EMBL-EBI

Principled annotation of quantitative models in Systems Biology

Nicolas Le Novère, EMBL-EBI

Computational model in SysBio

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

Computational model in SysBio

Not a bimolecular interaction

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

Computational model in SysBio

Not a bimolecular interaction

complexes

$$
\begin{aligned}
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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}] \\
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Computational model in SysBio

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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}
$$

complexes

Non-phos and phos of the same

Computational model in SysBio

Why not C2P?

Not a bimolecular interaction

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

complexes

Non-phos and phos of the same

Computational model in SysBio

Tyson JJ (1991)
Modeling the cell division cycle: cdc2 and cyclin interactions.
Proc. Natl. Acad. Sci. U.S.A. **88**: 7328-7332

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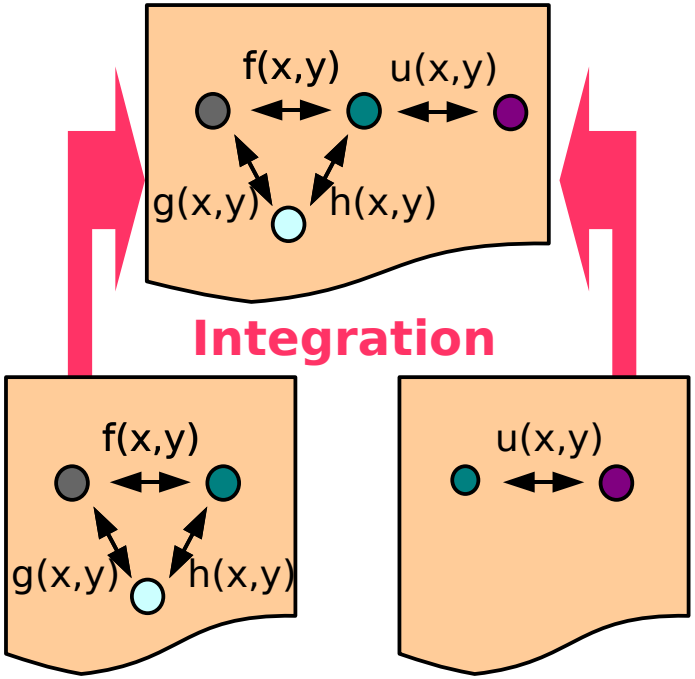
d[\mathrm{YP}]/dt &= k_6[\mathrm{M}] - k_7[\mathrm{YP}]
\end{aligned}
$$

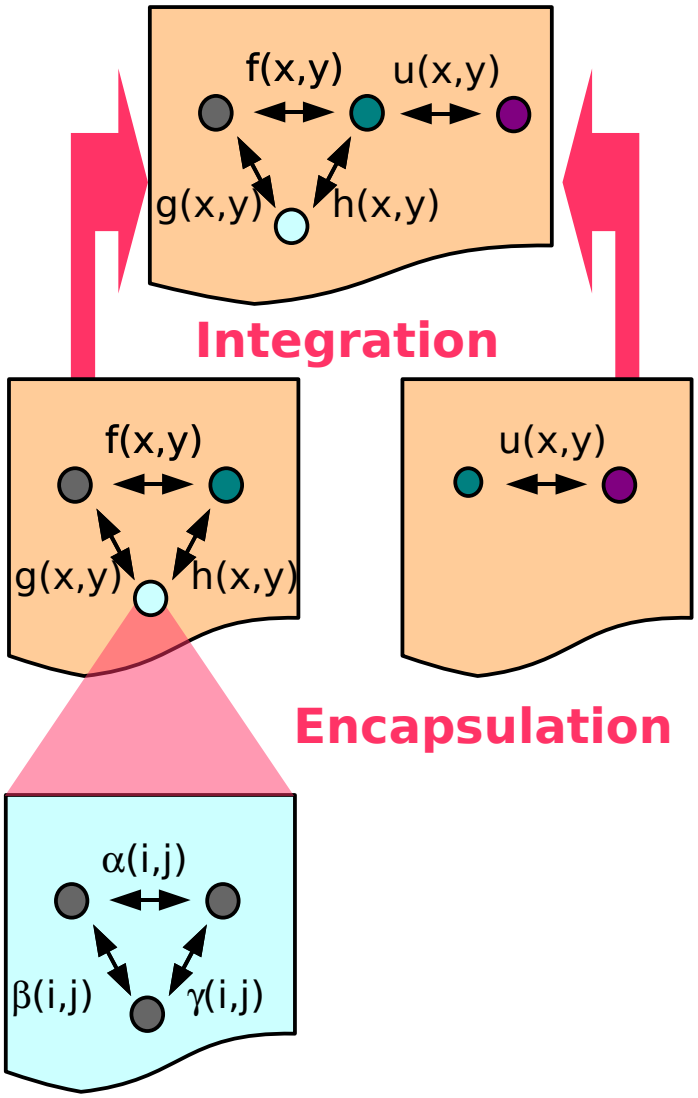
http://www.ebi.ac.uk/biomodels/

BIOMD0000000005

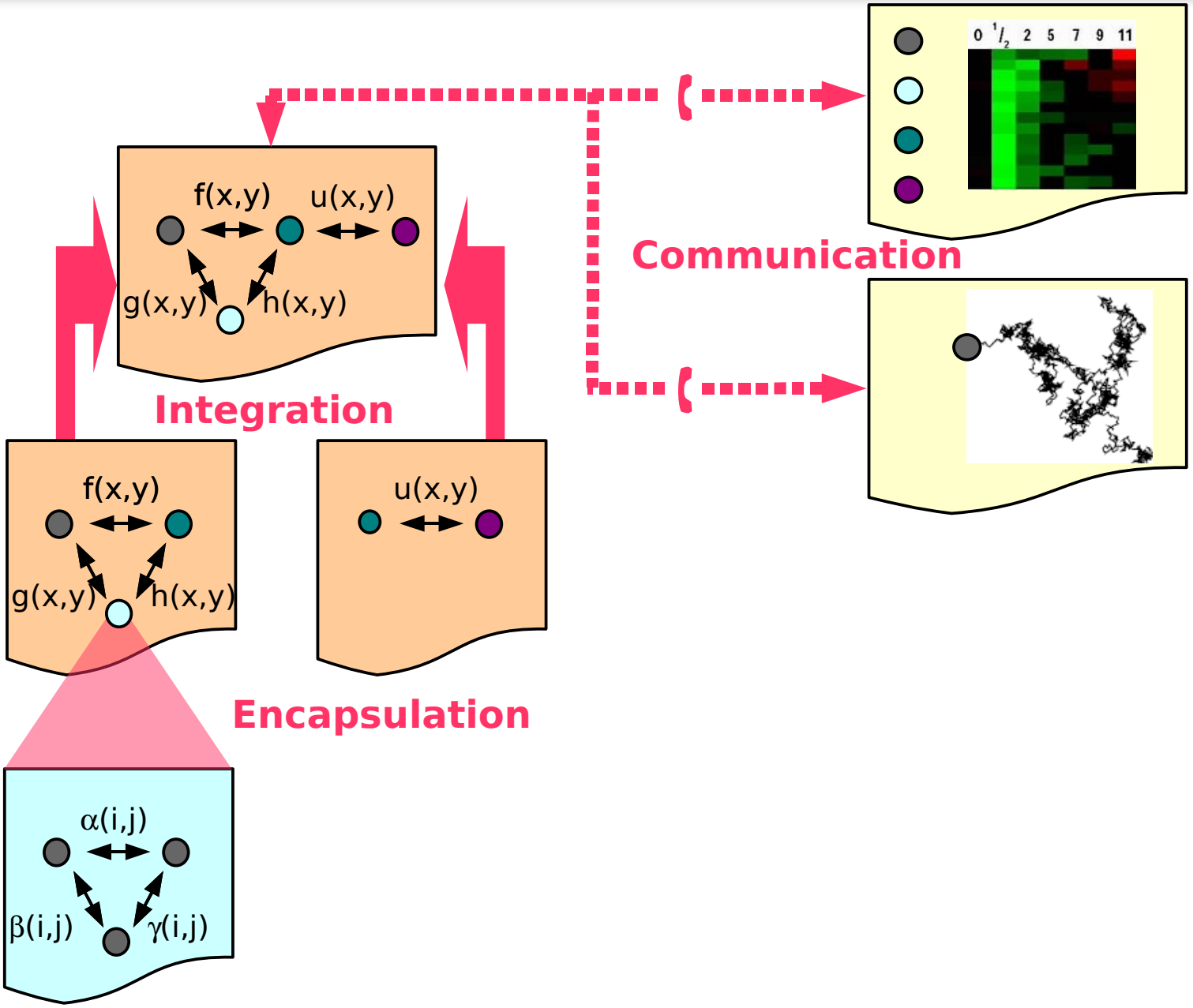
What do-we want to do with it



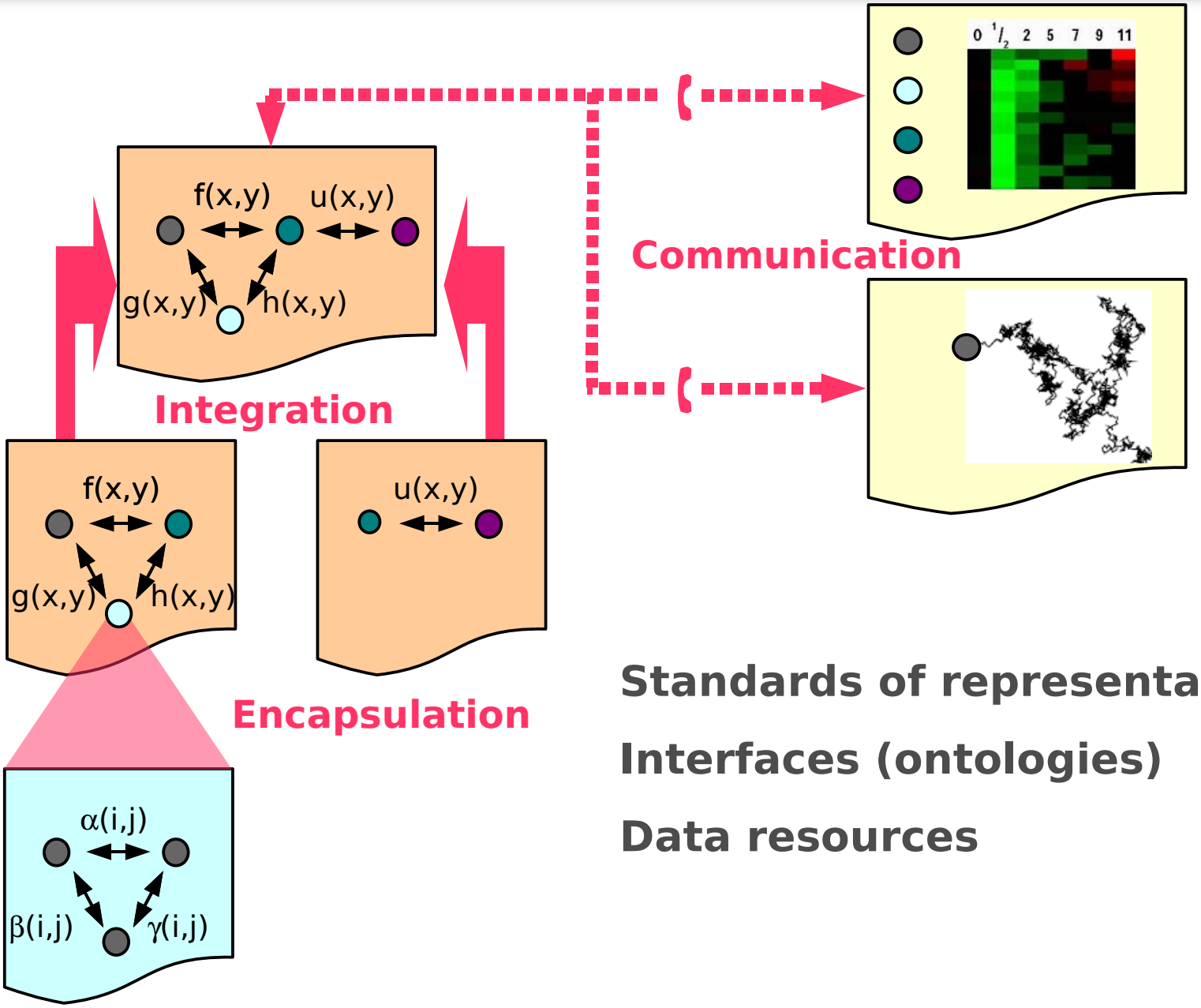
What do-we want to do with it



What do-we want to do with it



What do-we want to do with it



Standards of representation

Interfaces (ontologies)

Data resources

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.

None of this would be possible without the support of multiple agencies and organizations. Visit our **acknowledgments** page to learn about the visionary funding agencies that have backed SBML over the years.

SBML News

Old sbml.org failed

(2 Mar.'08) The old sbml.org server failed, so we had to unveil this new site even though some areas are unfinished.

LibSBML 3.1.1 released!

(25 Feb.'26) The latest version of **LibSBML**, an embeddable, portable API library for working with SBML content, is now available.

SBML Hackathon 2008

(19 Feb.'08) This year's SBML Hackathon will be April (6)–7–8 at **Stellenbosch University**.

Older news ...

Community News

Cell Cycle supports SBML

(12 Feb.'08) The **Cell Cycle Database** collects genes, proteins and models of the cell cycle and provides a user-friendly web interface. It supports SBML.

PottersWheel 1.5 released

(27 Jan.'08) **PottersWheel** is a multi-experiment fitting toolbox that supports SBML. The new version includes identifiability analysis.

SBToolbox^2 released

(18 Jan.'08) The rewritten **SBToolbox** and companion add-on package (SBPD) offer powerful features for biological modeling in MATLAB.

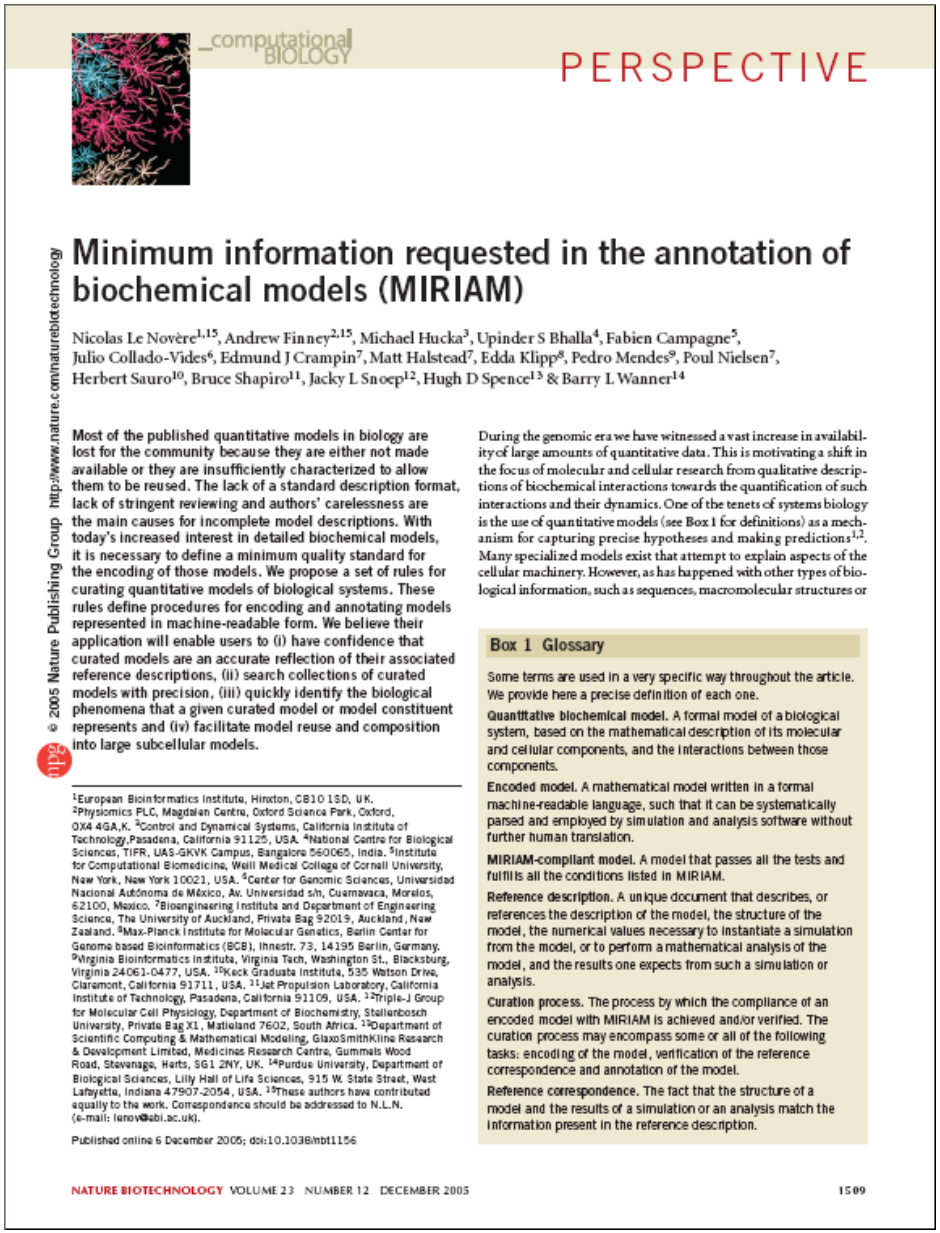
Older news ...

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

- 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, Claramont, 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.

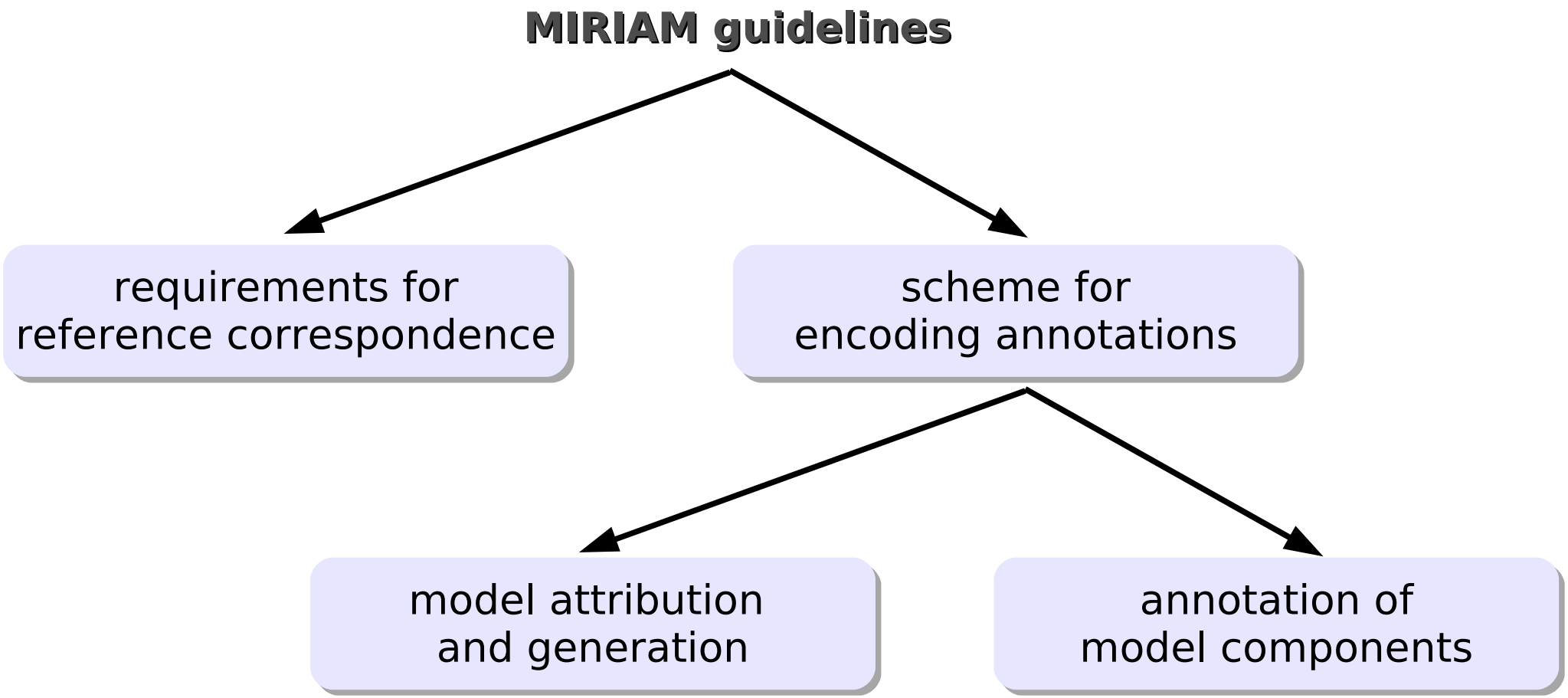
Encoded model. A mathematical model written in a formal machine-readable language, such that it can be systematically parsed and employed by simulation and analysis software without further human translation.

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.

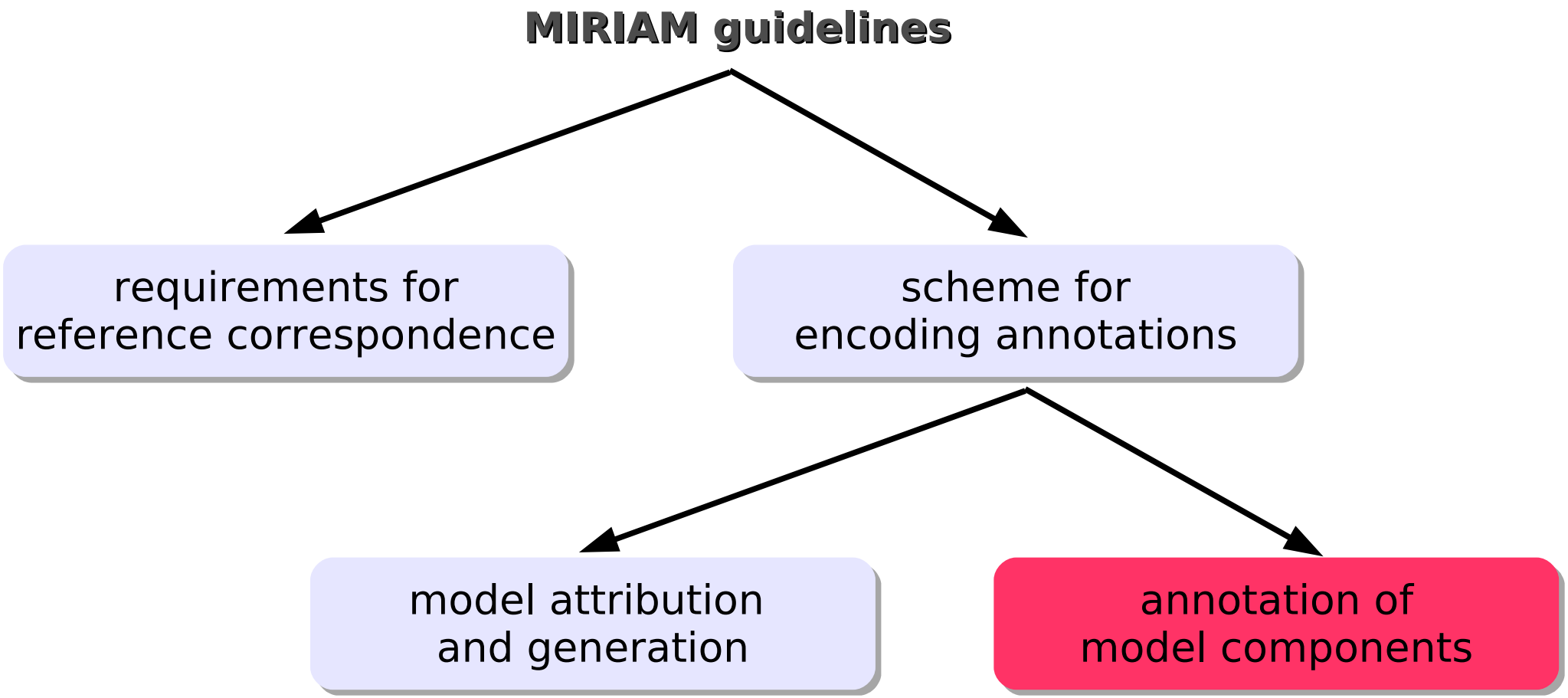

MIRIAM guidelines
requirements for reference correspondence
scheme for encoding annotations
model attribution and generation
annotation of model components

MIBBI Minimum Information for Biological and Biomedical Investigations

- Download a registration form for the MIBBI Portal (please return to chris.taylor[@]ebi.ac.uk)
- Download a summary spreadsheet of all registered projects
- Download the latest MIMI XML Schema
- Try the beta version of MICat — the searchable version of the MIBBI Portal

Registered projects (*20 listed as of 2007-11-22*)

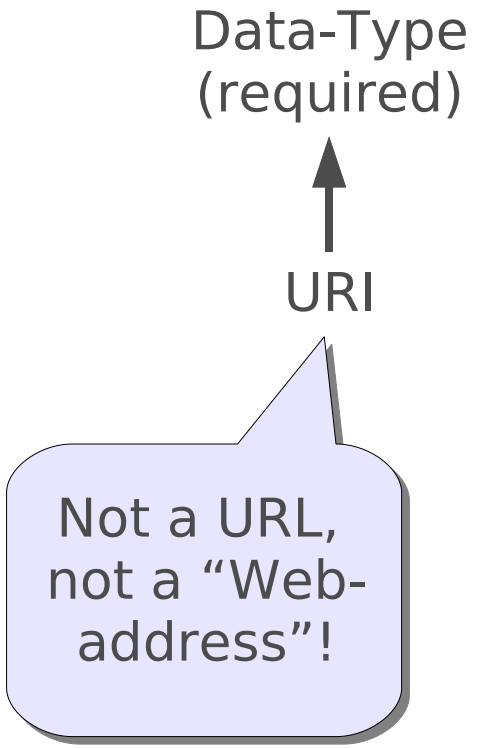
CIMR	*Core Information for Metabolomics Reporting*	Details	External Link
MIACA	*Minimal Information About a Cellular Assay*	Details	External Link
MIAME	*Minimum Information About a Microarray Experiment*	Details	External Link
MIAME/Env	*MIAME / Environmental transcriptomic experiment*	Details	External Link
MIAME/Nutr	*MIAME / Nutrigenomics*	Details	External Link
MIAME/Plant	*MIAME / Plant transcriptomics*	Details	External Link
MIAME/Tox	*MIAME / Toxicogenomics*	Details	External Link
MIAPA	*Minimum Information About a Phylogenetic Analysis*	Details	External Link
MIAPE	*Minimum Information About a Proteomics Experiment*	Details	External Link
MIARE	*Minimum Information About a RNAi Experiment*	Details	External Link
MIFlowCyt	*Minimum Information for a Flow Cytometry Experiment*	Details	External Link
MIGen	*Minimum Information about a Genotyping Experiment*	Details	External Link
MIGS	*Minimum Information about a Genome Sequence*	Details	External Link
MIMIX	*Minimum Information about a Molecular Interaction Experiment*	Details	External Link
MIMPP	*Minimal Information for Mouse Phenotyping Procedures*	Details	External Link
MINI	*Minimum Information about a Neuroscience Investigation*	Details	External Link
MIQAS	*Minimal Information for QTLs and Association Studies*	Details	External Link
MIRIAM	*Minimal Information Required In the Annotation of biochemical Models*	Details	External Link
MISFISHIE	*Minimum Information Specification For In Situ Hybridization and Immunohistochemistry Experiments*	Details	External Link
STRENDA	*Standards for Reporting Enzymology Data*	Details	External Link


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

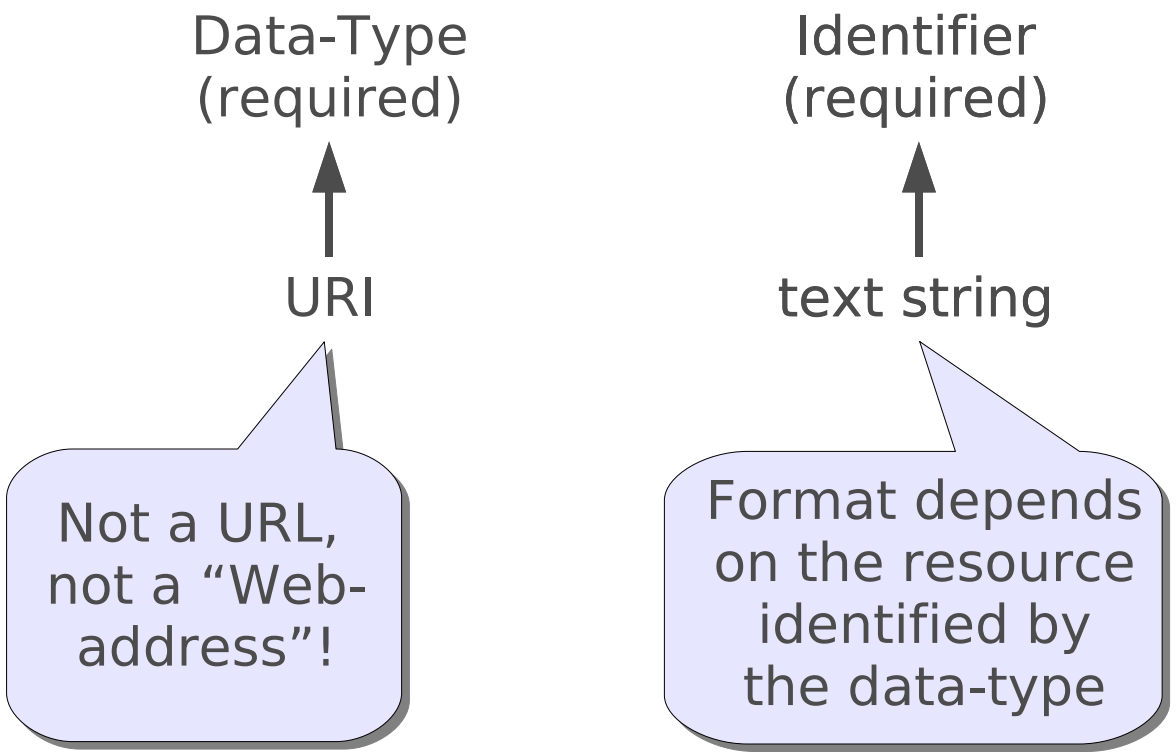
Characteristics of a useful identifier

- **Unique**
  an identifier must never be assigned to two different objects;
- **Perennial**
  the identifier is constant and its lifetime is permanent;
- **Standards compliant**
  must conform on existing standards, such as URI;
- **Resolvable**
  identifiers must be able to be transformed into locations of online resources storing the object or information about the object;
- **Free of use**
  everybody should be able to use and create identifiers, freely and at no cost.

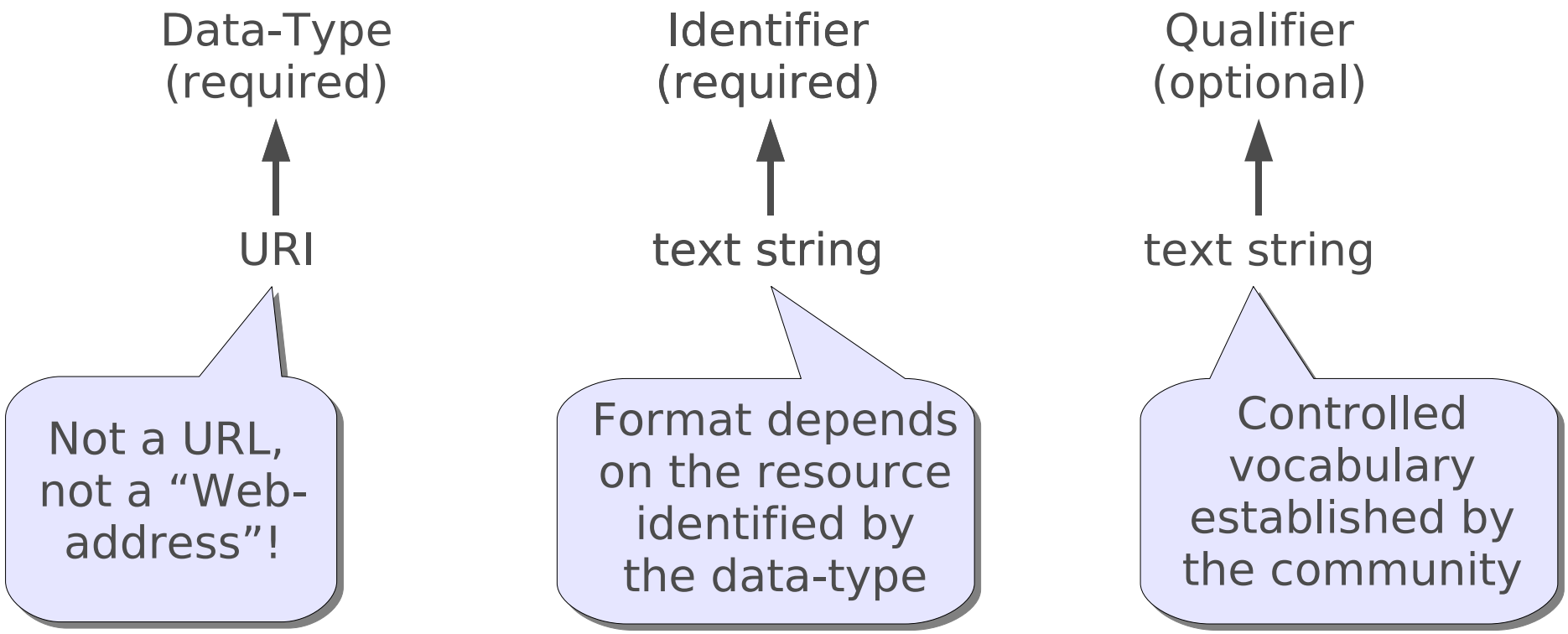
MIRIAM annotation



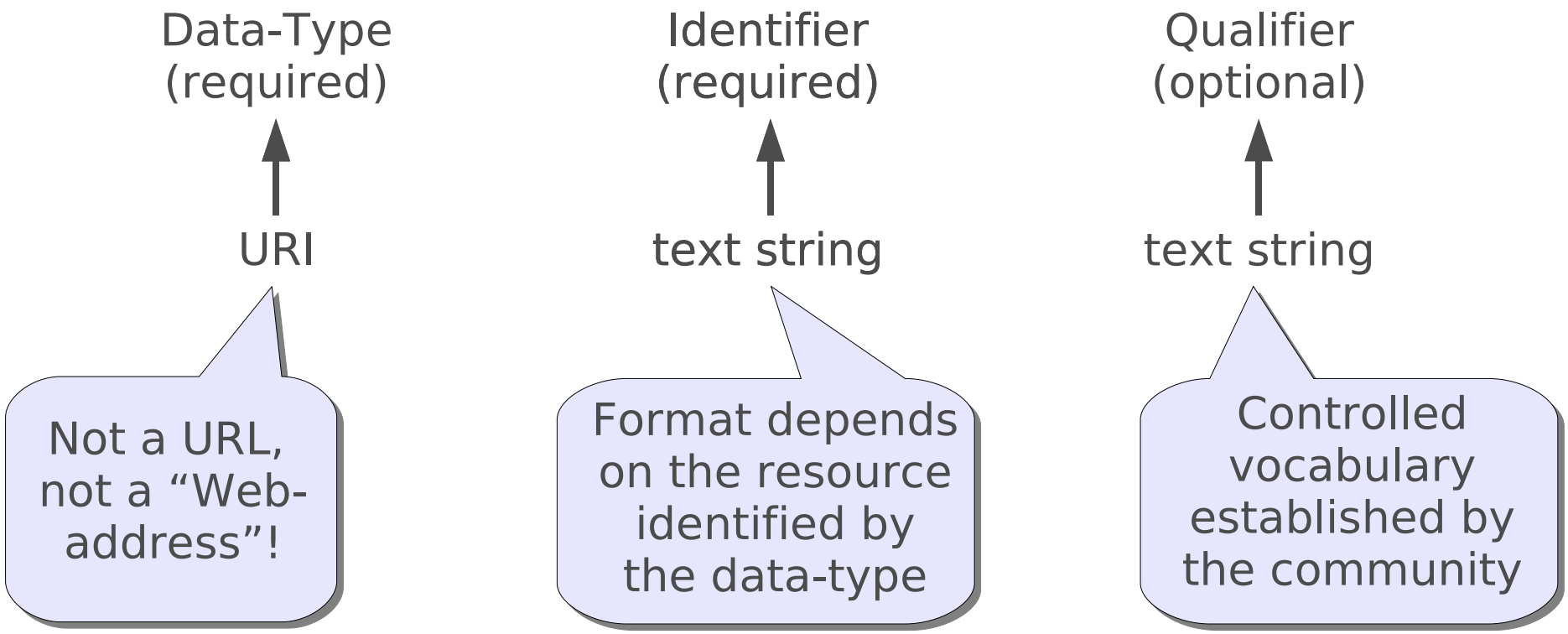
MIRIAM annotation



MIRIAM annotation



MIRIAM annotation



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

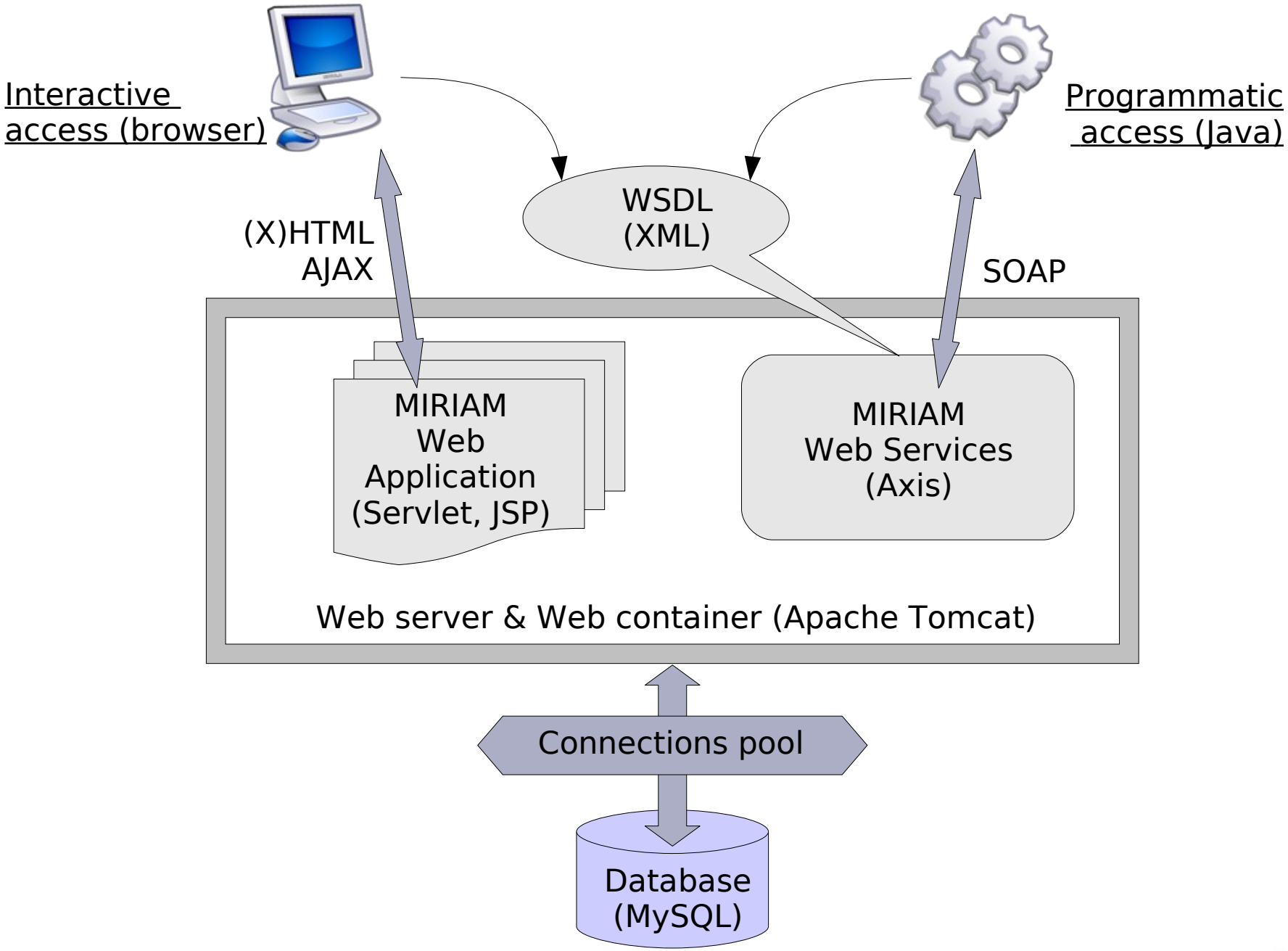
URL style: `http://www.MyResource.org/#MyIdentifier`

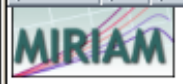
URN style: `urn:lsid:MyResource.org:MyIdentifier`

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.

MIRIAM Resources



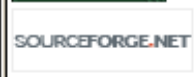


- Browse
- Query
- Submit new
- Export
- Sign In

- Web Services
  - WSDL
  - Services available
  - Library documentation
- Documents
  - MIRIAM Standard
  - FAQ
  - Media
  - News
  - BioModels Qualifiers

- MIRIAM on SourceForge

- Contact



MIRIAM

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

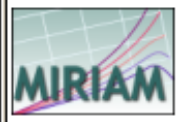
Browse the data-types

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

Name	URI	Definition
ArrayExpress	http://arrayexpress.org/	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	http://arxiv.org/	arXiv is an e-print service in the fields of physics, mathematics, non-linear science, computer science, and quantitative biology.
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 pathways.
KEGG Pathway	http://www.genome.jp/kegg/pathway/	KEGG PATHWAY is a collection of manually drawn pathway maps representing our knowledge on the molecular interaction and reaction networks.
KEGG Reaction	http://www.genome.jp/kegg/reaction/	KEGG reaction contains our knowledge on the universe of reactions that are relevant to life.
MIRIAM Resources	http://biomodels.net/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.

requirements for a MIRIAM-compliant data-type

- **Open access**
  Anybody can access any public data without restriction (no commercial licence; no login page etc.)
- **Atomicity**
  The granularity of the data distributed has to be appropriately selected (A database of “reactions” distributes reactions and not pathways) and consistent (e.g. classes or instances but not classes AND instances)
- **Identifier**
  An atomic data is associated to a unique and perennial identifier
- **Community recognition**
  The resource has to be “recognised” by the corresponding experimental community, be reasonably supported etc

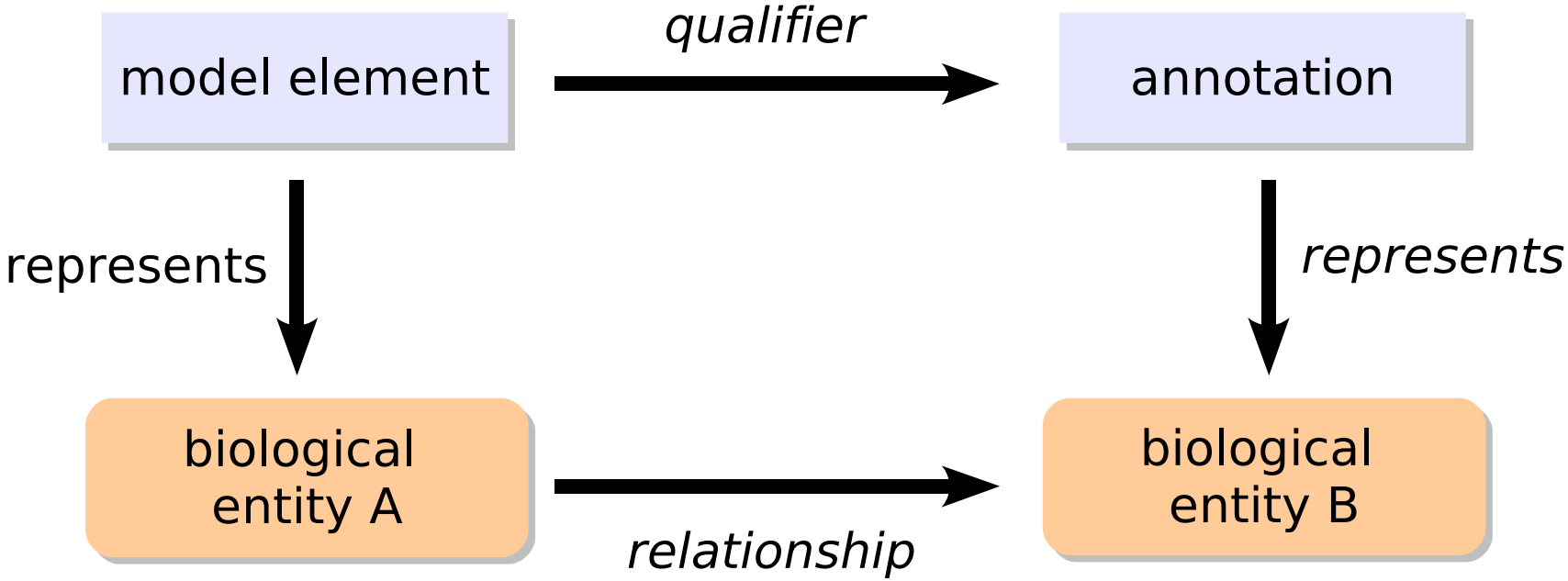


MIRIAM

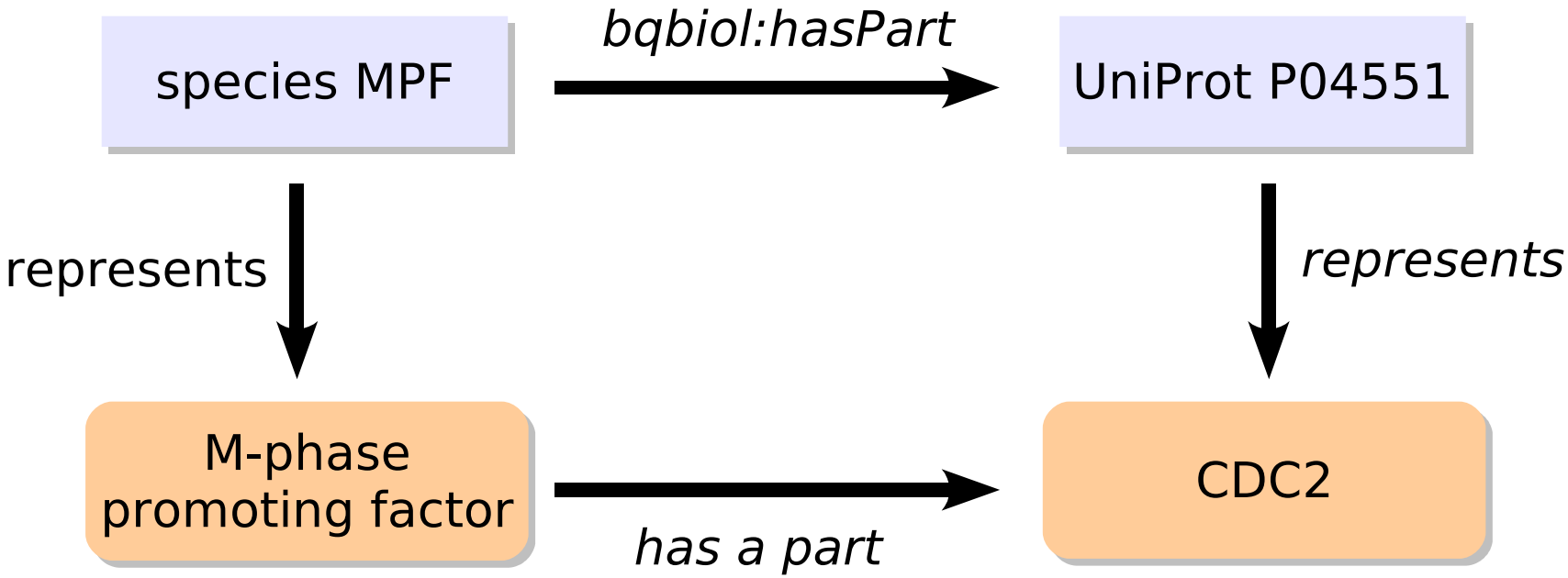
Data-type: ***Enzyme Nomenclature***

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+\.\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

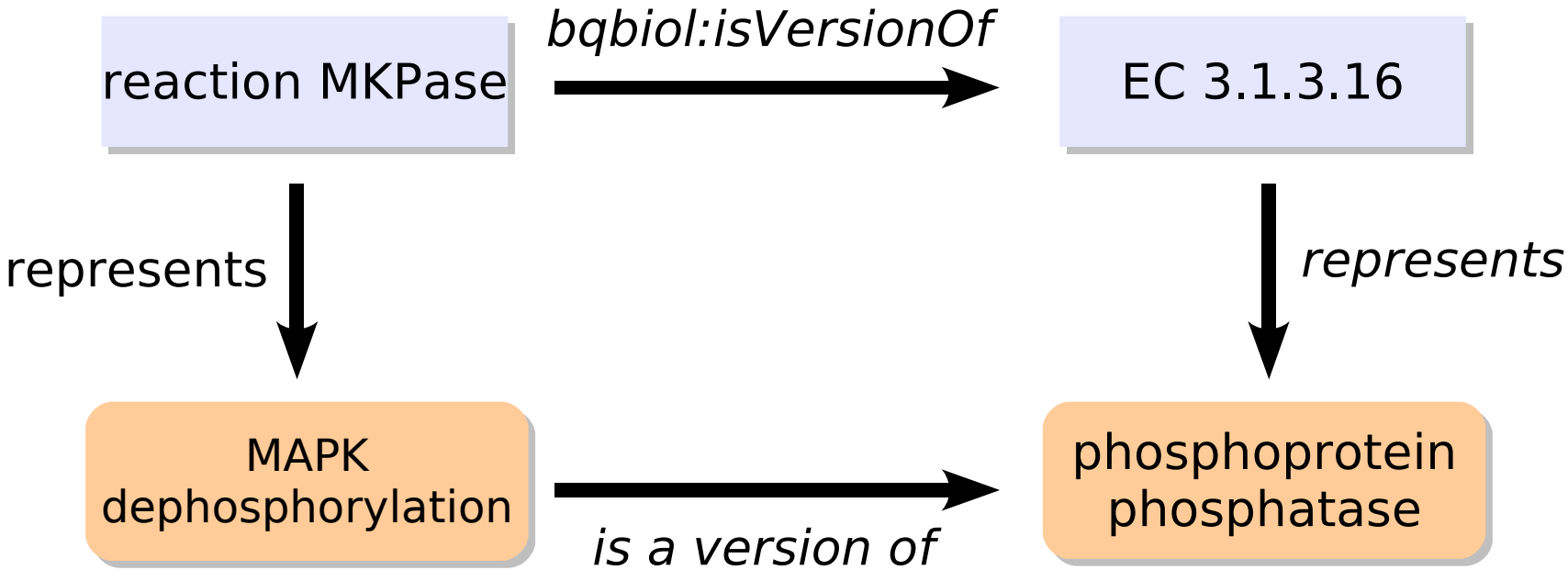
Qualification of annotation



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.

PROPOSED

- **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="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>
```

Computational model in SysBio

bqbiol:isVersionOf
Gene Ontology GO:0000079

bqbiol:isVersionOf
Gene Ontology GO:0006468
EC 3.1.3.16

bqbiol:isVersionOf
UniProt
CDC2_SCHPO

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

bqbiol:hasPart
UniProt CDC2_SCHPO
InterPro IPR006670

bqbiol:isVersionOf
Gene Ontology GO:0006470
EC 2.7.11.1

bqbiol:isVersionOf
InterPro
IPR006670

bqbiol:hasVersion
Reactome REACT_6216
Reactome REACT_6308

Hidden assumptions

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

$$S \xrightarrow{E} P \qquad v = \frac{kp.[E].[S]}{Km + [S]}$$

Import in a discrete simulator

Henri-Michaelis-Menten

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

Van Slyke-Cullen

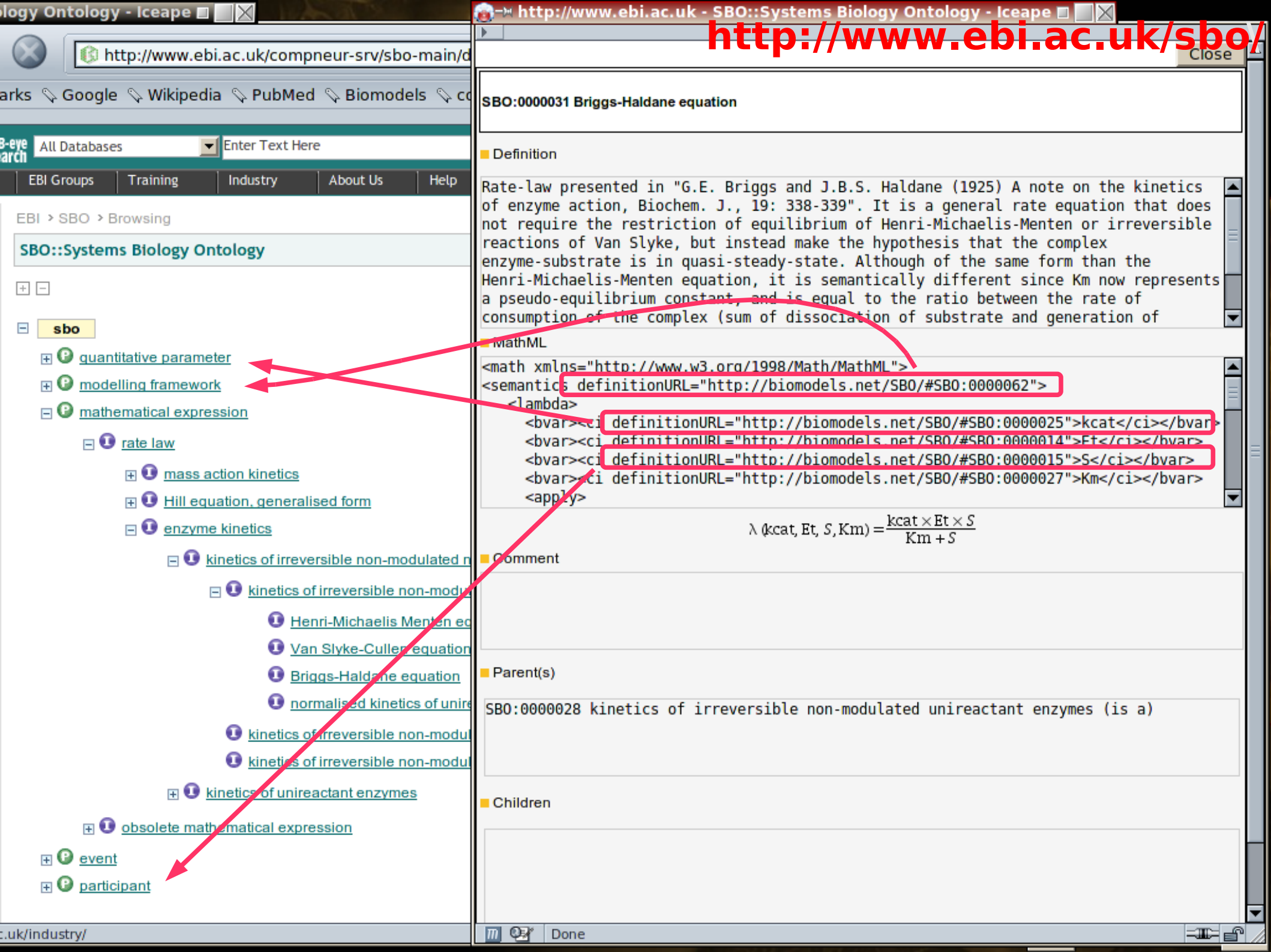
$$E+S \xrightarrow{k_1} ES \xrightarrow{k_p} E+P \; ; \; k_1 = k_p/K_m$$

Briggs-Haldane

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

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".


http://www.ebi.ac.uk/sbo/
http://www.ebi.ac.uk/compneur-srv/sbo-main/d
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
MathML
<math xmlns="http://www.w3.org/1998/Math/MathML">
<semantics definitionURL="http://biomodels.net/SBO/#SBO:0000062">
<lambda>
<bvar><ci definitionURL="http://biomodels.net/SBO/#SBO:0000025">kcat</ci></bvar>
<bvar><ci definitionURL="http://biomodels.net/SBO/#SBO:0000014">Et</ci></bvar>
<bvar><ci definitionURL="http://biomodels.net/SBO/#SBO:0000015">S</ci></bvar>
<bvar><ci definitionURL="http://biomodels.net/SBO/#SBO:0000027">Km</ci></bvar>
<apply>
λ (kcat, Et, S, Km) = kcat × Et × S / Km + S
Comment
Parent(s)
SBO:0000028 kinetics of irreversible non-modulated unireactant enzymes (is a)
Children
Done

SBML and SBO

```
<reaction sboTerm="SBO:0000172">
  <listOfReactants>
    <speciesReference species="S" sboTerm="SBO:0000015"/>
  </listOfReactants>
  <listOfProducts>
    <speciesReference species="P" sboTerm="SBO:0000011"/>
  </listOfProducts>
  <listOfModifiers>
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  </listOfModifiers>
  <kineticLaw sboTerm="SBO:0000031">
    <listOfParameters>
      <parameter id="K1" sboTerm="SBO:0000008"/>
      <parameter id="kp" sboTerm="SBO:0000025"/>
    </listOfParameters>
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        <divide/><apply>
                   <times/><ci>E</ci>
                           <ci>kp</ci>
                           <ci>S</ci>
                 </apply>
                 <apply>
                   <plus/><ci>K1</ci>
                          <ci>S</ci>
                 </apply>
      </apply>
    </math>
  </kineticLaw>
</reaction>
```

SBML and SBO

```
<reaction sboTerm="SBO:0000172">
  <listOfReactants>
    <speciesReference species="S" sboTerm="SBO:0000015"/>
  </listOfReactants>
  <listOfProducts>
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  </listOfProducts>
  <listOfModifiers>
    <speciesReference species="E" sboTerm="SBO:0000014"/>
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  <kineticLaw sboTerm="SBO:0000031">
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      <parameter id="kp" sboTerm="SBO:0000025"/>
    </listOfParameters>
    <math xmlns="http://www.w3.org/1998/Math/MathML">
      <apply>
        <divide/><apply>
                   <times/><ci>E</ci>
                           <ci>kp</ci>
                           <ci>S</ci>
                 </apply>
                 <apply>
                   <plus/><ci>K1</ci>
                          <ci>S</ci>
                 </apply>
      </apply>
    </math>
  </kineticLaw>
</reaction>
```

catalysis

substrate

product

catalyst

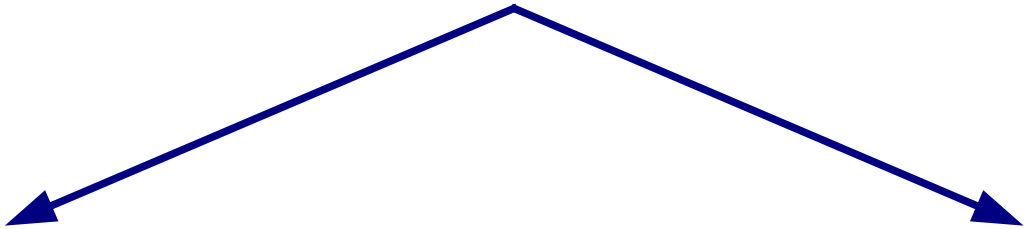
Briggs-Haldane equation

Km

kcat

SBML and SBO

```
<reaction sboTerm="SBO:0000172">
  <listOfReactants>
    <speciesReference species="A" sboTerm="SBO:0000015"/>
  </listOfReactants>
  <listOfProducts>
    <speciesReference species="B" sboTerm="SBO:0000011"/>
  </listOfProducts>
  <listOfModifiers>
    <speciesReference species="C" sboTerm="SBO:0000014"/>
  </listOfModifiers>
  <kineticLaw sboTerm="SBO:0000031">
    <listOfParameters>
      <parameter id="U" sboTerm="SBO:0000008"/>
      <parameter id="V" sboTerm="SBO:0000025"/>
    </listOfParameters>
  </kineticLaw>
</reaction>
```



continuous simulator

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

discrete simulator

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

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

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

SBML and SBO

```
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</listOfCompartments>
<listOfSpecies>
  <species id="A" sboTerm="SBO:0000247" />
  <species id="B" sboTerm="SBO:0000247" />
  <species id="C" sboTerm="SBO:0000014" />
</listOfSpecies>
<listOfReactions>
  <reaction sboTerm="SBO:0000172">
    <listOfReactants>
      <speciesReference species="A" sboTerm="SBO:0000015"/>
    </listOfReactants>
    <listOfProducts>
      <speciesReference species="B" sboTerm="SBO:0000011"/>
    </listOfProducts>
    <listOfModifiers>
      <speciesReference species="C" sboTerm="SBO:0000014"/>
    </listOfModifiers>
    <kineticLaw sboTerm="SBO:0000031">
      <listOfParameters>
        <parameter id="U" sboTerm="SBO:0000008"/>
        <parameter id="V" sboTerm="SBO:0000025"/>
      </listOfParameters>
    </kineticLaw>
  </reaction>
</listOfReactions>
```

functional compartment

simple chemical

simple chemical

enzyme

catalysis

substrate

product

catalyst

Briggs-Haldane equation

Km

kcat

SBML to BioPAX conversion using SBO

```
<listOfCompartments>
  <compartment id="C" sboTerm="SBO:0000289">
</listOfCompartments>
<listOfSpecies>
  <species id="A" sboTerm="SBO:0000247" />
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  <species id="C" sboTerm="SBO:0000014" />
</listOfSpecies>
<listOfReactions>
  <reaction sboTerm="SBO:0000172">
    <listOfReactants>
      <speciesReference species="A" sboTerm="SBO:0000015"/>
    </listOfReactants>
    <listOfProducts>
      <speciesReference species="B" sboTerm="SBO:0000011"/>
    </listOfProducts>
    <listOfModifiers>
      <speciesReference species="C" sboTerm="SBO:0000014"/>
    </listOfModifiers>
    <kineticLaw sboTerm="SBO:0000031">
      <listOfParameters>
        <parameter id="U" sboTerm="SBO:0000008"/>
        <parameter id="V" sboTerm="SBO:0000025"/>
      </listOfParameters>
    </kineticLaw>
  </reaction>
</listOfReactions>
```

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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</listOfCompartments>
<listOfSpecies>
  <species id="A" sboTerm="SBO:0000247" />
  <species id="B" sboTerm="SBO:0000247" />
  <species id="C" sboTerm="SBO:0000014" />
</listOfSpecies>
<listOfReactions>
  <reaction sboTerm="SBO:0000172">
    <listOfReactants>
      <speciesReference species="A" sboTerm="SBO:0000015"/>
    </listOfReactants>
    <listOfProducts>
      <speciesReference species="B" sboTerm="SBO:0000011"/>
    </listOfProducts>
    <listOfModifiers>
      <speciesReference species="C" sboTerm="SBO:0000014"/>
    </listOfModifiers>
    <kineticLaw sboTerm="SBO:0000031">
      <listOfParameters>
        <parameter id="U" sboTerm="SBO:0000008"/>
        <parameter id="V" sboTerm="SBO:0000025"/>
      </listOfParameters>
    </kineticLaw>
  </reaction>
</listOfReactions>
```
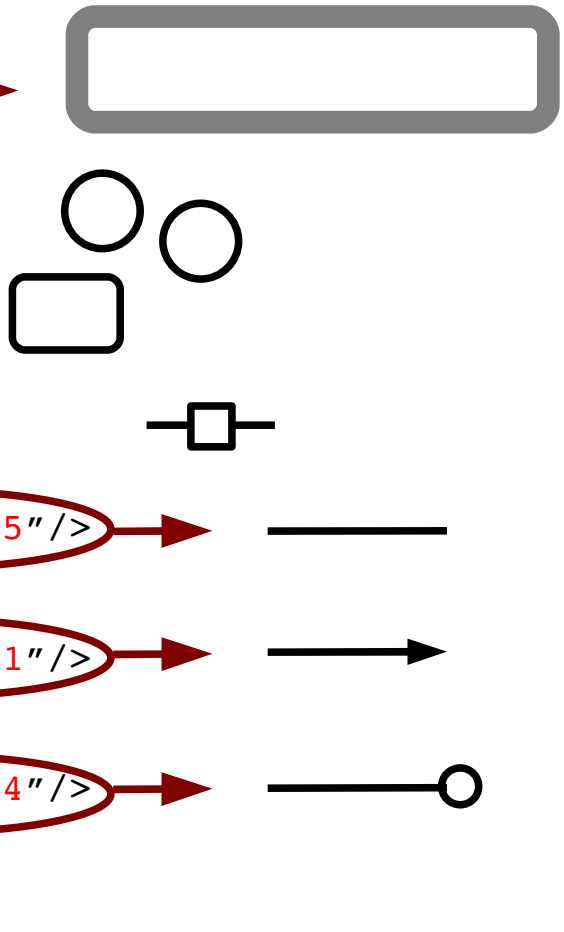



http://www.sbgn.org/

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 model

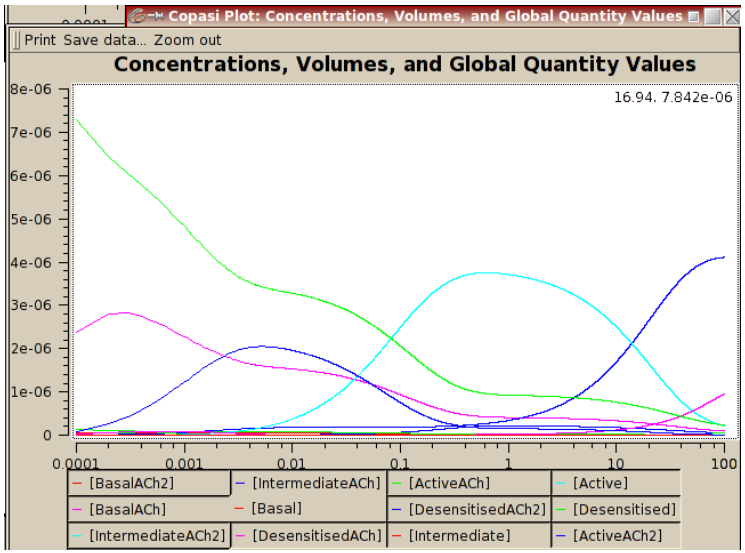
- A model is a mathematical description of the components of a system, their relationships, and the evolution of both.
  - ordinary differential equations (system evolution) $dX/dt = f(X)$
  - partial differential equation (system description) $\nabla X = g(X)$
  - algebraic equations (conservation laws) $h(X) = 0$
  - 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
  - ...

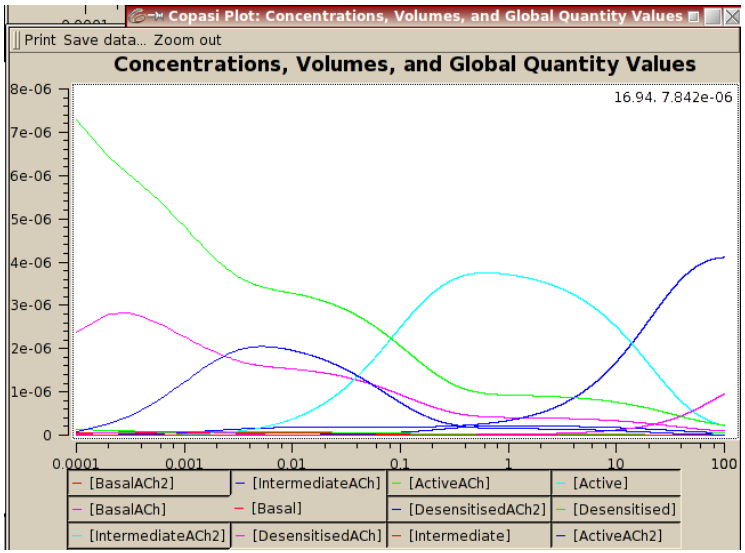
Some simulation results from COPASI

Edelstein et al 1996 (BIOMD0000000002)

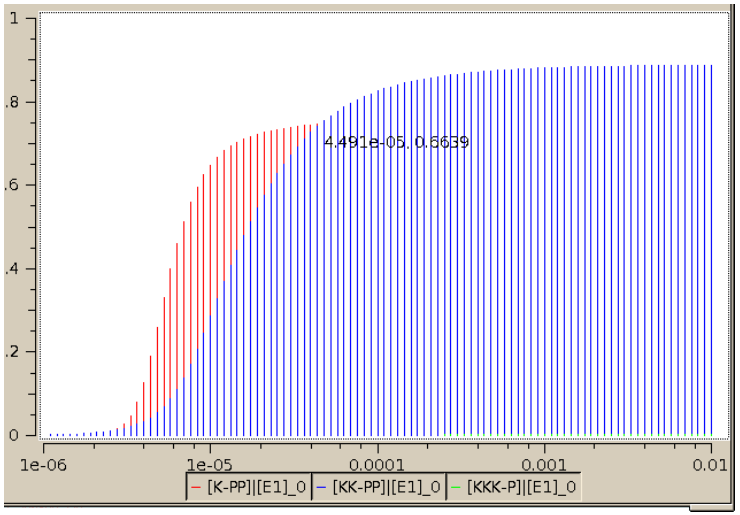


Some simulation results from COPASI

Edelstein et al 1996 (BIOMD0000000002)

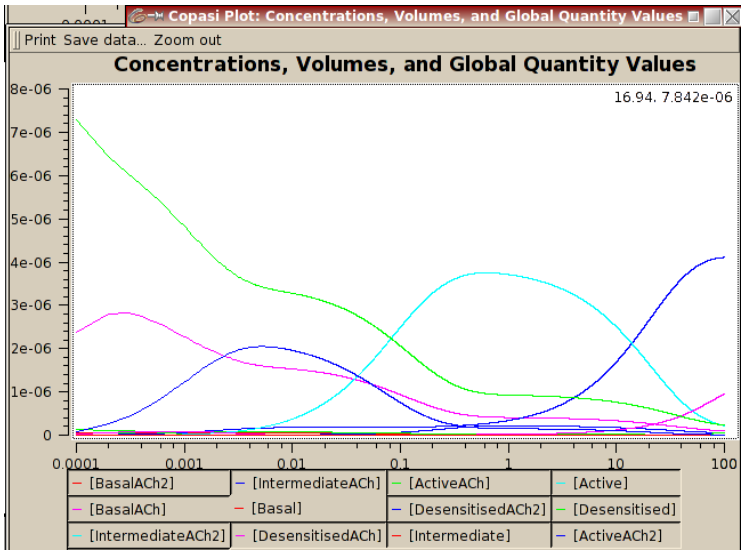


Huang & Ferrell (BIOMD0000000009)

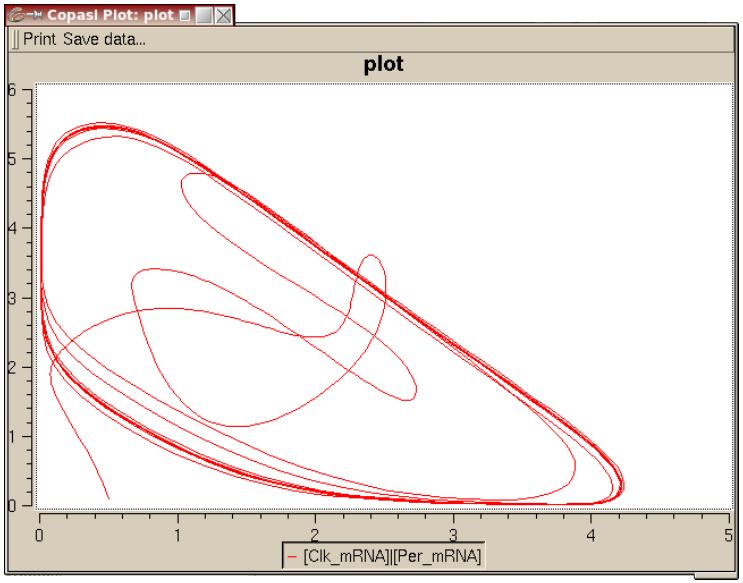


Some simulation results from COPASI

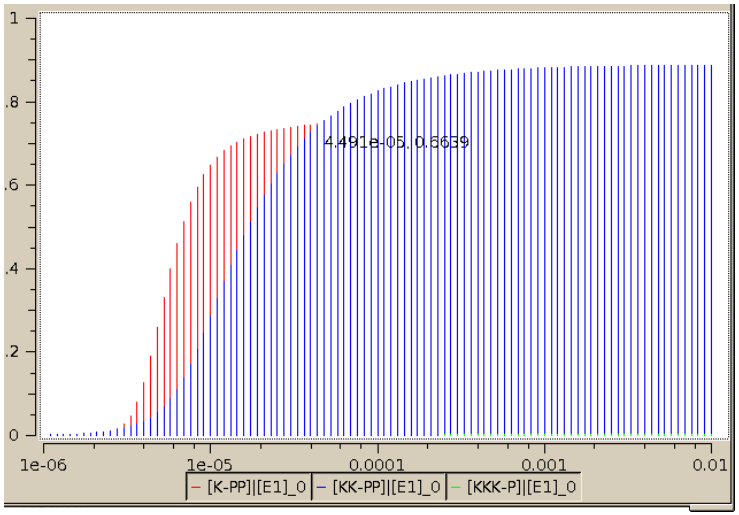
Edelstein et al 1996 (BIOMD0000000002)



Ueda, Hagiwara, Kitanol 2001 (BIOMD0000000022)

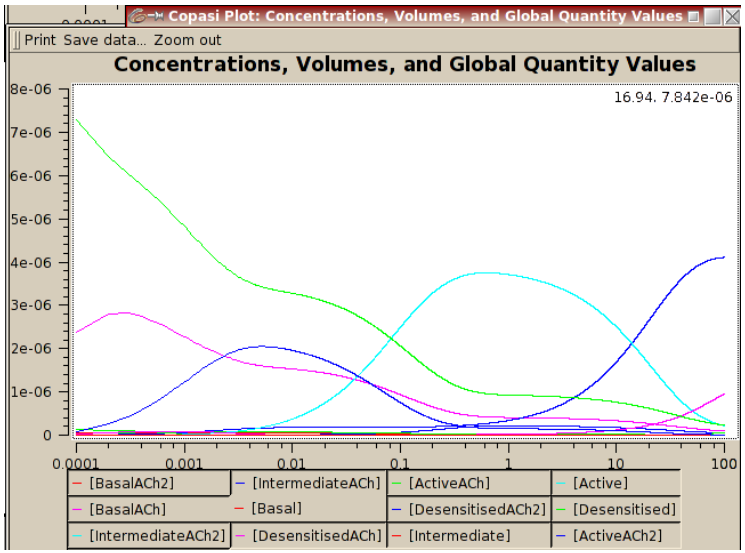


Huang & Ferrell (BIOMD0000000009)

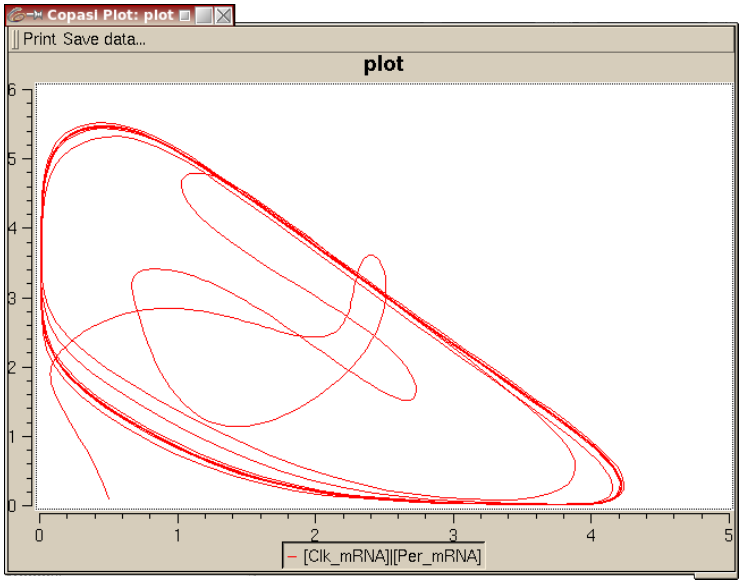


Some simulation results from COPASI

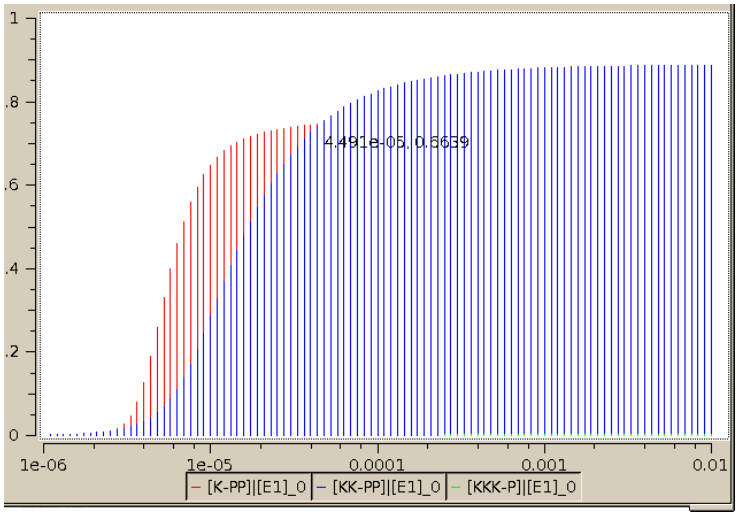
Edelstein et al 1996 (BIOMD0000000002)



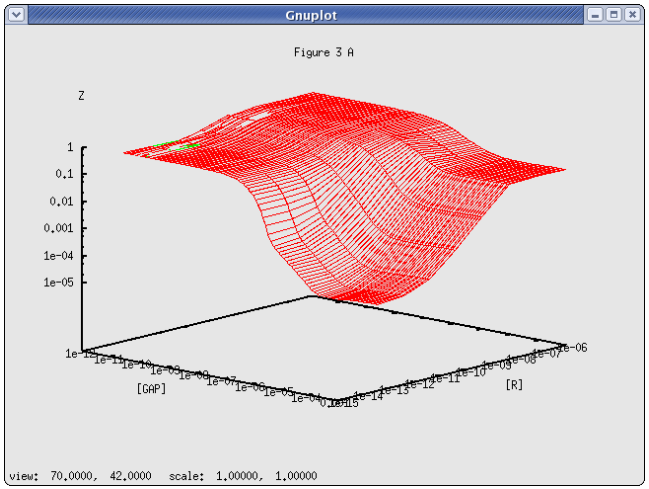
Ueda, Hagiwara, Kitanol 2001 (BIOMD0000000022)



Huang & Ferrell (BIOMD0000000009)



Bornheimer et al 2004 (BIOMD0000000086)



Minimum Information About a Simulation Experiment (MIASE)

https://sourceforge.net/projects/miase

MIASE aims at describing the information needed to run and repeat a numerical simulation experiment derived from a given quantitative model.

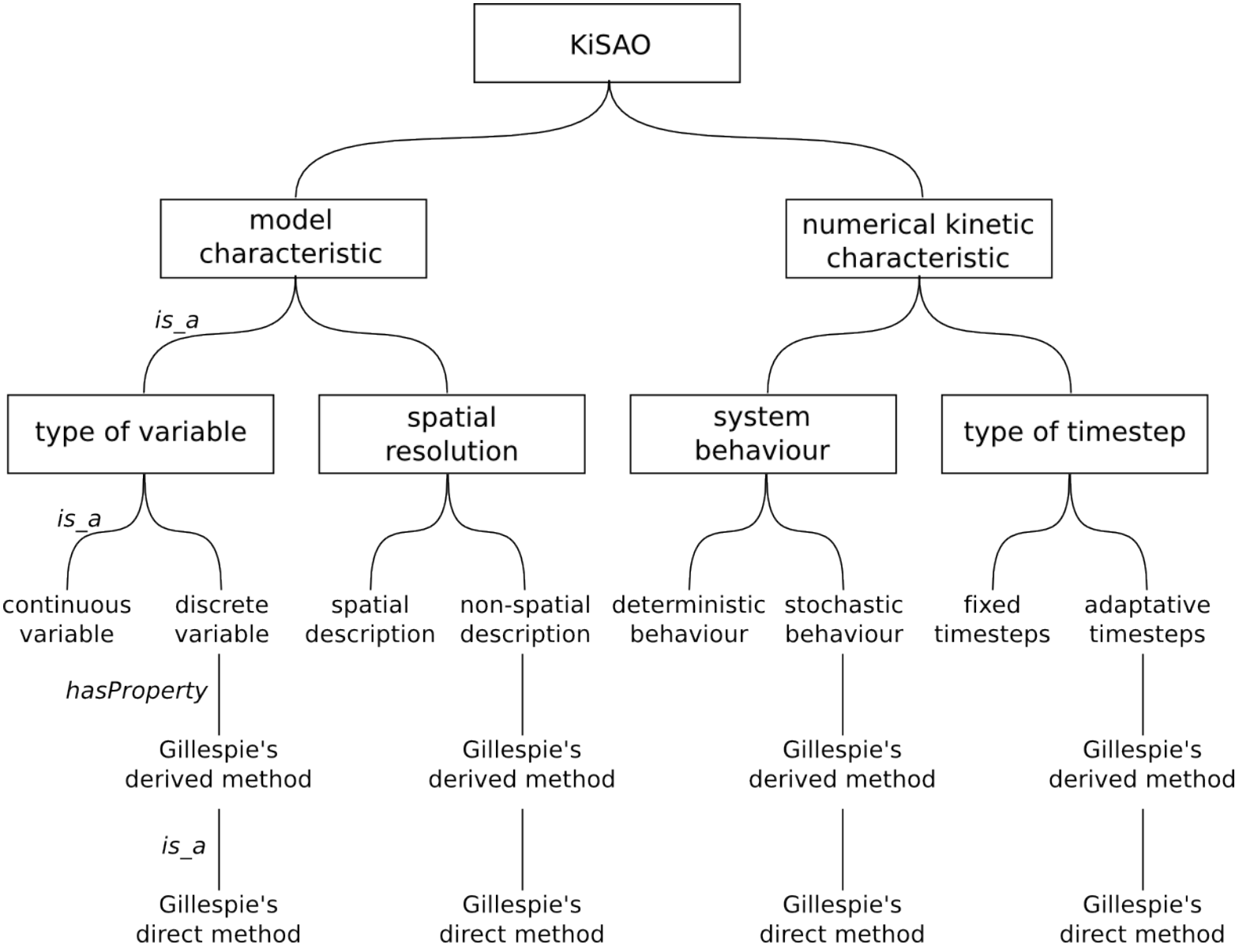
The project is divided into three parts:

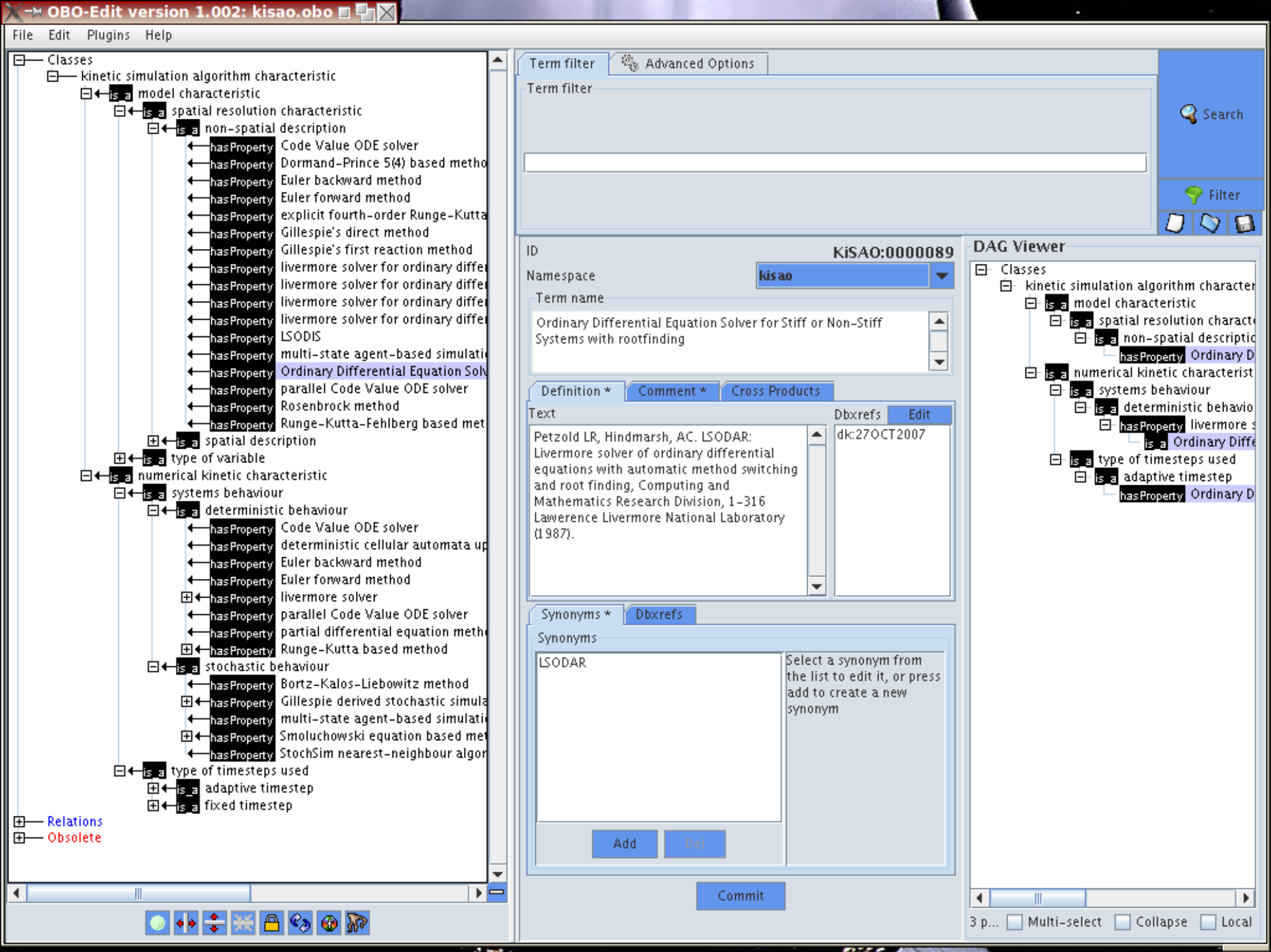
1. MIASE - The list of requested information to repeat a simulation result
   * Simulation settings (Type of simulation and the according parameters)
   * Simulation algorithm used to simulate a given model (see KiSAO)
   * Model references & model changes
   * Parameter settings
   * Desired output

2. KiSAO - Kinetic Simulation Algorithm Ontology
   * Classification of simulation algorithms & methods
   * Literature references
   * Relations between different simulation algorithms & methods

3. The MIASE Object Model
   * Formal representation of the requirements defined in MIASE
   * UML representation
   * XML Schema representation to encode MIASE information (MIASE-ML)

Kinetic Simulation Algorithm Ontology (KiSAO)

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Description of dynamics. Why?

- Comparison of simulation output with experimental datasets
- Retrieval of models based on their behaviours
  “Find-me one model that display an oscillation of period X”
- From Systems Biology to Synthetic biology and reverse

TErminology for the Description of DYnamics (https://sourceforge.net/projects/teddyontology)

- 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.

TeDDy is expressed in OWL

Contents

Ontology
All Resources
Class Hierarchy
All Classes

Teddy Entity
==Dynamical Behaviour
====Monotonic Behaviour
======Strictly Monotonic Behaviour
========Isotonic Behaviour
==========Linear Increasing Behaviour
==========Increasing Asymptotic Behavior
==========Diverging Increasing Behavior
========Antitonic Behaviour
==========Linear Decreasing Behaviour
==========Decreasing Asymptotic Behavior
======Steady State
====Non-Monotonic Behaviour
======Oscillation
========Non-Periodic Oscillating Behavior
========Periodic Oscillating Behavior
==========Single-Periodic Oscillating Behavior
============Sustained Oscillation
============Damped Oscillation
==========Mixed-Mode Oscillation
======Single Turnaround Behaviour
======Chaotic Behavior
======Bursting

Class: Dynamical Behaviour (TEDDY_0000001)

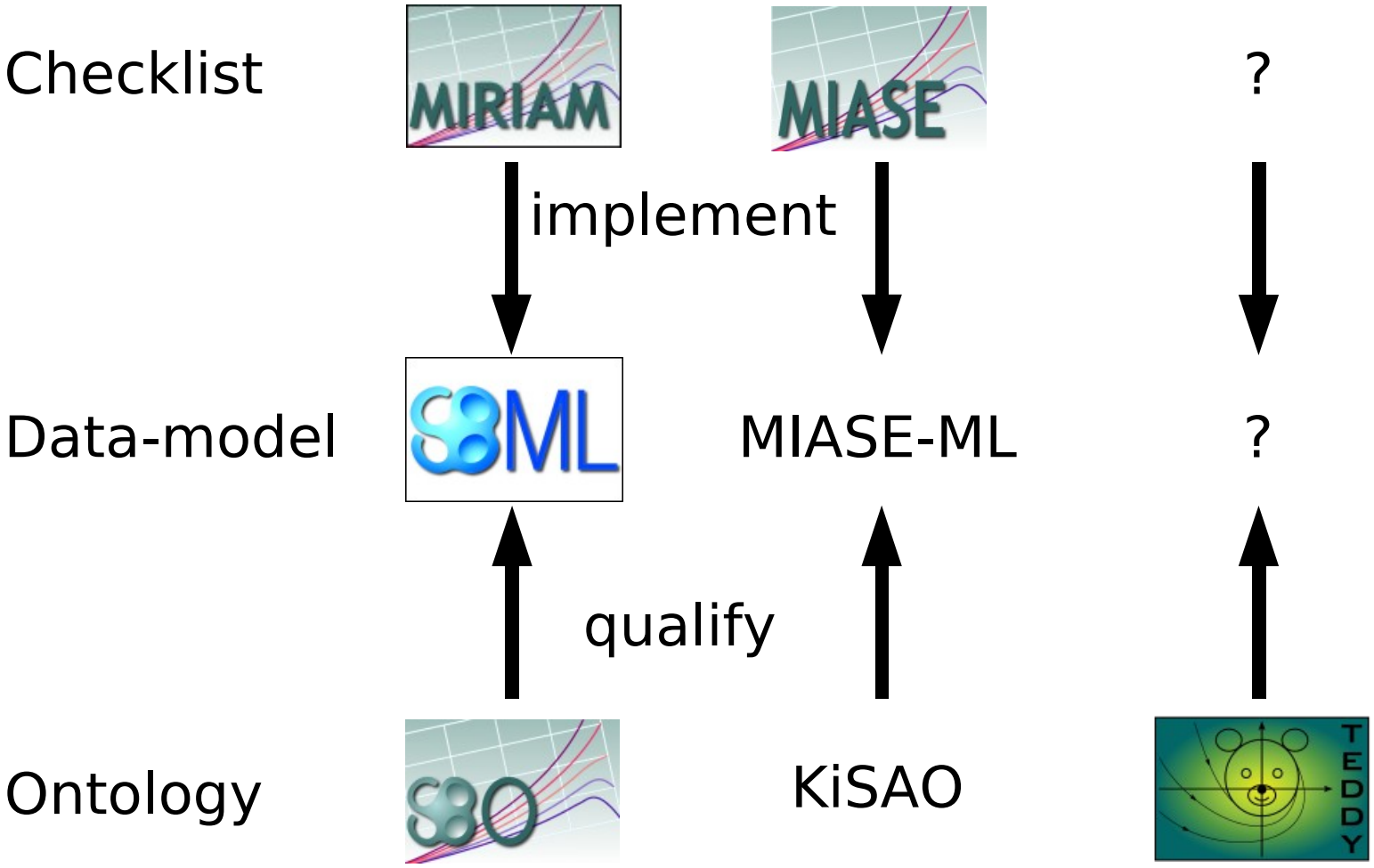
- owl:Thing
  - Teddy Entity
    - **Dynamical Behaviour**

Super Classes

Teddy Entity

Annotations

Curator_Comment	"The word 'dynamical' is used in order to emphasize the evolution of the state in time distinguishing the term form behaviour in ethology. 'Dynamical' will be omitted in sub-terms for convenience if confusion is impossible." [lang: en]
Curator_Comment	"This concept is used to name concrete behaviours of dynamical systems. Concrete refers to a specified interval of time in which the behaviour takes place." [lang: en]
Curator_Comment	"The set of possible states of a dynamical system has to be a metric space (Kuznetsov 1998, p.4). IMHO it's enough to require a totally ordered set." [lang: en]
Curator_Comment	"mathematical: A dynamical behaviour is a function from an ordered set (called Time) to a totally ordered set S (called State Space). " [lang: en]
Definition	"A Dynamical Behaviour is a temporal sequence of states of (a part of) a dynamical system. The set of possible states (state space) has to be a totally ordered set. A dynamical system is either a fully instantiated mathematical model or a particular biological entity." [lang: en]
Display_Name	Dynamical Behaviour


Checklist
MIRIAM
MIASE
?
implement
Data-model
SBML
MIASE-ML
?
qualify
Ontology
SBO
KiSAO
TEDDY

Acknowledgements

- EBI
  - Mélanie Courtot
  - Nick Juty
  - Christian Knuepfer
  - Dagmar Koehn
  - Camille Laibe
  - Nicolas Le Novère
- SBML team
  - Michael Hucka
  - Sarah Keating
- BioModels Database developers and curators

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The community of Systems Biology for their contributions, their software support and their comments.

What is ELIXIR?

- **ELIXIR** is an EU Framework 7 Preparatory Phase project
- Its mission is to construct and operate a ***sustainable*** infrastructure for biological information in Europe
- It comprises a 32-member consortium engaging many of Europe's main bioinformatics ***funding agencies*** and ***research institutes***
- The deliverables are ***memoranda*** of understanding to fund the ***implementation***
- The implementation will take many years and the estimated cost is ~***€500-800M***
- It is envisaged that the cost of implementation will be borne, mainly, by funding agencies within the ***member states*** and by ***structural*** or ***cohesion*** funds
- Interested parties should register as stake-holders:

www.elixir-europe.org

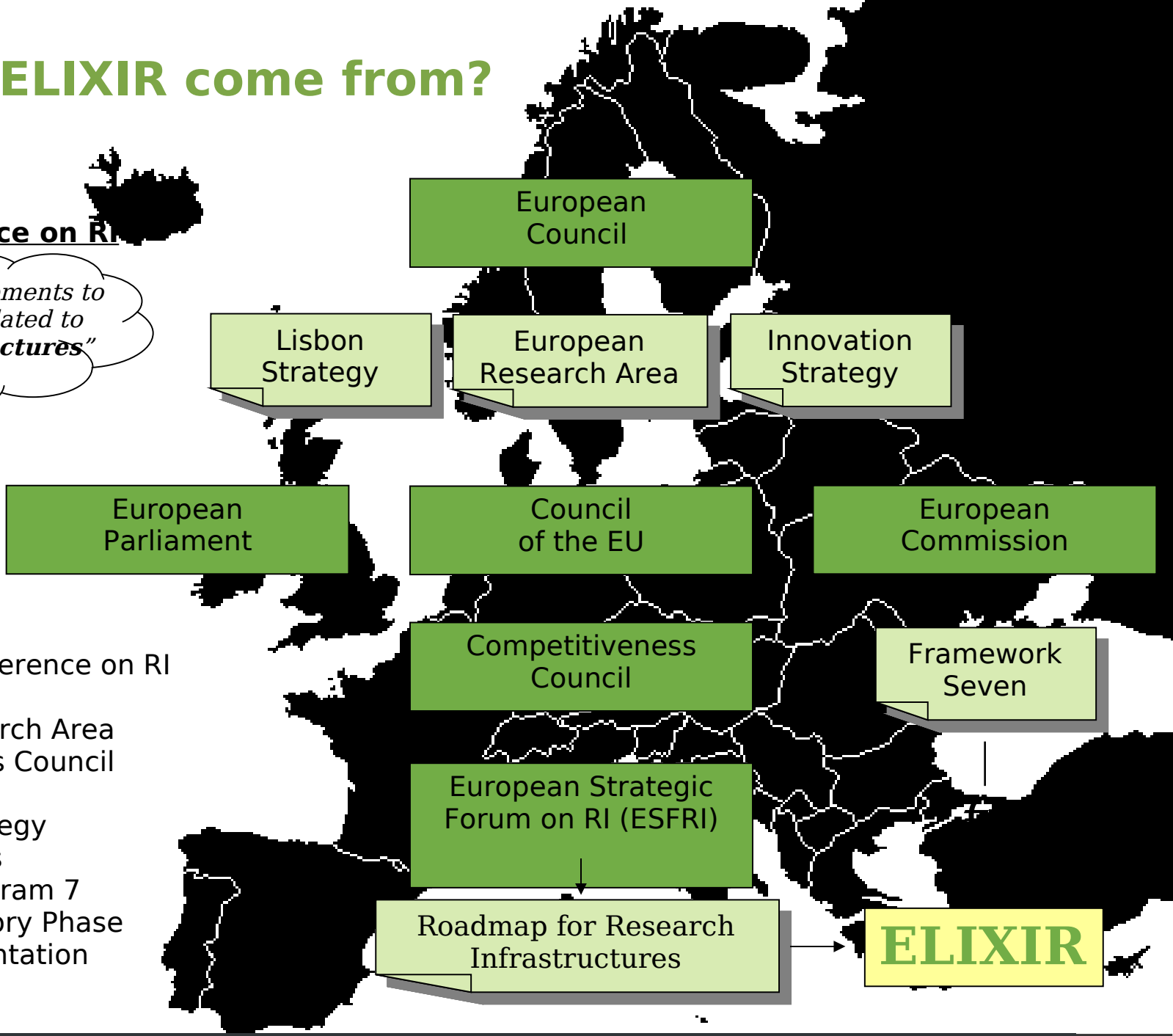
Where did ELIXIR come from?

Strasbourg Conference on RI

"...need new arrangements to support policies related to ***research infrastructures****"*

Timeline

- 2000 Strasbourg Conference on RI
- 2000 Lisbon strategy
- 2000 European Research Area
- 2002 Competitiveness Council
- 2002 ESFRI
- 2006 Innovation Strategy
- 2006 Roadmap for RIs
- 2007 Framework Program 7
- 2008 ELIXIR Preparatory Phase
- 2011 ELIXIR Implementation



What might ELIXIR be?

- A reliable ***distributed*** infrastructure to provide equality of access to biological information across all of Europe
- Sustainable funding for the ***core*** European biological data collections (genomes, sequences, structures, pathways etc)
- Sustainable funding the European components of the international biological data collaborations (INSDC, UNIPROT, ww-PDB etc)
- Processes for
  - developing ***new*** core data collections
  - supporting ***interoperability*** of bioinformatics tools
  - developing bioinformatics ***standards*** and ***ontologies***
- ***Enhanced*** use of biological information in Academic Research, the Pharmaceutical Industry, Biotechnology, Agriculture and for the Protection of the Environment