EMBL-EBI

Resources Européennes pour la biologie des systèmes

Nicolas Le Novère, EMBL-EBI

What is Systems Biology

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- **Systems Biology** is the study of a biological system taking into account all its constituents, *their relationships,* and *their evolution*. Nicolas Le Novère, now.
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- **Computational Systems Biology** is the construction of quantitative models that describe the behaviour of a system, on its own, or in response to its environment

What is a model

- A model is a mathematical description of the components of a system, their relationships, and the evolution of both.
  - ordinary differential equations (system evolution) $dX/dt = f(X)$
  - partial differential equation (system description) $\nabla X = g(X)$
  - algebraic equations (conservation laws) $h(X) = 0$
  - probability distributions $PX = i(X)$
  - master equation $dPX/dt = j(PX)$
  - cell automata/finite elements
  - ...

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
  - ...

EMBL-EBI

What does CSB aim to achieve?

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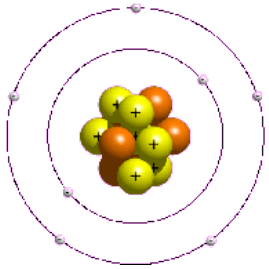
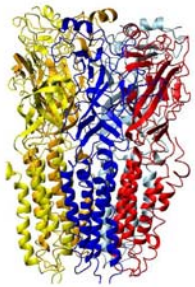
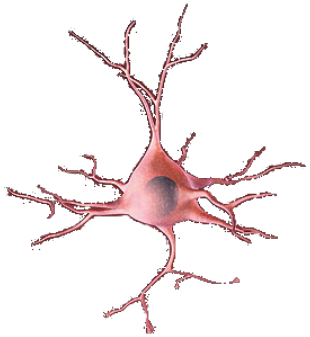
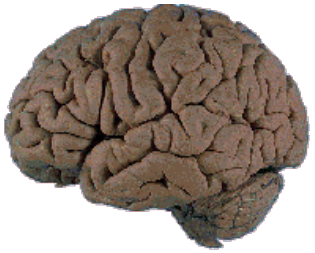
10^{-10} 10^{-8} 10^{-7} 10^{-5} 10^{-2} 10^{-0} m

spatial scale problem









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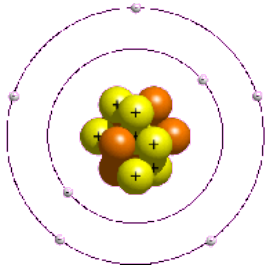
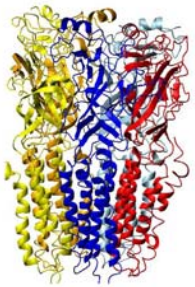
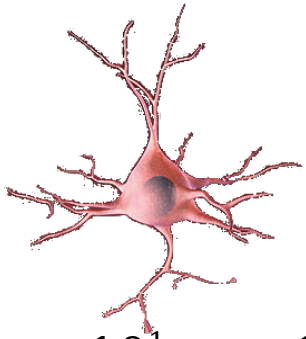
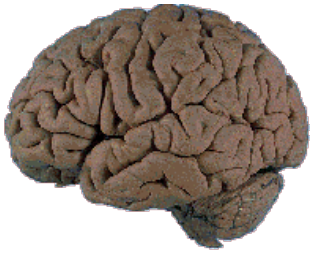





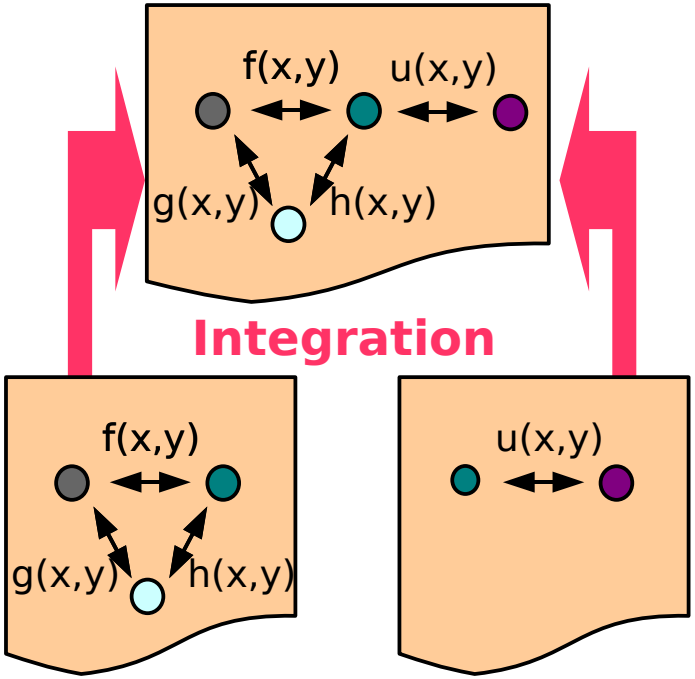

10^{-12} 10^{-6} 10^{-1} 10^{1} 10^{3} 10^{5} 10^{7} 10^{9} s

time scale problem

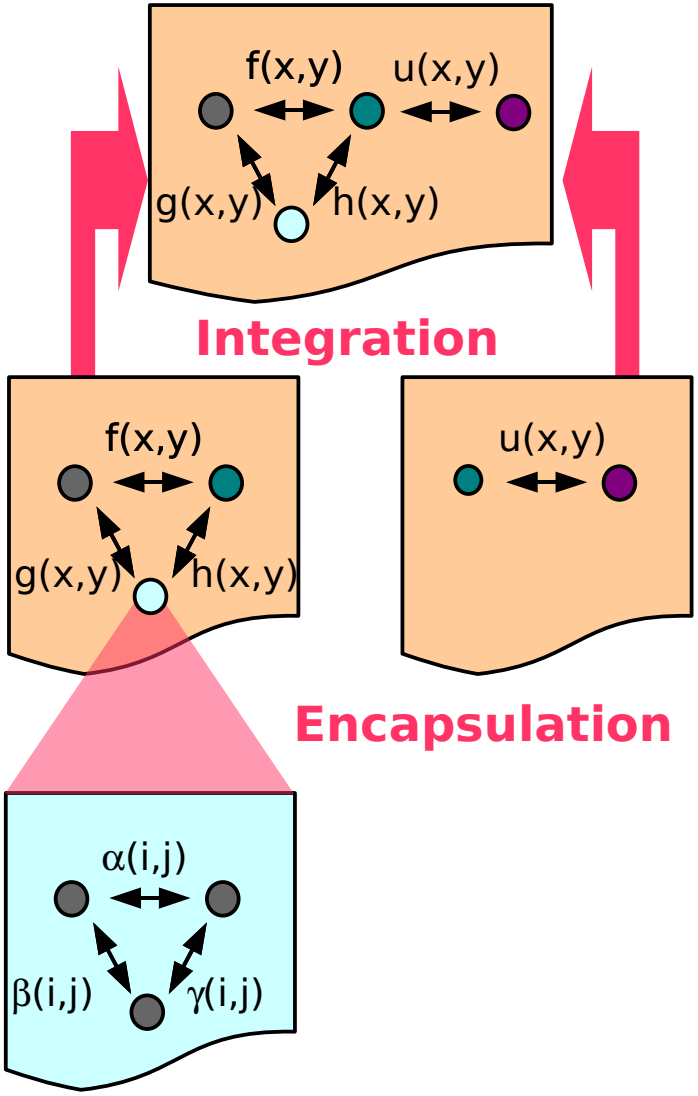
molecular dynamics
conformational transition
molecule diffusion
nerve signal
signalling cascade
gene regulation
circadian rhythm
cell cycle
reproduction
life cycle

Technical bottlenecks

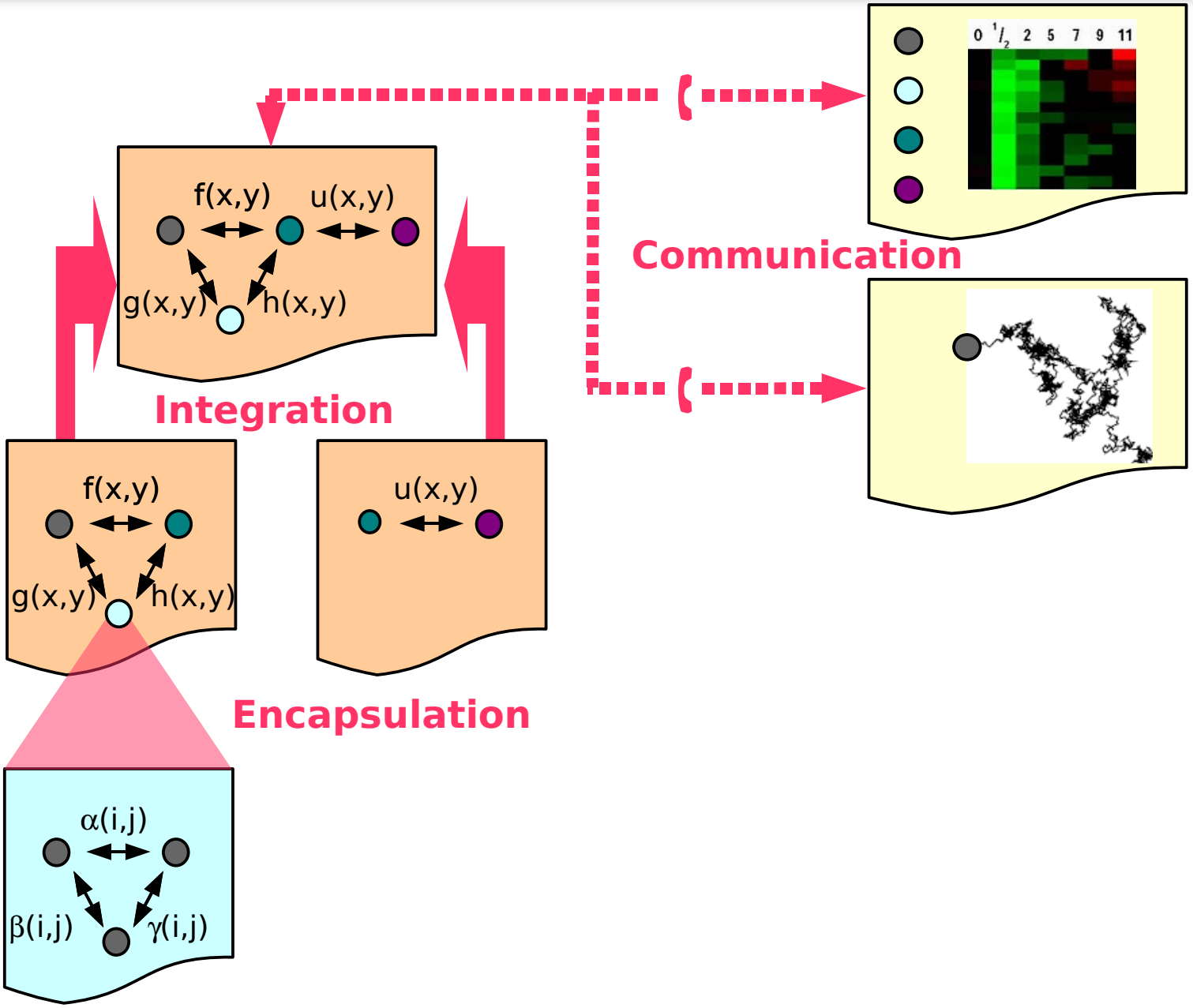
Technical bottlenecks



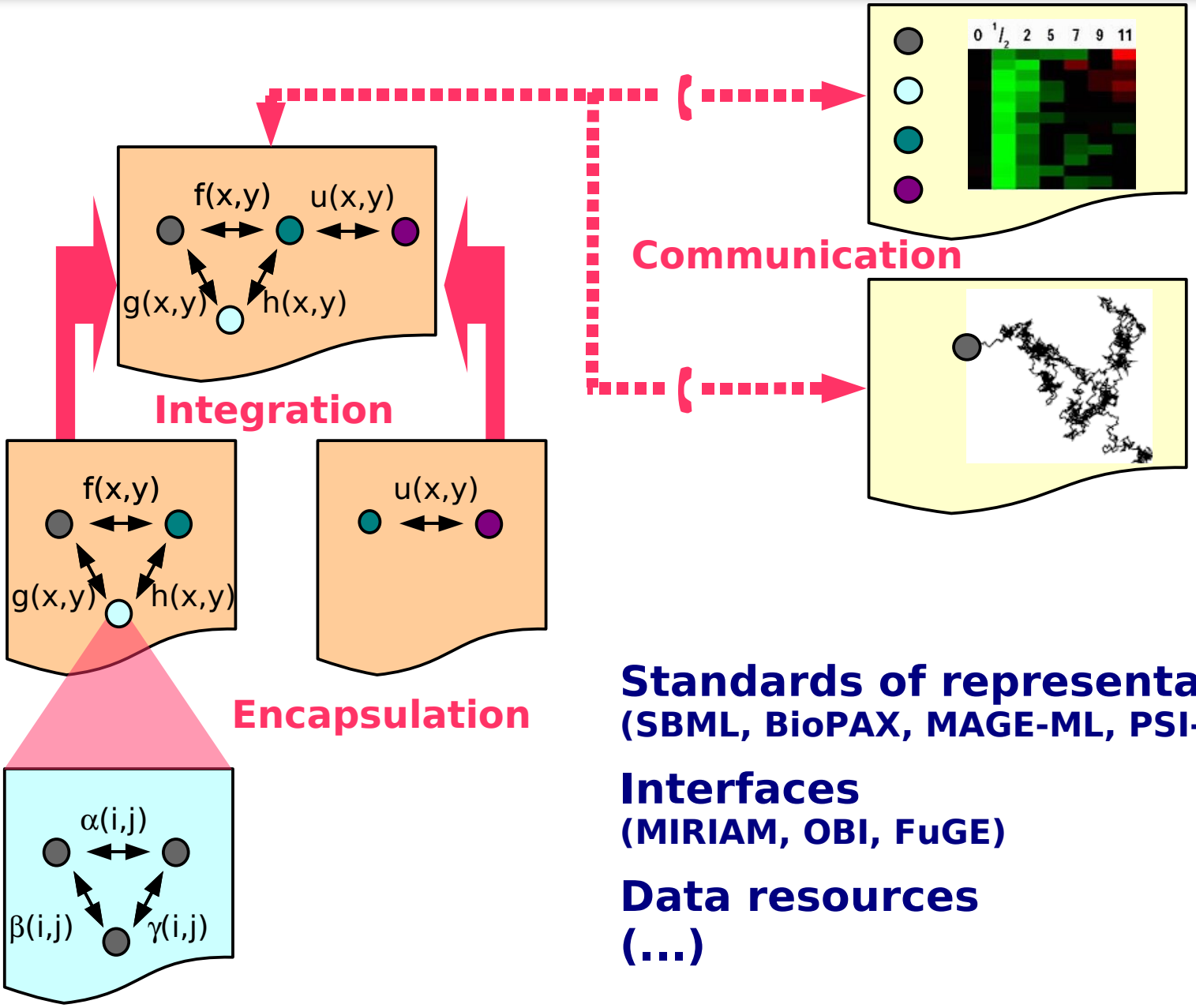
Technical bottlenecks



Technical bottlenecks



How to address them



Standards of representation
(SBML, BioPAX, MAGE-ML, PSI-MI etc.)

Interfaces
(MIRIAM, OBI, FuGE)

Data resources
(...)

SBML Systems Biology Markup Language

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 110 software systems**, including the following (where '*' indicates SBML support in development):

acslXtreme	Dizzy	Moleculizer	SBMLToolbox
BALSA	E-CELL	Monod	SBO
BASIS	ecellJ	Narrator	SBToolbox
BIOCHAM	ESS	NetBuilder	SBW
BioCharon	FluxAnalyzer	Oscill8	SCIpath
ByoDyn	Fluxor	PANTHER Pathway	semanticSBML
BioCyc	Genetdes	PathArt	Sigmoid*
BioGrid	Gepasi	Pathway Analyser	SigPath
BioModels	Gillespie2	PathwayLab	SigTran
BioNetGen	HSMB	Pathway Tools	SIMBA
BioPathwise	HybridSBML	PathwayBuilder	SimBiology
Bio Sketch Pad	INSILICO discovery	PATIKAweb	Simpathica
BioSens	JACOBIAN	PaVESy	SimPheny*
BioSPICE Dashboard	Jarnac	PET	SimWiz
BioSpreadsheet	JDesigner	PNK	SloppyCell
BioTapestry	JigCell	PottersWheel	SmartCell
BioUML	JSim	ProcessDB	SRS Pathway Editor
BSTLab	JWS Online	PROTON	StochSim
CADLIVE	Karyote*	pysbml	StochKit
CellDesigner	KEGG2SBML	PySCeS	STOCKS
Cellerator	Kineticon	Reactome	TERANODE Suite
Cell Illustrator	Kinsolver*	RMBNToolbox	Trelis
CellML2SBML	libSBML	RSBML	VANTED
Cellware	MathSBML	runSBML	Virtual Cell
CL-SBML	MesoRD	SABIO-RK	WebCell
CLEML	Meta-All	SBML ODE Solver	WinSCAMP
COPASI	MetaFluxNet	SBML-PET	Xholon
Cyto-Sim	MIRIAM	SBMLeditor	XPPAUT
Cytoscape	MMT2	SBMLR	
DBsolve	Modesto	SBMLSim	

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 environment, and (3) ensuring the survival of models (and the intellectual effort put into them) beyond the lifetime of the software used to create them.

Does Your Software Support SBML?

If you have implemented support for SBML in your tool, or you know of a package that is not listed above, please let us know and we'll

New version of SBW

(Oct. 25, 2007) The SBW Development Team has released **SBW version 2.7.6**. SBW is a software communications framework allowing different tools to be networked.

read more

New version of VCell

(Oct. 5, 2007) The **VCell** project has released both a stable and a new beta release of VCell. Among the new features are improved SBML compatibility.

read more

New version of COPASI

(Oct. 5, 2007) The **COPASI** project has released development version Build 23, featuring several new capabilities and improvements to SBML compatibility.

read more

SBML Level 2 Version 3 Release 2

(Sep. 27, 2007) **Release 2** of the SBML Level 2 Version 3 specification is now available. It corrects typos and small errors in Release 1.

read more

libSBML 3.0.0 released!

(Aug 31, 2007) **libSBML** 3.0.0 is now available. LibSBML is an embeddable, portable API library for reading, writing and manipulating files and data streams containing SBML content.

read more

See older news items.

```
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<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>
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            <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>
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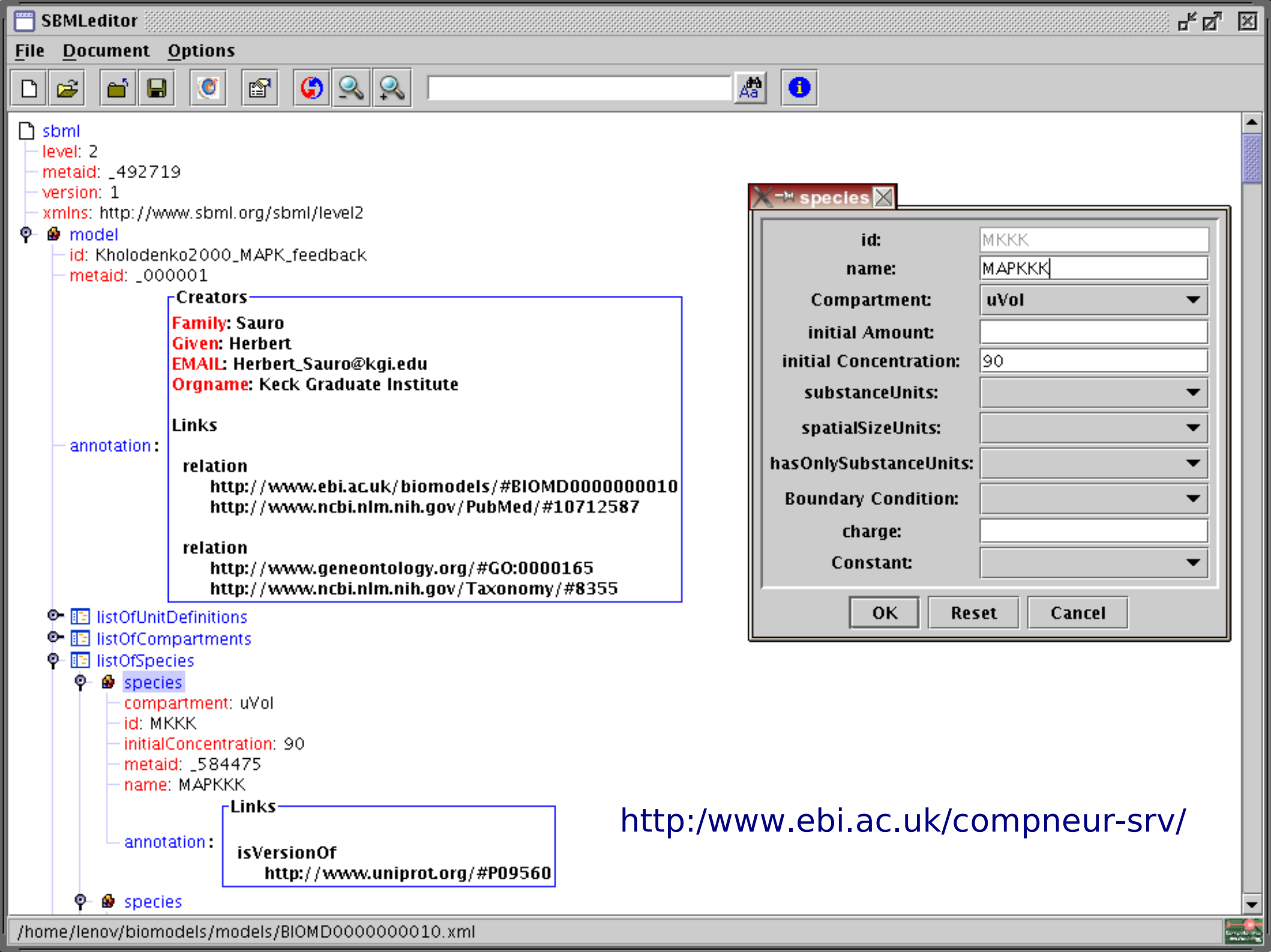
      </rdf:Description>
    </rdf:RDF>
  </annotation>
</species>
```


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

SBML is not limited to biochemistry!

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

➔ Remember, Systems Biology is scale-free!

New: SBML Level 2 Version 3

Hucka M, Finney AM, Hoops S, Keating SM, Le Novère N (2007)
Systems Biology Markup Language (SBML) Level 2:
Structures and Facilities for Model Definitions.
Available from *Nature Precedings*
<http://hdl.nature.com/10101/npre.2007.58.1>

- Released on June 16th 2007
- Simpler and cleaner (units ...)
- Generic entities (compartmentType, speciesType)
  ➔ path to generalised reactions
- Constraints and initialAssignments
- Controlled annotations (MIRIAM + SBO)
- Backward compatible with Level 2 Version 1
- More detailed and bug-free specification ... 164 pages, 10pt, small margin!

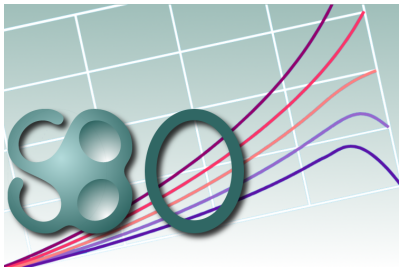
Is SBML enough? What's missing?

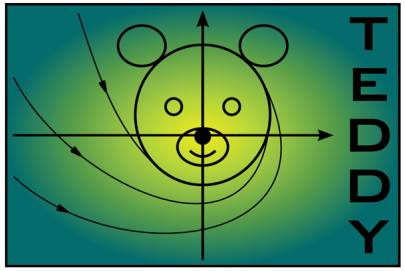
- An SBML model lists participants, but does not identify them.
- An SBML model contains mathematical expressions, but does not tell-us what they “mean”, and how they are derived.
- An SBML model constructed for a certain modelling approach cannot be used straight-away within another modelling framework.

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

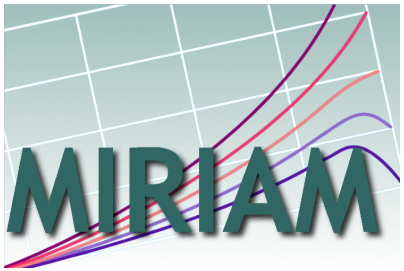
model semantics

behaviour semantics





SBML

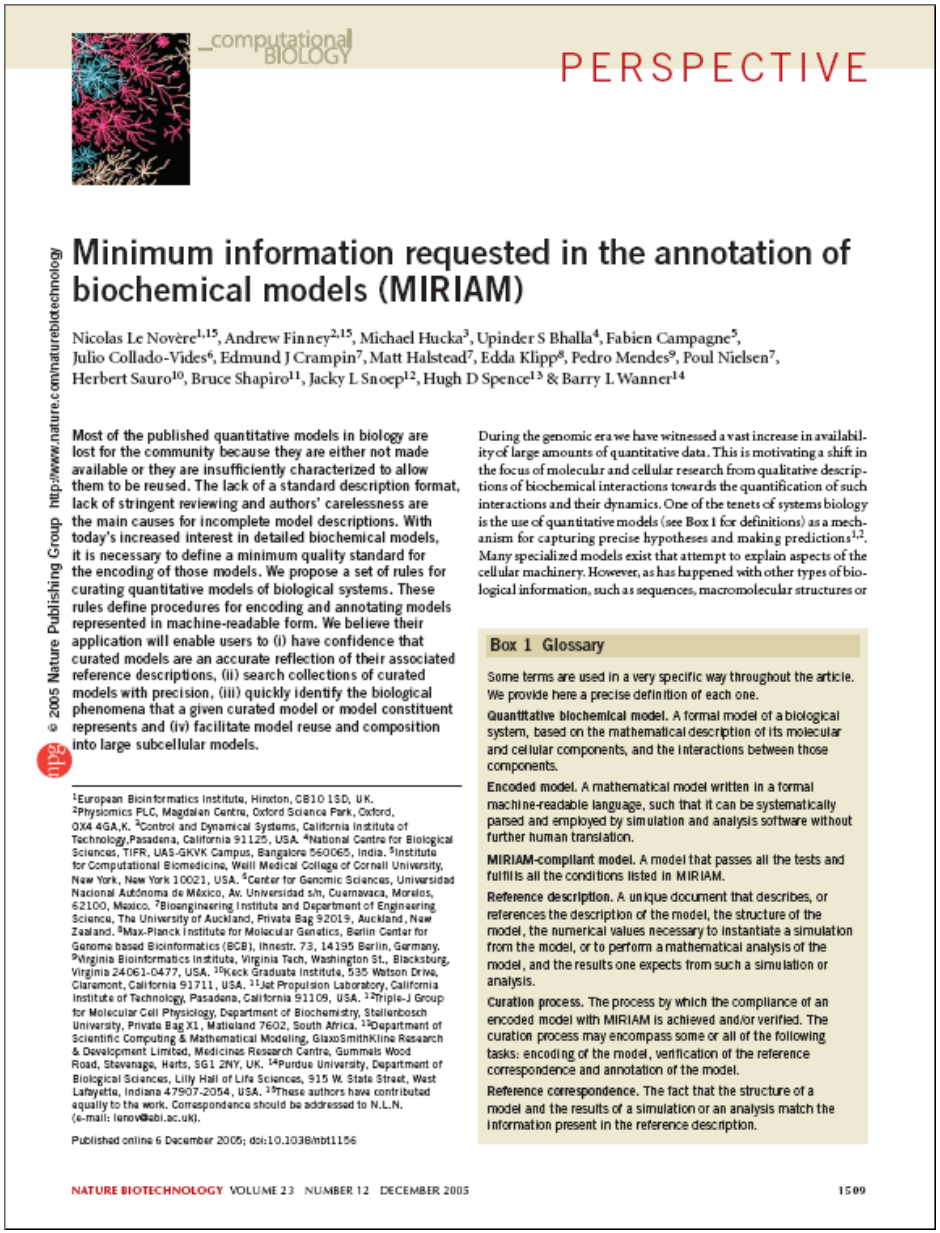


MIASE
KiSAO

biological semantics

simulation semantics

- Proposed guidelines for curation of quantitative models
  - Specifically about encoding & annotation
  - Limited to models that can be simulated
- Effort arose from a meeting organized by Andrew Finney during ICSB 2004
- Not specific to SBML; applicable to any structured model format



_computational BIOLOGY

PERSPECTIVE

Minimum information requested in the annotation of biochemical models (MIRIAM)

Nicolas Le Novère[1,15], Andrew Finney[2,15], Michael Hucka[3], Upinder S Bhalla[4], Fabien Campagne[5], Julio Collado-Vides[6], Edmund J Crampin[7], Matt Halstead[7], Edda Klipp[8], Pedro Mendes[9], Poul Nielsen[7], Herbert Sauro[10], Bruce Shapiro[11], Jacky L Snoep[12], Hugh D Spence[13] & Barry L Wanner[14]

Most of the published quantitative models in biology are lost for the community because they are either not made available or they are insufficiently characterized to allow them to be reused. The lack of a standard description format, lack of stringent reviewing and authors' carelessness are the main causes for incomplete model descriptions. With today's increased interest in detailed biochemical models, it is necessary to define a minimum quality standard for the encoding of those models. We propose a set of rules for curating quantitative models of biological systems. These rules define procedures for encoding and annotating models represented in machine-readable form. We believe their application will enable users to (i) have confidence that curated models are an accurate reflection of their associated reference descriptions, (ii) search collections of curated models with precision, (iii) quickly identify the biological phenomena that a given curated model or model constituent represents and (iv) facilitate model reuse and composition into large subcellular models.

[1]European Bioinformatics Institute, Hinxton, CB10 1SD, UK. [2]Physiomics PLC, Magdalen Centre, Oxford Science Park, Oxford, OX4 4GA,K. [3]Control and Dynamical Systems, California Institute of Technology,Pasadena, California 91125, USA. [4]National Centre for Biological Sciences, TIFR, UAS-GKVK Campus, Bangalore 560065, India. [5]Institute for Computational Biomedicine, Weill Medical College of Cornell University, New York, New York 10021, USA. [6]Center for Genomic Sciences, Universidad Nacional Autónoma de México, Av. Universidad s/n, Cuernavaca, Morelos, 62100, Mexico. [7]Bioengineering Institute and Department of Engineering Science, The University of Auckland, Private Bag 92019, Auckland, New Zealand. [8]Max-Planck Institute for Molecular Genetics, Berlin Center for Genome based Bioinformatics (BCB), Ihnestr. 73, 14195 Berlin, Germany. [9]Virginia Bioinformatics Institute, Virginia Tech, Washington St., Blacksburg, Virginia 24061-0477, USA. [10]Keck Graduate Institute, 535 Watson Drive, Claremont, California 91711, USA. [11]Jet Propulsion Laboratory, California Institute of Technology, Pasadena, California 91109, USA. [12]Triple-J Group for Molecular Cell Physiology, Department of Biochemistry, Stellenbosch University, Private Bag X1, Matieland 7602, South Africa. [13]Department of Scientific Computing & Mathematical Modeling, GlaxoSmithKline Research & Development Limited, Medicines Research Centre, Gunnels Wood Road, Stevenage, Herts, SG1 2NY, UK. [14]Purdue University, Department of Biological Sciences, Lilly Hall of Life Sciences, 915 W. State Street, West Lafayette, Indiana 47907-2054, USA. [15]These authors have contributed equally to the work. Correspondence should be addressed to N.L.N. (e-mail: lenov@ebi.ac.uk).

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During the genomic era we have witnessed a vast increase in availability of large amounts of quantitative data. This is motivating a shift in the focus of molecular and cellular research from qualitative descriptions of biochemical interactions towards the quantification of such interactions and their dynamics. One of the tenets of systems biology is the use of quantitative models (see Box 1 for definitions) as a mechanism for capturing precise hypotheses and making predictions[1,2]. Many specialized models exist that attempt to explain aspects of the cellular machinery. However, as has happened with other types of biological information, such as sequences, macromolecular structures or

Box 1 Glossary

Some terms are used in a very specific way throughout the article. We provide here a precise definition of each one.

Quantitative biochemical model. A formal model of a biological system, based on the mathematical description of its molecular and cellular components, and the interactions between those components.

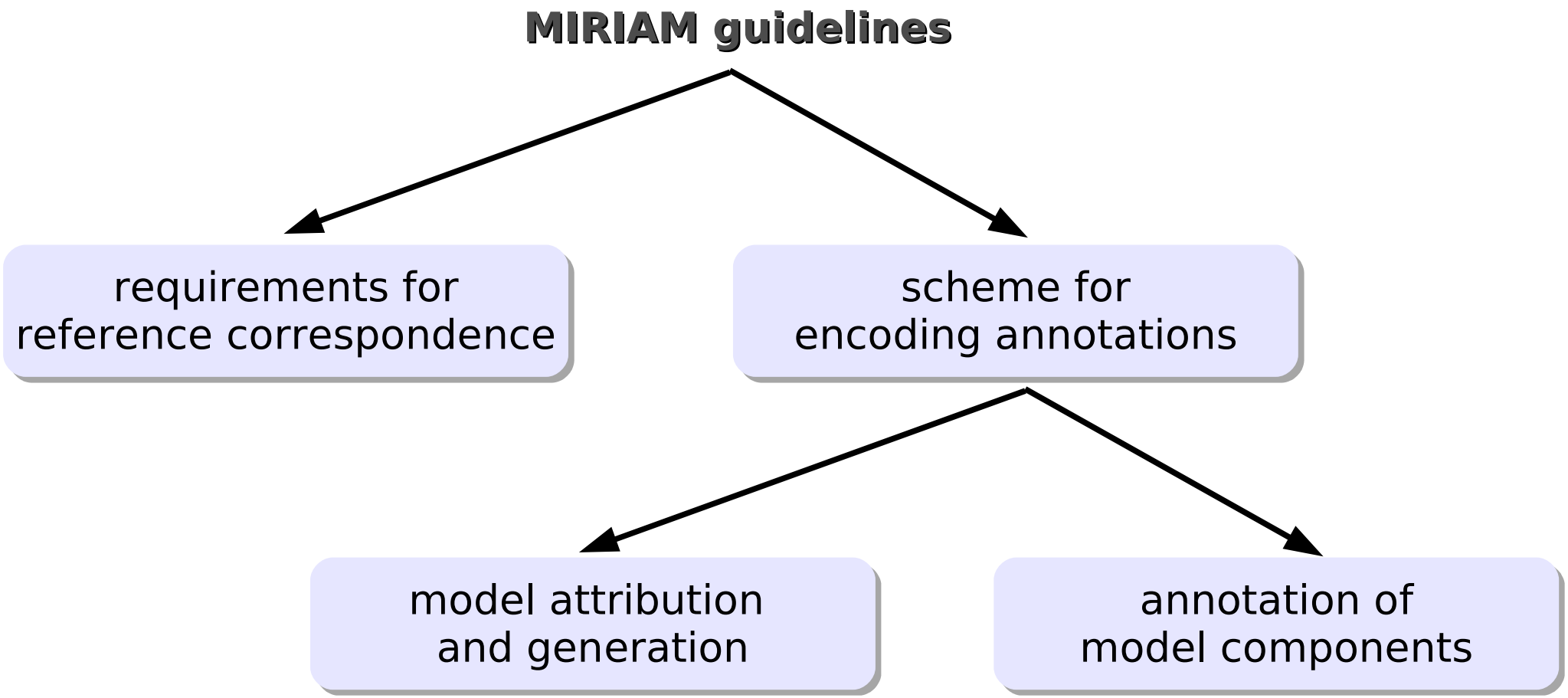
Encoded model. A mathematical model written in a formal machine-readable language, such that it can be systematically parsed and employed by simulation and analysis software without further human translation.

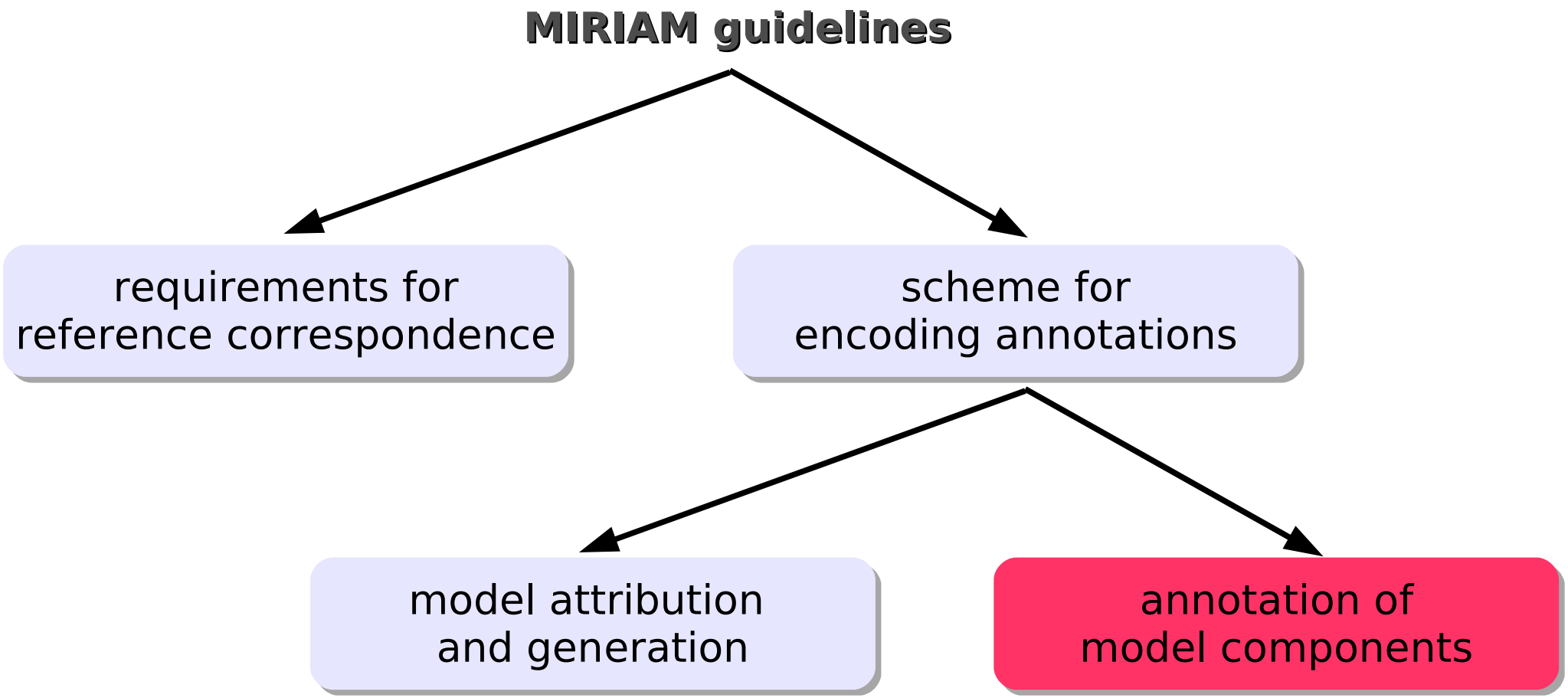
MIRIAM-compliant model. A model that passes all the tests and fulfills all the conditions listed in MIRIAM.

Reference description. A unique document that describes, or references the description of the model, the structure of the model, the numerical values necessary to instantiate a simulation from the model, or to perform a mathematical analysis of the model, and the results one expects from such a simulation or analysis.

Curation process. The process by which the compliance of an encoded model with MIRIAM is achieved and/or verified. The curation process may encompass some or all of the following tasks: encoding of the model, verification of the reference correspondence and annotation of the model.

Reference correspondence. The fact that the structure of a model and the results of a simulation or an analysis match the information present in the reference description.


MIRIAM guidelines
requirements for reference correspondence
scheme for encoding annotations
model attribution and generation
annotation of model components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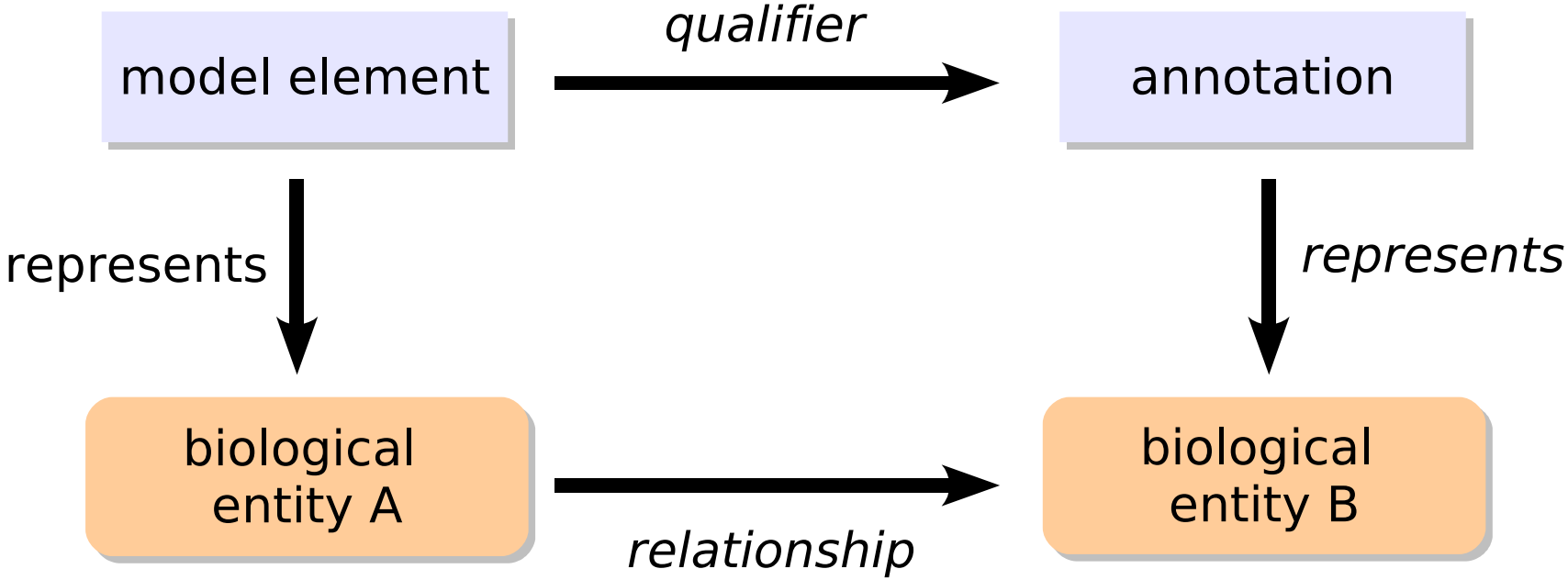
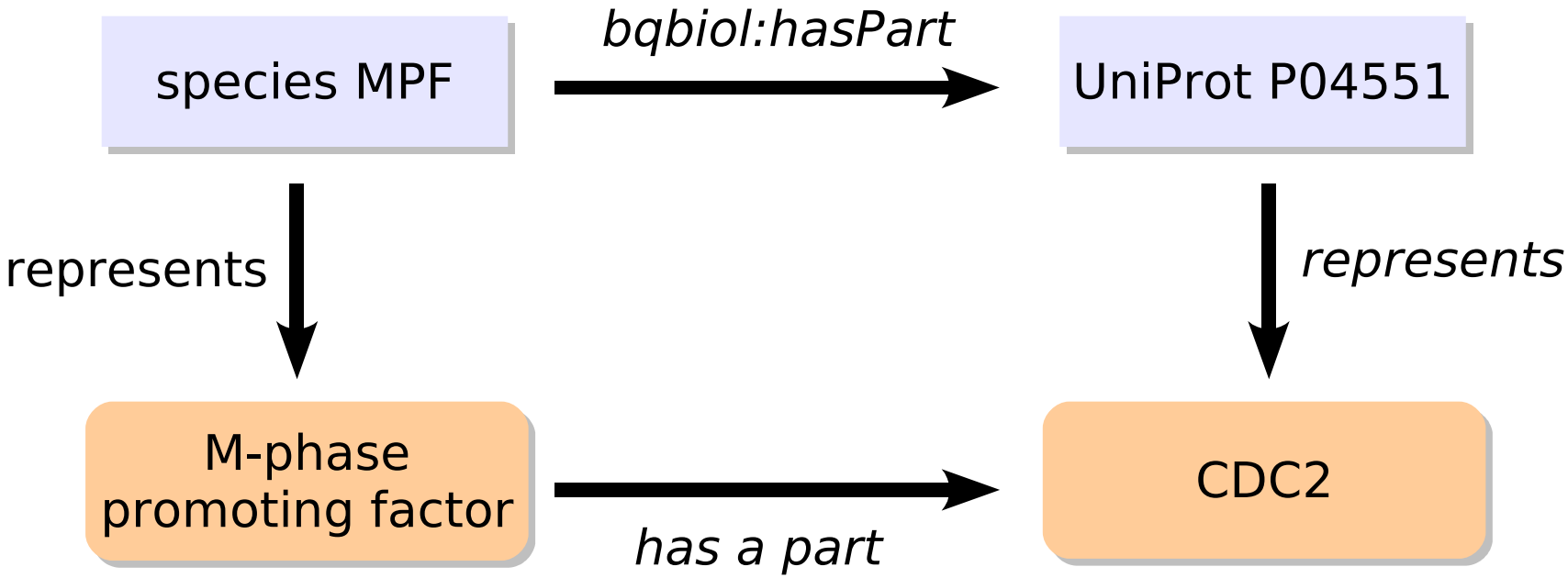
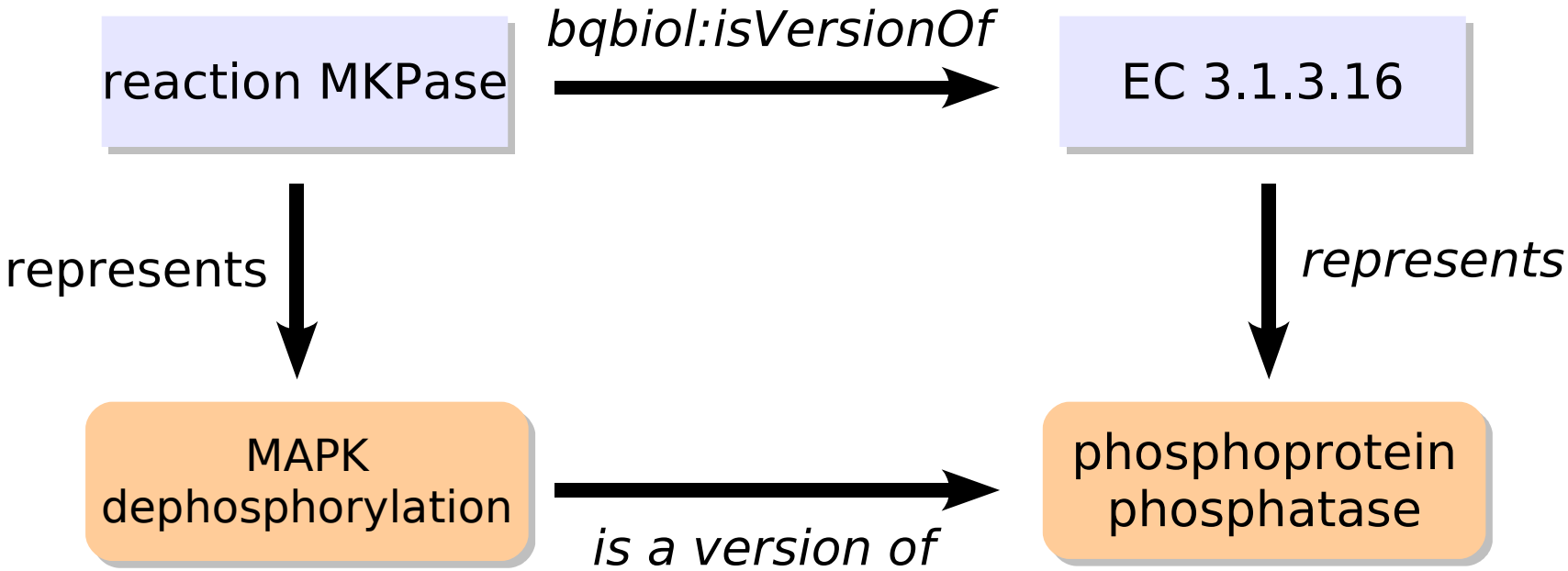
Qualification of annotation



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

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.

- Browse
- Query
- Submit new
- Export
- Sign In

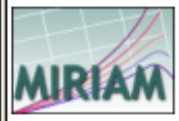
- News
- Web Services
- MIRIAM Standard
- BioModels Qualifiers
- FAQ
- MIRIAM on SourceForge
- Contact

MIRIAM

Browse the data-types

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

Name	URI	Definition
BIND	http://www.bind.ca/	BIND is a database of protein-protein interactions. This data-resource is not open-access.
BioModels Database	http://www.ebi.ac.uk/biomodels/	BioModels Database is a data resource that allows biologists to store, search and retrieve published mathematical models of biological interests.
ChEBI	http://www.ebi.ac.uk/chebi/	Chemical Entities of Biological Interest (ChEBI) is a freely available dictionary of molecular entities focused on 'small' chemical compounds.
CluSTr	http://www.ebi.ac.uk/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.
DOI	http://www.doi.org/	The Digital Object Identifier System is for identifying content objects in the digital environment.
Ensembl	http://www.ensembl.org/	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	http://www.ec-code.org/	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	http://www.flybase.org/	FlyBase is the database of the Drosophila Genome Projects and of associated literature.
Gene Ontology	http://www.geneontology.org/	The Gene Ontology project provides a controlled vocabulary to describe gene and gene product attributes in any organism.
ICD	http://www.who.int/classifications/icd/	The International Classification of Diseases is the international standard diagnostic classification for all general epidemiological and many health management purposes.
IntAct	http://www.ebi.ac.uk/intact/	IntAct provides a freely available, open source database system and analysis tools for protein interaction data.
InterPro	http://www.ebi.ac.uk/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.
KEGG Compound	http://www.genome.jp/kegg/compound/	KEGG compound contains our knowledge on the universe of chemical substances that are relevant to life.
KEGG Drug	http://www.genome.jp/kegg/drug/	KEGG DRUG contains chemical structures of drugs and additional information such as therapeutic categories and target molecules.
KEGG Glycan	http://www.genome.jp/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



- Browse
- Query
- Submit new
- Export
- Sign In

- News
- Web Services
- MIRIAM Standard
- BioModels Qualifiers
- FAQ
- MIRIAM on SourceForge
- Contact

MIRIAM

Data-type: ***Enzyme Nomenclature***

Name		
Identifier		MIR:00000004
Name		Enzyme Nomenclature
Synonyms		Enzyme Classification
		EC code
		EC
URIs		
Official URL		http://www.ec-code.org/
Official URN		urn:lsid:ec-code.org
Deprecated		http://www.ebi.ac.uk/IntEnz/
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		2007-03-09 16:00:07 GMT

SBML and MIRIAM

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  <annotation>
    <rdf:RDF
        xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#"
        xmlns:bqbiol="http://biomodels.net/biology-qualifiers/">
      <rdf:Description rdf:about="#cacam">
        <bqbiol:hasPart>
          <rdf:Bag>
            <rdf:li rdf:resource="http://www.uniprot.org/#P62158"/>
            <rdf:li rdf:resource="http://www.ebi.ac.uk/chebi/#CHEBI:29108"/>
          </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="http://www.ec-code.org/#2.7.11.25"/>
          </rdf:Bag>
        </bqbiol:isVersionOf>
```

annotation resolver

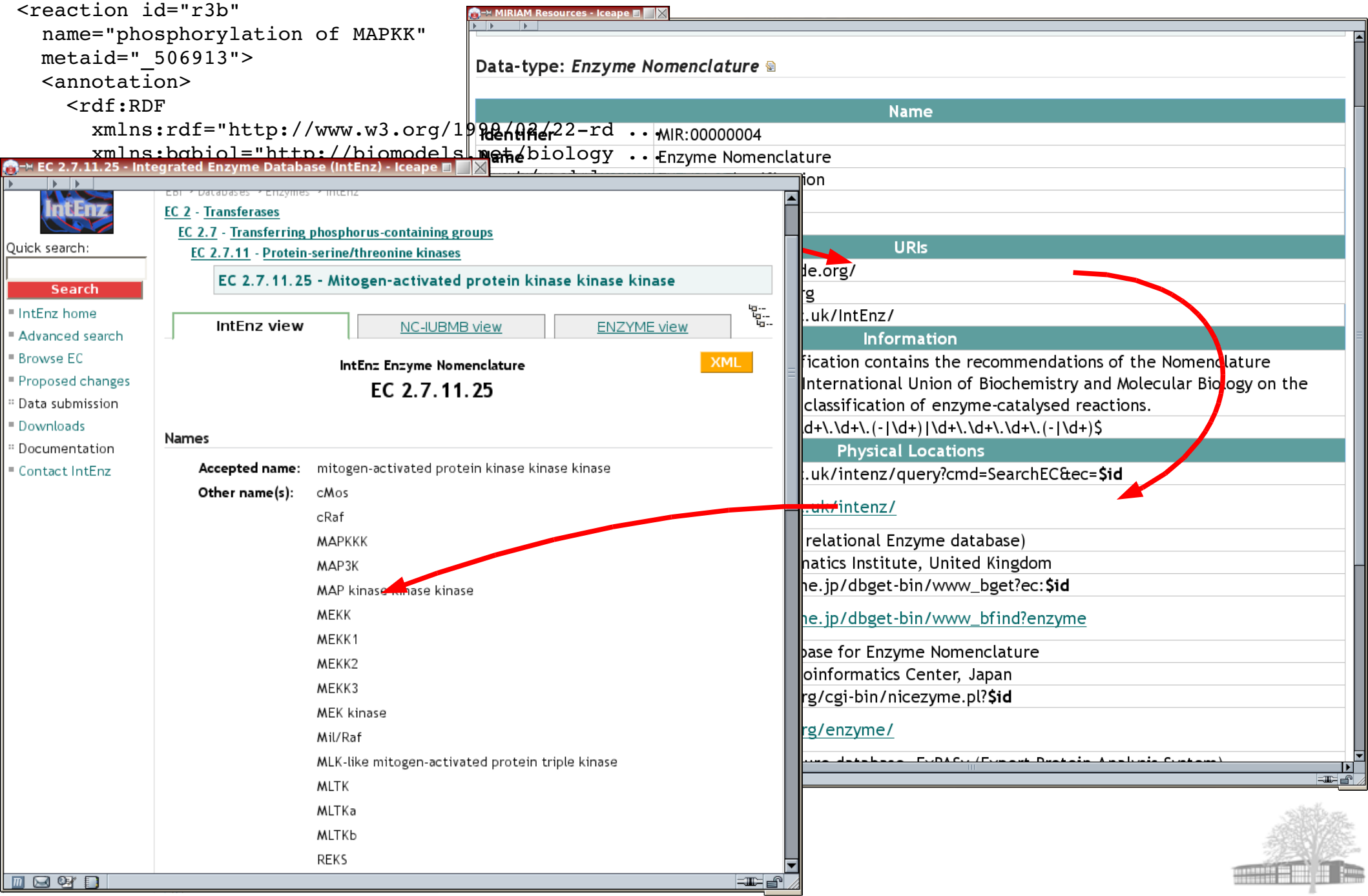
```
<reaction id="r3b"
  name="phosphorylation of MAPKK"
  metaid="_506913">
  <annotation>
    <rdf:RDF
      xmlns:rdf="http://www.w3.org/1999/02/22-rd ...
      xmlns:bqbiol="http://biomodels.net/biology ...
      xmlns:bqmodel="http://biomodels.net/model- ...
      <rdf:Description rdf:about="#_506913">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

MIRIAM Resources - Iceape

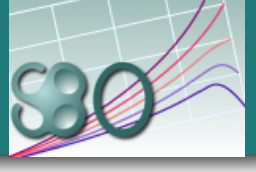
Data-type: ***Enzyme Nomenclature***

Name	
Identifier	MIR:00000004
Name	Enzyme Nomenclature
	Enzyme Classification
	EC code
	EC
URIs	
Official URL	http://www.ec-code.org/
Official URN	urn:lsid:ec-code.org
Deprecated	http://www.ebi.ac.uk/IntEnz/
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=**$id**
Resource #1 — **Data Resource**	http://www.ebi.ac.uk/intenz/
Resource #1 — **Information**	IntEnZ (Integrated relational Enzyme database)
Resource #1 — **Institution**	European Bioinformatics Institute, United Kingdom
Resource #2 — **Data Entry**	http://www.genome.jp/dbget-bin/www_bget?ec:**$id**
Resource #2 — **Data Resource**	http://www.genome.jp/dbget-bin/www_bfind?enzyme
Resource #2 — **Information**	KEGG Ligand Database for Enzyme Nomenclature
Resource #2 — **Institution**	Kyoto University Bioinformatics Center, Japan
Resource #3 — **Data Entry**	http://us.expasy.org/cgi-bin/nicezyme.pl?**$id**
Resource #3 — **Data Resource**	http://us.expasy.org/enzyme/
Resource #3 — **Information**	Enzyme nomenclature database. ExPASy (Expert Protein Analysis System)

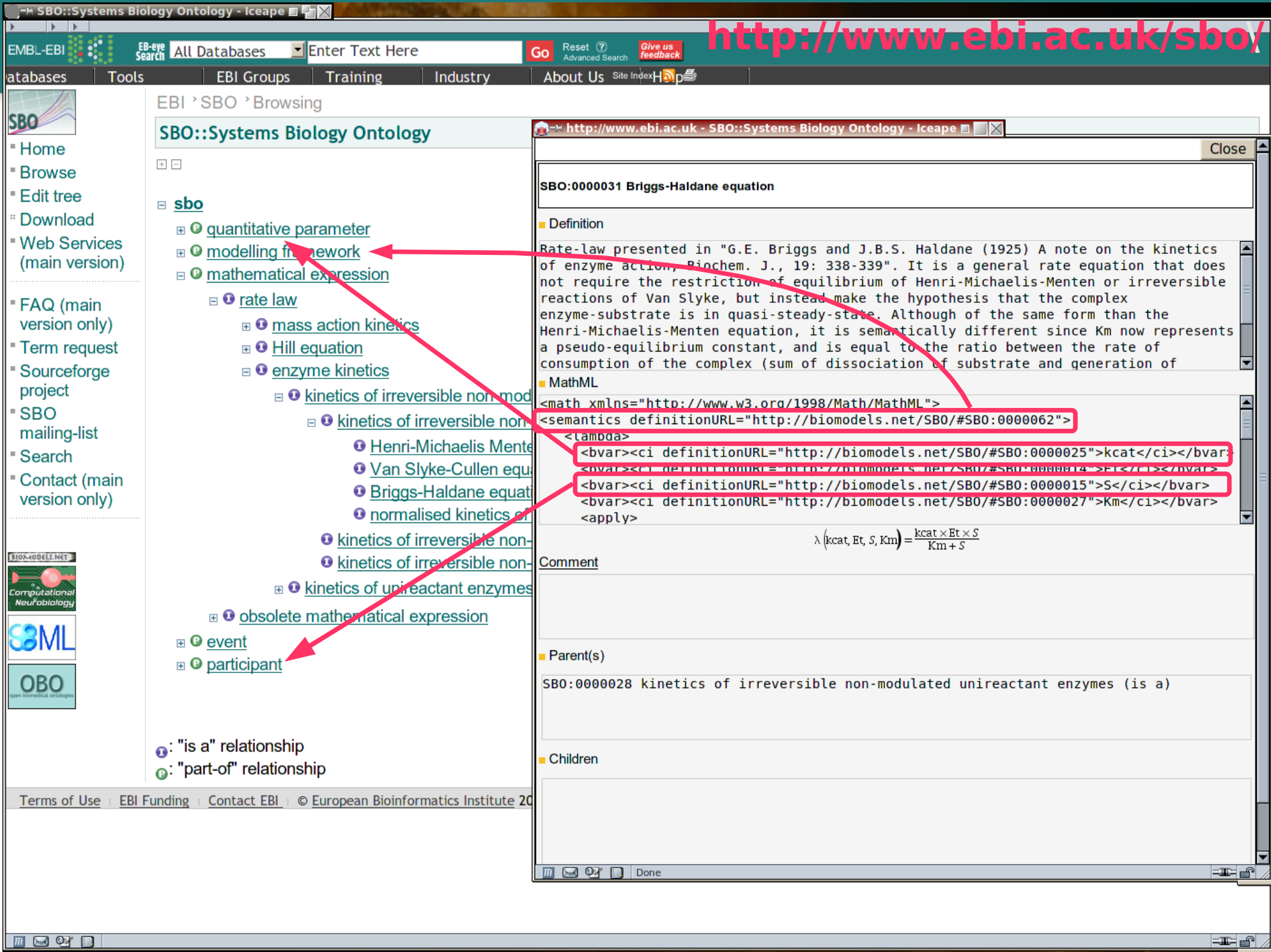
```
<reaction id="r3b"
  name="phosphorylation of MAPKK"
  metaid="_506913">
  <annotation>
    <rdf:RDF
      xmlns:rdf="http://www.w3.org/1999/02/22-rd
      xmlns:bqbiol="http://biomodels.net/biology
```



Systems Biology Ontology



- 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”.


SBO::Systems Biology Ontology - Iceape
http://www.ebi.ac.uk/sbo/
EMBL-EBI
All Databases
Enter Text Here
Go
Reset
Advanced Search
Give us feedback
Tools
EBI Groups
Training
Industry
About Us
Site Index
EBI › SBO › Browsing
SBO::Systems Biology Ontology
Home
Browse
Edit tree
Download
Web Services (main version)
FAQ (main version only)
Term request
Sourceforge project
SBO mailing-list
Search
Contact (main version only)
sbo
quantitative parameter
modelling framework
mathematical expression
rate law
mass action kinetics
Hill equation
enzyme kinetics
Henri-Michaelis Mente
Van Slyke-Cullen equa
Briggs-Haldane equati
normalised kinetics of
kinetics of irreversible non-
kinetics of irreversible non-
kinetics of unireactant enzymes
obsolete mathematical expression
event
participant
: "is a" relationship
: "part-of" relationship
Terms of Use
EBI Funding
Contact EBI
© European Bioinformatics Institute
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
MathML
<math xmlns="http://www.w3.org/1998/Math/MathML">
<semantics definitionURL="http://biomodels.net/SBO/#SBO:0000062">
<lambda>
<bvar><ci definitionURL="http://biomodels.net/SBO/#SBO:0000025">kcat</ci></bvar>
<bvar><ci definitionURL="http://biomodels.net/SBO/#SBO:0000015">S</ci></bvar>
<bvar><ci definitionURL="http://biomodels.net/SBO/#SBO:0000027">Km</ci></bvar>
<apply>
$\lambda(\mathrm{kcat}, \mathrm{Et}, S, \mathrm{Km}) = \frac{\mathrm{kcat} \times \mathrm{Et} \times S}{\mathrm{Km} + S}$
Comment
Parent(s)
SBO:0000028 kinetics of irreversible non-modulated unireactant enzymes (is a)
Children
Done

SBML and SBO

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    </kineticLaw>
  </reaction>
</listOfReactions>
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SBML and SBO

```
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  <compartment id="C" sboTerm="SBO:0000289">
</listOfCompartments>
<listOfSpecies>
  <species id="A" sboTerm="SBO:0000247" />
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<listOfReactions>
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    <kineticLaw sboTerm="SBO:0000031">
      <listOfParameters>
        <parameter id="U" sboTerm="SBO:0000008"/>
        <parameter id="V" sboTerm="SBO:0000025"/>
      </listOfParameters>
    </kineticLaw>
  </reaction>
</listOfReactions>
```

functional compartment

simple chemical

simple chemical

enzyme

catalysis

substrate

product

catalyst

Briggs-Haldane equation

Km

kcat

TErminology for the Description of DYnamics

- Dynamical behaviour of biological variables, including terms like “oscillation”, “bistability”, “steady-state”, “equilibrium” etc.
- Characteristics used to describe dynamics, such as “period” , “limit-cycle”, “Hopf bifurcation”etc.
- Functional role of model elements. Examples of terms are “negative feedback”, “integrator” etc.

Contents

Class: Temporal Behaviour (TEDDY_0000107)

- owl:Thing
  - Teddy Entity
    - Behaviour
      - **Temporal Behaviour**

Super Classes

Behaviour

Annotations

Definition	A **Temporal Behaviour** is a temporal sequence of states following the evolution operator of the dynamical system through a given initial state.
DisplayName	Temporal Behaviour
Reference	http://www.ebi.ac.uk/compneur-srv/teddy/literature.html#kuznetsov98-bifurcation_theory, p.8
Synonym	Orbit
Synonym	Phase Curve
Synonym	Trajectory

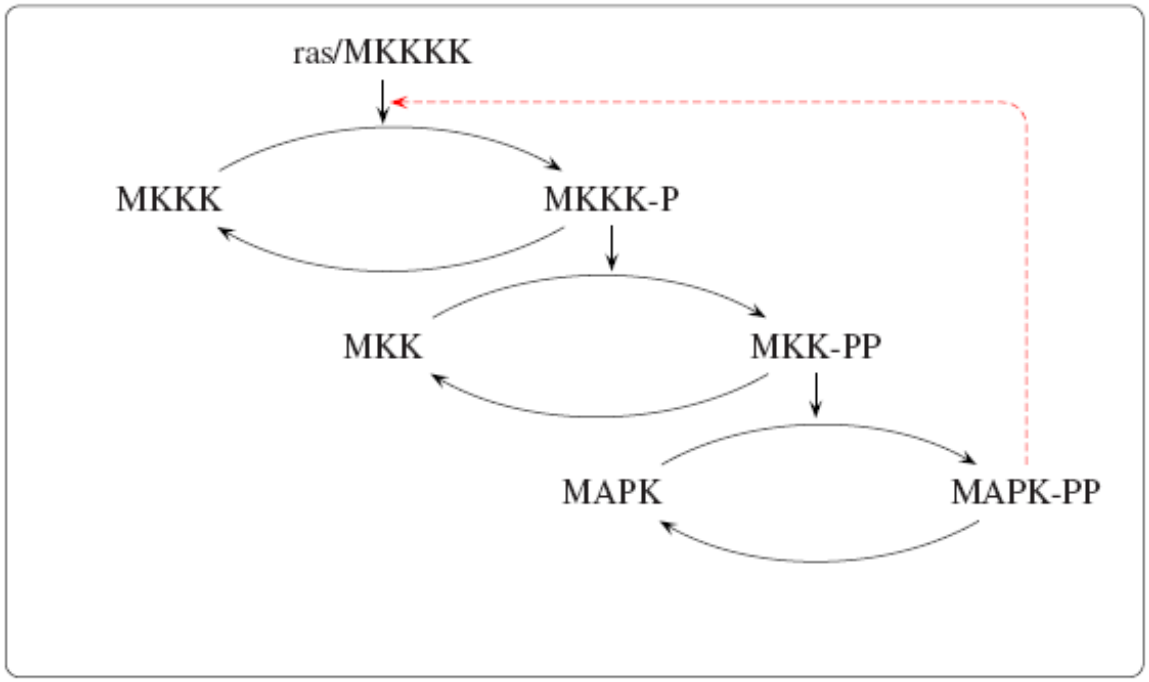
Usage

Class Description/Definition (Necessary Conditions)

Monotonic Behaviour, Non-Monotonic Behaviour

Release: rel-2007-09-03

Generated with OWLDoc, modified by Christian Knüpfer



$$\frac{\mathrm{d}[\mathrm{MKKK}]}{\mathrm{d}\,t} = \frac{V_1[\mathrm{MKKK}]}{K_1 + [\mathrm{MKKK}]} \times \left(1 + \frac{[\mathrm{MAPK\_PP}]}{K_I}\right)^{-m}$$

Bifurcation (TEDDY_0000053)

subClass

Positive Feedback (TEDDY_0000035)

Negative Feedback (TEDDY_0000034)

Saddle-Node Homoclinic Bifurcation (TEDDY_0000119)

dependsOn

$m < m_c$

hasSuperPart

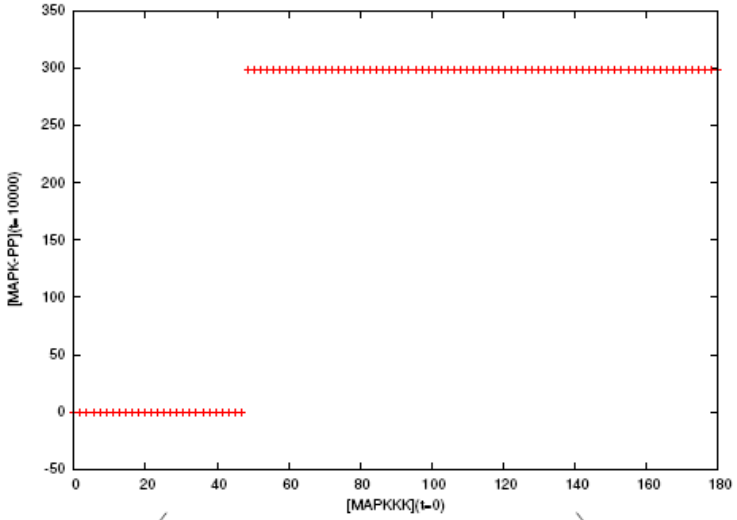
$m > m_c$

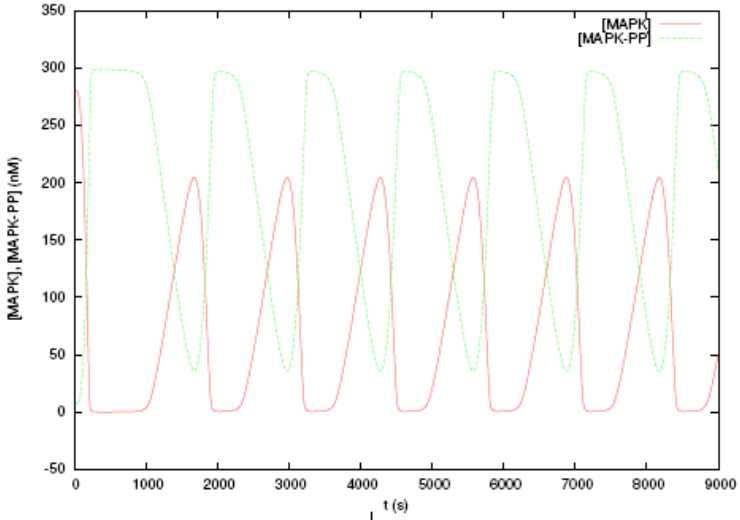
hasSubPart

dependsOn

Bistable Behaviour (TEDDY_0000110)

Stable Limit Cycle (TEDDY_0000114)





hasPart

hasPart

hasPart

Steady State (TEDDY_0000011)

Steady State (TEDDY_0000011)

Sustained Oscillation (TEDDY_0000062)

hasCharacteristic

hasCharacteristic

Low Magnitude (TEDDY_0000118)

High Magnitude (TEDDY_0000117)

EMBL-EBI

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

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

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

BioModels

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

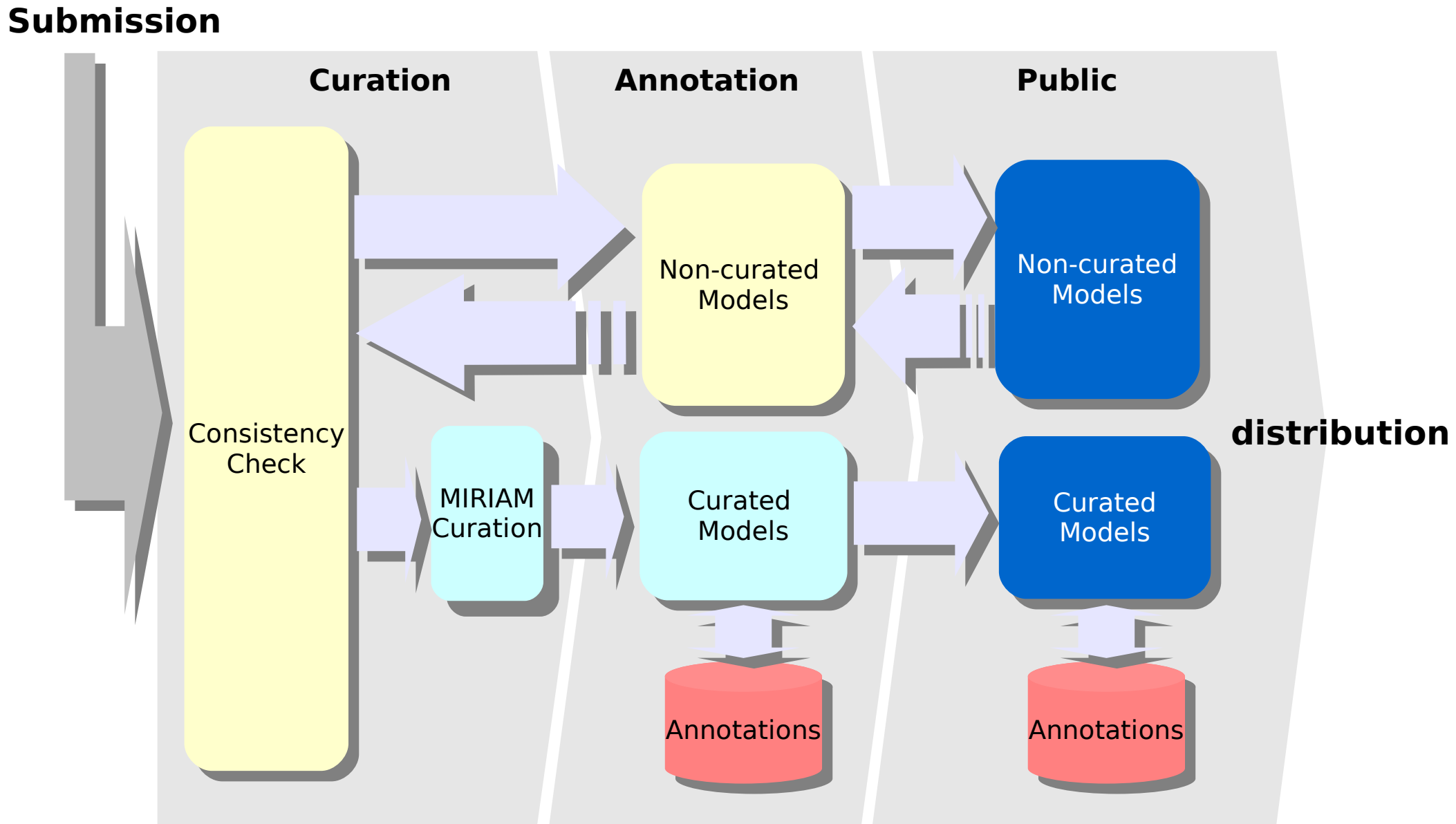
What is BioModels Database?

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

Where are the models coming from

- Existing model repositories
  - JWS Online
  - Database Of Quantitative Cell Signalling
  - CellML repository
  - the Virtual Cell
- Individuals
  - Members of the SBML community (developers+modellers)
  - Authors (prior to grant application, before publication etc.)
- Journals: Molecular Systems Biology, all PloS Journal, all BioMedCentral journals advise deposition
- BioModels DB curators encode new models from literature

Production pipeline



BioModels

- Curated Models
- Non-curated Models
- Search
- Simulate in JWS

- Submit Your Model

- Sign-in

- News
- Model of the Month
- Meetings
- Support
- Contact

BIOMODELS.NET

Computational Neurobiology | SBML | DOQCS Database of Quantitative Cellular Signaling | SBW | SBI | JWS online

BioModels Database

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

A Database of Annotated Published Models

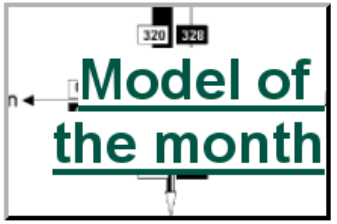
BioModels Database is a data resource that allows biologists to store, search and retrieve published mathematical models of biological interests. Models present in BioModels Database are annotated and linked to relevant data resources, such as publications, databases of compounds and pathways, controlled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

[Browse curated models] [Browse non-curated models] [Search] [Simulate in JWS Online]

05th June 2007 - Eighth Release! [More] [Download All Models Under SBML L2 V1 Format]

17th April 2007 - BioModels Database ranked first data resource for Systems Biology [More] [Original article]

4th December 2006 - BioModels Database and DOQCS join forces [More]



Acknowledgements

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

Model curators and annotators: Harish Dharuri, Enuo He, Nicolas Le Novère, Lu Li, Rainer Machne, Bruce Shapiro (Alumni: Maria Schilstra)

Developers: Mélanie Courtot, Camille Laibe, Chen Li (main developer), Lu Li, Nicolas Rodriguez (Alumni: Marco Donizelli, Arnaud Henry)

External contributors: BioModels Database would not exists without the continuous support of many people, whether by their contribution of models, of software, or by their constructive comments and criticisms. It is unfortunately impossible to acknowledge all of them here, without risking to be unfair. Therefore, a big collective thank-you all.

BioModels Database is built thanks to many third-party free software such as libSBML, Jakarta Tomcat, Xindice, Lucene, Xalan, Xerces, Axis, Jena and MySQL, plus all the free software coming with the GNU/Linux systems.

Main software used to curate models: CellDesigner, COPASI, Jarnac, MathSBML, RoadRunner, SBMLdeSolver, SBMLeditor, SBMLmerge and XPP-Aut.

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- Contact

BIOMODELS.NET

JWS online

Search - Models

Text Search

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

- *BioModels ID* → Search BioModels Database for *exact* BioModels identifiers (for example *BIOMD0000000001* or *BIOMD0000000022*).
- *Person* → Search BioModels Database for model submitter and/or creator(s) names, or model reference publication author(s) names (for example *Nicolas Le Novère*, *Nicolas*, *Bruce Shapiro* or *Shapiro*, *Edelstein* or *Novak*).
- *SBML Elements* → Search BioModels Database using the content of either "name" or "*notes*" SBML elements (for example *Edelstein* or *nicotinic*). Select the checkbox behind, if you want to find documents which matches the exact phrase; otherwise, all words will be searched as default.
- *Resource* → Search BioModels Database for related information found in the models reference publication or third-party resources, by either publication/resource identifier or text (for example *9256450* or *cyclin* for publication, *GO:0007049* or *cell cycle* for Gene Ontology, *P04551* or *cell division* for UniProt).
- *Resource ID* → Search BioModels Database for annotations, by third-party resource identifiers (for example *IPR002394* for InterPro, *hsa04080* for KEGG Pathway, *68910* for Reactome).

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

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

BioModels ID:

Person:

SBML Elements: ☐ match the **exact phrase**

Resource: Gene Ontology — map kinase

Resource:

Resource:

Publication
ChEBI
Gene Ontology
Taxonomy
UniProt

Resource ID:

Resource ID: BIND

Resource ID: BIND

BioModels

- Curated Models
- Non-curated Models
- Search
- Simulate in JWS

- Submit Your Model

- Sign-in

- News
- Model of the Month
- Meetings
- Support
- Contact

BIOMODELS.NET

Computational Neurobiology

SBML

DOQCS Database of Quantitative Cellular Signaling

SBW

SBI

JWS online

Search - Models

The search totally returned **15** models.

New Search

Show 10 Only

15 Curated Models returned.

BioModels ID	Name	Publication ID	Last Modified
BIOMD0000000009	Huang1996_MAPK_ultrasens	8816754	2006-12-29T00:54:48
BIOMD0000000010	Kholodenko2000_MAPK_feedback	10712587	2007-01-10T10:35:07
BIOMD0000000011	Levchenko2000_MAPK_noScaffold	10823939	2007-01-10T10:22:40
BIOMD0000000014	Levchenko2000_MAPK_Scaffold	10823939	2007-01-26T22:30:39
BIOMD0000000026	Markevich2004_MAPK_orderedElementary	14744999	2006-12-29T00:28:06
BIOMD0000000027	Markevich2004_MAPK_orderedMM	14744999	2006-12-29T00:28:55
BIOMD0000000028	Markevich2004_MAPK_phosphoRandomElementary	14744999	2006-12-29T00:39:36
BIOMD0000000029	Markevich2004_MAPK_phosphoRandomMM	14744999	2006-12-29T00:43:12
BIOMD0000000030	Markevich2005_MAPK_AllRandomElementary	14744999	2006-12-29T01:03:25
BIOMD0000000031	Markevich2004_MAPK_orderedMM2kinases	14744999	2006-12-29T21:41:12
BIOMD0000000032	Kofahl2004_pheromone	15300679	2007-06-08T11:42:52
BIOMD0000000033	Brown2004_NGF_EGF_signaling	14525003	2006-12-29T23:16:17
BIOMD0000000049	Sasagawa2005_MAPK	15793571	2007-03-02T23:37:04
BIOMD0000000084	Hornberg2005_ERKcascade	15634347	2007-01-03T05:59:37
BIOMD0000000099	Laub1998_SpontaneousOscillations	9843585	2007-04-30T21:59:10

New Search

- Curated Models
- Non-curated Models
- Search
- Simulate in JWS

- Submit Your Model

- Sign-in

- News
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- Support
- Contact

BIOMODELS.NET

BIOMD0000000010 - Kholodenko2000_MAPK_feedback

SBML L2 V1 | CellML | SciLab | XPP | BioPAX

Simulation Result | GIF Reaction Graph | SVG Reaction Graph | Dynamic Reaction Graph | JWS Online

Submit Model Comment/Bug

Reference Publication

Publication ID: 10712587

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

Model

Original Model: *Unspecified*
Submitter: Nicolas Le Novere
Submission Date: 2005-09-13T13:39:02
Last Modification Date: 2007-01-10T10:35:07
Creation Date: 2005-02-12T00:18:12
Creators: Herbert Sauro

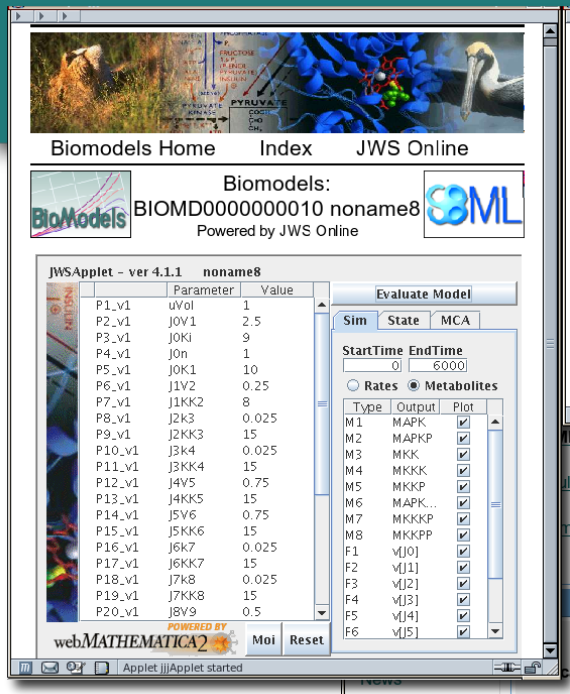
bqbiol:is	set #1	**Taxonomy**	Xenopus laevis
bqbiol:isVersionOf	set #1	**Gene Ontology**	MAPKKK cascade
bqbiol:isHomologTo	set #1	**Reactome**	REACT_634

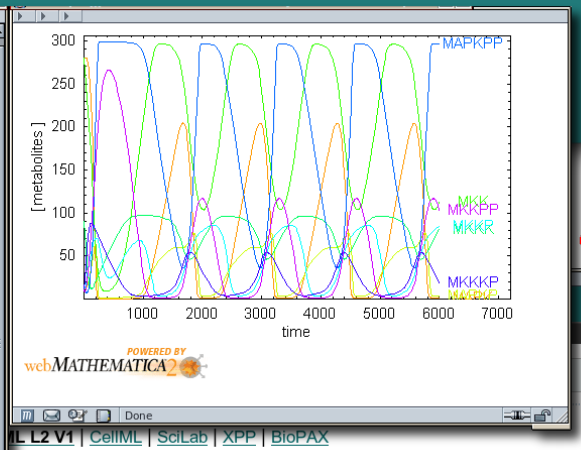
Compartments (1)

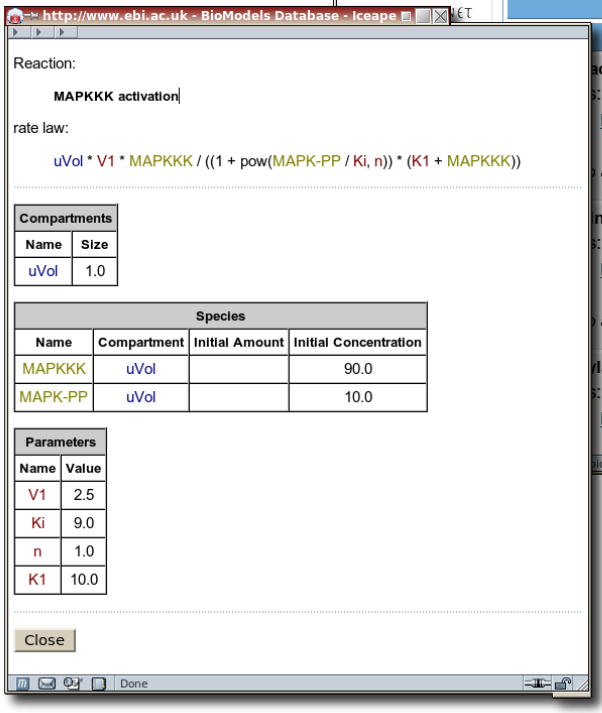
Species (8)

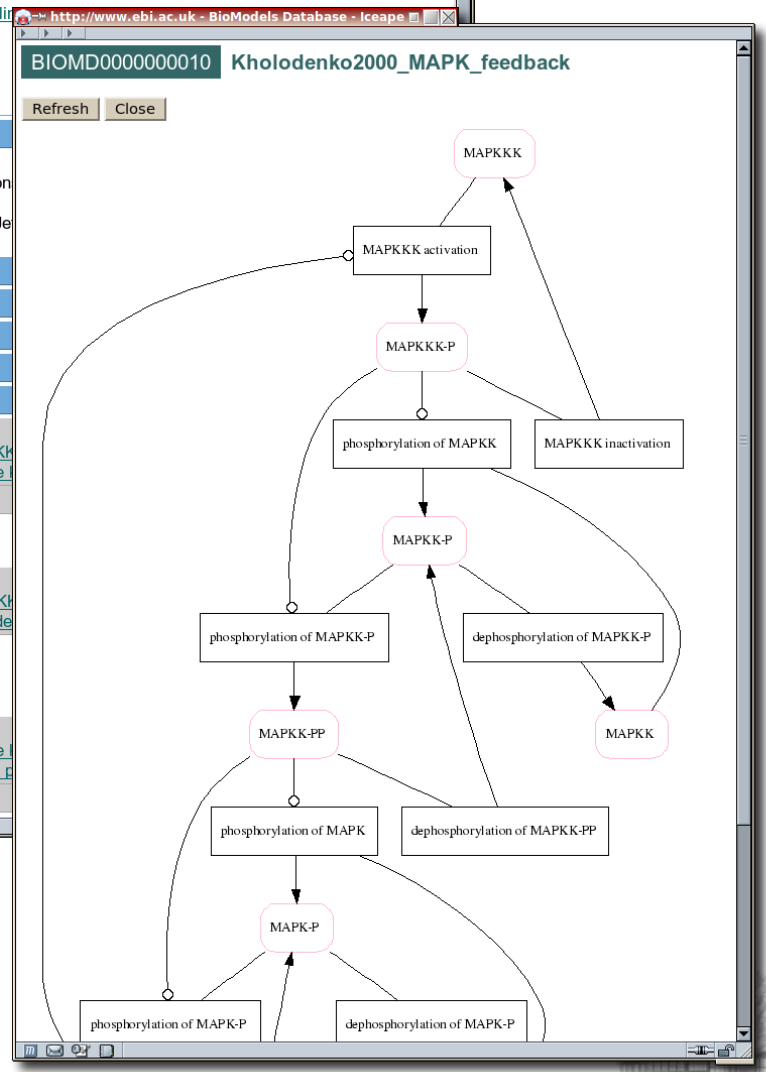
MAPKKK Compartment: uVol *Referred to as: MKKK*	bqbiol:isVersionOf	set #1	**UniProt**	RAF1_XENLA
MAPKKK-P Compartment: uVol *Referred to as: MKKK_P*	bqbiol:isVersionOf	set #1	**UniProt**	RAF1_XENLA
MAPKK Compartment: uVol *Referred to as: MKK*	bqbiol:isVersionOf	set #1	**UniProt**	MP2K1_XENLA
MAPKK-P	bqbiol:isVersionOf	set #1	**UniProt**	MP2K1_XENLA

Different views of a model









ML L2 V1 | CellML | SciLab | XPP | BioPAX

lation Result | GIF Reaction Graph | SVG Reaction Graph | Dynamic Reaction Graph | JWS Onlin

mit Model Comment/Bug

Reference Publication

cation ID: 10712587

Eur J Biochem 2000 Mar;267(6):1583-8.
Negative feedback and ultrasensitivity can bring about oscillation
Kholodenko BN.
Department of Pathology, Anatomy and Cell Biology, Thomas Je
Boris.Kholodenko@mail.tju.edu [more]

Model

Compartments (1)

Species (8)

Rules (0)

Reactions (10)

activation
MAPKKK
MAPKKK-P
MAPK-PP
as: J0

bqbiol:isVersionOf set #1 Enzyme Nomenclature 2.7.11.1
Gene Ontology activation of MAPKK
Gene Ontology MAP kinase kinase
bqbiol:isHomologTo set #1 Reactome REACT_525

inactivation
MAPKKK-P
MAPKKK
as: J1

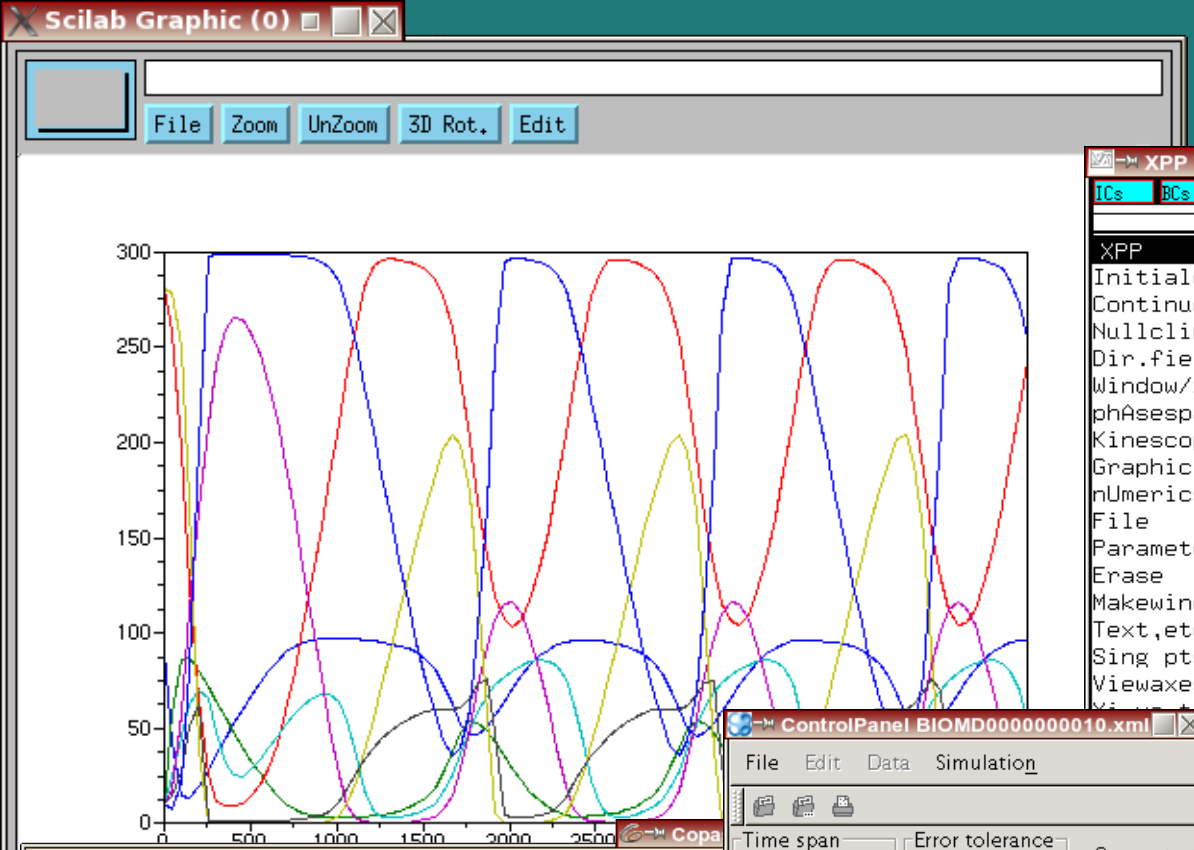
bqbiol:isVersionOf set #1 Enzyme Nomenclature 3.1.3.16
Gene Ontology inactivation of MAPKK
Gene Ontology protein amino acid de

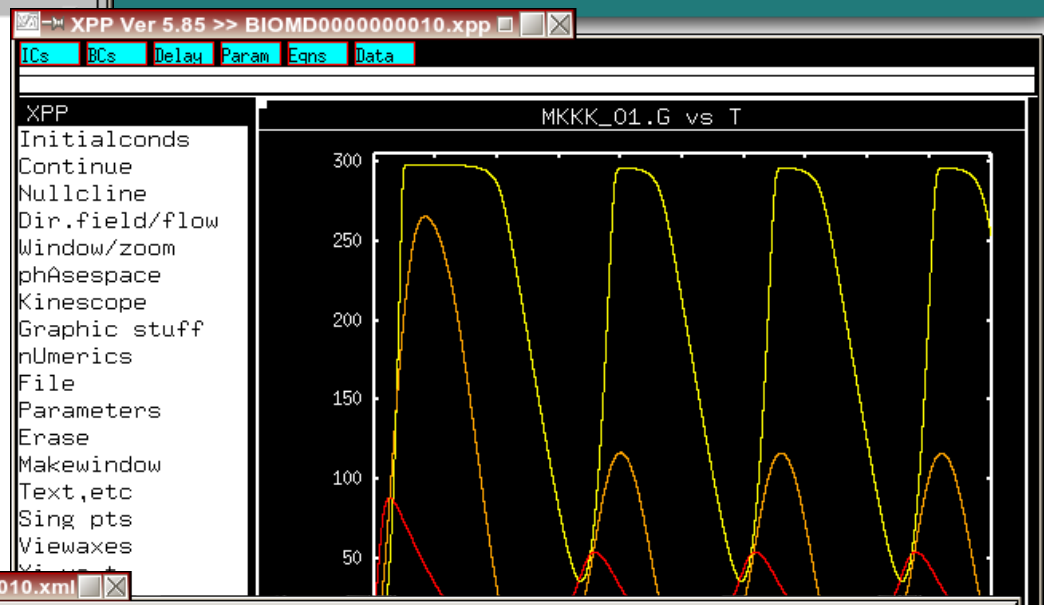
lation of MAPK
MAPKK
MAPKKK-P

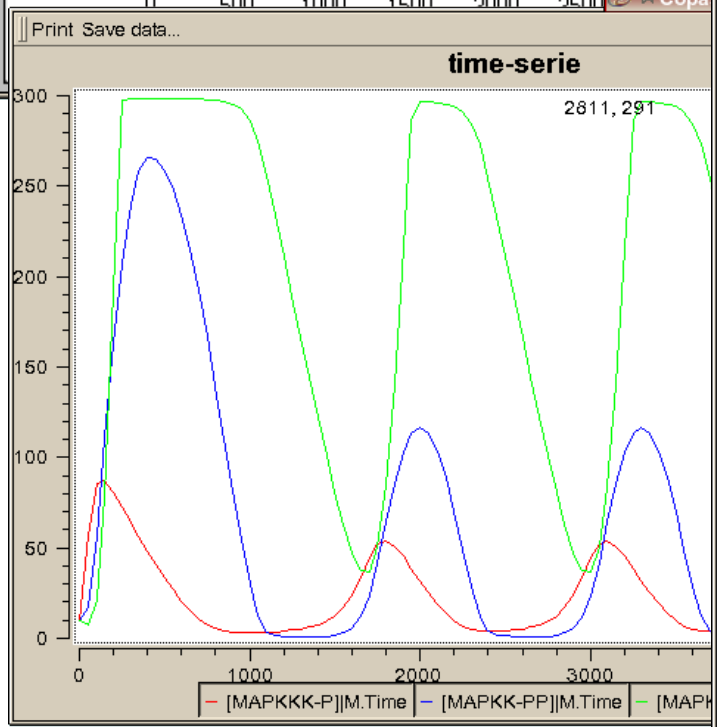
bqbiol:isVersionOf set #1 Enzyme Nomenclature 2.7.11.25
Gene Ontology MAP kinase kinase
Gene Ontology protein amino acid p
bqbiol:isHomologTo set #1 Reactome REACT_614

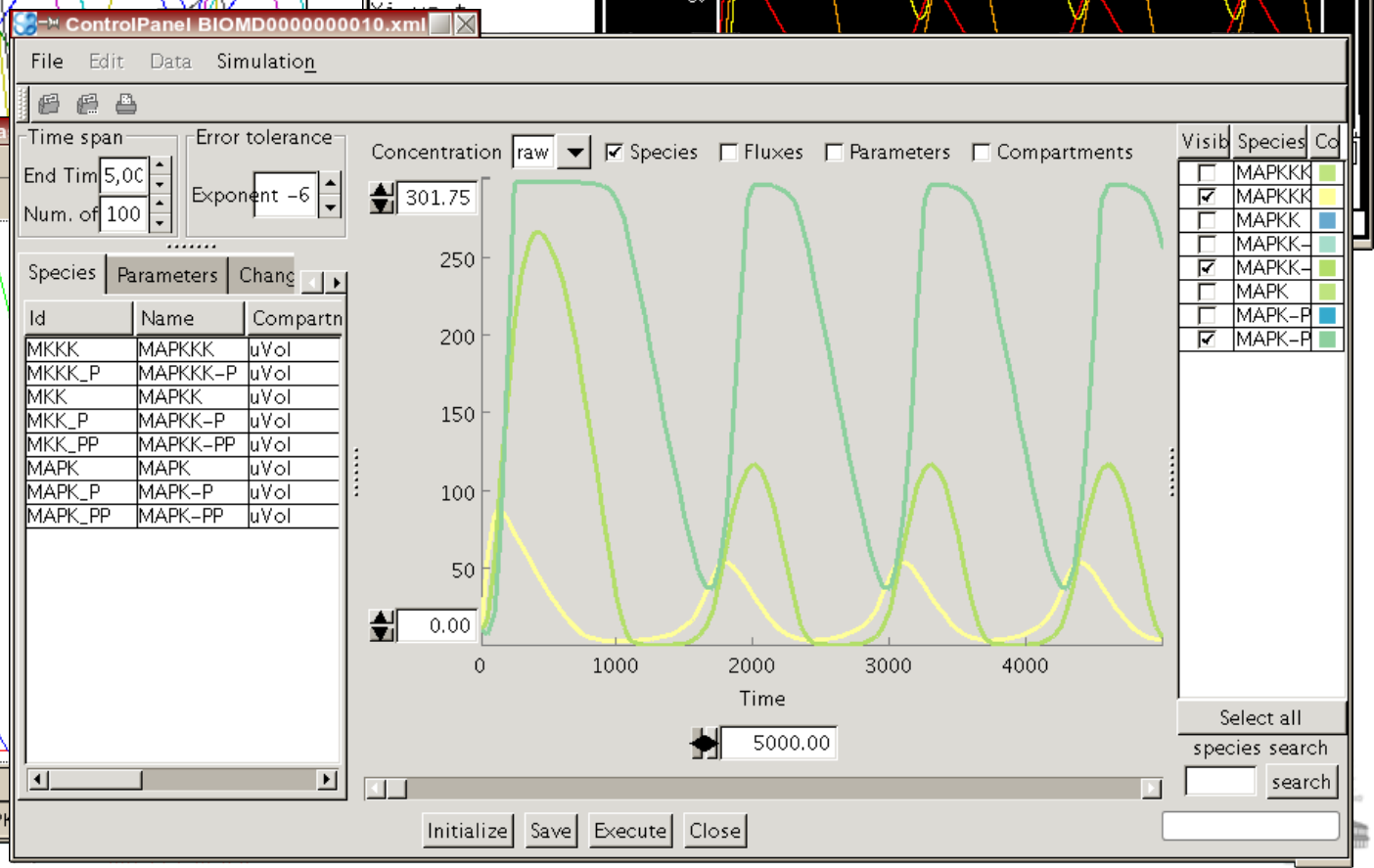
- Model of the Month
- Meetings
- Support
- Contact

Kholodenko 2000

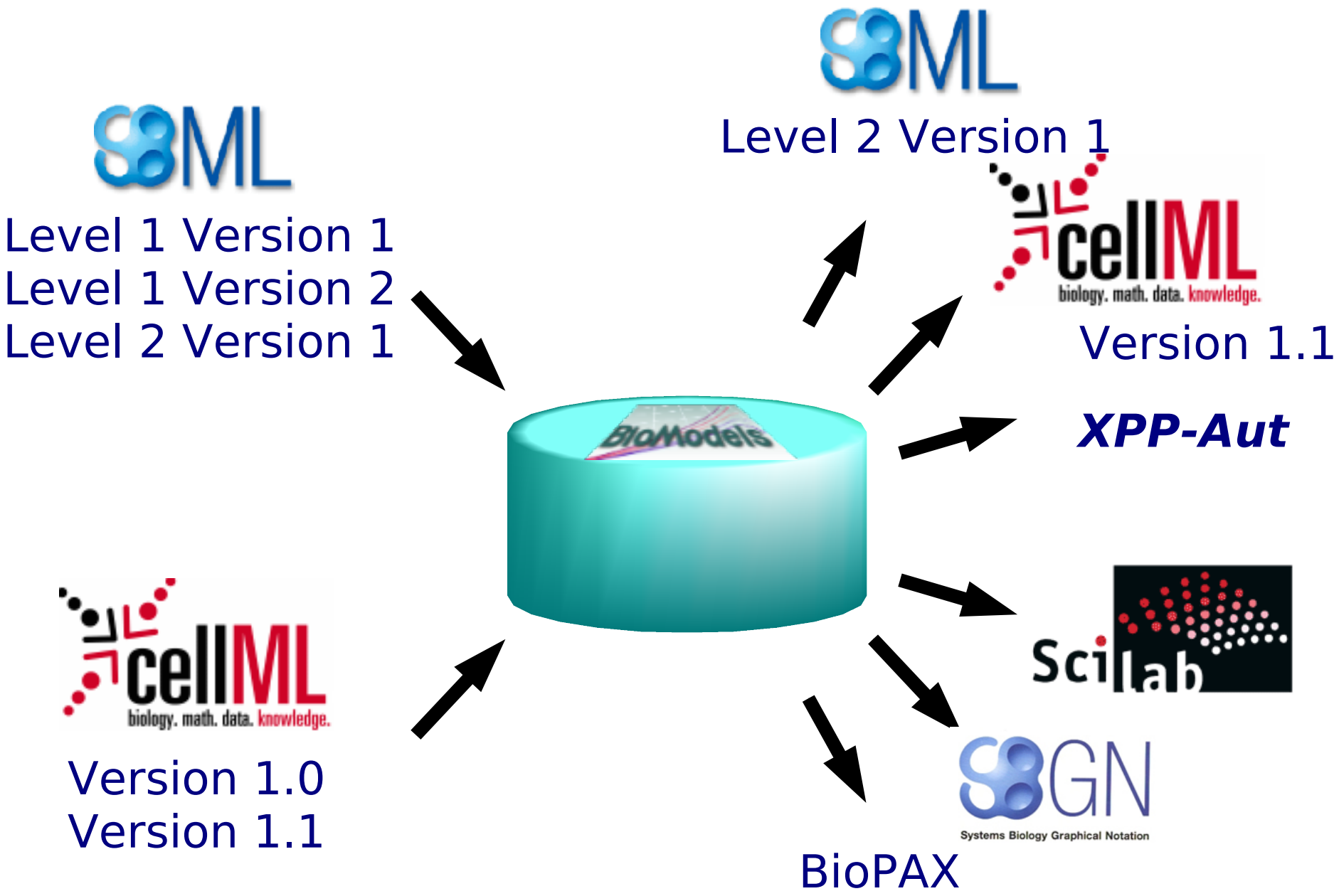








BioModels DB and interoperability in CSB



Browse - Curated models

This is a tree view of the models in BioModels Database based on Gene Ontology. To browse the models, please click ⊞ to expand the branch, or click ⊟ to collapse the branch. By double clicking the Gene Ontology term, the detail of the term will be displayed in a new window. By double clicking the BioModels Model ID, this page will be forwarded to the detail of selected model.

- biological_process
  - cellular process
    - cellular component organization and biogenesis
    - cell cycle
      - cell cycle process
      - mitotic cell cycle
        - BIOMD0000000003 - Goldbeter1991_MinMitOscil
        - BIOMD0000000004 - Goldbeter1991_MinMitOscil_ExplInact
        - BIOMD0000000005 - Tyson1991_CellCycle_6var
        - BIOMD0000000006 - Tyson1991_CellCycle_2var
        - BIOMD0000000007 - Novak1997_CellCycle
        - BIOMD0000000008 - Gardner1998_CellCycle_Goldbeter
        - BIOMD0000000056 - Chen2004_CellCycle
        - BIOMD0000000069 - Fuss2006_MitoticActivation
        - BIOMD0000000107 - Novak1993_M_phase_control
        - BIOMD0000000111 - Novak2001_FissionYeast_CellCycle
    - cell cycle process
    - regulation of cellular process
    - cellular metabolic process
    - cell communication
      - signal transduction
        - intracellular signaling cascade
          - protein kinase cascade
            - MAPKKK cascade
              - inactivation of MAPK activity
                - BIOMD0000000009 - Huang1996_MAPK_ultrasens
                - BIOMD0000000010 - Kholodenko2000_MAPK_feedback
                - BIOMD0000000011 - Levchenko2000_MAPK_noScaffold
                - BIOMD0000000014 - Levchenko2000_MAPK_Scaffold
                - BIOMD0000000026 - Markevich2004_MAPK_orderedElementary
                - BIOMD0000000027 - Markevich2004_MAPK_orderedMM
                - BIOMD0000000028 - Markevich2004_MAPK_phosphoRandomElementary
                - BIOMD0000000029 - Markevich2004_MAPK_phosphoRandomMM
                - BIOMD0000000030 - Markevich2005_MAPK_AllRandomElementary
                - BIOMD0000000031 - Markevich2004_MAPK_orderedMM2kinases
                - BIOMD0000000032 - Kofahl2004_pheromone
                - BIOMD0000000033 - Brown2004_NGF_EGF_signaling
                - BIOMD0000000049 - Sasagawa2005_MAPK
                - BIOMD0000000084 - Hornberg2005_ERKcascade
            - JAK-STAT cascade
            - second-messenger-mediated signaling

BioModels ID: *Unspecified*
Name: *N/A*
Publication ID: *N/A*
Last Modified: *N/A*

BIOMD0000000010 - Kholodenko2000_MAPK_feedback

SBML L2 V1 | CellML | SciLab | XPP | BioPAX

Simulation Result | GIF Reaction Graph | SVG Reaction Graph | Dynamic Reaction Graph | JWS Online

Submit Model Comment/Bug

Overview | Model | Math | Physical | Parameters | Submodel1

Create a submodel with selected elements — Deselect All

Model

Publication ID: 10712587 **Submission Date:** 2005-09-13T13:39:02+00:00 **Last Modification Date:** 2007-01-10T10:35:07+00:00:00 **Creation Date:** 2005-02-12T00:18:12+00:00:00

Mathematical expressions

Reactions

- [ ] MAPKKK activation
- [ ] MAPKKK inactivation
- [x] phosphorylation of MAPKK
- [x] phosphorylation of MAPKK-P
- [x] dephosphorylation of MAPKK-PP
- [x] dephosphorylation of MAPKK-P
- [ ] phosphorylation of MAPK
- [ ] phosphorylation of MAPK-P
- [ ] dephosphorylation of MAPK-PP
- [ ] dephosphorylation of MAPK-P

Variables

Compartments	Species
[x] uVol	[ ] MAPKKK
	[ ] MAPKKK-P
	[x] MAPKK
	[x] MAPKK-P
	[x] MAPKK-PP
	[ ] MAPK
	[ ] MAPK-P
	[ ] MAPK-PP

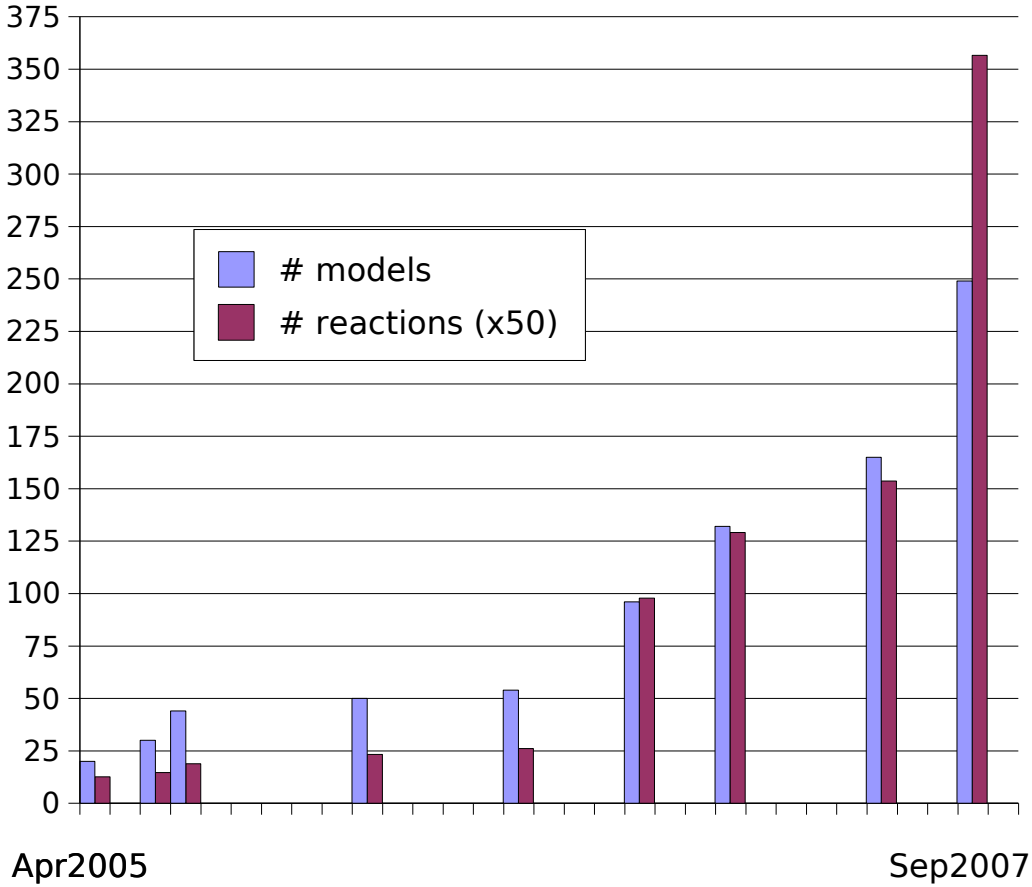
Create a submodel with selected elements — Deselect All

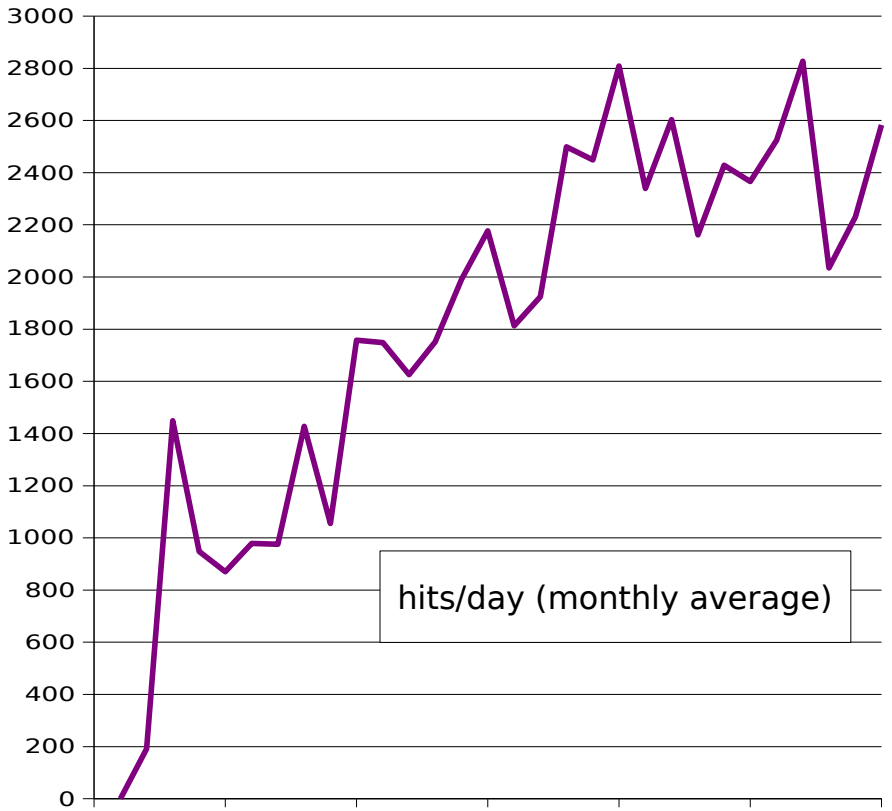
Submit Model Comment/Bug

Simulation Result | GIF Reaction Graph | SVG Reaction Graph | Dynamic Reaction Graph | JWS Online

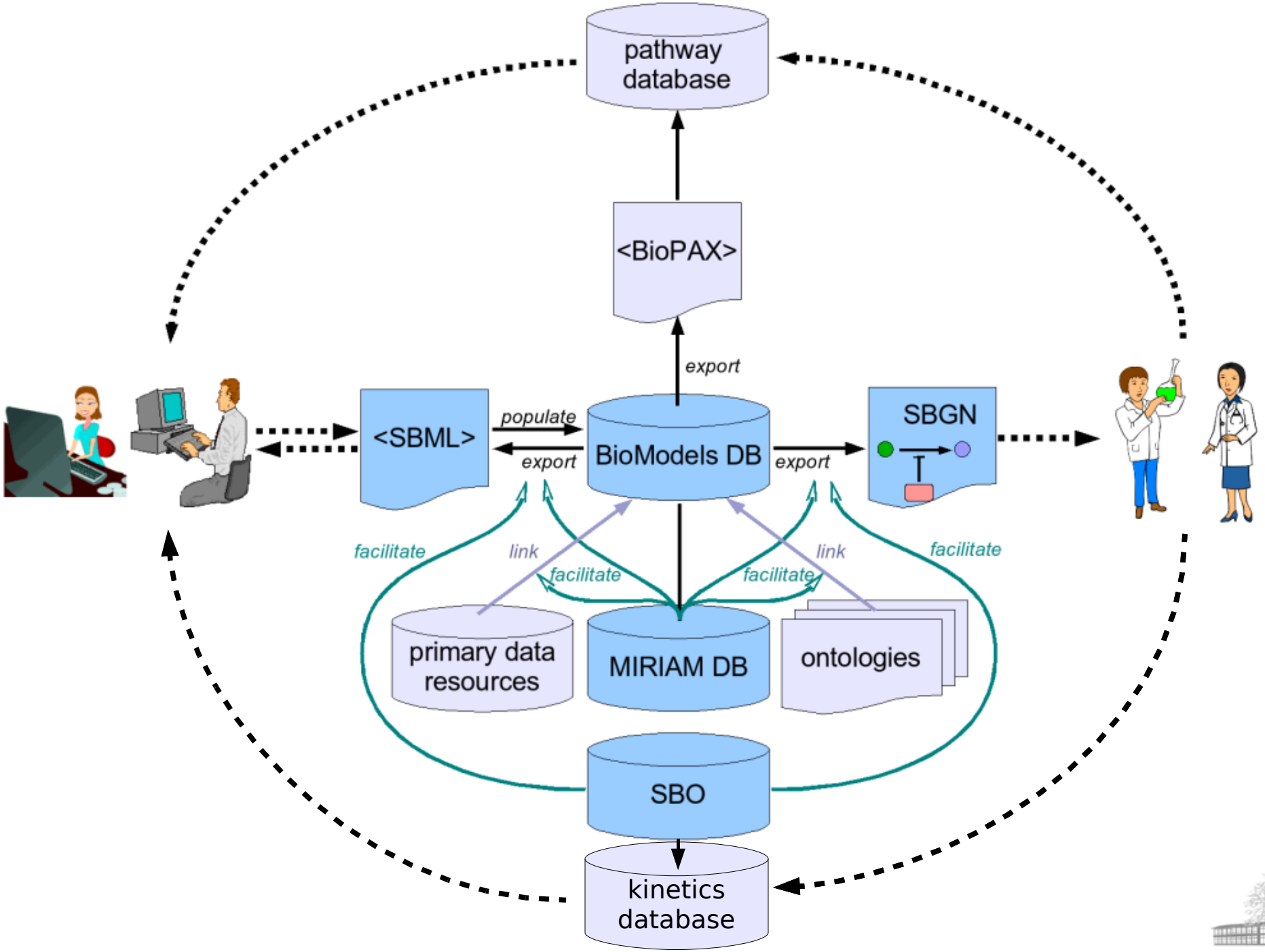
SBML L2 V1 | CellML | SciLab | XPP | BioPAX

Steady-increase of BioModels DB





A hub between keyboard and bench biologists

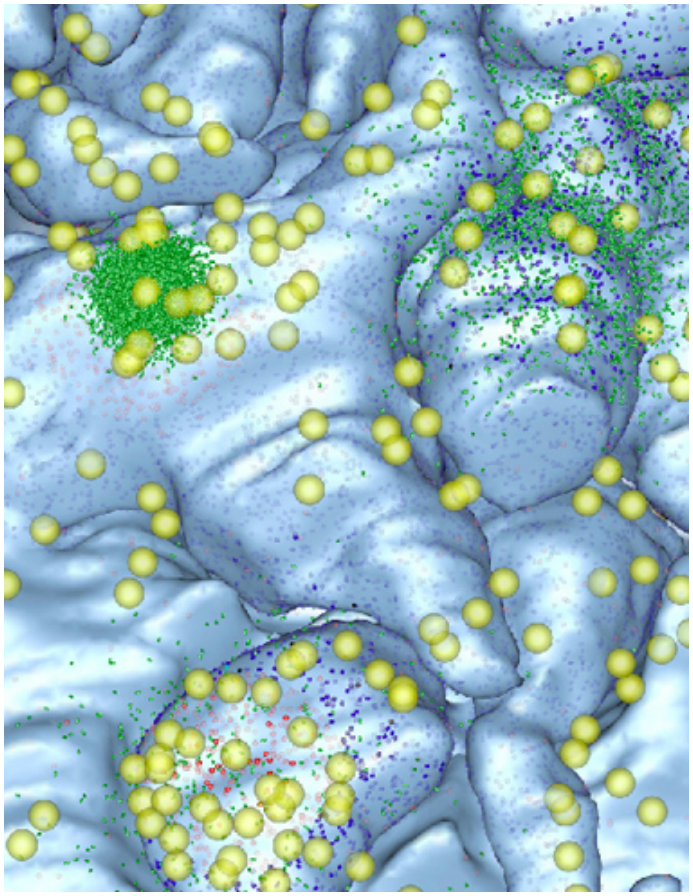


An international collaboration

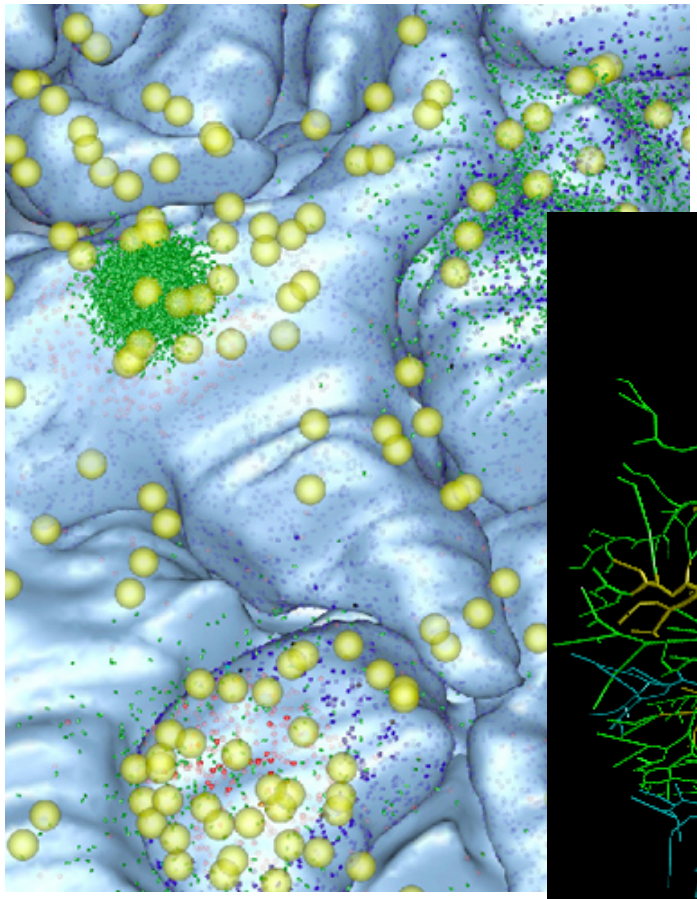
- EBI
  - Nicolas Le Novère
  - Mélanie Courtot
  - Marco Donizelli
  - Enuo He
  - Arnaud Henry
  - Christian Knüpfer
  - Dagmar Koehn
  - Camille Laibe
  - Chen Li
  - Lu Li
  - Nicolas Rodriguez
  - Melanie Stefan
- SBML team
  - Michael Hucka
  - Andrew Finney
  - Bruce Shapiro
  - Benjamin Borstein
  - Maria Schilstra
  - Sarah Keating
  - Harish Dharuri
- NCBS
  - Upinder Bhalla
  - Harsha Rani
- Keck Graduate Institute
  - Herbert Sauro
- Vienna TBI
  - Rainer Machne
- Systems Biology Institute
  - Hiroaki Kitano
  - Akira Funahashi
- JWS Online
  - Jacky Snoep
  - Hans Westerhoff
- Journals supporting BioModels Database
  - Molecular Systems Biology
  - PLoS Journals
  - BioMedCentral Journals
- Programs used for curation
  - CellDesigner/SBMLodeSolver
  - COPASI
  - Jarnac/JDesigner
  - MathSBML
  - SBMLeditor
  - XPP-Aut
  - RoadRunner

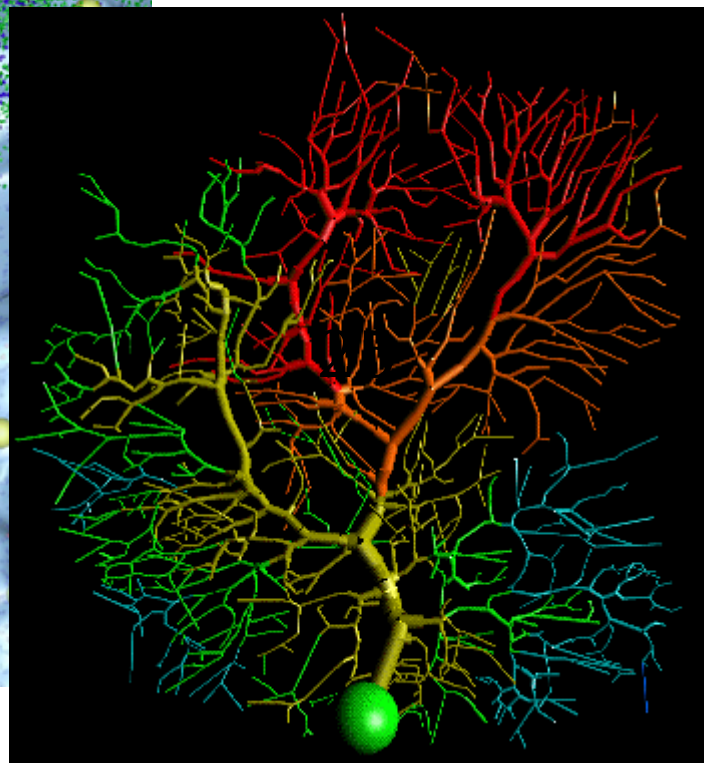
The community of Systems Biology for their contributions of models and comments.

Single-particle model

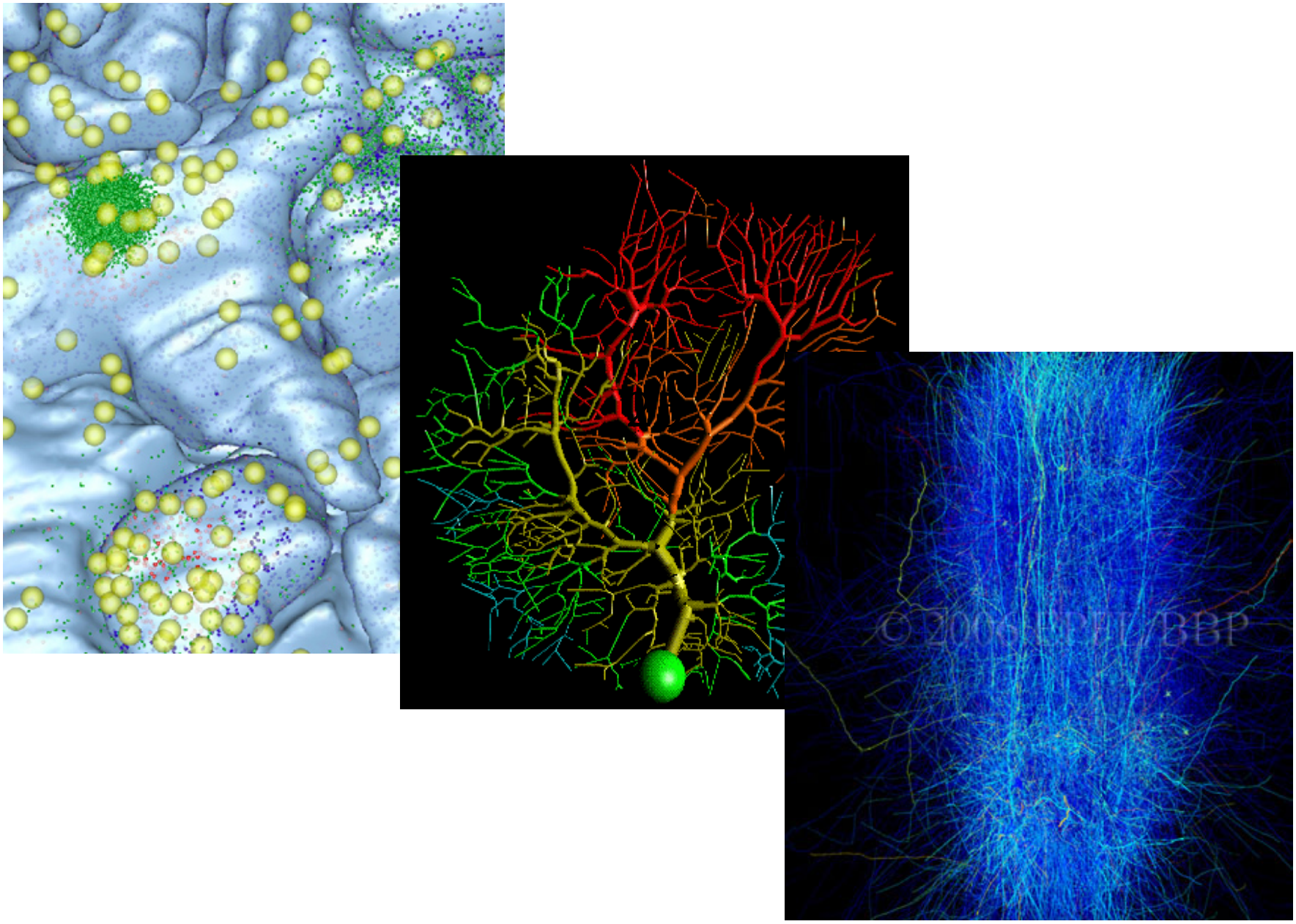


Whole-cell model





Tissue model



What type of quantitative data do-we need?

bottom-up approach

- literature
- reactions
- structures
- kinetics
- locations
- concentrations
- topologies
- morphologies
- existing models

top-down approach

- molecular interactomes
- metabolomes
- “functiomes” (e.g. kinomes)
- dynamics
- fluxiomes
- cellular phenotypes
- physiological datasets
- gene interactions
- histology

The EMBL-European Bioinformatics Institute

http://www.ebi.ac.uk

EMBL-EBI

What is the EMBL-EBI?

- Non-profit organization
- Part of the European Molecular Biology Laboratory
- Based on the Wellcome Trust Genome Campus near Cambridge, UK

Part of EMBL

The EBI is part of the European Molecular Biology Laboratory (EMBL), a basic research institute funded by public research monies from 19 member states.

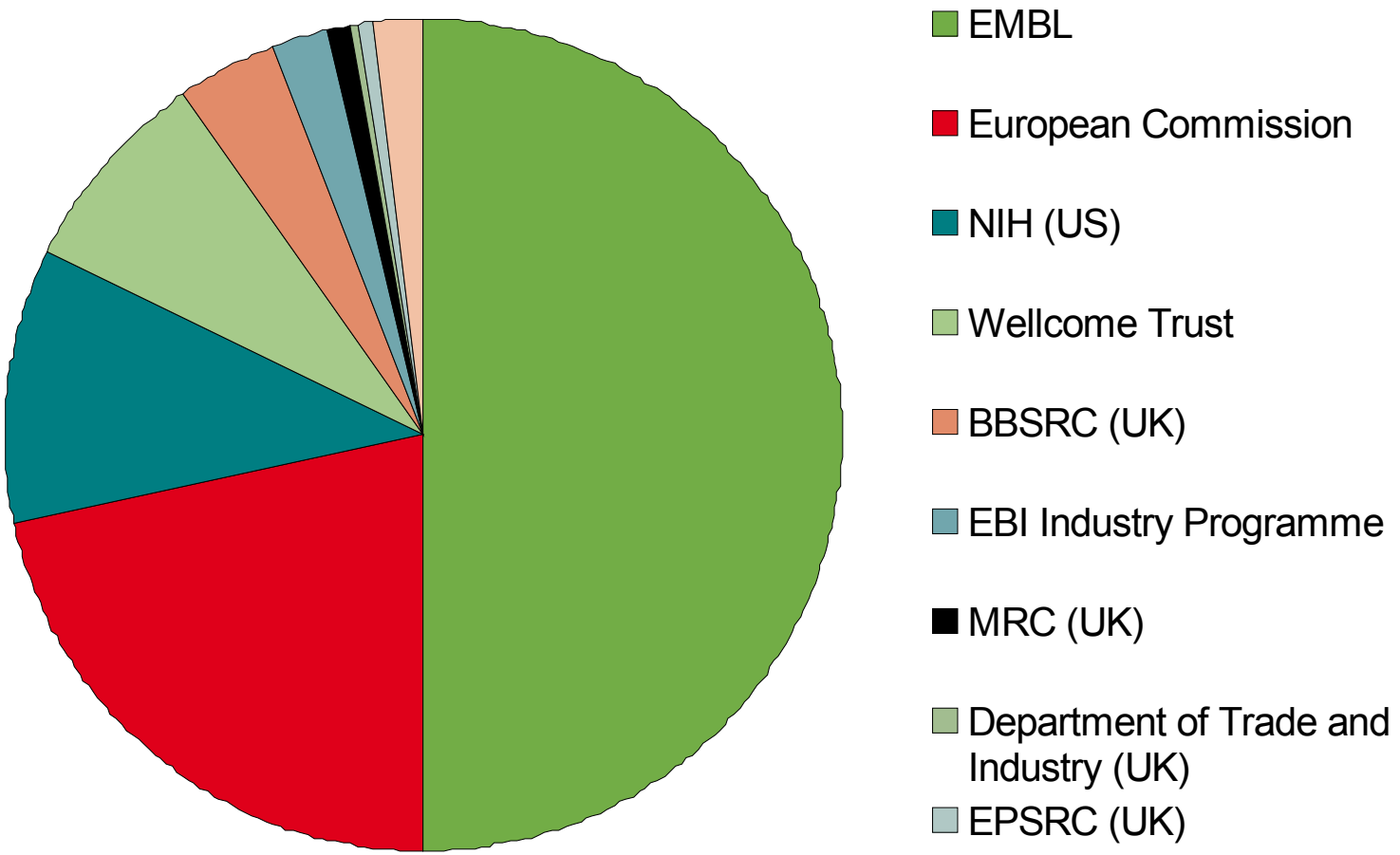
France is the 3rd biggest founder!

The EMBL-EBI's mission

- To provide **freely available data and bioinformatics services** to all facets of the scientific community in ways that promote scientific progress
- To contribute to the advancement of biology through basic investigator-driven **research** in bioinformatics
- To provide advanced bioinformatics **training** to scientists at all levels, from PhD students to independent investigators
- To help disseminate cutting-edge technologies to **industry**

Thanks to Don Powell, Wellcome Trust Sanger Institute, for providing this image.

Funding



In 2006 we received >€30 million in funding

Research groups

Goldman
Evolutionary sequence analysis

Rebholz-Schuhmann
Text mining

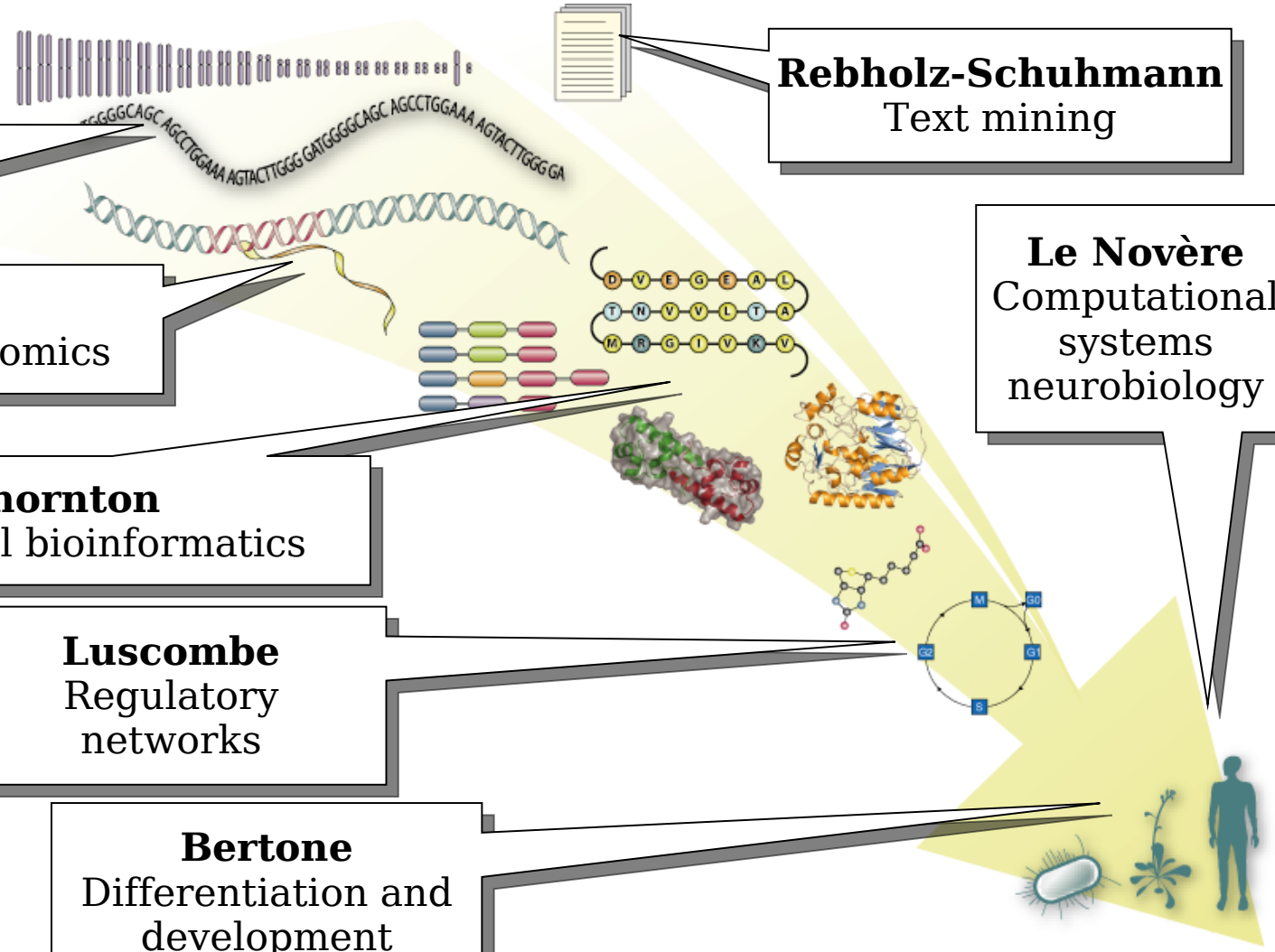
Huber
Functional genomics

Le Novère
Computational systems neurobiology

Thornton
Structural bioinformatics

Luscombe
Regulatory networks

Bertone
Differentiation and development



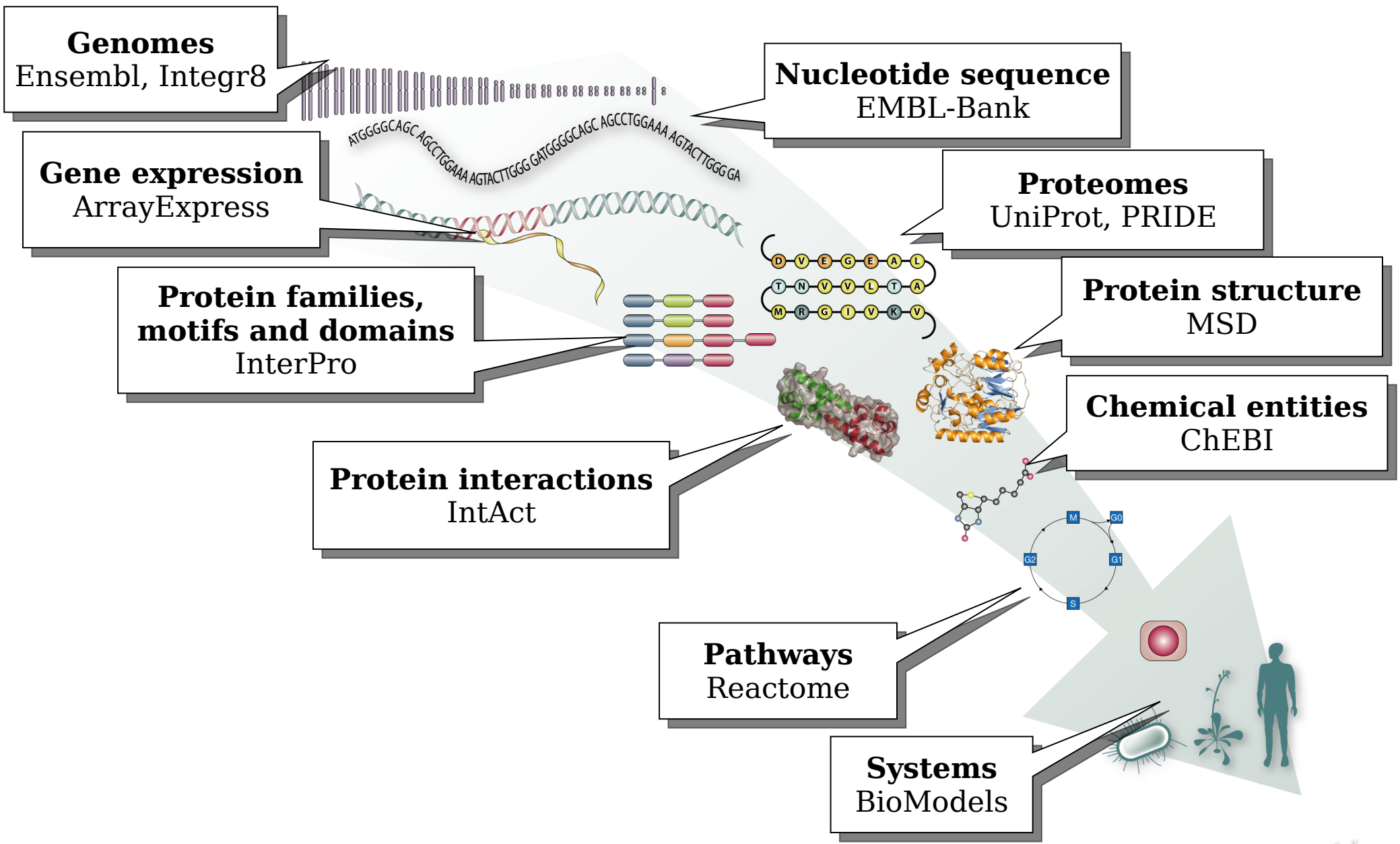
Key facts about services

- **European node** for globally coordinated data collection and dissemination projects
- Core databases produced in **collaboration** with other world leaders, including NCBI (US), National Institute of Genetics (Japan), Swiss Institute of Bioinformatics, Cold Spring Harbor Laboratory (US)
- The world's most **comprehensive** collection of molecular databases (>200)

Principles of service provision

- **Accessibility** – all data and tools freely available without restriction
- **Compatibility** – we develop and promote the use of standards in bioinformatics
- **Comprehensive data sets** – agreements with other data providers ensure that our resources contain comprehensive and up-to-date data; agreements with publishers ensure that published data are placed in a public repository at the earliest opportunity
- **Portability** – data and software can be downloaded and installed locally
- **Quality** – Our databases are enhanced through annotation and cross-referencing

Databases: molecules to systems



EMBL-EBI

Standards development

Genome annotation
Gene Ontology

Nucleotide sequence
www.insdc.org

Protein sequence
IPI

Transcriptomics
MIAME

Protein structure
PDB

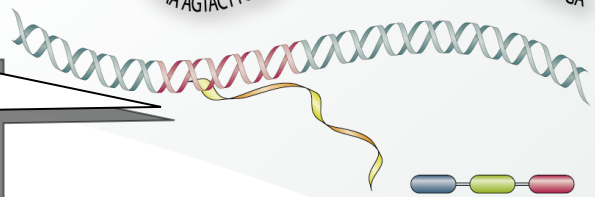
Proteomics
MIAPE, PSI

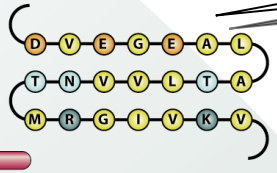
Systems modelling
SBML, SBO

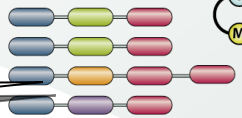
Cheminformatics
ChEBI

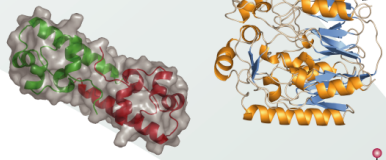
Metabolomics
www.metabolomicssociety.org

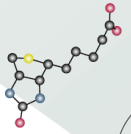
Pathways
BioPAX
SBGN

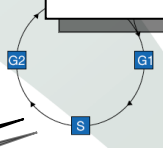


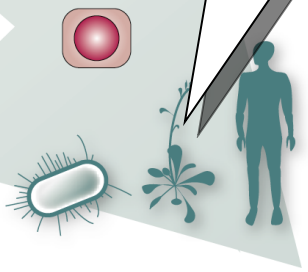








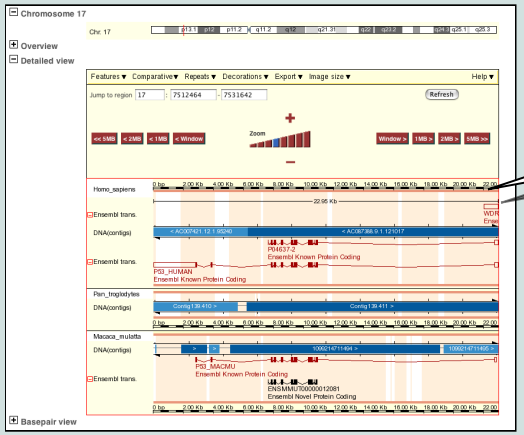




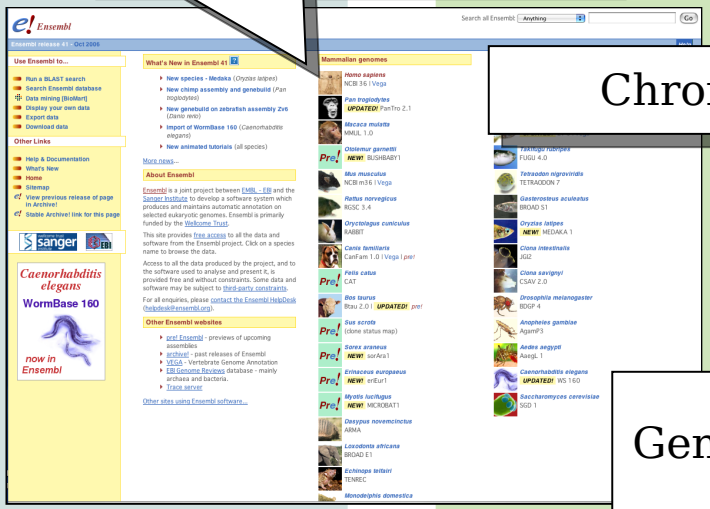
EMBL-EBI

Genomes: Ensembl

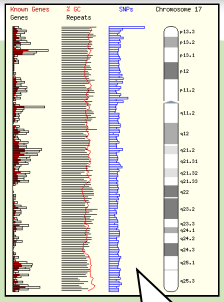
Multiple alignments



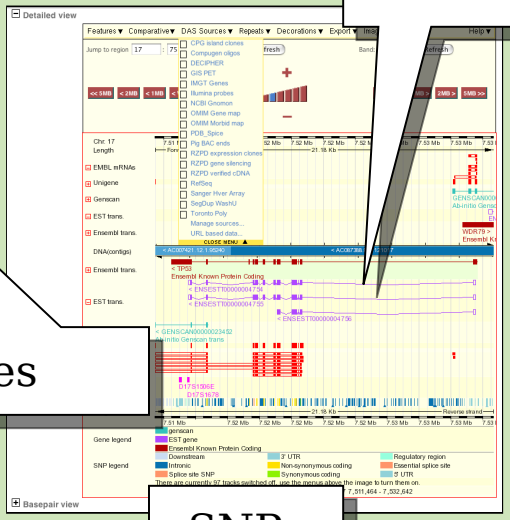
Pick a genome



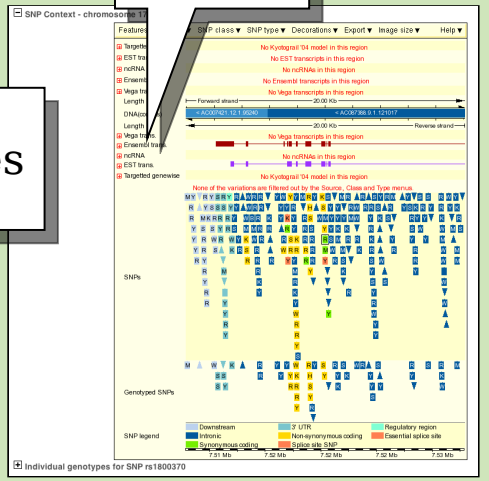
Chromosomes



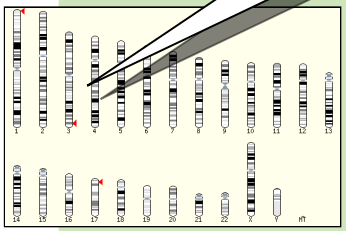
Genes



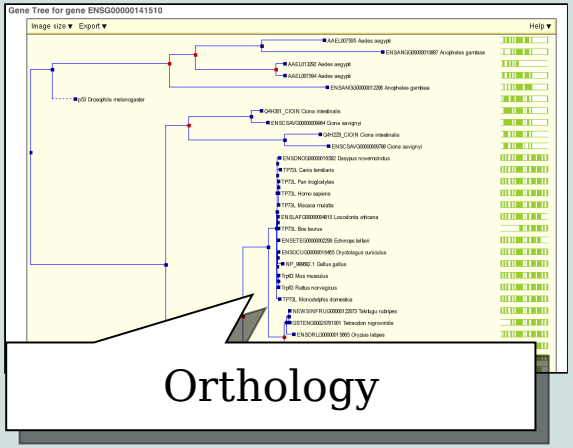
SNPs



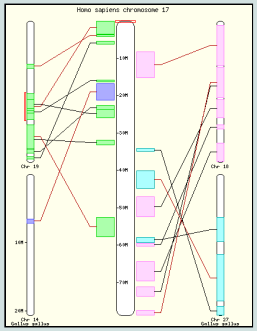
Gene families



Orthology



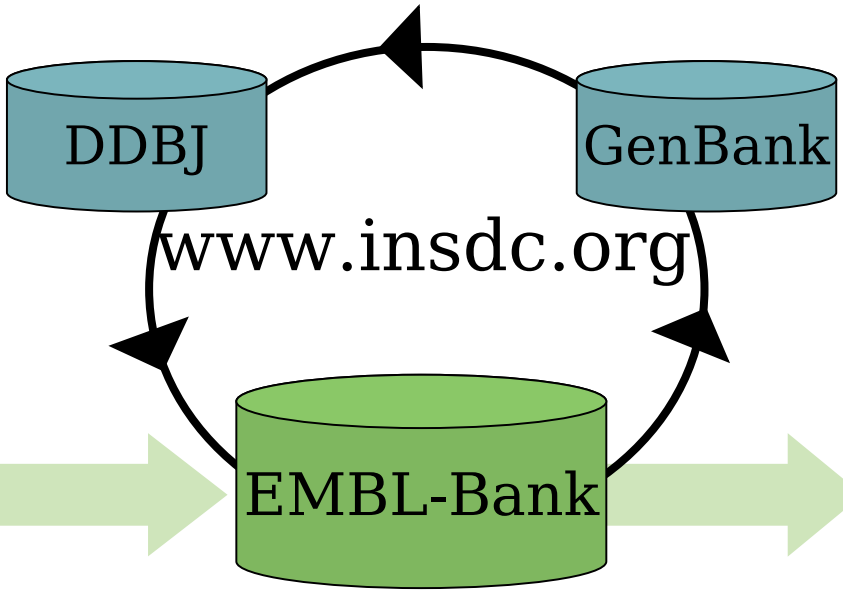
Synteny



Across species

Within species

Nucleotides: EMBL-Bank

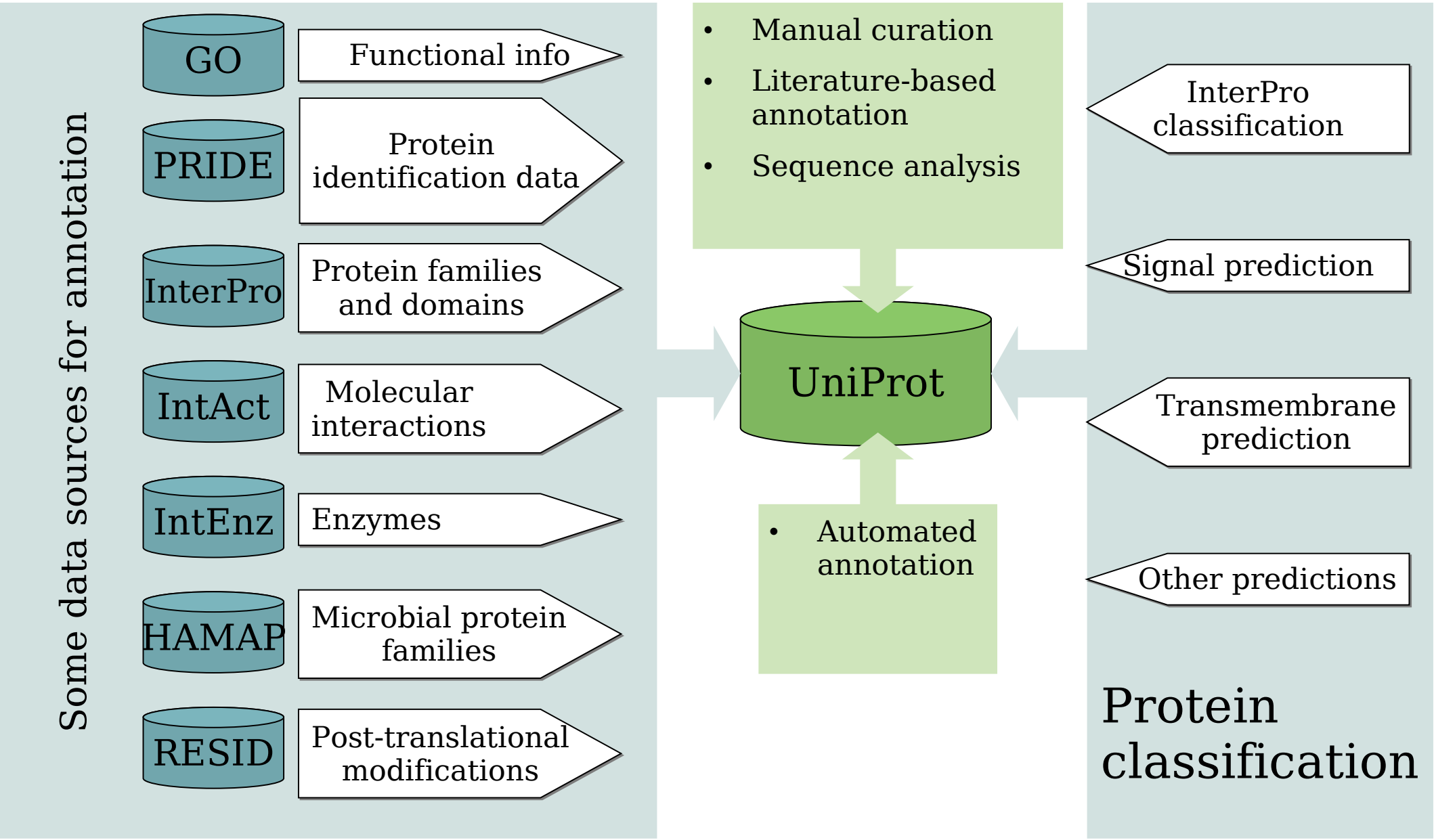


- Direct submissions
- Patents
- Genome-sequencing projects

- Updates
- Third-party annotation

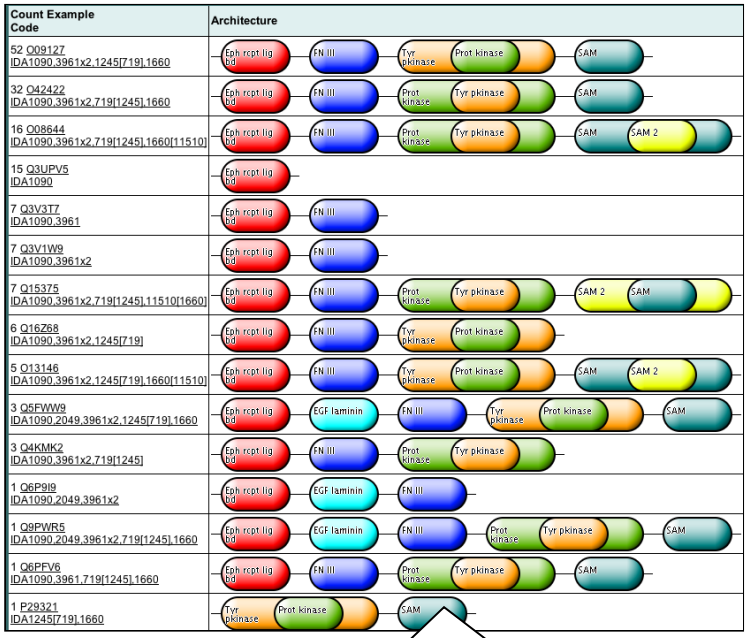
- Keyword and sequence searching
- Map-based search of environmental samples
- Downloads

Protein sequence: UniProt

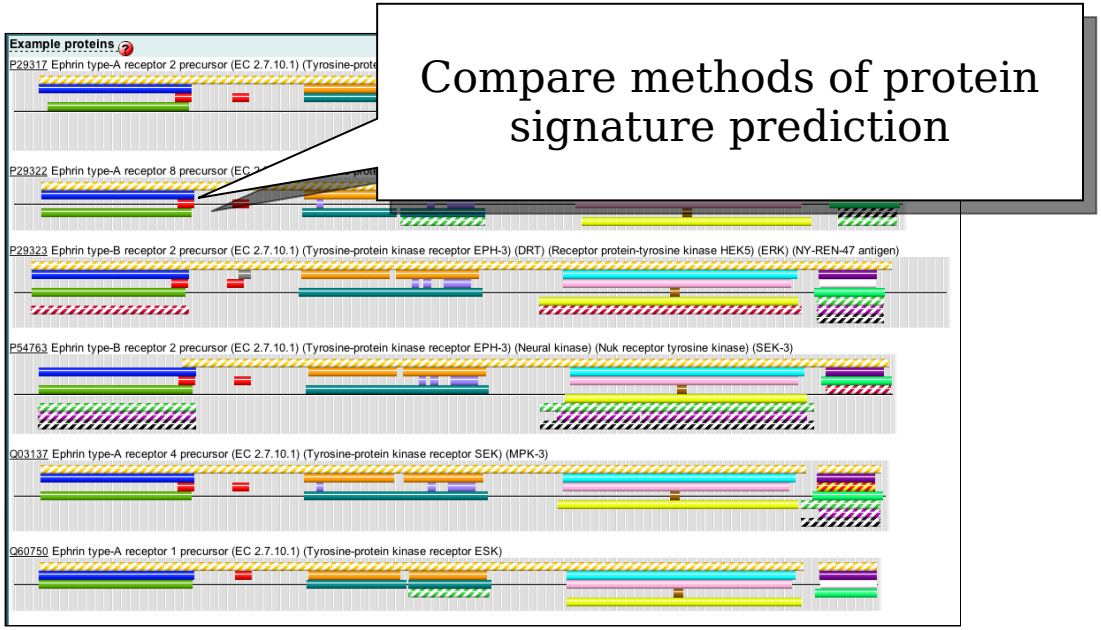


Protein families, motifs and domains: InterPro

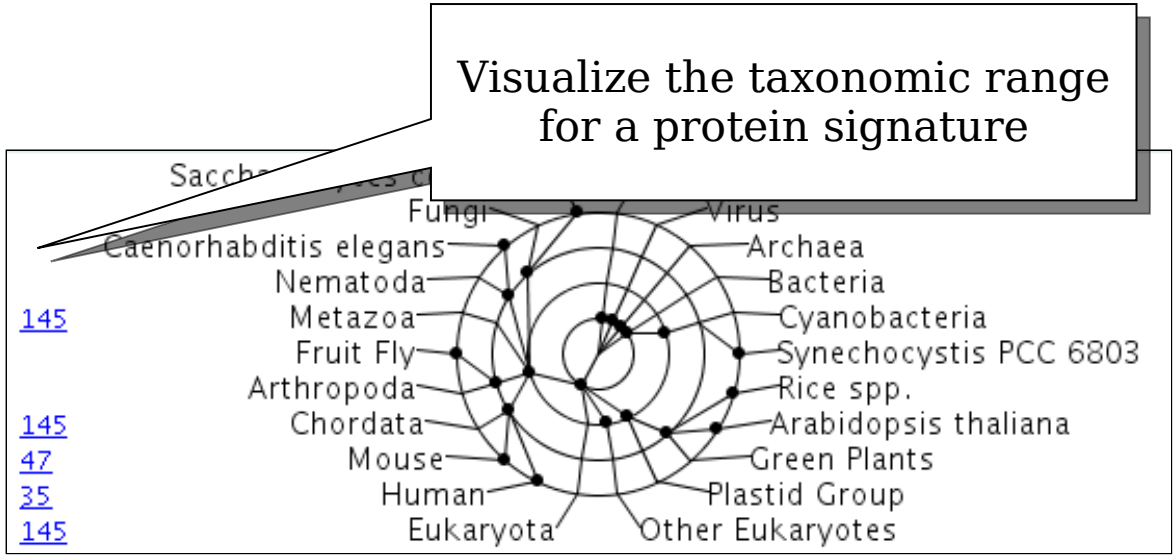
Powerful tool for protein classification, integrating several methods into one resource



View architectures of proteins containing a signature



Compare methods of protein signature prediction



Visualize the taxonomic range for a protein signature

What's new?

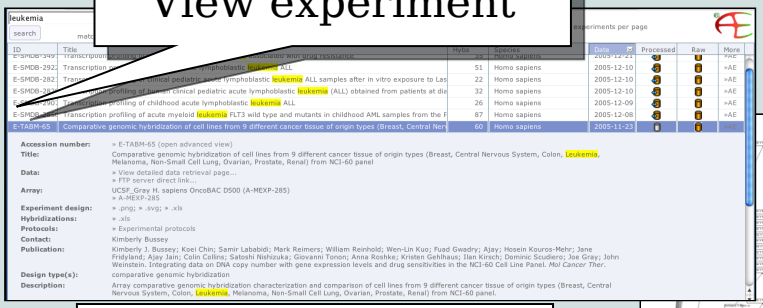
- Merging of all sequence resources (EMBLbank, Ensembl, Genomes, UniProt ...) in the PANDA group, headed by Rolf Apweiler (protein) and Ewin Birney (nucleotides)
- All genomes included in Ensembl (previously, only bilateria)
- Creation of a new resource to study human variation: The European Genotyping Archive

Transcriptomes: ArrayExpress

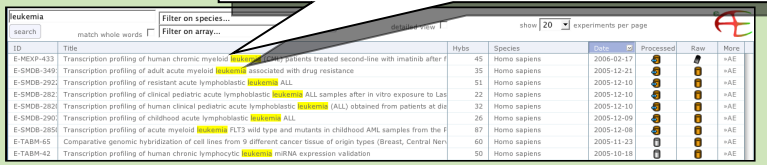
Search by keyword

Search by gene name

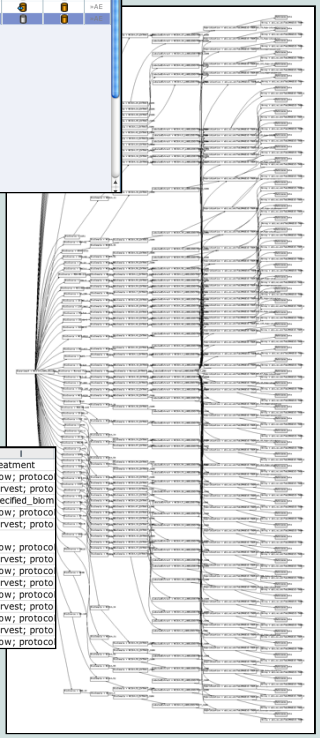
View experiment



Choose gene of interest

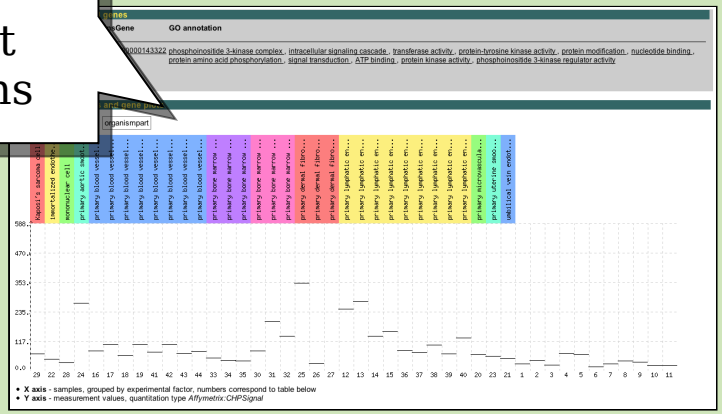


Link to sample properties and experiment design



	A	B	C	D	E	F	G	H	I
1	Sample name	Age	CellType	DiseaseState	Organism	OrganismPart	Sex	TimeUnit	Treatment
2	M14	unknown	melanocyte	melanoma	Homo sapiens	skin	unknown_sex	years	grow; protoco
3									harvest; proto
4	Normal Female DNA				Homo sapiens		female		specified_biom
5	SR	11	lymphocyte	lymphoma	Homo sapiens	blood	male	years	grow; protoco
6									harvest; proto
7	K-562	53	myeloid_proge	chronic myelogenous leukemia	Homo sapiens	blood	female	years	grow; protoco
8									harvest; proto
9	OVCAR-8	64	epithelial cell	carcinoma	Homo sapiens	ovary	female	years	grow; protoco
10									harvest; proto
11	OVCAR-3	60	epithelial cell	adenocarcinoma	Homo sapiens	ovary	female	years	grow; protoco
12									harvest; proto
13	HS 578T	74	epithelial cell	carcinosarcoma	Homo sapiens	breast	female	years	grow; protoco
14									harvest; proto
15	NCI-H460	unknown	epithelial cell	large cell carcinoma	Homo sapiens	lung	male	years	grow; protoco

View expression under different conditions

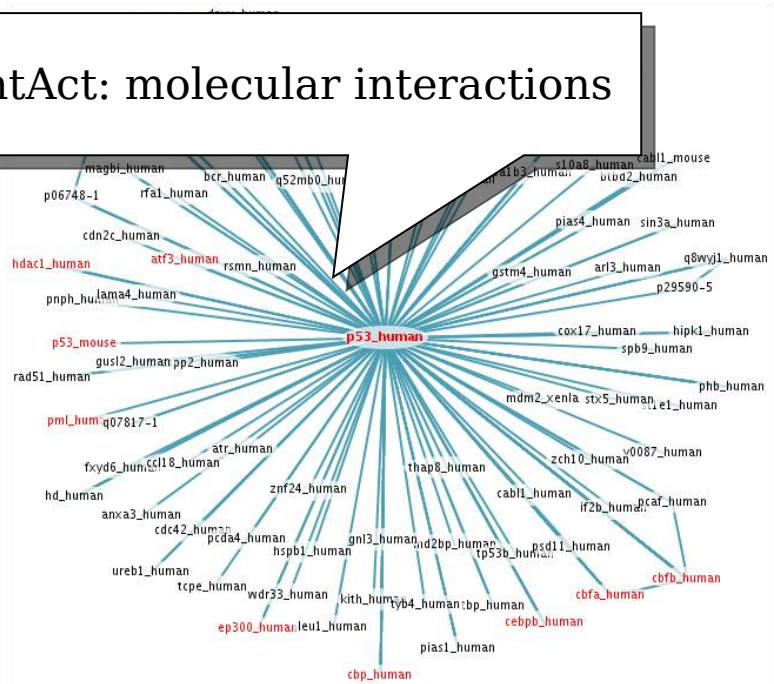


Search by experiment

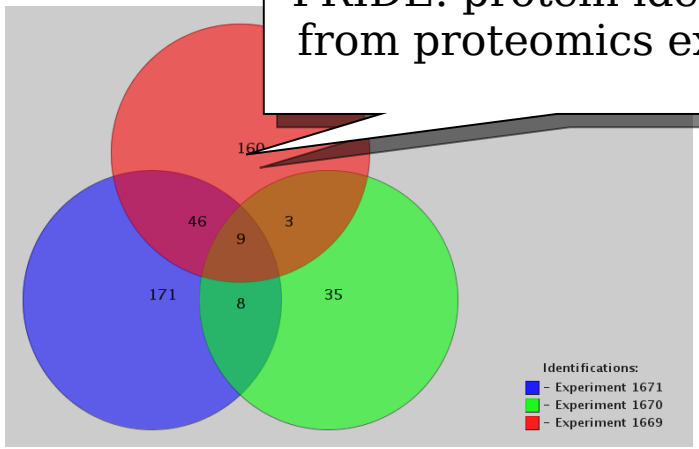
Search by gene

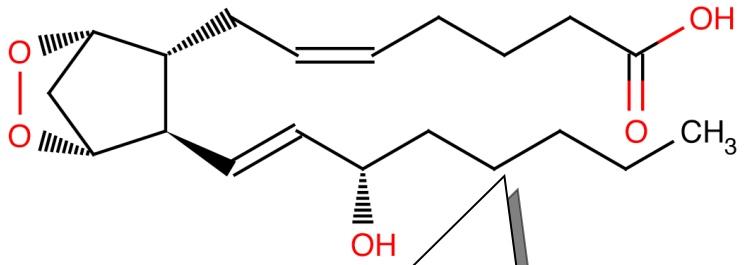
Proteomics and metabolomics

IntAct: molecular interactions

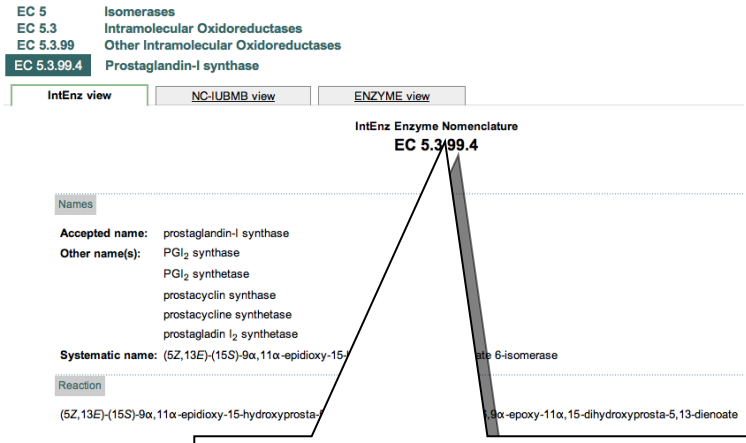


PRIDE: protein identifications from proteomics experiments





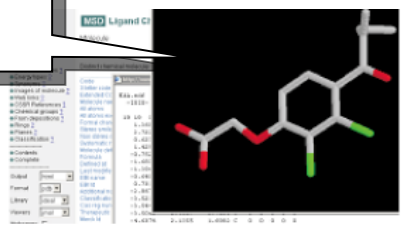
ChEBI: small molecules



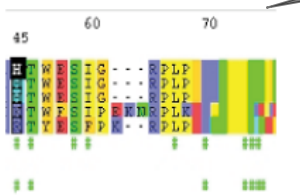
INTENZ: enzyme classification

Structures: MSD

Ligands

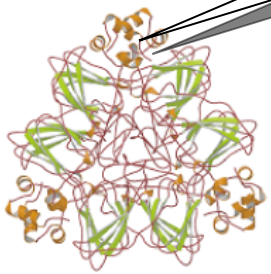


Sequence mapping

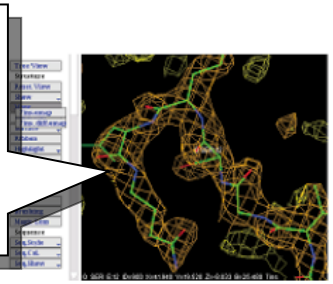


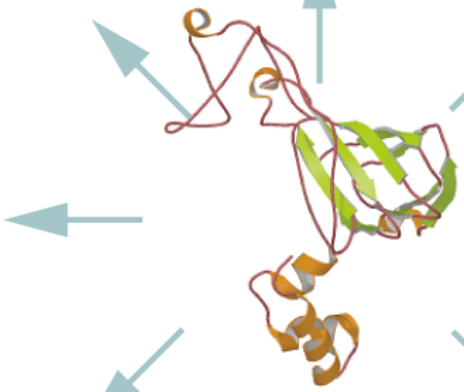
Linking to domain data

Assemblies

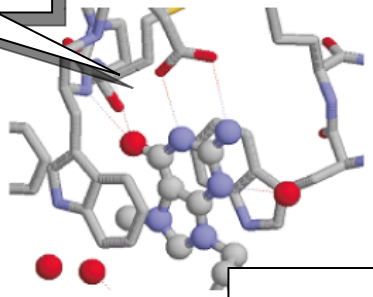


Electron density visualization

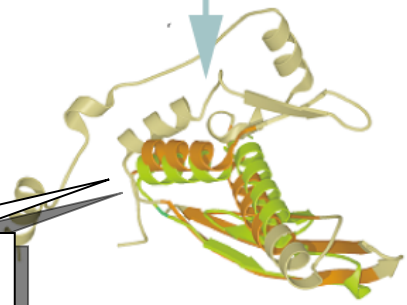


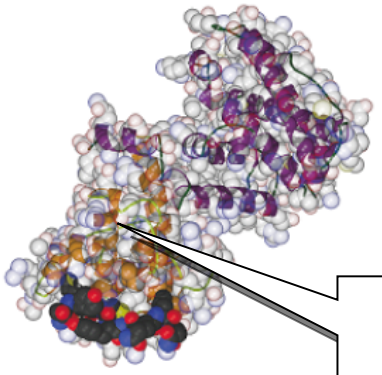


Active sites



Fold matching





Surface matching

Pathways: Reactome

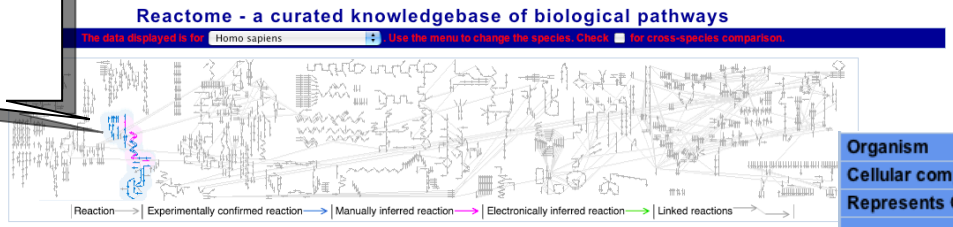
Select a pathway

Compare events in different species

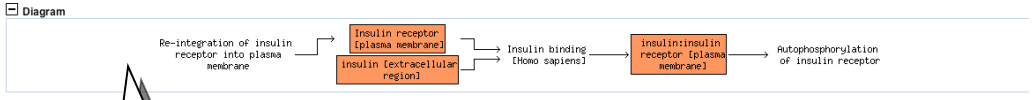
Link to source databases

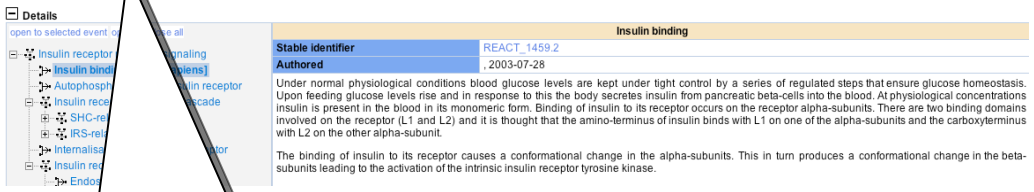
View reactions and events in detail

Export pathway to your favourite modelling software



Apoptosis	Cell Cycle Checkpoints	Cell Cycle, Mitotic	DNA Repa
DNA Replication	Electron Transport Chain	Gene Expression	HIV Infecti
Hemostasis	Immune System signaling	Influenza Infection	Insulin receptor media
Integration of pathways involved in energy metabolism	Lipid metabolism	Maintenance of Telomeres	Metabolism of amino acids containing mo
Carbohydrate metabolism	Notch Signaling Pathway	Nucleotide metabolism	Oxidative decarboxylation cycle
Post-translational modification of proteins	Transforming Growth Factor (TGF) beta signaling	Transcription	Translatio
mRNA Processing	Xenobiotic metabolism		



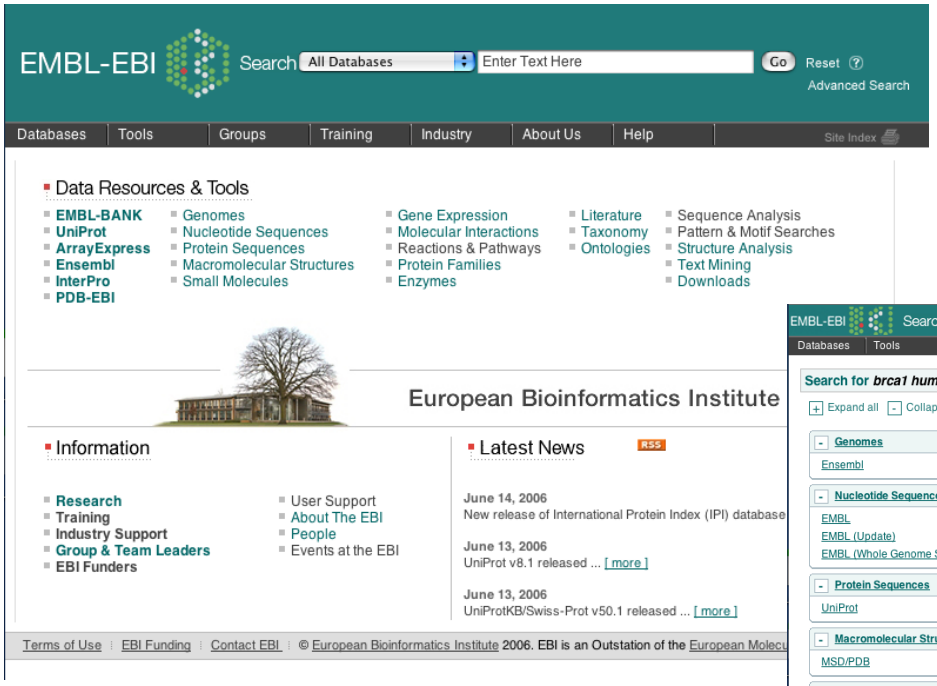


Organism	Hom ens
Cellular compartment	C SO
Represents GO biological process	Insulin receptor signaling pathway GO
Equivalent event(s) in other organism(s)	Insulin receptor mediated signaling [Drosophila melanogaster] Insulin receptor mediated signaling [Mus musculus] Insulin receptor mediated signaling [Rattus norvegicus] Insulin receptor mediated signaling [Gallus gallus] Insulin receptor mediated signaling [Tetraodon nigroviridis] Insulin r Insulin r Insulin r Insulin r Insulin r Insulin r Insulin r Insulin receptor r ing [Thalassiosira pseudonana] Insulin recepto gnaling [Arabidopsis thaliana] Insulin recep ed signaling [Oryza sativa] Insulin rec ulated signaling [Entamoeba histolytica] Insulin r or mediated signaling [Dictyostelium discoideum] Insuli eptor mediated signaling [Plasmodium falciparum]
Participating molecules	

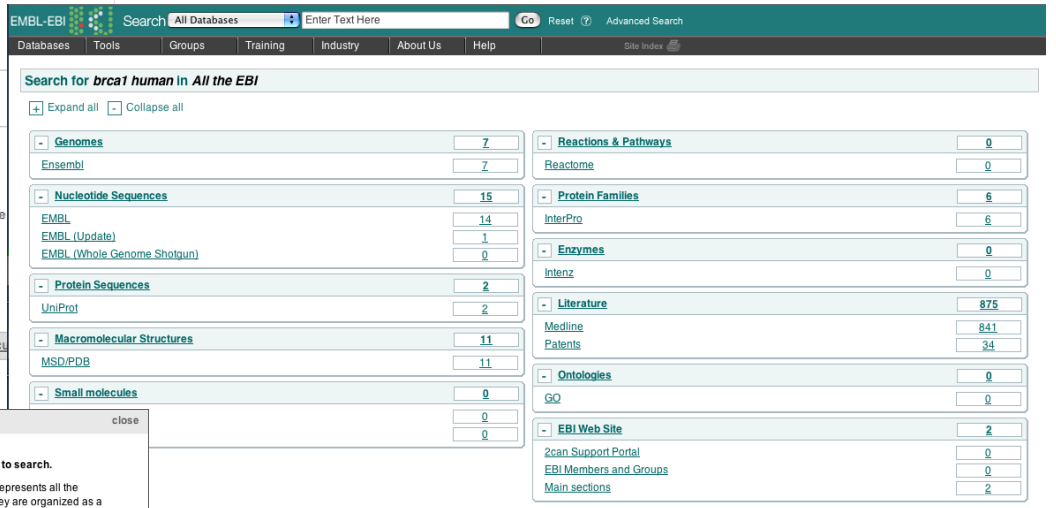
- 143B protein [cytosol] UEGKRRHHURR
- 3',5'-Cyclic AMP [cytosol] CCP
- 3-phosphoinositide dependent protein kinase-1 [plasma membrane] UEGKU
- 40S small ribosomal protein 6 [cytosol] UEGRRRRRHHHHHHUR
- 4E-BP [cytosol] UEGKRHUR
- 4E-BP1-P [cytosol] UEGKRHUR
- Activated PI3K [endosome membrane, plasma membrane]
- ADP [cytosol] CC
- AMP [cytosol] CC
- ATP [cytosol] CC
- ...

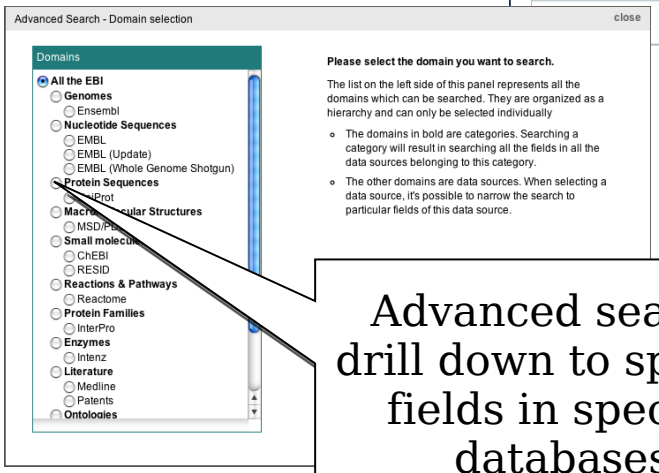
List all 96 particip

New website and search engine

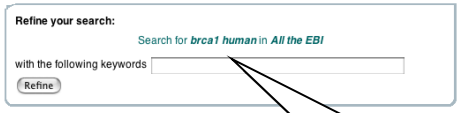


Search all main databases in on go





Advanced search: drill down to specific fields in specific databases



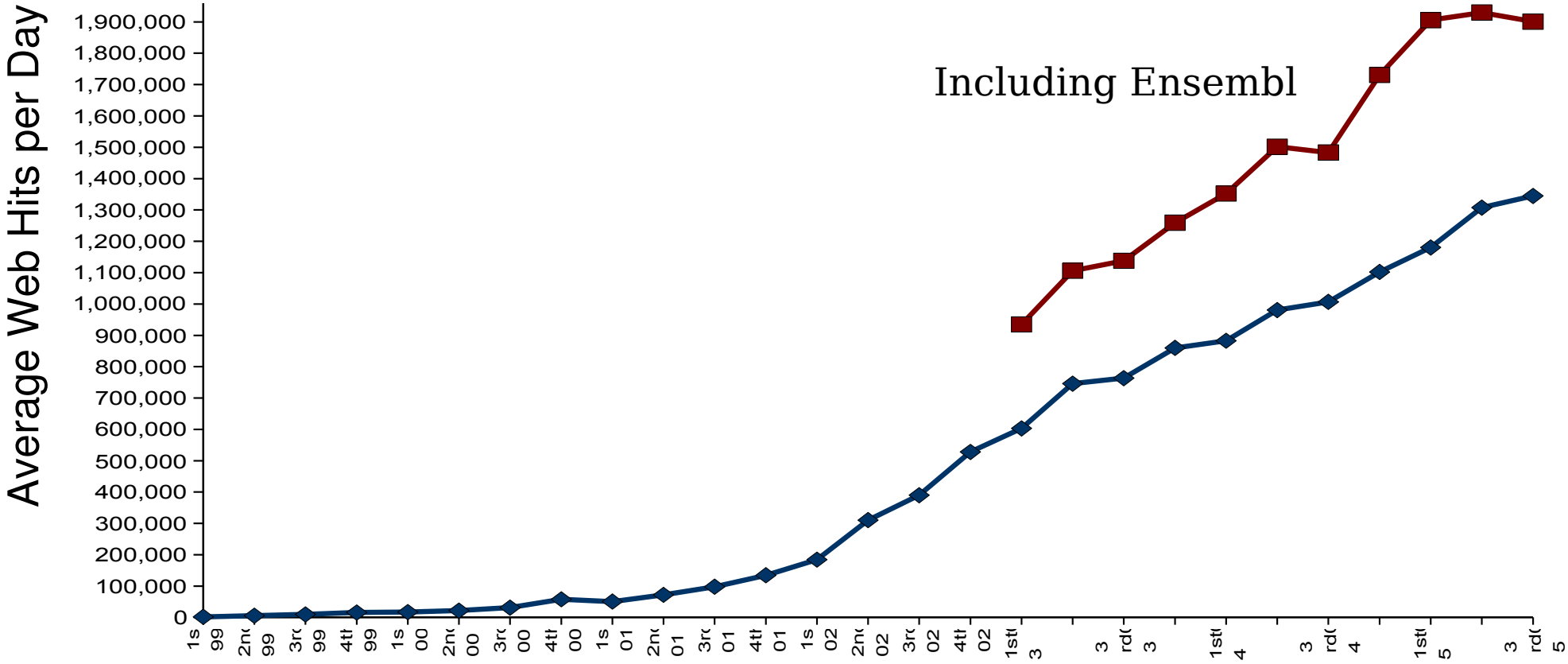
Refine your search

Data management

- ~1.6 million web requests per day (minus Ensembl)
- >250 000 unique hosts served per month
- ~3 million files downloaded per month
- ~110 TB data downloaded in 2006
- Millions of cross-references

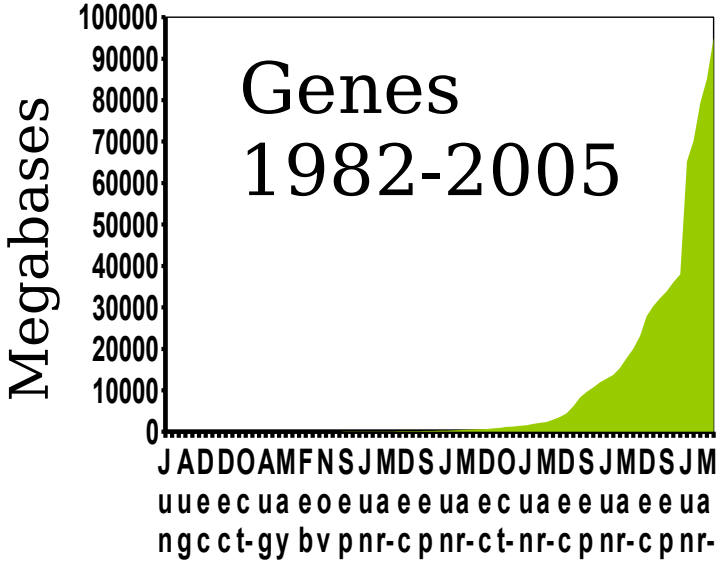
Statistics: end of 2006

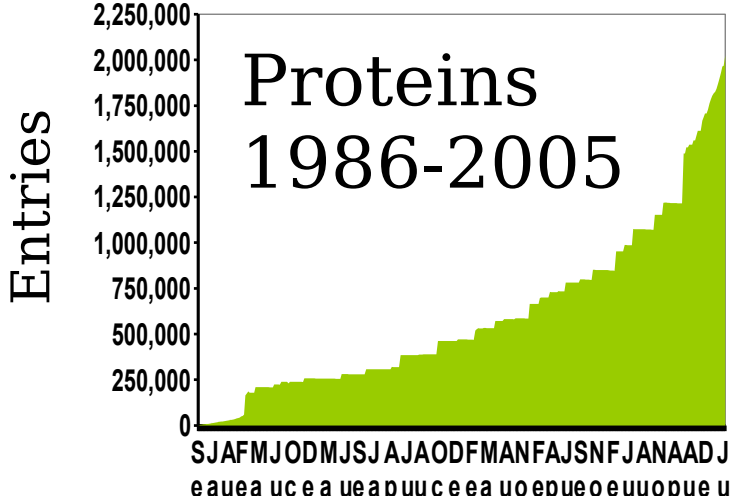
Steady increase in usage

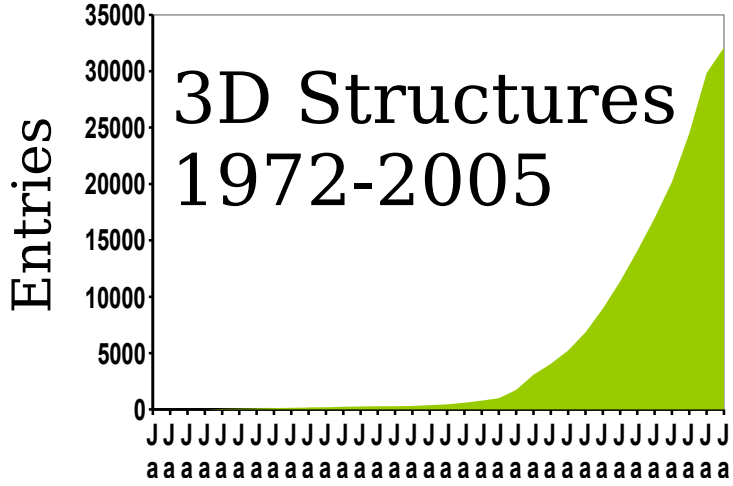


Note: Ensembl is a joint project with The Wellcome Trust Sanger Institute. Equivalent usage data have only been available since 2003.

Steady increase in data-set







What type of quantitative data do-we need?

bottom-up approach

- literature
- reactions
- structures
- kinetics
- locations
- concentrations
- topologies
- morphologies
- existing models

top-down approach

- molecular interactomes
- metabolomes
- “functiomes” (e.g. kinomes)
- dynamics
- fluxiomes
- cellular phenotypes
- physiological datasets
- gene interactions
- histology

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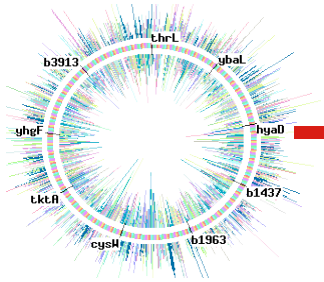
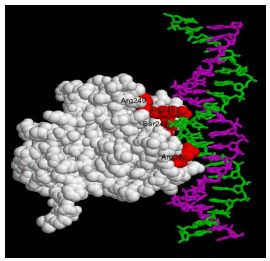
EMBL-EBI

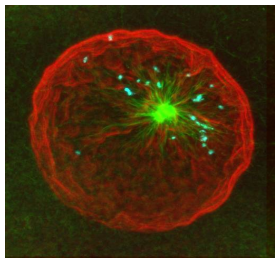
A European Infrastructure for Biological Information
ELIXIR (www.elixir-europe.org)



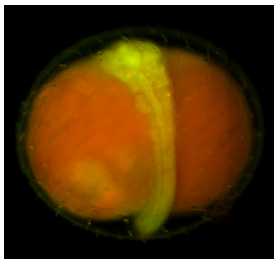
sequence



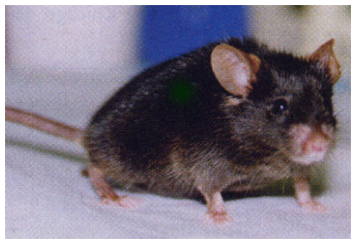
structure



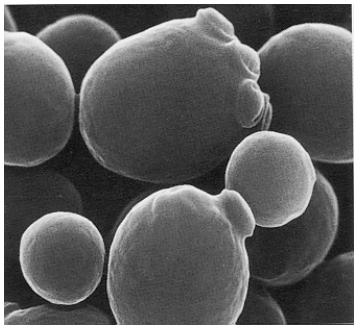
cell function



development



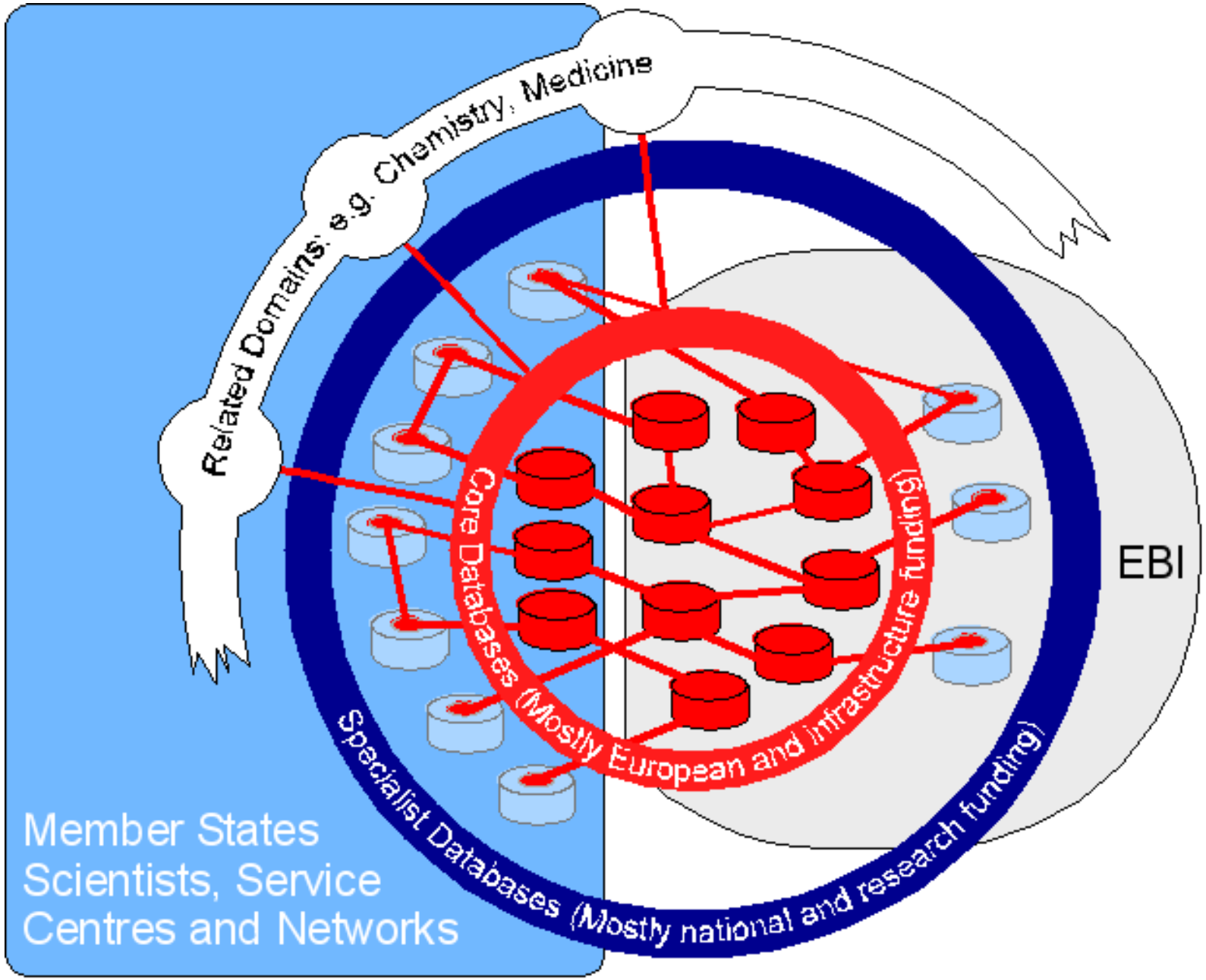
basic science



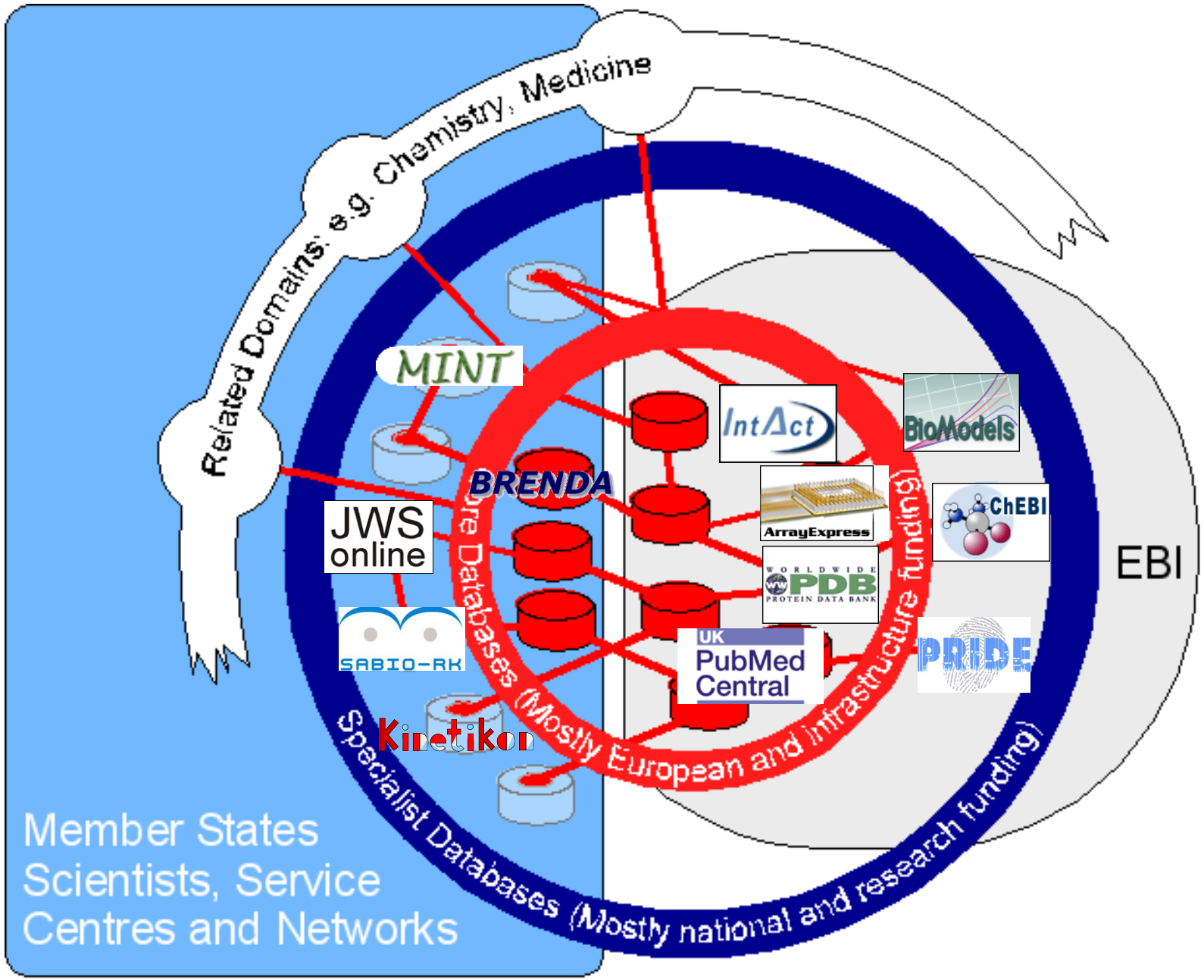
agronomy

human health

Structure of ELIXIR



Structure of ELIXIR



Key Components of ELIXIR

ELIXIR will provide

- A major upgrade of the current infrastructure, including construction of a European Biomolecular Data Centre.
- A trans-national infrastructure for biological information and service providers
- Infrastructure for biological information in the new accession states.
- The legal and financial framework for the construction and sustainable operation of this infrastructure.
- Coordination of Training and Outreach to optimise use of information

Rationale for ELIXIR

- Optimal Data Management
  - Coordinated Data Resources with improved access
  - Integration and interoperability of diverse heterogeneous data
- Forge Links to data in other related domains
- A single European voice to influence global decisions and maintain open access
- Enhance European competitiveness in bioscience industries
- Address need for Increased Funding & its Coordination

Benefits of ELIXIR

ELIXIR will contribute to European Systems Biology by:

- Optimising access and exploitation of biological data.
- Ensuring longevity of the data and protecting investments already made in research which collected the data.
- Increasing the competence and size of the already-large user community by strengthening national efforts in training and outreach.
- Enhance the global success and influence of Europe in Systems Biology research and industry.

Proposed Scale of Total Budget for ELIXIR

- Preparatory phase (ongoing) **2.5 M€**
- Construction phase
  - Data Resource Construction (ongoing)
  - Operation
  - Data Centre (building)
  - New Data Infrastructures (Accession States)

Total for 5 years **~ 800 M€**