Towards a public repository for pharmacodynamic/pharmacokinetic models?

Nicolas Le Novère, Camille Laibe, EMBL-EBI

EMBL-EBI

The models I am not going to talk about

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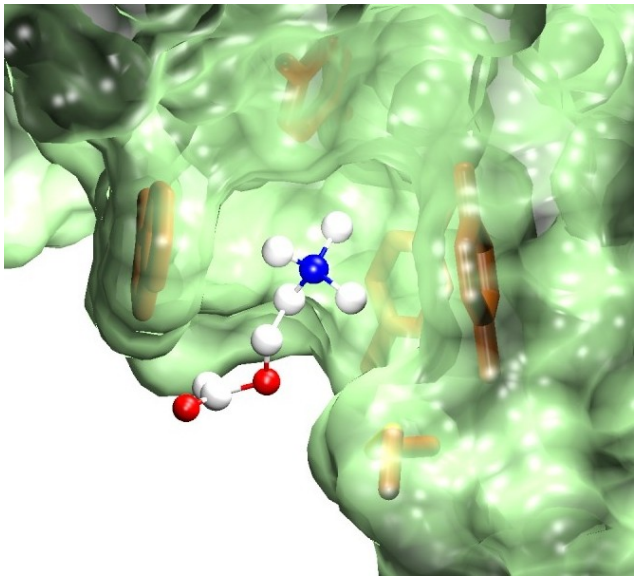
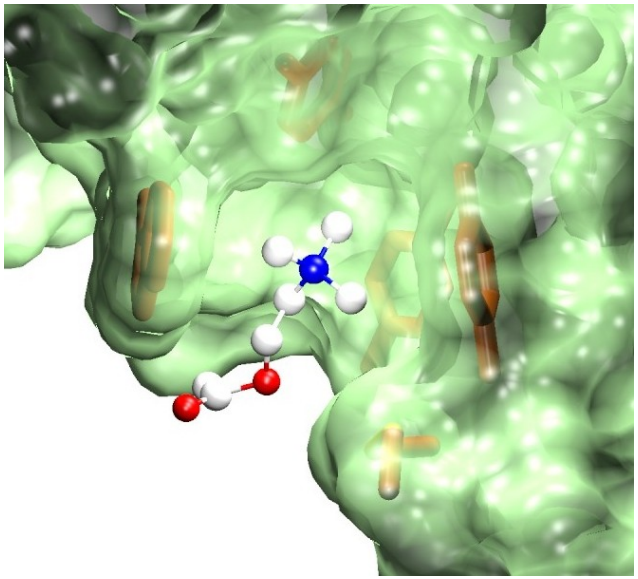
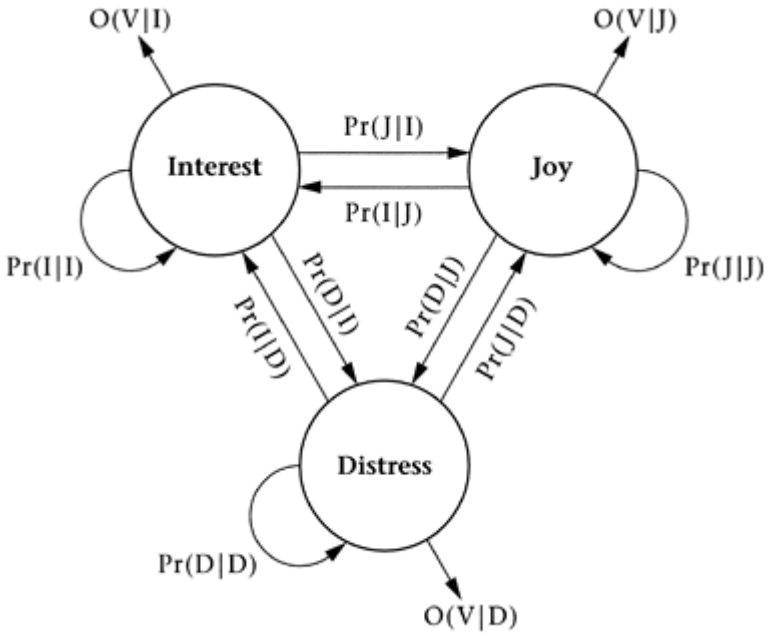
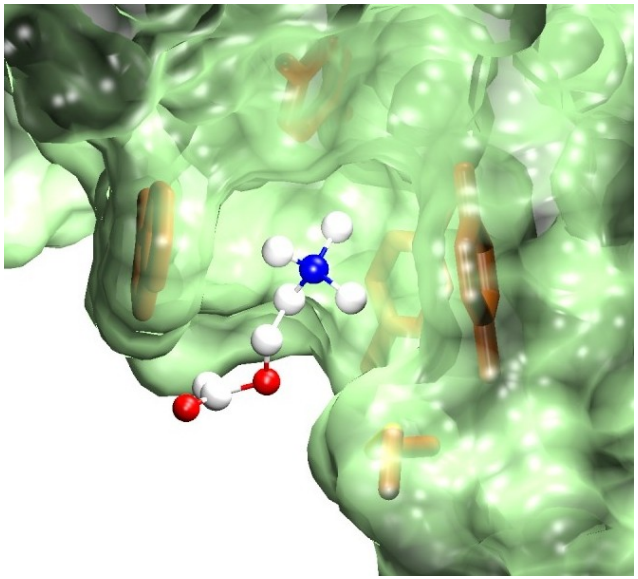


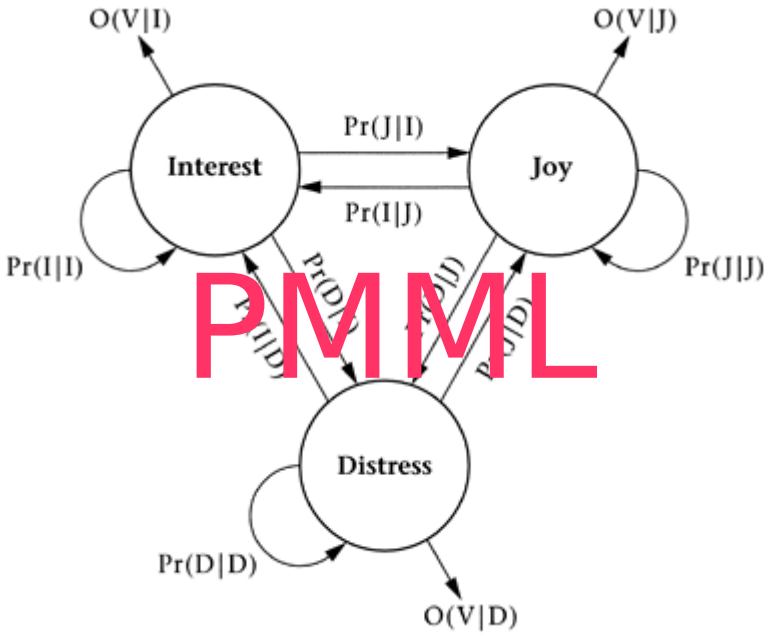
The models I am not going to talk about





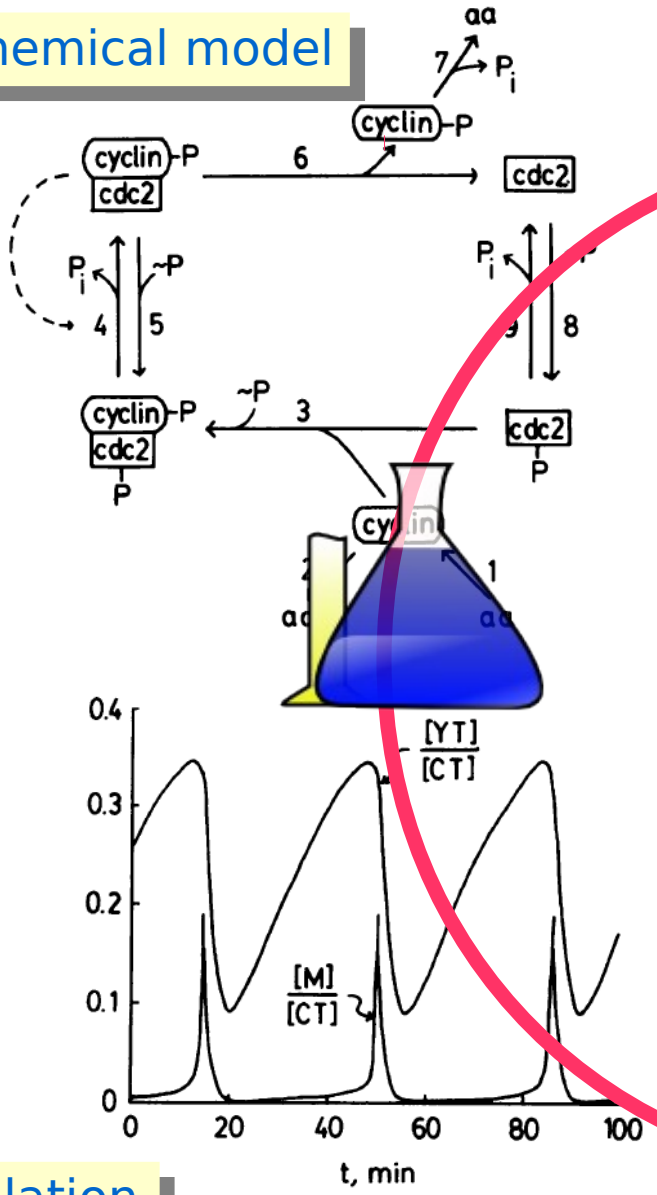
The models I am not going to talk about





The models I am going to talk about

biochemical 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		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

Definitions

- **Model**
  *"a **model** (M) for a **system** (S) and an **experiment** (E) is anything to which E can be applied in order to answer questions about S"* (Cellier 1991).
  Here we consider only numerical models, where the system S is described by mathematical relationships (quantitative or logical).

- **Pharmacodynamics**

  Study of the physiological effects of drugs on the body or on microorganisms or parasites within or on the body and the mechanisms of drug action and the relationship between drug concentration and effect.
  What a substance does to a body

- **Pharmacokinetics**

  Determination of the fate of substances administered externally to a living organism.
  What a body does to a substance

- **(L)ADME**

  (Liberation) Absorption, Distribution, Metabolism, and Excretion

Motivation for a public model repository

- Computational models, as with any other scientific production, must be not only “described” in the literature, but “**delivered**” to the community.
- Integrative Biology, Medicine and Pharmacology require the **integration** of computational models with **other type of information** publicly available.
- Modellers increasingly reuse and combine existing models. A **one stop-shop** allows them to access all “published” (large sense) models of interest.
- The number and complexity of quantitative models in biology are increasing rapidly. It often becomes **impractical and error-prone** to reimplement models from literature.
- Companies carefully built and enriched models for years. Their current willingness to share this knowledge is hinder by the lack of media to do so.

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- Companies carefully built and enriched models for years. Their current willingness to share this knowledge is hinder by the lack of media to do so.
- Existence of a population of users for a **freely available** repository
- Existence of a population of **submitters**
- Endorsement of **publishers** (advising deposition) and support of **industry** (submission and use)

Requirements for such a resource

For easy and efficient use of existing models:

- It must be possible to **encode** the models in **machine-readable** formats
- Models must be **accessible** and fully described (no black box)
- Users must be able to **trust** that the models are faithful and accurate
- The resource should not be a mere repository but a fully fledged **database** (annotations, search, online tools etc).
- Different levels and modes of access should be available, with mechanisms for changing the status of a model.
- Resource should neither focus on a particular biological substrate, process or species, nor specialise on a given modelling approach.

the Systems Biology Markup Language

- Way to exchange and reuse descriptions of quantitative models in biology
- Computer-readable format but not a programming or procedural language
- Built on other standards: MathML, XHTML, RDF, existing ontologies, ...
- Basic tools are provided to read, validate, write and process SBML. No need to re-invent the wheel. Let the user focus on science instead.
- Supported by a large and evolving community since 2000
  - active mailing lists (over 240 registered users and 5400 posts to sbml-discuss as of October 2009)
  - over 175 software systems claiming support
- Recommended by many journals (Public Library of Science, Nature Publishing Group, BioMed Central, ...)
- Level 3 is modular and extendible (core + packages)

SBML.org — The Systems Biology Markup Language

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

For the curious

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

For modelers

Are you looking for ready-to-run software that supports SBML? The **SBML Software Guide** lists over **175** systems today. Are you instead looking for ready-to-use models? Visit the **BioModels Database**, where you can find hundreds!

For software developers

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

No matter how you use SBML, we invite you to sign up for news updates either through our **RSS feed**, our **Twitter feed**, or one of the **mailing lists**, and get involved with community efforts to help keep improving SBML. You can also call attention to your project's support of SBML by displaying the **SBML logo**.

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

SBML News

SBMLeditor 1.3.4 released
(20 Nov.'09) **SBMLeditor** is a portable (written in Java), simple, low-level SBML editor. This release supports SBML L2v4 and the latest libSBML.

Review SBML on SourceForge!
(12 Nov.'09) SourceForge.net has a review system for projects. Please use it to **vote & comment** on the SBML project!

Call for SBML Editor nominations
(10 Nov.'09) The nomination phase for two new SBML Editors is **now open**.

Older news ...

Community News

BioMet Toolbox
(29 Oct.'09) **BioMet Toolbox** is a web-based toolbox for analyzing genome-scale models.

modelMaGe v. 1.0beta
(27 Oct.'09) **modelMaGe** can generate models and fit models to data.

CycSim supports SBML
(27 Oct.'09) **CycSim** is a pathway genome simulator supporting constraint-based models of metabolism.

Older news ...

>170 tools supporting SBML

SBML Software Matrix

This matrix provides an at-a-glance summary of software known to us to provide some degree of support for reading, writing, or otherwise working with SBML. The columns' meanings are explained below. For a list of longer descriptions grouped into themes, please see our **SBML Software Summary** page.

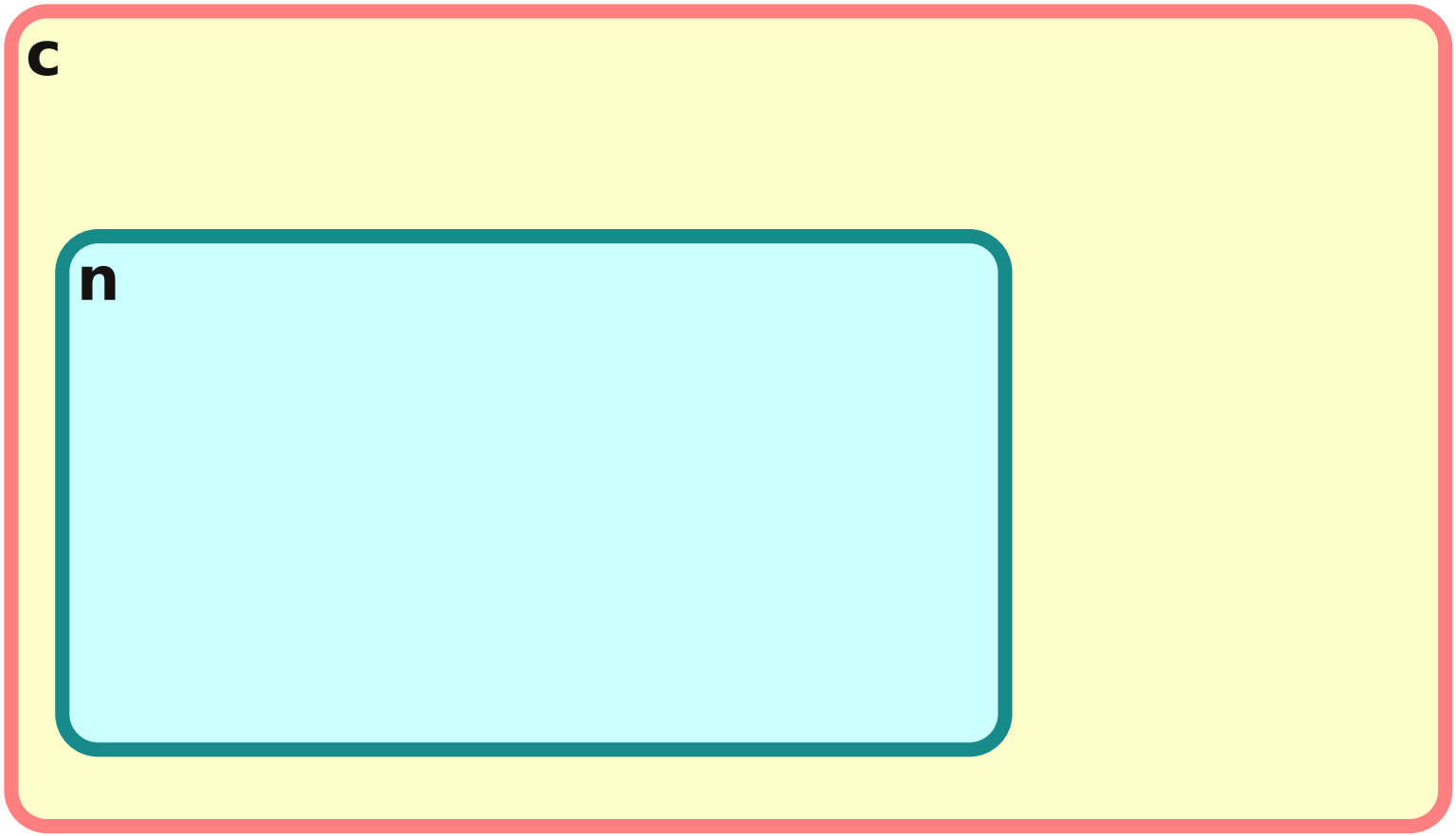
	Capabilities					Frameworks							API	Dep.	Platforms	SBML		Availabil.		
	Creation	Simulation	Analysis	Database	Utility	ODE	DAE	PDE	Stochastic	Events	Logical	Other				Import	Export	Open source	Academic use	Commercial use
acslXtreme	•														W	•			$	$
ALC	•					•	•		•			•			L, W, M, B		•	•	F	F
Asmparts	•				•	•									L,W	•	•	•	F	F
Antimony	•				•								C, C++		L, W, M	•	•	•	F	F
AutoSBW			•			•							SBW	SBW	L, W, M	•	•	•	F	F
AVIS												•		various	L	•		•	F	F
BALSA	•													Sigtran						
BASIS	•	•		•					•	•			WS		B	•	•	•	F	F
BetaWB	•	•	•						•	•					L,W,M		•		F	F
BiNoM	•		•		•							•			L, W, M	•	•	•	F	F
BiNoM Cytoscape Plugin	•		•		•							•		Cytoscape	L, W, M	•	•	•	F	F
BIOCHAM		•			•	•									L,W,M		•	•	F	F
BioCharon	•	•	•		•	•								CHARON						
Biological Networks	•		•		•										L,W,M	•	•		F	$
BioCyc				•													•		F	$
BioGrid																				

The columns of this table should be read in the following way:

- *Capabilities* summarizes the facilities that a package provides by itself (i.e., without invoking another package) for working with SBML: "Creation" = creating/editing models, "Simulation" = performing time-series simulation of models, "Analysis" = analyzing models (e.g., sensitivity analysis, flux-balance analysis, etc.), "Database" = providing a database of models, and "Utility" = providing other utility functions (e.g., translating SBML to/from other formats).

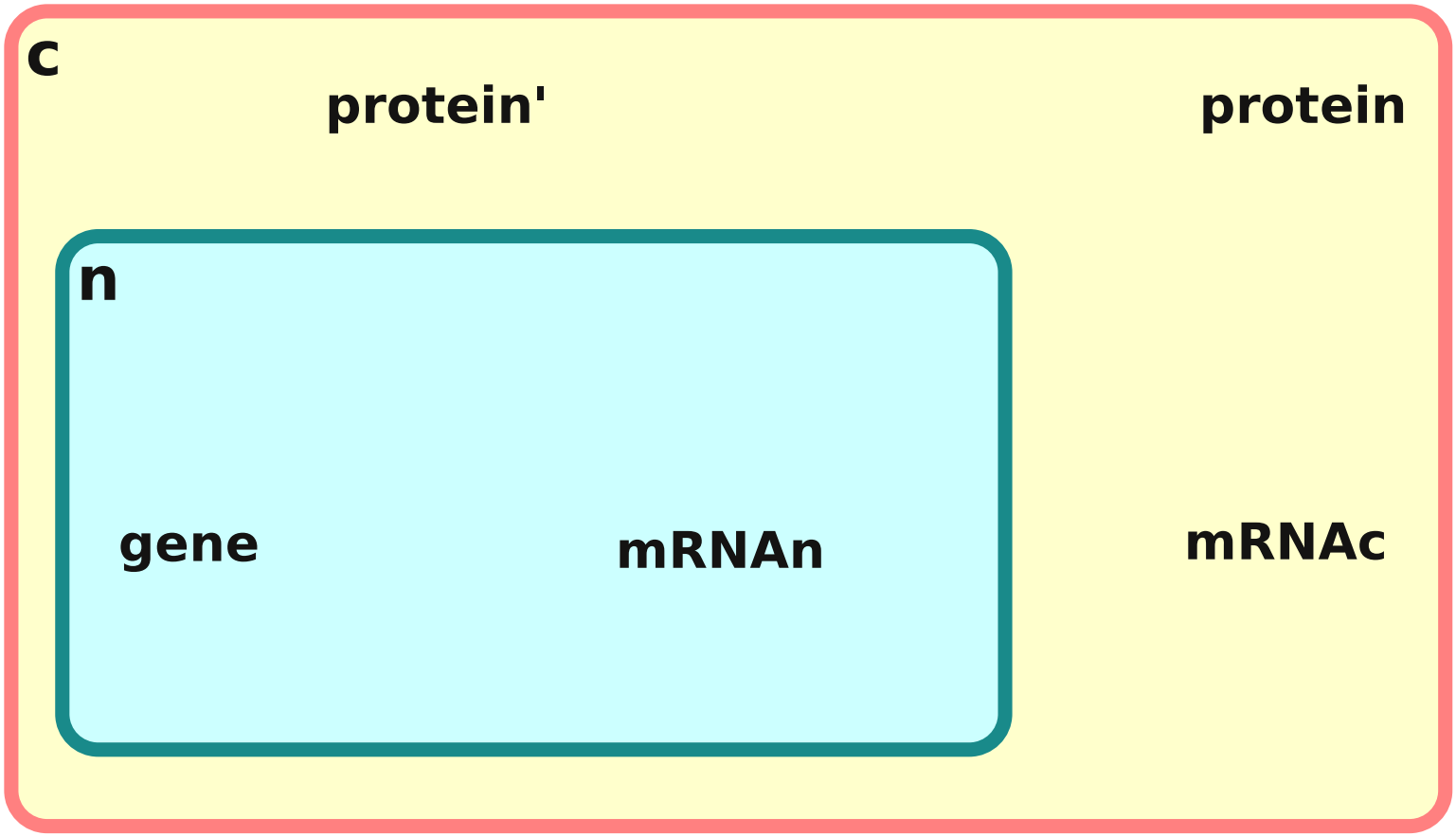
What can we encode in SBML Level 2?

containers (compartments)



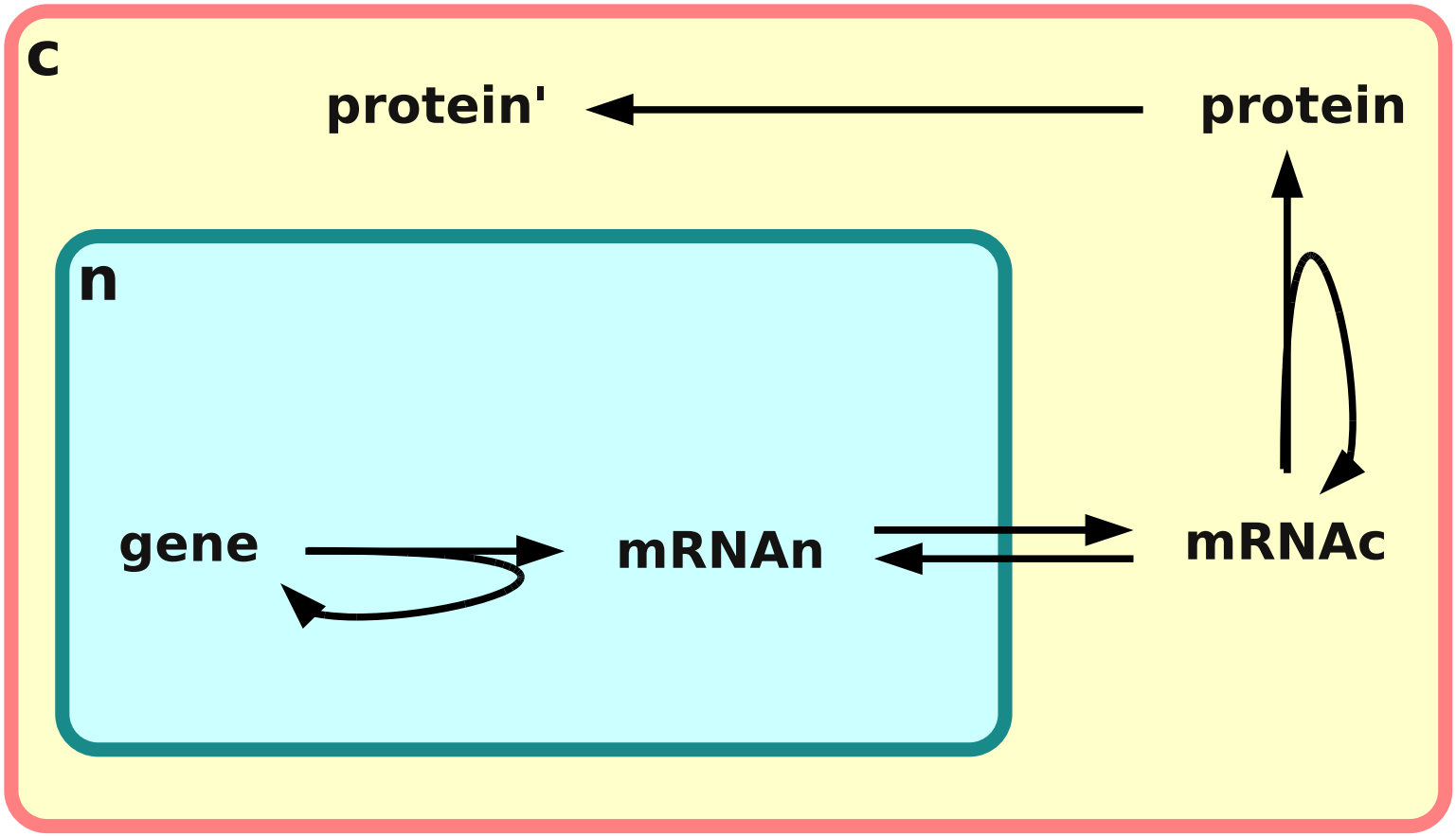
What can we encode in SBML Level 2?

species



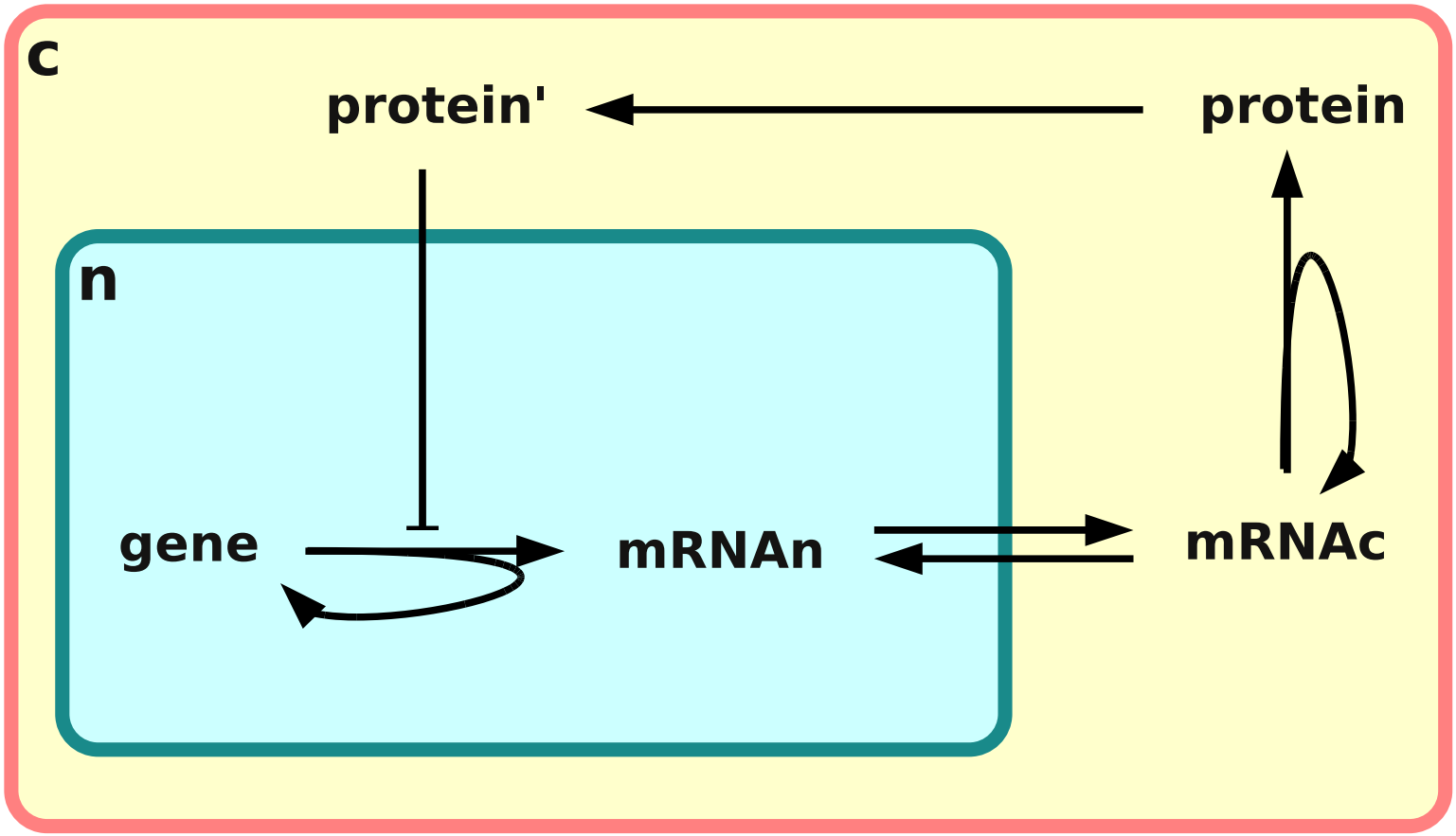
What can we encode in SBML Level 2?

reactions

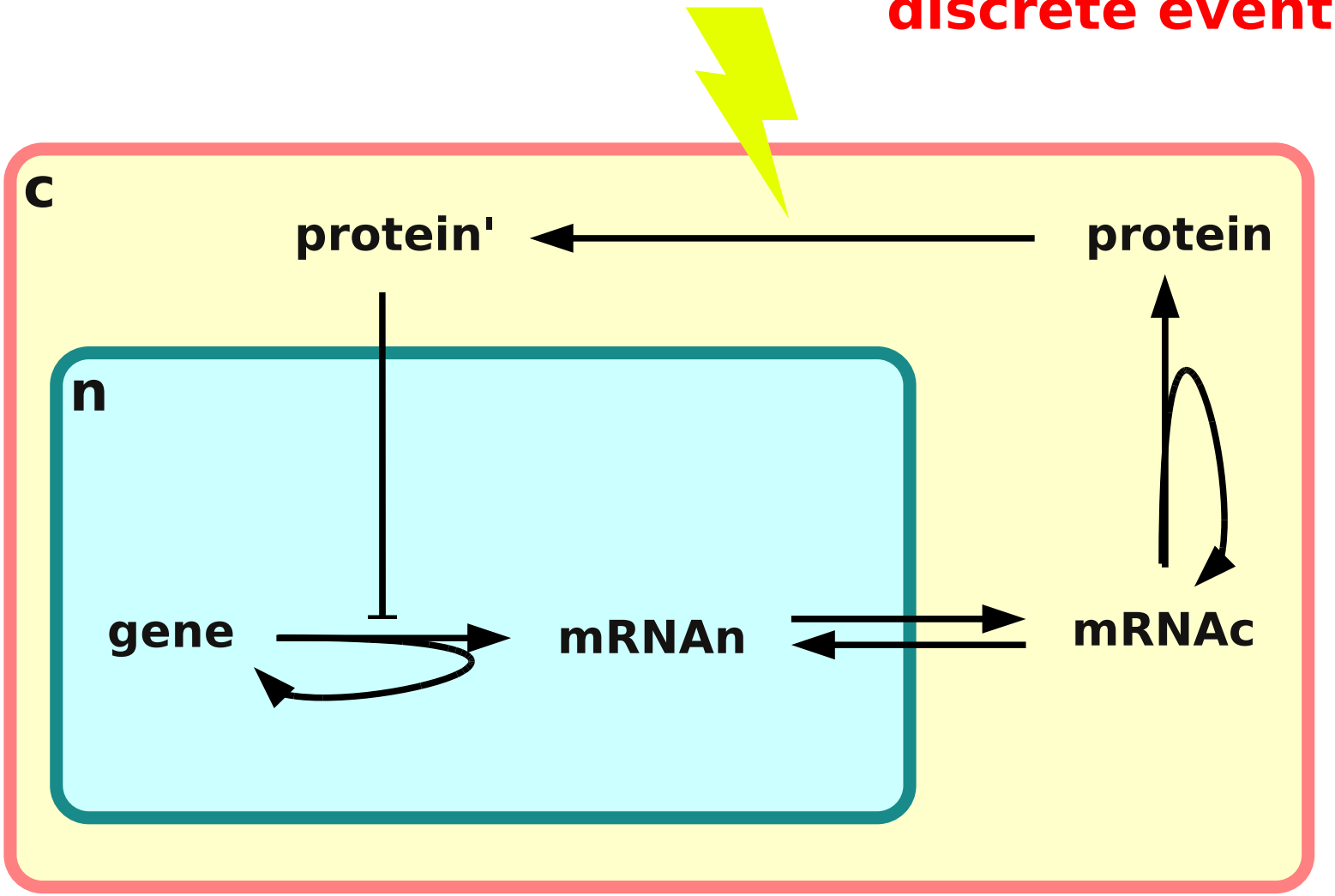


What can we encode in SBML Level 2?

modulations



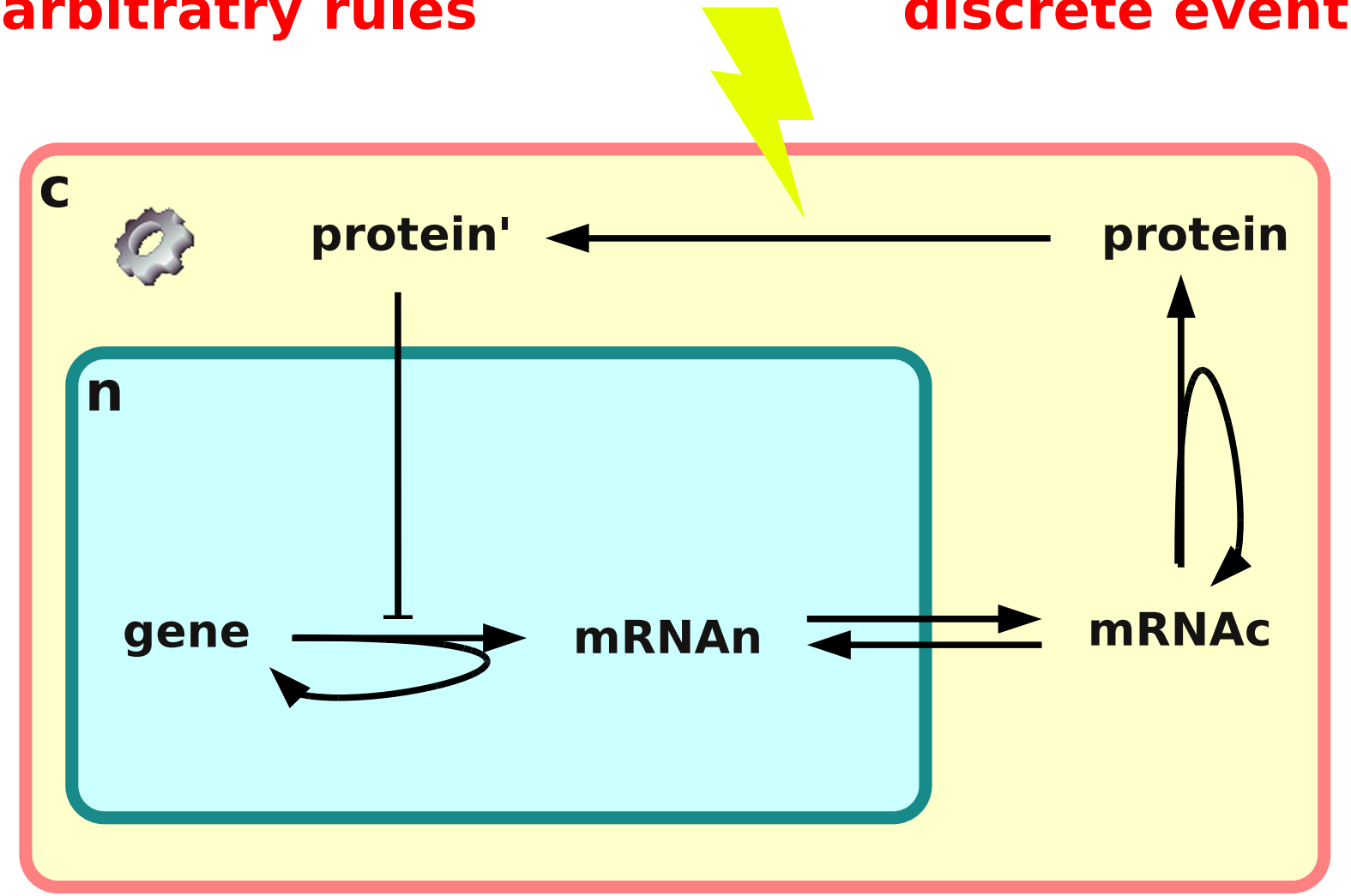
What can we encode in SBML?



What can we encode in SBML Level 2?

arbitratry rules

discrete events



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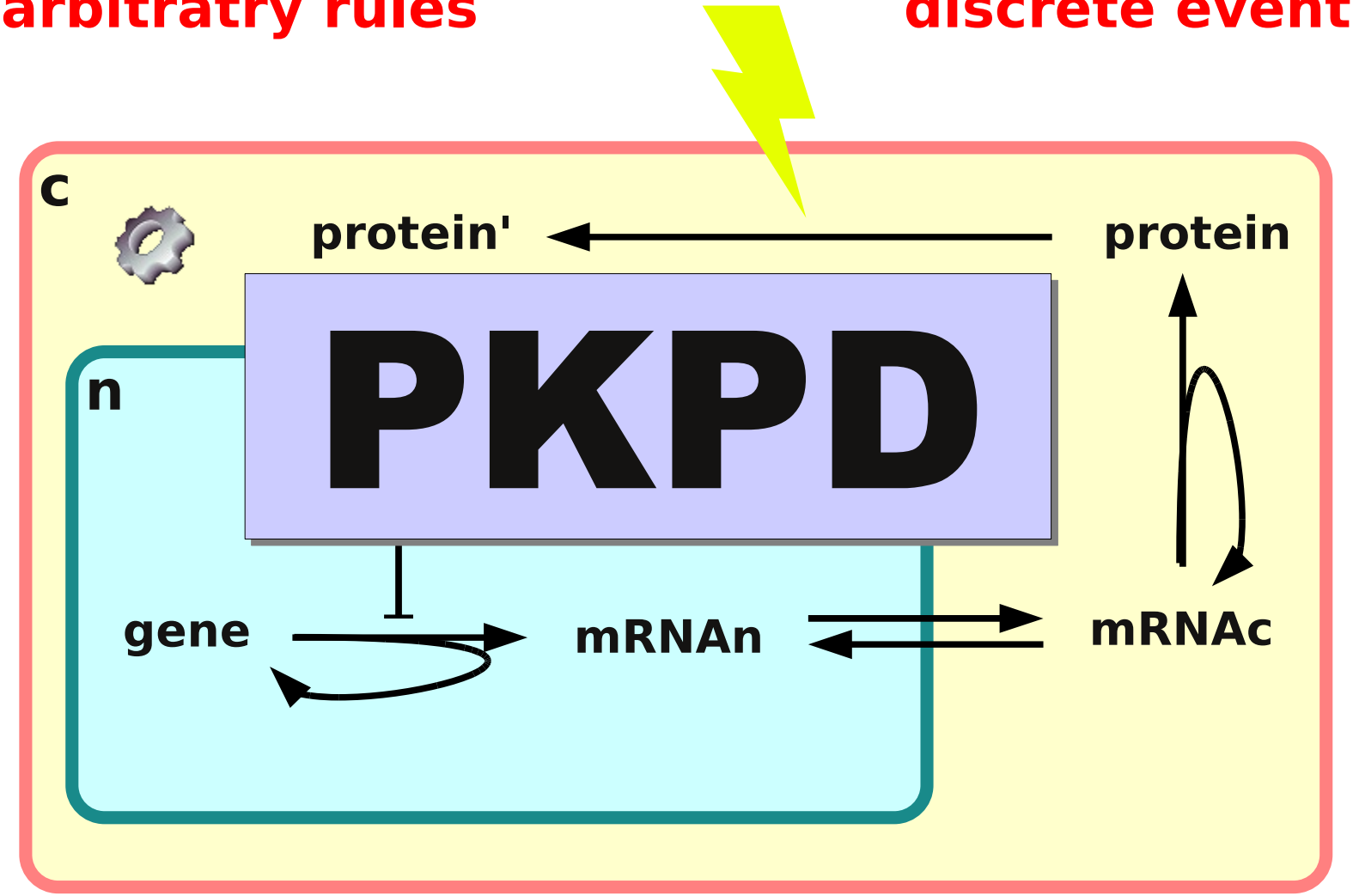


A → B

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml level="2" version="1" xmlns="http://www.sbml.org/sbml/level2">
  <model>
    <listOfCompartments>
      <compartment id="cell" />
    </listOfCompartments>
    <listOfSpecies>
      <species id="A" compartment="cell" initialConcentration="1"/>
      <species id="B" compartment="cell" initialConcentration="0"/>
    </listOfSpecies>
    <listOfParameters>
      <parameter id="kon" value="1"/>
    </listOfParameters>
    <listOfReactions>
      <reaction>
        <listOfReactants>
          <speciesReference species="A" />
        </listOfReactants>
        <listOfProducts>
          <speciesReference species="B" />
        </listOfProducts>
        <kineticLaw>
          <math xmlns="http://www.w3.org/1998/Math/MathML">
            <apply>
              <times />
              <ci>kon</ci>
              <ci>A</ci>
              <ci>cell</ci>
            </apply>
          </math>
        </kineticLaw>
      </reaction>
    </listOfReactions>
  </model>
</sbml>
```


A → B

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml level="2" version="1" xmlns="http://www.sbml.org/sbml/level2">
  <model>
    <listOfCompartments>
      <compartment id="cell" />
    </listOfCompartments>
    <listOfSpecies>
      <species id="A" compartment="cell" initialConcentration="1"/>
      <species id="B" compartment="cell" initialConcentration="0"/>
    </listOfSpecies>
    <listOfParameters>
      <parameter id="kon" value="1"/>
    </listOfParameters>
    <listOfReactions>
      <reaction>
        <listOfReactants>
          <speciesReference species="A" />
        </listOfReactants>
        <listOfProducts>
          <speciesReference species="B" />
        </listOfProducts>
        <kineticLaw>
          <math xmlns="http://www.w3.org/1998/Math/MathML">
            <apply>
              <times />
              <ci>kon</ci>
              <ci>A</ci>
              <ci>cell</ci>
            </apply>
          </math>
        </kineticLaw>
      </reaction>
    </listOfReactions>
  </model>
</sbml>
```


A more realistic example ...

```
<species
    id="A"
    name="α-tubulin"
    compartment="cell"
    initialAmount="1000"
    substanceUnits="item"
    hasOnlySubstanceUnits="true"
    boundaryCondition="true"
    constant="false"
    charge="0"
    metaid="PX"
    sboTerm="SBO:0000245" >
  <notes>
    <body xmlns="http://www.w3.org/1999/xhtml">
      <p>One of the components of a microtubule</p>
    </body>
  </notes>
  <annotation>
    <rdf:RDF
        xmlns:bqbiol="http://biomodels.net/biology-qualifiers/"
        xmlns:bqmodel="http://biomodels.net/model-qualifiers/"
        xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
      <rdf:Description rdf:about="#PX">
        <bqbiol:is>
          <rdf:Bag>
            <rdf:li rdf:resource="urn:miriam:uniprot:P68370"/>
            <rdf:li rdf:resource="urn:miriam:obo.go:GO%3A0045298"/>
          </rdf:Bag>
        </bqbiol:is>
      </rdf:Description>
    </rdf:RDF>
  </annotation>
</species>
```

externalisation of biological semantics

macromolecule

XHTML

RDF

reusing existing standards

SBML is not limited to biochemistry!

Rate Rules can describe the temporal evolution of any quantitative parameter, e.g. transmembrane voltage;

Events can describe any discontinuous change, e.g. neurotransmitter release or repolarisation;

A species is an entity participating to a reaction, **not always** a **chemical** entity. It can be a molecule, a cell, a tissue, an organism

SBML is suitable to encode models for biochemistry, physiology, and pharmacology

An example of PD model

```
<rateRule metaid="metaid_0000031" variable="Size">
  <math xmlns="http://www.w3.org/1998/Math/MathML">
    <apply>
      <times/>
      <apply>
        <minus/>
        <apply>
          <times/><ci> RateIn </ci><ci> Effect </ci>
        </apply>
        <apply>
          <times/><ci> Kover </ci><ci> Size </ci>
        </apply>
      </apply>
      <ci> Size </ci>
    </apply>
  </math>
</rateRule>
<assignmentRule metaid="metaid_0000027" variable="Effect">
  <math xmlns="http://www.w3.org/1998/Math/MathML">
    <apply>
      <minus/>
      <cn> 1 </cn>
      <apply>
        <divide/>
        <ci> Ce </ci>
        <apply>
          <plus/><ci> AE50 </ci><ci> Ce </ci>
        </apply>
      </apply>
    </apply>
  </math>
</assignmentRule>
```

Tham et al (2008) A pharmacodynamic model for the time course of tumor shrinkage by gemcitabine + carboplatin in non-small cell lung cancer patients. Clin Cancer Res. 2008 14(13): 4213-8.

$$\frac{Size}{dt} = (Rate_{in} \times Effect - K_{over} \times Size) \times Size$$

$$Effect = 1 - \frac{E_{max} - Ce}{Amt_{50} + Ce}$$

BioModels Home | Browse models | Submit | Curation | Administration | Support | About BioModels | Sign out | Search

BIOMD0000000234 - Tham2008_PDmode_TumourShrinkage

SBML formats | Other formats | Actions | Curation Comment

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

Reference Publication

Publication ID: 18594002

Clin Cancer Res 2008 Jul;14(13):4213-8.
A pharmacodynamic model for the time course of tumor shrinkage by gemcitabine + carboplatin in non-small cell lung cancer patients.
Tham LS, Wang L, Soo RA, Lee SC, Lee HS, Yong WP, Goh BC, Holford NH.
Department of Hematology-Oncology, National University Hospital, Singapore. Tham_lai_san@lilly.com [more]

Model

Original Model: *BIOMD0000000234.xml.origin*

Submitter: Nick Holford

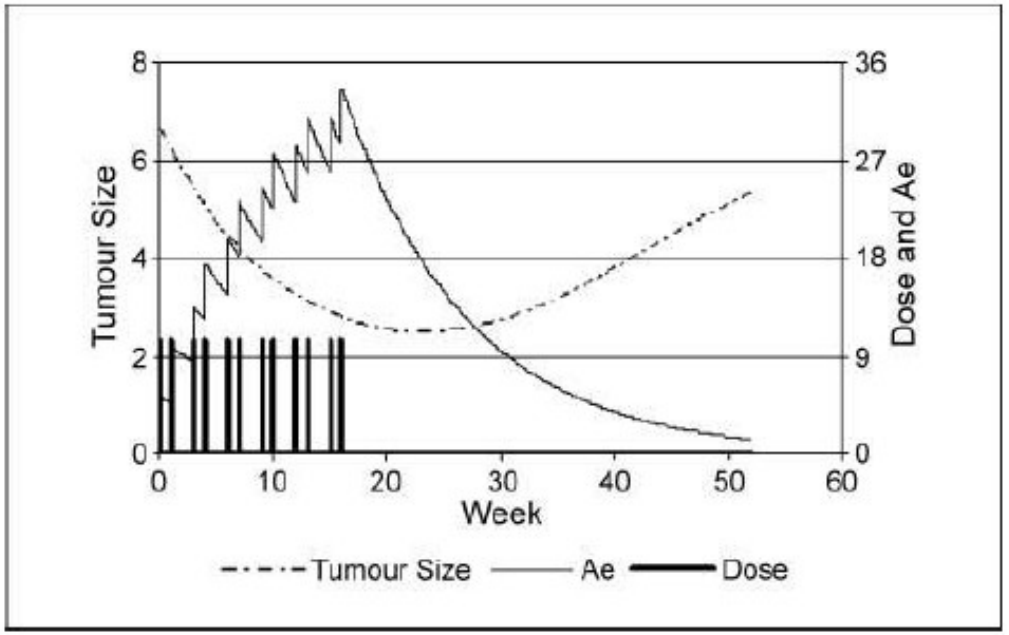
Submission ID: MODEL0911120001

Submission Date: 2009-11-16T19:41:59+00:00

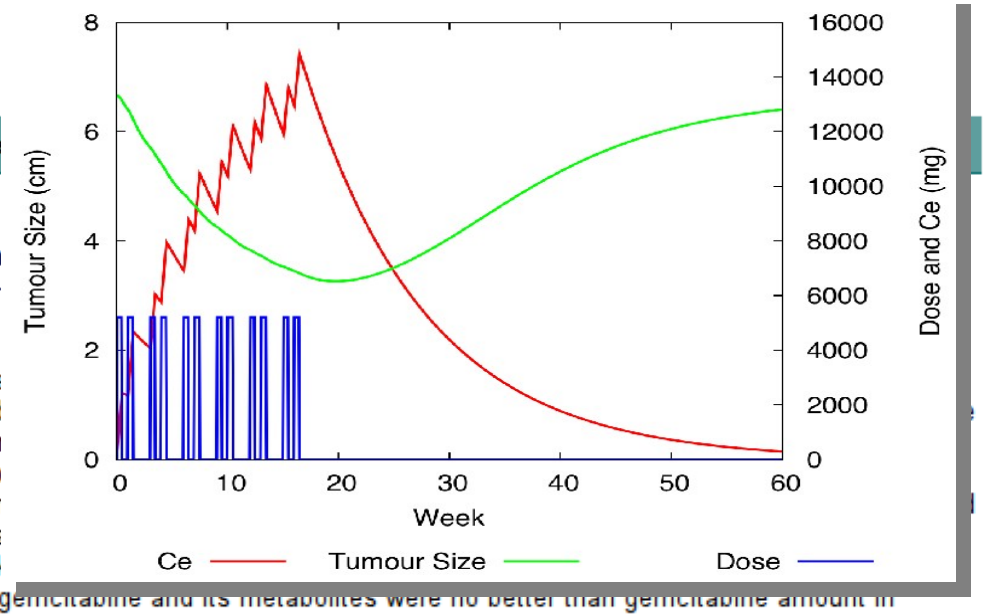
Last Modification Date: 2009-11-23T13:24:05+00:00

set #1	bqbiol:occursIn	**Taxonomy** Homo sapiens
set #2	bqbiol:isVersionOf	**ICD** C34 **OMIM** 211980

original article



reproduction with SBMLodeSolver



predicting tumor shrinkage in primary lung cancer lesions. Gemcitabine dose-based models did marginally better than treatment-based models that ignored doses of drug administered to patients. Modeling tumor shrinkage in primary lesions can be used to quantify individual sensitivity and response to antitumor effects of anticancer

A glimpse of SBML Level 3

Modular SBML, with core + optional packages

- Core package – draft specification available
- Graph Layout – specification finalised
- Complex species – specification finalised
- Groups - specification under discussion
- Model composition – specification under discussion
- Qualitative models – specification under discussion
- Graph rendering – specification proposed
- Distributions and ranges - specification proposed
- Arrays and sets – specifications proposed
- Geometry - specification proposed
- Spatial diffusion – needed
- Dynamic structures - needed

???

BioModels Database - 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.

Search | Go to the model | Advanced search

Browse models

- **Curated models** (231)
- **Browse models using GO**
- **Non-curated models** (198)

Simulate in JWS Online

Submit a model

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

http://biomodels.caltech.edu/

Mirror at California Institute of Technology http://biomodels.caltech.edu

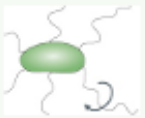
BioModels AT SourceForge http://sourceforge.net/projects/biomodels/

Web Services http://www.ebi.ac.uk/biomodels-main/webservices

Download archived models http://www.ebi.ac.uk/biomodels/models-main/tars/

Model of the month

September, 2009



Bacteria can move along chemical gradients, a process known as chemotaxis. A bacterial cell switches back and forth between two modes of movement: A "straight" mode in which the bacterium swims straight in one direction and a "tumble" mode in which the bacterium turns around by some acute angle.
Read more...

News

2nd September 2009 **Fifteenth release**
Download All Models Under SBML Format

16th June 2009 **Fourteenth release**
Download All Models Under SBML Format

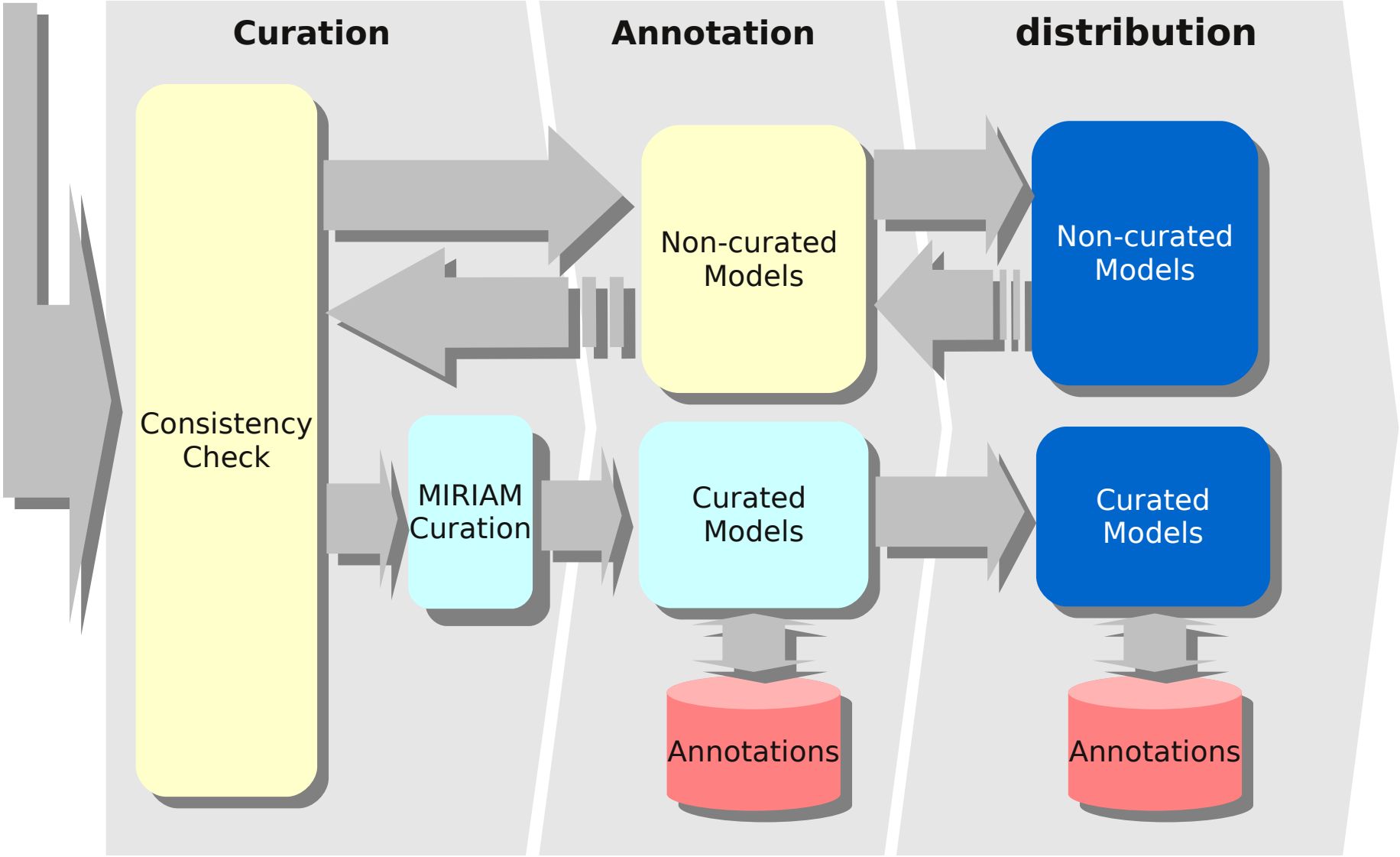
25th March 2009 **Thirteenth release**
Download All Models Under SBML Format

What is currently BioModels Database?

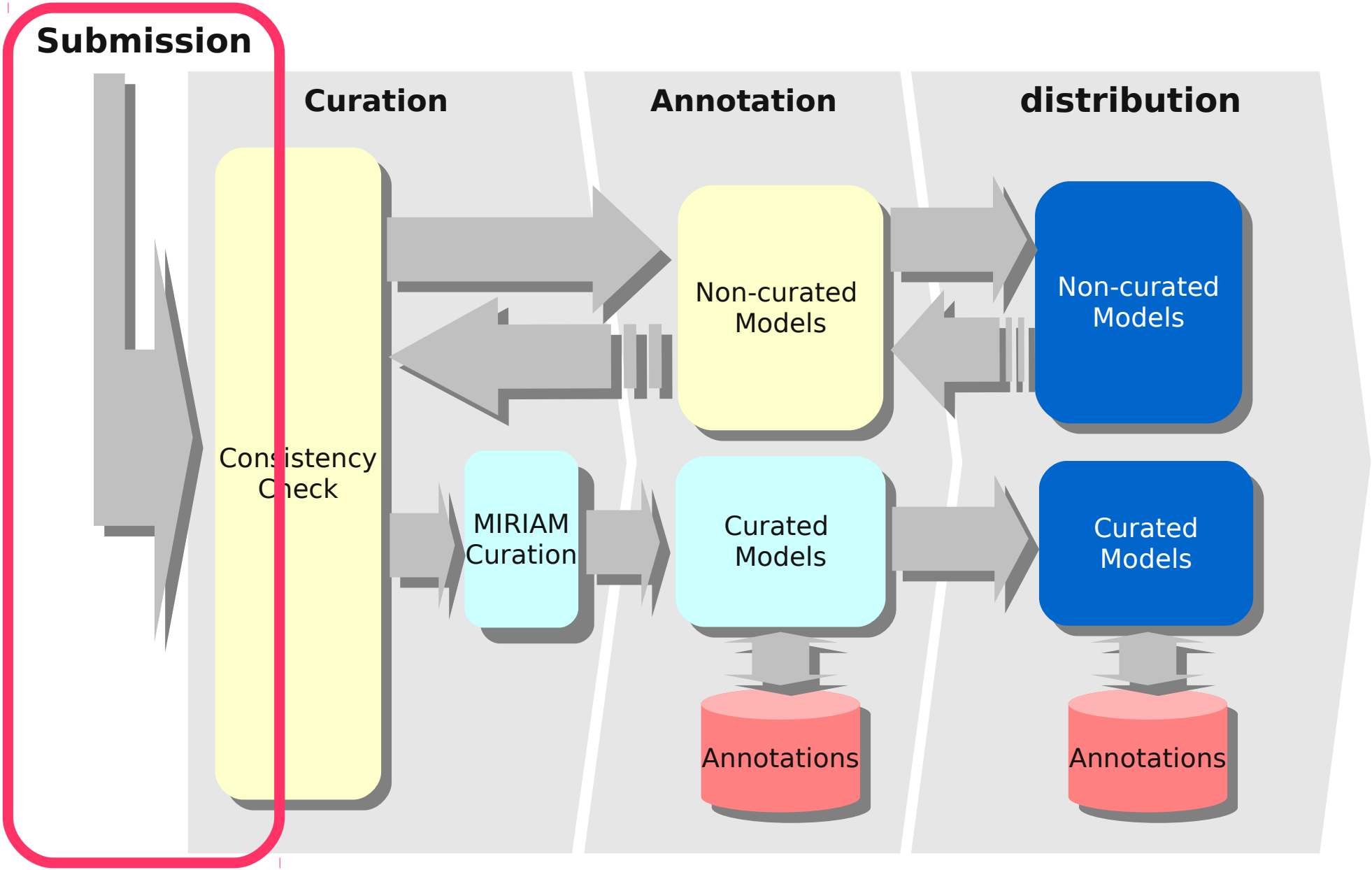
- Store and serve quantitative models of biomedical interest
- Only models described in the peer-reviewed scientific literature.
- Models are curated: computer software check the syntax, while human curators check the semantics.
- Models are simulated to ensure they provide the expected results
- Model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

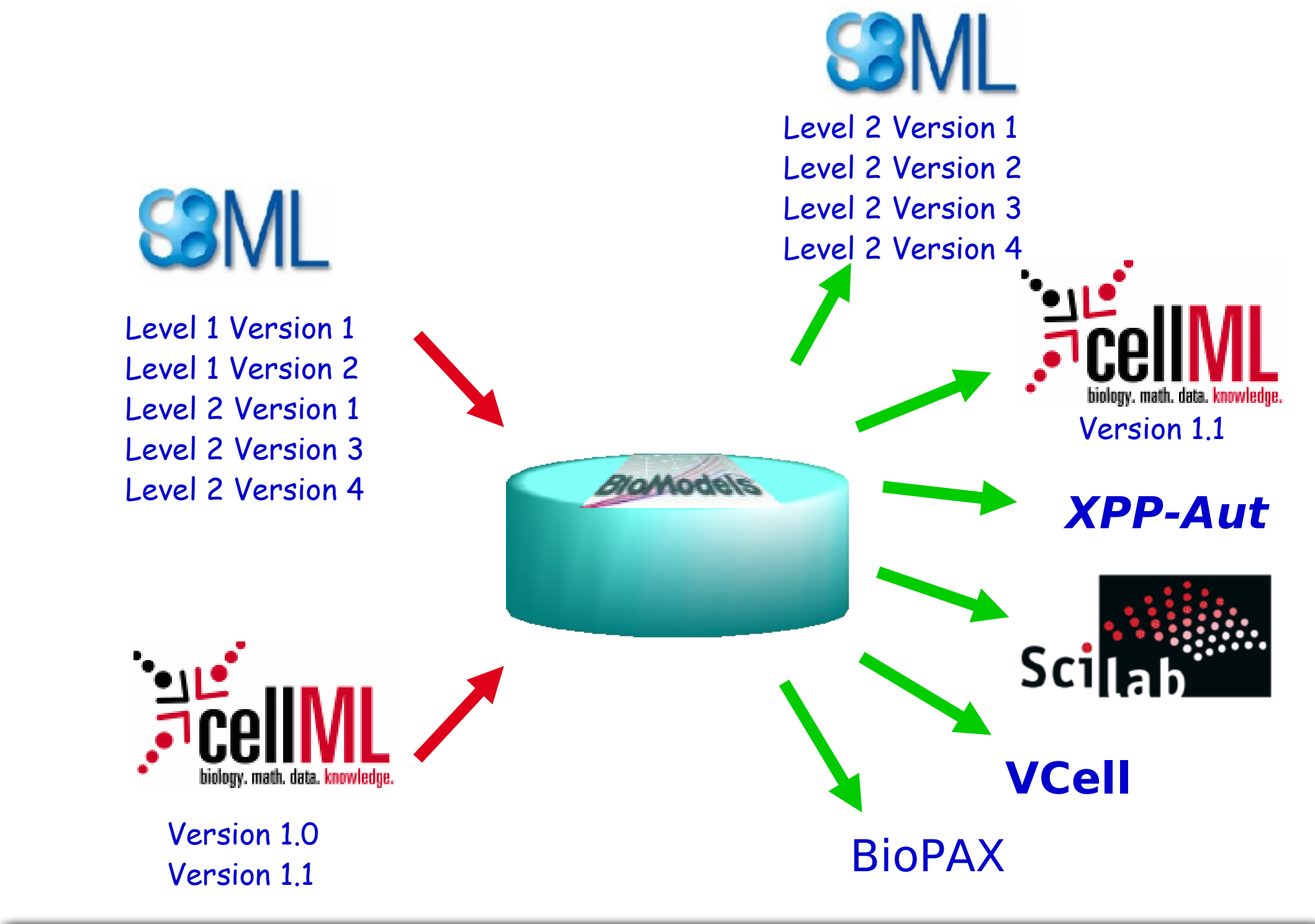
Current production pipeline

Submission



Submission

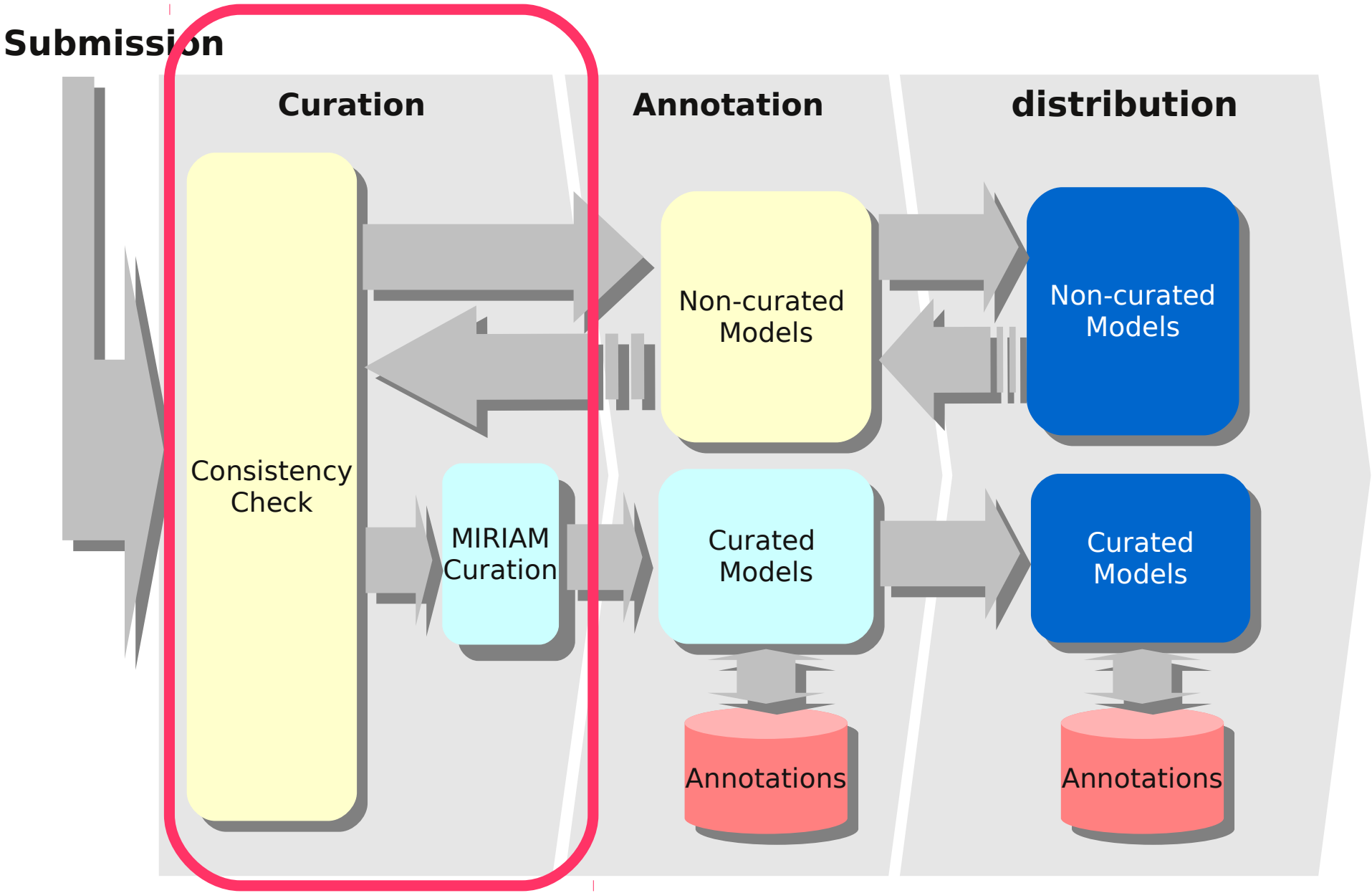

Submission
Curation
Annotation
distribution
Consistency Check
MIRIAM Curation
Non-curated Models
Curated Models
Annotations
Non-curated Models
Curated Models
Annotations


SBML
Level 1 Version 1
Level 1 Version 2
Level 2 Version 1
Level 2 Version 3
Level 2 Version 4
SBML
Level 2 Version 1
Level 2 Version 2
Level 2 Version 3
Level 2 Version 4
cellML
biology. math. data. knowledge.
Version 1.0
Version 1.1
BioModels
cellML
biology. math. data. knowledge.
Version 1.1
XPP-Aut
Scilab
VCell
BioPAX

Where do models come from?

- Submitted by curators
  - imported from other repositories (DOQCS, CellML)
  - reimplemented from literature
- From authors before grant application or publication
- Some scientific journals advise submission to BioModels DB:
  - Nature Molecular Systems Biology
  - Public Library of Science journals
  - BioMedCentral journals
- Various people curated models out of interest.

Curation


Submission
Curation
Annotation
distribution
Consistency Check
MIRIAM Curation
Non-curated Models
Curated Models
Annotations
Non-curated Models
Curated Models
Annotations

BioModels Database - SeaMonkey

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BIOMD0000000005 - Tyson1991_CellCycle_6var

SBML formats | Other formats | Actions | Submit Model

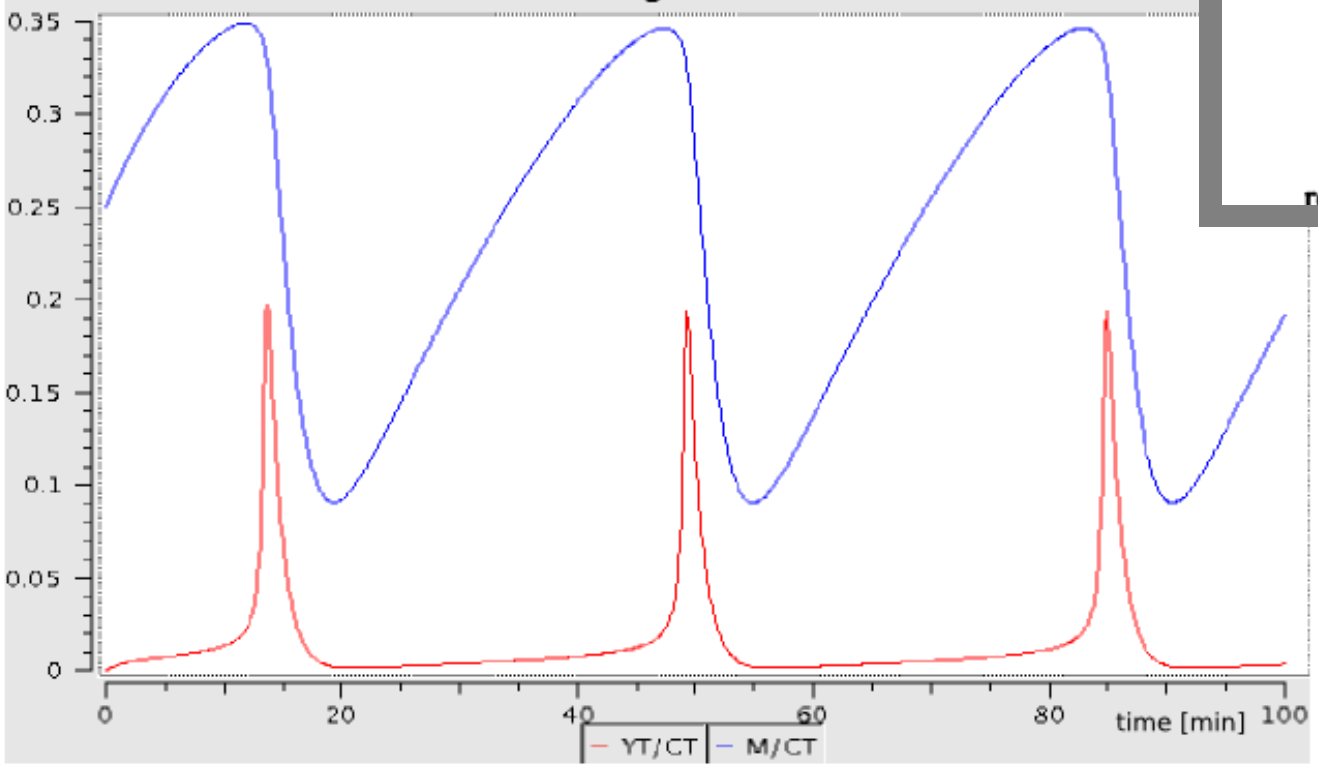
Model | Overview | Math | Physical entities

Curation result

2008-08-15T12:01:18+00:00

http://www.ebi.ac.uk - Curation Result - SeaMonkey

Figure 3A



Comment: Reproduction of Fig3A from the original publication (Tyson JJ 1991). Integrated and plot using Copasi v.4.4.

Done

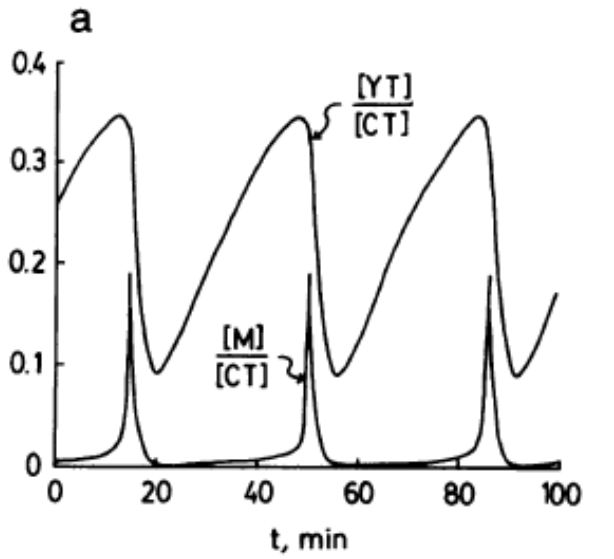


FIG. 3. Dynamical behavior of the cdc2–cycli
relative to total cdc2 ([CT] = [C2] + [CP] + [pM]

Curated and Non-curated Models

- Curated models – Comply with the MIRIAM guidelines
- Non-Curated models – valid SBML, not curated or annotated
  - Not MIRIAM compliant:

    cannot reproduce results published in the paper.

    differ in model structure

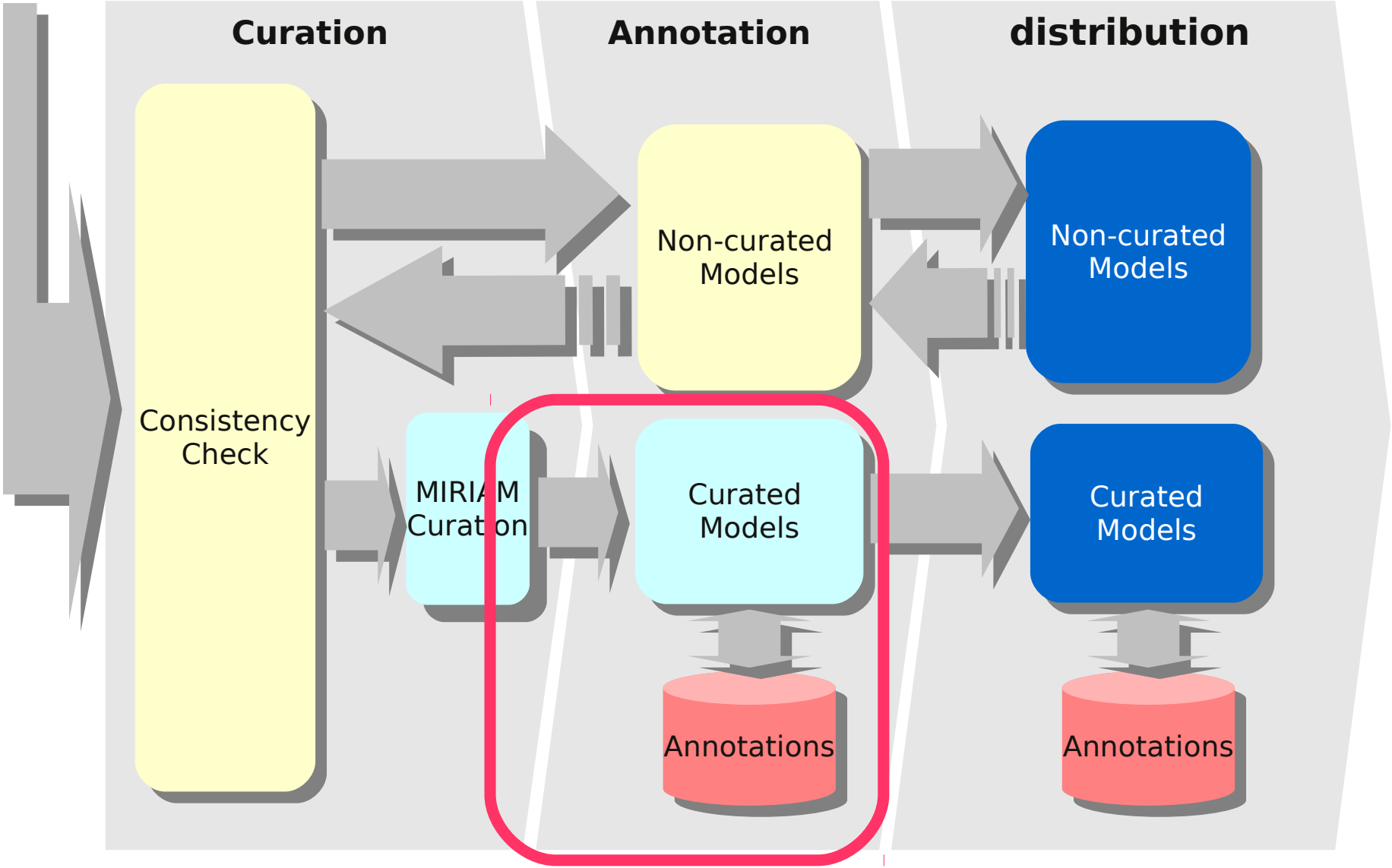
    non-kinetic models (eg. FBA, stoichiometric maps)
  - MIRIAM compliant:

    models contain kinetics that we cannot curate at present.

    models are yet to be curated

Annotation

Submission



BIOMD0000000005 - Tyson1991_CellCycle_6var

SBML formats | Other formats | Actions | Submit Model Comment/Bug

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

Reference Publication

Publication ID: 1831270

Proc Natl Acad Sci U S A 1991 Aug;88(16):7328-32.
Modeling the cell division cycle: cdc2 and cyclin interactions.
Tyson JJ.
Department of Biology, Virginia Polytechnic Institute and State University, Blacksburg 24061. [more]

Model

Original Model: *BIOMD0000000005.xml.origin*

Submitter: Nicolas Le Novère

Submission Date: 2005-09-13T12:31:08+00:00

Last Modification Date: 2009-02-25T14:58:48+00:00

Creation Date: 2005-02-08T18:28:27+00:00

Encoders: Bruce Shapiro
Vijayalakshmi Chelliah

	bqmodel:is	**Taxonomy** Fungi/Metazoa group
set #1	bqbiol:isVersionOf	**KEGG Pathway** sce04111 **Gene Ontology** mitotic cell cycle
	bqbiol:hasVersion	**Reactome** REACT_152

Notes

Cell Cycle Model; Tyson (1991, 6 variables)

Description

A model of the cell cycle based on the interactions between cdc2 and cyclin. The model has six dynamic variables: C2 (cdc2); CP (cdc2-P complex); pM (P-cyclin-cdc2-P complex); M (active MPF, P-cyclin-cdc2 complex); Y (cyclin); and YP (cyclin-P). Total cyclin concentration (YT) is the sum [YT]=[Y]+[YP]+[pM]+[M]

Reaction

Variable	ODE
C2	0
CP	1
pM	0.3
M	0
Y	0
YP	0

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BIOMD0000000005 - Tyson1991_CellCycle_6var

SBML formats | Other formats | Actions | Submit M

Model | Overview | Math | Physical entit

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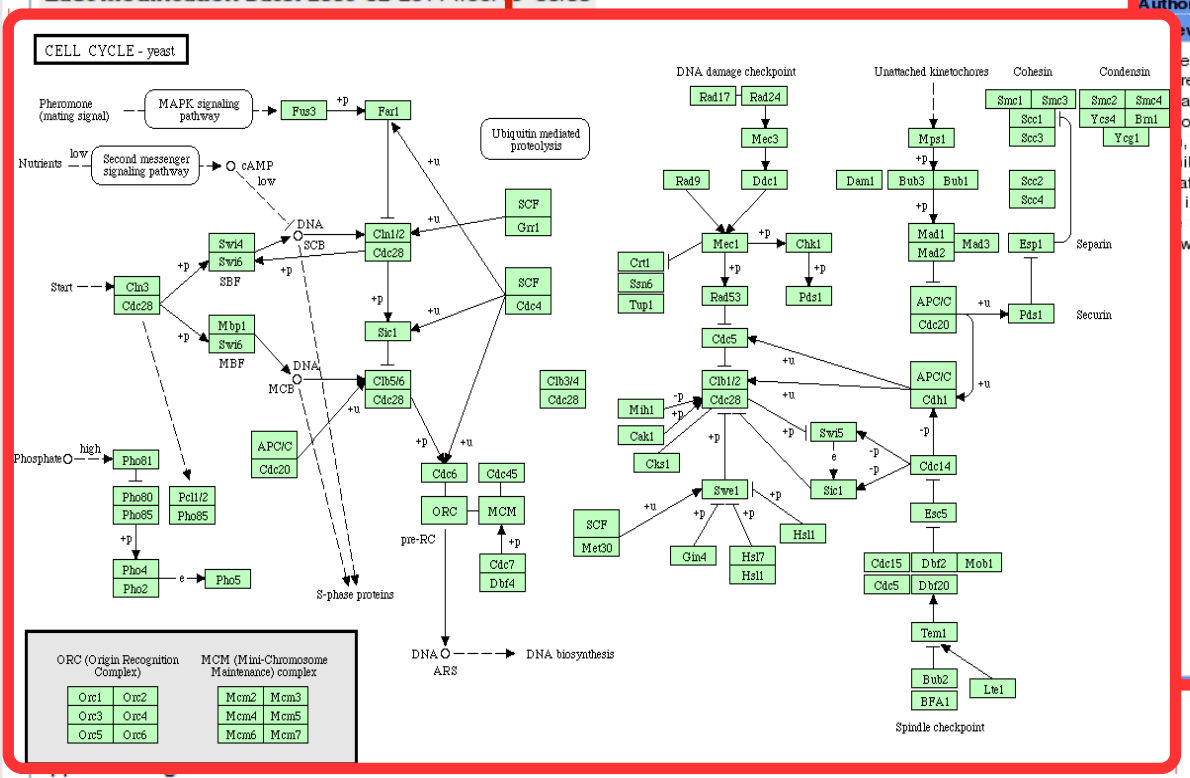
	bqmodel:is	**Taxonomy** Fungi/Metazoa grou
set #1	bqbiol:isVersionOf	**KEGG Pathway** sce04111
		Gene Ontology mitotic cell cycle
	bqbiol:hasVersion	**Reactome** REACT_152

Lineage	Taxonomy identifier	33154
• Eukaryota	Scientific name	Fungi/Metazoa group
	Common name	-
	Other NCBI synonyms	Opisthokonta opisthokonts
	Rank	no rank
	Number of UniProtKB/Swiss-Prot entries	114913
	Number of UniProtKB/TrEMBL entries	1459130

Taxonomy navigation

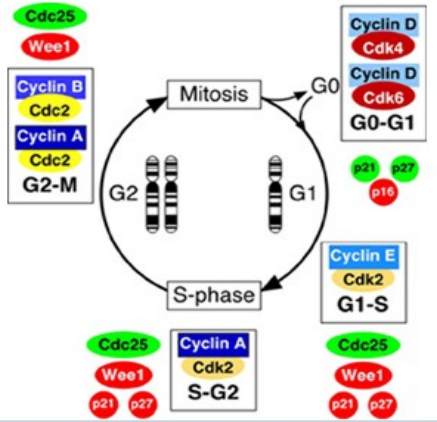
Up taxonomy tree	Down taxonomy tree
Eukaryota	• Choanoflagellida • Fungi • Fungi/Metazoa incertae sedis • Metazoa



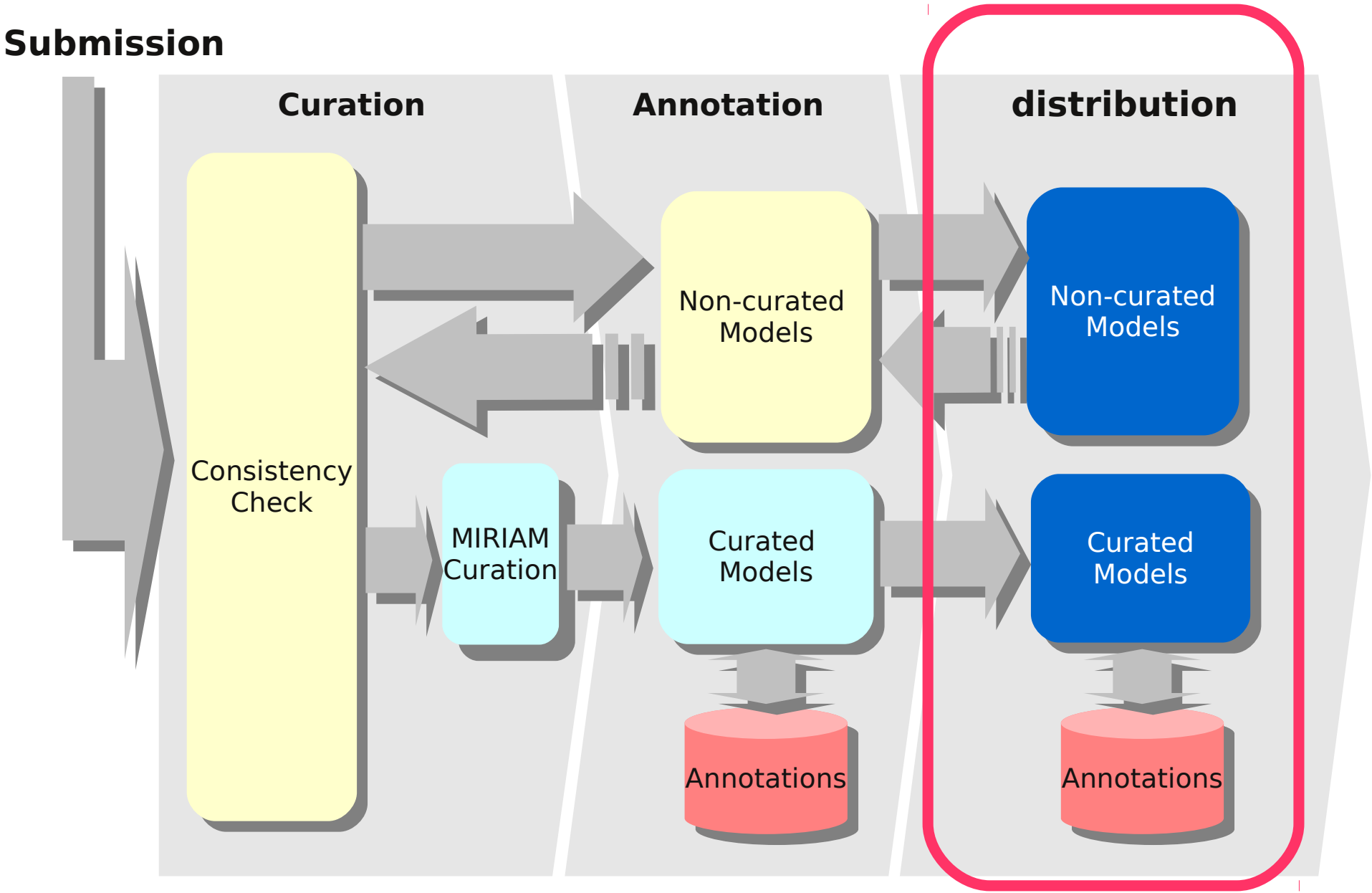
Cell Cycle, Mitotic

Stable identifier	REACT_152.2
Authored	O'Connell, M, Walworth, N, Bosco, G, 2005-01-01
ewed	Manfredi, J

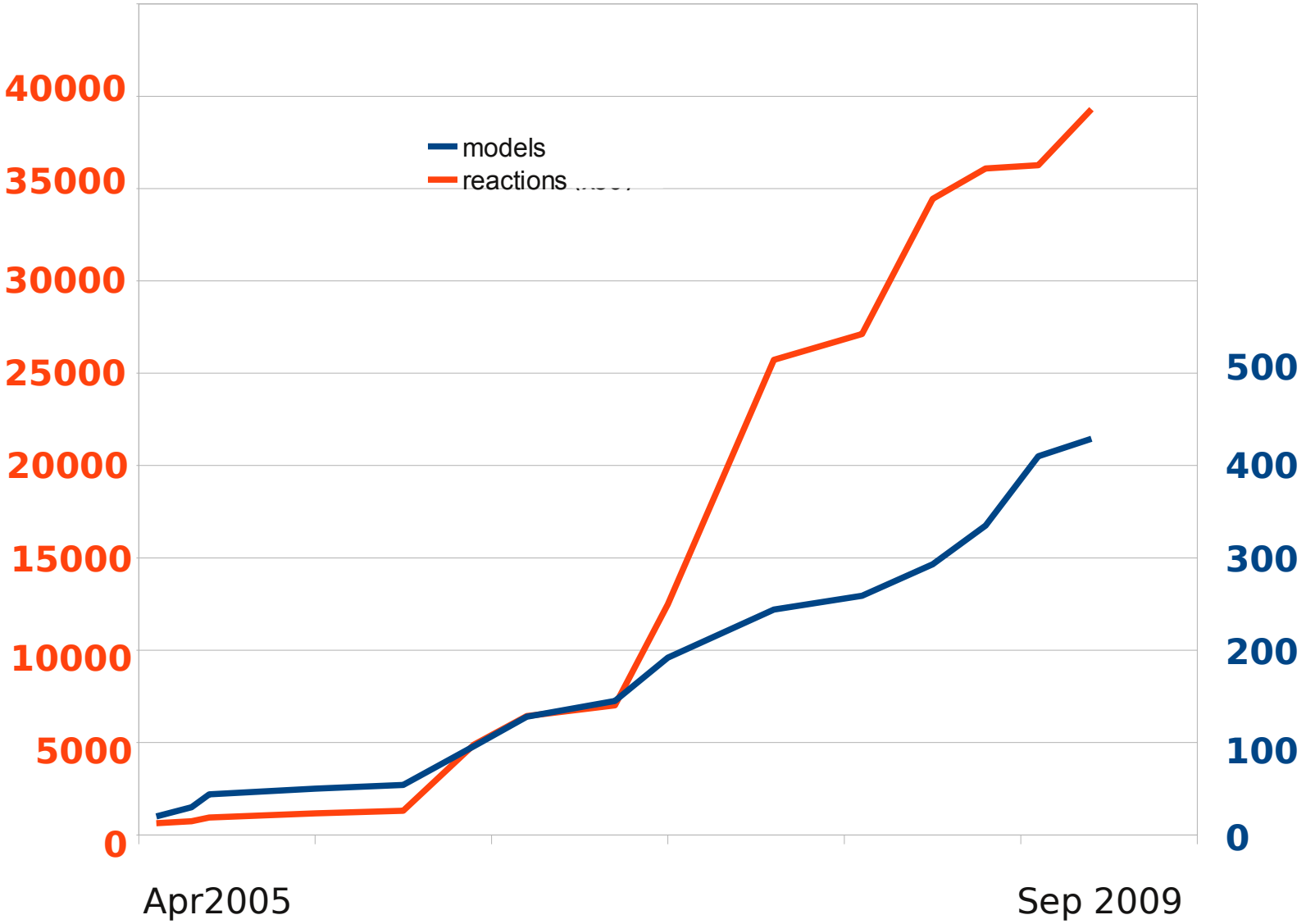
eplication of the genome and the subsequent segregation of chromosomes into daughter cells are controlled by
replication is carried out during a discrete temporal period known as the S (synthesis)-phase, and chromosome
ar architecture at mitosis. Two gap-phases separate these major cell cycle events: G1 between mitosis and S
opment of the human body, cells can exit the cell cycle for a period and enter a quiescent state known as G0,
, but undergo morphological development to carry out the wide variety of specialized functions of individual tissue
ily of protein serine/threonine kinases known as the cyclin-dependent kinases (CDKs) controls progression throu
atalytic subunit is dependent on binding to a cyclin partner. The human genome encodes several cyclins and se
in which they were identified. The oscillation of cyclin abundance is one important mechanism by which these en
relevant time and place. Additional regulatory proteins and post-translational modifications ensure that CDK
w window of activity.



Distribution



Steady-increase of BioModels Database



BIOMD0000000005 - Tyson1991_CellCycle_6var

SBML formats | Other formats | Actions | Submit Model Comment/Bug

- SBML L2 V1
- SBML L2 V2
- **SBML L2 V3**
- SBML L2 V4

Automatically generated using libsbml (http://sbml.org/Software/libSBML)

Curated version of the model

Publication ID: 1831270

Department of Biology, Virginia Polytechnic Institute and State University, Blacksburg 24061. [more]

Model

Original Model: *Unspecified*

Submitter: Nicolas Le Novère

Submission Date: 2005-09-13T12:31:08+00:00

Last Modification Date: 2009-02-25T14:58:48+00:00

Creation Date: 2005-02-08T18:28:27+00:00

Creators: Bruce Shapiro
Vijayalakshmi Chelliah

bqbiol:hasVersion **Reactome** REACT_152

Notes

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Reaction

Variable	ODE
C2	0
CP	1
pM	0.3
M	0
Y	0

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BIOMD0000000005 - Tyson1991_CellCycle_6var

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- SciLab
- XPP
- BioPAX
- VCell
- PDF

Model | Math | Physical entities

Publication ID: 1831270

Proc Natl Acad Sci U S A 1991 Aug;88(16):7328

Modeling the cell division cycle: cdc2 and cyclin

Tyson JJ.

Department of Biology, Virginia Polytechnic Insti

Original Model: *Unspecified*

Submitter: Nicolas Le Novère

Submission Date: 2005-09-13T12:31:08+00:00

Last Modification Date: 2009-02-25T14:58:48+00:00

Creation Date: 2005-02-08T18:28:27+00:00

Creators: Bruce Shapiro
Vijayalakshmi Chelliah

set #1	bqmodel:is	Taxonomy Fungi/Me
	bqbiol:isVersionOf	KEGG Pathway sce0
		Gene Ontology mitot
	bqbiol:hasVersion	Reactome REACT_

Notes

Cell Cycle Model; Tyson (1991, 6 variables)

Description

A model of the cell cycle based on the interactions between cdc2 and cyclin. The model has six dynamic variables: C2 (cdc2); CP (c MPF, P-cyclin-cdc2 complex); Y (cyclin); and YP (cyclin-P). Total cyclin concentration (YT) is the sum [YT]=[Y]+[YP]+[pM]+[M]

Reaction

Variable	ODE
C2	0
CP	1
pM	0.3
M	0
Y	0

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    xmlns:owl="http://www.w3.org/2002/07/owl#"
    xmlns="http://www.ebi.ac.uk/biomodels/biopax.owl#"
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```

SBML Model Report

Model name: "Tyson1991_CellCycle_6var"

SBML2LaTeX

9th February 2009

1 General Overview

This is a document in SBML Level 2 Version 3 format. This model was created by the following two authors: Bruce Shapiro[1] and Vijayalakshmi Chelliah[2] at February eighth 2005 at 6:28 p.m. and last modified at August 21st 2008 at 11:31 a.m. Table 1 gives an overview of the quantities of all components of this model.

Table 1: The SBML components in this model.
All components are described in more detail in the following sections.

Element	Quantity	Element	Quantity
compartment types	0	compartments	1
species types	0	species	9
events	0	constraints	0
reactions	9	function definitions	0
global parameters	0	unit definitions	5
rules	2	initial assignments	0

Model Notes

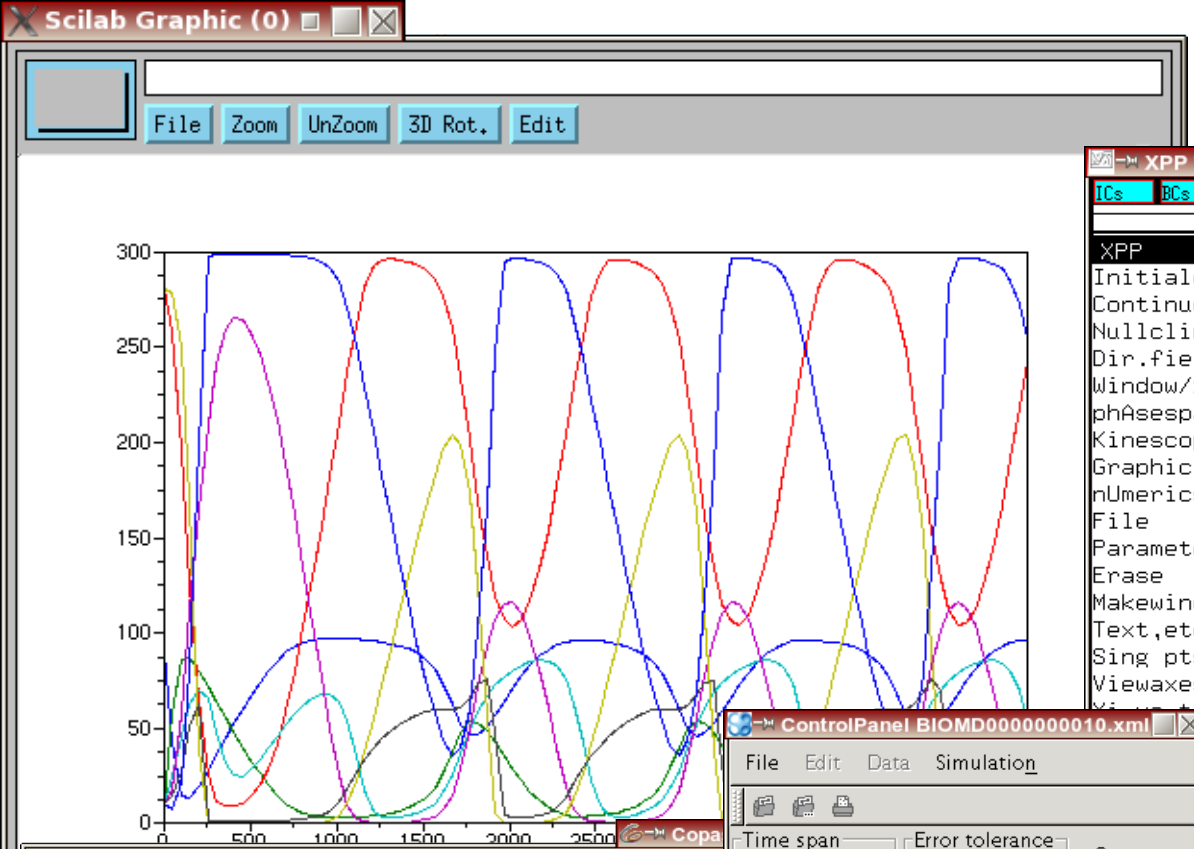
Cell Cycle Model; Tyson (1991, 6 variables)

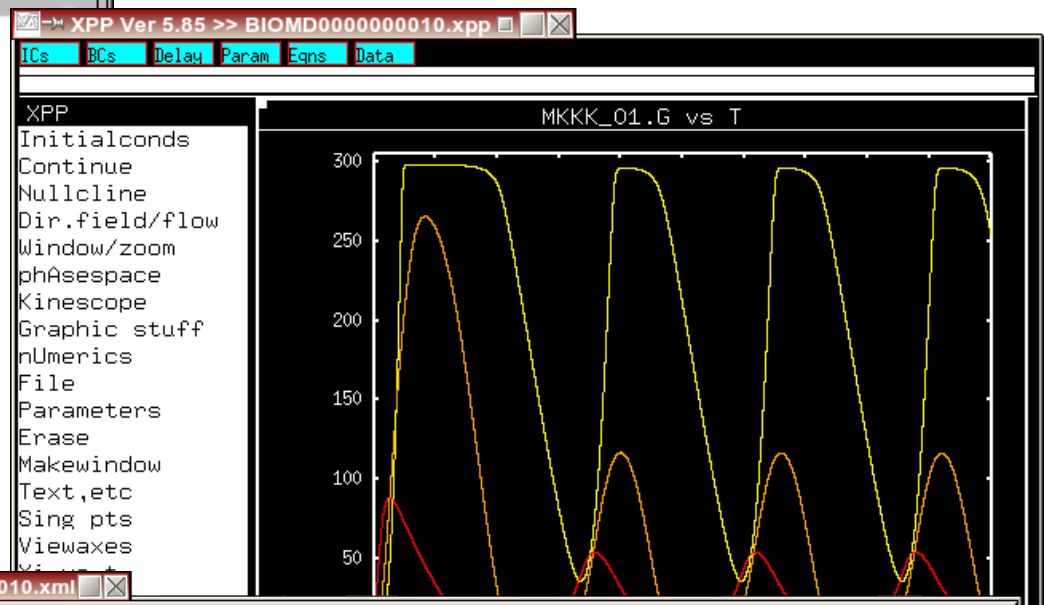
Description

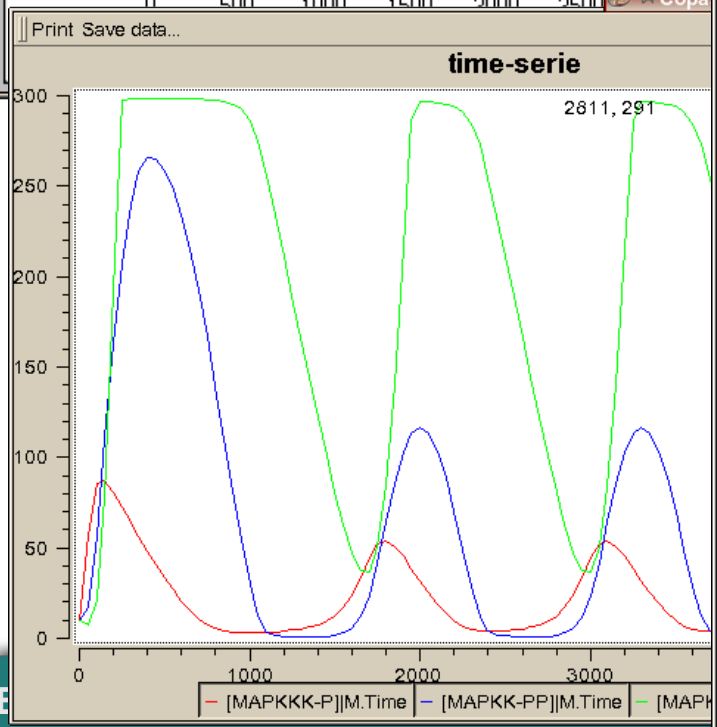
[1]NASA Jet Propulsion Laboratory, bshapiro@jpl.nasa.gov
[2]EMBL-EBI, viji@ebi.ac.uk

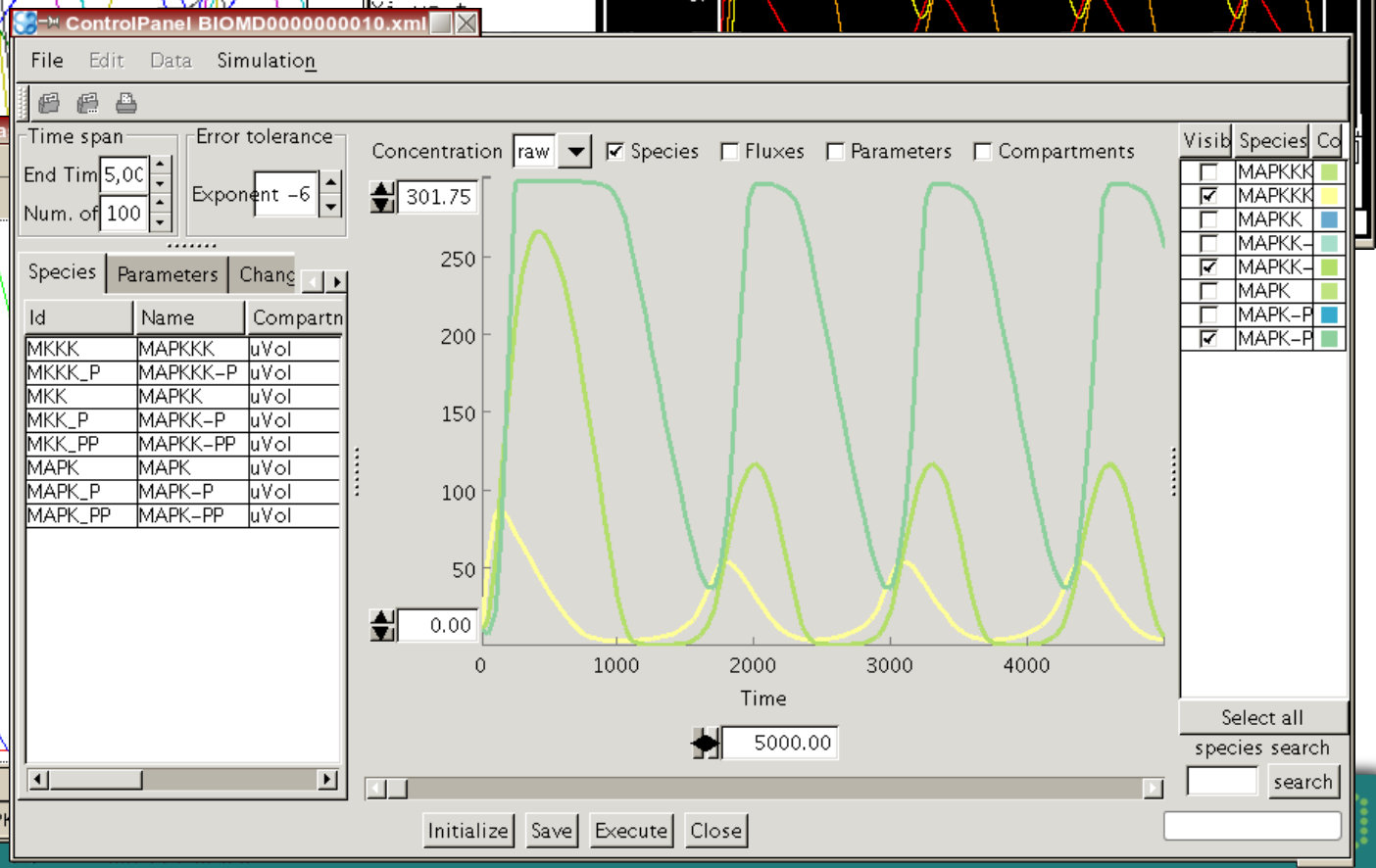
Produced by SBML2LaTeX 1

BIOMD0000000010









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BIOMD0000000005 - Tyson1991_CellCycle_6var

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- View GIF Reaction Graph
- View SVG Reaction Graph
- View Dynamic Reaction Graph
- View Model of Mo
- JWS Online Simulation
- BioModels Online Simulation

Model | Overview

Publication ID: 1831270

1991 Aug;8
cycle: cdc2
irginia Polyt

Original Model: *Unspecified*

Submitter: Nicolas Le Novère

Submission Date: 2005-09-13T12:31:08+00:00

Last Modification Date: 2009-02-25T14:58:48+00:00

Creation Date: 2005-02-08T18:28:27+00:00

Creators: Bruce Shapiro
Vijayalakshmi Chelliah

set #1	bqmodel:is	Taxonom
	bqbiol:isVersionOf	KEGG Pa Gene Ont
	bqbiol:hasVersion	Reactom

Cell Cycle Model; Tyson (1991, 6 variables)

Description

A model of the cell cycle based on the interactions between cdc2 and cyclin. The mod
P-cyclin-cdc2 complex); Y (cyclin); and YP (cyclin-P). Total cyclin concentration (YT)

Reaction

Variable	ODE
C2	0
CP	1
pM	0.3
M	0
Y	0

http://www.ebi.ac.uk/biomodels-main/publ-model-tab.do?cmd=MODEL:SIMU

Model - Simulation

For doing an online simulation, please select the species below. After specifying the *simulation time* and *print step*, and then click *Submit* to submit simulation job to our research cluster.

Click *Cancel* to close the window.

Cancel

Species

☐ EmptySet	☐ cdc2k	☑ cdc2k-P	☑ p-cyclin_cdc2
☐ p-cyclin_cdc2-p	☐ cyclin	☐ p-cyclin	☑ total_cyclin
☐ total_cdc2			

Simulation Time (use scientific notation e.g. 1

Print step: 1000

Submit

Done

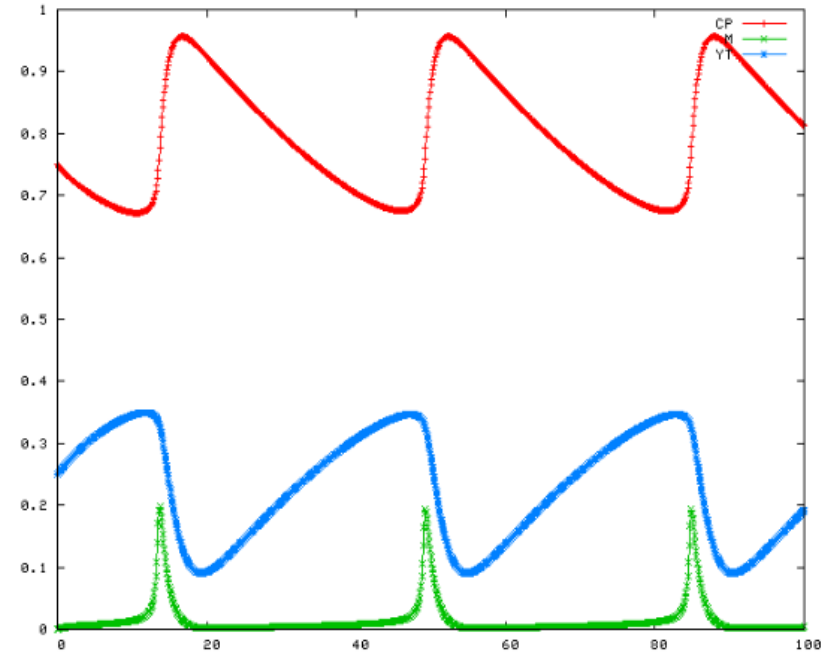
http://www.ebi.ac.uk/biomodels-main/publ-model-tab.do?cmd=MODEL:SIMU:RESULT

The simulation request has been submitted to the queue of our server cluster.

You could save following links and retrieve your simulation result later.

Link of simulation result:

http://www.ebi.ac.uk/biomodels-main/publ-model.do?cmd=SIMU:RETRIEVE&simuid=SIMU1234453623040



Close

http://www.ebi.ac.uk/biomodels/models-main/ode_simu/SIMU1234453623... zotero

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BIOMD0000000005 - Tyson1991_CellCycle_6var

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- View GIF Reaction Graph
- View SVG Reaction Graph
- View Dynamic Reaction Graph
- View Model of Month
- JWS Online Simulation
- BioModels Online Simulation

Model | Overview | Physical Entities | Parameters

Publication ID: 1831270

Reference Publication

1991 Aug;88(16):7328-32.

cycle: cdc2 and cyclin interactions.

irginia Polytechnic Institute and State University, BI

Original Model: *Unspecified*

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Submission Date: 2005-09-13T12:31:08+00:00

Last Modification Date: 2009-02-25T14:58:48+00:00

Creation Date: 2005-02-08T18:28:27+00:00

Creators: Bruce Shapiro, Vijayalakshmi Chelliah

Model

set #1	bqmodel:is	Taxonomy Fungi/Metazoa group
	bqbiol:isVersionOf	KEGG Pathway sce04111 Gene Ontology mitotic cell cycle
	bqbiol:hasVersion	Reactome REACT_152

Cell Cycle Model; Tyson (1991, 6

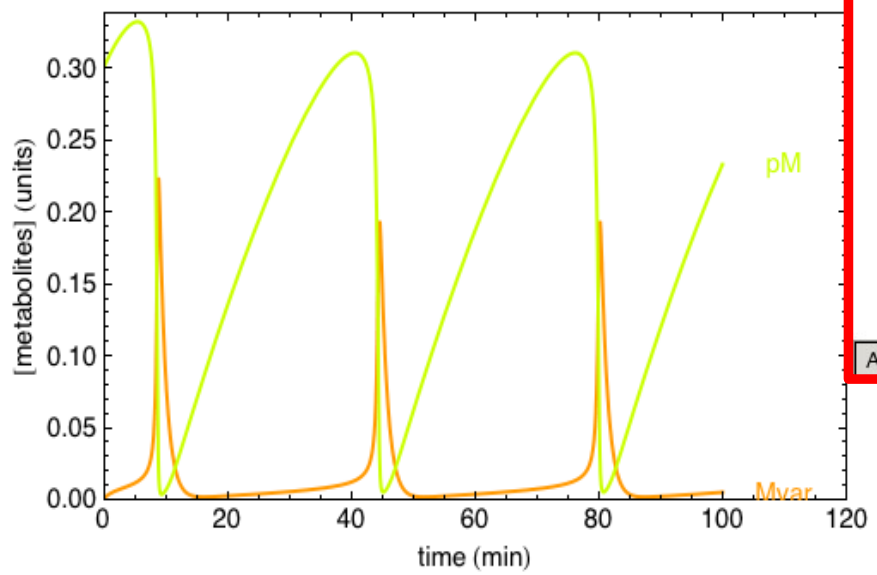
Description

A model of the cell cycle based or
P-cyclin-cdc2 complex); Y (cyclin)

Reaction

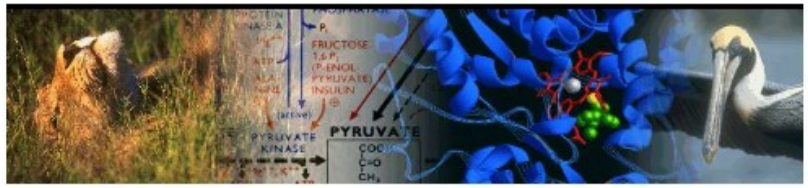
Variable	ODE
C2	0
CP	1
pM	0.3
M	0
Y	0

http://jjj.mib.ac.uk/webMathematica/Examples/PlotScript11.jsp?fun="JWS`



Download the results in text or comma separated value format (e.g. for Excel import):

http://jjj.mib.ac.uk/biomodels/Tyson1991/index.html



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Biomodels: BIOMD0000000005

Tyson1991

Powered by JWS Online

JWSApplet – ver 5.0.3 Tyson1991

	Parameter	Value
P1_v1	cell	1
P2_v1	k6	1
P3_v1	k8notP	1.0e6
P4_v1	k9	1000
P5_v1	k3	200
P6_v1	k5notP	0.
P7_v1	k1aa	0.015
P8_v1	k2	0.
P9_v1	k7	0.6
P10_v1	k4	180
P11_v1	k4prime	0.018
E1	EmptySet	0.
I1	C2[0]	0.
I2	CP[0]	1
I3	Mvar[0]	0.
I4	Y[0]	0.
I5	YP[0]	0.
I6	pM[0]	0.3

Evaluate Model

Sim | State

StartTime 0 EndTime 100

Rates Metabolites

Type	Output	Plot
M1	C2	
M2	CP	
M3	Mvar	✓
M4	Y	
M5	YP	
M6	pM	✓
F1	v[Rea...	
F2	v[Rea...	
F3	v[Rea...	
F4	v[Rea...	
F5	v[Rea...	
F6	v[Rea...	
F7	v[Rea...	

POWERED BY webMATHEMATICA2

Reset

Applet jjjApplet started

zotero

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BioModels Database: A Database of Annotated Published Models

Definitions:

"Reference Publication"
Document describing the structure of a model. This document is quoted within the model.
"Model Creators"
The individuals who wrote the model present in the BioModels Database, based on the reference publication. Model creators are listed within the model.
"Complete Dataset"
The entire content of the BioModels Database, including the models and their annotations.

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2. You may distribute verbatim copies of the complete dataset or a subset of the models, provided that you duplicate this copyright notice and the disclaimers shown below.

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a. Use the modified model only within your organization.
b. Contact BioModels team to include your modifications in the standard version of the model.
c. Rename the modified model, and remove both the BioModels Database identifier and any mention of the model creators.

DISCLAIMER

BioModels Web Services

Available features

Following are the currently available features in BioModels Web Services. In order to make using data in BioModels Database more conveniently, we will consider all requirements about new features.

```
java.lang.String helloBioModels()
          Say hello to BioModels
java.lang.String[] getAllCuratedModelsId()
```

Download

According to different cases, we provide two kinds of libraries for using BioModels Web Services. For downloading, please right click on the link and "*Save Target As*" or "*Save Link As*".

Name	Description	Size	Link
biomodelswslib-standalone.jar	standalone and includes all external dependencies and ready for use;	1.9M	http://www.ebi.ac.uk/compneur-srv/biomodels/softwares/biomodelswslib-standalone-1.11.jar
biomodelswslib.jar	light-weight, but needs other dependencies to work togeter.	6.4K	http://www.ebi.ac.uk/compneur-srv/biomodels/softwares/biomodelswslib-single-1.11.jar

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

- axis.jar
- jaxrpc.jar
- commons-logging-1.1.jar
- commons-discovery-0.2.jar
- saaj.jar
- wsdl4j-1.5.1.jar

Basics - Getting Started

Firstly, download the library we provided. I guess you already done it.

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

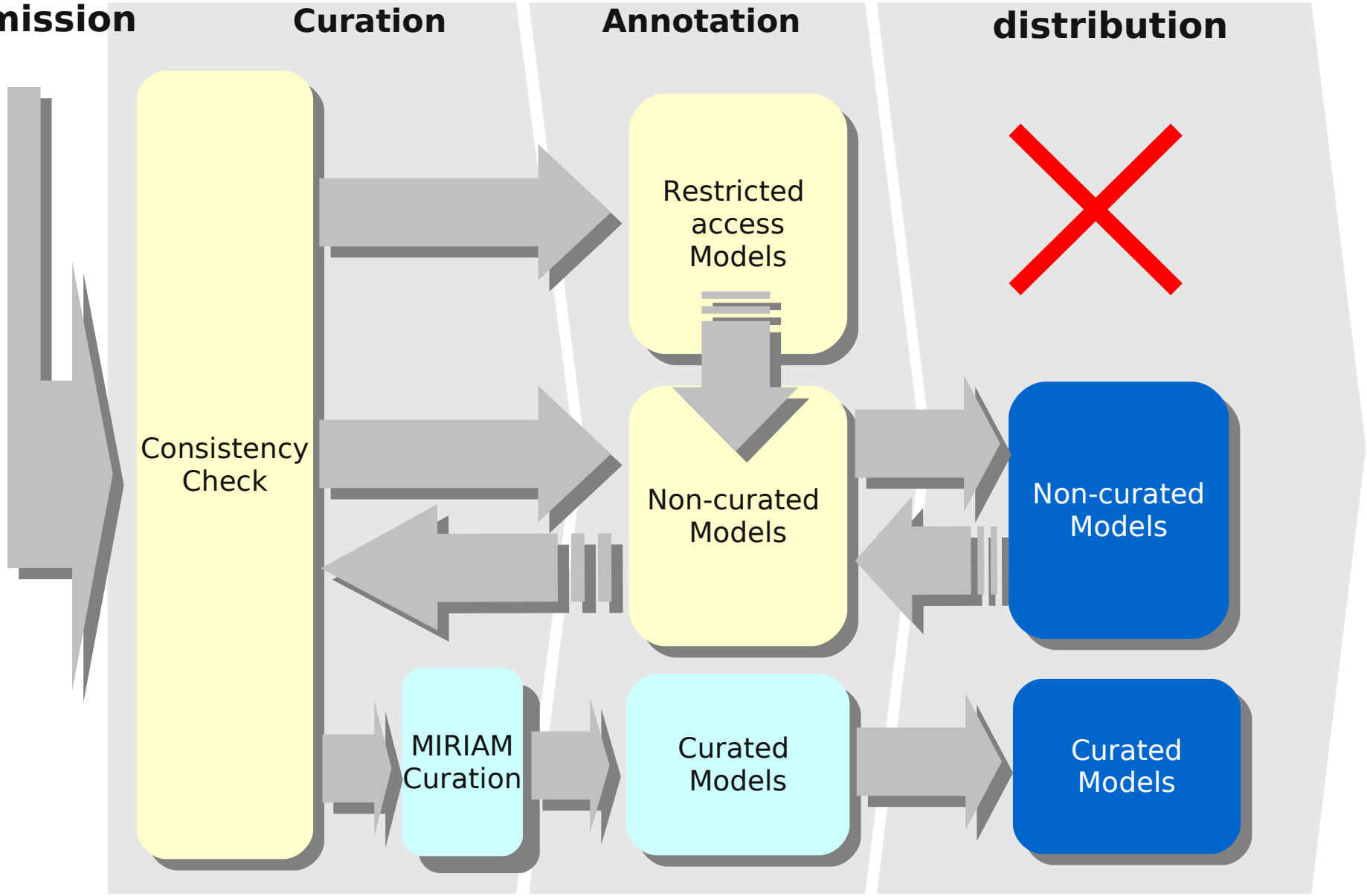
```
import uk.ac.ebi.biomodels.*;

public class HelloBioModels {
        public static void main(String args[]) throws Exception{
```

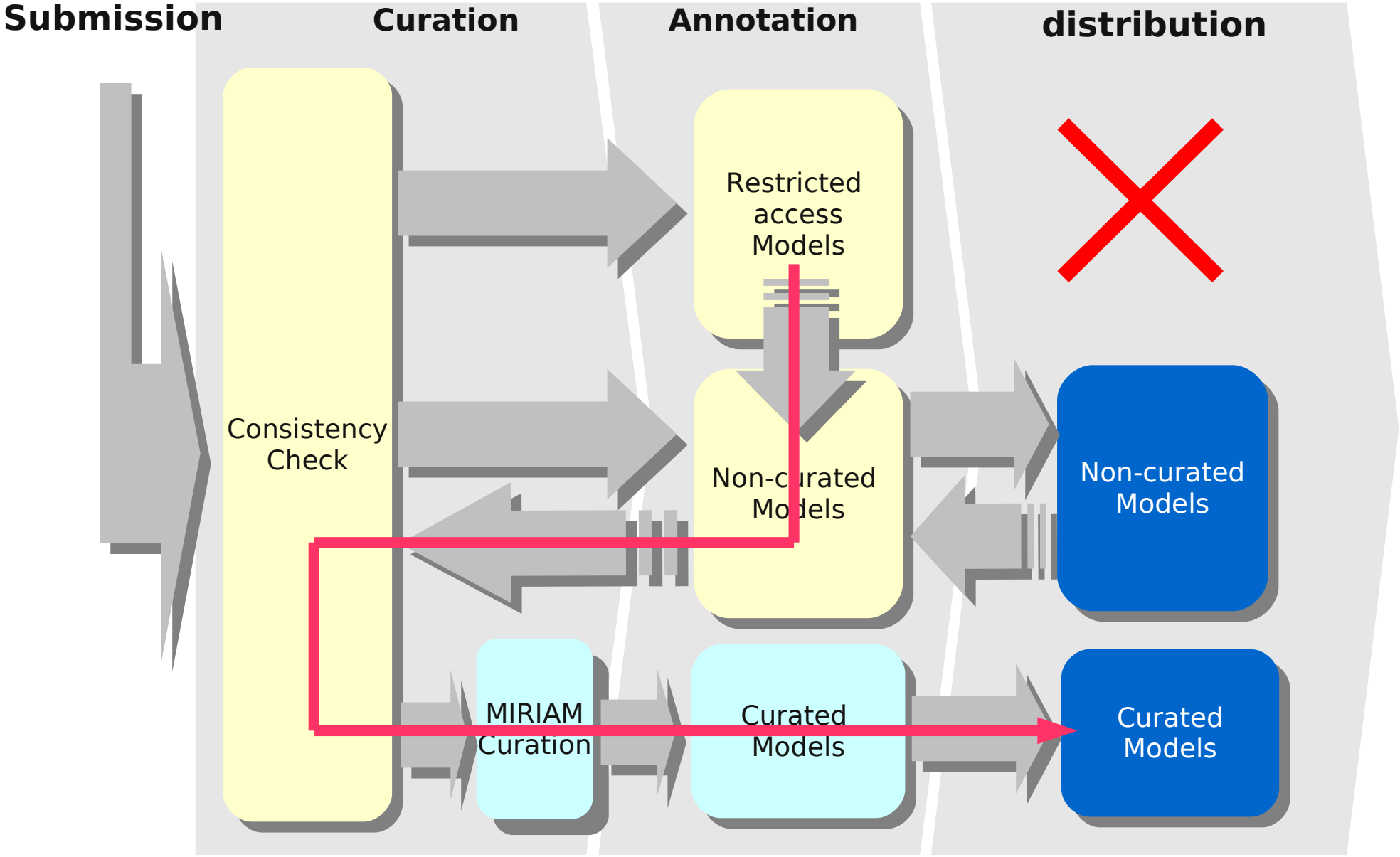
What do-we need to better serve Tox community

- Structure of BioModels Database: Model storage and access
  - Authenticated repositories with access to curation pipeline
    ☞ collaborative creation and annotation of models
  - Relaxation of the publication policy for the repositories above
  - Web access interface: Currently focus on reactions. We must enhance the coverage of rules and events

Modified production pipeline



Modified production pipeline



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  - Completing MIRIAM database with data resources used for toxicology.
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- **FUNDING**

Slides ommitted

BioModels.net group

Collaborators

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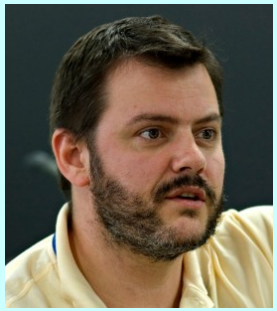
- Jacky Snoep (JWS Online, Stellenbosh university, ZA)
- Ion Moraru (Virtual Cell, UCHC, USA)
- Upinder Bhalla (DOQCS, NCBS, IN)

Journals supporting BioModels Database

- Molecular Systems Biology
- All PLoS Journals
- All BioMedCentral Journals

Programs used for curation

- CellDesigner/SBMLodeSolver
- COPASI
- Jarnac/JDesigner
- MathSBML
- RoadRunner
- SBMLeditor
- SBW
- XPP-Aut



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