Adding semantics in kinetic models of biochemical pathways

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Modelling is at the core of biology

- Computational modelling at the core of modern biology
  - Rise of functional genomics and systems biology
    Modern data are: high throughput, quantitative, quality-controlled
  - Number of models increasing quickly, very quickly
  - Size of the models is increasing with the data availability
  - “biologists” are more and more interested in challenging and using computer models

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  - Number of models increasing quickly, very quickly
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  - “biologists” are more and more interested in challenging and using computer models
- Computational modelling in biology is a mature and complex field
  - Constellation of different approaches and algorithms:
    - graph/topology – flux analysis – kinetic simulation
    - discrete – continuous
    - ODE - PDE
  - Alternative models to describe the same phenomena
    Bacterial chemotaxis, Cell cycle, MAPK, EGFR signalling,
  - Being not omniscient, one has to leverage on each other expertise

We need to reuse mathematical models

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

➔ Systems Biology Markup Language (SBML): A community maintained open XML standard to encode quantitative models of biological systems.

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

➔ MIME type application/sbml+xml
(RFC 3823 of the Internet Engineering Task Force)

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

A Free and Open Language

Advances in biotechnology are leading to larger, more complex quantitative models. The systems biology community needs information standards if models are to be shared, evaluated and developed cooperatively. SBML's widespread adoption **offers many benefits**, including: (1) enabling the use of multiple tools without rewriting models for each tool, (2) enabling models to be shared and published in a form other researchers can use even in a different software

New SBML Online Validator!

(March 6, 2008) SBML.org has a slick new online **SBML validator**, complete with remote API. Check it out!

read more

COPASI RC1

(February 21, 2008) **COPASI** is a biochemical modeling software package and successor to the popular Gepasi. It supports SBML.

read more

SBMLMerge Test Release

(February 18, 2008) **SBMLmerge** is a tool for assisting users in merging SBML files. It is now available for testing from the Max Planck Institute for Molecular Genetics.

read more

SABIO-RK Supports SBML

(February 15, 2008) The SABIO-Reaction Kinetics database from EML is a web-based system containing data about biochemical reactions. A beta test is under way now.

read more

MathSBML Vers. 2.5.7 Released!

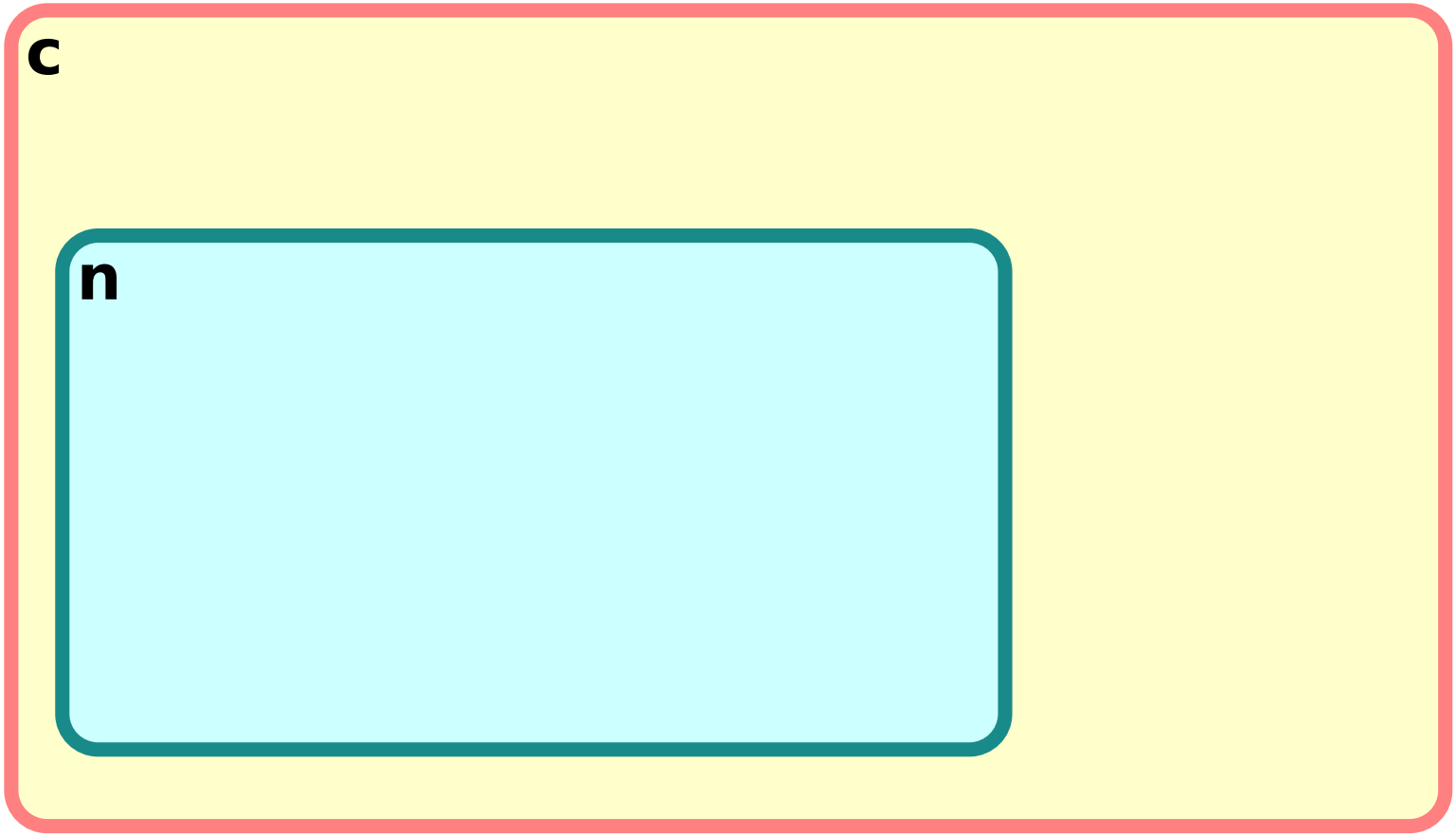
(February 4, 2008) The SBML Team released version 2.5.7 of **MathSBML**, a full-featured package for working with SBML in the Mathematica environment. The new version fixes a small bug in stoichiometry matrix calculations.

read more

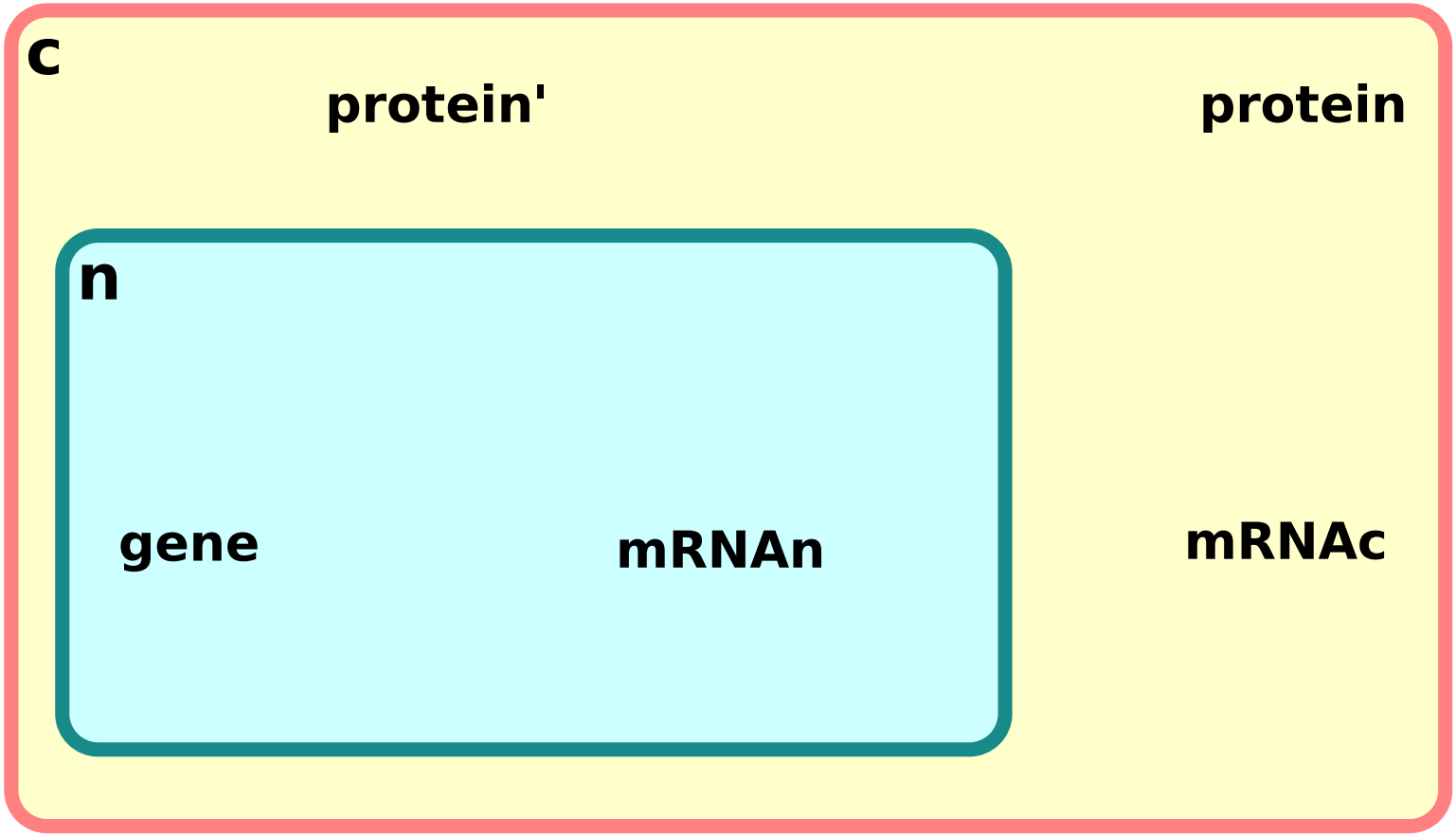
See older news items.

What can we encode in SBML?

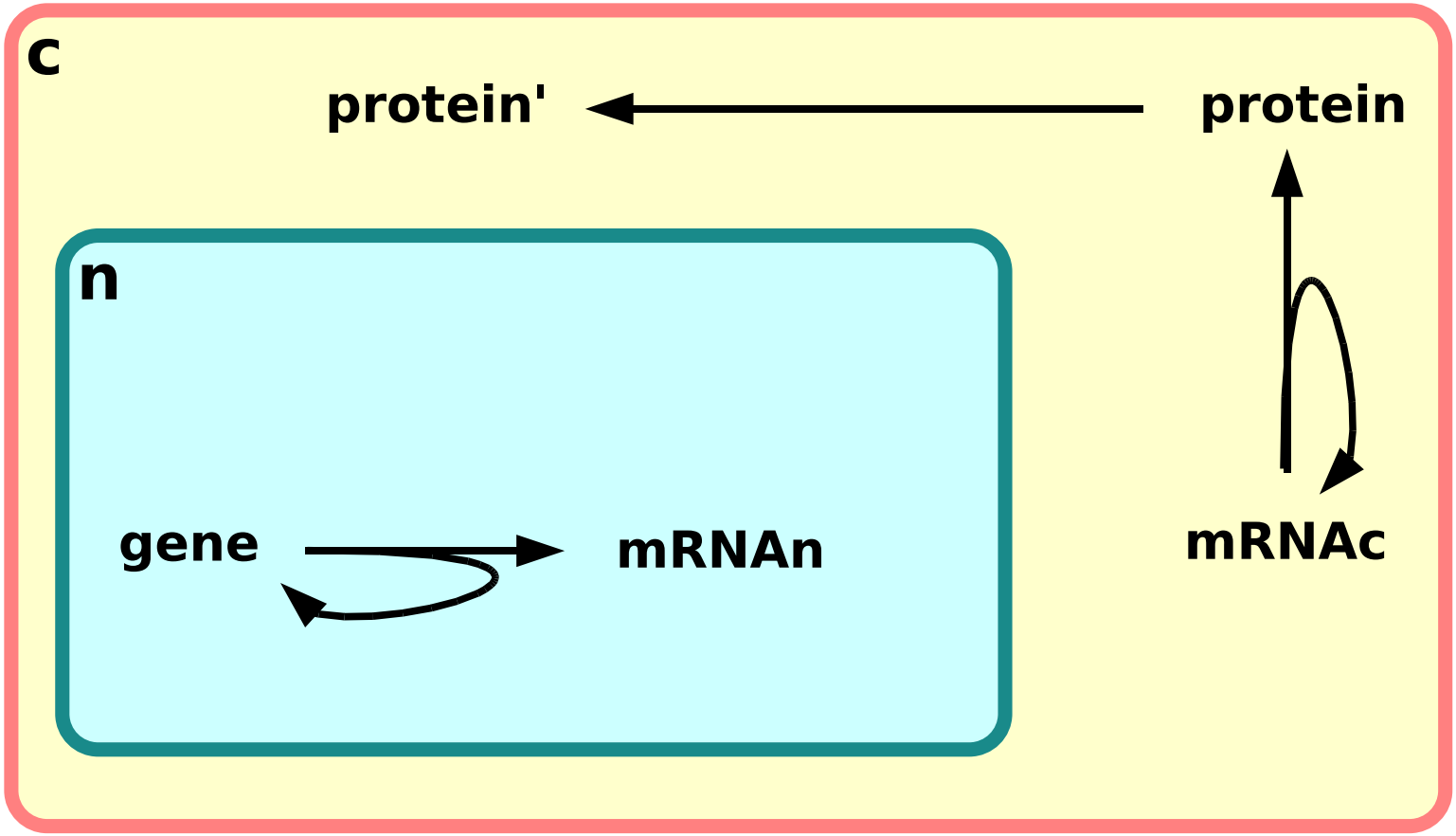
What can we encode in SBML?



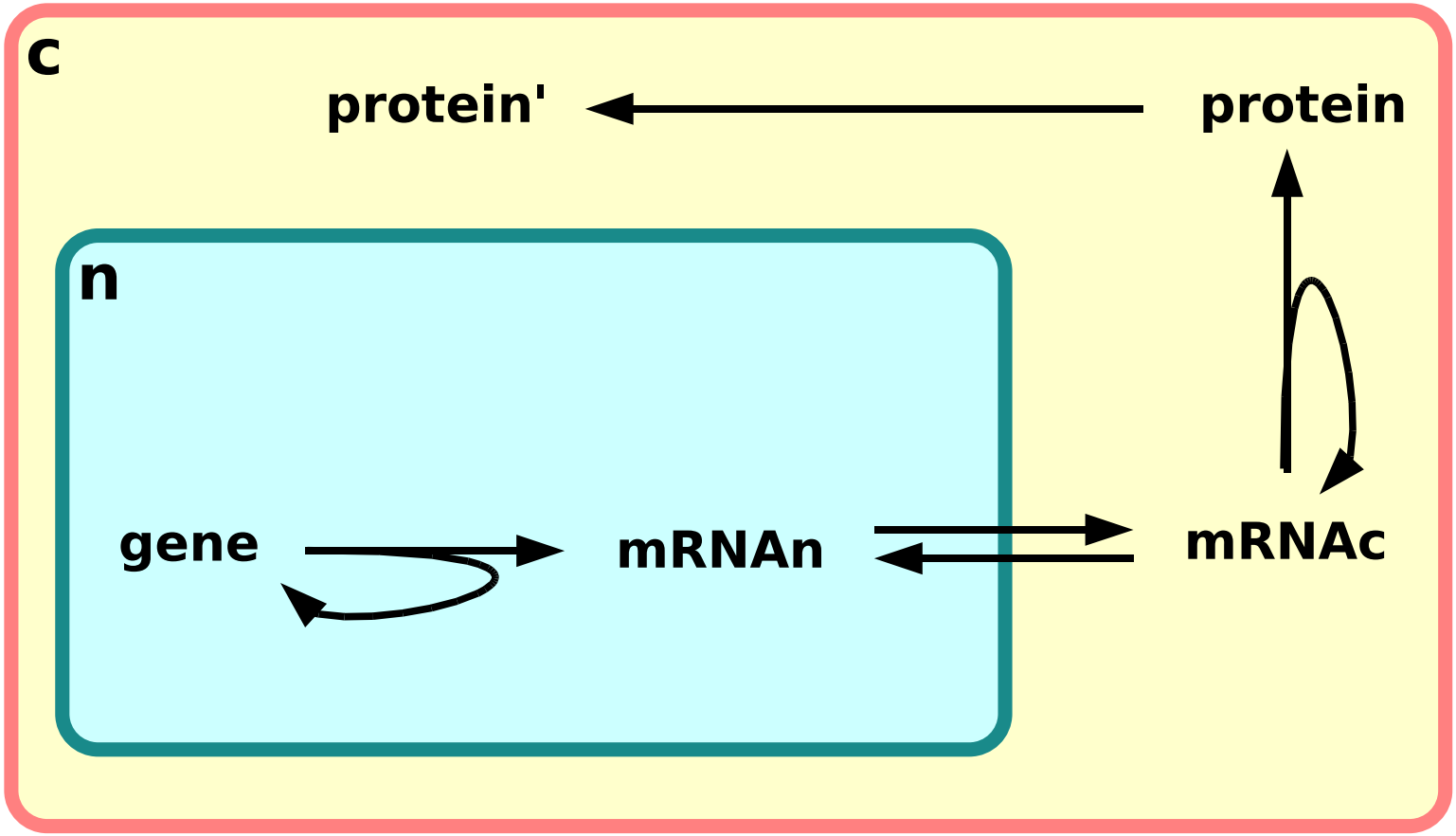
What can we encode in SBML?



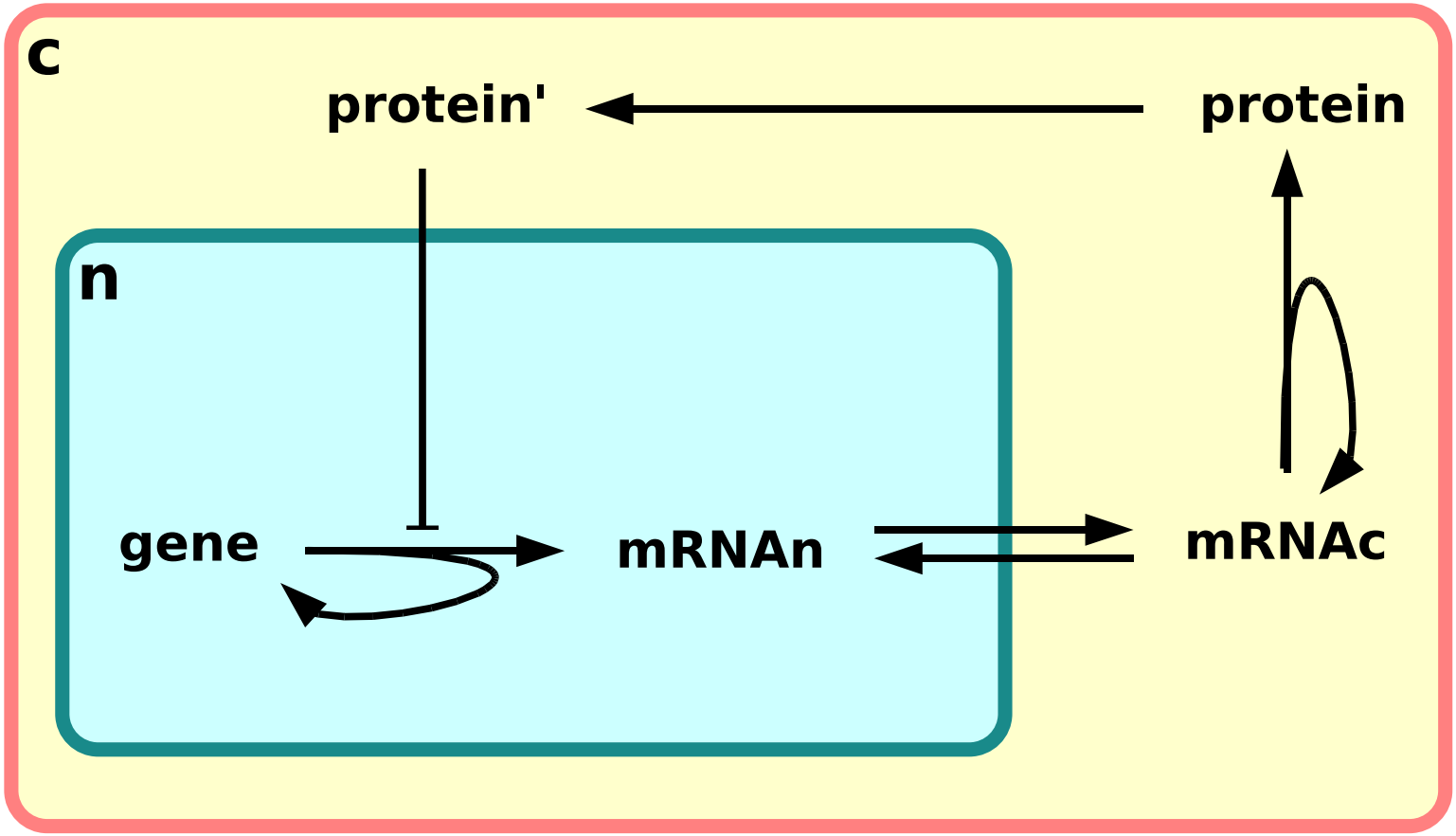
What can we encode in SBML?



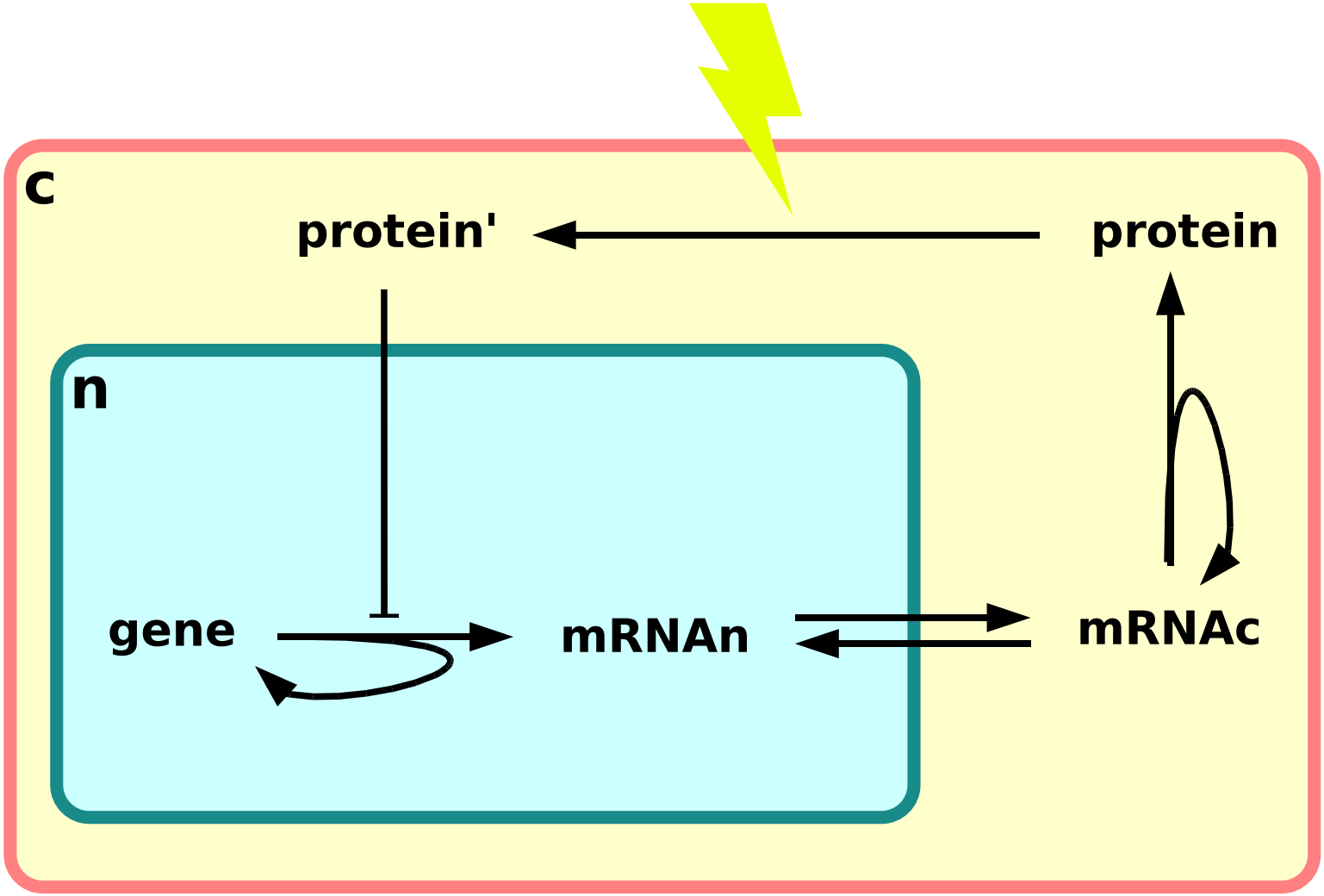
What can we encode in SBML?



What can we encode in SBML?



What can we encode in SBML?



```
<?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>
      <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>









      </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>









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

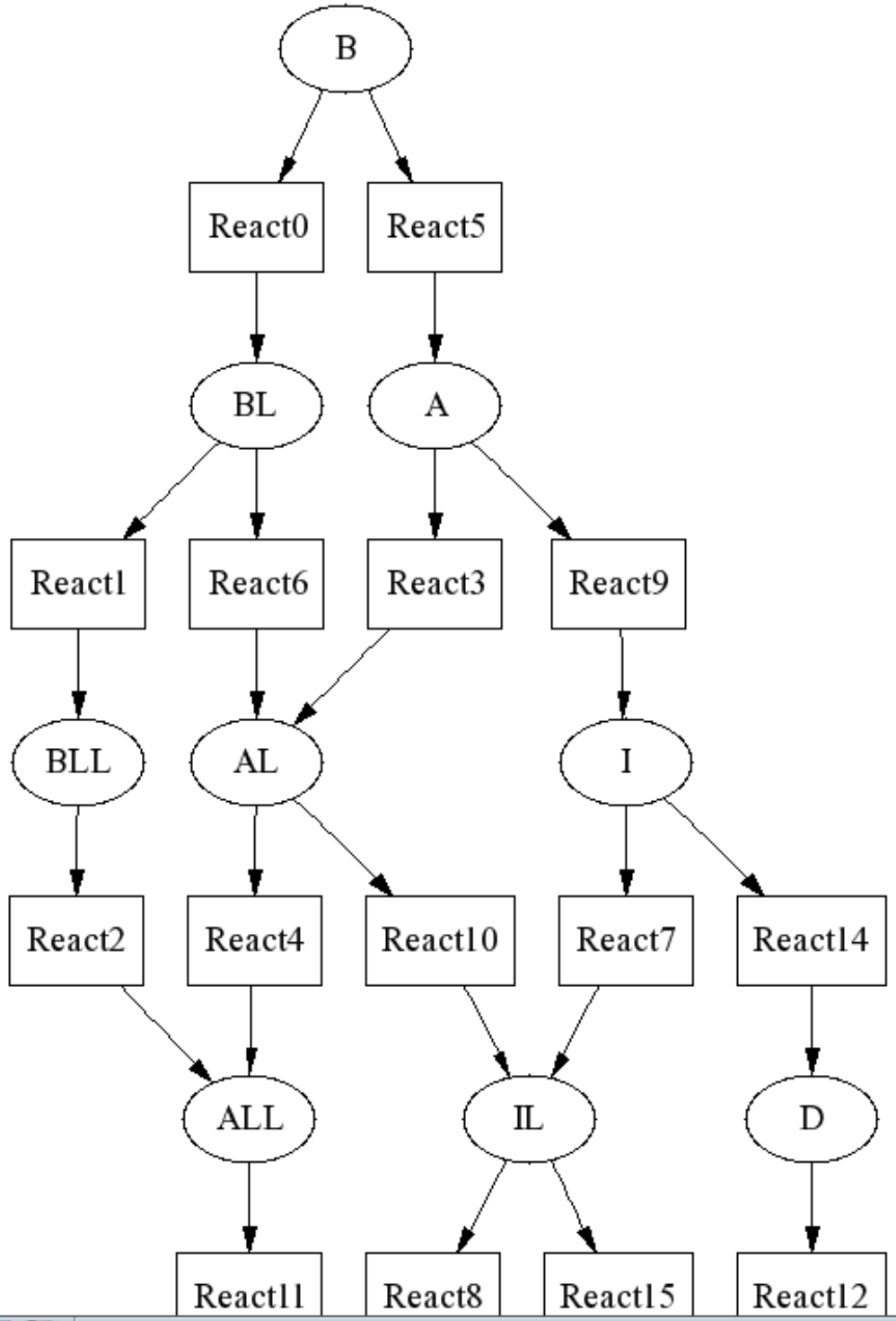
```
<?xml version="1.0" encoding="UTF-8"?>
<sbml level="2" version="1" xmlns="http://www.sbml.org/sbml/level2">
  <model>
    <listOfCompartments>
      <compartment id="cell" />
    </listOfCompartments>
    <listOfSpecies>
      <species id="A" compartment="cell" initialConcentration="1"/>
      <species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

SBML is not limited to biochemistry

```
<listOfCompartments>
  <compartment id="blood" />
</listOfCompartments>
<listOfSpecies>
  <species id="lympht" compartment="blood" initialConcentration="1"/>
  <species id="lymphb" compartment="blood" initialConcentration="1"/>
  <species id="plasmo" compartment="blood" initialConcentration="0"/>
</listOfSpecies>
<listOfParameters>
  <parameter id="kon" value="1"/>
</listOfParameters>
<listOfReactions>
  <reaction>
    <listOfReactants>
      <speciesReference species="lympht" />
      <speciesReference species="lymphb" />
    </listOfReactants>
    <listOfProducts>
      <speciesReference species="plasmo" />
    </listOfProducts>
    <kineticLaw>
      <math xmlns="http://www.w3.org/1998/Math/MathML">
        <apply>
          <times />
          <ci>kon</ci>
          <ci>lympht</ci>
          <ci>lymphb</ci>
          <ci>blood</ci>
        </apply>
      </math>
    </kineticLaw>
  </reaction>
</listOfReactions>
```

Systems Biology Markup Language - Diagram of EPSP_AChDynValue_SBML2.xml - Mozilla

No, it isn't!



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)

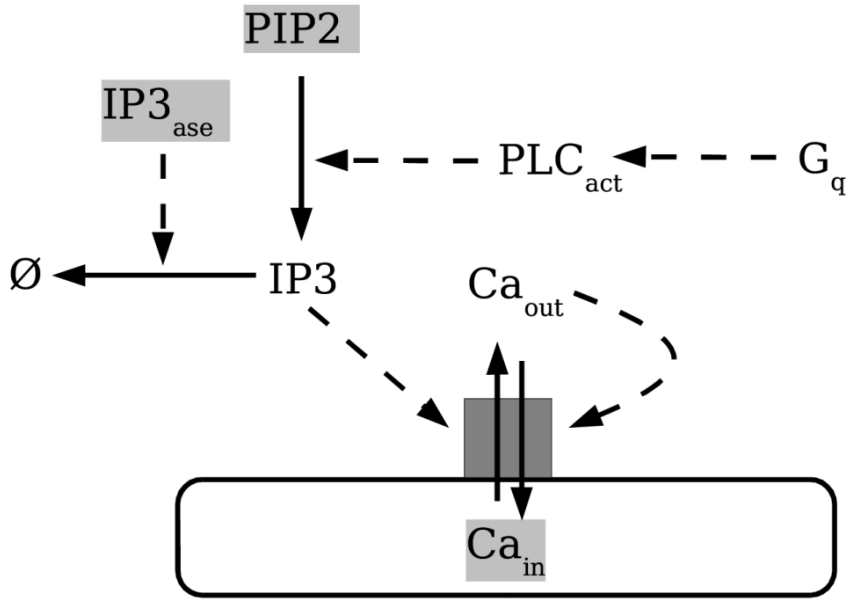
Attribution annotation

- 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.

Model example



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

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

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

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

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

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

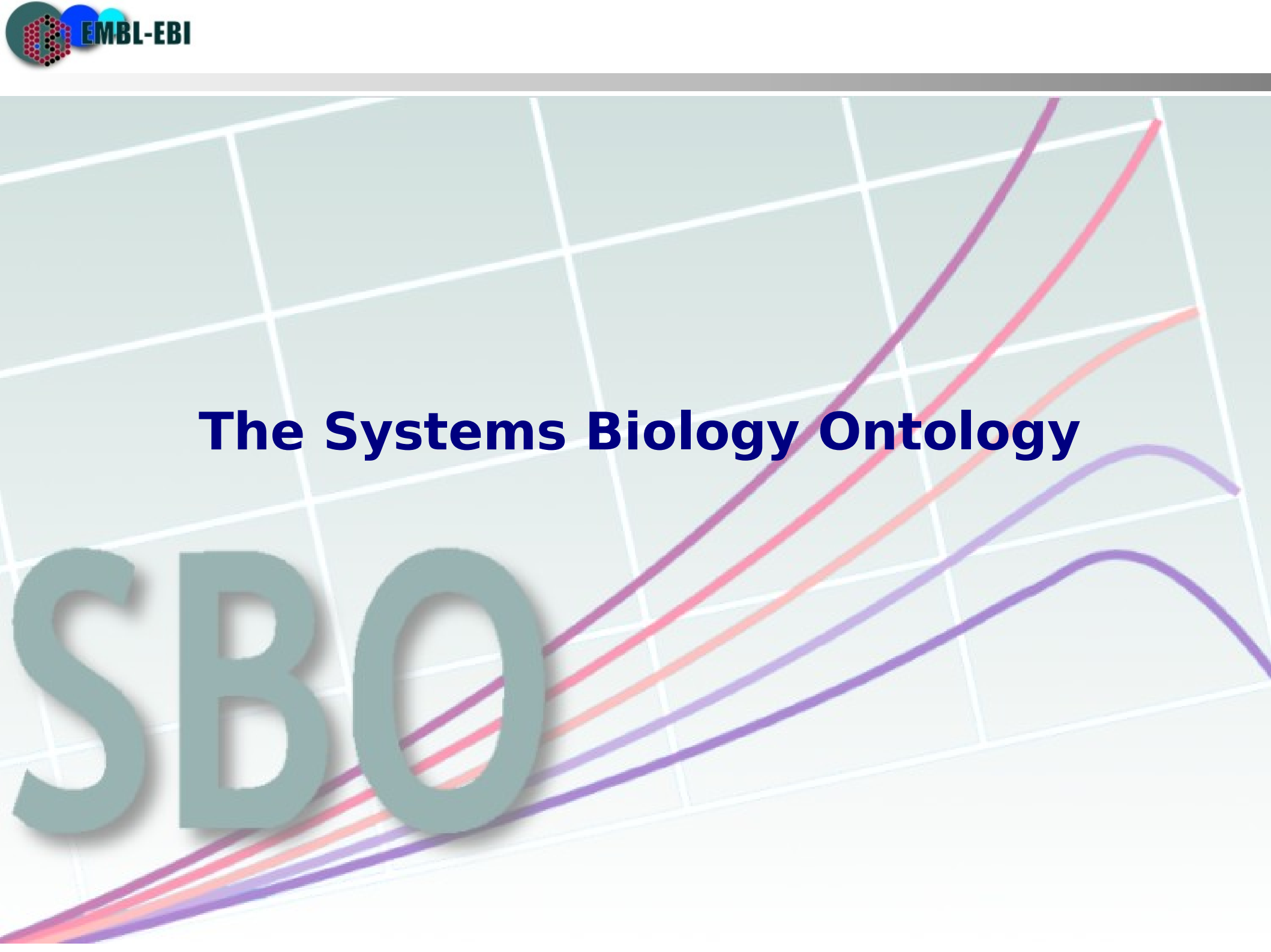
$$\frac{d[IP3]}{dt} = \frac{k_2[PLC_{act}] * [PIP2]}{Km_2 + [PIP2]} - \frac{k_3[IP3_{ase}] * [IP3]}{Km_3 + [IP3]}$$

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

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*

The Systems Biology Ontology



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

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

?

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

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

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

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`

- "An indexed dictionary". *Nicolas Le Novère. This presentation.*

- "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*

- ## 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 controlled vocabularies with defined relationships between terms. *Nicolas Le Novère. This presentation.*

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

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Computational Neurobiology

SBO Ontology Browser

SBO::Systems Biology Ontology

- sbo
  - rate law
    - mass action kinetics
    - kinetics of unireactant enzymes
      - Henri-Michelis Menten equation
      - Van Slyke-Cullen equation
      - Briggs-Haldane equation
    - obsolete rate law
  - quantitative parameter
    - kinetic constant
    - Michaelis constant
    - obsolete parameter
  - participant role
    - reactant
    - product
    - modifier
    - obsolete species role
  - modelling framework
    - continuous framework
    - discrete framework
    - obsolete modelling framework

SBO:0000029 Henri-Michelis Menten equation

Definition

First general rate equation for reactions involving enzymes, it was presented in "V. Henri. Lois Générales de l'Action des Diastases. Paris, Hermann, 1903.". The reaction is assumed to be made of a reversible of the binding of the substrate to the enzyme, followed by the breakdown of the complex generating the product. Ten years after Henri, Michaelis and Menten presented a variant of his equation, based on the hypothesis that the dissociation rate of the substrate was much larger than the rate of the product generation. Leonor Michaelis, Maud Menten (1913). Die Kinetik der

MathML

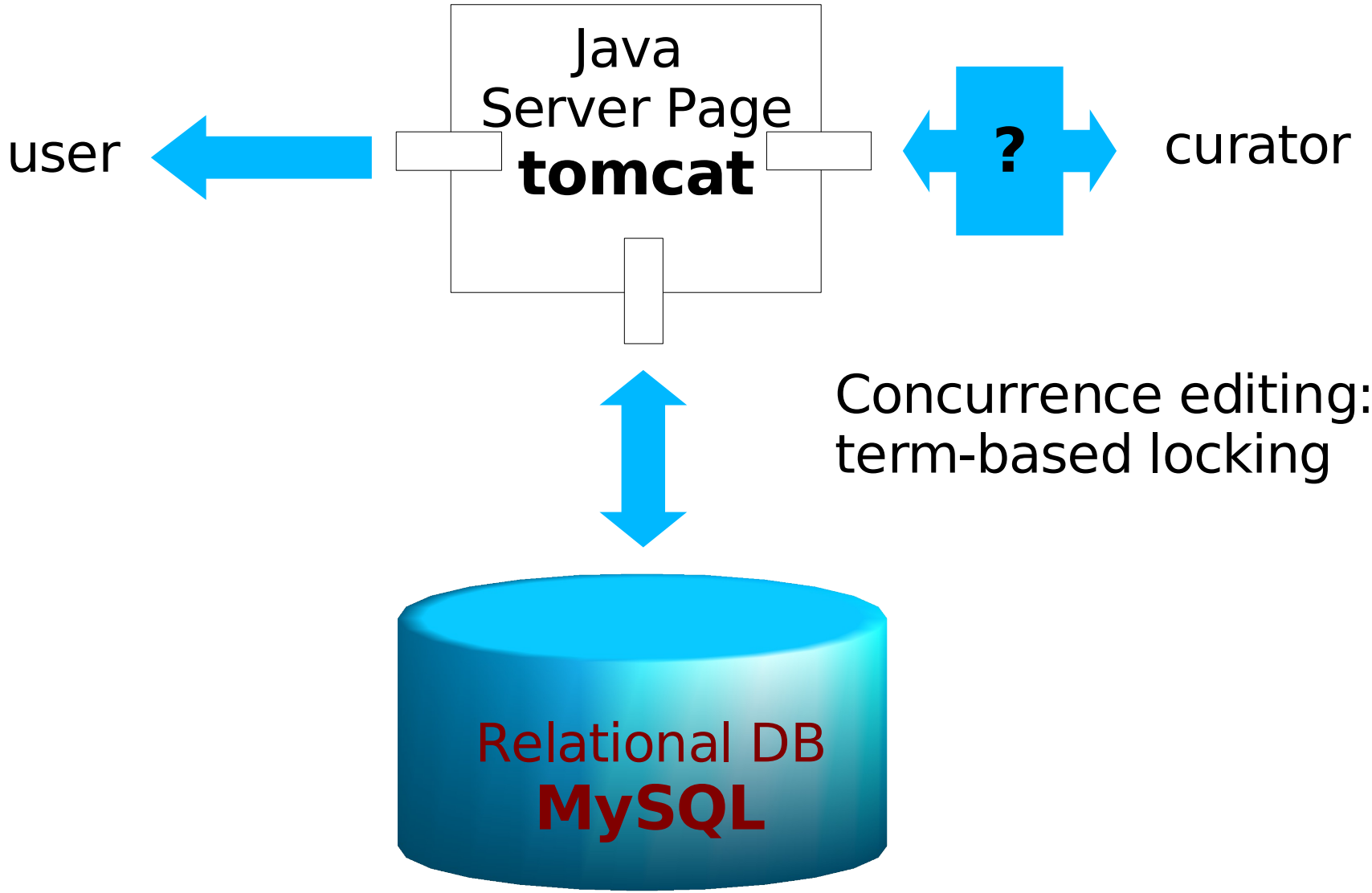
```
<math xmlns="http://www.w3.org/1998/Math/MathML">
   <lambda>
     <bvar><ci
definitionURL="http://biomodels.net/SBO/SBO:0000025">kcat</ci></bvar>
     <bvar><ci
definitionURL="http://biomodels.net/SBO/SBO:0000014">Et</ci></bvar>
     <bvar><ci
definitionURL="http://biomodels.net/SBO/SBO:0000015">S</ci></bvar>
```

Comment

Parent(s)

SBO:0000028 kinetics of unireactant enzymes (is a)

Edition/browsing interface



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

Revealing assumptions

```
SBO:0000000 ; Systems Biology Ontology
    > SBO:0000001 ; rate law
        % SBO:0000012 ; mass-action kinetics
        % SBO:0000028 ; kinetics of unireactant enzymes
            % SBO:0000029 ; Henri-Michaelis-Menten equation
            % SBO:0000030 ; Van Slyke equation
            % SBO:0000031 ; Briggs-Haldane equation
    > SBO:0000002 ; quantitative parameter
        % SBO:0000009 ; kinetic constant
            % SBO:0000016 ; unimolecular rate constant
                % SBO:0000022 ; forward unimolecular rate constant
                    % SBO:0000035 ; forward unimolecular rate constant,
                                    continuous case
                % SBO:0000025 ; catalytic rate constant
        % SBO:0000008 ; Michaelis constant
    > SBO:0000003 ; participant role
        % SBO:0000010 ; reactant
            % SBO:0000015 ; substrate
        % SBO:0000011 ; product
        % SBO:0000019 ; modifier
            % SBO:0000013 ; catalyst
                % SBO:0000014 ; enzyme
    > SBO:0000004 ; modelling framework
        % SBO:0000062 ; continuous framework
```

Revealed assumptions

```
<reaction>
   <listOfReactants>
     <speciesReference species="S" />
   </listOfReactants>
   <listOfProducts>
     <speciesReference species="P" />
   </listOfProducts>
   <listOfModifiers>
     <speciesReference species="E" />
   </listOfModifiers>
   <kineticLaw sboTerm="SBO:0000031">
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       <parameter id="Km"/>
       <parameter id="kp"/>
     </listOfParameters>
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         <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">
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    <speciesReference species="S" sboTerm="SBO:0000015"/>
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  <listOfProducts>
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  </listOfProducts>
  <listOfModifiers>
    <speciesReference species="E" sboTerm="SBO:0000014"/>
  </listOfModifiers>
  <kineticLaw sboTerm="SBO:0000031">
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                           <ci>S</ci>
                 </apply>
                 <apply>
                   <plus/><ci>Km</ci>
                          <ci>S</ci>
                 </apply>
      </apply>
    </math>
  </kineticLaw>
</reaction>
```

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">
      <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>
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           <divide/>
           <apply>
             <times/><ci>E</ci><ci>kp</ci><ci>S</ci>
           </apply>
           <apply>
             <plus/><ci>Km</ci><ci>S</ci>
           </apply>
         </apply>
       </lambda>
    </math>
```

Automatic conversion

```
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     <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>
```
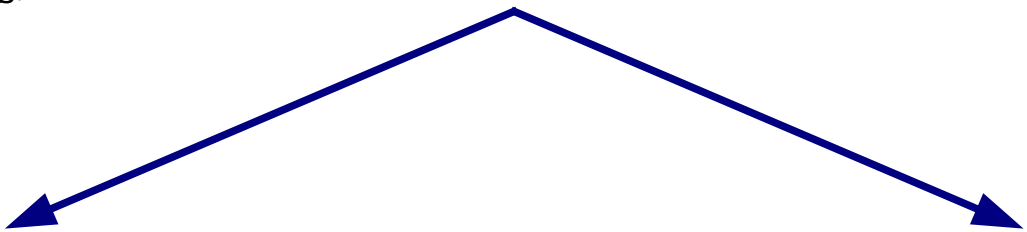



continuous simulator

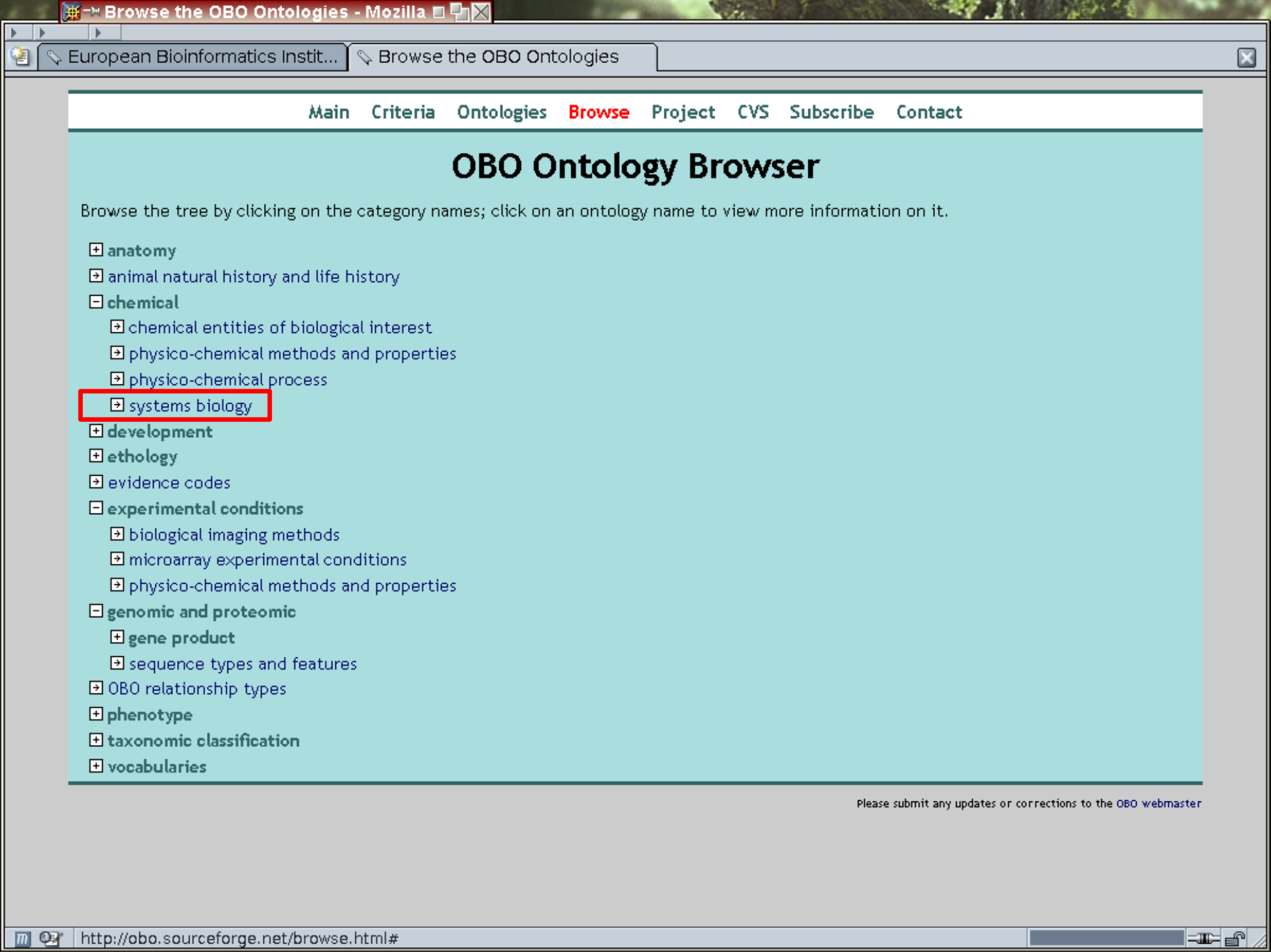
$$v = \frac{C \cdot V \cdot [A]}{(U + [A])}$$

discrete simulator

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

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

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


Browse the OBO Ontologies - Mozilla
European Bioinformatics Instit...
Browse the OBO Ontologies
Main Criteria Ontologies Browse Project CVS Subscribe Contact
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
Please submit any updates or corrections to the OBO webmaster
http://obo.sourceforge.net/browse.html#

SBO as metadata associated with measurements

- Annotation of experimental parameters to precisely identify them (kcat Vs. Vmax, Kp/Kd/IC50 etc.)
- Addition, when reporting a biochemical data, of the rate-law used to fit the measurements and, when relevant, of the underlying mechanistic
- Increase the awareness of assumptions when performing an experimental measurement
- Whatever you would fancy to use it for

The EBI team

Marco Donizelli, Chen Li:
Tomcat/Xindice/Web interface

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MySQL/Tomcat

Camille Laibe
WebServices

Lu Li:
Graph, CellML, XPP,
SciLab exports and curation

Arnaud Henry:
BioPAX export

Nicolas Le Novère:
Design and curation

An international collaboration

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  - Marco Donizelli
  - Mélanie Courtot
  - Lu Li
  - Chen Li
  - Nicolas Rodriguez
  - Alexander Broicher
  - Arnaud Henry
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  - 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
  - SBMLodeSolver
  - XPP-Aut