

# BioModels Database:

Repository of mathematical models of biological processes

[www.ebi.ac.uk/biomodels](http://www.ebi.ac.uk/biomodels)

Viji Chelliah ([viji@ebi.ac.uk](mailto:viji@ebi.ac.uk))

BioModels.net Team, EMBL-EBI

WTAC: In Silico Systems Biology

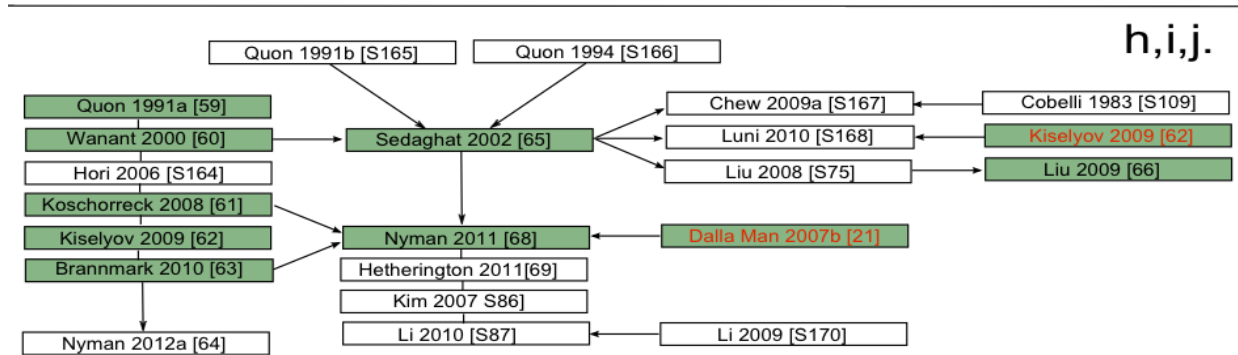
25<sup>th</sup> – 29<sup>th</sup> June 2013.

# Requirements for model repositories

- Modellers often need to

- search
- reuse
- reimplement
- combine..

existing models.



Example of models that are reused, reimplemented and combined

- Modellers get benefited by getting access to

- published models
- models in standard formats
- reliable (curation) and semantically (annotation) enriched model

# Outline

## BioModels

- In general (growth, model diversity, source)
- Model production pipeline
  - Submission
  - Curation and simulation
  - Annotation
  - Search, browse, model retrieval
- Iterative demo: Model components, features and submodels creation
- Usage

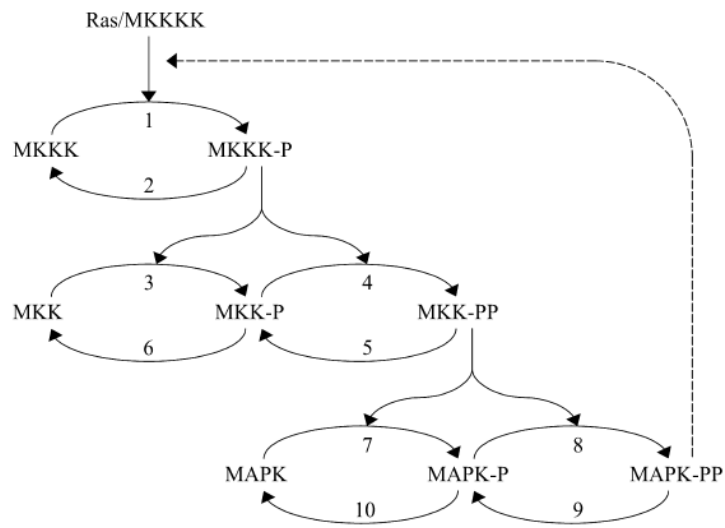
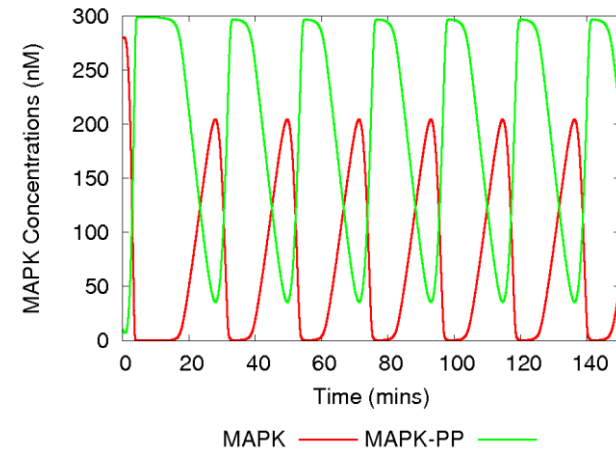


Table 2. Rate equations and parameter values of the MAPK cascade model. Concentrations and the Michaelis constants ( $K_1$ – $K_{10}$ ) are given in nM. The catalytic rate constants ( $k_3$ ,  $k_4$ ,  $k_7$ ,  $k_8$ ) and the maximal enzyme rates ( $V_1$ ,  $V_2$ ,  $V_5$ ,  $V_6$ ,  $V_9$ ,  $V_{10}$ ) are expressed in  $s^{-1}$  and  $nM \cdot s^{-1}$ , respectively.

Reaction number	Rate equation	Parameter values
1	$V_1 \cdot [MKKK] / ((1 + ([MAPK-PP]/K_1)^n) \cdot (K_1 + [MKKK]))$	$V_1 = 2.5$ ; $n = 1$ ; $K_1 = 9$ ; $K_1 = 10$ ;
2	$V_2 \cdot [MKKK-P] / (K_2 + [MKKK-P])$	$V_2 = 0.25$ ; $K_2 = 8$ ;
3	$k_3 \cdot [MKKK-P] \cdot [MKK] / (K_3 + [MKK])$	$k_3 = 0.025$ ; $K_3 = 15$ ;
4	$k_4 \cdot [MKKK-P] \cdot [MKK-P] / (K_4 + [MKK-P])$	$k_4 = 0.025$ ; $K_4 = 15$ ;
5	$V_5 \cdot [MKK-PP] / (K_5 + [MKK-PP])$	$V_5 = 0.75$ ; $K_5 = 15$ ;
6	$V_6 \cdot [MKK-P] / (K_6 + [MKK-P])$	$V_6 = 0.75$ ; $K_6 = 15$ ;
7	$k_7 \cdot [MKK-PP] \cdot [MAPK] / (K_7 + [MAPK])$	$k_7 = 0.025$ ; $K_7 = 15$ ;
8	$k_8 \cdot [MKK-PP] \cdot [MAPK-P] / (K_8 + [MAPK-P])$	$k_8 = 0.025$ ; $K_8 = 15$ ;
9	$V_9 \cdot [MAPK-PP] / (K_9 + [MAPK-PP])$	$V_9 = 0.5$ ; $K_9 = 15$ ;
10	$V_{10} \cdot [MAPK-P] / (K_{10} + [MAPK-P])$	$V_{10} = 0.5$ ; $K_{10} = 15$ ;

Total concentrations:  $[MKKK]_{total} = 100$ ;  $[MKK]_{total} = 300$ ;  $[MAPK]_{total} = 300$

output  
eg. time course



computer readable  
format, eg.



simulation software  
eg. Copasi



Kholodenko, *Eur J Biochem* (2000) 267: 1583-1588.



# BioModels Database

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BioModels Database serves as a reliable repository of computational models of biological processes. It hosts models described in peer-reviewed scientific literature and models generated automatically from pathway resources (Path2Models). A large number of models collected from literature are manually curated and semantically enriched with cross-references from external data resources. The resource allows scientific community to store, search and retrieve mathematical models of their interest. In addition, features such as generation of sub-models, online simulation, conversion of models into different representational formats, and [programmable access](#) via web services, are provided.

All models are provided under the terms of the [Creative Commons CC0 Public Domain Dedication](#), cf. our [terms of use](#). This means that the models are available freely for use, modification and distribution, to all users. More information about BioModels Database can be found in the [frequently asked questions](#) (FAQ).

## Models published in the literature

- [Browse curated models](#)
- [Browse curated models using GO](#)
- [Browse curated models using Taxonomy](#)
- [Browse non-curated models](#)

## Path2Models

## 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

June, 2013

The effect of different stresses that trigger p53 has been studied with a mathematical model of the negative feedback loop involving p53 and its inhibitor Mdm2.



[Please read more...](#)

## News Follow us on Twitter

18 June 2013 **25th release**

We are pleased to announce the [twenty-fifth release of BioModels Database](#)! The resource now publicly provides 143013 models. Numerous new models have been made available, several have been updated and various new features have been unveiled.

13 May 2013 **Bioinformatician position available**

We are seeking an outstanding **bioinformatician** to join the BioModels.net team. For more information and application instructions, please refer to the [job description page](#) (**closing date: 9 June 2013**).

5 March 2013 **Refreshed user interface**

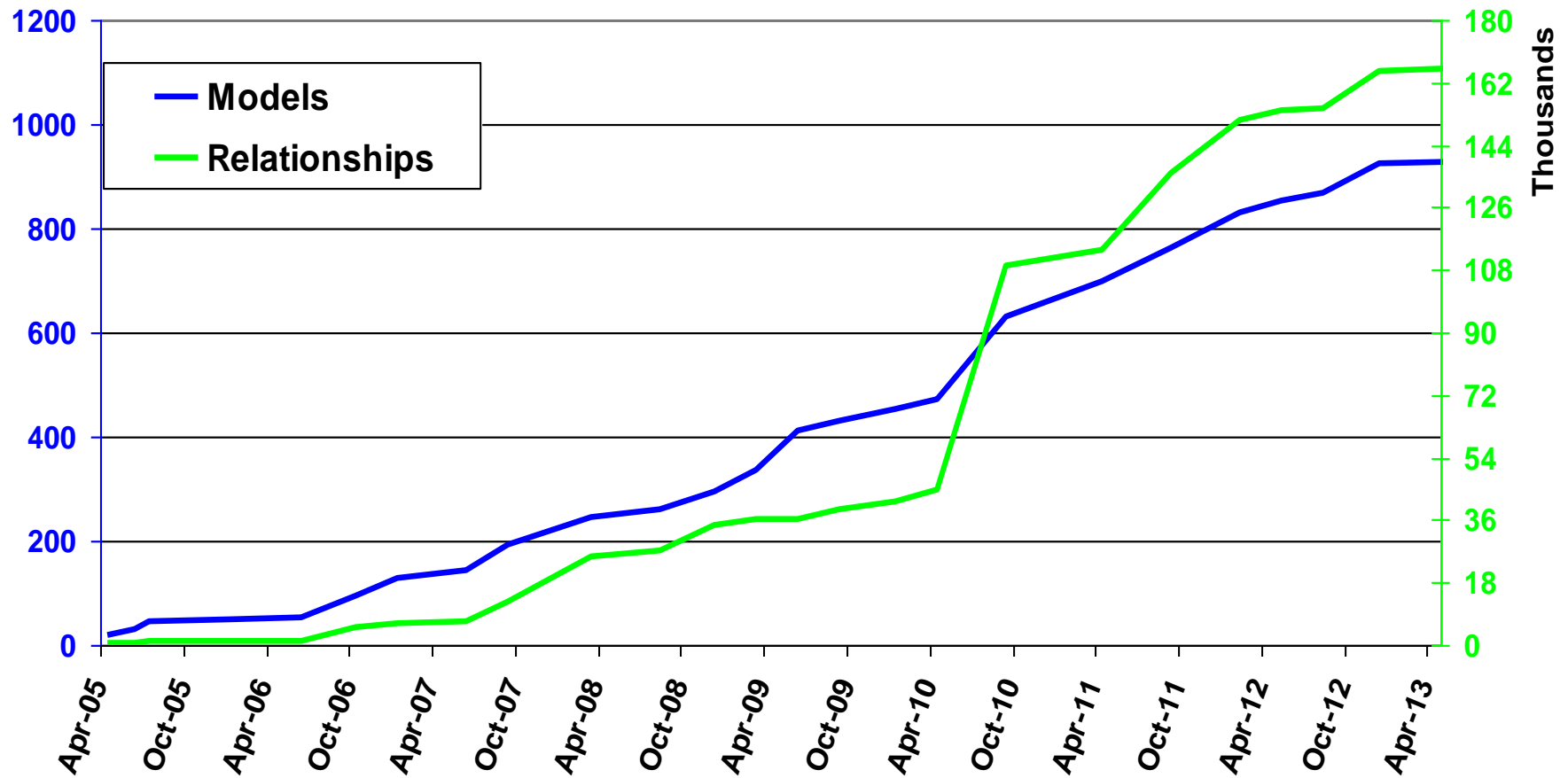
The user interface was slightly refreshed, in order to follow the new EBI look and feel.

Funded by:

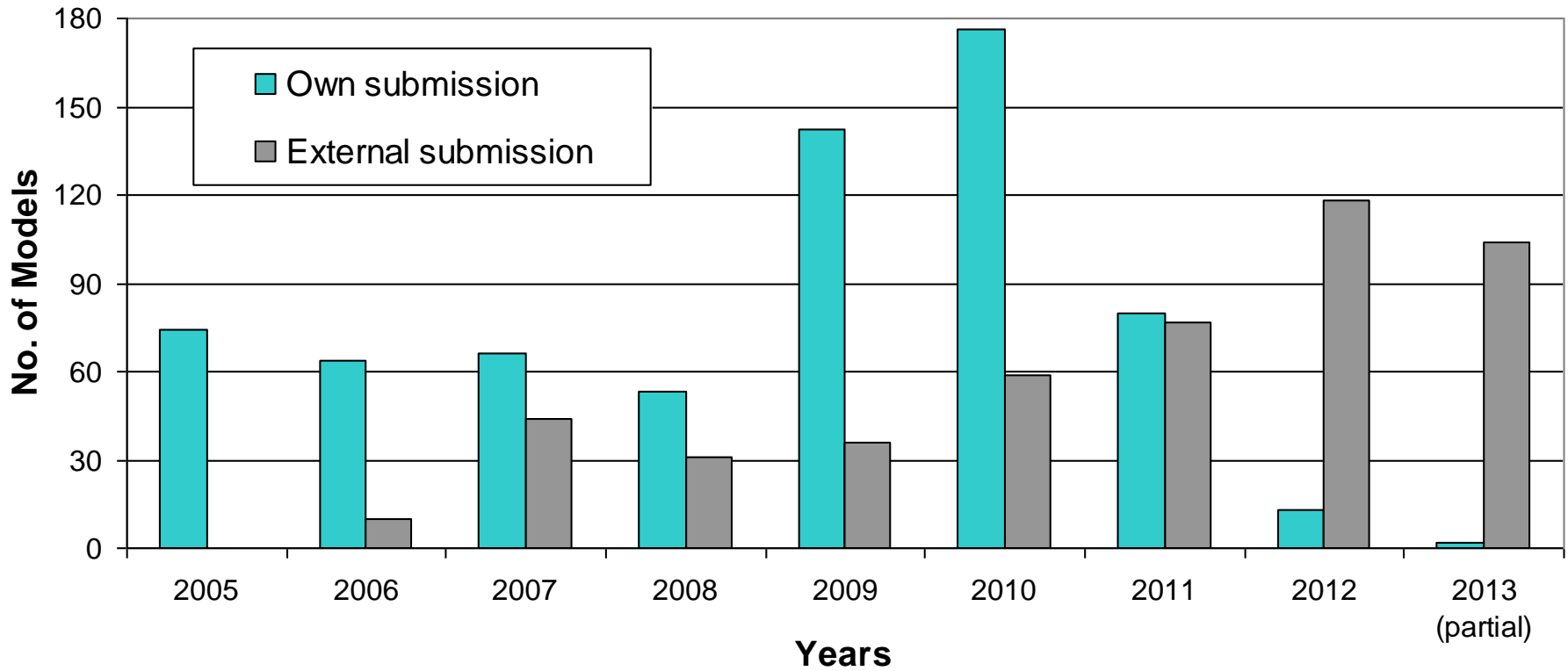


# BioModels Growth

Based on models from literature



# Submission statistics

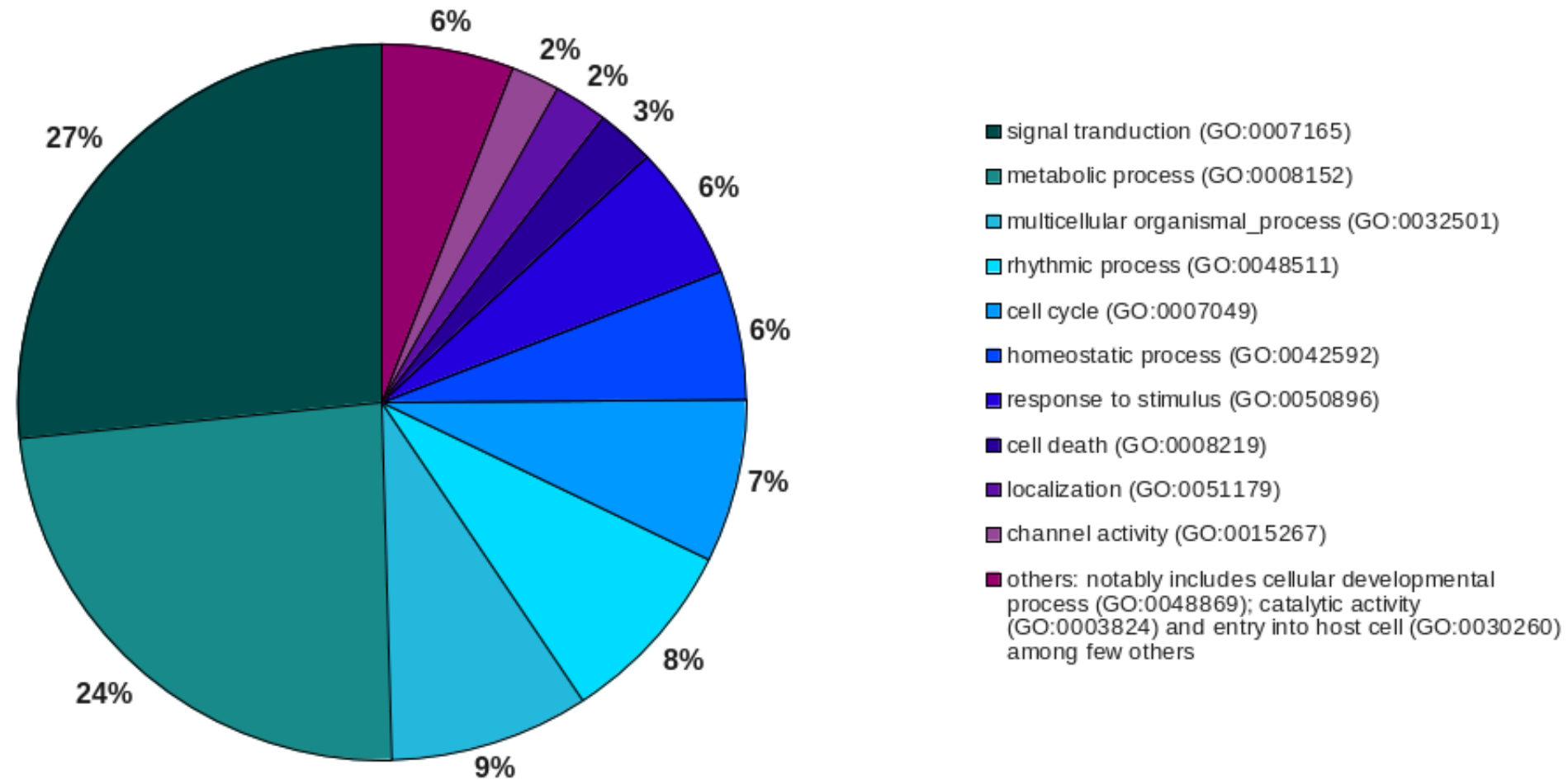


# Examples of models in BioModels Database?

- Biochemical models/Signal transduction models
  - Interaction between molecules in multicellular compartments
- Pharmacometric models
  - Tumour growth and treatment model
- Electrophysiology models
  - Membrane voltage, current flow, concentration of various ions in intra and extracellular compartments
- Disease models
  - Neurodegenerative, diabetes, blood coagulation, infectious disease models
- Ecosystem models
  - Interaction of living organism in a given environment



# Model classification based on GO terms



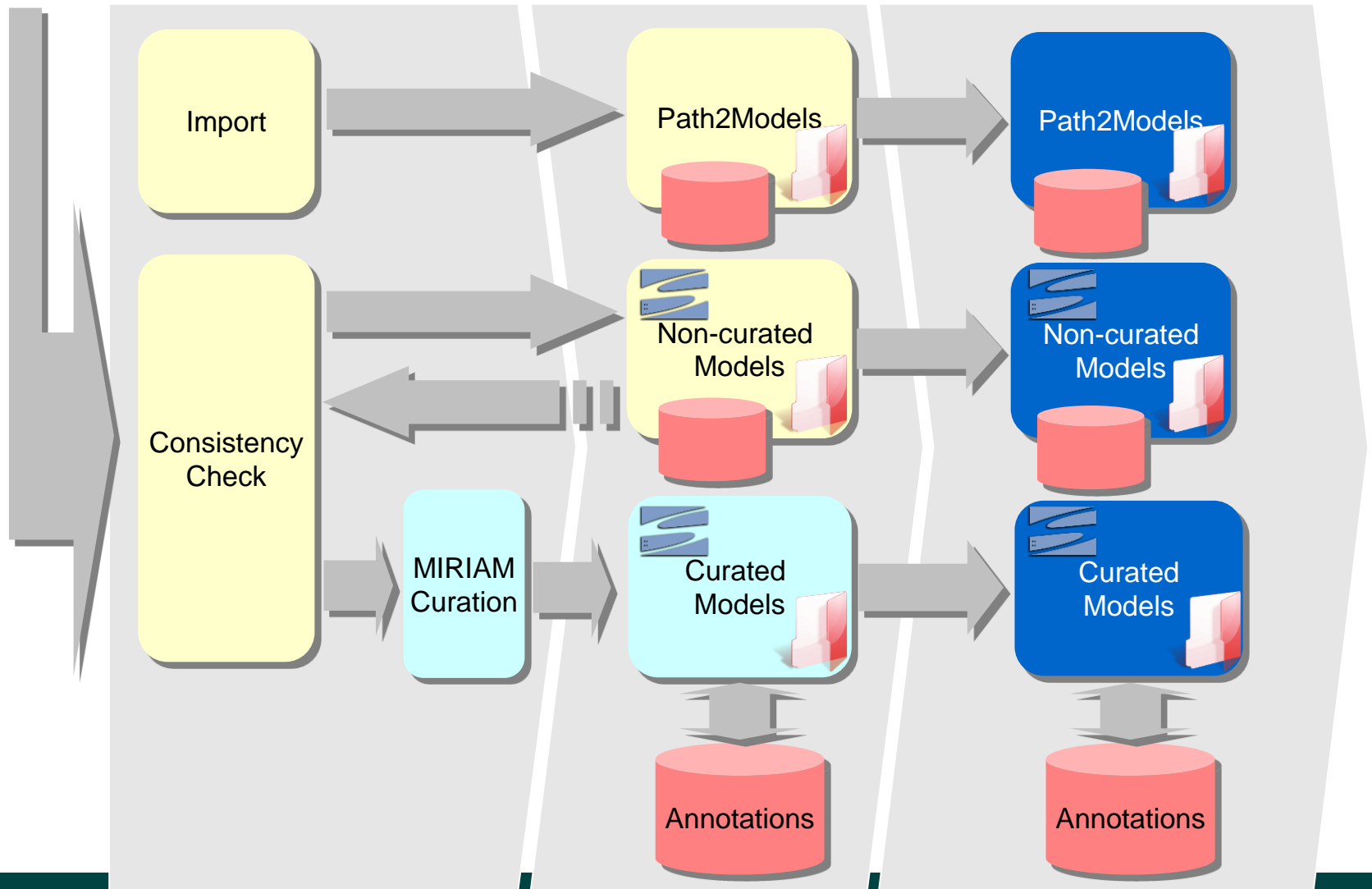
# Outline

## BioModels

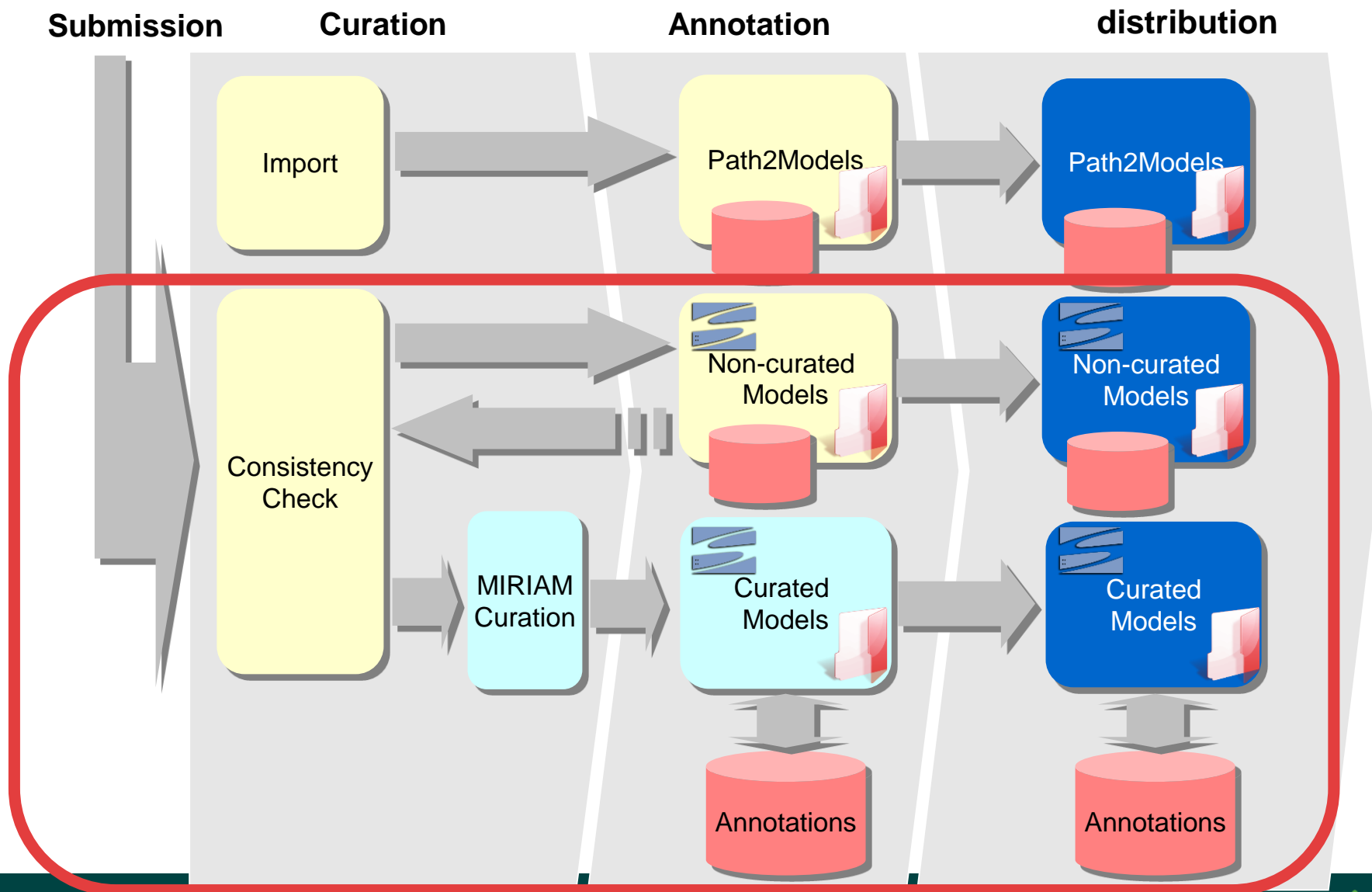
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# Current production pipeline

**Submission      Curation      Annotation      distribution**



# Current production pipeline





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model accession ID is unique and perennial  
and can be used as a reference in publications  
and for searching and retrieving the model

Dear **Vijayalakshmi**, your request to submit the model contained within the file:

**cellcycle.xml**

and with name:

**Tyson1991\_CellCycle\_6variable**

has been successfully completed.

The model has been assigned the unique ID:

**MODEL8232600906**

[Submit Another Model](#)

**Subject: BioModels Database - Notification of New Model Submission**

**From:** [biomodels-database-mailer@ebi.ac.uk](mailto:biomodels-database-mailer@ebi.ac.uk)

**Date:** 09:30

**To:** [viji@ebi.ac.uk](mailto:viji@ebi.ac.uk)

PLEASE DO NOT REPLY TO THIS EMAIL

Dear submitter,

Thank you for submitting the model Tyson1991\_CellCycle\_6variable, published in

Proc Natl Acad Sci U S A 1991 Aug;88(16):7328-32.  
Modeling the cell division cycle: cdc2 and cyclin interactions.  
Tyson JJ.

The model is now in the process pipeline with the unique accession **MODEL8232600906**. This identifier is unique and can be used, for instance in scientific publications or grant applications. Our team of curators will now verify the syntax and the semantic of the model. You will be notified when this is done and the model enters the annotation phase.

We welcome any updates, comments, or other notices about this or any other models. Please feel free to contact us at:

The BioModels Database team  
Computational Neurobiology  
EMBL-EBI  
Wellcome-Trust Genome Campus  
Hinxton Cambridge  
CB10 1SD  
United-Kingdom

E-mail: [biomodels-cura@ebi.ac.uk](mailto:biomodels-cura@ebi.ac.uk)

Tel: +44 (0)1223 494521

Fax: +44 (0)1223 494468

Thank you,  
The BioModels Database Team

BioModels Database is developed in collaboration by the teams of Nicolas Le Novère (EMBL-EBI, United-Kingdom), Michael Hucka (SBML Team, Caltech, USA), Herbert Sauro (Keck Graduate Institute, USA) and Jacky Snoep (JWS Online, Stellenbosch University, ZA), as part of the BioModels.net initiative. BioModels Database development is funded by the European Molecular Biology Laboratory and the National Institute of General Medical Sciences.

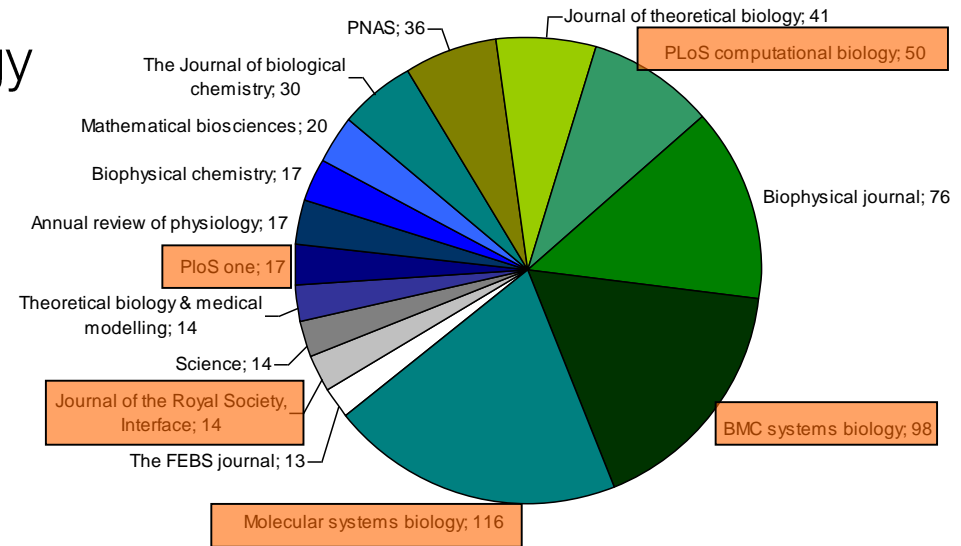
Please quote the reference publication associated with the model, when quoting a model present in the BioModels Database.

# Model provenance

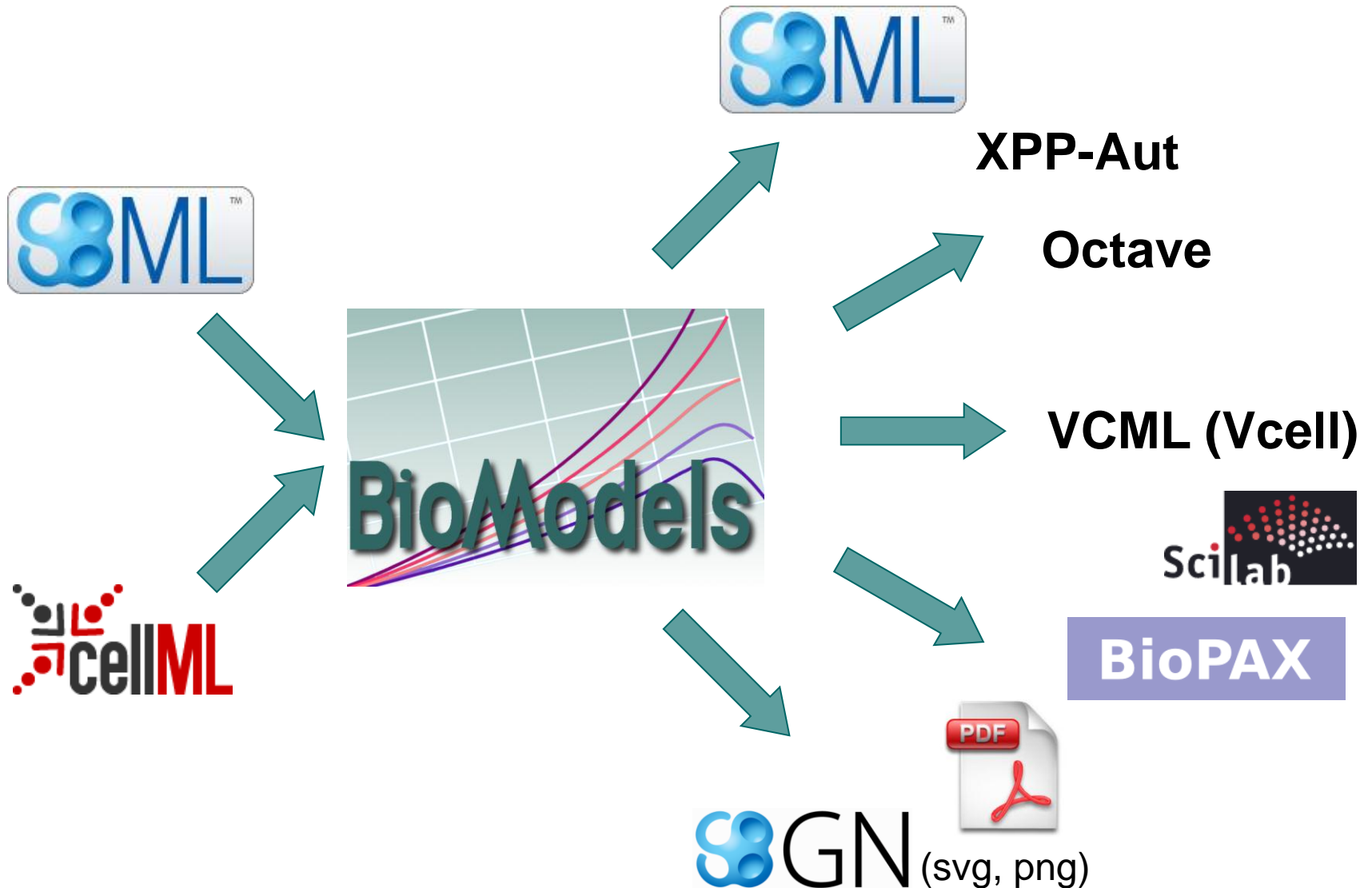
- From authors prior to submission

Supported by following journals (suggested submission to BioModels in author's instruction)

- Molecular Systems Biology
- PLoS journals
- BioMed Central journals
- RSC publications
- Submitted by curators
  - Implemented from literatures
  - Imported from supplementary materials of the article
- Exchange with other repositories (DOCQS, CellML, JWS online)
- From other people who curate models for their research



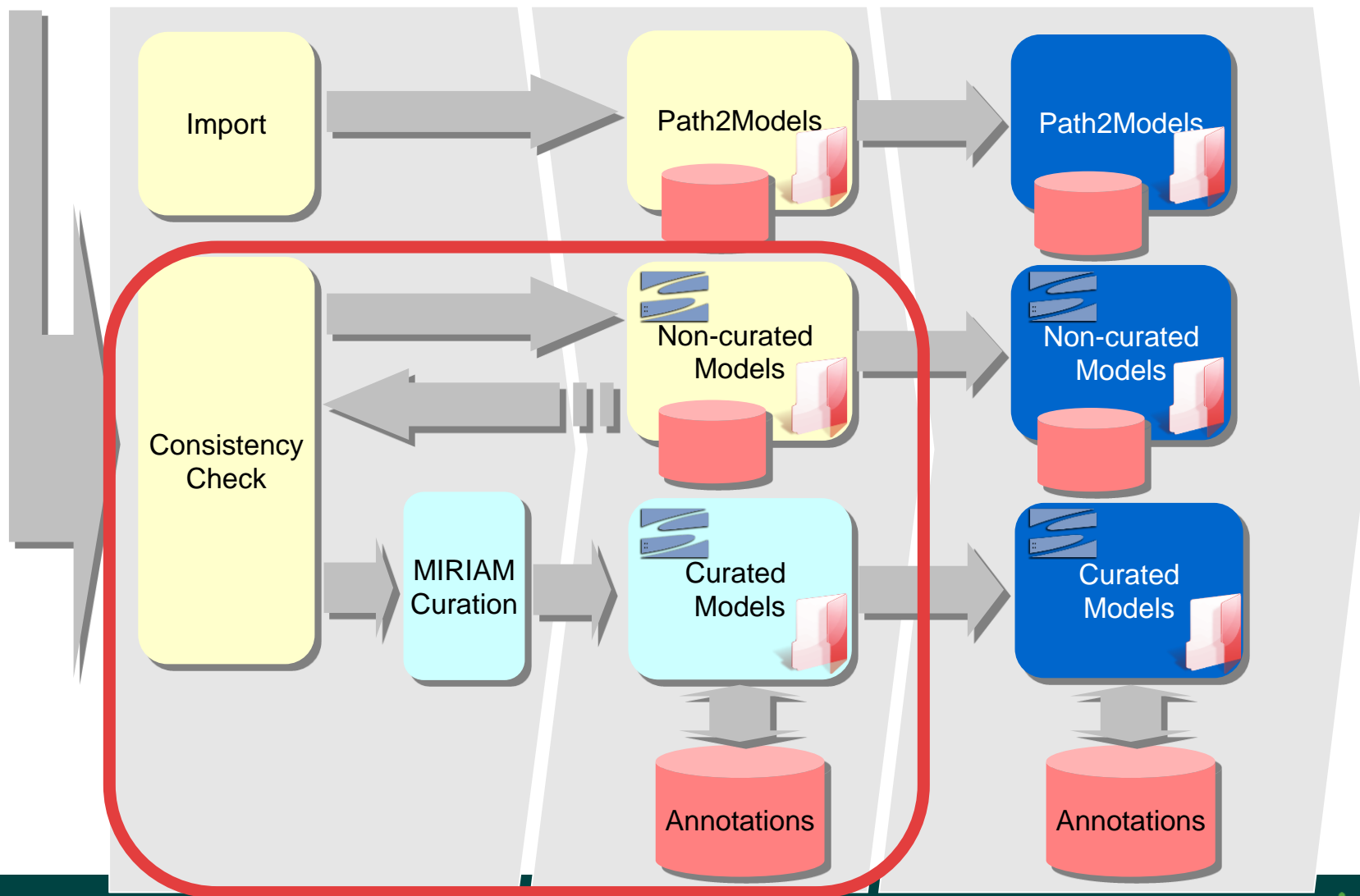
# Supported formats





# Model production pipeline

**Submission      Curation      Annotation      distribution**



BIOMD0000000005 - Tyson1991

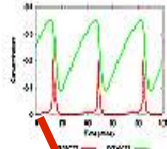
SBML formats

Other for  
generat

Model

Overv

Curation result



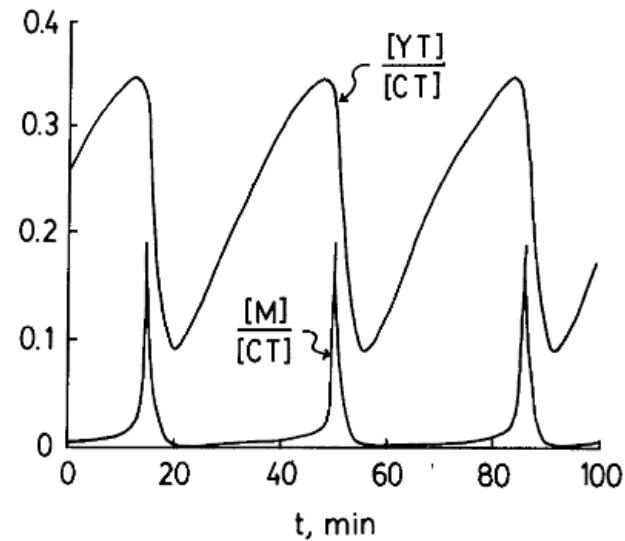
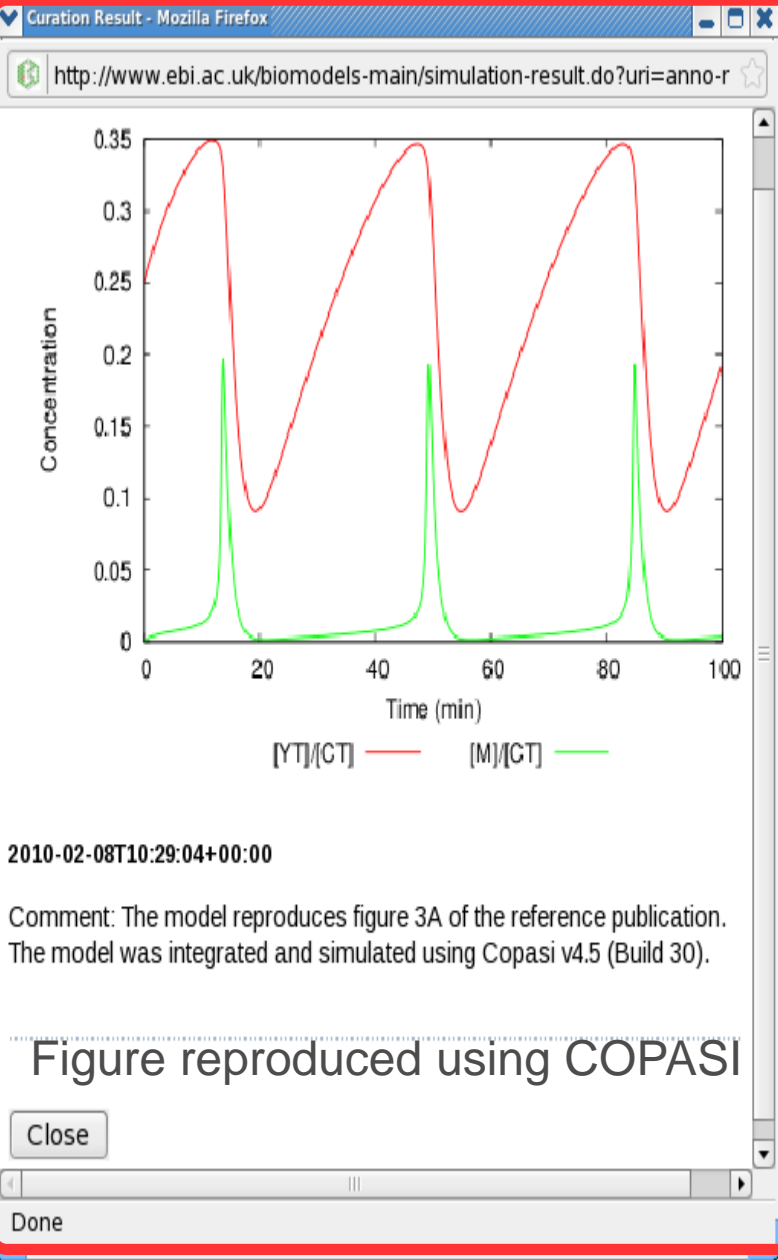
2010-02-08T10:29:04

Comment: The mo

Model history

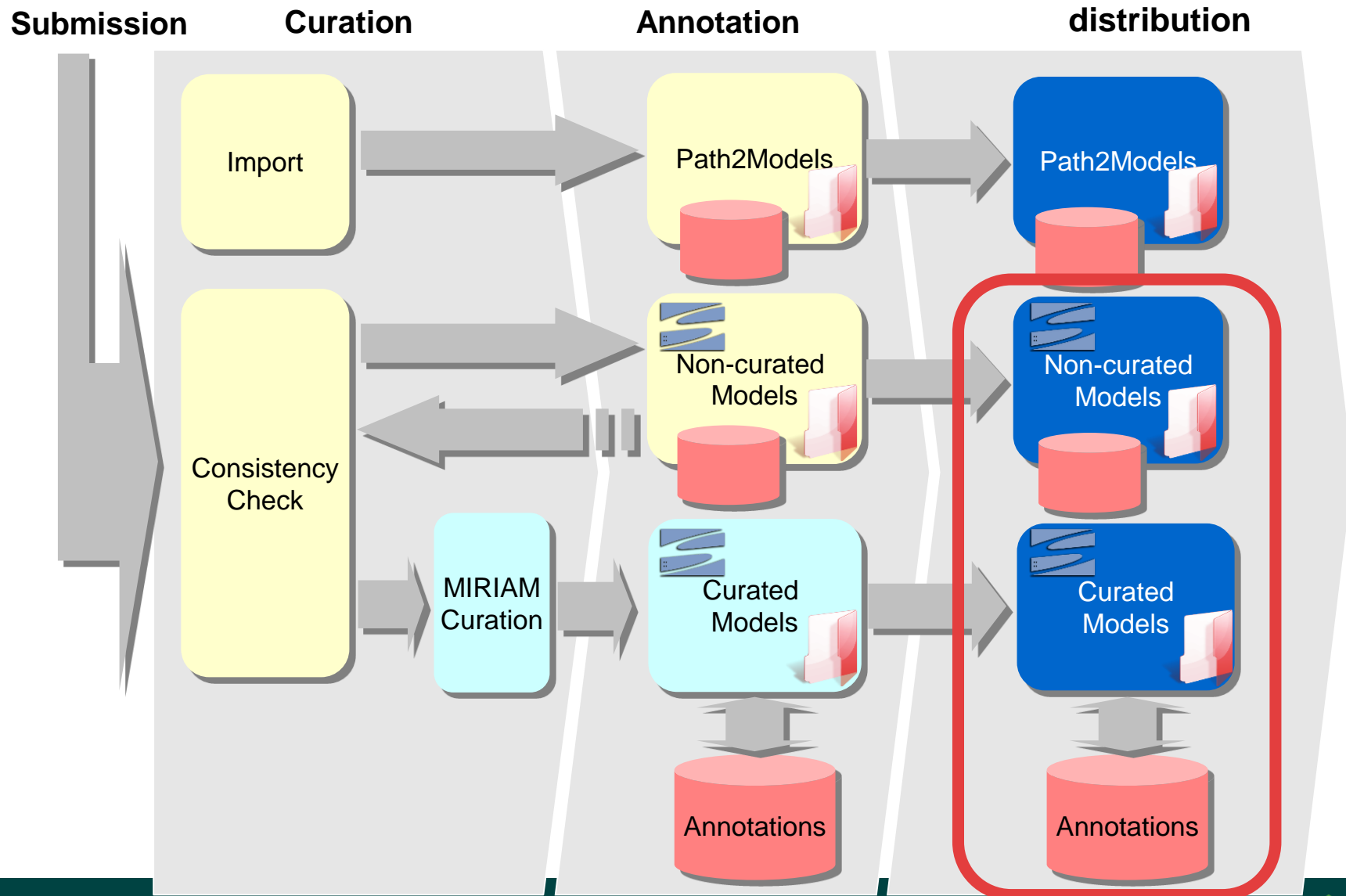
Rev	log message
<input type="checkbox"/> 36	changed to SBML l2_v4 a
<input type="checkbox"/> 3	the latest version when im
<input type="checkbox"/> 2	original models.

Compare Revisions



original article

# Model production pipeline



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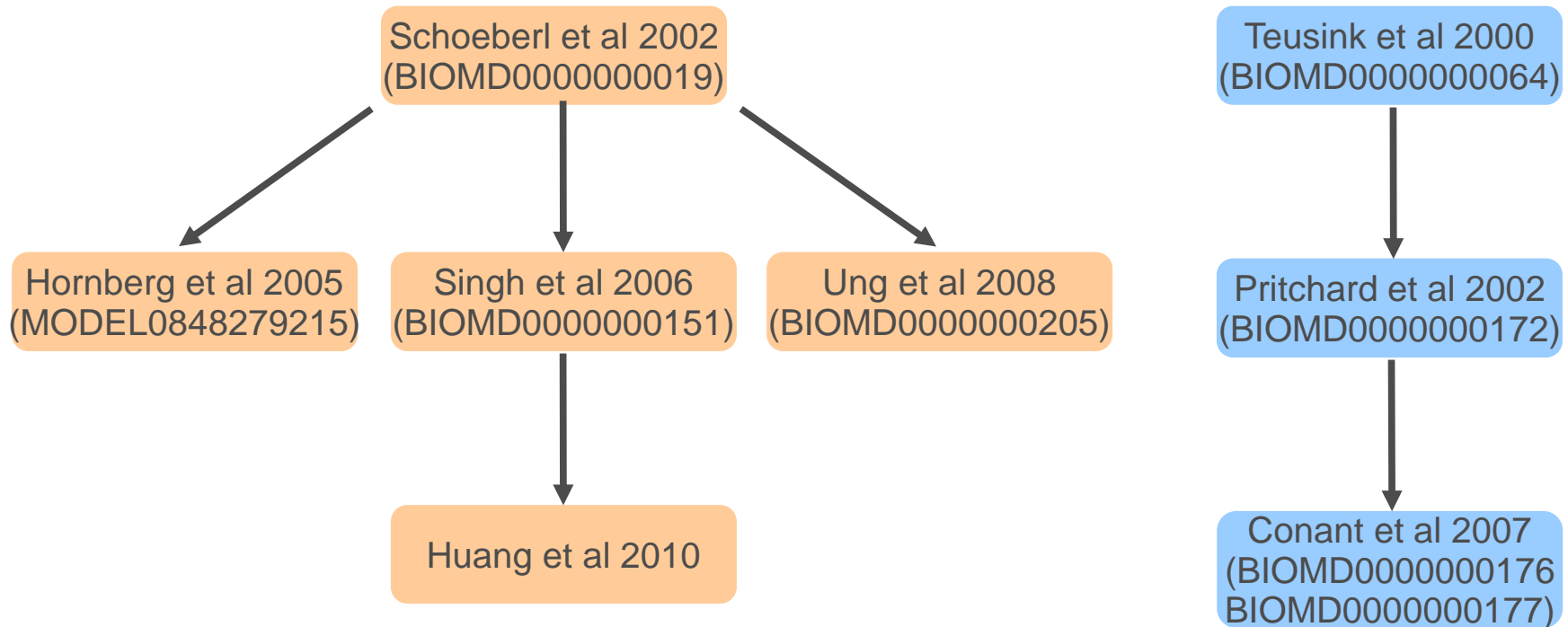
# BioModels Usage

Benchmarking modelling and simulation tools

- SBMLsimulator
- ByoDyn
- BioUML
- CellDesigner
- Systems Biology Workbench
- Virtual Cell
- ...


































# BioModels Usage

Direct model reuse eg: EGFR signalling and glycolysis



# BioModels Usage

## Clustering and merging of models using annotations (Schulz et al. 2010)

Model	BioModel	Similarity	P-value	Overlap	P-value	
Huang1996_MAPK_ultrasens	BIOMD0000000009	1.000	$\leq 1e-3$	30	0.0e+00	
Levchenko2000_MAPK_noScaffold	BIOMD0000000011	0.930	$\leq 1e-3$	28	0.0e+00	
Levchenko2000_MAPK_Scaffold	BIOMD0000000014	0.874	$\leq 1e-3$	26	0.0e+00	
Kholodenko2000_MAPK_feedback	BIOMD0000000010	0.830	$\leq 1e-3$	20	0.0e+00	
Markevich2004_MAPK_orderedElementary	BIOMD0000000026	0.749	$\leq 1e-3$	16	2.9e-15	
Markevich2004_MAPK_phosphoRandomElementary	BIOMD0000000028	0.692	$\leq 1e-3$	15	9.1e-14	
Markevich2004_MAPK_AIRandomElementary	BIOMD0000000030	0.692	$\leq 1e-3$	15	9.1e-14	
Markevich2004_MAPK_orderedMM	BIOMD0000000027	0.691	$\leq 1e-3$	12	9.8e-10	
Markevich2004_MAPK_orderedMM2kinases	BIOMD0000000031	0.691	$\leq 1e-3$	12	9.8e-10	
Markevich2004_MAPK_phosphoRandomMM	BIOMD0000000029	0.626	$\leq 1e-3$	11	1.6e-08	
Hornberg2005_ERKcascade	BIOMD0000000084	0.523	$\leq 1e-3$	9	2.7e-06	
McClean2007_CrossTalk	BIOMD0000000116	0.453	$\leq 1e-3$	8	2.7e-05	
Kofahl2004_pheromone	BIOMD0000000032	0.441	$\leq 1e-3$	12	9.8e-10	
Goldbeter1991_MinMitOscil_ExpInact	BIOMD0000000004	0.389	$\leq 1e-3$	3	1.5e-01	
Brown2004_NGF_EGF_signaling	BIOMD0000000033	0.371	$\leq 1e-3$	9	2.7e-06	
Ung2008_EGFR_Endocytosis	BIOMD0000000205	0.363	$\leq 1e-3$	8	2.7e-05	
Kim2007_Wnt_ERK_Crosstalk	BIOMD0000000149	0.355	$\leq 1e-3$	10	2.2e-07	
Goldbeter1991_MinMitOscil	BIOMD0000000003	0.349	$\leq 1e-3$	3	1.5e-01	
Sasagawa2005_MAPK	BIOMD0000000049	0.339	$\leq 1e-3$	9	2.7e-06	
Swat2004_Mammalian_G1_S_Transition	BIOMD0000000228	0.317	$\leq 1e-3$	2	4.0e-01	
Tyson1991_CellCycle_6var	BIOMD0000000005	0.304	$\leq 1e-3$	4	4.2e-02	
Goldbeter1995_CircClock	BIOMD0000000016	0.274	$\leq 1e-3$	4	4.2e-02	
Novak1997_CellCycle	BIOMD0000000007	0.259	$\leq 1e-3$	1	7.6e-01	
Novak2001_FissionYeast_CellCycle	BIOMD0000000111	0.255	$\leq 1e-3$	2	4.0e-01	
Leloup1999_CircClock	BIOMD0000000021	0.246	$\leq 1e-3$	4	4.2e-02	
Birtwistle2007_ErbB_Signalling	BIOMD0000000175	0.236	$\leq 1e-3$	1	7.6e-01	
Neves2008_Cell_Shape	BIOMD0000000182	0.222	$\leq 1e-3$	6	1.6e-03	
Leloup1998_CircClock_LD	BIOMD0000000171	0.219	$\leq 1e-3$	4	4.2e-02	
Veening2008_DegU_Regulation	BIOMD0000000240	0.211	4.0e-03	2	4.0e-01	
Chen2004_CellCycle	BIOMD0000000056	0.209	4.0e-03	4	4.2e-02	
Fernandez2006_ModelA	BIOMD0000000152	0.207	5.0e-03	2	4.0e-01	
Fisher2006_NFAT_Activation	BIOMD0000000123	0.199	7.0e-03	2	4.0e-01	
Hatakeyama2003_MAPK	BIOMD0000000146	0.198	7.0e-03	1	7.6e-01	

**Figure 3** Results of a semantic model search in BioModels Database. Starting from the kinase cascade model of Huang and Ferrell (1996), a ranked list of similar models was retrieved automatically. The first 15 models contain complete kinase cascades or parts of them. The top hit is the query model itself.



# Thanks to:

- EMBL-EBI
- Developers
  - Mélanie Courtot, Alexander Broicher, Finja Büchel, [Marco Donizelli](#), Marine Dumousseau, Gael Jalowicki, [Mihai Glont](#), Ron Henkel, Arnaud Henri, [Sarah Keating](#), Christian Knuepfer, [Camille Laibe](#), [Chen Li](#), Lu Li, Florian Mittag, Kedar Nath Natarajan, Jean-Baptiste Pettit, [Nicolas Rodriguez](#), Karim Tazibt, Martijn van Iersel, Dagmar Waltemath, [Sarala Wimalaratne](#), Yangyang Zhao, Anna Zhukova
- Curators
  - Ishan Ajmera, [Viji Chelliah](#), Harish Dharuri, Lukas Endler, Enuo He, [Nick Juty](#), Michael Schubert, Melanie Stefan
- [Henning Hermjakob](#), Janet Thornton
- Babraham Institute
  - [Nicolas Le Novère](#) (Visiting Scientist at EBI)
- External contributions
  - Collaborators
    - Upi Bhalla, Andreas Dräger, Jürgen Eils, [Mike Hucka](#), Hiroaki Kitano, Ion Moraru, Julio Saez-Rodriguez, Herbert Sauro, Maria Schilstra, Falk Schreiber, Jacky Snoep, Neil Swainston
  - Scientific Advisory Board
    - Upi Bhalla, [Carole Goble](#), [Thomas Lemberger](#), [Pedro Mendes](#), Ion Moraru, [Wolfgang Müller](#), [Philippe Sanseau](#), Herbert Sauro, Jacky Snoep
  - All the computational systems biology community.

# Current funders

