From art to engineering: two decades of standards and tools towards digital organisms

Nicolas Le Novère
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Cambridge, UK
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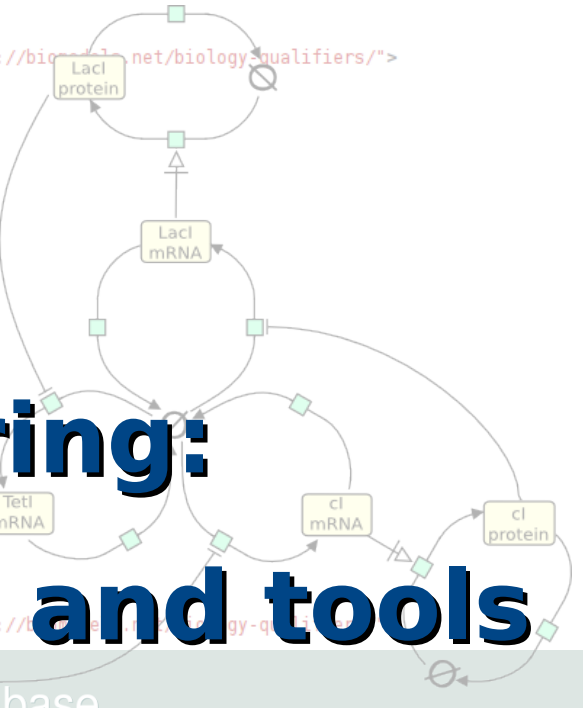
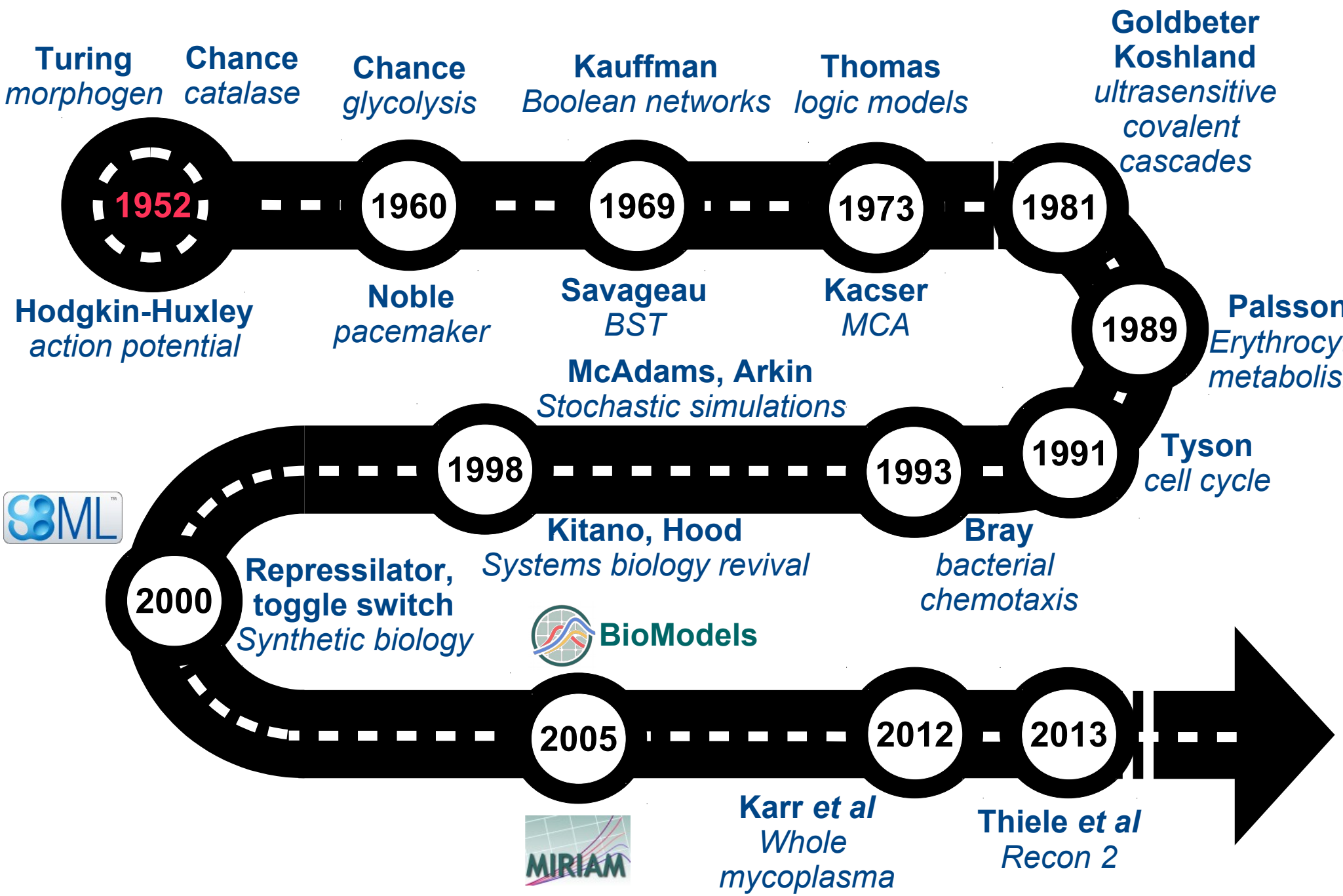
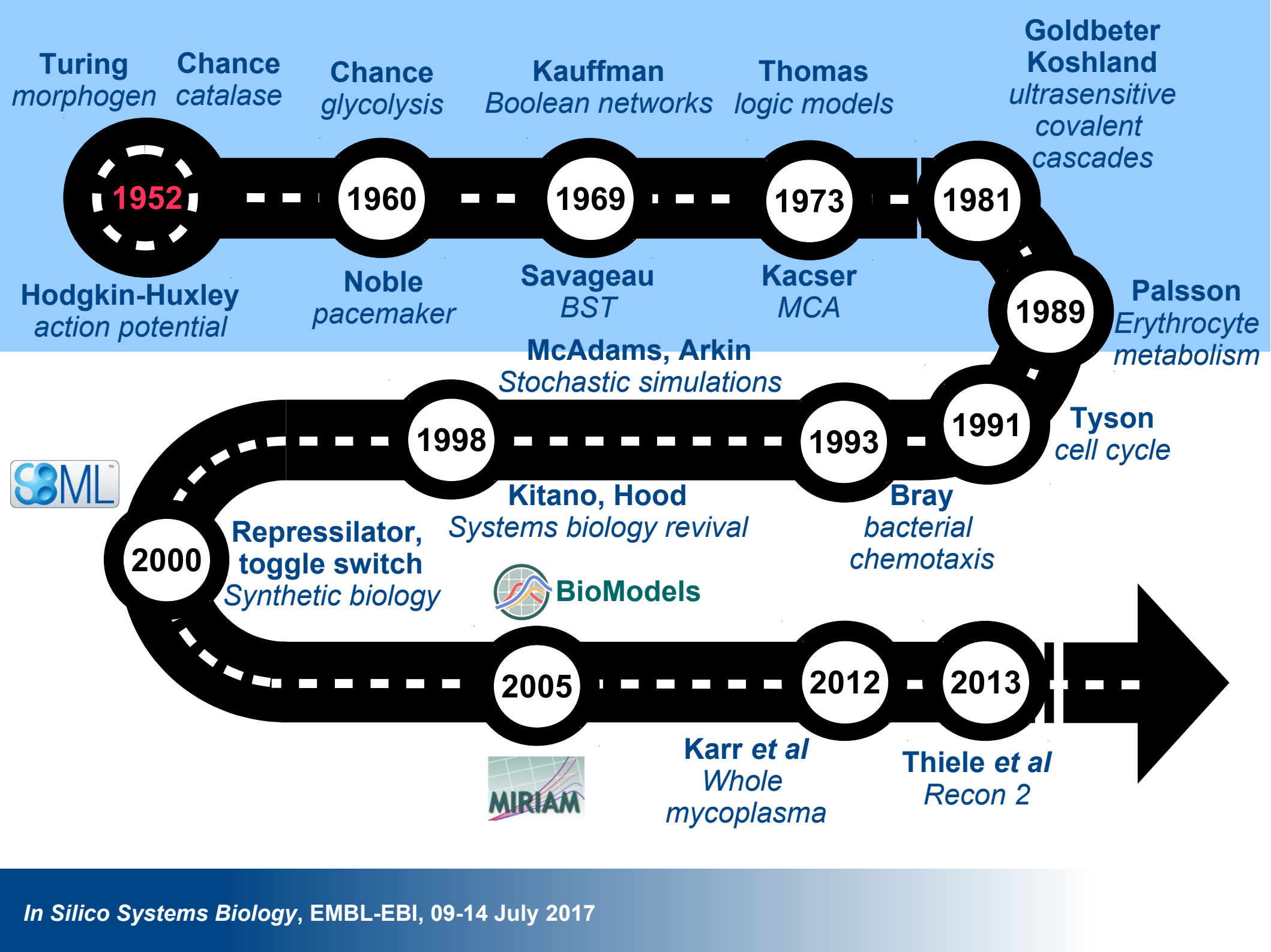



Turing
morphogen
Chance
catalase
Chance
glycolysis
Kauffman
Boolean networks
Thomas
logic models
Goldbeter
Koshland
ultrasensitive
covalent
cascades
1952
1960
1969
1973
1981
Hodgkin-Huxley
action potential
Noble
pacemaker
Savageau
BST
Kacser
MCA
1989
Palsson
Erythrocyte
metabolism
McAdams, Arkin
Stochastic 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
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Boolean networks
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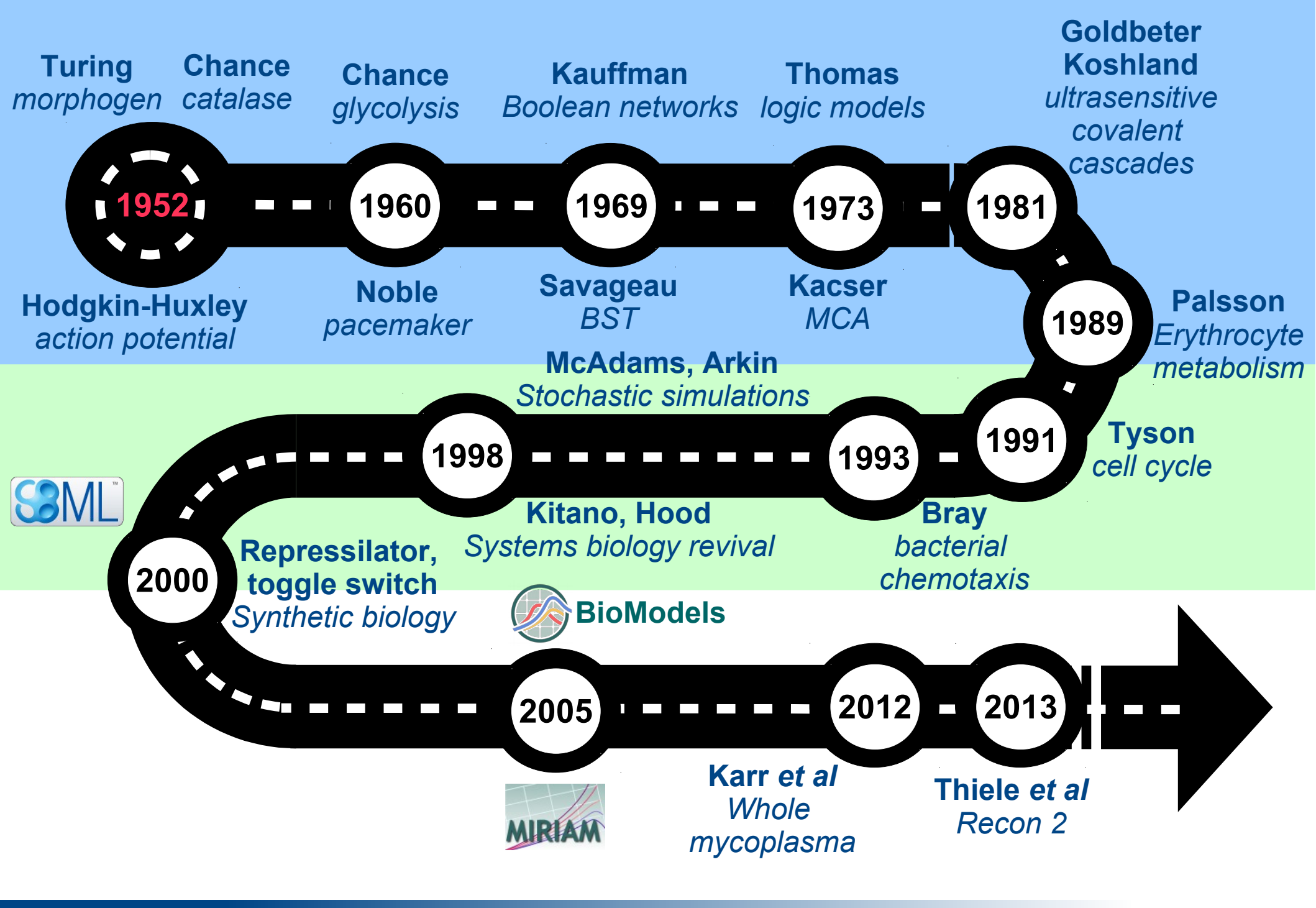
Recon 2


Turing
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Chance
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Kauffman
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logic models
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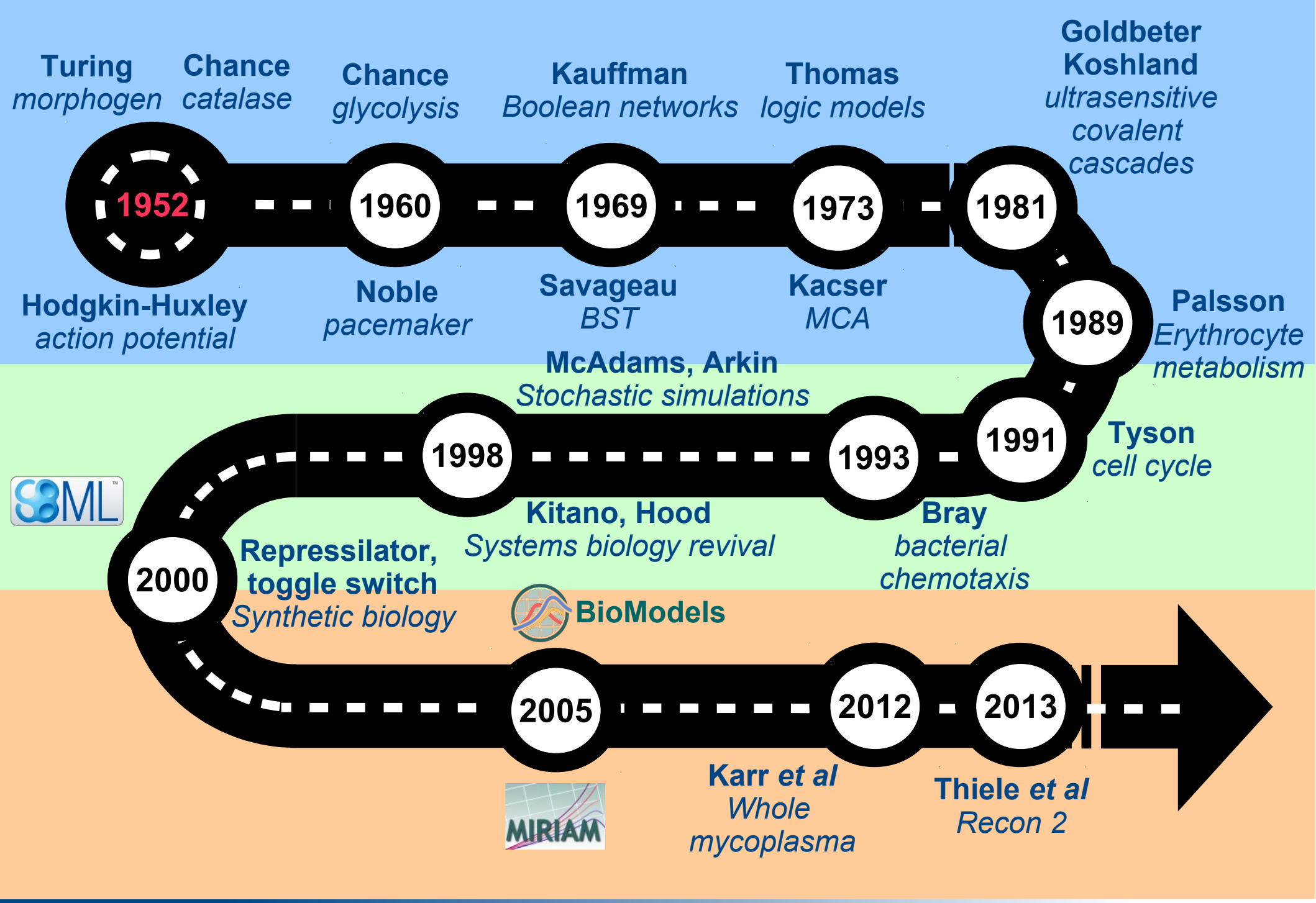
Recon 2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Kauffman
Boolean networks
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2000
Repressilator,
toggle switch
Synthetic biology
BioModels
2005
2012
2013
MIRIAM
Karr et al
Whole
mycoplasma
Thiele et al
Recon 2

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

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

combine the computational modeling in biology network

COMBINE 2017 | Standards | Events | Documents | About | Forums | Search

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lenov

- My account
- Create content
  - CoLoMoTo Page
  - HTML Page
  - Mediawiki Page
  - 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]

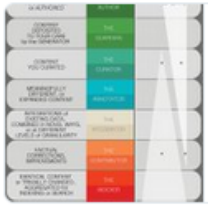
To discuss the goals, organization and operation of COMBINE, subscribe to [https://groups.google.com/forum/?hl=en-GB#!forum/combine-discuss COMBINE discuss]. To report issues about the co.mbine.org website, send a mail to combine-support @ googlegroups.com

http://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

A language to describe computational models in biology

	Model descriptions
Data-models	SBML™

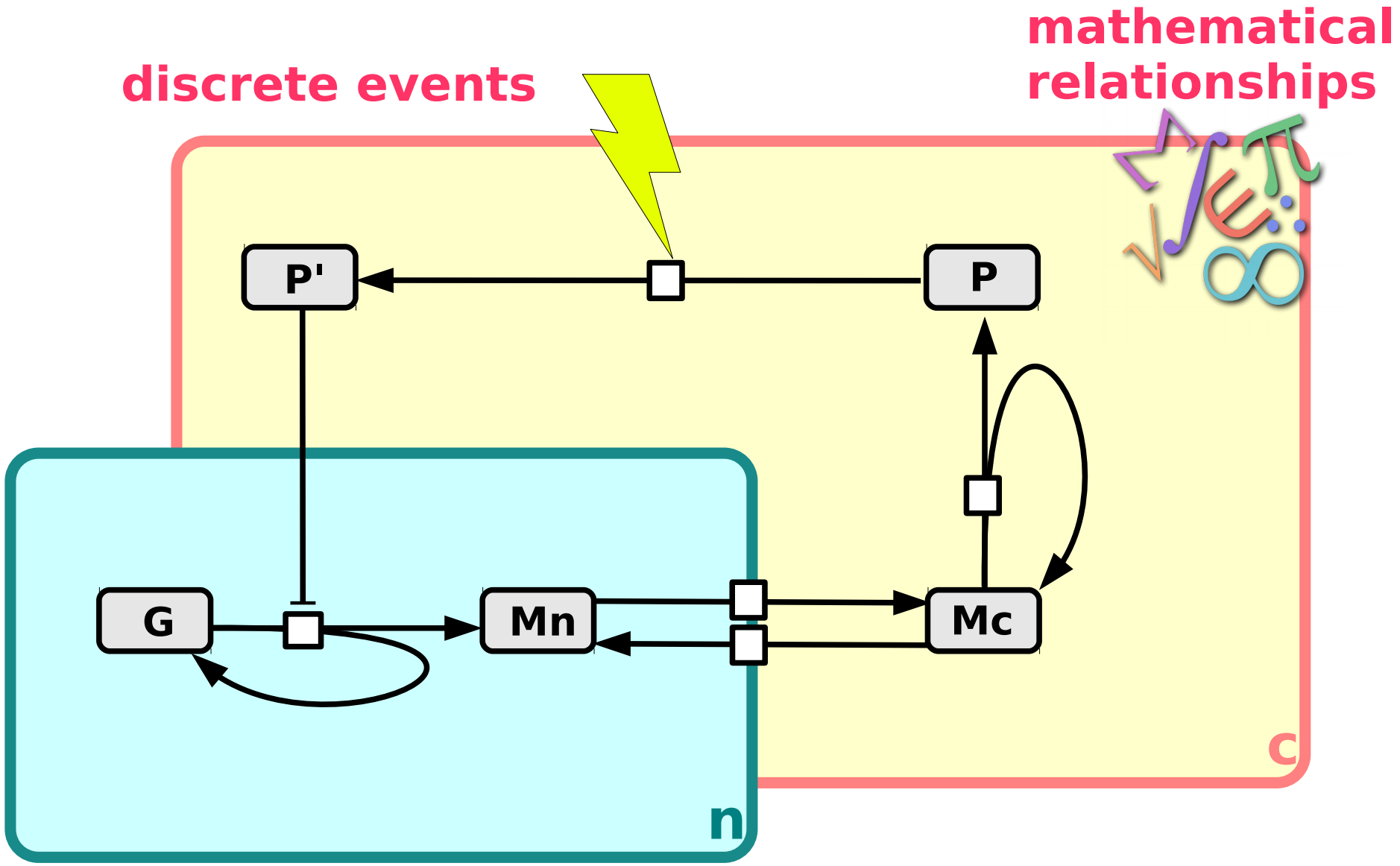
Born in Caltech 2000

John Doyle

Hiroaki Kitano

Hamid Bolouri | Mike Hucka | Andrew Finney | Herbert Sauro

What can we encode in SBML (core)?

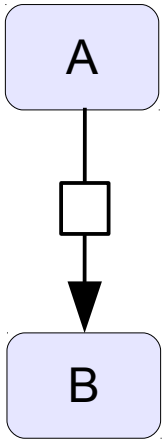


Structure of SBML core

```
<?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

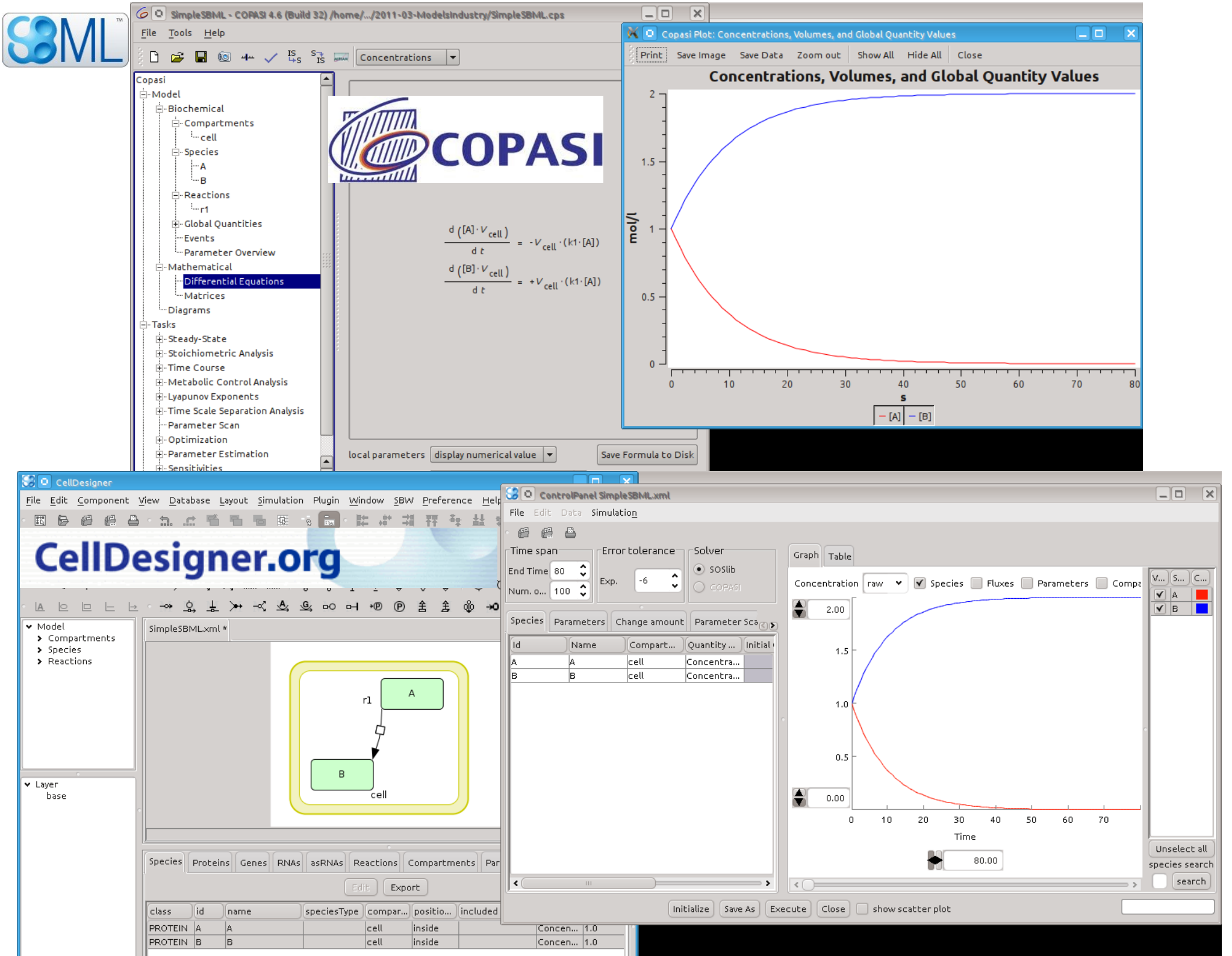
relationships



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

```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
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
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

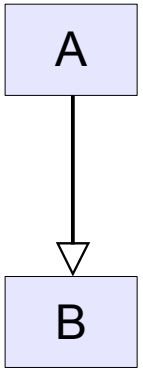
A not so simple SBML file (Recon2)

- 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
- Complex species – public specification
- Graph rendering – specification finalised
- Spatial diffusion – specification finalised
- Distributions and ranges – specification finalised
- Arrays and sets – draft specification available
- Dynamic structures – draft specification available
- Extended math – under discussion

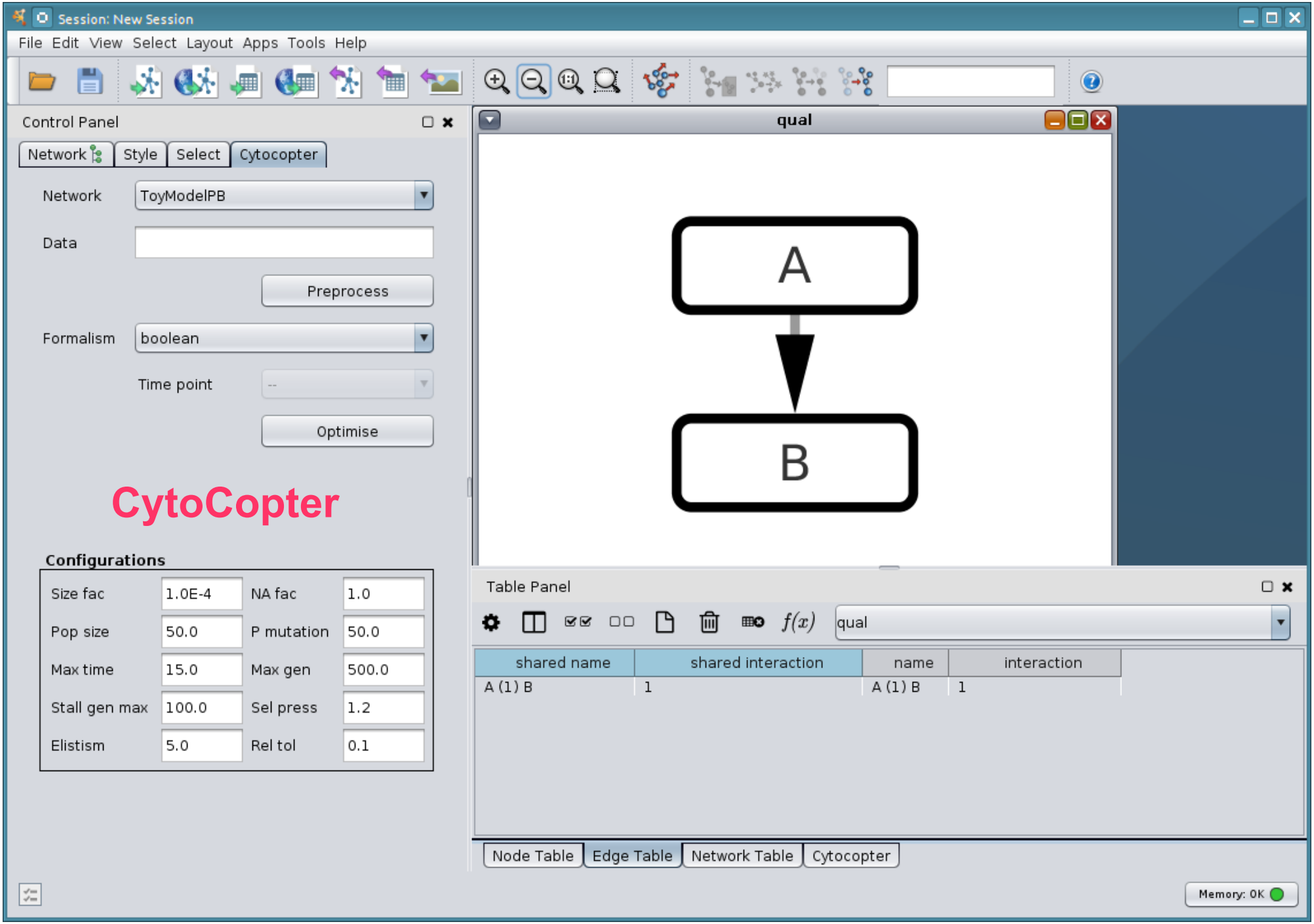
SBML Level 3 is modular

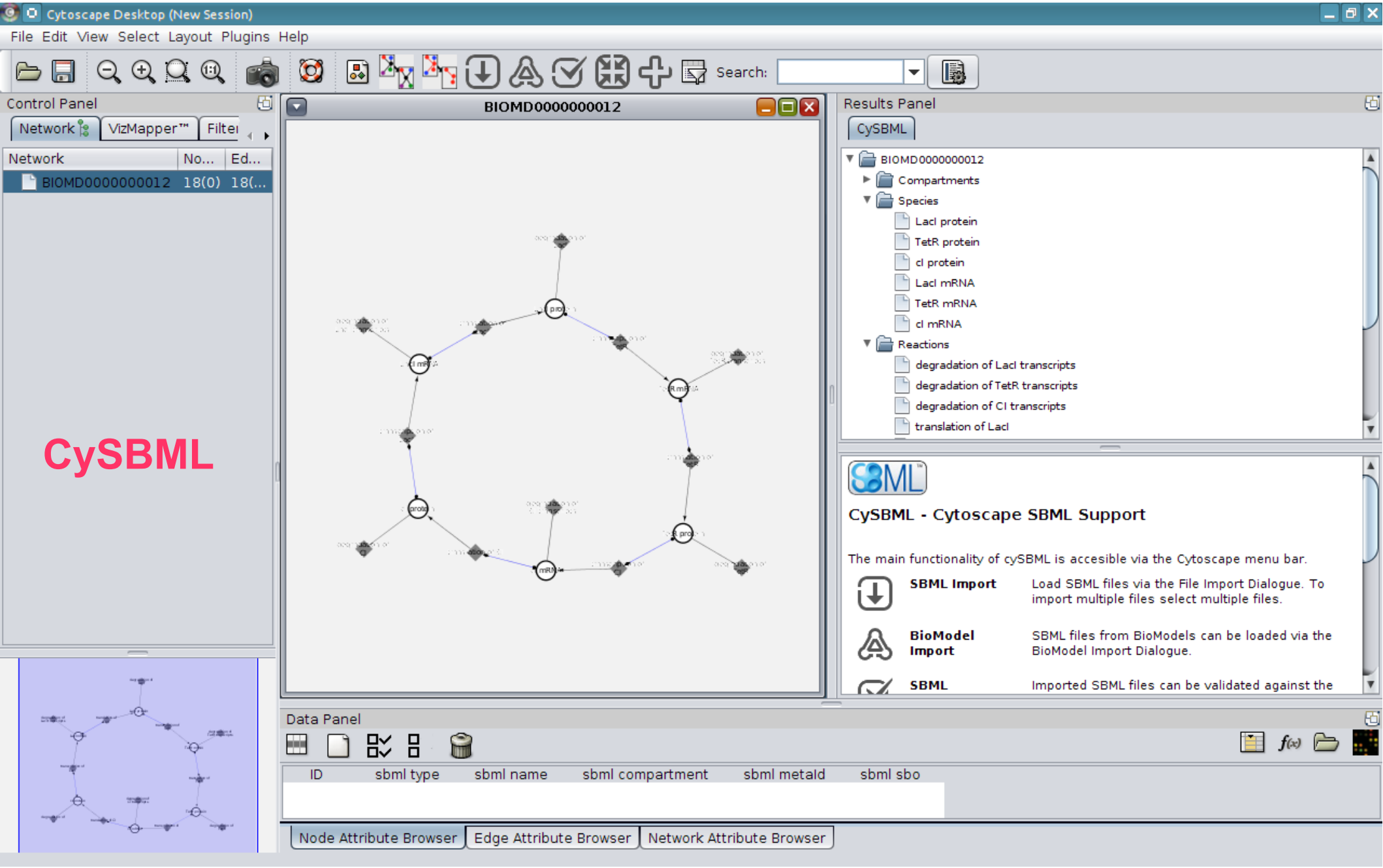


$$A \geqslant 1 \Rightarrow B = 1$$

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.org The Systems Biology Markup Language

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Parent pages: SBML.org

SBML Software Guide

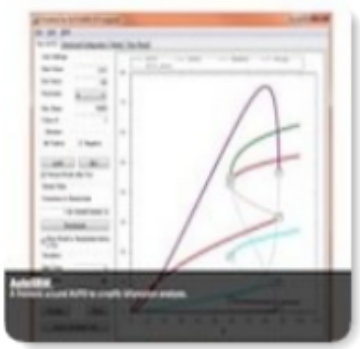
The following pages describe SBML-compatible software packages known to us. We offer different ways of viewing the information, all drawn from the same underlying data collected from the systems' developers via our **software survey**. The *Matrix* provides a table listing all known software and a variety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

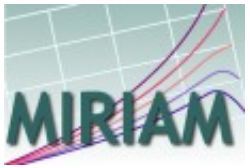
More on Friday

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



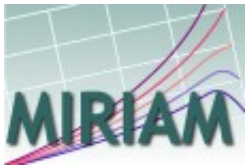
- Encoded in public standard format ☑
- Single reference description ☑
- Reflect biological processes ☑
- Simulatable and reproduce results ☑

- 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 ☑

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 ☑

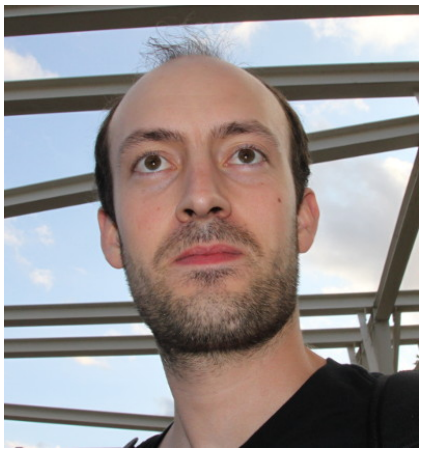
- Model components identified ☑
- Cross reference as triplets {collection, record, qualifier} ☑
- Collection and record in one agreed-upon URI ☑

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

Identifiers.org (aka new MIRIAM URIs)

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

protocol — type of URI — collection — record

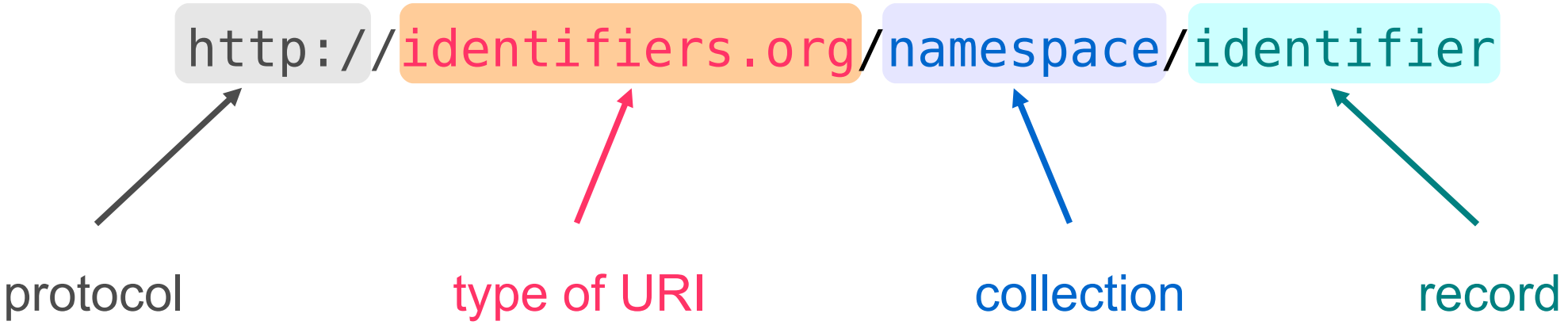


Camille Laibe

Nick Juty

Sarala Wimalaratne

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


Unique
Persistent
Resolvable
Maintained
Homogeneous
Human readable

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.

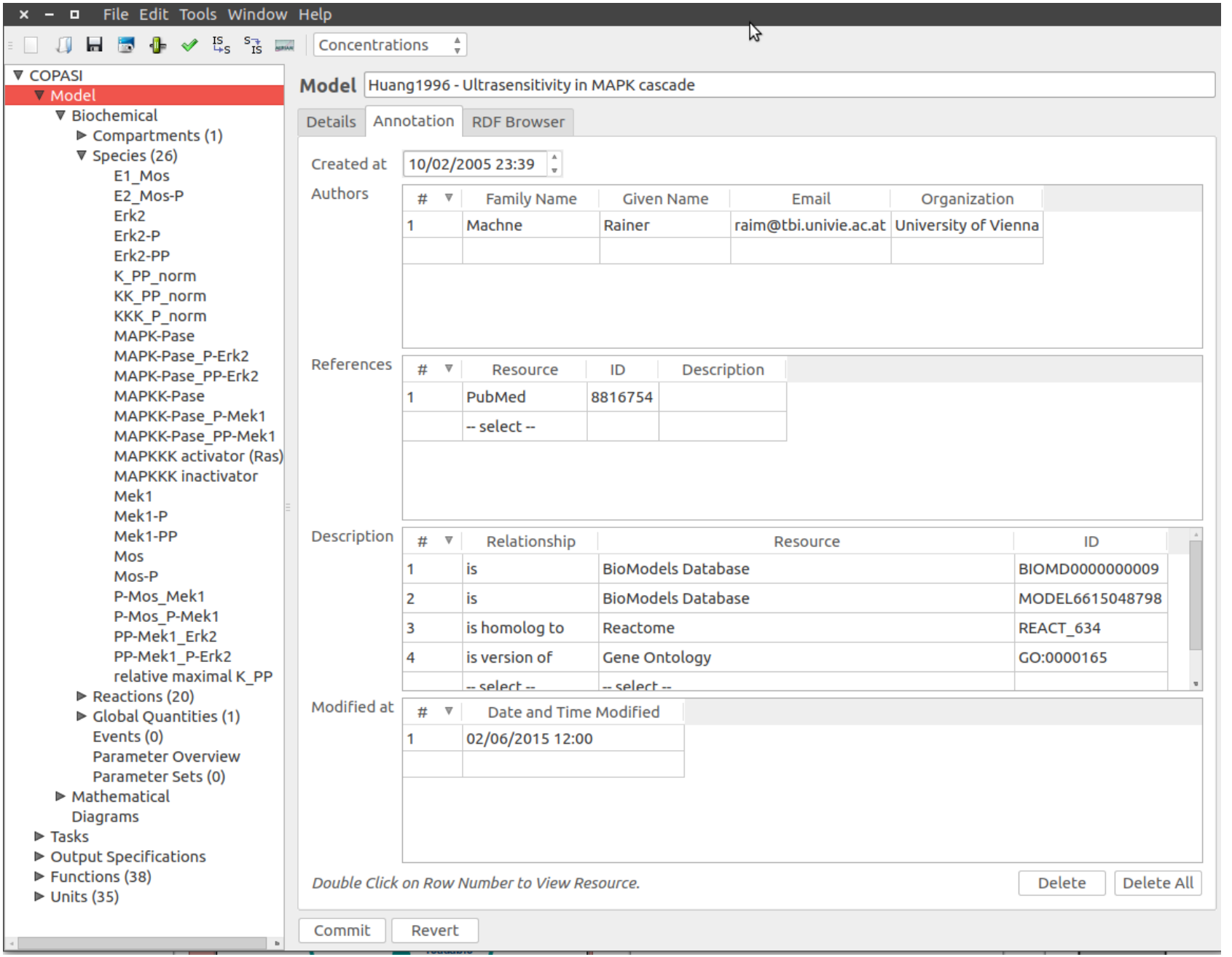
Web services

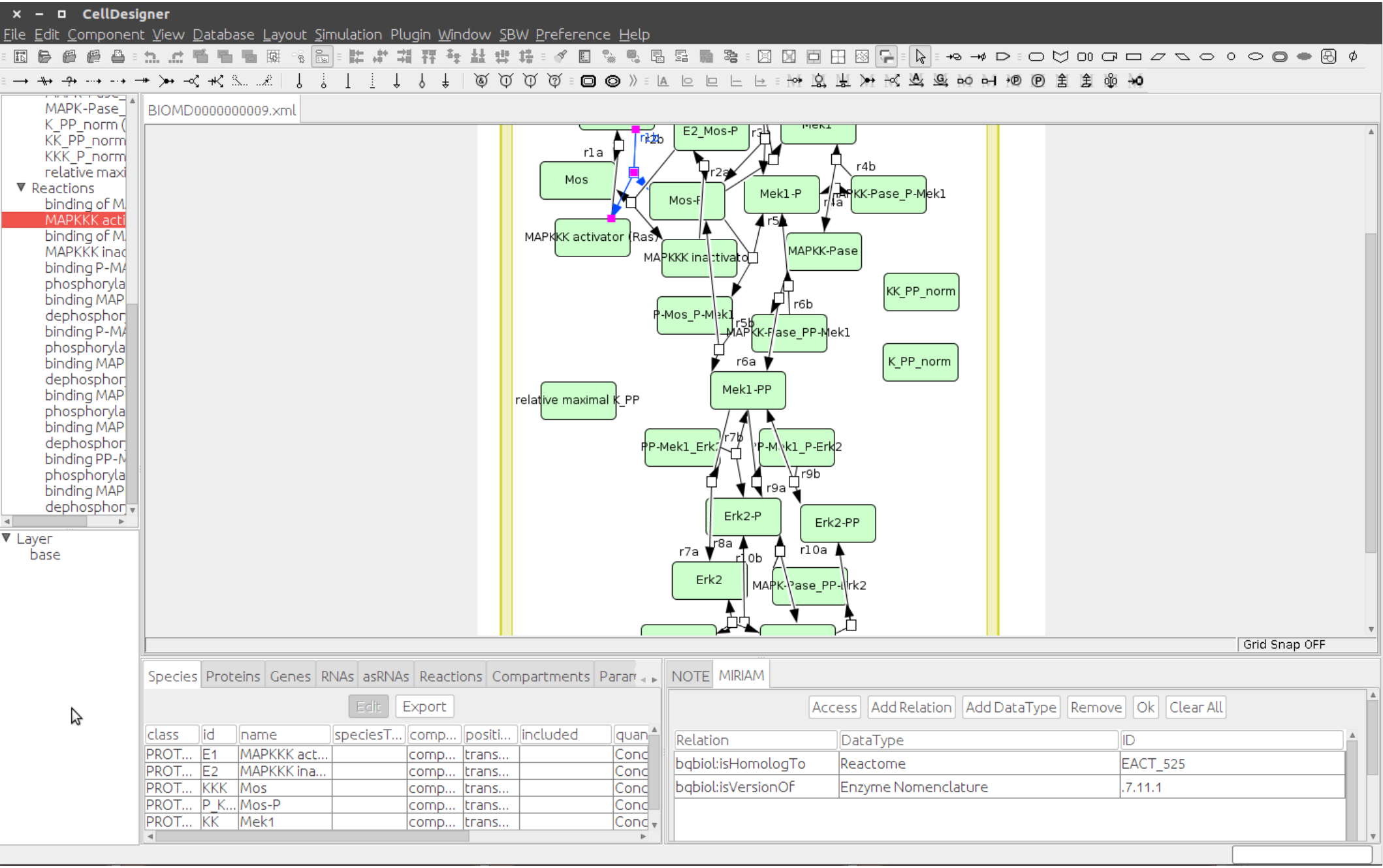
REST Web Services for programmatic access.

Download

Registry's content in XML is available here.

More on Friday


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
BIOMD0000000009.xml
MAPK-Pase_
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KK_PP_norm
KKK_P_norm
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Reactions
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binding MAP
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dephosphor
binding PP-M
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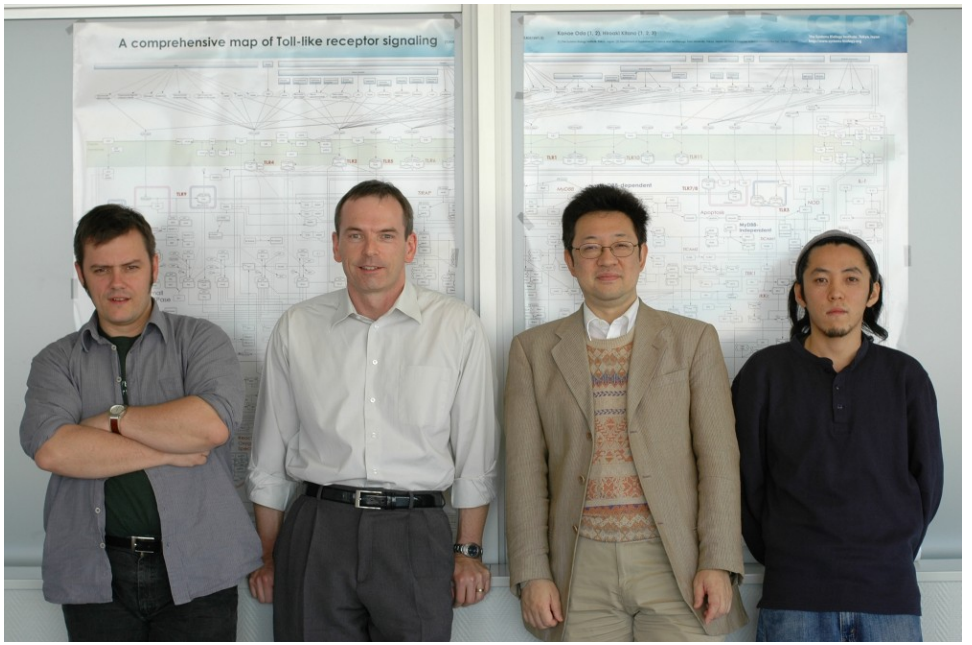
binding MAP
dephosphor
Layer
base
E2_Mos-P
r1a
r1b
r2b
r2a
r4b
Mos
Mos-P
Mek1-P
MAPKK-Pase_P-Mek1
r4a
r5
MAPKKK activator (Ras)
MAPKKK inactivator
MAPKK-Pase
KK_PP_norm
P-Mos_P-Mek1
r6b
r5b
MAPKK-Pase_PP-Mek1
r6a
K_PP_norm
Mek1-PP
relative maximal K_PP
PP-Mek1_Erk2
P-Mek1_P-Erk2
r7b
r9b
r9a
Erk2-P
Erk2-PP
r8a
r7a
r10a
r10b
Erk2
MAPK-Pase_PP-Erk2
Grid Snap OFF
Species Proteins Genes RNAs asRNAs Reactions Compartments Param
Edit Export
class id name speciesT... comp... positi... included quan
PROT... E1 MAPKKK act... comp... trans... Conc
PROT... E2 MAPKKK ina... comp... trans... Conc
PROT... KKK Mos comp... trans... Conc
PROT... P_K... Mos-P comp... trans... Conc
PROT... KK Mek1 comp... trans... Conc
NOTE MIRIAM
Access Add Relation Add DataType Remove Ok Clear All
Relation DataType ID
bqbiol:isHomologTo Reactome EACT_525
bqbiol:isVersionOf Enzyme Nomenclature .7.11.1

The interface with all biologists

	Model descriptions
Minimal requirements	MIRIAM
Data-models	SBML, SBGN
Terminologies	SBO

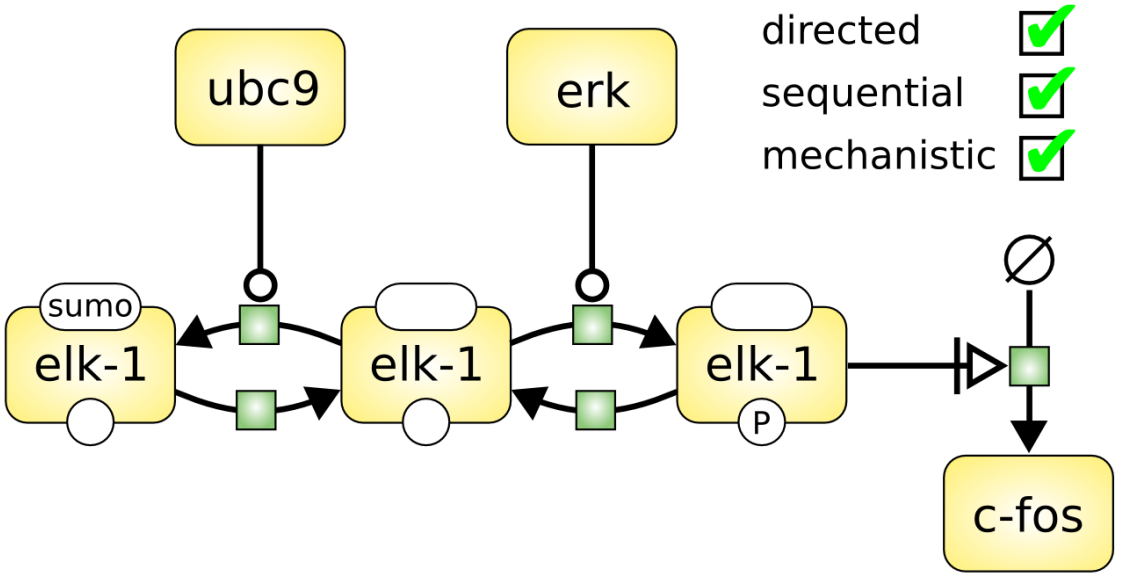
Born in Tokyo 2005



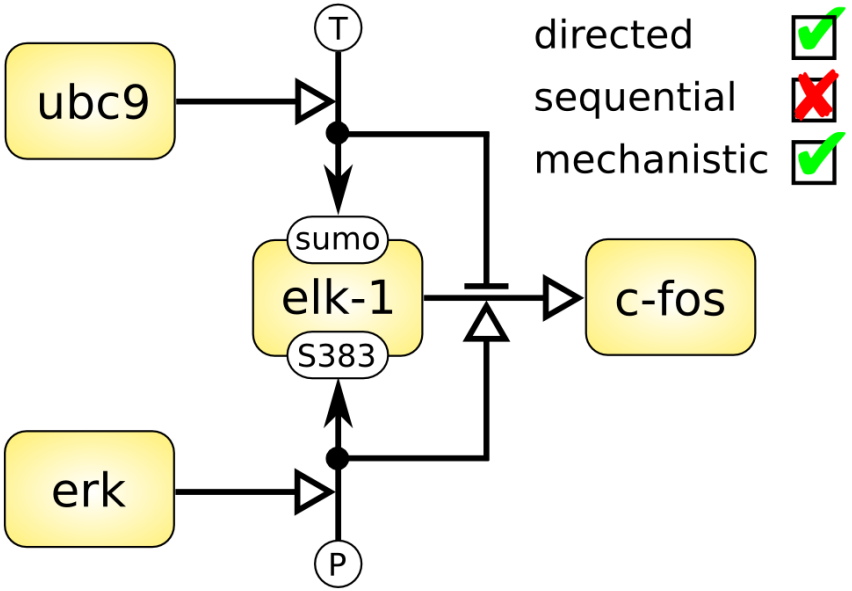
Akira Funahashi

One standard
Three languages

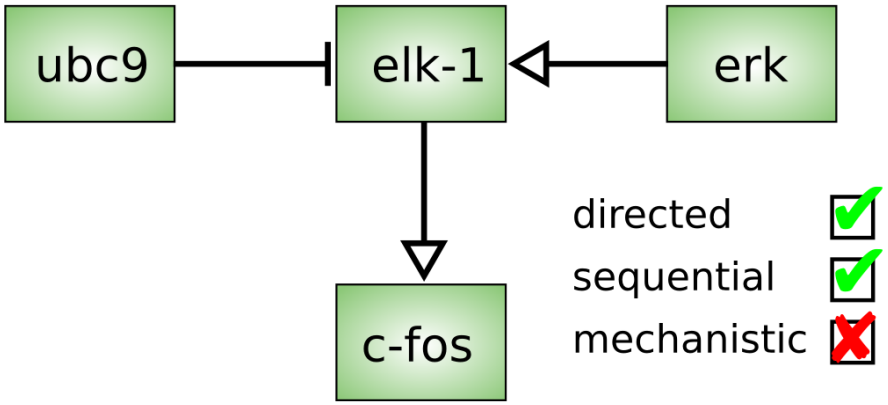
process descriptions



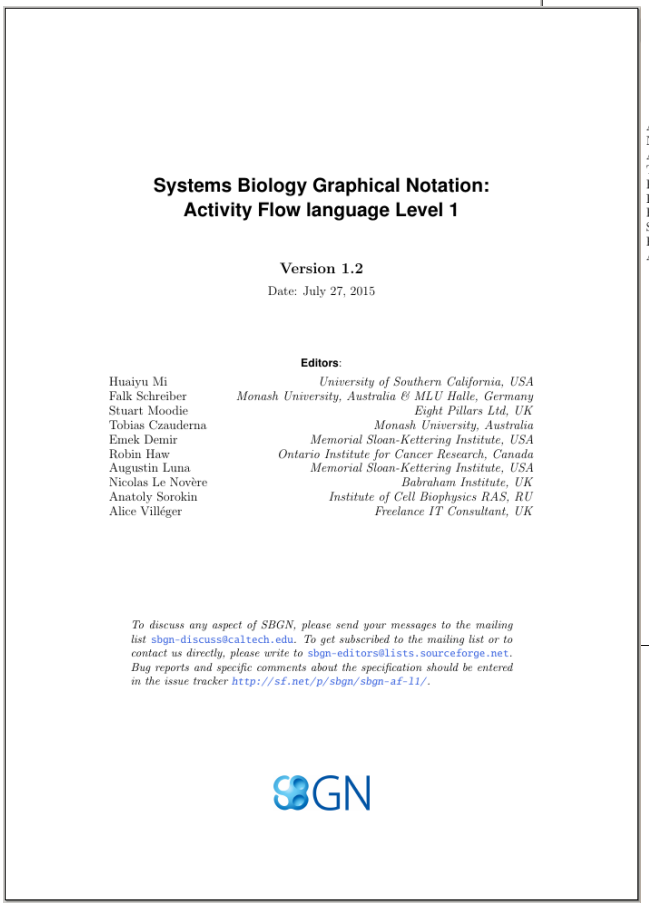
entity relationships



activity flows



http://sbgn.org/



Systems Biology Graphical Notation:
Activity Flow language Level 1

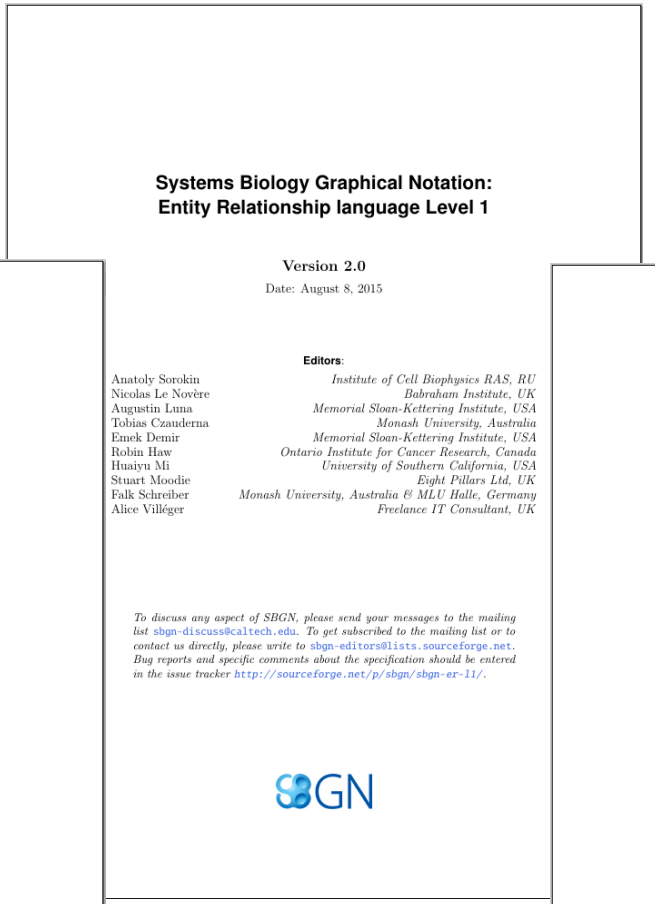
Version 1.2

Date: July 27, 2015

Editors:

Huaiyu Mi	*University of Southern California, USA*
Falk Schreiber	*Monash University, Australia & MLU Halle, Germany*
Stuart Moodie	*Eight Pillars Ltd, UK*
Tobias Czauderna	*Monash University, Australia*
Emek Demir	*Memorial Sloan-Kettering Institute, USA*
Robin Haw	*Ontario Institute for Cancer Research, Canada*
Augustin Luna	*Memorial Sloan-Kettering Institute, USA*
Nicolas Le Novère	*Babraham Institute, UK*
Anatoly Sorokin	*Institute of Cell Biophysics RAS, RU*
Alice Villéger	*Freelance IT Consultant, UK*

To discuss any aspect of SBGN, please send your messages to the mailing list sbgn-discuss@caltech.edu. *To get subscribed to the mailing list or to contact us directly, please write to* sbgn-editors@lists.sourceforge.net. *Bug reports and specific comments about the specification should be entered in the issue tracker* http://sf.net/p/sbgn/sbgn-af-ll/.



Systems Biology Graphical Notation:
Entity Relationship language Level 1

Version 2.0

Date: August 8, 2015

Editors:

Anatoly Sorokin	*Institute of Cell Biophysics RAS, RU*
Nicolas Le Novère	*Babraham Institute, UK*
Augustin Luna	*Memorial Sloan-Kettering Institute, USA*
Tobias Czauderna	*Monash University, Australia*
Emek Demir	*Memorial Sloan-Kettering Institute, USA*
Robin Haw	*Ontario Institute for Cancer Research, Canada*
Huaiyu Mi	*University of Southern California, USA*
Stuart Moodie	*Eight Pillars Ltd, UK*
Falk Schreiber	*Monash University, Australia & MLU Halle, Germany*
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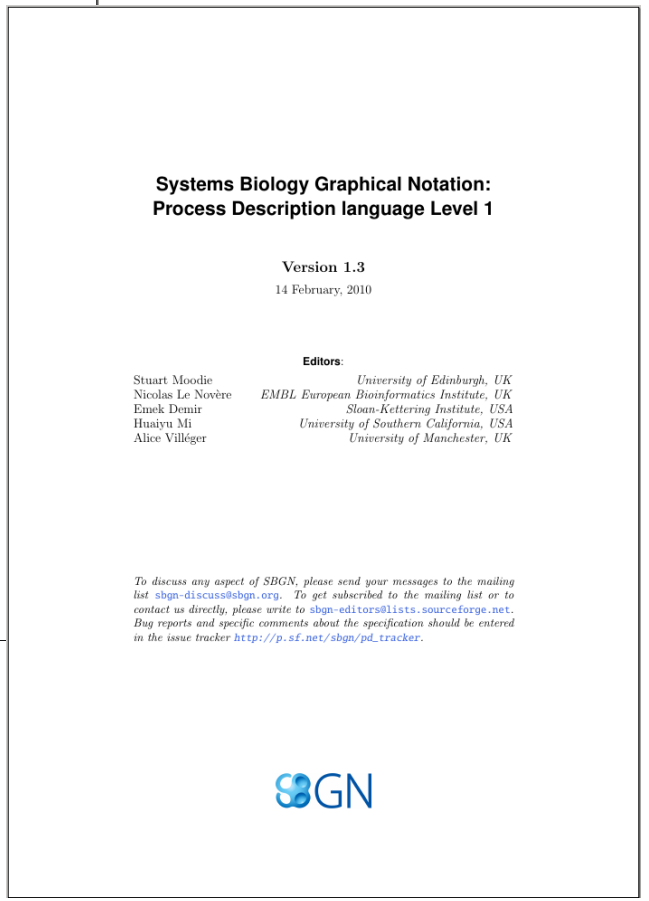


Systems Biology Graphical Notation:
Process Description language Level 1

Version 1.3

14 February, 2010

Editors:

Stuart Moodie	*University of Edinburgh, UK*
Nicolas Le Novère	*EMBL European Bioinformatics Institute, UK*
Emek Demir	*Sloan-Kettering Institute, USA*
Huaiyu Mi	*University of Southern California, USA*
Alice Villéger	*University of Manchester, UK*

To discuss any aspect of SBGN, please send your messages to the mailing list sbgn-discuss@sbgn.org. *To get subscribed to the mailing list or to contact us directly, please write to* sbgn-editors@lists.sourceforge.net. *Bug reports and specific comments about the specification should be entered in the issue tracker* http://p.sf.net/sbgn/pd_tracker.

```xml
<?xml version="1.0" encoding="UTF-8"?>
<sbgn xmlns="http://sbgn.org/libsbgn/0.3">
  <map version="http://identifiers.org/combine.specifications/
  sbgn.pd.level-1.version-1.3" id="map1">
        <bbox x="0" y="0" w="363" h="253"/>
        <glyph class="simple chemical" id="glyph1">
              <label text="Ethanol"/> <!-- fontsize="" etc -->
              <!-- Line breaks are allowed in the text attribute -->
              <bbox x="40" y="120" w="60" h="60"/>
        </glyph>
        <glyph class="simple chemical" id="glyph_ethanal">
              <label text="Ethanal" />
              <bbox x="220" y="110" w="60" h="60"/>
        </glyph>
        <glyph class="macromolecule" id="glyph_adh1">
              <label text="ADH1" />
              <bbox x="106" y="20" w="108" h="60"/>
        </glyph>
        <glyph class="simple chemical" id="glyph_h">
              <label text="H+" />
              <bbox x="220" y="190" w="60" h="60"/>
        </glyph>
        <glyph class="simple chemical" id="glyph_nad">
              <label text="NAD+" />
              <bbox x="40" y="190" w="60" h="60"/>
        </glyph>
        <glyph class="simple chemical" id="glyph_nadh">
              <label text="NADH" />
              <bbox x="300" y="150" w="60" h="60"/>
        </glyph>

        <glyph class="process" orientation="horizontal" id="pn1">
              <bbox x="148" y="168" w="24" h="24"/>
              <port x="136" y="180" id="pn1.1"/>
              <port x="184" y="180" id="pn1.2"/>
        </glyph>

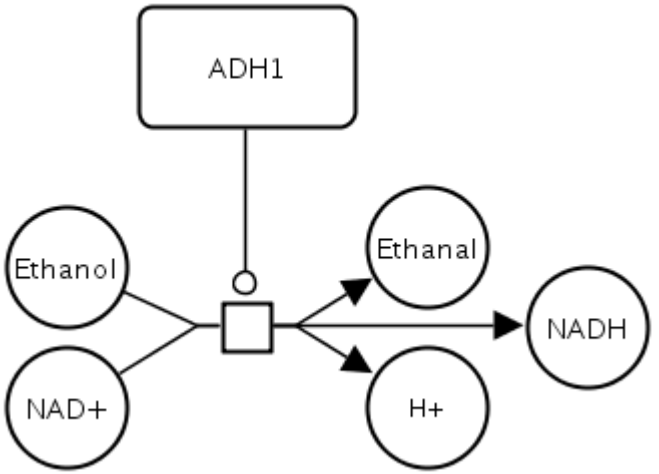
        <arc class="consumption" source="glyph1" target="pn1.1"
        id="a01">
              <start x="98" y="160" />
              <end x="136" y="180" />
        </arc>

        <arc class="production" source="pn1.2" target="glyph_nadh"
        id="a02">
              <start x="184" y="180" />
              <end x="300" y="180" />
        </arc>

        <arc class="catalysis" source="glyph_adh1" target="pn1"
        id="a03">
              <start x="160" y="80" />
              <end x="160" y="168" />
        </arc>

        <arc class="production" source="pn1.2" target="glyph_h"
        id="a04">
              <start x="184" y="180" />
              <end x="224" y="202" />
        </arc>
        <arc class="production" source="pn1.2" target="glyph_ethanal"
        id="a05">
              <start x="184" y="180" />
              <end x="224" y="154" />
```

SBGN-ML



LibSBGN

Edit New Page

Matthias König edited this page on 30 Sep 2016 · 13 revisions

LibSBGN library

LibSBGN is the library for writing and reading SBGN-ML, a XML-based file format dedicated to the description of SBGN maps.

Source code: https://github.com/sbgn/libsbgn
Latest release: https://github.com/sbgn/libsbgn/releases

Features

LibSBGN is a library that deals with SBGN maps. It currently supports:

- Reading / writing the SBGN-ML file format (XML-based format for description of SBGN maps)
- Validation of semantical and syntactical correctness
- Conversion to other formats such as SBML and BioPAX
- Support for Java and C++

Documentation

Pages 89

SBGN

Systems Biology Graphical Notation

###Home

###Events

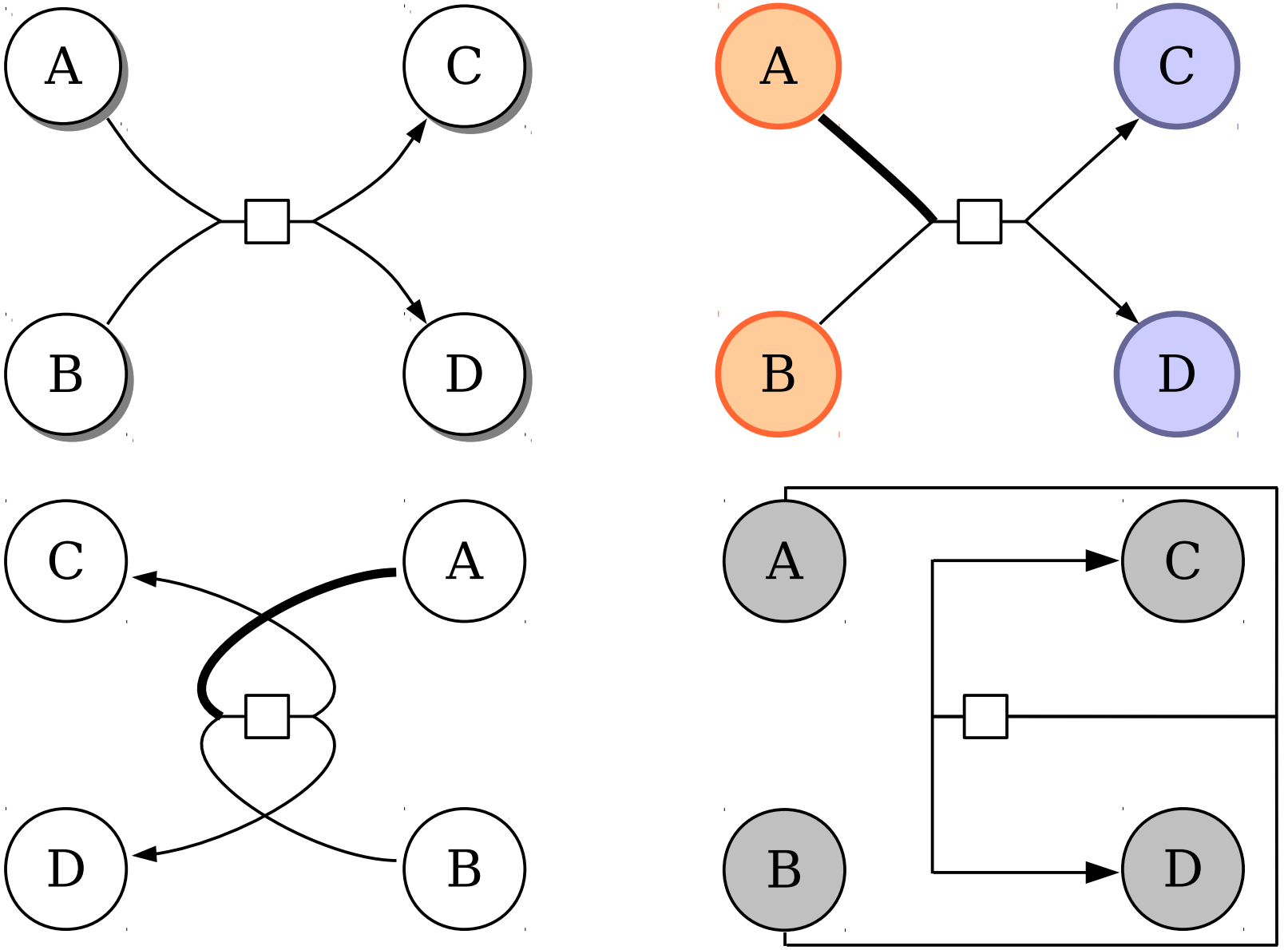
- Logistics
- Notes

###Editor Meeting Notes

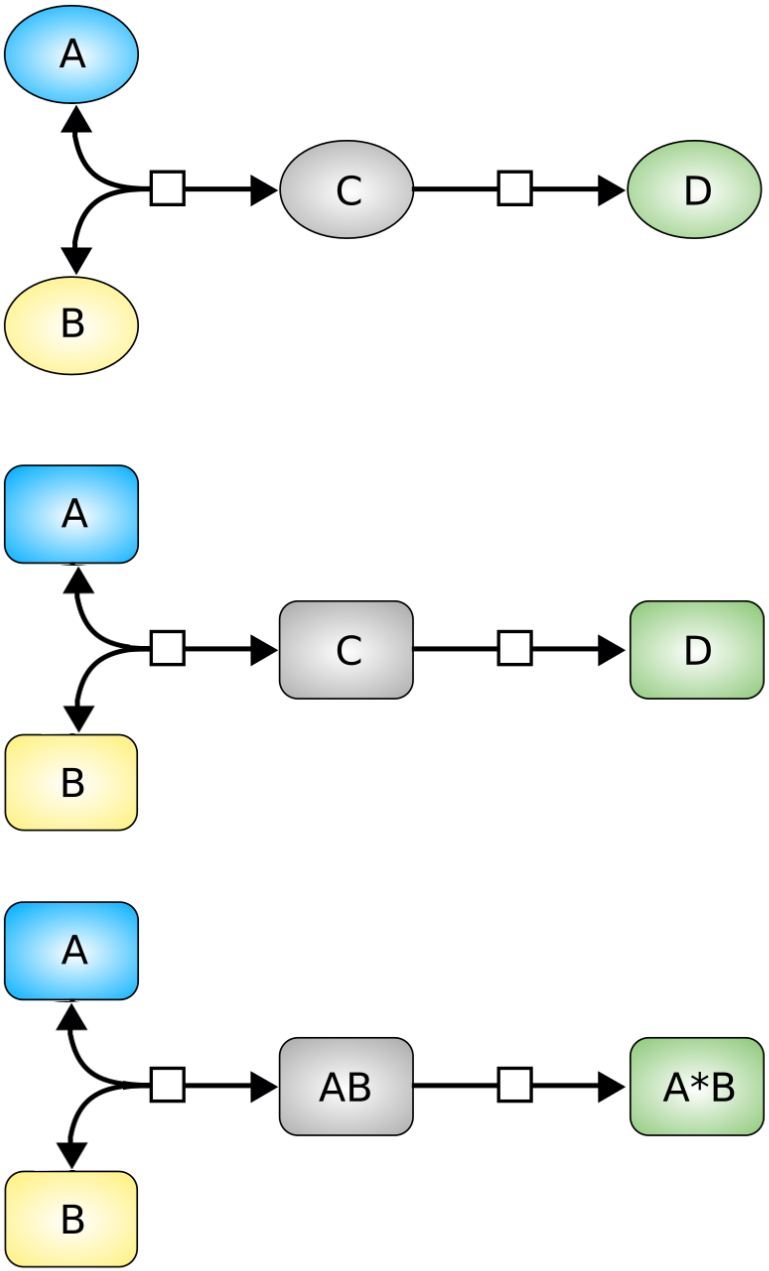
###LibSBGN

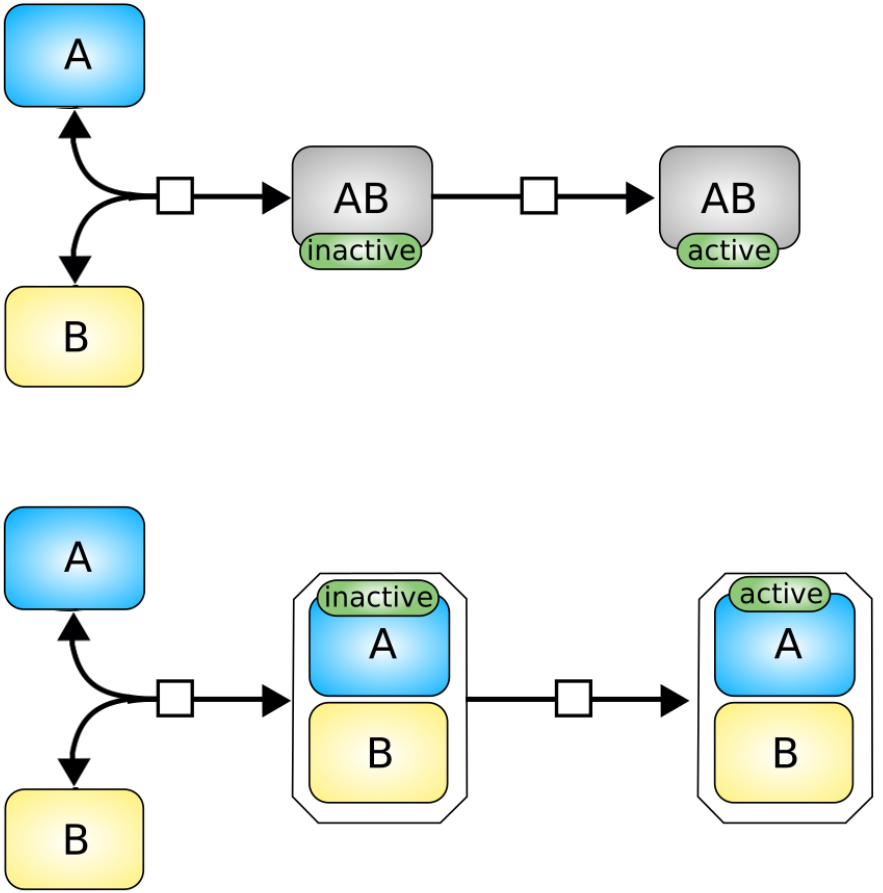
###Specification Development

All those diagrams are identical

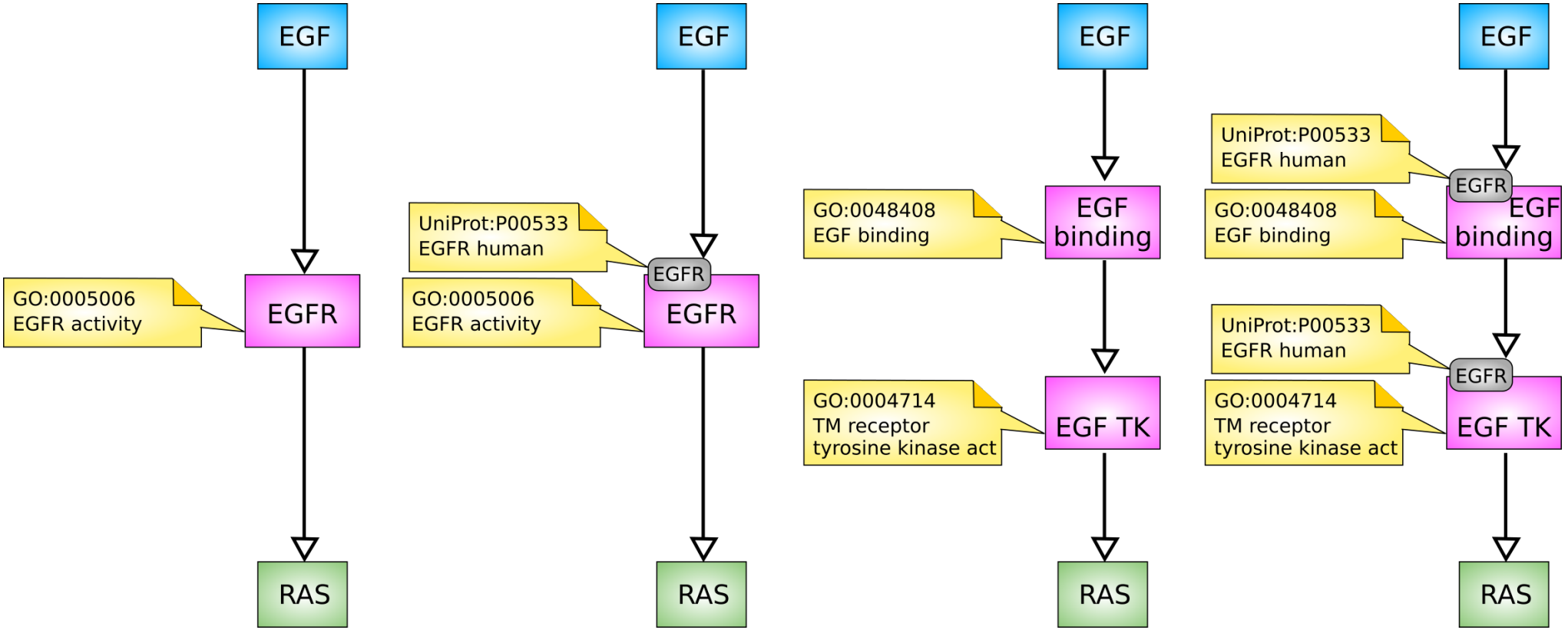


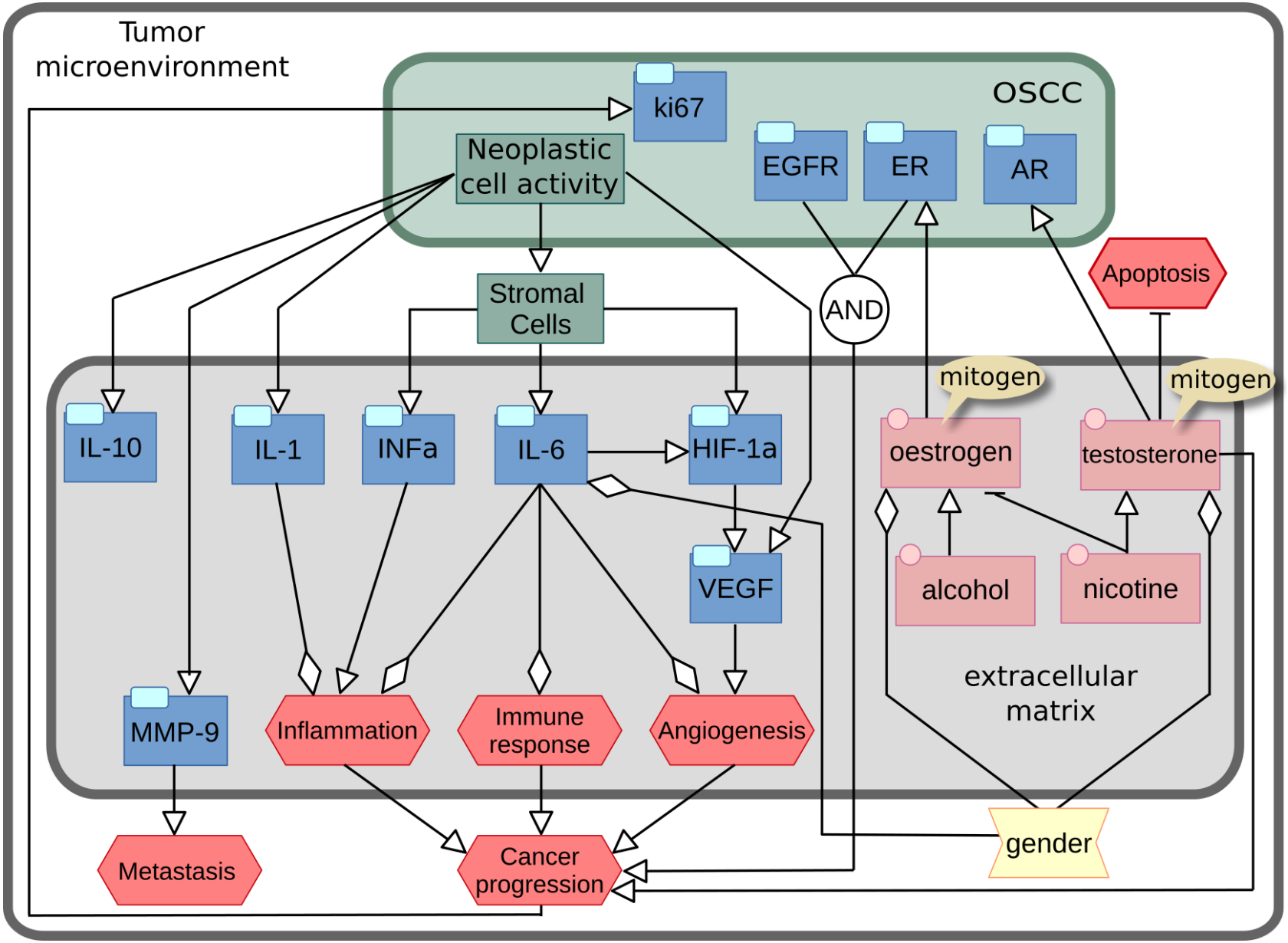
Variable granularity

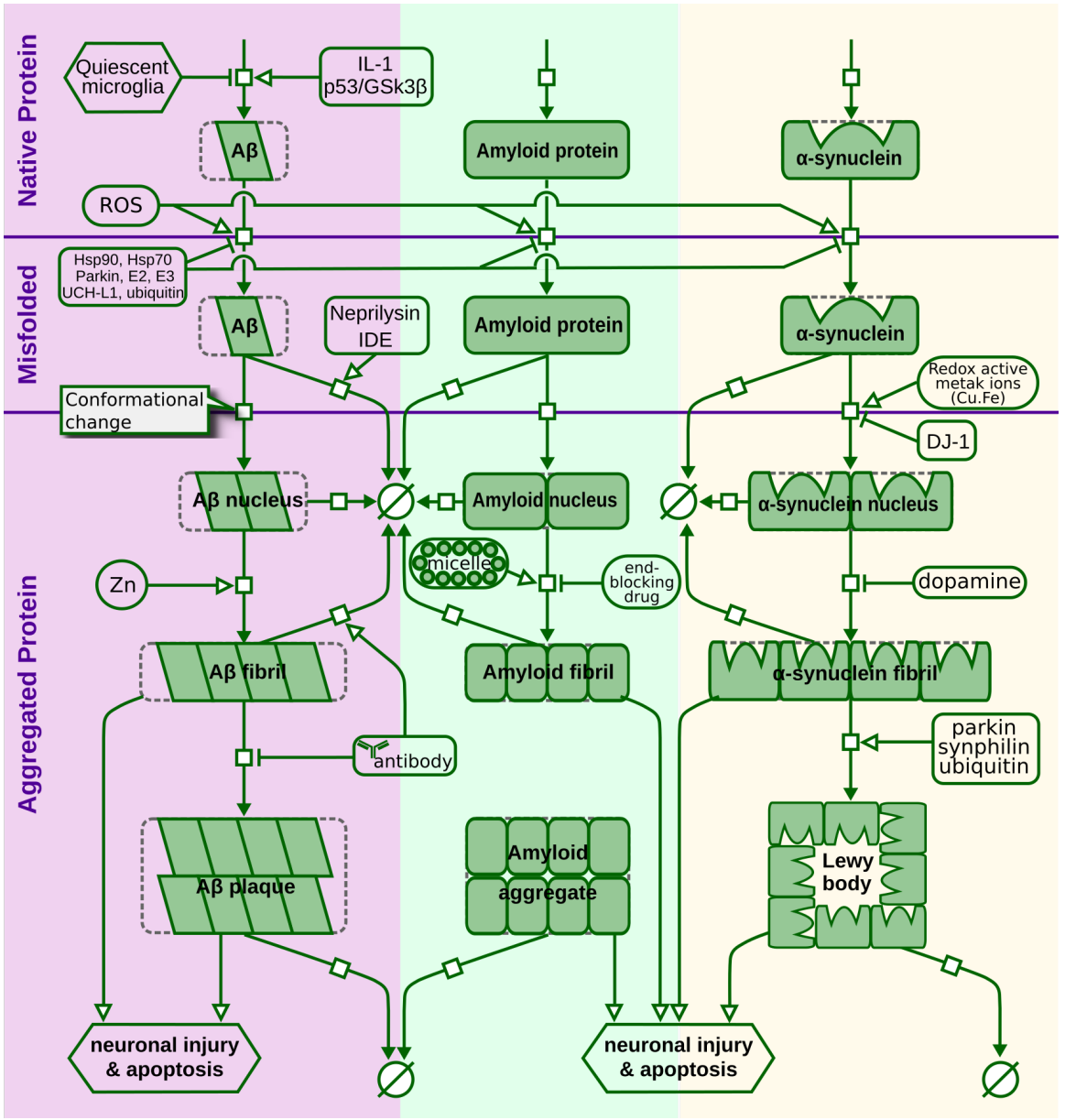


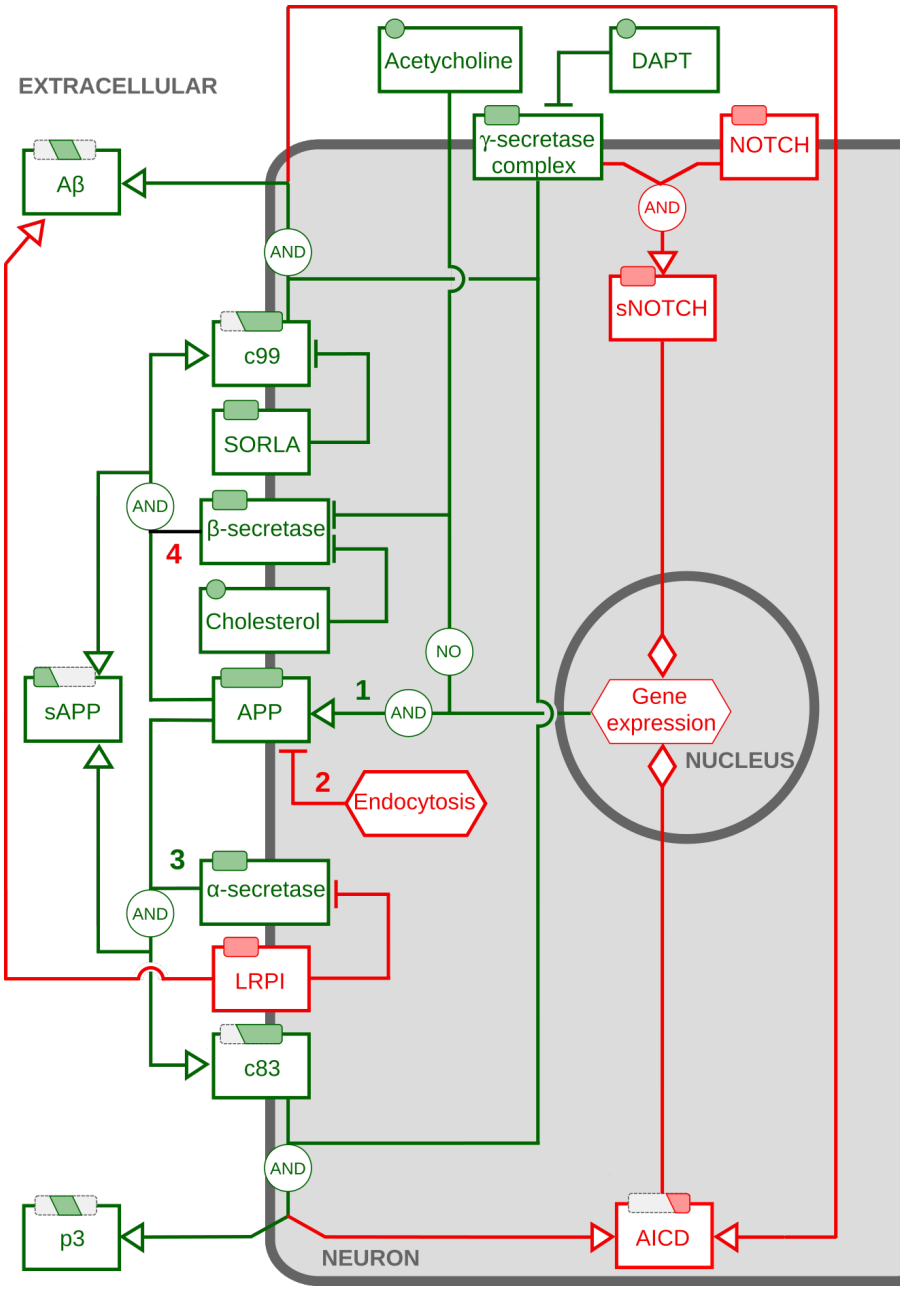


There Is More Than One Way To Do It




Tumor microenvironment
OSCC
ki67
Neoplastic cell activity
EGFR
ER
AR
Apoptosis
Stromal Cells
AND
mitogen
mitogen
IL-10
IL-1
INFa
IL-6
HIF-1a
oestrogen
testosterone
VEGF
alcohol
nicotine
extracellular matrix
MMP-9
Inflammation
Immune response
Angiogenesis
Metastasis
Cancer progression
gender


Native Protein
Misfolded
Aggregated Protein
Quiescent microglia
IL-1
p53/GSk3β
Aβ
Amyloid protein
α-synuclein
ROS
Hsp90, Hsp70
Parkin, E2, E3
UCH-L1, ubiquitin
Neprilysin
IDE
Redox active metak ions (Cu.Fe)
Conformational change
DJ-1
Aβ nucleus
Amyloid nucleus
α-synuclein nucleus
micelle
end-blocking drug
Zn
dopamine
Aβ fibril
Amyloid fibril
α-synuclein fibril
antibody
parkin
synphilin
ubiquitin
Aβ plaque
Amyloid aggregate
Lewy body
neuronal injury & apoptosis
neuronal injury & apoptosis

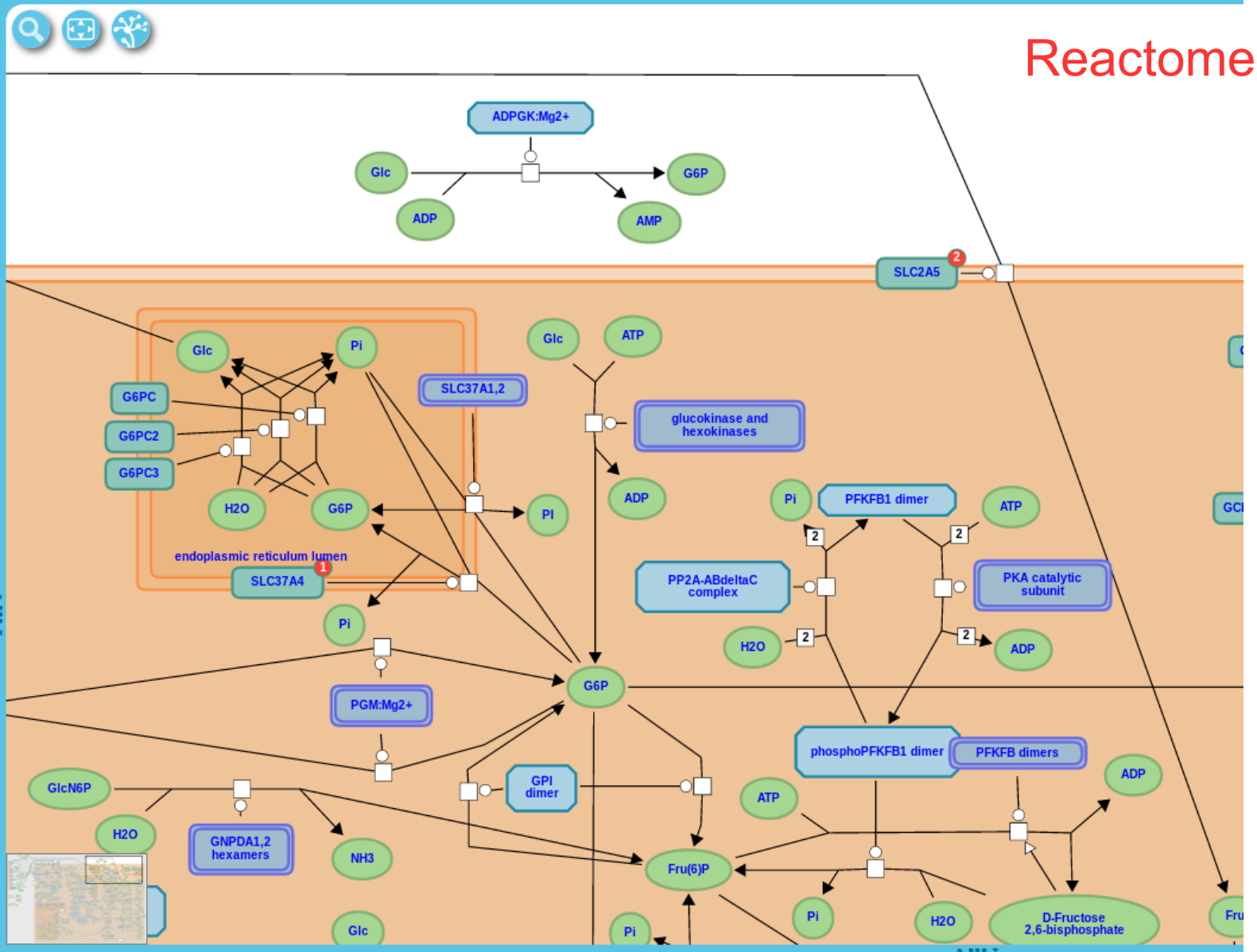

EXTRACELLULAR
Acetycholine
DAPT
γ-secretase complex
NOTCH
Aβ
AND
sNOTCH
c99
SORLA
AND
β-secretase
4
Cholesterol
NO
sAPP
APP
1
AND
Gene expression
NUCLEUS
2
Endocytosis
3
α-secretase
AND
LRPI
c83
AND
p3
NEURON
AICD

REACTOME 3.4 60

Pathways for: **Homo sapiens**

Event Hierarchy:

- Cell Cycle
- Cell-Cell communication
- Cellular responses to external stimuli
- Chromatin organization
- Circadian Clock
- Developmental Biology
- Digestion and absorption
- Disease
- DNA Repair
- DNA Replication
- Extracellular matrix organization
- Gene expression (Transcription)
- Hemostasis
- Immune System
- **Metabolism**
  - **Metabolism of carbohydrates**
    - Digestion of dietary carbohydrate
      - CHIA hydrolyses chitin
      - CHIT1 hydrolyses CHIT to 3xADGF
    - Hexose transport
    - Glucose metabolism
      - Glycolysis
      - Gluconeogenesis
        - Exchange of alpha-ketoglutarate
      - Glycogen synthesis
      - Glycogen breakdown (glycog
        - ADPGK:Mg2+ phosphorylates G
        - GNPDA1,2 hexamers deaminat
        - BPGM dimer isomerises 1,3BPG
    - Fructose metabolism
    - Lactose synthesis
    - Galactose catabolism
    - Pentose phosphate pathway (he
    - 5-Phosphoribose 1-diphosphate bi
    - Glycosaminoglycan metabolism
    - Catabolism of glucuronate to xylulc
    - Lysosomal oligosaccharide catabo
  - Inositol phosphate metabolism
  - Metabolism of lipids



Description | Molecules | Structures | Expression | Analysis | Downloads

Metabolism of carbohydrates | Species: Homo sapiens

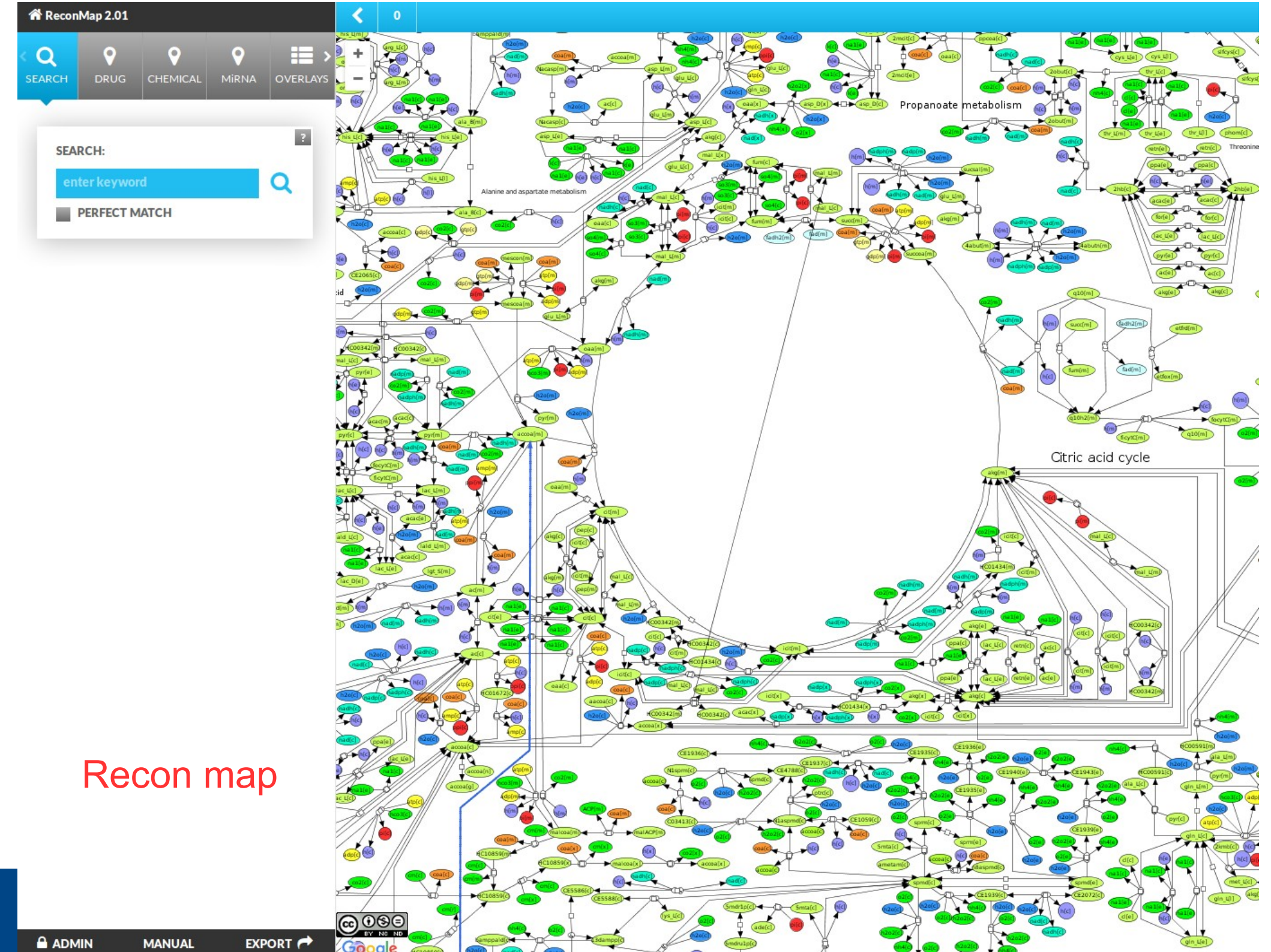
Stable Identifier

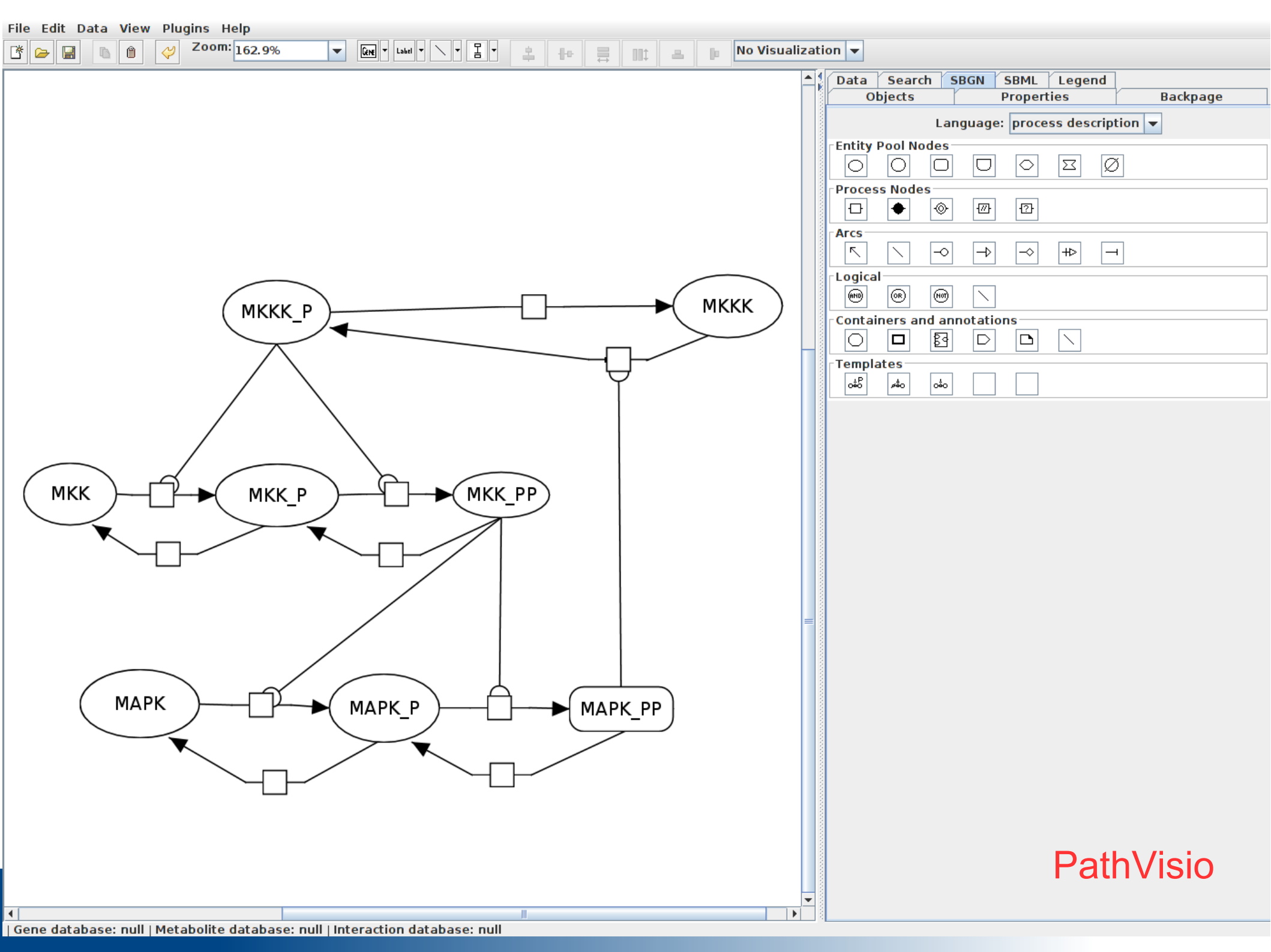
R-HSA-71387.5

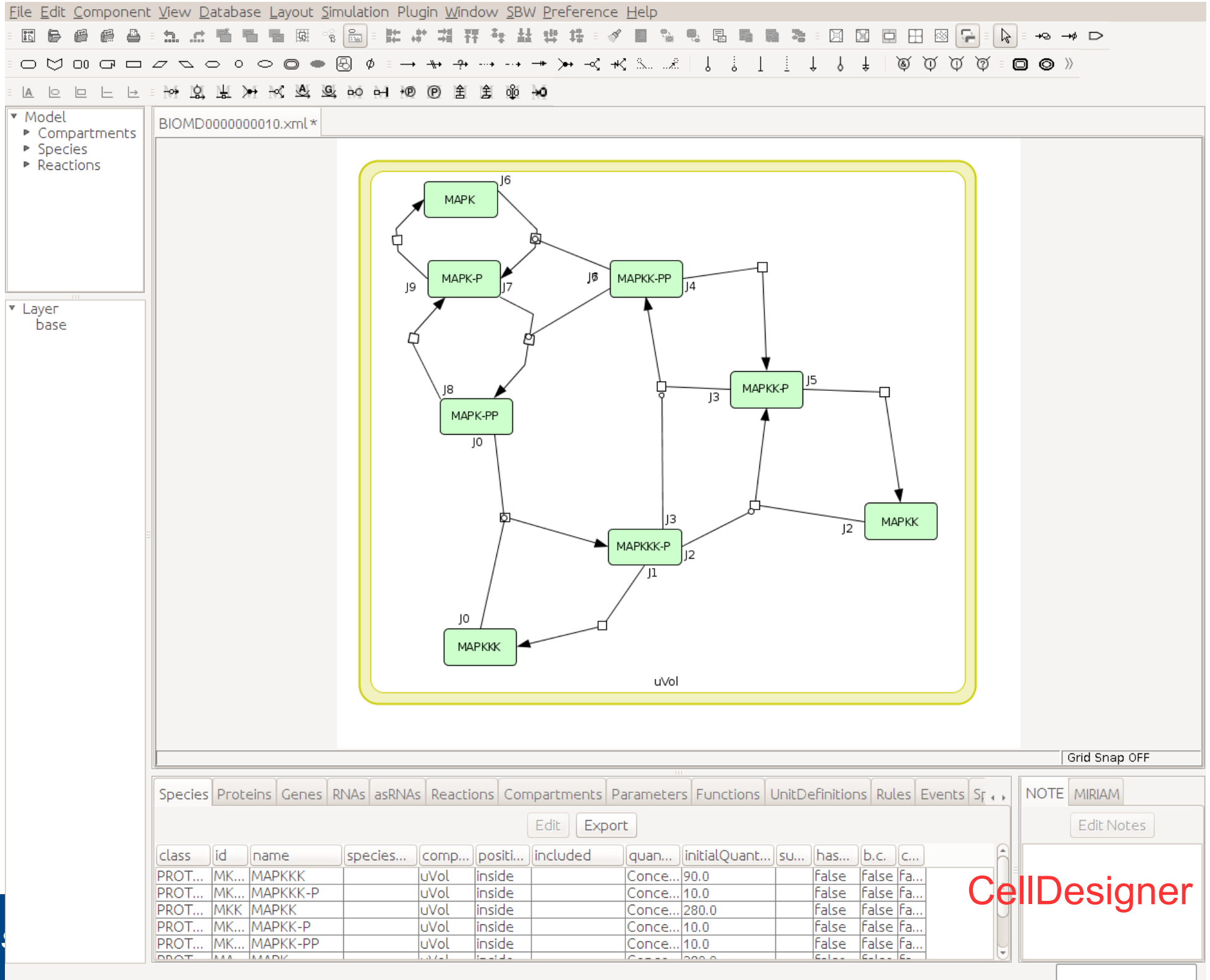
Summation

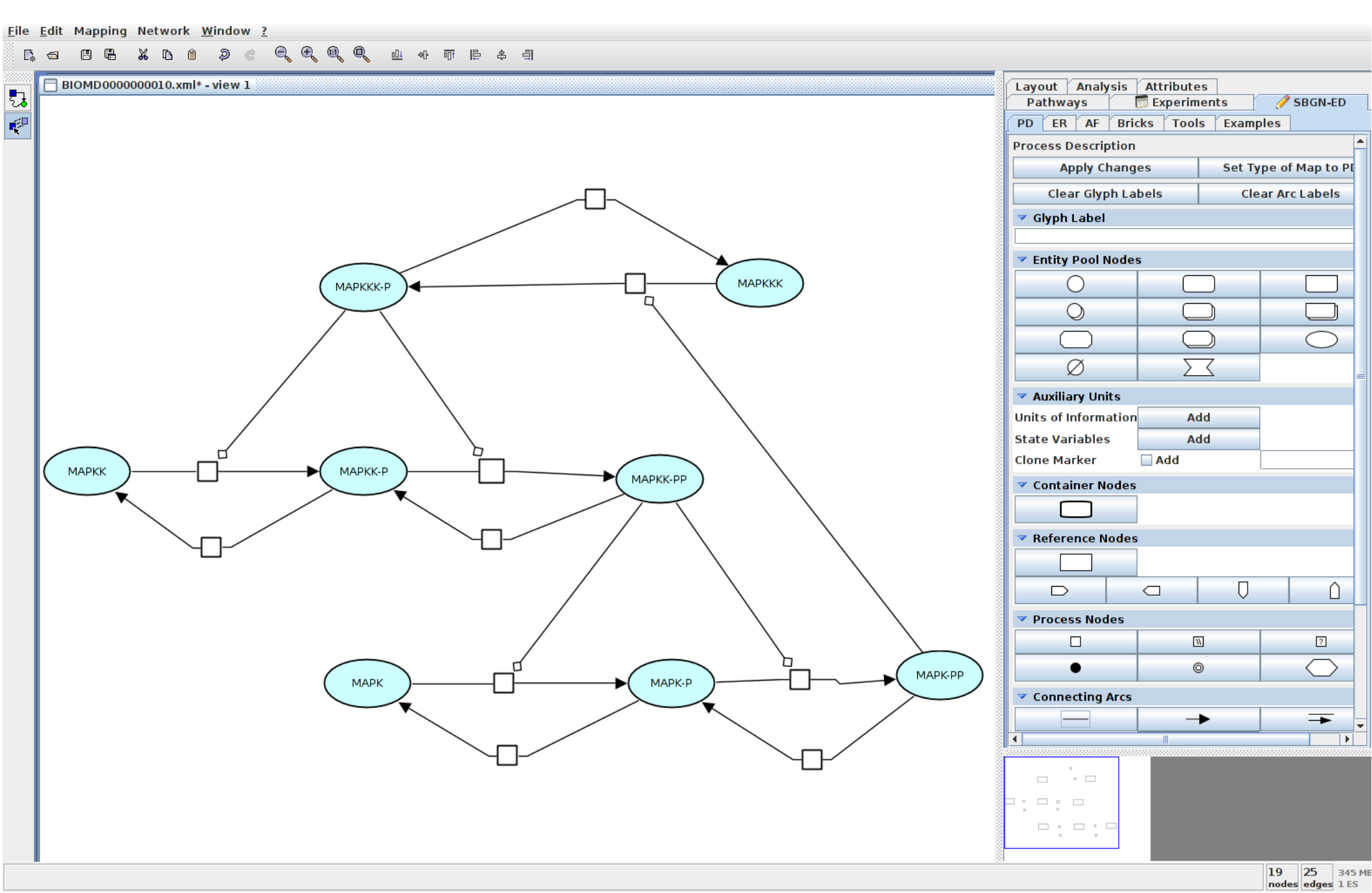
These pathways together are responsible for: 1) the extraction of energy and carbon skeletons for biosyntheses from dietary sugars and related molecules; 2) the short-term storage of gluc
from pyruvate during extended fasts.

View computationally predicted event in


ReconMap 2.01
SEARCH
DRUG
CHEMICAL
MiRNA
OVERLAYS
SEARCH:
enter keyword
PERFECT MATCH
Propanoate metabolism
Alanine and aspartate metabolism
Citric acid cycle
Threonine
Recon map
ADMIN
MANUAL
EXPORT


File Edit Data View Plugins Help
Zoom: 162.9%
No Visualization
Data Search SBGN SBML Legend
Objects Properties Backpage
Language: process description
Entity Pool Nodes
Process Nodes
Arcs
Logical
Containers and annotations
Templates
MKKK_P
MKKK
MKK
MKK_P
MKK_PP
MAPK
MAPK_P
MAPK_PP
PathVisio
Gene database: null | Metabolite database: null | Interaction database: null

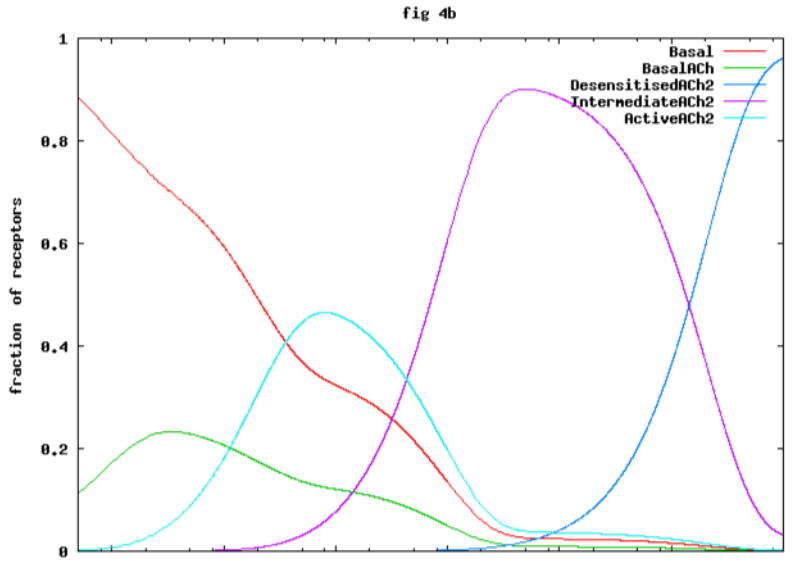

File Edit Component View Database Layout Simulation Plugin Window SBW Preference Help
Model
Compartments
Species
Reactions
Layer
base
BIOMD0000000010.xml*
MAPK
MAPK-P
MAPKK-PP
MAPK-PP
MAPKK-P
MAPKK
MAPKKK-P
MAPKKK
J0
J1
J2
J3
J4
J5
J6
J7
J8
J9
uVol
Grid Snap OFF
Species
Proteins
Genes
RNAs
asRNAs
Reactions
Compartments
Parameters
Functions
UnitDefinitions
Rules
Events
Edit
Export
class
id
name
species...
comp...
positi...
included
quan...
initialQuant...
su...
has...
b.c.
PROT... MK... MAPKKK uVol inside Conce... 90.0 false false
PROT... MK... MAPKKK-P uVol inside Conce... 10.0 false false
PROT... MKK MAPKK uVol inside Conce... 280.0 false false
PROT... MK... MAPKK-P uVol inside Conce... 10.0 false false
PROT... MK... MAPKK-PP uVol inside Conce... 10.0 false false
NOTE
MIRIAM
Edit Notes
CellDesigner


File Edit Mapping Network Window ?
BIOMD0000000010.xml* - view 1
MAPKKK-P
MAPKKK
MAPKK
MAPKK-P
MAPKK-PP
MAPK
MAPK-P
MAPK-PP
Layout
Analysis
Attributes
Pathways
Experiments
SBGN-ED
PD
ER
AF
Bricks
Tools
Examples
Process Description
Apply Changes
Set Type of Map to PD
Clear Glyph Labels
Clear Arc Labels
Glyph Label
Entity Pool Nodes
Auxiliary Units
Units of Information
Add
State Variables
Add
Clone Marker
Add
Container Nodes
Reference Nodes
Process Nodes
Connecting Arcs
19 nodes
25 edges
345 MB
1 ES

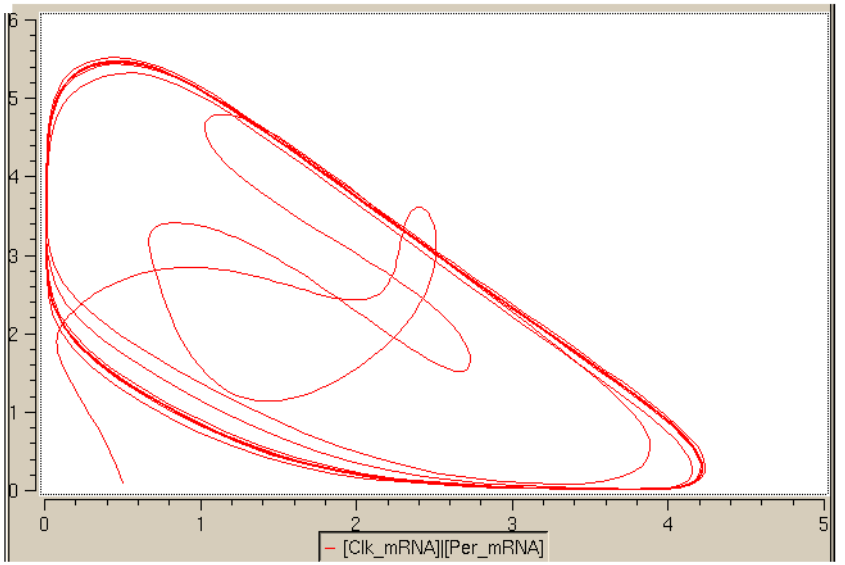
Vanted

Surely, this is enough?

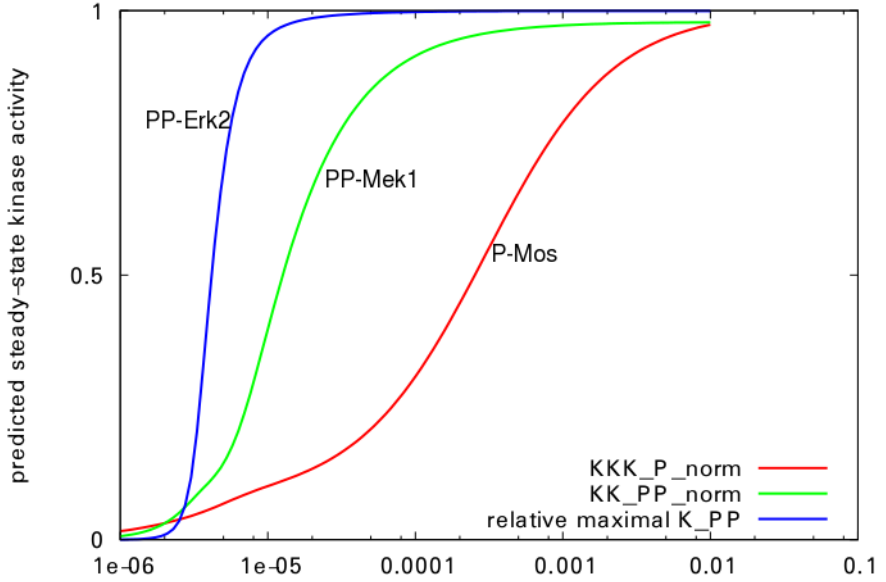
Simulation experiment = model + what to do with it



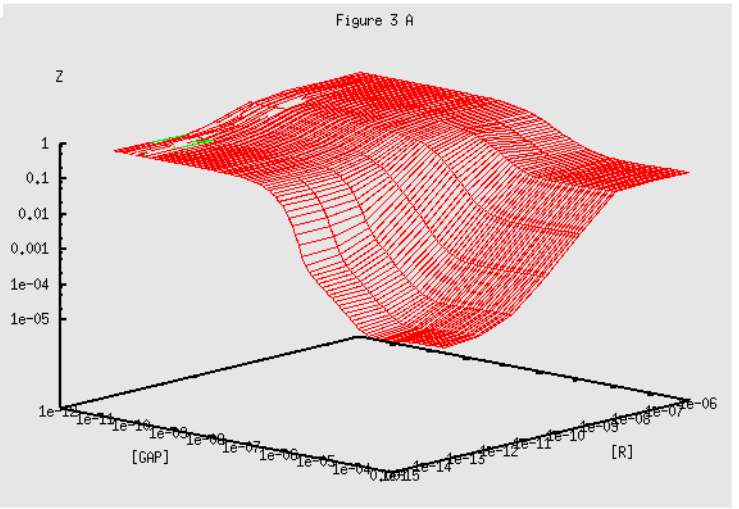
Edelstein et al 1996 (BIOMD0000000002)



Ueda, Hagiwara, Kitano 2001 (BIOMD0000000022)

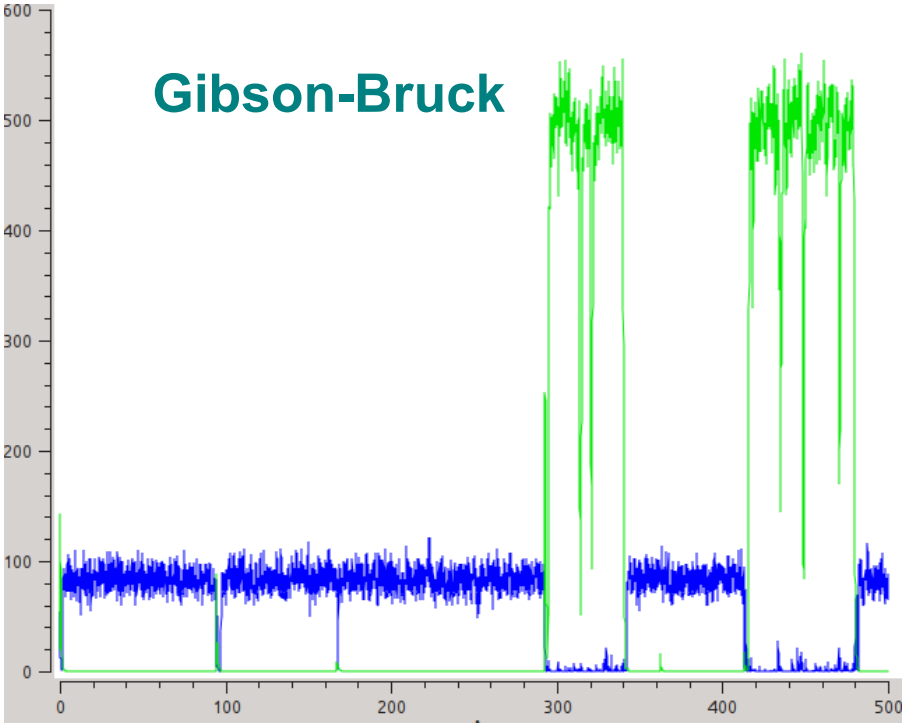


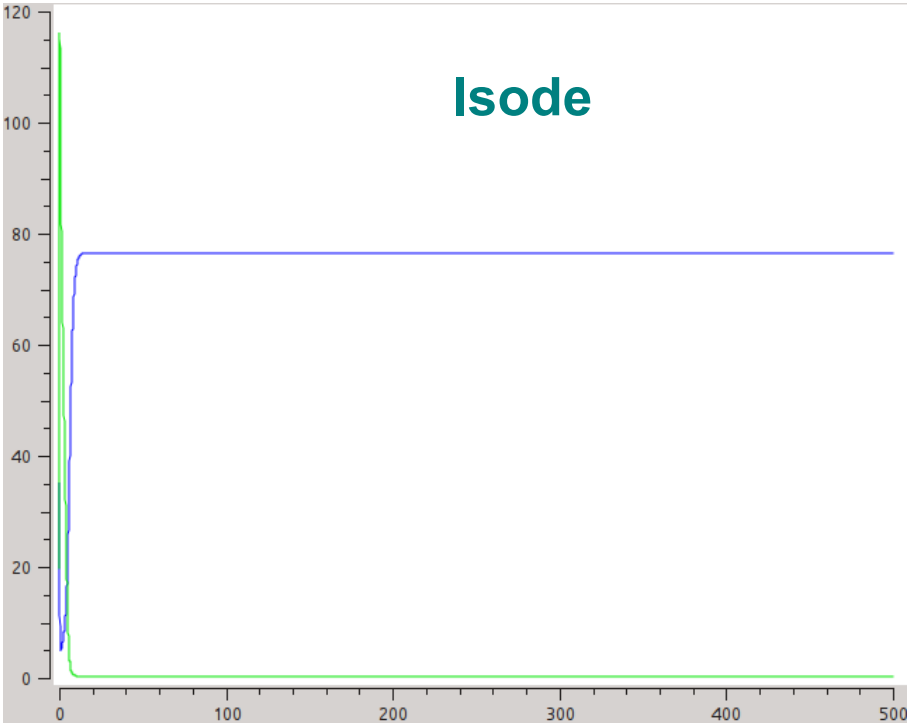
Huang & Ferrell (BIOMD0000000009)

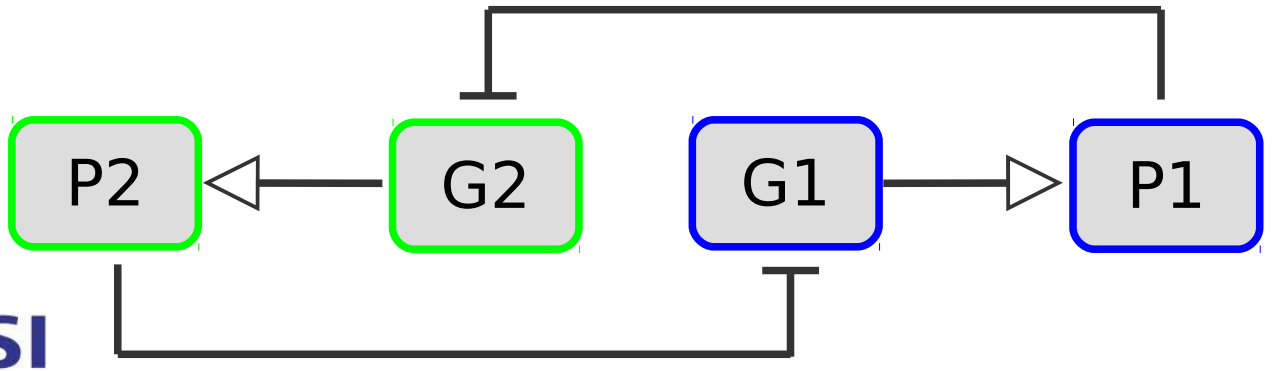


Bornheimer et al 2004 (BIOMD0000000086)

Choice of algorithm affects behaviour





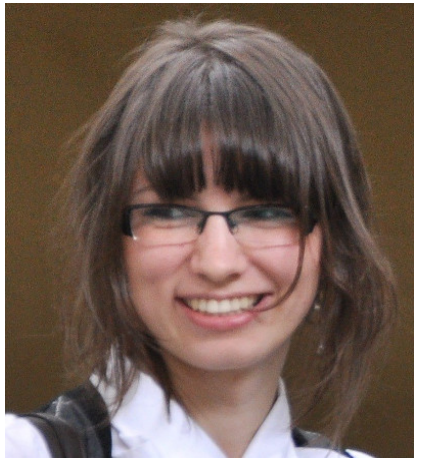


COPASI

Description of simulations and analyses

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

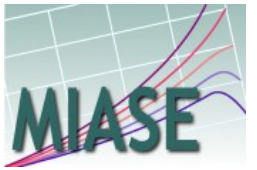
Dagmar Waltemath



Anna Zhukova

Born in Hinxton 2007

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 results
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

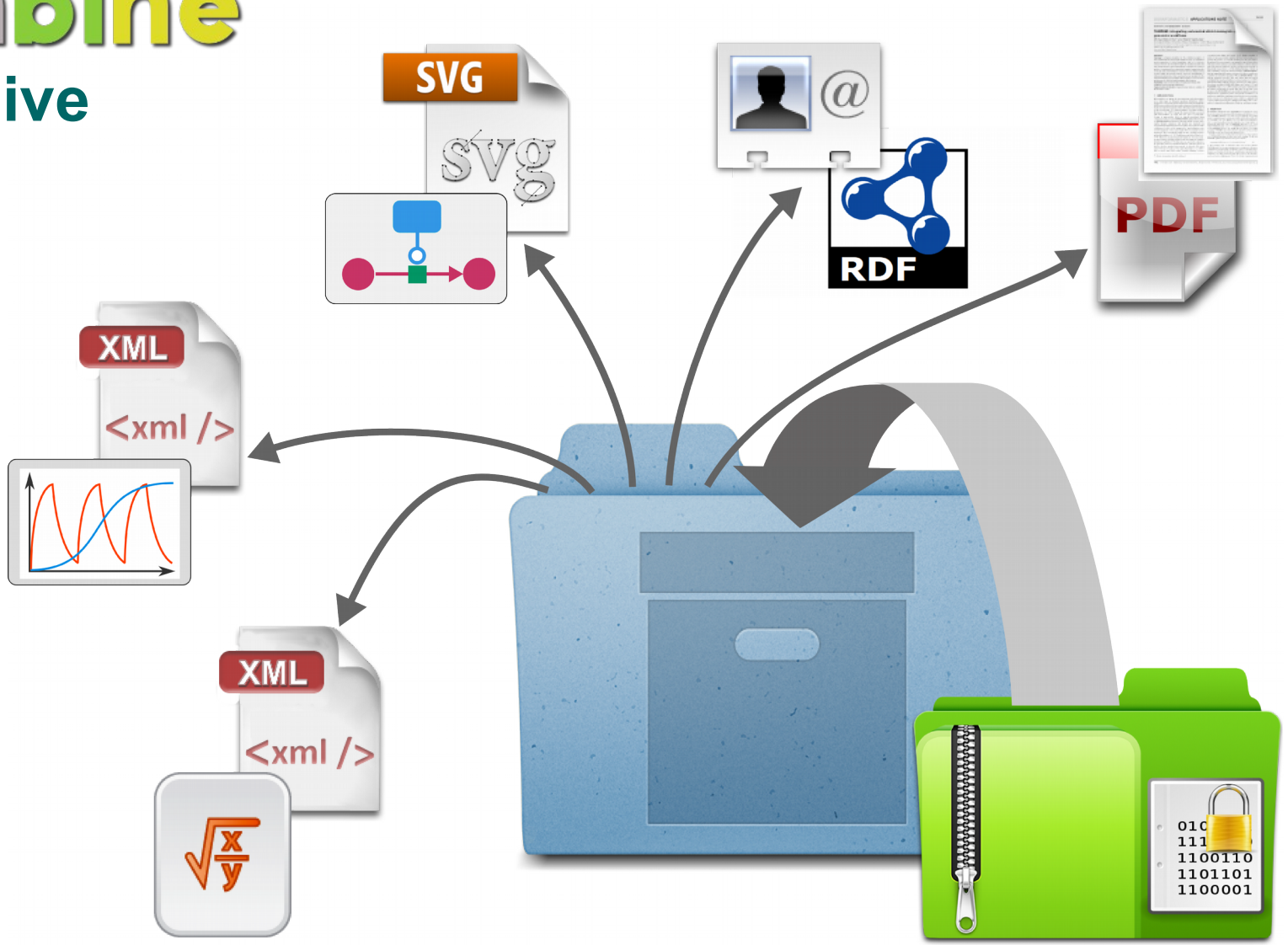
- modelling and simulation algorithm
  - Bayesian inference algorithm
  - CVODE-like method
    - CVODE
    - PVODE
  - algorithm using adaptive timesteps
  - algorithm using continuous variables
  - algorithm using deterministic rules
  - algorithm using discrete variables
  - algorithm using fixed 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)*

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."

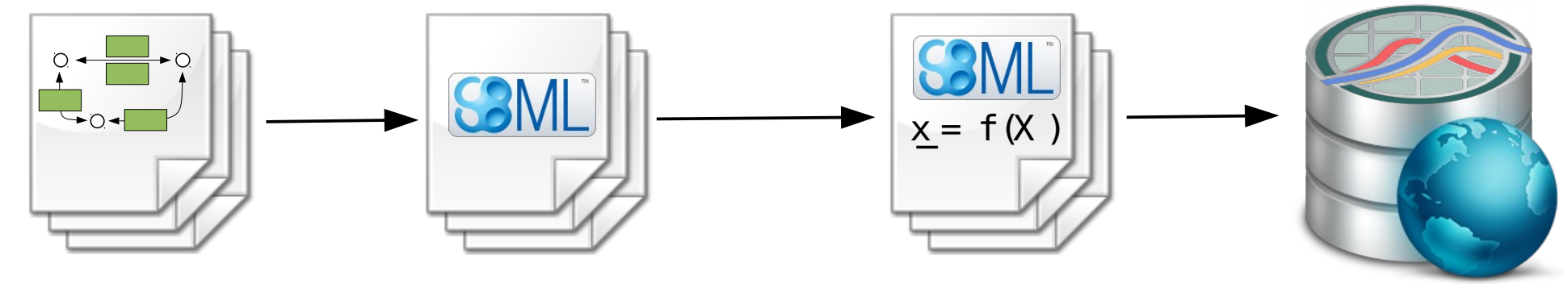
Biomathematician, 2007

"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

+

→

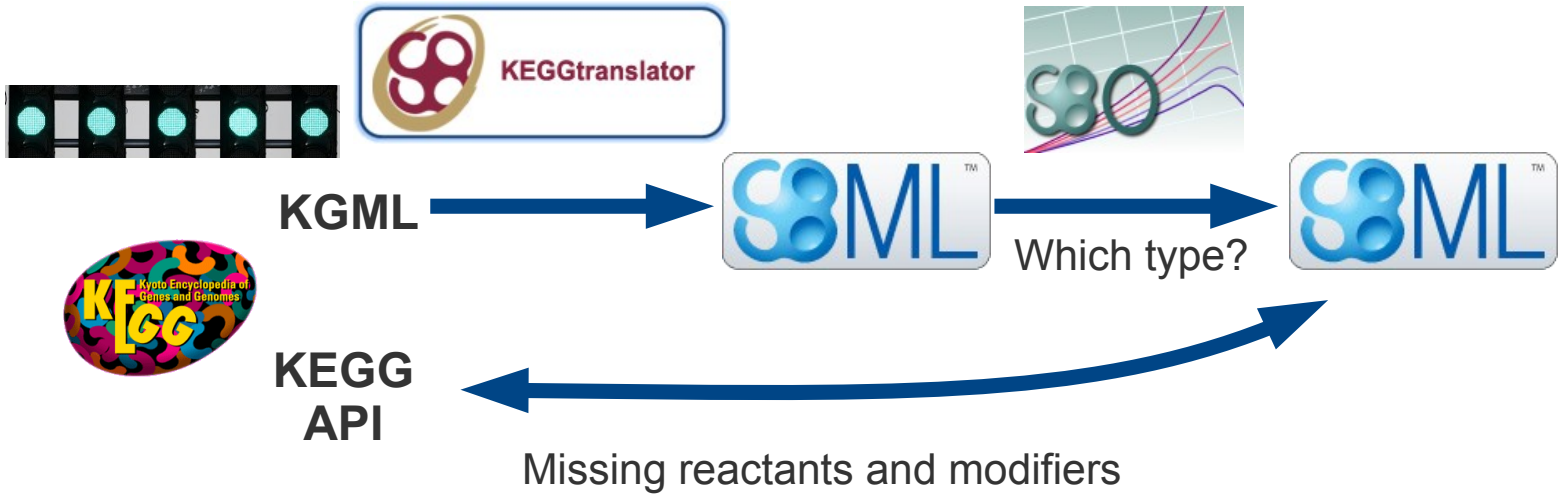
Flux Balance Analysis
of whole genome reconstructions

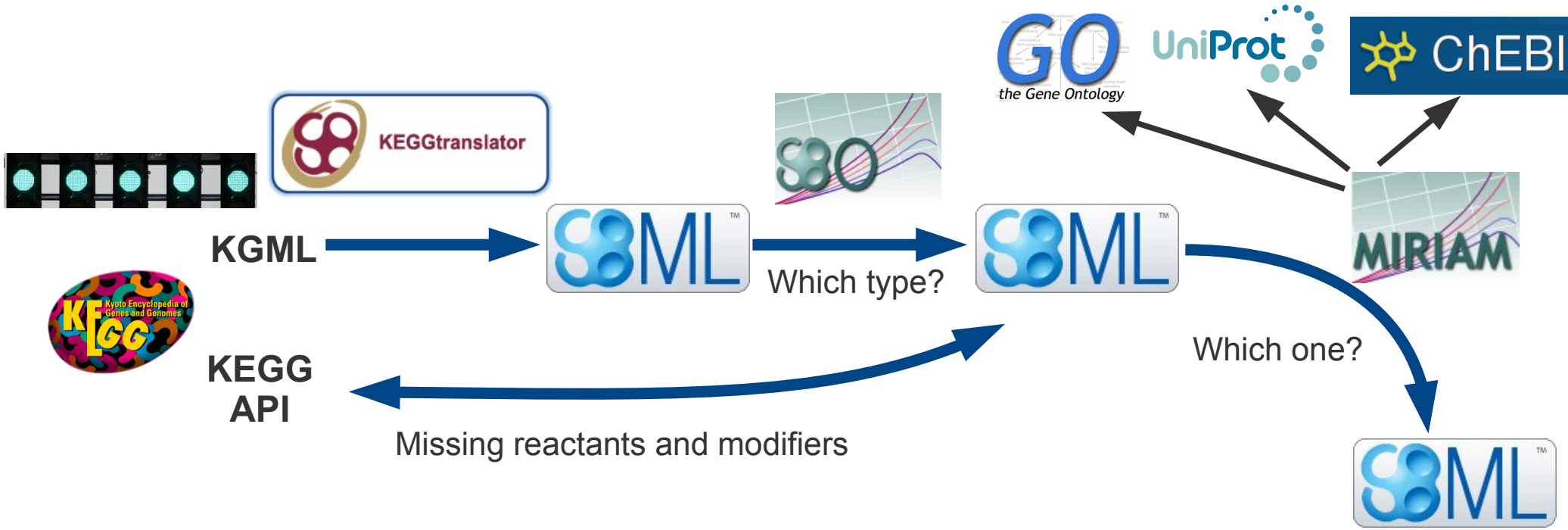
KEGGtranslator

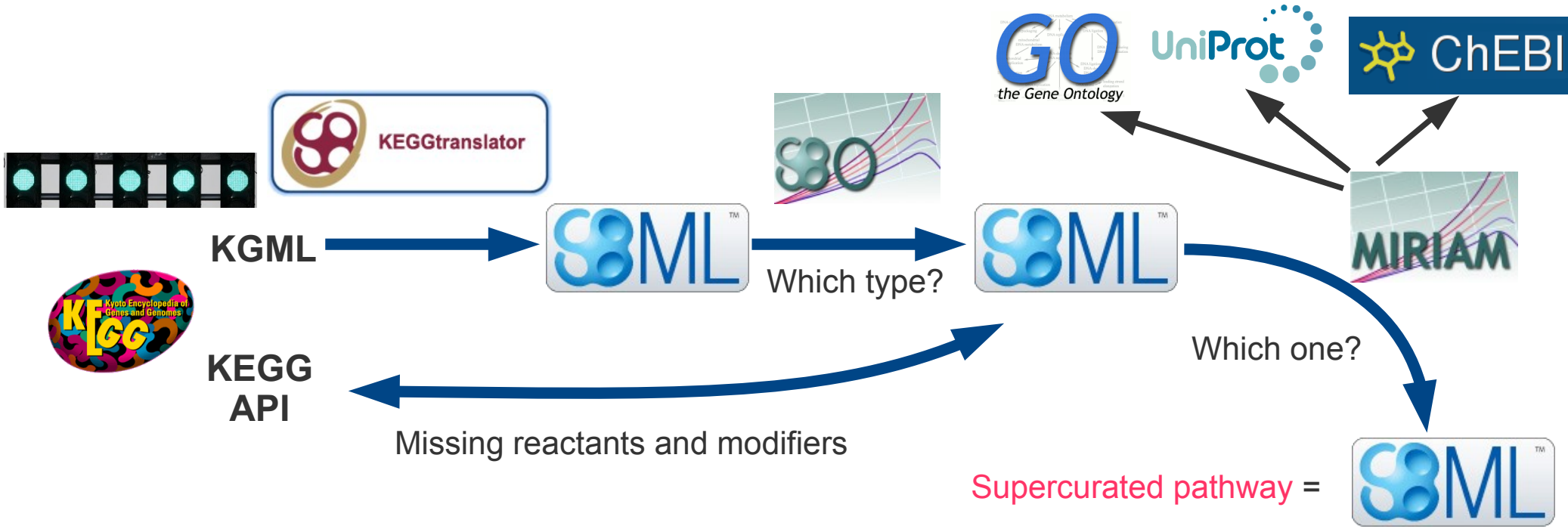
KGML → SBML

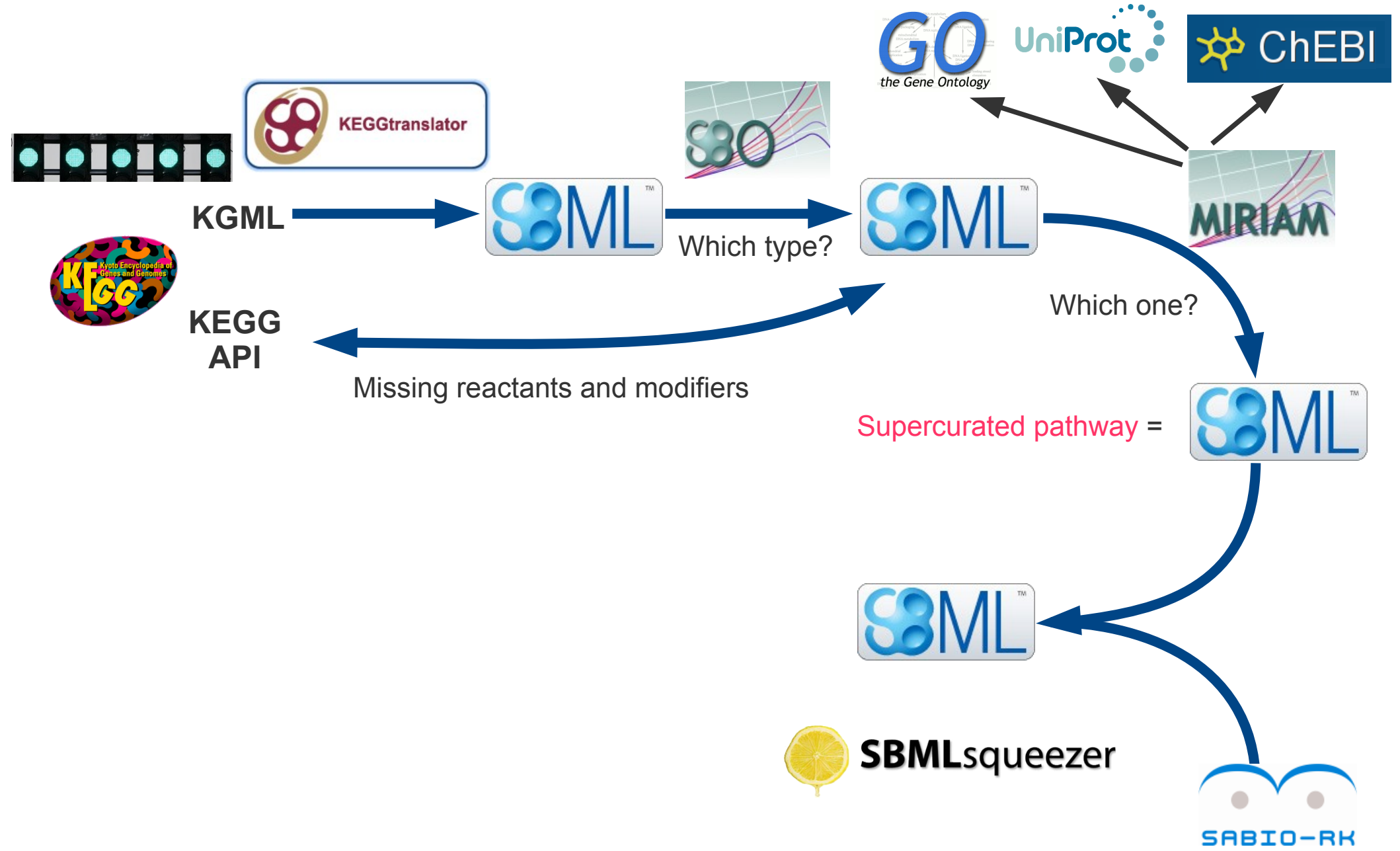
Kyoto Encyclopedia of Genes and Genomes

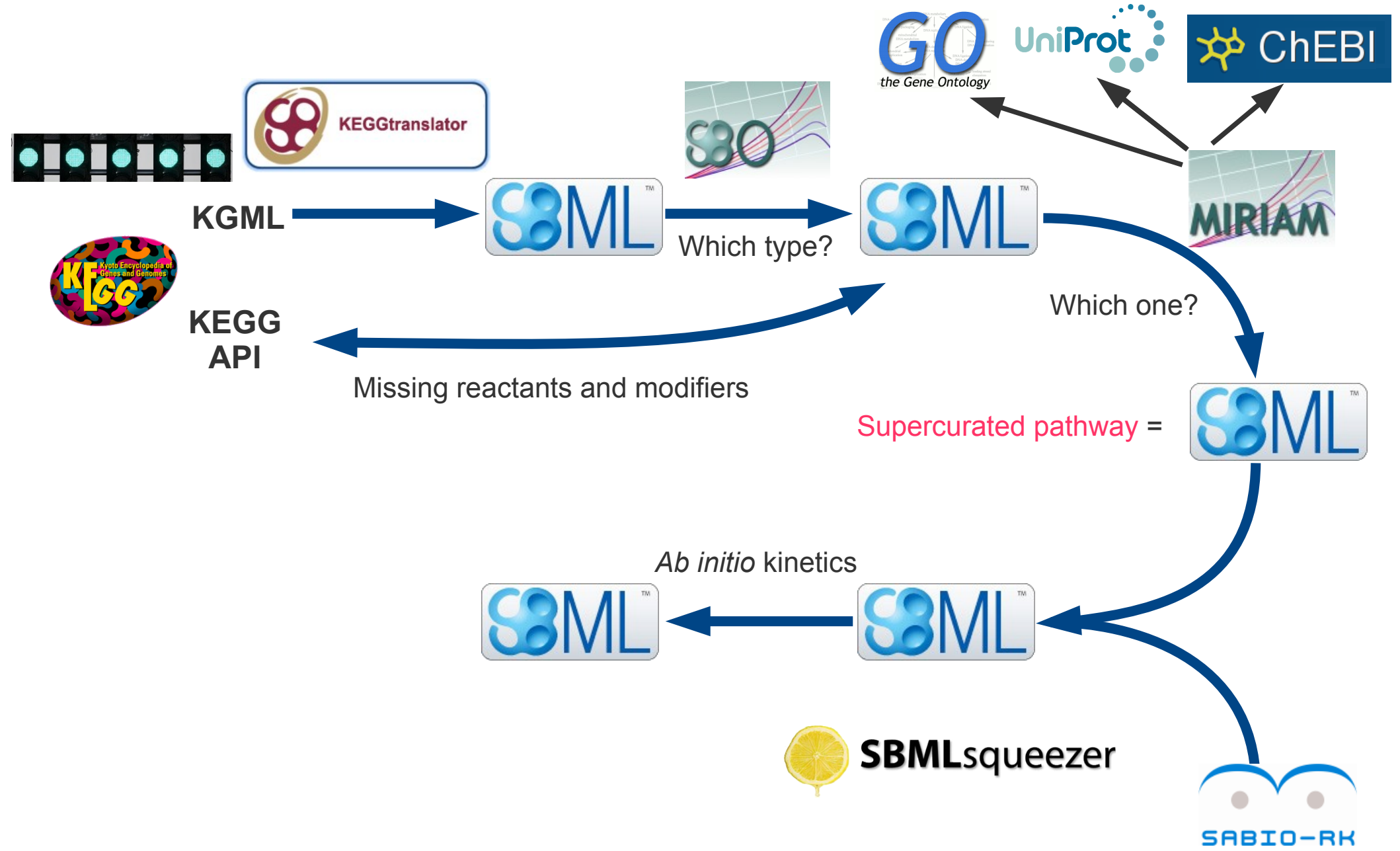

KEGGtranslator
KGML
Which type?

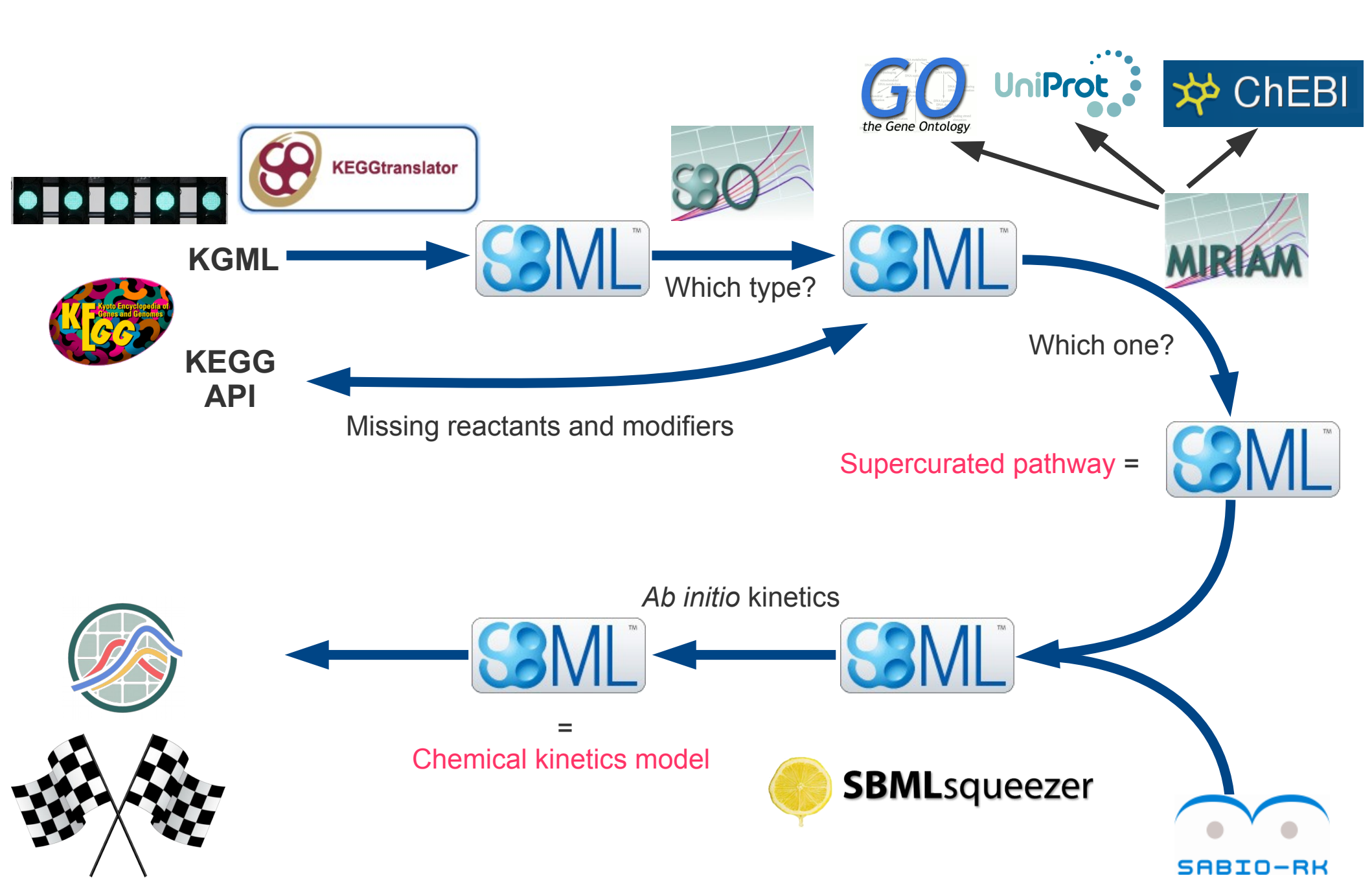

KEGGtranslator
KGML
Which type?
KEGG
API
Missing reactants and modifiers


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


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


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

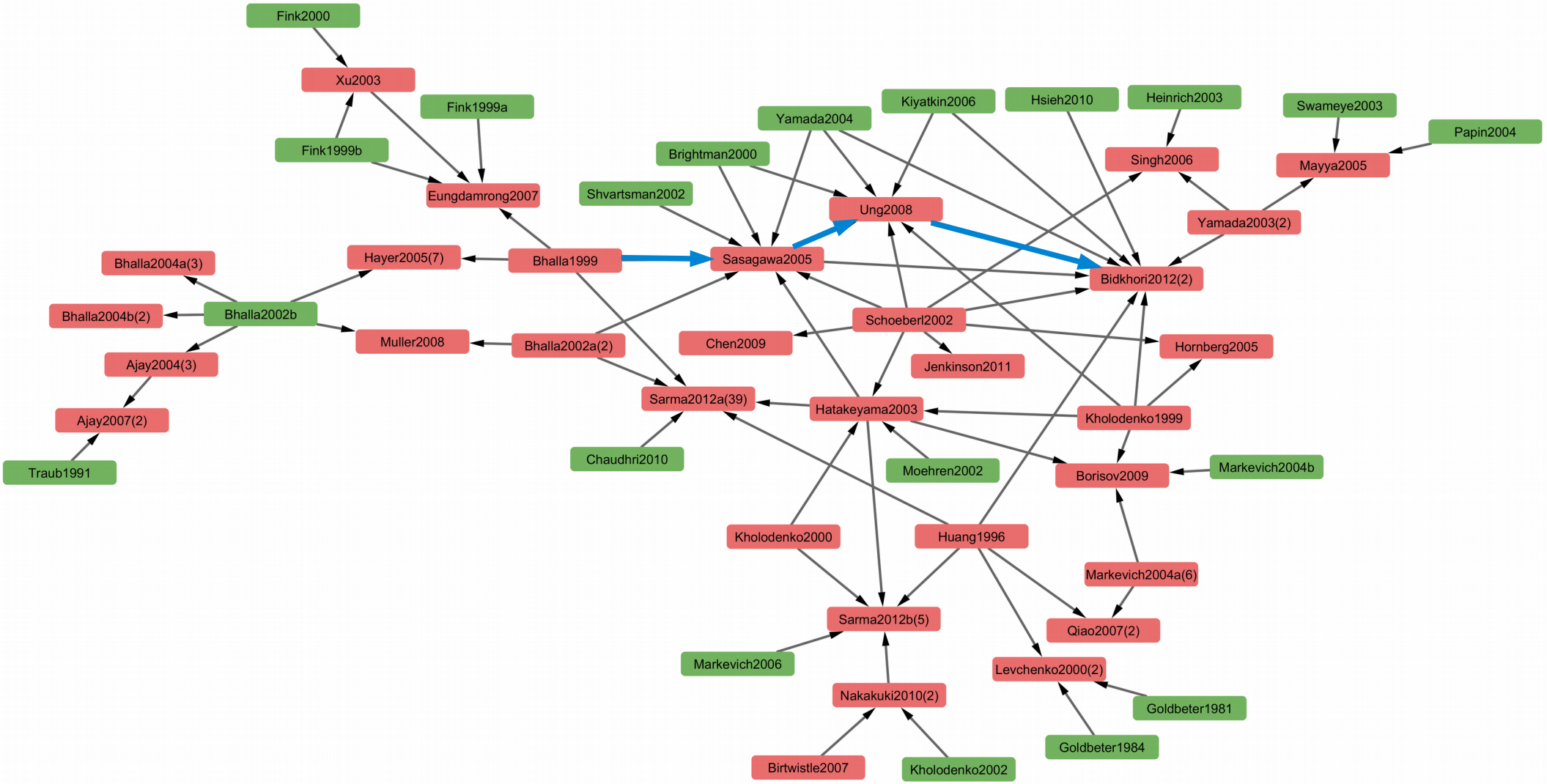

GO
the Gene Ontology
UniProt
ChEBI
KEGGtranslator
SBO
KGML
SBML
Which type?
SBML
MIRIAM
KEGG
API
Which one?
Missing reactants and modifiers
Supercurated pathway =
SBML
Ab initio kinetics
SBML
SBML
SBMLsqueezer
SABIO-RK


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

REUSE

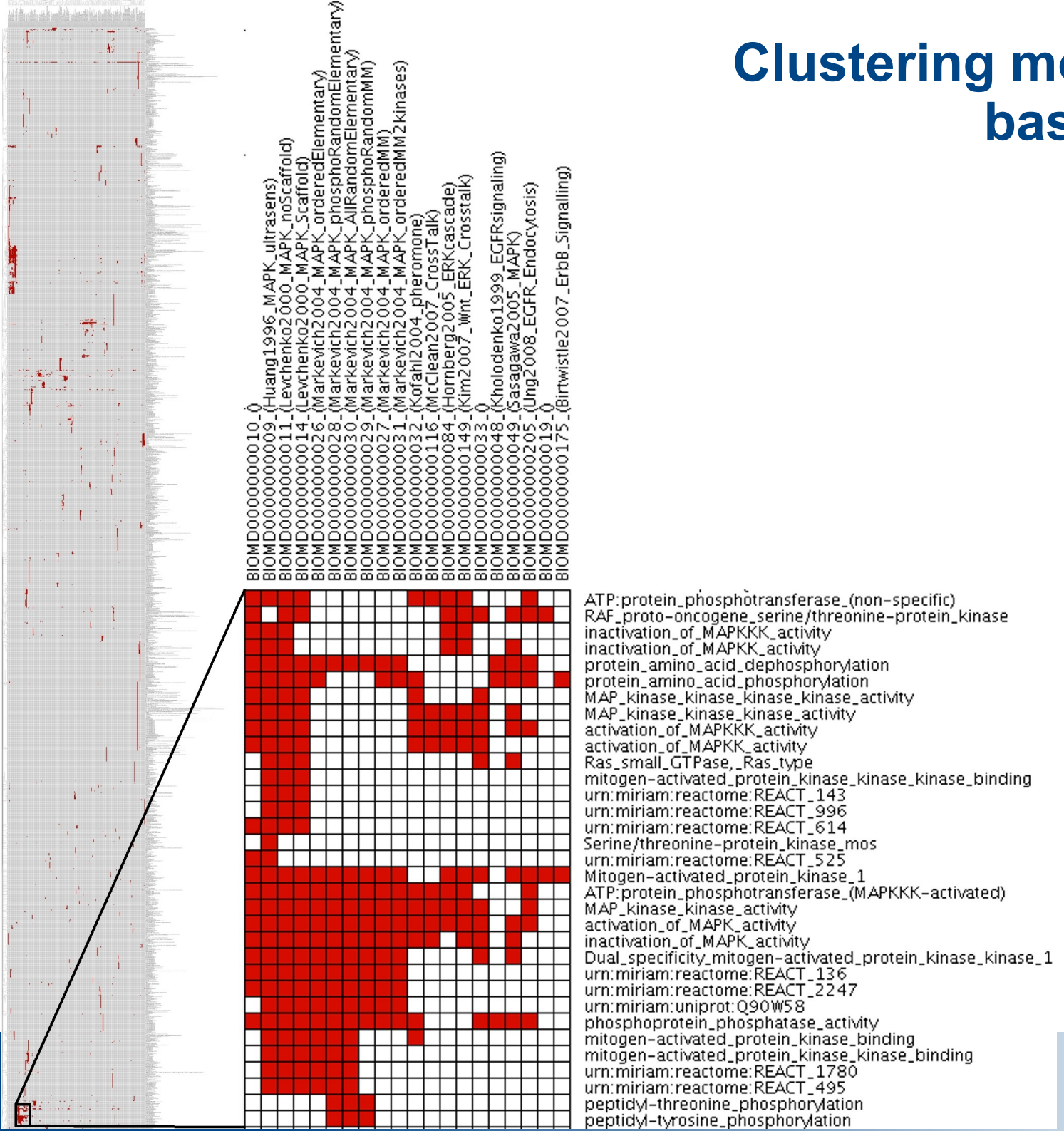
In Silico Systems Biology, EMBL-EBI, 09-14 July 2017

Erb receptor signalling



DISCOVER

Clustering models (and data) based on metadata



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

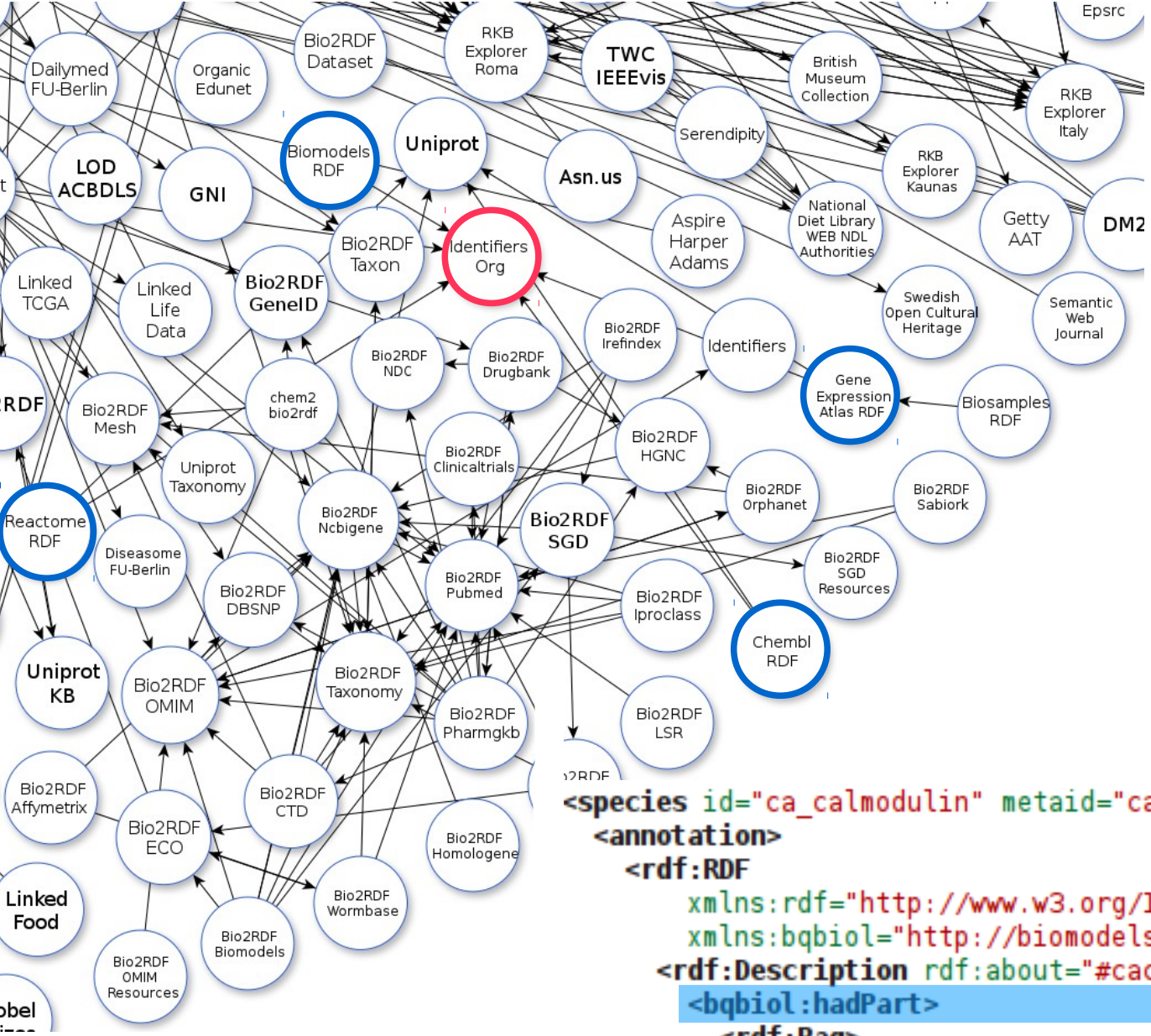
Ranking and retrieval of models

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	BIOMD0000000140	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

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

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  <annotation>
    <rdf:RDF
        xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#"
        xmlns:bqbiol="http://biomodels.net/biology-qualifiers/">
      <rdf:Description rdf:about="#cacam">
        <bqbiol:hadPart>
          <rdf:Bag>
            <rdf:li rdf:resource="http://identifiers.org/uniprot/62158"/>
            <rdf:li rdf:resource="http://identifiers.org/chebi/CHEBI:29108"/>
          </rdf:Bag>
        </bqbiol:hasPart>
      </rdf:Description>
```