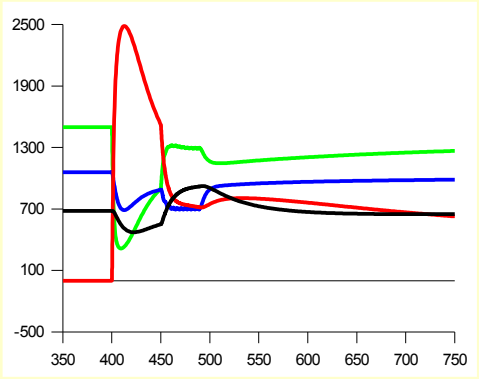
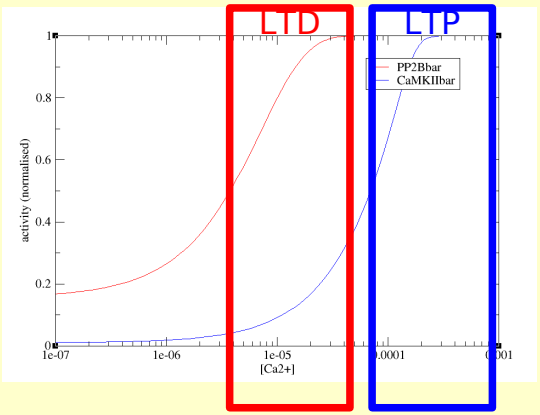
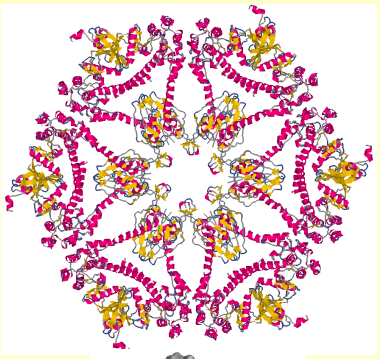

衆聲
探象之圖
modellers
Biological system
Blind monks and an elephant

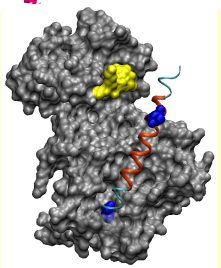
Group themes and projects

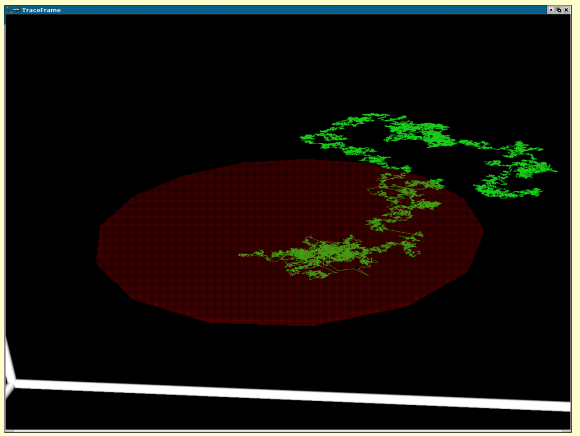
Computational Neurobiology







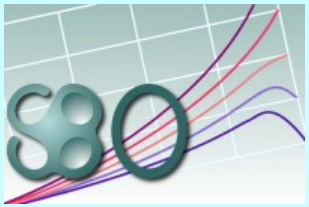


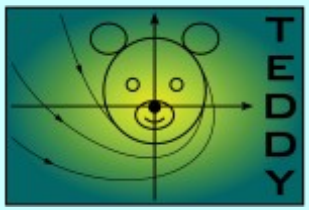


Systems Biology

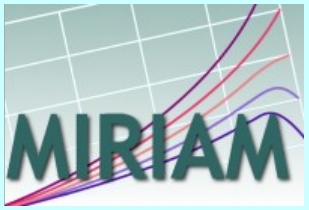
SBML

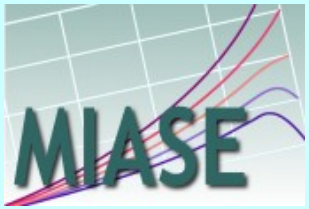
SBGN
Systems Biology Graphical Notation





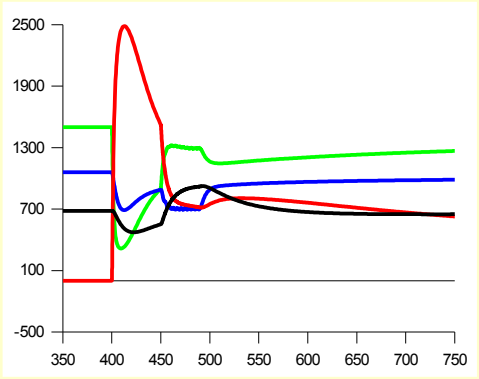
KISAO

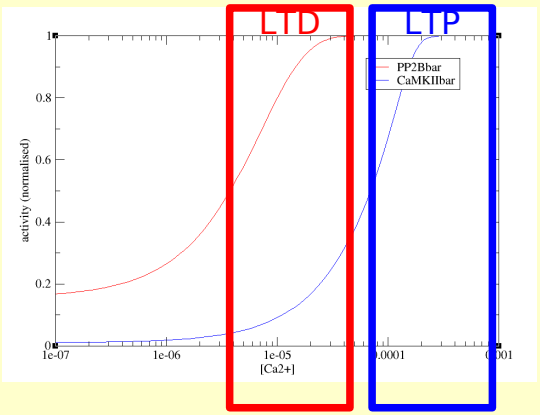


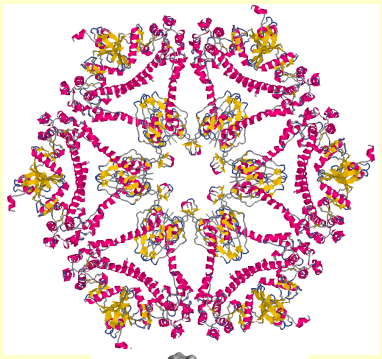


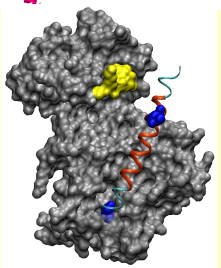
Group themes and projects

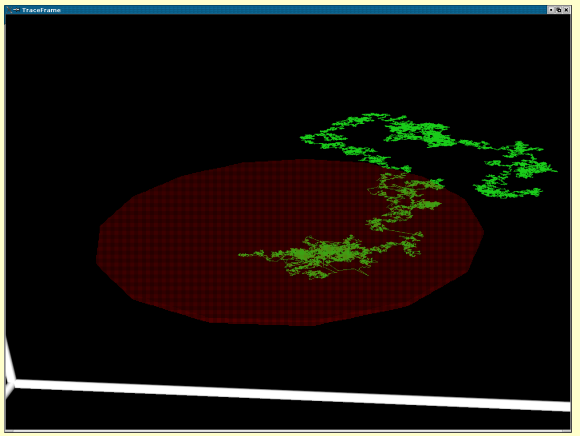
Computational Neurobiology











Systems Biology

SBML

SBGN
Systems Biology Graphical Notation

SBO

TEDDY

KISAO

MIRIAM

MIASE

e-MeP

Ligand-Gated Ion Channel database

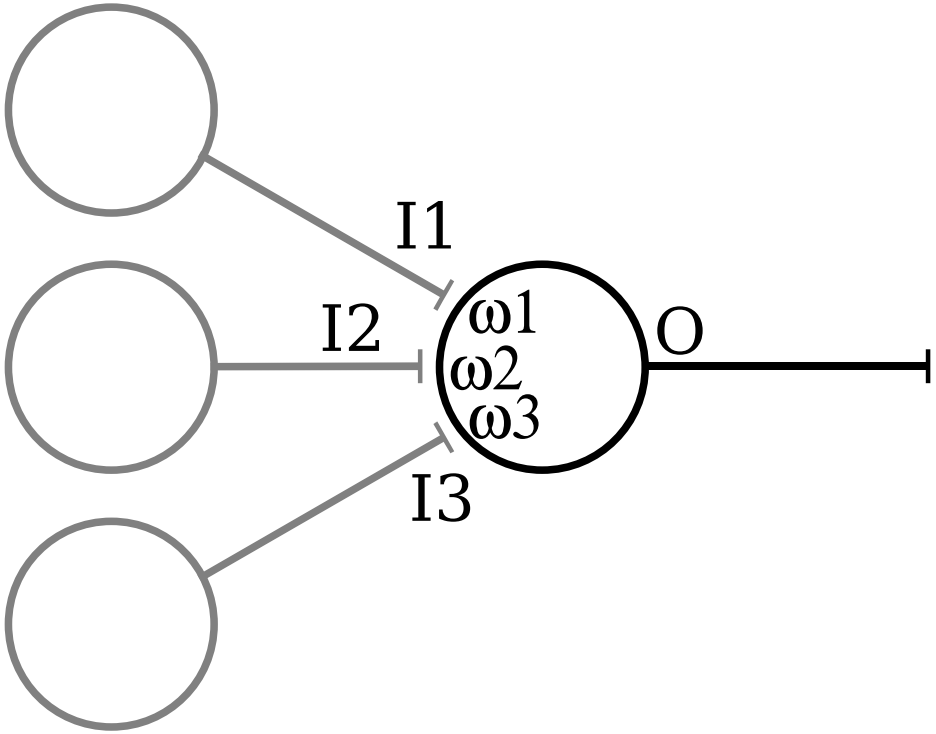
BioModels

What is a model in computational (neuro)biology?

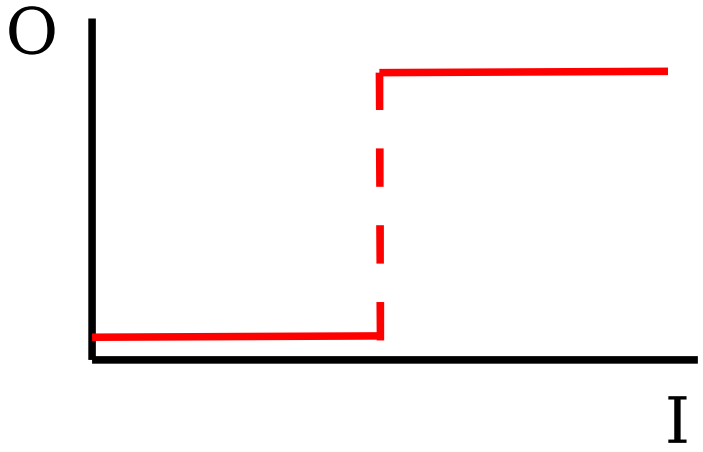
What is a model? A preliminary definition

A model is a quantitative description of a system, or the components of a system and their relationships, and their evolution

Artificial neuron: theoretical

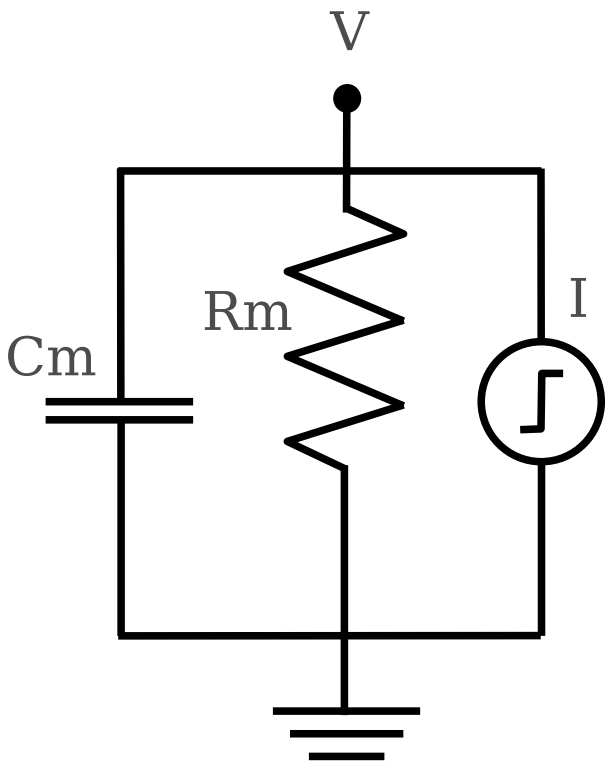


$$O = H\sum_i \omega_i I_i$$

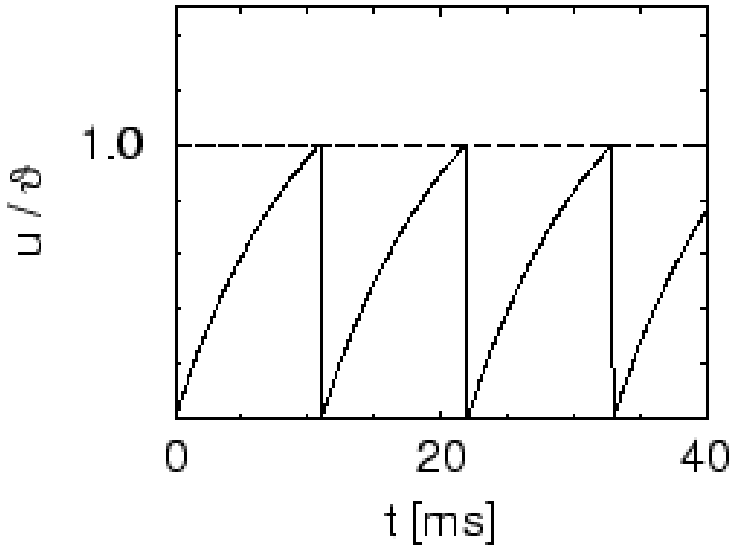


McCulloch, Pitts (1943) *Bull Math Biophys* 5: 115-133.

Leaky integrate and fire: phenomenological



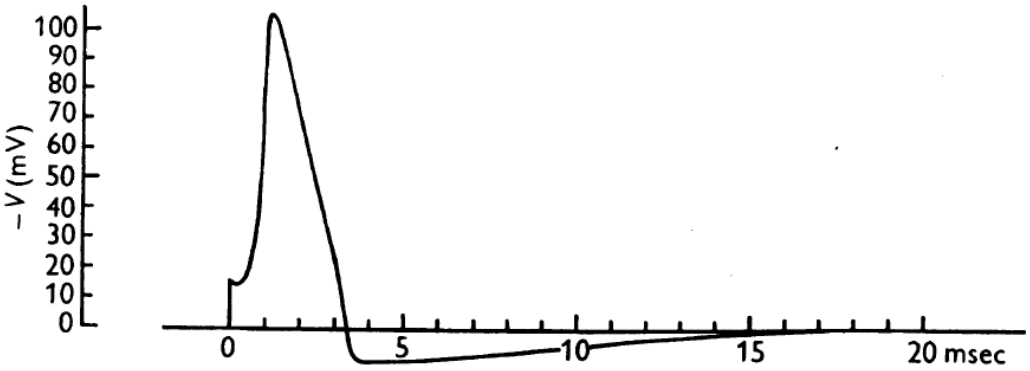
$$Cm\frac{dV}{dt} = -\frac{V}{Rm} + I$$

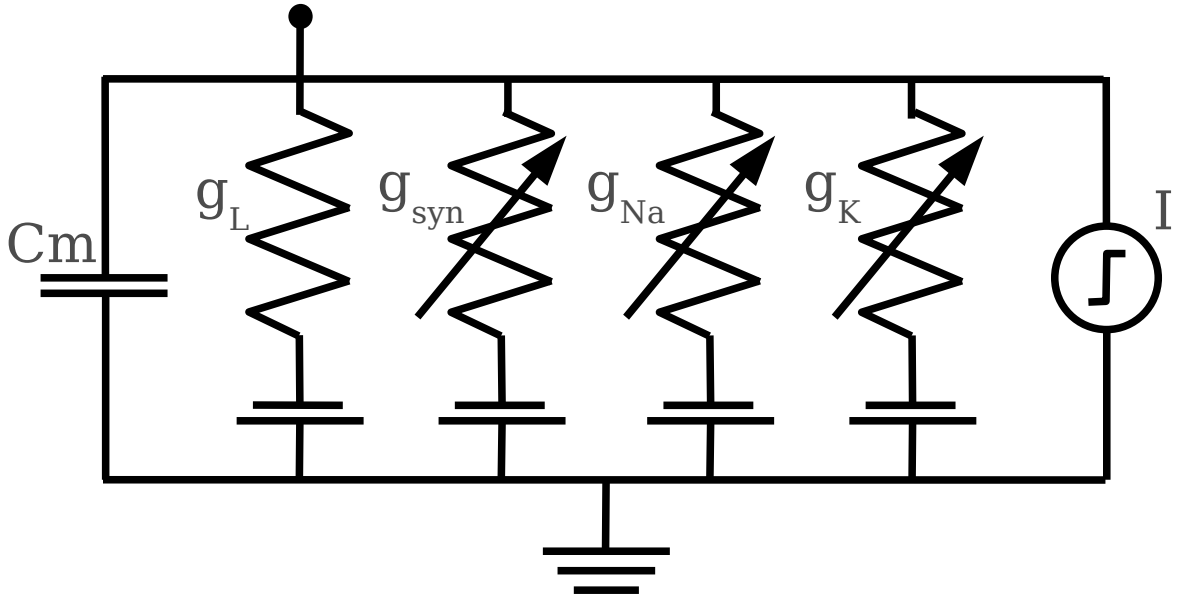


Lapicque (1907) *J Physiol Pathol Gen* 9: 620-635.

Conductance-based: mechanistic

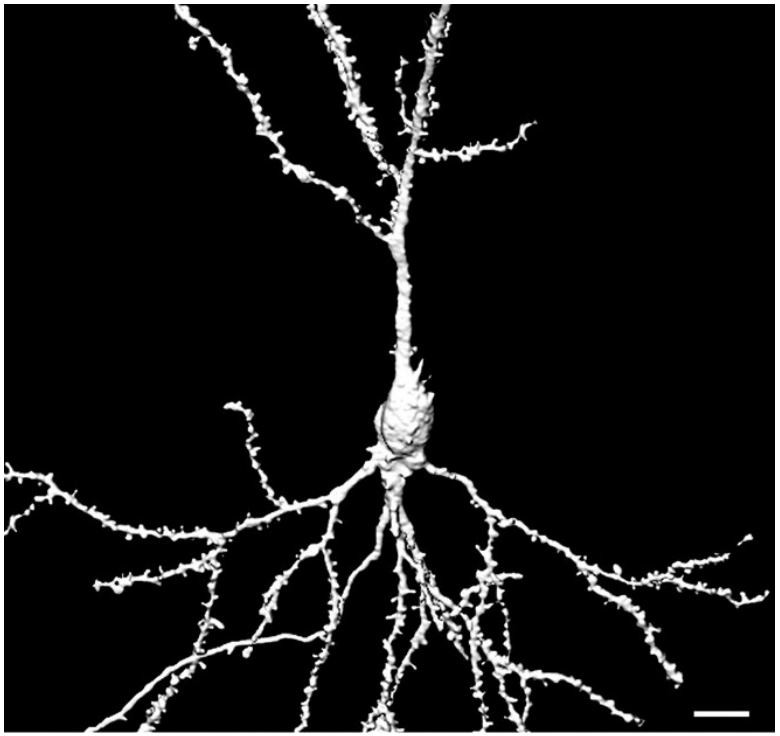
$$
\begin{aligned}
Cm\frac{dV}{dt} &= -g_L(V - E_L) - \bar{g}_{Na}m^3h(V_V - E_{Na}) - \bar{g}_K n^4(V - E_K) \\
\frac{dm}{dt} &= \alpha_m(V)(1 - m) - \beta_m(V)m \\
\frac{dh}{dt} &= \alpha_h(V)(1 - h) - \beta_h(V)h \\
\frac{dn}{dt} &= \alpha_n(V)(1 - n) - \beta_n(V)n
\end{aligned}
$$

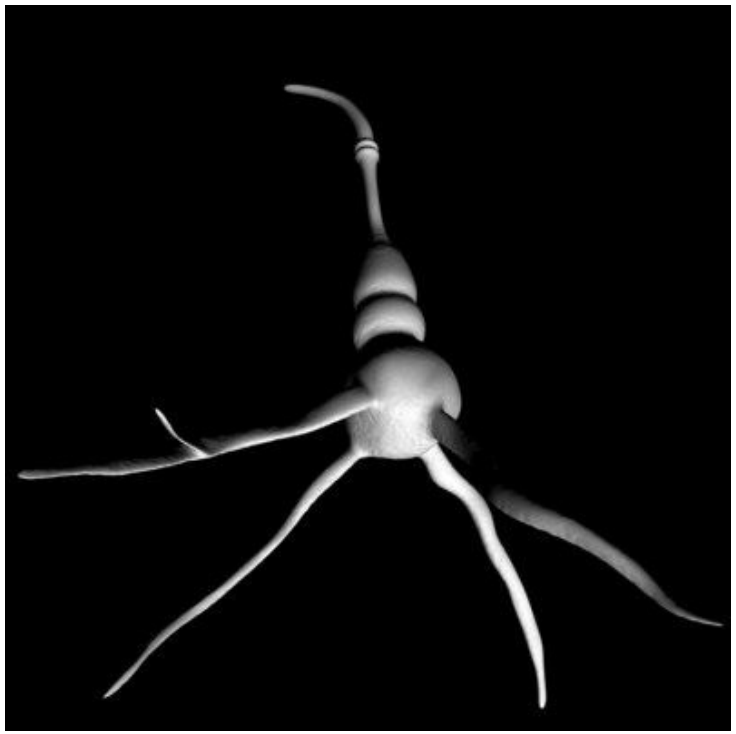




Hodgkin, Huxley (1953) *J Physiol* 117: 500-544

3D-model: descriptive



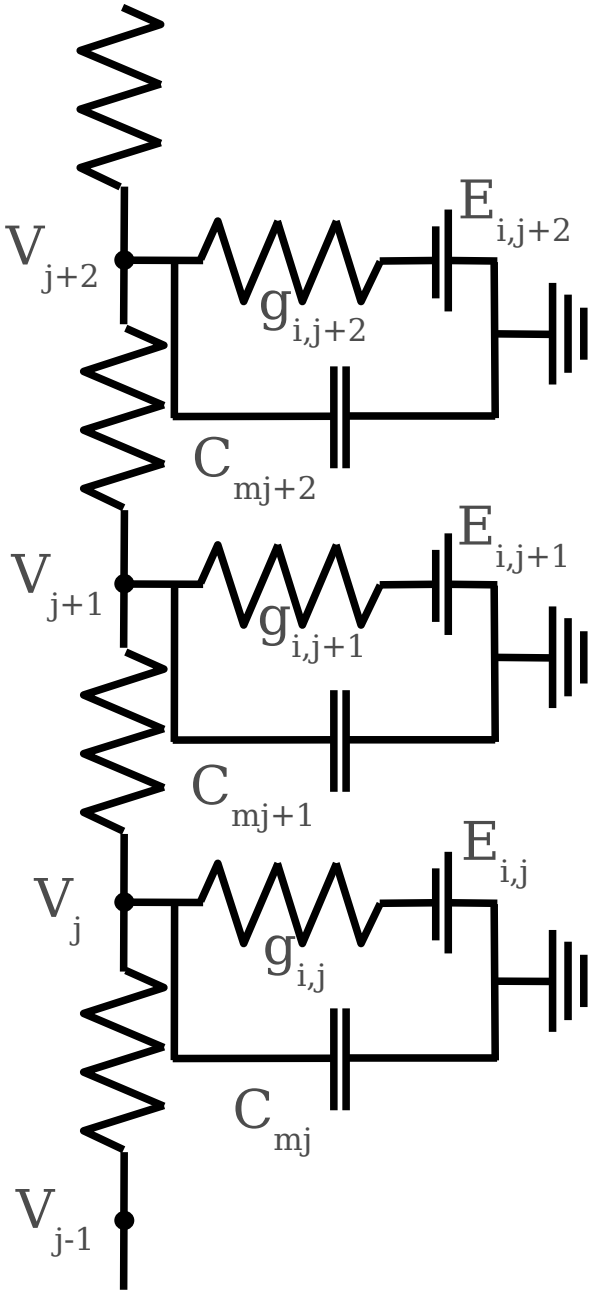


Richards et al (2005) *PNAS* 102: 6166-6171

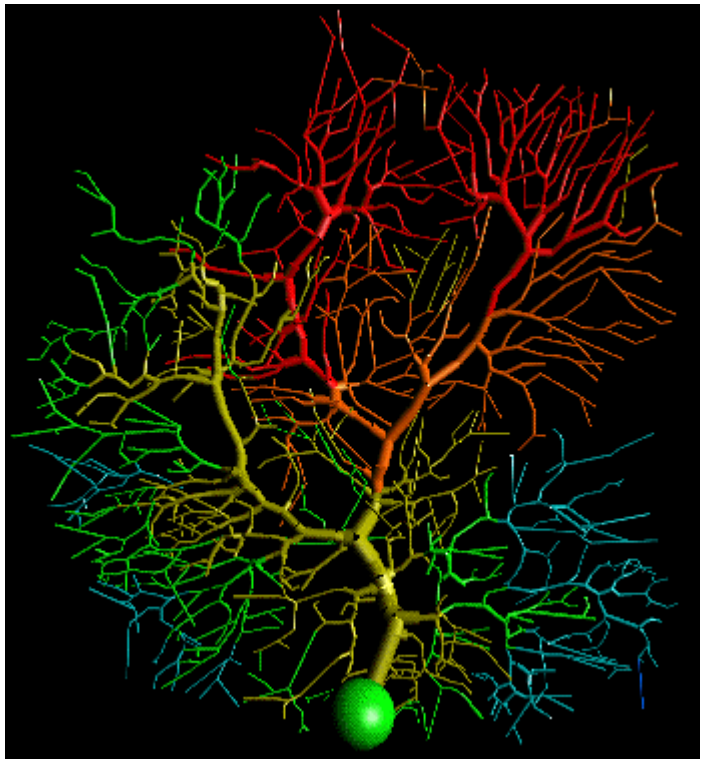
What is a model? A more relaxed definition

A model is a quantitative description of a system, or the components of a system and their relationships

Cable approximation



Rall (1959) *Exp Neurol* 1: 491-527.



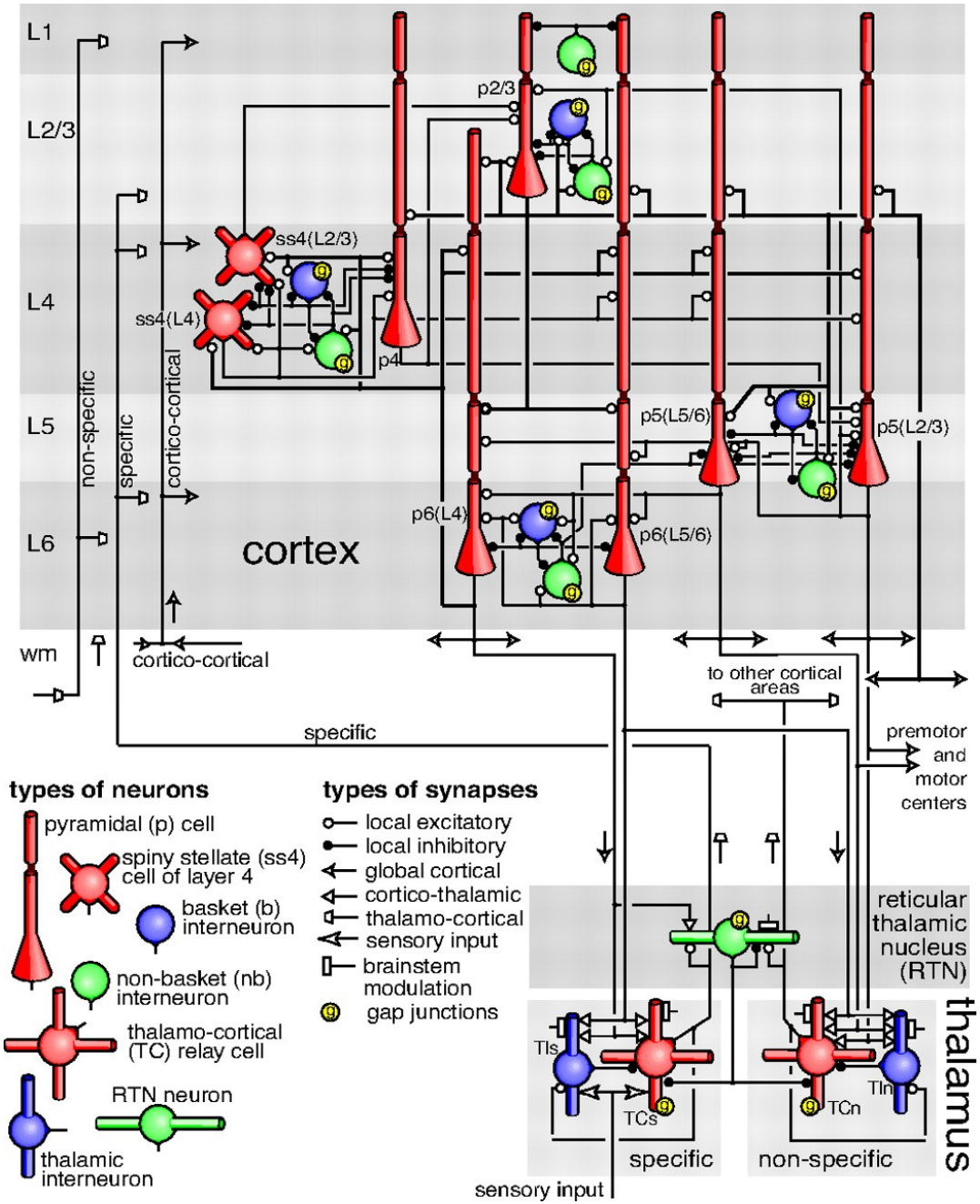
The Purkinje Neuron

- 1 Neuron
- > 3000 compartments

De Schutter (1994) *J Physiol* 71: 375-400.

$$Cm\frac{dV_j}{dt} = -\sum_i g_i j[V_j - E_i] + \sum_k \frac{V_k - V_j}{R_j k} + I$$

Connectivity: Qualitative



Izhikevich, Edelman (2008) *PNAS* 105: 3593-3598

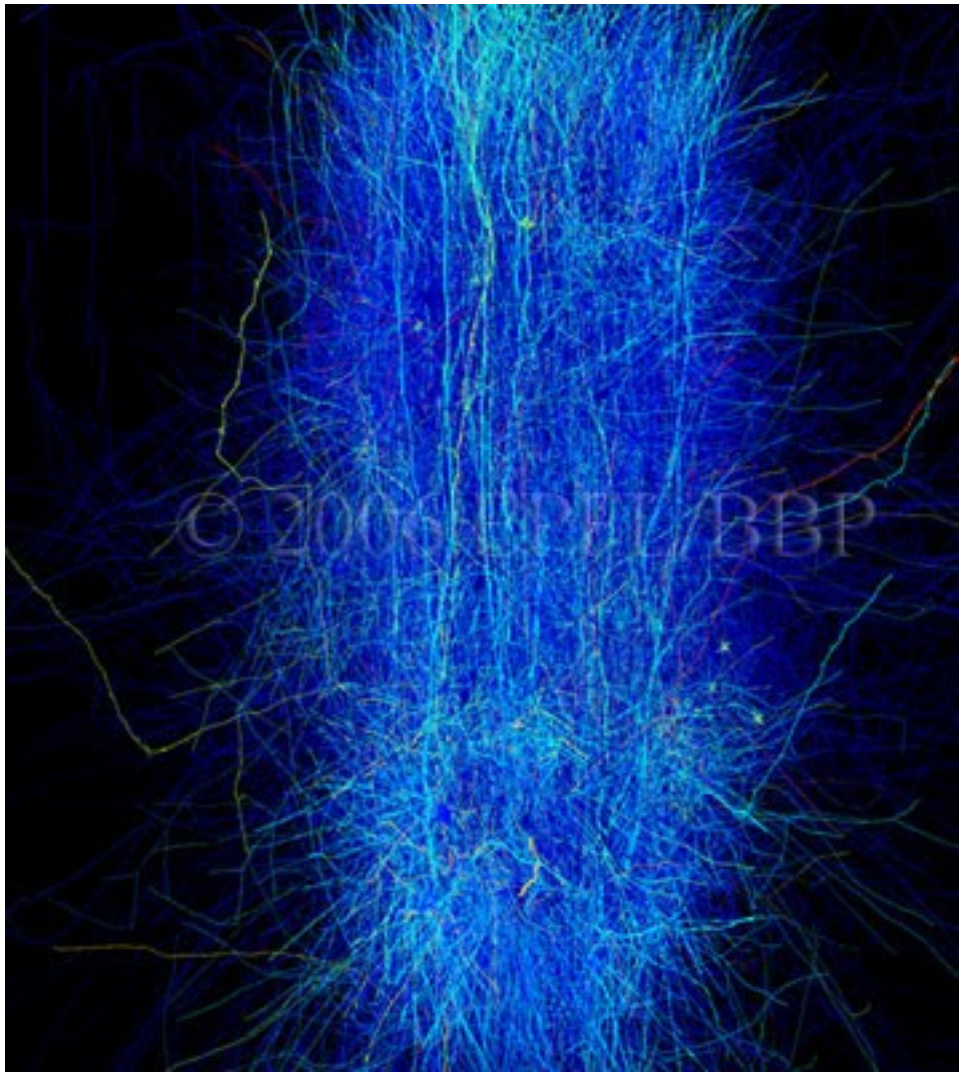
What is a model? A final definition?

A model is a formal description of a system, or the components of a system and their relationships

Functional assembly

- 10 000 Neurons
- ~100 compartments

The neocortical column of the blue-brain project

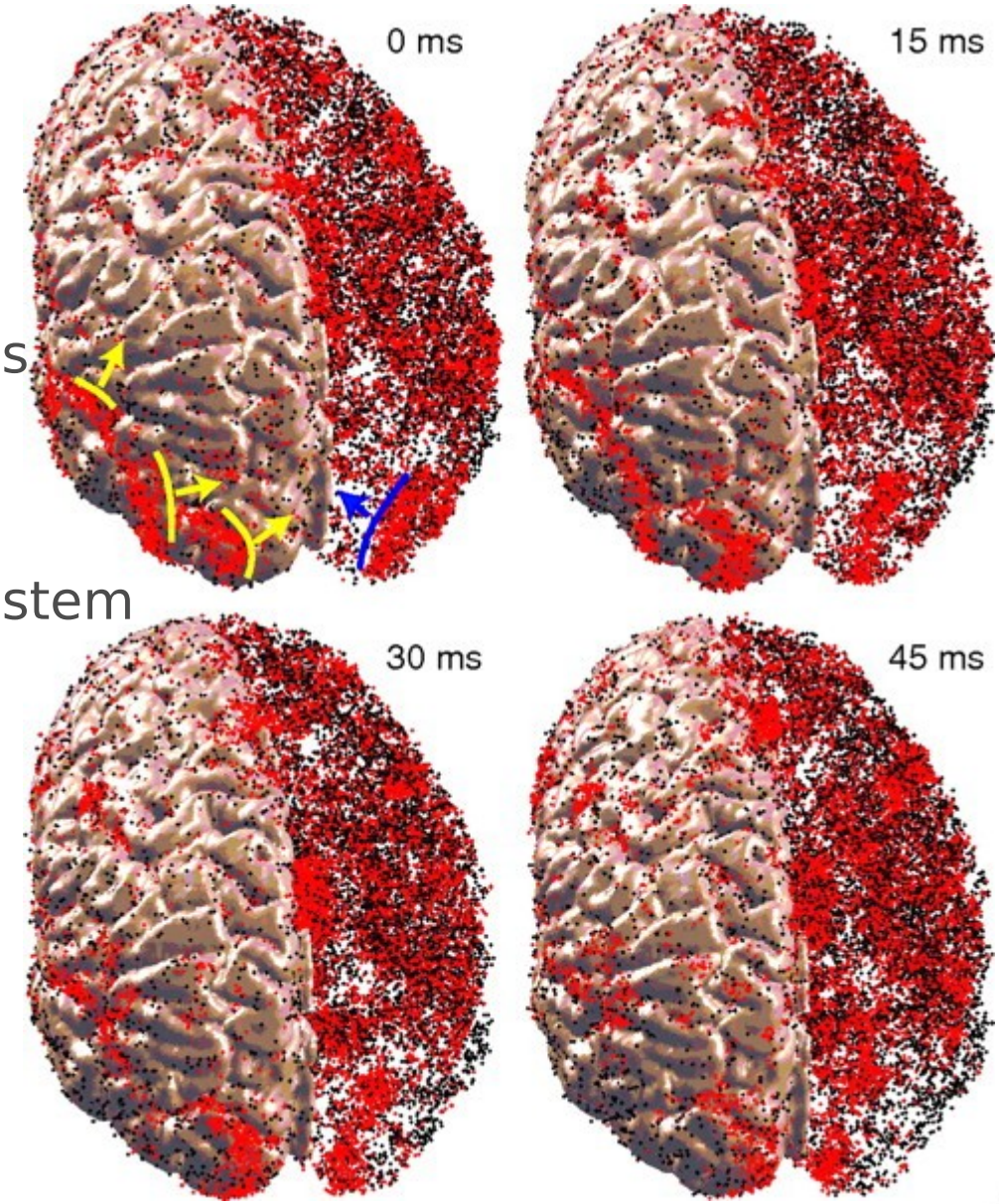


Markram (2006) *Nat Rev Neurosci* 7: 153-160.

A whole organ

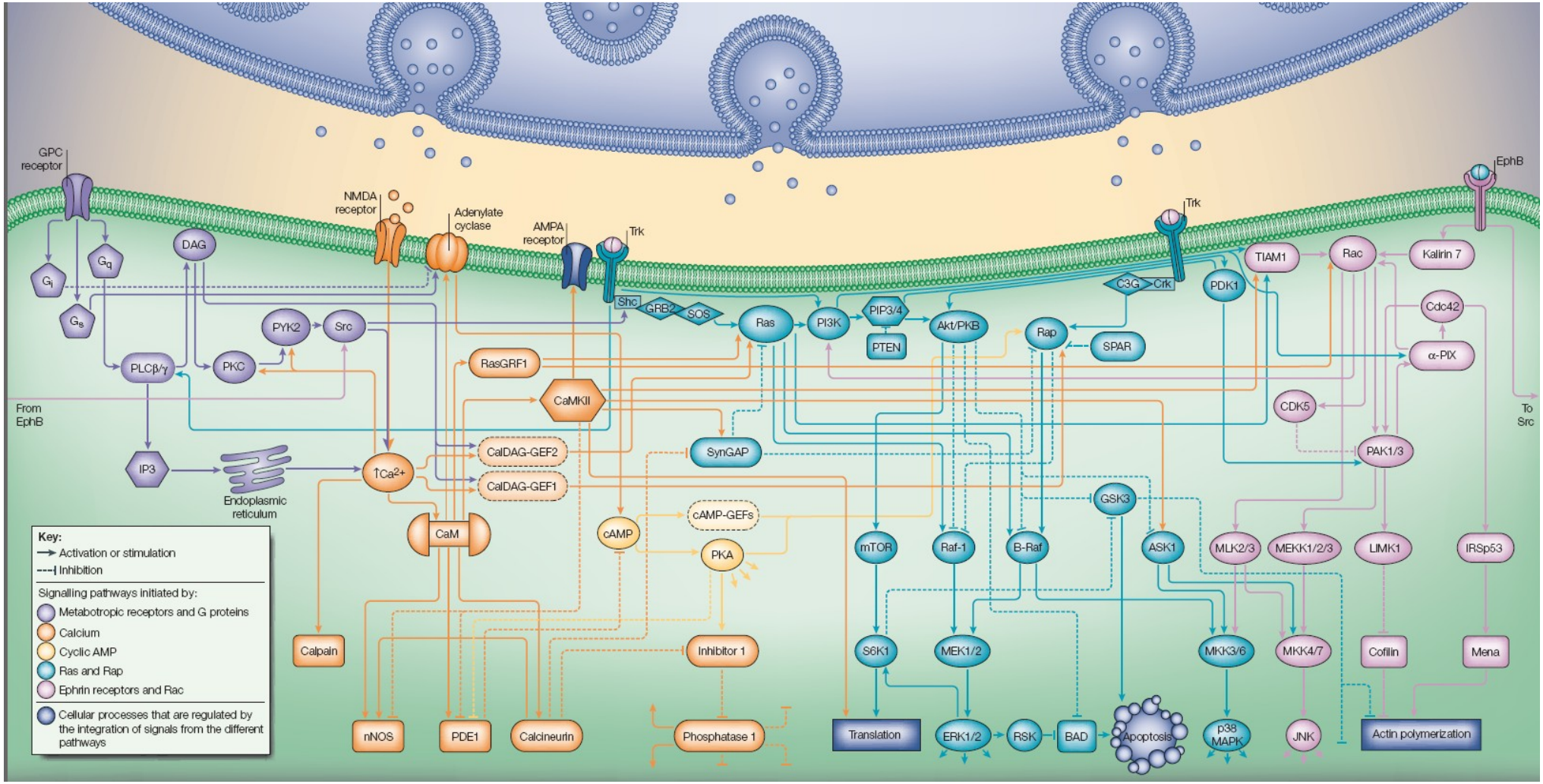
- 1 000 000 Neurons
- 10-50 compartments
- 1 000 000 000 synapses

The thalamo-cortical system



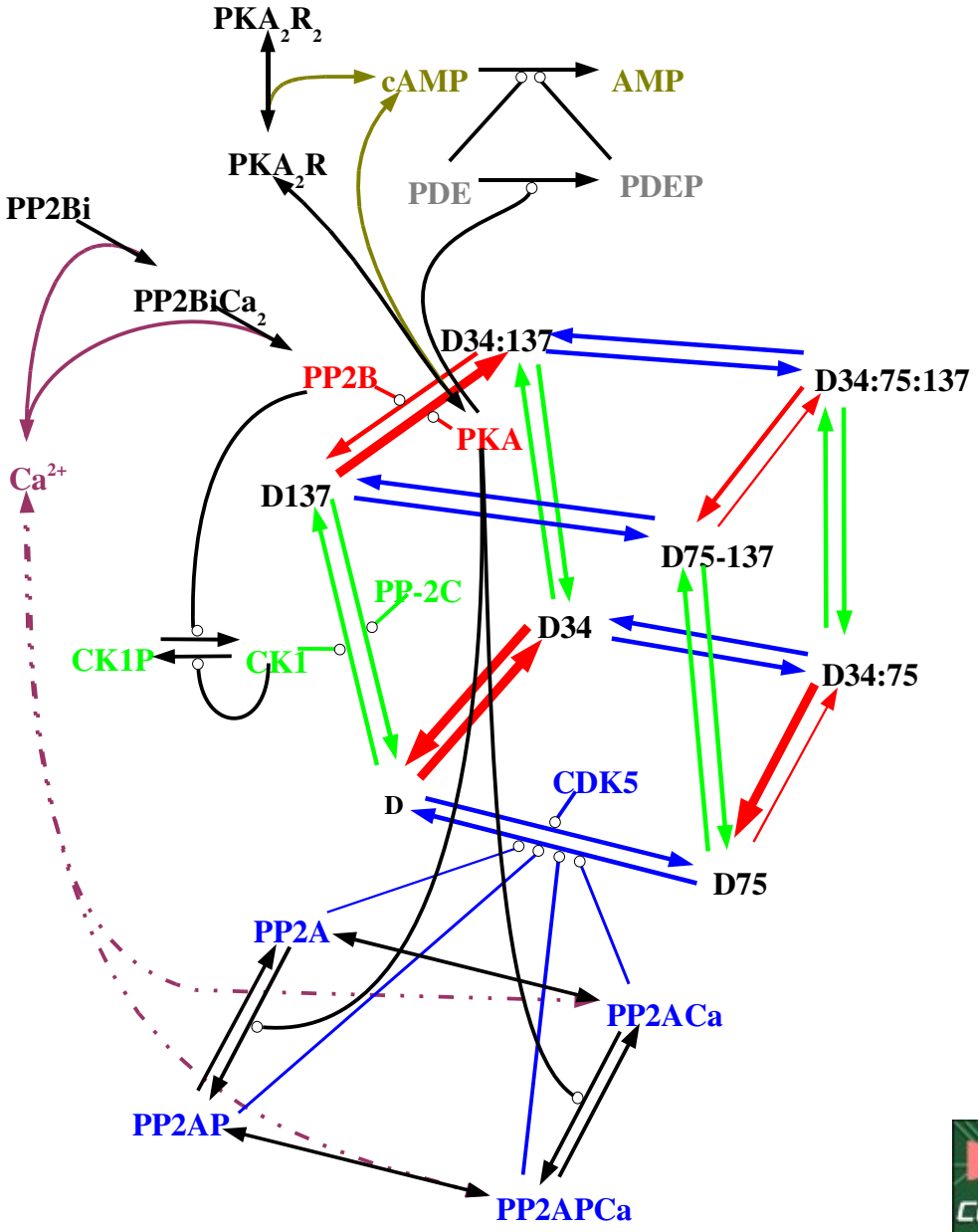
Izhikevich, Edelman (2008) *PNAS* 105: 3593-3598

Signalling pathways: logic

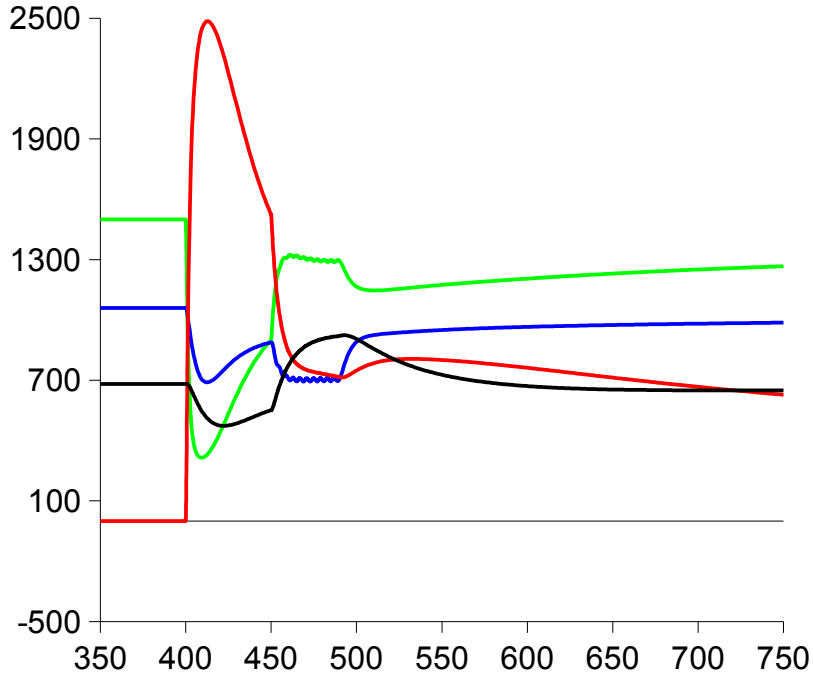


Kennedy et al (2005) *Nat Rev Neurosci* 6

Signalling pathways: ODEs



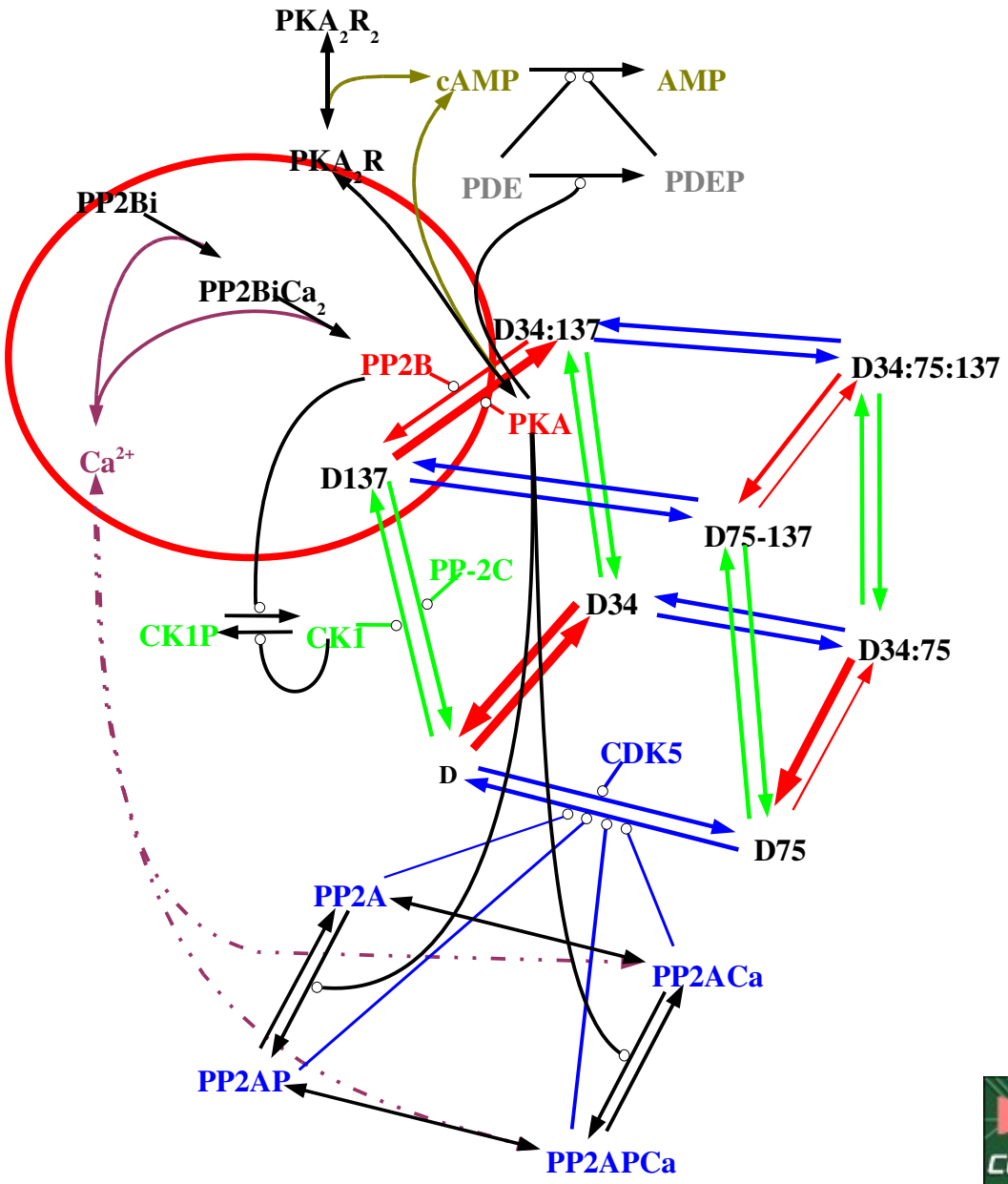
$$\frac{dX_i}{dt} = \sum_j n_{ij} f(X_0, X_1, ..., X_n)$$



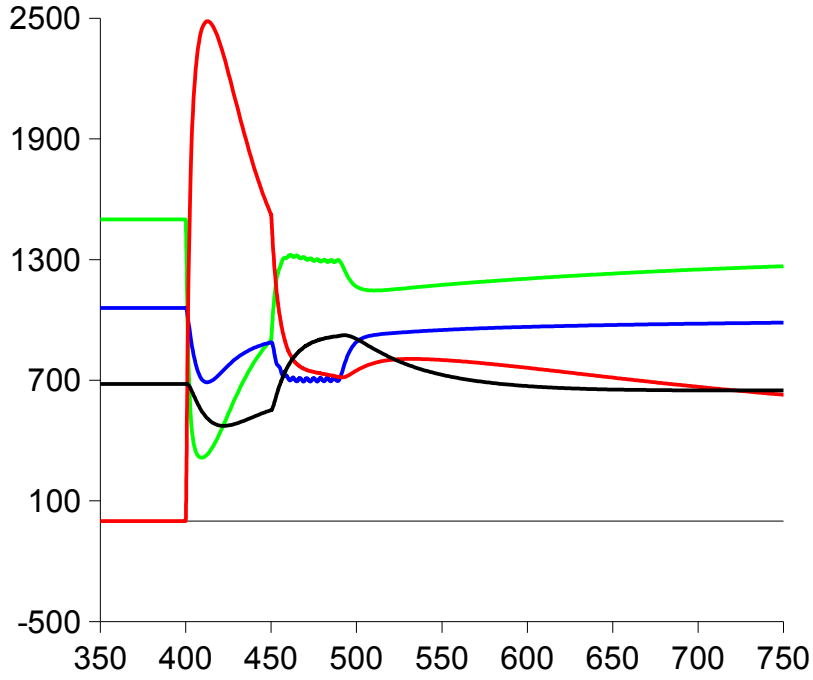
Computational Neurobiology

Fernandez et al (2006)
PLoS Comp Biol 2: e176

Signalling pathways: ODEs



$$\frac{dX_i}{dt} = \sum_j n_{ij} f(X_0, X_1, ..., X_n)$$

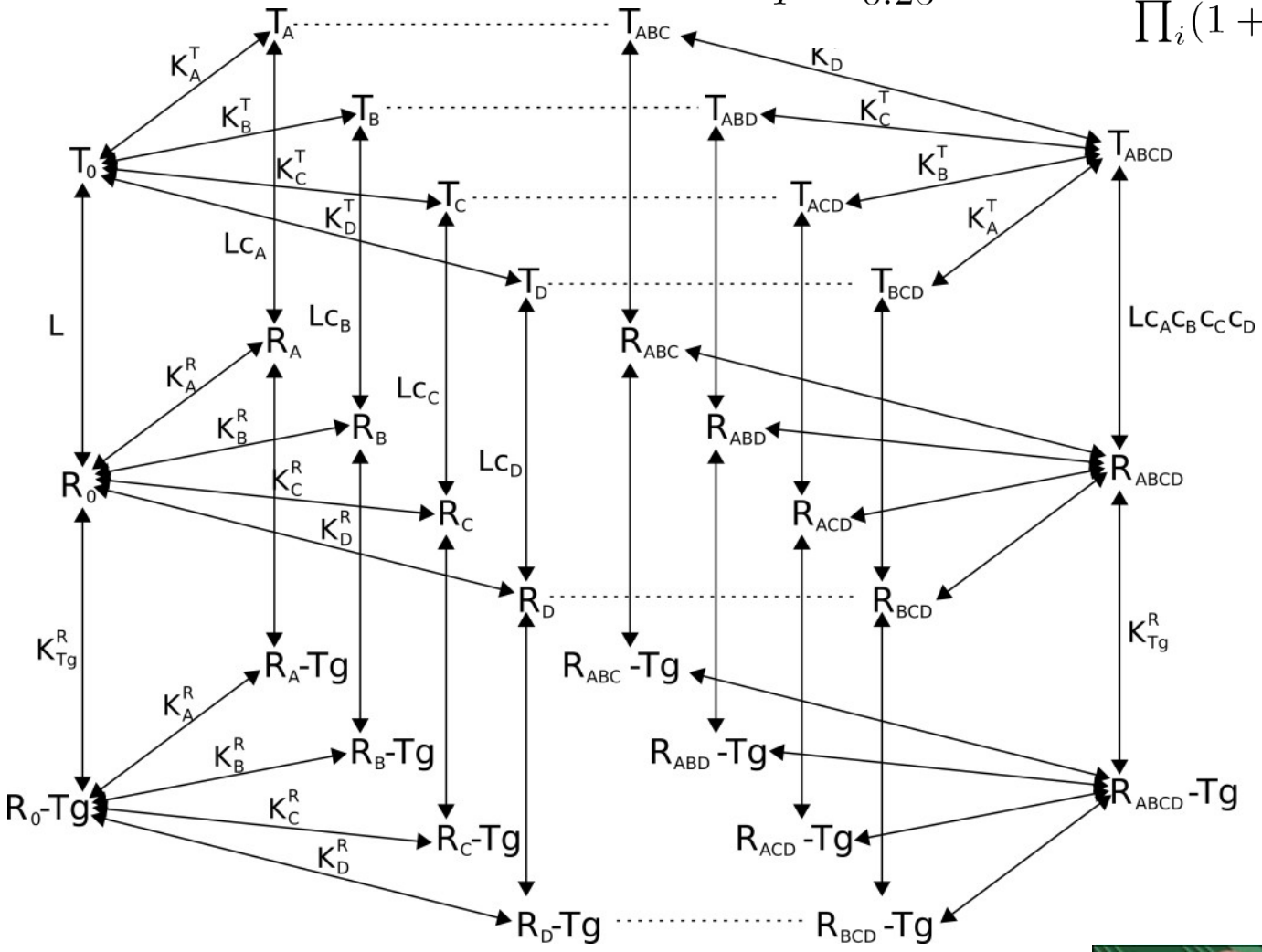


Computational Neurobiology

Fernandez et al (2006)
PLoS Comp Biol 2: e176

Biophysical models of signalling

$$\bar{Y} = 0.25 \frac{\sum_i \left(\alpha_i \prod_j (1+\alpha_j)\right) + L \sum_i \left(c_i \alpha_i \prod_j (1+c_j \alpha_j)\right)}{\prod_i (1+\alpha_i) + L \prod_i (1+c_i \alpha_i)}$$



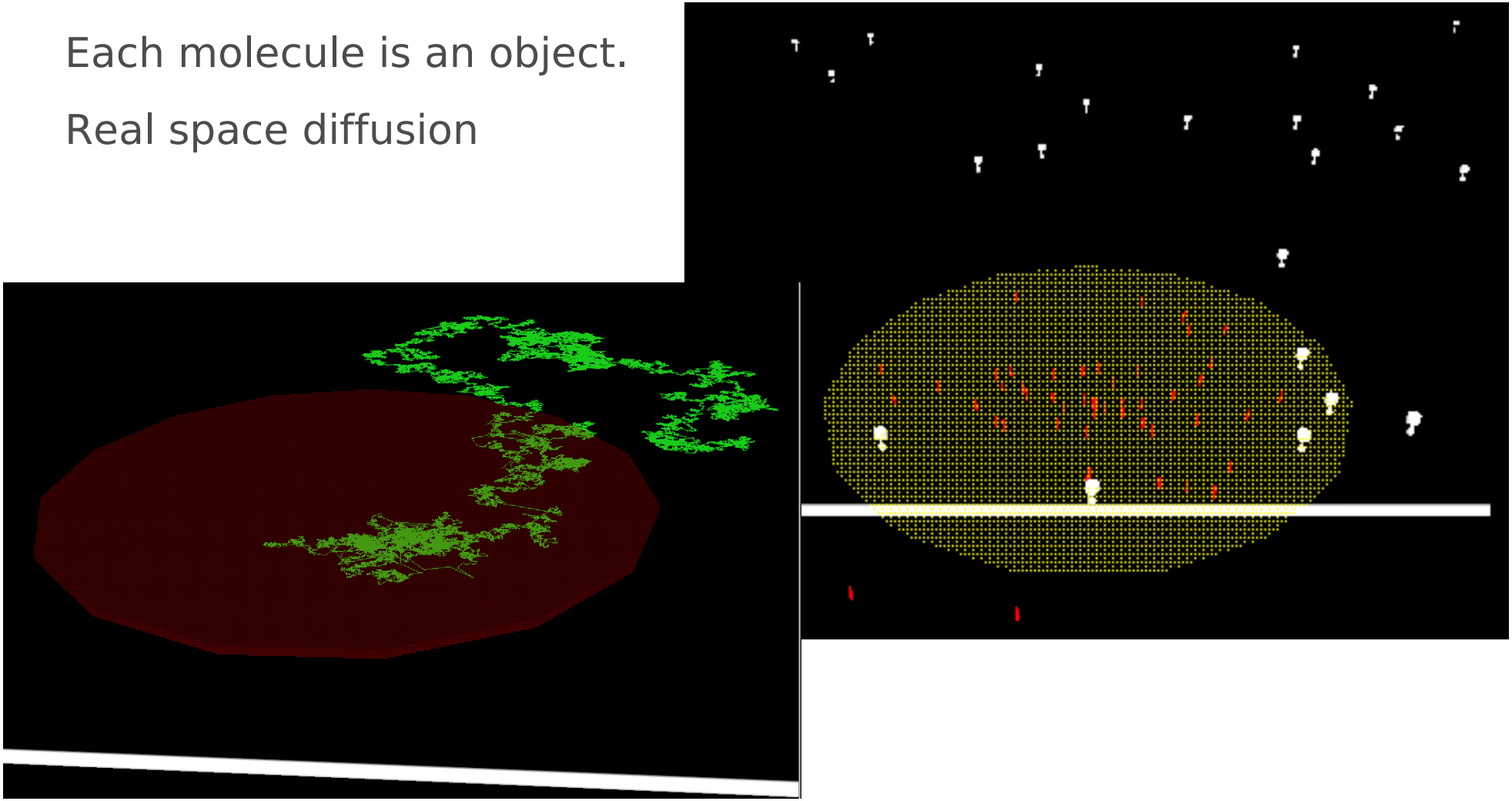
Computational Neurobiology

Stefan et al (2008)
PNAS, in the press

Agent-based models

Each molecule is an object.

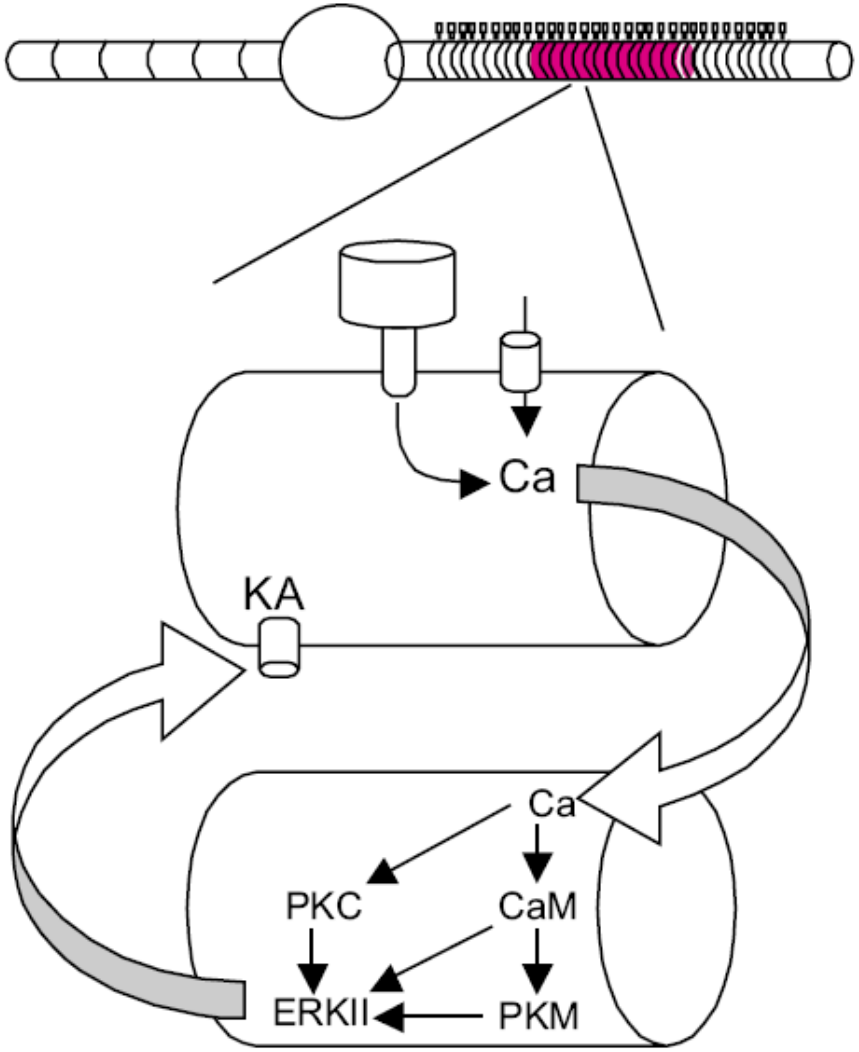
Real space diffusion

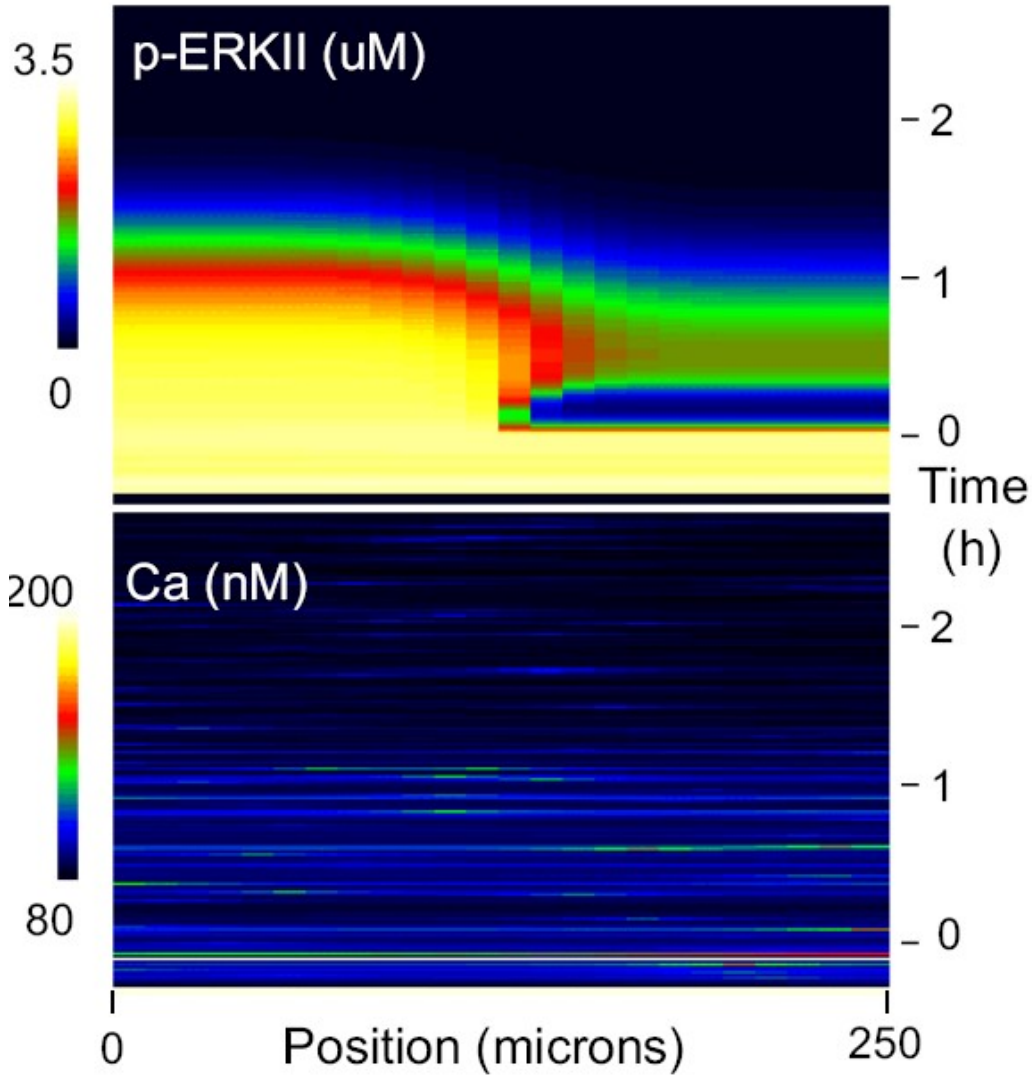


Computational Neurobiology

Tolle (2006)
Curr Bioinfo 1: 315-320

Signalling in multi-compartment models





Upinder Bhalla (personal communication)

Cellular network

Molecular network

Electrical behaviour

Multi-compartment model

Biochemical processes

Neuronal system

Geometry and topology

Space and diffusion

Quantitative representation

Logical interactions and inferences

Qualitative representation

What do-we need to understand each other?

- Standard formats
  - BioPAX
  - Systems Biology Markup Language (SBML)
  - Systems Biology Graphical Notation (SBGN)
- Guidelines
  - Minimum Information Requested In the Annotation of Models
  - Minimum Information About a Simulation Experiment
- Ontologies
  - BioPAX ...
  - Systems Biology Ontology
  - Kinetic Simulation Algorithm Ontology (KiSAO)
  - Terminology for the Description of Dynamics (TeDDy)

SBML.org — The Systems Biology Markup Language

The **Systems Biology Markup Language** (**SBML**) is a computer-readable format for representing models of biochemical reaction networks in software. It's applicable to models of metabolism, cell-signaling, and many others. SBML has been evolving since mid-2000 thanks to an international community of software developers and users. This website is the portal for the global SBML development effort; here you can find information about all aspects of SBML.

For the curious

What *is* SBML? Read our **basic introduction** and then perhaps browse the **mailing lists** to get a sense for what's currently going on in the world of SBML.

For modelers

Are you looking for ready-to-run software that supports SBML? Take a look at our **SBML Software Guide**. Are you instead looking for ready-to-use models? Visit the **BioModels Database**, where you can find hundreds of tried and tested models.

For software developers

Are you interested in developing SBML support for your software? Read our **basic introduction** and then the **SBML specifications** to understand how to use SBML. After that, you may want to look at **libSBML**, an API library supporting many programming languages.

Whether you use SBML as a modeler or a developer, we invite you to sign up for news updates either through our **RSS feed** or one of the **mailing lists**, and get involved with community efforts to help keep SBML improving.

SBML News

SBML.org problems
(29 May '08) A security break-in on the server, followed by a disk failure, caused SBML.org to be off-line for two days while we rebuilt it.

New SBML FAQ
(7 May '08) A greatly revised and rewritten list of FAQs and answers for SBML is **now available**.

New mailing list introduced
(6 May '08) A new mailing list, **libsbml-development**, now exists for discussions of libSBML improvement and development.

Older news ...

Community News

SBToolbox^2 version 2.0
(6 Jun.'08) The latest version of **SBToolbox** adds GUIs, new optimization methods, and new sensitivity analysis methods.

Cell Illustrator 4.0
(14 May.'08) **BioBase** has released version 4.0 of **Cell Illustrator**. It supports importing SBML.

COPASI user workshop
(23 Apr.'08) The **COPASI** team will hold a 3-day workshop July 22–24, 2008, at the VBI in Virginia.

Older news ...

What is a SBML?

- Website: SBML is a computer-readable format for representing models of biochemical reaction networks [...]. It's applicable to models of metabolism, cell-signaling, and many others.

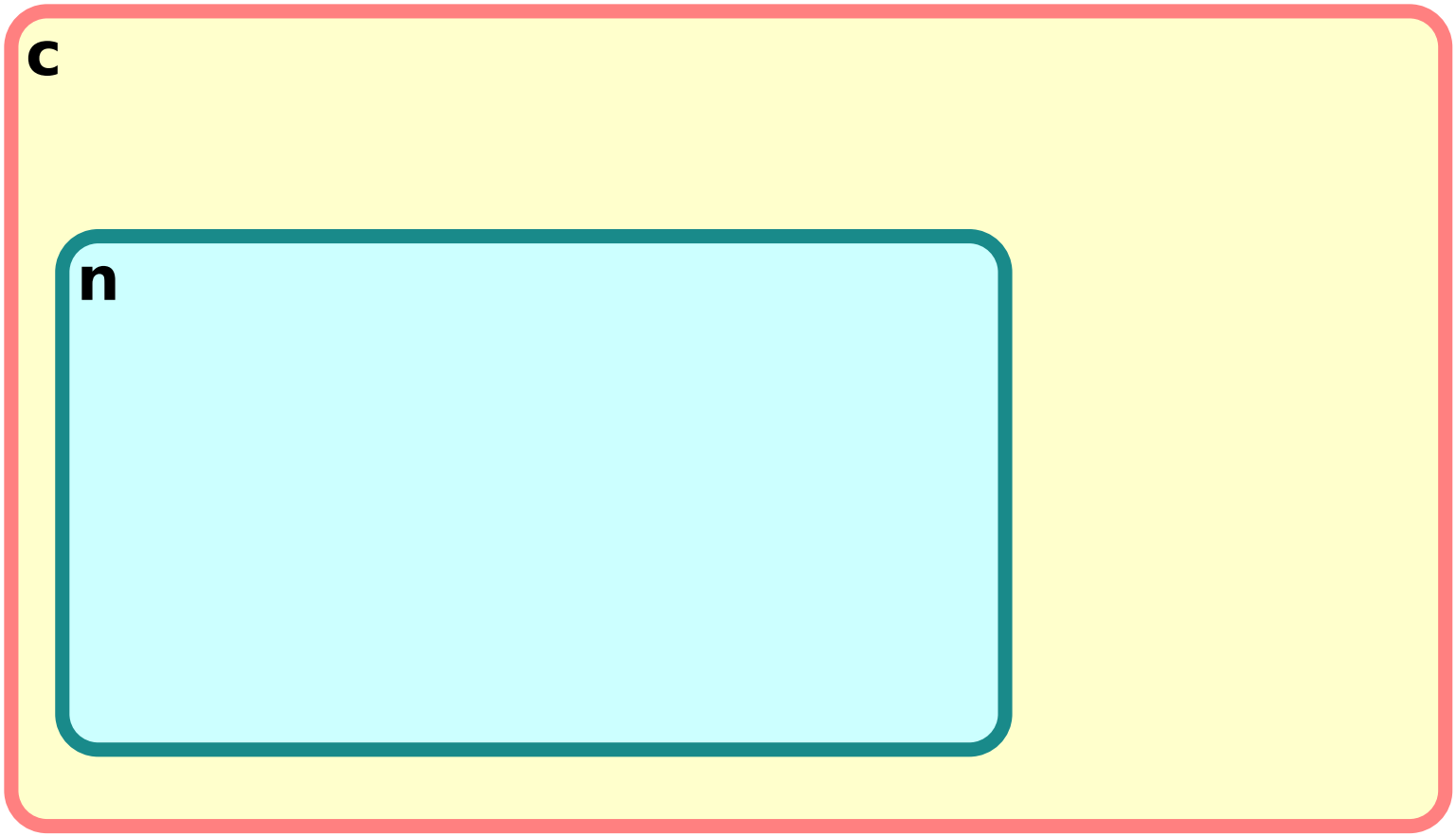
What is a SBML?

- Website: SBML is a computer-readable format for representing models of biochemical reaction networks [...]. It's applicable to models of metabolism, cell-signaling, and many others.
- SBML allows to encode models of biological processes unambiguously, so that any simulation software interpret them the same way.
- SBML core element is the reaction, not the variable. The final mathematical representation is built by the reading software.
- SBML is neutral when it comes to simulation approaches and algorithms.

What can we encode in SBML?

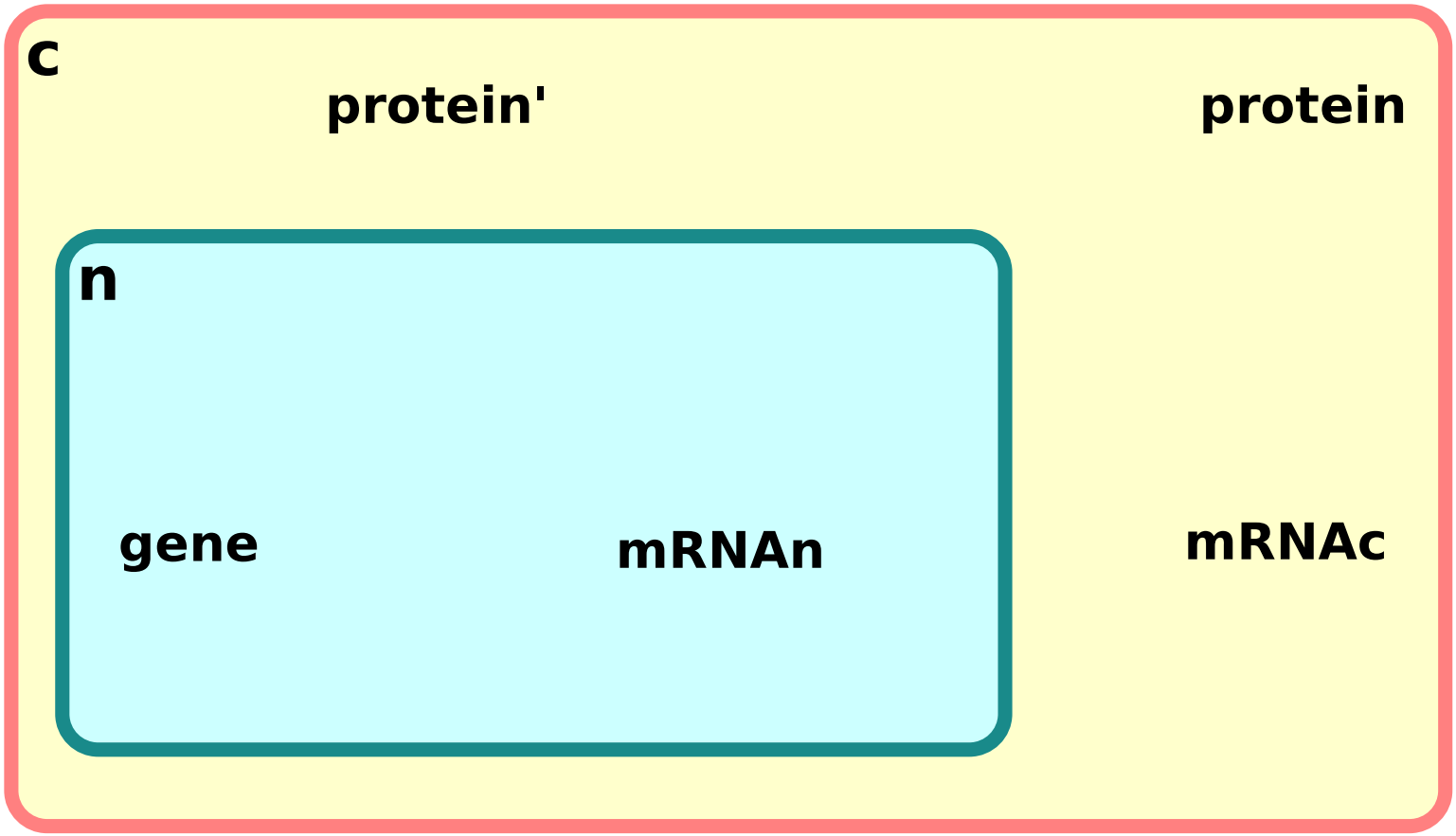
What can we encode in SBML?

Well-stirred compartments



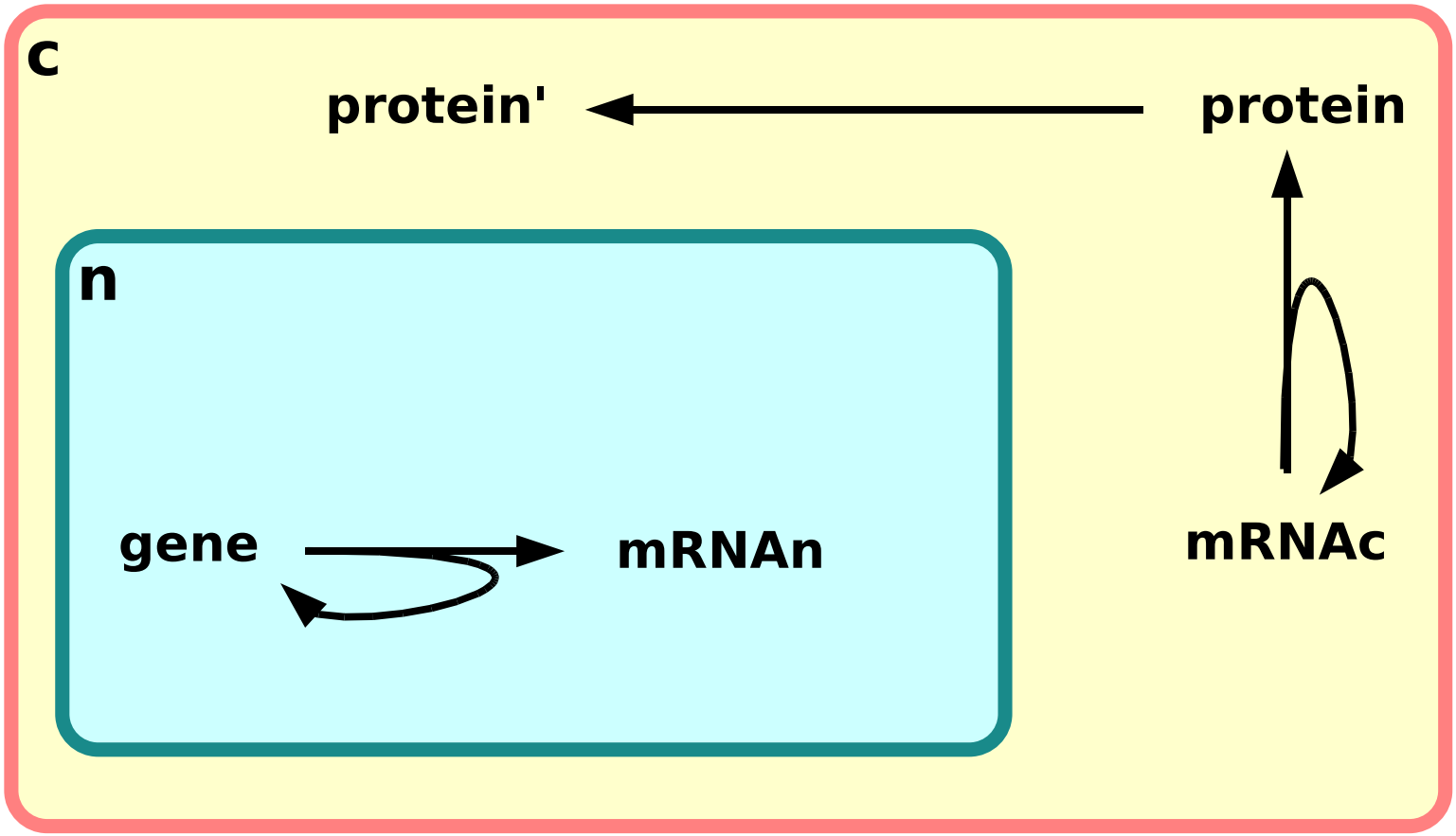
What can we encode in SBML?

Entity pools



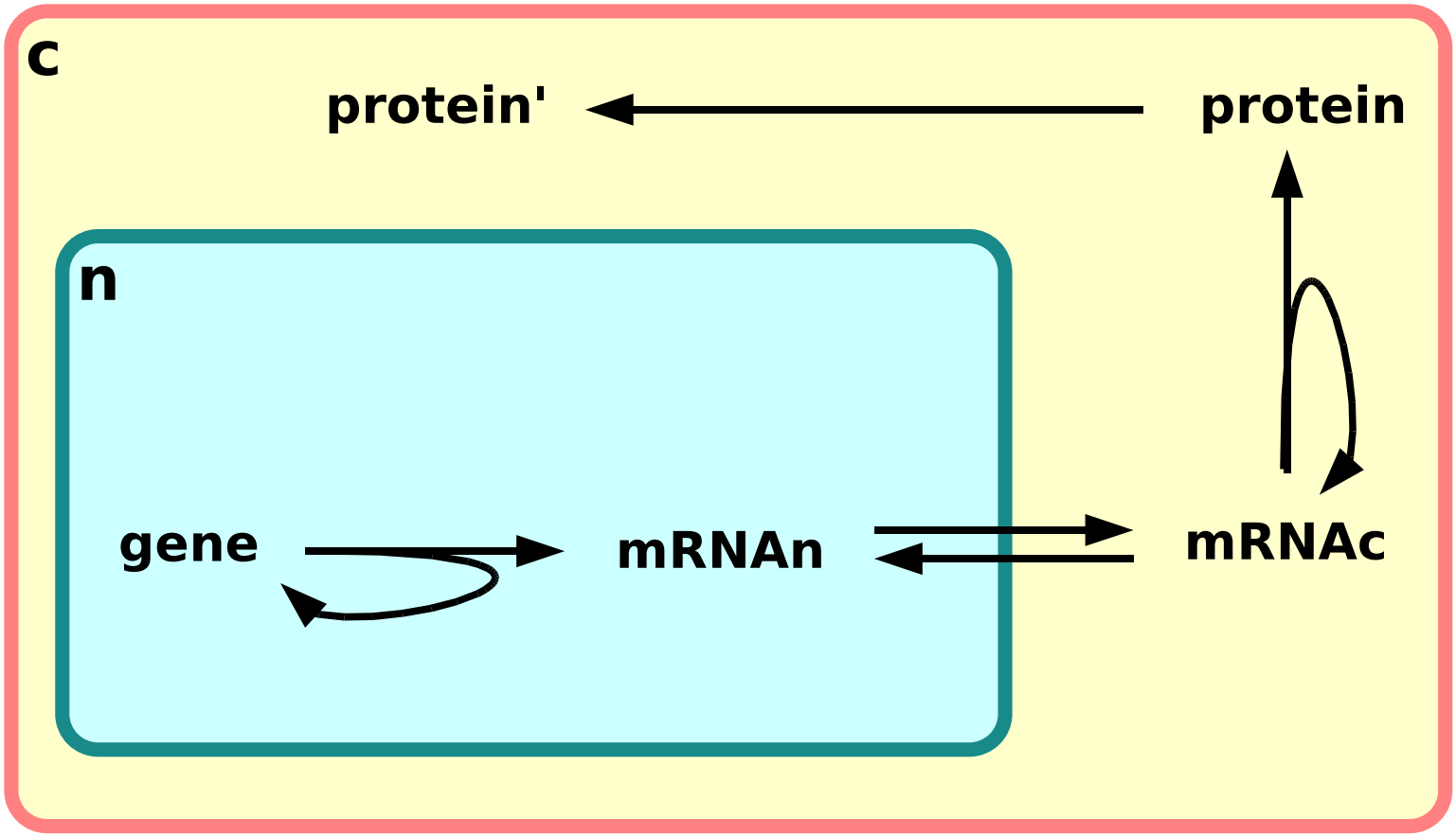
What can we encode in SBML?

reactions



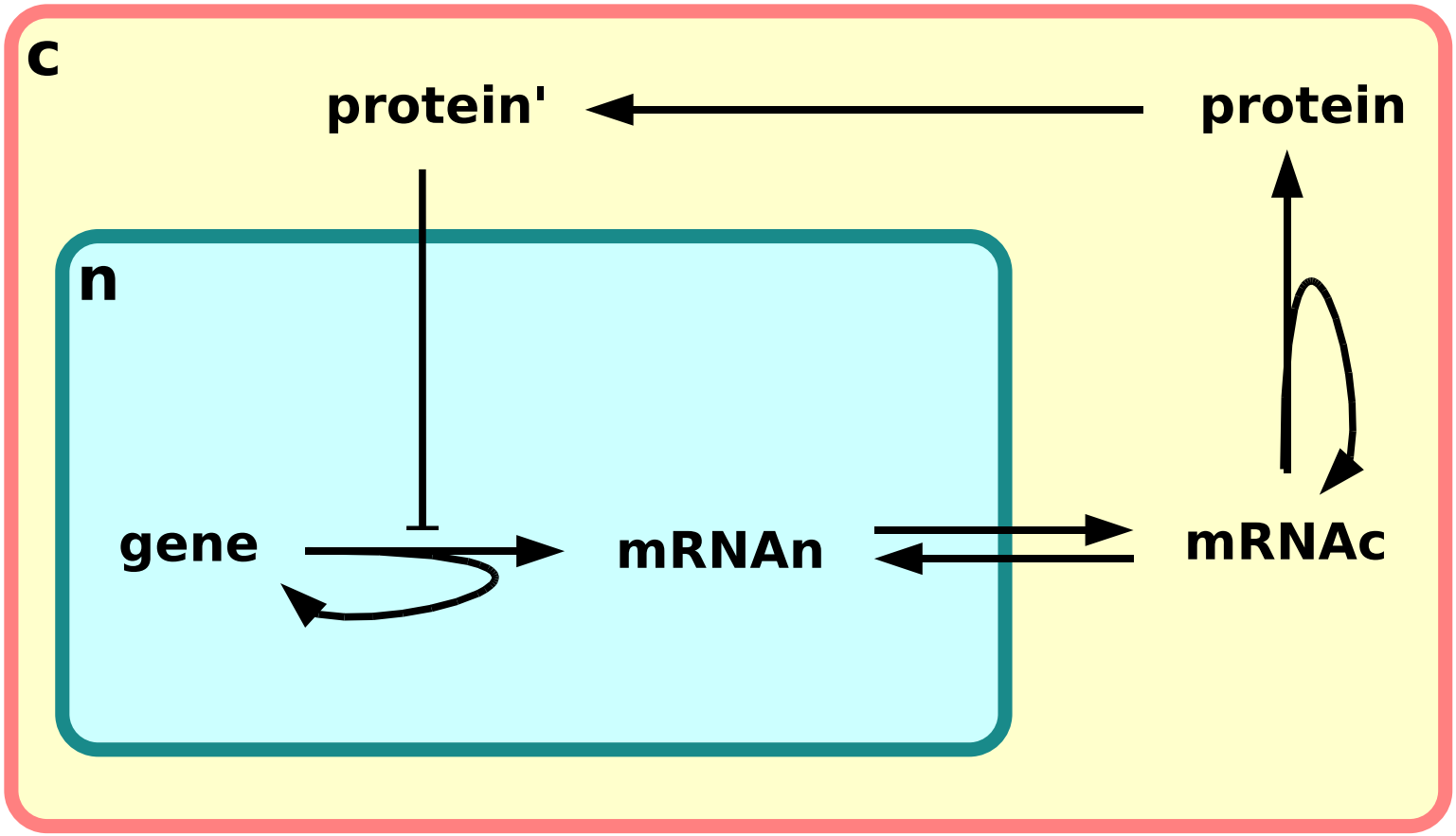
What can we encode in SBML?

reactions

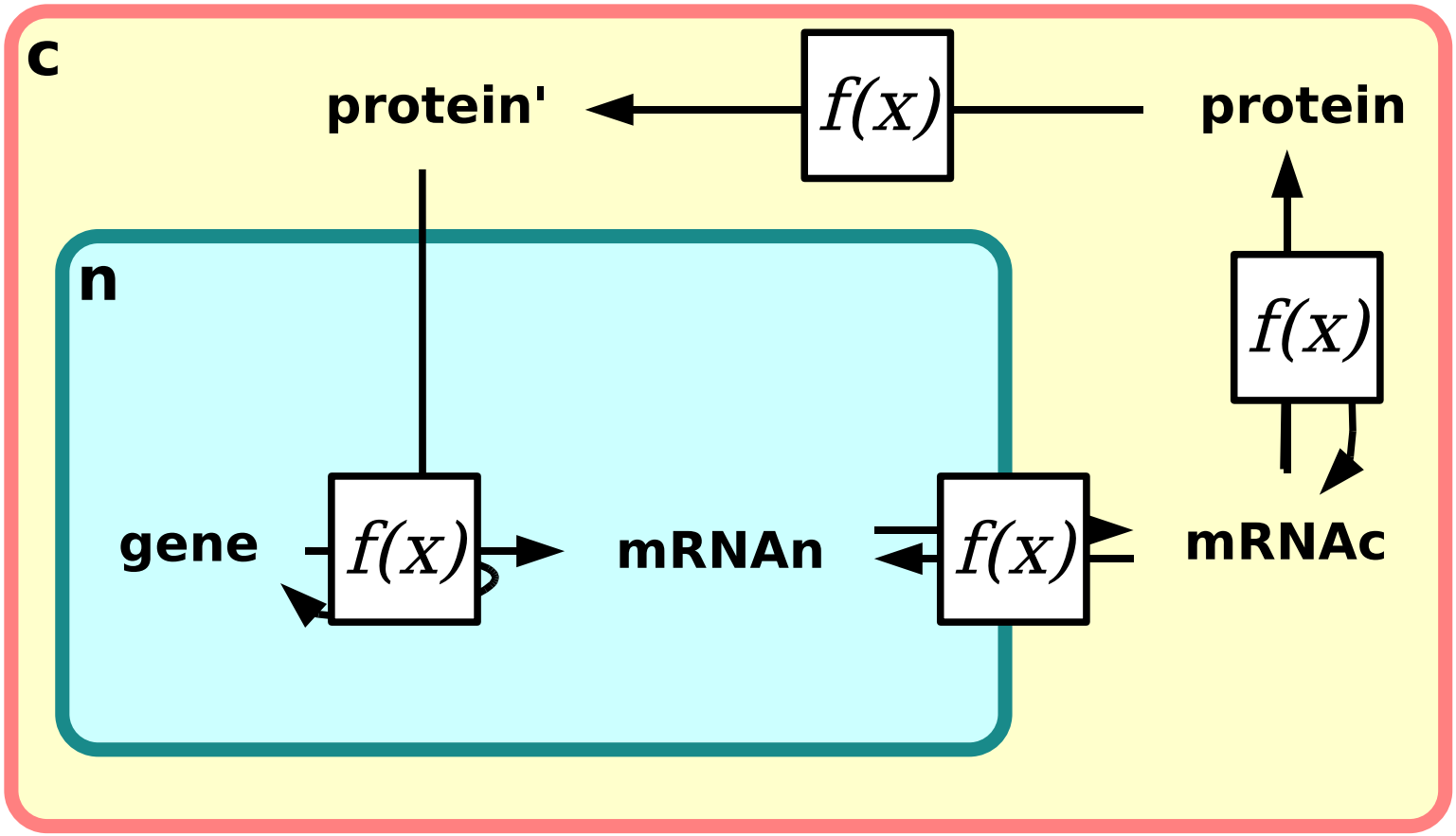


What can we encode in SBML?

modulations

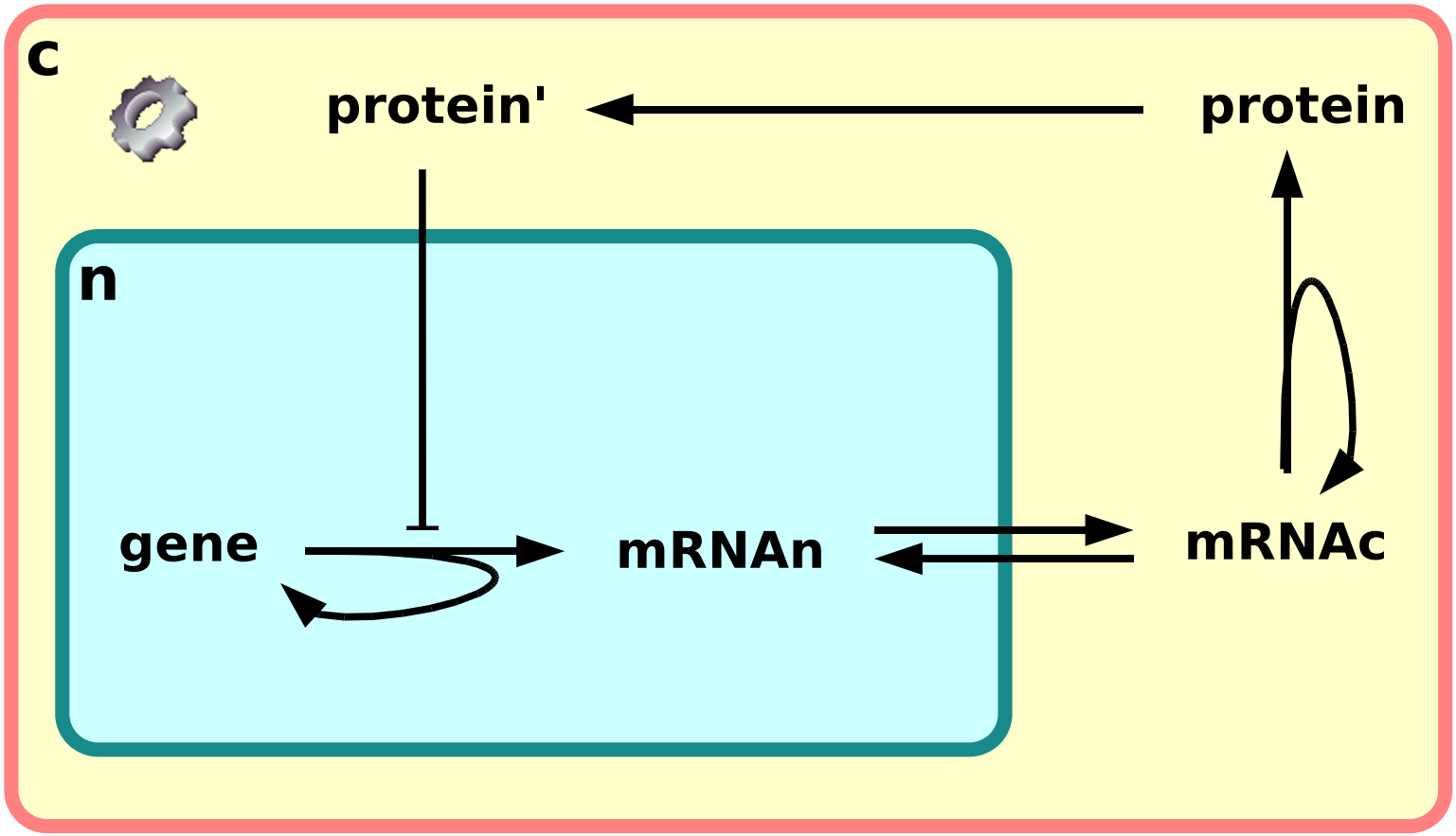


What can we encode in SBML?



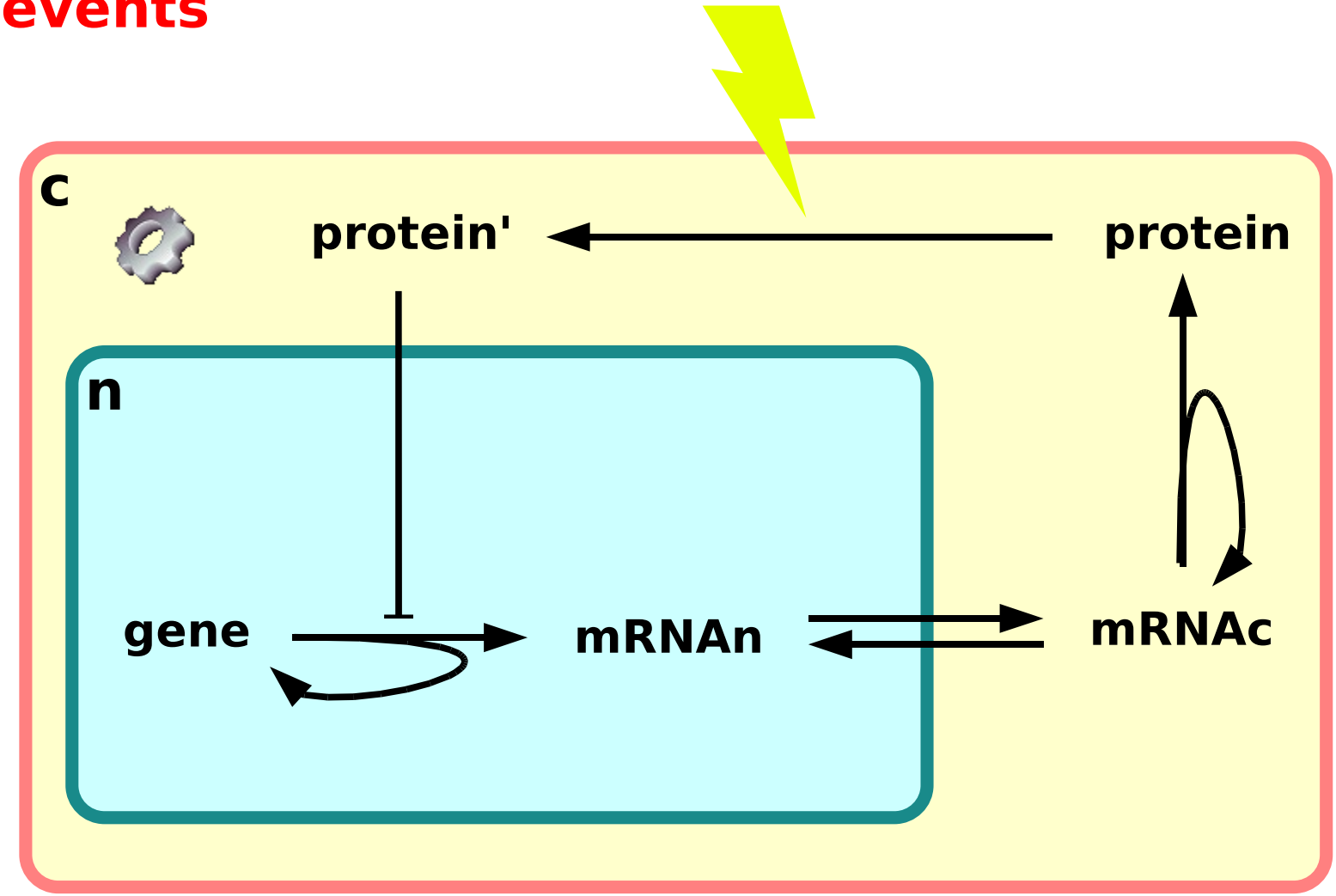
What can we encode in SBML?

rules



What can we encode in SBML?

events



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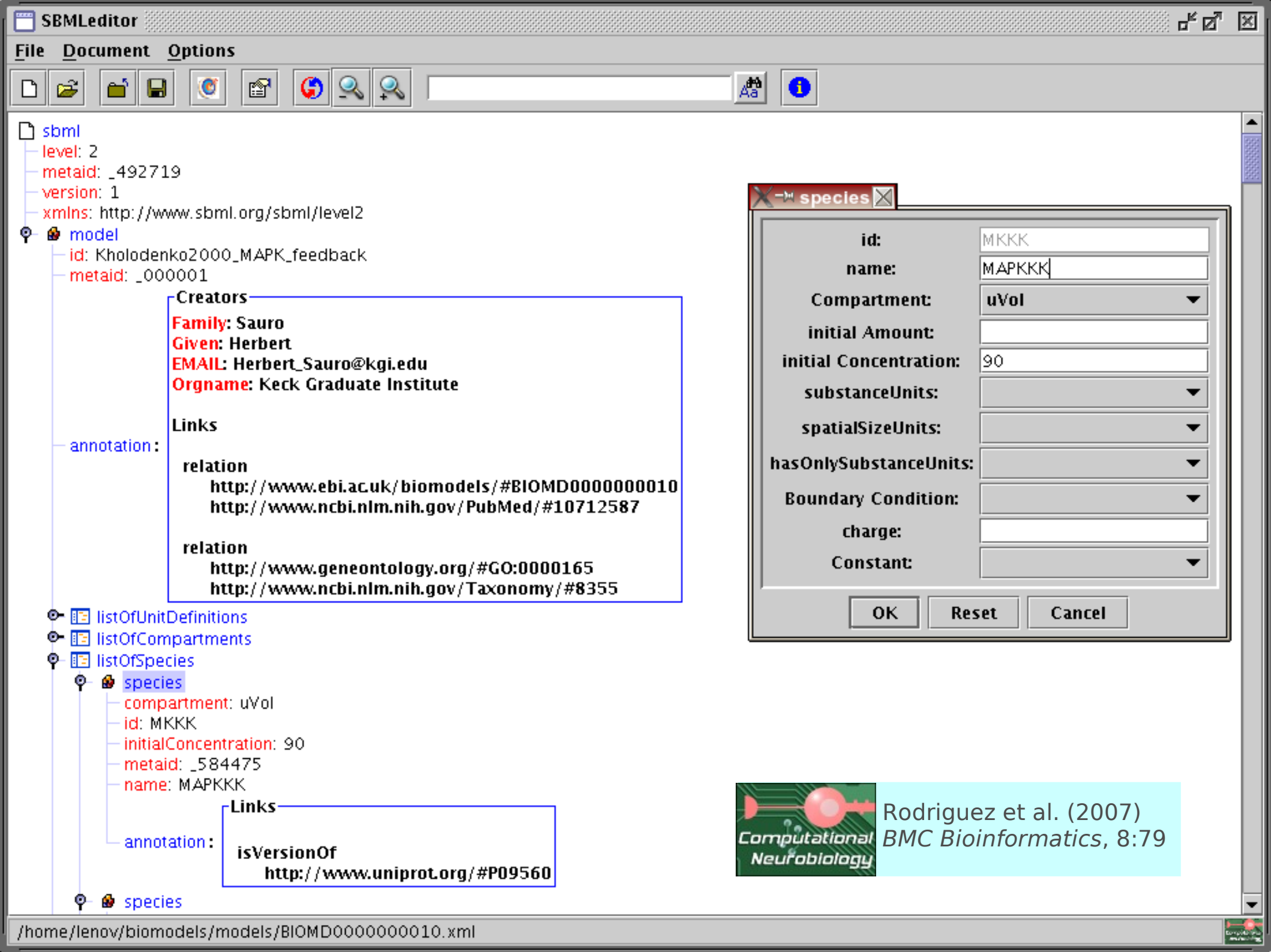
    <listOfCompartments>
      <compartment id="cell" />
    </listOfCompartments>
    <listOfSpecies>
      <species id="A" compartment="cell" initialConcentration="1"/>
      <species id="B" compartment="cell" initialConcentration="0"/>
    </listOfSpecies>
    <listOfParameters>
      <parameter id="kon" value="1"/>
    </listOfParameters>
    <listOfReactions>
      <reaction>
        <listOfReactants>
          <speciesReference species="A" />
        </listOfReactants>
        <listOfProducts>
          <speciesReference species="B" />
        </listOfProducts>
        <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
annotation:
Creators
Family: Sauro
Given: Herbert
EMAIL: Herbert_Sauro@kgi.edu
Orgname: Keck Graduate Institute
Links
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
annotation:
Links
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
Computational Neurobiology
Rodriguez et al. (2007)
BMC Bioinformatics, 8:79
/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!

SBML Levels

- **Level 1 (March 2001)**
  - Predefined kinetics functions
  - One type of reactive substance
  - ISO646 encoding

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

- **Level 2 (June 2003)**
  - Function definitions
  - Modifier species
  - Events
  - All math in MathML
  - Unicode encoding

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

- **Level 3 (dev started)**

Newest: SBML Level 2 Version 3 release 2

- Released on September 26th 2007
- Simpler and cleaner (units ...)
- Generic entities (compartmentType, speciesType)
  ➔ path to generalised reactions
- Constraints and initialAssignments
- Controlled (MIRIAM) annotations (+ links to SBO)
- Backward compatible with Level 2 Version 1
- More detailed and bug-free specification ... 166 pages, 10pt, small margin.

Hucka et al (2007) *Nat Precedings*
DOI:10101/npre.2007.58.2

SBML Level 3

- Modular SBML, with common core + optional packages
- Graph Layout (certain; already in use in Level 2 as annotation, shared by several software)
- Generalised reactions [one definition for all compartments] (probable)
- Model composition [models based on submodels] (probable)
- Complex species (multi-components multistates) (probable)
- Formal modeling [logical, petri-net etc.] (probable)
- Arrays or sets of entities (maybe)
- Geometry of physical entities (maybe)
- Spatial anisotropy and movements (maybe)
- Dynamic compartments (maybe)
- ???

SBML development process

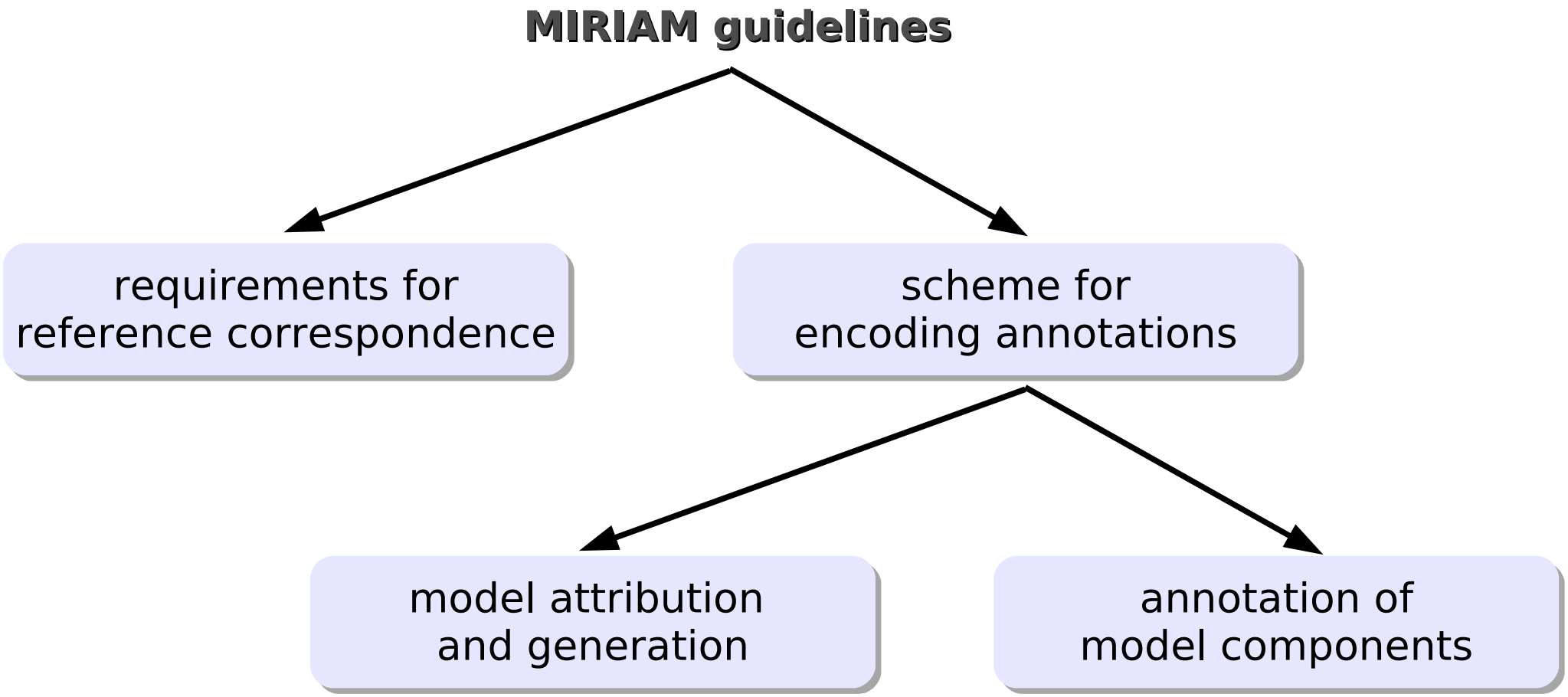
- Editorial board
  - 1 chair (head of SBML-team)
  - 5 elected editors. Single 3 year term.
- One SBML “forum” a year
  - General discussion about the evolution of the language
  - Presentation of SBML-compliant software
- One SBML “hackathon” a year
  - Development of SBML-supporting tools
  - Implementation of SBML-support
  - Writing of specification
- Communication tools
  - SBML-announce mailing list
  - SBML-discuss mailing list
  - Sourceforge trackers to debug the specification

Is SBML enough? What's missing?

- An SBML model *lists* participants, but does not *identify* them.
- An SBML model contains mathematical expressions, but does not tell-us what they *mean*, and how they are derived.
- An SBML model constructed for a certain modelling approach may not be usable straight-away within another modelling framework.

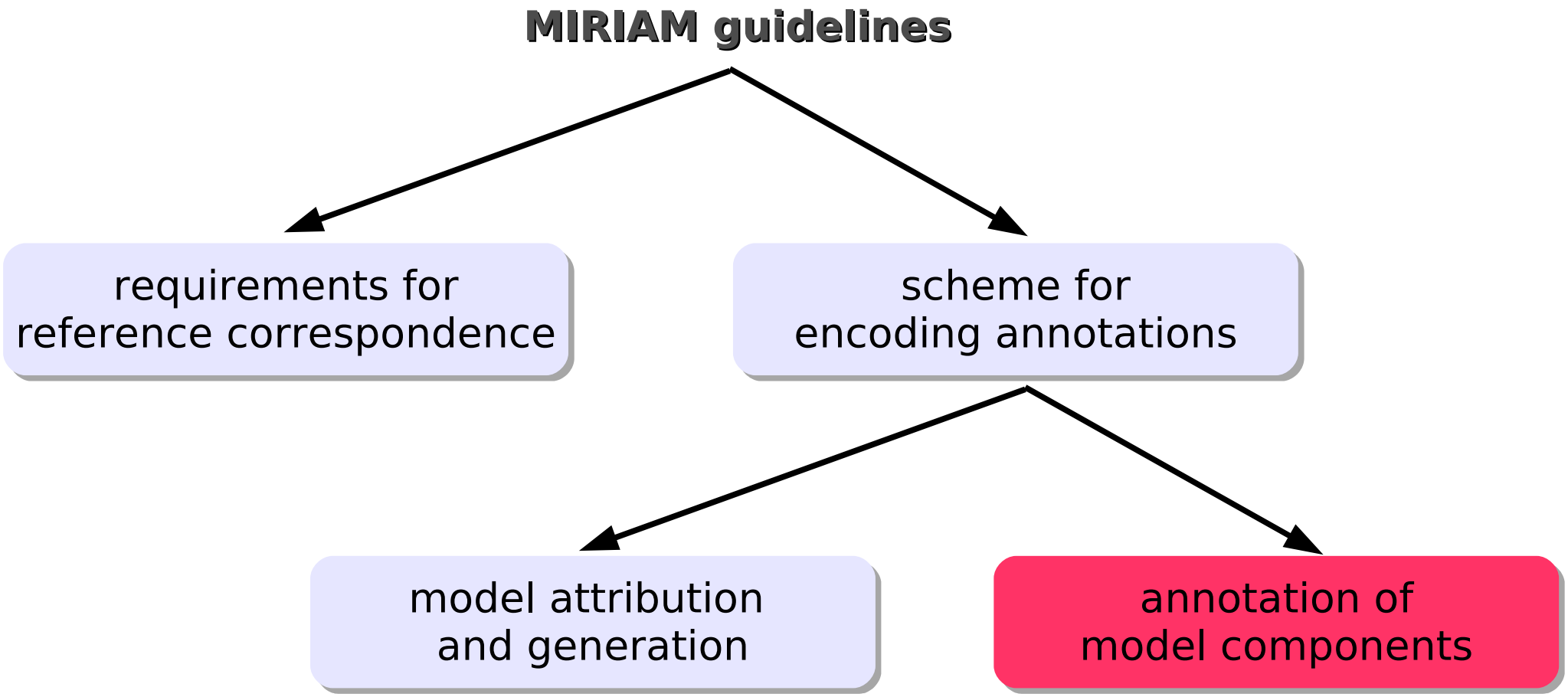
⇒ **SBML models cannot be easily searched**
SBML models cannot be easily converted
SBML models cannot be easily merged

Minimum Information Requested in the Annotation of Models(MIRIAM)

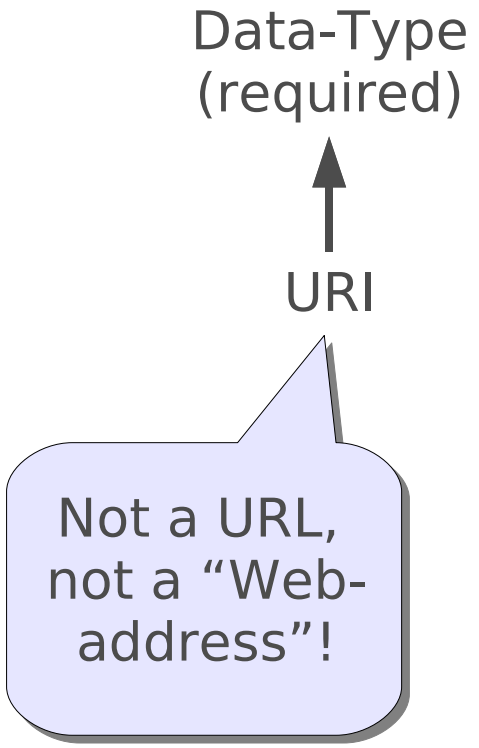


Le Novère et al (2005)
Nat Biotech 23: 1509-1515

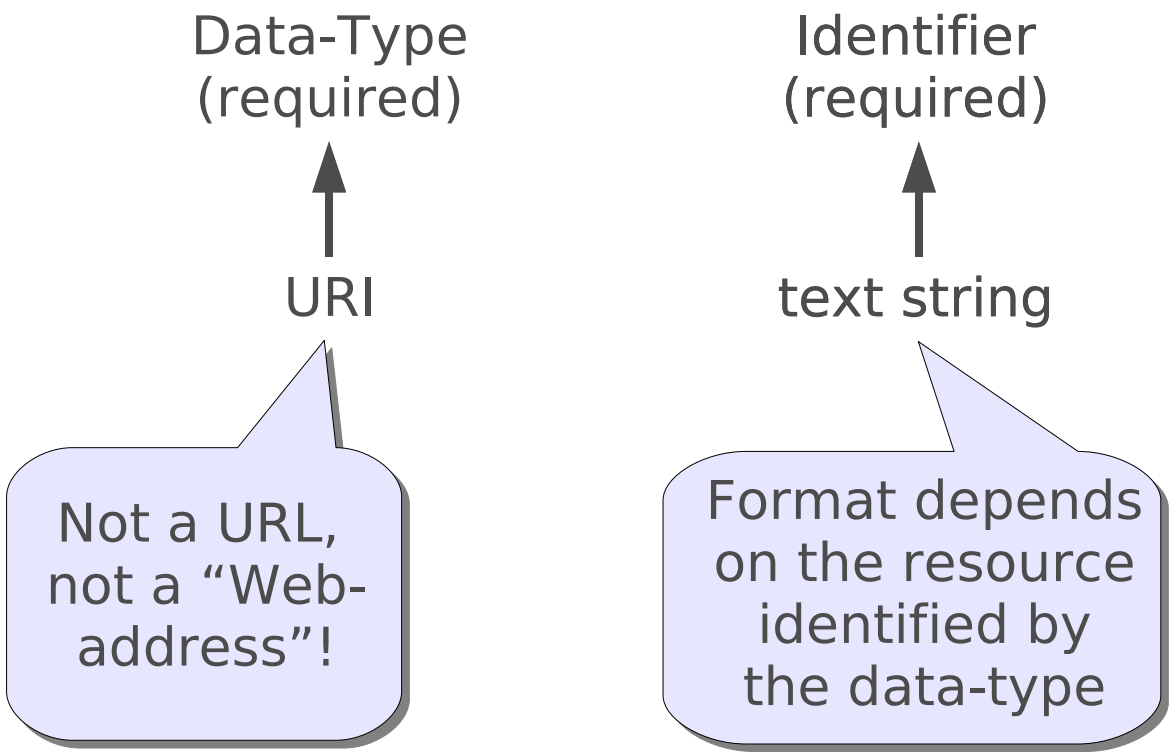
Minimum Information Requested in the Annotation of Models(MIRIAM)



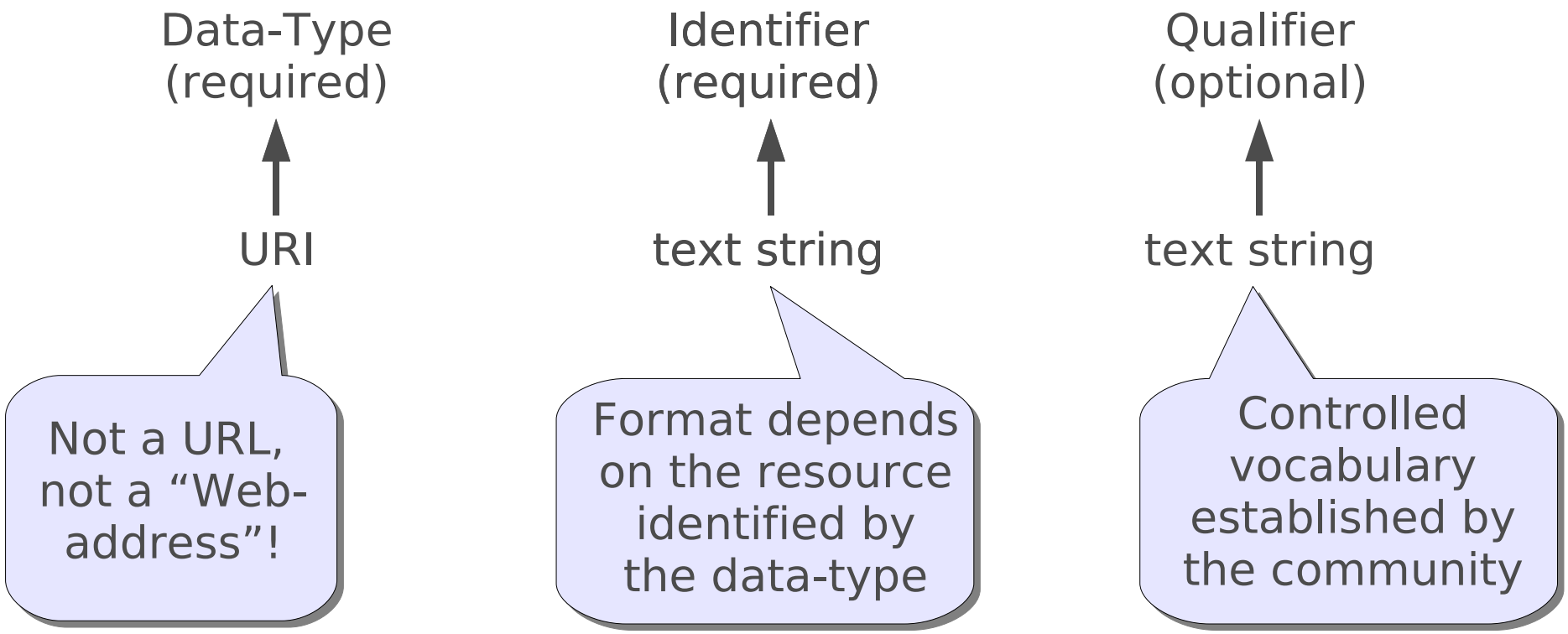
MIRIAM annotation



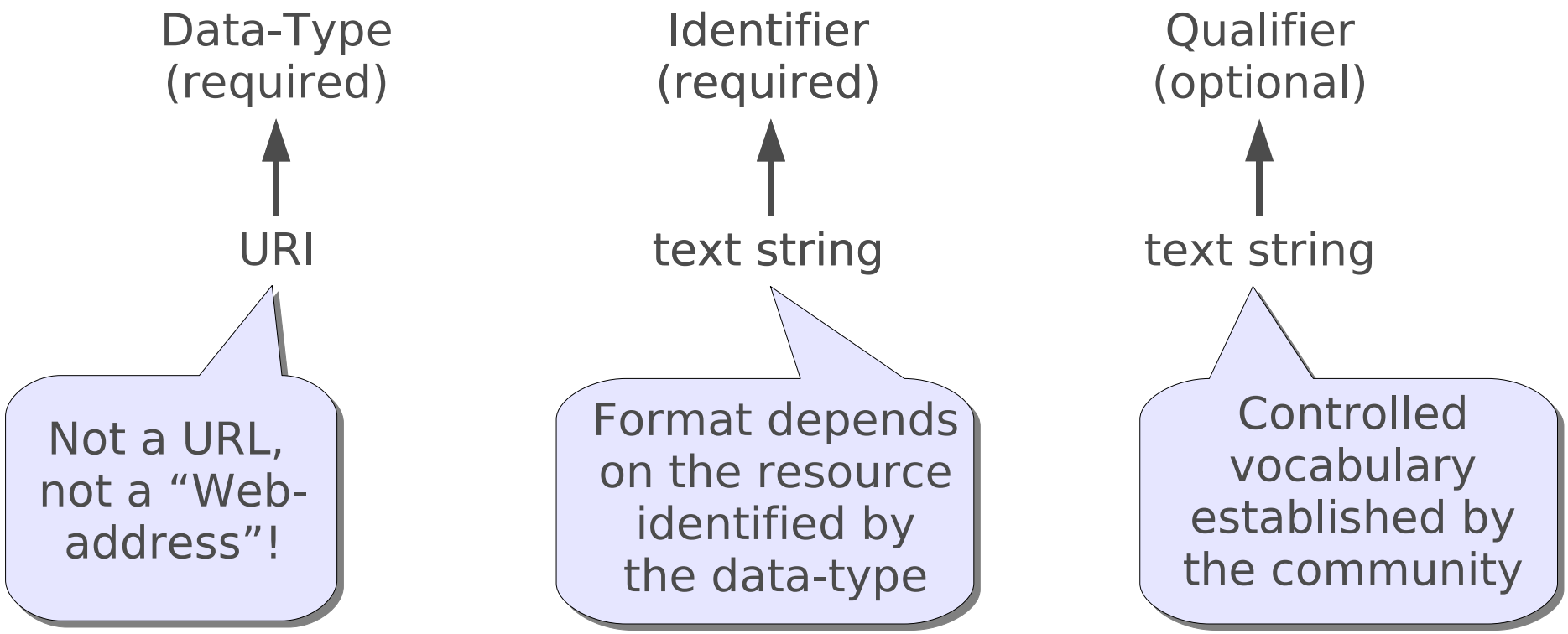
MIRIAM annotation



MIRIAM annotation



MIRIAM annotation



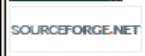
The data-type and the identifier can be combined in a single URI

`urn:miriam:MyResource:MyIdentifier`

MIRIAM Resources

- **MIRIAM Database**
  Core element of the resource, storing all the information about the data-types and associated information;
- **MIRIAM Web Services**
  SOAP-based application programming interface (API) for querying MIRIAM Database
- **MIRIAM Library**
  Library to use MIRIAM Web Services
- **MIRIAM Web Application**
  Interactive web interface for browsing and querying MIRIAM Database, and submit or edit data-types.

Laibe, Le Novère (2007)
BMC Systems Biology, 1: 58



MIRIAM

Browse the data-types

Brief overview of the different data-types stored in *MIRIAM Database*.

Name	URI	Definition
ArrayExpress	urn:miriam:arrayexpress	ArrayExpress is a public repository for microarray data, which is aimed at storing MIAME-compliant data in accordance with Microarray Gene Expression Data (MGED) recommendations.
arXiv	urn:miriam:arxiv	arXiv is an e-print service in the fields of physics, mathematics, non-linear science, computer science, and quantitative biology.
BIND	urn:miriam:bind	BIND is a database of protein-protein interactions. This data-resource is not open-access.
BioModels Database	urn:miriam:biomodels.db	BioModels Database is a data resource that allows biologists to store, search and retrieve published mathematical models of biological interests.
ChEBI	urn:miriam:obo.chebi	Chemical Entities of Biological Interest (ChEBI) is a freely available dictionary of molecular entities focused on 'small' chemical compounds.
CluSTr	urn:miriam:clustr	The CluSTr database offers an automatic classification of UniProt Knowledgebase and IPI proteins into groups of related proteins. The clustering is based on analysis of all pairwise comparisons (Smith-Waterman) between protein sequences.
Database of Interacting Proteins	urn:miriam:dip	The database of interacting protein (DIP) database stores experimentally determined interactions between proteins. It combines information from a variety of sources to create a single, consistent set of protein-protein interactions
DOI	urn:miriam:doi	The Digital Object Identifier System is for identifying content objects in the digital environment.
Ensembl	urn:miriam:ensembl	Ensembl is a joint project between EMBL - EBI and the Sanger Institute to develop a software system which produces and maintains automatic annotation on selected eukaryotic genomes.
Enzyme Nomenclature	urn:miriam:ec-code	The Enzyme Classification contains the recommendations of the Nomenclature Committee of the International Union of Biochemistry and Molecular Biology on the nomenclature and classification of enzyme-catalysed reactions.
FlyBase	urn:miriam:flybase	FlyBase is the database of the Drosophila Genome Projects and of associated literature.
Gene Ontology	urn:miriam:obo.go	The Gene Ontology project provides a controlled vocabulary to describe gene and gene product attributes in any organism.
HMDB	urn:miriam:hmdb	The Human Metabolome Database (HMDB) is a database containing detailed information about small molecule metabolites found in the human body.It contains or links 1) chemical 2) clinical and 3) molecular biology/biochemistry data.
ICD	urn:miriam:icd	The International Classification of Diseases is the international standard diagnostic classification for all general epidemiological and many health management purposes.
IntAct	urn:miriam:intact	IntAct provides a freely available, open source database system and analysis tools for protein interaction data.
InterPro	urn:miriam:interpro	InterPro is a database of protein families, domains and functional sites in which identifiable features found in known proteins can be applied to unknown protein sequences.
IPI	urn:miriam:ipi	The International Protein Index) provides complete nonredundant data sets representing the human, mouse and rat proteomes, built from the Swiss-Prot, TrEMBL, Ensembl and RefSeq databases
KEGG Compound	urn:miriam:kegg.compound	KEGG compound contains our knowledge on the universe of chemical substances that are relevant to life.
KEGG Drug	urn:miriam:kegg.drug	KEGG DRUG contains chemical structures of drugs and additional information such as therapeutic categories and target molecules.
KEGG Glycan	urn:miriam:kegg.glycan	KEGG GLYCAN, a part of the KEGG LIGAND database, is a collection of experimentally determined glycan structures. It contains all unique structures taken from CarbBank, structures entered from recent publications, and structures present in KEGG pathways.
KEGG Pathway	urn:miriam:kegg.pathway	KEGG PATHWAY is a collection of manually drawn pathway maps representing our knowledge on the molecular interaction and reaction networks.
KEGG Reaction	urn:miriam:kegg.reaction	KEGG reaction contains our knowledge on the universe of reactions that are relevant to life.
MINT	urn:miriam:mint	The Molecular INTeraction database (MINT) stores, in a structured format, information about molecular interactions by extracting experimental details from work published in peer-reviewed journals.
MIRIAM Resources	urn:miriam:miriam	MIRIAM Resources is an online resource created to catalogue the data-types (Gene Ontology, Taxonomy or PubMed are some examples), their URIs and the corresponding physical URLs, whether these are controlled vocabularies or databases.
Mouse Genome Database	urn:miriam:mgd	The Mouse Genome Database (MGD) project includes data on gene characterization, nomenclature, mapping, gene homologies among mammals, sequence links, phenotypes, allelic variants and mutants, and strain data.
Nucleotide Sequence Database	urn:miriam:insdc	The International Nucleotide Sequence Database Collaboration (INSDC) consists of a joint effort to collect and disseminate databases containing DNA and RNA sequences.
OMIM	urn:miriam:omim	Online Mendelian Inheritance in Man is a catalog of human genes and genetic disorders.
Pfam	urn:miriam:pfam	The Pfam database contains information about protein domains and families. For each entry a protein sequence alignment and a Hidden Markov Model is stored.
PIRSF	urn:miriam:pirsf	The PIR SuperFamily concept is being used as a guiding principle to provide comprehensive and non-overlapping clustering of UniProtKB sequences into a hierarchical order to reflect their evolutionary relationships.
PROSITE	urn:miriam:prosite	PROSITE consists of documentation entries describing protein domains, families and functional sites as well as associated patterns and profiles to identify them.
Protein Data Bank	urn:miriam:pdb	The Protein Data Bank is the single worldwide archive of structural data of biological macromolecules.
PubChem-compound	urn:miriam:pubchem.compound	PubChem provides information on the biological activities of small molecules. It is a component of NIH's Molecular Libraries Roadmap Initiative. PubChem Substance archives chemical structures. records.
PubChem-substance	urn:miriam:pubchem.substance	PubChem provides information on the biological activities of small molecules. It is a component of NIH's Molecular Libraries Roadmap Initiative. PubChem Substance archives chemical substance records.
PubMed	urn:miriam:pubmed	PubMed is a service of the U.S. National Library of Medicine that includes citations from MEDLINE and other life science journals for biomedical articles back to the 1950s.
Rat Genome Database	urn:miriam:rgd	Rat Genome Database seeks to collect, consolidate, and integrate data generated from ongoing rat genetic and genomic research efforts and make these data widely available to the scientific community.
Reactome	urn:miriam:reactome	The Reactome project is a collaboration to develop a curated resource of core pathways and reactions in human biology.
RefSeq	urn:miriam:refseq	The Reference Sequence (RefSeq) collection aims to provide a comprehensive, integrated, non-redundant set of sequences, including genomic DNA, transcript (RNA), and protein products.
RESID	urn:miriam:resid	The RESID Database of Protein Modifications is a comprehensive collection of annotations and structures for protein modifications including amino-terminal, carboxyl-terminal and peptide chain cross-link post-translational modifications.
SABIO-RK Reaction	urn:miriam:sabiork.reaction	SABIO-RK is a relational database system that contains information about biochemical reactions, their kinetic equations with their parameters, and the experimental conditions under which these parameters were measured

MIRIAM

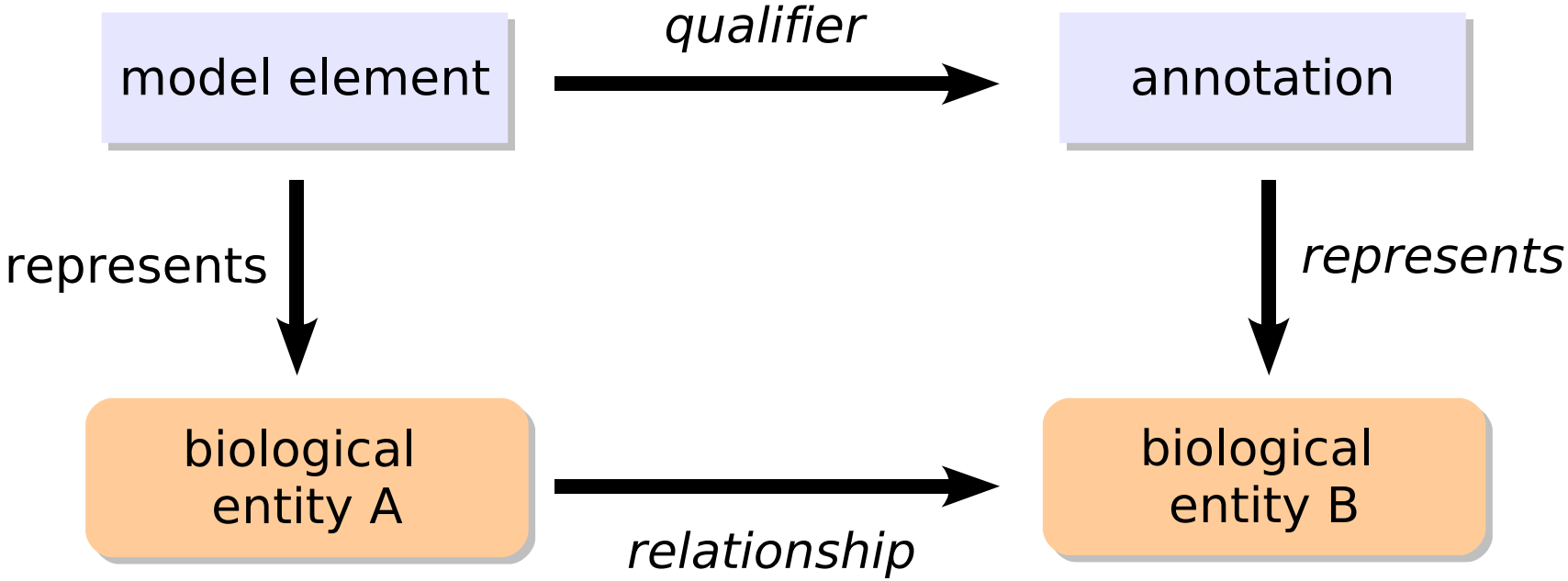
Data type: *Enzyme Nomenclature*

Name		
Identifier		MIR:00000004
Name		Enzyme Nomenclature
Synonyms		Enzyme Classification
		EC code
		EC
URIs		
Official URN		urn:miriam:ec-code
Deprecated		http://www.ec-code.org/
		http://www.ebi.ac.uk/IntEnz/
		urn:lsid:ec-code.org
Information		
Definition		The Enzyme Classification contains the recommendations of the Nomenclature Committee of the International Union of Biochemistry and Molecular Biology on the nomenclature and classification of enzyme-catalysed reactions.
Identifier Pattern		^\d+|\d+\.(-|\d+)|\d+\.\d+\.(-|\d+)|\d+\.\d+\.\d+\.(-|\d+)$
Physical Locations		
Resource #1	**Data Entry**	http://www.ebi.ac.uk/intenz/query?cmd=SearchEC&ec=**$id**
	Data Resource	http://www.ebi.ac.uk/intenz/
	Information	IntEnZ (Integrated relational Enzyme database)
	Institution	European Bioinformatics Institute, United Kingdom
Resource #2	**Data Entry**	http://www.genome.jp/dbget-bin/www_bget?ec:**$id**
	Data Resource	http://www.genome.jp/dbget-bin/www_bfind?enzyme
	Information	KEGG Ligand Database for Enzyme Nomenclature
	Institution	Kyoto University Bioinformatics Center, Japan
Resource #3	**Data Entry**	http://us.expasy.org/cgi-bin/nicezyme.pl?**$id**
	Data Resource	http://us.expasy.org/enzyme/
	Information	Enzyme nomenclature database, ExPASy (Expert Protein Analysis System)
	Institution	Swiss Institute of Bioinformatics, Switzerland
Documentation		
URL(s)		http://www.chem.qmul.ac.uk/iubmb/enzyme/
		⊞ http://srs.ebi.ac.uk/srsbin/cgi-bin/wgetz?-view+MedlineFull+[medline-PMID:10812475]
Miscellaneous		
Date of creation		2006-08-14 19:38:06 GMT
Date of last modification		2008-04-14 00:32:21 GMT

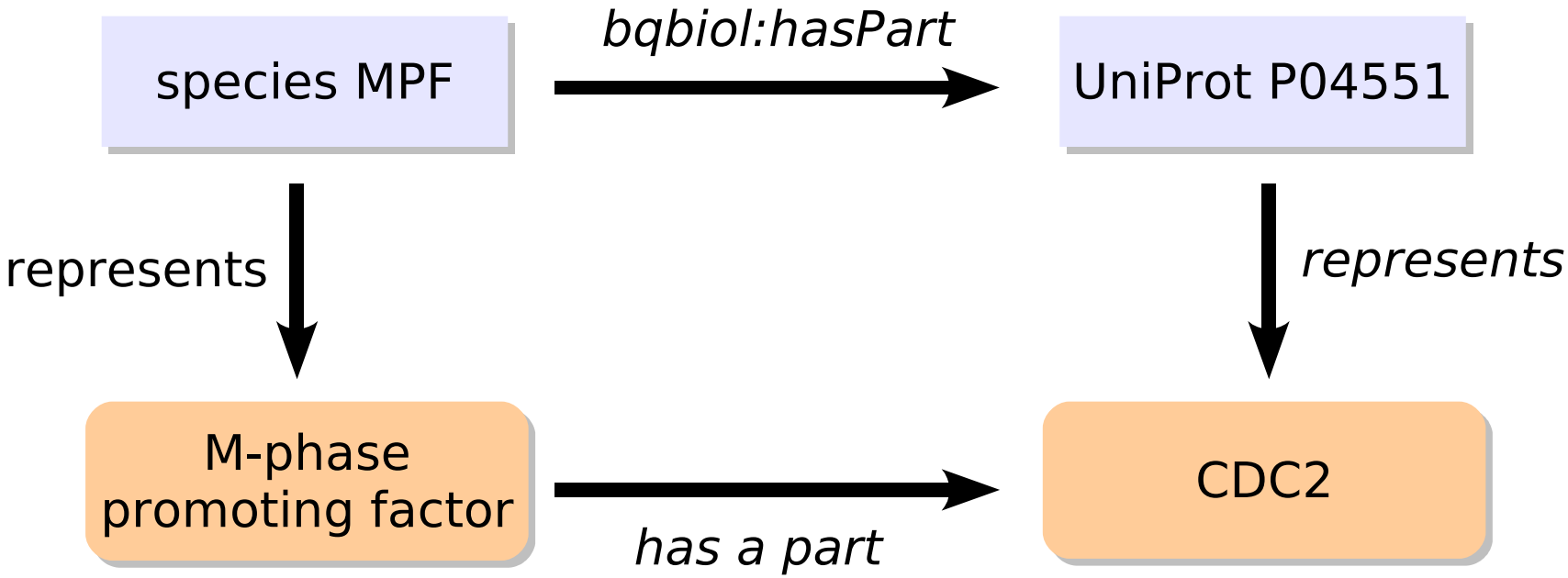
Go back

Examples of annotations using this data type

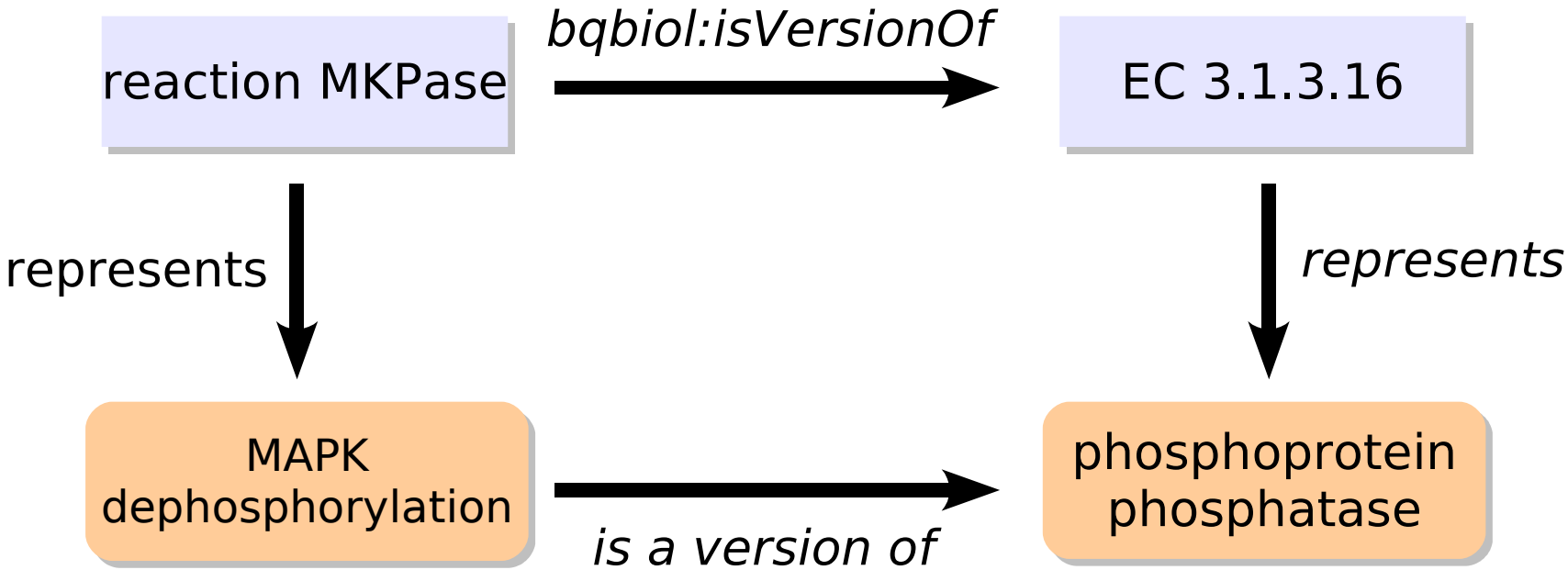
Qualification of annotation



Qualification of annotation



Qualification of annotation



Current BioModels.net Qualifiers

- **bqmodel:is** The modelling object represented by the model component is the subject of the referenced resource.
- **bqmodel:isDescribedBy** The modelling object represented by the component of the encoded model is described by the referenced resource.
- **bqbiol:is** The biological entity represented by the model component is the subject of the referenced resource.
- **bqbiol:hasPart** The biological entity represented by the model component includes the subject of the referenced resource, either physically or logically.
- **bqbiol:isPartOf** The biological entity represented by the model component is a physical or logical part of the subject of the referenced resource
- **bqbiol:isVersionOf** The biological entity represented by the model component is a version or an instance of the subject of the referenced resource.
- **bqbiol:hasVersion** The subject of the referenced resource is a version or an instance of the biological entity represented by the model component.
- **bqbiol:isHomologTo** The biological entity represented by the model component is homolog, to the subject of the referenced resource, i.e. they share a common ancestor.
- **bqbiol:isDescribedBy** The biological entity represented by the model component is described by the referenced resource.

Current BioModels.net Qualifiers

NEW

- **bqbiol:encodes** The biological entity represented by the model component encodes, directly or by transitivity the subject of the referenced resource.
- **bqbiol:isEncodedBy** The biological entity represented by the model component is encoded, directly, or by transitivity, by the subject of the referenced resource.
- **bqbiol:occursIn** The biological entity represented by the model component takes place in the subject of the referenced resource.

SBML and MIRIAM

```
<species id="Ca_calmodulin" metaid="cacam">
  <annotation>
    <rdf:RDF
        xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#"
        xmlns:bqbiol="http://biomodels.net/biology-qualifiers/">
      <rdf:Description rdf:about="#cacam">
        <bqbiol:hasPart>
          <rdf:Bag>
            <rdf:li rdf:resource="urn:miriam:uniprot:P62158"/>
            <rdf:li rdf:resource="urn:miriam:obo.chebi:CHEBI%3A29108"/>
          </rdf:Bag>
        </bqbiol:hasPart>
      </rdf:Description>
    </rdf:RDF>
  </annotation>
</species>
```

annotation resolver

```
<reaction id="r3b"
  name="phosphorylation of MAPKK"
  metaid="_506913">
  <annotation>
    <rdf:RDF
      xmlns:rdf="http://www.w3.org/1999/02/22-rd ...
      xmlns:bqbiol="http://biomodels.net/biology ...
      xmlns:bqmodel="http://biomodels.net/model- ...
      <rdf:Description rdf:about="#_506913">
        <bqbiol:isVersionOf>
          <rdf:Bag>
<rdf:li  rdf:resource="urn:miriam:ec-code:2.7.11.25"/>
          </rdf:Bag>
        </bqbiol:isVersionOf>
```

annotation resolver

```
<reaction id="r3b"
  name="phosphorylation of MAPKK"
  metaid="_506913">
  <annotation>
    <rdf:RDF
      xmlns:rdf="http://www.w3.org/1999/02/2
      xmlns:bqbiol="http://biomodels.net/bio
      xmlns:bqmodel="http://biomodels.net/mo
      <rdf:Description rdf:about="#_506913">
        <bqbiol:isVersionOf>
          <rdf:Bag>
<rdf:li  rdf:resource="urn:miriam:ec-code:2.
          </rdf:Bag>
        </bqbiol:isVersionOf>
```

MIRIAM Resources - Iceape

Data type: *Enzyme Nomenclature*

Name		
Identifier		MIR:00000004
Name		Enzyme Nomenclature
Synonyms		Enzyme Classification
		EC code
		EC
URIs		
Official URN		urn:miriam:ec-code
Deprecated		http://www.ec-code.org/
		http://www.ebi.ac.uk/IntEnz/
		urn:lsid:ec-code.org
Information		
Definition		The Enzyme Classification contains the recommendations of the Nomenclature Committee of the International Union of Biochemistry and Molecular Biology on the nomenclature and classification of enzyme-catalysed reactions.
Identifier Pattern		^\d+|\d+\.(-|\d+)|\d+\.\d+\.(-|\d+)|\d+\.\d+\.\d+\.(-|\d+)$
Physical Locations		
Resource #1	**Data Entry**	http://www.ebi.ac.uk/intenz/query?cmd=SearchEC&ec=**$id**
	Data Resource	http://www.ebi.ac.uk/intenz/
	Information	IntEnZ (Integrated relational Enzyme database)
	Institution	European Bioinformatics Institute, United Kingdom
Resource #2	**Data Entry**	http://www.genome.jp/dbget-bin/www_bget?ec:**$id**
	Data Resource	http://www.genome.jp/dbget-bin/www_bfind?enzyme
	Information	KEGG Ligand Database for Enzyme Nomenclature
	Institution	Kyoto University Bioinformatics Center, Japan
Resource #3	**Data Entry**	http://us.expasy.org/cgi-bin/nicezyme.pl?**$id**
	Data Resource	http://us.expasy.org/enzyme/
	Information	Enzyme nomenclature database, ExPASy (Expert Protein Analysis System)
	Institution	Swiss Institute of Bioinformatics, Switzerland
Documentation		
URL(s)		http://www.chem.qmul.ac.uk/iubmb/enzyme/
		⊞ http://srs.ebi.ac.uk/srsbin/cgi-bin/wgetz?-view+MedlineFull+[medline-PMID:10812475]
Miscellaneous		
Date of creation		2006-08-14 19:38:06 GMT

```
<reaction id="r3b"
  name="phosphorylation of MAPKK"
  metaid="_506913">
  <annotation>
    <rdf:RDF
      xmlns:rdf="http://www.w3.org/1999/02/2
      xmlns:bqbiol="http://biomodels.net/bio
```

MIRIAM Resources - Iceape

Data type: *Enzyme Nomenclature*

Name	
Identifier	MIR:00000004
Name	Enzyme Nomenclature
	Enzyme Classification
Synonyms	EC code

URIs
iam:ec-code
www.ec-code.org/
www.ebi.ac.uk/IntEnz/
:ec-code.org

Information
yme Classification contains the recommendations of the Nomenclature tee of the International Union of Biochemistry and Molecular Biology on the lature and classification of enzyme-catalysed reactions.
+\.(-|\d+)|\d+\.\d+\.(-|\d+)|\d+\.\d+\.\d+\.(-|\d+)$

Physical Locations
www.ebi.ac.uk/intenz/query?cmd=SearchEC&ec=$id
www.ebi.ac.uk/intenz/
Integrated relational Enzyme database)
n Bioinformatics Institute, United Kingdom
www.genome.jp/dbget-bin/www_bget?ec:$id
www.genome.jp/dbget-bin/www_bfind?enzyme
gand Database for Enzyme Nomenclature
niversity Bioinformatics Center, Japan
us.expasy.org/cgi-bin/nicezyme.pl?$id
us.expasy.org/enzyme/
nomenclature database, ExPASy (Expert Protein Analysis System)
stitute of Bioinformatics, Switzerland

Documentation
www.chem.qmul.ac.uk/iubmb/enzyme/
/srs.ebi.ac.uk/srsbin/cgi-bin/wgetz?-view+MedlineFull+[medline-PMID:10812475]

Miscellaneous
-14 19:38:06 GMT

EC 2.7.11.25 - Integrated Enzyme Database (IntEnz) - Iceape

IntEnz

Quick search:

Search

- IntEnz home
- Advanced search
- Browse EC
- Proposed changes
- Data submission
- Downloads
- Documentation
- Contact IntEnz

EBI > Databases > Enzymes > IntEnz

EC 2 - Transferases

EC 2.7 - Transferring phosphorus-containing groups

EC 2.7.11 - Protein-serine/threonine kinases

EC 2.7.11.25 - Mitogen-activated protein kinase kinase kinase

IntEnz view | NC-IUBMB view | ENZYME view

XML

IntEnz Enzyme Nomenclature

EC 2.7.11.25

Names

Accepted name: mitogen-activated protein kinase kinase kinase

Other name(s): cMos
cRaf
MAPKKK
MAP3K
MAP kinase kinase kinase
MEKK
MEKK1
MEKK2
MEKK3
MEK kinase
Mil/Raf
MLK-like mitogen-activated protein triple kinase
MLTK
MLTKa
MLTKb
REKS

EMBL-EBI

Can-this be understood by biologists?

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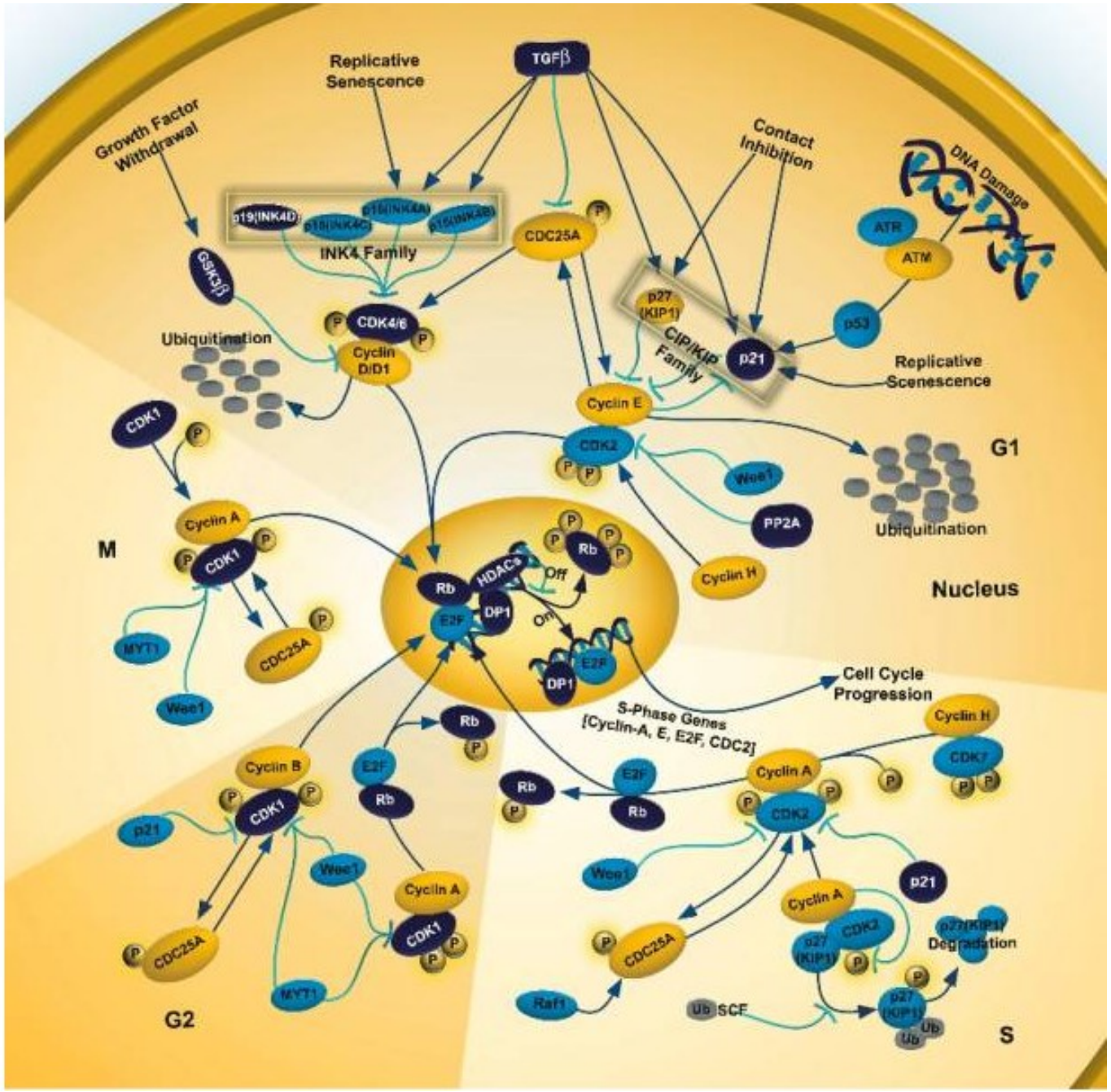
Can-this be understood by biologists?

$$
\begin{aligned}
d[\mathrm{C2}]/dt &= k_6[\mathrm{M}] - k_8[\sim P][\mathrm{C2}] + k_9[\mathrm{CP}] \\
d[\mathrm{CP}]/dt &= -k_3[\mathrm{CP}][\mathrm{Y}] + k_8[\sim P][\mathrm{C2}] - k_9[\mathrm{CP}] \\
d[\mathrm{pM}]/dt &= k_3[\mathrm{CP}][\mathrm{Y}] - [\mathrm{pM}]F([\mathrm{M}]) + k_5[\sim P][\mathrm{M}] \\
d[\mathrm{M}]/dt &= [\mathrm{pM}]F([\mathrm{M}]) - k_5[\sim P][\mathrm{M}] - k_6[\mathrm{M}] \\
d[\mathrm{Y}]/dt &= k_1[\mathrm{aa}] - k_2[\mathrm{Y}] - k_3[\mathrm{CP}][\mathrm{Y}] \\
d[\mathrm{YP}]/dt &= k_6[\mathrm{M}] - k_7[\mathrm{YP}]
\end{aligned}
$$

EMBL-EBI

Can-this be understood by biologists?



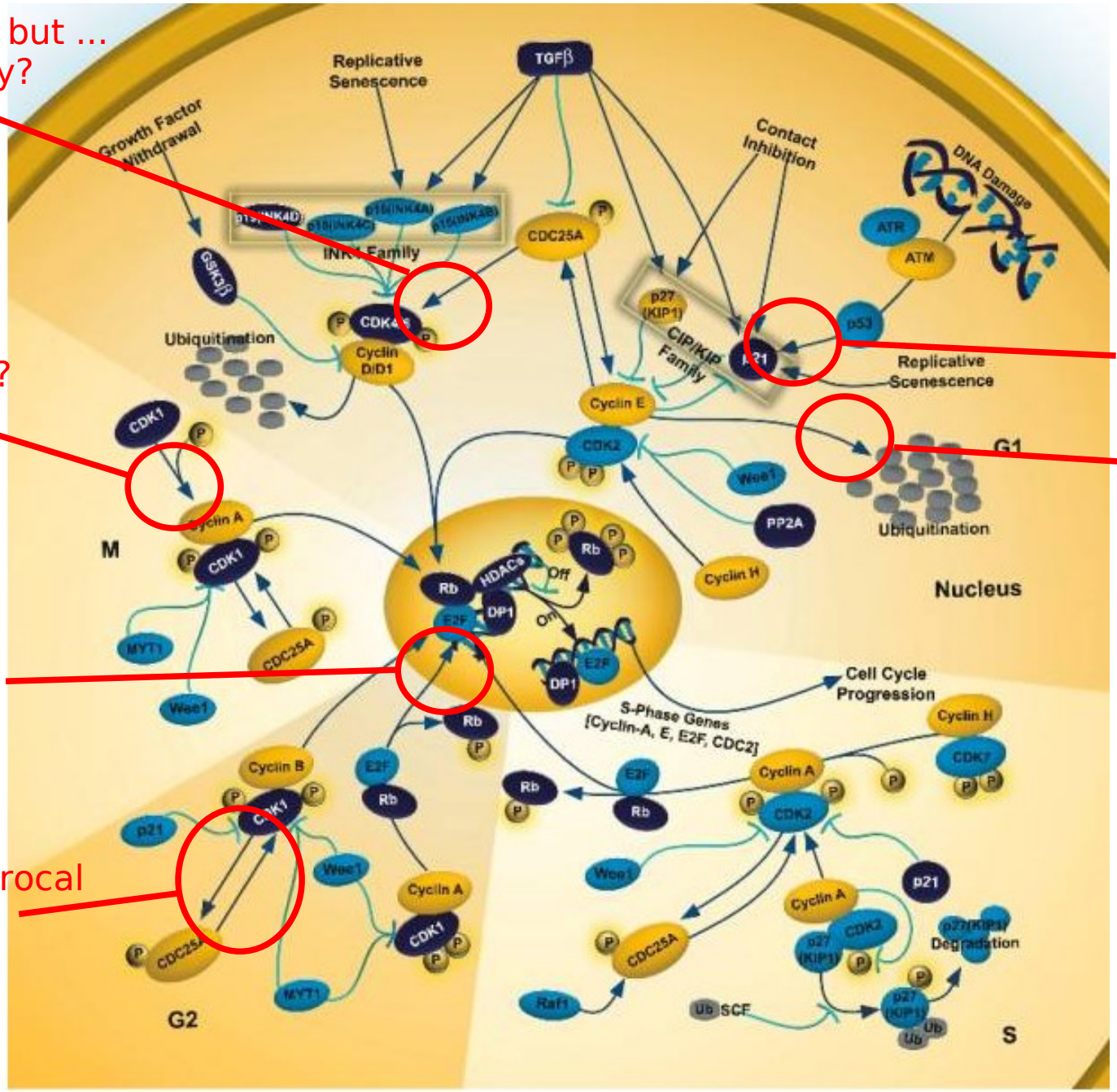
Can-this be understood by biologists?

Stimulates? but ... what exactly?

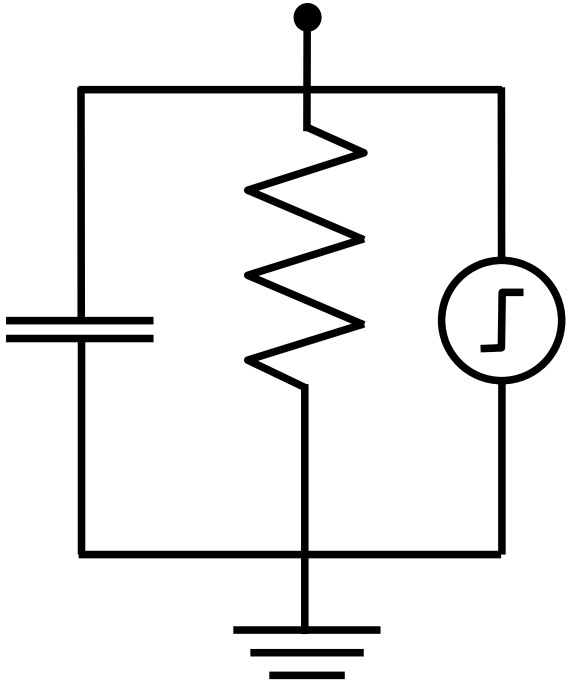
Associates into?

Translocates?

No idea. Reciprocal stimulation?



“Everyone” understands that



Enters
The Systems Biology Markup Language

What is SBGN?

- A way to unambiguously describe biochemical and cellular events in a graphical way
- Limited amount of symbols ☞ Smooth learning curve
- Can graphically represent quantitative models, biochemical pathways, at different levels of granularity
- Developed over three years by a growing community
- Three languages
  - Process Diagrams ☞ one state = one glyph, biochemical level
  - Entity Relationships ☞ one entity = one glyph, biochemical level
  - Activity Flow ☞ conveptual level
- http://www.sbgn.org/

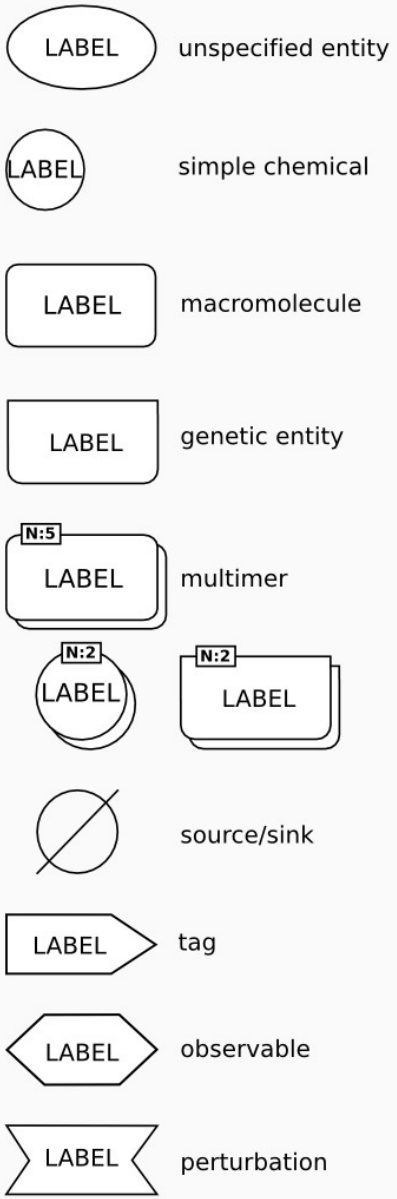
Computational Neurobiology

Le Novère et al (2008) *unpublished*

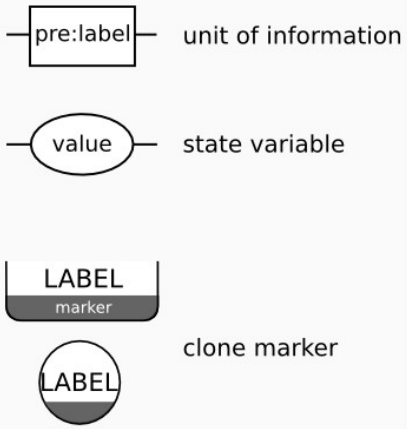
EMBL-EBI

SBGN Process Diagram L1 reference card

Entity Pool Nodes



Auxiliary units



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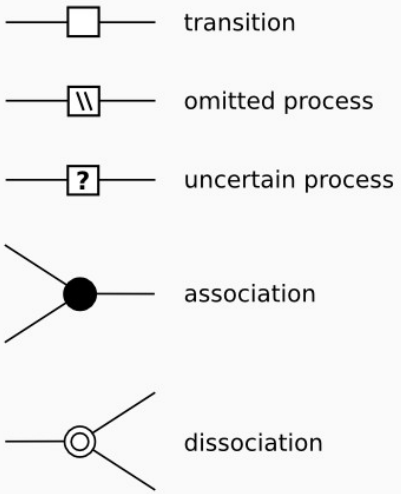
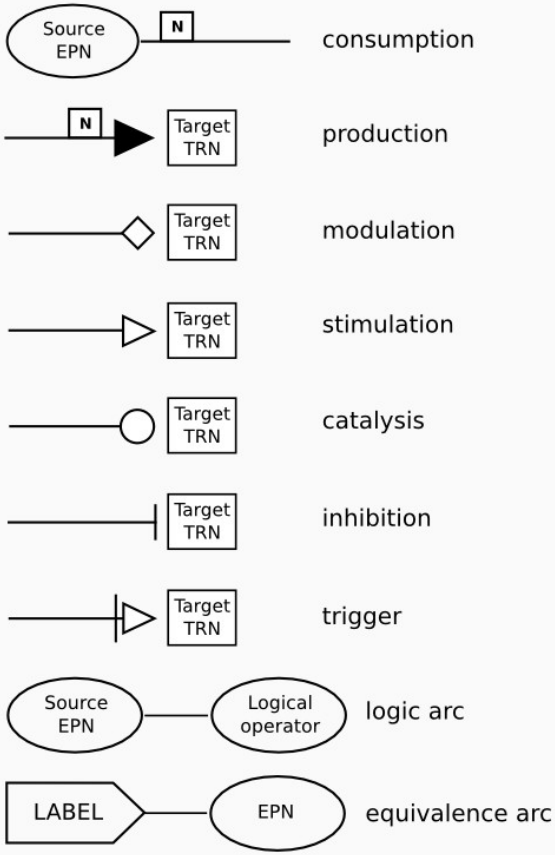
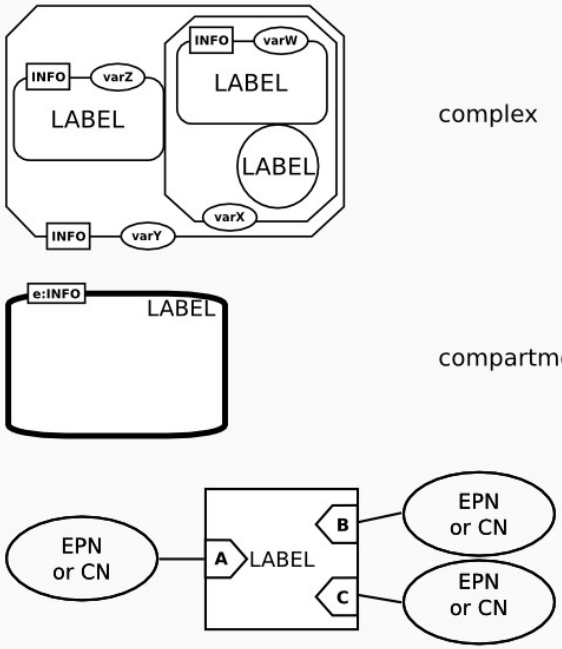


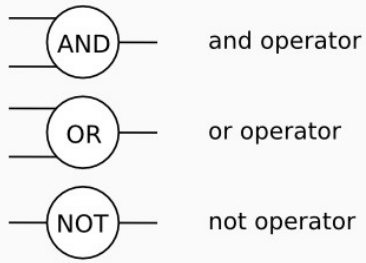
Connecting Arcs



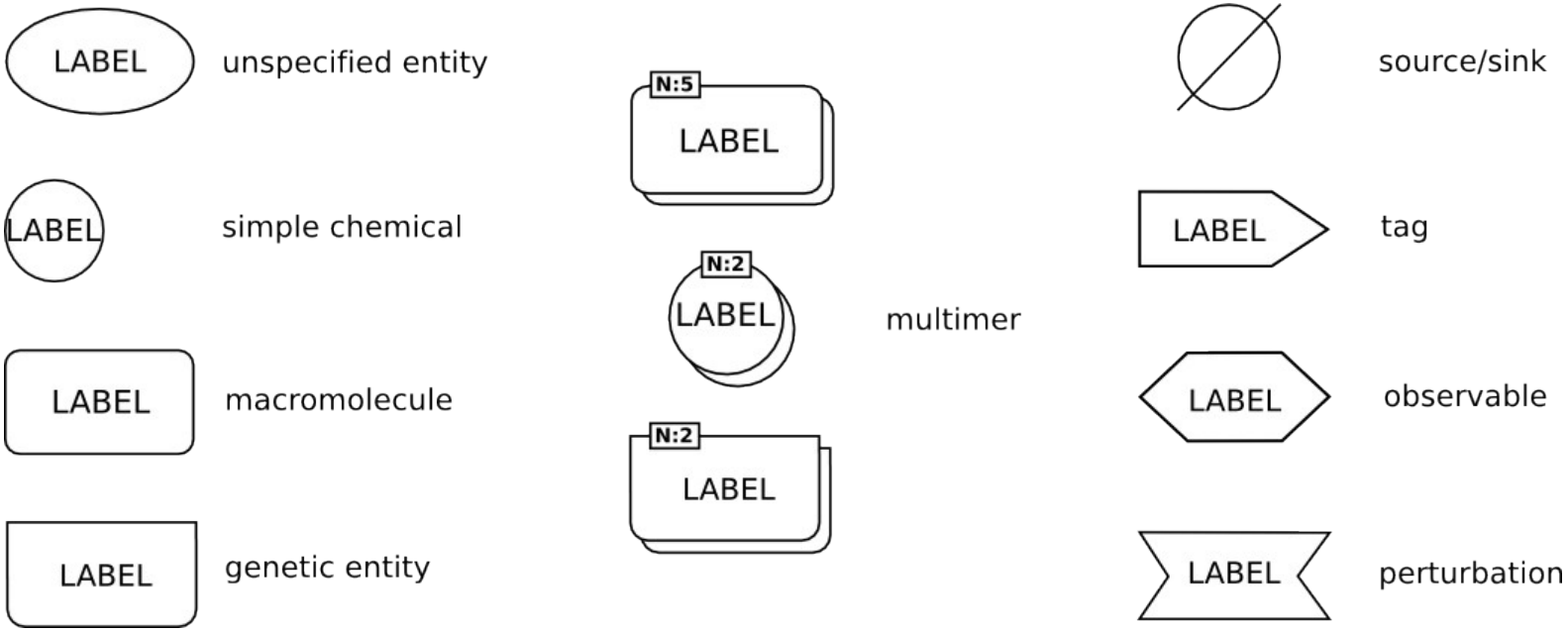
Container Nodes



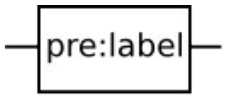
Logical Operators



Entity Pool Nodes



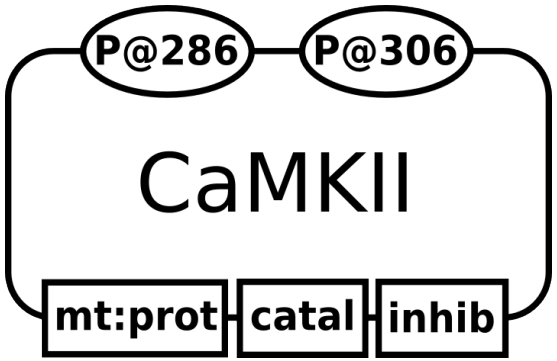
Auxiliary Units



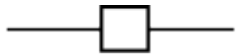
unit of information

state variable

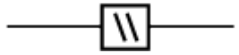
clone marker



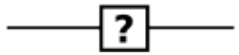
Process Nodes



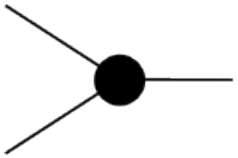
transition



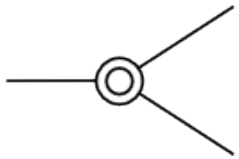
omitted process



uncertain process

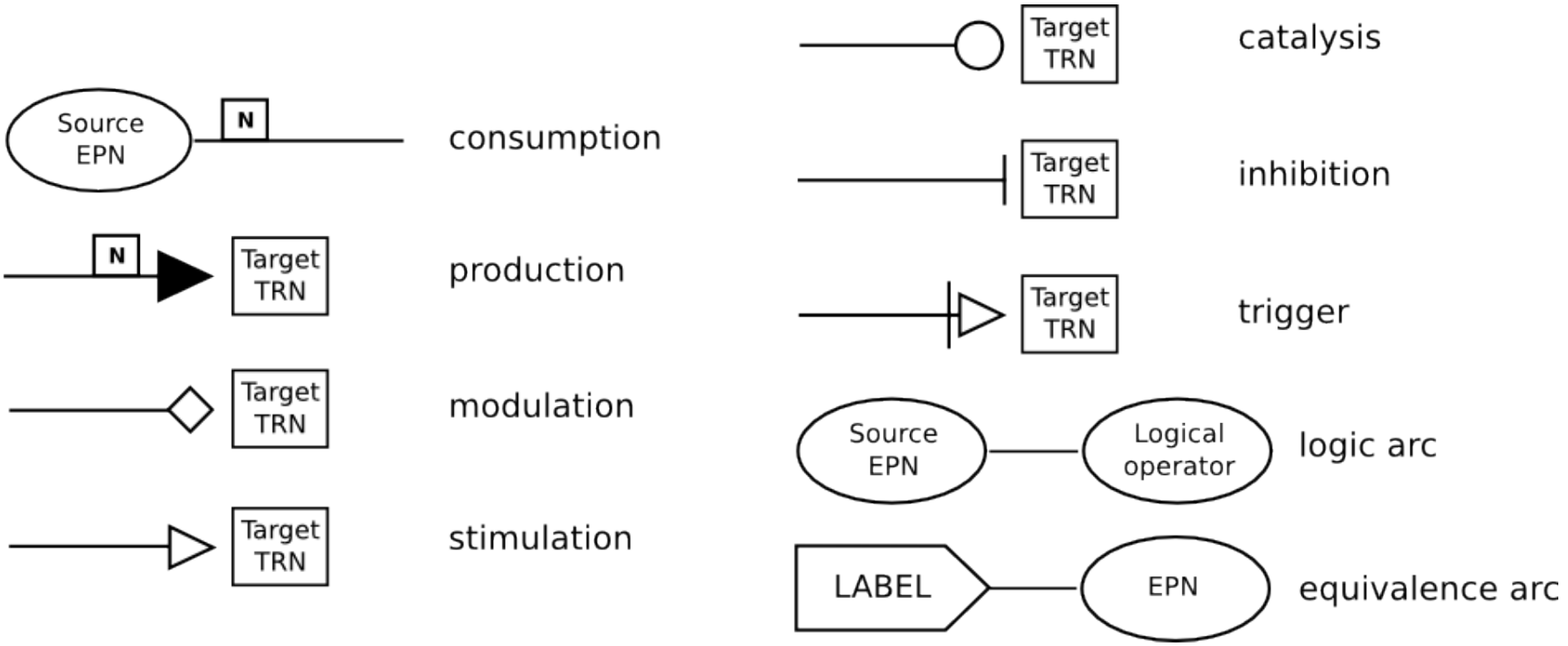


association

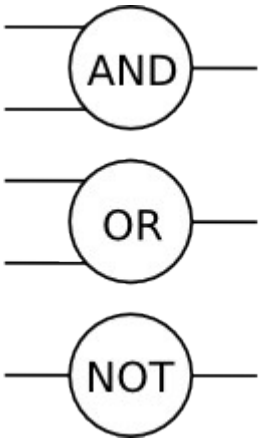


dissociation

Connecting Arcs



Logical Operators

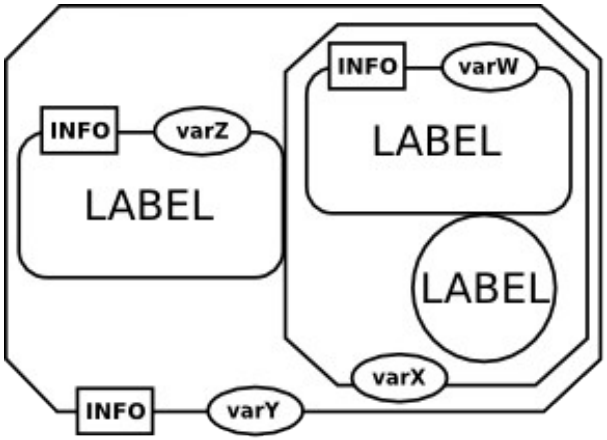


and operator

or operator

not operator

Containers



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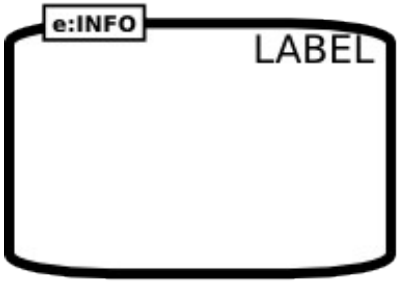
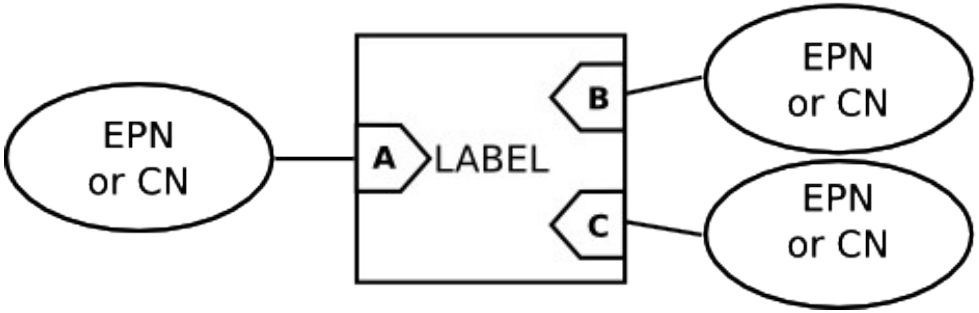
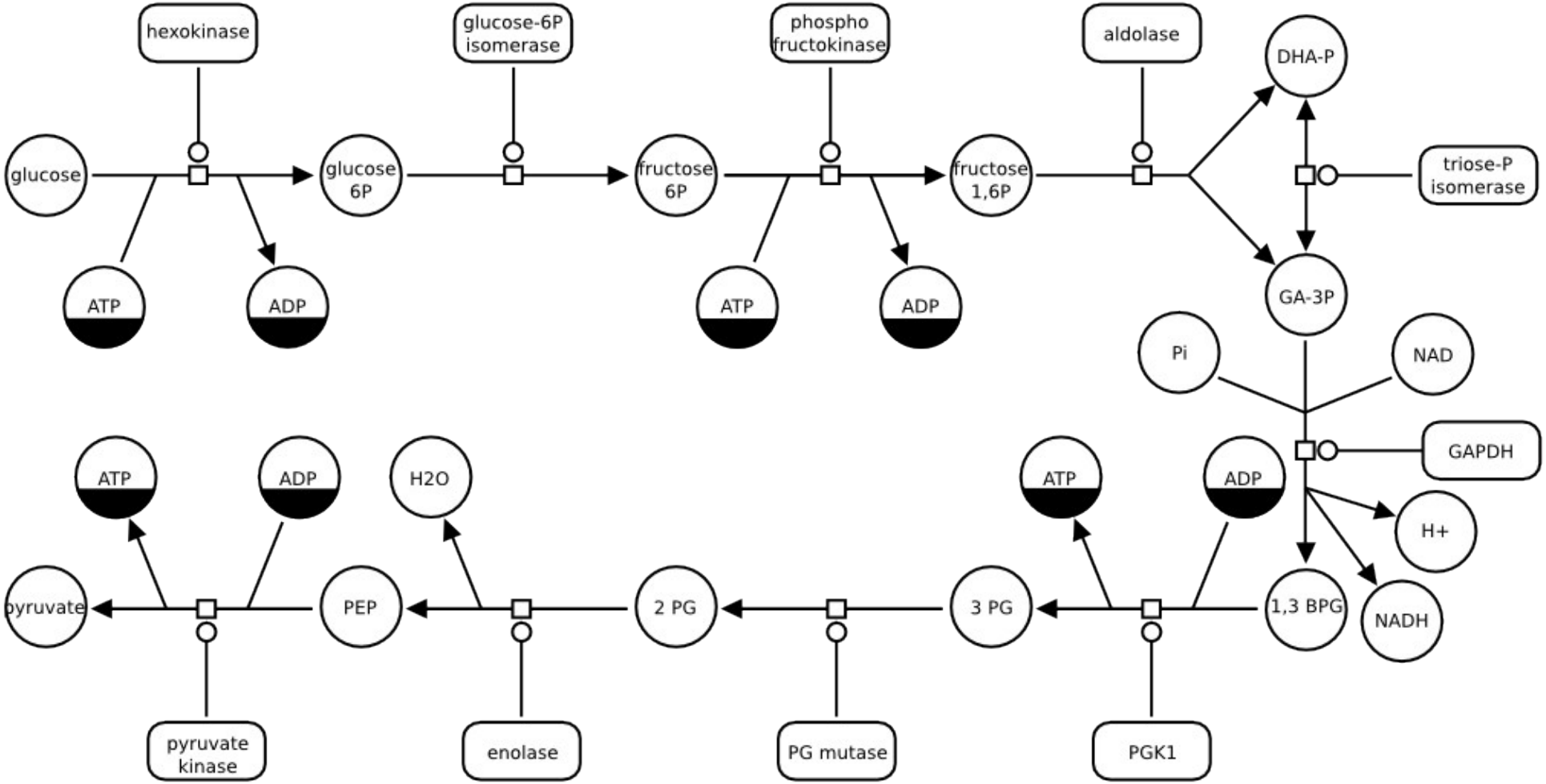


compartment

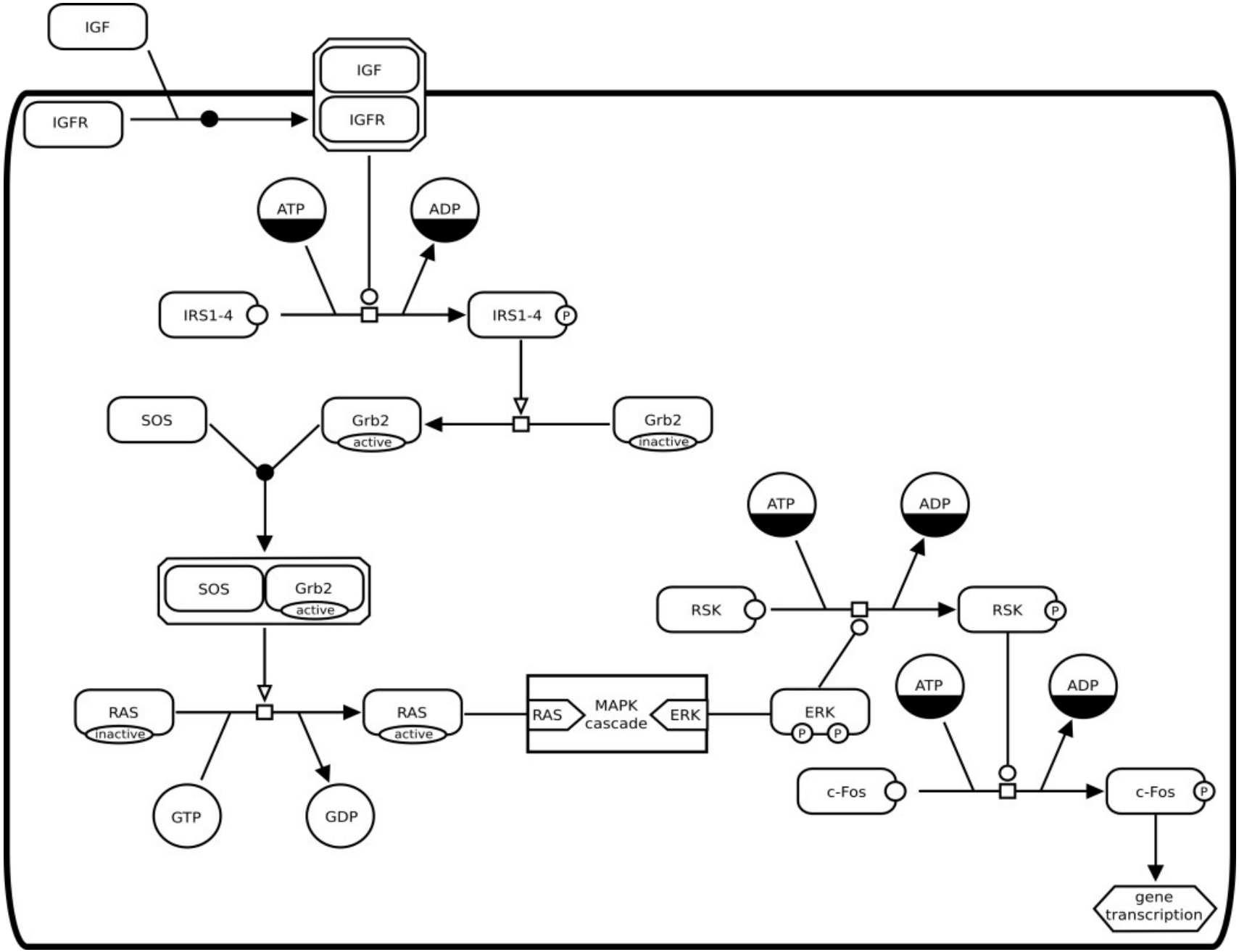


submap

Metabolic pathway



Submaps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ATP
ADP
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SOS
Grb2
active
Grb2
inactive
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active
ATP
ADP
RSK
RSK
P
RAS
inactive
RAS
active
RAS
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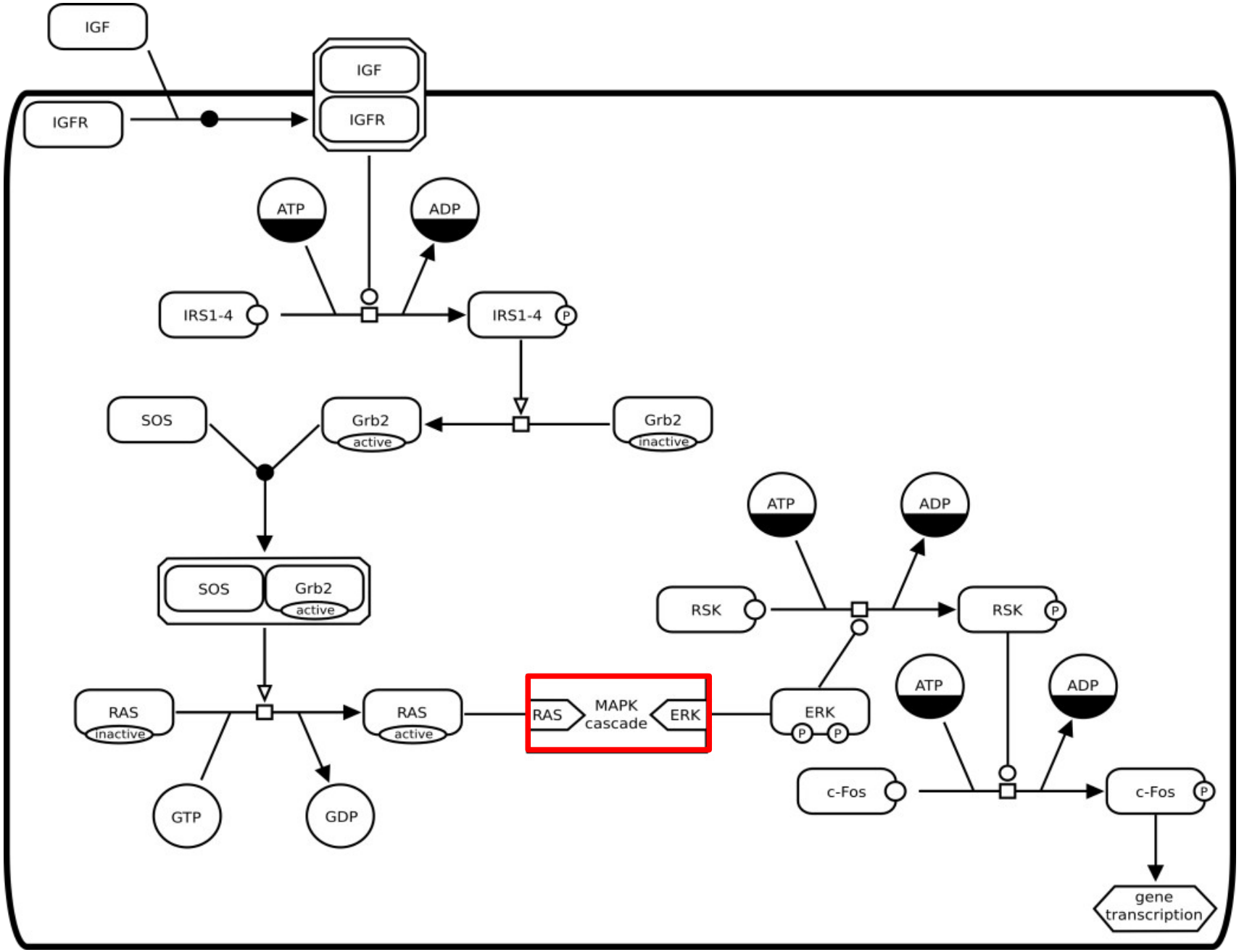
c-Fos
c-Fos
P
gene
transcription

Submaps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active
ATP
ADP
RSK
RSK
P
RAS
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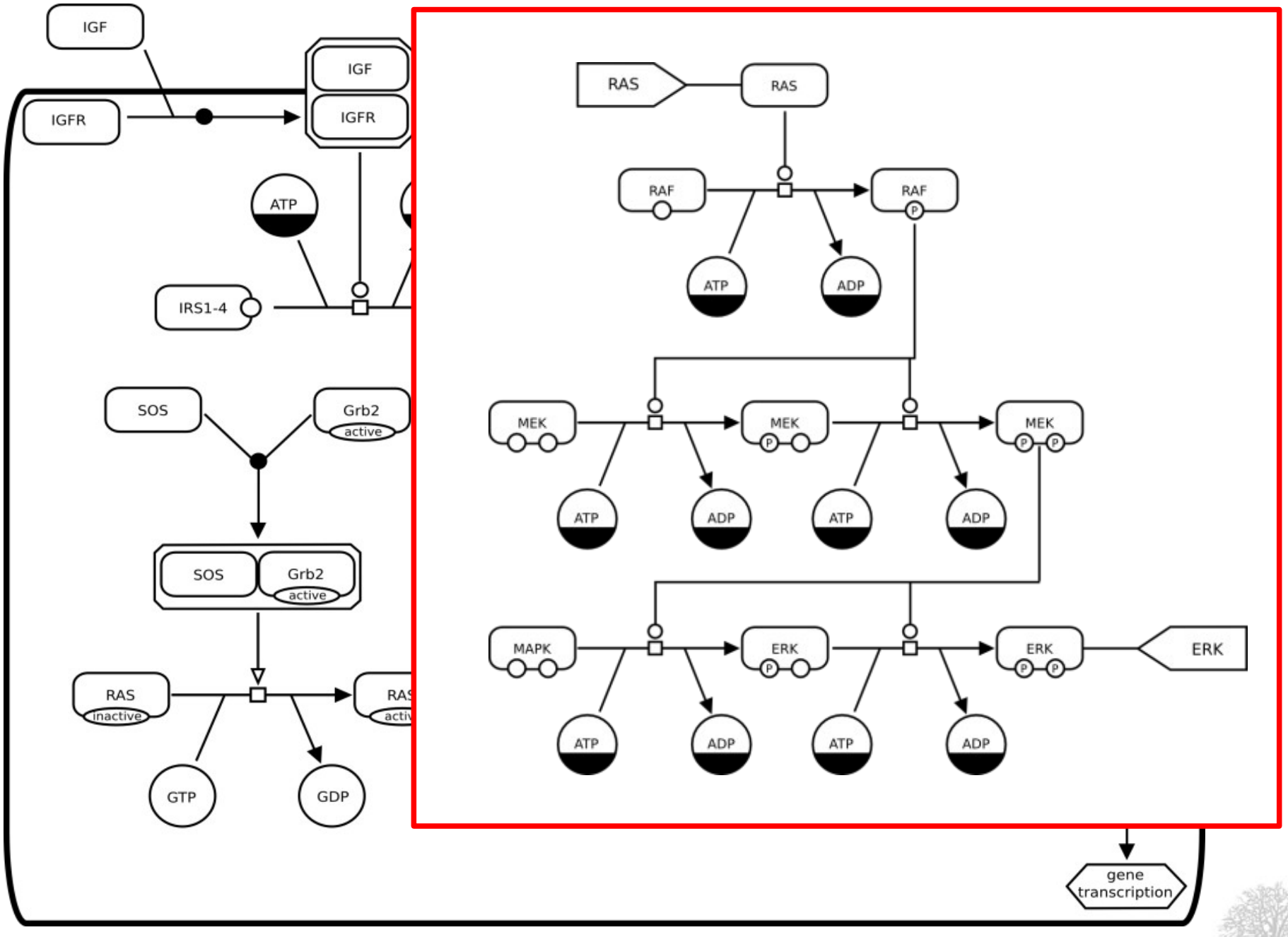
c-Fos
P
gene
transcription

Submaps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MEK
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P
MEK
P
P
ATP
ADP
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P
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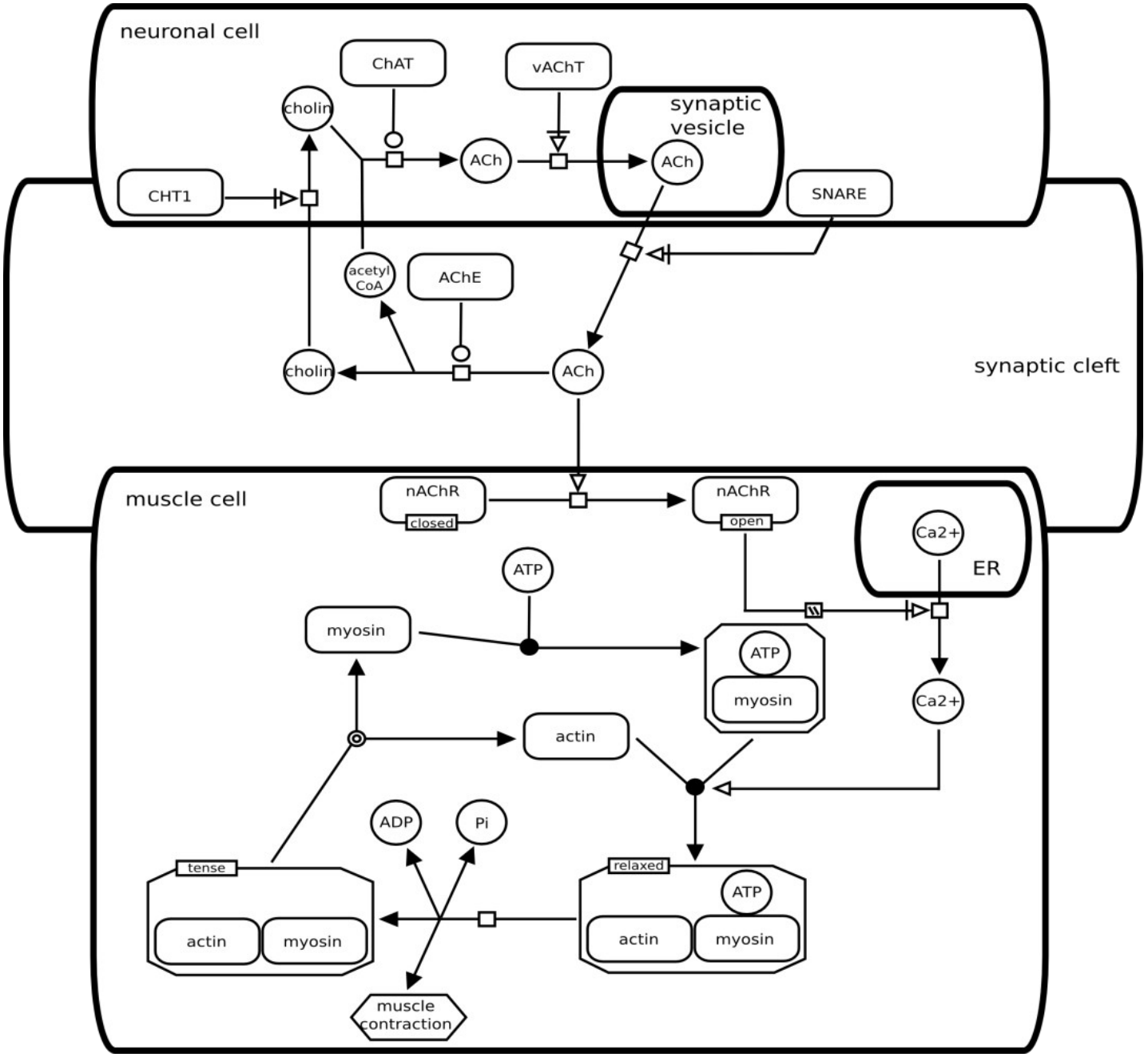
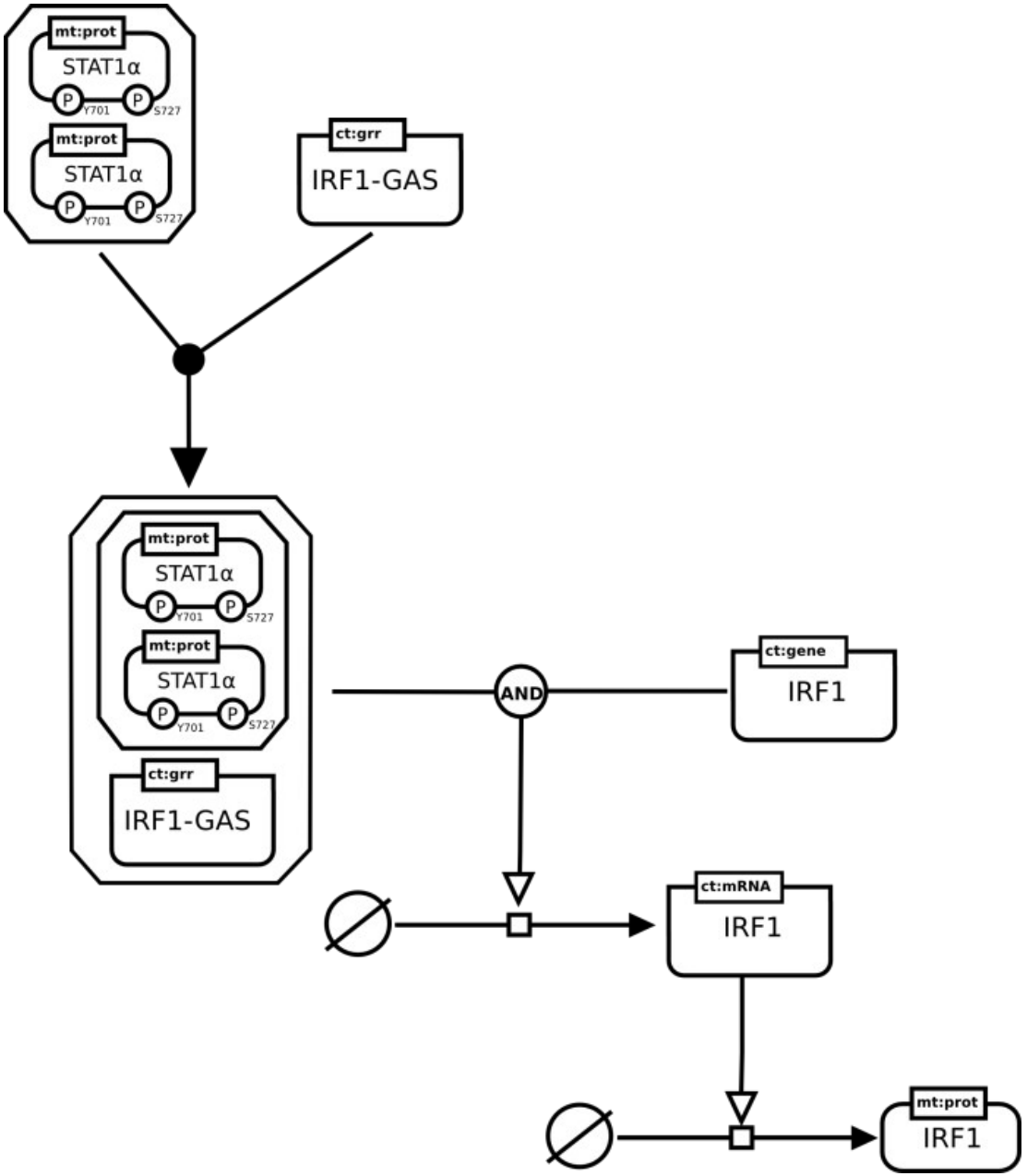
ERK
ATP
ADP
ATP
ADP
gene
transcription

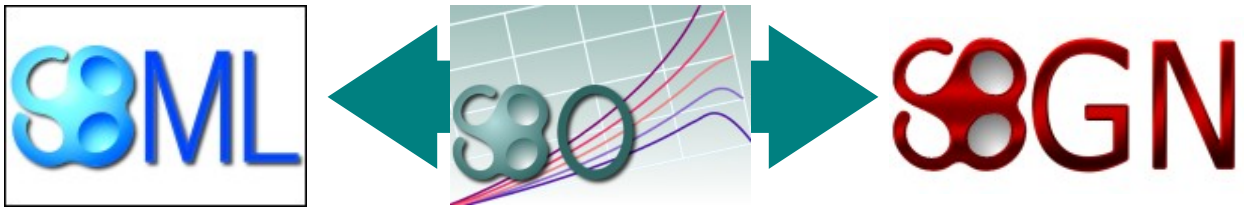
Multi-cellular example



Genetic regulation




SBML
?
SBGN

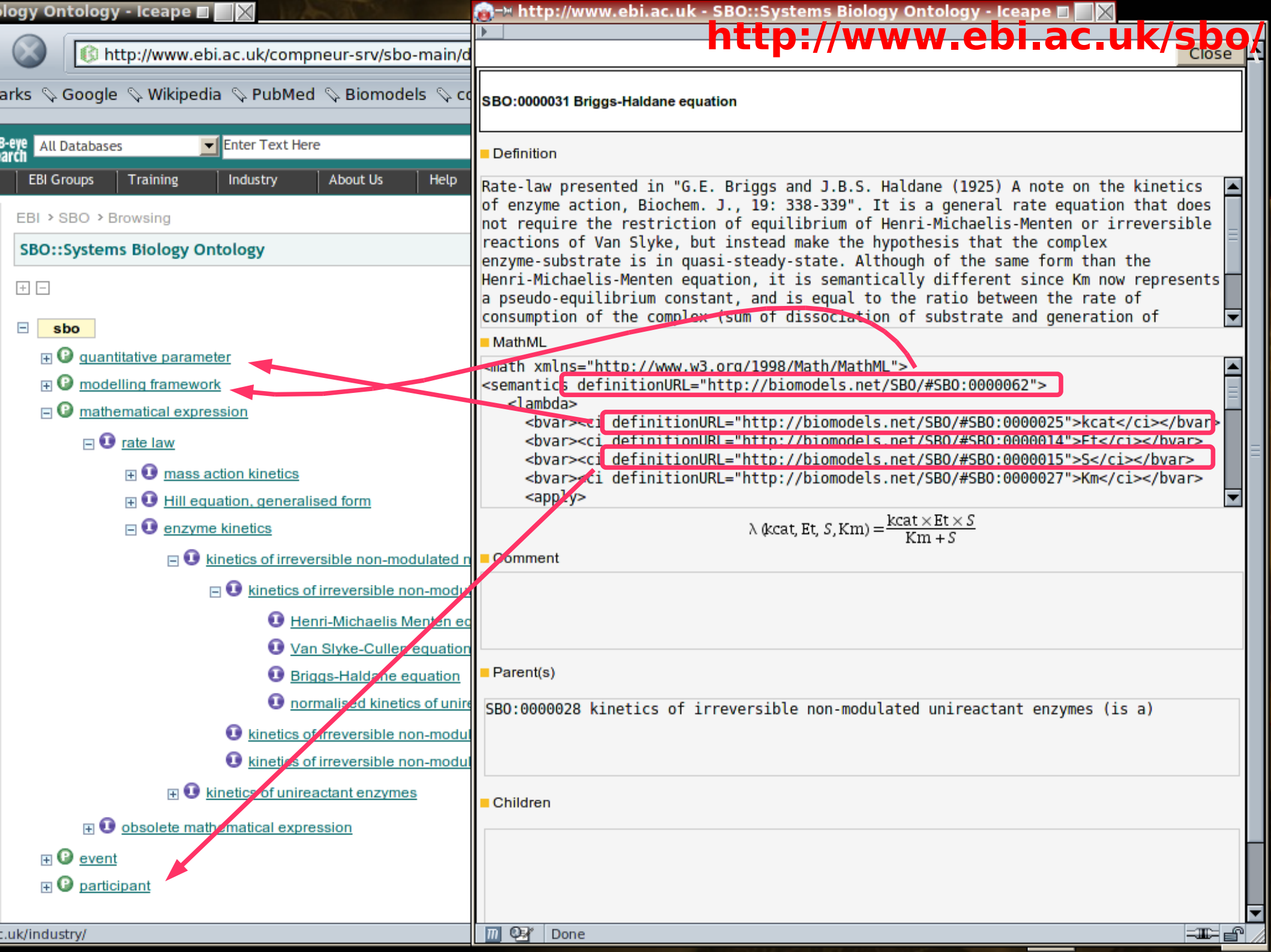


Computational Neurobiology

Le Novère et al (2007)
Proc ESCEC2

Systems Biology Ontology vocabularies

- Types and roles of reaction participants, including terms like "substrate", "catalyst" etc., but also "macromolecule", or "channel"
- Parameter used in quantitative models. This vocabulary includes terms like "Michaelis constant" , "forward unimolecular rate constant"etc. A term may contain a precise mathematical expression stored as a MathML lambda function. The variables refer to other parameters.
- Mathematical expressions. Examples of terms are "mass action kinetics", "Henri-Michaelis-Menten equation" etc. A term may contain a precise mathematical expression stored as a MathML lambda function. The variables refer to the other vocabularies.
- Modelling framework to precise how to interpret the rate-law. E.g. "continuous modelling", "discrete modelling" etc.
- Event type, such as "catalysis" or "addition of a chemical group".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Google
Wikipedia
PubMed
Biomodels
All Databases
Enter Text Here
EBI Groups
Training
Industry
About Us
Help
EBI › SBO › Browsing
SBO::Systems Biology Ontology
sbo
quantitative parameter
modelling framework
mathematical expression
rate law
mass action kinetics
Hill equation, generalised form
enzyme kinetics
kinetics of irreversible non-modulated u
kinetics of irreversible non-modu
Henri-Michaelis Menten eq
Van Slyke-Cullen equation
Briggs-Haldane equation
normalised kinetics of unire
kinetics of irreversible non-modul
kinetics of irreversible non-modul
kinetics of unireactant enzymes
obsolete mathematical expression
event
participant
http://www.ebi.ac.uk - SBO::Systems Biology Ontology - Iceape
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: 338-339". 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 pseudo-equilibrium constant, and is equal to the ratio between the rate of consumption of the complex (sum of dissociation of substrate and generation of
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Children
Done

SBML and SBO

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functional compartment

simple chemical

simple chemical

enzyme

catalysis

substrate

product

catalyst

Briggs-Haldane equation

Km

kcat

SBML to BioPAX conversion using SBO

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GO annotation

Small molecule

Small molecule

Protein

catalysis

physicalEntityParticipant

physicalEntityParticipant

physicalEntityParticipant

http://www.biopax.org/

SBML to SBGN conversion using SBO

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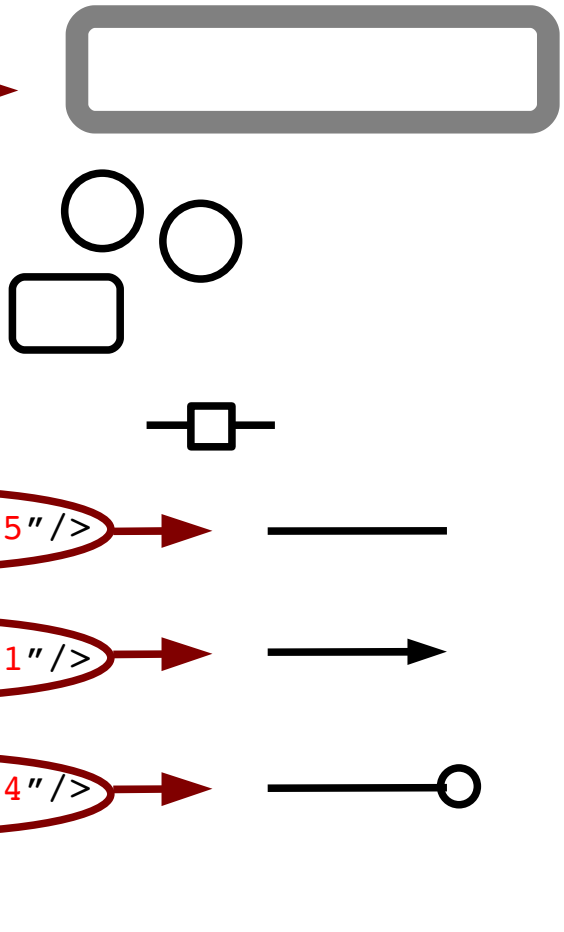


http://www.sbgn.org/

Systems Biology Ontology

Assignee: (?) Any | Status: (?) Any | Category: (?) Any | Group: (?) Any

Show only: Submitter username (show mine) : | Summary keyword:

Sort By: (?) ID | Descending | Browse

List of suggested SBO term creations or modification.

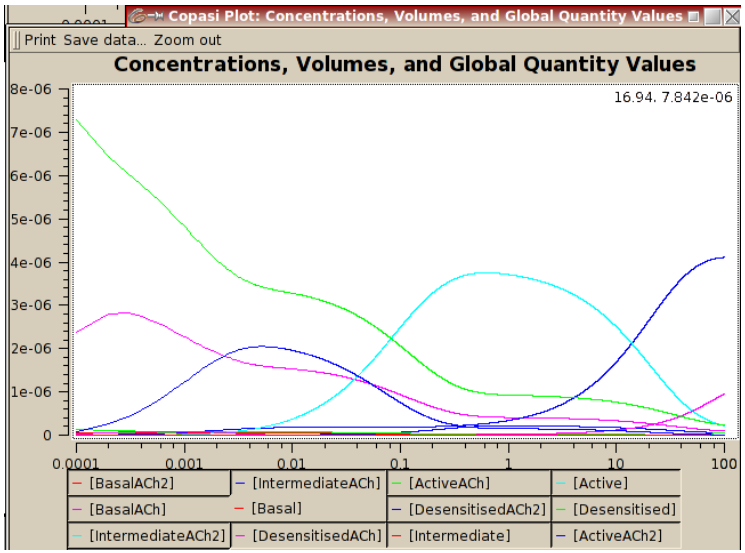
Request ID	Summary	Open Date	Priority	Status	Assigned To	Submitted By
1682477	create types of simple chemicals needed by SBGN	* 2007-03-16 23:17	5	Open	lenov	lenov
1672292	types of RNAs	* 2007-03-02 09:55	5	Closed	lenov	lenov
1599415	transporter	* 2006-11-19 23:38	5	Closed	nobody	lenov
1598503	Acid dissociation constant	* 2006-11-17 17:02	5	Closed	nobody	golebiewskim
1598488	pK	* 2006-11-17 16:47	5	Closed	nobody	golebiewskim
1598430	Equilibrium constant	* 2006-11-17 16:00	5	Closed	nobody	golebiewskim
1598416	EC50 and IC50	* 2006-11-17 15:44	5	Closed	nobody	golebiewskim
1598404	Catalytic efficiency	* 2006-11-17 15:16	5	Closed	nobody	golebiewskim
1597770	move enzyme	* 2006-11-16 14:44	5	Closed	nobody	lenov

What is a simulation

- A simulation is the instantiation of a model over time, using a given algorithmic approach, and a particular software: A model can beget simulations giving different results!
  - Logical (boolean or discrete) approach
  - Deterministic approach
  - Stochastic approach
  - Fixed timesteps
  - Adaptative timesteps
  - ...
- Plus ... range of simulations
  - parameter scan
  - parameter search/optimisation
  - phase-plane analysis
  - bifurcation analysis
  - ...

Some simulation results from COPASI

Edelstein et al 1996 (BIOMD0000000002)



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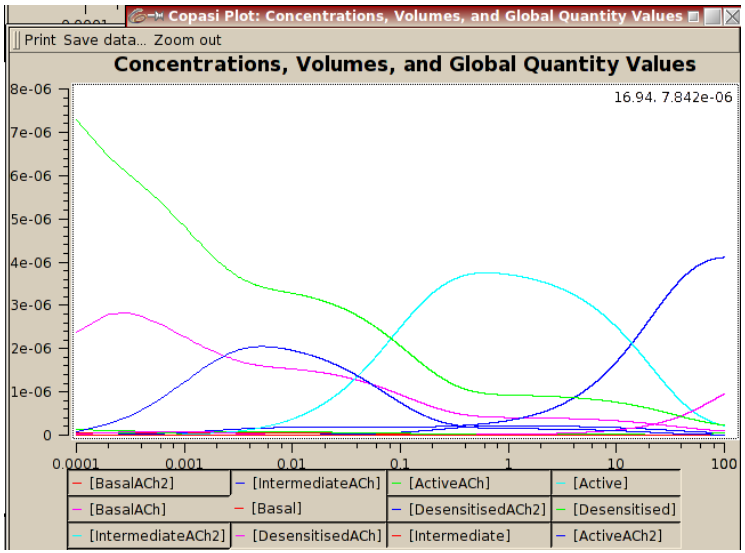
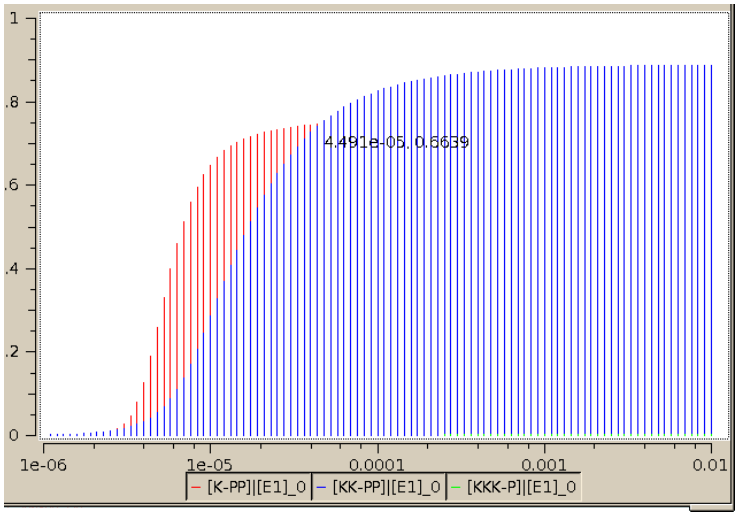
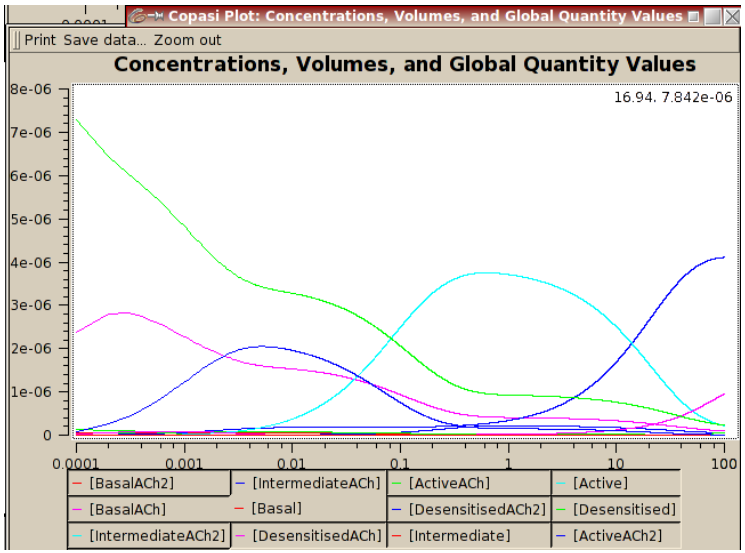


Huang & Ferrell (BIOMD0000000009)

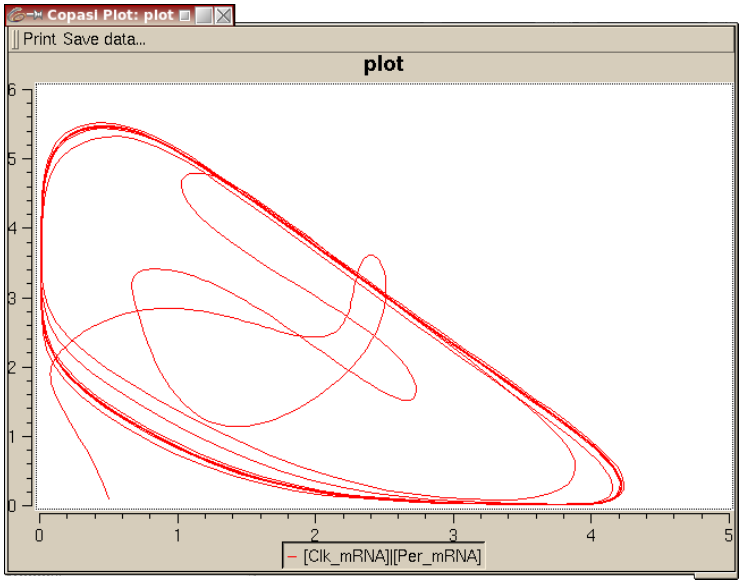


Some simulation results from COPASI

Edelstein et al 1996 (BIOMD0000000002)



Ueda, Hagiwara, Kitanol 2001 (BIOMD0000000022)



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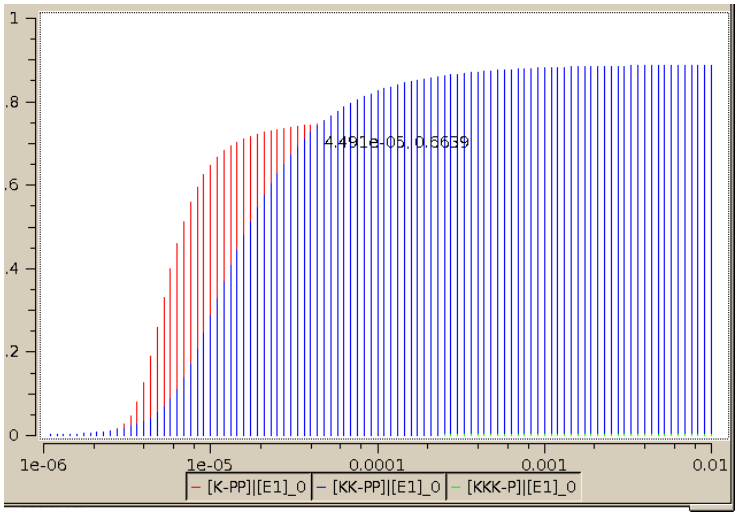

Some simulation results from COPASI

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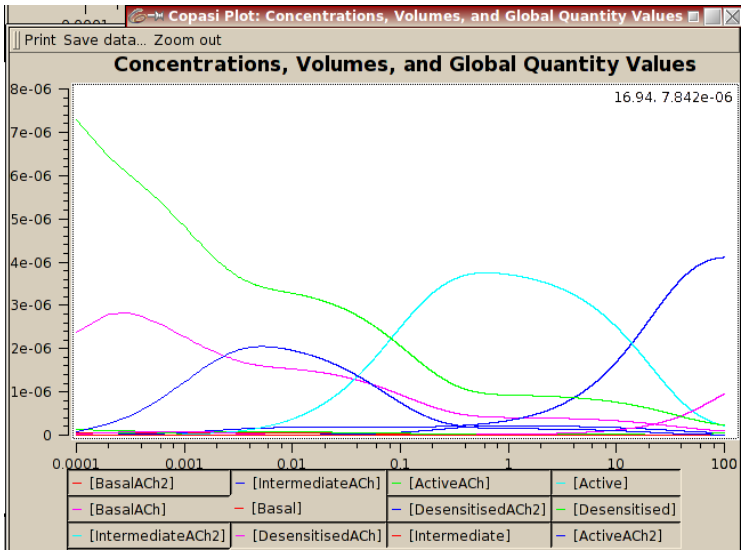
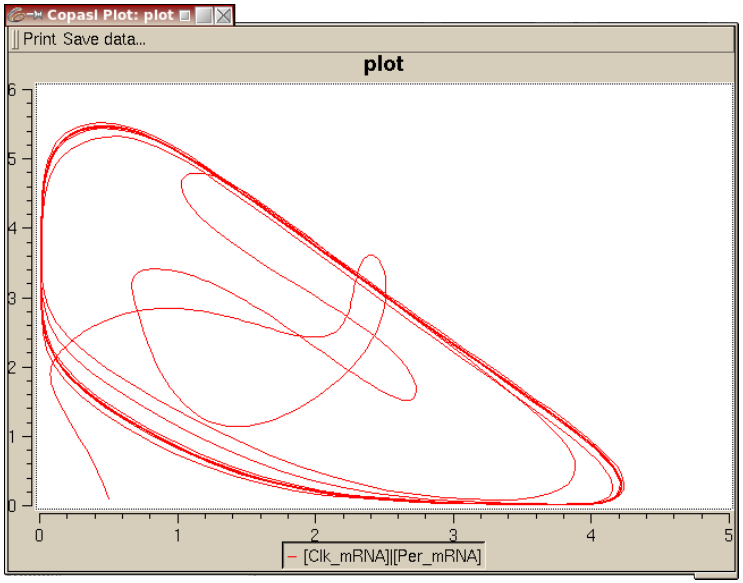


Ueda, Hagiwara, Kitanol 2001 (BIOMD0000000022)



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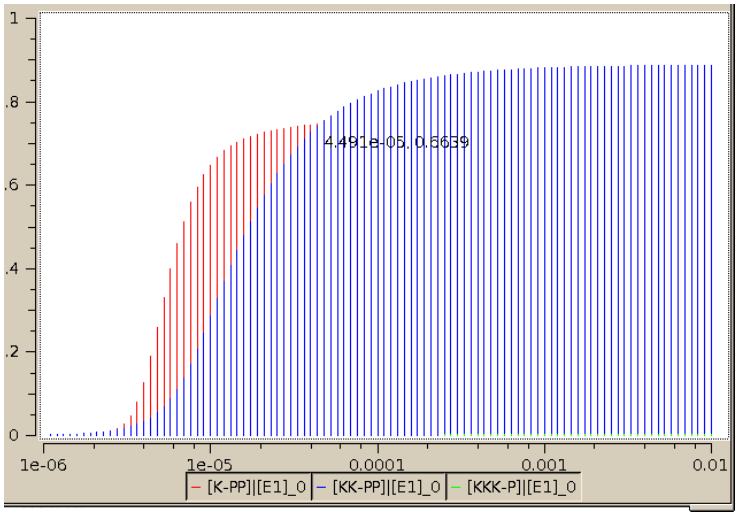
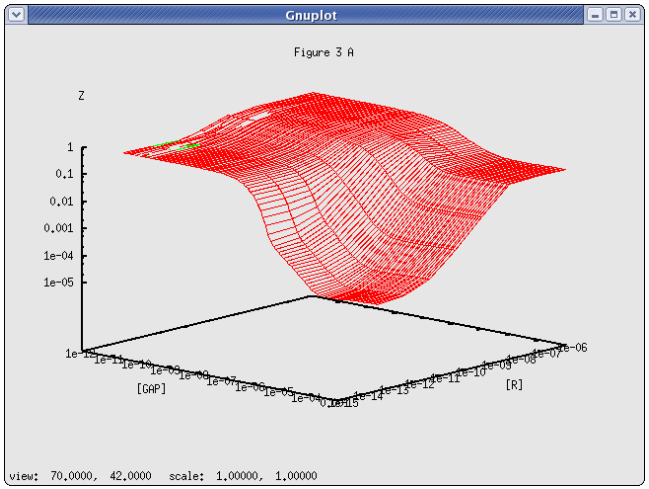


Bornheimer et al 2004 (BIOMD0000000086)



Minimum Information About a Simulation Experiment (MIASE)

- ## Information about the models simulated
  MIASE recommends to explicitly define all models used in a simulation by providing a specific name and the source of each model. In order to get a desired simulation result, it is often not sufficient to use models as such. That is why, changes that have to be applied to the model before simulation have to be described. Examples of such changes can be the assignment of a new value (e.g. constant, initial concentration), or the change of a mathematical expression (e.g. using different enzyme kinetics). simulation settings (type of simulation and the corresponding parameters)

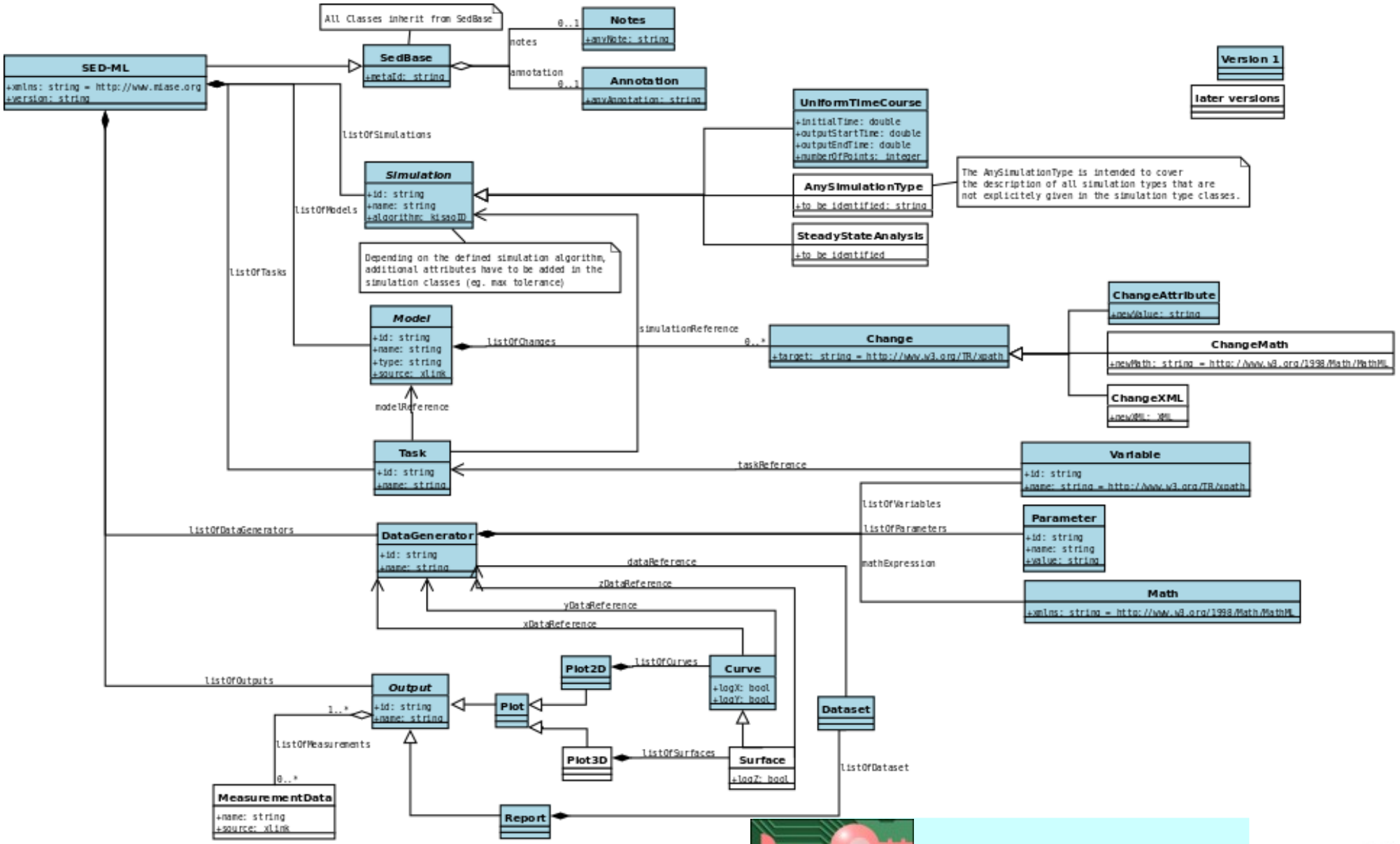
- ## Information about the simulation methods used
  Each simulation can be characterized by certain types of simulation procedures to be run (steady-state, timecourse etc.) and the simulation algorithms used to perform them. The information has to be sufficiently detailed so that no arbitrary choices have to be made when setting up the simulations.

- ## Information about the tasks performed
  Once simulation settings and changes on the models have been stored, the simulation tasks to be undertaken in order to complete the simulation experiment need to be specified. Typically, that will involve describing how a simulation procedure has to be applied to a specific model, and in which order.

- ## Information about the outputs produced
  It is often necessary to define the transformations that have to be applied to the raw output of the simulation tasks, and how to provide the final results. These results can be numerical or graphical. For instance, a model of a periodic process can provide just timecourses showing oscillations; or it can, on the contrary, provide phase diagrams, which are more explicit in describing the relationship between variables. An even more striking example of the necessity for output definitions is the bifurcation diagram.

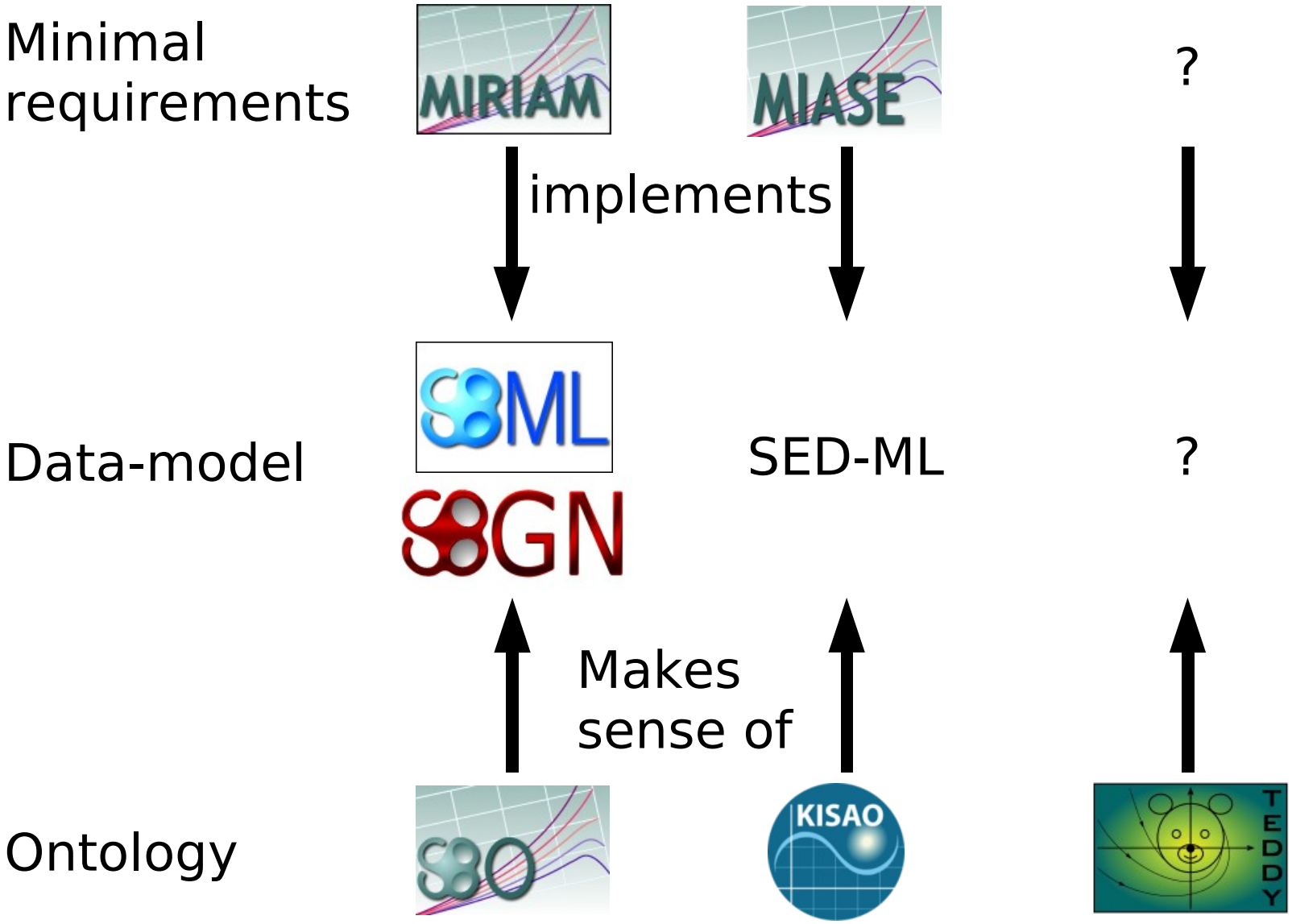
EMBL-EBI

Simulation Experiment Description ML



Computational Neurobiology

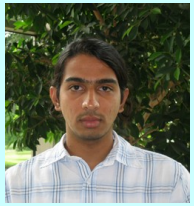
Köhn, Le Novère (2008)
CMSB 2008


Minimal requirements
MIRIAM
MIASE
?
implements
Data-model
SBML
SED-ML
?
SBGN
Makes sense of
Ontology
SBO
KISAO
TEDDY

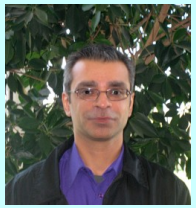
EMBL-EBI

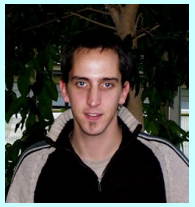
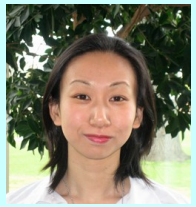
Acknowledgements





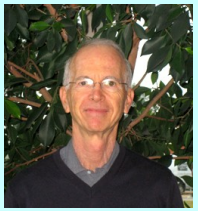









MIRIAM

MIASE

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  - Andrew Finney
  - Stefan Hoops
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  - Anatoly Sorokin

The whole community of
Computational Systems Biology