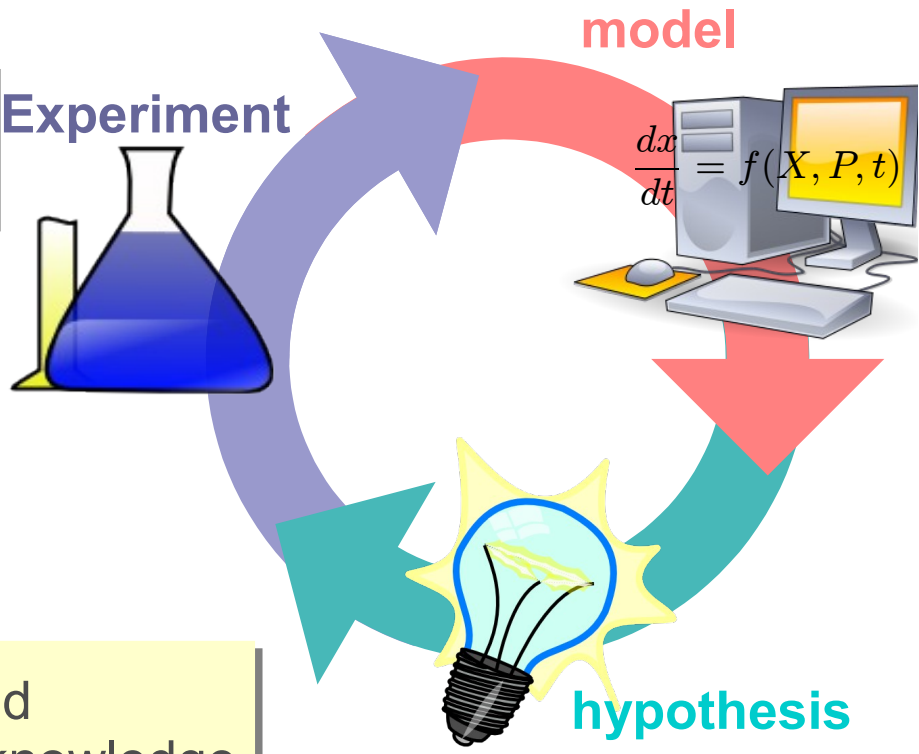
Models For All

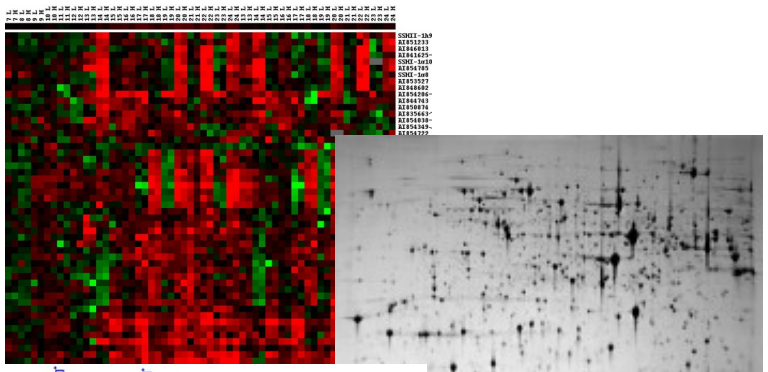
Standards for describing the whole life-cycle of modeling in the life sciences

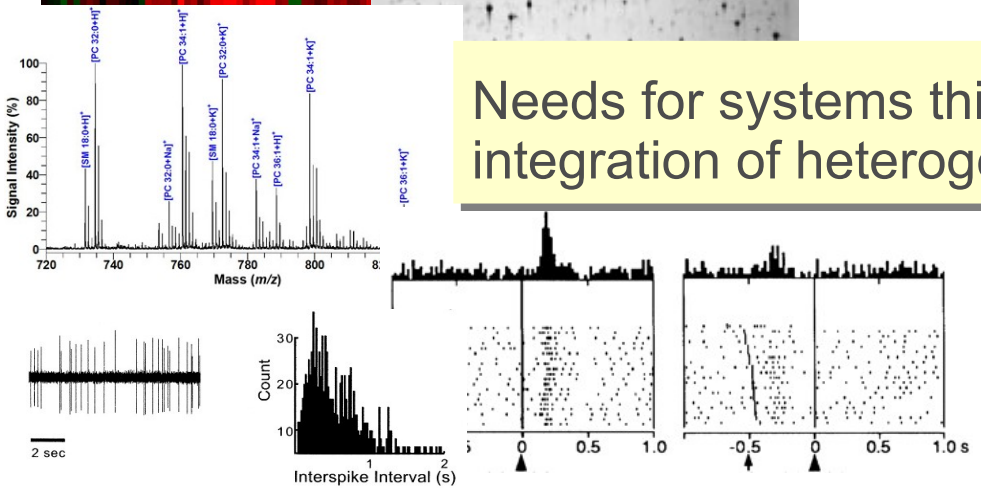
Nicolas Le Novère, EMBL-EBI

New way of doing biomedical research

Needs for interplay between models and reality tests

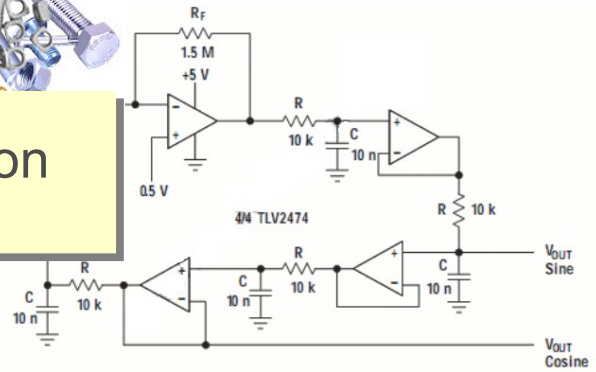




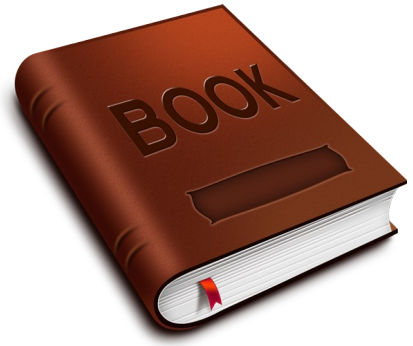


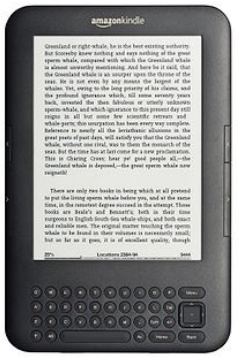
Needs for systems thinking and integration of heterogeneous knowledge

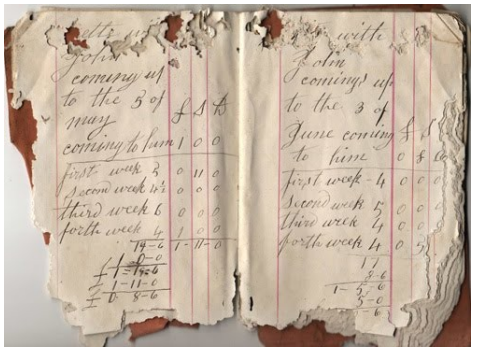
Needs for cooperation and standardisation

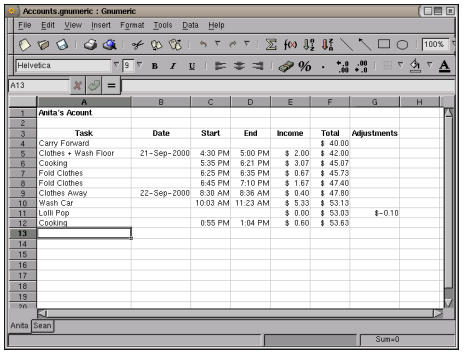


What are standards good for?







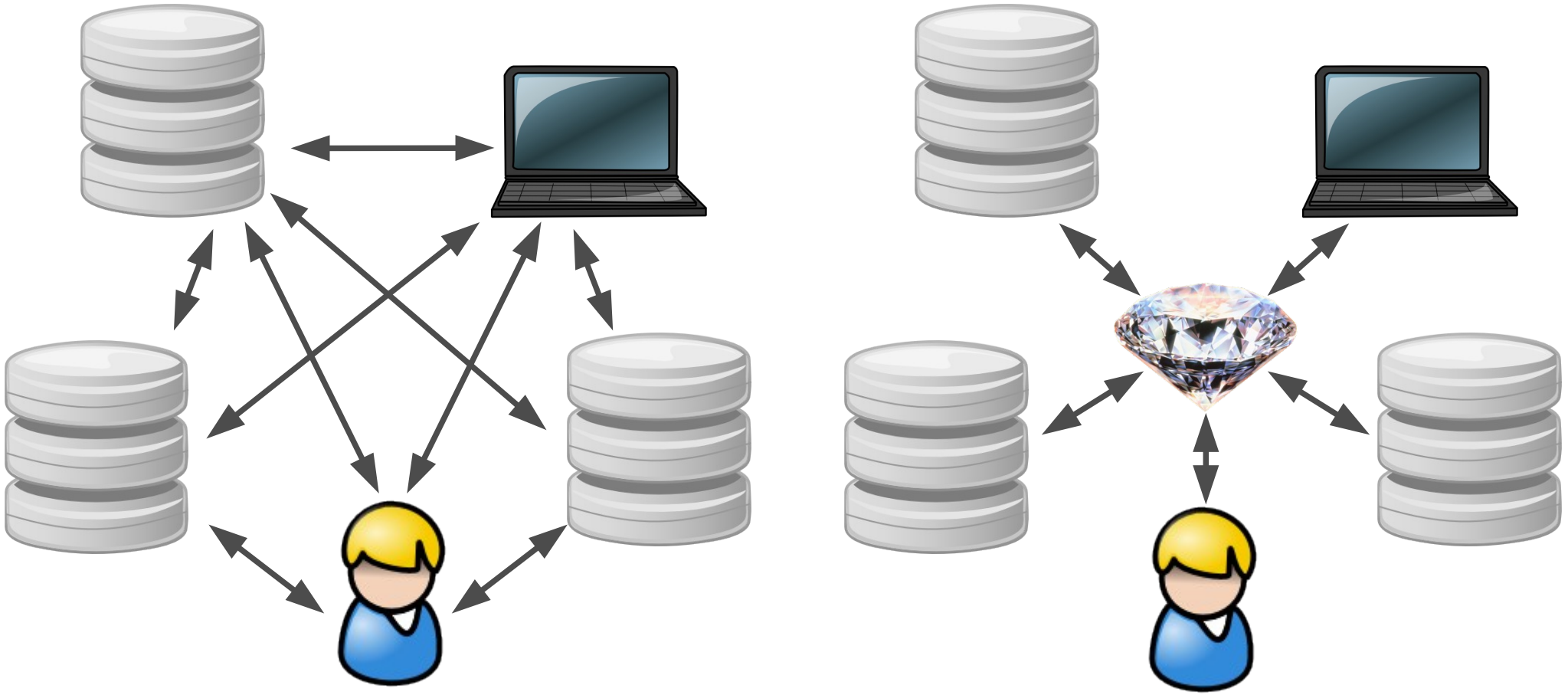


$$\int_1^t \frac{dx}{x}$$

```
<int/>
  <bvar><ci>x</ci></bvar>
  <lowlimit><cn>1</cn></lowlimit>
  <uplimit><ci>t</ci></uplimit>
  <apply>
    <divide/>
      <cn>1</cn>
      <ci>x</ci>
  </apply>
</int>
```

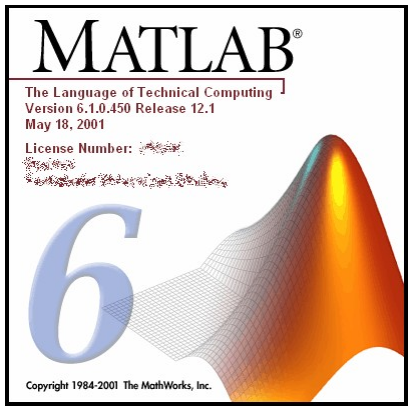
Formal languages can be read and written by computers

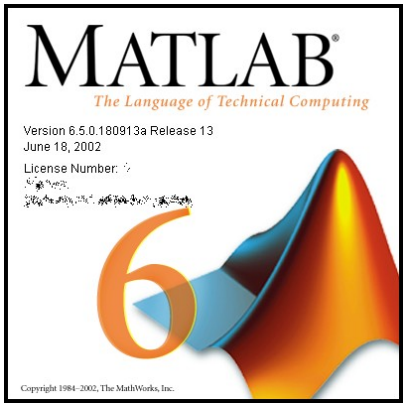
What are standards good for?

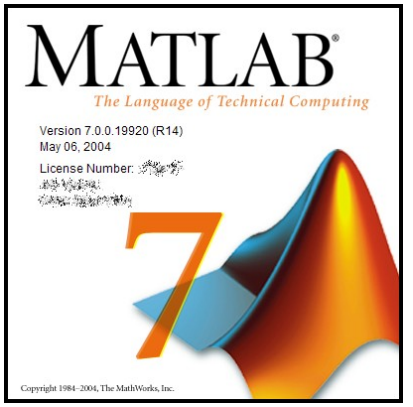


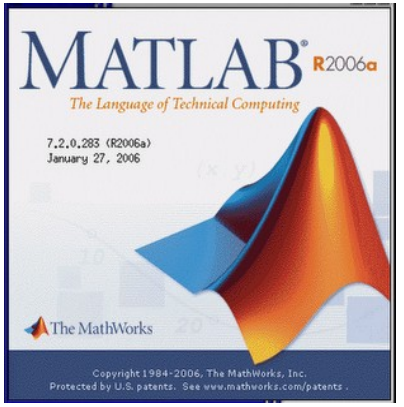
N tools require N conversions for exchange and not N(N-1)/2

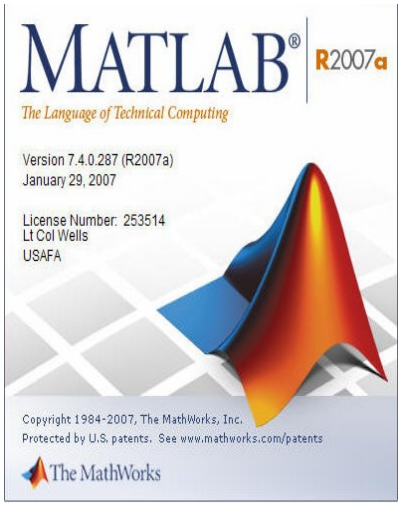
What are standards good for?

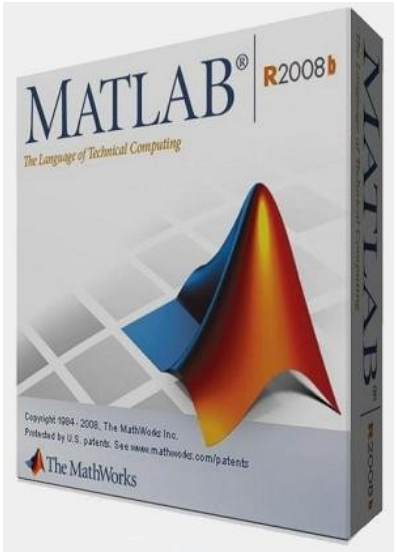


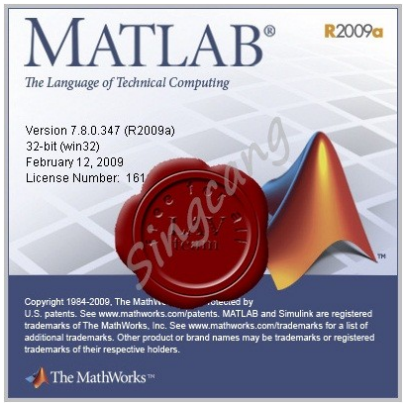


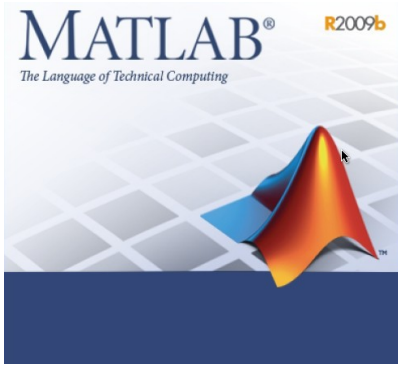


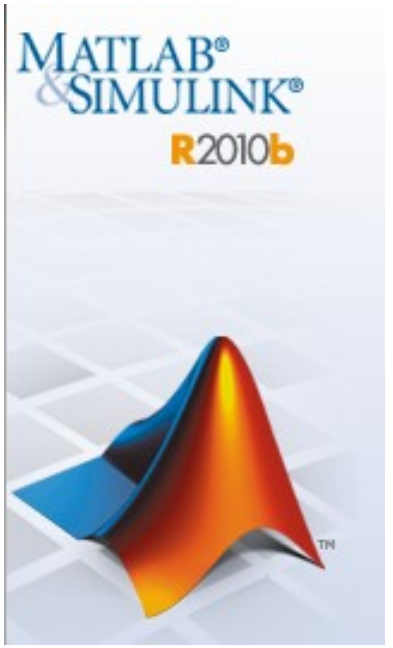


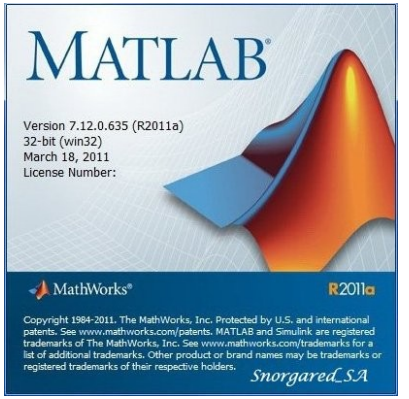






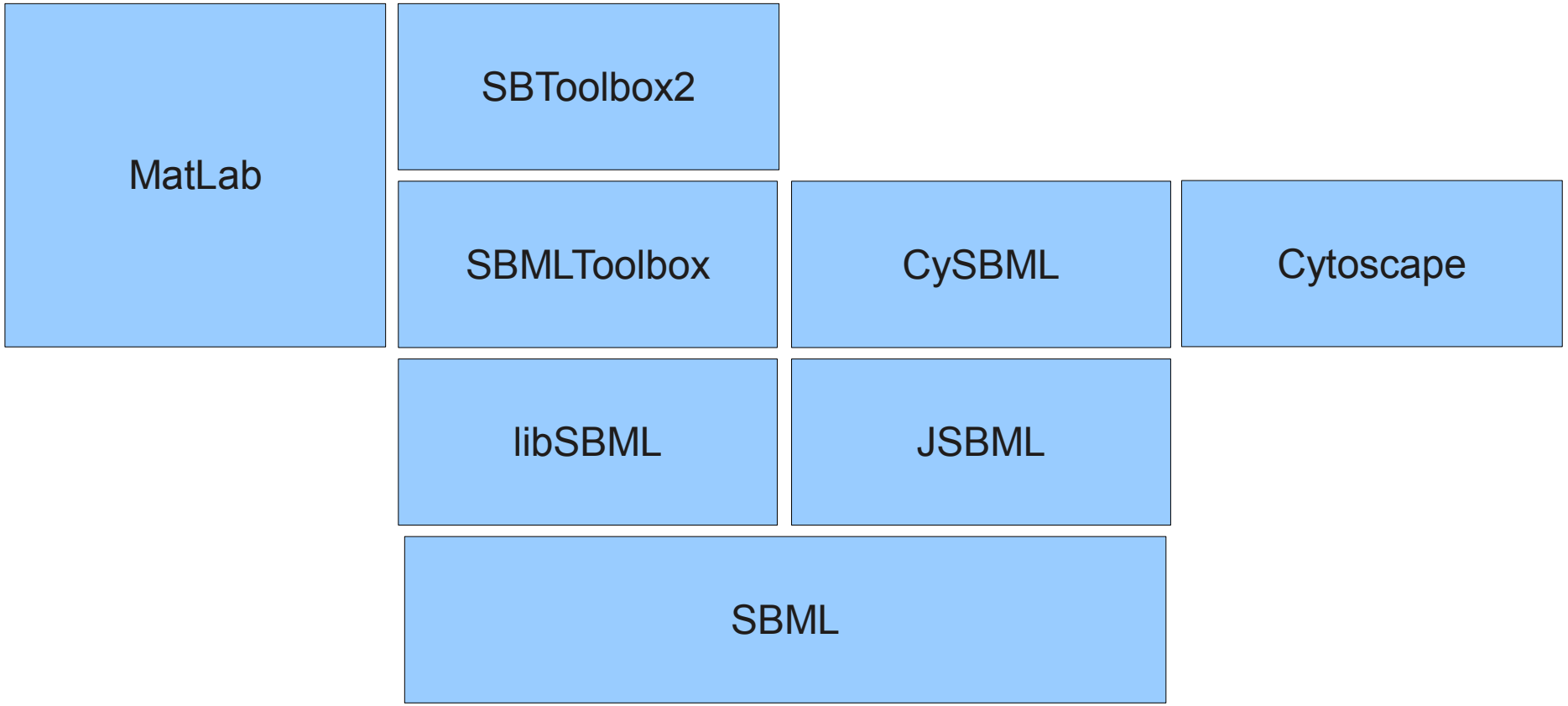






Open standards are more stable than proprietary formats

What are standards good for?



Open standards can be built on. They generate new science

Three types of standards

Minimal requirements	What to encode in order to share experiments and understand results 
Data-models	How to encode the information defined above in a computer-readable manner 
Terminologies	Structured represention of knowledge, with concept definitions and their relationships 

Three types of standards

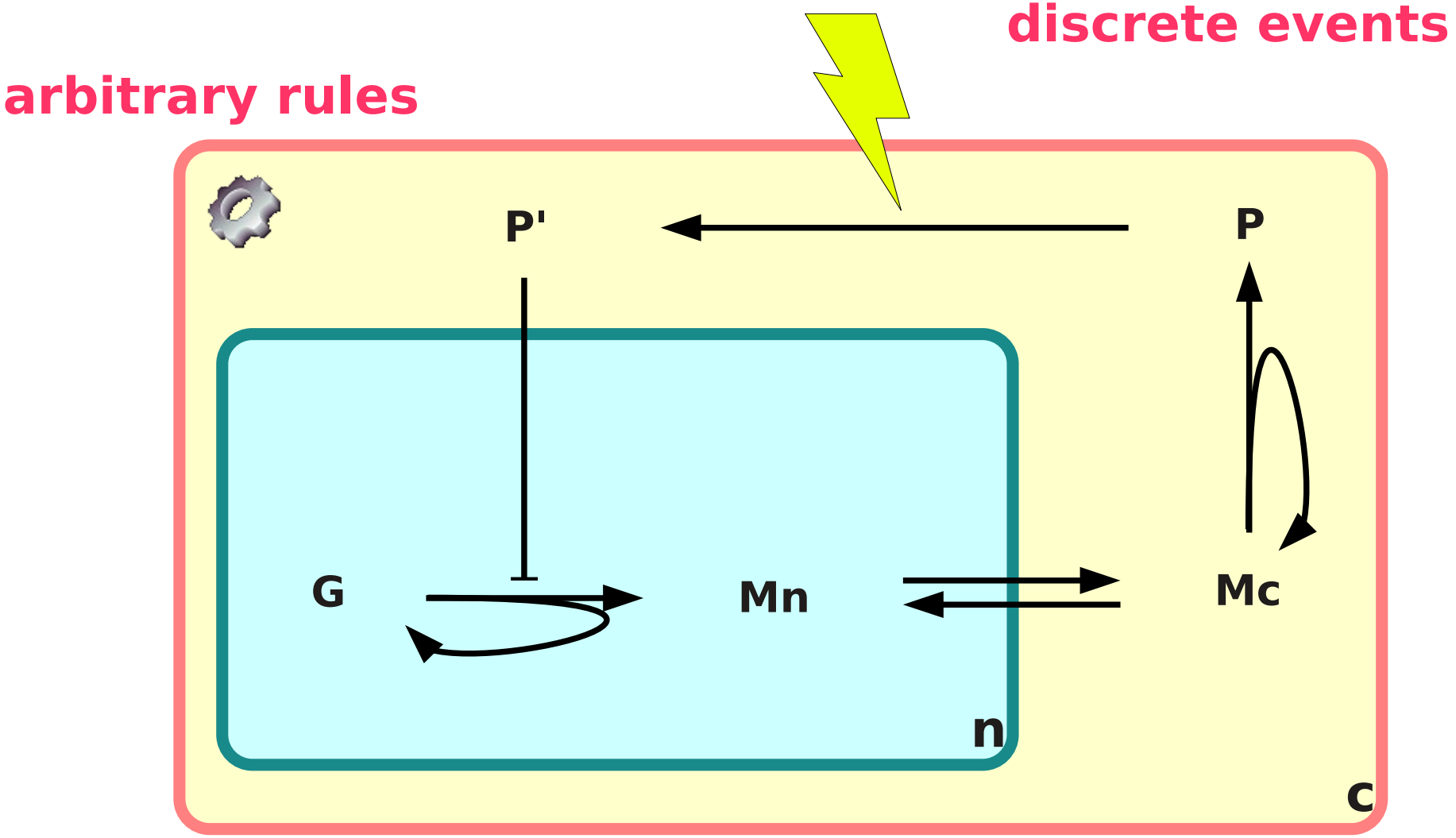
Minimal requirements	What to encode in order to share experiments and understand results 
Data-models	How to encode the information defined above in a computer-readable manner 
Terminologies	Structured represention of knowledge, with concept definitions and their relationships 

A language to describe computational models in biology

	Model descriptions
Data-models	

Born in Caltech 2000

What can we encode in SBML (core)?



Why the Extensible Markup Language (XML)?

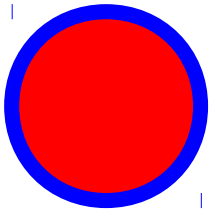
- **HTML**

```
A <strong>strong word</strong> and an
<a href=”http://www.w3.org/”>hyperlink</a>
```

A **strong word** and an hyperlink

- **SVG**

```
<circle r="100" fill="red"
stroke="blue" stroke-width="10"  />
```



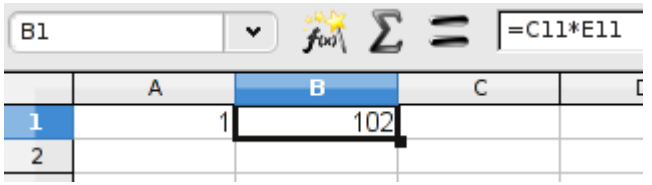
- **MathML**

```
<apply>
  <int/>
  <bvar><ci> x </ci></bvar>
  <lowlimit><cn> 0 </cn></lowlimit>
  <uplimit><ci> a </ci></uplimit>
  <apply><ci> f </ci><ci> x </ci></apply>
</apply>
```

$$\int_0^a f(x)\,dx$$

- **Excel**

```
<row r="1">
  <c r="A1"><v>1</v></c>
  <c r="B1">
    <f>C11*E11</f>
    <v>102</v>
  </c>
</row>
```



Why the Extensible Markup Language (XML)?

- Easy to define and validate
  - Rapid prototyping, processing tools can be generated and thrown away
- Existence of a very large toolkit
  - Libraries in every programming languages
  - A very large number of description formats in life sciences are in XML
- Associated technologies
  - Definition: XML Schema, Schematron (themselves XML)
  - Conversion: XSLT (using XSL in XML)
  - Linking: XPath and XQuery

Global structure of a SBML file

variables

relationships

```
<?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>
```

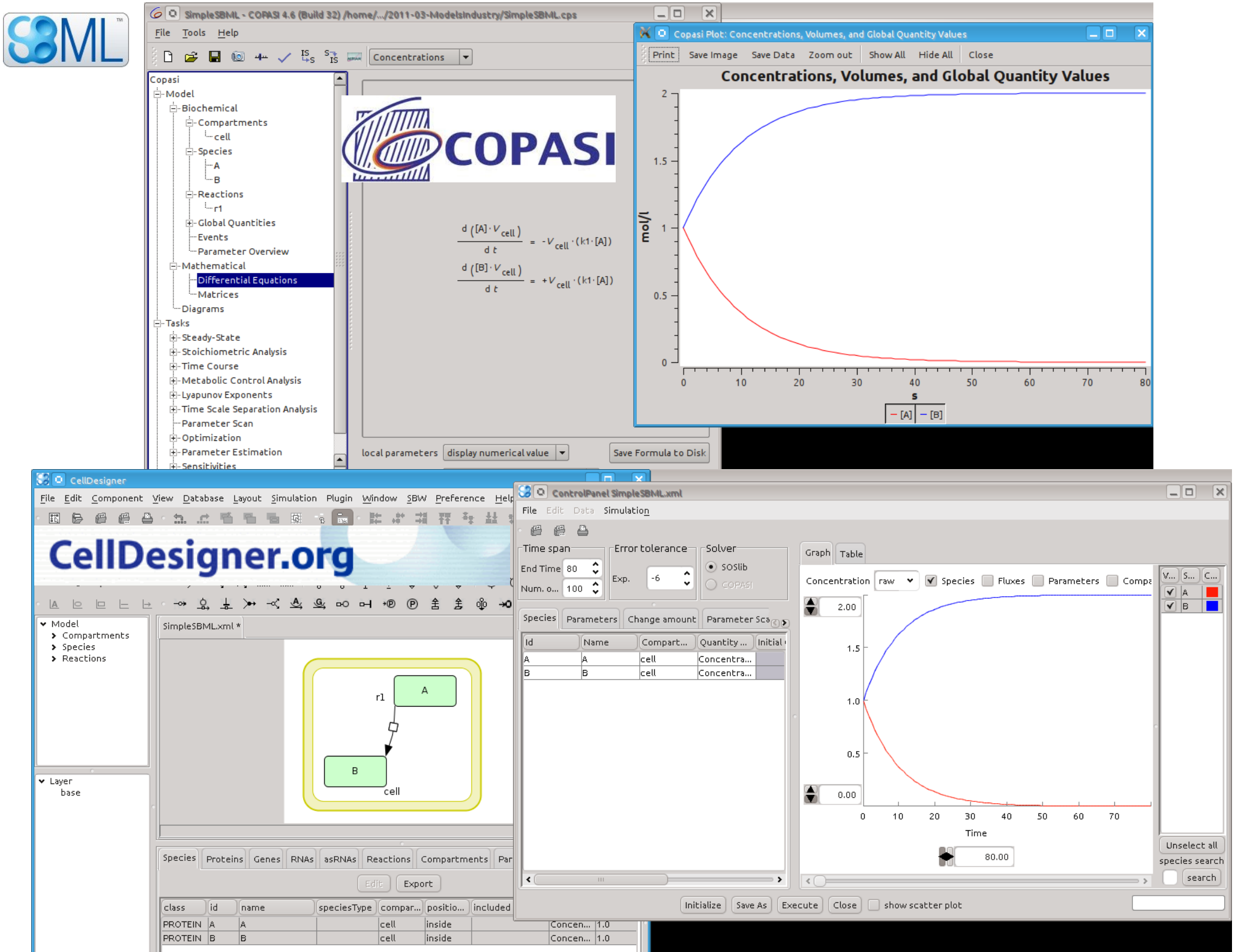
A very simple SBML file (A ⟶ B)

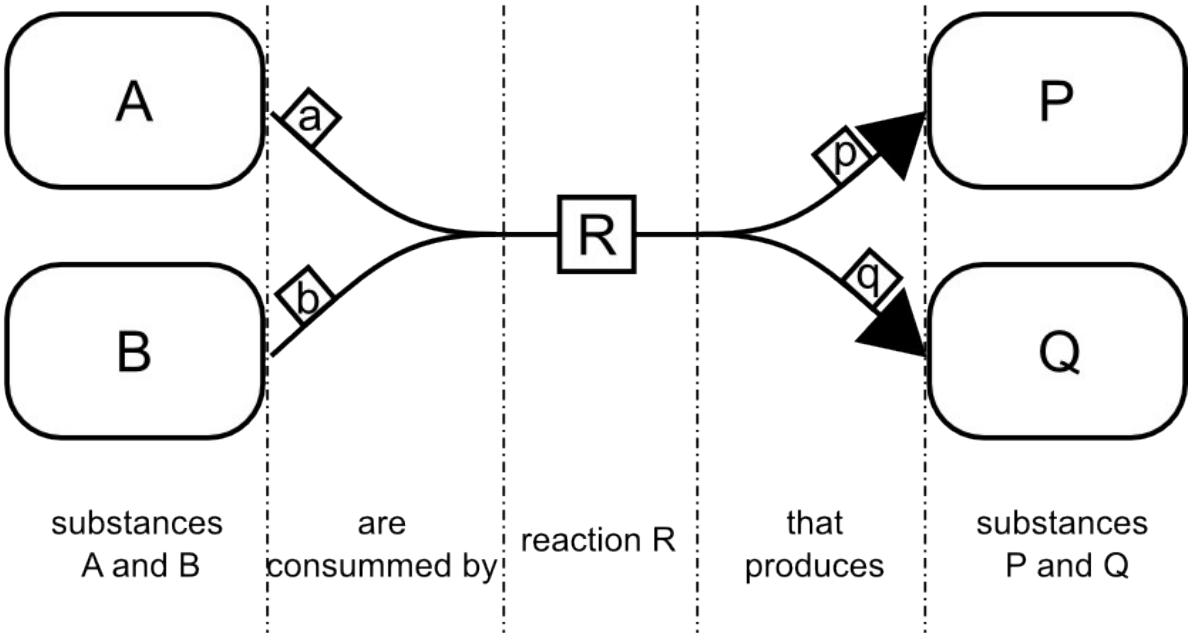
```
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns="http://www.sbml.org/sbml/level2/version4" level="2" version="4">
  <model name="Simple Model">
    <listOfCompartments>
      <compartment id="cell" size="1" />
    </listOfCompartments>
    <listOfSpecies>
      <species id="A" compartment="cell" 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 (A ⟶ B)

```
<?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>
```

MathML


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
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



SBML

Species | Species Reference | Kinetic Law | Species Reference | Species

A more realistic example ...

```
<species·
    id="A"·
    name="a-tubulin"
    compartment="cell"
    initialAmount="1000"
    substanceUnits="item"
    hasOnlySubstanceUnits="true"
    boundaryCondition="true"
    constant="false"
    charge="0"
    metaid="PX"
    sboTerm="SBO:0000245" >
  <notes>
    <body xmlns="http://www.w3.org/1999/xhtml">
      <p>One of the components of a microtubule</p>
    </body>
  </notes>
  <annotation>
    <rdf:RDF·
        xmlns:bqbiol="http://biomodels.net/biology-qualifiers/"·
        xmlns:bqmodel="http://biomodels.net/model-qualifiers/"
        xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
      <rdf:Description rdf:about="#PX">
        <bqbiol:is>
          <rdf:Bag>
            <rdf:li rdf:resource="urn:miriam:uniprot:P68370"/>
            <rdf:li rdf:resource="urn:miriam:obo.go:GO%3A0045298"/>
          </rdf:Bag>
        </bqbiol:is>
      </rdf:Description>
    </rdf:RDF>
  </annotation>
</species>
```

A more realistic example ...

```
<species·
    id="A"·
    name="a-tubulin"
    compartment="cell"
    initialAmount="1000"
    substanceUnits="item"
    hasOnlySubstanceUnits="true"
    boundaryCondition="true"
    constant="false"
    charge="0"
    metaid="PX"
    sboTerm="SBO:0000245" >
  <notes>
    <body xmlns="http://www.w3.org/1999/xhtml">
      <p>One of the components of a microtubule</p>
    </body>
  </notes>
  <annotation>
    <rdf:RDF·
        xmlns:bqbiol="http://biomodels.net/biology-qualifiers/"·
        xmlns:bqmodel="http://biomodels.net/model-qualifiers/"
        xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
      <rdf:Description rdf:about="#PX">
        <bqbiol:is>
          <rdf:Bag>
            <rdf:li rdf:resource="urn:miriam:uniprot:P68370"/>
            <rdf:li rdf:resource="urn:miriam:obo.go:GO%3A0045298"/>
          </rdf:Bag>
        </bqbiol:is>
      </rdf:Description>
    </rdf:RDF>
  </annotation>
</species>
```

biological semantics: macromolecule

XHTML

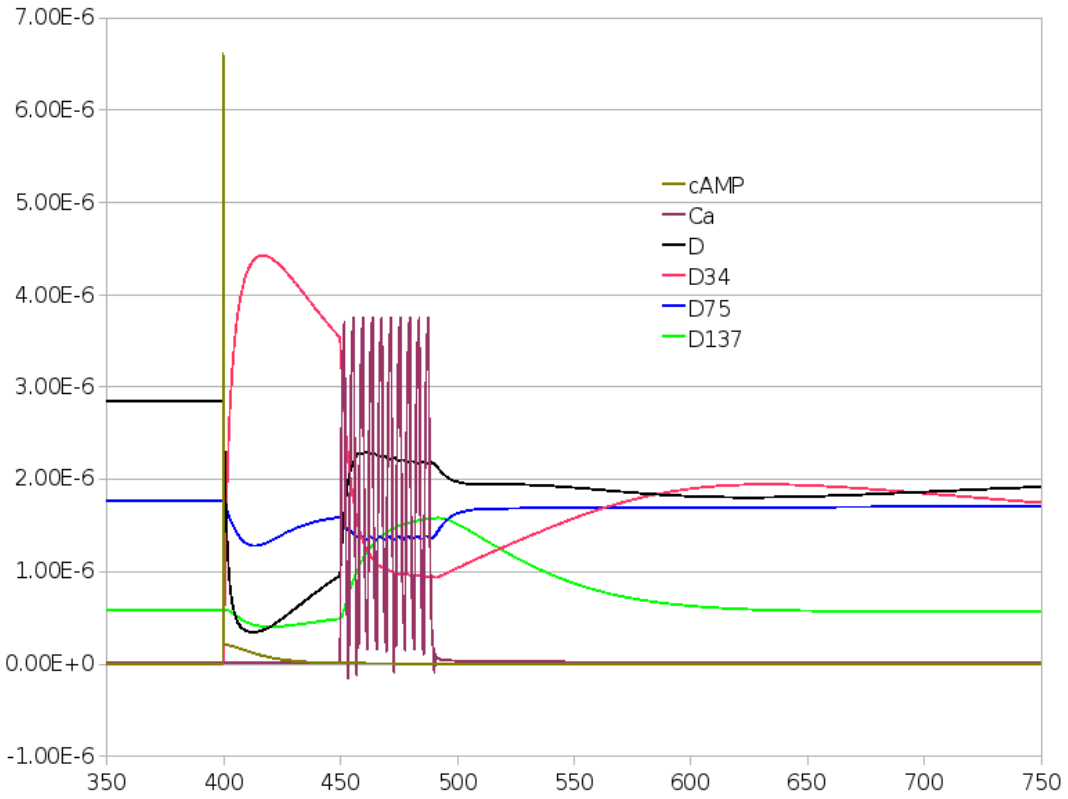
RDF

SBML is not limited to biochemistry!

- A species is a pool of entities participating to a reaction, **not always** a **chemical** entity
  - It can be a pool of molecules
  - It can be a pool of cells
  - It can be a pool of organs
  - It can be a population of organi
- Rate Rules can describe the temporal evolution of any quantitative parameter, e.g. transmembrane voltage, tumour size etc.
- Events can describe any discontinuous change, e.g. neurotransmitter release, repolarisation, cell division etc.

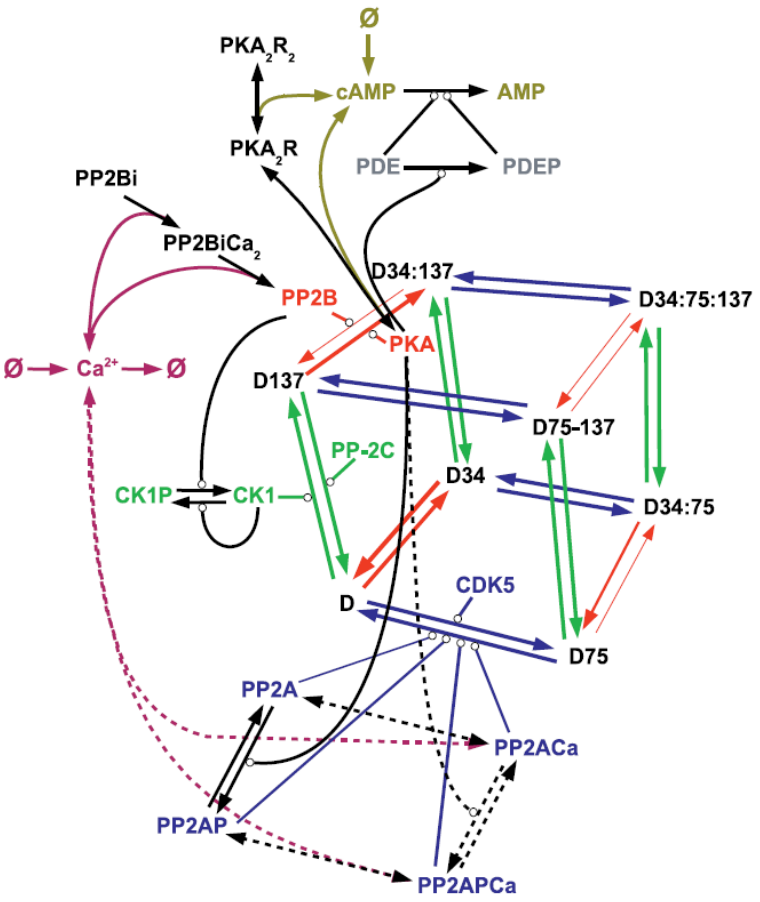
➔ SBML is about process descriptions

Biochemical models



Fernandez et al. DARPP-32 is a robust integrator of dopamine and glutamate signals
PLoS Comput Biol (2006) 2: e176.

BioModels **BIOMD0000000153**

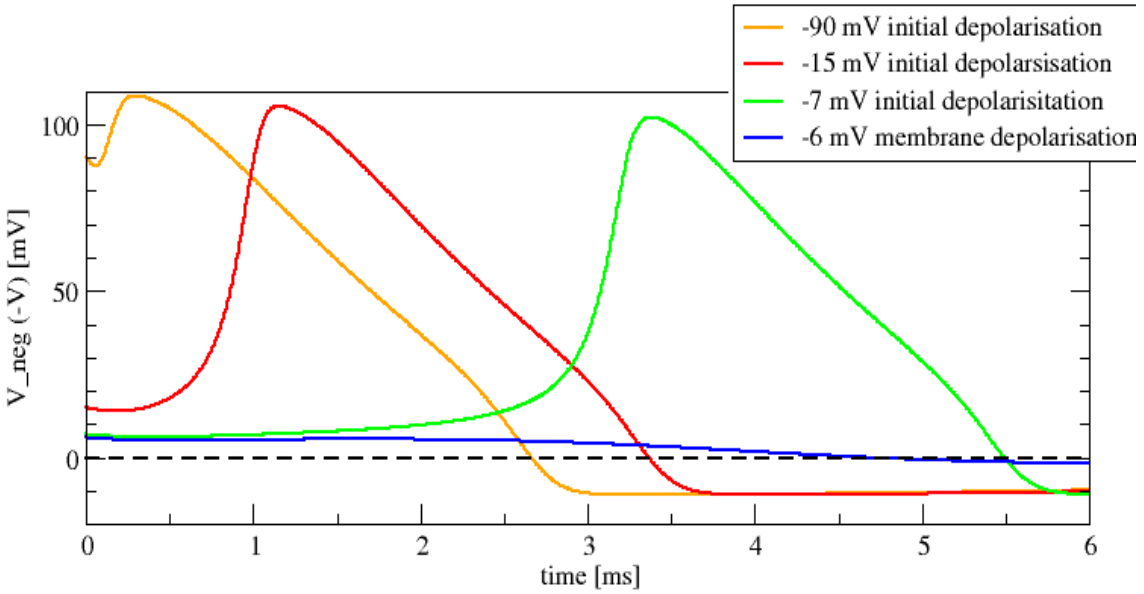


reaction:

$$v_{on1} = k_{on1} \times [D] \times [CDK5] \times Vol$$

➜ Vijayalakshmi Chelliah, Friday 11:30am

Conductance-based model



Hodgkin AL, Huxley AF.
A quantitative description of membrane current and its application to conduction and excitation in nerve.
J Physiol (1952) 117:500-544.

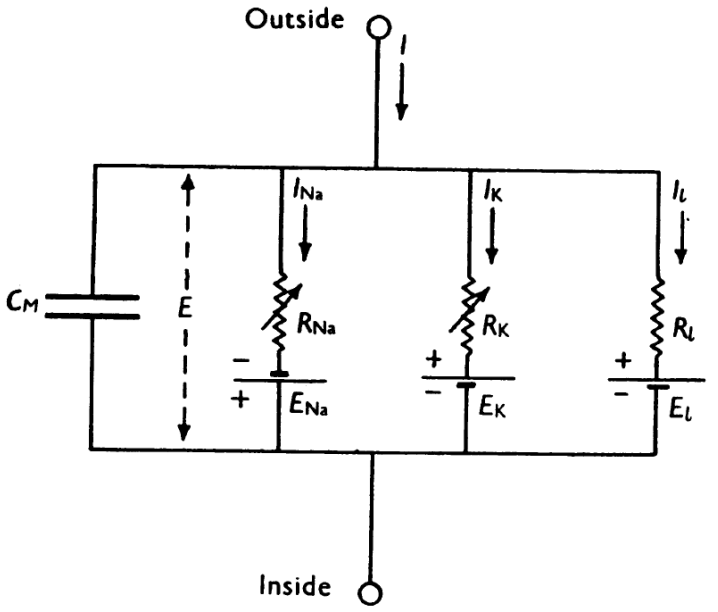
BIOMD0000000020

rate rule:

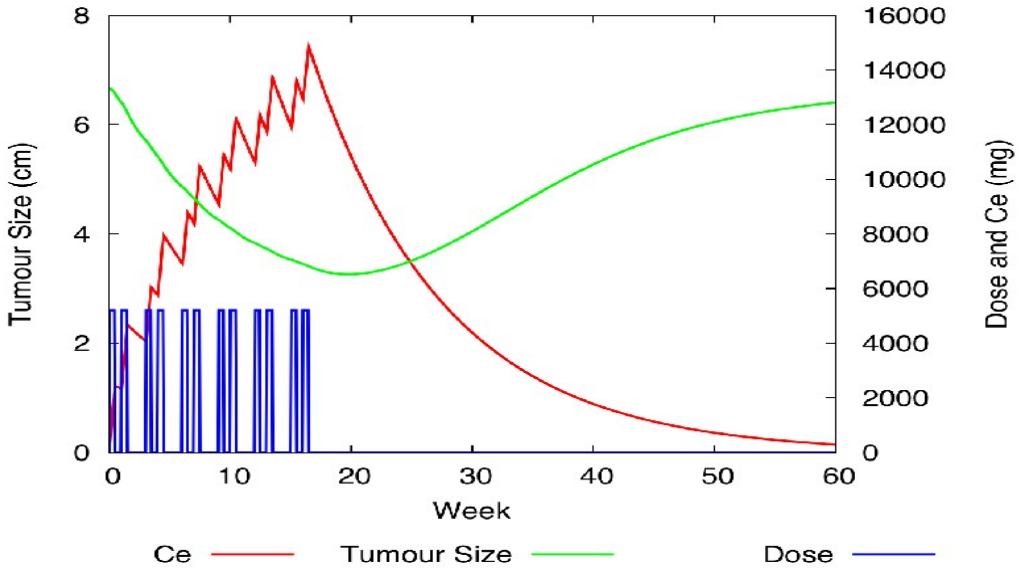
$$\frac{dv}{dt} = \frac{I - (i_{Na} + i_K + i_L)}{C_m}$$

assignment rule:

$$i_{Na} = g_{Na} \times m^3 \times h \times (V - E_{Na})$$



Pharmacometrics models



Tham et al (2008) A pharmacodynamic model for the time course of tumor shrinkage by gemcitabine + carboplatin in non-small cell lung cancer patients. *Clin Cancer Res*. 2008 14(13): 4213-8.

BIOMD0000000234

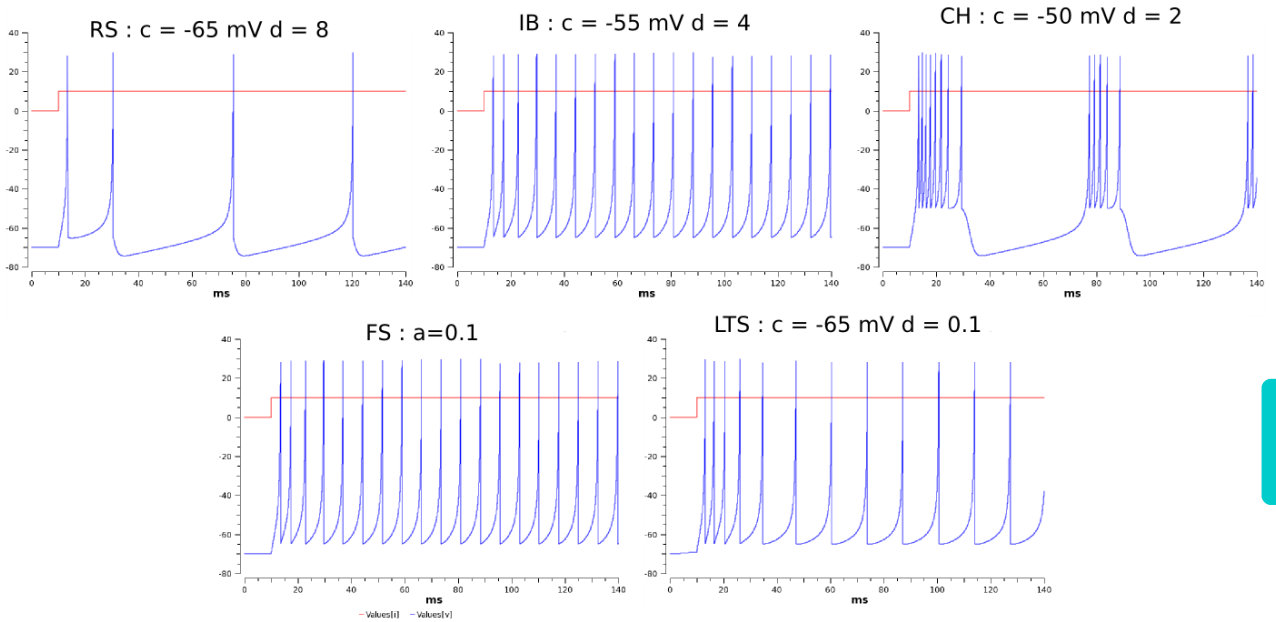
rate rule:

$$\frac{dSize}{dt} = (Rate_{in} \times Effect - K_{over} \times Size) \times Size$$

assignment rule:

$$Effect = 1 - \frac{E_{max} \times Ce}{Amt_{50} + Ce}$$

Single-compartment neurons



Izhikevich EM. Simple model of spiking neurons. *IEEE Trans Neural Netw* (2003) 14(6):1569-1572.

BIOMD0000000127

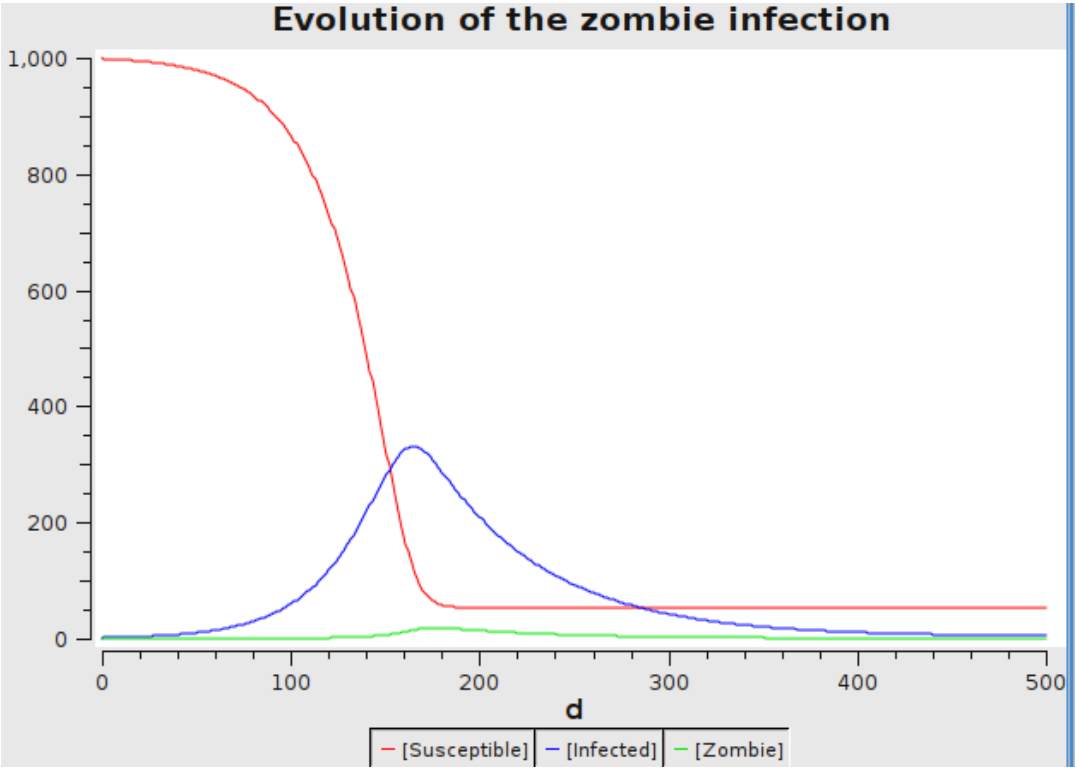
rate rule:

$$\frac{dv}{dt} = 0.04^2 + 5 \times V + 140 - U + i$$

event:

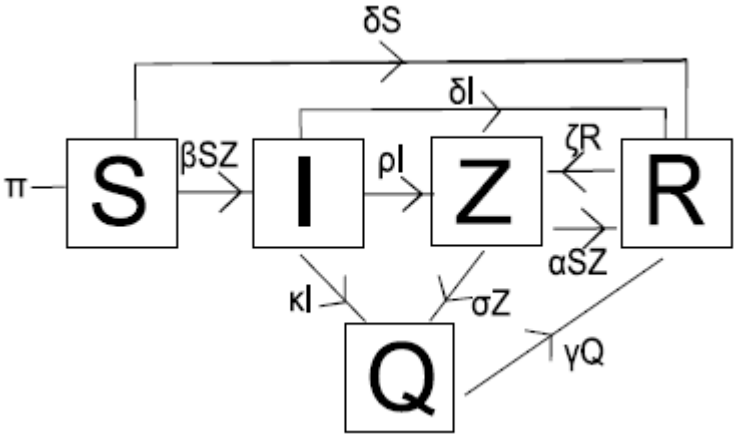
$$\text{when } v > V_{thresh} \begin{cases} v = c \\ U = U + d \end{cases}$$

Spread of infection diseases ...



Munz P et al. When zombies attack!: Mathematical modelling of an outbreak of zombie infection. in "Infectious Disease Modelling Research Progress", (2009)133-150

BioModels MODEL1008060001

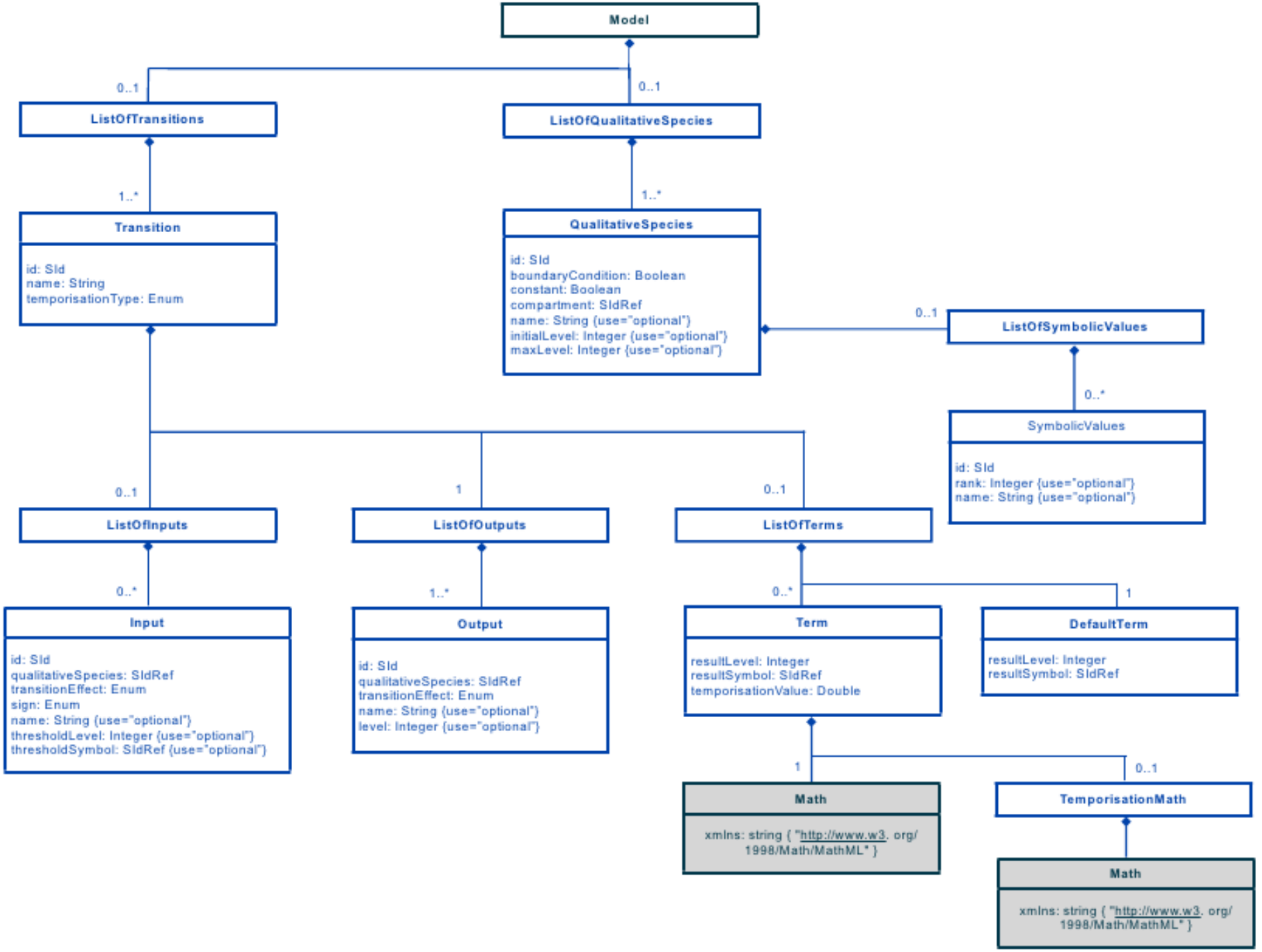


SBML Level 3 packages

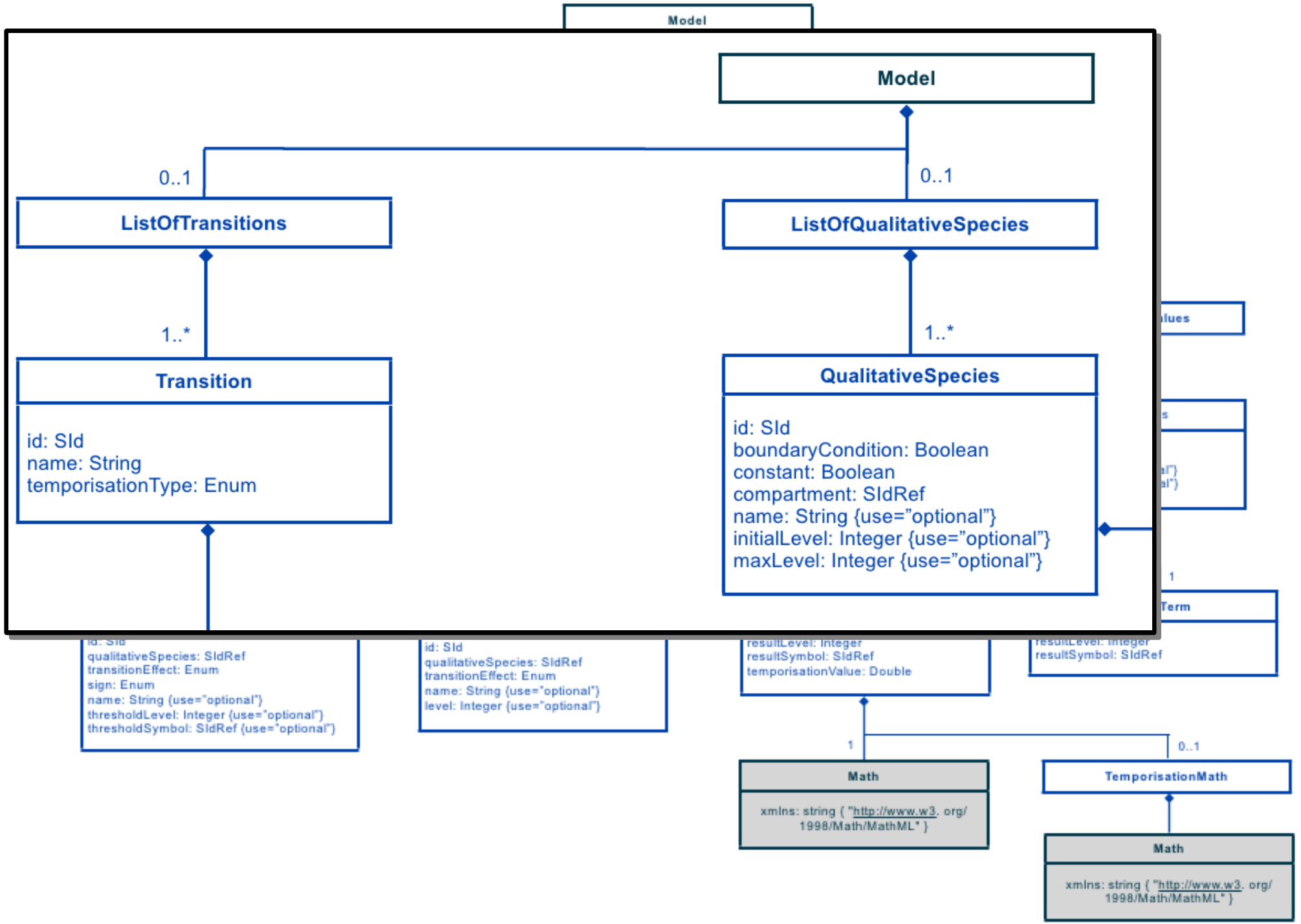
- Core package – public specification
- Graph Layout – specification finalised
- Complex species – specification finalised
- Groups - specification finalised
- Model composition – specification finalised
- Qualitative models – specification finalised
- Flux balance constraint – specification finalised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

???

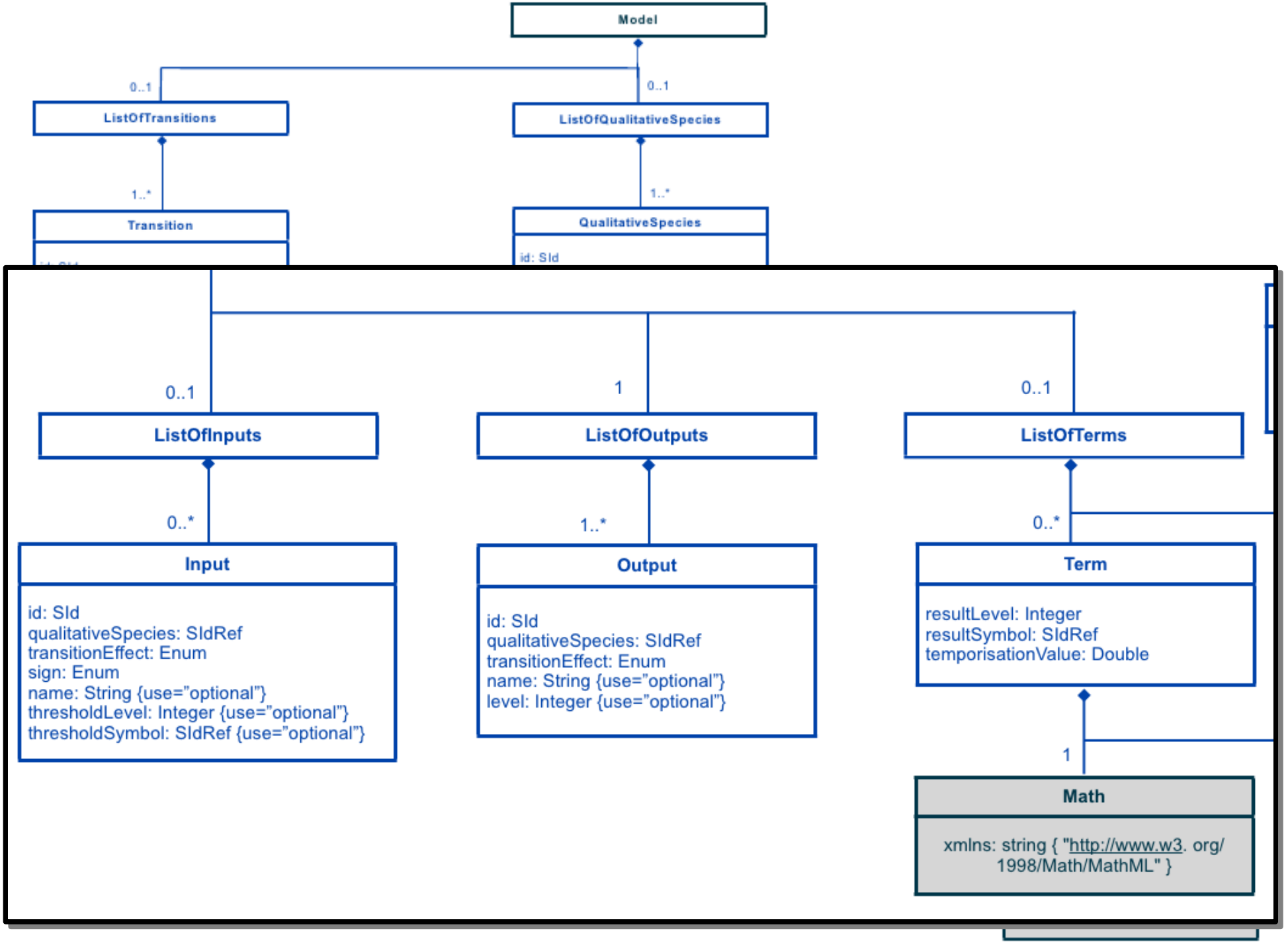
The *qual* package



The *qual* package



The *qual* package



SBML definition and API

- SBML syntax and semantics are very precisely defined
  - SBML specification document: Level 3 Version 1 = 167 pages, small margins
  - XML schema (L1 and L2) and Schematron (forthcoming for L3)
  - Hundreds of validation rules to check compliance
- A standard Application Programming Interface with two implementations
  - LibSBML in C and C++, with binding to C#, Java, Python, Perl, MatLab, Octave, Ruby
  - JSBML, native Java version
- Test suite of 5514 models either testing a feature or a documented error

➜ Sarah Keating, Nicolas Rodriguez, Friday 9am

SBML Software Guide

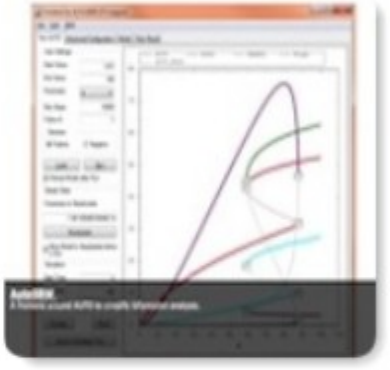
The following pages describe SBML-compatible software packages known to us. We offer different ways of viewing the information, all drawn from the same underlying data collected from the systems' developers via our **software survey**. The *Matrix* provides a table listing all known software and a variety 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: **232**.

Go to the SBML Software Matrix

Go to the SBML Software Summary

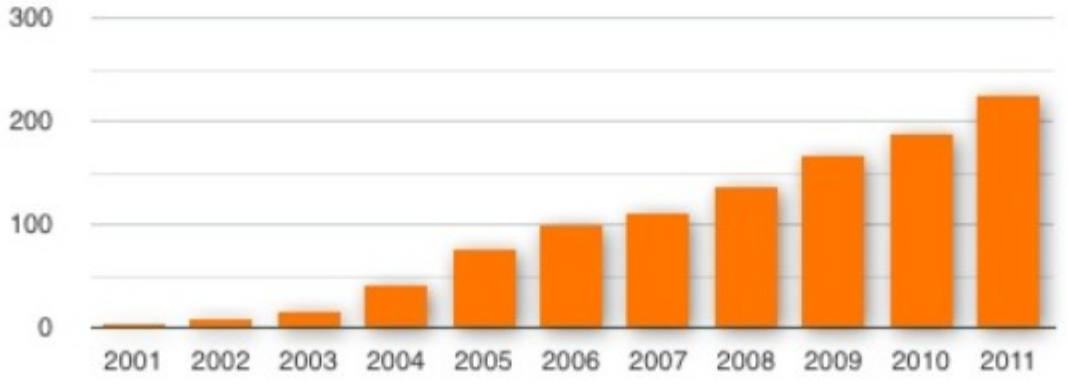
Go to the SBML Software Showcase



Please **use the survey form** to notify us about additions and suggestions.

Historical trend

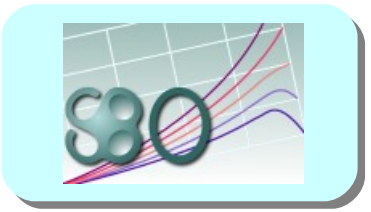
The following graph shows the total number of known SBML-compatible software packages each year, as counted by the SBML Team. The counts shown are for approximately the middle of each year.



SBML supporting tools

- Simulators
  - Discrete stochastic (25)
  - Continuous deterministic (42)
  - Spatial (4)
- Modelling and simulation environments (29)
  - Based on Mathematica (3)
  - Based on Matlab (12)
  - Based on Python/SciPy (9)
  - Based on R (3)
- Flux/metabolic analysis (16)
- Integrated framework (3)
- Libraries (3)
- Model Management, Data Integration, and Analysis (12)
- Model development tools (18)
- Model visualisation (7)
- Model Repositories, Test Suites, and Databases (16)
- Converters (7)
- Analysis and utility (12)

Adding the semantics to the syntax

	Model descriptions
Minimal requirements	
Data-models	
Terminologies	

Born in Heidelberg 2004

SBML and MIRIAM cross-references

```
<species id="ca_calmodulin" metaid="cacam">
  <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>
    </rdf:RDF>
  </annotation>
</species>
```

http://biomodels.net/miriam/

➜ Nick Juty, Friday 12am

Systems Biology Ontology

- Download
- Recent changes
- Term request
- Edit tree
- Web Services
- FAQ
- News
- Project on SourceForge
- Contact

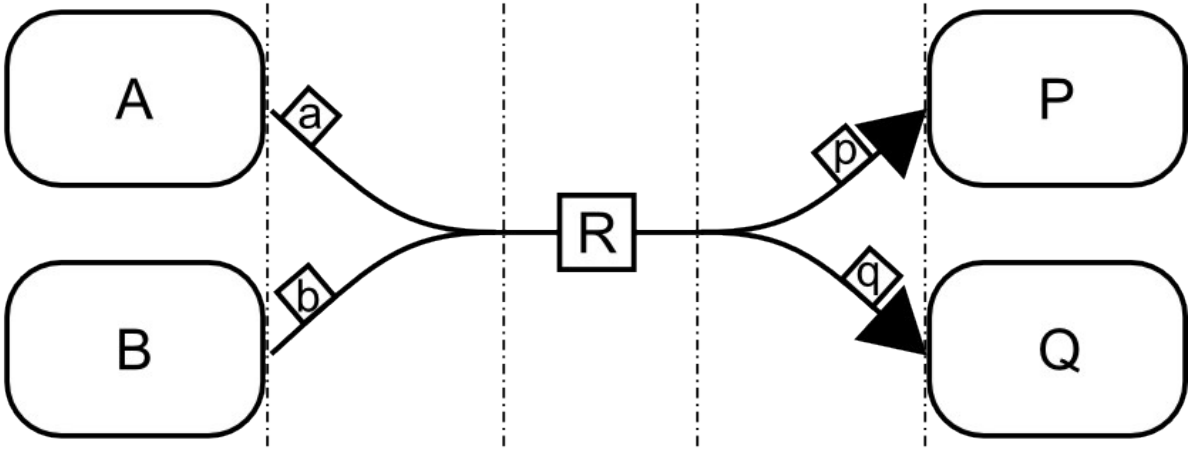
BIOMODELS.NET

- **SBO:0000000 - systems biology representation**
  - SBO:0000064 - mathematical expression
    - SBO:0000355 - conservation law
    - SBO:0000474 - convenience function
    - SBO:0000001 - rate law
    - SBO:0000391 - steady state expression
  - SBO:0000544 - metadata representation
  - SBO:0000004 - modelling framework
  - SBO:0000231 - occurring entity representation
  - SBO:0000003 - participant role
  - SBO:0000236 - physical entity representation
  - SBO:0000545 - systems description parameter
    - SBO:0000546 - qualitative systems description parameter
    - SBO:0000002 - quantitative systems description parameter
      - SBO:0000492 - amplitude
      - SBO:0000542 - basic reproductive ratio
      - SBO:0000380 - biochemical coefficient
      - SBO:0000258 - capacitance
      - SBO:0000257 - conductance
      - SBO:0000254 - electrical resistance
      - SBO:0000308 - equilibrium or steady-state characteristic

Essential activator

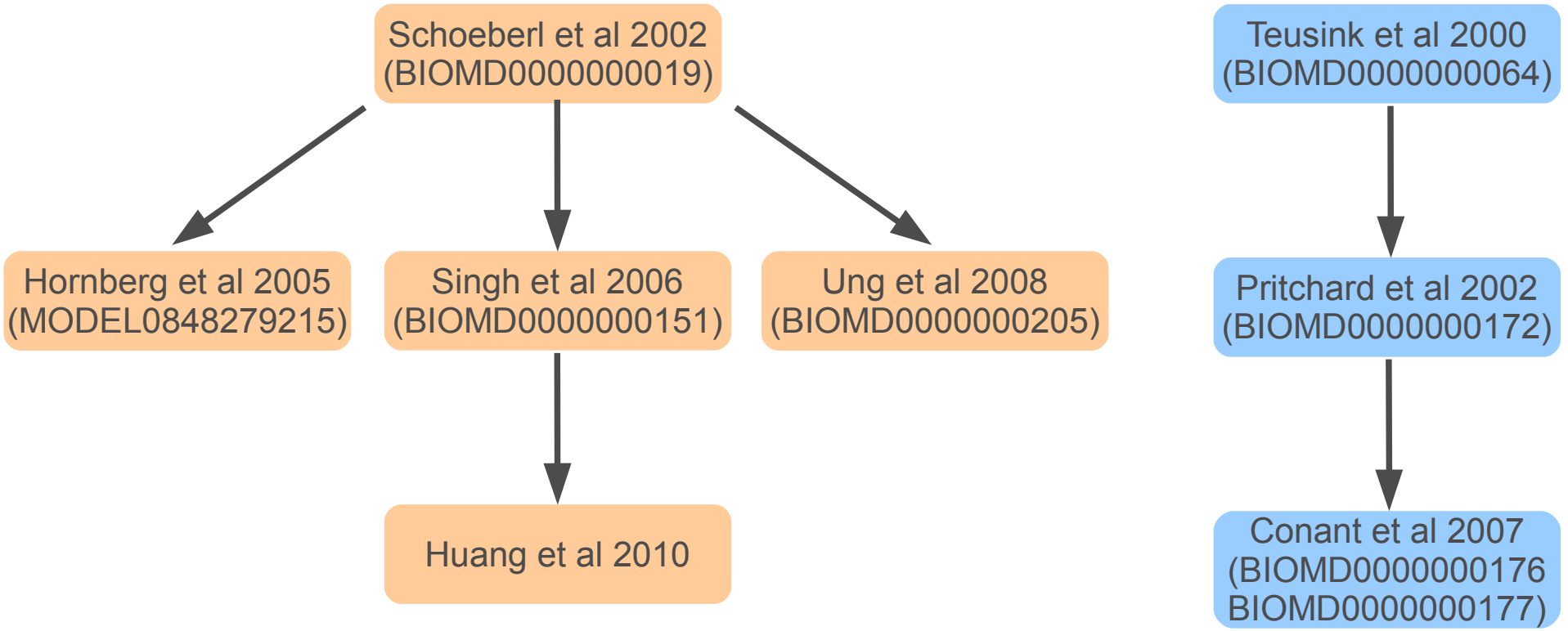
```
<listOfModifiers>
    <modifierSpeciesReference
      sboTerm="SBO:0000461"
      species="Y"/>
 </listOfModifiers>
```

http://www.ebi.ac.uk/sbo/



substances A and B	are consummed by	reaction R	that produces	substances P and Q
SBO:0000240 material entity	SBO:0000394 consumption	SBO:0000375 process	SBO:0000393 production	SBO:0000240 material entity
Species	Species Reference	Kinetic Law	Species Reference	Species

Direct model re-use: e.g. EGFR signalling and glycolysis



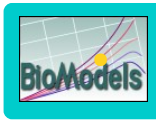
Standard formats generate new research

- Herrgård et al (2008) A consensus yeast metabolic network reconstruction obtained from a community approach to systems biology. *Nature Biotechnol*, 26: 1155-1160

MODEL0072364382: 2152 species, 1857 reactions

  - stoichiometric map, no concentrations, no kinetics

- Smallbone et al (2010) Towards a genome-scale kinetic model of cellular metabolism. *BMC Syst Biol*, 4:6



MODEL1001200000: 1748 species, 1059 reactions

  - Concentrations and flux from BioModels Database
  - Constraint-based model and simplified linlog kinetics

- Dobson et al (2010) Further developments towards a genome-scale metabolic model of yeast. *BMC Syst Biol,* 4:145

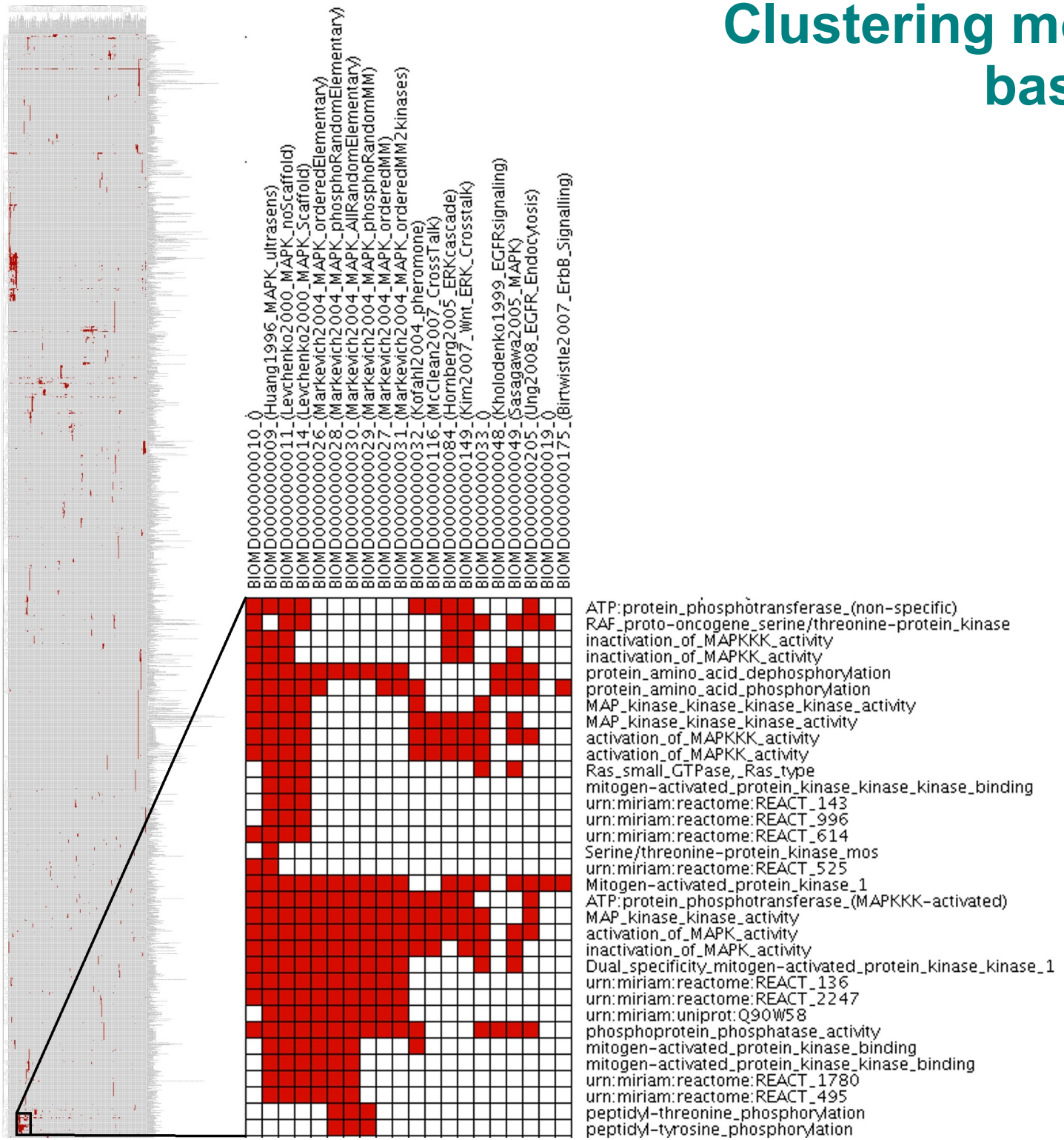
MODEL1012110000: 2657 species, 1865 reactions

- Li et al (2010) Systematic integration of experimental data and models in systems biology. *BMC Bioinfo,* 11: 582

MODEL1012110001

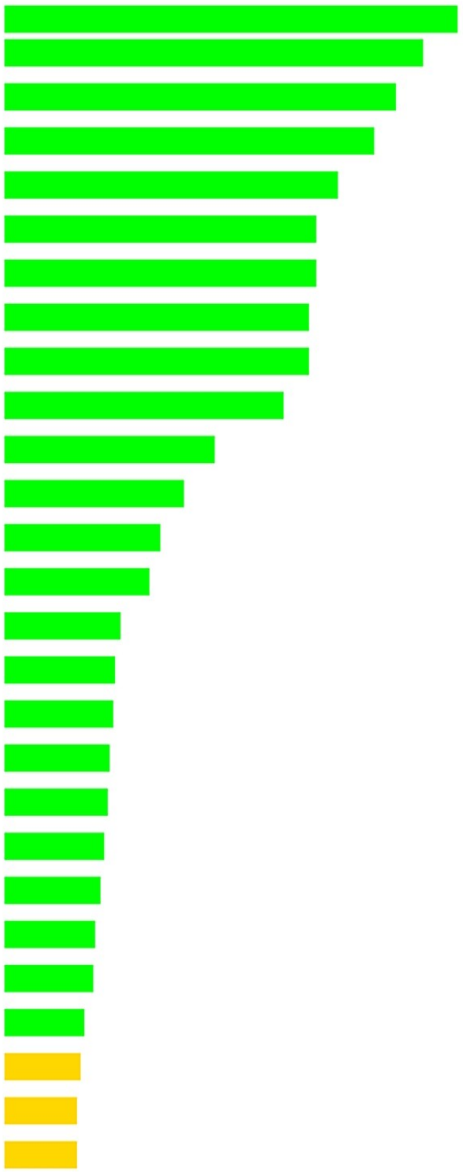
  - Workflows using experimental kinetic information database (SABIO-RK) plus metabolomics and proteomics database
  - Full quantitative chemical kinetics descriptions

Clustering models (and data) based on metadata



Ranking and retrieval of models

Model	BioModel	Score	p-val num
Huang1996_MAPK_ultrasens	BIOMD0000000009	1.000	< 1/1000
Levchenko2000_MAPK_noScaffold	BIOMD0000000011	0.925	< 1/1000
Levchenko2000_MAPK_Scaffold	BIOMD0000000014	0.865	< 1/1000
Kholodenko2000_MAPK_feedback	BIOMD0000000010	0.816	< 1/1000
Markevich2004_MAPK_orderedElementary	BIOMD0000000026	0.737	< 1/1000
Markevich2004_MAPK_phosphoRandomElementary	BIOMD0000000028	0.690	< 1/1000
Markevich2004_MAPK_AllRandomElementary	BIOMD0000000030	0.690	< 1/1000
Markevich2004_MAPK_orderedMM	BIOMD0000000027	0.673	< 1/1000
Markevich2004_MAPK_orderedMM2kinases	BIOMD0000000031	0.673	< 1/1000
Markevich2004_MAPK_phosphoRandomMM	BIOMD0000000029	0.617	< 1/1000
Hornberg2005_ERKcascade	BIOMD0000000084	0.468	< 1/1000
McClean2007_CrossTalk	BIOMD0000000116	0.397	< 1/1000
Kofahl2004_pheromone	BIOMD0000000032	0.348	< 1/1000
Kim2007_Wnt_ERK_Crosstalk	BIOMD0000000149	0.323	< 1/1000
Brown2004_NGF_EGF_signaling	BIOMD0000000033	0.260	< 1/1000
Goldbeter1995_CircClock	BIOMD0000000016	0.244	< 1/1000
Sasagawa2005_MAPK	BIOMD0000000049	0.240	< 1/1000
Ung2008_EGFR_Endocytosis	BIOMD0000000205	0.234	< 1/1000
Leloup1999_CircClock	BIOMD0000000021	0.229	< 1/1000
Goldbeter1991_MinMitOscil_ExplInact	BIOMD0000000004	0.222	< 1/1000
Goldbeter1991_MinMitOscil	BIOMD0000000003	0.214	< 1/1000
Leloup1998_CircClock_LD	BIOMD0000000171	0.201	< 1/1000
Tyson1991_CellCycle_6var	BIOMD0000000005	0.199	< 1/1000
Veening2008_DegU_Regulation	BIOMD0000000240	0.180	< 1/1000
Neves2008_Cell_Shape	BIOMD0000000182	0.168	4.0e-03
Fisher2006_Ca_Oscillation_dpdnt_NFAT_dynamics	BIOMD0000000122	0.164	5.0e-03
Leloup2003_CircClock_DD	BIOMD0000000073	0.163	5.0e-03

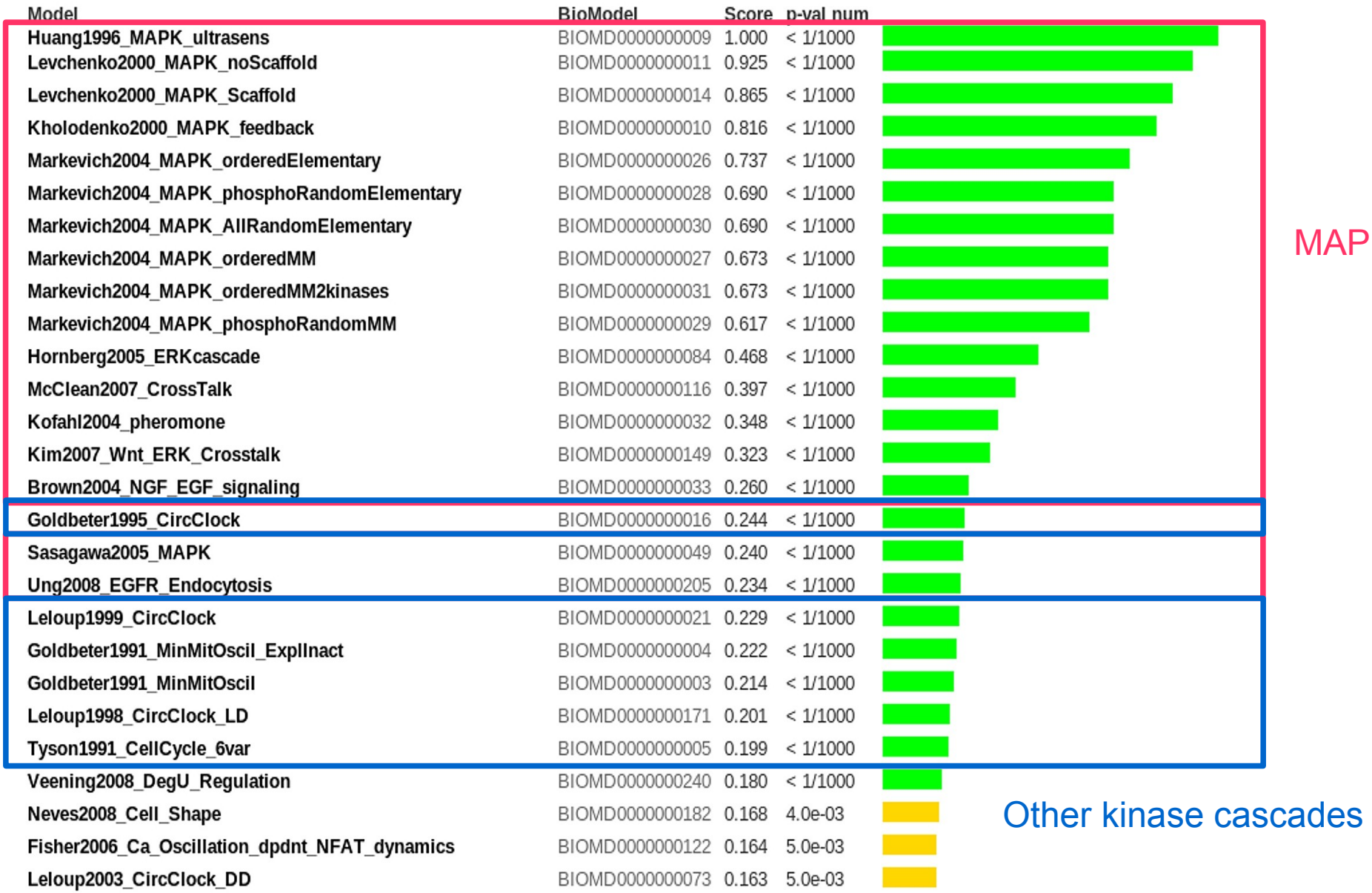


Ranking and retrieval of models

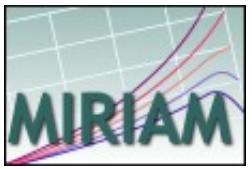
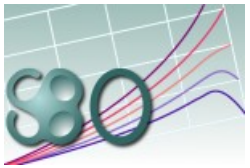
Model	BioModel	Score	p-val num
Huang1996_MAPK_ultrasens	BIOMD0000000009	1.000	< 1/1000
Levchenko2000_MAPK_noScaffold	BIOMD0000000011	0.925	< 1/1000
Levchenko2000_MAPK_Scaffold	BIOMD0000000014	0.865	< 1/1000
Kholodenko2000_MAPK_feedback	BIOMD0000000010	0.816	< 1/1000
Markevich2004_MAPK_orderedElementary	BIOMD0000000026	0.737	< 1/1000
Markevich2004_MAPK_phosphoRandomElementary	BIOMD0000000028	0.690	< 1/1000
Markevich2004_MAPK_AllRandomElementary	BIOMD0000000030	0.690	< 1/1000
Markevich2004_MAPK_orderedMM	BIOMD0000000027	0.673	< 1/1000
Markevich2004_MAPK_orderedMM2kinases	BIOMD0000000031	0.673	< 1/1000
Markevich2004_MAPK_phosphoRandomMM	BIOMD0000000029	0.617	< 1/1000
Hornberg2005_ERKcascade	BIOMD0000000084	0.468	< 1/1000
McClean2007_CrossTalk	BIOMD0000000116	0.397	< 1/1000
Kofahl2004_pheromone	BIOMD0000000032	0.348	< 1/1000
Kim2007_Wnt_ERK_Crosstalk	BIOMD0000000149	0.323	< 1/1000
Brown2004_NGF_EGF_signaling	BIOMD0000000033	0.260	< 1/1000
Goldbeter1995_CircClock	BIOMD0000000016	0.244	< 1/1000
Sasagawa2005_MAPK	BIOMD0000000049	0.240	< 1/1000
Ung2008_EGFR_Endocytosis	BIOMD0000000205	0.234	< 1/1000
Leloup1999_CircClock	BIOMD0000000021	0.229	< 1/1000
Goldbeter1991_MinMitOscil_ExplInact	BIOMD0000000004	0.222	< 1/1000
Goldbeter1991_MinMitOscil	BIOMD0000000003	0.214	< 1/1000
Leloup1998_CircClock_LD	BIOMD0000000171	0.201	< 1/1000
Tyson1991_CellCycle_6var	BIOMD0000000005	0.199	< 1/1000
Veening2008_DegU_Regulation	BIOMD0000000240	0.180	< 1/1000
Neves2008_Cell_Shape	BIOMD0000000182	0.168	4.0e-03
Fisher2006_Ca_Oscillation_dpdnt_NFAT_dynamics	BIOMD0000000122	0.164	5.0e-03
Leloup2003_CircClock_DD	BIOMD0000000073	0.163	5.0e-03

MAPK

Ranking and retrieval of models



The interface with all biologists

	Model descriptions
Minimal requirements	
Data-models	  BioPAX
Terminologies	

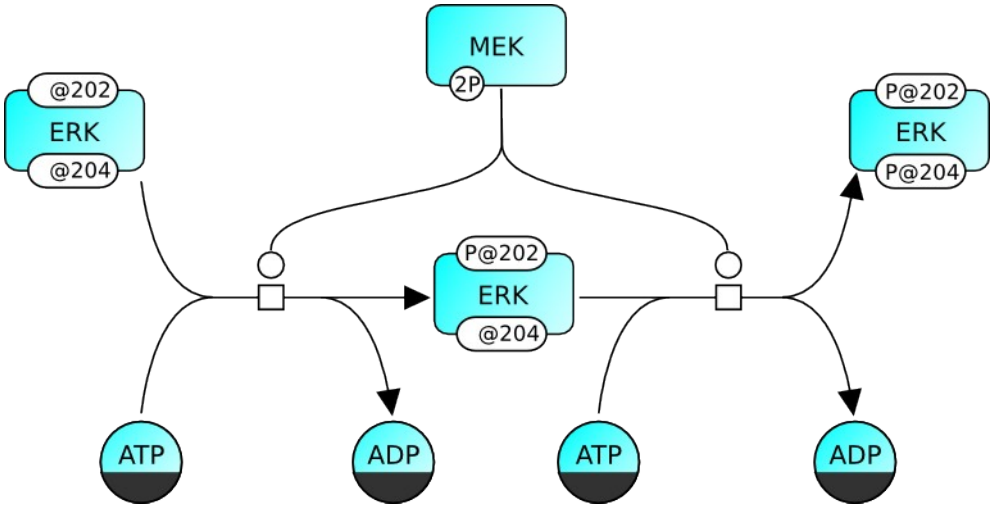
Born in Tokyo 2005

What is SBGN?

- 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 and growing software support
- Developed over four years by a diverse community, including biologists, modellers, computer scientists etc.

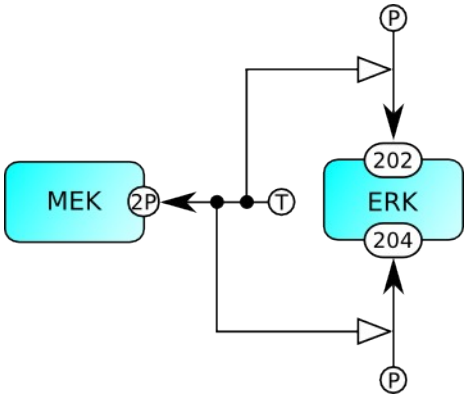
Graph trinity: three languages in one notation

Process Descriptions



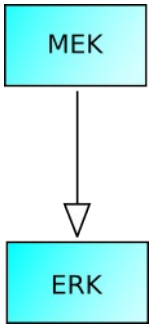
- Unambiguous
- Mechanistic
- Sequential
- Combinatorial explosion

Entity Relationships



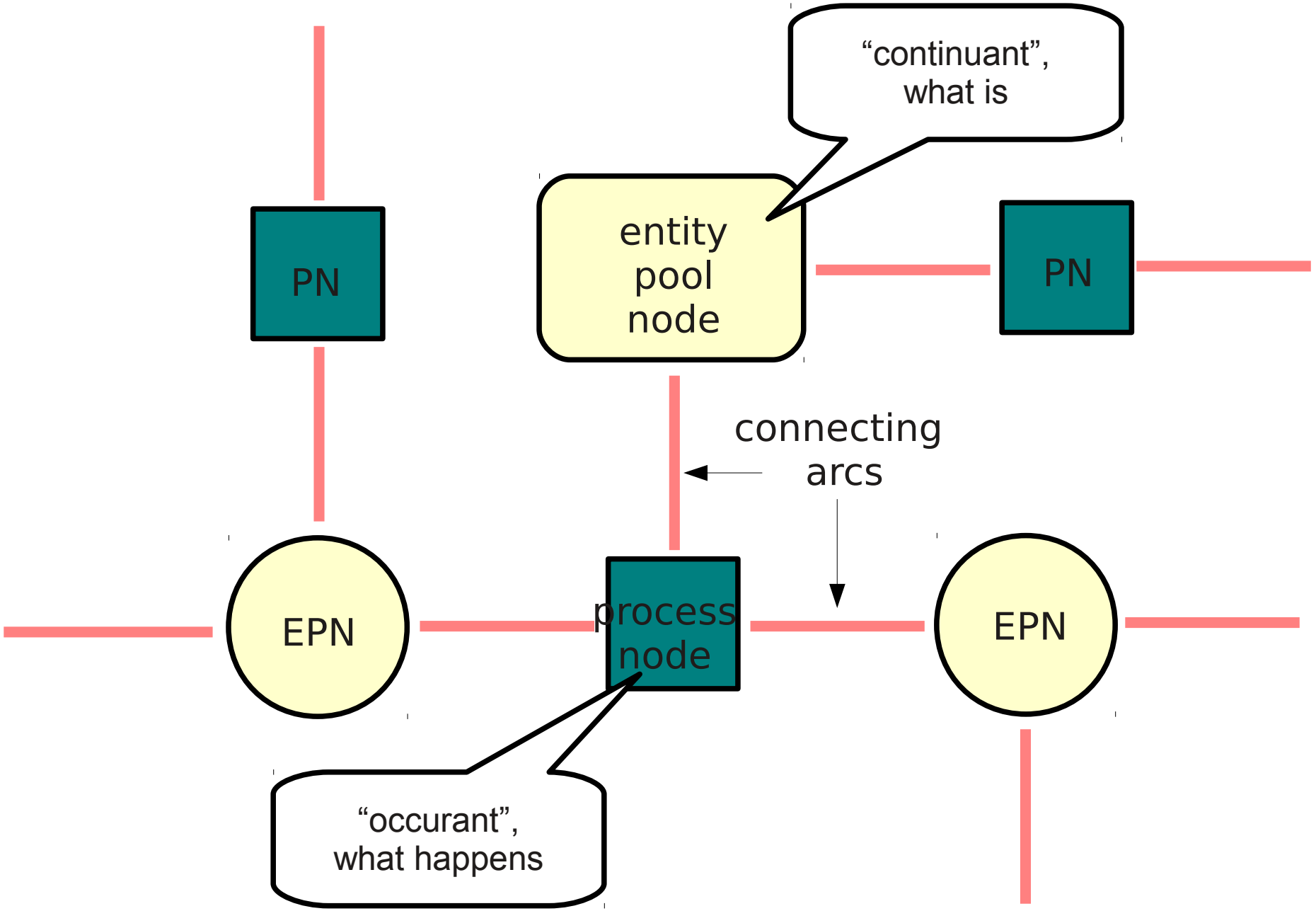
- Unambiguous
- Mechanistic
- Non-sequential
- Independence of relationships

Activity Flows

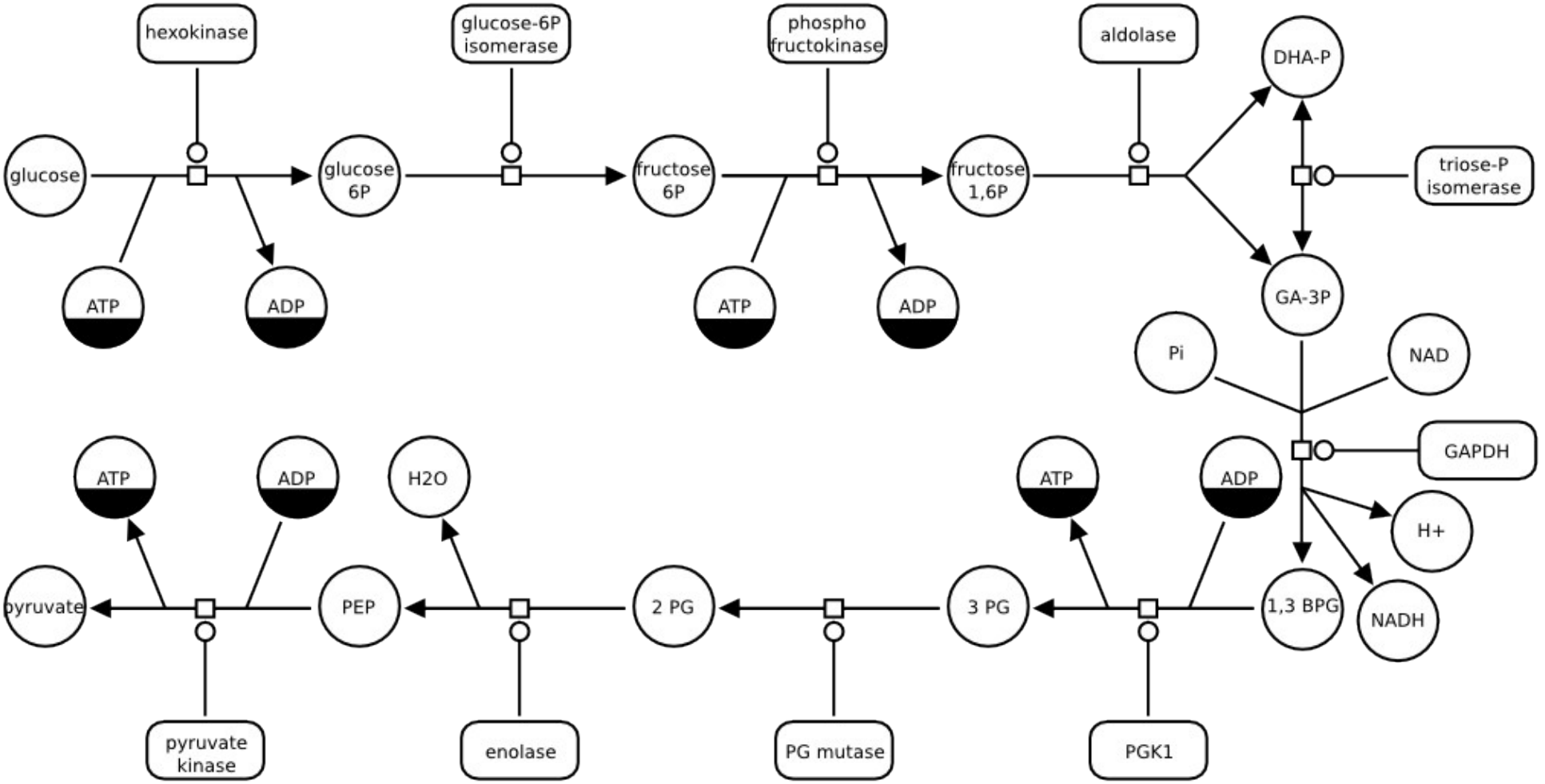


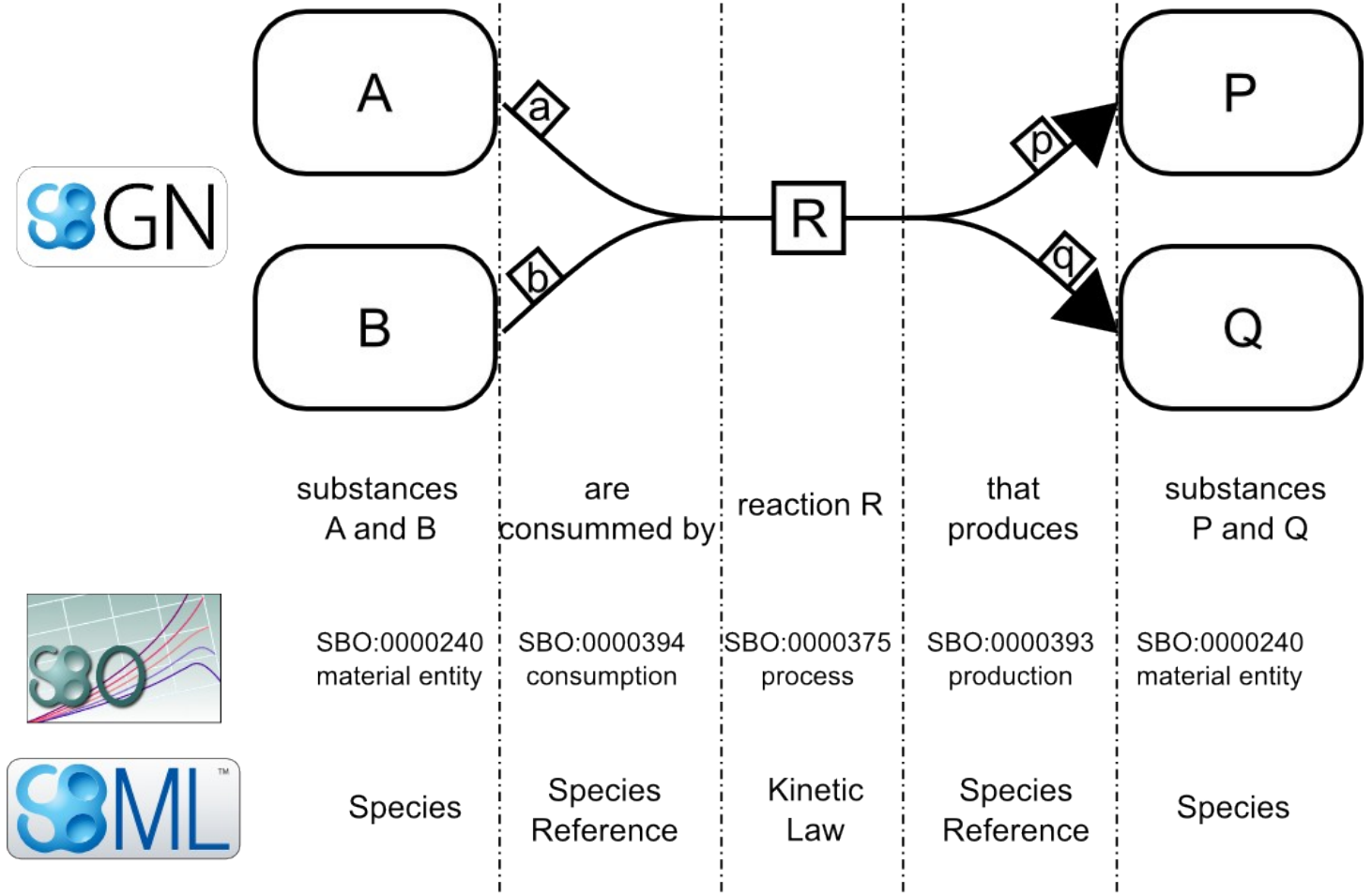
- Ambiguous
- Conceptual
- Sequential

Process Descriptions are bipartite graphs

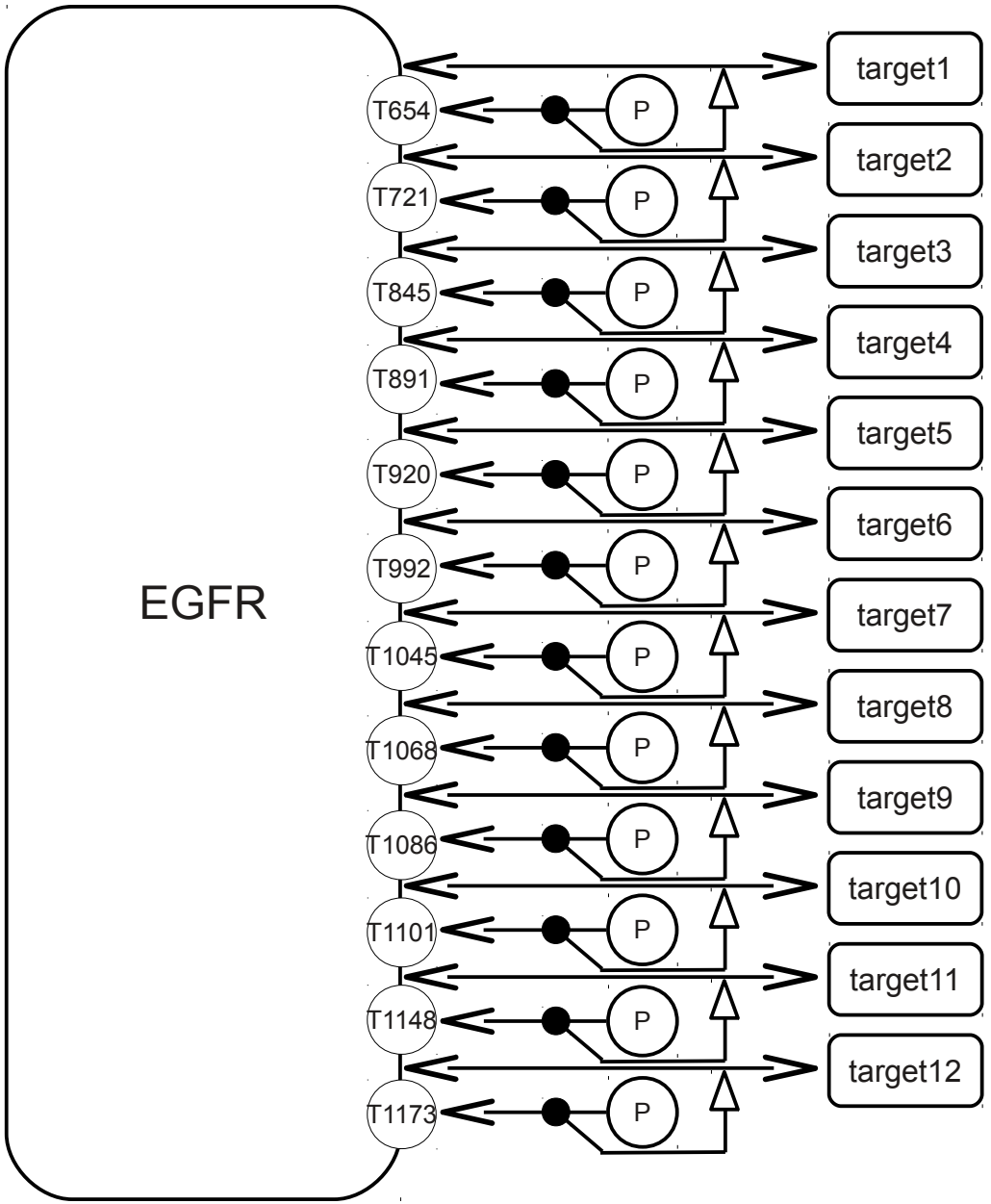


Metabolic network in Process Description Language




A
B
a
b
R
p
q
P
Q
substances A and B
are consummed by
reaction R
that produces
substances P and Q
SBO:0000240 material entity
SBO:0000394 consumption
SBO:0000375 process
SBO:0000393 production
SBO:0000240 material entity
Species
Species Reference
Kinetic Law
Species Reference
Species

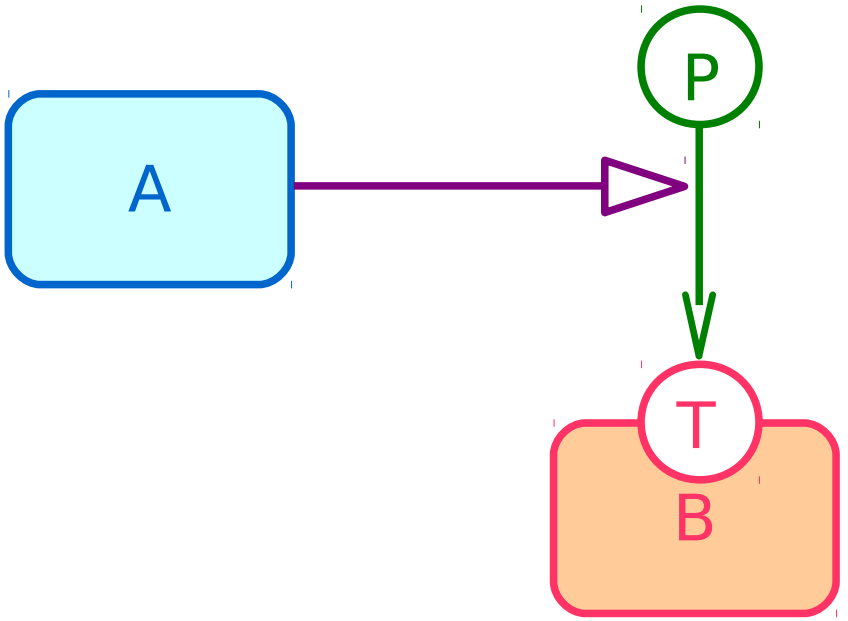
Multi-state and combinatorial explosion



Process Descriptions:
“once a state variable value,
always a state variable value”

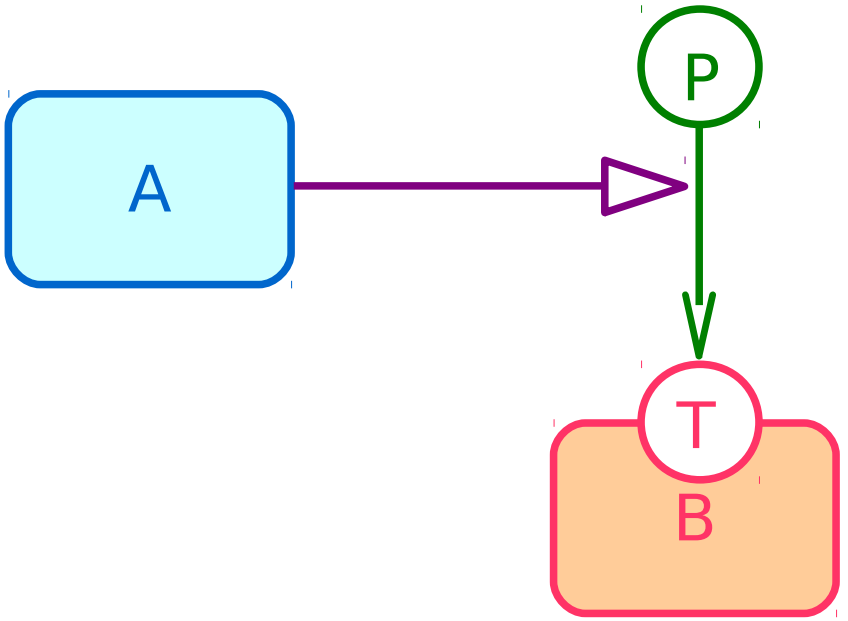
2^{12} = 4096 states
(i.e. EPN glyphs) for EGFR
and 4096 complexes between
EGFR and targets

Entity Relationships can be viewed as rules



If A exists, the assignment of the value P to the state variable T of B is increased

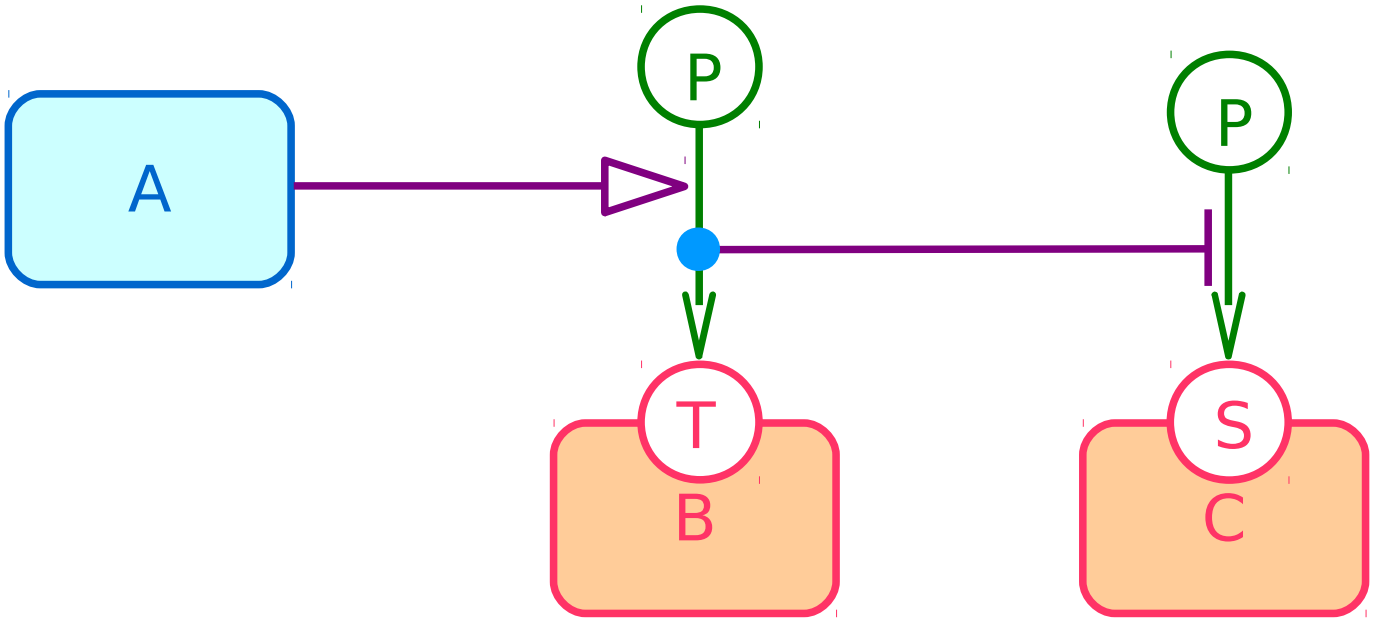
Entity Relationships can be viewed as rules



If A exists, the assignment of the value P to the state variable T of B is increased

(A stimulates the phosphorylation of B on the threonine)

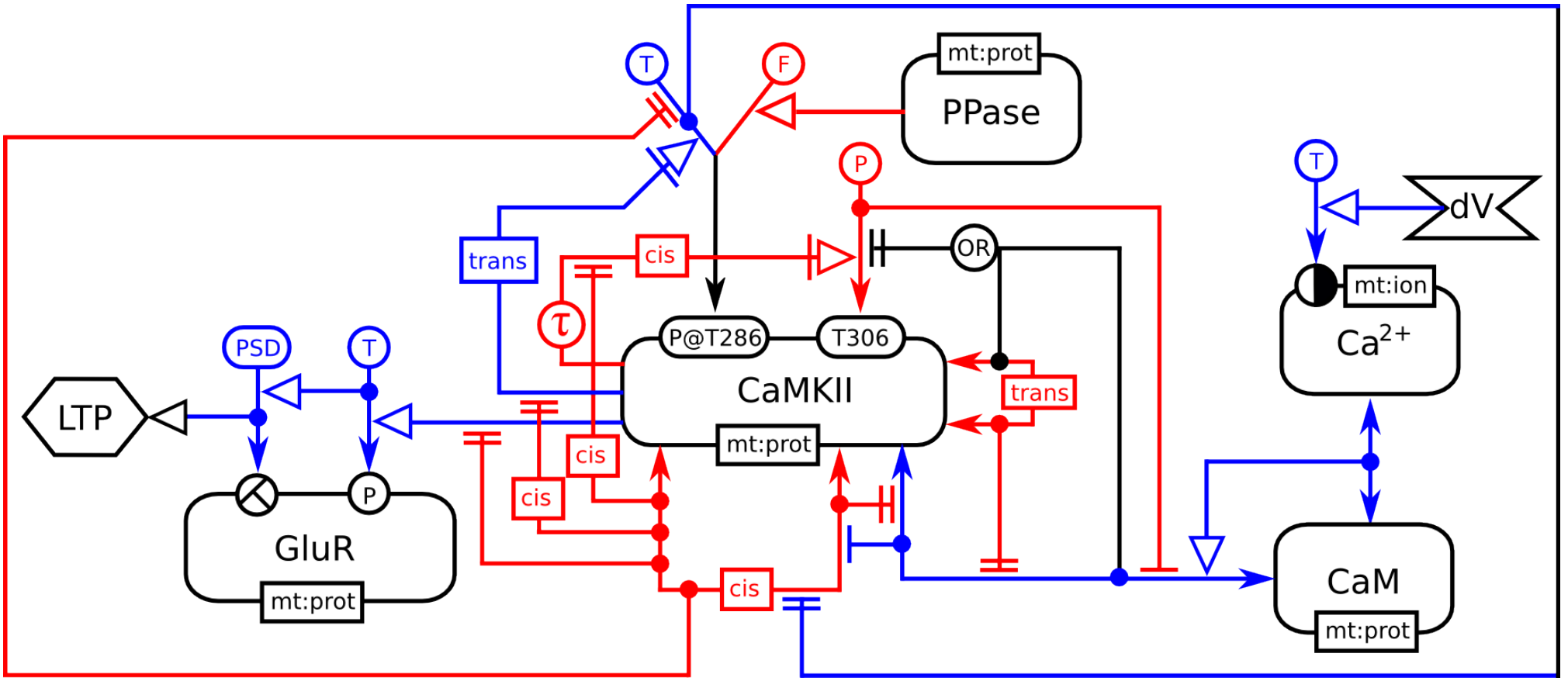
Entity Relationships can be viewed as rules



If A exists, the assignment of the value P to the state variable T of B is increased

If P is assigned to the state variable T of B, the assignment of the value P to the state variable S of B is decreased

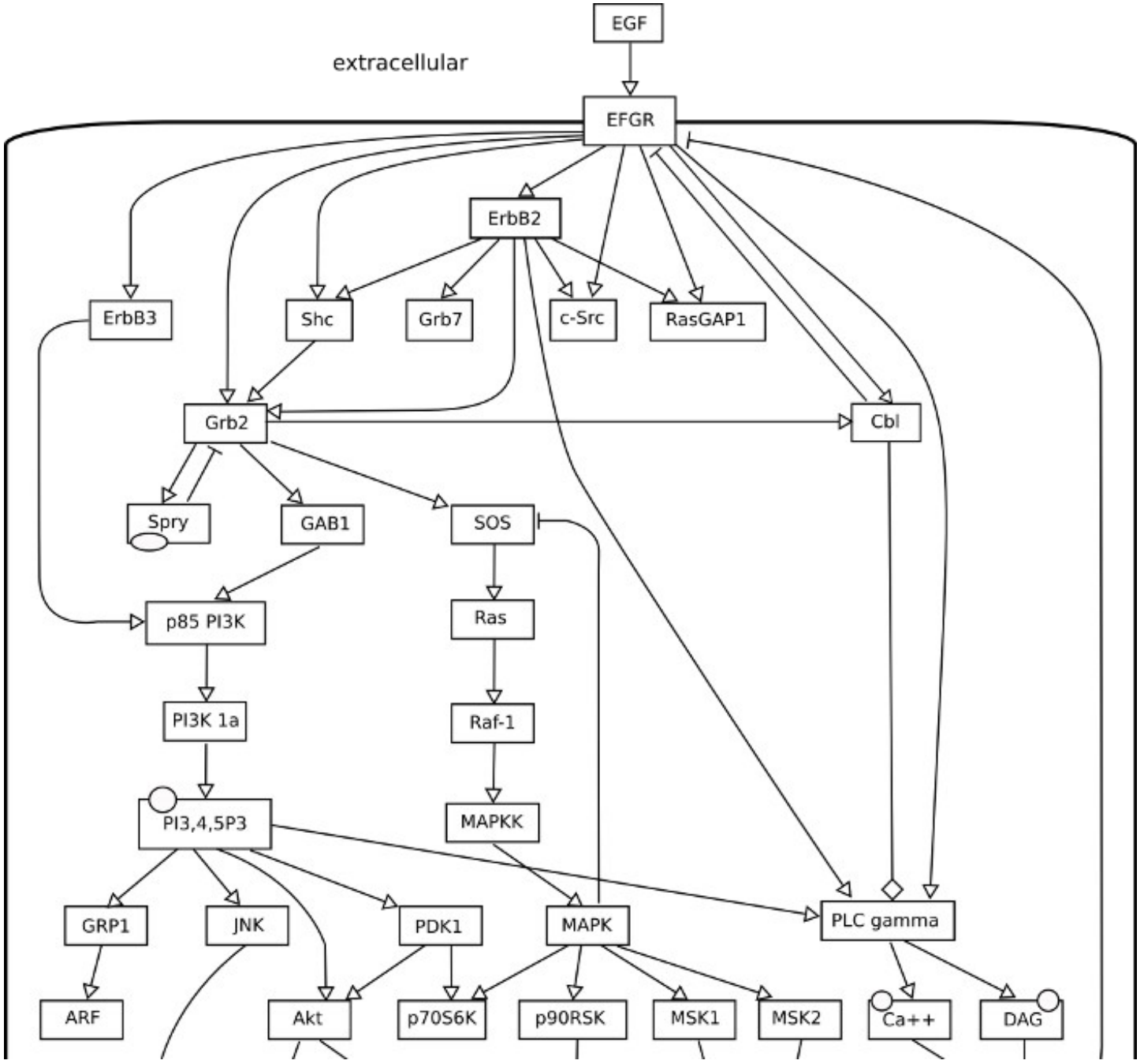
SBGN ER map of calcium-regulated synaptic plasticity



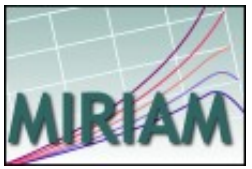
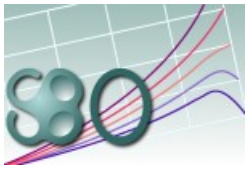
increases synaptic weight

decreases synaptic weight

Example of Activity Flow map



Merging biologist semantics for database

	Model descriptions
Minimal requirements	
Data-models	  BioPAX
Terminologies	

Biological Pathway Exchange format - BioPAX

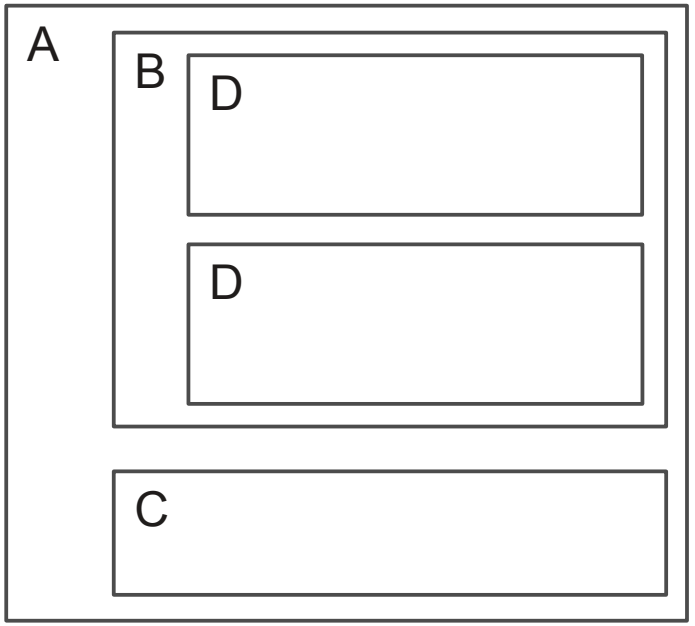
- **RDF/OWL**-based language to represent biological pathways at the molecular and cellular level
- Covers molecular and genetic interactions, metabolic network, signalling pathways, gene regulatory networks
- **Interactions**: Control (Catalysis, Modulation, TemplateReactionRegulation), Conversion (BiochemicalReaction, ComplexAssembly, Degradation, Transport, TransportWithBiochemicalReaction), GeneticInteraction, MolecularInteraction, TemplateReaction
- **Physical entities**: Complex, DNA, DNARegion, Protein, RNA, RNARegion, SmallMolecule
- **Utility classes**: BioSource, ChemicalStructure, ControlledVocabulary, DeltaG, EntityFeature, EntityReference, Evidence, ExperimentalForm, kPrime, PathwayStep, Provenance, Score, SequenceLocation, Stoichiometry, Xref

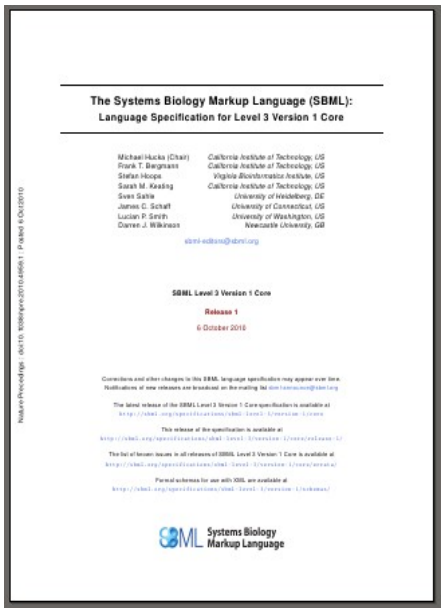
Resource Description Framework - RDF

- Language of the semantic web
- Semantic entirely embedded in the language (does not require external schemas and specifications)
- Series of statements

Subject	Predicate	Object
EGFR	*located_in*	plasma membrane
P00533 (UniProt)	OBO_REL:0000008 (OBO Relation ontology)	GO:0005886 (Gene Ontology)

“XML” Vs RDF



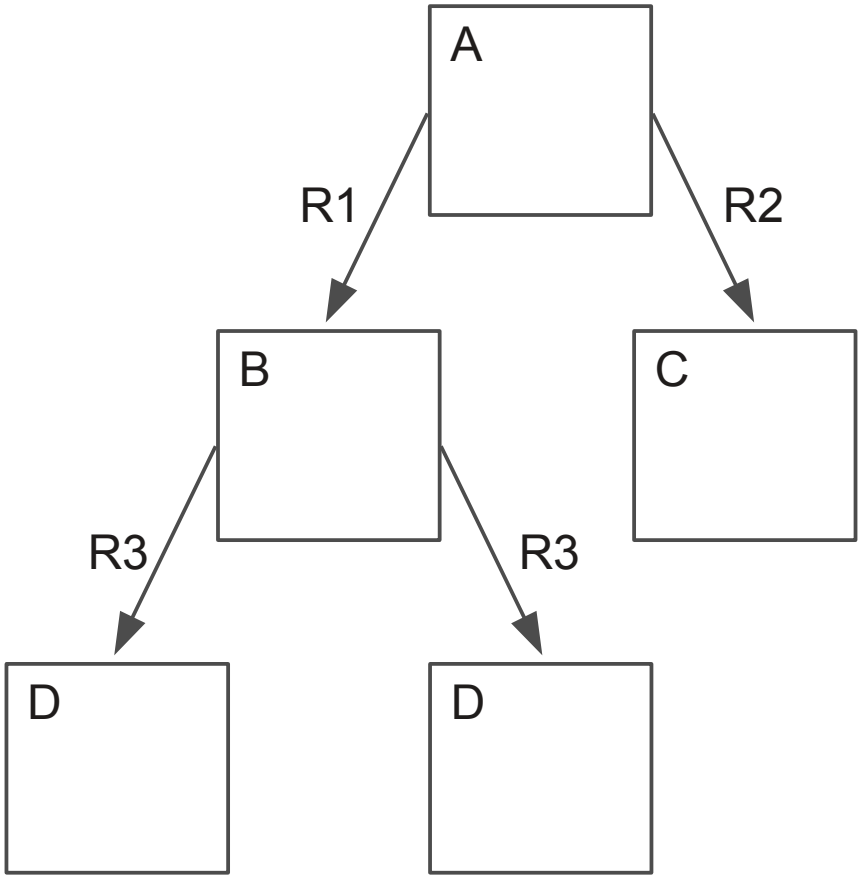


The Systems Biology Markup Language (SBML):
Language Specification for Level 3 Version 1 Core

SBML Level 3 Version 1 Core

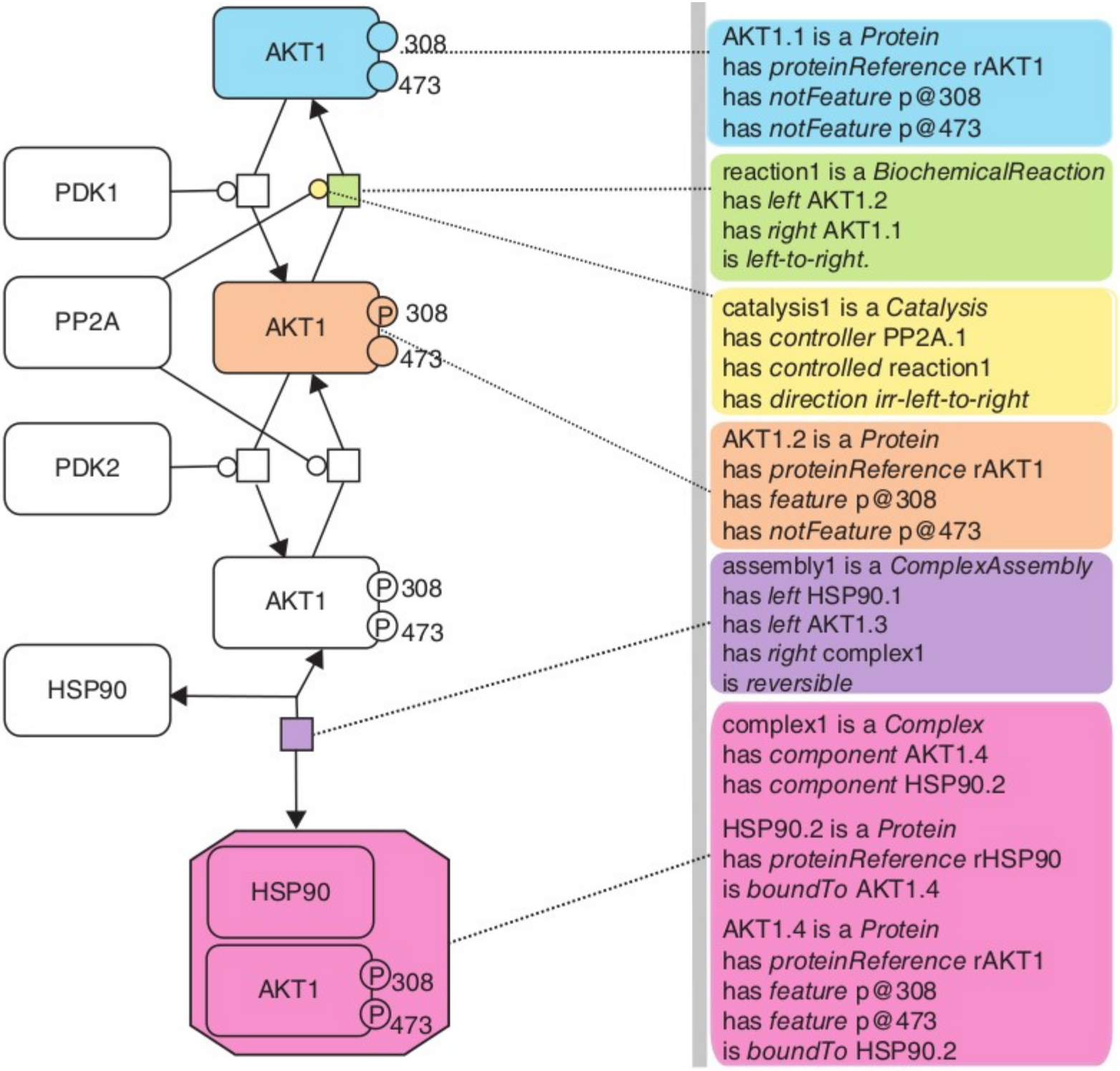
Release 1

6 October 2010

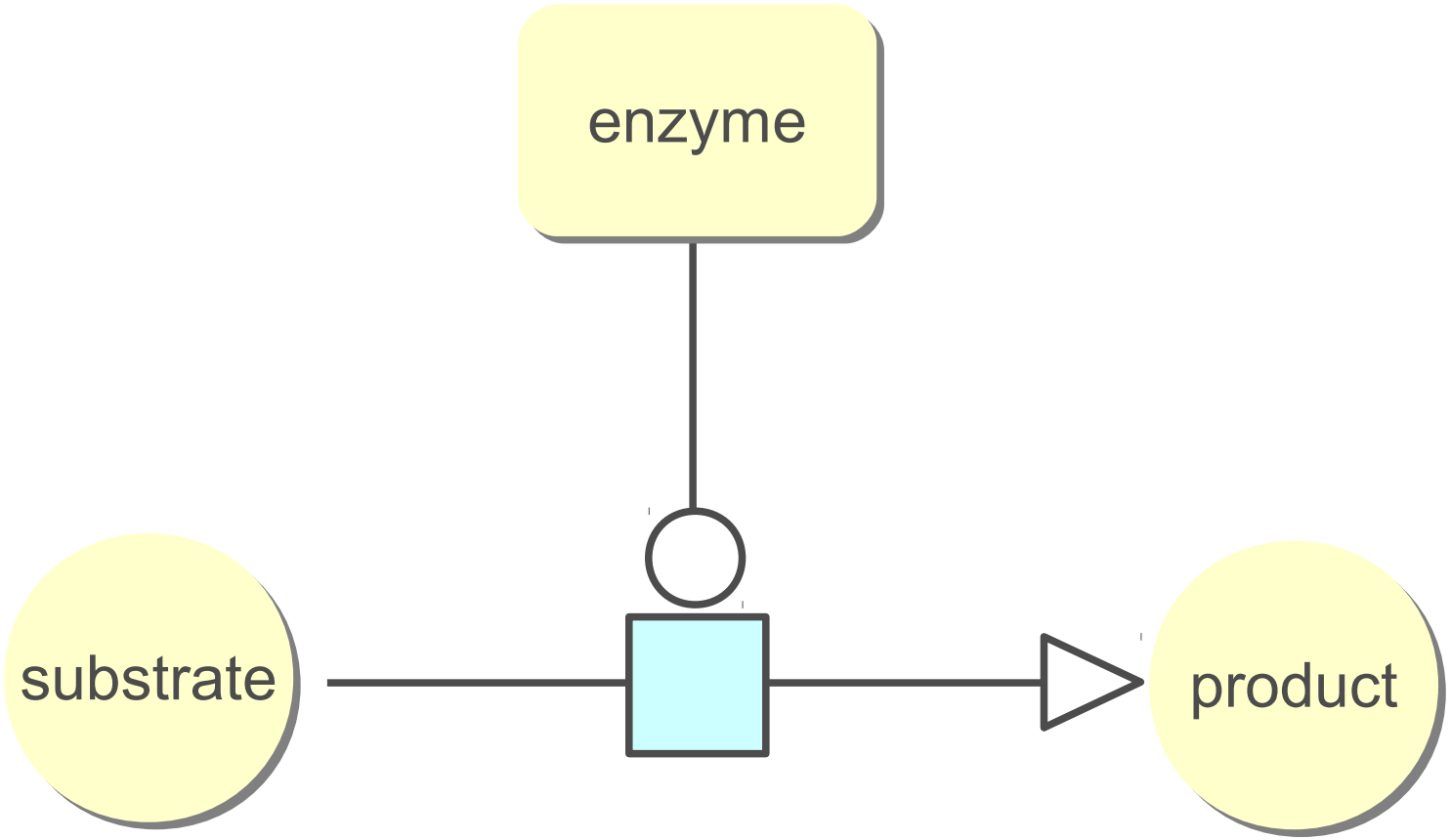


Web Ontology Language - OWL

- BioPAX contains classes, relations and properties, constraints, objects, values.
- Classes are arranges in a specialisation hierarchy. E.g. a “protein” is a “physical entity”
- Classes may have properties of specific types. The types are linked to other classes by relations. E.g. “reaction X” has *participant* “protein P”. An attribute is a property that has a simple type.
- Constraints define allowable values and connexions. E.g. “MOLECULAR_WT” must be a positive real number
- Objects are instances of classes.


AKT1
308
473
PDK1
PP2A
AKT1
P
308
473
PDK2
AKT1
P
308
P
473
HSP90
HSP90
AKT1
P
308
P
473
AKT1.1 is a Protein
has proteinReference rAKT1
has notFeature p@308
has notFeature p@473
reaction1 is a BiochemicalReaction
has left AKT1.2
has right AKT1.1
is left-to-right.
catalysis1 is a Catalysis
has controller PP2A.1
has controlled reaction1
has direction irr-left-to-right
AKT1.2 is a Protein
has proteinReference rAKT1
has feature p@308
has notFeature p@473
assembly1 is a ComplexAssembly
has left HSP90.1
has left AKT1.3
has right complex1
is reversible
complex1 is a Complex
has component AKT1.4
has component HSP90.2
HSP90.2 is a Protein
has proteinReference rHSP90
is boundTo AKT1.4
AKT1.4 is a Protein
has proteinReference rAKT1
has feature p@308
has feature p@473
is boundTo HSP90.2

A catalysis in BioPAX



A catalysis in BioPAX

```
<!-- physicalEntities -->

<bp:smallMolecule rdf:ID="smallMolecule1" />
<bp:smallMolecule rdf:ID="smallMolecule2" />
<bp:protein rdf:ID="protein1">

<!-- physicalEntityParticipants -->

<bp:physicalEntityParticipant rdf:ID="substrate">
    <bp:STOICHIOMETRIC-COEFFICIENT>1.0</bp:STOICHIOMETRIC-COEFFICIENT>
    <bp:PHYSICAL-ENTITY rdf:resource=”#smallMolecule1” />
</bp:physicalEntityParticipant>
<bp:physicalEntityParticipant rdf:ID="product">
    <bp:STOICHIOMETRIC-COEFFICIENT>1.0</bp:STOICHIOMETRIC-COEFFICIENT>
    <bp:PHYSICAL-ENTITY rdf:resource=”#smallMolecule2” />
</bp:physicalEntityParticipant>
<bp:physicalEntityParticipant rdf:ID="enzyme">
    <bp:PHYSICAL-ENTITY rdf:resource=”#protein1” />
</bp:physicalEntityParticipant>

<!-- physicalInteractions -->

<bp:biochemicalReaction rdf:ID="biochemicalReaction1">
    <bp:LEFT rdf:resource=”#substrate”>
    <bp:RIGHT rdf:resource=”#product”>
</bp:biochemicalReaction>
<bp:catalysis rdf:ID="catalysis1">
    <bp:CONTROLLER rdf:resource=”#enzyme” />
    <bp:CONTROLLED rdf:resource=”#biochemicalReaction1”
</bp:catalysis>
```

A catalysis in BioPAX

```
<!-- physicalEntityParticipants -->

<bp:physicalEntityParticipant rdf:ID="substrate">
    <bp:STOICHIOMETRIC-COEFFICIENT>1.0</bp:STOICHIOMETRIC-COEFFICIENT>
    <bp:PHYSICAL-ENTITY>
        <bp:smallMolecule rdf:ID="smallMolecule1" />
    </bp:PHYSICAL-ENTITY>
</bp:physicalEntityParticipant>
<bp:physicalEntityParticipant rdf:ID="product">
    <bp:STOICHIOMETRIC-COEFFICIENT>1.0</bp:STOICHIOMETRIC-COEFFICIENT>
    <bp:PHYSICAL-ENTITY>
        <bp:smallMolecule rdf:ID="smallMolecule2" />
    </bp:PHYSICAL-ENTITY>
</bp:physicalEntityParticipant>
<bp:physicalEntityParticipant rdf:ID="enzyme">
    <bp:PHYSICAL-ENTITY>
        <bp:protein rdf:ID="protein1">
    </bp:PHYSICAL-ENTITY>
</bp:physicalEntityParticipant>

<!-- physicalInteractions -->

<bp:biochemicalReaction rdf:ID="biochemicalReaction1">
    <bp:LEFT rdf:resource=”#substrate”>
    <bp:RIGHT rdf:resource=”#product”>
</bp:biochemicalReaction>
<bp:catalysis rdf:ID="catalysis1">
    <bp:CONTROLLER rdf:resource=”#enzyme” />
    <bp:CONTROLLED rdf:resource=”#biochemicalReaction1”
</bp:catalysis>
```

A catalysis in BioPAX

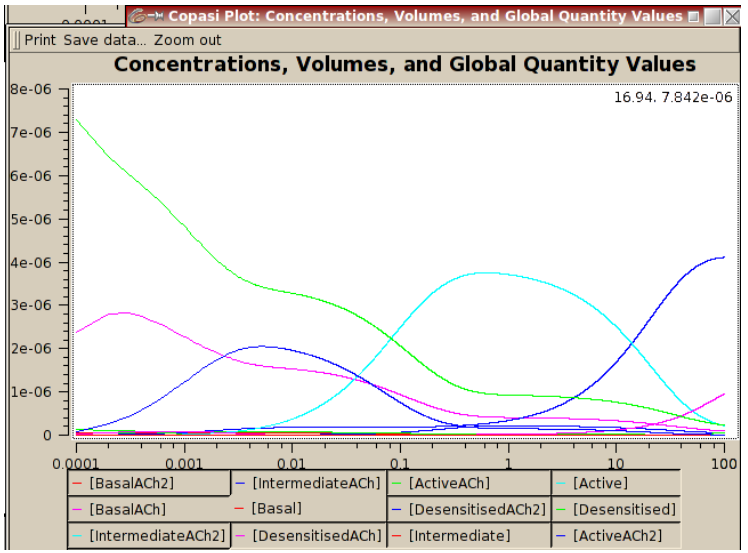
```
<!-- physicalInteractions -->

<bp:biochemicalReaction rdf:ID="biochemicalReaction1">
    <bp:LEFT>
        <bp:physicalEntityParticipant>
            <bp:STOICHIOMETRIC-COEFFICIENT>1.0</bp:STOICHIOMETRIC-COEFFICIENT>
            <bp:PHYSICAL-ENTITY>
                <bp:smallMolecule rdf:ID="smallMolecule1" />
            </bp:PHYSICAL-ENTITY>
        </bp:physicalEntityParticipant>
    </bp:LEFT>
    <bp:RIGHT>
        <bp:physicalEntityParticipant rdf:ID="product">
            <bp:STOICHIOMETRIC-COEFFICIENT>1.0</bp:STOICHIOMETRIC-COEFFICIENT>
            <bp:PHYSICAL-ENTITY>
                <bp:smallMolecule rdf:ID="smallMolecule2" />
            </bp:PHYSICAL-ENTITY>
        </bp:physicalEntityParticipant>
    </bp:RIGHT>
</bp:biochemicalReaction>

<bp:catalysis rdf:ID="catalysis1">
    <bp:CONTROLLER/>
        <bp:physicalEntityParticipant rdf:ID="enzyme">
            <bp:PHYSICAL-ENTITY>
                <bp:protein rdf:ID="protein1">
            </bp:PHYSICAL-ENTITY>
        </bp:physicalEntityParticipant>
    </bp:CONTROLLER>
    <bp:CONTROLLED rdf:resource=”#biochemicalReaction1”
</bp:catalysis>
```

A catalysis in BioPAX

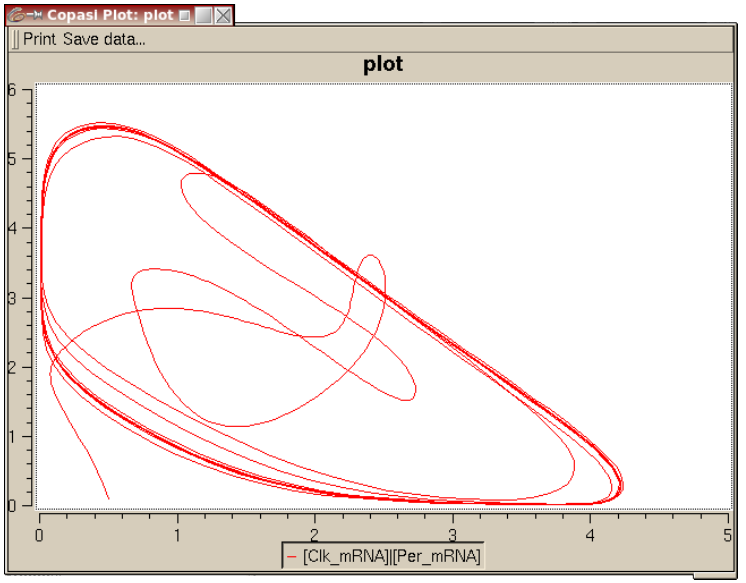
```
<!-- physicalInteractions -->

<bp:catalysis rdf:ID="catalysis1">
    <bp:CONTROLLER/>
        <bp:physicalEntityParticipant rdf:ID="enzyme">
            <bp:PHYSICAL-ENTITY>
                <bp:protein rdf:ID="protein1">
            </bp:PHYSICAL-ENTITY>
        </bp:physicalEntityParticipant>
    </bp:CONTROLLER>
    <bp:CONTROLLED>
        <bp:biochemicalReaction rdf:ID="biochemicalReaction1">
            <bp:LEFT>
                <bp:physicalEntityParticipant>
                    <bp:STOICHIOMETRIC-COEFFICIENT>1.0</bp:STOICHIOMETRIC-COEFFICIENT>
                    <bp:PHYSICAL-ENTITY>
                        <bp:smallMolecule rdf:ID="smallMolecule1" />
                    </bp:PHYSICAL-ENTITY>
                </bp:physicalEntityParticipant>
            </bp:LEFT>
            <bp:RIGHT>
                <bp:physicalEntityParticipant rdf:ID="product">
                    <bp:STOICHIOMETRIC-COEFFICIENT>1.0</bp:STOICHIOMETRIC-COEFFICIENT>
                    <bp:PHYSICAL-ENTITY>
                        <bp:smallMolecule rdf:ID="smallMolecule2" />
                    </bp:PHYSICAL-ENTITY>
                </bp:physicalEntityParticipant>
            </bp:RIGHT>
        </bp:biochemicalReaction>
    </bp:CONTROLLED>
</bp:catalysis>
```

Reproduction of published simulation results

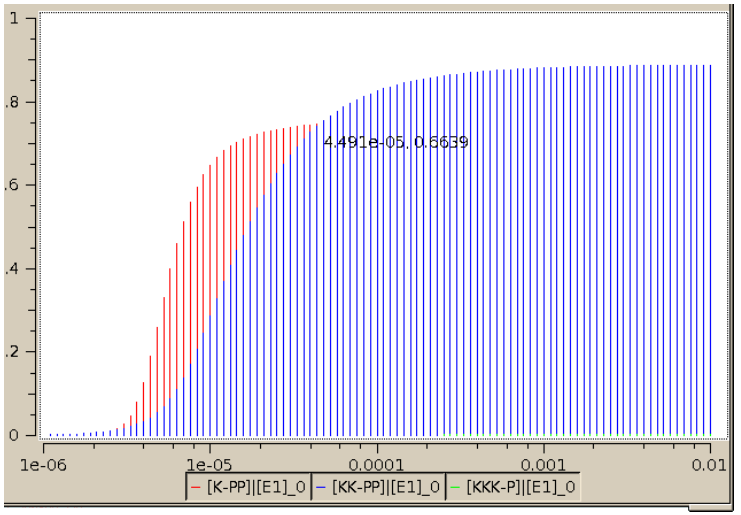
Edelstein et al 1996 (BIOMD0000000002)



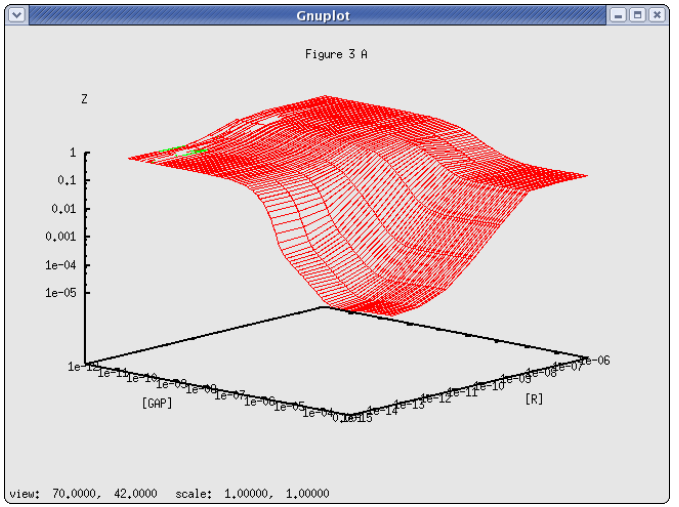
Ueda, Hagiwara, Kitano 2001 (BIOMD0000000022)



Huang & Ferrell (BIOMD0000000009)



Bornheimer et al 2004 (BIOMD0000000086)



Description of simulations and analyses

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

Born in Hinxton 2007

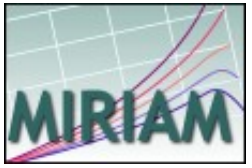
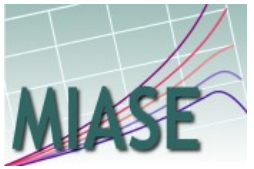
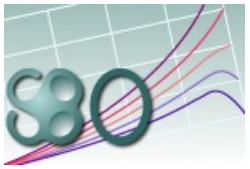
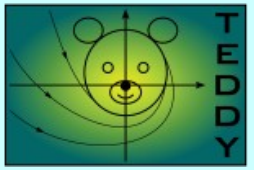
Description of model simulation and analysis

Minimum Information About a Simulation Experiment (MIASE) common set of information a modeller needs to provide in order to enable the execution and reproduction of a numerical simulation experiment, derived from a given set of quantitative models

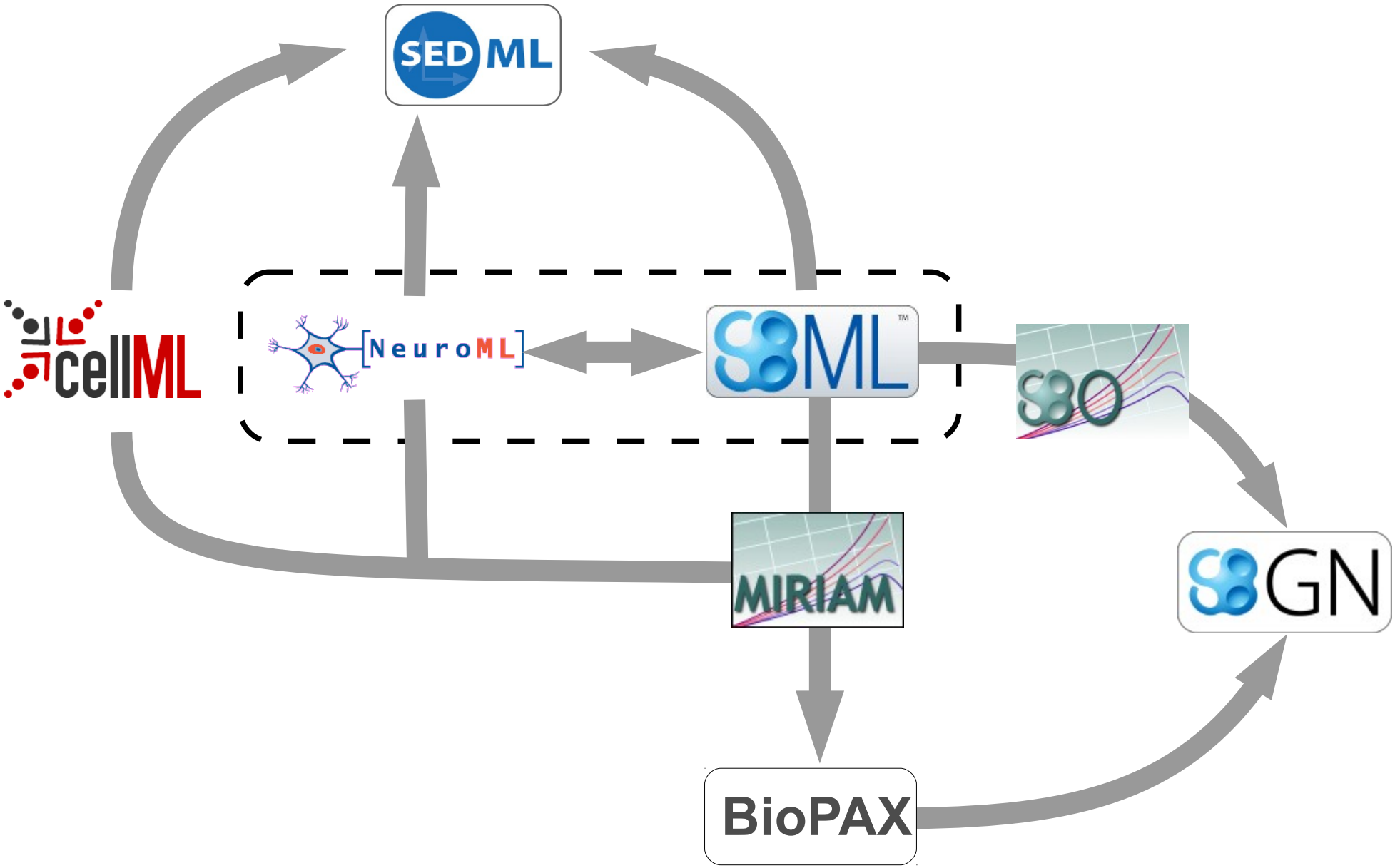
Simulation Experiment Description Markup Language (SED-ML) XML-based format for encoding simulation experiments, following the requirements defined in the MIASE guidelines

Kinetic Simulation Algorithm Ontology (KiSAO) covers the most important simulation algorithms and simulation methods used to simulate biological kinetic models and puts those algorithms and methods into relation

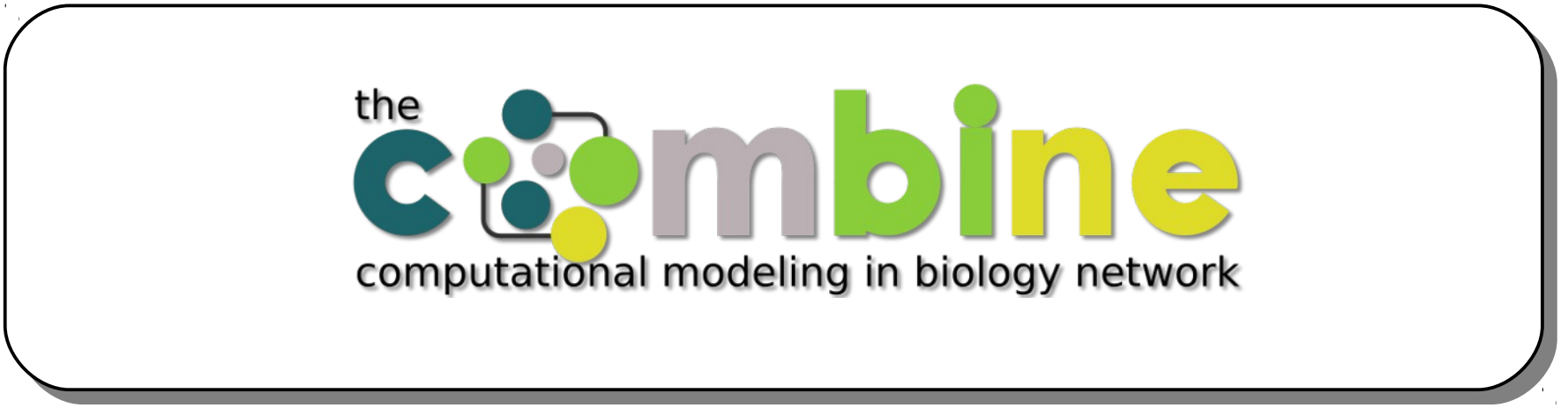
Characterising dynamical behaviours

	Model descriptions	Simulations and analysis	results
Minimal requirements			
Data-models	  BioPAX		NuML
Terminologies			

Existing standards interoperability



Overarching standardisation structure

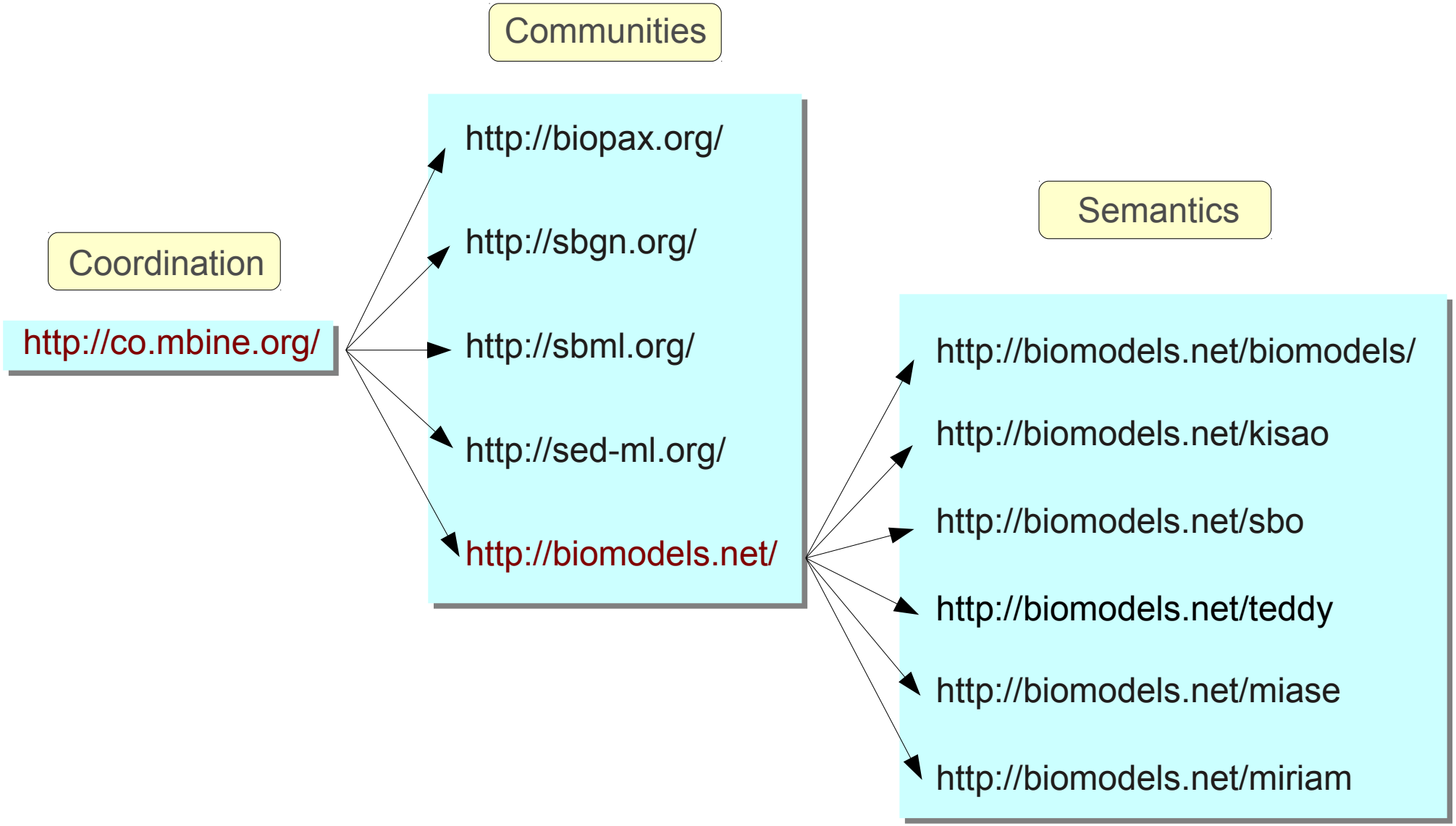


The “WorldWide Web consortium” of modelling in biology
http://co.mbine.org/

- HARMONY 2012
  - 21 to 25 May 2012, Maastricht
  - http://co.mbine.org/events/HARMONY_2012
  - 59 attendees
- COMBINE 2012
  - 14 to 19 August 2012, Toronto
  - http://co.mbine.org/events/COMBINE_2012

- Standard Operating Procedures
  - Technical requirements
  - Governance
- Single voice
  - Discussions with Industry
  - Financial support

Where to find more information?



Acknowledgements

Visionary: **Hiroaki Kitano**

SBML editors: Frank Bergmann, *Andrew Finney, Stefan Hoops*, ***Michael Hucka***, Nicolas Le Novère, Sarah Keating, Chris Myers, *Sven Sahle*, *Herbert Sauro*, Jim Schaff, Lucian Smith, *Darren Wilkinson*

SBGN editors: Emek Demir, Nicolas Le Novère, *Huaiyu Mi*, *Stuart Moodie*, Falk Schreiber, Anatoly Sorokin, Alice Villéger

SED-ML editors: Richard Adams, Franck Bergmann, *Nicolas Le Novère,* Andrew Miller, David Nickerson, Dagmar Waltemath

BioPAX editors: Emek Demir, Peter d'Eustachio, Huaiyu MI, Oliver Ruebenacker, Andrea Splendiani

Metadata: Mélanie Courtot, Nick Juty, Camille Laibe, Anna Zhukova

The whole community of Computational Systems Biology

The EBI group Computational Systems Neurobiology