EMBL-EBI

Computational models in Systems Biology

Nicolas Le Novère

EMBL-EBI

What is Computational Systems Biology?

What is Computational Systems Biology?

- « *Je tiens impossible de connaître les parties sans connaître le tout, non plus que de connaître le tout sans connaître particulièrement les parties* » Blaise Pascal, Pensées, 1660.

- *“[A system consists of] a dynamic order of parts and processes standing in mutual interaction. [...] The fundamental task of biology [is] the discovery of the laws of biological systems*" Ludwig von Bertalanfy, Kritische Theorie der Formbildung, 1928

What is Computational Systems Biology

For us and for today ...

What is Computational Systems Biology

For us and for today ...

- **Systems Biology** is the study of a biological systems taking into account all its constituents, *their relationships* and *their evolution*

What is Computational Systems Biology

For us and for today ...

- **Systems Biology** is the study of a biological systems taking into account all its constituents, *their relationships* and *their evolution*

- **Computational Systems Biology** is the construction of quantitative models that describe the behaviour of a system, on its own, or in response to its environment

What is a model? A simulation?

- A model is a mathematical description of the components of a system, their relationships, and the evolution of both.
  - ordinary differential equations (system evolution) $dX/dt = f(X)$
  - partial differential equation (system description) $\nabla X = g(X)$
  - algebraic equations (conservation laws) $h(X) = 0$
  - probability distributions $PX = i(X)$
  - master equation $dPX/dt = j(PX)$
  - cell automata/finite elements
  - ...

What is a model? A simulation?

- A simulation is the instantiation of a model over time, using a given algorithmic approach, and a particular software: A model can generate simulations giving different results!
  - Logical (boolean or discrete) approach
  - Deterministic approach
  - Stochastic approach
  - Fixed timesteps
  - Adaptative timesteps
  - ...
- Plus ... range of simulations
  - parameter scan
  - parameter search/optimisation
  - phase-plane analysis
  - bifurcation analysis
  - ...

SBML Systems Biology Markup Language

The Systems Biology Markup Language (SBML) is a computer-readable format for representing **models of biochemical reaction networks**. SBML is applicable to metabolic networks, cell-signaling pathways, regulatory networks, and many others.

Internationally Supported and Widely Used

SBML has been evolving since mid-2000 through the efforts of an international group of software developers and users. Today, SBML is **supported by over 110 software systems**, including the following (where '*' indicates SBML support in development):

BALSA
BASIS
BIOCHAM
BioCharon
ByoDyn
BioCyc
BioGrid
BioModels
BioNetGen
BioPathwise
Bio Sketch Pad
BioSens
BioSPICE Dashboard
BioSpreadsheet
BioTapestry
BioUML
BSTLab
CADLIVE
CellDesigner
Cellerator
Cell Illustrator
CellML2SBML
Cellware
CL-SBML
CLEML
COPASI
Cyto-Sim
Cytoscape
DBsolve
Dizzy
E-CELL
ecellJ
ESS
FluxAnalyzer
Fluxor
Gepasi
Gillespie2
HSMB
HybridSBML
INSILICO discovery
JACOBIAN
Jarnac
JDesigner
JigCell
JSim
JWS Online
Karyote*
KEGG2SBML
Kineticon
Kinsolver*
libSBML
MathSBML
MesoRD
Meta-All
MetaFluxNet
MIRIAM
MMT2
Modesto
Moleculizer
Monod
Narrator
NetBuilder
Oscill8
PANTHER Pathway
PathArt
Pathway Analyser
PathwayLab
Pathway Tools
PathwayBuilder
PATIKAweb
PaVESy
PET
PNK
PottersWheel
ProcessDB
PROTON
pysbml
PySCeS
Reactome
RSBML
runSBML
SABIO-RK
SBML ODE Solver
SBML-PET
SBMLeditor
SBMLmerge
SBMLR
SBMLSim
SBMLToolbox
SBO
SBToolbox
SBW
SCIpath
Sigmoid*
SigPath
SigTran
SIMBA
SimBiology
Simpathica
SimPheny*
SimWiz
SloppyCell
SmartCell
SRS Pathway Editor
StochSim
StochKit
STOCKS
TERANODE Suite
Trelis
VANTED
Virtual Cell
WebCell
WinSCAMP
Xholon
XPPAUT

A Free and Open Language

Advances in biotechnology are leading to larger, more complex quantitative models. The systems biology

COPASI 4.1 Build 21 Released

(May 21, 2007) **COPASI** version 4.1 (build 21) has been released. COPASI is a free, general simulator for systems biology with a large number of features.

read more

SBML Hackathon 2007!

(April 3, 2007) This year's **SBML Hackathon** will be held at the University of Newcastle, UK. Please join us and don't forget to register ASAP!

read more

VANTED supports SBML

(April 3, 2007) **VANTED** is a network editing and visualization system with features for network-integrated visualization of data from experiments and simulations.

read more

RSBML, a package for R

(March 29, 2007) **RSBML** is a package that allows SBML to be imported into R either as an S4 object or a Bioconductor graph object.

read more

Xholon supports SBML

(March 27, 2007) **Xholon** is an open-source, general-purpose modeling and simulation tool. It can read models created using UML, among other things.

read more

See older news items.

What is SBML?

"*The goal of SBML is to help people to disagree as precisely as possible*". Ed Franck, Argonne National Laboratory

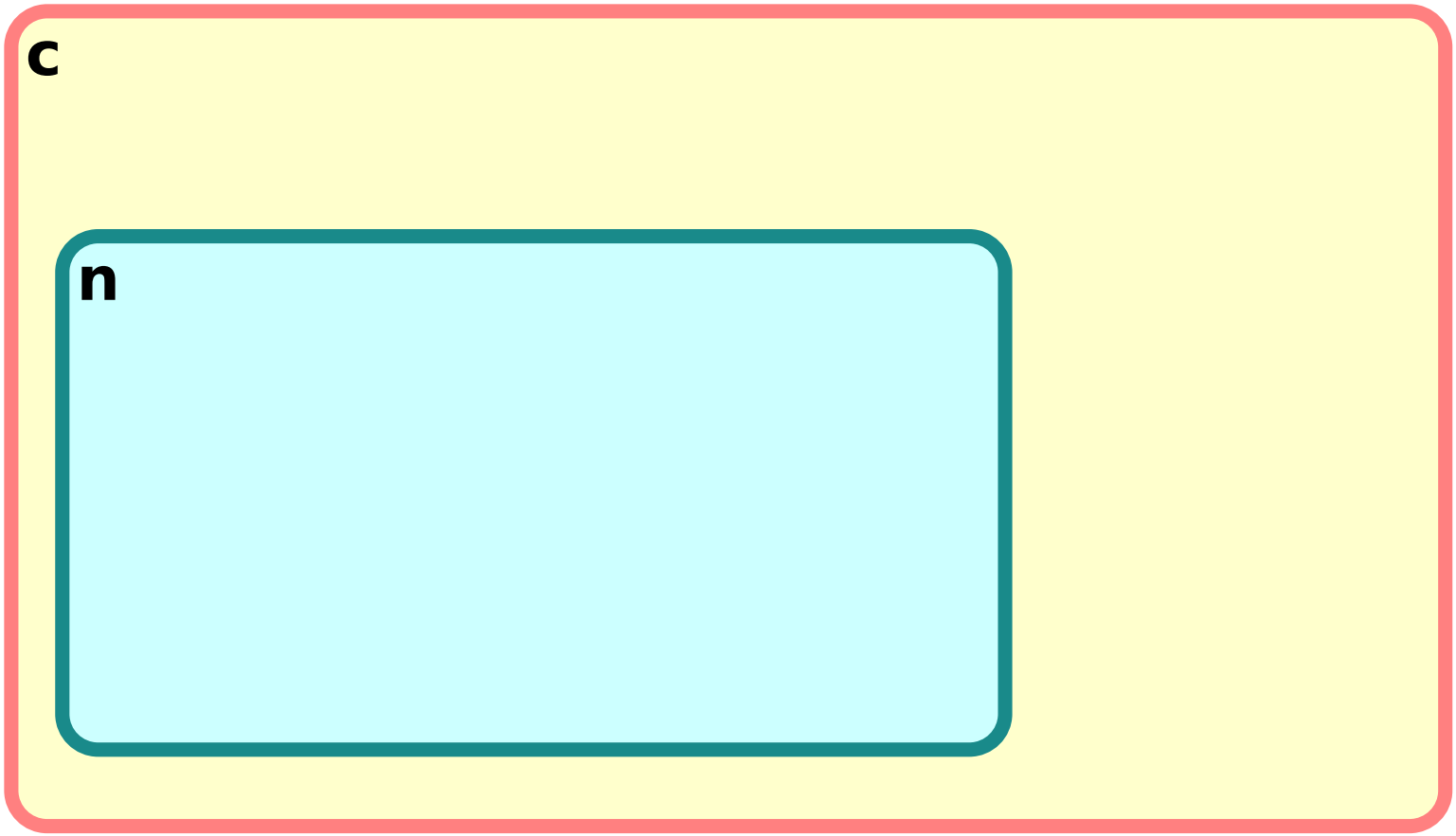
What is SBML?

SBML is a computer readable format for representing models describing the dynamical behaviour of biological entities

What can we encode in SBML?

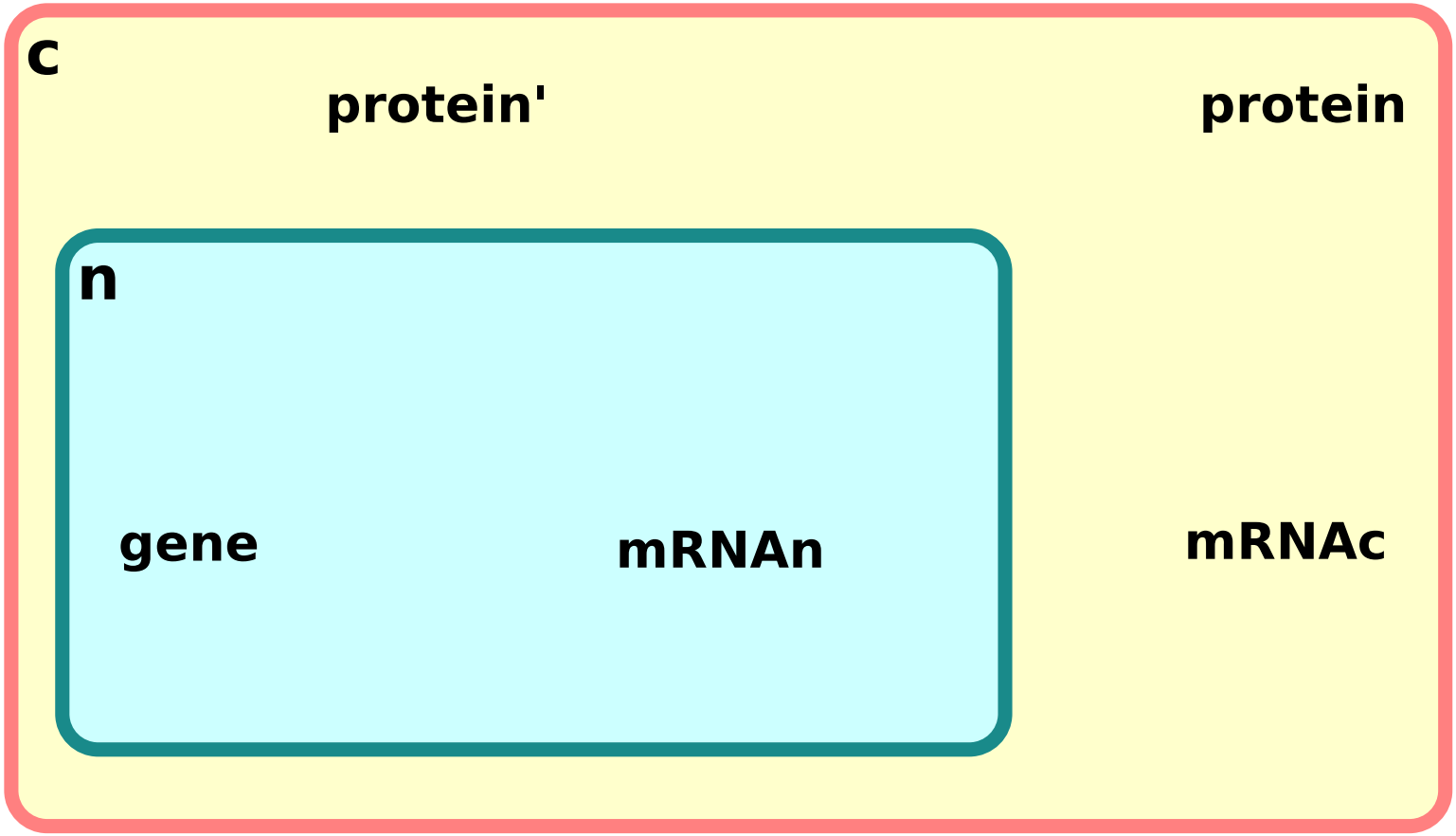
What can we encode in SBML?

compartments



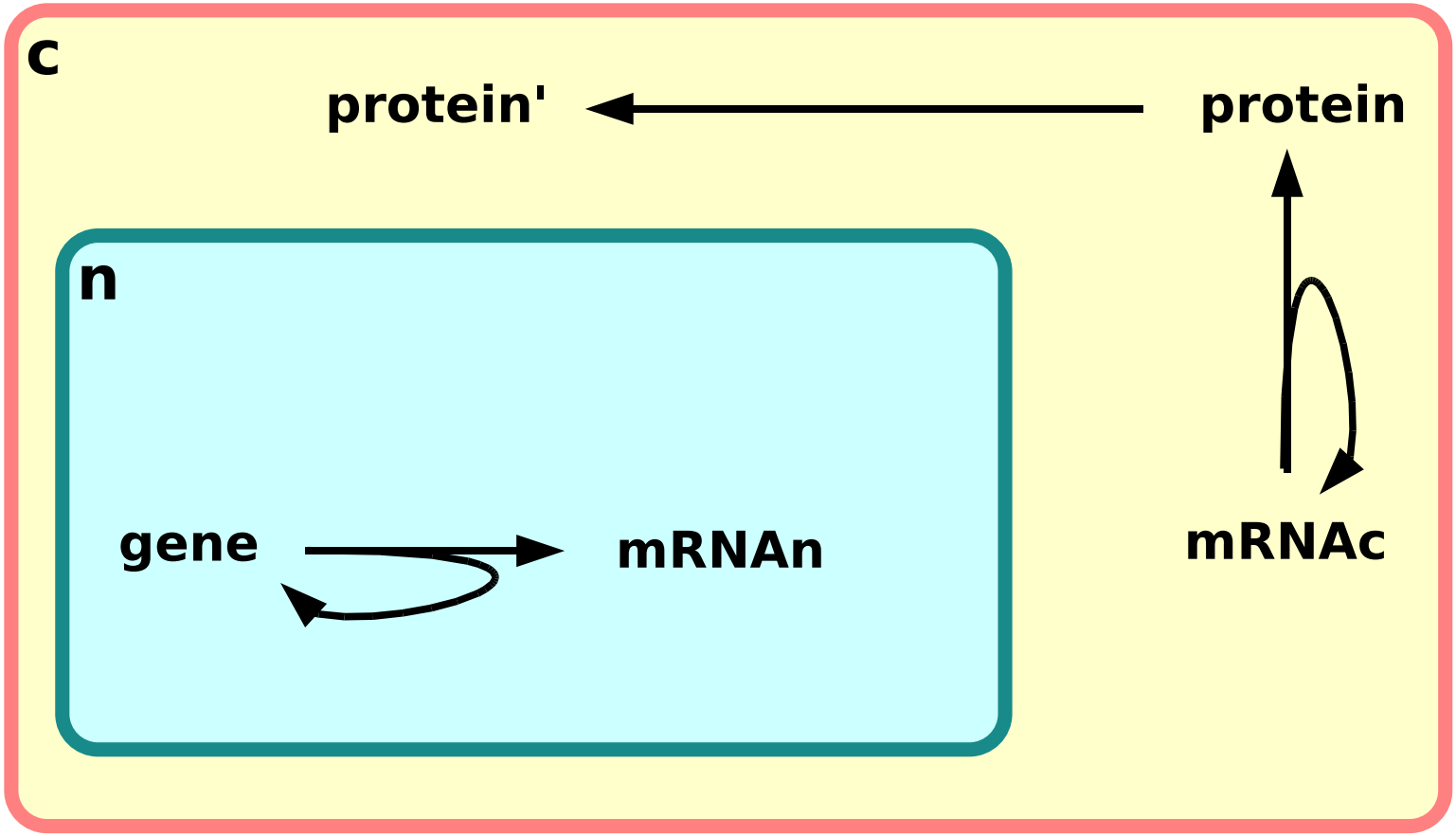
What can we encode in SBML?

species



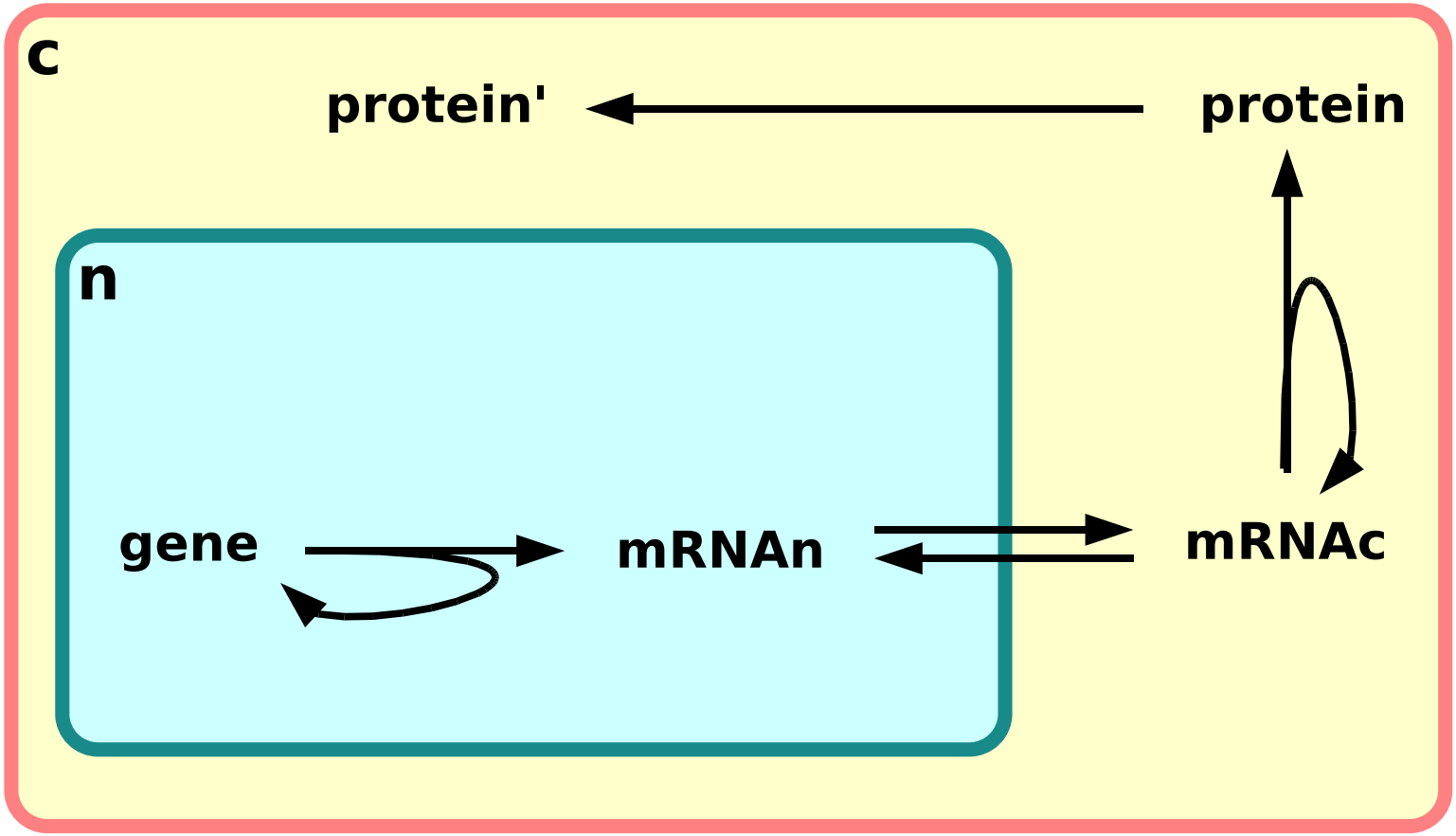
What can we encode in SBML?

reactions



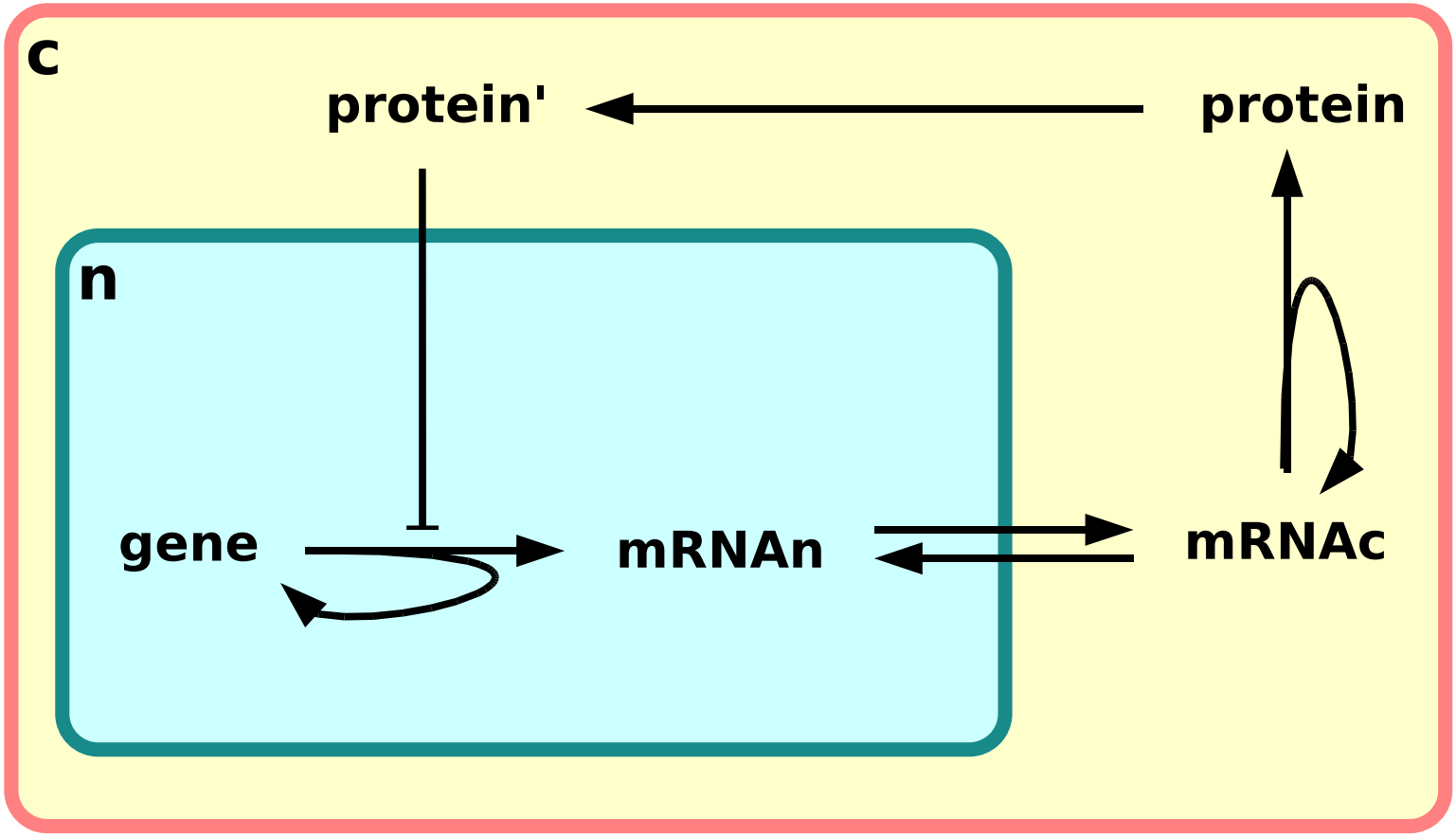
What can we encode in SBML?

reactions



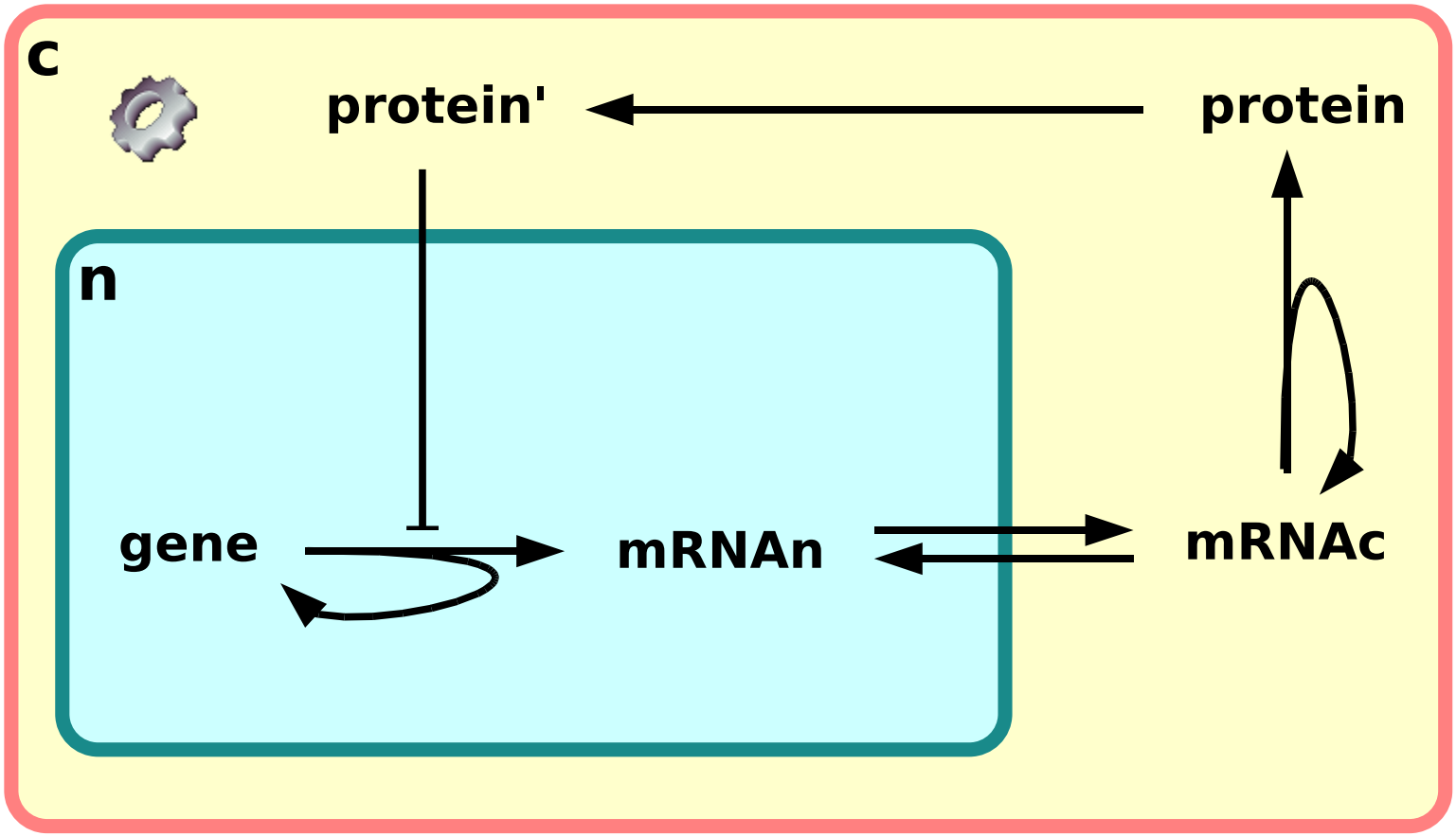
What can we encode in SBML?

modulations



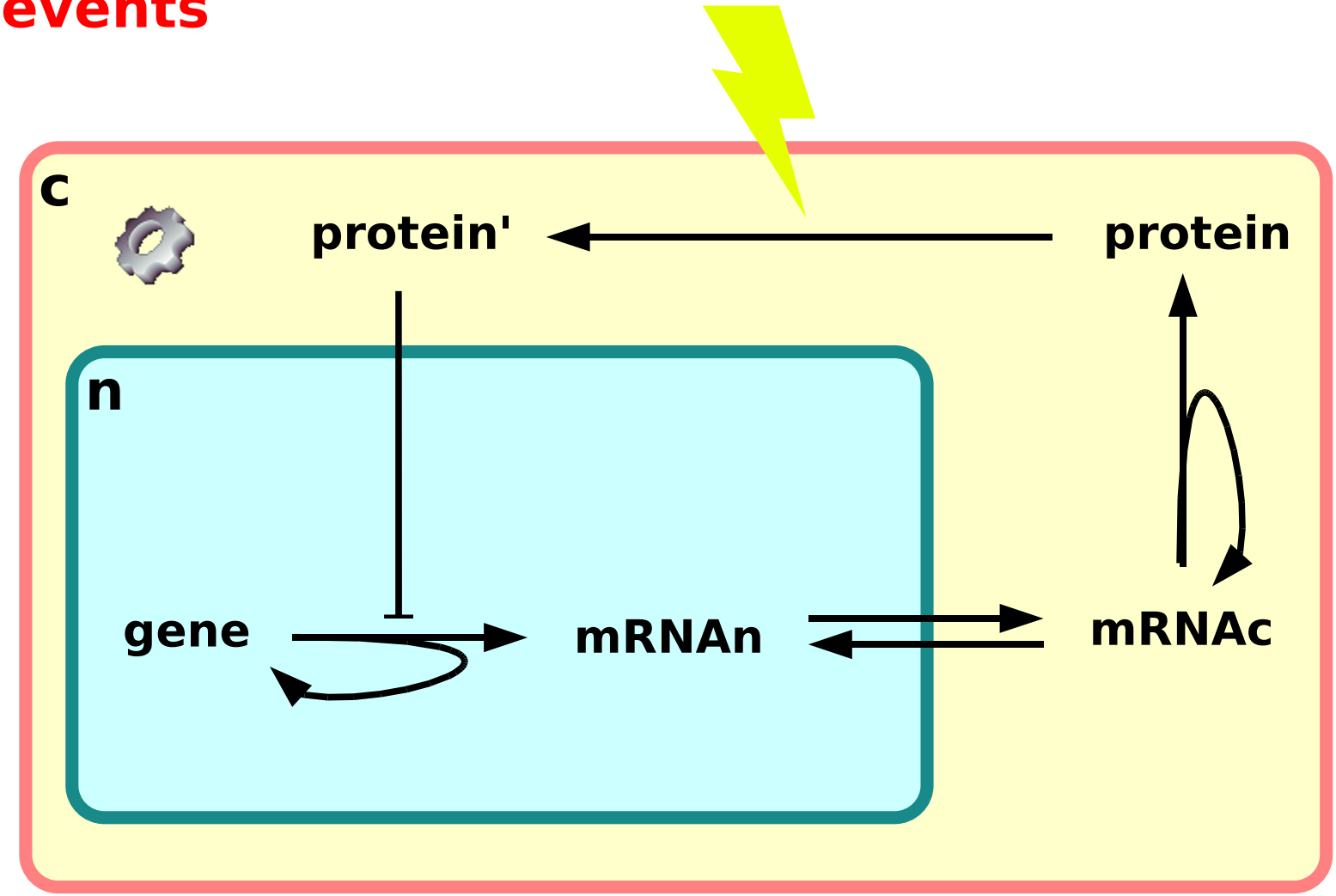
What can we encode in SBML?

rules



What can we encode in SBML?

events



SBML and XML

- The Systems Biology Markup Language is defined as a set of classes represented in the Unified Modelling Language (UML)
- In practise it is used as serialised using
  - An XML schema 1) lists all the elements and attributes, 2) specifies the containment relationships between them, 3) precises the datatype of each
  - An additional set of constraints is listed in the specification and implemented as a list of consistency checks

What the heck is XML?

- The eXtensible Markup Language (XML) is a text-format that allow to define languages to store structured information
- An XML language is made-up of elements and attributes:

```
<element1 attribute1="valeur1" attribute2="valeur2">
    <element2 attribute1="valeur3" />
</element1>
```

- An XML language can be defined in another XML language called XML schema. An XML file can be transformed into something else using other XML files called XML style-sheets
- Thanks to a strict namespace system, one can build XML files using several XML languages
- There are a constellation of tools to help processing XML languages
- Most known example of XML language is XHTML, the language used to designed webpages.

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml level="2" version="1" xmlns="http://www.sbml.org/sbml/level2">
  <model>









  </model>
</sbml>
```

```
<?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>









  </model>
</sbml>
```

```
<?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>









  </model>
</sbml>
```

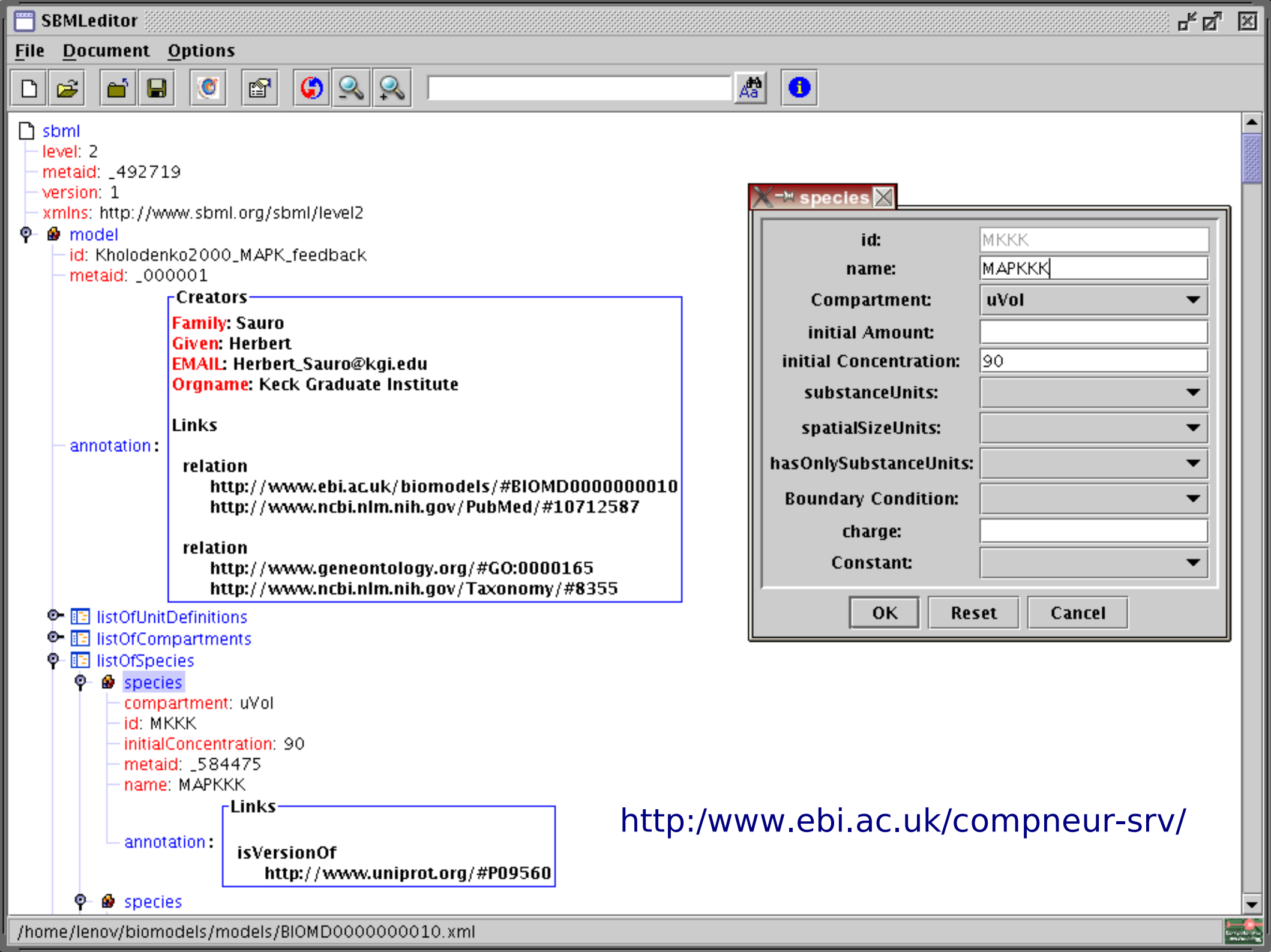
```
<?xml version="1.0" encoding="UTF-8"?>
<sbml level="2" version="1" xmlns="http://www.sbml.org/sbml/level2">
  <model>
    <listOfCompartments>
      <compartment id="cell" />
    </listOfCompartments>
    <listOfSpecies>
      <species id="A" compartment="cell" initialConcentration="1"/>
      <species id="B" compartment="cell" initialConcentration="0"/>
    </listOfSpecies>
    <listOfParameters>
      <parameter id="kon" value="1"/>
    </listOfParameters>
    <listOfReactions>
      <reaction>









      </reaction>
    </listOfReactions>
  </model>
</sbml>
```

```
<?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>









      </reaction>
    </listOfReactions>
  </model>
</sbml>
```

```
<?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" >
  <notes>
    <body xmlns="http://www.w3.org/1999/xhtml">
      <p>One of the components of 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="http://www.uniprot.org/#P68370"/>
            <rdf:li rdf:resource="http://www.geneontology.org/#GO:0045298"/>
          </rdf:Bag>
        </bqbiol:is>
      </rdf:Description>
    </rdf:RDF>
  </annotation>
</species>
```


SBMLeditor
File Document Options
sbml
level: 2
metaid: _492719
version: 1
xmlns: http://www.sbml.org/sbml/level2
model
id: Kholodenko2000_MAPK_feedback
metaid: _000001
Creators
Family: Sauro
Given: Herbert
EMAIL: Herbert_Sauro@kgi.edu
Orgname: Keck Graduate Institute
Links
annotation:
relation
http://www.ebi.ac.uk/biomodels/#BIOMD0000000010
http://www.ncbi.nlm.nih.gov/PubMed/#10712587
relation
http://www.geneontology.org/#GO:0000165
http://www.ncbi.nlm.nih.gov/Taxonomy/#8355
listOfUnitDefinitions
listOfCompartments
listOfSpecies
species
compartment: uVol
id: MKKK
initialConcentration: 90
metaid: _584475
name: MAPKKK
Links
annotation:
isVersionOf
http://www.uniprot.org/#P09560
species
species
id: MKKK
name: MAPKKK
Compartment: uVol
initial Amount:
initial Concentration: 90
substanceUnits:
spatialSizeUnits:
hasOnlySubstanceUnits:
Boundary Condition:
charge:
Constant:
OK
Reset
Cancel
http:/www.ebi.ac.uk/compneur-srv/
/home/lenov/biomodels/models/BIOMD0000000010.xml

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;
- A species is an entity participating to a reaction, **not always** a **chemical** entity:
  - It can be a molecule
  - It can be a cell
  - It can be an organ
  - It can be an organism

➔ Remember, Systems Biology is scale-free!

New: SBML Level 2 Version 3

- Released on June 16th 2007
- Simpler and cleaner (units ...)
- Generic entities (compartmentType, speciesType)
  ➔ path to generalised reactions
- Constraints and initialAssignments
- Controlle annotations (MIRIAM + SBO)
- Backward compatible with Level 2 Version 1
- More detailed and bug-free specification ... 164 pages, 10pt, small margin.

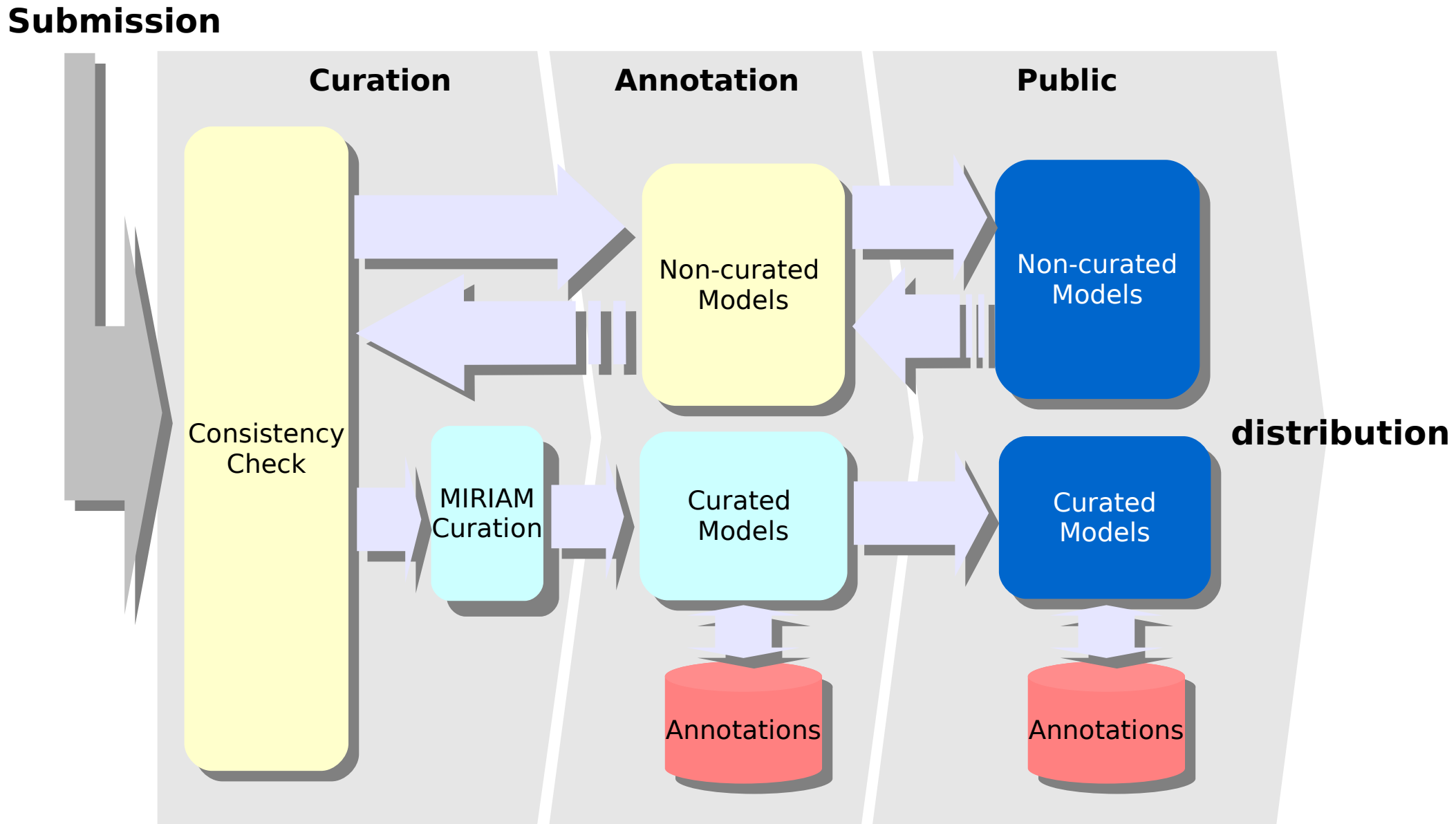
SBML Level 3

- Modular SBML, with core + optional packages
- Graph Layout
- Generalised reactions (probable)
- Model composition (probable)
- Complex species (probable)
- Arrays or sets (maybe)
- Geometry (maybe)
- Movements (maybe)
- Dynamic compartments (maybe)
- ???

What is BioModels Database?

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

Production pipeline



- Curated Models
- Non-curated Models
- Search
- Simulate in JWS

- Submit Your Model

- Sign-in

- News
- Model of the Month
- Meetings
- Support
- Contact

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BioModels Database

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

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.

[Browse curated models] [Browse non-curated models] [Search] [Simulate in JWS Online]

05th June 2007 - Eighth Release! [More] [Download All Models Under SBML L2 V1 Format]

17th April 2007 - BioModels Database ranked first data resource for Systems Biology [More] [Original article]

4th December 2006 - BioModels Database and DOQCS join forces [More]

Model of the month

Acknowledgements

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

Model curators and annotators: Harish Dharuri, Enuo He, Nicolas Le Novère, Lu Li, Rainer Machne, Bruce Shapiro (Alumni: Maria Schilstra)

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

External contributors: BioModels Database would not exists without the continuous support of many people, whether by their contribution of models, of software, or by their constructive comments and criticisms. It is unfortunately impossible to acknowledge all of them here, without risking to be unfair. Therefore, a big collective thank-you all.

BioModels Database is built thanks to many third-party free software such as libSBML, Jakarta Tomcat, Xindice, Lucene, Xalan, Xerces, Axis, Jena and MySQL, plus all the free software coming with the GNU/Linux systems.

Main software used to curate models: CellDesigner, COPASI, Jarnac, MathSBML, RoadRunner, SBMLdeSolver, SBMLeditor, SBMLmerge and XPP-Aut.

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Search - Models

Text Search

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

- *BioModels ID* → 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.
- *Resource* → Search BioModels Database for related information found in the models reference publication or third-party resources, by either publication/resource identifier or text (for example *9256450* or *cyclin* for publication, *GO:0007049* or *cell cycle* for Gene Ontology, *P04551* or *cell division* for UniProt).
- *Resource ID* → Search BioModels Database for annotations, by third-party resource identifiers (for example *IPR002394* for InterPro, *hsa04080* for KEGG Pathway, *68910* for Reactome).

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

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

BioModels ID:

Person:

SBML Elements: ☐ match the **exact phrase**

Resource: Gene Ontology — map kinase

Resource: Publication / ChEBI / Gene Ontology / Taxonomy / UniProt

Resource:

Resource ID:

Resource ID: BIND

Resource ID: BIND

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Search - Models

The search totally returned **15** models.

New Search

Show 10 Only

15 Curated Models returned.

BioModels ID	Name	Publication ID	Last Modified
BIOMD0000000009	Huang1996_MAPK_ultrasens	8816754	2006-12-29T00:54:48
BIOMD0000000010	Kholodenko2000_MAPK_feedback	10712587	2007-01-10T10:35:07
BIOMD0000000011	Levchenko2000_MAPK_noScaffold	10823939	2007-01-10T10:22:40
BIOMD0000000014	Levchenko2000_MAPK_Scaffold	10823939	2007-01-26T22:30:39
BIOMD0000000026	Markevich2004_MAPK_orderedElementary	14744999	2006-12-29T00:28:06
BIOMD0000000027	Markevich2004_MAPK_orderedMM	14744999	2006-12-29T00:28:55
BIOMD0000000028	Markevich2004_MAPK_phosphoRandomElementary	14744999	2006-12-29T00:39:36
BIOMD0000000029	Markevich2004_MAPK_phosphoRandomMM	14744999	2006-12-29T00:43:12
BIOMD0000000030	Markevich2005_MAPK_AllRandomElementary	14744999	2006-12-29T01:03:25
BIOMD0000000031	Markevich2004_MAPK_orderedMM2kinases	14744999	2006-12-29T21:41:12
BIOMD0000000032	Kofahl2004_pheromone	15300679	2007-06-08T11:42:52
BIOMD0000000033	Brown2004_NGF_EGF_signaling	14525003	2006-12-29T23:16:17
BIOMD0000000049	Sasagawa2005_MAPK	15793571	2007-03-02T23:37:04
BIOMD0000000084	Hornberg2005_ERKcascade	15634347	2007-01-03T05:59:37
BIOMD0000000099	Laub1998_SpontaneousOscillations	9843585	2007-04-30T21:59:10

New Search

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BIOMD0000000010 - Kholodenko2000_MAPK_feedback

SBML L2 V1 | CellML | SciLab | XPP | BioPAX

Simulation Result | GIF Reaction Graph | SVG Reaction Graph | Dynamic Reaction Graph | JWS Online

Submit Model Comment/Bug

Reference Publication

Publication ID: 10712587

Eur J Biochem 2000 Mar;267(6):1583-8.
Negative feedback and ultrasensitivity can bring about oscillations in the mitogen-activated protein kinase cascades.
Kholodenko BN.
Department of Pathology, Anatomy and Cell Biology, Thomas Jefferson University, Philadelphia, PA 19107, USA. Boris.Kholodenko@mail.tju.edu [more]

Model

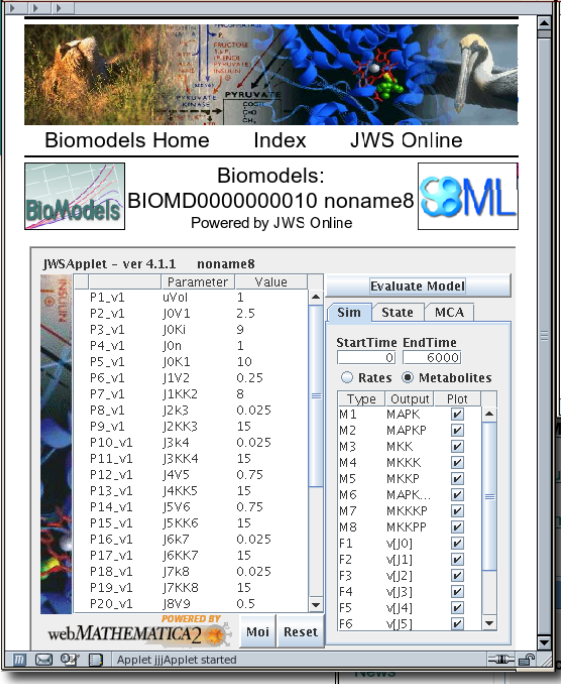
Original Model: *Unspecified*	bqbiol:is	set #1	**Taxonomy** Xenopus laevis
Submitter: Nicolas Le Novere	bqbiol:isVersionOf	set #1	**Gene Ontology** MAPKKK cascade
Submission Date: 2005-09-13T13:39:02	bqbiol:isHomologTo	set #1	**Reactome** REACT_634
Last Modification Date: 2007-01-10T10:35:07			
Creation Date: 2005-02-12T00:18:12			
Creators: Herbert Sauro			

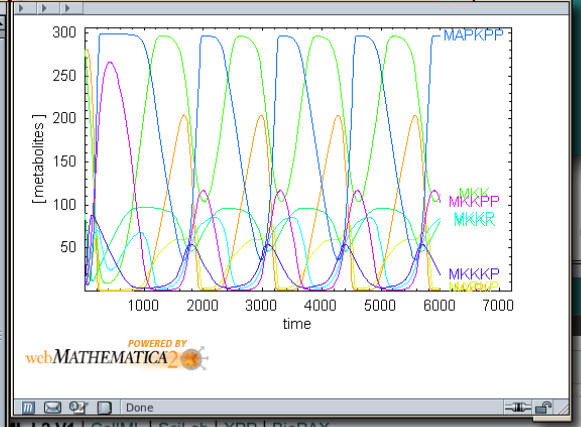
Compartments (1)

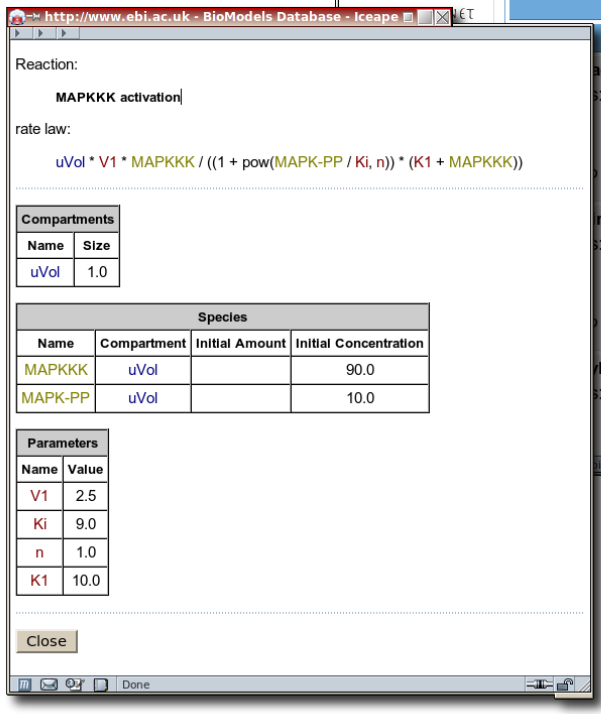
Species (8)

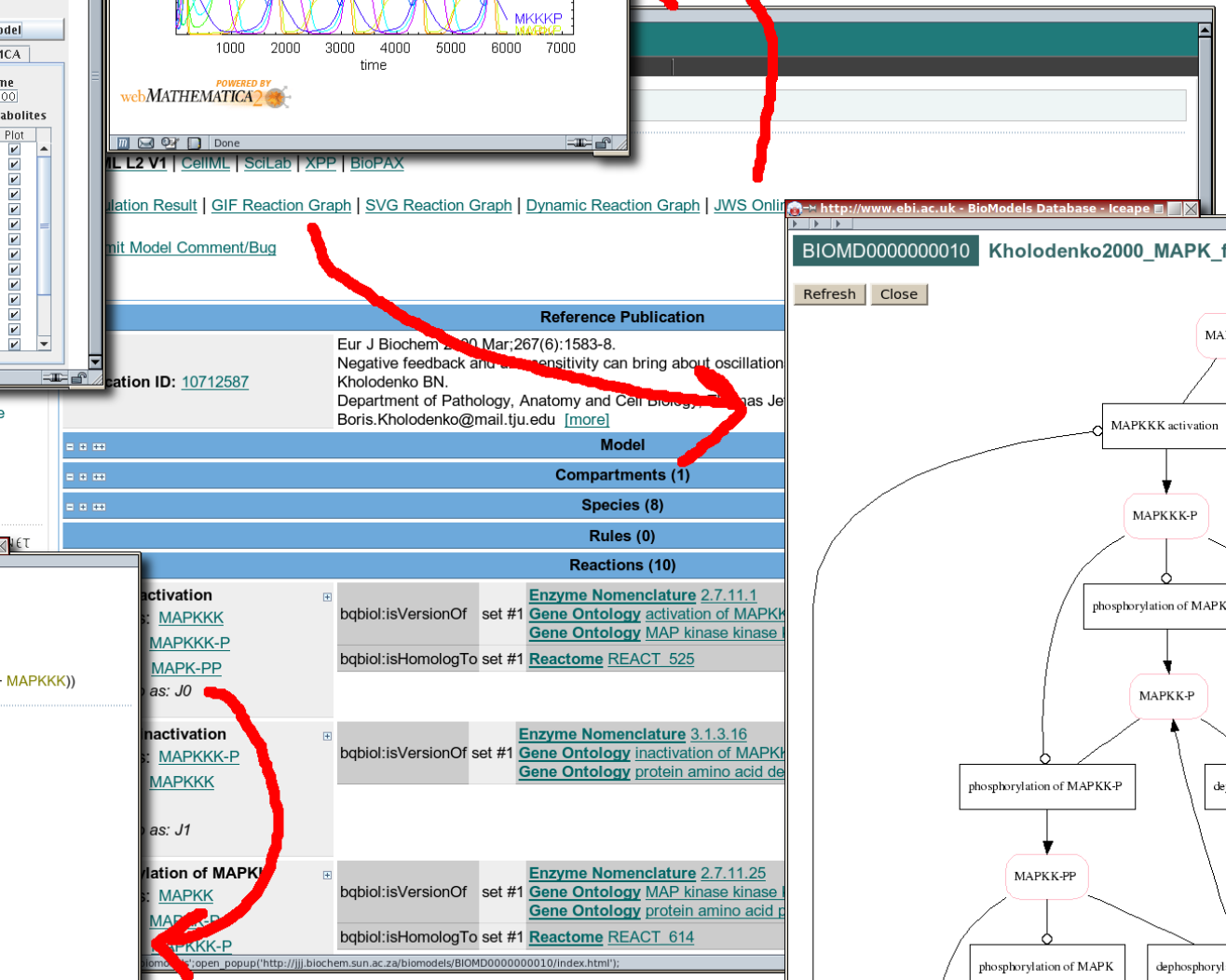
MAPKKK Compartment: uVol *Referred to as: MKKK*	bqbiol:isVersionOf	set #1	**UniProt** RAF1_XENLA
MAPKKK-P Compartment: uVol *Referred to as: MKKK_P*	bqbiol:isVersionOf	set #1	**UniProt** RAF1_XENLA
MAPKK Compartment: uVol *Referred to as: MKK*	bqbiol:isVersionOf	set #1	**UniProt** MP2K1_XENLA
MAPKK-P	bqbiol:isVersionOf	set #1	**UniProt** MP2K1_XENLA

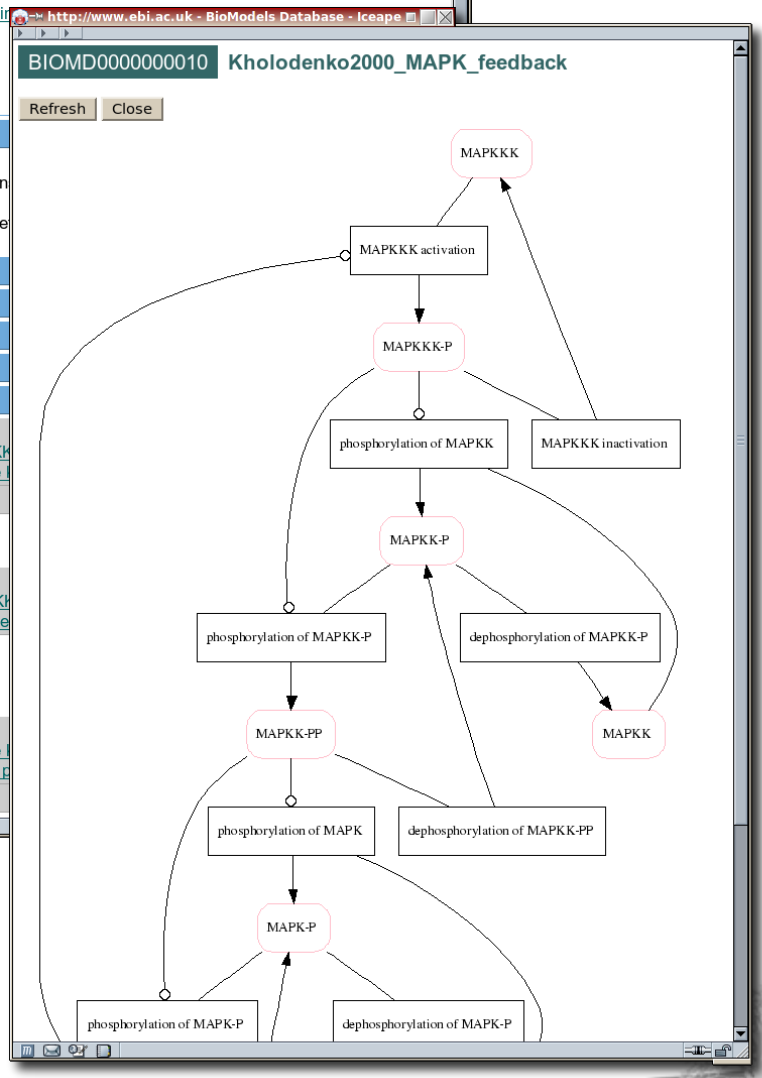
Different views of a model



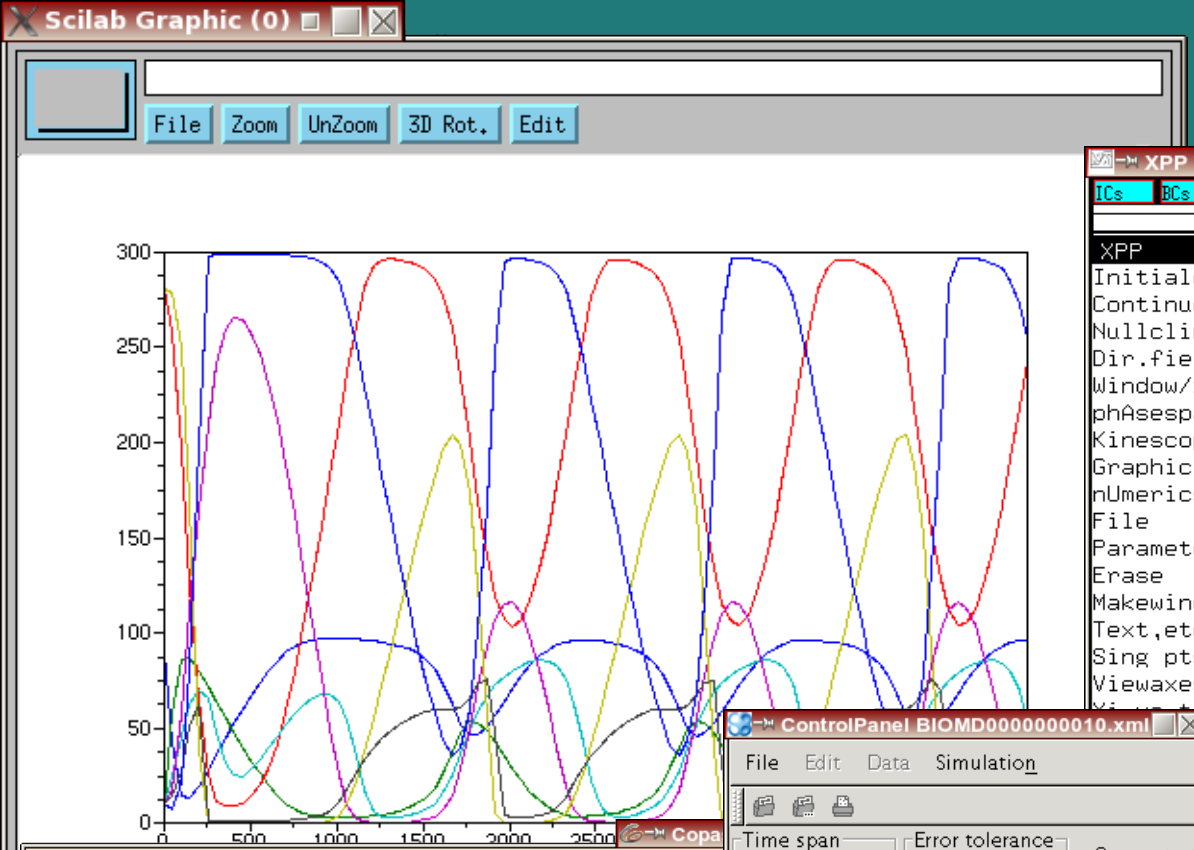


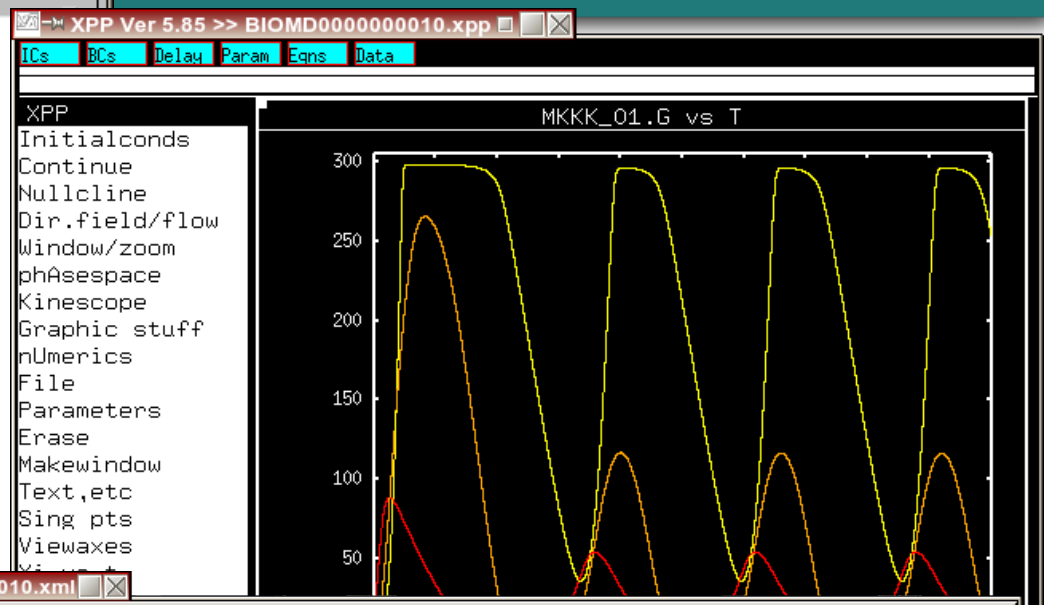


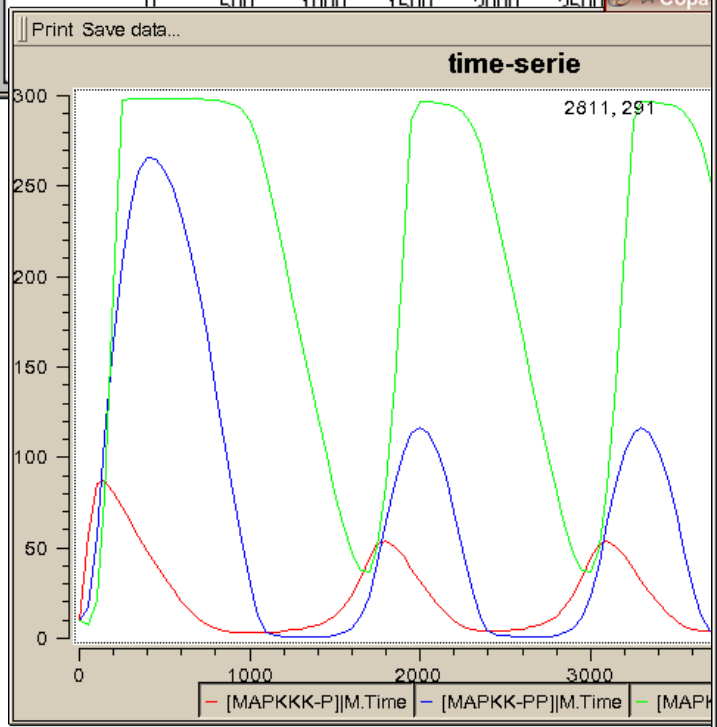


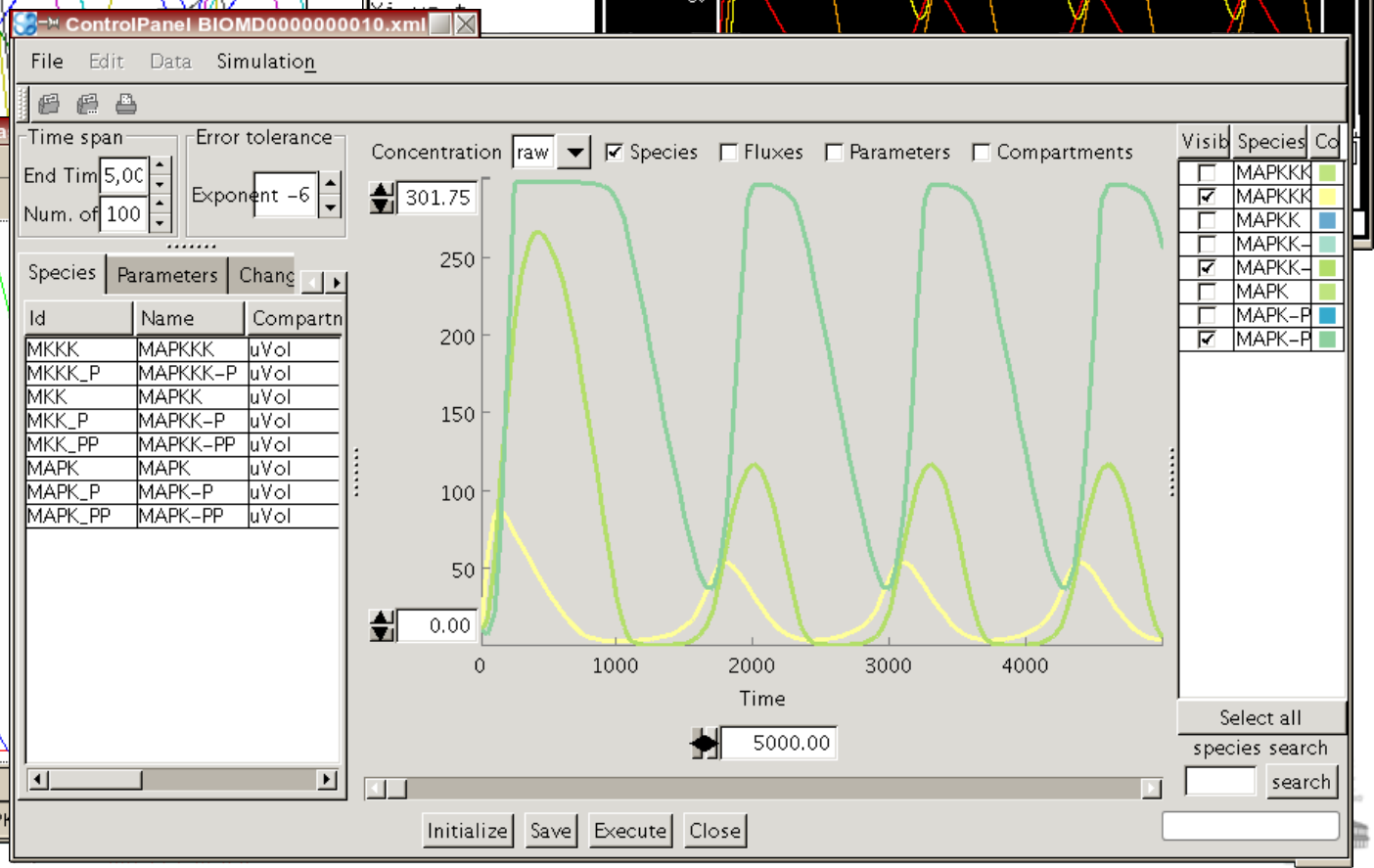


Kholodenko 2000

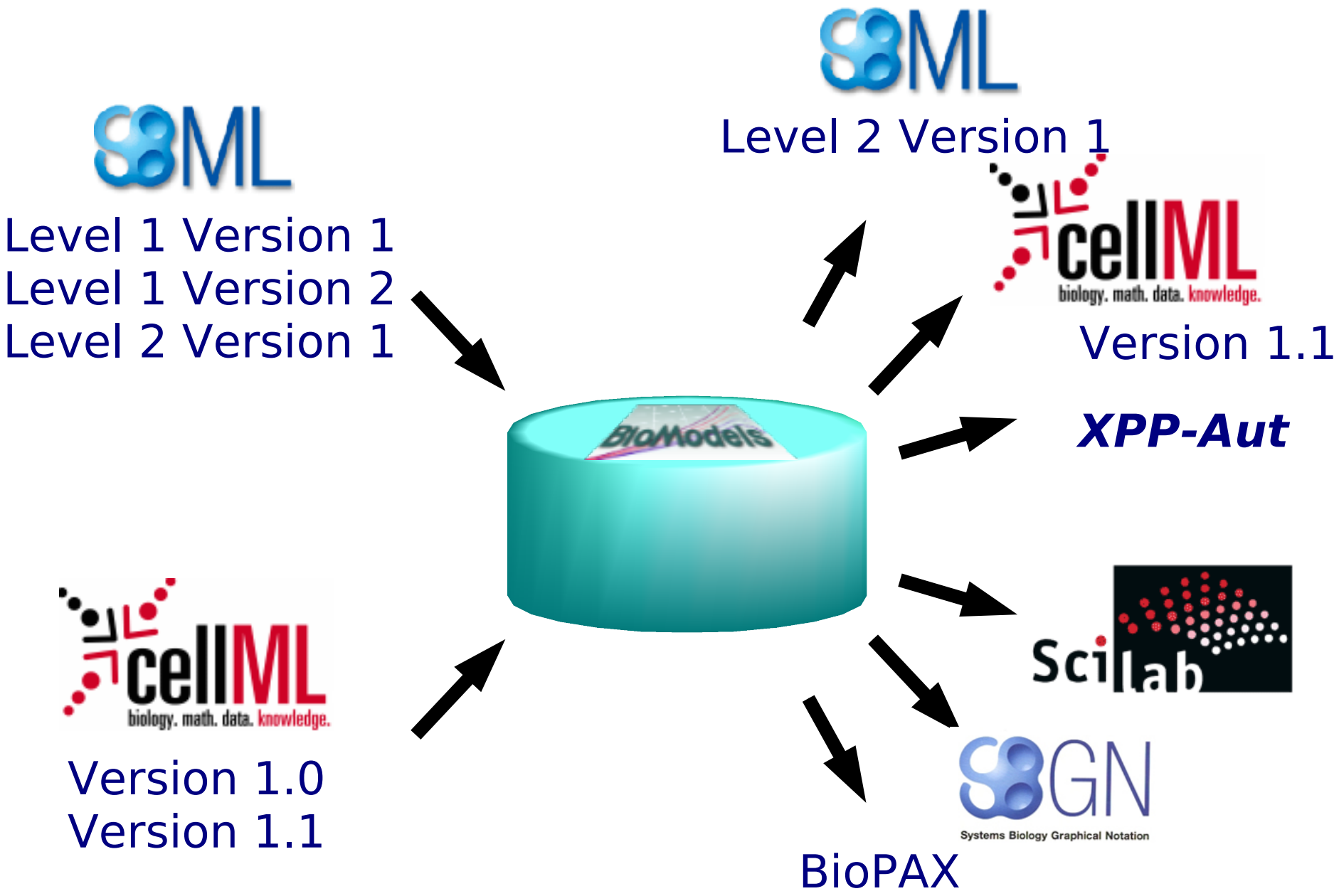








BioModels DB and interoperability in CSB



The BioModels Database team

Nicolas Le Novère

Michael Hucka

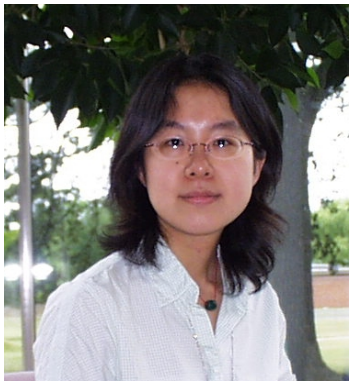
Development

Marco Donizelli

Chen Li

Arnaud Henry

Lu Li



Curation

Harish Dharuri

Enuo He

Bruce Shapiro

Rainer Machne

An international collaboration

- EBI
  - **Nicolas Le Novère**
  - Mélanie Courtot
  - Marco Donizelli
  - Arnaud Henry
  - Christian Knuepfer
  - Chen Li
  - Lu Li
  - Camille Laibe
  - Nicolas Rodriguez
  - Alexander Broicher
- SBML team (Caltech)
  - **Michael Hucka**
  - **Andrew Finney**
  - Benjamin Borstein
  - Harish Dharuri
  - Enuo He
  - Sarah Keating
  - Maria Schilstra
  - Bruce Shapiro
- NCBS (Bangalore)
  - Upinder Bhalla
  - Harsha Rani
- University of Washington
  - Herbert Sauro
- Vienna TBI
  - Rainer Machne
  - Christof Flamm
  - James Lu
- Systems Biology Institute (Tokyo)
  - Hiroaki Kitano
  - Akira Funahashi
- JWS Online (Stellenbosh+Amsterdam)
  - Jacky Snoep
  - Hans Westerhoff
- 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
  - XPP-Aut

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

We will use COPASI, developed by:
Virginia Bioinformatics Institute
European Medial Laboratory

http://www.copasi.org/

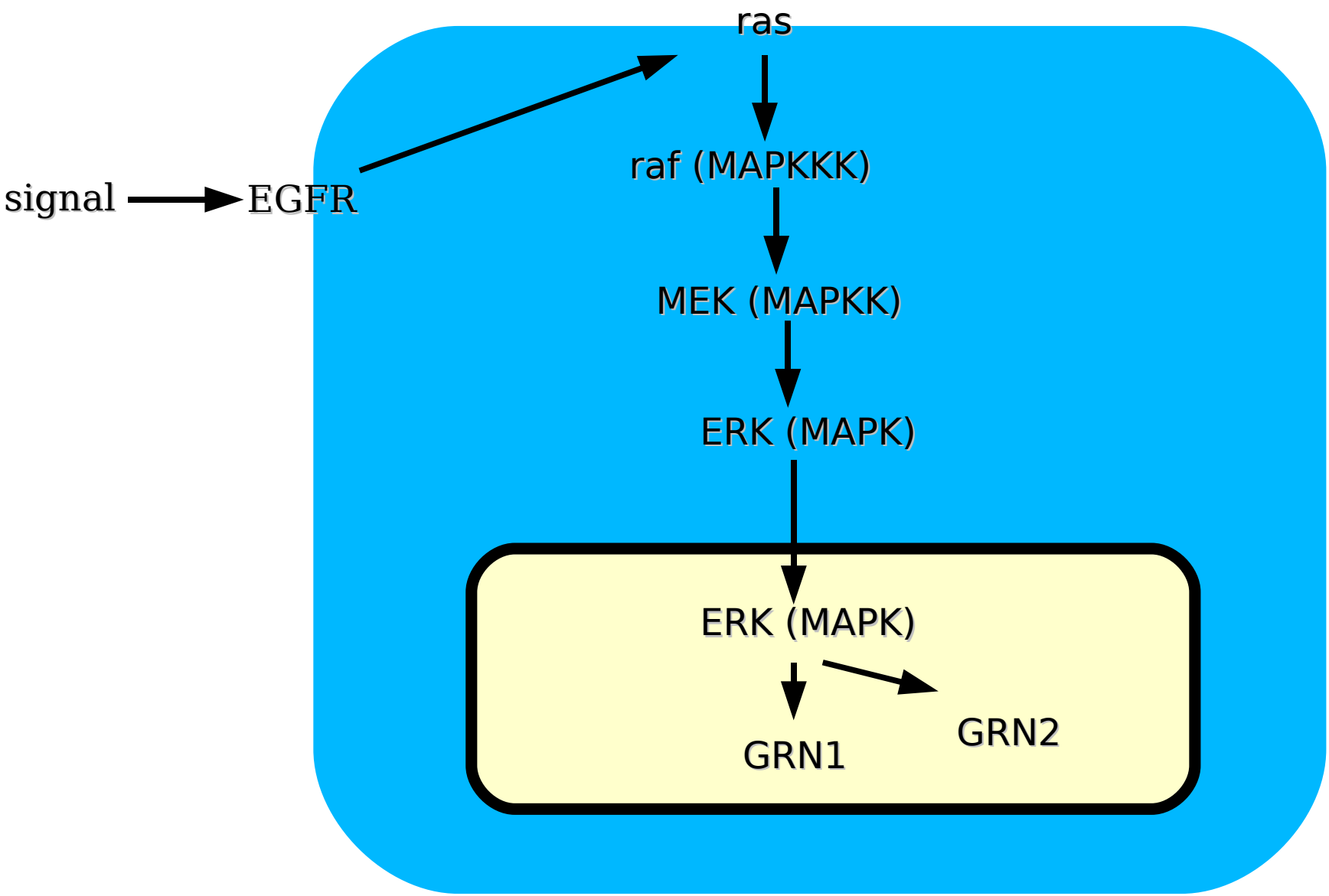
Download:
http://www.copasi.org/tiki-index.php?page=SecureDownload

documentation:
http://www.copasi.org/static/userguide/copasi.xhtml

MAPK cascade

- Mitogen Activated Protein kinase
  ->mitosis, differentiation, cell survival, apoptosis
  => CANCER
- Integration of many signalling pathways
- Activation of many regulatory networks
- Model systems in computational biology

MAPK cascade



Proc. Natl. Acad. Sci. USA
Vol. 78, No. 11, pp. 6840–6844, November 1981
Biochemistry

An amplified sensitivity arising from covalent modification in biological systems

(protein modification/metabolic regulation/switch mechanism/enzyme cascades)

ALBERT GOLDBETER† AND DANIEL E. KOSHLAND, JR.

Department of Biochemistry, University of California, Berkeley, California 94720

Contributed by Daniel E. Koshland, Jr., August 11, 1981

ABSTRACT **The transient and steady-state behavior of a reversible covalent modification system is examined. When the modifying enzymes operate outside the region of first-order kinetics, small percentage changes in the concentration of the effector controlling either of the modifying enzymes can give much larger percentage changes in the amount of modified protein. This amplification of the response to a stimulus can provide additional sensitivity in biological control, equivalent to that of allosteric proteins with high Hill coefficients.**

Biological systems must respond to internal and external variations such as the depletion of nutrients, the variations in hormone levels, and the reception of sensory signals. The stimuli are processed to change the activities of enzymes controlling pathways in the biological system. Two basic phenomena play a large role in this processing: allosteric changes in protein conformation and covalent modification of proteins.

Since the findings of Cori and Green (1) and Krebs and

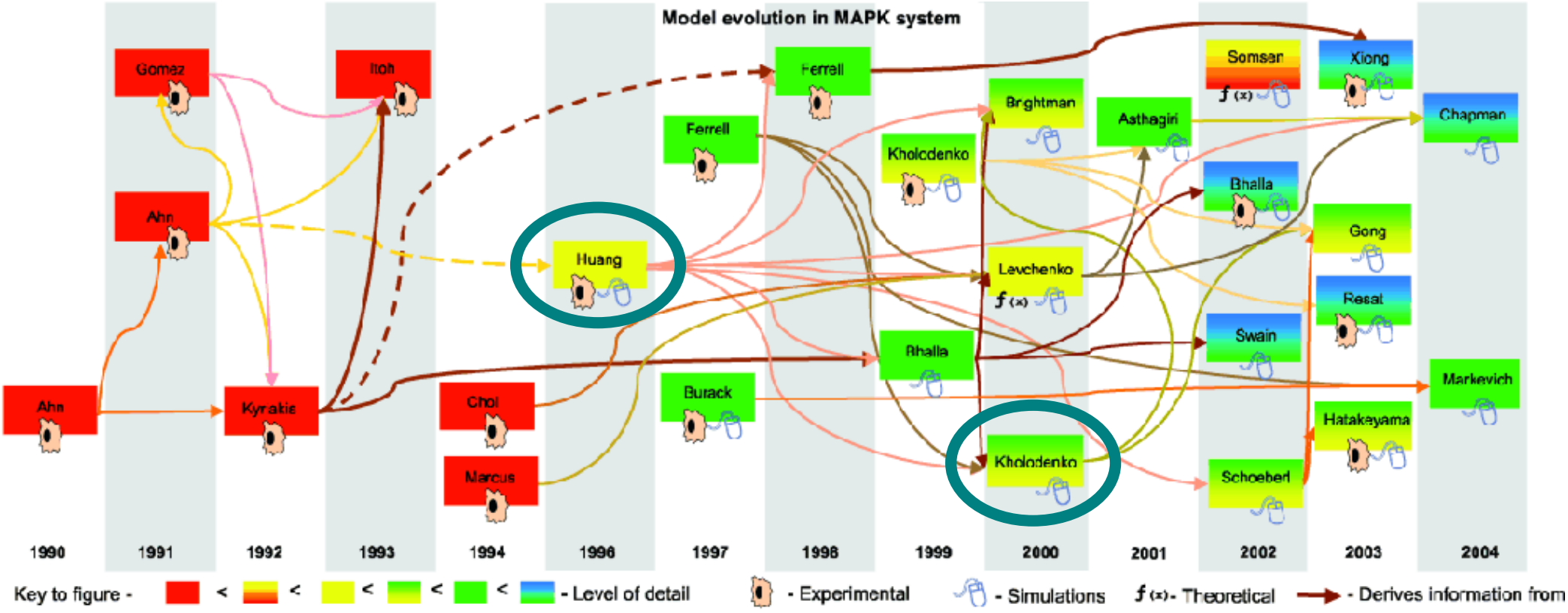
ture of covalent regulation was possible, if the differential equations could be solved analytically outside the first-order region.

This analysis has been achieved, and the results reveal that there is an added sensitivity inherent in covalent modification schemes when one or more of the converter enzymes operate in the "zero-order" region—i.e., region of saturation with respect to protein substrate. Thus there is a property of covalent systems that, in the absence of allosteric cooperativity and multiple inputs, can generate sensitivity equivalent to cooperative enzymes with high Hill coefficients. The derivations leading to and the implications of this finding are discussed below. For convenience, we shall use the term "ultrasensitivity" to describe an output response that is more sensitive to change in stimulus than the hyperbolic (Michaelis–Menten) equation.

Steady-state behavior of modification system

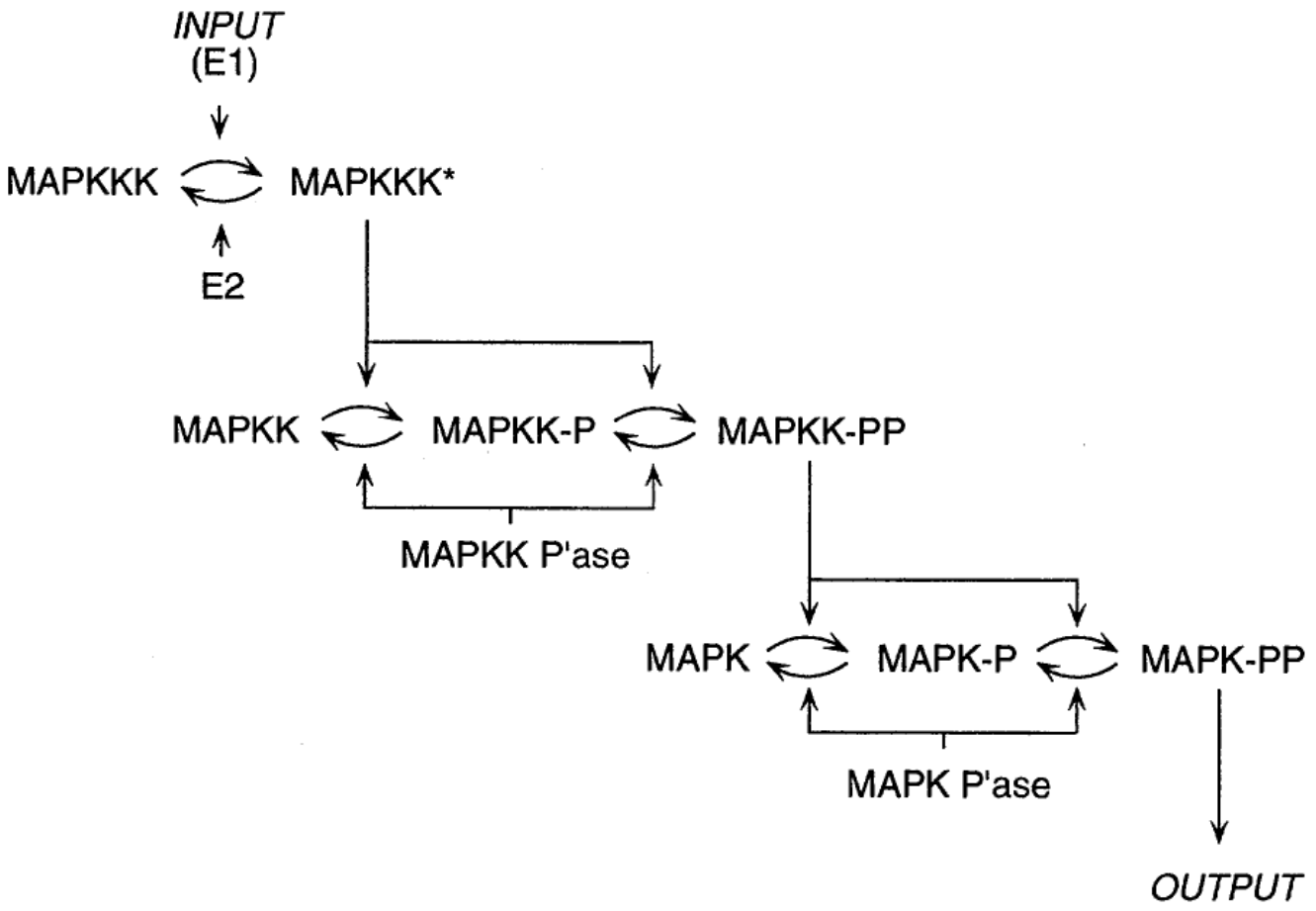
We shall consider a covalent modification system in which a

History of MAPK models

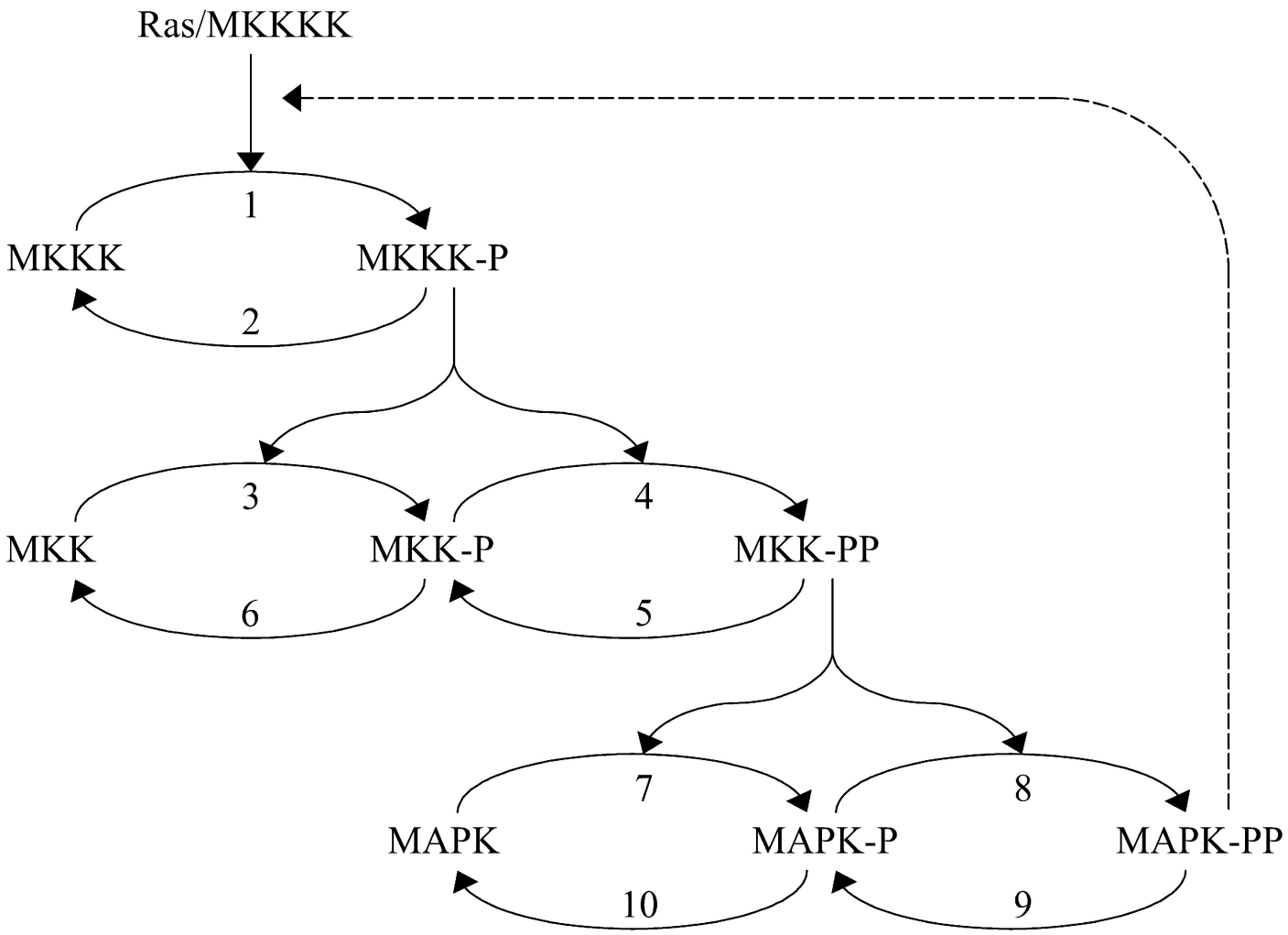


Vayttaden, Ajay, Bhalla (2004) A spectrum of models of signalling pathways. *Chembiochem* 5: 1365-1374.

Huang and Ferrell



Huang and Ferrell (1996) Ultrasensitivity in the mitogen-activated protein kinase cascade. *Proc Natl Acad Sci USA* 93: 10078-10083.



Kholodenko (2000) Negative feedback and ultrasensitivity can bring about oscillations in the mitogen-activated protein kinase cascades. *Eur J Biochem* 267: 1583-1588.

Choose the right formalism

$$E + S \underset{kas}{\overset{kds}{\rightleftharpoons}} ES \underset{kcat'}{\overset{kcat}{\rightleftharpoons}} EP \underset{kdp}{\overset{kap}{\rightleftharpoons}} E + P \qquad \frac{d[P]}{dt} = kdp[EP] - kap[E][P]$$

Choose the right formalism

$$E + S \underset{kas}{\overset{kds}{\rightleftharpoons}} ES \underset{kcat'}{\overset{kcat}{\rightleftharpoons}} EP \underset{kdp}{\overset{kap}{\rightleftharpoons}} E + P \qquad \frac{d[P]}{dt} = kdp[EP] - kap[E][P]$$

$$E + S \underset{kas}{\overset{kds}{\rightleftharpoons}} ES \xrightarrow{kcat} EP \underset{kdp}{\overset{kap}{\rightleftharpoons}} E + P$$

catalysis irreversible

Choose the right formalism

$$E + S \underset{kas}{\overset{kds}{\rightleftharpoons}} ES \underset{kcat'}{\overset{kcat}{\rightleftharpoons}} EP \underset{kdp}{\overset{kap}{\rightleftharpoons}} E + P \qquad \frac{d[P]}{dt} = kdp[EP] - kap[E][P]$$

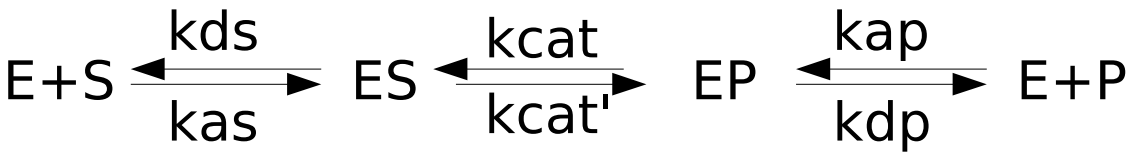
$$E + S \underset{kas}{\overset{kds}{\rightleftharpoons}} ES \xrightarrow{kcat} EP \underset{kdp}{\overset{kap}{\rightleftharpoons}} E + P$$

catalysis irreversible

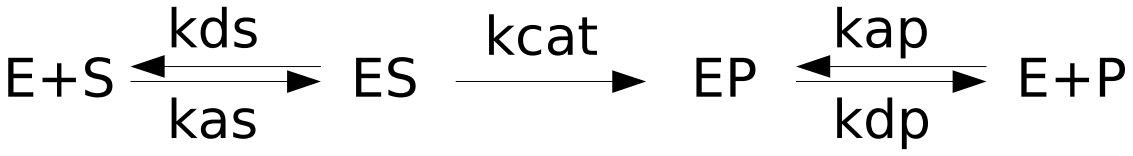
$$E + S \underset{ksd}{\overset{ksa}{\rightleftharpoons}} ES \xrightarrow{kcat} E + P$$

product is consumed before rebinding

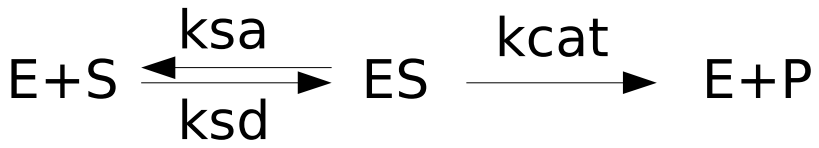
Choose the right formalism



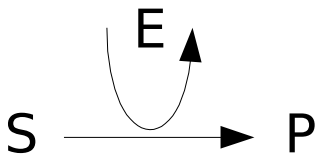
$$\frac{d[P]}{dt} = kdp[EP] - kap[E][P]$$



catalysis irreversible



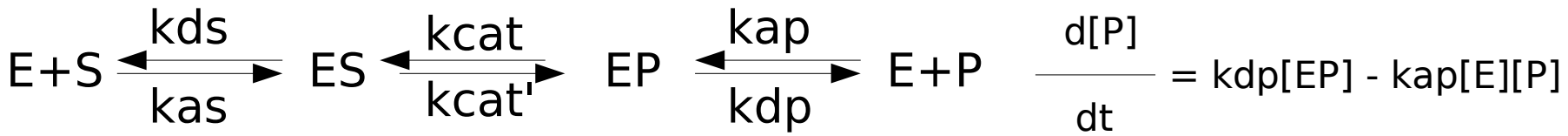
product is consumed before rebinding



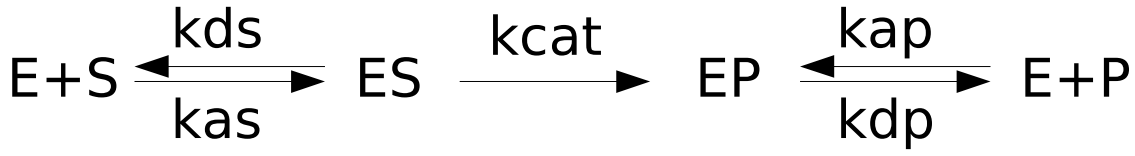
steady-state

$$\frac{d[P]}{dt} = \frac{[E]\,kcat}{1 + \frac{Km}{[S]}}$$

Choose the right formalism



$$\frac{d[P]}{dt} = kdp[EP] - kap[E][P]$$



catalysis irreversible

Huang and Ferrell

product is consumed before rebinding

Kholodenko

$$\frac{d[P]}{dt} = \frac{[E]\,kcat}{1 + \frac{Km}{[S]}}$$

Briggs-Haldane (Michaelis-Menten)

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} ES \xrightarrow{k_2} E + P$$

$$[ES] = \frac{k_1[E][S]}{k_{-1} + k_2}$$

$$K_m = \frac{k_{-1} + k_2}{k_1}$$

$$[ES] = \frac{[E][S]}{K_m}$$

$$\frac{d[P]}{dt} = k_2[ES]$$

$$[E]=[E_0]-[ES]$$

$$[ES] = \frac{([E_0] - [ES])[S]}{K_m}$$

$$[ES]\frac{K_m}{[S]} = [E_0] - [ES]$$

$$[ES](1 + \frac{K_m}{[S]}) = [E_0]$$

$$[ES] = [E_0]\frac{1}{1 + \frac{K_m}{[S]}}$$

$$\frac{d[P]}{dt} = k_2[E_0]\frac{[S]}{K_m + [S]} = V_{max}\frac{[S]}{K_m + [S]}$$

Briggs-Haldane

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} ES \xrightarrow{k_2} E + P$$

$$\frac{d[ES]}{dt} = k_1[E][S] - k_{-1}[ES] - k_2[ES] = 0$$

steady-state!!!

$$[ES] = \frac{k_1[E][S]}{k_{-1} + k_2}$$

$$K_m = \frac{k_{-1} + k_2}{k_1}$$

$$[ES] = \frac{[E][S]}{K_m}$$

$$\frac{d[P]}{dt} = k_2[ES]$$

$$[E]=[E_0]-[ES]$$

$$[ES] = \frac{([E_0] - [ES])[S]}{K_m}$$

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$$[ES] = [E_0]\frac{1}{1 + \frac{K_m}{[S]}}$$

$$\frac{d[P]}{dt} = k_2[E_0]\frac{[S]}{K_m + [S]} = V_{max}\frac{[S]}{K_m + [S]}$$