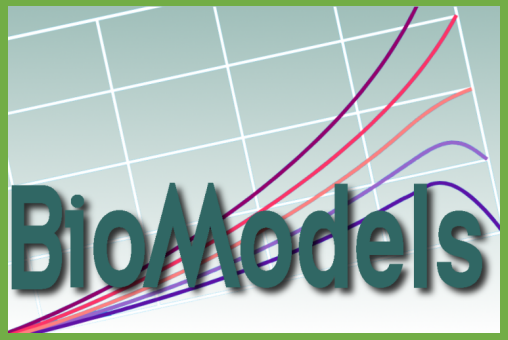
Management and provision of computational models



Camille Laibe

EMBL-EBI

Data Management workshop, 19-20th March 2012, Vienna

- **BioModels.net team**

Technology part of the *Computational Systems Neurobiology* group (Nicolas Le Novère) at EMBL-EBI

- **Standards:** Minimal Information Required In the Annotation of Models (MIRIAM), Minimal Information About a Simulation Experiment (MIASE), Systems Biology Graphical Notation (SBGN), …
- **Formats:** Systems Biology Markup Language (SBML), Simulation Experiment Description Markup Language (SED-ML), ...
- **Ontologies:** Systems Biology Ontology (SBO), Kinetic Simulation Algorithm Ontology (KiSAO), TErminology for the Description of DYnamics (TEDDY), …
- **Services:** **BioModels Database**, MIRIAM Registry, Identifiers.org, ...
- **Tools:** libSBML, JSBML, SBFC, SBMLeditor, …

What is a model?

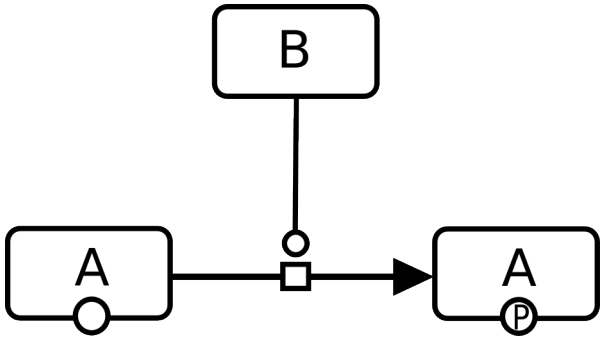
- **Model**

  provides a description of a biological system, taking into account the necessary constituents and their relationships

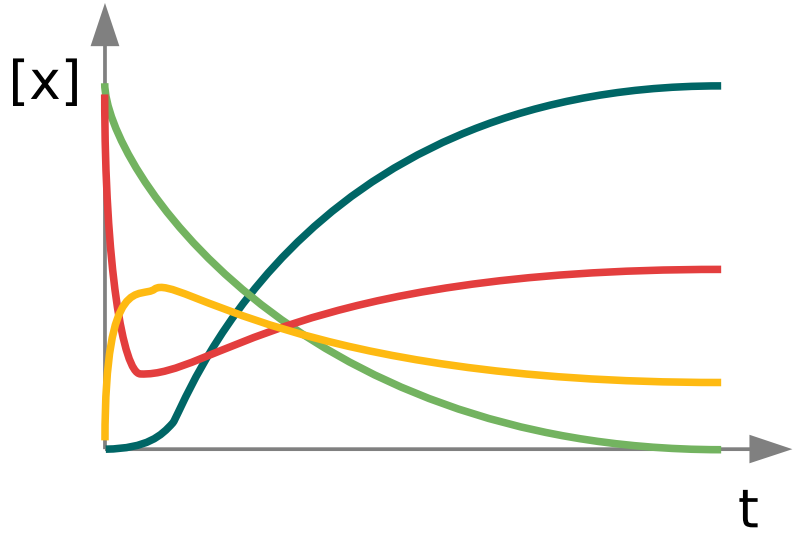
- **Quantitative/mathematical/computational model**

  describes a system using mathematical concepts and language and allows the study of its **dynamic behaviour** (for instance: time and/or space) by mean of simulations

Basic (biochemical) model example

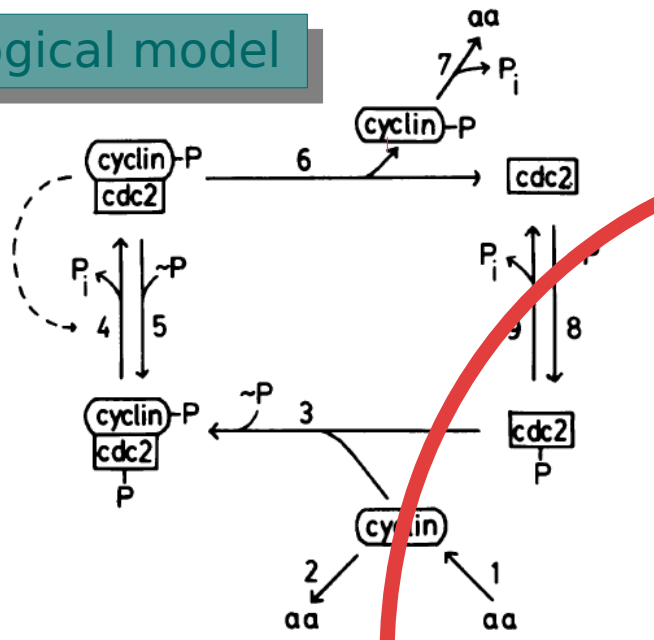


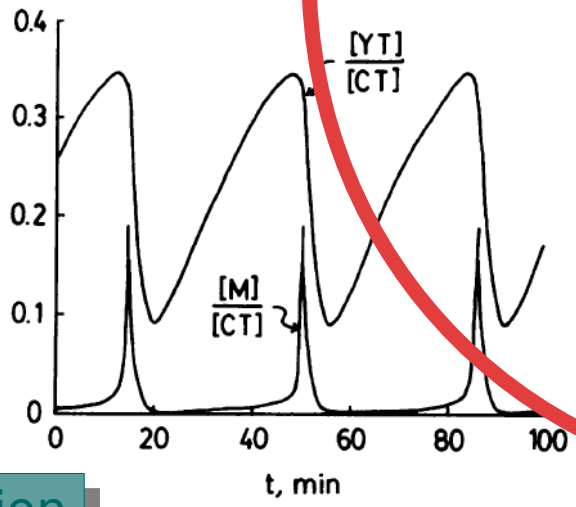
$$
\begin{aligned}
d[A]/dt &= -k_1[B][A] + k_2[A\_B] \\
d[Ap]/dt &= +k_3[A\_B] \\
d[B]/dt &= -k_1[B][A] + k_2[A\_B] + k_3[A\_B] \\
d[A\_B]/dt &= +k_1[B][A] - k_2[A\_B] - k_3[A\_B]
\end{aligned}
$$



How to build a model?

biological model





simulation

mathematical model

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

Parameter	Value	Notes
$k_1[aa]/[CT]$	0.015 min^{-1}	*
k_2	0	†
$k_3[CT]$	200 min^{-1}	*
k_4	10–1000 min^{-1} (adjustable)	
k_4'	0.018 min^{-1}	
$k_5[\sim P]$	0	‡
k_6	0.1–10 min^{-1} (adjustable)	
k_7	0.6 min^{-1}	†
$k_8[\sim P]$	$>> k_9$	§
k_9	$>> k_6$	§

computational model

Tyson et al (1991) PNAS 88(1):7328-32

Nature Precedings : doi:10.1038/npre.2012.7013.1 : Posted 22 Mar 2012

Why are models useful?

- quantitative / dynamic understanding of biological systems
  - integration of data from various scales
  - make clear the current state of knowledge
  - effective way of highlighting gaps in the knowledge
- prediction of the behaviour of systems under certain conditions
  - sometimes the only tool available
- design novel experiments
- …

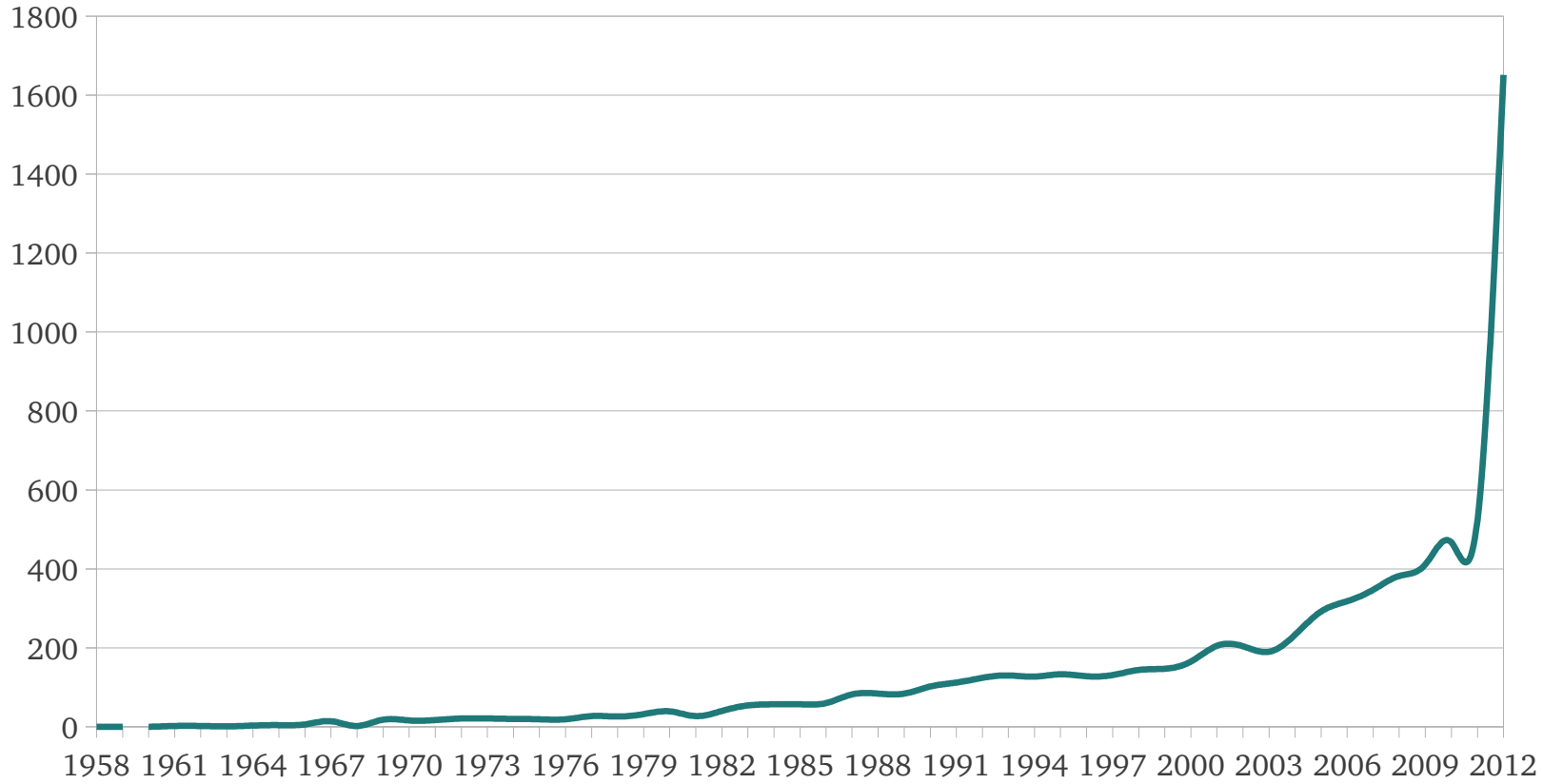
Why are models useful?

- quantitative / dynamic understanding of biological systems
  - integration of data from various scales
  - make clear the current state of knowledge
  - effective way of highlighting gaps in the knowledge
- prediction of the behaviour of systems under certain conditions
  - sometimes the only tool available
- design novel experiments
- …

Models are significant tools in Systems Biology

EMBL-EBI

Models availability



UK PUBMED CENTRAL

Number of results returned for “computational model” for a given year on UKPMC

Requirements for storage and exchange

Modellers need to:

- **find**
- **understand**
- **reuse**
- **combine**

existing models

Requirements for storage and exchange

Modellers need to:

- **find**
- **understand**
- **reuse**
- **combine**

existing models

This requires:

- **standard formats**

- Access to **published** models
- **reliable** models: **curated and annotated**

BioModels Database - A Database of Annotated Published Models

BioModels Database is a repository of peer-reviewed, published, computational models. These mathematical models are primarily from the field of systems biology, but more generally are those of biological interest. This resource allows biologists to store, search and retrieve published mathematical models. In addition, models in the database can be used to generate sub-models, can be simulated online, and can be converted between different representational formats. This resource also features programmatic access via Web Services.

All unmodified models in the database are available freely for use and distribution, to all users. This resource is developed and maintained by the BioModels.net initiative. More information about BioModels Database can be found in the Frequently Asked Questions.

Search | Go to model | Advanced Search

Browse models

- Curated models (366)
- Browse models using GO
- Non-curated models (398)

Simulate in JWS Online

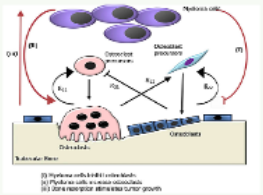
Submit a model

Links

- Main instance at EMBL-EBI, UK
- Mirror at Caltech, USA
- Project on SourceForge
- Web Services
- Download archived models

Model of the month

January, 2012



In normal bone remodeling, the coupling between bone resorption and formation mediated by osteoclasts and osteoblasts respectively, are tightly regulated. The dysregulation in bone remodeling that occurs in myelome bone disease are described here.. *Read more...*

News

1st September 2011 **Twentieth Release of BioModels Database!**
Download all models in the SBML format

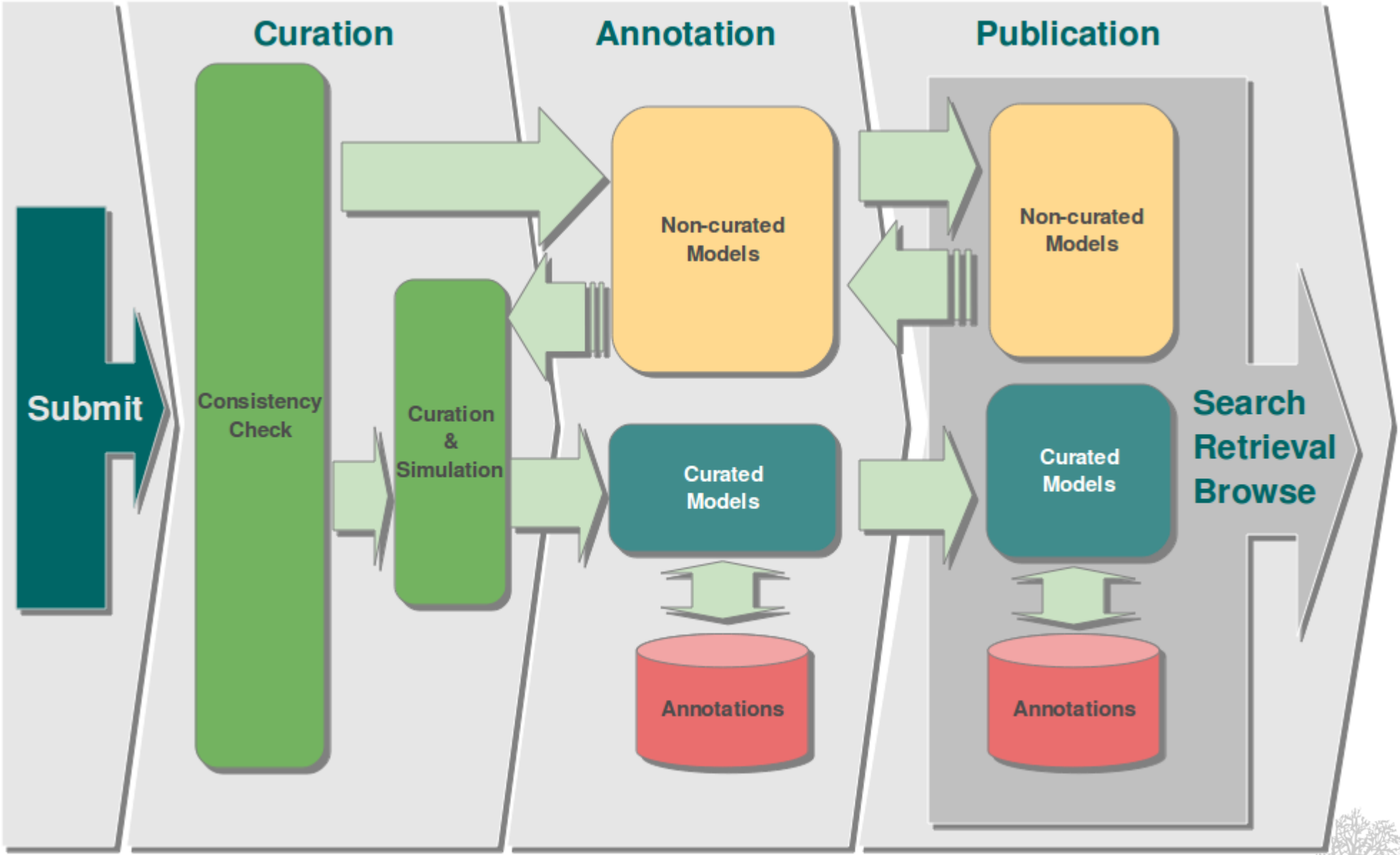
15 April 2011 **Nineteenth Release!**
Download All Models Under SBML Format

4 February 2011 **JUMMP: JUst a Model Management Platform**
To provide the worldwide community with a modern tool for the collaborative creation and sharing of models in an efficient and secured way, the Jürgen Fils and Nicolas Le Novère groups are announcing the JUMMP project. It is planned that JUMMP will be used as the software infrastructure running BioModels Database. Read more...

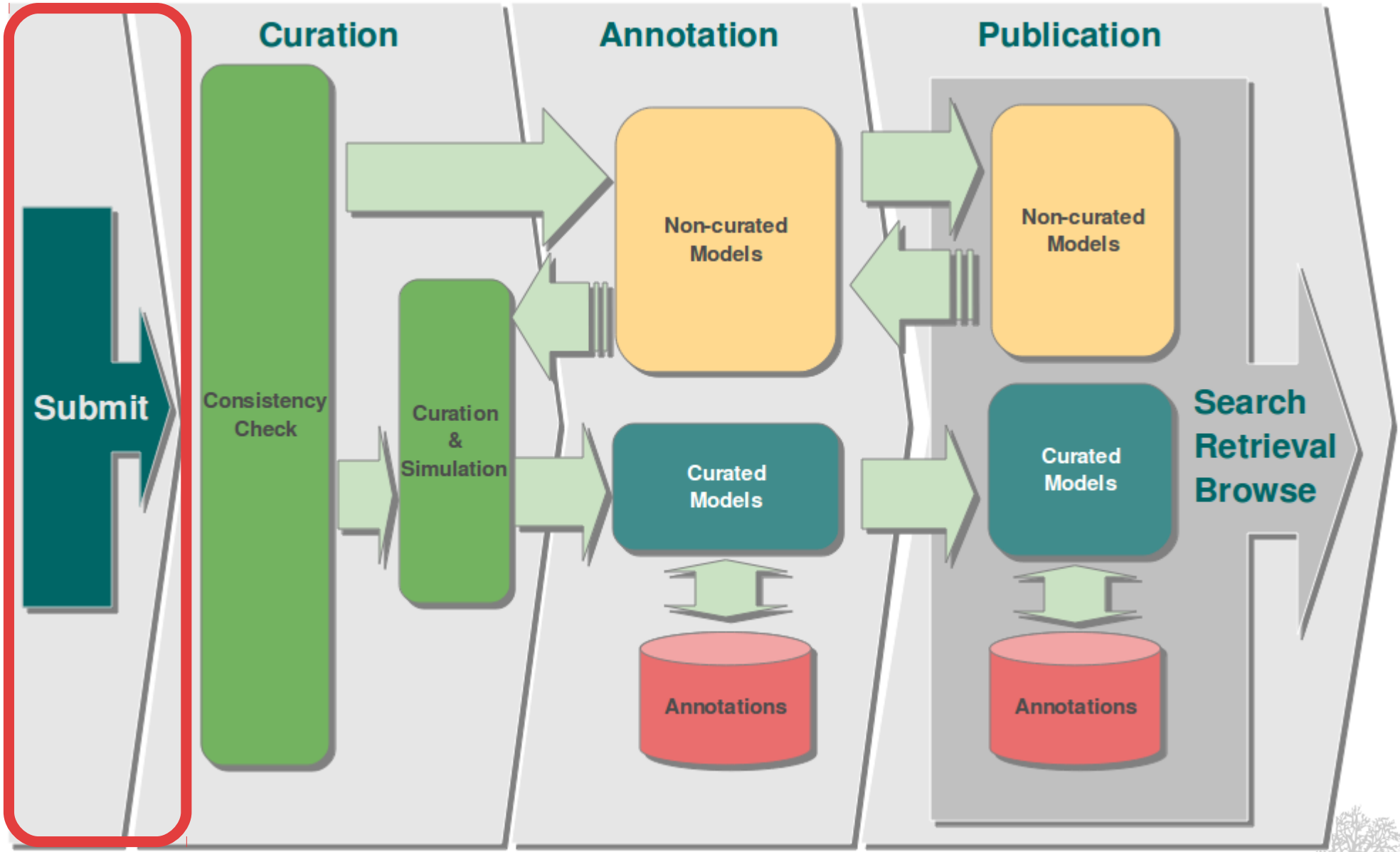
Examples of models in BioModels Database

- Biochemical models
  - interactions between molecules in multiple cellular compartments
- Pharmacometrics models
  - tumor growth and treatment response
- Single-compartment neurons
  - membrane voltage, current flow, concentrations of various ions intra- and extracellularly
- Spread of infectious diseases
  - outbreak of zombie infection
- Ecosystem models
  - interaction of living organisms in a given environment
- ...

Production pipeline



Model submission



Models provenance

- From **authors** prior to publication

  Supported (listed in instructions for authors) by **> 300 journals**, including:

  - Molecular Systems Biology
  - All PLoS journals
  - All BioMedCentral journals
  - …

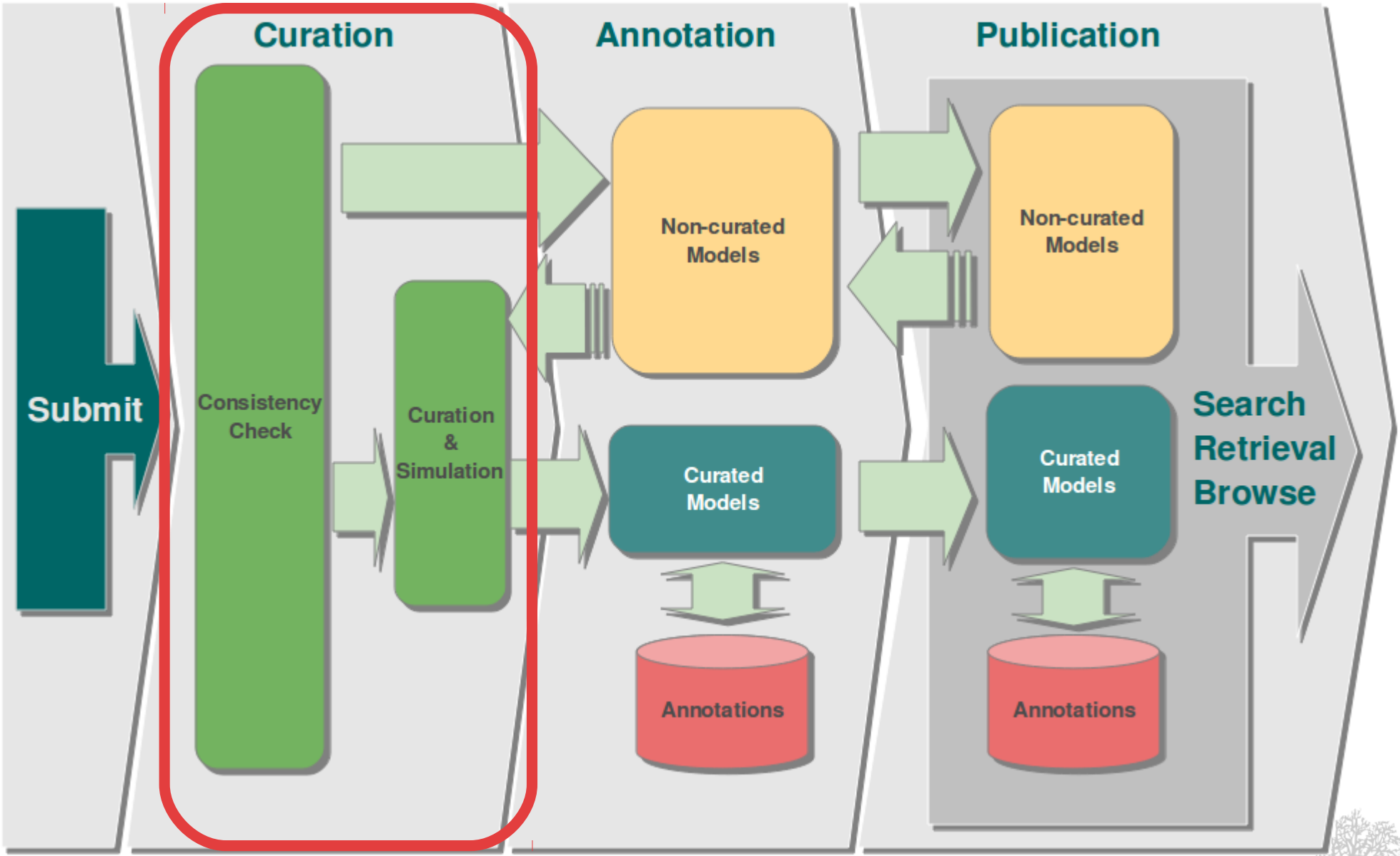
- Submitted by **curators**

  - implemented from literature
  - imported from journal supplementary materials
  - exchanged with other repositories

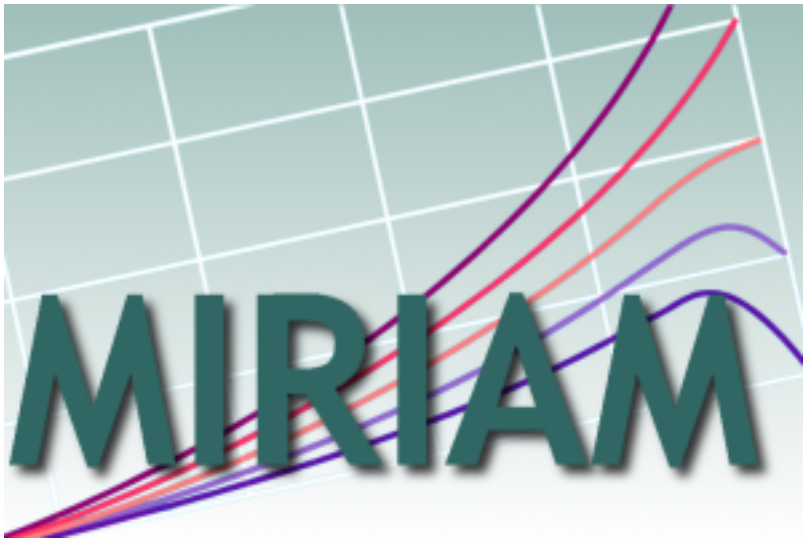
    (DOQCS, CellML Model Repository, JWS Online, ...)

- Provided by other **people** curating models out of interest

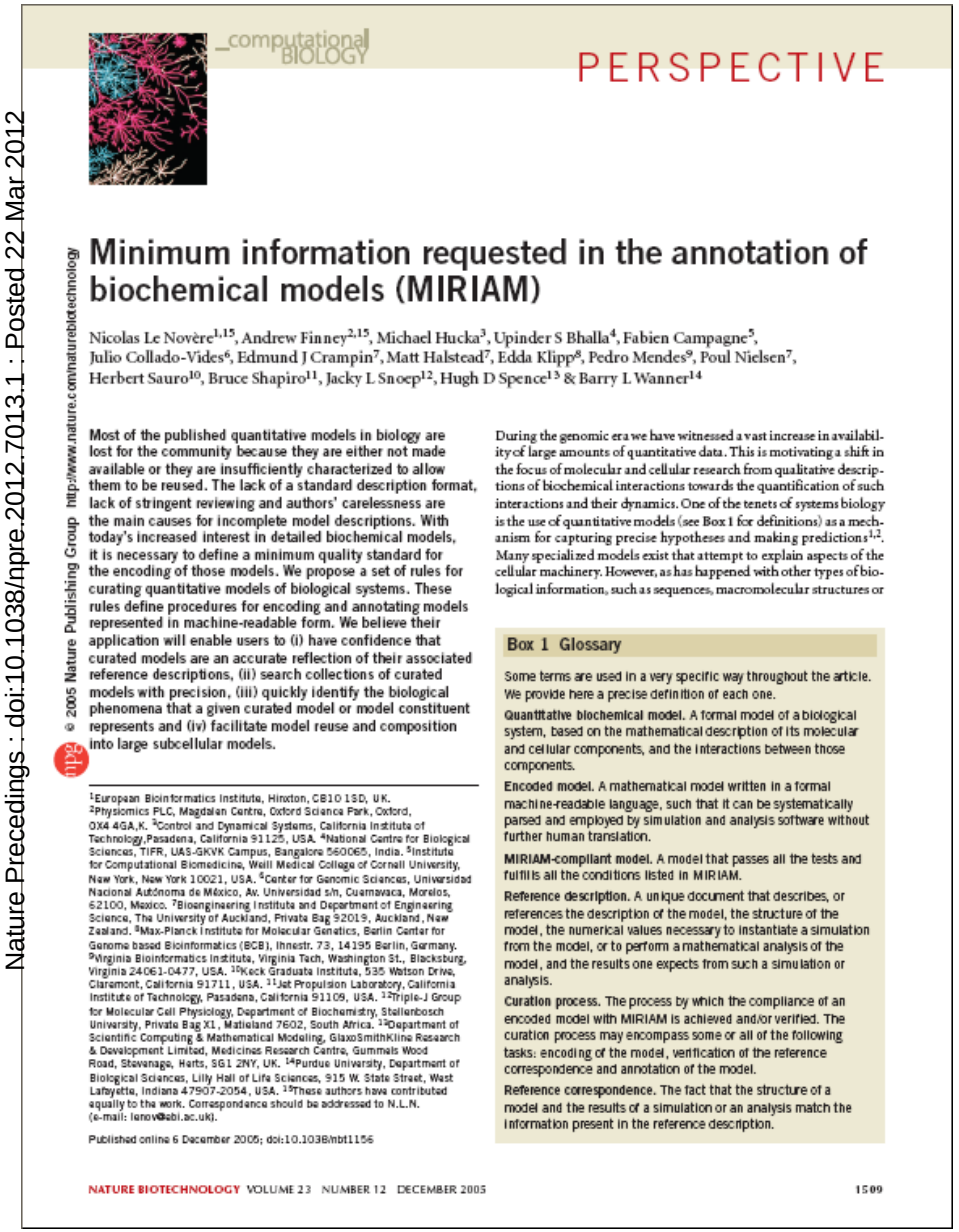
Curation



The Minimum Information Required In the Annotation of a Model



http://biomodels.net/miriam/



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).

Published online 6 December 2005; doi:10.1038/nbt1156

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.

- set of guidelines for the curation and annotation of quantitative models
- about encoding and annotation
- applicable to **any structured model format**

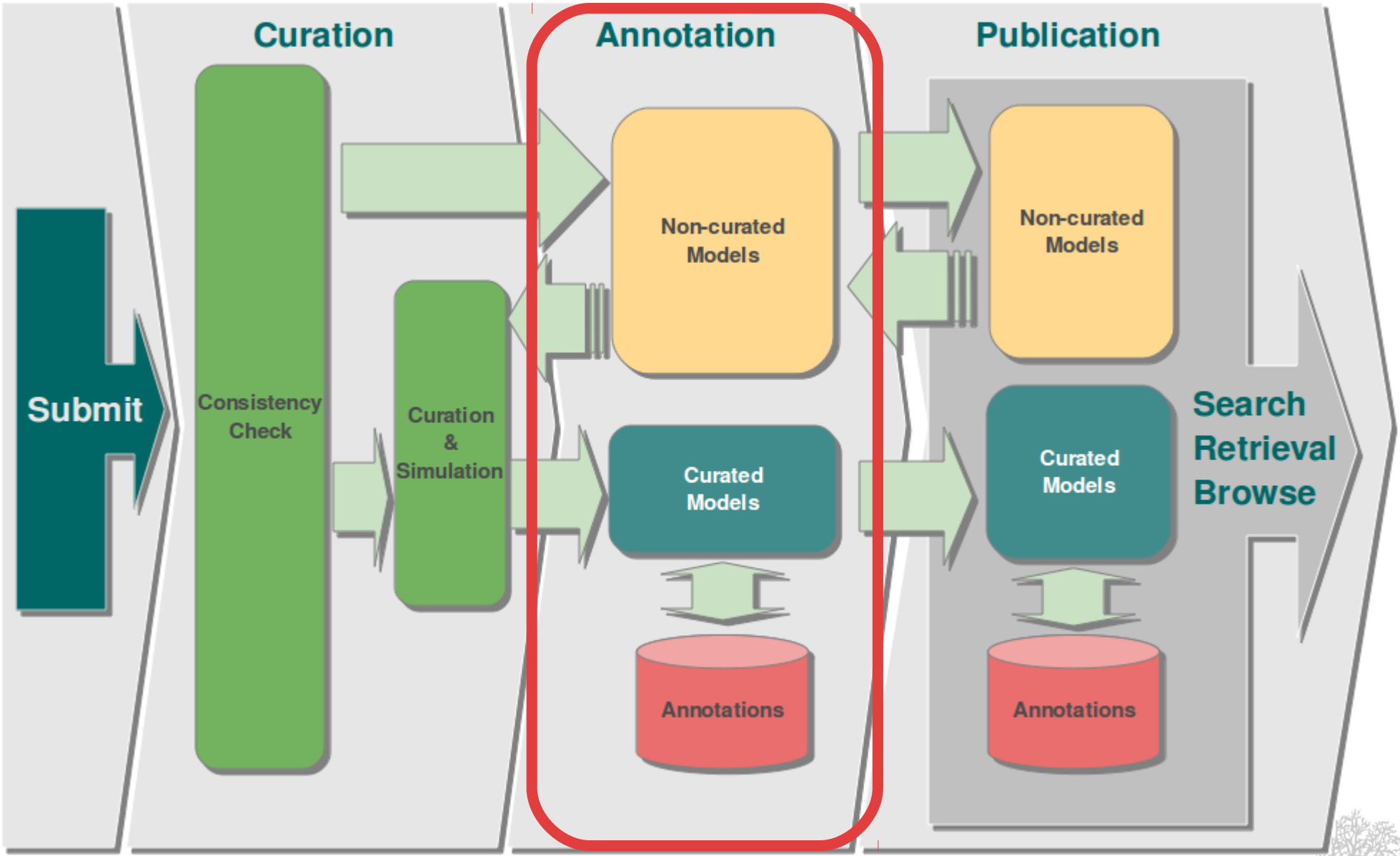
cf. Nicolas Le Novère *et al.* **Minimum Information Requested in the Annotation of biochemical Models (MIRIAM)**. *Nature Biotechnology*, 2005

MIRIAM Compliance

Models **must** (among other things):

- be encoded in a public machine-readable format
- be clearly linked to a single publication
- reflect the structure of the biological processes described in the reference paper (list of reactions, ...)
- be instantiable in a simulation (possess initial conditions, ...)
- be able to reproduce the results given in the reference paper
- contain creator's contact details
- annotated: **each model constituent must be unambiguously identified**

Annotation



Curated and non-curated branches

- **Curated branch**

MIRIAM compliant models

- **Non-curated branch**

valid SBML but not curated or annotated

  - not MIRIAM compliant models
    - cannot reproduce published results
    - different model structure
    - non kinetic model (FBA, stoichiometric maps, ...)
  - MIRIAM compliant models
    - models contain kinetic that we cannot curate up to now
    - work in progress, will be moved to curated branch in the near future

Why are annotations important?

Annotations, and generally **metadata**, are essential for:

- understanding data
- reusing data
- comparing data
- integrating data
- converting data
- providing efficient search strategies
- ...

Why are annotations important?

Annotations, and generally **metadata**, are essential for:

- understanding data
- reusing data
- comparing data
- integrating data
- converting data
- providing efficient search strategies
- ...

→ *true for any kind of data!*

Identifiers for annotations

- **Unique and unambiguous**

  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

Towards globally unique identifiers

Namespace

Identifies a data collection

from a shared list of *namespaces*

Entity identifier

Identifies a data entry within the data collection

provided by the data collection

unique within the data collection

format defined by the data collection

Provision of URIs for annotations

- **MIRIAM Registry**
  - catalogue of **data collections** and their associated **namespace**
  - provides **perennial identifiers** for annotation and cross-referencing purposes

Human calmodulin: P62158 in UniProt

→ `urn:miriam:uniprot:P62158`

Alcohol dehydrogenase: 1.1.1.1 in Enzyme Nomenclature

→ `urn:miriam:ec-code:1.1.1.1`

Activation of MAPKK activity: GO:0000186 in Gene Ontology

→ `urn:miriam:obo.go:GO%3A0000186`

Provision of URIs for annotations

- **MIRIAM Registry**
  - catalogue of **data collections** and their associated **namespace**
  - provides **perennial identifiers** for annotation and cross-referencing purposes

Identifiers.org

- built on the information stored in the **Registry**
- provides **directly resolvable URIs**

Human calmodulin: P62158 in UniProt

↳ http://identifiers.org/uniprot/P62158

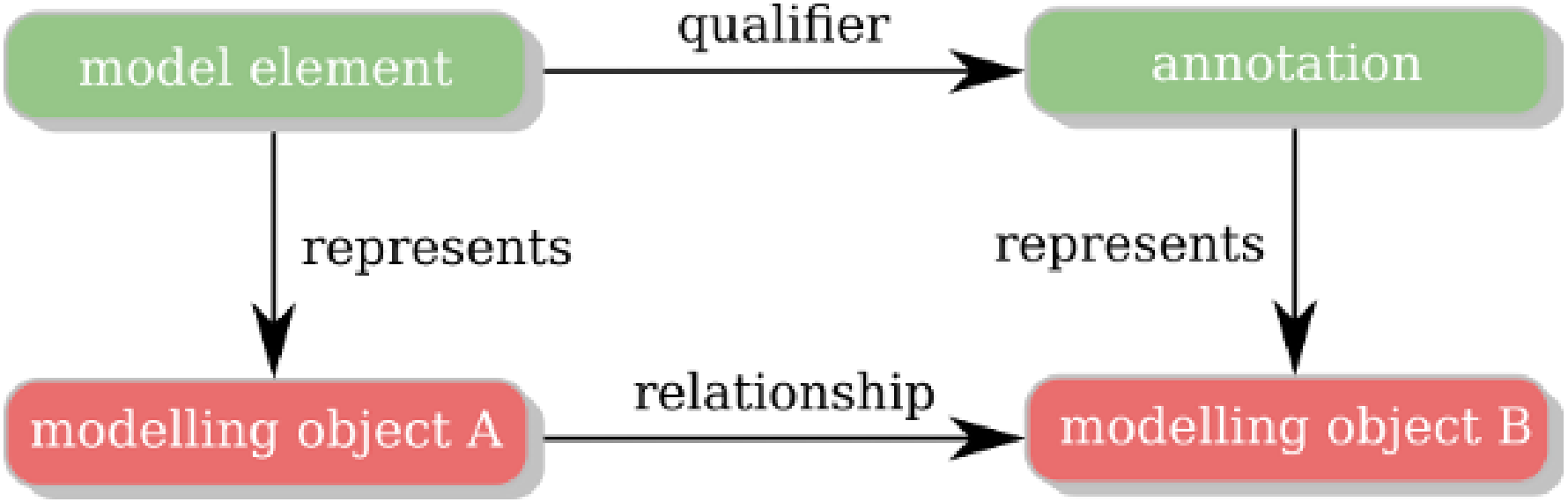
Alcohol dehydrogenase: 1.1.1.1 in Enzyme Nomenclature

↳ http://identifiers.org/ec-code/1.1.1.1

Activation of MAPKK activity: GO:0000186 in Gene Ontology

↳ http://identifiers.org/obo.go/GO:0000186

Qualified annotation



BioModels.net qualifiers

- bqmodel:is
- bqmodel:isDerivedFrom
- bqmodel:isDescribedBy

- bqbiol:is
- bqbiol:isDescribedBy
- bqbiol:hasPart
- bqbiol:hasProperty
- bqbiol:isPartOf

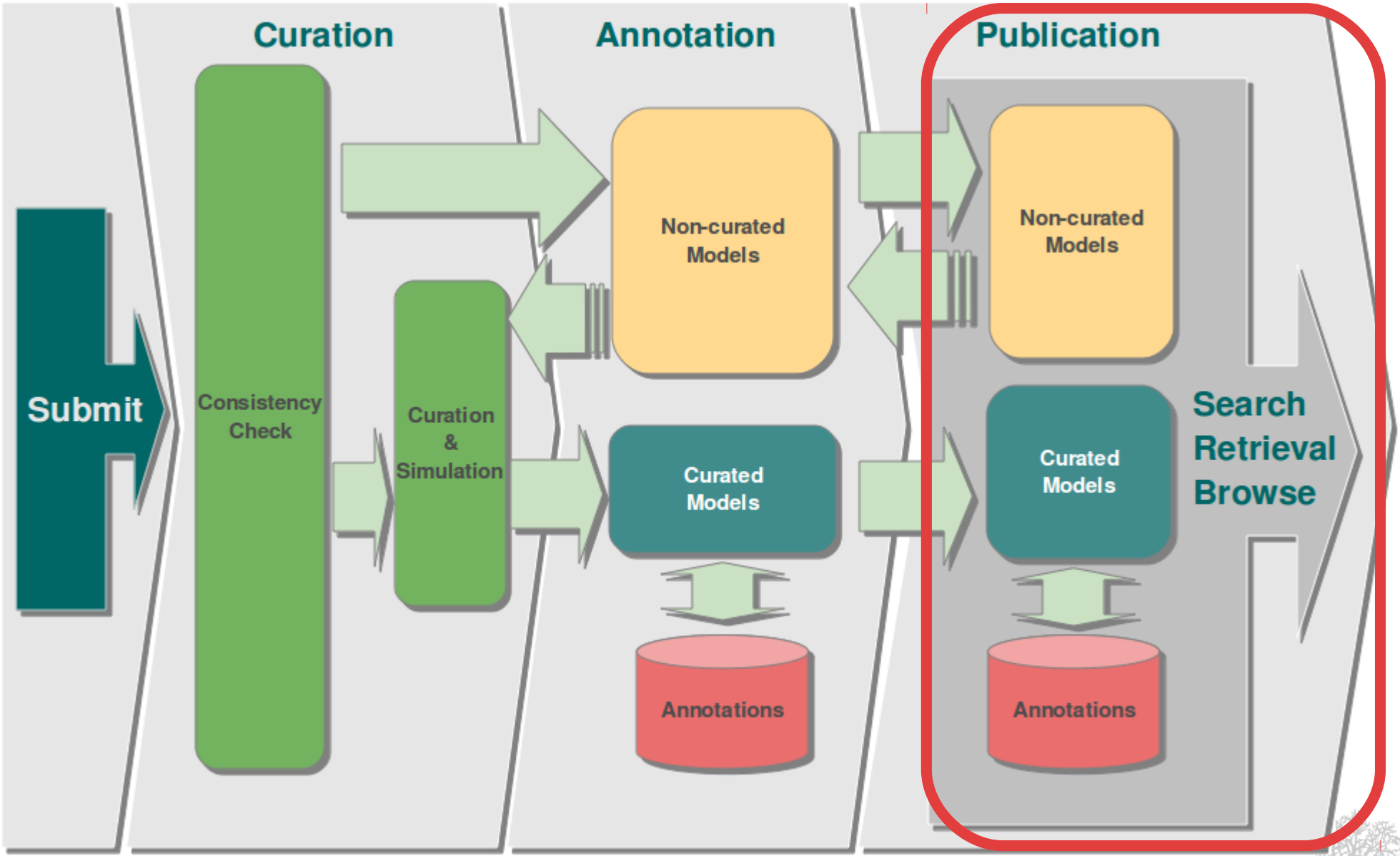
- bqbiol:isPropertyOf
- bqbiol:isVersionOf
- bqbiol:hasVersion
- bqbiol:isHomologTo
- bqbiol:isDescribedBy
- bqbiol:encodes
- bqbiol:isEncodedBy
- bqbiol:occursIn
- [...]

http://biomodels.net/qualifiers/

Annotations in SBML


```
[...]
<species metaid="metaid_0000006"
         id="L_EGFR"
         compartment="compartment"
         initialConcentration="0">
  <annotation>
    <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22rdfsyntaxns#"
             xmlns:bqbiol="http://biomodels.net/biologyqualifiers/">
      <rdf:Description rdf:about="#metaid_0000006">
        <bqbiol:hasPart>
          <rdf:Bag>
            <rdf:li rdf:resource="http://identifiers.org/uniprot/P07522" />
            <rdf:li rdf:resource="http://identifiers.org/uniprot/Q9QX70" />
          </rdf:Bag>
        </bqbiol:hasPart>
      </rdf:Description>
    </rdf:RDF>
  </annotation>
</species>
[...]
```

Publication



Browse - Curated models

The following fields are used to describe a model:

- *BioModels ID* → A unique string of characters associated with the model, which will never be re-used even if the model is deleted from the BioModels Database.
- *Name* → The name of the model, as written in the model itself by its creator(s).
- *Publication ID* → The unique identifier of the reference publication describing the model, specified either as a PubMed identifier (linked to the EBI Medline database), or as a DOI (linked to the original publication through a DOI resolver), or as an URL. Being all published, all models must have one publication identifier, and the same identifier can be shared amongst several models if they have been described in the same publication.
- *Last Modified* → The date when the model was last modified.

To view a model, simply click on the correspondant BioModels ID provided within the leftmost column of the row corresponding to the model.

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 ⇨

10 | 50 | 100 | All

BioModels ID	Name	Publication ID	Last Modified
BIOMD0000000279	Komarova2005_PTHaction_OsteoclastOsteoblastCoupling	15860557	2011-12-20T15:45:46+00:00
BIOMD0000000403	Ayati2010_BoneRemodelingDynamics_WithTumour+DrugTreatment	20406449	2011-12-20T14:45:58+00:00
BIOMD0000000402	Ayati2010_BoneRemodelingDynamics_WithTumour	20406449	2011-12-20T14:43:23+00:00
BIOMD0000000401	Ayati2010_BoneRemodelingDynamics_NormalCondition	20406449	2011-12-20T14:40:44+00:00
BIOMD0000000305	Kolomeisky2003_MyosinV_Processivity	12609867	2011-11-04T14:34:07+00:00
BIOMD0000000356	Nyman2011_M3Hierarachical_InsulinGlucosedynamics	21572040	2011-11-01T17:27:21+00:00
BIOMD0000000137	Sedaghat2002_InsulinSignalling_noFeedback	12376338	2011-11-01T17:19:19+00:00
BIOMD0000000343	Brannmark2010_InsulinSignalling_Mifamodel	20421297	2011-11-01T17:18:37+00:00
BIOMD0000000379	DallaMan2007_MealModel_GlucoseInsulinSystem	17926672	2011-11-01T13:42:58+00:00
BIOMD0000000362	Butenas2004_BloodCoagulation	15039440	2011-09-02T10:16:08+00:00

List of models

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.

- GO:0008150 - biological_process (314)
  - GO:0009987 - cellular process (280)
    - GO:0051641 - cellular localization (48)
    - GO:0050794 - regulation of cellular process (172)
    - GO:0007049 - cell cycle (27)
      - GO:0051726 - regulation of cell cycle (23)
        - GO:0000075 - cell cycle checkpoint (10)
        - GO:0000079 - regulation of cyclin-dependent protein kinase activity (11)
        - GO:0007346 - regulation of mitotic cell cycle (13)
        - GO:0010564 - regulation of cell cycle process (13)
        - GO:0045786 - negative regulation of cell cycle (15)
        - GO:0045787 - positive regulation of cell cycle (12)
        - BIOMD0000000168 - Obeyesekere1999_CellCycle
        - BIOMD0000000195 - Tyson2001_Cell_Cycle_Regulation
        - BIOMD0000000242 - Bai2003_G1phaseRegulation
      - GO:0000278 - mitotic cell cycle (23)
      - GO:0022402 - cell cycle process (11)
      - GO:0045786 - negative regulation of cell cycle (15)
      - GO:0045787 - positive regulation of cell cycle (12)
      - GO:0004693 - cyclin-dependent protein kinase activity (9)
      - BIOMD0000000196 - Srividhya2006_CellCycle
      - BIOMD0000000265 - Conradie2010_RPControl_CellCycle
    - GO:0022402 - cell cycle process (11)
    - GO:0016043 - cellular component organization (89)
    - GO:0007154 - cell communication (26)
    - GO:0044237 - cellular metabolic process (227)
    - GO:0051301 - cell division (4)
    - GO:0048523 - negative regulation of cellular process (31)
    - GO:0019725 - cellular homeostasis (36)
    - GO:0048869 - cellular developmental process (6)
    - GO:0051716 - cellular response to stimulus (111)

BioModels ID: BIOMD0000000195
Name: Tyson2001_Cell_Cycle_Regulation
Publication ID: 11371178
Last Modified: 2009-03-16T14:37:30+00:00
SBML L2 V3

Model browsing via GO terms

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.

- GO:0008150 - biological_process (314)
  - GO:0009987 - cellular process (280)
    - GO:0051641 - cellular localization (48)
    - GO:0050794 - regulation of cellular process (172)
    - GO:0007049 - cell cycle (27)
      - GO:0051726 - regulation of cell cycle (23)
        - GO:0000075 - cell cycle checkpoint (10)
        - GO:0000079 - regulation of cyclin-dependent protein kinase activity (11)
        - GO:0007346 - regulation of mitotic cell cycle (13)
        - GO:0010564 - regulation of cell cycle process (13)
        - GO:0045786 - negative regulation of cell cycle (15)
        - GO:0045787 - positive regulation of cell cycle (12)
        - BIOMD0000000168 - Obeyesekere1999_CellCycle
        - BIOMD0000000195 - Tyson2001_Cell_Cycle_Regulation
        - BIOMD0000000242 - Bai2003_G1phaseRegulation
      - GO:0000278 - mitotic cell cycle (23)
      - GO:0022402 - cell cycle process (11)
      - GO:0045786 - negative regulation of cell cycle (15)
      - GO:0045787 - positive regulation of cell cycle (12)
      - GO:0004693 - cyclin-dependent protein kinase activity (9)
      - BIOMD0000000196 - Srividhya2006_CellCycle
      - BIOMD0000000265 - Conradie2010_RPControl_CellCycle
    - GO:0022402 - cell cycle process (11)
    - GO:0016043 - cellular component organization (89)
    - GO:0007154 - cell communication (26)
    - GO:0044237 - cellular metabolic process (227)
    - GO:0051301 - cell division (4)
    - GO:0048523 - negative regulation of cellular process (31)
    - GO:0019725 - cellular homeostasis (36)
    - GO:0048869 - cellular developmental process (6)
    - GO:0051716 - cellular response to stimulus (111)

BioModels ID: BIOMD0000000195
Name: Tyson2001_Cell_Cycle_Regulation
Publication ID: 11371178
Last Modified: 2009-03-16T14:37:30+00:00
SBML L2 V3

Model browsing via GO terms

BioModels Database - A Database of Annotated Published Models

BioModels Database is a repository of peer-reviewed, published, computational models. These mathematical models are primarily from the field of systems biology, but more generally are those of biological interest. This resource allows biologists to store, search and retrieve published mathematical models. In addition, models in the database can be used to generate sub-models, can be simulated online, and can be converted between different representational formats. This resource also features programmatic access via Web Services.

All unmodified models in the database are available freely for use and distribution, to all users. This resource is developed and maintained by the BioModels.net initiative. More information about BioModels Database can be found in the Frequently Asked Questions.

Advanced Search

Search | Go to model

Browse models

- Curated models (366)
- Browse models using GO
- Non-curated models (398)

Simulate in JWS Online

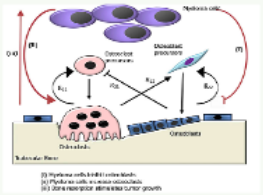
Submit a model

Links

- Main instance at EMBL-EBI, UK
- Mirror at Caltech, USA
- Project on SourceForge
- Web Services
- Download archived models

Model of the month

January, 2012



In normal bone remodeling, the coupling between bone resorption and formation mediated by osteoclasts and osteoblasts respectively, are tightly regulated. The dysregulation in bone remodeling that occurs in myelome bone disease are described here.. *Read more...*

News

1st September 2011 **Twentieth Release of BioModels Database!**
Download all models in the SBML format

15 April 2011 **Nineteenth Release!**
Download All Models Under SBML Format

4 February 2011 **JUMMP: JUst a Model Management Platform**
To provide the worldwide community with a modern tool for the collaborative creation and sharing of models in an efficient and secured way, the Jürgen Eils and Nicolas Le Novère groups are announcing the JUMMP project. It is planned that JUMMP will be used as the software infrastructure running BioModels Database. Read more...

Model search

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

- *BioModels identifier* → 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.
- *Annotation (full text)* → 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:0000278* or *cell cycle* for Gene Ontology, *P04551* or *cell division* for UniProt).
- *Annotation (identifier)* → Search BioModels Database for annotations, by third-party resource identifiers (for example *IPR002394* for InterPro, *hsa04080* for KEGG Pathway, *68910* for Reactome).

Apart from the *BioModels identifier* -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 identifier:

Person:

SBML elements: match the **exact phrase**

Annotation (full text): UniProt

Annotation (full text): Publication

Annotation (full text): Gene Ontology

Annotation (identifier): PubChem-compound

Annotation (identifier): KEGG Reaction

Annotation (identifier): Enzyme Nomenclature

Compose by: and or

Search Rese

Advanced model search

BIOMD0000000003 - Goldbeter1991_MinMitOscil

Download SBML | Other formats (auto-generated) | Actions | Submit Model Comment/Bug

Model | Overview | Math | Physical entities | Parameters | Curation

Reference Publication

Publication ID: 1833774

Goldbeter A.
A minimal cascade model for the mitotic oscillator involving cyclin and cdc2 kinase.
Proc Natl Acad Sci U S A 1991 Oct;88(20):9107-11.
Faculté des Sciences, Université Libre de Bruxelles, Belgium. [more]

Model

Original Model: *BIOMD0000000003.xml.origin*

Submitter: Nicolas Le Novère

Submission ID: MODEL6614271263

Submission Date: 13 Sep 2005 12:24:56 UTC

Last Modification Date: 17 Mar 2010 00:25:38 UTC

Creation Date: 06 Feb 2005 23:39:40 UTC

Encoders: Bruce Shapiro
Vijayalakshmi Chelliah

set #1	bqbiol:occursIn	**Taxonomy** Amphibia
set #2	bqbiol:isVersionOf	**KEGG Pathway** hsa04110 **Gene Ontology** mitotic cell cycle
	bqbiol:isHomologTo	**Reactome** REACT_152

Notes

This a model from the article:
A minimal cascade model for the mitotic oscillator involving cyclin and cdc2 kinase.
Goldbeter A *Proc. Natl. Acad. Sci. U.S.A.* 1991:88(20):9107-11 1833774,
Abstract:
A minimal model for the mitotic oscillator is presented. The model, built on recent experimental advances, is based on the cascade of post-translational modification that modulates the activity of cdc2 kinase during the cell cycle. The model pertains to the situation encountered in early amphibian embryos, where the accumulation of cyclin suffices to trigger the onset of mitosis. In the first cycle of the bicyclic cascade model, cyclin promotes the activation of cdc2 kinase through reversible dephosphorylation, and in the second cycle, cdc2 kinase activates a cyclin protease by reversible phosphorylation. That cyclin activates cdc2 kinase while the kinase triggers the degradation of cyclin has suggested that oscillations may originate from such a negative feedback loop [Félix, M. A., Labbé, J. C., Dorée, M., Hunt, T. & Karsenti, E. (1990) Nature (London) 346, 379-382]. This conjecture is corroborated by the model, which indicates that sustained oscillations of the limit cycle type can arise in the cascade, provided that a threshold exists in the activation of cdc2 kinase by cyclin and in the activation of cyclin proteolysis by cdc2 kinase. The analysis shows how miotic oscillations may readily arise from time lags associated with these thresholds and from the delayed negative feedback provided by cdc2-induced cyclin degradation. A mechanism for the origin of the thresholds is proposed in terms of the phenomenon of zero-order ultrasensitivity previously described for biochemical systems regulated by covalent modification.

BIOMD0000000003 - Goldbeter1991_MinMitOscil

Download SBML | Other formats (auto-generated) | Actions | Submit Model Comment/Bug

Model | Overview | Math | Physical entities | Parameters | Curation

Reference Publication

Publication ID: 1833774

Goldbeter A.
A minimal cascade model for the mitotic oscillator involving cyclin and cdc2 kinase.
Proc Natl Acad Sci U S A 1991 Oct;88(20):9107-11.
Faculté des Sciences, Université Libre de Bruxelles, Belgium. [more]

Model

Original Model: *BIOMD0000000003.xml.origin*

Submitter: Nicolas Le Novère

Submission ID: MODEL6614271263

Submission Date: 13 Sep 2005 12:24:56 UTC

Last Modification Date: 17 Mar 2010 00:25:38 UTC

Creation Date: 06 Feb 2005 23:39:40 UTC

Encoders: Bruce Shapiro
Vijayalakshmi Chelliah

set #1	bqbiol:occursIn	**Taxonomy** Amphibia
set #2	bqbiol:isVersionOf	**KEGG Pathway** hsa04110 **Gene Ontology** mitotic cell cycle
	bqbiol:isHomologTo	**Reactome** REACT_152

Notes

This a model from the article:
A minimal cascade model for the mitotic oscillator involving cyclin and cdc2 kinase.
Goldbeter A *Proc. Natl. Acad. Sci. U.S.A.* 1991:88(20):9107-11 1833774,
Abstract:
A minimal model for the mitotic oscillator is presented. The model, built on recent experimental advances, is based on the cascade of post-translational modification that modulates the activity of cdc2 kinase during the cell cycle. The model pertains to the situation encountered in early amphibian embryos, where the accumulation of cyclin suffices to trigger the onset of mitosis. In the first cycle of the bicyclic cascade model, cyclin promotes the activation of cdc2 kinase through reversible dephosphorylation, and in the second cycle, cdc2 kinase activates a cyclin protease by reversible phosphorylation. That cyclin activates cdc2 kinase while the kinase triggers the degradation of cyclin has suggested that oscillations may originate from such a negative feedback loop [Félix, M. A., Labbé, J. C., Dorée, M., Hunt, T. & Karsenti, E. (1990) Nature (London) 346, 379-382]. This conjecture is corroborated by the model, which indicates that sustained oscillations of the limit cycle type can arise in the cascade, provided that a threshold exists in the activation of cdc2 kinase by cyclin and in the activation of cyclin proteolysis by cdc2 kinase. The analysis shows how miotic oscillations may readily arise from time lags associated with these thresholds and from the delayed negative feedback provided by cdc2-induced cyclin degradation. A mechanism for the origin of the thresholds is proposed in terms of the phenomenon of zero-order ultrasensitivity previously described for biochemical systems regulated by covalent modification.

BIOMD0000000003 - Goldbeter1991_MinMitOscil

Reference Publication

Publication ID: 1833774

Goldbeter A.
A minimal cascade model for the mitotic oscillator involving cyclin and cdc2 kinase.
Proc Natl Acad Sci U S A 1991 Oct;88(20):9107-11.
Faculté des Sciences, Université Libre de Bruxelles, Belgium. [more]

Model

Original Model: *BIOMD0000000003.xml.origin*

Submitter: Nicolas Le Novère

Submission ID: MODEL6614271263

Submission Date: 13 Sep 2005 12:24:56 UTC

Last Modification Date: 17 Mar 2010 00:25:38 UTC

Creation Date: 06 Feb 2005 23:39:40 UTC

Encoders: Bruce Shapiro
Vijayalakshmi Chelliah

set #1	bqbiol:occursIn	**Taxonomy** Amphibia
set #2	bqbiol:isVersionOf	**KEGG Pathway** hsa04110 **Gene Ontology** mitotic cell cycle
	bqbiol:isHomologTo	**Reactome** REACT_152

Notes

This a model from the article:
A minimal cascade model for the mitotic oscillator involving cyclin and cdc2 kinase.
Goldbeter A *Proc. Natl. Acad. Sci. U.S.A.* 1991:88(20):9107-11 1833774,
Abstract:
A minimal model for the mitotic oscillator is presented. The model, built on recent experimental advances, is based on the cascade of post-translational modification that modulates the activity of cdc2 kinase during the cell cycle. The model pertains to the situation encountered in early amphibian embryos, where the accumulation of cyclin suffices to trigger the onset of mitosis. In the first cycle of the bicyclic cascade model, cyclin promotes the activation of cdc2 kinase through reversible dephosphorylation, and in the second cycle, cdc2 kinase activates a cyclin protease by reversible phosphorylation. That cyclin activates cdc2 kinase while the kinase triggers the degradation of cyclin has suggested that oscillations may originate from such a negative feedback loop [Félix, M. A., Labbé, J. C., Dorée, M., Hunt, T. & Karsenti, E. (1990) Nature (London) 346, 379-382]. This conjecture is corroborated by the model, which indicates that sustained oscillations of the limit cycle type can arise in the cascade, provided that a threshold exists in the activation of cdc2 kinase by cyclin and in the activation of cyclin proteolysis by cdc2 kinase. The analysis shows how miotic oscillations may readily arise from time lags associated with these thresholds and from the delayed negative feedback provided by cdc2-induced cyclin degradation. A mechanism for the origin of the thresholds is proposed in terms of the phenomenon of zero-order ultrasensitivity previously described for biochemical systems regulated by covalent modification.

BIOMD0000000003 - Goldbeter1991_MinMitOscil

Download SBML | Other formats (auto-generated) | Actions | Submit Model Comment/Bug

Model | Overview | Math | Physical entities | Parameters | Curation

Reference Publication

Publication ID: 1833774

Goldbeter A.
A minimal cascade model for the mitotic oscillator involving cyclin and cdc2 kinase.
Proc Natl Acad Sci U S A 1991 Oct;88(20):9107-11.
Faculté des Sciences, Université Libre de Bruxelles, Belgium. [more]

Model

Original Model: *BIOMD0000000003.xml.origin*

Submitter: Nicolas Le Novère

Submission ID: MODEL6614271263

Submission Date: 13 Sep 2005 12:24:56 UTC

Last Modification Date: 17 Mar 2010 00:25:38 UTC

Creation Date: 06 Feb 2005 23:39:40 UTC

Encoders: Bruce Shapiro
Vijayalakshmi Chelliah

set #1	bqbiol:occursIn	**Taxonomy** Amphibia
set #2	bqbiol:isVersionOf	**KEGG Pathway** hsa04110 **Gene Ontology** mitotic cell cycle
	bqbiol:isHomologTo	**Reactome** REACT_152

Notes

This a model from the article:
A minimal cascade model for the mitotic oscillator involving cyclin and cdc2 kinase.
Goldbeter A *Proc. Natl. Acad. Sci. U.S.A.* 1991:88(20):9107-11 1833774,
Abstract:
A minimal model for the mitotic oscillator is presented. The model, built on recent experimental advances, is based on the cascade of post-translational modification that modulates the activity of cdc2 kinase during the cell cycle. The model pertains to the situation encountered in early amphibian embryos, where the accumulation of cyclin suffices to trigger the onset of mitosis. In the first cycle of the bicyclic cascade model, cyclin promotes the activation of cdc2 kinase through reversible dephosphorylation, and in the second cycle, cdc2 kinase activates a cyclin protease by reversible phosphorylation. That cyclin activates cdc2 kinase while the kinase triggers the degradation of cyclin has suggested that oscillations may originate from such a negative feedback loop [Félix, M. A., Labbé, J. C., Dorée, M., Hunt, T. & Karsenti, E. (1990) Nature (London) 346, 379-382]. This conjecture is corroborated by the model, which indicates that sustained oscillations of the limit cycle type can arise in the cascade, provided that a threshold exists in the activation of cdc2 kinase by cyclin and in the activation of cyclin proteolysis by cdc2 kinase. The analysis shows how miotic oscillations may readily arise from time lags associated with these thresholds and from the delayed negative feedback provided by cdc2-induced cyclin degradation. A mechanism for the origin of the thresholds is proposed in terms of the phenomenon of zero-order ultrasensitivity previously described for biochemical systems regulated by covalent modification.

BIOMD0000000003 - Goldbeter1991_MinMitOscil

Download SBML | Other formats (auto-generated) | Actions | Submit Model Comment/Bug

Model | Overview | Math | **Physical entities** | Parameters | Curation

cell	Spatial dimensions: 3 Compartment size: 1.0 *(Units: volume)*
Cyclin *Compartment: cell*	Initial concentration: 0.01 *(Units: substance)*
Annotations: *(SBO: polypeptide chain)*	set #1 bqbiol:isVersionOf **UniProt** CCNC_XENLA **InterPro** IPR006670
CDC-2 Kinase *Compartment: cell*	Initial concentration: 0.01 *(Units: substance)*
Cyclin Protease *Compartment: cell*	Initial concentration: 0.01 *(Units: substance)*

BioModels Home | Models | Submit | Support | About BioModels | Contact us | Search

BIOMD0000000003 - Goldbeter1991_MinMitOscil

Download SBML | Other formats (auto-generated) | Actions | Submit Model Comment/Bug

Model | Overview | Math | **Physical entities** | Parameters | Curation

cell Spatial dimensions: 3 Compartment size: 1.0 *(Units: volume)*

Cyclin

Compartment: cell

Initial concentration: 0.01 *(Units: substance)*

Annotations:
(SBO: polypeptide chain)

et #1 bqbiol:isVersionO

UniProt CCNC_XENLA

Browse
Search
Download
Recent changes

Term request
Edit tree

Web Services
FAQ
News
Project on SourceForge
Contact

Term: SBO:0000252

Name
polypeptide chain

Definition
Naturally occurring macromolecule formed by the rep
ribosome. CHEBI:16541

Comment
Name changed on January 10 2007 by Nicolas Le N
Novere.

Miscellaneous
Date of creation:
10 November 2006, 15:38
Date of last modification:
10 January 2007, 13:49

Parent(s)
SBO:0000246 *information macromolecule* (is a)

Children

UniProt › UniProtKB

Search | Blast * | Align | Retrieve | ID

Search in Protein Knowledgebase (UniProtKB) **Query**

Q4KLA0 (CCNC_XENLA) Reviewed, UniProtKB/Swiss-Prot
Last modified November 16, 2011. Version 37. History...

Clusters with 100%, 90%, 50% identity | Documents (1) | Third-party

Names · Attributes · General annotation · Ontologies · Sequence
Documents | Customize order

Names and origin

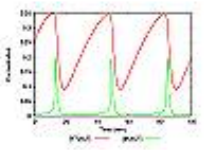
Protein names	*Recommended name:* **Cyclin-C**
Gene names	Name:**ccnc**
Organism	**Xenopus laevis (African clawed frog)**
Taxonomic identifier	8355 [NCBI]
Taxonomic lineage	Eukaryota › Metazoa › Chordata › Craniata › V Mesobatrachia › Pipoidea › Pipidae › Xenopod

BIOMD0000000005 - Tyson1991_CellCycle_6var

Download SBML | Other formats (auto-generated) | Actions | Submit Model Comment/Bug

Model | Overview | Math | Physical entities | Parameters | **Curation**

Representative curation result(s)



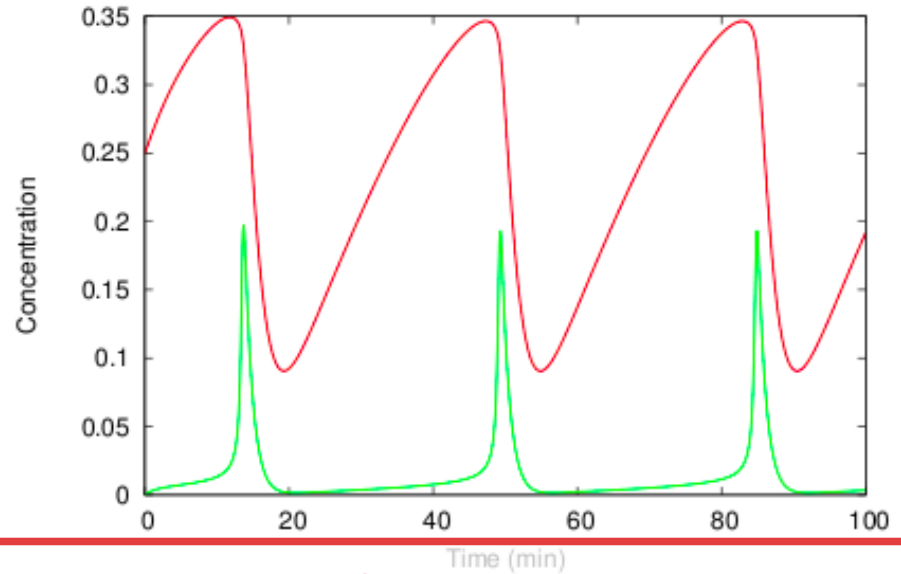
Curator's comment: (*updated:* 08 Feb 2010 10:29:04 GMT)

The model reproduces figure 3A of the reference publication. The model was integrated and simulated using Copasi v4.5 (Build 30).

Representative curation result(s) - Mozilla Firefox

www.ebi.ac.uk/biomodels-main/simulation-result.do?uri=publ-model.do&mid=E

Representative curation result(s)



Computational Systems Neurobiology Group, European Bi

Curation information

BIOMD0000000005 - Tyson1991_CellCycle_6var

Download SBML | Other formats (auto-generated) | Actions | Submit Model Comment/Bug

Model | Overview

Publication ID: 1831270

Original Model: *BIOMD0000000005.xml.origin*

Submitter: Nicolas Le Novère

Submission ID: MODEL6614644188

Submission Date: 13 Sep 2005 12:31:08 UTC

Last Modification Date: 24 May 2010 16:33:07

Creation Date: 08 Feb 2005 18:28:27 UTC

Encoders: Bruce Shapiro
Vijayalakshmi Chelliah

This a model from the article:
Modeling the cell division cycle: cdc2 and cyc
Tyson JJ *Proc. Natl. Acad. Sci. U.S.A.*1991; 88(1
Abstract:
The proteins cdc2 and cyclin form a heterodime
cyclin is constructed. Simulation and analysis of
as a spontaneous oscillator, or as an excitable s
cycles in early embryos, and the excitable switc

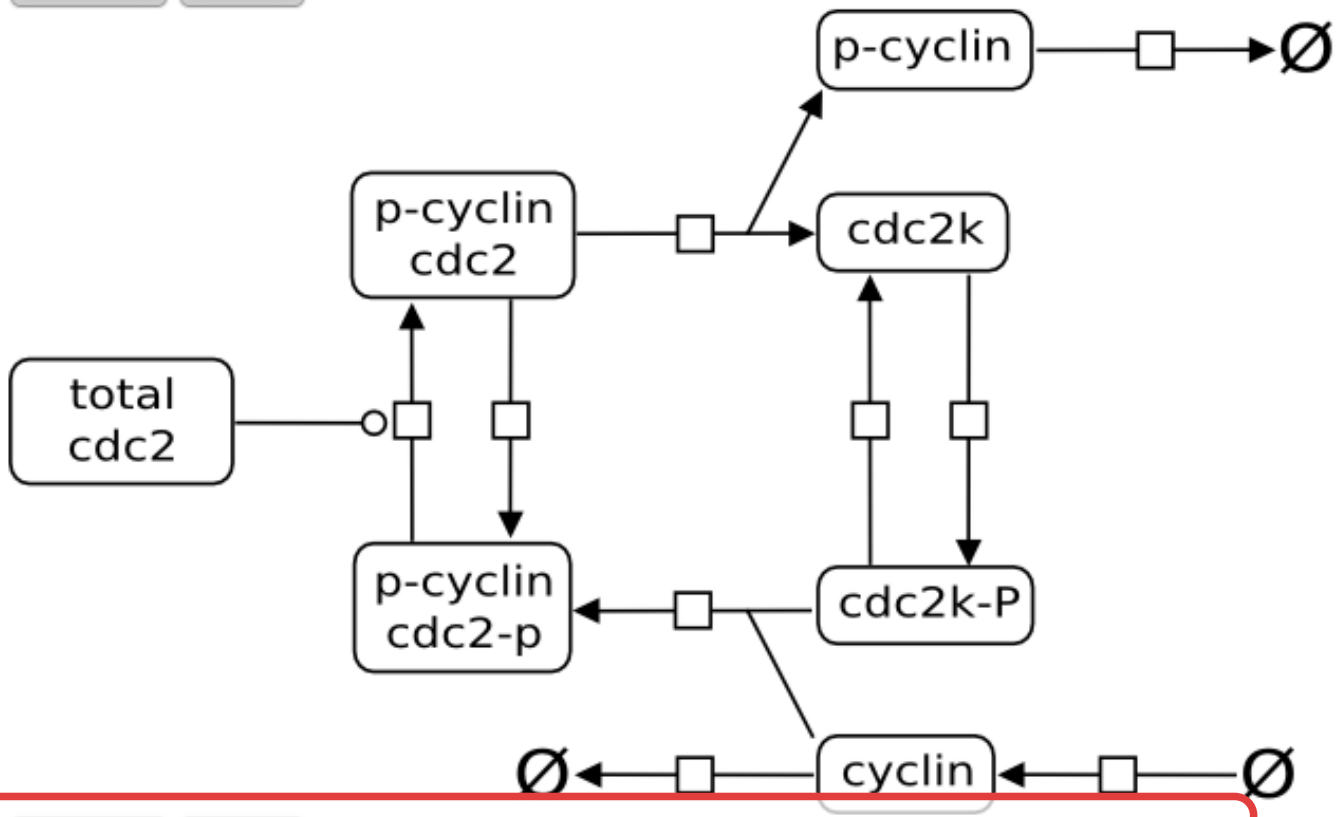
This model originates from BioModels Database
Team.
For more information see the terms of use.
To cite BioModels Database, please use: Li C, Donizelli M, Rodriguez N, Dharuri H, Endler L, Chelliah V, Li L, He E, Henry A, Stefan MI, Snoep JL, Hucka M, Le Novère N, Laibe C

BioModels Database - Mozilla Firefox

www.ebi.ac.uk/biomodels/models-main/publ/BIOMD0000000005/BIOMD0000000005.html

BIOMD0000000005

Refresh Close



Refresh Close

Graphical export

BIOMD0000000005 - Tyson1991_CellCycle_6var

Download SBML | Other formats (auto-generated) | Actions | Submit Model Comment/Bug

Actions menu:
- View Bitmap Reaction Graph
- View SVG Reaction Graph
- View Dynamic Reaction Graph
- View Model of Month
- JWS Online Simulation
- BioModels Online Simulation

Model | Overview | Math | Parameters | Curation

Publication ID: 1831270

Tyson JJ.
Modeling the cell d ctions.
Proc Natl Acad Sci
Department of Biology, Virginia Polytechnic Institute and State University, Blacksburg 24061. [more]

Model

Original Model: *BIOMD0000000005.xml.origin*

Submitter: Nicolas Le Novère

Submission ID: MODEL6614644188

Submission Date: 13 Sep 2005 12:31:08 UTC

Last Modification Date: 24 May 2010 16:33:07 UTC

Creation Date: 08 Feb 2005 18:28:27 UTC

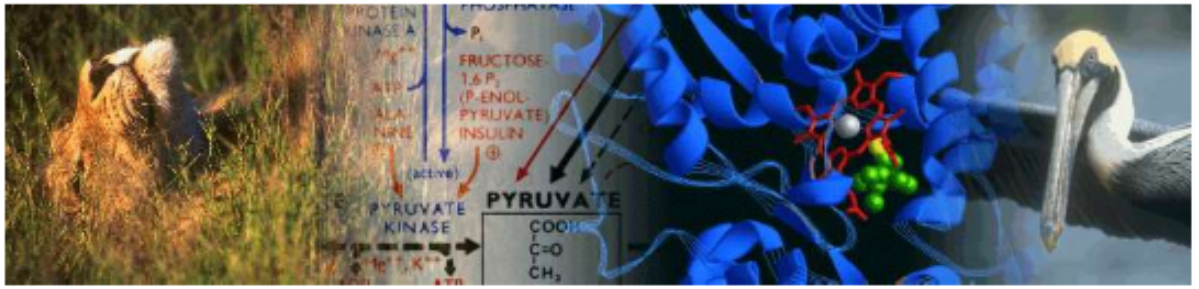
Encoders: Bruce Shapiro
Vijayalakshmi Chelliah

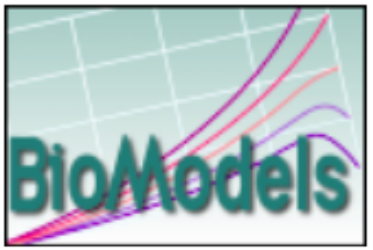
	bqbiol:occursIn	**Taxonomy** Opisthokonta
set #1	bqbiol:isVersionOf	**KEGG Pathway** sce04111 **Gene Ontology** mitotic cell cycle
	bqbiol:hasVersion	**Reactome** REACT_152

Notes

This a model from the article:
Modeling the cell division cycle: cdc2 and cyclin interactions.
Tyson JJ *Proc. Natl. Acad. Sci. U.S.A.*1991; 88(16); 7328-32 1831270,
Abstract:
The proteins cdc2 and cyclin form a heterodimer (maturation promoting factor) that controls the major events of the cell cycle. A mathematical model for the interactions of cdc2 and cyclin is constructed. Simulation and analysis of the model show that the control system can operate in three modes: as a steady state with high maturation promoting factor activity, as a spontaneous oscillator, or as an excitable switch. We associate the steady state with metaphase arrest in unfertilized eggs, the spontaneous oscillations with rapid division cycles in early embryos, and the excitable switch with growth-controlled division cycles typical of nonembryonic cells.

Online simulation





Biomodels: BIOMD0000000005 Tyson1991

Parame...	Value
cell	1.0
k6	1.0
k8notP	10000...
k9	1000.0
k3	200.0
k5notP	0.0
k1aa	0.015
k2	0.0
k7	0.6
k4	180.0
k4prime	0.018
EmptyS...	0.0
C2[0]	0.0
CP[0]	1.0
Mvar[0]	0.0
Y[0]	0.0
YP[0]	0.0
pM[0]	0.3

Evaluate Model

Sim State

Start value 0

End value 100

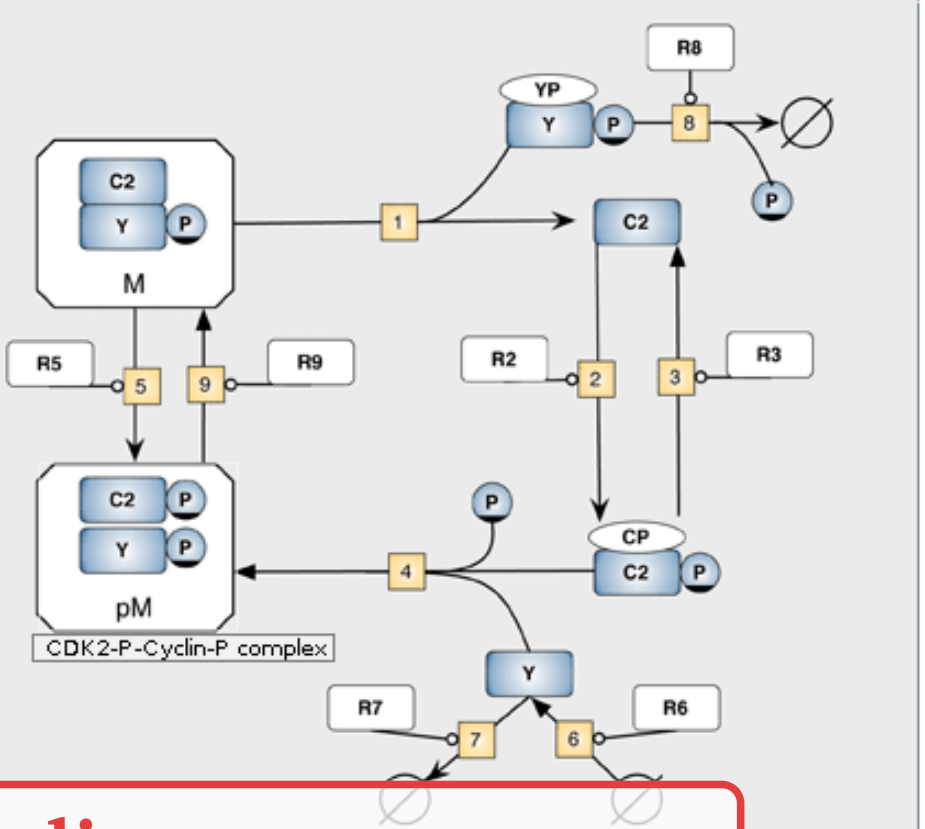
Rates

Metabolites

Select values

C2
CP
Mvar
Y
YP
pM

Param Reset



JWS Online

Applet started.

BIOMD0000000003 - Goldbeter1991_MinMitOscil

Download SBML | Other formats (auto-generated) | Actions | Submit Model Comment/Bug

Model | **Overview** | Math | Physical entities | Parameters | Curation

Create a submodel with selected elements — Deselect All

Model

Publication ID: 1833774 **Submission Date:** 13 Sep 2005 12:24:56 UTC **Last Modification Date:** 17 Mar 2010 00:25:38 UTC **Creation Date:** 06 Feb 2005 23:39:40 UTC

Mathematical expressions

Reactions

creation of cyclin	default degradation of cyclin	cdc2 kinase triggered degration of cyclin	activation of cdc2 kinase
deactivation of cdc2 kinase	activation of cyclin protease	deactivation of cyclin protease	

Rules

Assignment Rule (variable: V1)	Assignment Rule (variable: V3)

Physical entities

Compartments	Species		
cell	Cyclin	CDC-2 Kinase	Cyclin Protease

Global parameters

V1	V3	VM1	VM3
Kc			

Sub-model creation

BIOMD0000000003 - Goldbeter1991_MinMitOscil

Download SBML | Other formats (auto-generated) | Actions | Submit Model Comment/Bug

Model | **Overview** | Math | Physical entities | Parameters | Curation

Create a submodel with selected elements — Deselect All

Model

Publication ID: 1833774 | **Submission Date:** 13 Sep 2005 12:24:56 UTC | **Last Modification Date:** 17 Mar 2010 00:25:38 UTC | **Creation Date:** 06 Feb 2005 23:39:40 UTC

Mathematical expressions

Reactions

☑ creation of cyclin	☐ default degradation of cyclin	☐ cdc2 kinase triggered degration of cyclin	☐ activation of cdc2 kinase
☑ deactivation of cdc2 kinase	☐ activation of cyclin protease	☐ deactivation of cyclin protease	

Rules

Assignment Rule (variable: V1)	Assignment Rule (variable: V3)

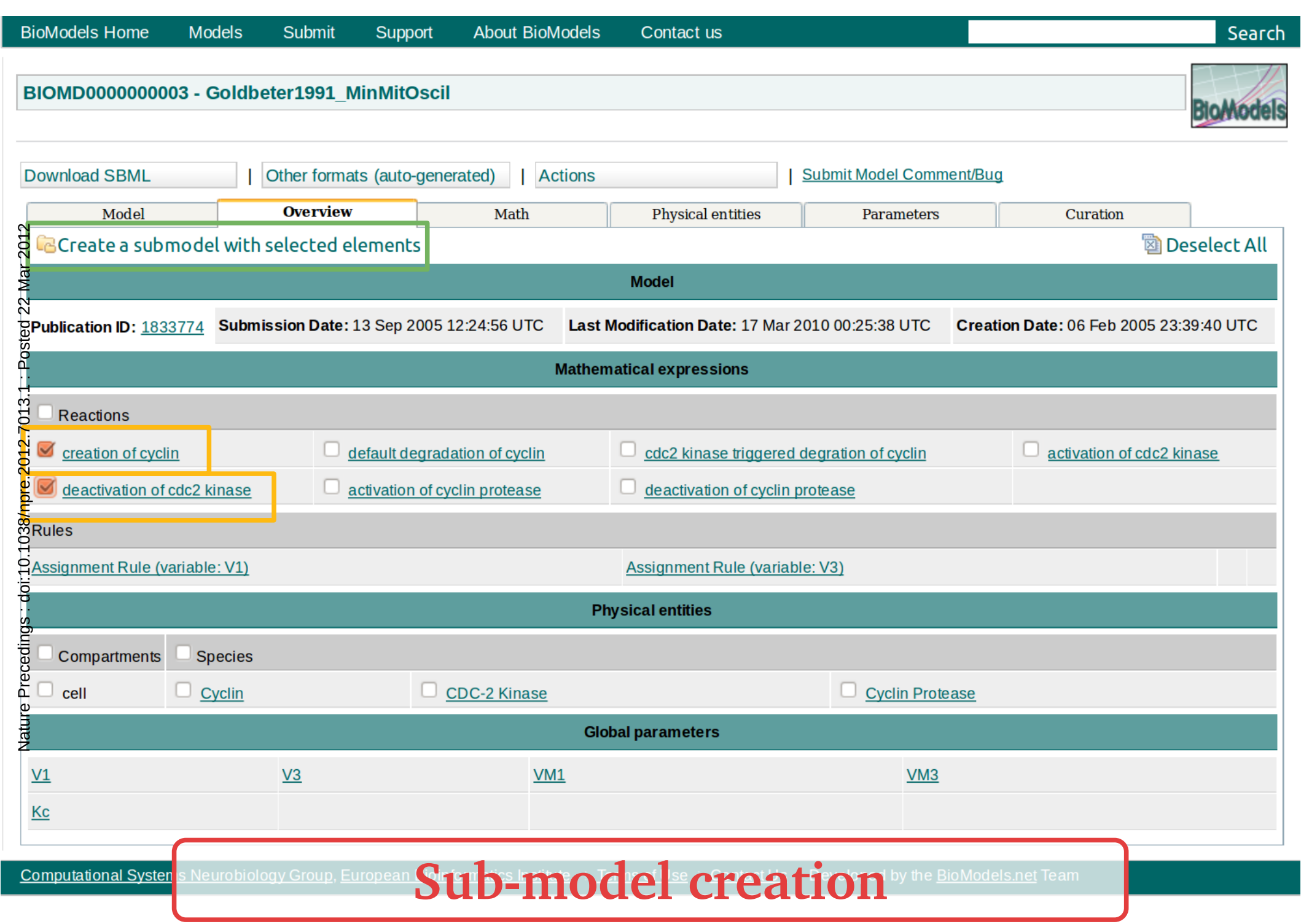
Physical entities

Compartments	Species		
☐ cell	☐ Cyclin	☐ CDC-2 Kinase	☐ Cyclin Protease

Global parameters

V1	V3	VM1	VM3
Kc			

Sub-model creation



BIOMD0000000003 - Goldbeter1991_MinMitOscil

Download SBML | Other formats (auto-generated) | Actions | Submit Model Comment/Bug

Overview | Math | Physical entities | Parameters | Curation | **Submodel1**

View the submodel in SBML — Save as

Reactions (2)	
creation of cyclin	→ [Cyclin];
deactivation of cdc2 kinase	[CDC-2 Kinase] → ;

Compartments (1)		
cell	set #1	bqbiol:is Gene Ontology cell
Referred to as: cell		

Species (2)	
Cyclin *Compartment: cell*	Initial concentration: 0.01 *(Units: substance)*
CDC-2 Kinase *Compartment: cell*	Initial concentration: 0.01 *(Units: substance)*

Rules (2)	
Assignment Rule	V1 = C * VM1 * pow(C + Kc, -1)
Assignment Rule	V3 = M * VM3

Sub-model creation

BIOMD0000000003 - Goldbeter1991_MinMitOscil

Download SBML | Other formats (auto-generated) | Actions | Submit Model Comment/Bug

Overview | Math | Physical entities | Parameters | Curation | **Submodel1**

View the submodel in SBML — Save as

Reactions (2)	
creation of cyclin	→ [Cyclin];
deactivation of cdc2 kinase	[CDC-2 Kinase] → ;

Compartments (1)		
cell	set #1	bqbiol:is Gene Ontology cell
Referred to as: cell		

Species (2)	
Cyclin *Compartment: cell*	Initial concentration: 0.01 *(Units: substance)*
CDC-2 Kinase *Compartment: cell*	Initial concentration: 0.01 *(Units: substance)*

Rules (2)	
Assignment Rule	V1 = C * VM1 * pow(C + Kc, -1)
Assignment Rule	V3 = M * VM3

Sub-model creation

Ayati et al., (2010). A mathematical model of bone remodeling dynamics for normal bone cell populations and myeloma bone disease.

January 2012, model of the month by *Vijayalakshmi Chelliah*
Original model: BIOMD0000000401, BIOMD0000000402, BIOMD0000000403

Bone is a dynamic tissue that is constantly being remodeled in order to maintain a healthy skeleton, which serves to support and protect vital internal organs. Besides its structural function, it has an essential metabolic function serving as a reserve of calcium and phosphate needed for the maintenance of the serum homeostasis.

Bone remodeling requires the coordinated action of four major types of bone cells: bone lining cells, osteocytes, osteoclasts (bone-resorping cells) and osteoblasts (bone-forming cells), organized in bone multicellular units (BMU). The process involves the removal of old or damaged bone by osteoclasts followed by the formation of new bone matrix by osteoblasts that subsequently become mineralized. The remodeling cycle consists of three consecutive phases: resorption, during which osteoclasts digest old bone; reversal, when mononuclear cells appear on the bone surface; and formation, when osteoblasts lay down new bone until the resorped bone is completely replaced. The coupling between bone resorption and formation, mediated by osteoclasts and osteoblasts respectively, are tightly regulated. Dysregulation of the above cycle causes various metabolic bone diseases such as osteoporosis, renal osteodystrophy, osteopetrosis, Paget's disease and rickets (or osteomalacia) [1].

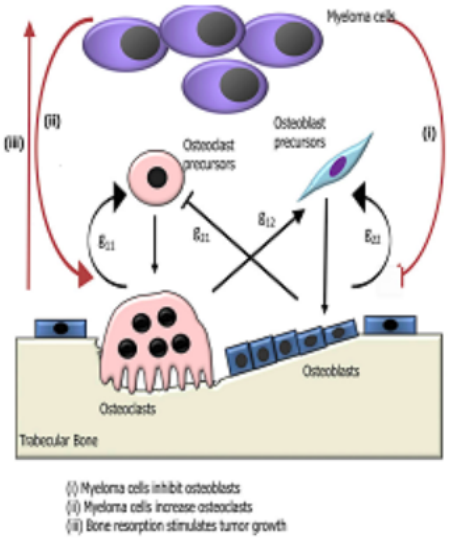
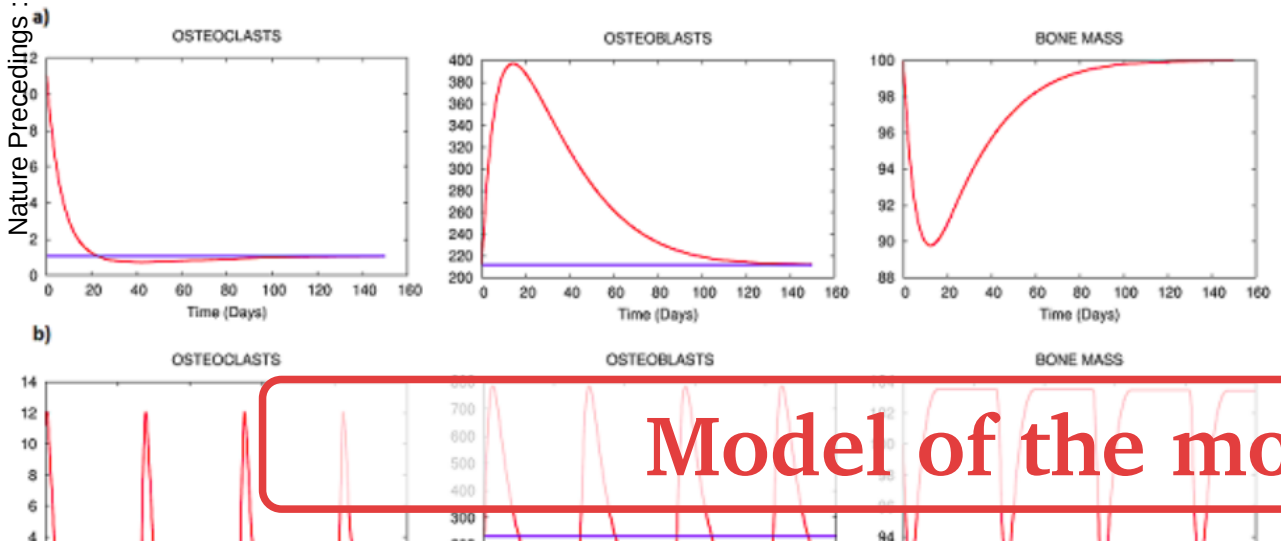


Figure 1: The effect of myeloma on the autocrine and paracrine signaling in the osteoclast and osteoblast cell populations in the presence of tumour is illustrated schematically. Figure taken from [2].



Mathematical modeling of bone remodeling has focused on various aspects, taking into account several key pathways that are involved in this process. Ayati *et al.* (2010) [2,BIOMD0000000401-3], have modelled the influence of tumour growth on bone remodeling. In particular, the influence of tumour growth on the autocrine and paracrine signaling of osteoclast and osteoblast cell population is well explored in this article. Patients with multiple myeloma have abnormal bone remodeling, i.e. the resorption and formation become uncoupled, with the end being an increase in bone resorption and a decrease in bone formation (causing weaker bones). **Figure 1** shows schematically the effects of myeloma on the autocrine and paracrine signaling in the osteoclast and osteoblast cell populations in the presence of tumour.

Ayati et al. (2010), have used the already existing mathematical models of bone remodeling described by Komarova et al., 2003 [3, BIOMD0000000148] and Komarova 2005 [4, BIOMD0000000279],

Model of the month

BIOMD0000000049 - Sasagawa2005_MAPK

Download SBML | Other formats (auto-generated) | Actions | Submit Model Comment/Bug

Model | Overview | Math | Physical entities | Parameters | Curation

Publication ID: 15793571

Sasagawa S, Ozaki Y, Fujita K, Kuroda S.
Prediction and validation of the distinct dynamics of transient and sustained ERK activation.
Nat Cell Biol 2005 Apr;7(4):365-73.
Undergraduate Program for Bioinformatics and Systems Biology, Graduate School of Information Science and Technology, Univers

Original Model: *BIOMD0000000049.xml.origin*

Submitter: Shinya Kuroda

Submission ID: MODEL6624243033

Submission Date: 12 Jan 2006 13:42:52 UTC

Last Modification Date: 10 Jun 2011 18:18:14 UTC

Creation Date: 21 Dec 2005 10:59:39 UTC

Encoders: Lu Li
Shinya Kuroda

set #1	bqbiol:isVersionOf	Gene Ontology epidermal growth factor receptor signaling pathway Gene Ontology Ras protein signal transduction Gene Ontology nerve growth factor receptor signaling pathway Gene Ontology MAPKKK cascade
	bqbiol:occursIn	Taxonomy Rattus

This a model from the article:
Prediction and validation of the distinct dynamics of transient and sustained ERK activation.
Sasagawa S, Ozaki Y, Fujita K, Kuroda S *Nat. Cell Biol.*[2005 Apr; Volume: 7 (Issue: 4)]: 365-73 15793571,
Abstract:
To elucidate the hidden dynamics of extracellular-signal-regulated kinase (ERK) signalling networks, we developed a simulation model of ERK signalling networks by constraining in si
not on their final concentrations, whereas sustained ERK activation depends on the final concentration of NGF but not on the temporal rate of increase. These ERK dynamics depend or
concentration of growth factors, and encode these distinct physical properties into transient and sustained ERK activation, respectively.

Dynamics of active Ras, active Rap1 and phosphorylated ERK were [illegible] with [illegible]

BioModels Web Services

Available features

With BioModels Web Services, users can access the up-to-date resources in BioModels Database without installing a local copy of the database. There are a range of available features for searching and retrieving models. Furthermore, some features can help users to extract interesting parts from a large model and construct them into a submodel. For any comments or new feature enquiries, please feel free to contact us.

- Available features
- javadoc
- WSDL

The WSDL (Web Services Description Language) defines and describes the available features in an XML format file. This enables third-party sofware to automate parsing all available features of BioModels Web Services. Comparing with WSDL, Javadoc is API documentation which provides more information to the developers.

Download

We provide two versions of the library for querying BioModels Database Web Services. These are available for download from the SourceForge project download page (latest release: 2.12):

- light version (you need a couple of external jars to use it)
- standalone version (all the dependencies are already included in the jar)

These are the dependencies only needed by light-weight library.

- axis.jar (version 1.4)
- commons-discovery.jar (version 0.4)
- commons-logging.jar (version 1.1.1)
- jaxrpc.jar
- mail.jar (version 1.4.3)
- saaj.jar
- wsdl4j.jar (version 1.6.2)

Note: you can find the latest version of each of these packages on their official web site.

Java 1.5 (or newer) is required in order to use the library.

Basics - Getting Started

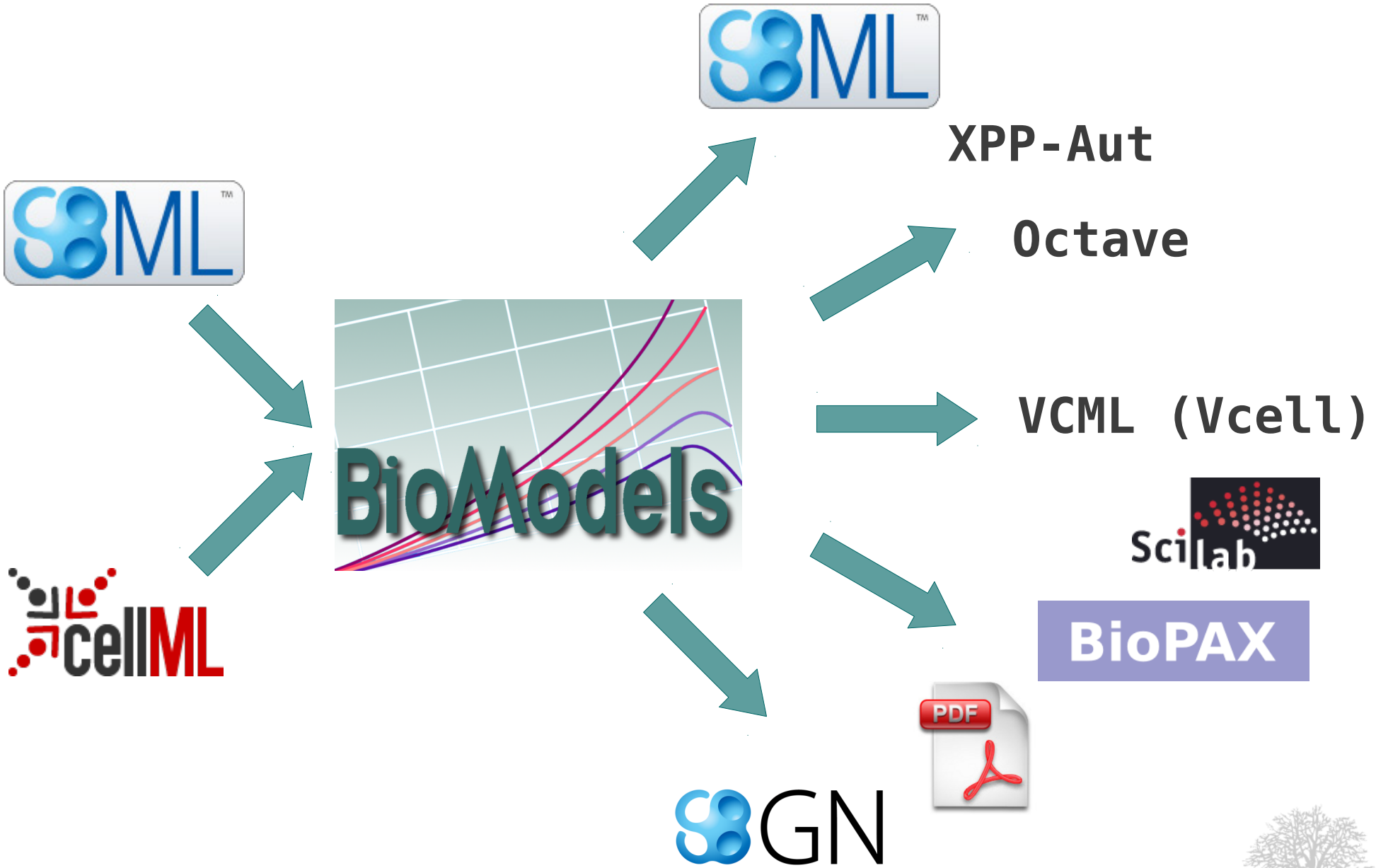
First, download the library we provide.

Assuming that you downloaded the biomodels-wslib_standalone.jar, let's write a simple HelloBioModels.java to test if it works on your environment.

```
import uk.ac.ebi.biomodels.*;
```

Supported formats

Nature Precedings : doi:10.1038/npre.2012.7013.1 : Posted 22 Mar 2012

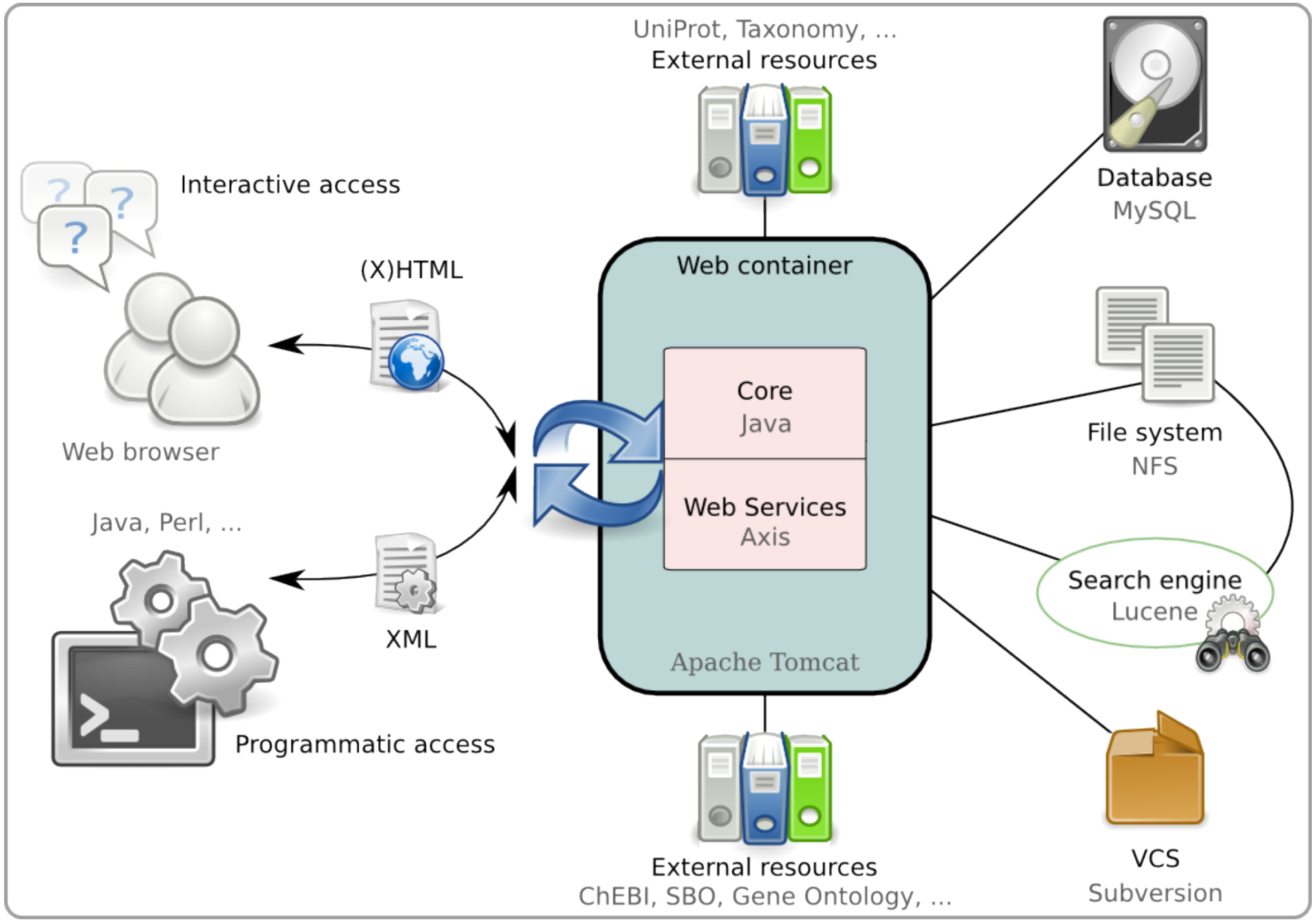


Converter framework

- **System Biology Format Converter**
- generic framework that potentially allows any conversion between two formats
- aims to be easily extended
- currently supported: conversion from SBML to SBGN-ML, BioPAX Level 2 and Level 3, XPP, Octave, Dot, ...
- allows the combination of several existing converters (conversion pipeline)
- collaborative project developed in Java
- online conversion service:
  - http://www.ebi.ac.uk/compneur-srv/converters/ (*beta*)

http://sourceforge.net/projects/sbfc

Current infrastructure



Nature Precedings : doi:10.1038/npre.2012.7013.1 : Posted 22 Mar 2012

Technologies

- Java
- Apache Tomcat
- Apache HTTP Server
- MySQL server
- Subversion
- Apache Lucene
- SOSlib
- Gnuplot
- several converters
- numerous libraries
- Bash scripts
- ...

http://sourceforge.net/projects/biomodels/

http://www.ebi.ac.uk/biomodels-main/develop

Current development model

- **Open source**

  GNU General Public License

  sources available from SourceForge.net

- main development and maintenance work done at **EMBL-EBI**

  (BioModels.net team)

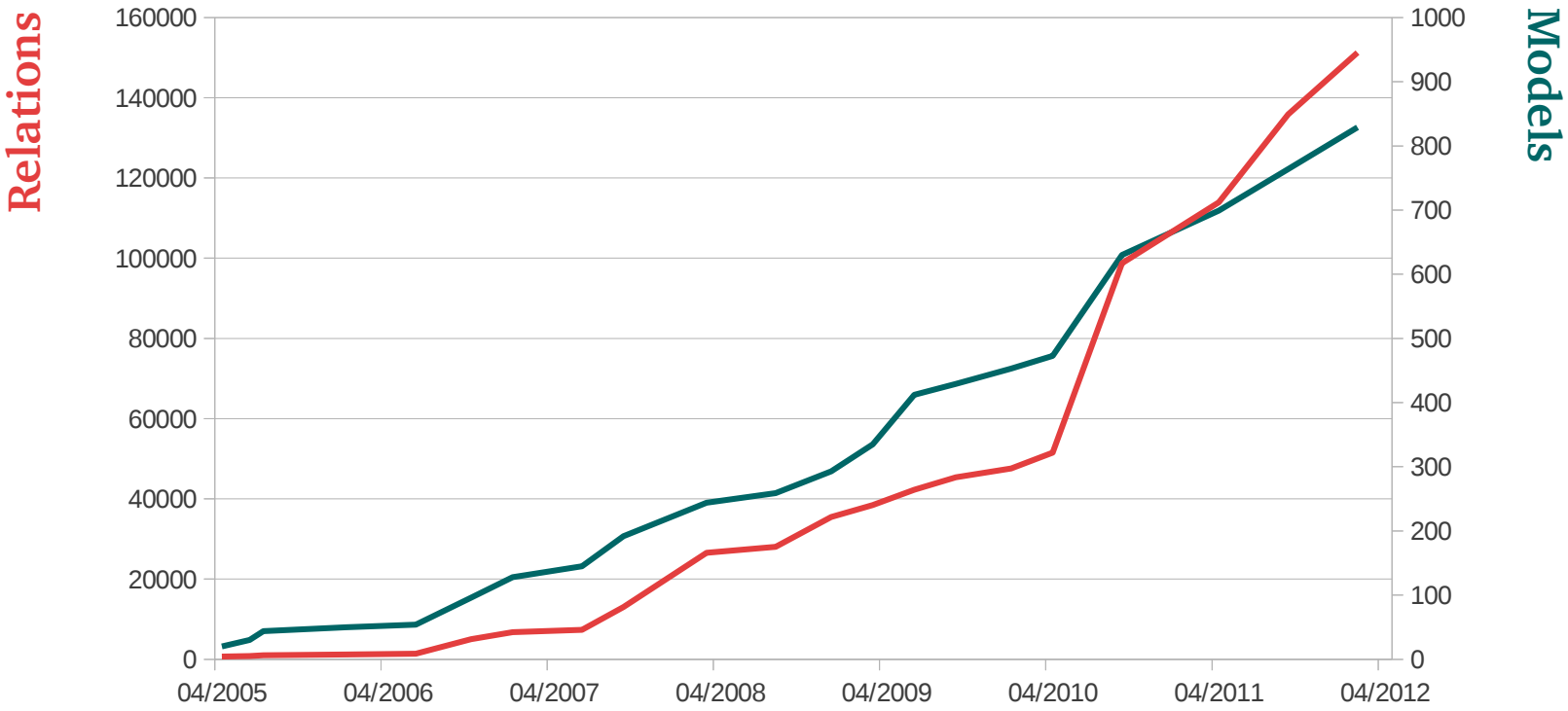
- main instance running at **EMBL-EBI** (UK)

  and one mirror at **Caltech** (USA)

(new) challenges

Content evolution

Nature Precedings : doi:10.1038/npre.2012.7013.1 : Posted 22 Mar 2012



Evolution of the content of BioModels Database

Increasing size and complexity of models

- Global reconstruction of the human metabolic network (MODEL6399676120)

  17919 species
- Genome-scale human metabolic modeling (MODEL1105100000)

  25600 species, 4894 reactions
- Global model for the yeast molecular interaction network (MODEL3883569319)

  130325 species, 36265 annotations

Challenges

- storage infrastructure
  - suitability of some technologies
  - performance

Challenges

- annotation
  - semi-automatic annotation

Annotation and merging of SBML models with semanticSBML. Krause F, Uhlendorf J., Lubitz T., Schulz M., Klipp E., Liebermeister W. Bioinformatics (2009)

Saint: a lightweight integration environment for model annotation. Lister, A. L., Pocock, M., Taschuk, M. & Wipat, A. Bioinformatics (2009)

  - collaborative annotation

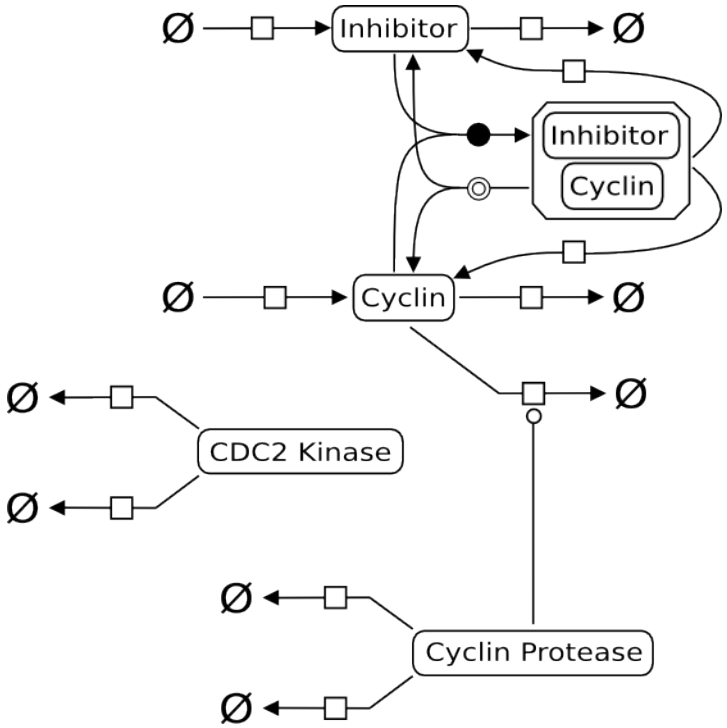
Payao: a community platform for SBML pathway model curation. Matsuoka Y , Ghosh S , Kikuchi N , Kitano H. Bioinformatics (2010)

BioCatalogue: a universal catalogue of web services for the life sciences. Bhagat J, Tanoh F, Nzuobontane E, Laurent T, Orlowski J, Roos M, Wolstencroft K, Aleksejevs S, Stevens R, Pettifer S, Lopez R, Goble CA. Nucleic Acids Res (2010)

The Pfam protein families database. M. Punta, P.C. Coggill, R.Y. Eberhardt, J. Mistry, J. Tate, C. Boursnell, N. Pang, K. Forslund, G. Ceric, J. Clements, A. Heger, L. Holm, E.L.L. Sonnhammer, S.R. Eddy, A. Bateman, R.D. Finn. Nucleic Acids Research (2012)

Challenges

- display
  - textual
  - graphical



Challenges

- search engines
  - speed
  - ranked results
  - making full use of annotations (e.g. ontologies and classifications)

Ranked Retrieval of Computational Biology Models. Henkel R., Endler L., Le Novère N., Peters A., Waltemath D. BMC Bioinformatics (2010)

Retrieval, alignment, and clustering of computational models based on semantic annotations. Schulz M., Krause F., Le Novere N., Klipp E., Liebermeister W. Molecular Systems Biology (2011)

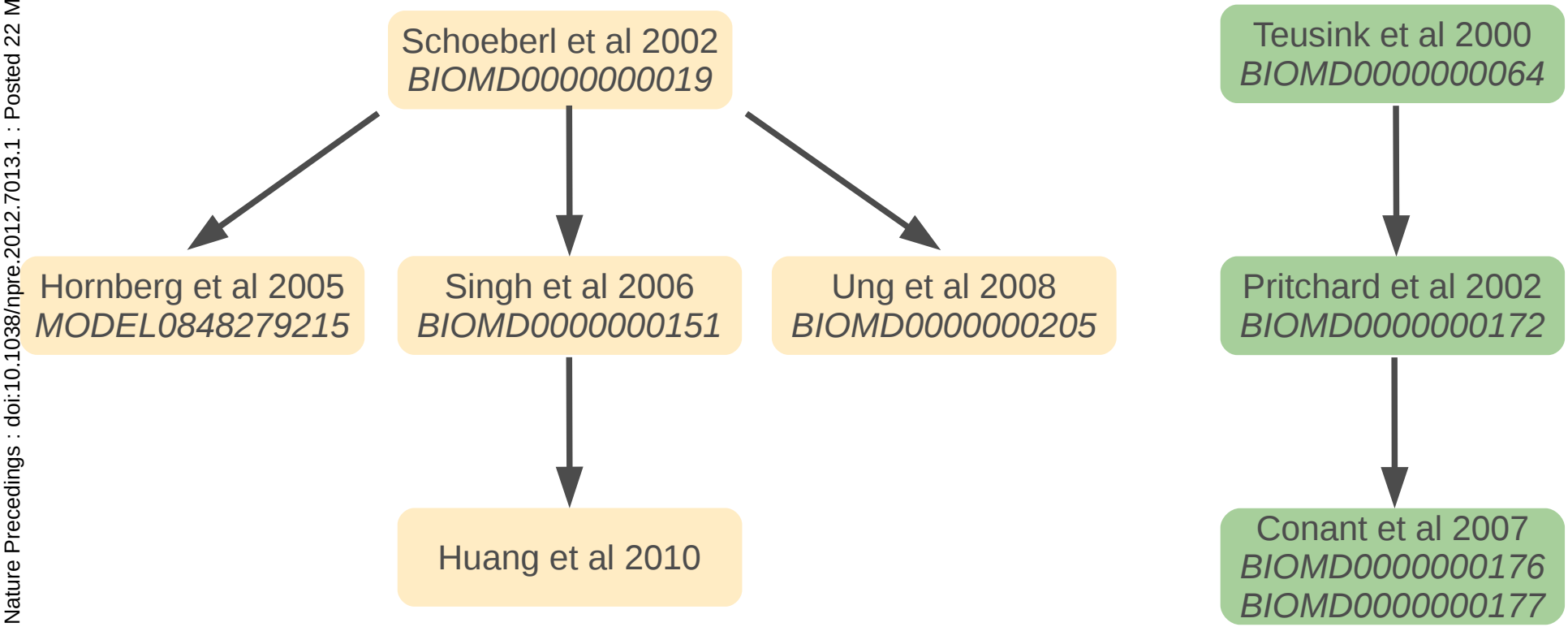
Challenges

- collaborative model development
  - model versioning
  - model comparison
  - ...

Version control of pathway models using XML patches. Saffrey P, Orton R. BMC Systems Biology (2009)

Revision history aware repositories of computational models of biological systems. Miller, A.K., Yu, T., Britten, R., Cooling, M.T., Lawson, J., Cowan, D., Garny, A., Halstead, M.D., Hunter, P.J., Nickerson, D.P., Nunns, G., Wimalaratne, S.M., Nielsen, P.M. BMC Bioinformatics (2011)

New ways to build models



Challenges

- linked (open) data
  - structured data
  - URIs
  - SPARQL endpoints
  - …

Bio2RDF: Towards a mashup to build bioinformatics knowledge systems. Belleau F, Nolin MA, Tourigny N, Rigault P, Morissette J. Journal of Biomedical Informatics (2008)

An infrastructure for ontology-based information systems in biomedicine: RICORDO case study. Wimalaratne SM, Grenon P, Hoehndorf R, Gkoutos GV, de Bono B. Bioinformatics (2012)

Challenges

- data integration, verification by reasoning, querying, ...
  - OWL

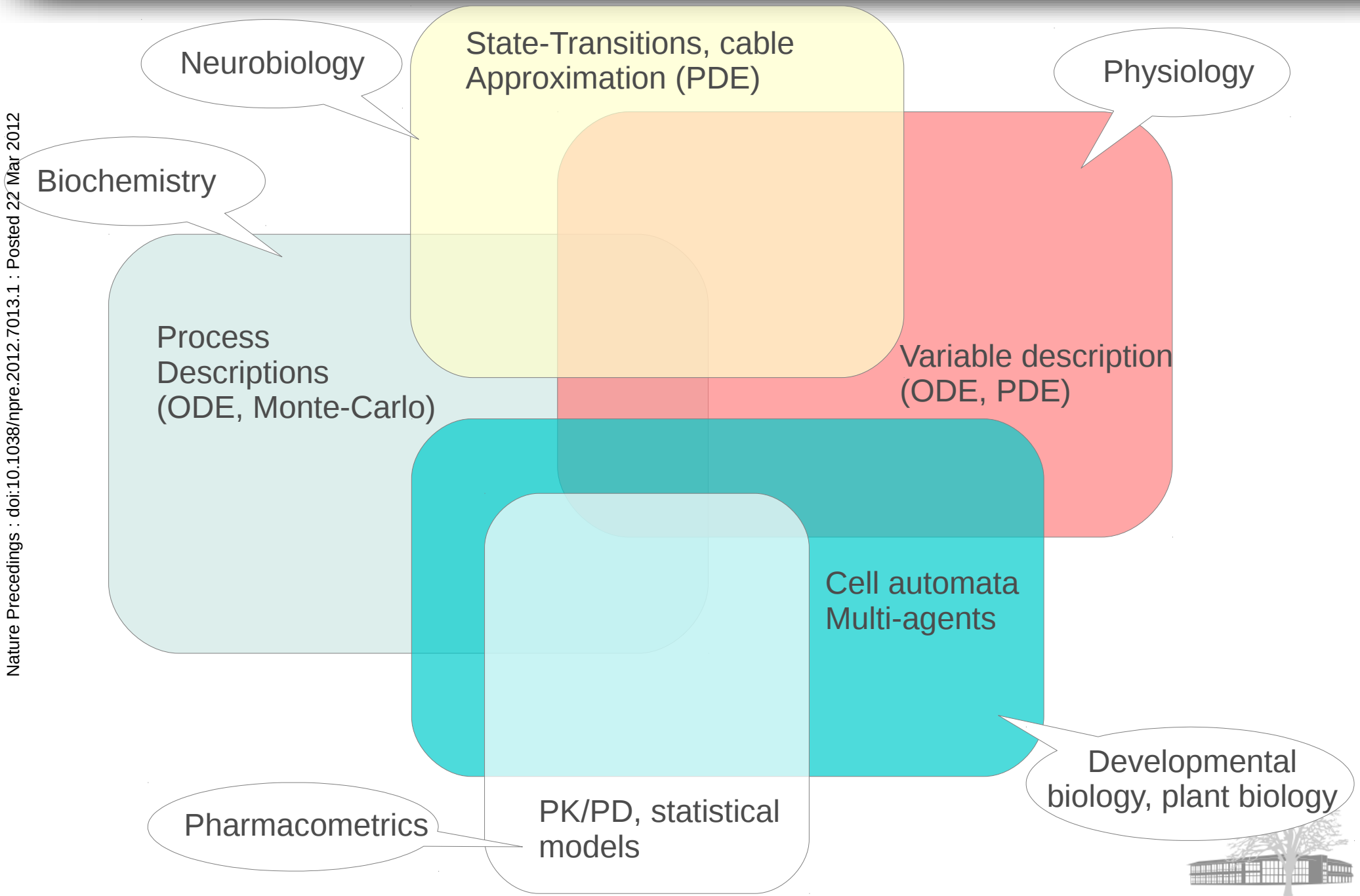
Annotation of SBML models through rule-based semantic integration. Lister AL, Lord P, Pocock M, Wipat A. J Biomed Semantics (2010)

Integrating systems biology models and biomedical ontologies. Hoehndorf R, Dumontier M, Gennari JH, Wimalaratne S, de Bono B, Cook DL, Gkoutos GV. BMC Syst Biol (2011)

Challenges

- different communities
  - new formats but similar needs

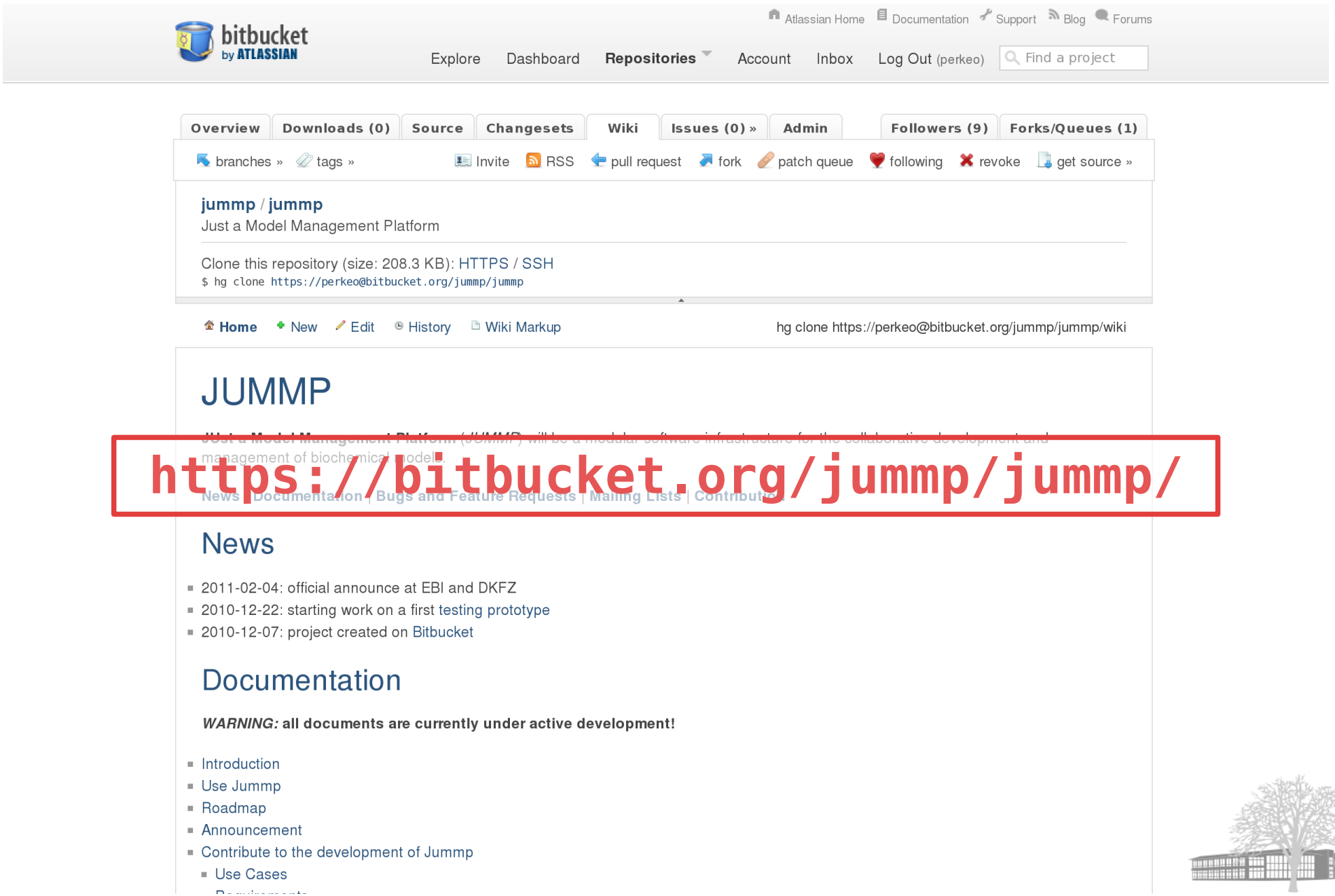
Numerous modelling approaches



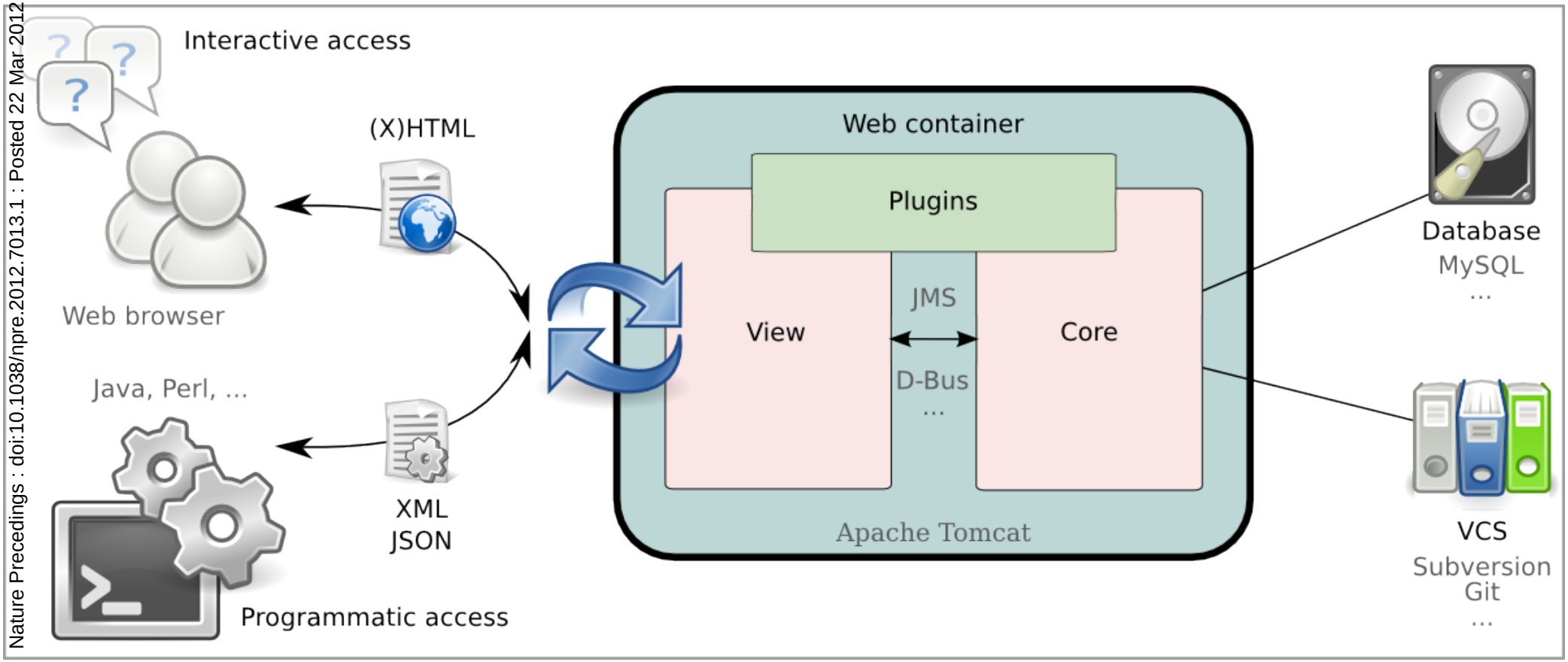
New infrastructure requirements

- **Features**
  - format independent
  - full model versioning
  - ranked search results (making full use of annotations)
  - private secured access to the pipeline for the models you submitted
  - collaboration: model sharing and development
  - standard access for reviewers (before model publication)
- **Software**
  - easy deployment and reuse (independent of EBI infrastructure)
  - easy to extend (usage of plugins)
  - improved performance (more and larger models)
  - improved security
  - customisable theme
  - ...

JUMMP: JUst a Model Management Platform



JUMMP: architecture



Technologies

- Groovy
- Grails (Spring, Hibernate, …)
- Spring Security
- Hibernate Search
- Apache ActiveMQ / D-Bus
- jQuery, jQuery UI
- JSBML
- Subversion / Git
- …

Development model

- new application focused on **security**, **performance** and **flexibility**
- multiple instances running in various institutes (various projects using the software to run their infrastructure)
- EBI (and its mirrors) remains the location where models are **publicly** available

- **community** developed project
  - initially undertaken by:
    - European Bioinformatics Institute (EBI)
    - German Cancer Research Center (DKFZ)

JUMMP: acknowledgements

- Jürgen Eils
- Martin Gräßlin
- Jochen Schramm
- Michael Hoehl

Acknowledgements

Nature Precedings : doi:10.1038/npre.2012.7013.1 : Posted 22 Mar 2012

BioModels.net Team:

- Viji Chelliah
- Mihai Glont
- Nick Juty
- Sarah Keating
- **Camille Laibe**
- Nicolas Le Novère
- Stuart Moodie
- Nicolas Rodriguez
- Maciej Swat
- Yangyang Zhao

EMBL

BBSRC bioscience for the future

NIGMS

ELIXIR

camille.laibe@ebi.ac.uk