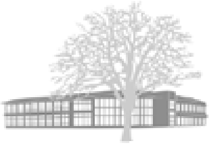
MIRIAM and Biomodels DB: Curation and Exchange of Quantitative Models

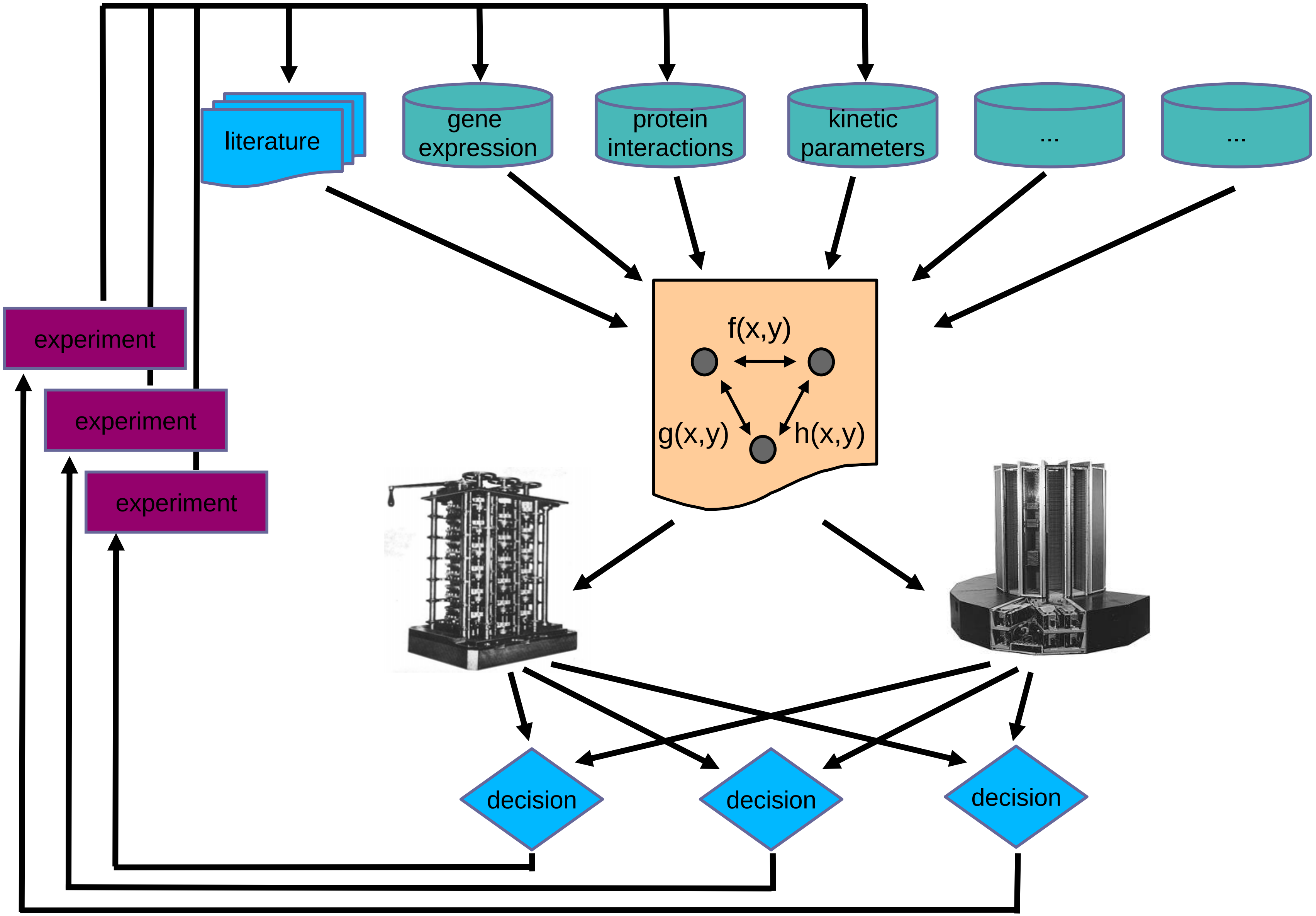
Nicolas Le Novère, EMBL-EBI, United-Kingdom

The Seventh International Conference on Systems Biology

October 9-13 2006, Yokohama, Japan



The model as an integrator of knowledge



literature

gene expression

protein interactions

kinetic parameters

...

...

f(x,y)

g(x,y)

h(x,y)

experiment

experiment

experiment

decision

decision

decision

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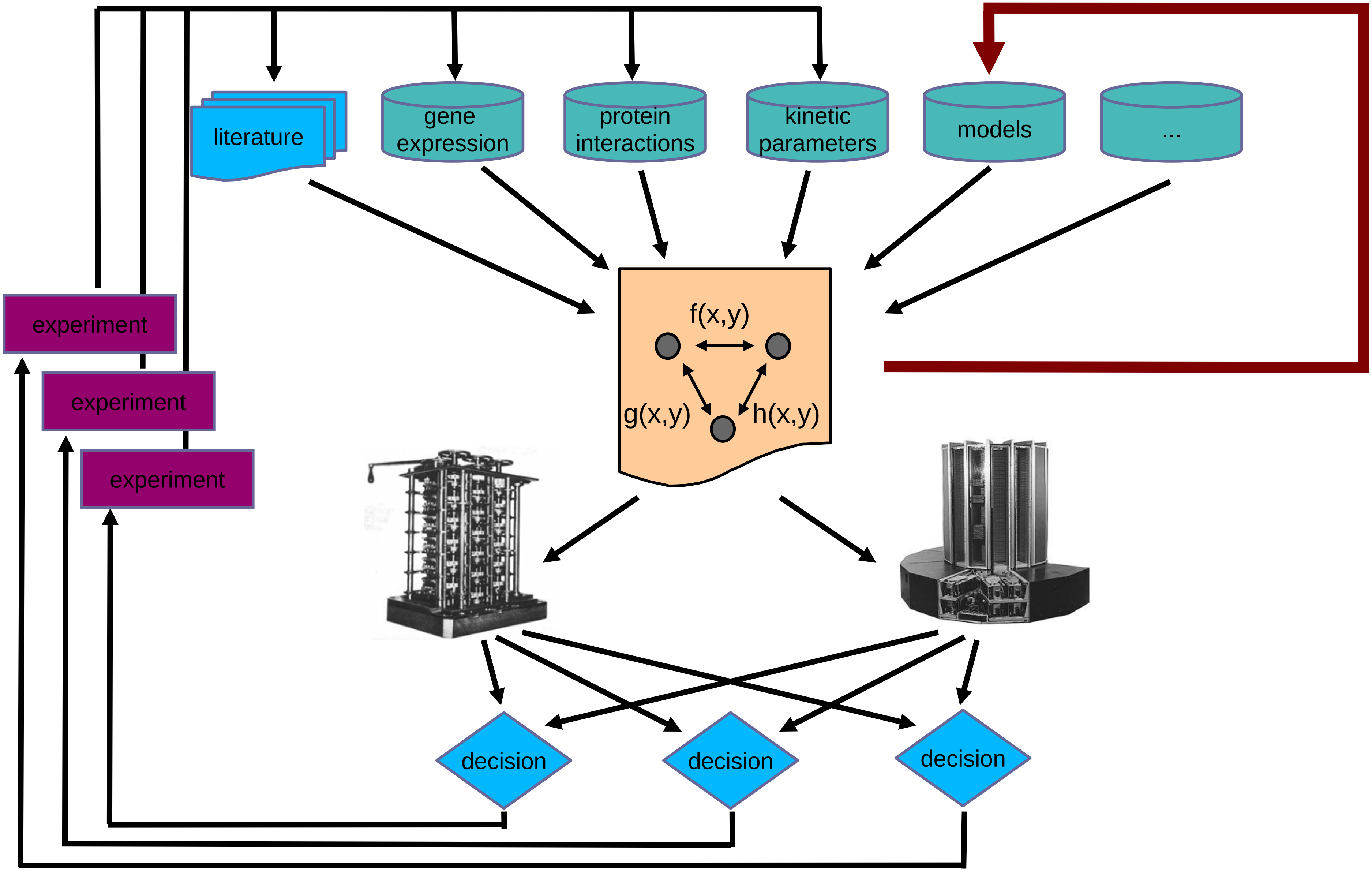

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Requirements for a successful exchange

- We need to encode the models in a computer-edible way
  - Structured formats → easily “parsable”; mirror the model structure;
  - Public formats → Published specifications, freely re-usable
  - Community-developed formats ...

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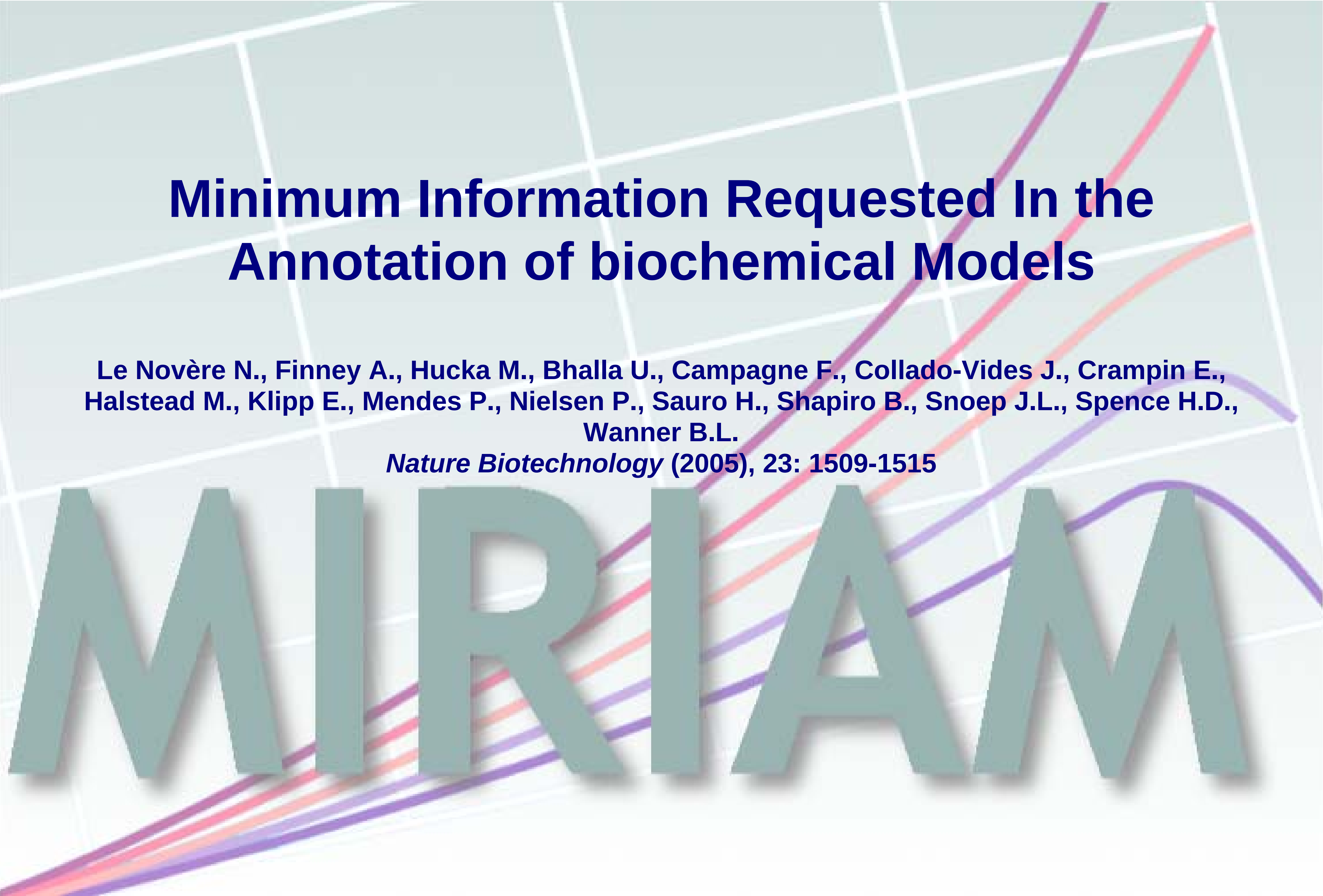
  - Public formats ⇒ Published specifications, freely re-usable
  - Community-developed formats ...
- We need to make the content human-edible ⇒ semantics
  - You want other people to appreciate your work!
  - Standards of content and annotation
  - Ontologies to relate model components and biological information

Minimum Information Requested In the Annotation of biochemical Models

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

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



Reference correspondence

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

Attribution annotation

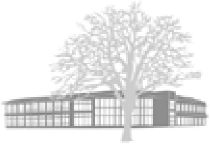
- The model has to be named.
- A citation of the reference description must be joined (complete citation, unique identifier, unambigous URL). The citation should permit to identify the *authors* of the model.
- The name and contact of model *creators* must be joined.
- The date and time of creation and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

External resource annotation

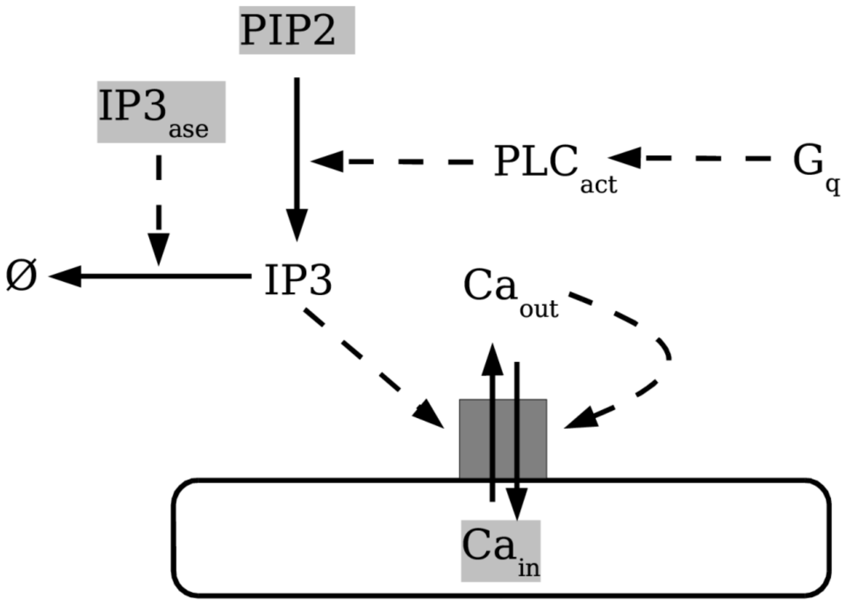
- The annotation must permit to unambiguously relate a piece of knowledge to a model constituent.

- The referenced information should be described using a triplet {data-type, identifier, qualifier}
  - The data-type should be written as a Unique Resource Identifier (URI)
  - The identifier is analysed within the framework of the data-type.
  - Data-type and Identifier can be combined in a single URI
    http://www.myResource.org/#myIdentifier
    urn:lsid:myResource.org:myIdentifier
  - Qualifiers (optional) should refine the link between the model constitutent and the piece of knowledge: “has a”, “is version of”, “is homolog to” etc.

- The community has to agree on a set of standard valid URIs. A database and the associated API (WebServices) have been developed at the EBI to provide the generation and interpretation of URIs.



Model example



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

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

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

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

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

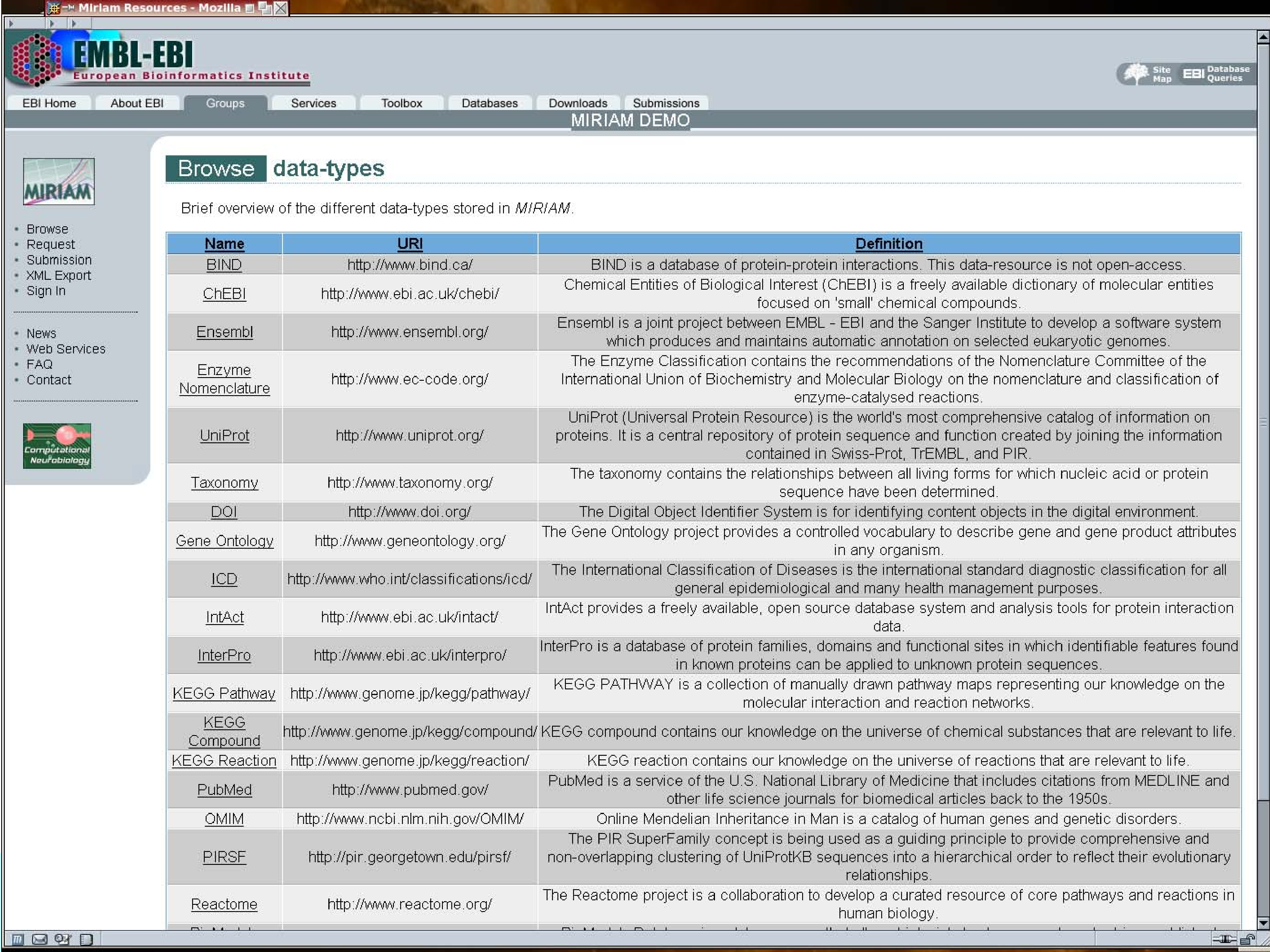
$$\frac{d[Ca_{out}]}{dt} = \frac{k_1[IP3R] * ([Ca_{in}] - [Ca_{out}])}{Km_1 + |[Ca_{in}] - [Ca_{out}]|} * \frac{[IP3]^m}{K_A + [IP3]^m}$$

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

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

---

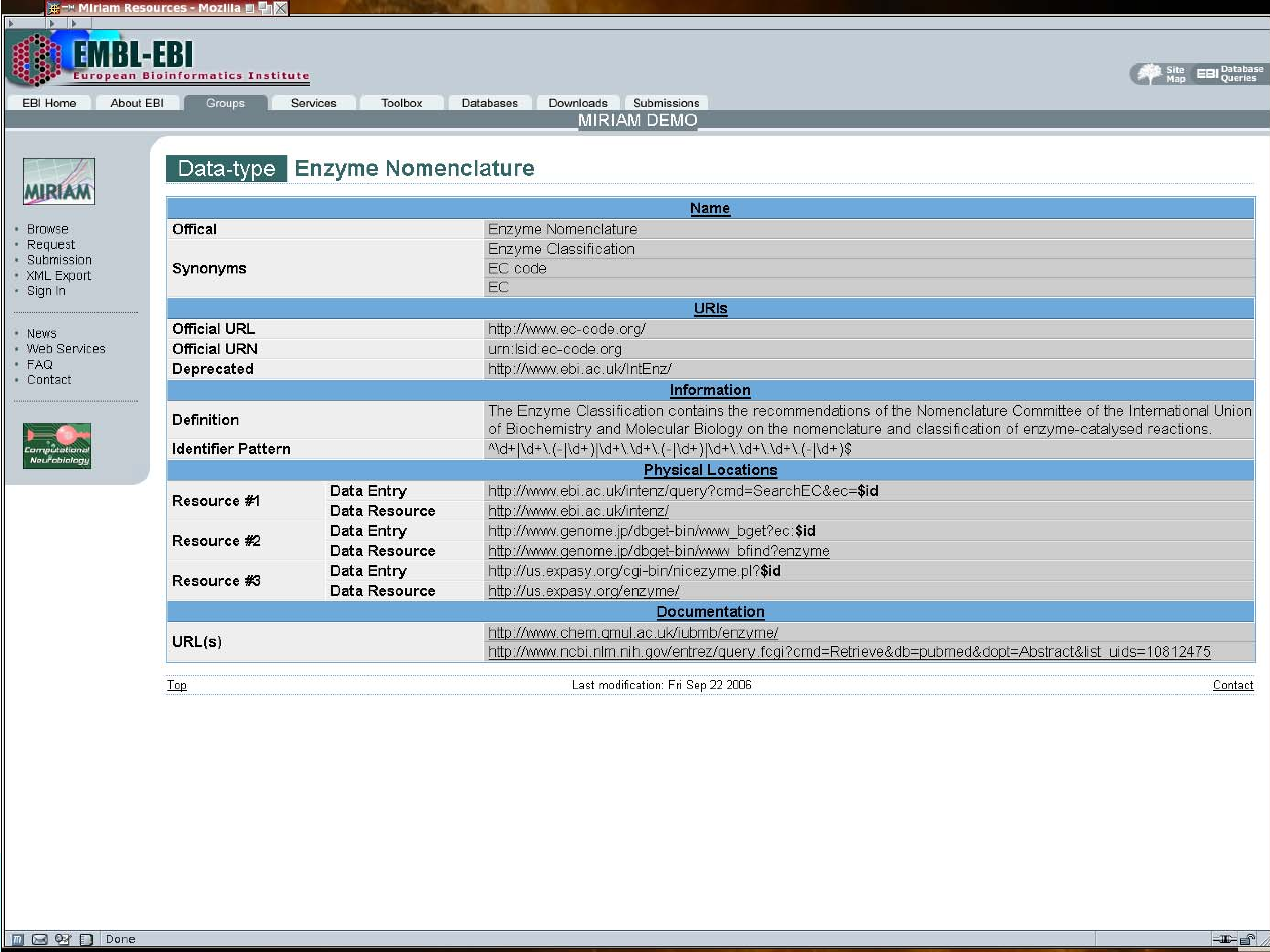
creators	Joe User (juser@eden.com), Anne Other (aother@eden.com)			
creation date	01 January 0000			
last modification	31 May 2005			
Constituent	**Data Type**	**Identifier**	**Qualifier**	**Meaning**
model	http://www.pubmed.gov/	0000000		
	http://www.taxonomy.org/	9606		*Homo sapiens*
	http://www.geneontology.org/	GO:0007204	IsVersionOf	*positive regulation of cytosolic ca2+ concentration*
	http://www.geneontology.org/	GO:0051279	IsVersionOf	*regulation of release of sequestered ca2+ into cytop*
	http://www.genome.jp/kegg/pathway	hsa04020	IsPartOf	*Calcium signaling pathway—H sapiens*
	http://www.genome.jp/kegg/pathway	hsa04070	IsPartOf	*Phosphatidylinositol signaling system—H sapiens*
compartment ER	http://www.geneontology.org/	GO:0005790		*smooth endoplasmic reticulum*
reactant Ca_{in}	http://www.ebi.ac.uk/chebi/	CHEBI:29108		*calcium(2+)*
compartment cytoplasm	http://www.geneontology.org/	GO:0005737		*cytoplasm*
reactant Ca_{out}	http://www.ebi.ac.uk/chebi/	CHEBI:29108		*calcium(2+)*
reactant IP3	http://www.ebi.ac.uk/chebi/	CHEBI:16595		*1D-myo-inositol 1,4,5-tris(dihydrogen phosphate)*
reactant PIP2	http://www.ebi.ac.uk/chebi/	CHEBI:18348		*1-phosphatidyl-1D-myo-inositol 4,5-bisphosphate*
reactant IP3R	http://www.uniprot.org/	Q14643	HasVersion	*Inositol 1,4,5-trisphosphate receptor type 1*
	http://www.uniprot.org/	Q14571	HasVersion	*Inositol 1,4,5-trisphosphate receptor type 2*
	http://www.uniprot.org/	Q14573	HasVersion	*Inositol 1,4,5-trisphosphate receptor type 3*
reactant PLC_{act}	http://www.uniprot.org/	Q9NQ66	IsVersionOf	*PIP2 phosphodiesterase* $\beta 1$
reactant PLC_{tot}	http://www.uniprot.org/	Q9NQ66		*PIP2 phosphodiesterase* $\beta 1$
reactant $\mathrm{IP3}_{ase}$	http://www.uniprot.org/	Q14642		*Type I inositol-1,4,5-trisphosphate 5-phosphatase*
reactant G_{q}	http://www.uniprot.org/	Q6NT27		*Guanine nucleotide binding protein Gq*
reaction $\mathrm{Ca}_{release}$	http://www.geneontology.org/	GO:0005220		*IP3-sensitive calcium-release channel activity*
	http://www.geneontology.org/	GO:0008095	IsVersionOf	*IP3 receptor activity*
reaction $\mathrm{IP3}_{production}$	http://www.geneontology.org/	GO:0004435	IsVersionOf	*phosphoinositide phospholipase C activity*
	http://www.ec-code.org/	3.1.4.11	IsVersionOf	*phosphoinositide phospholipase C*
reaction $\mathrm{IP3}_{degradation}$	http://www.ec-code.org/	3.1.3.56	IsVersionOf	*inositol-polyphosphate 5-phosphatase*
reaction $\mathrm{PLC}_{activation}$	http://www.geneontology.org/	GO:0007200		*G-protein signaling coupled to IP3 2nd messenger*



Browse data-types

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

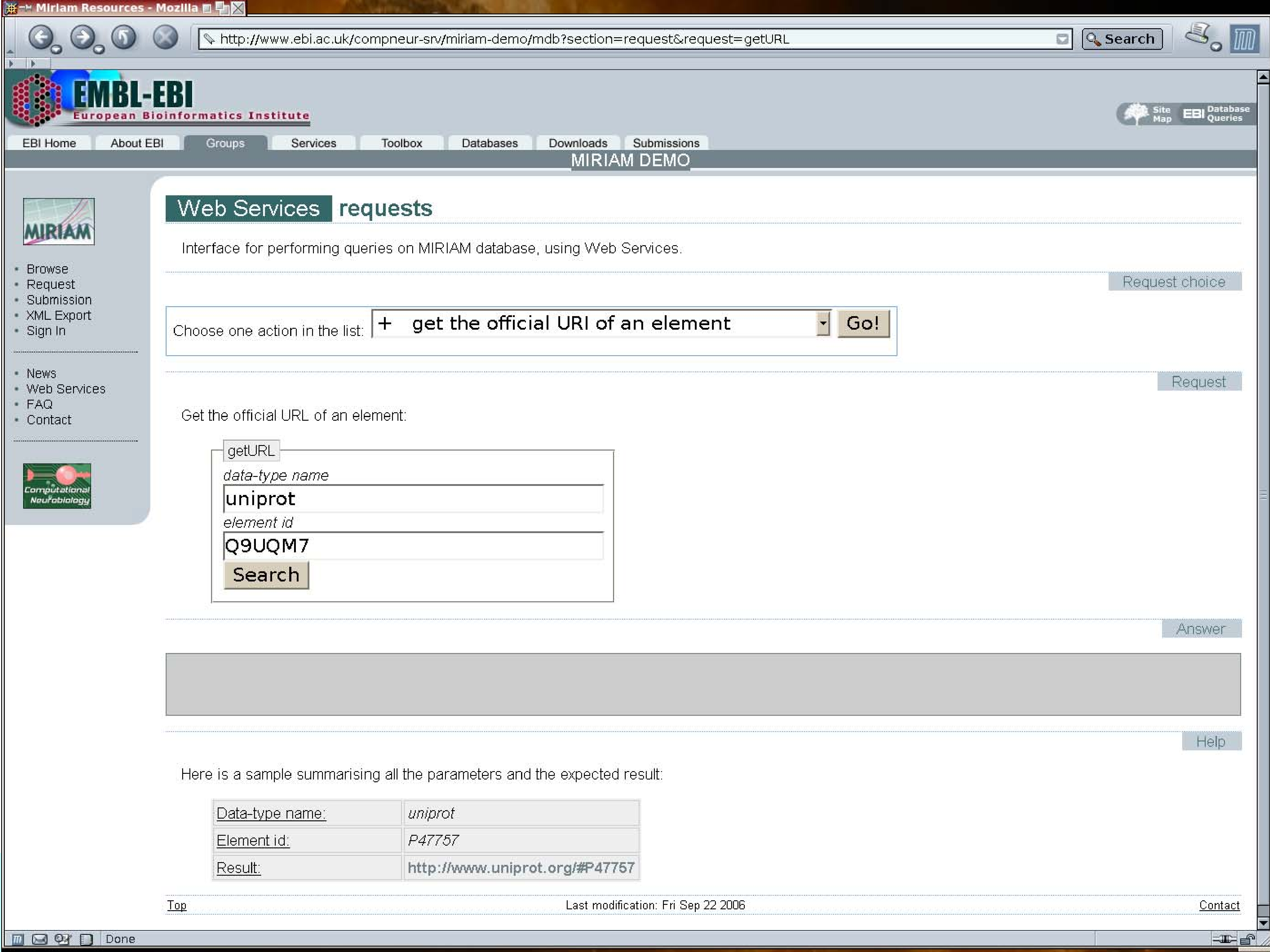
Name	URI	Definition
BIND	http://www.bind.ca/	BIND is a database of protein-protein interactions. This data-resource is not open-access.
ChEBI	http://www.ebi.ac.uk/chebi/	Chemical Entities of Biological Interest (ChEBI) is a freely available dictionary of molecular entities focused on 'small' chemical compounds.
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.
UniProt	http://www.uniprot.org/	UniProt (Universal Protein Resource) is the world's most comprehensive catalog of information on proteins. It is a central repository of protein sequence and function created by joining the information contained in Swiss-Prot, TrEMBL, and PIR.
Taxonomy	http://www.taxonomy.org/	The taxonomy contains the relationships between all living forms for which nucleic acid or protein sequence have been determined.
DOI	http://www.doi.org/	The Digital Object Identifier System is for identifying content objects in the digital environment.
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 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 Compound	http://www.genome.jp/kegg/compound/	KEGG compound contains our knowledge on the universe of chemical substances that are relevant to life.
KEGG Reaction	http://www.genome.jp/kegg/reaction/	KEGG reaction contains our knowledge on the universe of reactions that are relevant to life.
PubMed	http://www.pubmed.gov/	PubMed is a service of the U.S. National Library of Medicine that includes citations from MEDLINE and other life science journals for biomedical articles back to the 1950s.
OMIM	http://www.ncbi.nlm.nih.gov/OMIM/	Online Mendelian Inheritance in Man is a catalog of human genes and genetic disorders.
PIRSF	http://pir.georgetown.edu/pirsf/	The PIR SuperFamily concept is being used as a guiding principle to provide comprehensive and non-overlapping clustering of UniProtKB sequences into a hierarchical order to reflect their evolutionary relationships.
Reactome	http://www.reactome.org/	The Reactome project is a collaboration to develop a curated resource of core pathways and reactions in human biology.



Data-type Enzyme Nomenclature

Name		
Offical		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=**$id**
	Data Resource	http://www.ebi.ac.uk/intenz/
Resource #2	**Data Entry**	http://www.genome.jp/dbget-bin/www_bget?ec:**$id**
	Data Resource	http://www.genome.jp/dbget-bin/www_bfind?enzyme
Resource #3	**Data Entry**	http://us.expasy.org/cgi-bin/nicezyme.pl?**$id**
	Data Resource	http://us.expasy.org/enzyme/
Documentation		
URL(s)		http://www.chem.qmul.ac.uk/iubmb/enzyme/ http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10812475

Top Last modification: Fri Sep 22 2006 Contact



http://www.ebi.ac.uk/compneur-srv/miriam-demo/mdb?section=request&request=getURL

Web Services requests

Interface for performing queries on MIRIAM database, using Web Services.

Choose one action in the list: + get the official URI of an element

Get the official URL of an element:

getURL

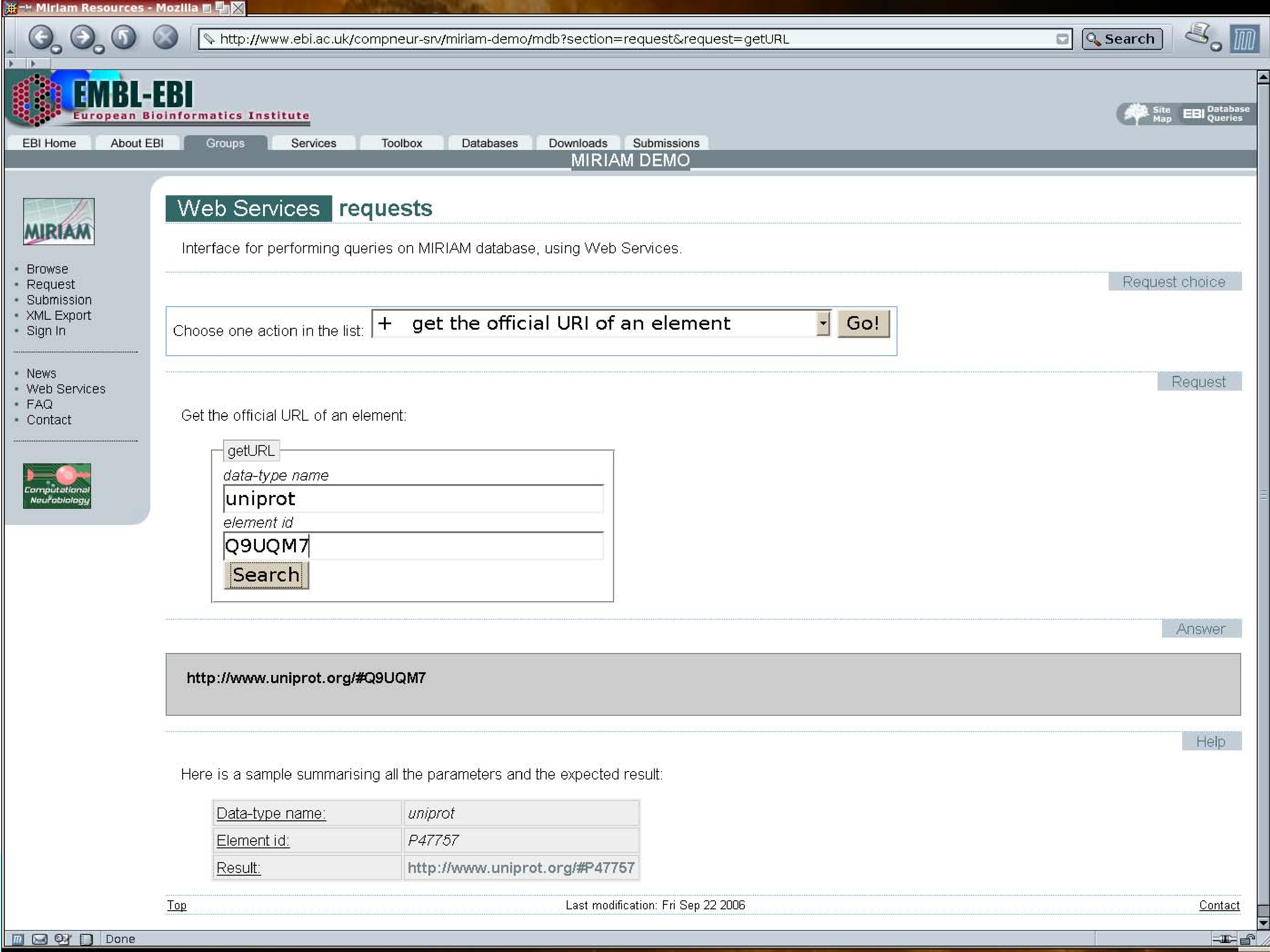
data-type name: uniprot

element id: Q9UQM7

Here is a sample summarising all the parameters and the expected result:

Data-type name:	*uniprot*
Element id:	*P47757*
Result:	**http://www.uniprot.org/#P47757**

Last modification: Fri Sep 22 2006



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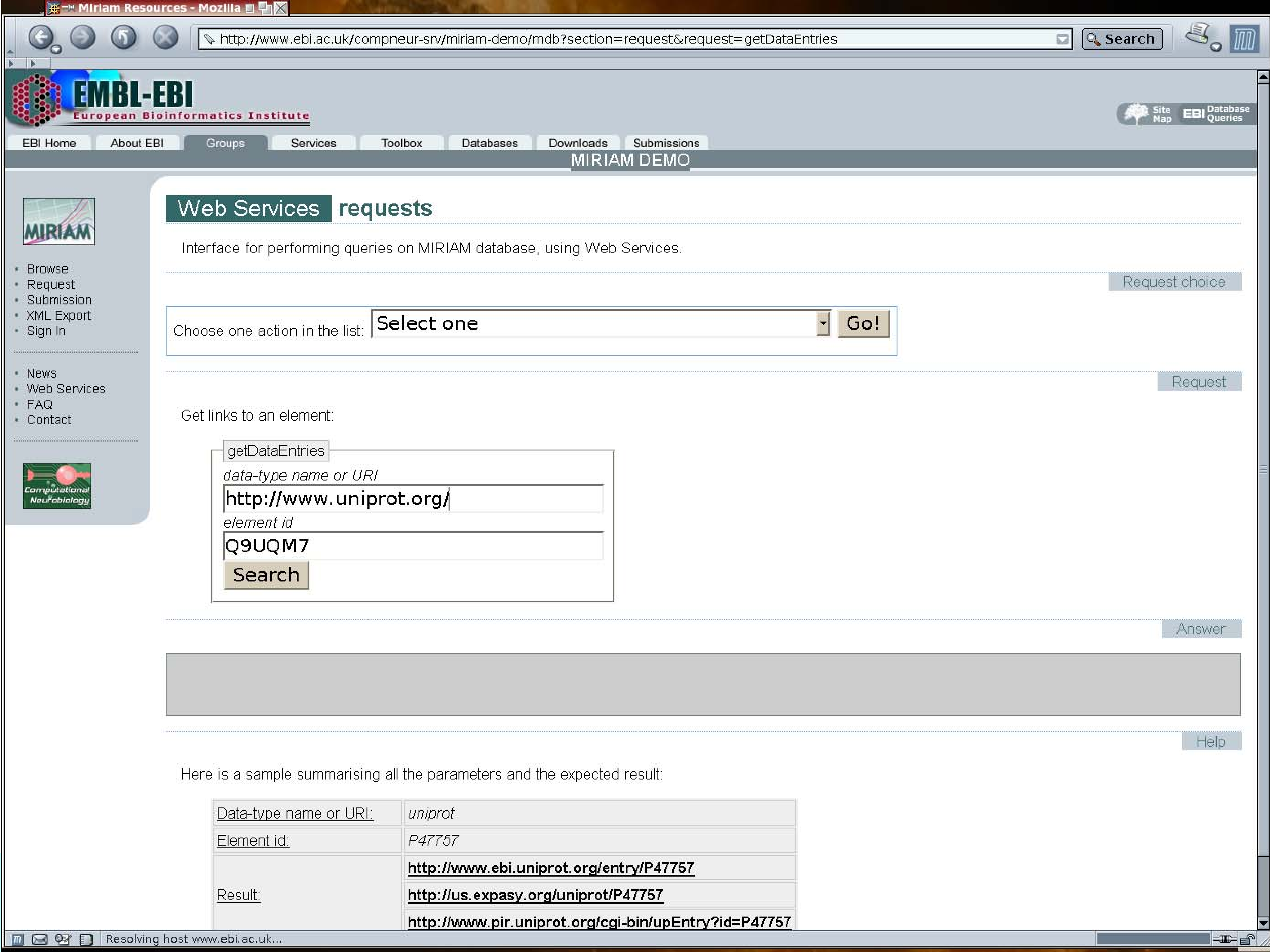


Web Services requests

Interface for performing queries on MIRIAM database, using Web Services.

Request choice

Choose one action in the list: Select one [Go!]

Request

Get links to an element:

getDataEntries

data-type name or URI

http://www.uniprot.org/

element id

Q9UQM7

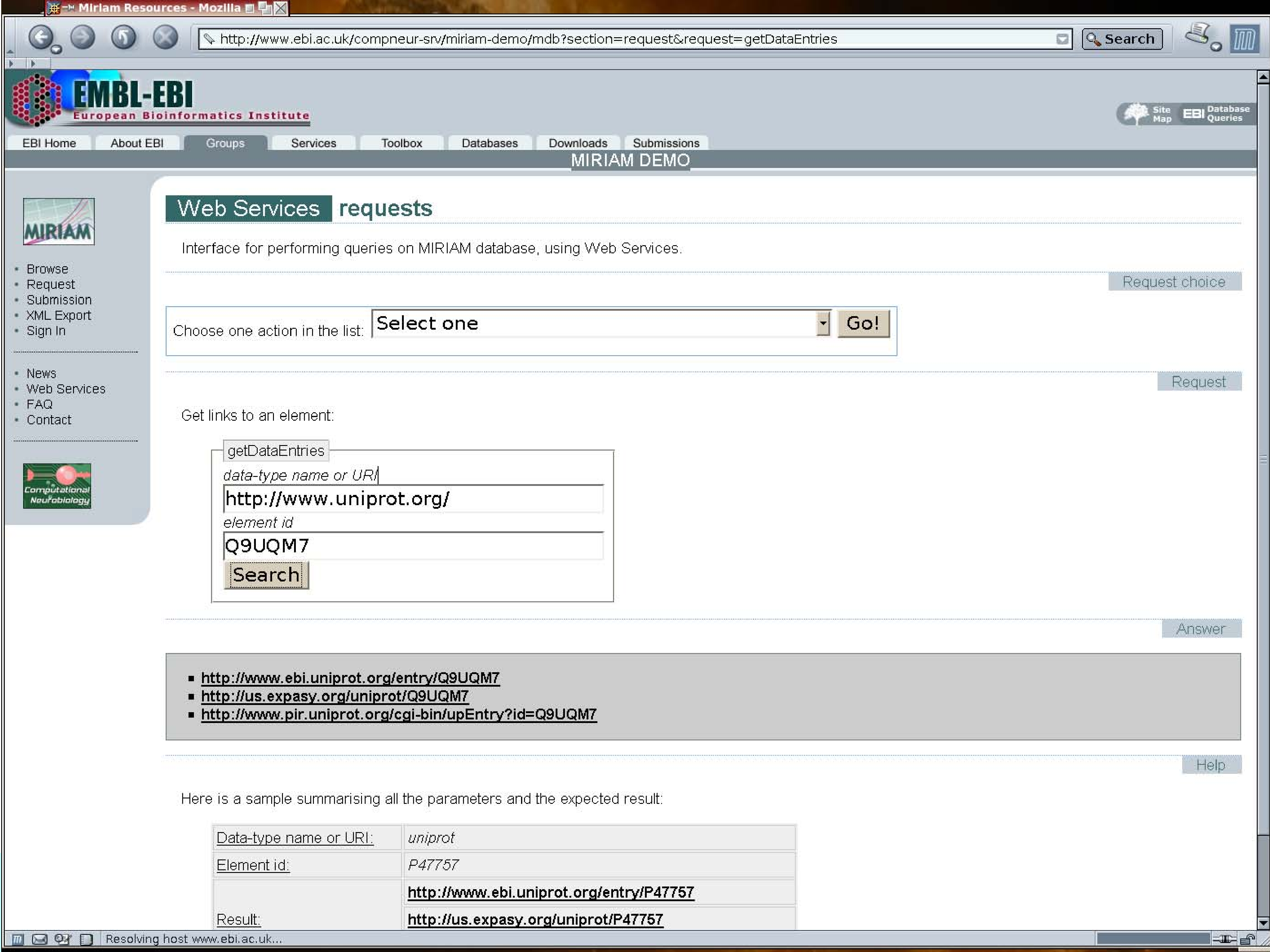
[Search]

Answer

Help

Here is a sample summarising all the parameters and the expected result:

Data-type name or URI:	*uniprot*
Element id:	*P47757*
Result:	**http://www.ebi.uniprot.org/entry/P47757** **http://us.expasy.org/uniprot/P47757** **http://www.pir.uniprot.org/cgi-bin/upEntry?id=P47757**



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data-type name or URI
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element id
Q9UQM7

- http://www.ebi.uniprot.org/entry/Q9UQM7
- http://us.expasy.org/uniprot/Q9UQM7
- http://www.pir.uniprot.org/cgi-bin/upEntry?id=Q9UQM7

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Data-type name or URI:	*uniprot*
Element id:	*P47757*
	http://www.ebi.uniprot.org/entry/P47757
Result:	http://us.expasy.org/uniprot/P47757

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  - You want other people to appreciate your work!
  - Standards of content and annotation
  - Ontologies to relate model components and biological information
- We need to make the models available
  - Personal websites
  - Publisher's websites
  - Curated repository/databases

Requirements for a unified model resource

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

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

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

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

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

What is BioModels Database?

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

Where are the models coming from

I) Existing model repositories

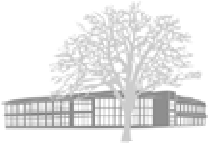
- SBML repository
- JWS Online
- E-Cell Developer Network
- CellML repository

II) Individuals

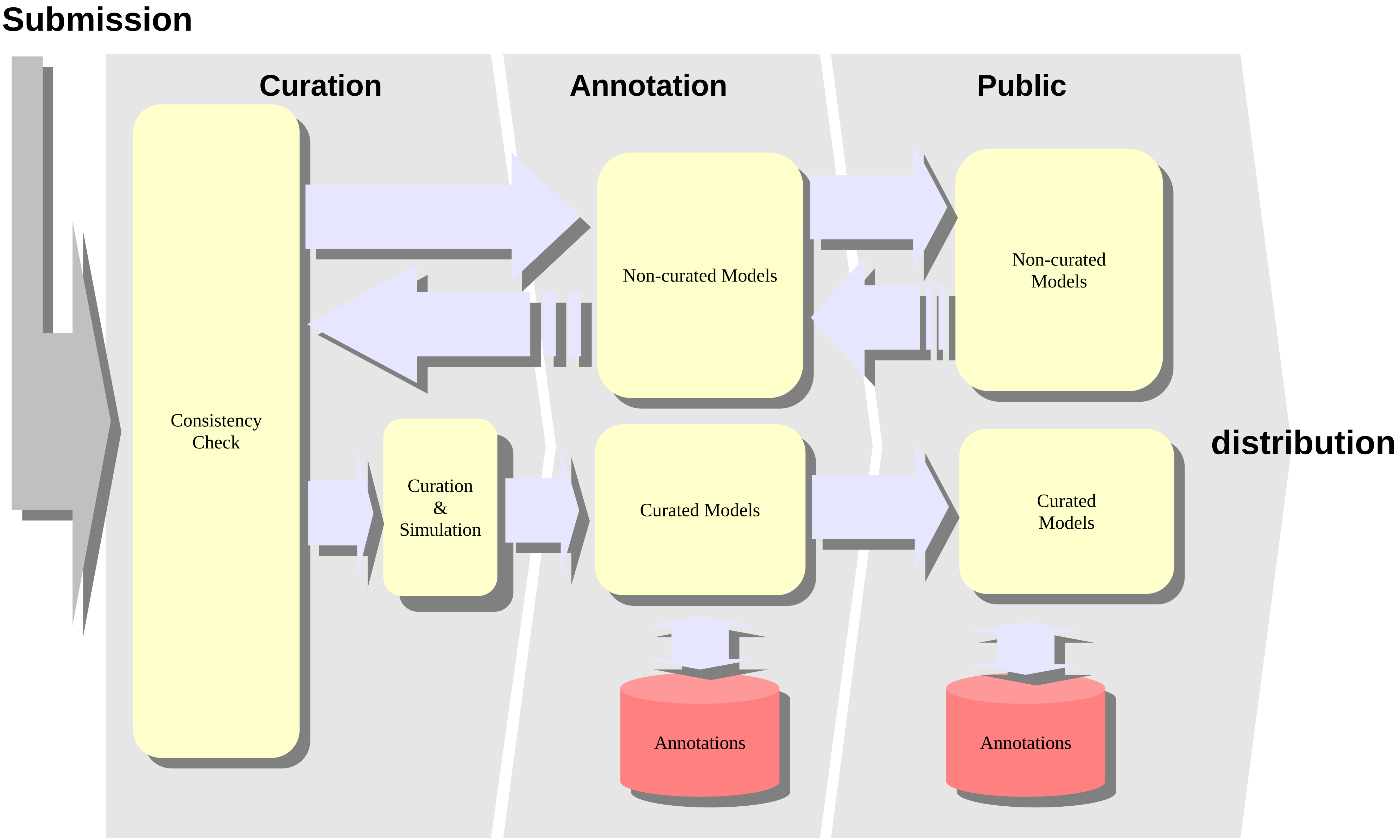
- Members of the SBML community (developers+modellers)
- Authors (prior to grant application, before publication etc.)

III) Journals (Molecular Systems Biology and PloS Computational Biology advise deposition)

IV) BioModels DB curators encode new models from literature



Structure of BioModels Database


Submission

Curation

Annotation

Public

Consistency Check

Curation & Simulation

Non-curated Models

Curated Models

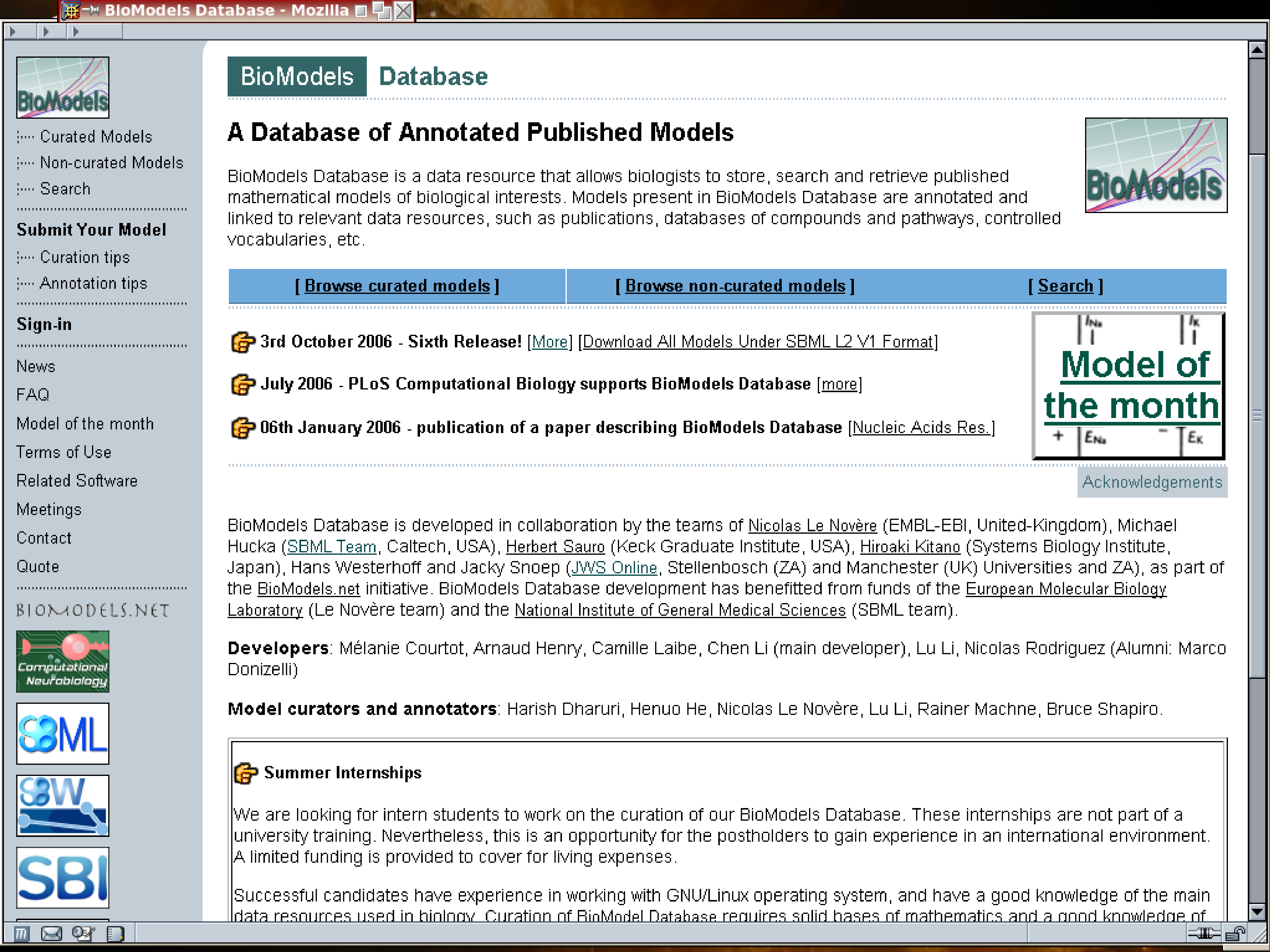
Annotations

Non-curated Models

Curated Models

Annotations

distribution



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.

3rd October 2006 - Sixth Release! [More] [Download All Models Under SBML L2 V1 Format]

July 2006 - PLoS Computational Biology supports BioModels Database [more]

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

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

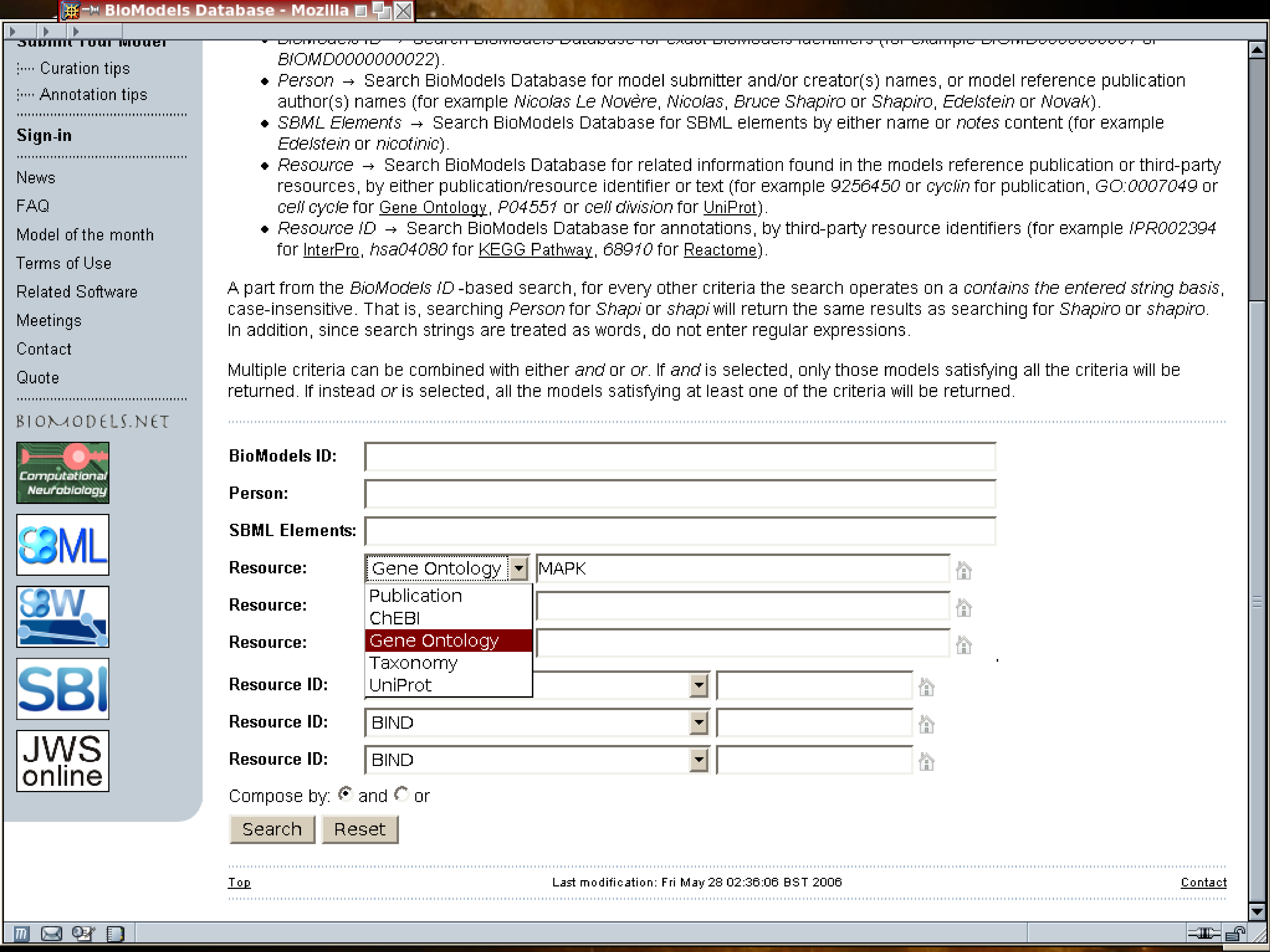
Developers: Mélanie Courtot, Arnaud Henry, Camille Laibe, Chen Li (main developer), Lu Li, Nicolas Rodriguez (Alumni: Marco Donizelli)

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

Summer Internships

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

Successful candidates have experience in working with GNU/Linux operating system, and have a good knowledge of the main data resources used in biology. Curation of BioModel Database requires solid bases of mathematics and a good knowledge of



- BioModels ID → Search BioModels Database for exact BioModels identifiers (for example BIOMD0000000007 or BIOMD0000000022).
- *Person* → Search BioModels Database for model submitter and/or creator(s) names, or model reference publication author(s) names (for example *Nicolas Le Novère*, *Nicolas*, *Bruce Shapiro* or *Shapiro*, *Edelstein* or *Novak*).
- *SBML Elements* → Search BioModels Database for SBML elements by either name or *notes* content (for example *Edelstein* or *nicotinic*).
- *Resource* → Search BioModels Database for related information found in the models reference publication or third-party resources, by either publication/resource identifier or text (for example *9256450* or *cyclin* for publication, *GO:0007049* or *cell cycle* for Gene Ontology, *P04551* or *cell division* for UniProt).
- *Resource ID* → Search BioModels Database for annotations, by third-party resource identifiers (for example *IPR002394* for InterPro, *hsa04080* for KEGG Pathway, *68910* for Reactome).

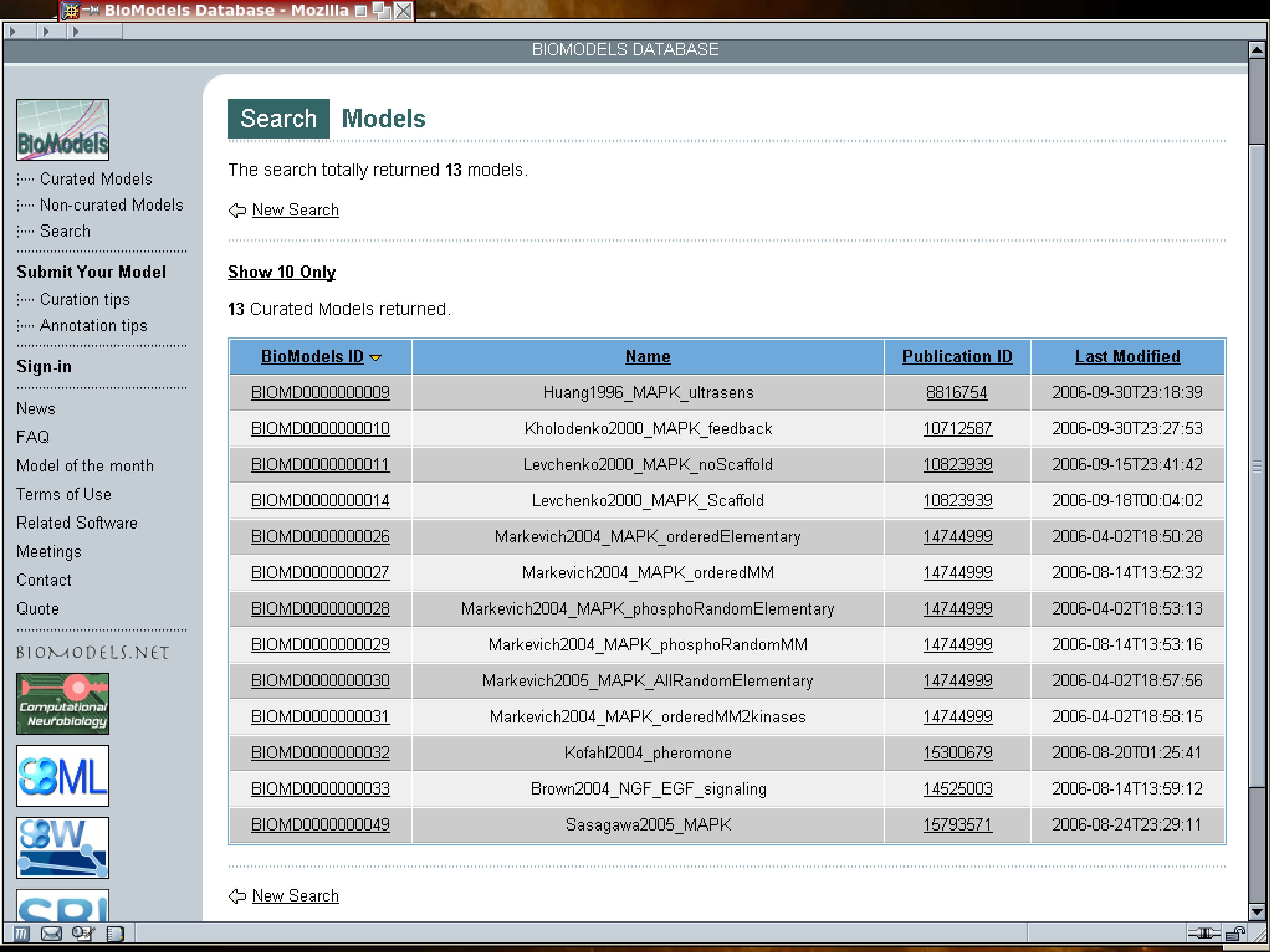
A part from the *BioModels ID* -based search, for every other criteria the search operates on a *contains the entered string basis*, case-insensitive. That is, searching *Person* for *Shapi* or *shapi* will return the same results as searching for *Shapiro* or *shapiro*. In addition, since search strings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

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

BioModels ID:		
Person:		
SBML Elements:		
Resource:	Gene Ontology	MAPK
Resource:		
Resource:		
Resource ID:		
Resource ID:	BIND	
Resource ID:	BIND	

Compose by: ● and ○ or

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



Search Models

The search totally returned **13** models.

New Search

Show 10 Only

13 Curated Models returned.

BioModels ID	Name	Publication ID	Last Modified
BIOMD0000000009	Huang1996_MAPK_ultrasens	8816754	2006-09-30T23:18:39
BIOMD0000000010	Kholodenko2000_MAPK_feedback	10712587	2006-09-30T23:27:53
BIOMD0000000011	Levchenko2000_MAPK_noScaffold	10823939	2006-09-15T23:41:42
BIOMD0000000014	Levchenko2000_MAPK_Scaffold	10823939	2006-09-18T00:04:02
BIOMD0000000026	Markevich2004_MAPK_orderedElementary	14744999	2006-04-02T18:50:28
BIOMD0000000027	Markevich2004_MAPK_orderedMM	14744999	2006-08-14T13:52:32
BIOMD0000000028	Markevich2004_MAPK_phosphoRandomElementary	14744999	2006-04-02T18:53:13
BIOMD0000000029	Markevich2004_MAPK_phosphoRandomMM	14744999	2006-08-14T13:53:16
BIOMD0000000030	Markevich2005_MAPK_AllRandomElementary	14744999	2006-04-02T18:57:56
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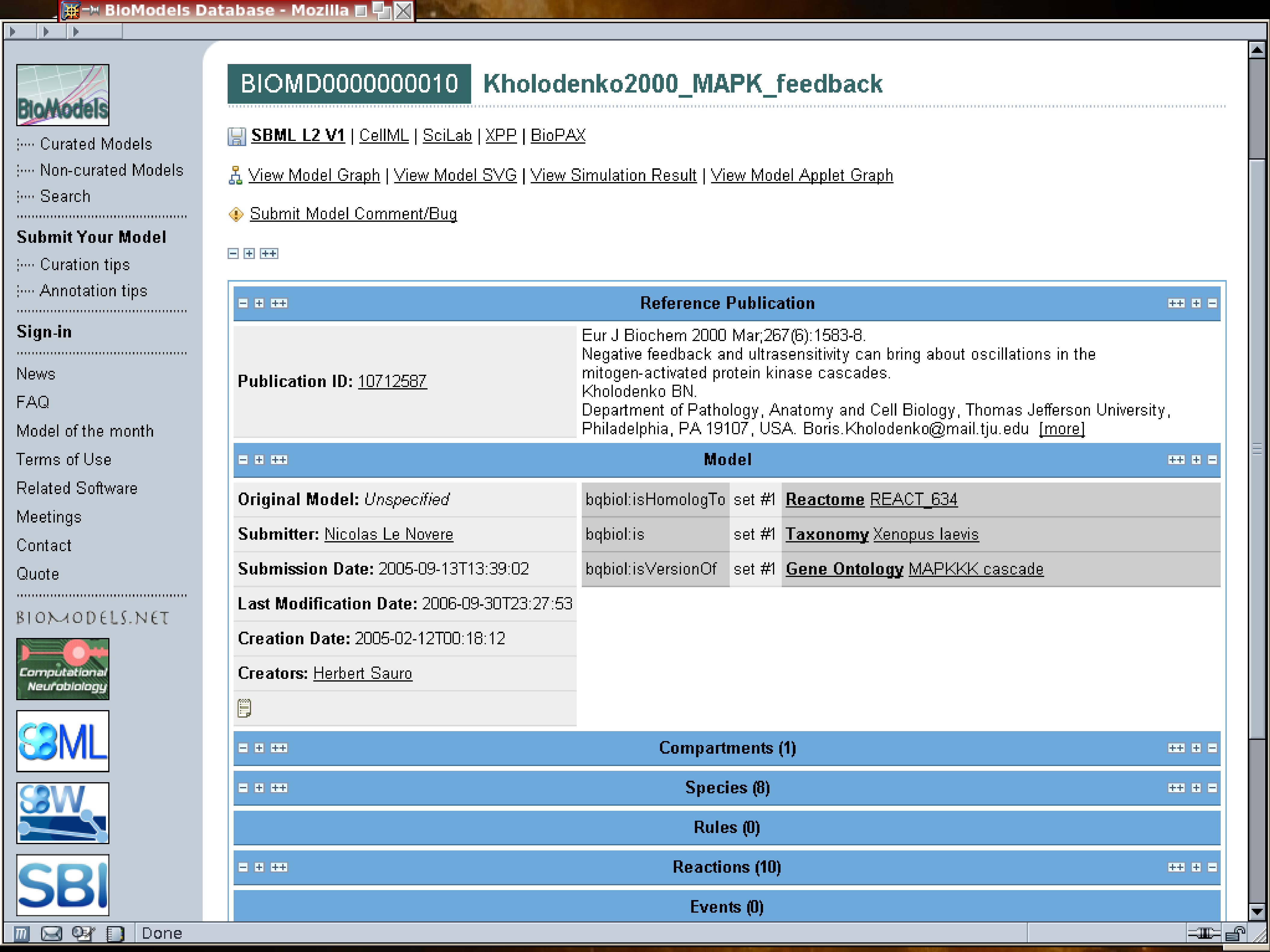
BIOMD0000000032	Kofahl2004_pheromone	15300679	2006-08-20T01:25:41
BIOMD0000000033	Brown2004_NGF_EGF_signaling	14525003	2006-08-14T13:59:12
BIOMD0000000049	Sasagawa2005_MAPK	15793571	2006-08-24T23:29:11

New Search



BIOMD0000000010 Kholodenko2000_MAPK_feedback

SBML L2 V1 | CellML | SciLab | XPP | BioPAX

View Model Graph | View Model SVG | View Simulation Result | View Model Applet Graph

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*	bqbiol:isHomologTo	set #1	**Reactome** REACT_634
Submitter: Nicolas Le Novere	bqbiol:is	set #1	**Taxonomy** Xenopus laevis
Submission Date: 2005-09-13T13:39:02	bqbiol:isVersionOf	set #1	**Gene Ontology** MAPKKK cascade
Last Modification Date: 2006-09-30T23:27:53			
Creation Date: 2005-02-12T00:18:12			
Creators: Herbert Sauro			

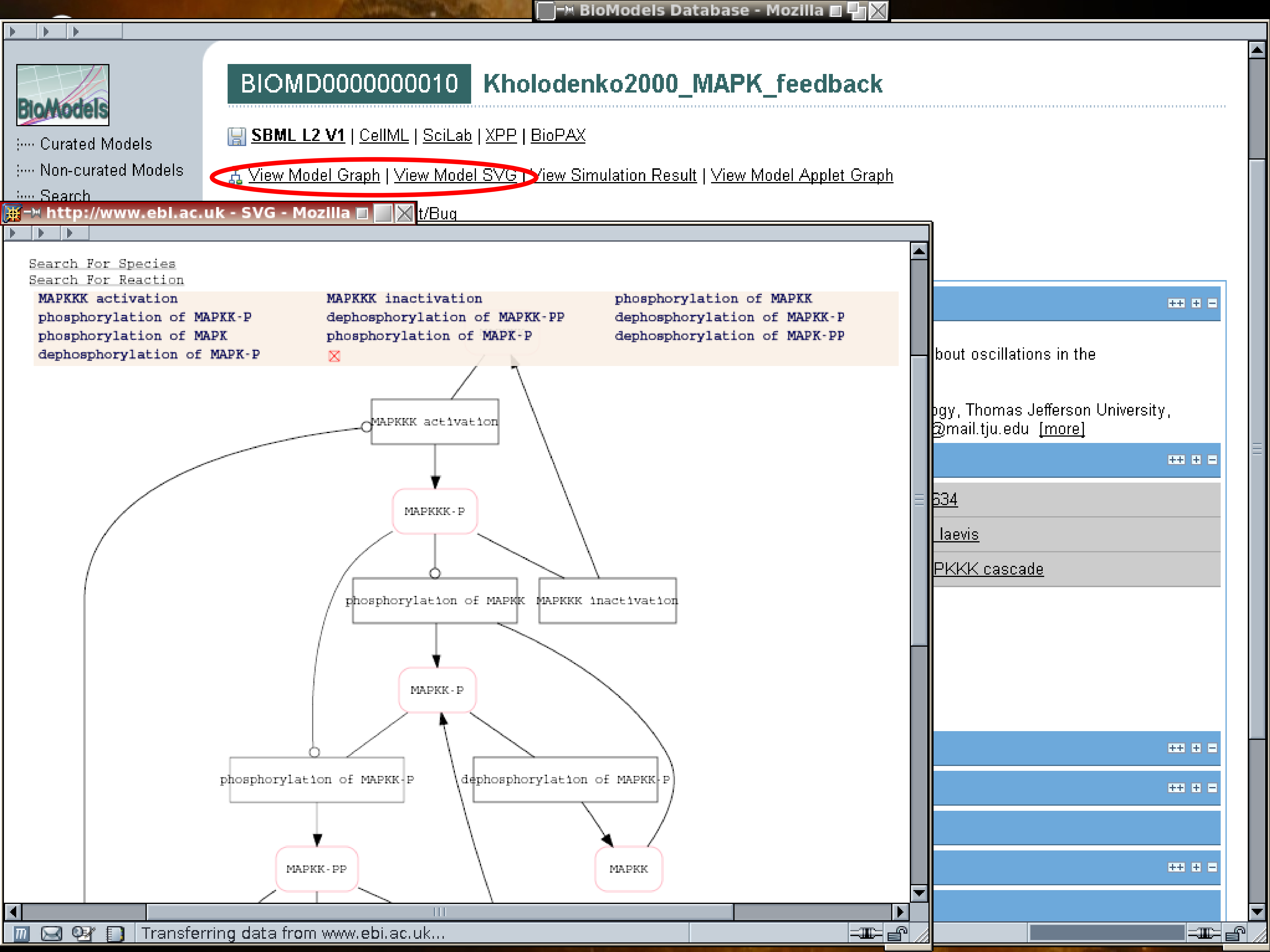
Compartments (1)

Species (8)

Rules (0)

Reactions (10)

Events (0)



BIOMD0000000010 Kholodenko2000_MAPK_feedback

SBML L2 V1 | CellML | SciLab | XPP | BioPAX

View Model Graph | View Model SVG | View Simulation Result | View Model Applet Graph

Search For Species
Search For Reaction

MAPKKK activation	MAPKKK inactivation	phosphorylation of MAPKK
phosphorylation of MAPKK-P	dephosphorylation of MAPKK-PP	dephosphorylation of MAPKK-P
phosphorylation of MAPK	phosphorylation of MAPK-P	dephosphorylation of MAPK-PP
dephosphorylation of MAPK-P		

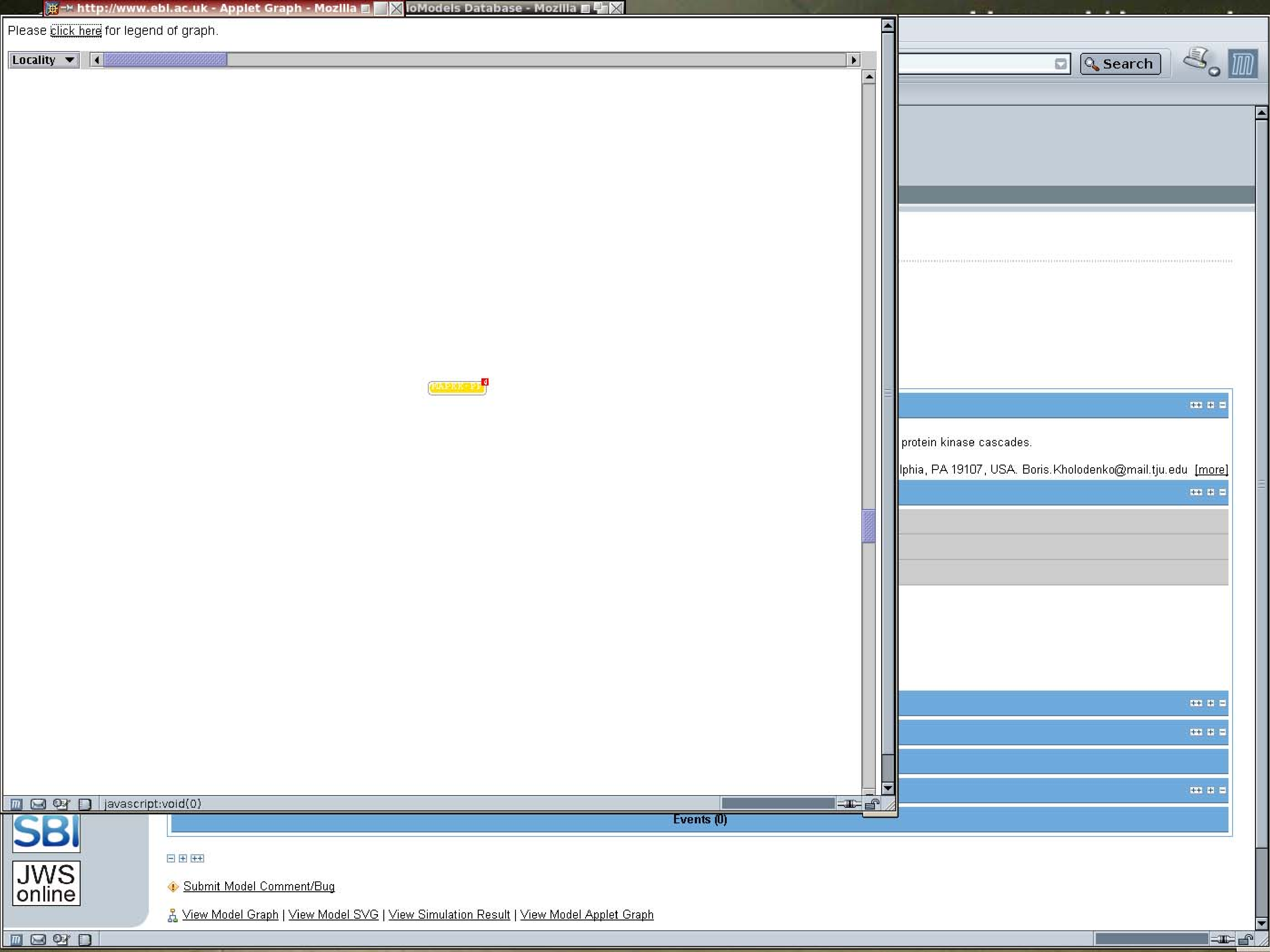
bout oscillations in the

gy, Thomas Jefferson University,
@mail.tju.edu [more]

634

laevis

PKKK cascade



Please click here for legend of graph.

protein kinase cascades.

lphia, PA 19107, USA. Boris.Kholodenko@mail.tju.edu [more]

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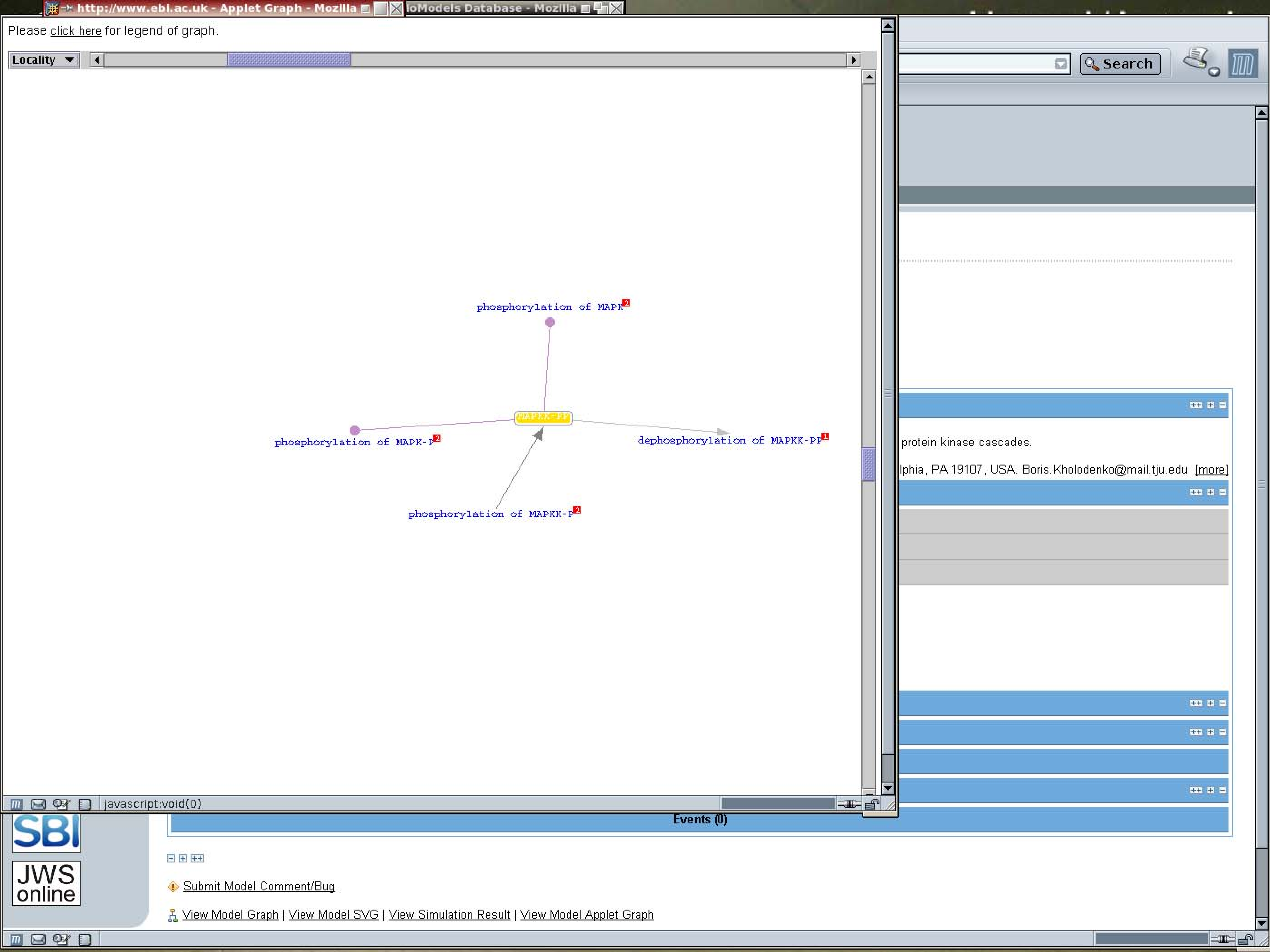

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protein kinase cascades.

lphia, PA 19107, USA. Boris.Kholodenko@mail.tju.edu [more]

Events (0)

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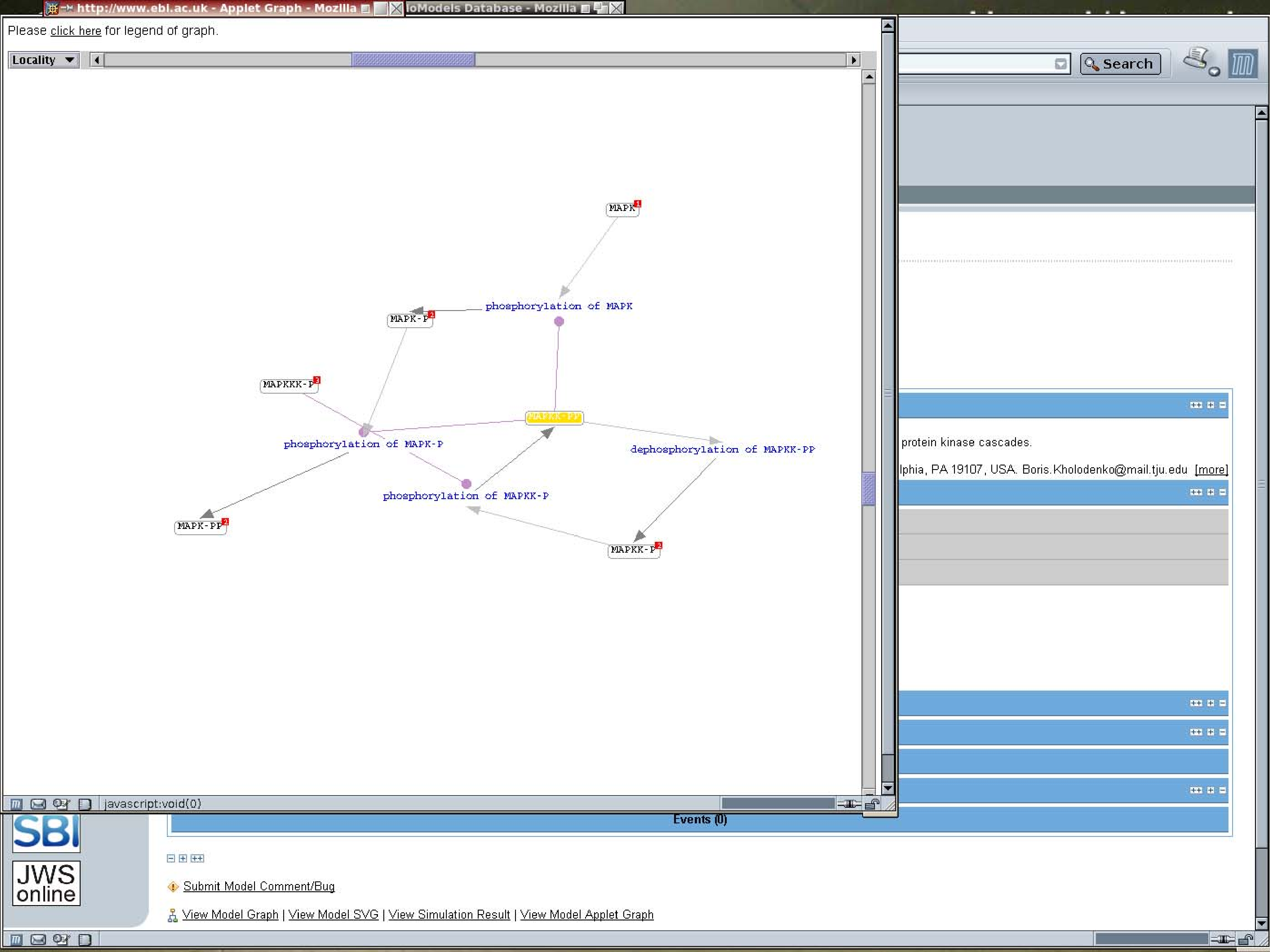

Please click here for legend of graph.

javascript:void(0)

protein kinase cascades.

lphia, PA 19107, USA. Boris.Kholodenko@mail.tju.edu [more]

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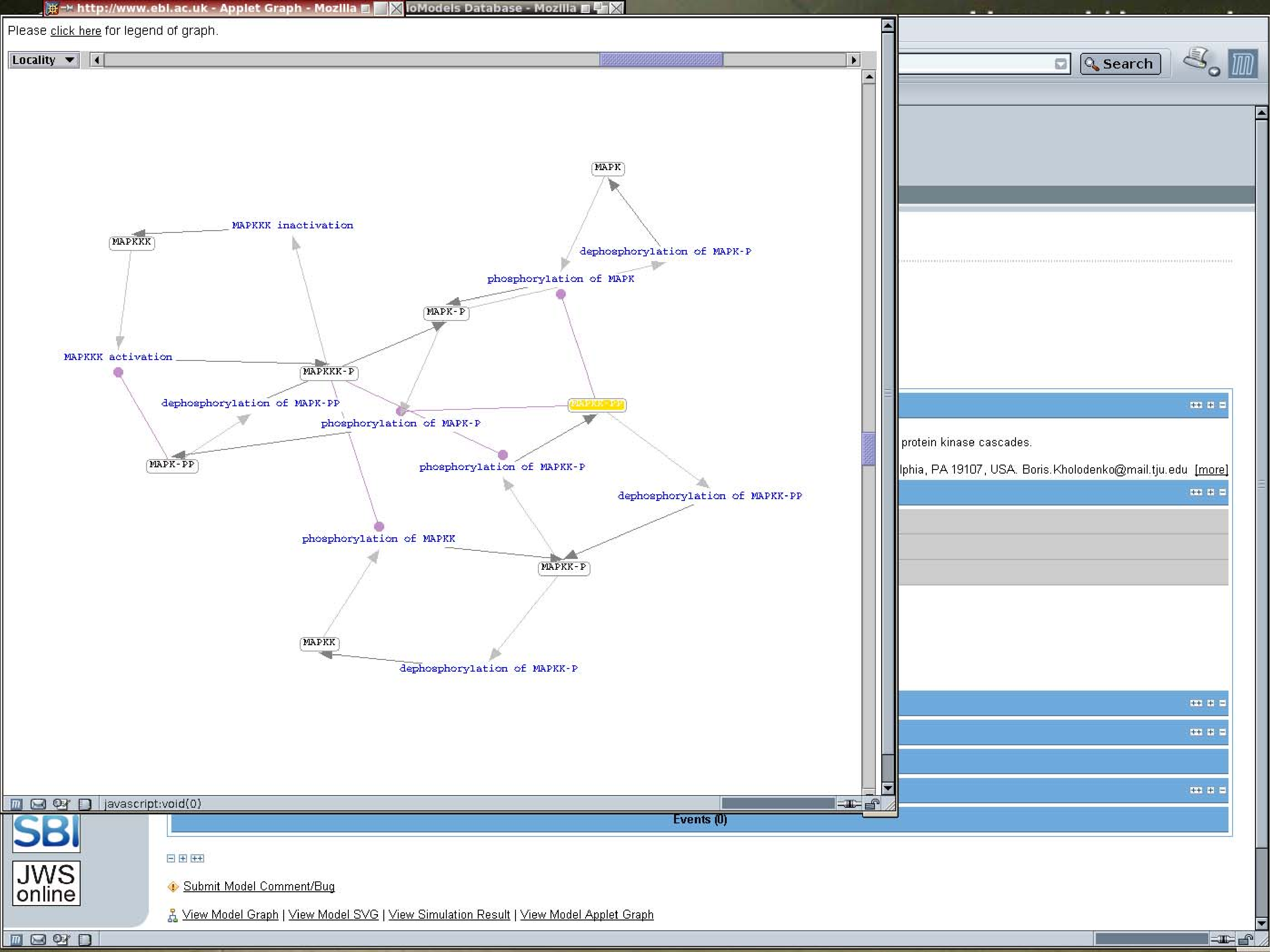

Please click here for legend of graph.

protein kinase cascades.

lphia, PA 19107, USA. Boris.Kholodenko@mail.tju.edu [more]

Events (0)

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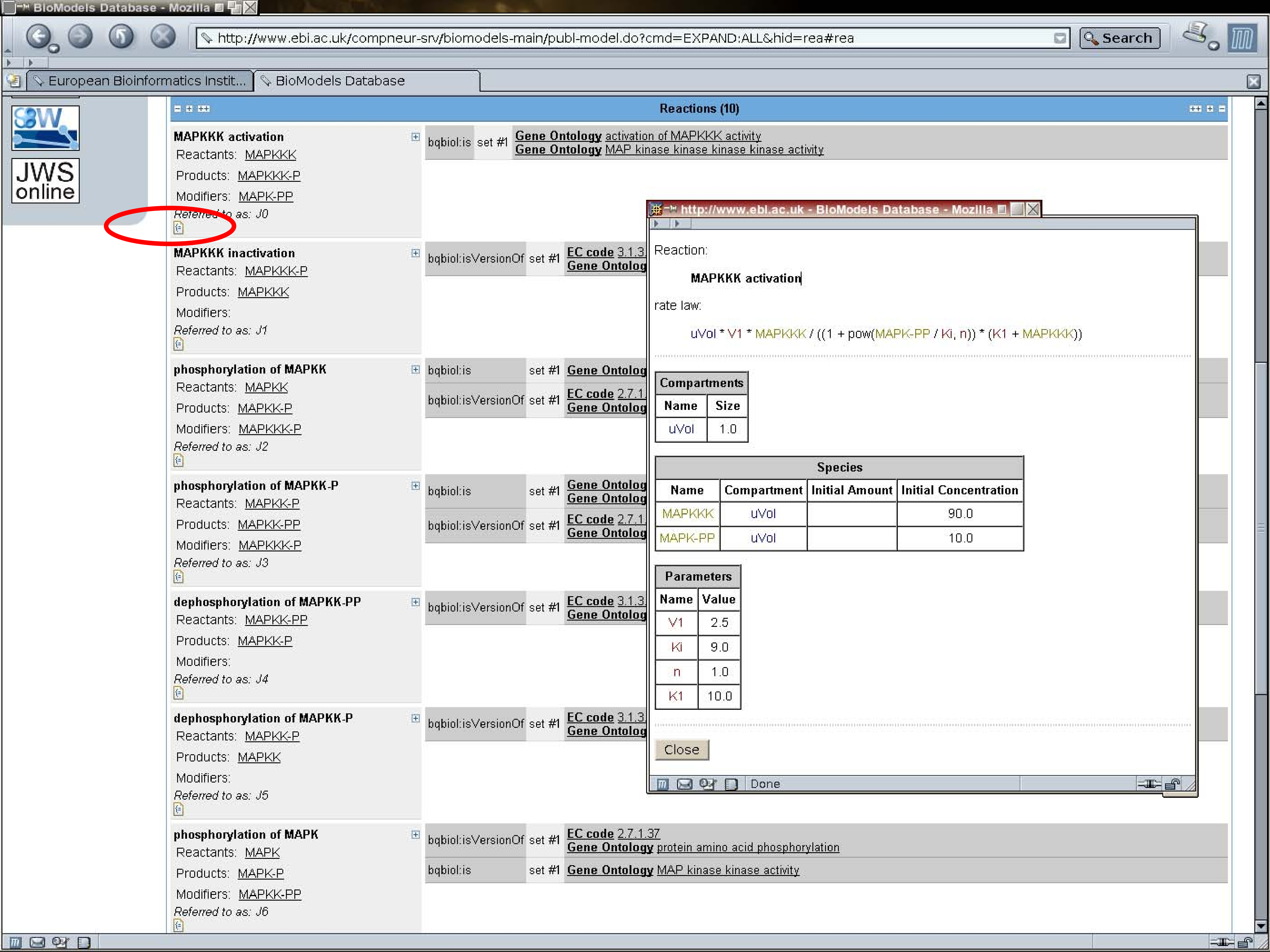


Reactions (10)

Reaction	Qualifier	Set	Annotation
MAPKKK activation Reactants: MAPKKK Products: MAPKKK-P Modifiers: MAPK-PP *Referred to as: J0*	bqbiol:is	set #1	**Gene Ontology** activation of MAPKKK activity **Gene Ontology** MAP kinase kinase kinase kinase activity
MAPKKK inactivation Reactants: MAPKKK-P Products: MAPKKK Modifiers: *Referred to as: J1*	bqbiol:isVersionOf	set #1	**EC code** 3.1.3 **Gene Ontolog**
phosphorylation of MAPKK Reactants: MAPKK Products: MAPKK-P Modifiers: MAPKKK-P *Referred to as: J2*	bqbiol:is	set #1	**Gene Ontolog**
	bqbiol:isVersionOf	set #1	**EC code** 2.7.1 **Gene Ontolog**
phosphorylation of MAPKK-P Reactants: MAPKK-P Products: MAPKK-PP Modifiers: MAPKKK-P *Referred to as: J3*	bqbiol:is	set #1	**Gene Ontolog** **Gene Ontolog**
	bqbiol:isVersionOf	set #1	**EC code** 2.7.1 **Gene Ontolog**
dephosphorylation of MAPKK-PP Reactants: MAPKK-PP Products: MAPKK-P Modifiers: *Referred to as: J4*	bqbiol:isVersionOf	set #1	**EC code** 3.1.3 **Gene Ontolog**
dephosphorylation of MAPKK-P Reactants: MAPKK-P Products: MAPKK Modifiers: *Referred to as: J5*	bqbiol:isVersionOf	set #1	**EC code** 3.1.3 **Gene Ontolog**
phosphorylation of MAPK Reactants: MAPK Products: MAPK-P Modifiers: MAPKK-PP *Referred to as: J6*	bqbiol:isVersionOf	set #1	**EC code** 2.7.1.37 **Gene Ontology** protein amino acid phosphorylation
	bqbiol:is	set #1	**Gene Ontology** MAP kinase kinase activity

Reaction:

MAPKKK activation

rate law:

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

Compartments

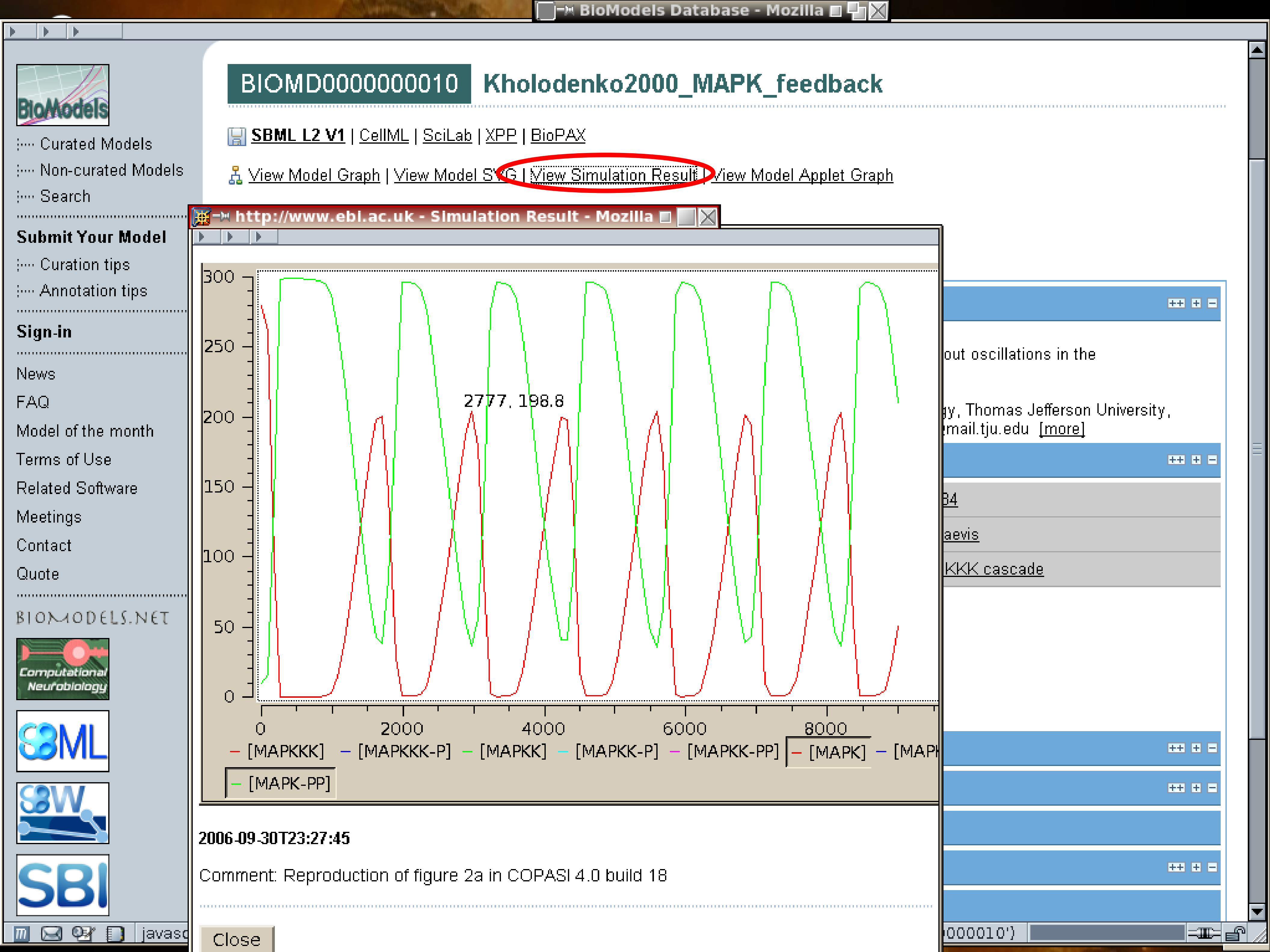
Name	Size
uVol	1.0

Species

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

Parameters

Name	Value
V1	2.5
Ki	9.0
n	1.0
K1	10.0



BIOMD0000000010 Kholodenko2000_MAPK_feedback

out oscillations in the

gy, Thomas Jefferson University,
mail.tju.edu [more]

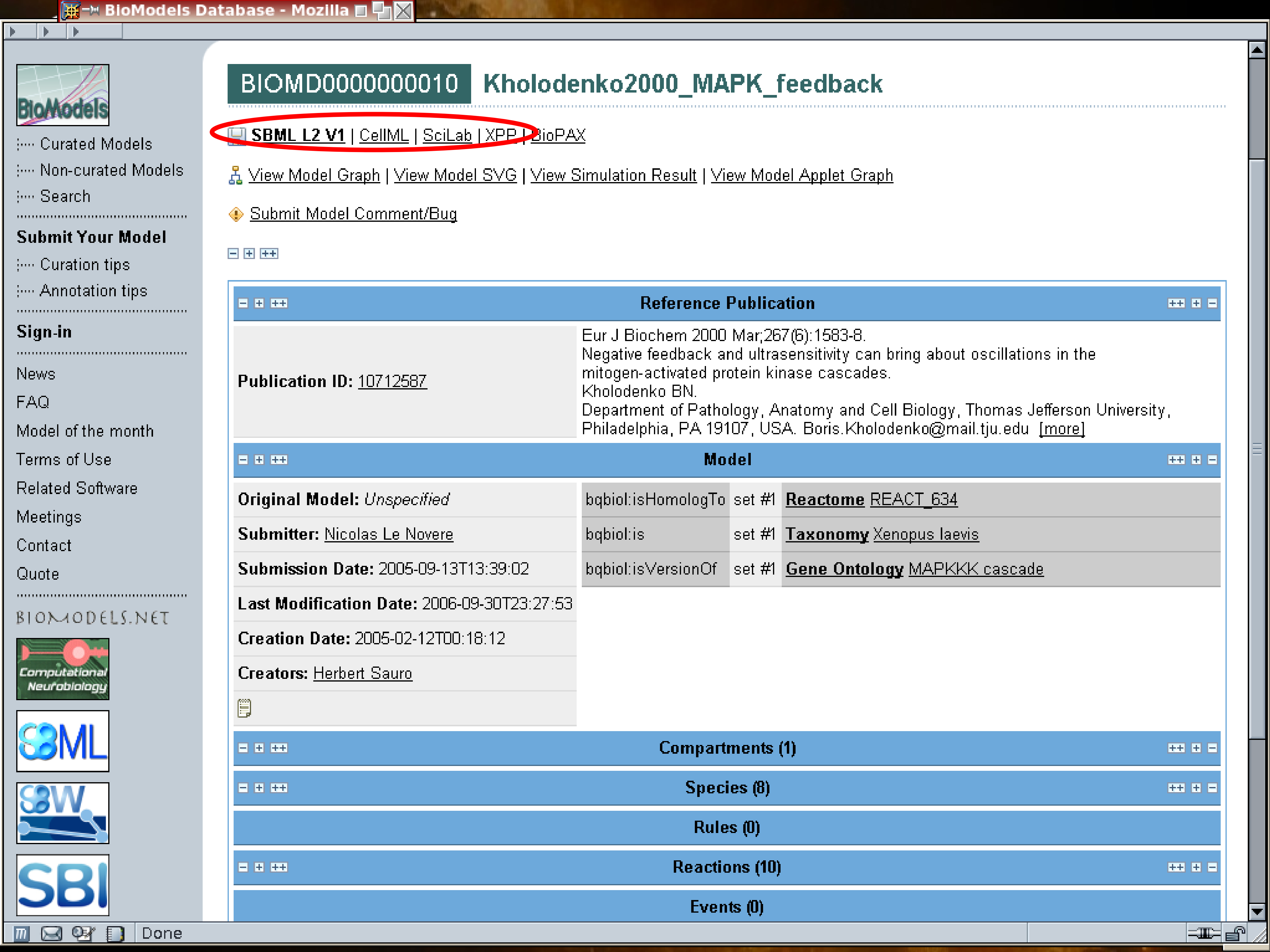
34

aevis

KKK cascade

2006-09-30T23:27:45

Comment: Reproduction of figure 2a in COPASI 4.0 build 18



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Reference Publication

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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: 2006-09-30T23:27:53

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

Creators: Herbert Sauro

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

Compartments (1)

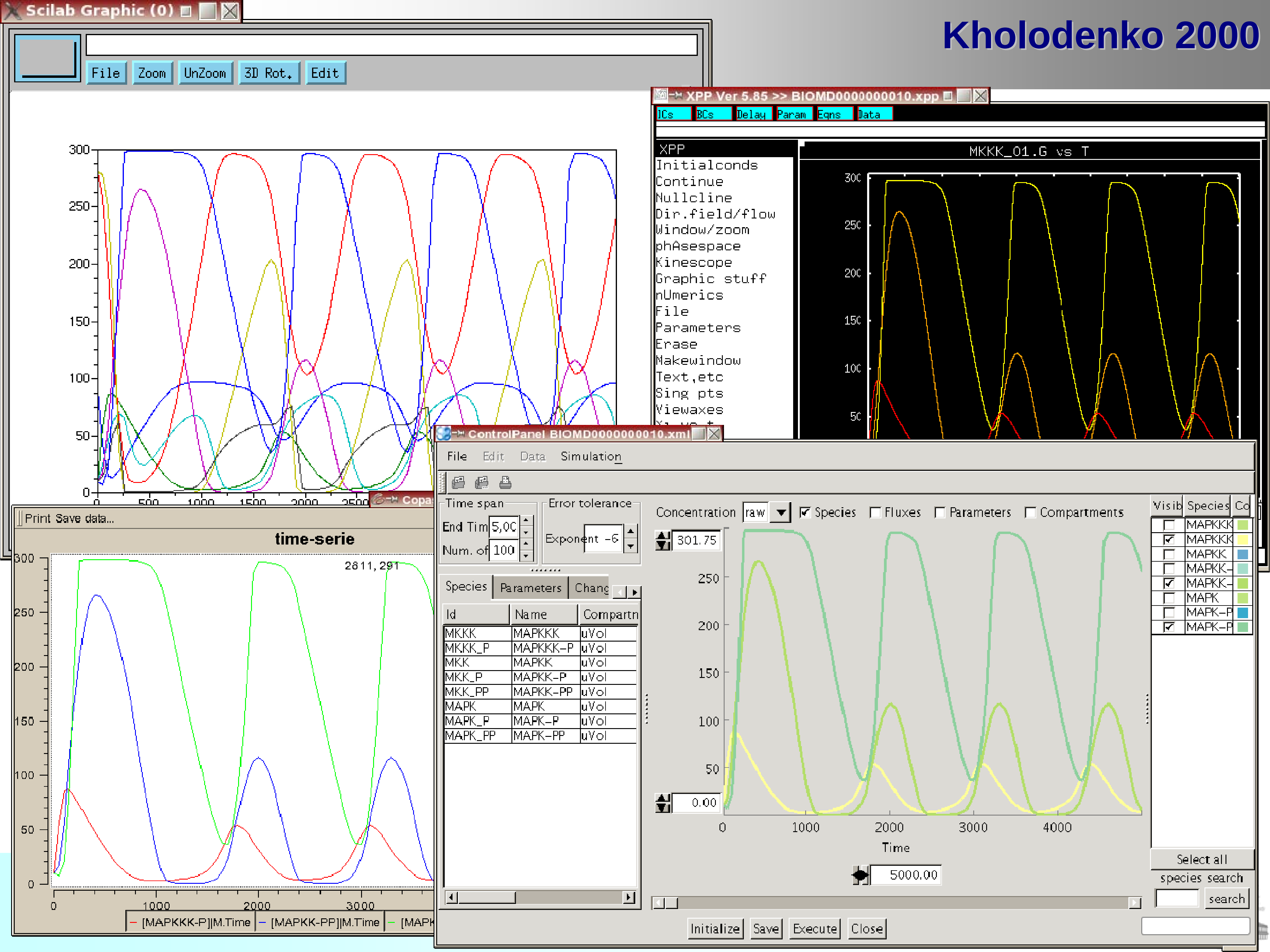
Species (8)

Rules (0)

Reactions (10)

Events (0)

Kholodenko 2000



Time span

End Tim 5,00

Num. of 100

Error tolerance

Exponent -6

Concentration raw

☑ Species ☐ Fluxes ☐ Parameters ☐ Compartments

Id	Name	Compartn
MKKK	MAPKKK	uVol
MKKK_P	MAPKKK-P	uVol
MKK	MAPKK	uVol
MKK_P	MAPKK-P	uVol
MKK_PP	MAPKK-PP	uVol
MAPK	MAPK	uVol
MAPK_P	MAPK-P	uVol
MAPK_PP	MAPK-PP	uVol

Visib	Species	Co
☐	MAPKKK	🟩
☑	MAPKKK	🟨
☐	MAPKK	🟦
☐	MAPKK-	🟩
☑	MAPKK-	🟩
☐	MAPK	🟩
☐	MAPK-P	🟦
☑	MAPK-P	🟩

Problem children

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

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BioModels ID ▾	Name	Publication ID	Last Modified
MODEL0995500644	Rodriguez2005_denovo_pyrimidine_biosynthesis	15784266	2006-09-30T21:48:57
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MODEL5662377562	Feist2006_methanogenesis_OptiAcetate	10.1038/msb4100046...	2006-10-02T16:46:28
MODEL5662398146	Feist2006_methanogenesis_OptiH2-CO2	10.1038/msb4100046...	2006-10-02T16:47:09
MODEL5662425708	Feist2006_methanogenesis_OptiPyruvate	10.1038/msb4100046...	2006-10-02T16:50:56
MODEL5974712823	FangeElf2006_MinSystem_MesoRD	16846247	2006-09-29T22:28:23
MODEL6623597435	Fuentes2005_ZymogenActivation	15634334	2006-09-29T22:39:28
MODEL6623610941	Hornberg2005_ERKcascade	15634347	2006-09-29T22:50:28
MODEL6623617994	Lambeth2002_Glycogenolysis	12220081	2006-09-30T21:46:54
MODEL6623628741	Kolomeisky2003_myosin	12609867	2006-09-29T23:36:52
MODEL6624091635	Hoefnagel2002_Glycolysis	12241048	2006-09-29T22:45:45
MODEL6624139162	Cronwright2003_GlycerolSynthesis	12200299	2006-09-29T22:34:13
MODEL6624199343	Martins2001_glyoxalase	11453985	2006-10-02T10:53:31
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MODEL8293171637	Yeast_glycolysis_model_of_Pritchard_and_Kell	12180966	2006-09-30T21:49:59
MODEL8568434338	Raman2006_MycolicAcid	16261191	2006-09-29T23:24:10
MODEL8583955822	Singh_Ghosh2006_TCA_eco_glucose	10.1186/1742-4682-3-...	2006-09-29T23:47:42
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MODEL8584292730	Singh_Ghosh2006_TCA_mtu_model1	10.1186/1742-4682-3-...	2006-09-29T23:48:15
MODEL8584468482	Singh_Ghosh2006_TCA_mtu_model2	10.1186/1742-4682-3-...	2006-09-29T23:49:52

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MODEL5662377562	Feist2006_methanogenesis_OptiAcetate	10.1038/msb4100046...	2006-10-02T16:46:28
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MODEL5662425708	Feist2006_methanogenesis_OptiPyruvate	10.1038/msb4100046...	2006-10-02T16:50:56
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MODEL6623610941	Hornberg2005_ERKcascade	15634347	2006-09-29T22:50:28
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MODEL6623628741	Kolomeisky2003_myosin	12609867	2006-09-29T23:36:52
MODEL6624091635	Hoefnagel2002_Glycolysis	12241048	2006-09-29T22:45:45
MODEL6624139162	Cronwright2003_GlycerolSynthesis	12200299	2006-09-29T22:34:13
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MODEL8584137422	Singh_Ghosh2006_TCA_eco_acetate	10.1186/1742-4682-3-...	2006-09-29T23:47:20
MODEL8584292730	Singh_Ghosh2006_TCA_mtu_model1	10.1186/1742-4682-3-...	2006-09-29T23:48:15
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MODEL8584468482	Singh_Ghosh2006_TCA_mtu_model2	10.1186/1742-4682-3-...	2006-09-29T23:49:52

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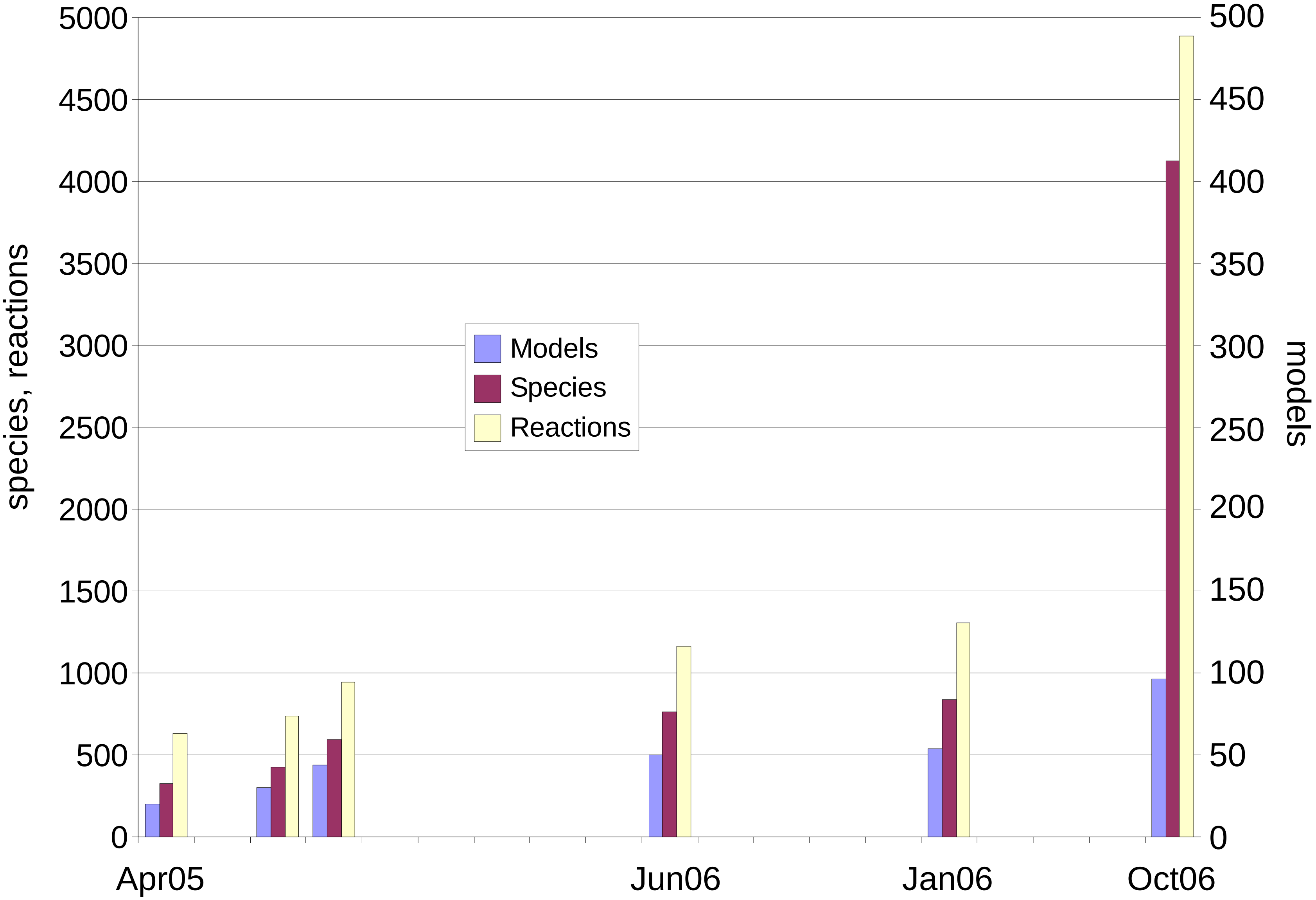
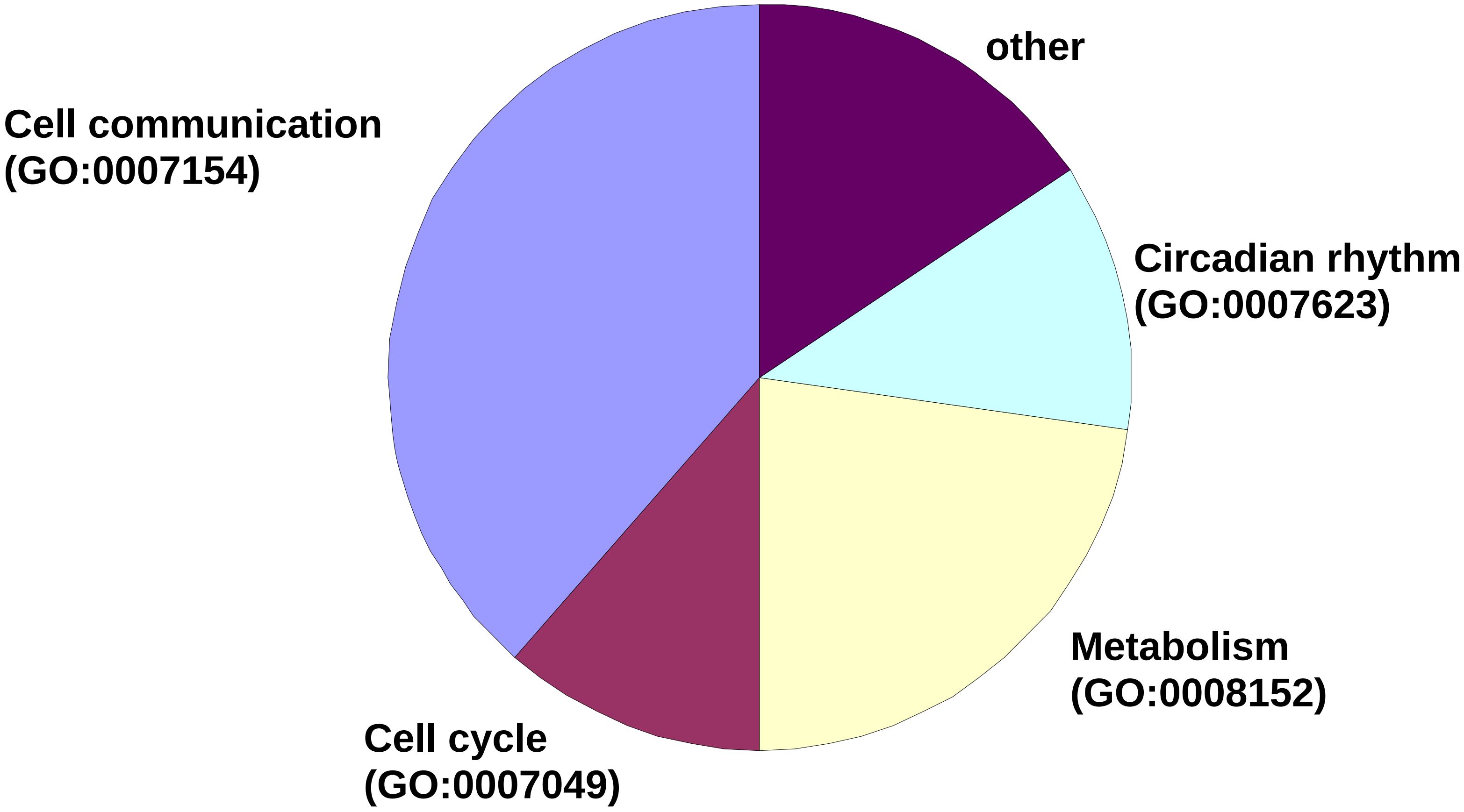


Topical repartition



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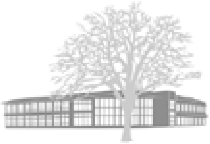
- Encode those models in SBML
- Annotate them extensively using MIRIAM guidelines
- Share them using BioModels Database



The BioModels.net team


Enuo He


Melanie Courtot

Nicolas
Le Novere

Lu Li


Marco Donizelli

Chen Li


Harish
Dharuri

Camille Laibe

Arnaud Henry

Michael
Hucka

An international collaboration

- EBI
  - Nicolas Le Novère
  - Marco Donizelli
  - Mélanie Courtot
  - Lu Li
  - Chen Li
  - Nicolas Rodriguez
  - Alexander Broicher
  - Arnaud Henry
  - Camille Laibe
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  - Bruce Shapiro
  - Benjamin Borstein
  - Maria Schilstra
  - Sarah Keating
  - Harish Dharuri
- Keck Graduate Institute
  - Herbert Sauro
- Systems Biology Institute
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  - Akira Funahashi
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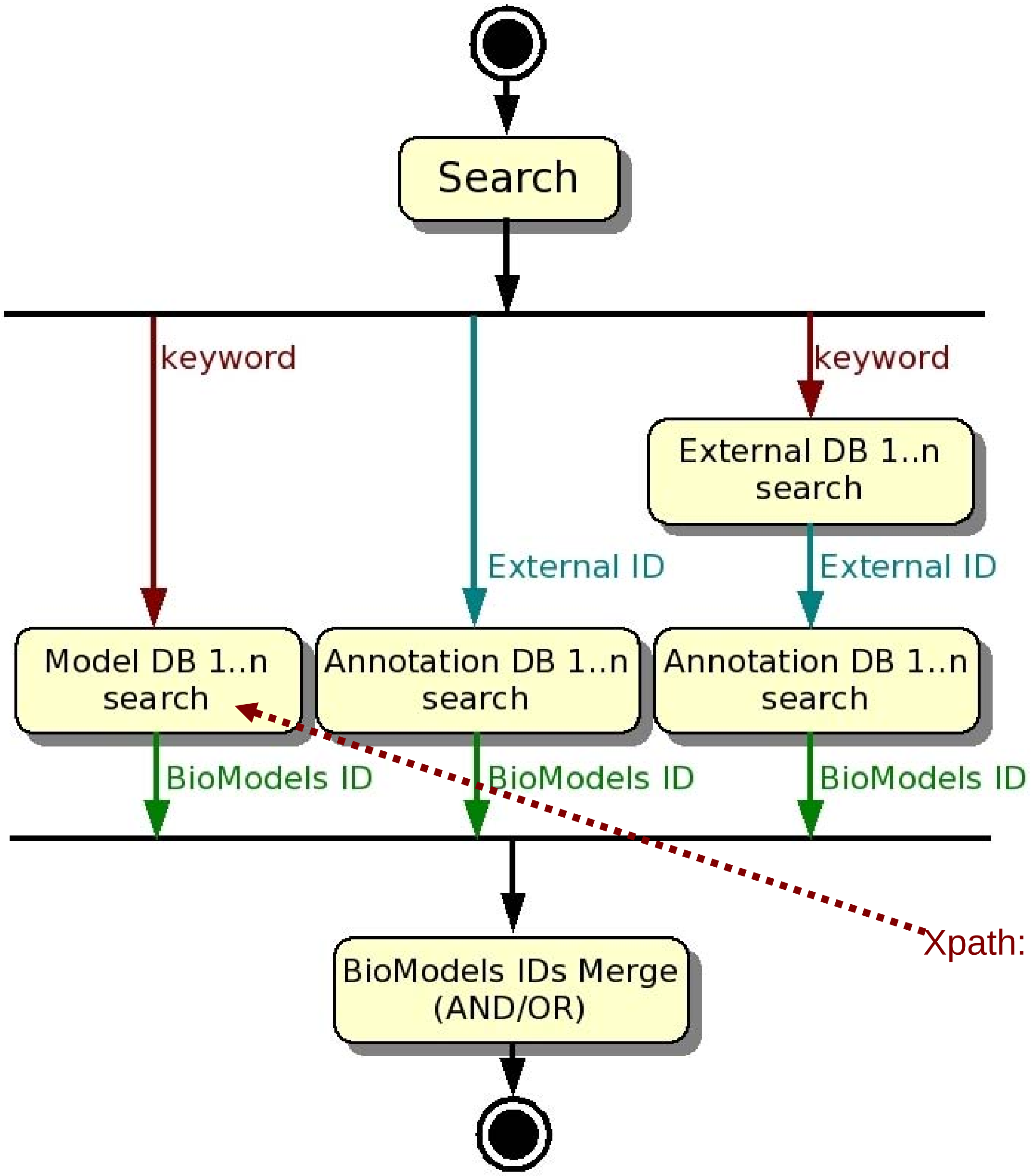
  - Jarnac/JDesigner
  - MathSBML
  - SBMLeditor
  - XPP-Aut

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

Search strategy



Search

keyword

External ID

keyword

External DB 1..n search

External ID

Model DB 1..n search

Annotation DB 1..n search

Annotation DB 1..n search

BioModels ID

BioModels ID

BioModels ID

BioModels IDs Merge (AND/OR)

← GO, UniProt Oracle database
ChEBI, PubMed WebServices

← BioModels MySQL database

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