Bioinformatics resources and standards for modeling neuronal signalling

Nicolas Le Novère, EMBL-EBI, United-Kingdom

We need to reuse computational models

- As such
  - Non-specialists need to use models relevant for their research, directly with their simulation software, without messing with their structure.
  - Modelling literates need to reuse existing models rather than rewrite them from scratch.
  - Various software that are used during the modelling process, such as graphical designers, simulation engines and plotters or renderers, should be able to communicate.

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  - Various software that are used during the modelling process, such as graphical designers, simulation engines and plotters or renderers, should be able to communicate.
- For integration purpose
  - Very large pathways cannot be built in one shot. We need to built on pre-existing efforts
  - Different approaches: time-series (continuous, discrete), MCA, FBA, logical descriptions etc.
  - Different spatial scales: nanometer (channel) to meter (axon)
  - Different real time scales: microsecond (channel opening) to weeks (LTP)
  - (Different simulation time scale: single-particle tracking to ODE)

Requirements for a successful exchange

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  - Structured formats ➔ easily “parsable”; mirror the model structure;
  - Public formats ➔ Published specifications, freely re-usable
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- We need to make the models available
  - Personal websites
  - Publisher's websites
  - Curated repository/databases

Standard of representation

- http://www.cellml.org/

Fixed specification; Based on modules; scalable; ... complex

-

http://www.neuroml.org/

-

http://www.neuroml.org/

Flexible (expendable set of classes/schemas); scalable;

- BrainML.org http://brainml.org/

Models are XML-schemas

- BioPAX http://www.biopax.org/

No kinetics; deep semantics;

SBML.org - The home site for the Systems Biology Markup Language - Mozilla
Home | Bookmarks | Biomodels | compneur | Google | PubMed | SBO::Systems ...

SBML Systems Biology Markup Language

Google
Search this site

The Systems Biology Markup Language (SBML) is a computer-readable format for representing **models of biochemical reaction networks**. SBML is applicable to metabolic networks, cell-signaling pathways, regulatory networks, and many others.

Internationally Supported and Widely Used

SBML has been evolving since mid-2000 through the efforts of an international group of software developers and users. Today, SBML is **supported by over 90 software systems**, including the following (where '*' indicates SBML support in development):

BALSA	DBsolve	Moleculizer	SBMLR
BASIS	Dizzy	Monod	SBMLSim
BIOCHAM	E-CELL	Narrator	SBMLToolbox
BioCharon	ecellJ	NetBuilder	SBliD
ByoDyn	ESS	Oscill8	SBToolbox
biocyc2SBML	FluxAnalyzer	PANTHER Pathway	SBW
BioGrid	Fluxor	PathArt	SCIpath
BioModels	Gepasi	PathScout	Sigmoid*
BioNetGen	Gillespie2	PathwayLab	SigPath
BioPathway Explorer	INSILICO discovery	Pathway Tools	SigTran
Bio Sketch Pad	JACOBIAN	PathwayBuilder	SIMBA
BioSens	Jarnac	PATIKAweb	SimBiology
BioSPICE Dashboard	JDesigner	PaVESy	Simpathica
BioSpreadsheet	JigCell	PET	SimWiz
BioTapestry	JSim	PNK	SloppyCell
BioUML	JWS Online	Reactome	SmartCell
BSTLab	Karyote*	ProcessDB	SRS Pathway Editor
CADLIVE	KEGG2SBML	PROTON	StochSim
CellDesigner	Kinsolver*	pysbml	StochKit
Cellerator	libSBML	PySCeS	STOCKS
CellML2SBML	MathSBML	runSBML	TERANODE Suite
Cellware	MesoRD	SABIO-RK	Trelis
CL-SBML	MetaboLogica	SBML ODE Solver	Virtual Cell
CLEML	MetaFluxNet	SBML-PET	WebCell
COPASI	MMT2	SBMLeditor	WinSCAMP
Cytoscape	Modesto	SBMLmerge	XPPAUT

A Free and Open Language

SBML-PET Announced

(May 8, 2006) **SBML-PET** is a parameter estimation tool that uses SBML and can work with a variety of types of models.

read more

JSim supports SBML

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SBW 2.5.5 Released

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JACOBIAN
Jarnac
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JigCell
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PATIKAweb
PaVESy
PET
PNK
Reactome
ProcessDB
PROTON
pysbml
PySCeS
runSBML
SABIO-RK
SBML ODE Solver
SBMLeditor
SBMLmerge
SBMLR
SBMLSim
SBMLToolbox
SBIiD
SBToolbox
SBW
SCIpath
Sigmoid*
SigPath
SigTran
SIMBA
SimBiology
Simpathica
SimWiz
SloppyCell
SmartCell
SRS Pathway Editor
StochSim
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What can we encode in SBML?

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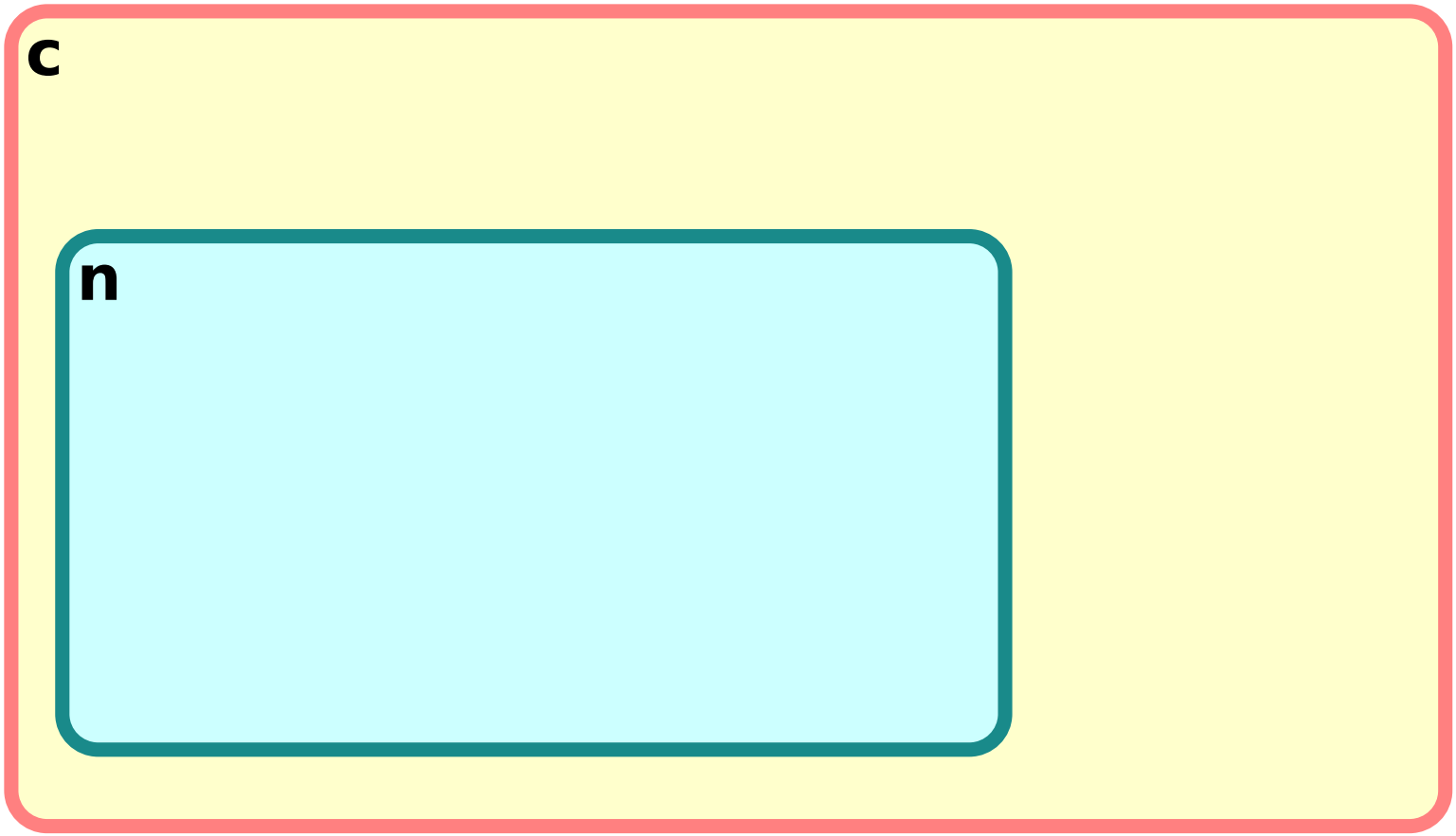
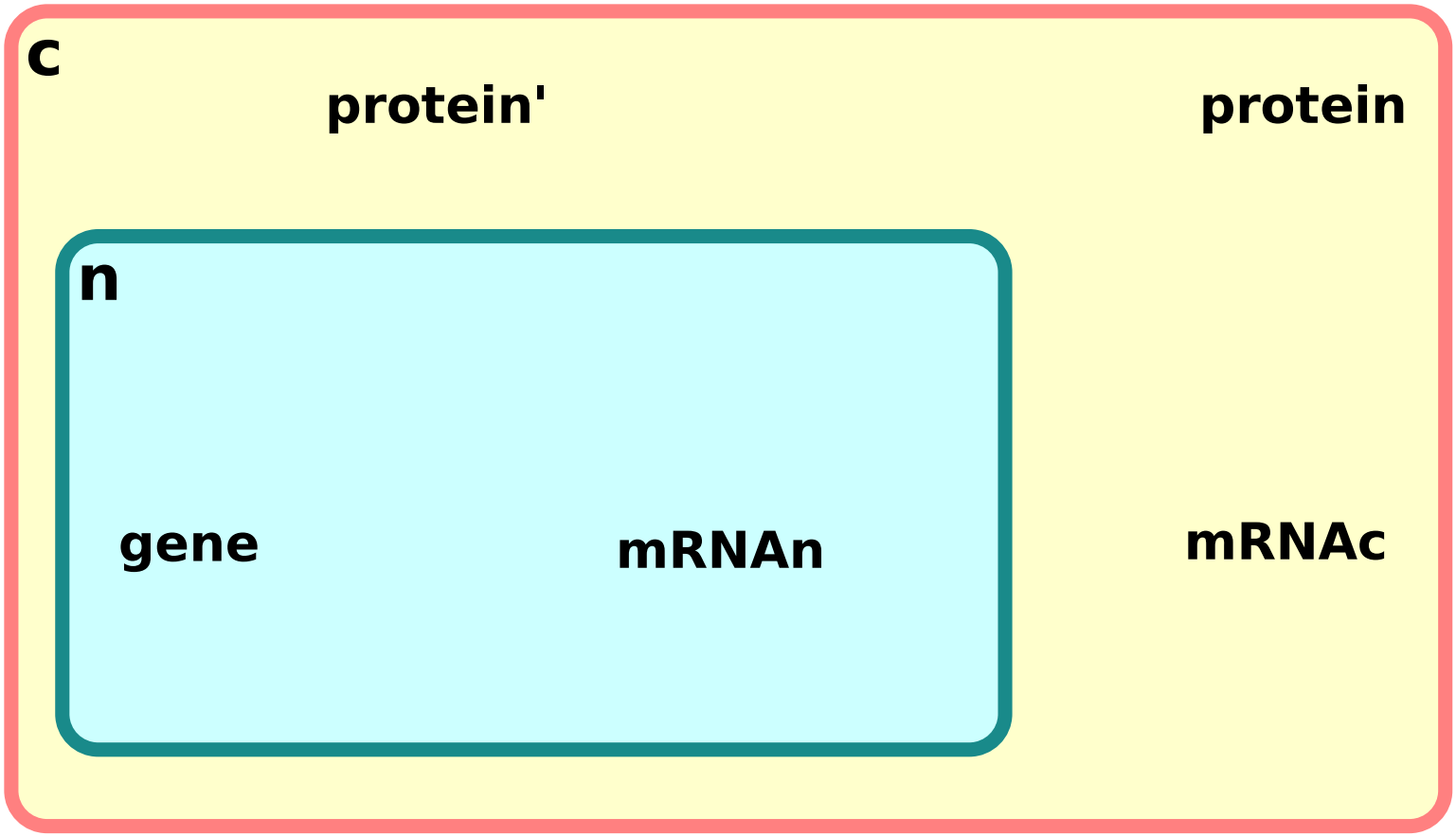
compartments



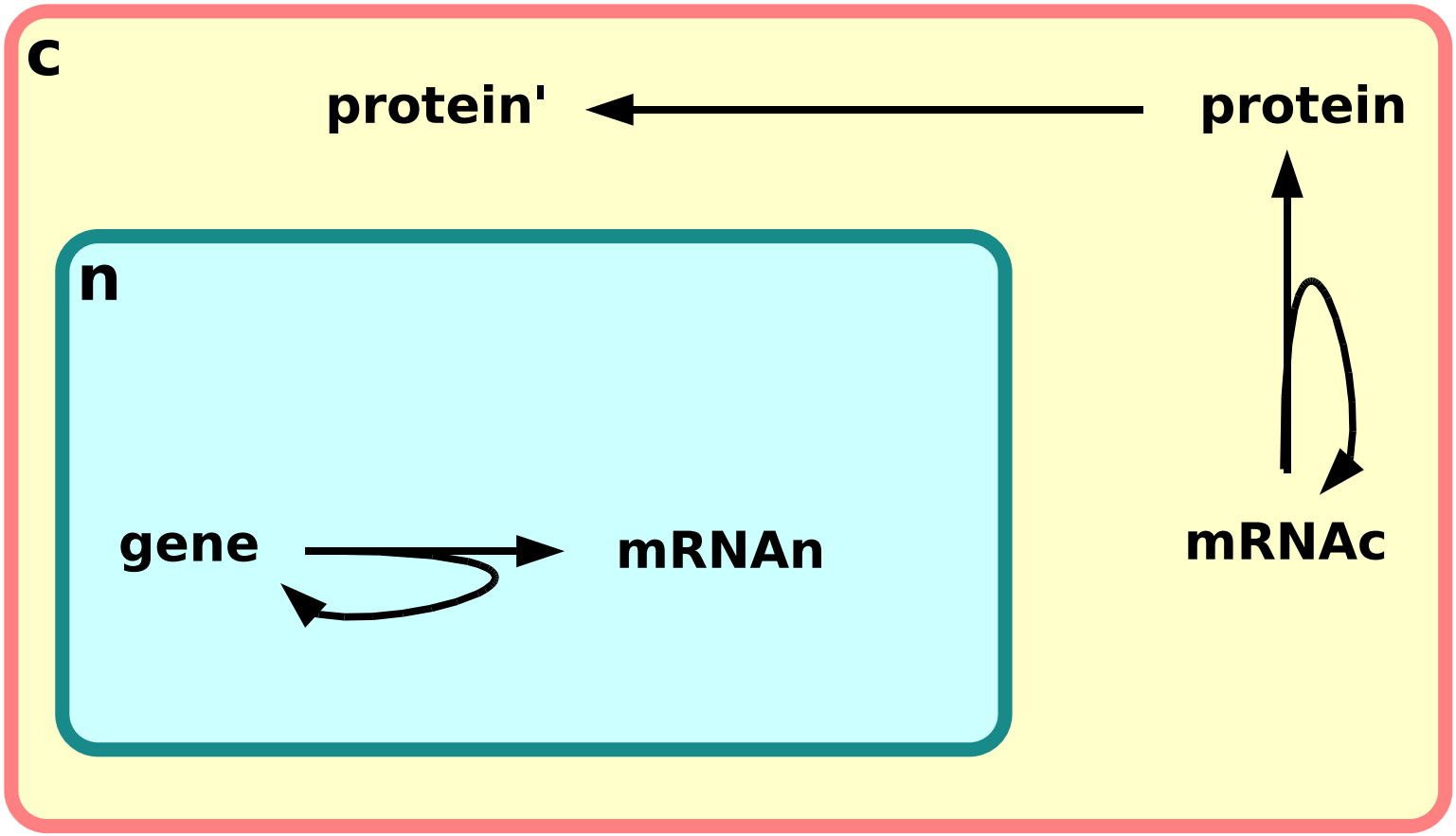
What can we encode in SBML?

species



What can we encode in SBML?

reactions



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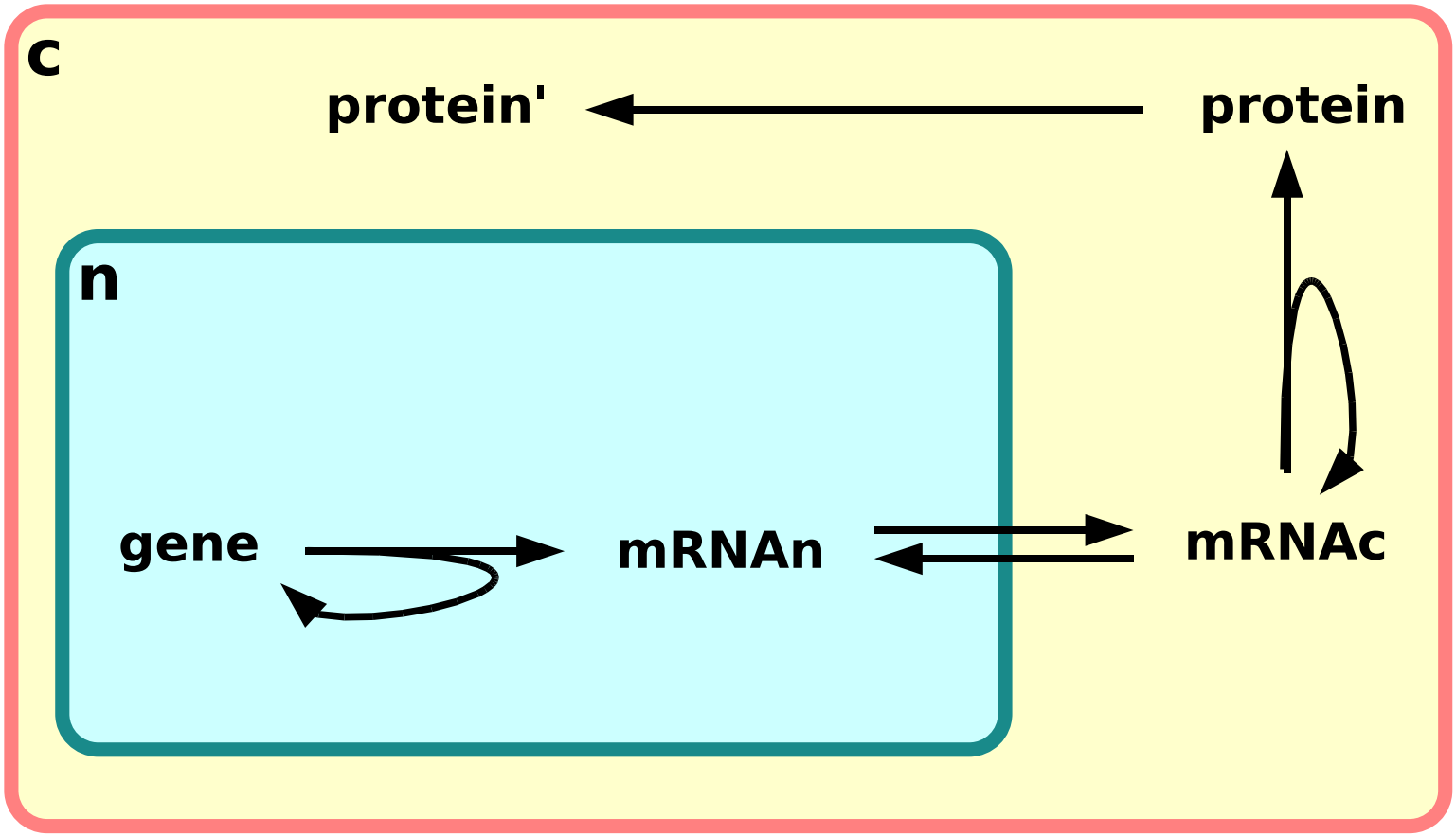
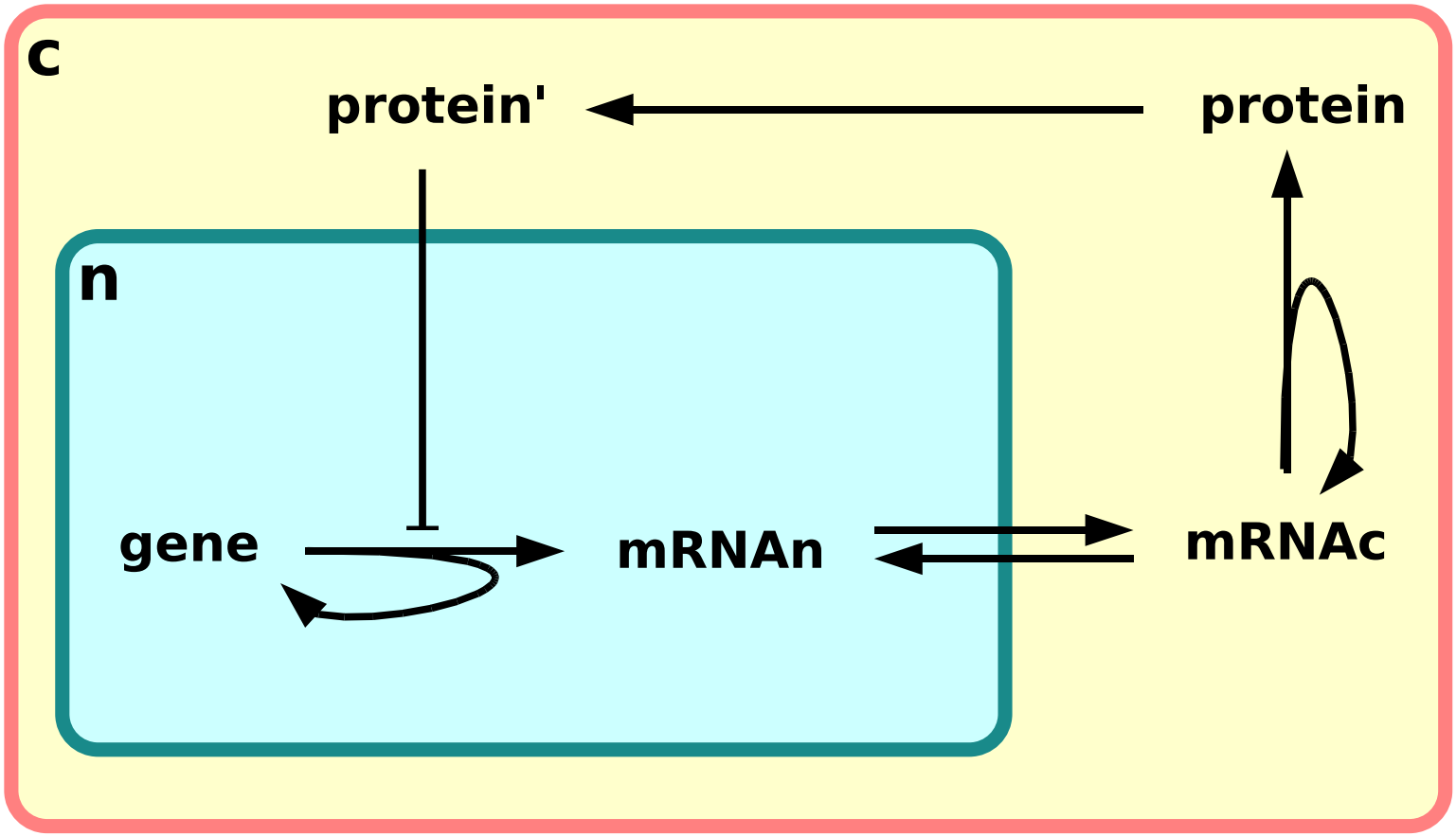


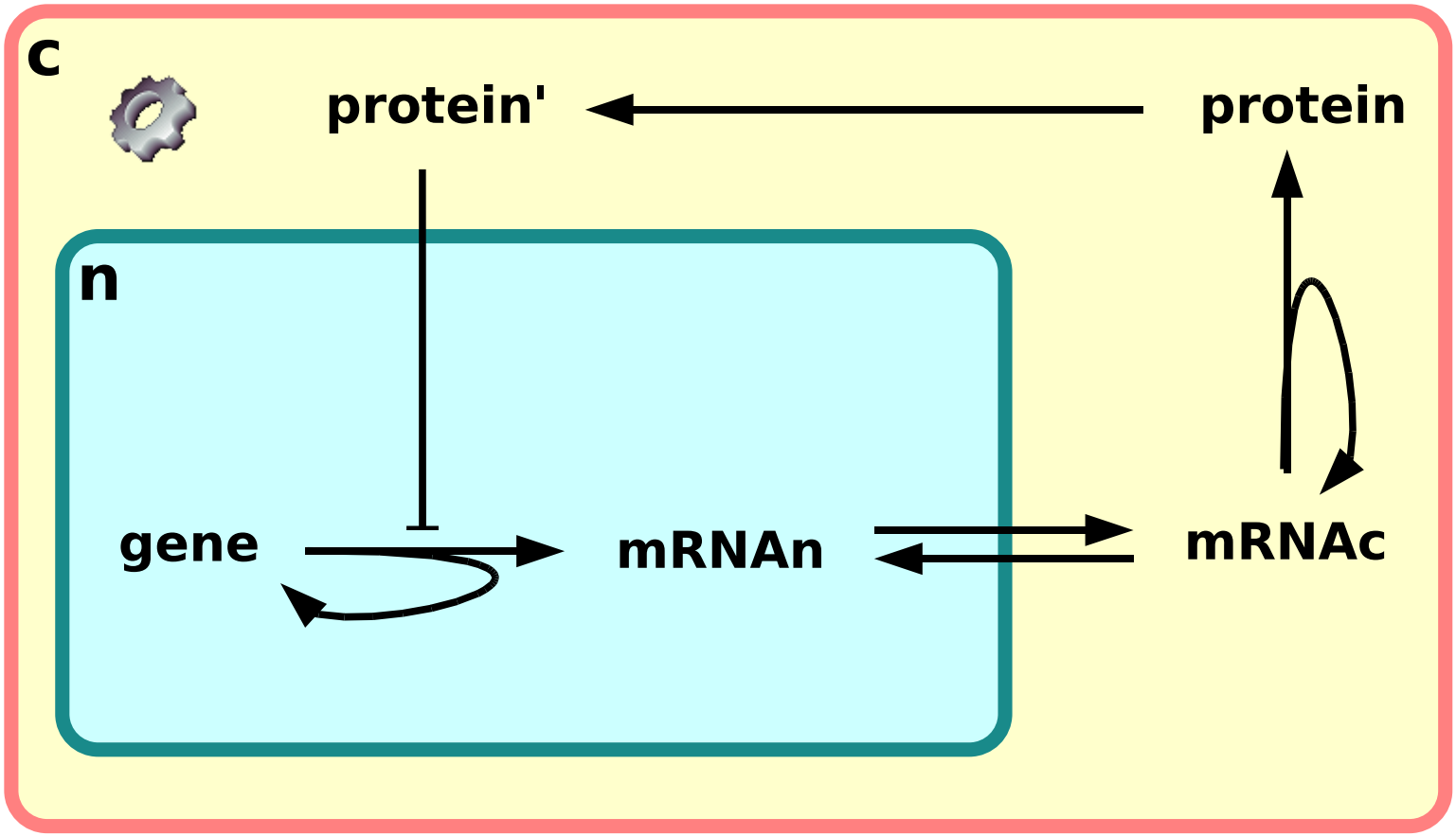
What can we encode in SBML?

modulations



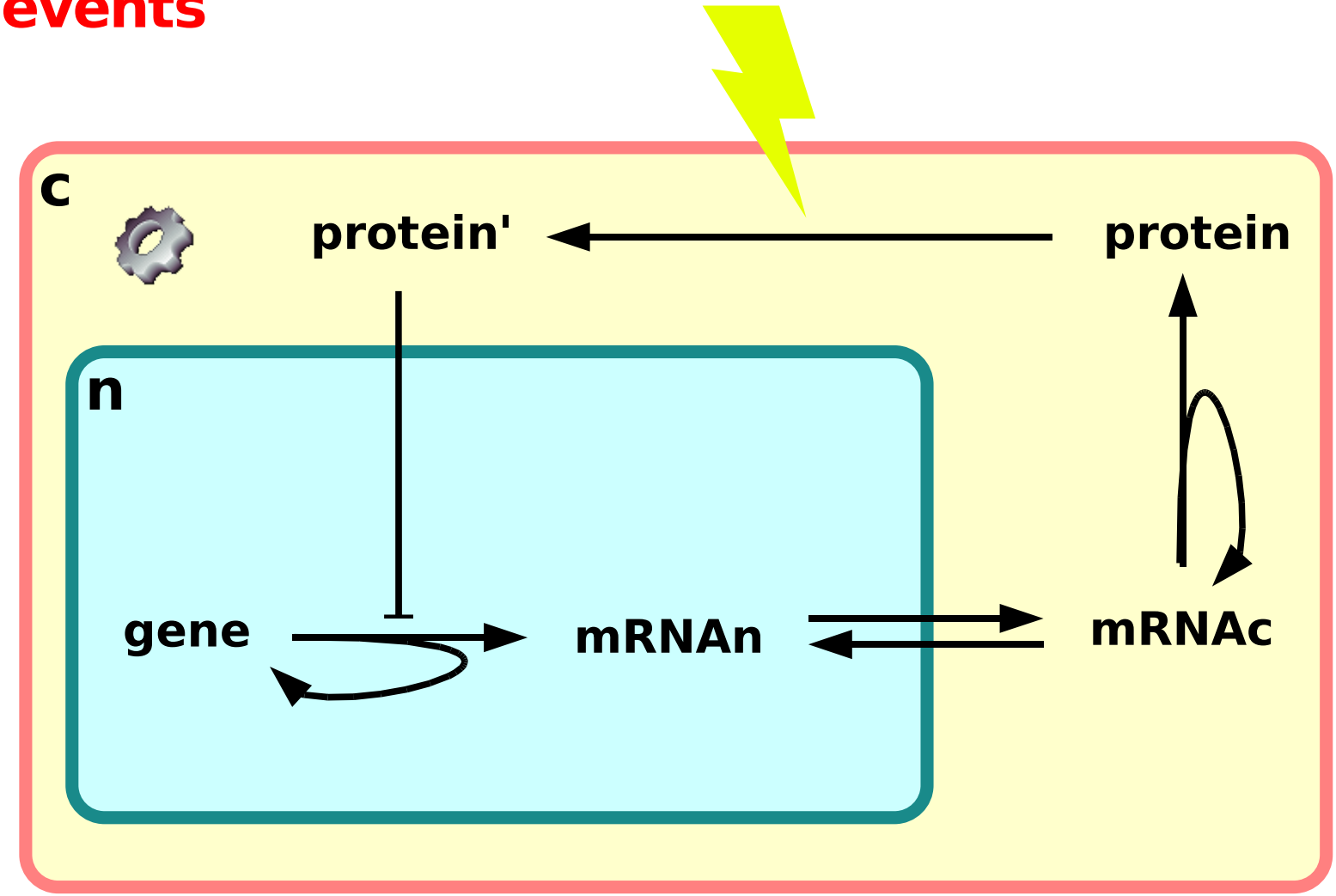
What can we encode in SBML?

rules



What can we encode in SBML?

events



SBML and XML

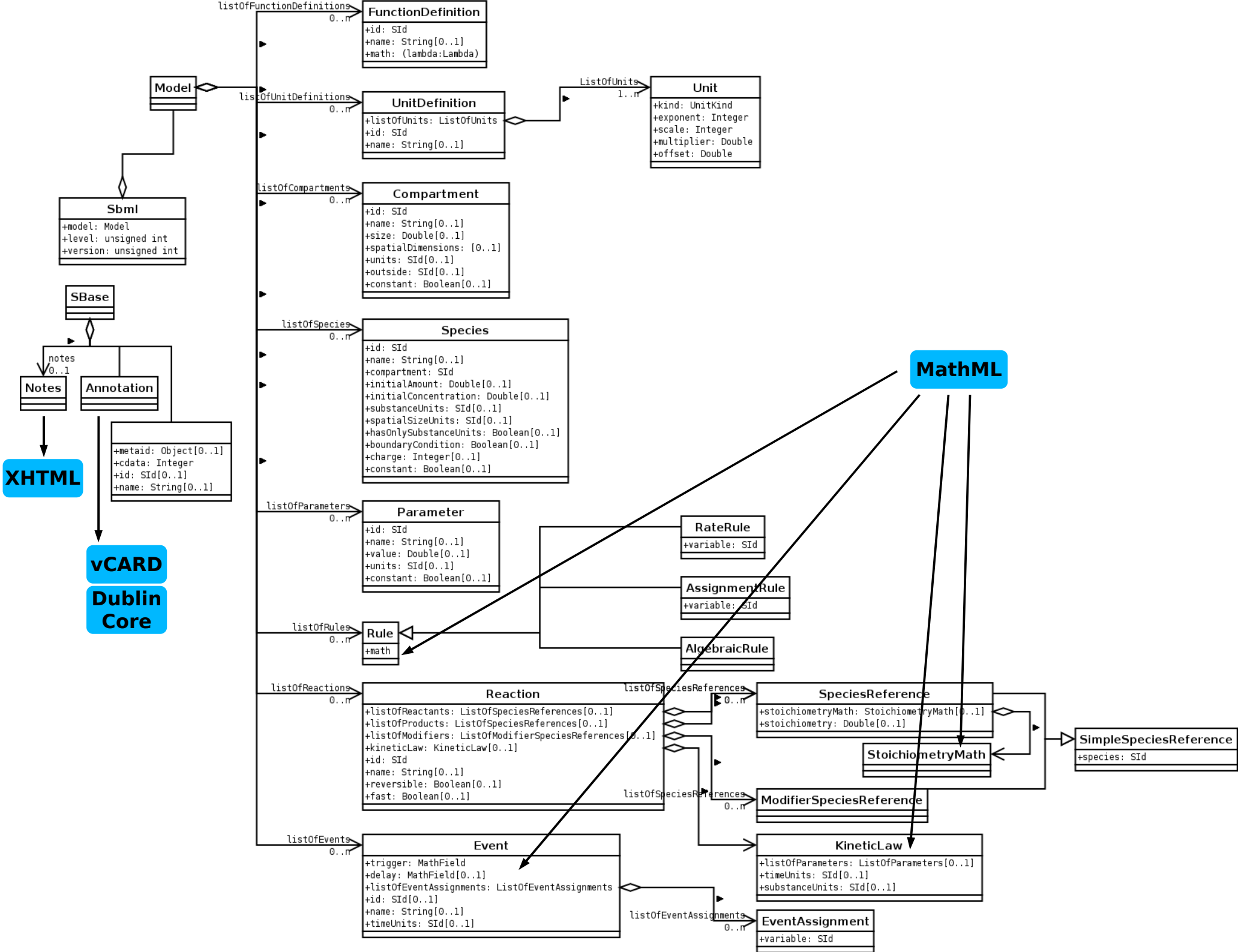
- the Systems Biology Markup Language is defined as a set of classes represented in the Unified Modelling Language (UML)
- In practise it is used as serialised using
  - An XML schema 1) lists all the elements and attributes, 2) specifies the containment relationships between them, 3) precises the datatype of each
  - An additional set of constraints is listed in the specification and implemented as a list of consistency checks

What the heck is XML?

- The eXtensible Markup Language (XML) is a text-format that allow to define languages to store structured information
- An XML language is made-up of elements and attributes:

```
<element1 attribute1="valeur1" attribute2="valeur2">
    <element2 attribute1="valeur3" />
</element1>
```

- An XML language can be defined in another XML language called XML schema. An XML file can be transformed into something else using other XML files called XML style-sheets
- Thanks to a strict namespace system, one can build XML files using several XML languages
- There are a constellation of tools to help processing XML languages
- Most known example of XML language is XHTML, the language used to designed webpages.


listOfFunctionDefinitions
0..n
FunctionDefinition
+id: SId
+name: String[0..1]
+math: (lambda:Lambda)
Model
listOfUnitDefinitions
0..n
UnitDefinition
+listOfUnits: ListOfUnits
+id: SId
+name: String[0..1]
ListOfUnits
1..n
Unit
+kind: UnitKind
+exponent: Integer
+scale: Integer
+multiplier: Double
+offset: Double
Sbml
+model: Model
+level: unsigned int
+version: unsigned int
listOfCompartments
0..n
Compartment
+id: SId
+name: String[0..1]
+size: Double[0..1]
+spatialDimensions: [0..1]
+units: SId[0..1]
+outside: SId[0..1]
+constant: Boolean[0..1]
SBase
notes
0..1
Notes
Annotation
+metaid: Object[0..1]
+cdata: Integer
+id: SId[0..1]
+name: String[0..1]
XHTML
vCARD
Dublin Core
listOfSpecies
0..n
Species
+id: SId
+name: String[0..1]
+compartment: SId
+initialAmount: Double[0..1]
+initialConcentration: Double[0..1]
+substanceUnits: SId[0..1]
+spatialSizeUnits: SId[0..1]
+hasOnlySubstanceUnits: Boolean[0..1]
+boundaryCondition: Boolean[0..1]
+charge: Integer[0..1]
+constant: Boolean[0..1]
MathML
listOfParameters
0..n
Parameter
+id: SId
+name: String[0..1]
+value: Double[0..1]
+units: SId[0..1]
+constant: Boolean[0..1]
RateRule
+variable: SId
AssignmentRule
+variable: SId
listOfRules
0..n
Rule
+math
AlgebraicRule
listOfReactions
0..n
Reaction
+listOfReactants: ListOfSpeciesReferences[0..1]
+listOfProducts: ListOfSpeciesReferences[0..1]
+listOfModifiers: ListOfModifierSpeciesReferences[0..1]
+kineticLaw: KineticLaw[0..1]
+id: SId
+name: String[0..1]
+reversible: Boolean[0..1]
+fast: Boolean[0..1]
listOfSpeciesReferences
0..n
SpeciesReference
+stoichiometryMath: StoichiometryMath[0..1]
+stoichiometry: Double[0..1]
SimpleSpeciesReference
+species: SId
StoichiometryMath
listOfSpeciesReferences
0..n
ModifierSpeciesReference
listOfEvents
0..n
Event
+trigger: MathField
+delay: MathField[0..1]
+listOfEventAssignments: ListOfEventAssignments
+id: SId[0..1]
+name: String[0..1]
+timeUnits: SId[0..1]
KineticLaw
+listOfParameters: ListOfParameters[0..1]
+timeUnits: SId[0..1]
+substanceUnits: SId[0..1]
listOfEventAssignments
0..n
EventAssignment
+variable: SId

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml level="2" version="1" xmlns="http://www.sbml.org/sbml/level2">
  <model>




  </model>
</sbml>
```

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml level="2" version="1" xmlns="http://www.sbml.org/sbml/level2">
  <model>
    <listOfCompartments>
      <compartment id="cell" />
    </listOfCompartments>









  </model>
</sbml>
```

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml level="2" version="1" xmlns="http://www.sbml.org/sbml/level2">
  <model>
    <listOfCompartments>
      <compartment id="cell" />
    </listOfCompartments>
    <listOfSpecies>
      <species id="A" compartment="cell" initialConcentration="1"/>
      <species id="B" compartment="cell" initialConcentration="0"/>
    </listOfSpecies>









  </model>
</sbml>
```

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml level="2" version="1" xmlns="http://www.sbml.org/sbml/level2">
  <model>
    <listOfCompartments>
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    </listOfCompartments>
    <listOfSpecies>
      <species id="A" compartment="cell" initialConcentration="1"/>
      <species id="B" compartment="cell" initialConcentration="0"/>
    </listOfSpecies>
    <listOfParameters>
      <parameter id="kon" value="1"/>
    </listOfParameters>
    <listOfReactions>
      <reaction>









      </reaction>
    </listOfReactions>
  </model>
</sbml>
```

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml level="2" version="1" xmlns="http://www.sbml.org/sbml/level2">
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    <listOfCompartments>
      <compartment id="cell" />
    </listOfCompartments>
    <listOfSpecies>
      <species id="A" compartment="cell" initialConcentration="1"/>
      <species id="B" compartment="cell" initialConcentration="0"/>
    </listOfSpecies>
    <listOfParameters>
      <parameter id="kon" value="1"/>
    </listOfParameters>
    <listOfReactions>
      <reaction>
        <listOfReactants>
          <speciesReference species="A" />
        </listOfReactants>
        <listOfProducts>
          <speciesReference species="B" />
        </listOfProducts>









      </reaction>
    </listOfReactions>
  </model>
</sbml>
```
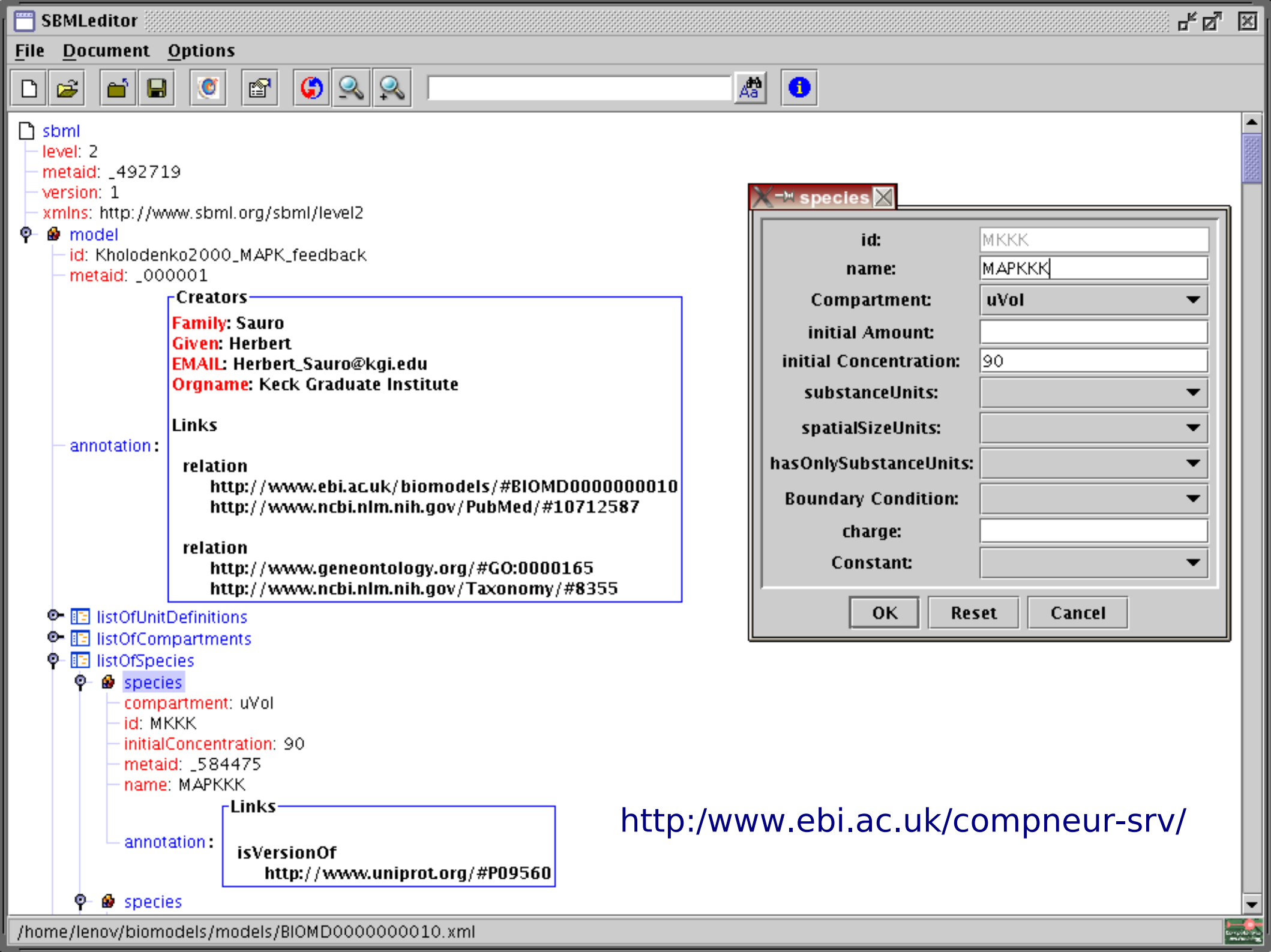

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml level="2" version="1" xmlns="http://www.sbml.org/sbml/level2">
  <model>
    <listOfCompartments>
      <compartment id="cell" />
    </listOfCompartments>
    <listOfSpecies>
      <species id="A" compartment="cell" initialConcentration="1"/>
      <species id="B" compartment="cell" initialConcentration="0"/>
    </listOfSpecies>
    <listOfParameters>
      <parameter id="kon" value="1"/>
    </listOfParameters>
    <listOfReactions>
      <reaction>
        <listOfReactants>
          <speciesReference species="A" />
        </listOfReactants>
        <listOfProducts>
          <speciesReference species="B" />
        </listOfProducts>
        <kineticLaw>
          <math xmlns="http://www.w3.org/1998/Math/MathML">
            <apply>
              <times />
              <ci>kon</ci>
              <ci>A</ci>
              <ci>cell</ci>
            </apply>
          </math>
        </kineticLaw>
      </reaction>
    </listOfReactions>
  </model>
</sbml>
```

A more realistic example ...

```
<species
    id="A"
    name="α-tubulin"
    compartment="cell"
    initialAmount="1000"
    substanceUnits="item"
    hasOnlySubstanceUnits="true"
    boundaryCondition="true"
    constant="false"
    charge="0"
    metaid="PX" >
  <notes>
    <body xmlns="http://www.w3.org/1999/xhtml">
      <p>One of the components of 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="http://www.uniprot.org/#P68370"/>
            <rdf:li rdf:resource="http://www.geneontology.org/#GO:0045298"/>
          </rdf:Bag>
        </bqbiol:is>
      </rdf:Description>
    </rdf:RDF>
  </annotation>
</species>
```


SBMLeditor
File Document Options
sbml
level: 2
metaid: _492719
version: 1
xmlns: http://www.sbml.org/sbml/level2
model
id: Kholodenko2000_MAPK_feedback
metaid: _000001
Creators
Family: Sauro
Given: Herbert
EMAIL: Herbert_Sauro@kgi.edu
Orgname: Keck Graduate Institute
Links
annotation:
relation
http://www.ebi.ac.uk/biomodels/#BIOMD0000000010
http://www.ncbi.nlm.nih.gov/PubMed/#10712587
relation
http://www.geneontology.org/#GO:0000165
http://www.ncbi.nlm.nih.gov/Taxonomy/#8355
listOfUnitDefinitions
listOfCompartments
listOfSpecies
species
compartment: uVol
id: MKKK
initialConcentration: 90
metaid: _584475
name: MAPKKK
Links
annotation:
isVersionOf
http://www.uniprot.org/#P09560
species
species
id: MKKK
name: MAPKKK
Compartment: uVol
initial Amount:
initial Concentration: 90
substanceUnits:
spatialSizeUnits:
hasOnlySubstanceUnits:
Boundary Condition:
charge:
Constant:
OK
Reset
Cancel
http:/www.ebi.ac.uk/compneur-srv/
/home/lenov/biomodels/models/BIOMD0000000010.xml

SBML is not limited to biochemistry!

- Rate Rules can describe the temporal evolution of any quantitative parameter, e.g. transmembrane voltage;
- Events can describe any discontinuous change, e.g. neurotransmitter release;
- A species is an entity participating to a reaction, **not always** a **chemical** entity:
  - It can be a molecule
  - It can be a cell
  - It can be an organ
  - It can be an organism

➔ Systems Biology is scale-free!

Example 2: neuron differentiation

```
<listOfCompartments>
  <compartment id="brain" />
</listOfCompartments>
<listOfSpecies>
  <species id="glia" compartment="brain" initialConcentration="1"/>
  <species id="neuroblast" compartment="brain" initialConcentration="1"/>
  <species id="neuron" compartment="brain" initialConcentration="0"/>
</listOfSpecies>
<listOfParameters>
  <parameter id="K" value="1"/>
</listOfParameters>
<listOfReactions>
  <reaction>
    <listOfReactants>
      <speciesReference species="neuroblast" />
    </listOfReactants>
    <listOfProducts>
      <speciesReference species="neuron" />
    </listOfProducts>
   <listOfModifiers>
      <modifierSpeciesReference species="glia" />
    </listOfModifiers>
    <kineticLaw>
      <math xmlns="http://www.w3.org/1998/Math/MathML">
        <apply>
          [...]
        </apply>
      </math>
    </kineticLaw>
  </reaction>
</listOfReactions>
```

Example 1: Hodking-Huxley

```
<rateRule metaid="metaid_0000048" variable="V">
  <notes><p xmlns="http://www.w3.org/1999/xhtml">dV/dt = (I - (i_Na + i_K + i_L))/Cm</p></notes>
  <math xmlns="http://www.w3.org/1998/Math/MathML">
    <apply>
      <divide/>
      <apply>
        <minus/>
        <ci> I </ci>
        <apply>
          <plus/><ci> i_Na </ci><ci> i_K </ci><ci> i_L </ci>
        </apply>
      </apply>
      <ci> Cm </ci>
    </apply>
  </math>
</rateRule>
<assignmentRule metaid="metaid_0000042" variable="i_Na">
  <notes><p xmlns="http://www.w3.org/1999/xhtml">i_Na = g_Na * m^3.0 * h * (V - E_Na)</p></notes>
  <math xmlns="http://www.w3.org/1998/Math/MathML">
    <apply>
      <times/>
      <ci> g_Na </ci>
      <apply>
        <power/><ci> m </ci><cn> 3.0 </cn>
      </apply>
      <ci> h </ci>
      <apply>
        <minus/><ci> V </ci><ci> E_Na </ci>
      </apply>
    </apply>
  </math>
</assignmentRule>
```

An example of piecewise assignment

- calcium flux depends on glutamate concentration

```
<listOfRules>
    <assignmentRule variable="calcium_influx">
        <math xmlns="http://www.w3.org/1998/Math/MathML">
            <apply>
                <piece>
                    <cn>15</cn>
                    <apply>
                        <gt/>
                        <ci>glutamate</ci>
                        <cn>1</cn>
                    </apply>
                </piece>
                <otherwise>
                    <cn>0</cn>
                </otherwise>
            </apply>
        </math>
    </assignmentRule>
</listOfRules>
```

An example of event

- release of neurotransmitter if [Ca]i intra gets above threshold

```
<listOfEvents>
    <event id="release”>
        <trigger>
            <math xmlns="http://www.w3.org/1998/Math/MathML">
                <apply>
                    <gt/>
                       <ci>calcium</ci>
                       <ci>100</ci>
                </apply>
            </math>
        </trigger>
        <listOfEventAssignments>
            <eventAssignment variable="glutamate">
                <math xmlns="http://www.w3.org/1998/Math/MathML">
                    <cn>e-3</cn>
                </math>
            </eventAssignment>
        </listOfEventAssignements>
</listOfEvents>
```

SBML Levels

- **Level 1 (March 2001)**
  - Predefined kinetics functions
  - One type of reactive substance
  - ISO646 encoding
- **Level 2 (June 2003)**
  - Function definitions
  - Modifier species
  - Events
  - All math in MathML
  - Unicode encoding
- **Level 3 (?)**

Hucka et al (2003)
Bioinformatics 19: 524-531

Hucka et al (2004)
IEE Systems Biology 1: 41-53

SBML Level 2 Version 2

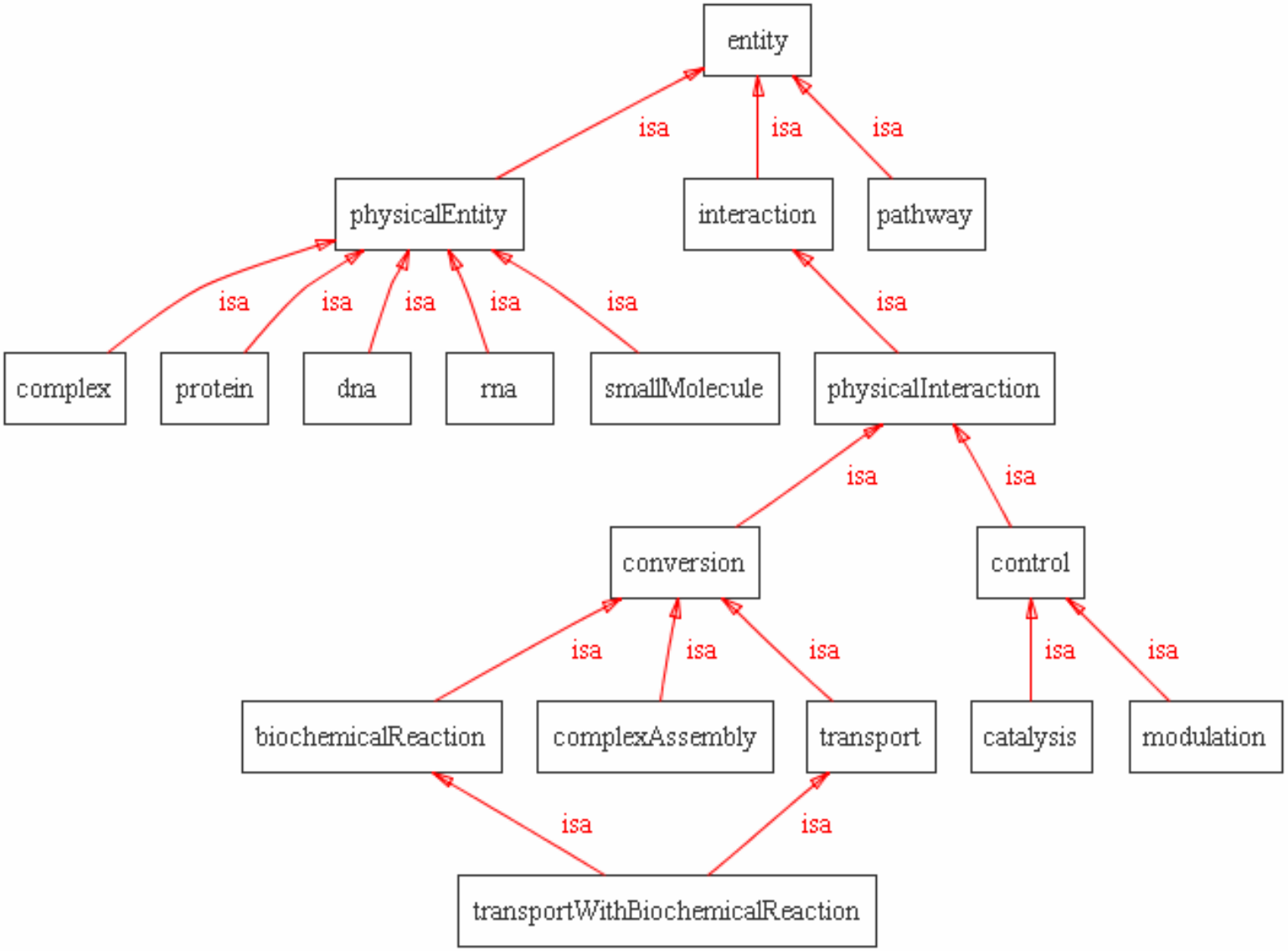
- Finalised on April 8th 2006
- Simpler and cleaner (units ...)
- Generics (compartmentType, speciesType)
  ➔ path to generalised reactions
- Constraints and initialAssignments
- Backward compatible with Level 2 Version 1
- More detailed and bug-free specification ... 130 pages

SBML Level 3

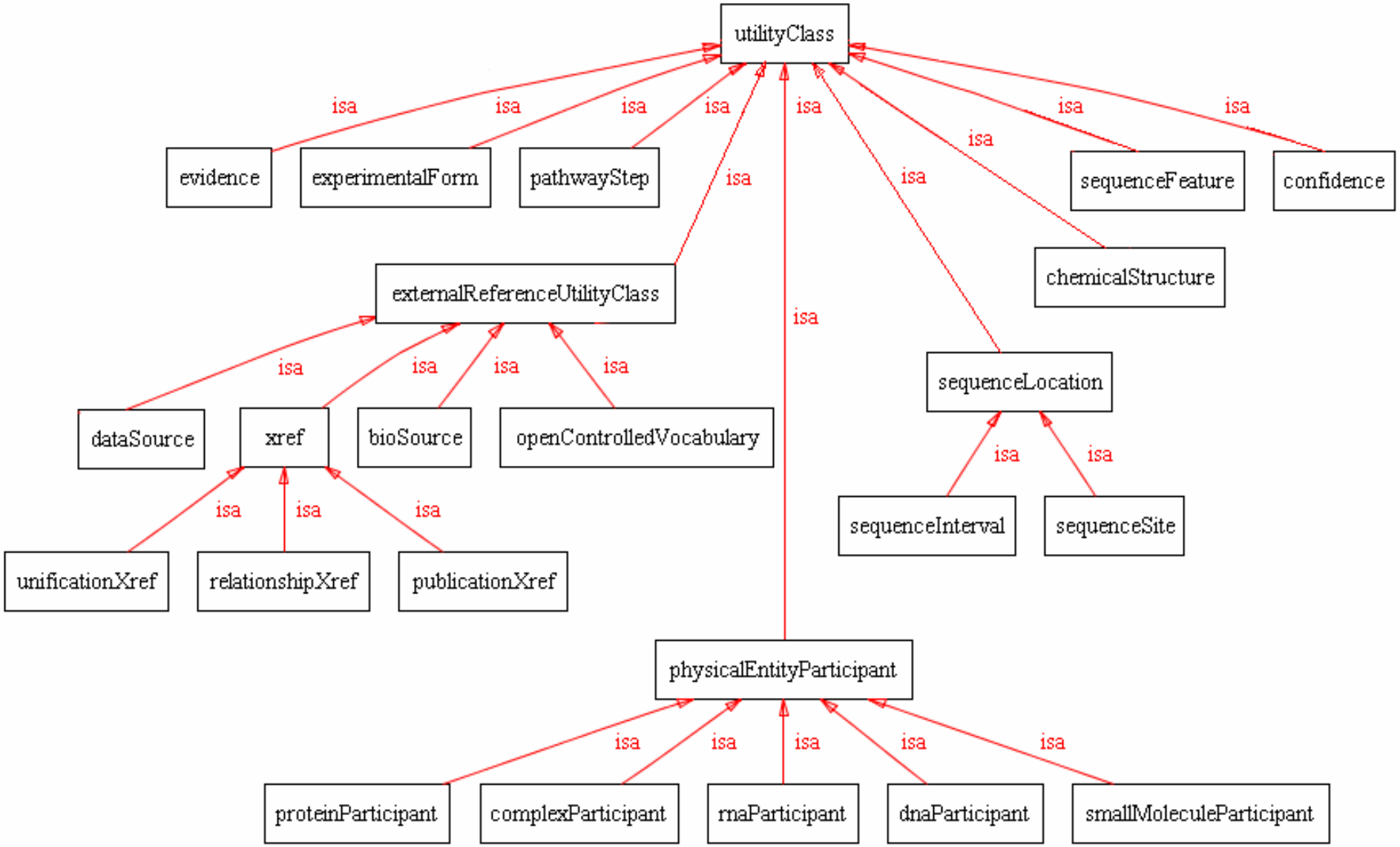
- Modular SBML, with core + optional packages (probable)
- Generalised reactions
- Graph Layout (certain; already in use in Level 2 as annotation, shared by several software)
- Model composition (probable)
- Complex species (probable)
- Arrays or sets (maybe)
- Geometry (maybe)
- Movements (maybe)
- Dynamic compartments (maybe)
- ???

- Format to represent metabolic networks and signalling pathways
- Set of classes representing the physical entities and their relationships
  - Subclassing allows different levels of abstraction/precision
- Defined using the Ontology Web Language (OWL)
  - BioPAX classed are defined in OWL
  - Each BioPAX file is an OWL file
  - Rich semantics allowing complex treatments (e.g. searches)
- OWL is based on an XML serialisation of the Resource Description Framework (RDF)
  - Explicit relationships between elements rather than only containment

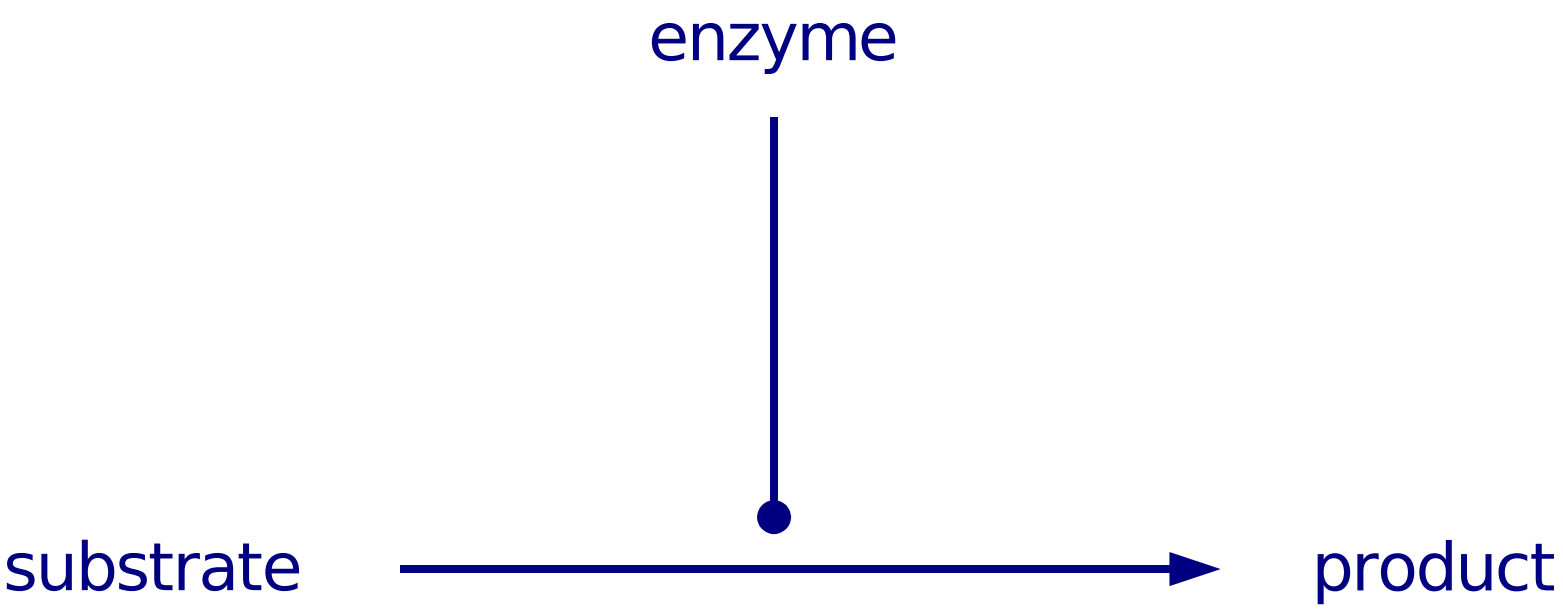
Core classes



Utility classes



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>

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```

A catalysis in BioPAX

```
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<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>
```

Semantics and visual representations

- A activates B?
- A converts into B?
- A causes the production of B?

Semantics and visual representations

- A activates B?
- A converts into B?
- A causes the production of B?

- A inhibits B?
- A inhibits the production of B?

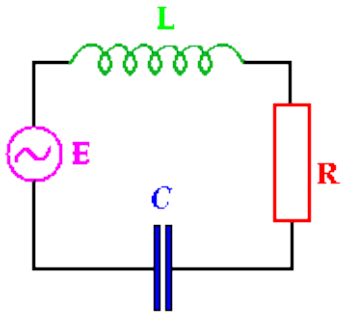
Semantics and visual representations

- A activates B?
- A converts into B?
- A causes the production of B?

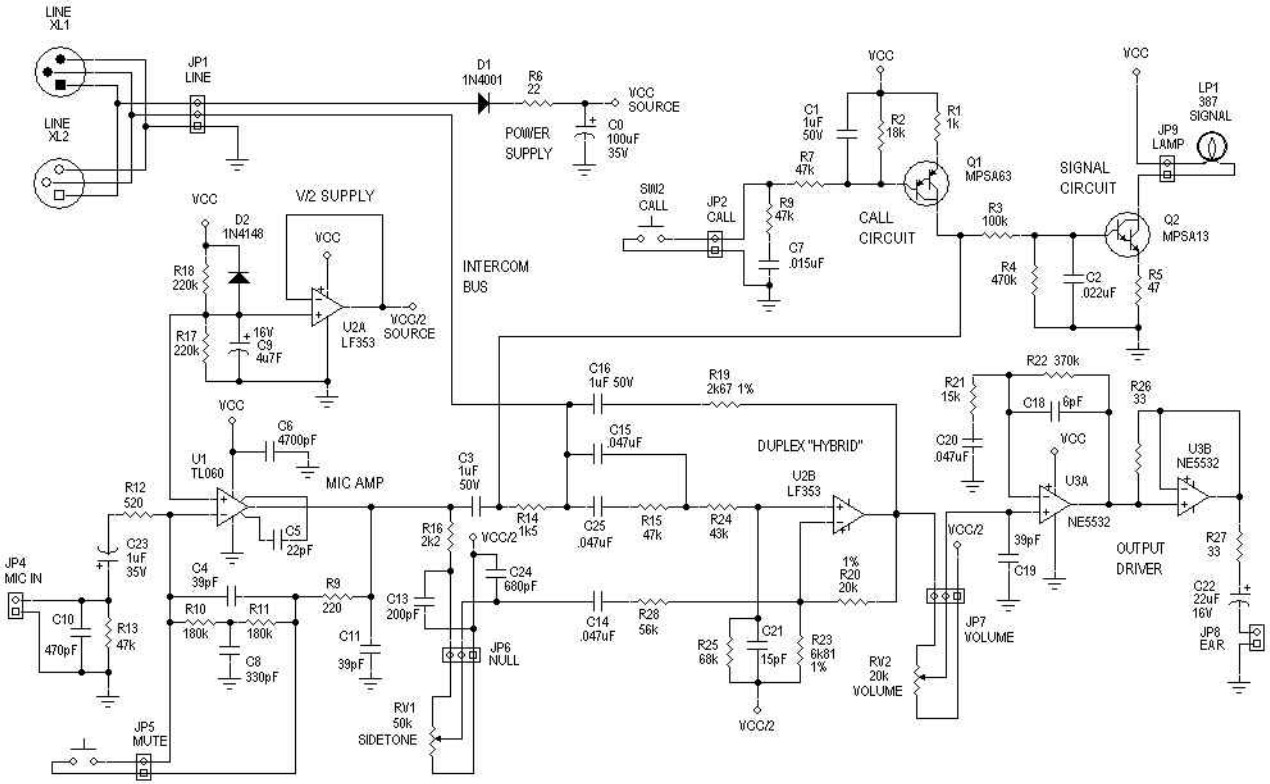
- A inhibits B?
- A inhibits the production of B?

- A modulates B?
- A catalyses the production of B?

Solution from another discipline



Solution from another discipline



Systems Biology Graphical Notation

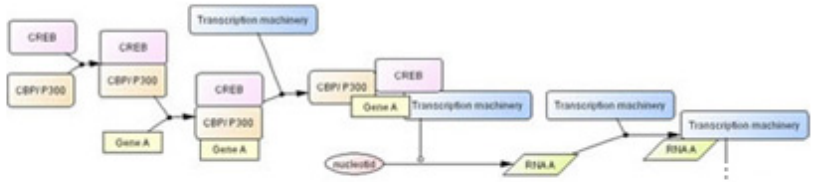
SBGN - Mozilla

File Edit View Go Bookmarks Tools Window Help

http://www.sbgn.org/ Search

Home Bookmarks SBO BioModels Google

SBGN



Systems Biology Graphical Notation

Home | Contacts | Workshops

A Visual Notation for Network Diagrams

Systems Biology has become an essential part of 21st century biological research. It is an approach that has been accepted internationally everywhere from academic research departments to industrial pharmaceutical companies. A conerstone of this movement is the use of computational modeling, a crucial tool for helping us cope with the vast size and complexity of natural organisms. The use of quantitative computational models by experimental scientists promises to pave the way for more rigorous analyses of biological functions, and ultimately will lead to new and better treatments for disease. But for this to happen, the computational models themselves must reach a wider audience.

An important first step is to reach agreement on how to communicate models. For models at the level of cellular biochemical reaction networks, the **Systems Biology Markup Language** has become a de facto machine-readable format for exchanging models between software tools. SBML is a critical enabler of research in computational systems biology, but it works at the software level; is not intended for humans to read and write.

About this Site:

This site is devoted to the Systems Biology Graphical Notation (SBGN). The international SBGN project aims to bring consistency and uniformity to the graphical expression of network diagrams in biology, in the same way that electronic circuit diagrams are standardized in electrical engineering.

Search

- Kurt Kohn's entity relationships's Diagram

  Kohn et al. Molecular Interaction Maps of Bioregulatory Networks: A General Rubric for Systems Biology. ...

- CellDesigner's Process Diagrams

  Kitano et al. Using Process Diagrams for the graphical representation of biological networks. *Nat Biotech*, 23: 961-966.

Entity relationship representation

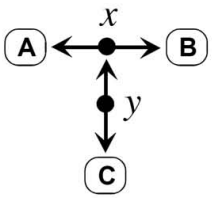
Elementary molecular species

(a) *Protein A* A molecular species named "Protein A".

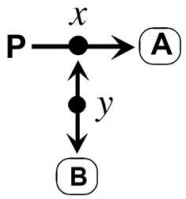
(b) **Protein A** *domain 1* *domain 2*
Domain representation of Protein A.

(c) *promoter A* A DNA site named "promoter A".

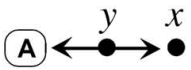
Complex molecular species

(d) 

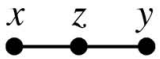
Node x is the **A:B** complex (the consequence of **A** binding to **B**); node y is the (**A:B**):**C** complex.

(e) 

Node x is phosphorylated **A**; node y is phosphorylated **A** bound to **B.**

(f) 

The isolated node x is an abbreviation for another copy of **A.** Node y is the homodimer **A:A**.

(g) 

State-combination symbol: z is the combination of states defined by x and y (see examples).

Reaction symbols

(a) Non-covalent binding (reversible)

(b) Covalent modification.

(b') Covalent bond (see Figure 13 & text).

(c) Stoichiometric conversion

(d) Products appear without loss of reactants.

(e) Transcription

(f) Cleavage of a covalent bond.

(g) Degradation

(h) Reaction *in trans.*

Contingency symbols

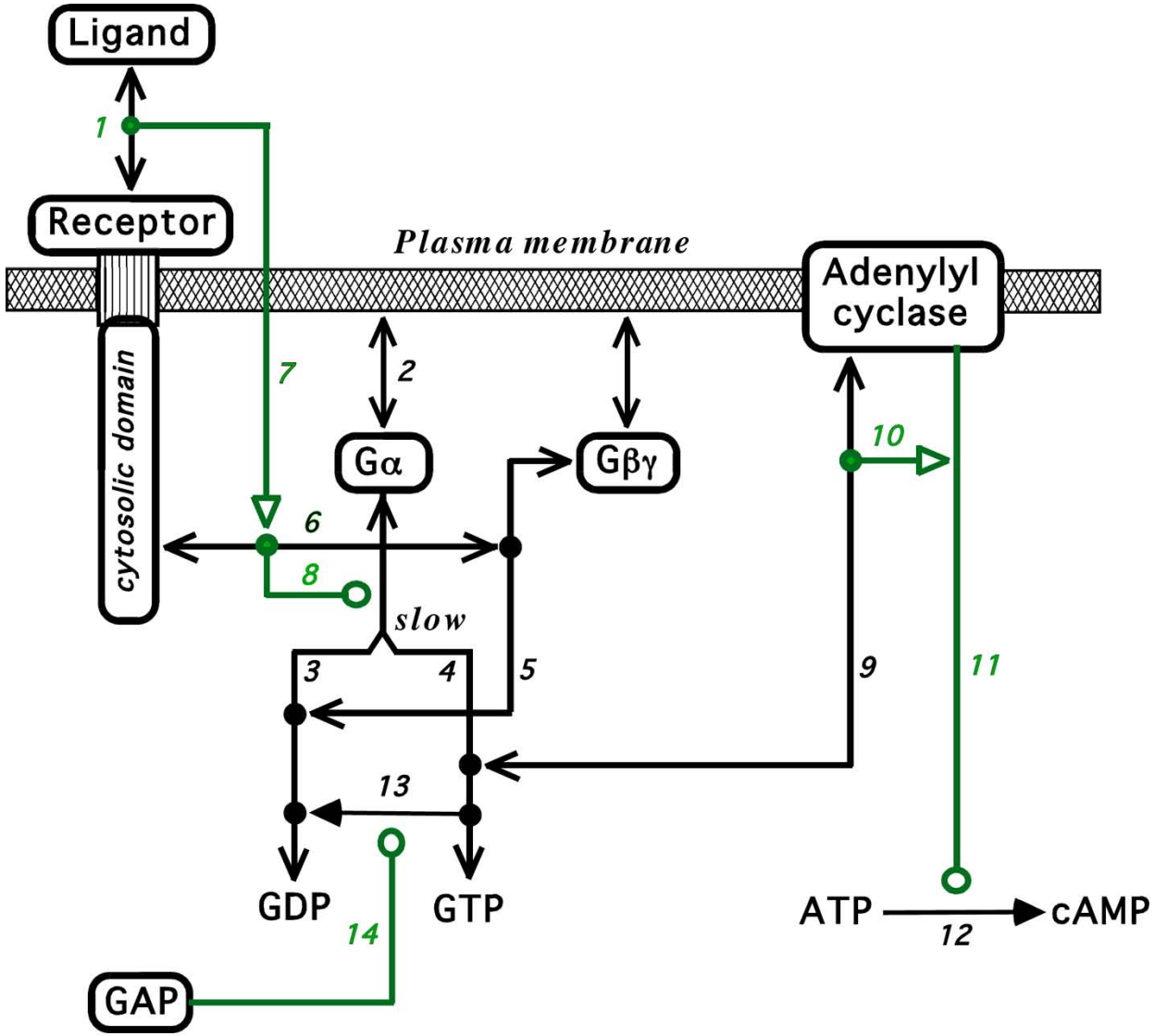
(i) Stimulation

(j) Requirement

(k) Inhibition

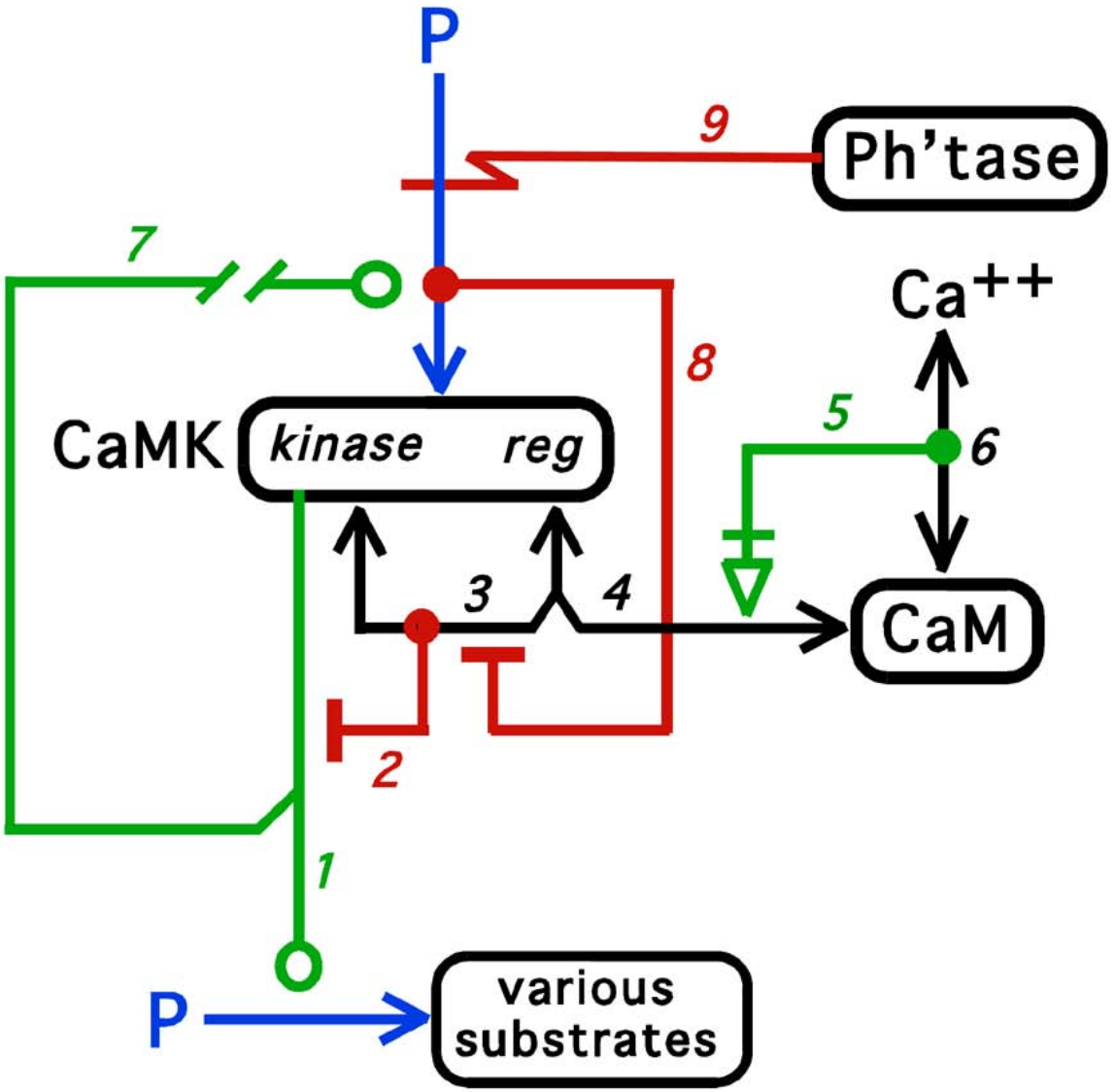
(l) Enzymatic catalysis

Entity relationship representation

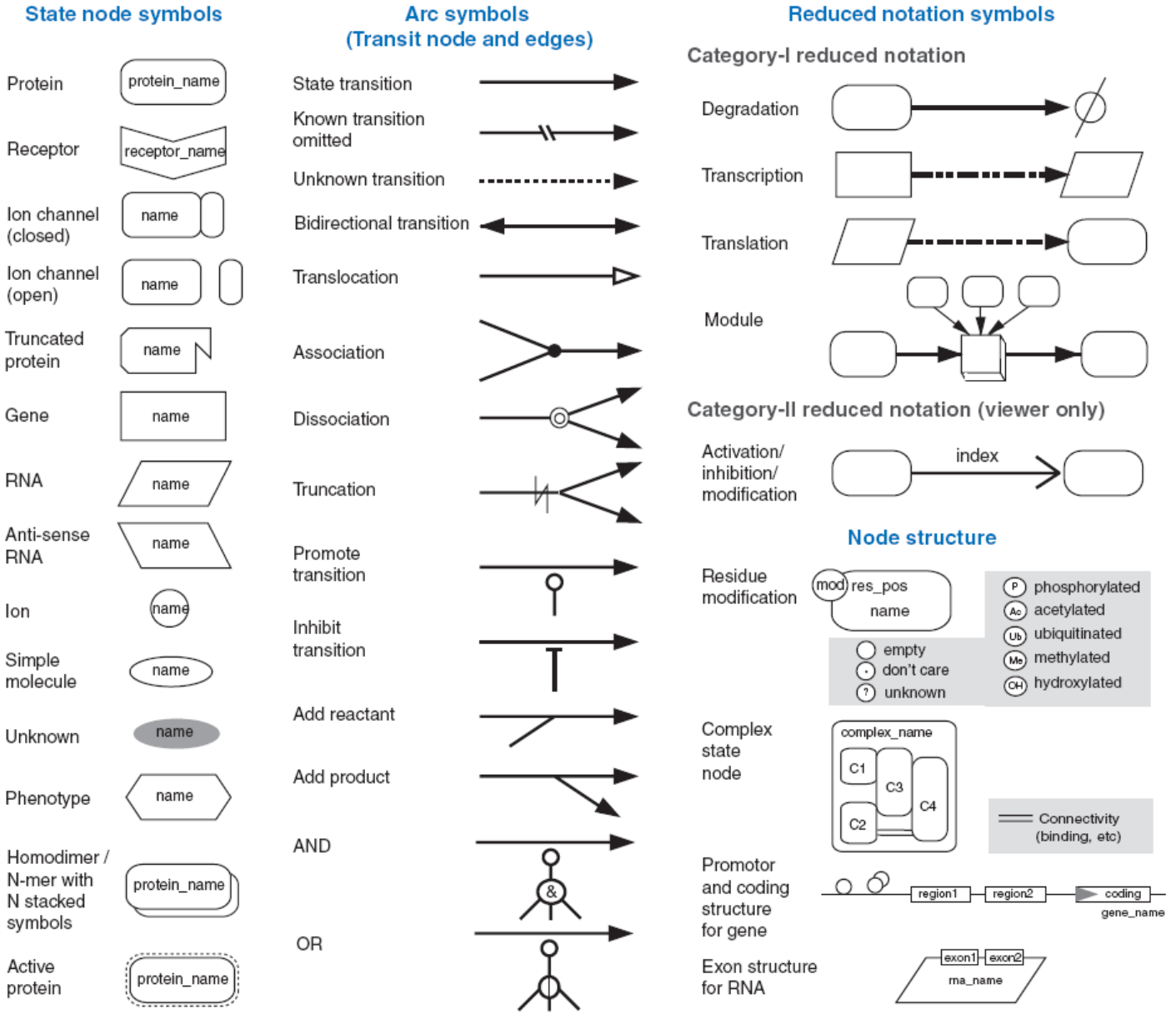


MIM def fig 11-b (Gprot)

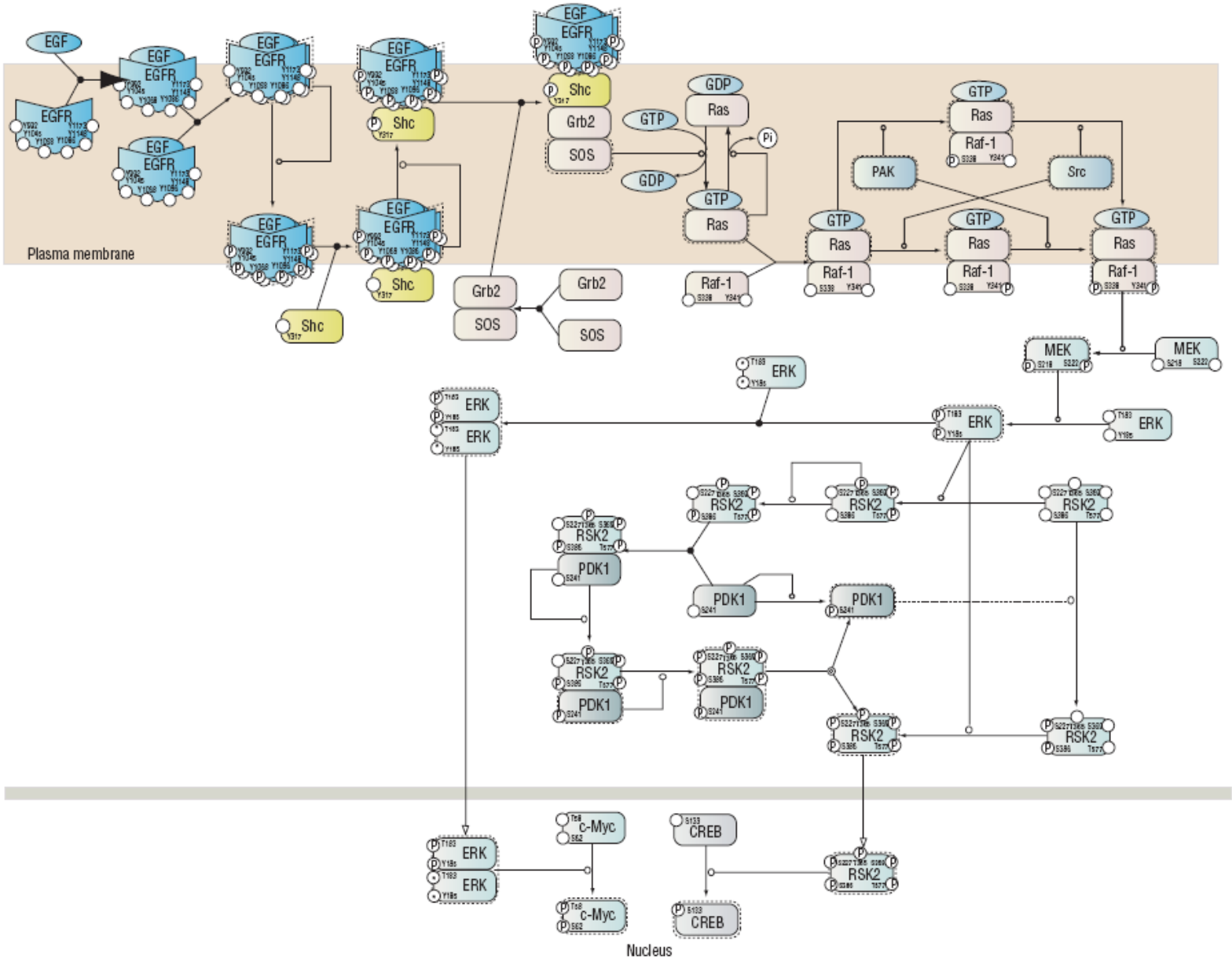
Entity relationship representation



Process Diagram



Process Diagram



Is SBGN usable?

- No ...
- Work in progress: Agreement on the existence of two notations. Ontologies are on their way to define the concepts behind the glyphs
- First draft should be agreed in the second meeting at the ICSB in Yokohama

BIOMODELS.NET

The Next Step After Standard Formats

For computational modeling to become more widely used in biological research, researchers must be able to exchange and share their results. The development and broad acceptance of common model representation formats such as **SBML** is a crucial step in that direction, allowing researchers to exchange and build upon each other's work with greater ease and accuracy.

The BioModels.net project is another step: an international effort to (1) define agreed-upon standards for model curation, (2) define agreed-upon vocabularies for annotating models with connections to biological data resources, and (3) provide a free, centralized, publicly-accessible database of annotated, computational models in SBML and other structured formats.

Helping to Define Community Standards

To facilitate assembling useful collections of quantitative models of biological phenomena, it is crucial to establish standards for the vocabularies used in model annotations as well as criteria for minimum quality levels of those models. The BioModels.net project aims to bring together a community of interested researchers to address these issues. We are working towards defining these standards through white papers and process definitions. All of the products of our efforts are open and freely available through this site.

Standards and Processes Developed Hand-in-Hand with a New Database

The database component of BioModels.net is especially designed for working with *annotated* computational models: each model is carefully reviewed and augmented by human annotators on the BioModels.net team to add metadata linking the model elements to other biological databases and resources. The **BioModels database at the EBI** system goes far beyond other collections of models by being a *true* database, featuring browsing, cross-referencing, searching, and (coming soon) facilities for visualization, exporting models in different formats, and remote API access.

Minimum Information Requested In the Annotation of biochemical Models

Le Novère N., Finney A., Hucka M., Bhalla U., Campagne F., Collado-Vides J., Crampin E., Halstead M., Klipp E., Mendes P., Nielsen P., Sauro H., Shapiro B., Snoep J.L., Spence H.D., Wanner B.L.

Nature Biotechnology **(2005), 23: 1509-1515**

MIRIAM

Reference correspondence

- The model must be encoded in a public, standardized, machine-readable format (SBML, CellML, GENESIS ...)
- The model must comply with the standard in which it is encoded!
- The model must be clearly related to a single reference description. If a model is composed from different parts, there should still be a description of the derived/combined model.
- The encoded model structure must reflect the biological processes listed in the reference description.
- The model must be instantiated in a simulation: All quantitative attributes have to be defined, including initial conditions.
- When instantiated, the model must be able to reproduce all results given in the reference description within an epsilon (algorithms, round-up errors)

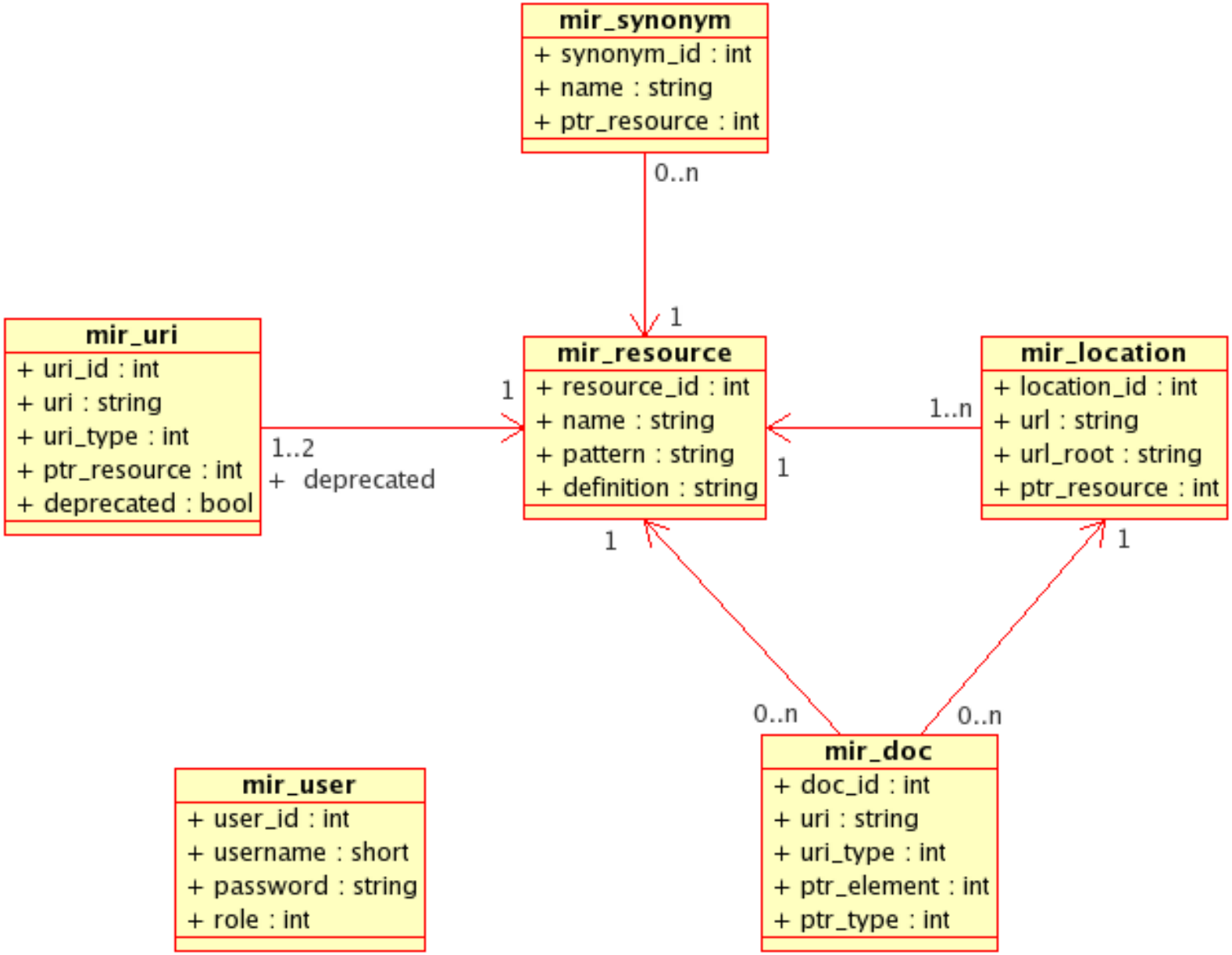
Attribution annotation

- The model has to be named.
- A citation of the reference description must be joined (complete citation, unique identifier, unambigous URL). The citation should permit to identify the *authors* of the model.
- The name and contact of model *creators* must be joined.
- The date and time of creation and last modification should be specified. An history is useful but not required.
- The model should be linked to a precise statement about the terms of distribution. MIRIAM does not require “freedom of use” or “no cost”.

External resource annotation

- The annotation must permit to unambiguously relate a piece of knowledge to a model constituent.
- The referenced information should be described using a triplet {data-type, identifier, qualifier}
  - The data-type should be written as a Unique Resource Identifier (URI). Either a URL (webpage) or a URN (e.g. LSID). Not necessarily a physical location.
  - The identifier is analysed by the software within the framework of the data-type.
  - Data-type and Identifier can be combined in a single URI
    http://www.myResource.org/#myIdentifier
    urn:lsid:myResource.org:myIdentifier
  - Qualifiers (optional) should refine the link between the model constitutent and the piece of knowledge: “has a”, “is version of”, “is homolog to” etc.
- The community will have to agree on a set of standard valid URIs. A database and the associated API (WebServices) have been developed at the EBI.

MIRIAM database

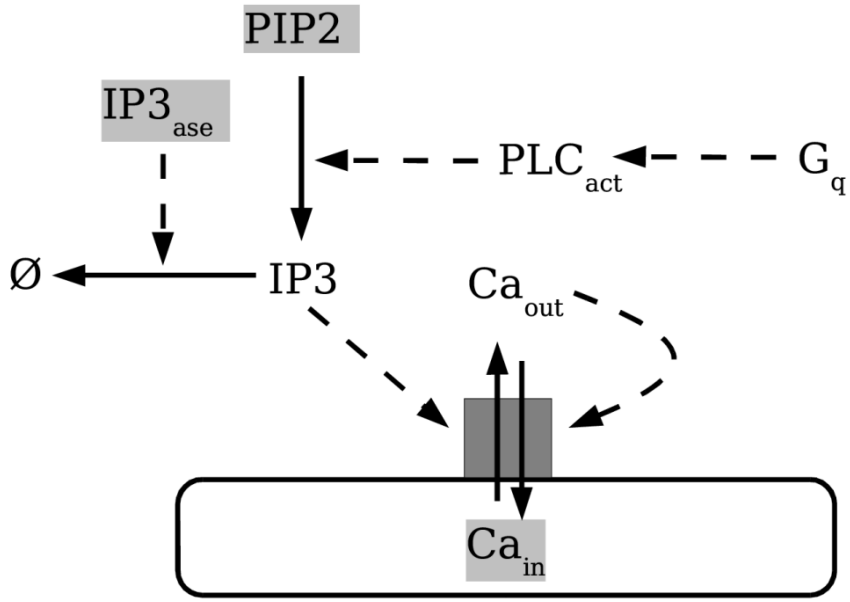


MIRIAM database

- getURI(name, ID)
  {uniprot,P12345} → `http://www.uniprot.org/#P122345`
- getURL(URI)
  {http://www.ec-code.org/#1.1.1.1} →

  `http://www.ebi.ac.uk/intenz/query?cmd=SearchEC&ec=1.1.1.1`
  `http://us.expasy.org/cgi-bin/nicezyme.pl?1.1.1.1`
  `http://www.genome.jp/dbget-bin/www-bget?ec:1.1.1.1`
- validate(URI)
  {http://www.uniprot.org/#P123Z5} →
  "Invalid URI! Either the root URI or the accession is wrong "

Model example



$$k_1 = k_2 = k_3 = 1\ s^{-1}$$

$$Km_1 = 10^{-7}\ M, Km_2 = 10^{-8}, Km_3 = 2.10^{-6}\ M$$

$$K_A = 10^{-11}, m = 4, n = 3, \alpha = 0.001$$

$$\frac{d[Ca_{out}]}{dt} = \frac{k_1[IP3R] * ([Ca_{in}] - [Ca_{out}])}{Km_1 + |[Ca_{in}] - [Ca_{out}]|} * \frac{[IP3]^m}{K_A + [IP3]^m}$$

$$\frac{d[IP3]}{dt} = \frac{k_2[PLC_{act}] * [PIP2]}{Km_2 + [PIP2]} - \frac{k_3[IP3_{ase}] * [IP3]}{Km_3 + [IP3]}$$

$$\frac{d[PLC_{act}]}{dt} = \frac{[G_q]^n}{\alpha + [G_q]^n} * [PLC_{tot}]$$

$$[Ca_{in}] = [IP3R] = [PLC_{tot}] = [PIP2] = [IP3_{ase}] = 0.001\ M$$

$$[G_q] = 0.01\ M, [Ca_{out}] = [IP3] = [PLC_{act}] = 0\ M$$

creators	Joe User (juser@eden.com), Anne Other (aother@eden.com)
creation date	01 January 0000
last modification	31 May 2005

Constituent	Data Type	Identifier	Qualifier	Meaning
model	http://www.pubmed.gov/	0000000		
	http://www.ncbi.nlm.nih.gov/Taxonomy/	9606		*Homo sapiens*
	http://www.geneontology.org/	GO:0007204	IsVersionOf	*positive regulation of cytosolic [ca^{2+}]*
	http://www.geneontology.org/	GO:0051279	IsVersionOf	*regulation of release of sequestered ca^{2+} into cytop*
	http://www.genome.jp/kegg/pathway/	hsa04020	IsPartOf	*Calcium signaling pathway - H sapiens*
	http://www.genome.jp/kegg/pathway/	hsa04070	IsPartOf	*Phosphatidylinositol signaling system - H sapiens*
compartment ER	http://www.geneontology.org/	GO:0005790		*smooth endoplasmic reticulum*
reactant Ca_{in}	http://www.ebi.ac.uk/chebi/	CHEBI:29108		*calcium(2+)*
cytoplasm	http://www.geneontology.org/	GO:0005737		*cytoplasm*
reactant Ca_{out}	http://www.ebi.ac.uk/chebi/	CHEBI:29108		*calcium(2+)*
reactant IP3	http://www.ebi.ac.uk/chebi/	CHEBI:16595		*1D-myo-inositol 1,4,5-tris(dihydrogen phosphate)*
reactant PIP2	http://www.ebi.ac.uk/chebi/	CHEBI:18348		*1-phosphatidyl-1D-myo-inositol 4,5-bisphosphate*
reactant IP3R	http://www.uniprot.org/	Q14643	HasVersion	*Inositol 1,4,5-trisphosphate receptor type 1*
	http://www.uniprot.org/	Q14571	HasVersion	*Inositol 1,4,5-trisphosphate receptor type 2*
	http://www.uniprot.org/	Q14573	HasVersion	*Inositol 1,4,5-trisphosphate receptor type 3*
reactant PLC_{act}	http://www.uniprot.org/	Q9NQ66	IsVersionOf	*PIP2 phosphodiesterase β1*
reactant PLC_{tot}	http://www.uniprot.org/	Q9NQ66		*PIP2 phosphodiesterase β1*
reactant $IP3_{ase}$	http://www.uniprot.org/	Q14642		*Type I inositol-1,4,5-trisphosphate 5-phosphatase*
reactant G_q	http://www.uniprot.org/	Q6NT27		*Guanine nucleotide binding protein Gq*
reaction $Ca_{release}$	http://www.geneontology.org/	GO:0005220		*IP3-sensitive calcium-release channel activity*
	http://www.geneontology.org/	GO:0008095	IsVersionOf	*IP3 receptor activity*
reaction $IP3_{production}$	http://www.geneontology.org/	GO:0004435	IsVersionOf	*phosphoinositide phospholipase C activity*
	http://www.ebi.ac.uk/intenz/	3.1.4.11	IsVersionOf	*phosphoinositide phospholipase C*
reaction $IP3_{degradation}$	http://www.ebi.ac.uk/intenz/	3.1.3.56	IsVersionOf	*inositol-polyphosphate 5-phosphatase*
reaction $PLC_{activation}$	http://www.geneontology.org/	GO:0007200		*G-protein signaling coupled to IP3 2nd messenger*

creators	Joe User (juser@eden.com), Anne Other (aother@eden.com)
creation date	01 January 0000
last modification	31 May 2005

What is common?

Constituent	Data Type	Identifier	Qualifier	Meaning
model	http://www.pubmed.gov/	0000000		
	http://www.ncbi.nlm.nih.gov/Taxonomy/	9606		*Homo sapiens*
	http://www.geneontology.org/	GO:0007204	IsVersionOf	*positive regulation of cytosolic [ca^{2+}]*
	http://www.geneontology.org/	GO:0051279	IsVersionOf	*regulation of release of sequestered ca^{2+} into cytop*
	http://www.genome.jp/kegg/pathway/	hsa04020	IsPartOf	*Calcium signaling pathway - H sapiens*
	http://www.genome.jp/kegg/pathway/	hsa04070	IsPartOf	*Phosphatidylinositol signaling system - H sapiens*
compartment ER	http://www.geneontology.org/	GO:0005790		*smooth endoplasmic reticulum*
reactant Ca_{in}	http://www.ebi.ac.uk/chebi/	CHEBI:29108		*calcium(2+)*
cytoplasm	http://www.geneontology.org/	GO:0005737		*cytoplasm*
reactant Ca_{out}	http://www.ebi.ac.uk/chebi/	CHEBI:29108		*calcium(2+)*
reactant IP3	http://www.ebi.ac.uk/chebi/	CHEBI:16595		*1D-myo-inositol 1,4,5-tris(dihydrogen phosphate)*
reactant PIP2	http://www.ebi.ac.uk/chebi/	CHEBI:18348		*1-phosphatidyl-1D-myo-inositol 4,5-bisphosphate*
reactant IP3R	http://www.uniprot.org/	Q14643	HasVersion	*Inositol 1,4,5-trisphosphate receptor type 1*
	http://www.uniprot.org/	Q14571	HasVersion	*Inositol 1,4,5-trisphosphate receptor type 2*
	http://www.uniprot.org/	Q14573	HasVersion	*Inositol 1,4,5-trisphosphate receptor type 3*
reactant PLC_{act}	http://www.uniprot.org/	Q9NQ66	IsVersionOf	*PIP2 phosphodiesterase β1*
reactant PLC_{tot}	http://www.uniprot.org/	Q9NQ66		*PIP2 phosphodiesterase β1*
reactant $IP3_{ase}$	http://www.uniprot.org/	Q14642		*Type I inositol-1,4,5-trisphosphate 5-phosphatase*
reactant G_q	http://www.uniprot.org/	Q6NT27		*Guanine nucleotide binding protein Gq*
reaction $Ca_{release}$	http://www.geneontology.org/	GO:0005220		*IP3-sensitive calcium-release channel activity*
	http://www.geneontology.org/	GO:0008095	IsVersionOf	*IP3 receptor activity*
reaction $IP3_{production}$	http://www.geneontology.org/	GO:0004435	IsVersionOf	*phosphoinositide phospholipase C activity*
	http://www.ebi.ac.uk/intenz/	3.1.4.11	IsVersionOf	*phosphoinositide phospholipase C*
reaction $IP3_{degradation}$	http://www.ebi.ac.uk/intenz/	3.1.3.56	IsVersionOf	*inositol-polyphosphate 5-phosphatase*
reaction $PLC_{activation}$	http://www.geneontology.org/	GO:0007200		*G-protein signaling coupled to IP3 2nd messenger*

Some definitions

- Controlled Vocabularies
- "Organized lists of words and phrases, or notation systems, that are used to initially tag content, and then to find it through navigation or search." *Amy J. Warner. A Taxonomy Primer.* http://www.lexonomy.com/publications/aTaxonomyPrimer.html
- "A set of codes, managed by some authority (eg a person or an organisation), employing some mechanism". Misha Wolf on *IPTC internal developer forum for the News Metadata Framework WG*
- "An indexed dictionary". *Nicolas Le Novère. This presentation.*
- Ontology
- "(Computers) A systematic arrangement of all of the important categories of objects or concepts which exist in some field of discourse, showing the relations between them. When complete, an ontology is a categorization of all of the concepts in some field of knowledge, including the objects and all of the properties, relations, and functions needed to define the objects and specify their actions. A simplified ontology may contain only a **hierarchical** classification (a **taxonomy**)" *The Collaborative International Dictionary of English v.0.48*
- A set of elements of knowledge linked with sense-bearing relationships. *Nicolas Le Novère. This presentation.*

AmiGO http://www.geneontology.org/

Search GO

Exact Match

Terms

Gene Symbol/Name

Submit Query

Advanced Query

Query By Sequence

Gene Product Filters

Species

All
A. aeolicus
A. fulgidus

Datasource

All
FlyBase
SGD

Evidence Code

All Curator Approved
IC
IMP

Set Filters

XML
Flat File
Permalink

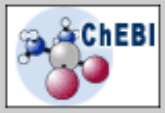
Last updated: 2005-08-21

Graphical View

- all : all (218850)
  - GO:0008150 : biological_process (145098)
    - GO:0009987 : cellular process (91236)
      - GO:0007154 : cell communication (15496)
        - GO:0007267 : cell-cell signaling (1894)
          - GO:0019226 : transmission of nerve impulse (1230)
            - **GO:0007268 : synaptic transmission (1124)**
              - GO:0007270 : nerve-nerve synaptic transmission (92)
              - GO:0007274 : neuromuscular synaptic transmission (33)
              - GO:0045213 : neurotransmitter receptor metabolism (32)
              - GO:0001505 : regulation of neurotransmitter levels (547)
              - GO:0050803 : regulation of synapse structure and function (49)
    - GO:0007582 : physiological process (96419)
      - GO:0050874 : organismal physiological process (9314)
        - GO:0050877 : neurophysiological process (4743)
          - GO:0019226 : transmission of nerve impulse (1230)
            - **GO:0007268 : synaptic transmission (1124)**
              - GO:0007270 : nerve-nerve synaptic transmission (92)
              - GO:0007274 : neuromuscular synaptic transmission (33)
              - GO:0045213 : neurotransmitter receptor metabolism (32)
              - GO:0001505 : regulation of neurotransmitter levels (547)
              - GO:0050803 : regulation of synapse structure and function (49)
  - **GO:0005575 : cellular_component (131714)**
    - **GO:0005623 : cell (96196)**
      - GO:0045177 : apical part of cell (293)
      - GO:0043190 : ATP-binding cassette (ABC) transporter complex (145)
      - GO:0045178 : basal part of cell (38)
      - GO:0005933 : bud (294)
      - GO:0000267 : cell fraction (2094)
      - **GO:0042995 : cell projection (1119)**
        - GO:0005930 : axoneme (69)
        - GO:0005932 : basal body (29)
        - GO:0005903 : brush border (72)
        - GO:0031253 : cell projection membrane (0)
        - GO:0005929 : cilium (91)
        - GO:0035230 : cytoneme (0)
        - GO:0030175 : filopodium (34)
        - GO:0019861 : flagellum (251)
        - GO:0030027 : lamellipodium (197)
        - GO:0005937 : mating projection (86)
        - GO:0005902 : microvillus (40)
        - **GO:0043005 : neuron projection (236)**
          - GO:0030424 : axon (115)
          - **GO:0030425 : dendrite (106)**
            - GO:0043198 : dendritic shaft (5)
            - GO:0043197 : dendritic spine (5)
        - GO:0031143 : pseudopodium (20)
        - GO:0001726 : ruffle (76)

ChEBI Result

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



Quick Search

Example: water

Search Help?

- ChEBI Home
- Advanced Search
- User Manual
- FAQ's
- Downloads
- SourceForge Forum
- Contact ChEBI

General Information	
ChEBI Name	**acetylcholine**
ChEBI ID	**CHEBI:15355**

Ontology

CHEBI:23091 chemical_ontology
- CHEBI:24432 grouped_by_functions
  - CHEBI:25512 neurotransmitters
    - CHEBI:15355 acetylcholine
- CHEBI:24431 grouped_by_chemistry
  - CHEBI:25367 molecules
    - CHEBI:25700 organic molecules
      - CHEBI:32952 amines
        - CHEBI:22879 biogenic amines
          - CHEBI:22227 acylcholines
            - CHEBI:15355 acetylcholine

Parents and children

IUPAC Name
2-acetyloxy-*N*,*N*,*N*-trimethylethanaminium

Synonyms	Sources
acetylcholine	IntEnz
Acetylcholine	KEGG COMPOUND
O-acetylcholine	ChEBI
O-acetylcholine	IntEnz
O-Acetylcholine	KEGG COMPOUND

Database Link	Database
C01996	KEGG COMPOUND

Registry Number	Type	Source
51-84-3	CAS Registry Number	KEGG COMPOUND

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

IntEnz
Home
News
Advanced search
Proposed enzymes
Display information
About IntEnz
Future development

EC 3
EC 3.1
EC 3.1.1

Go

Show classification

Printer-friendly view

IUBMB Enzyme Nomenclature

EC 3.1.1.7

Common name: acetylcholinesterase

Reaction: acetylcholine + H_2O = choline + acetate

Other name(s): AcCholE
acetyl.β-methylcholinesterase
acetylcholine hydrolase
acetylthiocholinesterase
choline esterase I
cholinesterase
true cholinesterase

Systematic name: acetylcholine acetylhydrolase

Comments: Acts on a variety of acetic esters; also catalyses transacetylations.

Links to other databases: BRENDA, ERGO, GO, KEGG, NIST 74

CAS Registry Number: 9000-81-1

References:

1. Augustinsson, K.-B. Cholinesterases. A study in comparative enzymology. *Acta Physiol. Scand.* 15 (1948)
2. Bergmann, F., Rimon, S. and Segal, R. Effect of pH on the activity of eel esterase towards different substrates. *Biochem. J.* 68 (1958) 493-499.
3. Cilliv, G. and Ozand, P.T. Human erythrocyte acetylcholinesterase purification, properties and kinetic behavior. *Biochim. Biophys. Acta* 284 (1972) 136-156. [PMID: 5073758]
4. Leuzinger, W., Baker, A.L. and Cauvin, E. Acetylcholinesterase. II. Crystallization, absorption spectra, isoionic point. *Proc. Natl. Acad. Sci. USA* 59 (1968) 620-623. [PMID: 5238989]
5. Nachmansohn, D. and Wilson, I.B. The enzymic hydrolysis and synthesis of acetylcholine. *Adv. Enzymol. Relat. Subj. Biochem.* 12 (1951) 259-339.
6. Zittle, C.A., DellaMonica, E.S., Custer, J.H. and Krikorian, R. Purification of human red cell acetylcholinesterase by electrophoresis, ultracentrifugation and gradient extraction. *Arch. Biochem. Biophys.* 56 (1955) 469-475.

[EC 3.1.1.7 created 1961]

InterPro Parent-Child tree for InterPro Entry IPR006201

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

InterPro entries can be related to each other in a parent-child relationship. See the user manual for more information.

Any domains (InterPro entries) in which an entry in this tree is found or contains is shown. Click on the accession number to go to the primary entry, click on the name to go to that entry's parent-child tree.

- IPR006201 : Neurotransmitter-gated ion-channel CONTAINS: (IPR006029:Neurotransmitter-gated ion-channel transmembrane region, IPR006202:Neurotransmitter-gated ion-channel ligand-binding)
  - IPR002394 : Nicotinic acetylcholine receptor CONTAINS: (IPR006029:Neurotransmitter-gated ion-channel transmembrane region, IPR006202:Neurotransmitter-gated ion-channel ligand-binding)
  - IPR006028 : Gamma-aminobutyric acid A receptor CONTAINS: (IPR006029:Neurotransmitter-gated ion-channel transmembrane region, IPR006202:Neurotransmitter-gated ion-channel ligand-binding)
    - IPR001390 : Gamma-aminobutyric-acid A receptor, alpha subunit CONTAINS: (IPR006029:Neurotransmitter-gated ion-channel transmembrane region, IPR006202:Neurotransmitter-gated ion-channel ligand-binding)
    - IPR002289 : Gamma-aminobutyric-acid A receptor, beta subunit CONTAINS: (IPR006029:Neurotransmitter-gated ion-channel transmembrane region, IPR006202:Neurotransmitter-gated ion-channel ligand-binding)
    - IPR005437 : Gamma-aminobutyric-acid A receptor, gamma subunit CONTAINS: (IPR006029:Neurotransmitter-gated ion-channel transmembrane region, IPR006202:Neurotransmitter-gated ion-channel ligand-binding)
    - IPR008057 : Gamma-aminobutyric-acid A receptor, Rho CONTAINS: (IPR006029:Neurotransmitter-gated ion-channel transmembrane region, IPR006202:Neurotransmitter-gated ion-channel ligand-binding)
    - IPR008098 : Gamma-aminobutyric-acid A receptor delta subunit CONTAINS: (IPR006029:Neurotransmitter-gated ion-channel transmembrane region, IPR006202:Neurotransmitter-gated ion-channel ligand-binding)
    - IPR008099 : Gamma-aminobutyric-acid A receptor epsilon subunit CONTAINS: (IPR006029:Neurotransmitter-gated ion-channel transmembrane region, IPR006162:Phosphopantetheine attachment site, IPR006202:Neurotransmitter-gated ion-channel ligand-binding)
    - IPR008100 : Gamma-aminobutyric-acid A receptor pi subunit CONTAINS: (IPR006029:Neurotransmitter-gated ion-channel transmembrane region, IPR006202:Neurotransmitter-gated ion-channel ligand-binding)
    - IPR008101 : Gamma-aminobutyric-acid A receptor theta subunit CONTAINS: (IPR006029:Neurotransmitter-gated ion-channel transmembrane region, IPR006202:Neurotransmitter-gated ion-channel ligand-binding)
  - IPR008060 : Glycine receptor beta CONTAINS: (IPR006029:Neurotransmitter-gated ion-channel transmembrane region, IPR006202:Neurotransmitter-gated ion-channel ligand-binding)
  - IPR008128 : Glycine receptor alpha1 CONTAINS: (IPR006029:Neurotransmitter-gated ion-channel transmembrane region, IPR006202:Neurotransmitter-gated ion-channel ligand-binding)
  - IPR008129 : Glycine receptor alpha2 CONTAINS: (IPR006029:Neurotransmitter-gated ion-channel transmembrane region, IPR006202:Neurotransmitter-gated ion-channel ligand-binding)
  - IPR008130 : Glycine receptor alpha3 CONTAINS: (IPR006029:Neurotransmitter-gated ion-channel transmembrane region, IPR006202:Neurotransmitter-gated ion-channel ligand-binding)
  - IPR008132 : 5-hydroxytryptamine 3 receptor CONTAINS: (IPR006029:Neurotransmitter-gated ion-channel transmembrane region, IPR006202:Neurotransmitter-gated ion-channel ligand-binding)
    - IPR008133 : 5-hydroxytryptamine 3 receptor, A subunit CONTAINS: (IPR006029:Neurotransmitter-gated ion-channel transmembrane region, IPR006202:Neurotransmitter-gated ion-channel ligand-binding)
    - IPR008134 : 5-hydroxytryptamine 3 receptor, B subunit CONTAINS: (IPR006029:Neurotransmitter-gated ion-channel transmembrane region, IPR006202:Neurotransmitter-gated ion-channel ligand-binding)

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

Homo sapiens (Human)

Lineage	Taxonomy identifier	9606	External information
• Eukaryota • Metazoa • Chordata • Craniata • Vertebrata • Euteleostomi • Mammalia • Eutheria • Euarchontoglires • Primates • Catarrhini • Hominidae • Homo	Organism identification code	HUMAN	http://www.ebi.ac.uk/integr8/QuickSearch.do?action=doOrgSearch&organismName=homo+sapi http://www.mnh.si.edu/anthro/humanorigins/ha/sap.htm
	Scientific name	Homo sapiens	
	Common name	Human	
	Synonym	-	
	Other NCBI synonyms	man	
	Rank	species	
	Number of UniProt/Swiss-Prot entries	12838	
	Number of UniProt/TrEMBL entries	57516	

Taxonomy navigation	
Up taxonomy tree	Down taxonomy tree
Homo	• Homo sapiens neanderthalensis

Source of data : Swiss-Prot *NCBI taxonomy for this taxon*

PhyloCode - Mozilla
File Edit View Go Bookmarks Tools Window Help
http://www.ohiou.edu/phylocode/
Search
"definition of ontology" - Google Se... | dict.org- ontology | DopaNet Neuronal Ontology Browser | PhyloCode

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Download Current Draft of PhyloCode

PDF Version
Word Version

Previous Drafts:

April 2000 draft
PDF version
Word version

October 2003 draft
PDF version
Word version

December 2003 draft

PhyloCode

The PhyloCode is a formal set of rules governing phylogenetic nomenclature. It is designed to name the parts of the tree of life by explicit reference to phylogeny. The PhyloCode will go into operation in a few years, but the exact date has not yet been determined. It is designed so that it may be used concurrently with the existing codes based on rank-based nomenclature (ICBN, ICZN, etc.). We anticipate that many people whose research concerns phylogeny will find phylogenetic nomenclature advantageous.

The PhyloCode grew out of a workshop at Harvard University in August 1998, where decisions were made about its scope and content. Many of the workshop participants, together with several other people who subsequently joined the project, have served as an advisory group (see the PhyloCode preface for a list of the people involved). In April 2000, a draft was made public on this web site and comments were solicited from the scientific community. All comments were forwarded to the advisory group, and many of them elicited discussion.

A second workshop was held at Yale University in July 2002, at which some modifications were made in the rules and recommendations of the PhyloCode. An important decision made at the Yale workshop is that the rules governing clade names and those governing species names will be published in separate documents, and the timing of implementation of the two documents will be independent. The rules for clade names will almost certainly be implemented before those for species names because the latter have not yet been drafted. Only clade names are covered by the current version of the PhyloCode. As a result, the examples in the current version use binomials governed by the rank-based codes when species names are cited in the phylogenetic definitions of clade names.

The First International Phylogenetic Nomenclature Meeting, which took place July 6-9, 2004 in Paris, was attended by about 70 systematic and evolutionary biologists from 11 nations. The program can be downloaded from the left side of this page. The participants are grateful to the Organizing Committee, and particularly its Chair, Michel Laurin, for the care and effort that was devoted to making the meeting an enjoyable and stimulating event. This was the first open, multi-day conference that focused entirely on phylogenetic nomenclature. Papers presented at the meeting will form the core of a book whose publication, tentatively scheduled for 2006, will coincide with the implementation of the PhyloCode. This book will represent the official starting point of phylogenetic nomenclature as implemented in the PhyloCode. The Paris meeting also provided the venue for the inauguration of a new association, the International Society for Phylogenetic Nomenclature (ISPN). The ISPN membership will elect the Committee on Phylogenetic Nomenclature, the

http://www.ohiou.edu/phylocode/PhyloCode2b.pdf

Hidden assumptions

- $E+S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_p} E+P$; Rapid equilibrium

  Henri-Michaelis-Menten: $$v = \frac{E \cdot k_p \cdot [S]}{(K_m + [S])}; K_m = \frac{k_{-1}}{k_1}$$

- $E+S \xrightarrow{k_1} ES \xrightarrow{k_p} E+P$; Total duration equal sum of duration

  Van Slyke-Cullen: $$v = \frac{E \cdot k_p \cdot [S]}{(K_m + [S])}; K_m = \frac{k_p}{k_1}$$

- $E+S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_p} E+P$; Quasi-steady state

  Briggs-Haldane: $$v = \frac{E \cdot k_p \cdot [S]}{(K_m + [S])}; K_m = \frac{(k_{-1} + k_p)}{k_1}$$

Hidden assumptions

```
<reaction>
   <listOfReactants>
     <speciesReference species="S" />
   </listOfReactants>
   <listOfProducts>
     <speciesReference species="P" />
   </listOfProducts>
   <listOfModifiers>
     <speciesReference species="E" />
   </listOfModifiers>
   <kineticLaw>
     <listOfParameters>
       <parameter id="Km"/>
       <parameter id="kp"/>
     </listOfParameters>
     <math xmlns="http://www.w3.org/1998/Math/MathML">
       <apply>
         <divide/><apply>
                    <times/><ci>E</ci>
                            <ci>kp</ci>
                            <ci>S</ci>
                  </apply>
                  <apply>
                    <plus/><ci>Km</ci>
                           <ci>S</ci>
                  </apply>
       </apply>
     </math>
   </kineticLaw>
 </reaction>
```

$E+S \rightarrow E+P$

Import in a discrete simulator

$$E+S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_p} E+P \; ; \; k_1 = k_{-1}/K_m$$

$$E+S \xrightarrow{k_1} ES \xrightarrow{k_p} E+P \; ; \; k_1 = k_p/K_m$$

$$E+S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_p} E+P \; ; \; k_1 = (k_{-1}+k_p)/K_m$$

The Systems Biology Ontology

SBO

http://www.ebi.ac.uk/compneur-srv/sbo/

Classifications Vs. Ontologies

- Each term is associated to a perennial identifier. Once created a term is never destroyed. It can be merged with other, or made obsolete, but it still exists.
- An ontology is an evolving structure: It can cope with an increase or refinement of knowledge. No need to reconstruct everything as with the taxonomies.
- An ontology is a Direct Acyclic Graph, and not a hierarchy. A term can possess more than one parent.
- Ontologies are stored in standard machine-readable formats. They can be subjected to automatic treatments.

Systems Biology Ontology vocabularies

- A taxonomy of the roles of reaction participants, including the following terms: “substrate”, “catalyst” etc.

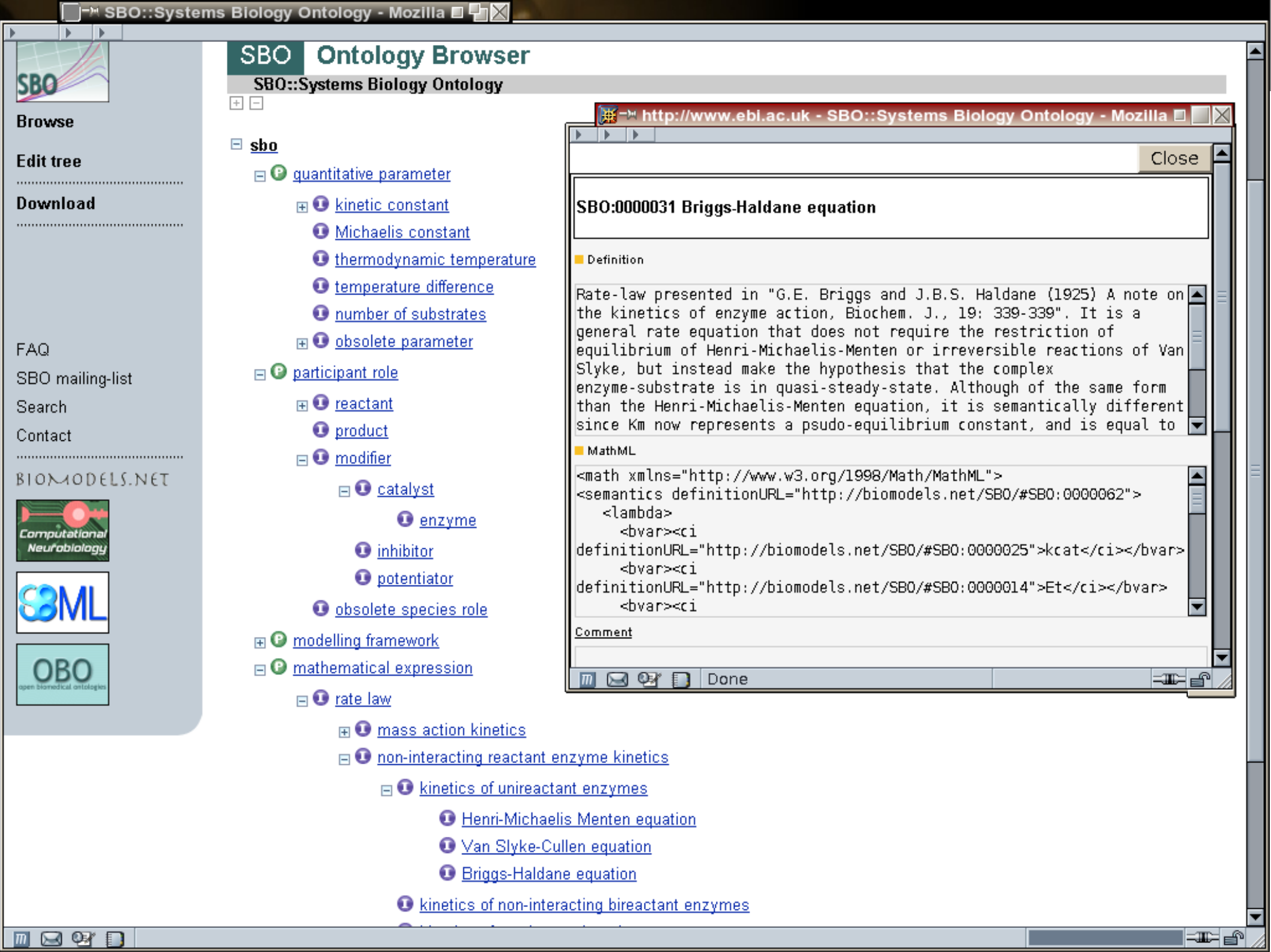
- A CV for parameter roles in quantitative models. This CV includes terms like “Michaelis constant” , “forward unimolecular rate constant”etc.

- A classification of rate laws. This CV is a taxonomy of kinetic rate equations. Examples of terms in this CV are “mass action kinetics”, “Henri-Michaelis-Menten equation” etc. Each term contains a precise mathematical expression stored as a MathML lambda function. The variables refer to the CVs described above.

- A list of modelling framework to precise how to interpret the rate-law. E.g. “continuous modelling”, “discrete modelling” etc.

SBO term

id	SBO:\d{7}	minOccurs=1	maxOccurs=1
name	unicode string	minOccurs=1	maxOccurs=1
def	unicode string	minOccurs=0	maxOccurs=1
is_a	SBO:\d{7}	minOccurs=0	minOccurs=n
part_of	SBO:\d{7}	minOccurs=0	maxOccurs=1
synonyms	unicode string	minOccurs=0	minOccurs=n
mathml	MathML lambda function	minOccurs=0	maxOccurs=1


SBO::Systems Biology Ontology - Mozilla
SBO Ontology Browser
SBO::Systems Biology Ontology
Browse
Edit tree
Download
FAQ
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Search
Contact
BIOMODELS.NET
Computational Neurobiology
SBML
OBO
sbo
quantitative parameter
kinetic constant
Michaelis constant
thermodynamic temperature
temperature difference
number of substrates
obsolete parameter
participant role
reactant
product
modifier
catalyst
enzyme
inhibitor
potentiator
obsolete species role
modelling framework
mathematical expression
rate law
mass action kinetics
non-interacting reactant enzyme kinetics
kinetics of unireactant enzymes
Henri-Michaelis Menten equation
Van Slyke-Cullen equation
Briggs-Haldane equation
kinetics of non-interacting bireactant enzymes
http://www.ebi.ac.uk - SBO::Systems Biology Ontology - Mozilla
Close
SBO:0000031 Briggs-Haldane equation
Definition
Rate-law presented in "G.E. Briggs and J.B.S. Haldane (1925) A note on the kinetics of enzyme action, Biochem. J., 19: 339-339". It is a general rate equation that does not require the restriction of equilibrium of Henri-Michaelis-Menten or irreversible reactions of Van Slyke, but instead make the hypothesis that the complex enzyme-substrate is in quasi-steady-state. Although of the same form than the Henri-Michaelis-Menten equation, it is semantically different since Km now represents a psudo-equilibrium constant, and is equal to
MathML
<math xmlns="http://www.w3.org/1998/Math/MathML">
<semantics definitionURL="http://biomodels.net/SBO/#SBO:0000062">
<lambda>
<bvar><ci definitionURL="http://biomodels.net/SBO/#SBO:0000025">kcat</ci></bvar>
<bvar><ci definitionURL="http://biomodels.net/SBO/#SBO:0000014">Et</ci></bvar>
<bvar><ci
Comment
Done

Complete description of a rate-law term

```
[Term]
id: SBO:0000031
name: Briggs-Haldane equation
def: "Rate-law presented in "G.E. Briggs and J.B.S. Haldane (1925) A note on the kinetics
of enzyme action, Biochem. J., 19: 339-339". It is a general rate equation that does not
require the restriction of equilibrium of Henri-Michaelis-Menten or irreversible reactions
of Van Slyke, but instead make the hypothesis that the complex enzyme-substrate is in
quasi-steady-state. Although of the same form than the Henri-Michaelis-Menten equation, it
is semantically different since Km now represents a psudo-equilibrium constant, and is
equal to the ratio between the rate of consumption of the complex (sum of dissociation of
substrate and generation of product) and the association rate of the enzyme and the
substrate.
is_a: SBO:0000011 ; kinetics of unireactant enzymes
MathML: <math xmlns="http://www.w3.org/1998/Math/MathML">
    <semantics definitionURL="http://biomodels.net/SBO/#SBO:0000062">
      <lambda>
      <bvar><ci definitionURL="http://www.biomodels.net/SBO/#SBO:0000015">S</ci></bvar>
      <bvar><ci definitionURL="http://www.biomodels.net/SBO/#SBO:0000014">E</ci></bvar>
      <bvar><ci definitionURL="http://www.biomodels.net/SBO/#SBO:0000025">kp</ci></bvar>
      <bvar><ci definitionURL="http://www.biomodels.net/SBO/#SBO:0000008">Km</ci></bvar>
         <apply>
           <divide/>
           <apply>
             <times/><ci>E</ci><ci>kp</ci><ci>S</ci>
           </apply>
           <apply>
             <plus/><ci>Km</ci><ci>S</ci>
           </apply>
         </apply>
       </lambda>
     </semantics>
   </math>
```

New SBML attribute: sboTerm

- syntax: <elementX sboTerm=”SBO:ddddddd” >
- present in:
  - model
  - initialAssignment (new element of L2V2)
  - rule
  - constraint (new element of L2V2)
  - reaction
  - speciesReference and modifierSpeciesReference
  - kineticLaw
  - parameter

Revealed assumptions

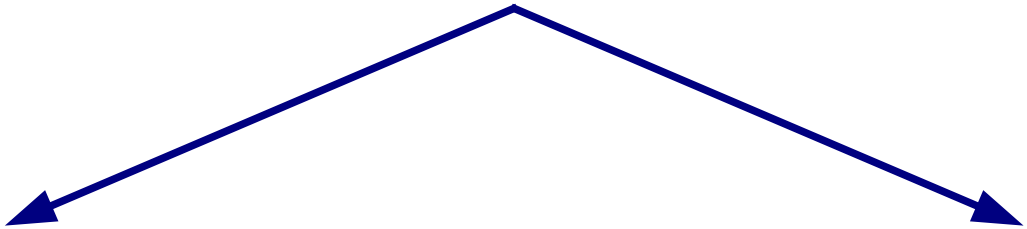
```
<reaction>
   <listOfReactants>
     <speciesReference species="S" />
   </listOfReactants>
   <listOfProducts>
     <speciesReference species="P" />
   </listOfProducts>
   <listOfModifiers>
     <speciesReference species="E" />
   </listOfModifiers>
   <kineticLaw sboTerm="SBO:0000031">
     <listOfParameters>
       <parameter id="Km"/>
       <parameter id="kp"/>
     </listOfParameters>
     <math xmlns="http://www.w3.org/1998/Math/MathML">
       <apply>
         <divide/><apply>
                    <times/><ci>E</ci>
                            <ci>kp</ci>
                            <ci>S</ci>
                  </apply>
                  <apply>
                    <plus/><ci>Km</ci>
                           <ci>S</ci>
                  </apply>
       </apply>
     </math>
   </kineticLaw>
 </reaction>
```

Revealed assumptions

```
<reaction sboTerm="SBO:0000062">
   <listOfReactants>
     <speciesReference species="S" sboTerm="SBO:0000015"/>
   </listOfReactants>
   <listOfProducts>
     <speciesReference species="P" sboTerm="SBO:0000011"/>
   </listOfProducts>
   <listOfModifiers>
     <speciesReference species="E" sboTerm="SBO:0000014"/>
   </listOfModifiers>
   <kineticLaw sboTerm="SBO:0000031">
     <listOfParameters>
       <parameter id="Km" sboTerm="SBO:0000008"/>
       <parameter id="kp" sboTerm="SBO:0000025"/>
     </listOfParameters>
     <math xmlns="http://www.w3.org/1998/Math/MathML">
       <apply>
         <divide/><apply>
                    <times/><ci>E</ci>
                            <ci>kp</ci>
                            <ci>S</ci>
                  </apply>
                  <apply>
                    <plus/><ci>Km</ci>
                           <ci>S</ci>
                  </apply>
       </apply>
     </math>
   </kineticLaw>
 </reaction>
```

Automatic conversion

```
<reaction sboTerm="SBO:0000062">
  <listOfReactants>
    <speciesReference species="A" sboTerm="SBO:0000015"/>
  </listOfReactants>
  <listOfProducts>
    <speciesReference species="B" sboTerm="SBO:0000011"/>
  </listOfProducts>
  <listOfModifiers>
    <speciesReference species="C" sboTerm="SBO:0000014"/>
  </listOfModifiers>
  <kineticLaw sboTerm="SBO:0000031">
    <listOfParameters>
      <parameter id="U" sboTerm="SBO:0000008"/>
      <parameter id="V" sboTerm="SBO:0000025"/>
    </listOfParameters>
  </kineticLaw>
</reaction>
```



continuous simulator

$$v = \frac{C \cdot V \cdot [A]}{(U + [A])}$$

discrete simulator

$$v1 = \frac{(k_{-1} + V)}{U} \cdot [A] \cdot [C]$$

$$v2 = k_{-1} \cdot [D]$$

$$v3 = V \cdot [D]$$

OBO Ontology Browser

Browse the tree by clicking on the category names; click on an ontology name to view more information on it.

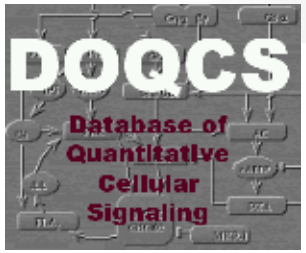
- **anatomy**
- animal natural history and life history
- **chemical**
  - chemical entities of biological interest
  - physico-chemical methods and properties
  - physico-chemical process
  - systems biology
- **development**
- **ethology**
- evidence codes
- **experimental conditions**
  - biological imaging methods
  - microarray experimental conditions
  - physico-chemical methods and properties
- **genomic and proteomic**
  - **gene product**
  - sequence types and features
- OBO relationship types
- **phenotype**
- **taxonomic classification**
- **vocabularies**

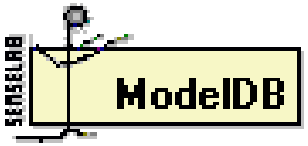
Primary data

This list is incomplete and biased! Use it as a starting point

- Signalling pathways and metabolic networks
  - KEGG: http://www.genome.jp/kegg/
  - Reactome: http://www.reactome.org/
  - BioCyc: http://biocyc.org/
- Functional parameters
  - BRENDA: http://www.brenda.uni-koeln.de/
  - SABIO-RK: http://sabio.villa-bosch.de/SABIORK/
- Morphology
  - Cell-Centered Database: http://ccdb.ucsd.edu/
  - Synapse Web: http://synapses.mcg.edu/
- Electrophysiology
  - Neurodatabase.org: http://neurodatabase.org/

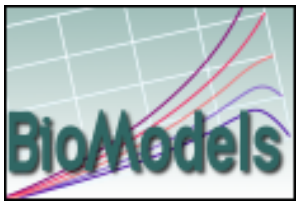
Models repositories for modelling neurons

- 

[GENESIS][curation][search]
- 

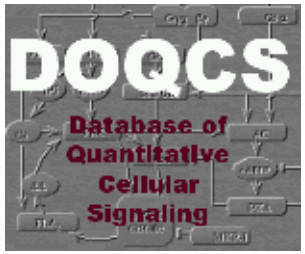
of SenseLab [NEURON, GENESIS ...][search]
-

models repository [CellML][curation...][search]
- JWS online [SBML, Pysces][curation]
-

Developer Network [E-Cell, SBML]
- 

BioModels Database [CellML, SBML][curation...][search]

Database of Quantitative Cellular Signalling



- Main page: http://doqcs.ncbs.res.in/
- Location: National Center for Biological Sciences (Bangalore, India)
- Team: Upinder Bhalla

DOQCS
Database of Quantitative Cellular Signaling

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Enter a Search String

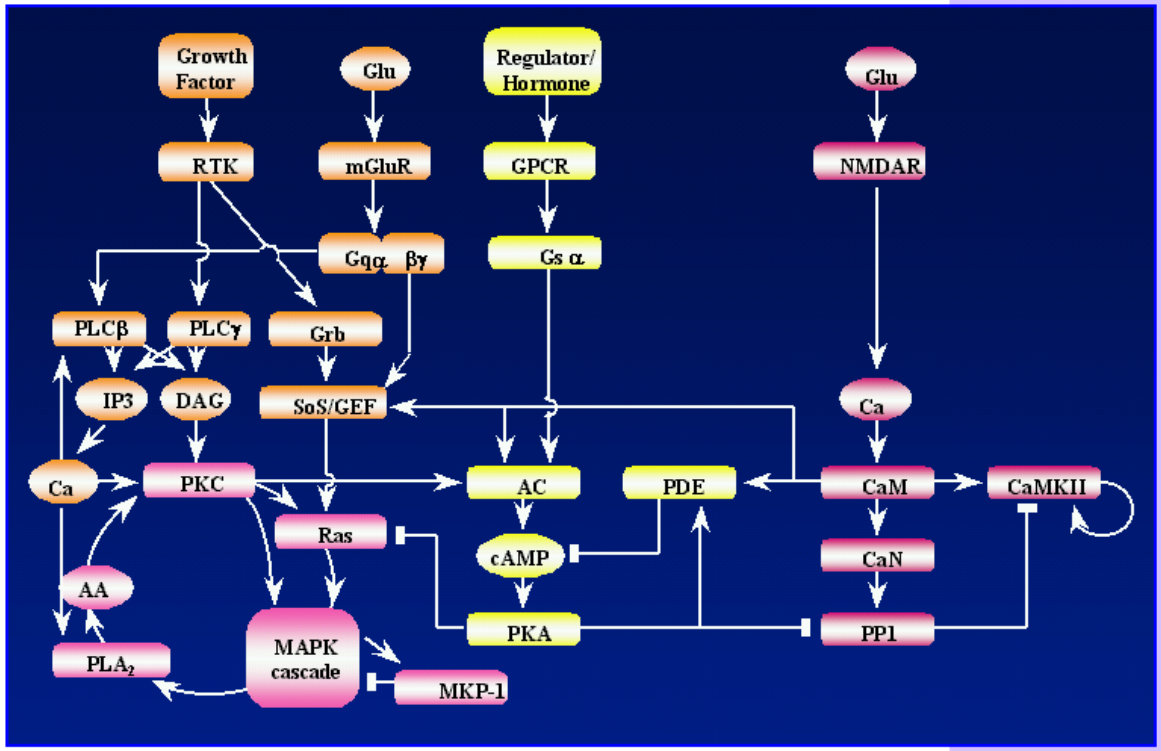
Special character and *space* not allowed in the query term. Search string should be at least 2 characters long.

Search in: ALL | Search for | Match: Anything | By: Name | submit

The Database of Quantitative Cellular Signaling is a repository of models of signaling pathways. It includes reaction schemes, concentrations, rate constants, as well as annotations on the models. The database provides a range of search, navigation, and comparison functions.

Quick Pathway Navigation

General cellular signaling



Click on the pathway block to view pathway parameters.

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DOQCS
Database of Quantitative Cellular Signaling

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Search in: ALL | Search for | Match: Anything | By: Name | submit

Result: 1 - 12 of 12 rows are displayed

Pathway List for mapk

Default ordering is done according to Pathway Name.Table header can be used for changing the default ordering.

indicates that ordering is done according to ascending or descending order.

Entries are color tagged depending on Network or Pathway

	Pathway Name / Pathway No.	Accession Name / Accession No.	Accession Type	Related Pathway	Pathway statistics	mapk statistics	Source / Entry Date
1	MAPK Pathway No. 6	fig2_egfr Accession No. 1	Network	24, 35, 56, 61, 75, 139, 142, 182, 193, 211, 230	Molecule = 9 Enzyme = 4 Reaction = 0	Molecule = 1 Enzyme = 0 Reaction = 0	Bhalla US and Iyengar R. Science (1999) 283(5400):381-7. (peer-reviewed publication)/ 2001-11-07
	This network was used to generate figure 2 in Bhalla US and Iyengar R. Science (1999) 283(5400):381-7. It consists of the MAPK cascade in a feedback loop with PKC, and receives input from the EGFR in the synapse. Demonstration script files for generating the figures in the paper, including figure 2, are available here.						
2	MAPK Pathway No. 24	fig4_synapse Accession No. 3	Network	6, 35, 56, 61, 75, 139, 142, 182, 193, 211, 230	Molecule = 9 Enzyme = 4 Reaction = 0	Molecule = 1 Enzyme = 0 Reaction = 0	Bhalla US and Iyengar R. Science (1999) 283(5400):381-7. (peer-reviewed publication)/ 2001-11-07
	This is the composite model of 4 kinases: PKC, MAPK, PKA and CaMKII and numerous regulatory pathways involved in synaptic signaling. From Bhalla US and Iyengar R. Science (1999) 283(5400):381-7.This model comes from figure 4 of that paper. Demonstration script files for generating the figures in the paper, including figure 4, are available here.						
3	MAPK Pathway No. 35	• mkp1_feedback_effects Accession No. 4	Network	6, 24, 56, 61, 75, 139, 142, 182, 193, 211, 230	Molecule = 16 Enzyme = 9 Reaction = 8	Molecule = 1 Enzyme = 0 Reaction = 0	Bhalla US et al. Science (2002) 297(5583):1018-23. (peer-reviewed publication)/ 2001-11-07
	The Mitogen Activated Protein Kinase (MAPK) cascade model here includes both the MAPK cascade and its regulation by two forms of MKP. MKP-1 is induced upon MAPK activation, whereas MKP-2 is treated as a steady level of protein. The phosphatase Protein phosphatase 2 A (PP2A) is also included in this model to balance the activity of the kinases.						
4	MAPK Pathway No. 56	3d_fold_model Accession No. 8	Network	6, 24, 35, 61, 75, 139, 142, 182, 193, 211, 230	Molecule = 9 Enzyme = 4 Reaction = 0	Molecule = 1 Enzyme = 0 Reaction = 0	Bhalla US and Iyengar R. Science (1999) 283(5400):381-7. (peer-reviewed publication)/ 2001-11-08
	This model is an annotated version of the synaptic signaling network. The primary reference is Bhalla US and Iyengar R. Science (1999) 283(5400):381-7 but several of the model pathways have been updated Bhalla US, Ram PT, Iyengar R. Science. 2002 Aug 9;297(5583):1018-23.						
5	MAPK Pathway No. 61	• MAPK_MKP1_oscillation Accession No. 9	Network	6, 24, 35, 56, 75, 139, 142, 182, 193, 211, 230	Molecule = 15 Enzyme = 9 Reaction = 7	Molecule = 1 Enzyme = 0 Reaction = 0	Bhalla US, Iyengar R. Chaos (2001) 11(1):221-226. (peer-reviewed publication)/ 2001-11-08
	This model relates to figure 5 in Bhalla US, Iyengar R. Chaos (2001) 11(1):221-226. It includes the model used for figures 2-4 and also has MKP-1 induction by MAPK activity in the synapse. PP2A is set to 0.16 uM and MKP synthesis is varied from 5x to 40 x basal to get a range of interesting behaviours.						
6	MAPK Pathway No. 75	• Synaptic_Network Accession No. 16	Network	6, 24, 35, 56, 61, 139, 142, 182, 193, 211, 230	Molecule = 9 Enzyme = 4 Reaction = 0	Molecule = 1 Enzyme = 0 Reaction = 0	Bhalla US and Iyengar R. Science (1999) 283(5400):381-7. (peer-reviewed publication)/ 2001-12-12
	The Mitogen Activated Protein Kinase (MAPK) cascade model here includes both the MAPK cascade and its regulation by MKP-1. MKP-1 is induced upon MAPK activation, whereas MKP-2 is treated as a steady level of protein. For the purposes of this version of the model, MKP-1 is kept at a fixed starting value. The phosphatase Protein phosphatase 2 A (PP2A) is also included in this model to balance the activity of the kinases.						
7	MAPK	MAPK_osc		6, 24, 35, 56, 61, 75,	Molecule = 15	Molecule = 1	Boris N. Kholodenko Eur J Biochem. (2000)

Quantitative Cellular Signaling

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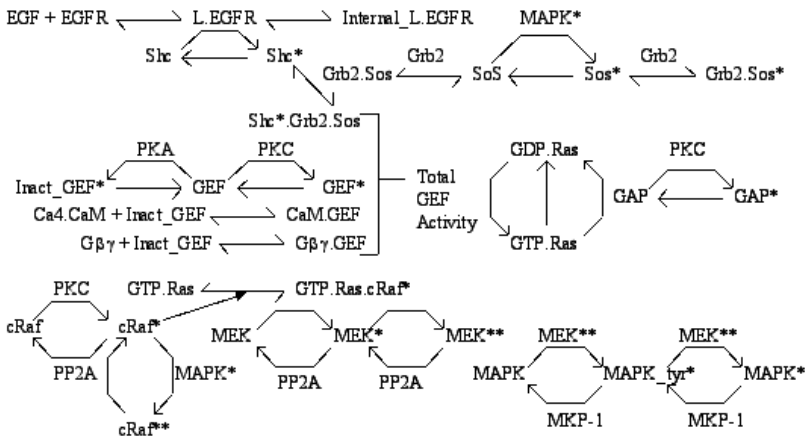
Accession Type:
Network

- EGFR_MAPK
  - Shared_Object_EGFR_MAPK
  - MAPK
    - Molecule
    - Enzyme
  - Ras
  - EGFR
  - Sos

Parameters for MAPK (Pathway Number)

Pathway Layout



Pathway Basic Parameters

Pathway Name	MAPK
Pathway Entry Number	230
Accession Number	58
Accession Name	EGFR_MAPK
Species	Generic mammalian
Tissue	Neuronal
CellCompartment	Synapse
Related Pathways	6, 24, 35, 56, 61, 75, 139, 142, 182, 193, 211
Notes	Model of MAPK activation by EGFR in the synapse. Demonstration programs using this model are available here. Primary citation:Bhalla US. Biophys J. (2004) 87(2):745-53.

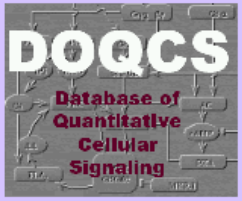
Statistics

Molecules	Enzyme sites	Reactions
9	4	0

Conversion format

This pathway is part of accession 58 and is completely specified in the file acc58.g.
There is no separate files for just this pathway.

Format	File
Native Format (GENESIS format)	acc58.g
GENESIS Format (Annotated version)	Anno_acc58.g
MATLAB format	acc58.m



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Accession Type:
Network

- EGFR_MAPK
  - Shared_Object_EGFR_MAPK
  - MAPK
    - Molecule
    - Enzyme
  - Ras
  - EGFR
  - Sos

Enter a Search String

Special character and *space* not allowed in the query term. Search string should be at least 2 characters long.

Search in: ALL | Search for | Match: Anything | By: Name | submit

Enzyme List for pathway *MAPK* (Pathway Number 230)

	Molecule Name/ Site Name	Km (uM)	kcat (s-1)	Ratio (k2/k3)	Enzyme Type	Substrate	Product
1	**Enzyme Activity:** MAPKKthr **Enzyme Molecule:** MAPKK*	0.0462963	0.15	4	explicit E-S complex	MAPK-tyr	MAPK*
	Rate consts same as for MAPKKtyr.						
2	**Enzyme Activity:** MAPKKtyr **Enzyme Molecule:** MAPKK*	0.0462963	0.15	4	explicit E-S complex	MAPK	MAPK-tyr
	The actual MAPKK is 2 forms from Seger et al JBC 267:20 14373(1992) Vmax = 150nmol/min/mg From Haystead et al FEBS 306(1):17-22 we get Km=46.6nM for at least one of the phosphs. Putting these together: k3=0.15/sec, scale to get k2=0.6. k1=0.75/46.6nM=2.7e-5						
3	**Enzyme Activity:** Raf-GTP-Ras*.1 **Enzyme Molecule:** Raf-GTP-Ras*	0.159091	0.105	4	explicit E-S complex	MAPKK	MAPKK-ser
	Kinetics are the same as for the craf-1* activity, ie., k1=1.1e-6, k2=.42, k3 =0.105 These are based on Force et al PNAS USA 91 1270-1274 1994. These parms cannot reach the observed 4X stim of MAPK. So lets increase the affinity, ie, raise k1 10X to 1.1e-5 Lets take it back down to where it was. Back up to 5X: 5.5e-6						
4	**Enzyme Activity:** Raf-GTP-Ras*.2 **Enzyme Molecule:** Raf-GTP-Ras*	0.159091	0.105	4	explicit E-S complex	MAPKK-ser	MAPKK*
	Same kinetics as other c-raf activated forms. See Force et al PNAS 91 1270-1274 1994. k1 = 1.1e-6, k2 = .42, k3 = 1.05 raise k1 to 5.5e-6						

Pathway Details | Molecule List | Enzyme List | Reaction List

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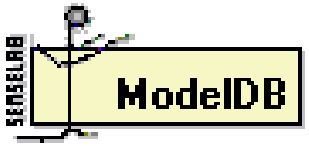
SenseLab's ModelDB



- Main page: http://senselab.med.yale.edu/senselab/modeldb/
- Location: Yale University School of Medicine (New Haven, USA)
- Team: Gordon Sheperd

ModelDB - Mozilla
European Bioinformatics Instit... | ModelDB

SenseLab ModelDB NeuronDB

ModelDB provides an accessible location for storing and efficiently retrieving computational neuroscience models. ModelDB is tightly coupled with NeuronDB. Models can be coded in any language for any environment, though ModelDB has been initially constructed for use with NEURON and GENESIS. Model code can be viewed before downloading and browsers can be set to auto-launch the models. **Help**

Submit a new model entry

Find models by	Find models for	Find models of
• model name	• Neuron type	• Networks
• first author	• Current	• Neurons
• each author	• Receptor	• Synapses
	• Transmitters	• Neuromuscular Junctions
	• Topic	• Axons
	• Simulators	• Ion Channels

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Find models containing the following [ ] Search

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Login to access your models
Related Resources

Total site hits since January 1, 2005: **637,222**

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SenseLab ModelDB NeuronDB

Models that contain the Model Type : *Neuron or other electrically excitable cell*

(An electrically excitable cell such as a Neuron, Heart, Muscle, Sensory, or Endocrine cell.)

Models	Description
A Model for Interaural Time Difference Sensitivity in the Medial Superior Olive (Zhou et al 2005)	This model simulates responses of neurons to interaural time difference (ITD) in the medial superior olive (MSO) of the mammalian brainstem. The model has a bipolar cell structure and incorporates two anatomic observations in the MSO: (1) the axon arises from the dendrite that receives ipsilateral inputs and (2) inhibitory synapses are located primarily on the soma in adult animals. Fine adjustment of the best ITD is achieved by the interplay of somatic sodium currents and synaptic inhibitory currents. The model suggests a mechanism for dynamically "fine-tuning" the ITD sensitivity of MSO cells by the opponency between depolarizing sodium currents and hyperpolarizing inhibitory currents.
Active dendrites and spike propagation in a hippocampal interneuron (Saraga et al 2003)	We create multi-compartment models of an Oriens-Lacunosum/Moleculare (O-LM) hippocampal interneuron using passive properties, channel kinetics, densities and distributions specific to this cell type, and explore its signaling characteristics. We find that spike initiation depends on both location and amount of input, as well as the intrinsic properties of the interneuron. Distal synaptic input always produces strong back-propagating spikes whereas proximal input could produce both forward and back-propagating spikes depending on the input strength. Please see paper for more details. Fernanda.Saraga@utoronto.ca
Activity dependent regulation of pacemaker channels by cAMP (Wang et al 2002)	Demonstration of the physiological consequences of the cyclic allosteric gating scheme for Ih mediated by HCN2 in thalamocortical relay cells.
Artificial neuron model (Izhikevich 2003)	A model is presented that reproduces spiking and bursting behavior of known types of cortical neurons. The model combines the biologically plausibility of Hodgkin–Huxley-type dynamics and the computational efficiency of integrate-and-fire neurons. Using this model, one can simulate tens of thousands of spiking cortical neurons in real time (1 ms resolution) using a desktop PC.
Auditory nerve model with linear tuning (Heinz et al 2001)	A method for calculating psychophysical performance limits based on stochastic neural responses is introduced and compared to previous analytical methods for evaluating auditory discrimination of tone frequency and level. The method uses signal detection theory and a computational model for a population of auditory nerve (AN) fiber responses. Please see paper for details.
Breakdown of accmmodation in nerve: a possible role for INAp (Hennings et al 2005)	The present modeling study suggests that persistent, low-threshold, rapidly activating sodium currents have a key role in breakdown of accommodation, and that breakdown of accommodation can be used as a tool for studying persistent sodium current under normal and pathological conditions. See paper for more and details.
Bursting activity of neuron R15 in Aplysia (Canavier et al 1991, Butera et al 1995)	An equivalent circuit model of the R15 bursting neuron in Aplysia has been combined with a fluid compartment model, resulting in a model that incorporates descriptions of most of the membrane ion channels that are known to exist in the somata of R15, as well as providing a Ca2+ balance on the cell. ... (from the second paper) we have implemented proposed mechanisms for the modulation of two ionic currents (IR and ISI) that play key roles in regulating its spontaneous electrical activity. The model was sufficient to simulate a wide range of endogenous activity in the presence of various concentrations of 5-HT or DA. See papers for more and details.
CA1 Pyramidal Neuron: Synaptic Scaling (London, Segev 2001)	London and Segev (2001) discuss location dependent and location independent synaptic scaling in a model CA1 neuron with passive dendrites. The freely available text is followed by a critique by Maggee and Cook who comment that the London and Segev model is accurate and informative and however needs to be augmented by active channels in dendrites. Note: the zip files for this model are stored at the nature neuroscience website - Click above Supplementary Source Code in the readme.html in the model files
CA1 Pyramidal Neuron: slow Na+ inactivation (Migliore 1996)	Model files from the paper: M. Migliore, Modeling the attenuation and failure of action potentials in the dendrites of hippocampal neurons, Biophys. J. 71:2394-403 (1996). Please see the below readme file for installation and use instructions. Contact michele.migliore@pa.ibf.cnr.it if you have any questions about the implementation of the model.
CA1 pyramidal neuron (Migliore et al 1999)	Hippocampal CA1 pyramidal neuron model from the paper M.Migliore, D.A Hoffman, J.C. Magee and D. Johnston (1999) Role of an A-type K+ conductance in the back-propagation of action potentials in the dendrites of hippocampal pyramidal neurons, J. Comput. Neurosci. 7, 5-15. Instructions are provided in the below README file.Contact michele.migliore@pa.ibf.cnr.it if you have any questions about the implementation of the model.
CA1 pyramidal neuron:	We developed a CA1 pyramidal cell model calibrated with a broad spectrum of in vitro data. Using simultaneous dendritic and somatic recordings, and

ModelDB: Dopaminergic cell bursting model (Kuznetsov et al 2006) - Mozilla
European Bioinformatics Instit... | ModelDB: Dopaminergic cell ...

SenseLab ModelDB

Dopaminergic cell bursting model (Kuznetsov et al 2006)

Dopaminergic neurons of the midbrain fire spontaneously at rates <10/s and ordinarily will not exceed this range even when driven with somatic current injection. During spontaneous bursting behaving animals, and bursts generated by dendritic application of N-methyl-D-aspartate (NMDA) agonists, transient firing attains rates well above this range. We suggest a way such highfrequ We have extended the coupled oscillator model of the dopaminergic neuron, which represents the soma and dendrites as electrically coupled compartments with different natural spiking frequen (voltage-dependent) synaptic conductance. Both soma and dendrites contain a simplified version of the calcium-potassium mechanism known to be the mechanism for slow spontaneous oscillat of its voltage dependence, NMDA receptor activation acts to amplify the effect on the soma of the high-frequency oscillation of the dendrites, which is normally too weak to exert a large influenc
Reference: Kuznetsov AS, Kopell NJ, Wilson CJ (2005) Transient high-frequency firing in a coupled-oscillator model of the mesencephalic dopaminergic neuron. *J Neurophysiol* : - [PubMed]

Citations Citation Browser

Model Information (*Click on a link to find other models with that property*)

Model Type:	Neuron or other electrically excitable cell;
Cell Type(s):	
Channel(s):	I K,Ca; I Calcium;
Receptor(s):	AMPA; NMDA;
Transmitter(s):	
Simulation Environment:	XPP;
Model Concept(s):	Activity Patterns; Bursting; Oscillations; Action Potentials;
Implementer(s):	

Search NeuronDB for information about: AMPA; NMDA; I Calcium; I K,Ca;

Model files Download zip file | Download the below displayed file | Help downloading and running models

- \
  - kuzkopwil2006
    - readme.txt
    - screenshot.jpg
    - KuzKopWil2006.ode

```
#this is the two compartment model with a brief NMDA activation

alphan(V)=-0.0032*tk*(V+5.)/(exp(-(V+5.)/10.) - 1.)
betan(V)=0.05*tk*exp(-((V+10.)/16.))

alpham(V)=-0.32*(V+31.)/(exp(-(V+31.)/4.) - 1.)
betam(V)=0.28*(V+4.)/(exp((V+4.)/5.) - 1.)
minf(v)=alpham(v)/(alpham(v)+betam(v))
alphah(V)=0.2*th*exp(-((V+47.)/18.))
betah(V)=25.*th/(1.+(exp(-(V+24.)/5.)))

gNa1(v,h)=gbarNa1*(minf(v)**3)*h
gK2(n)=gbarK2*(n**4)
gK1(x)=gbarK1/(1. + exp(-(x-vHk)/vSk))


v1'=i1+gCa1(v1)*(ECa-v1)+(gKCa1(u1)+gk1(v1)+gK2(n1))*(EK-v1)+gL1*(EL1-v1)+gNa1(v1,h1)*(ENa-v1)+nd*gc*(v2-v1)*r1*r2*r2/(r1*r1+r2*r
u1'= 2.*buf1*(gCa1(v1)*(ECa - v1)/H - u1/tC1)/r1
n1'= alphan(v1)*(1.-n1)-betan(v1)*n1
h1'= alphah(v1)*(1.-h1)-betah(v1)*h1

v2'=gCa1(v2)*(ECa-v2)+(gKCa1(u2)+gK1(v2)+gK2(n2))*(EK-v2)+gL1*(EL1-v2)+gNa1(v2,h2)*(ENa-v2)+gc*(v1-v2)*r1*r1*r2/(r1*r1+r2*r2)+gnm
```

Done

Requirements for a unified model resource

- Neither focussed on a particular biological substrate or process, nor specialised on a given modelling approach
- Real “searchable“ database rather than mere repository
- Models thoroughly verified, structure and results, and annotated
- International collaboration rather than a one-group effort
- Long-term commitment and secure funding
- Freely available and reusable

BioModels Database: A Free, Centralized Database of Curated, Published, Quantitative Kinetic Models of Biochemical and Cellular Systems

Le Novère N., Bornstein B., Broicher A., Courtot M., Donizelli M., Dharuri H., Li L., Sauro H., Schilstra M., Shapiro B., Snoep J.L., Hucka M.

Nucleic Acids Research, (2006), 34: D689-D691

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

What is BioModels Database?

- Store and serve quantitative models of biomedical interest
- Only models described in the peer-reviewed scientific literature.
- Models are curated: computer software check the syntax, while human curators check the semantics.
- Models are simulated to check the reference correspondence
- Model components are annotated, to improve identification and retrieval.
- Models are accepted in several formats, and served in several others.
- Aims to be the “Swiss-Prot” of quantitative modelling.

Where are the models coming from

I) Repositories

- SBML repository
- JWS Online
- E-Cell Developer Network
- CellML repository

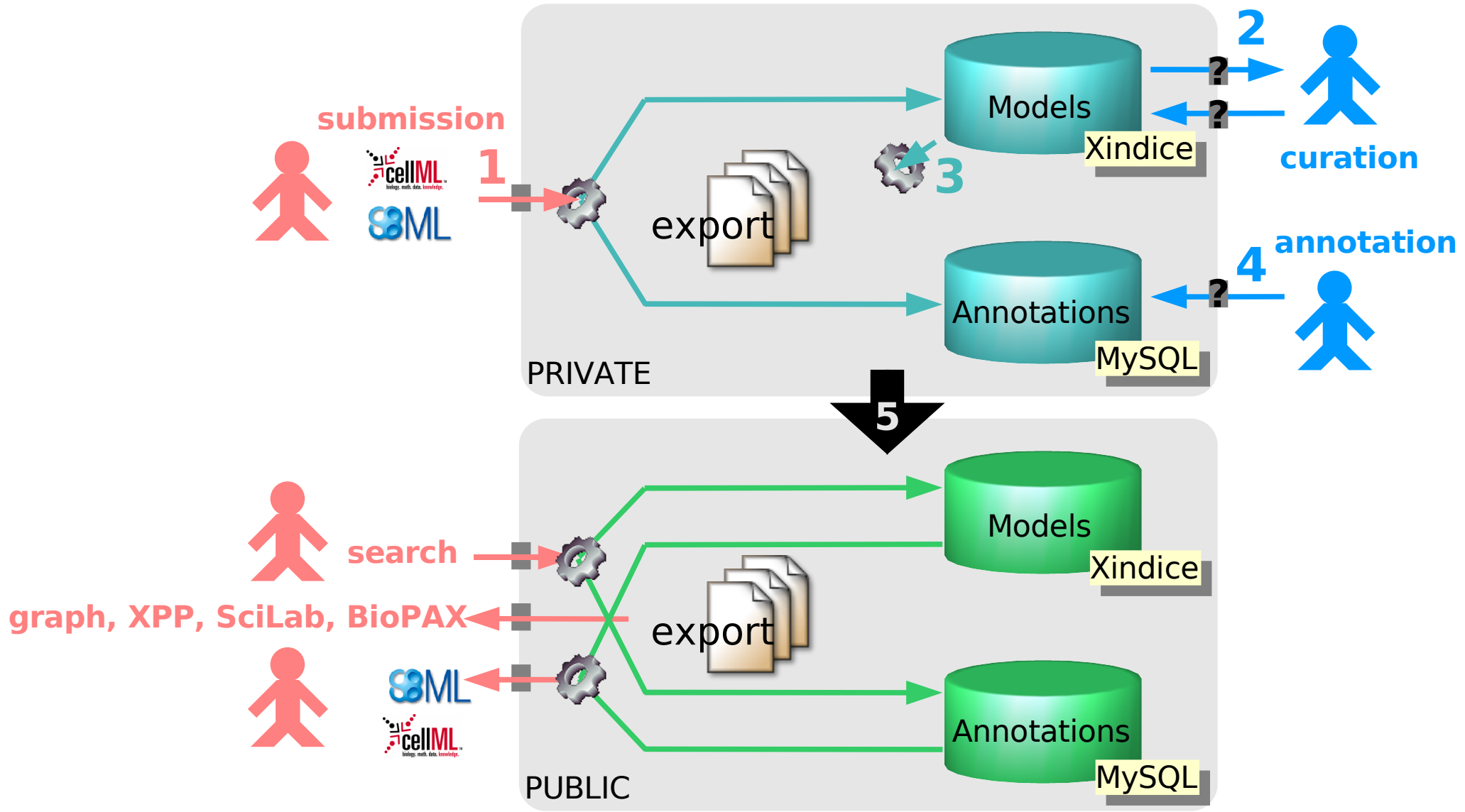
II) Individuals

- Members of the SBML community (developers+modellers)
- Authors (prior to grant application, before publication etc.)

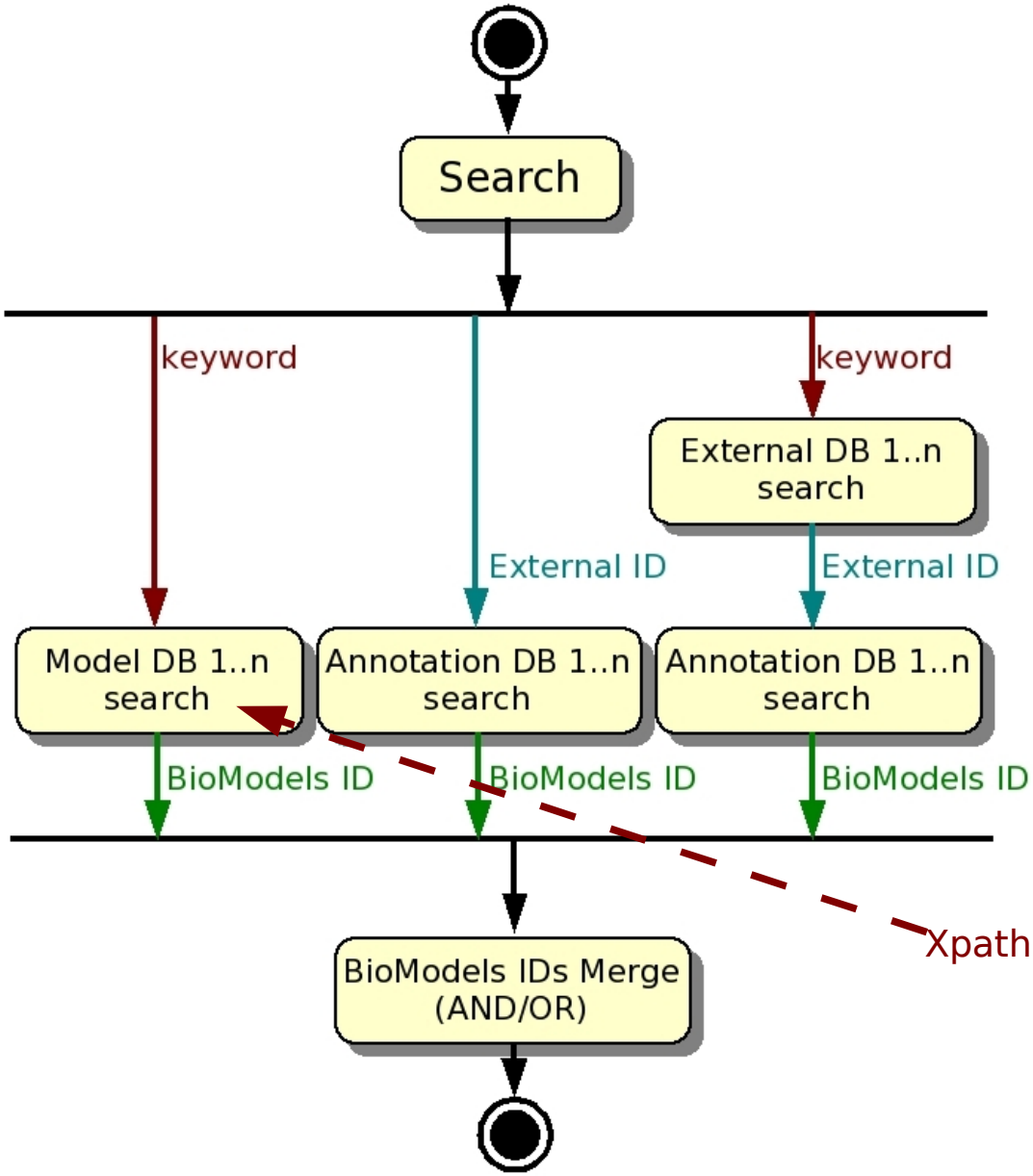
III) Supported by Nature Publishing Group. MSB advices deposition, and forward supplementary material

IV) BioModels DB curators encode new models from literature

Structure of BioModels Database



Search strategy



GO, UniProt Oracle database
ChEBI, PubMed WebServices

BioModels MySQL database

Xpath:
```
//sbml:*[contains(@id,'TEXT')]
| //sbml:*[contains(@name,'TEXT')]
| //xhtml:*[contains(text(),'TEXT')]
```

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BioModels Database

A Database of Annotated Published Models

BioModels Database is a data resource that allows biologists to store, search and retrieve published mathematical models of biological interests. Models present in BioModels Database are annotated and linked to relevant data resources, such as publications, databases of compounds and pathways, controlled vocabularies, etc.

[Browse] | [Search]

5th June 2006 - Fifth Release! [More] [Download All Models Under SBML L2 V1 Format]

06th January 2006 - publication of a paper describing BioModels Database [Nucleic Acids Res.]

06th December 2005 - publication of MIRIAM, a standard for model curation and annotation [Press Release][article in Nature Biotechnology]

Acknowledgements

BioModels Database is developed in collaboration by the teams of Nicolas Le Novère (EMBL-EBI, United-Kingdom), Michael Hucka (SBML Team, Caltech, USA), Herbert Sauro (Keck Graduate Institute, USA), Hiroaki Kitano (Systems Biology Institute, Japan) and Jacky Snoep (JWS Online, Stellenbosch University, ZA), as part of the BioModels.net initiative. BioModels Database development has benefitted from funds of the European Molecular Biology Laboratory (Le Novère team) the National Institute of General Medical Sciences (SBML team).

Developers: Mélanie Courtot, Arnaud Henry, Camille Laibe, Chen Li, Lu Li (alumni: Marco Donizelli)

Model curators and annotators: Harish Dharuri, Nicolas Le Novère, Lu Li and Bruce Shapiro.

Summer Internships

We are looking for summer interns to work on the curation of our BioModels Database. These internships are not part of a university training. Nevertheless, this is an opportunity for the postholders to gain experience in an international environment. A limited funding is provided to cover for living expenses.

Successful candidates have experience in working with GNU/Linux operating system, and have a good knowledge of the main data resources used in biology. Curation of BioModel Database requires solid bases of mathematics and a good knowledge of chemical kinetics. Candidates with a dual training in physics and computing would be ideal.

External contributors: Upinder Bhalla, Christoph Flamm, Ryan Gutenkunst, Adam Halasz, Ken Lau, Rainer Machné, Marc Poolman, Tomas Radivoyevitch, Birgit Schoeberl, Oleg Sokolsy, Molecular Systems Biology (models), Ben Bornstein, Sarah Keating, Joanne Matthews, Nicolas Rodriguez, Maria Schilstra (software), Samuel Bandara, Alexander Broicher, Les Grivell, Noriko Hiroi, Boris Kholodenko, Ursula Kummer, Adrian Lopez Garcia de Lomana, Yukiko Matsuoka , Robert Phair, Tjeerd Olde Scheper, Henning Schmidt, Paul Smolen (miscellaneous).

The BioModels Database makes heavy use of third-party free software such as libSBML, developed by Ben Bornstein and Sarah Keating, Jakarta Tomcat, Xindice, Xalan, Xerces and MySQL.

Transferring data from www.ebi.ac.uk...

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Search Models

Text Search

You can search BioModels Database for models using one or more of the following criteria:

- *BioModels ID* → Search BioModels Database for *exact* BioModels identifiers (for example *BIOMD0000000001* or *BIOMD0000000022*).
- *Person* → Search BioModels Database for model submitter and/or creator(s) names, or model reference publication author(s) names (for example *Nicolas Le Novère*, *Nicolas*, *Bruce Shapiro* or *Shapiro*, *Edelstein* or *Novak*).
- *SBML Elements* → Search BioModels Database for SBML elements by either name or *notes* content (for example *Edelstein* or *nicotinic*).
- *Resource* → Search BioModels Database for related information found in the models reference publication or third-party resources, by either publication/resource identifier or text (for example *9256450* or *cyclin* for publication, *GO:0007049* or *cell cycle* for Gene Ontology, *P04551* or *cell division* for UniProt).
- *Resource ID* → Search BioModels Database for annotations, by third-party resource identifiers (for example *IPR002394* for InterPro, *hsa04080* for KEGG Pathway, *68910* for Reactome).

A part from the *BioModels ID* -based search, for every other criteria the search operates on a *contains the entered string basis*, case-insensitive. That is, searching *Person* for *Shapi* or *shapi* will return the same results as searching for *Shapiro* or *shapiro*. In addition, since search strings are treated as words, do not enter regular expressions.

Multiple criteria can be combined with either *and* or *or*. If *and* is selected, only those models satisfying all the criteria will be returned. If instead *or* is selected, all the models satisfying at least one of the criteria will be returned.

BioModels ID:

Person:

SBML Elements:

Resource: Gene Ontology — MAPK

Resource:

Resource:

Publication
ChEBI
Gene Ontology
Taxonomy
UniProt

Resource ID:

Resource ID: BIND

Resource ID: BIND

Compose by: and or

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Search Models

The search returned **13** models.

New Search

Show 10 Only

BioModels ID	Name	Publication ID	Last Modified	
BIOMD0000000009	Huang1996_MAPK_ultrasens	8816754	2006-06-13T23:09:10	SBML L2 V1
BIOMD0000000010	Kholodenko2000_MAPK_feedback	10712587	2006-04-07T22:02:49	SBML L2 V1
BIOMD0000000011	Levchenko2000_MAPK_noScaffold	10823939	2006-01-31T10:04:06	SBML L2 V1
BIOMD0000000014	Levchenko2000_MAPK_Scaffold	10823939	2006-01-31T10:08:46	SBML L2 V1
BIOMD0000000026	Markevich2004_MAPK_orderedElementary	14744999	2006-04-02T18:50:28	SBML L2 V1
BIOMD0000000027	Markevich2004_MAPK_orderedMM	14744999	2006-01-31T10:12:00	SBML L2 V1
BIOMD0000000028	Markevich2004_MAPK_phosphoRandomElementary	14744999	2006-04-02T18:53:13	SBML L2 V1
BIOMD0000000029	Markevich2004_MAPK_phosphoRandomMM	14744999	2006-04-02T18:55:05	SBML L2 V1
BIOMD0000000030	Markevich2005_MAPK_AllRandomElementary	14744999	2006-04-02T18:57:56	SBML L2 V1
BIOMD0000000031	Markevich2004_MAPK_orderedMM2kinases	14744999	2006-04-02T18:58:15	SBML L2 V1
BIOMD0000000032	Kofahl2004_pheromone	15300679	2006-03-24T13:34:26	SBML L2 V1
BIOMD0000000033	Brown2004_NGF_EGF_signaling	14525003	2006-05-03T13:02:33	SBML L2 V1
BIOMD0000000049	Sasagawa2005_MAPK	15793571	2006-03-07T11:36:34	SBML L2 V1

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BIOMD0000000010 Kholodenko2000_MAPK_feedback

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Reference Publication

Publication ID: 10712587

Eur J Biochem 2000 Mar;267(6):1583-8.
Negative feedback and ultrasensitivity can bring about oscillations in the mitogen-activated protein kinase cascades.
Kholodenko BN.
Department of Pathology, Anatomy and Cell Biology, Thomas Jefferson University, Philadelphia, PA 19107, USA. Boris.Kholodenko@mail.tju.edu

Model

Submitter: Nicolas Le Novere

Submission Date: 2005-09-13T13:39:02

Last Modification Date: 2006-04-07T22:02:49

Creation Date: 2005-02-12T00:18:12

Creators: Herbert Sauro

bqbiol:is set #1
Gene Ontology MAPKKK cascade
Taxonomy Xenopus laevis

Compartments (1)

Species (8)

Rules (0)

Reactions (10)

Events (0)

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Publication ID: 10712587

Eur J Biochem 2000 Ma
Negative feedback and u
Kholodenko BN.
Department of Patholog

Submitter: Nicolas Le Novere

bqbiol:is set #1 **Gene Taxon**

Submission Date: 2005-09-13T13:39:02

Last Modification Date: 2006-04-07T22:02:49

Creation Date: 2005-02-12T00:18:12

Creators: Herbert Sauro

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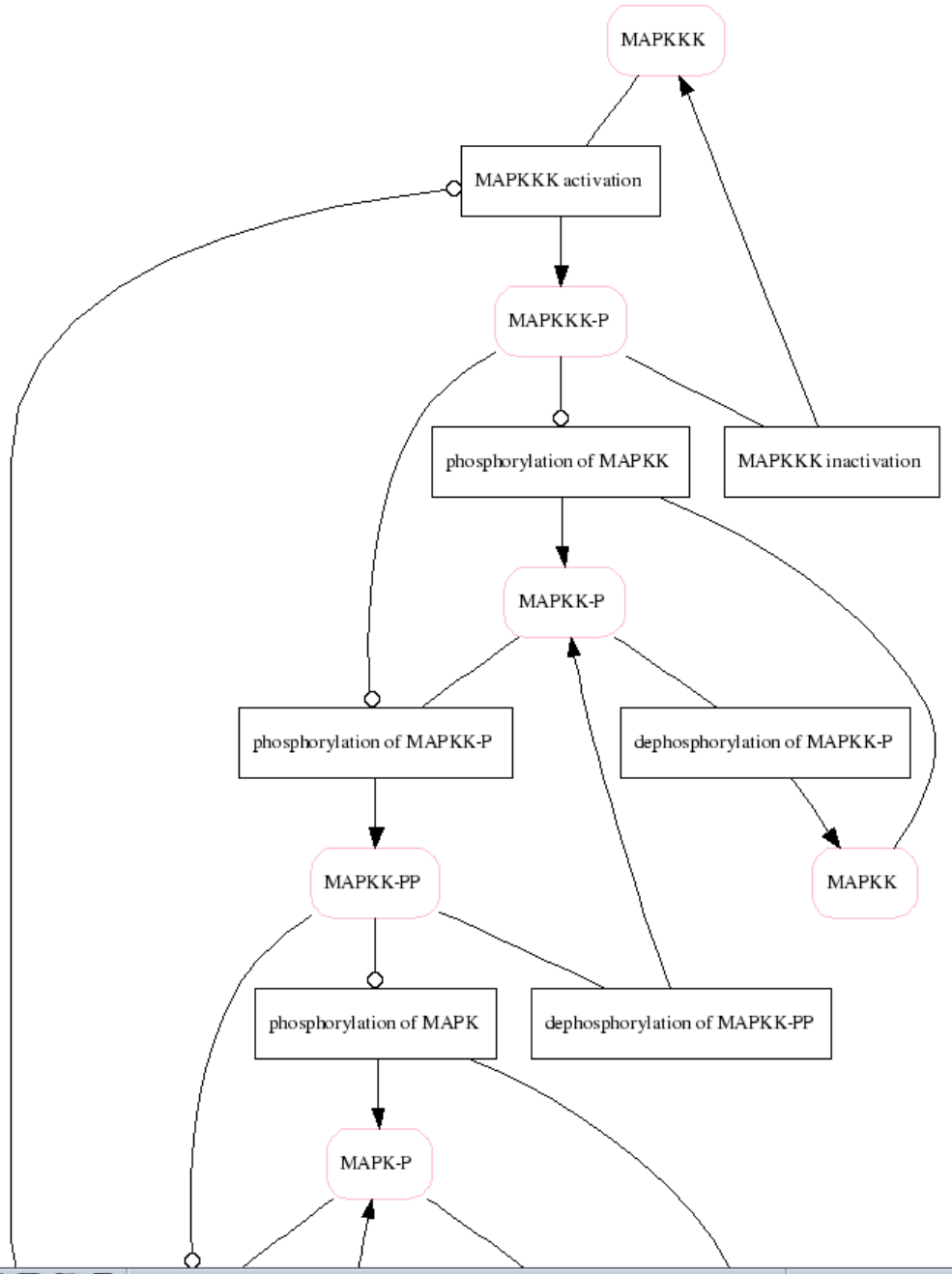

Last modification: Fri May 28 02:36:06 BST 2006

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Reactions (10)

MAPKKK activation
Reactants: MAPKKK
Products: MAPKKK-P
Modifiers: MAPK-PP
Referred to as: J0

bqbiol:is set #1 **Gene Ontology** activation of MAPKKK activity
Gene Ontology MAP kinase kinase kinase activity

MAPKKK inactivation
Reactants: MAPKKK-P
Products: MAPKKK
Modifiers:
Referred to as: J1

bqbiol:isVersionOf set #1 **EC code** 3.1.3.
Gene Ontolog

phosphorylation of MAPKK
Reactants: MAPKK
Products: MAPKK-P
Modifiers: MAPKKK-P
Referred to as: J2

bqbiol:is set #1 **Gene Ontolog**
bqbiol:isVersionOf set #1 **EC code** 2.7.1.
Gene Ontolog

phosphorylation of MAPKK-P
Reactants: MAPKK-P
Products: MAPKK-PP
Modifiers: MAPKKK-P
Referred to as: J3

bqbiol:is set #1 **Gene Ontolog**
Gene Ontolog
bqbiol:isVersionOf set #1 **EC code** 2.7.1.
Gene Ontolog

dephosphorylation of MAPKK-PP
Reactants: MAPKK-PP
Products: MAPKK-P
Modifiers:
Referred to as: J4

bqbiol:isVersionOf set #1 **EC code** 3.1.3.
Gene Ontolog

dephosphorylation of MAPKK-P
Reactants: MAPKK-P
Products: MAPKK
Modifiers:
Referred to as: J5

bqbiol:isVersionOf set #1 **EC code** 3.1.3.
Gene Ontolog

phosphorylation of MAPK
Reactants: MAPK
Products: MAPK-P
Modifiers: MAPKK-PP
Referred to as: J6

bqbiol:isVersionOf set #1 **EC code** 2.7.1.37
Gene Ontology protein amino acid phosphorylation
bqbiol:is set #1 **Gene Ontology** MAP kinase kinase activity

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Reaction:

MAPKKK activation

rate law:

uVol * V1 * MAPKKK / ((1 + pow(MAPK-PP / Ki, n)) * (K1 + MAPKKK))

Compartments	
Name	**Size**
uVol	1.0

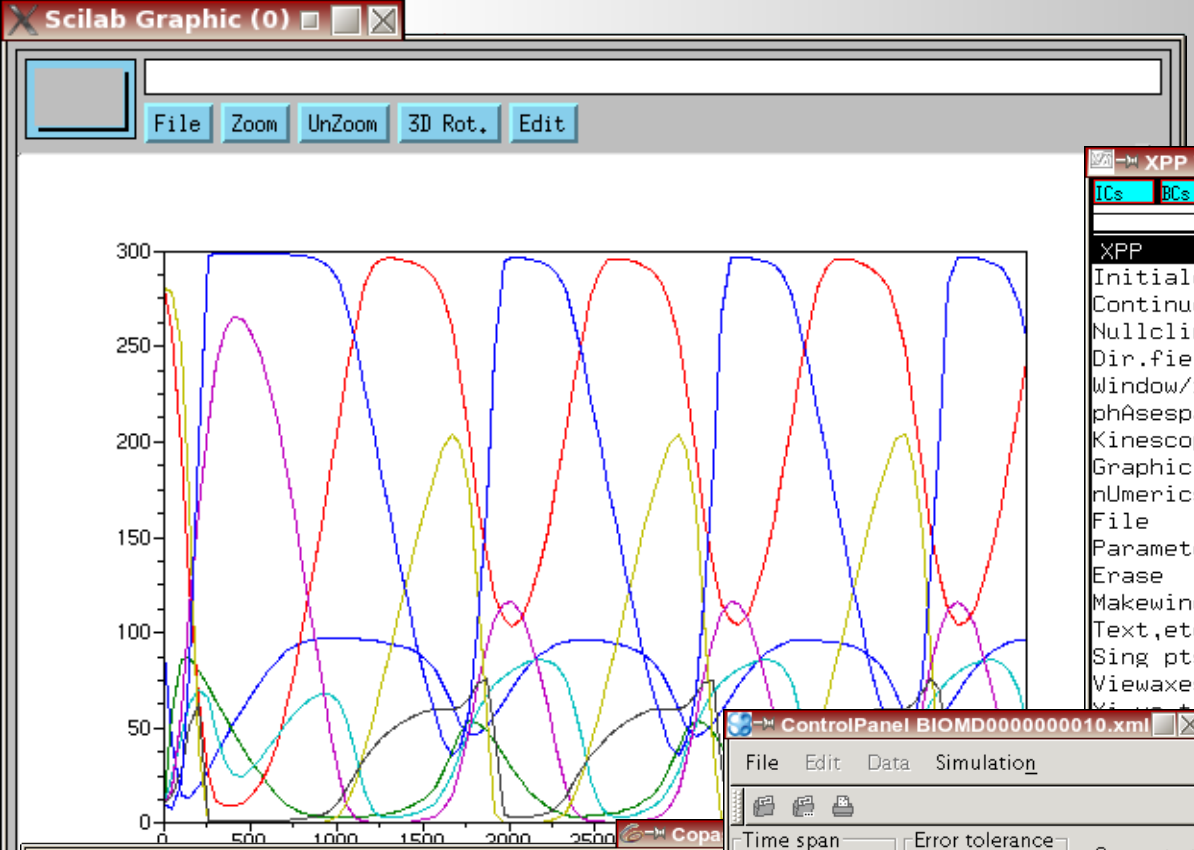
Species			
Name	**Compartment**	**Initial Amount**	**Initial Concentration**
MAPKKK	uVol		90.0
MAPK-PP	uVol		10.0

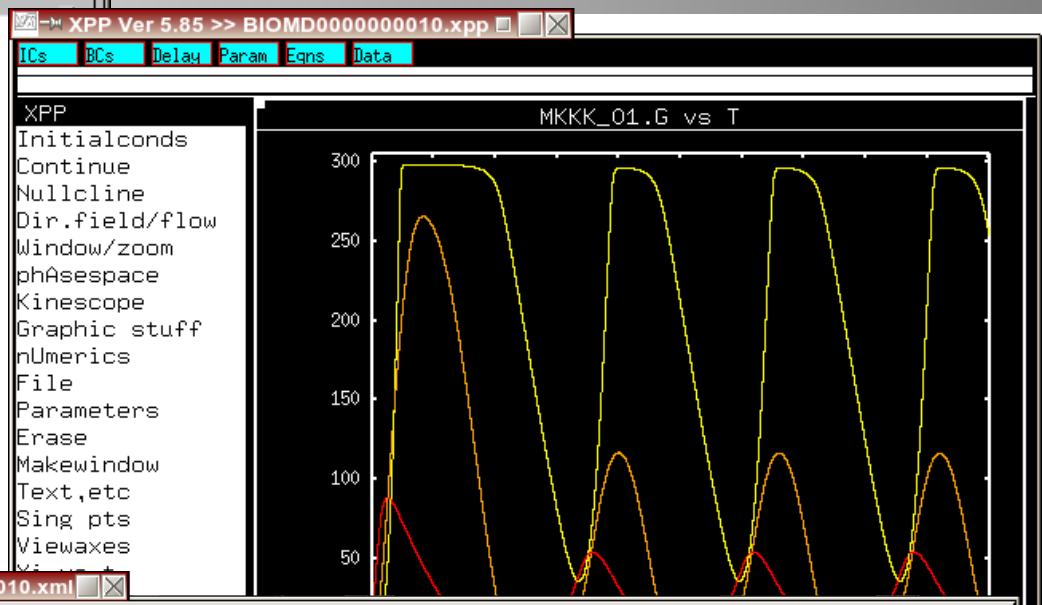
Parameters	
Name	**Value**
V1	2.5
Ki	9.0
n	1.0
K1	10.0

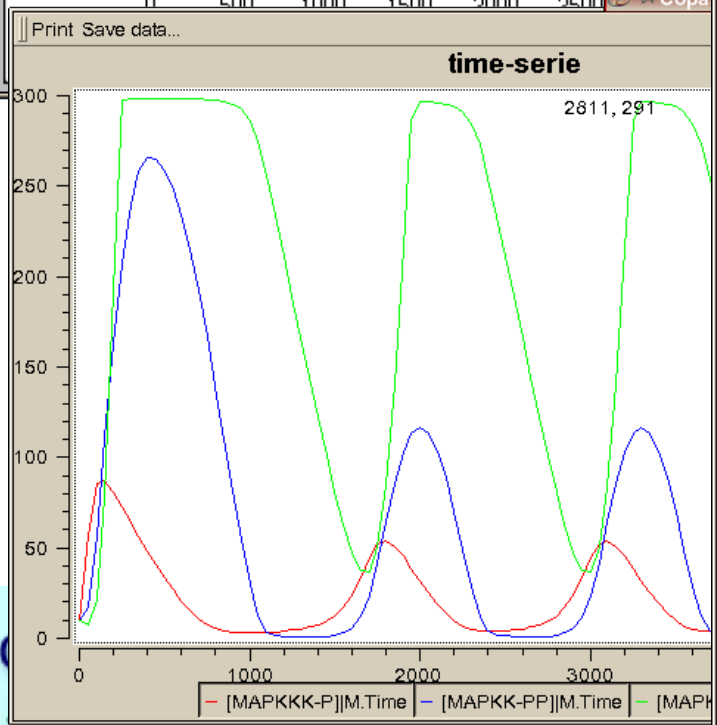
Close

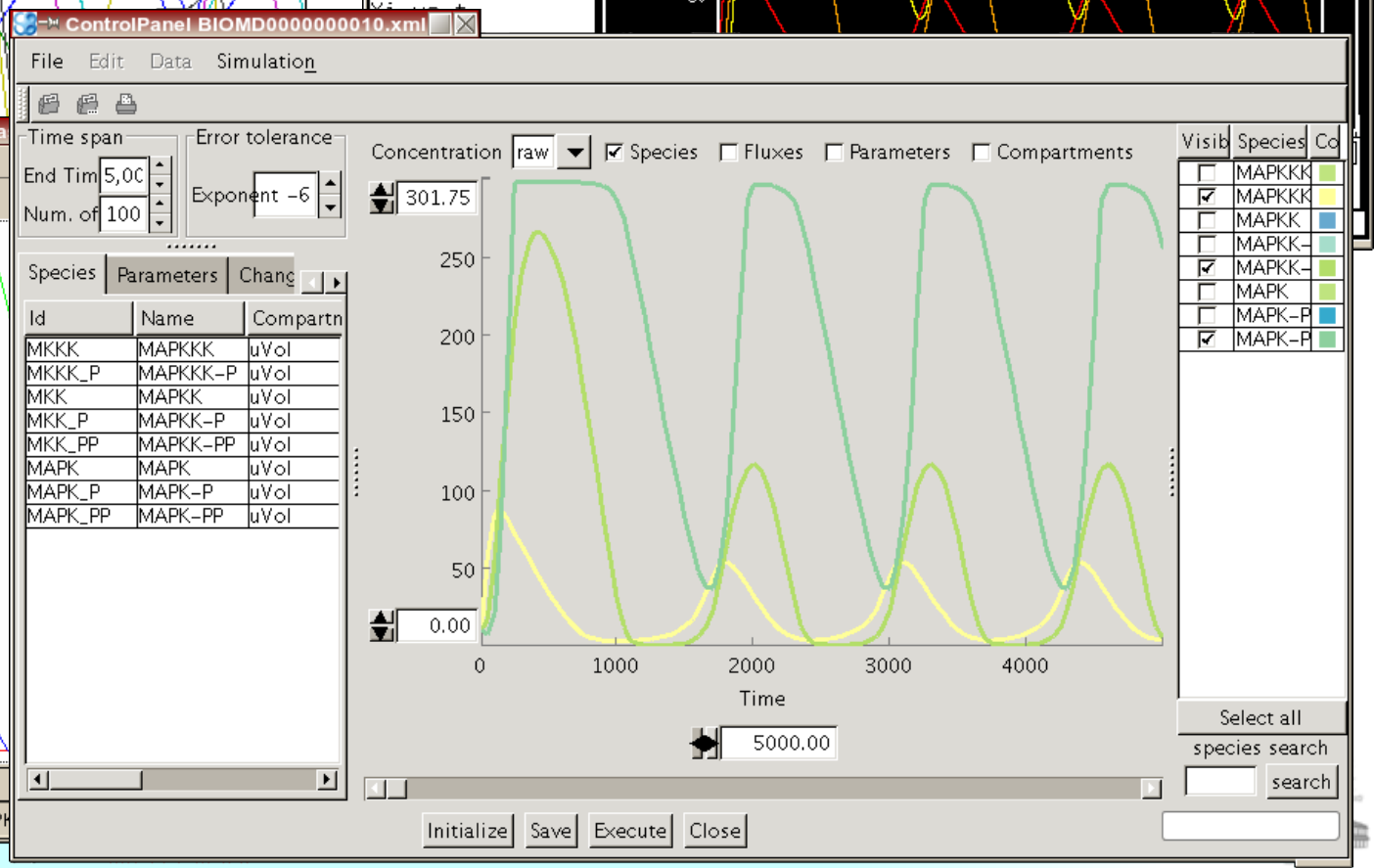
Done

Kholodenko 2000







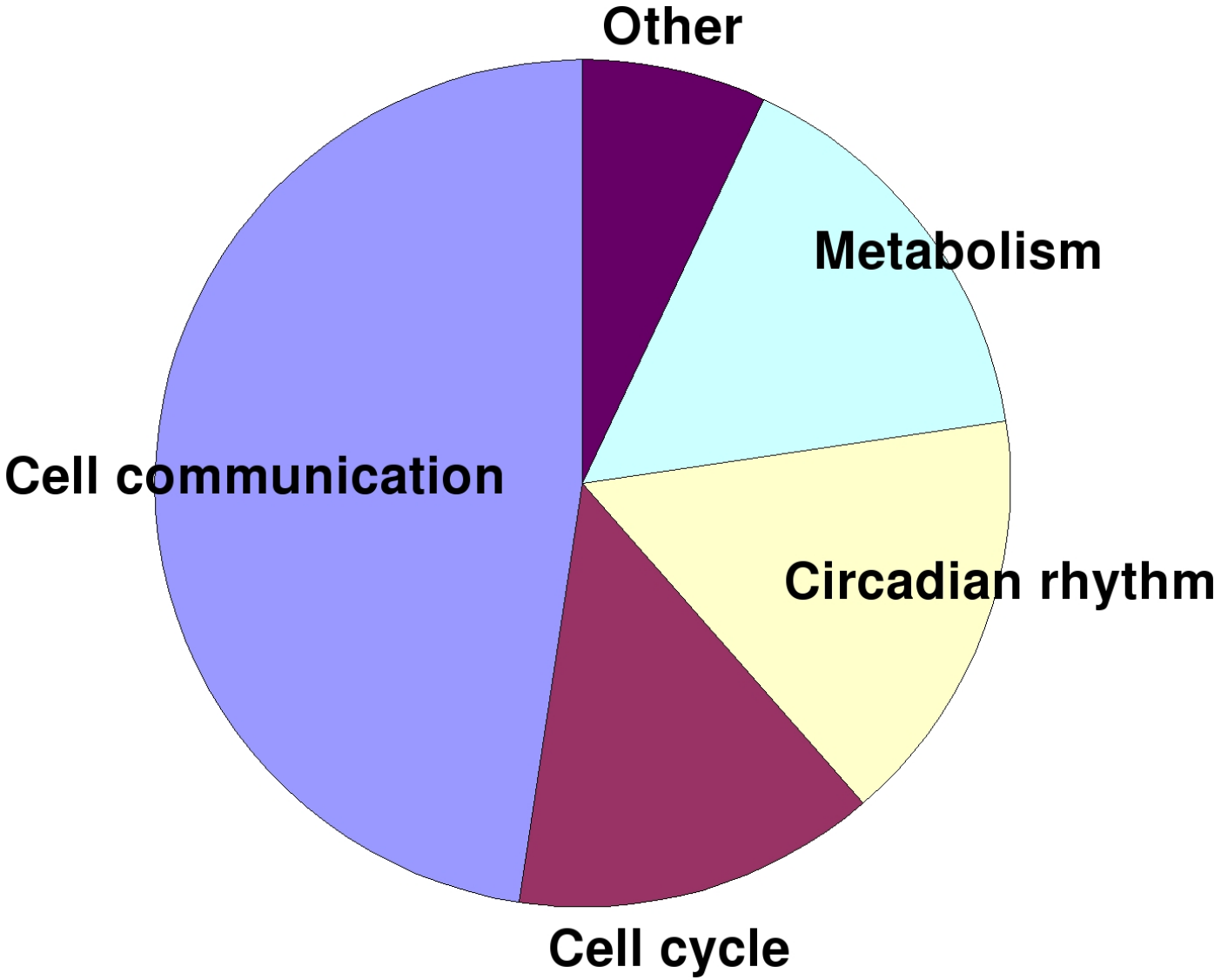


Steady increase

Release	# models	# reactions	#annotations
11 April 2005	20	631	1084
01 June 2005	30	736	1609
28 July 2005	44	943	2373
30 January 2006	50	1163	3126
05 June 2006	54	1307	3542

- Around 30 models in the curation pipeline
- Important legacy from JWS Online (~20), CellML Repository (~200) and DOCQS (~200)

Topical repartition



Neurobiology-related: 1, 2 (channel conformation), 20 (HH), 33 (EGF/NGF) + circadian rhythms?

unsolicited mirrors

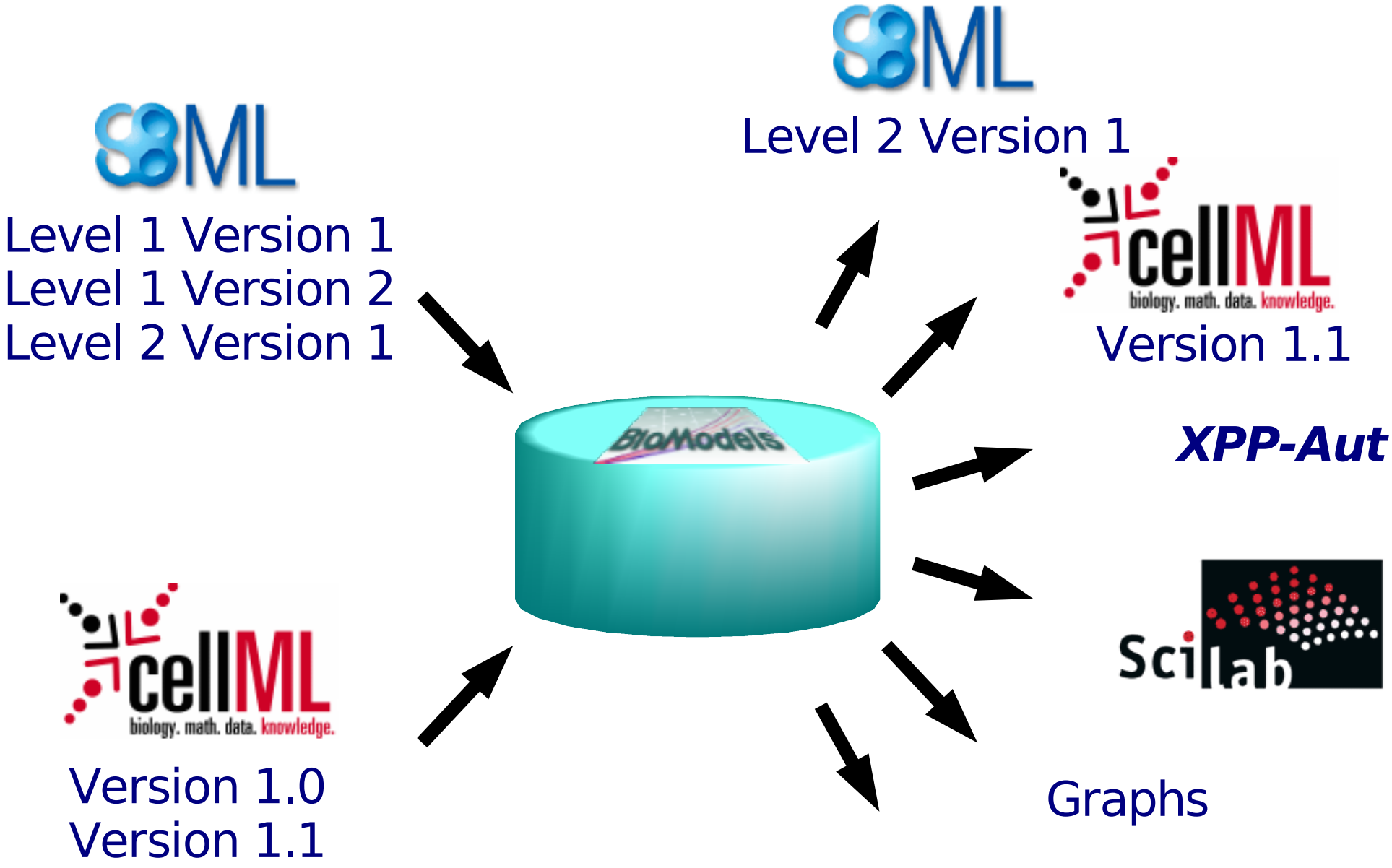
- CellDesigner:
  http://www.systems-biology.org/cd/features/BioModelsNet.html
- SIGMOID:
  http://www.sigmoid.org/models/ModelBrowse.do
- JSIM:
  http://nsr.bioeng.washington.edu/cgi-bin/butterw/jsquery.cgi?d=biomodels

We are happy about that! Feel-free to do the same!

Problem children

- Non-MIRIAM compliant models
  - SBML is correct
  - quantitative
  - simulatable
  - structure is not correct; results are not correct; missing information
- Non time-series: Ex models from B Palsson:
  - SBML is syntactically correct
  - quantitative
  - SBML is semantically incorrect
  - non-simulatable
- Spatial models: e.g. VCell, SmartCell, MesoRD
  - SBML is correct
  - only part of the information is in SBML

Versatility



The EBI team

Marco Donizelli, Chen Li:

Tomcat/Xindice/Web interface

Melanie Courtot:

MySQL/Tomcat

Lu Li:

Curation plus Graph, CellML, XPP and SciLab exports

Camille Laibe

WebServices

Arnaud Henry:

BioPAX export

Nicolas Le Novère:

Design and curation

An international collaboration

- EBI
  - Nicolas Le Novère
  - Marco Donizelli
  - Mélanie Courtot
  - Lu Li
  - Chen Li
  - Nicolas Rodriguez
  - Alexander Broicher
  - Arnaud Henry
  - Camille Laibe
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  - Maria Schilstra
  - Sarah Keating
  - Harish Dharuri
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  - Herbert Sauro
- Systems Biology Institute
  - Hiroaki Kitano
  - Akira Funahashi
- Stellenbosh University
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  - Ursula Kummer
  - Ken Lau
  - Adrian Lopez Garcia de Lomana
  - Rainer Machné
  - Yukiko Matsuoka
  - Joanne Matthews
  - Robert Phair
  - Marc Poolman
  - Carole Proctor
  - Tomas Radivoyevitch
  - Birgit Schoeberl
  - Oleg Sokolsy
  - Joanne Matthews
  - Tjeerd olde Scheper
  - Birgit Schoeberl
  - Henning Schmidt
  - Paul Smolen
  - Darren Wilkinson
  - Molecular Systems Biology
- Programs used for curation
  - CellDesigner
  - COPASI
  - Jarnac/JDesigner
  - MathSBML
  - SBMLeditor
  - SBMLodeSolver
  - XPP-Aut