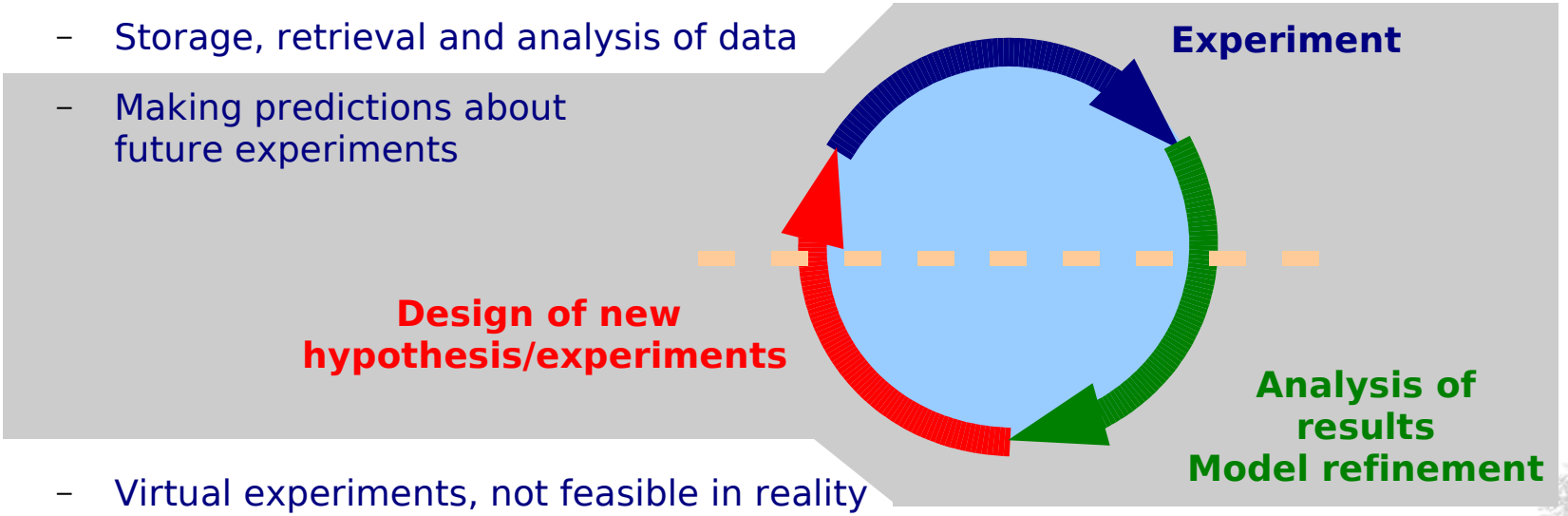
Quantitative models in Systems Biology: Generation, curation and exchange

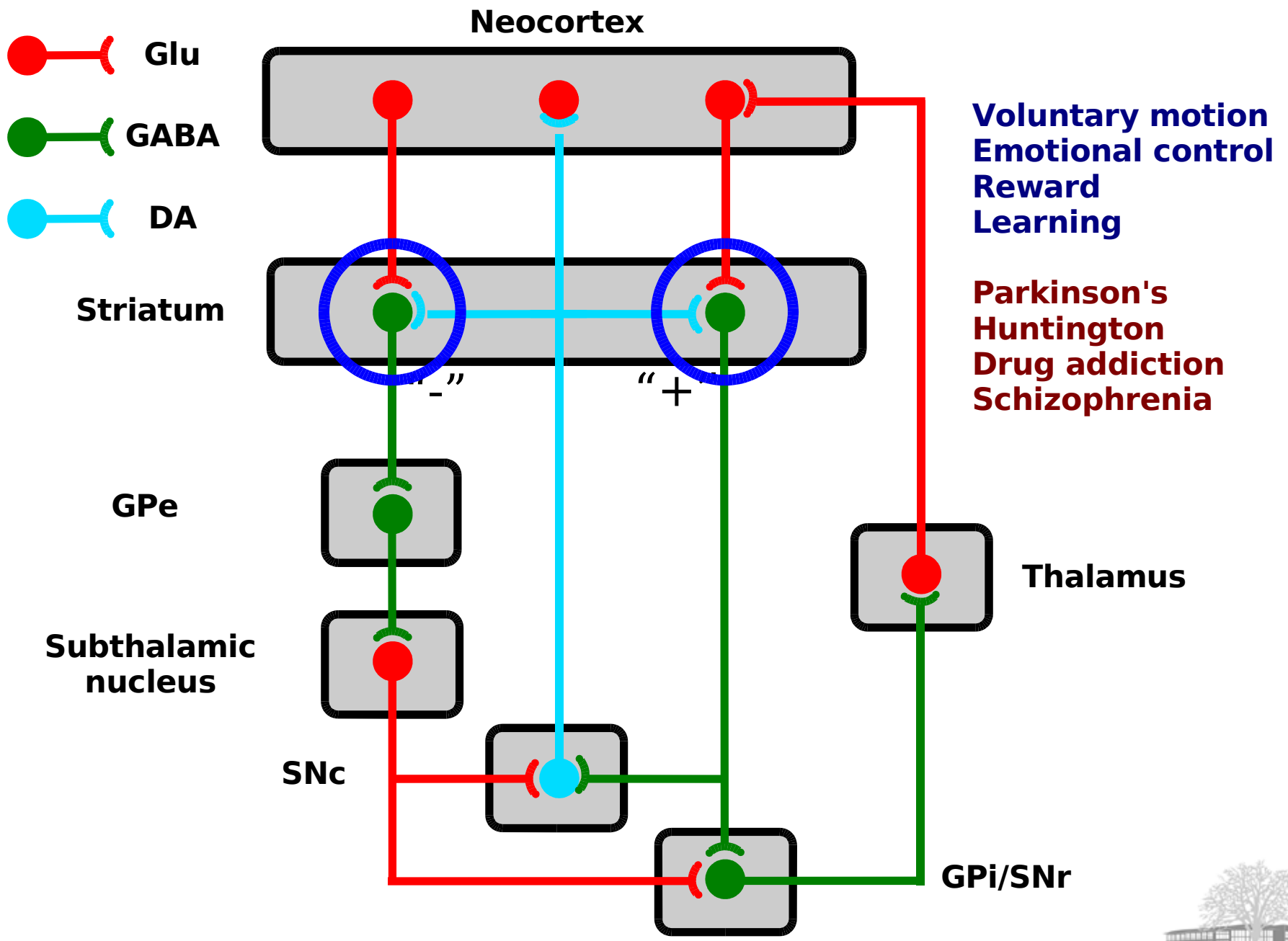
Why computer simulations in Biology

- Complexity of biological systems
  - Structural complexity: molecular and cellular levels
  - Functional complexity: network of relations
- Limitations of analytical approaches
  - Intractable system of equations
  - Existence of chaotic behaviours
  - Experiments often provides snapshots of processes
- Faster and cheaper computers
- Computing can complement experimental investigations by:
  - Storage, retrieval and analysis of data
  - Making predictions about future experiments

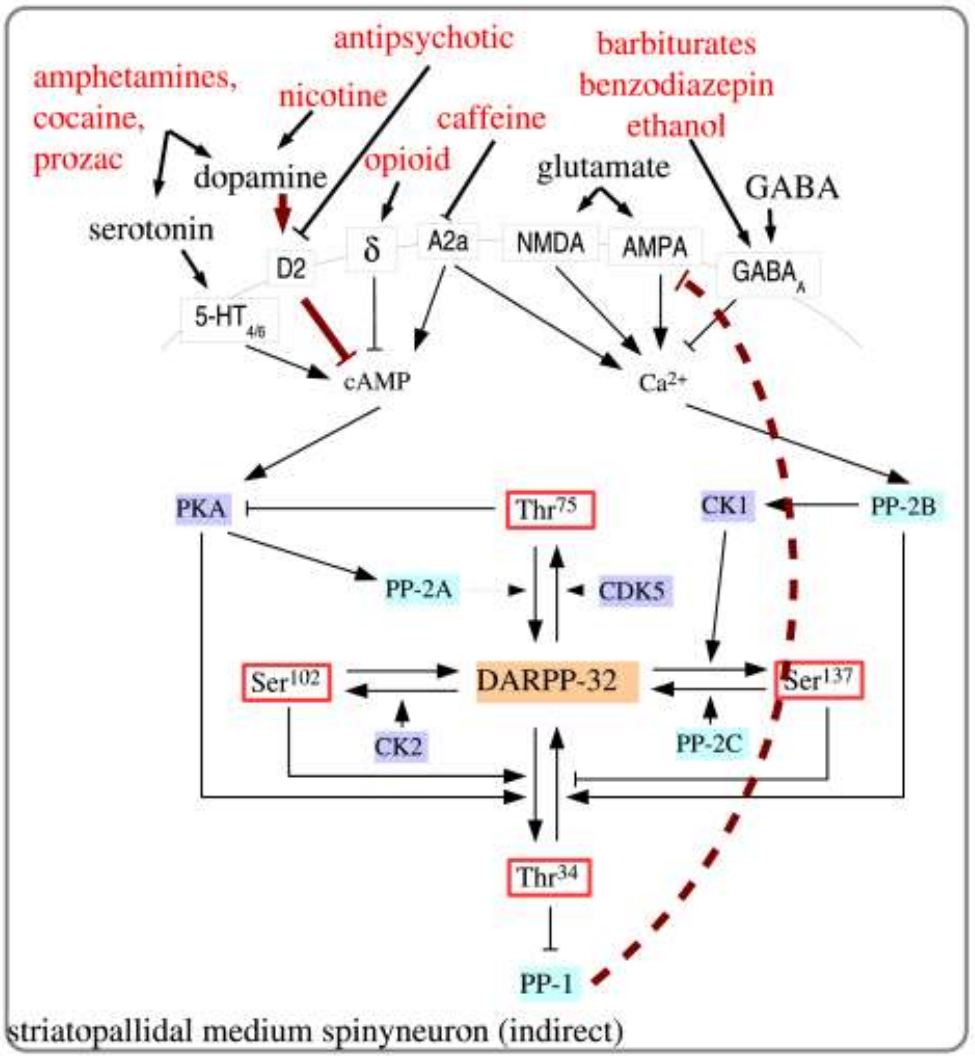


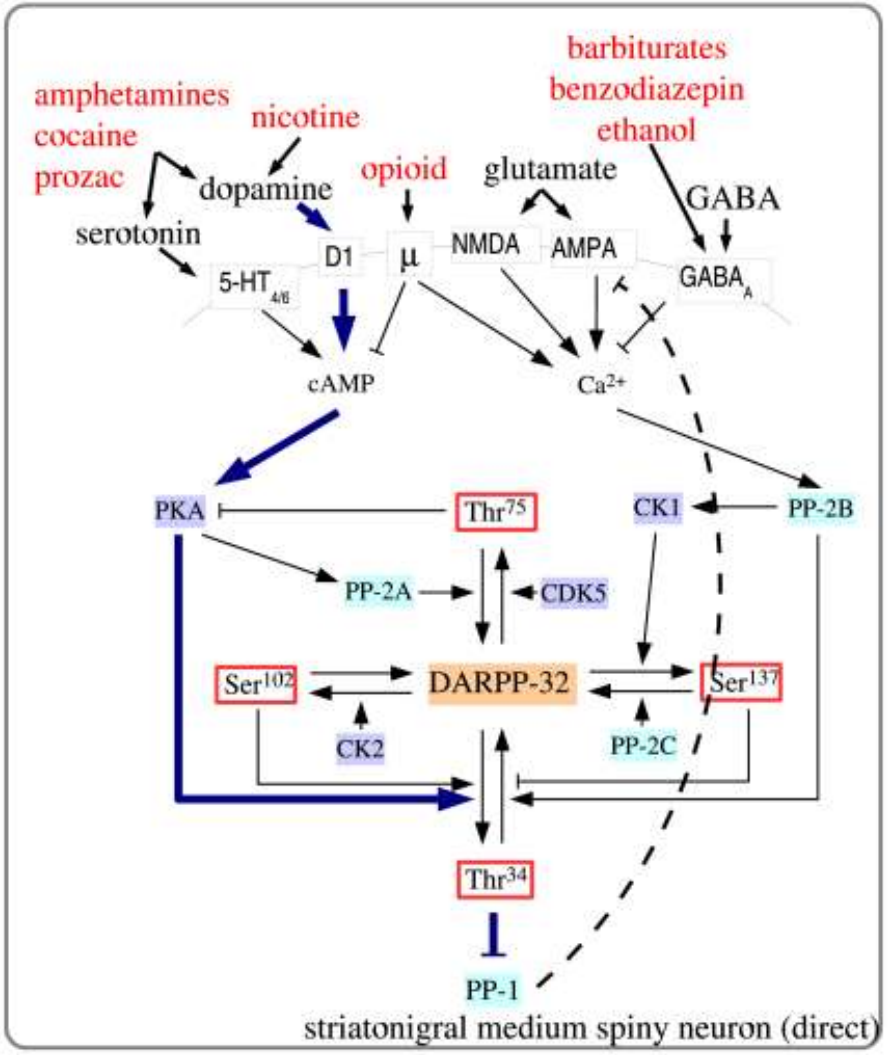
  - Virtual experiments, not feasible in reality

Dopamine mesotelencephalic pathway



DARPP-32, a signal integrator

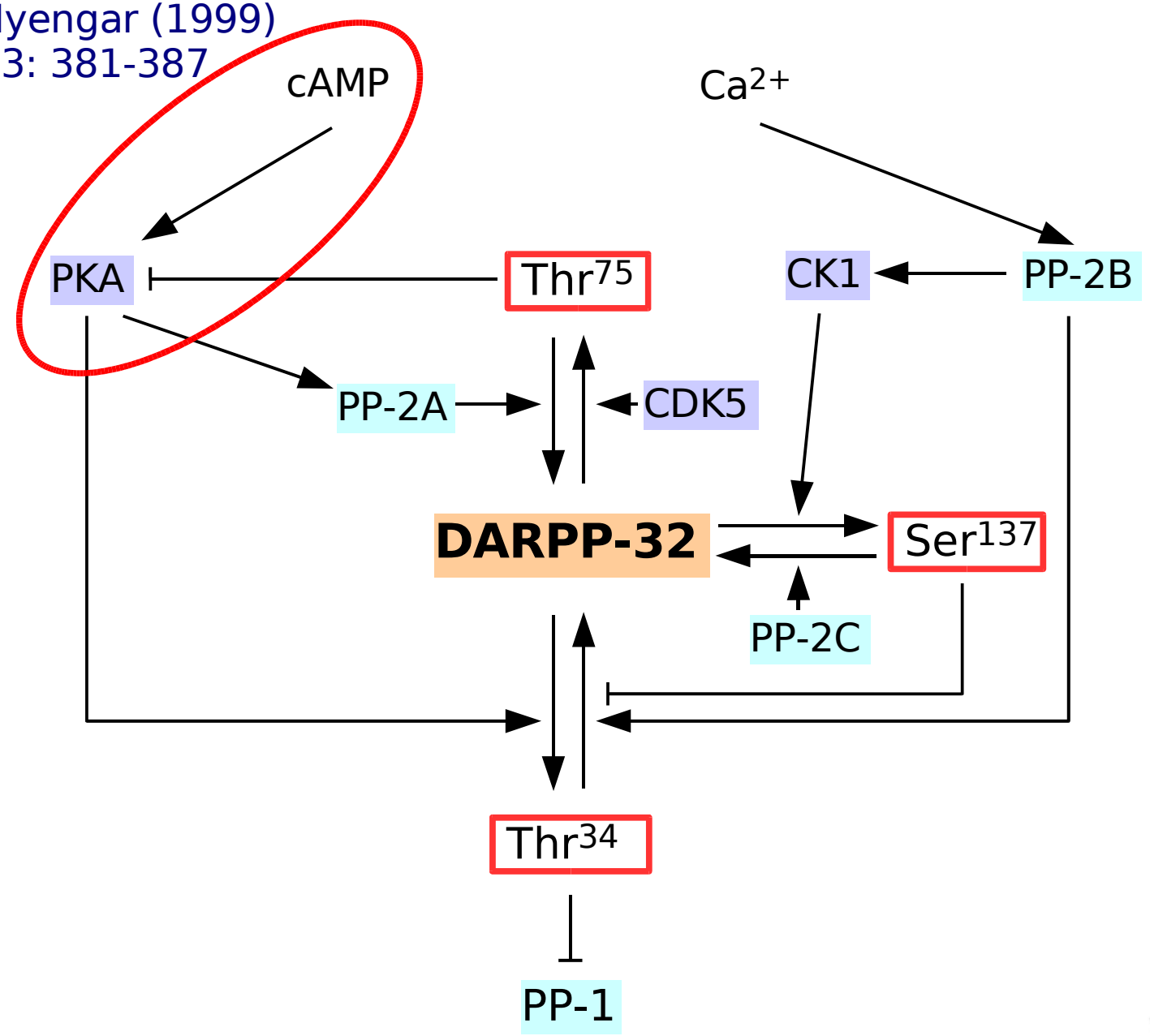




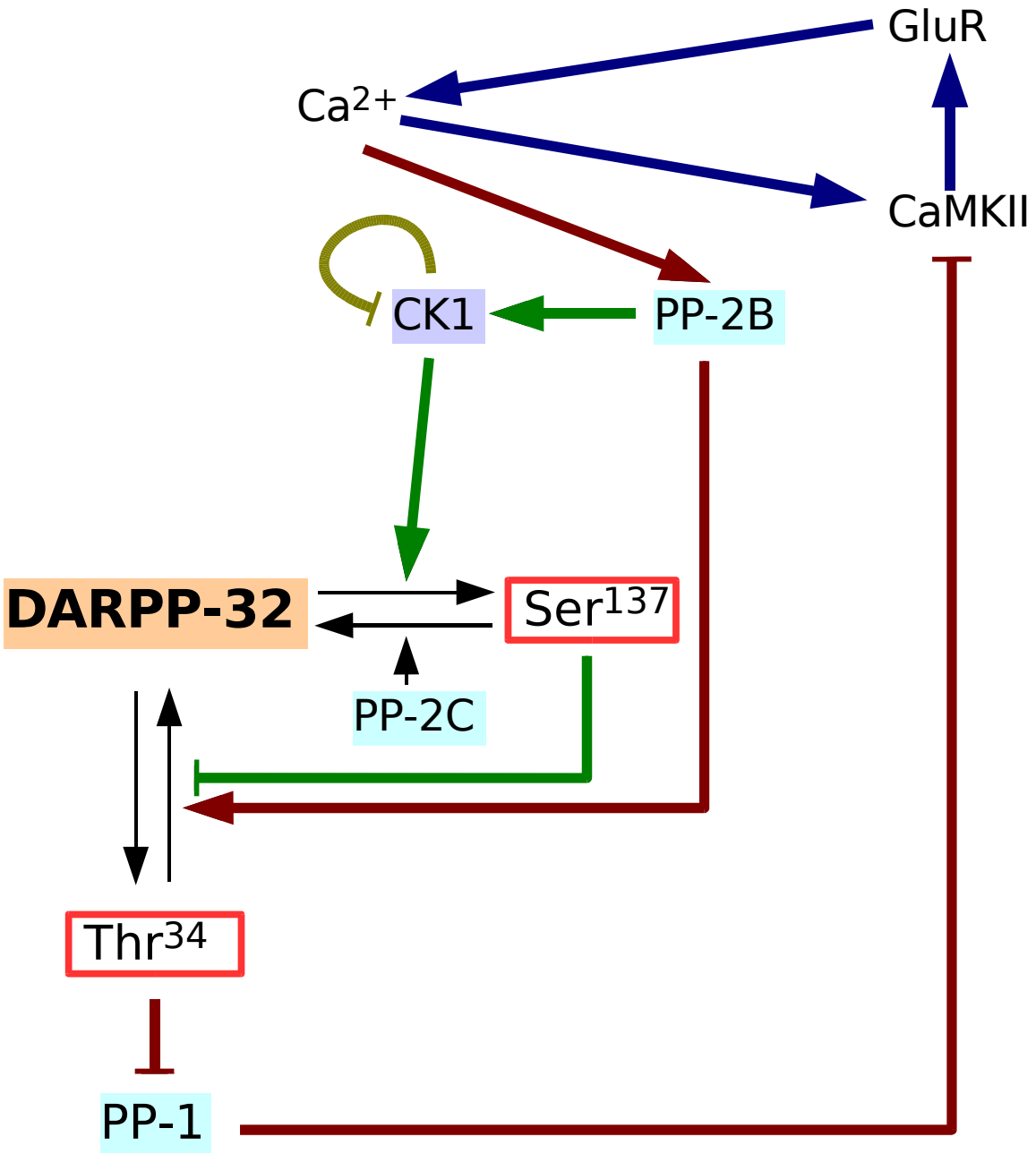
Computational Neurobiology

Model of DARPP-32 regulation

Bhalla and Iyengar (1999)
Science, 283: 381-387



Negative loops: “russian dolls”



The complete model

64 species, 121 reactions

- D + CDK5 D_CDK5 → D75 + CDK5
- D75 + PP2A D75_PP2A → D + PP2A
- D75 + PP2AP D75_PP2AP → D + PP2AP
- D137 + CDK5 D137_CDK5 → D75-137 + CDK5
- D75-137 + PP2A D75-137_PP2A → D137 + PP2A
- D75-137 + PP2AP D75-137_PP2AP → D137 + PP2AP
- D34 + CDK5 D34_CDK5 → D34-75 + CDK5
- D34-75 + PP2A D34-75_PP2A → D34 + PP2A
- D34-75 + PP2AP D34-75_PP2AP → D34 + PP2AP
- D34-137 + CDK5 D34-137_CDK5 → D34-75_137 + CDK5
- D34-75-137 + PP2A D34-75-137_PP2A → D34-137 + PP2A
- D34-75-137 + PP2AP D34-75-137_PP2AP → D34-137 + PP2AP

- D + CK1 D_CK1 → D137 + CK1
- D137 + PP2C D137_PP2C → D + PP2C
- D75 + CK1 D75_CK1 → D75-137 + CK1
- D75-137 + PP2C D75-137_PP2C → D75 + PP2C
- D34 + CK1 D34_CK1 → D34-137 + CK1
- D34-75 + PP2C D34-75_PP2C → D75 + PP2C
- D34-75 + CK1 D34-75_CK1 → D34-75-137 + CK1
- D34-75-137 + PP2C D34-75-137_PP2C → D34-75 + PP2C

- D + PKA D_PKA → D34 + PKA
- D34 + PP2B D34_PP2B → D + PP2B
- D75 + PKA D75_PKA → D34-75 + PKA
- D34-75 + PP2B D34-75_PP2B → D75 + PP2B
- D137 + PKA D137_PKA → D34-137 + PKA
- D75-137 + PKA D75-137_PKA → D34-75-137 + PKA

- CK1 + CK1 CK1_CK1 → CK1P + CK1
- CK1P + PP2B CK1P_PP2B → CK1 + PP2B
- PP2Bi + 2Ca PP2Bi_Ca2
- PP2Bi_Ca + 2Ca PP2B

- D75 + PKA D75_PKA
- D34-75 + PKA D34-75_PKA
- D34-75-137 + PKA D34-75-137_PKA

- R2_PKA2 + cAMP cAMP_R2_PKA2
- cAMP_R2_PKA2 + cAMP cAMP2_R2_PKA2
- cAMP2_R2_PKA2 + cAMP cAMP3_R2_PKA2
- cAMP3_R2_PKA2 + cAMP cAMP4_R2_PKA2
- cAMP4_R2_PKA2 cAMP4_R2_PKA + PKA
- cAMP4_R2_PKA cAMP4_R2 + PKA
- PKA + PDE PKA_PDE → PKA + PDEP
- cAMP + PDE cAMP_PDE → AMP + PDE
- cAMP + PDEP cAMP_PDEP → AMP + PDEP

Ordinary Differential Equation approach

$$E + S \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} ES \xrightarrow{k_{cat}} E + P$$

$$d[S]/dt = k_{off}[ES] - k_{on}[E][S]$$

$$d[P]/dt = k_{cat}[ES]$$

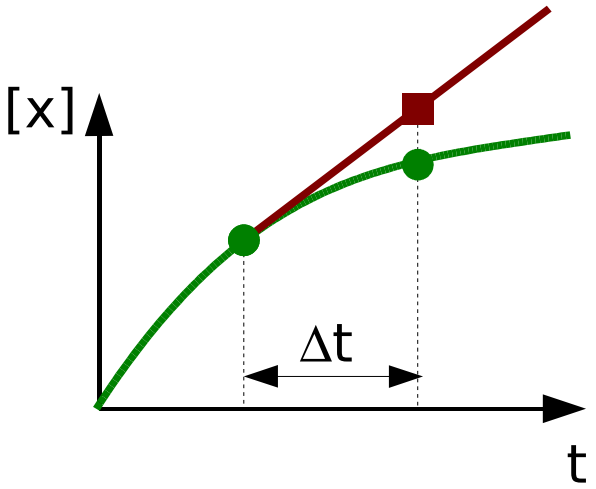
$$d[E]/dt = k_{cat}[ES]$$

$$d[ES]/dt = k_{on}[E][S] - k_{off}[ES] - k_{cat}[ES]$$

Euler method:

$$d[x]/dt \approx ([x]_{t+\Delta t} - [x]_t) / \Delta t$$

$$[x]_{t+\Delta t} \approx [x]_t + d[x]/dt \,.\, \Delta t$$



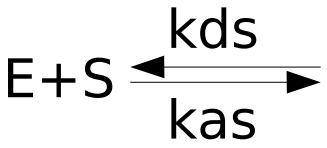
$$[P]_{t+\Delta t} = [P]_t + k_{cat}[ES]_t \,.\, \Delta t$$

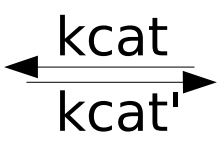
$$[E]_{t+\Delta t} = [E]_t + k_{cat}[ES]_t \,.\, \Delta t$$

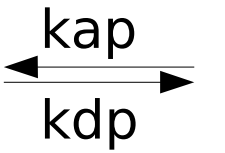
$$[S]_{t+\Delta t} = [S]_t + (k_{off}[ES]_t - k_{on}[E]_t[S]_t) \,.\, \Delta t$$

$$[ES]_{t+\Delta t} = [S]_t + (k_{on}[ES]_t - (k_{on}+k_{cat})[E]_t[S]_t) \,.\, \Delta t$$

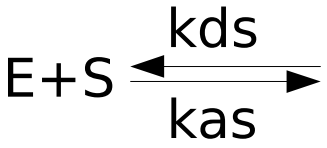
Choose the right formalism

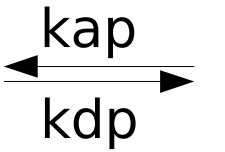




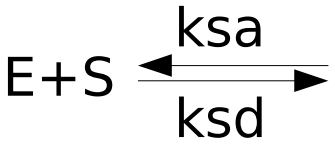


$$\frac{d[P]}{dt} = kdp[EP] - kap[E][P]$$

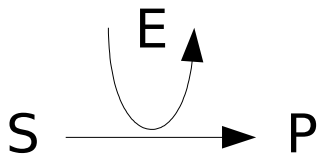




catalysis irreversible



product is consumed before rebinding



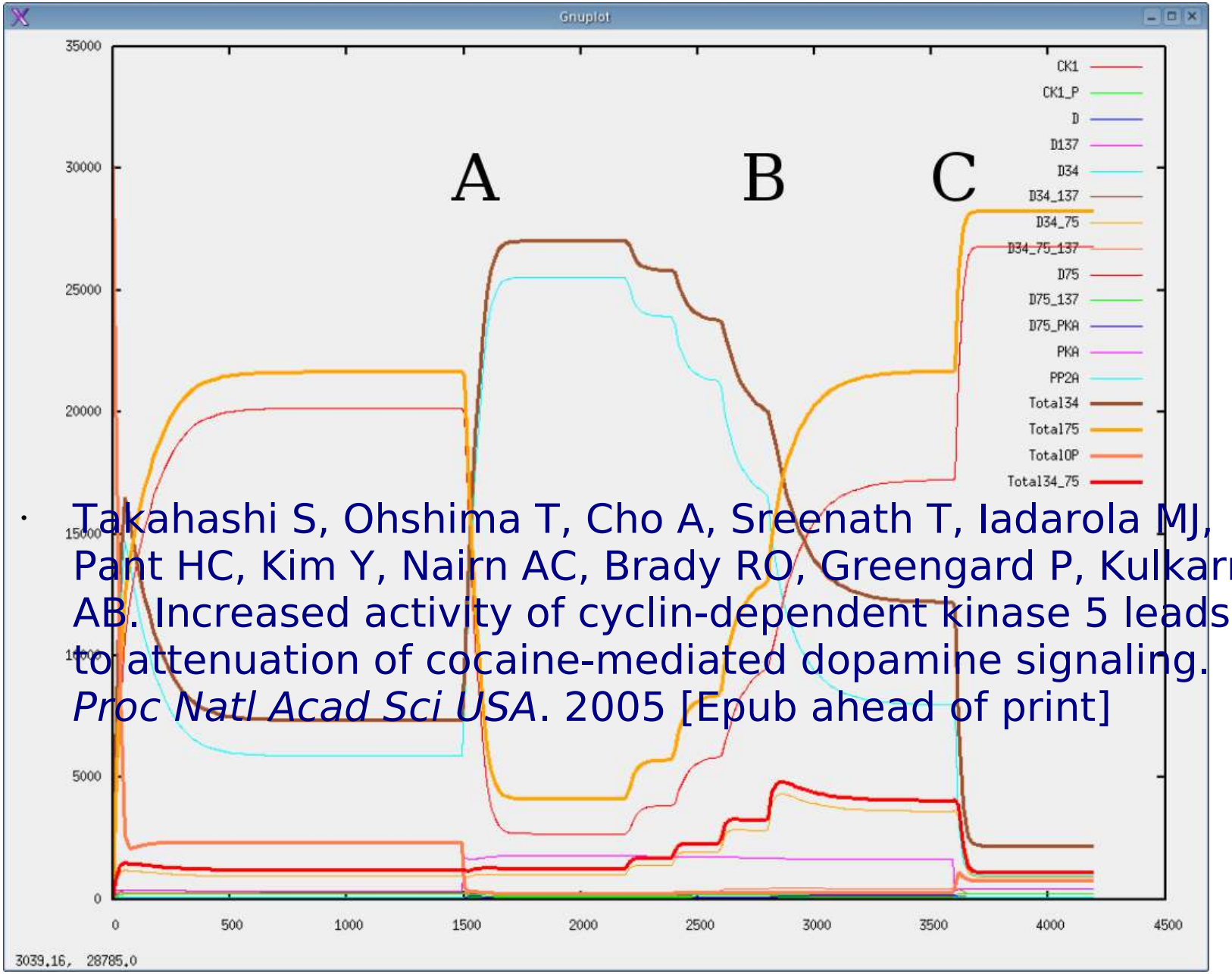
steady-state

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

Leonor Michaelis, Maud Menten (**1913**).
Die Kinetik der Intertinwerkung, Biochem. Z. 49:333-369.

G. E. Briggs and J. B. S. Haldane (**1925**)
A note on the kinetics of enzyme action, Biochem. J., 19, 339-339.

Effect of CDK5 activity



- Takahashi S, Ohshima T, Cho A, Sreenath T, Iadarola MJ, Pant HC, Kim Y, Nairn AC, Brady RO, Greengard P, Kulkarni AB. Increased activity of cyclin-dependent kinase 5 leads to attenuation of cocaine-mediated dopamine signaling. *Proc Natl Acad Sci USA*. 2005 [Epub ahead of print]

We need to reuse those mathematical models

- Non-specialists need to use models relevant for their research with simulation software without messing with their structure.
- Modeling literates need to reuse existing models rather than rewrite them from scratch.
- Various software used during the modelling process, such as graphical designers, simulation engines and plotters or renderers, should be able to communicate.

→ Systems Biology Markup Language (SBML): A community maintained open XML standard to encode quantitative models of biological systems.

→ MIME type application/sbml+xml
(RFC 3823 of the Internet Engineering Task Force)

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 75 software systems**, including the following (where '*' indicates SBML support in development):

BALSA	Cytoscape	MATLAB SBToolbox	SBMLeditor
BASIS	DBsolve	MathSBML	SBMLR
BIOCHAM	Dizzy	MesoRD	SBMLToolbox
BioCharon	E-CELL	MetaboLogica	SBW
biocyc2SBML	ecellJ	MetaFluxNet	SCIpath
BioGrid	ESS	MMT2	Sigmoid*
BioNetGen	FluxAnalyzer	Modesto	SigPath
BioPathways Explorer	Fluxor	Moleculizer	SigTran
Bio Sketch Pad	Gepasi	Monod	SIMBA
BioSPICE Dashboard	INSILICO discovery	NetBuilder	Simpathica
BioSpreadsheet	Jarnac	PANTHER Pathway	SimWiz
BioTapestry	JDesigner	PathArt	SmartCell
BioUML	JigCell	PathScout	StochSim
BSTLab	JSIM	Pathway Tools	STOCKS
CADLIVE	JWS*	PathwayBuilder	TERANODE Suite
CellDesigner	Karyote*	PaVESy	Trelis
Cellerator	KEGG2SBML	Reactome	Virtual Cell
Cellware	Kinsolver*	ProcessDB*	WinSCAMP
CL-SBML	libSBML	PySCeS*	
COPASI	LION Target Engine	SBML ODE Solver	

A Free and Open Language

Advances in biotechnology are leading to larger, more complex quantitative models. The systems biology community needs information standards if models are to be shared, evaluated and developed cooperatively. SBML's widespread adoption **offers many benefits**, including: (1) enabling the use of multiple tools without rewriting models for each tool, (2) enabling models to be shared and published in a form other researchers can use even in a different software environment, and (3) ensuring the survival of models (and the intellectual effort put into them) beyond the lifetime of the software used to create them.

Does Your Software Support SBML?

MATLAB SBToolbox

(March 15, 2005) Henning Schmidt at the Fraunhofer-Chalmers Research Centre in Sweden has created a new **Systems Biology Toolbox for MATLAB**.

read more

SBMLeditor

(March 4, 2005) A new low-level editor, **SBMLeditor**, has been released by Nicolas Le Novère's group at the EBI.

read more

Teranode Design Suite 2.5

(Feb 2, 2005) Teranode has updated their **Design Suite** with powerful new features including KEGG and MATLAB support.

read more

Recent presentations & posters

(Jan 20, 2005) We've added a number of recent presentations and posters to the SBML.org documents page.

read more

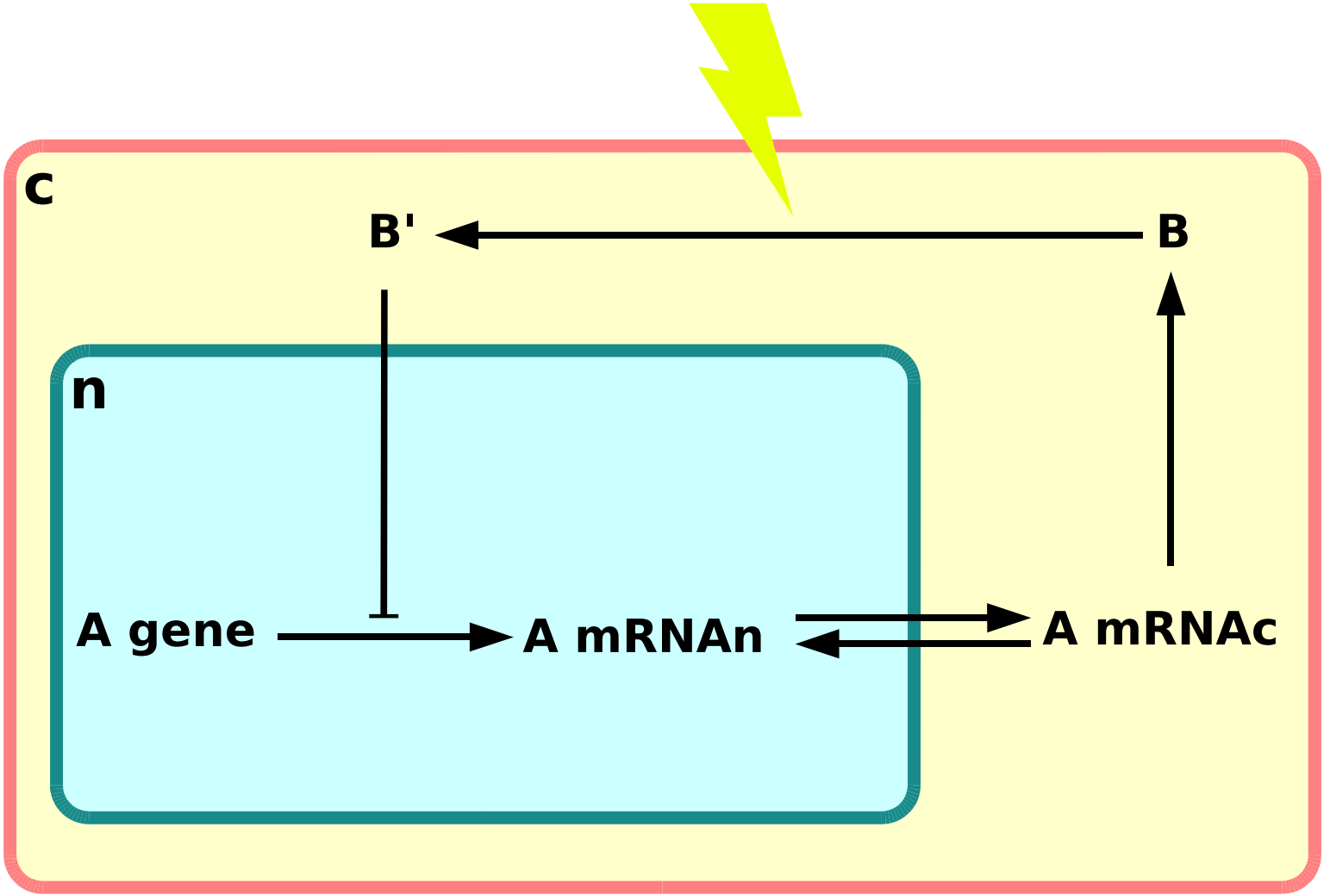
Announcement: SIMBA

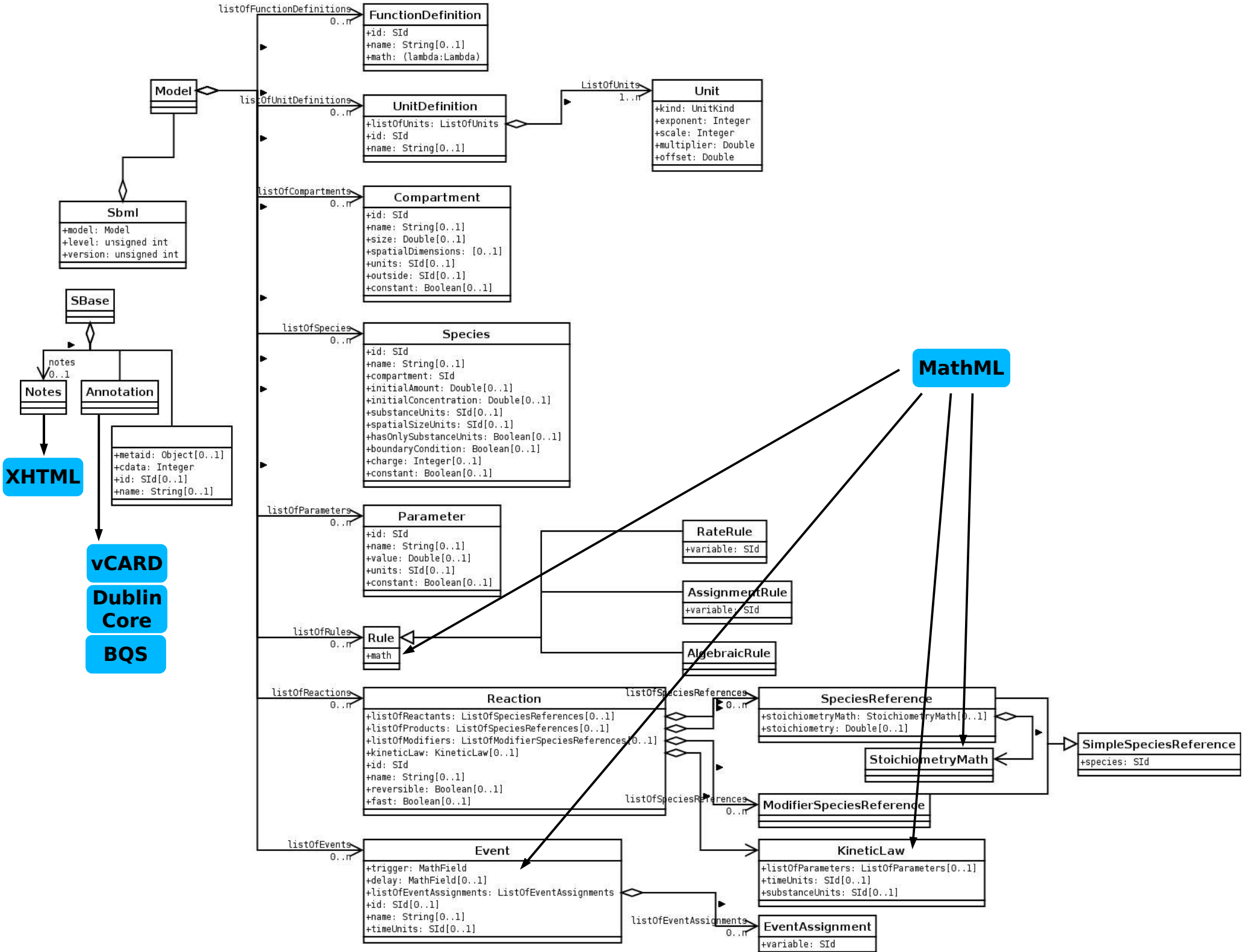
(Jan 5, 2005) **SIMBA** is a package from *ifak system GmbH* designed for dynamical simulation of wastewater treatment. At ICSB 2004, they announced support for SBML.

read more

See older news items.

What can we encode in SBML?




listOfFunctionDefinitions
0..n
FunctionDefinition
+id: SId
+name: String[0..1]
+math: (lambda:Lambda)
Model
listOfUnitDefinitions
0..n
UnitDefinition
+listOfUnits: ListOfUnits
+id: SId
+name: String[0..1]
ListOfUnits
1..n
Unit
+kind: UnitKind
+exponent: Integer
+scale: Integer
+multiplier: Double
+offset: Double
Sbml
+model: Model
+level: unsigned int
+version: unsigned int
listOfCompartments
0..n
Compartment
+id: SId
+name: String[0..1]
+size: Double[0..1]
+spatialDimensions: [0..1]
+units: SId[0..1]
+outside: SId[0..1]
+constant: Boolean[0..1]
SBase
notes
0..1
Notes
Annotation
XHTML
+metaid: Object[0..1]
+cdata: Integer
+id: SId[0..1]
+name: String[0..1]
vCARD
Dublin Core
BQS
listOfSpecies
0..n
Species
+id: SId
+name: String[0..1]
+compartment: SId
+initialAmount: Double[0..1]
+initialConcentration: Double[0..1]
+substanceUnits: SId[0..1]
+spatialSizeUnits: SId[0..1]
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+boundaryCondition: Boolean[0..1]
+charge: Integer[0..1]
+constant: Boolean[0..1]
MathML
listOfParameters
0..n
Parameter
+id: SId
+name: String[0..1]
+value: Double[0..1]
+units: SId[0..1]
+constant: Boolean[0..1]
RateRule
+variable: SId
AssignmentRule
+variable: SId
listOfRules
0..n
Rule
+math
AlgebraicRule
listOfReactions
0..n
Reaction
+listOfReactants: ListOfSpeciesReferences[0..1]
+listOfProducts: ListOfSpeciesReferences[0..1]
+listOfModifiers: ListOfModifierSpeciesReferences[0..1]
+kineticLaw: KineticLaw[0..1]
+id: SId
+name: String[0..1]
+reversible: Boolean[0..1]
+fast: Boolean[0..1]
listOfSpeciesReferences
0..n
SpeciesReference
+stoichiometryMath: StoichiometryMath[0..1]
+stoichiometry: Double[0..1]
StoichiometryMath
SimpleSpeciesReference
+species: SId
listOfSpeciesReferences
0..n
ModifierSpeciesReference
listOfEvents
0..n
Event
+trigger: MathField
+delay: MathField[0..1]
+listOfEventAssignments: ListOfEventAssignments
+id: SId[0..1]
+name: String[0..1]
+timeUnits: SId[0..1]
KineticLaw
+listOfParameters: ListOfParameters[0..1]
+timeUnits: SId[0..1]
+substanceUnits: SId[0..1]
listOfEventAssignments
0..n
EventAssignment
+variable: SId

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




</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>
  </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>
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      <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>
      </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>
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      <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>
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        </listOfReactants>
        <listOfProducts>
          <speciesReference species="B" />
        </listOfProducts>
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            <apply>
              <times />
              <ci>kon</ci>
              <ci>A</ci>
              <ci>cell</ci>
            </apply>
          </math>
        </kineticLaw>
      </reaction>
    </listOfReactions>
  </model>
</sbml>
```


A more realistic example

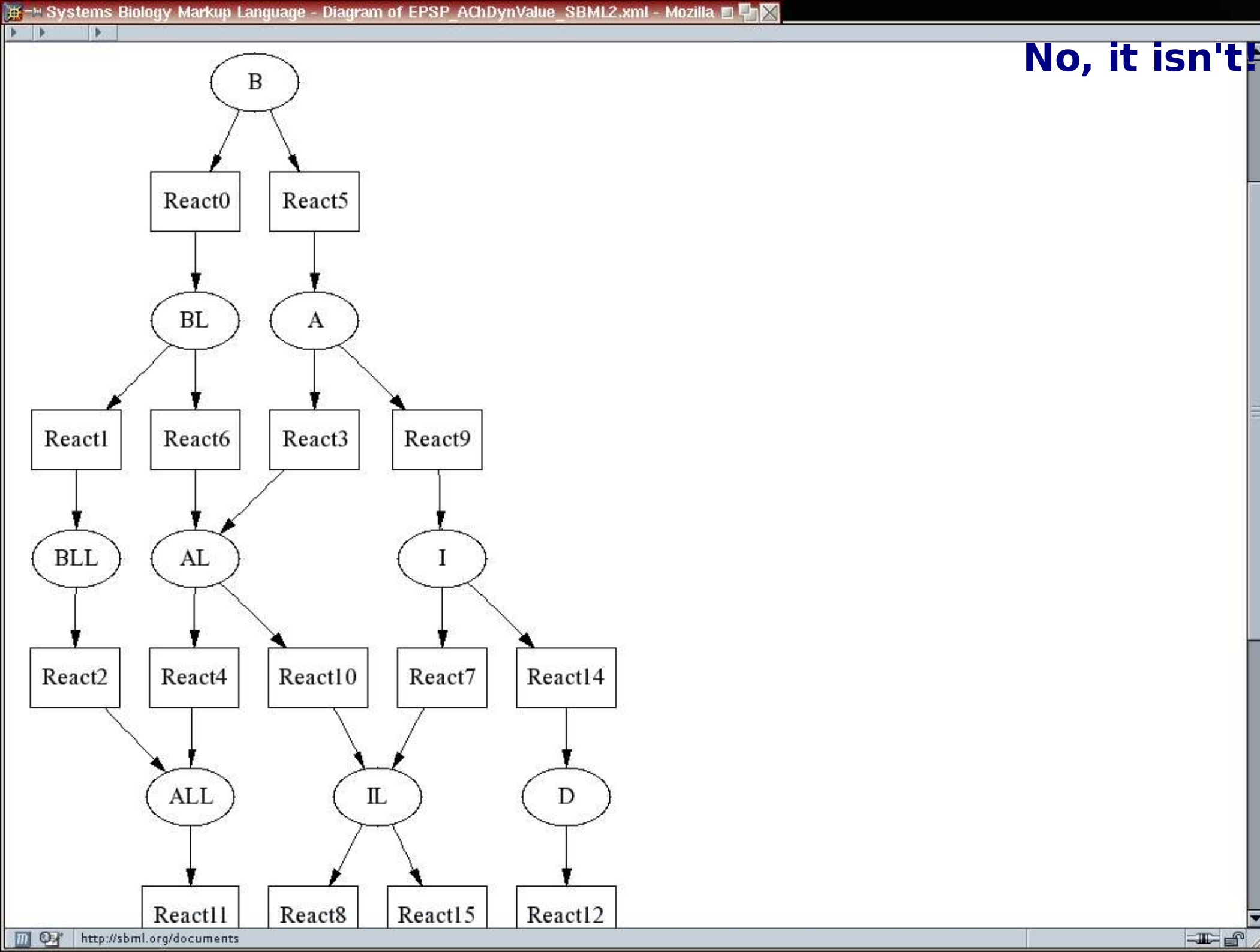
```
<species
   id=”A”
   name=”a-tubulin”
   compartment=”cell”
   initialAmount=”1000”
   substanceUnits=”item”
   hasOnlySubstanceUnits=”true”
   boundaryCondition=”true”
   constant=”false”
   charge=”0”>
  <notes>
   <body xmlns=”http://www.w3.org/1999/xhtml”>
     <p>One of the components of microtubule</p>
   </body>
  </notes>
  <annotation>
   <rdf:RDF
      xmlns:dc="http://purl.org/dc/elements/1.1/"
      xmlns:dcterms="http://purl.org/dc/terms/"
      xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
     <rdf:Description rdf:about="#PX">
      <dc:relation>
        <rdf:Bag>
          <rdf:li rdf:resource="http://www.uniprot.org/#P68370"/>
          <rdf:li rdf:resource=”http://www.geneontology.org/#0045298”/>
        </rdf:Bag>
      </dc:relation>
     </rdf:Description>
   </rdf:RDF>
  </annotation>
</species>
```

SBML Levels

- **Level 1 (March 2001)**
  - Predefined kinetics functions
  - One type of reactive substance
  - ISO646 encoding
- **Level 2 (June 2003)**
  - Function definitions
  - Modifier species
  - Events
  - All math in MathML
  - Unicode encoding
- **Level 3 (?)**
  - Modular SBML (“packages”)
  - Graph layout
  - Multi-component species
  - Model composition
  - Arrays of elements

Hucka et al (2003)
Bioinformatics 19: 524-531

Hucka et al (2004)
IEE Systems Biology 1: 41-53


Systems Biology Markup Language - Diagram of EPSP_AChDynValue_SBML2.xml - Mozilla
No, it isn't!
B
React0
React5
BL
A
React1
React6
React3
React9
BLL
AL
I
React2
React4
React10
React7
React14
ALL
IL
D
React11
React8
React15
React12
http://sbml.org/documents

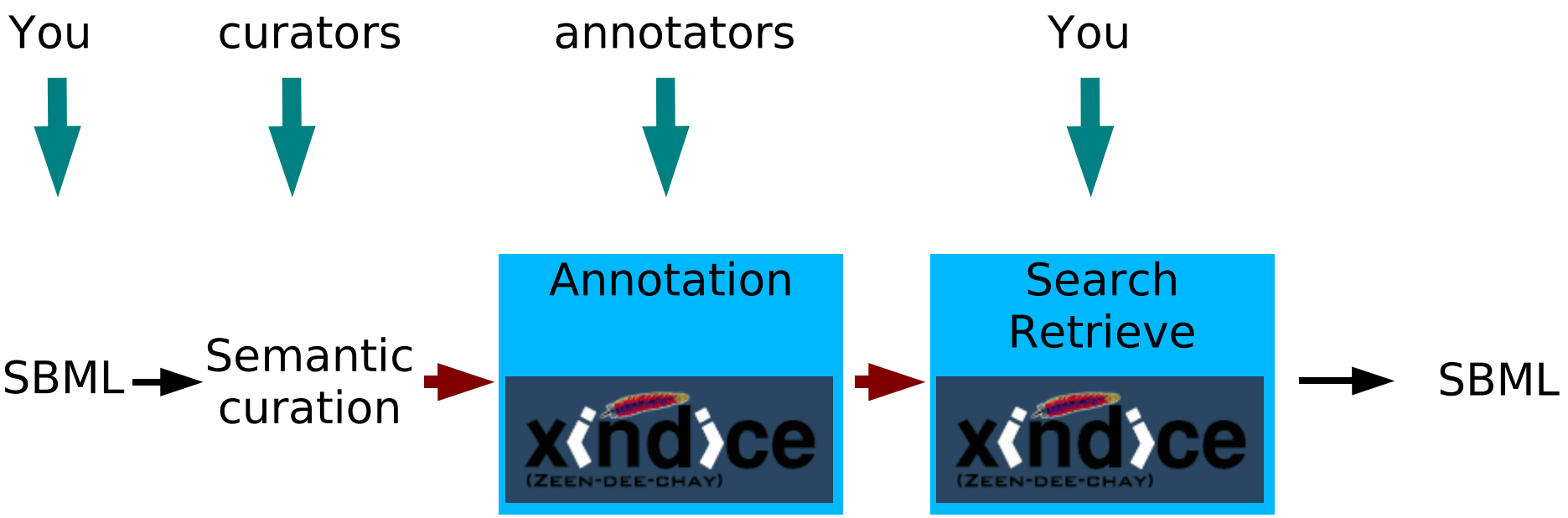
What can we do?

- Bench biologists need to find models relevant for their research.
- Modellers need to reuse existing models, or portions of models, rather than rewrite them from scratch. Model composition on a large scale will be possible only if we have such a model “shopping cart”.
- But ...
  - No true database of models, only repositories, sometimes with side information.
  - Poor quality control on the models available online (JWS excepted).
  - No annotation of models: reactants are A,B,C, reactions 1, 2, 3 etc.
  - Lack of standards on production, curation and annotation of models.
- ⇒ Biomodels.net: collaboration between Caltech, EMBL-EBI, SBI, JWS etc. etc.
  - MIRIAM:
    Minimum Information Requested In the Annotation of Models
  - Controlled vocabularies:
    - Parameters: Kd, Ka, Kp, IC50 ARE DIFFERENT!
    - “Michaelis-Menten”, “Mass Action Law” etc.
  - Biomodels database, a database of “Systems Biology Models”

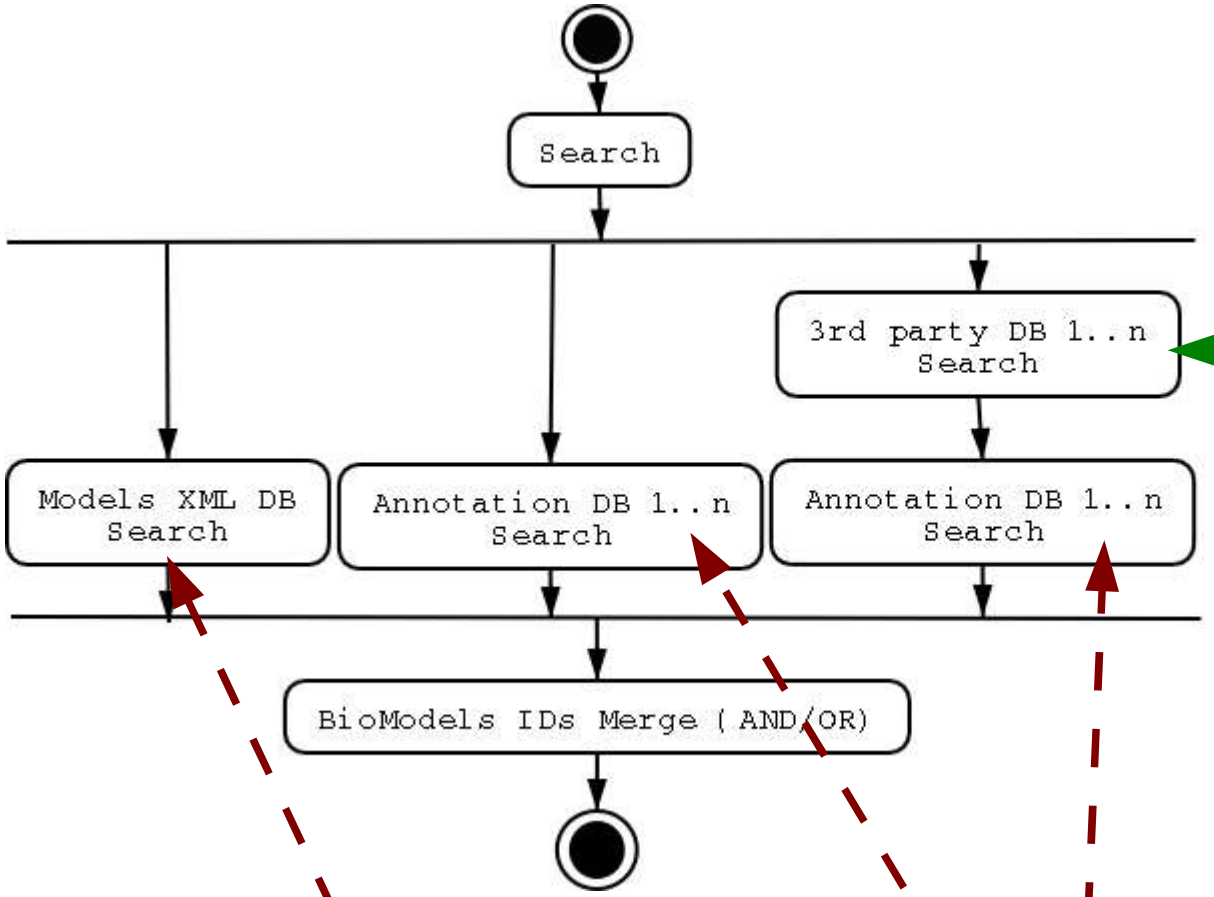
Model annotation

model	Submitter, Creators, publication, Gene Ontology, KEGG pathway, OMIM, Reactome, Taxonomy
compartment	Gene Ontology
species	ChEBI, Ensembl, Gene Ontology, InterPro, KEGG compound, OMIM, Taxonomy, UniProt
rule	BIND, EC code, Gene Ontology, IntAct, KEGG pathway, KEGG Reaction, Reactome
reaction	BIND, EC code, Gene Ontology, IntAct, KEGG pathway, KEGG Reaction, Reactome
event	BIND, EC code, Gene Ontology, IntAct, KEGG pathway, KEGG Reaction, Reactome

Structure of Biomodels



Search strategy



GO Oracle database
PubMed webservices

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

//dc:relation//ref:li[contains(@rdf:resource,'URI')
                      and contains(@rdf:resource,'ID')]
```

BIOMODELS.NET

BioModels Database

Submit Your Model

BioModels Annotation

- Browse
- Search
- Submit
- Replace
- Delete
- Annotate

Contact

Computational Neurobiology

Search Models

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

- *BioModels ID* → Search BioModels Annotation for BioModels identifiers, for example *BIOMD0000000003*, *00003* or *3*.
- *Person* → Search BioModels Annotation for submitter and/or creator names, for example *Nicolas Le Novère*, *Nicolas*, *Bruce Shapiro* or *Shapiro*.
- *SBML Elements* → Search BioModels Annotation for SBML elements by either name or *notes* content, for example *Edelstein* or *nicotinic*.
- *Resource* → Search BioModels Annotation for related information found in third-party resources by either resource identifier or text, for example *9256450* or *cyclin* for PubMed, *GO:0007049* or *cell cycle* for Gene Ontology.
- *Resource ID* → Search BioModels Annotation for annotations with third-party resource identifiers, for example *CHEBI:15422* or *15422* for ChEBI, *68910* or *69278* for Reactome, *P04551* or *4551* for UniProt.

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

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

BioModels ID:

Person:

SBML Elements:

Resource: Gene Ontology — cell cycle

Resource: PubMed

Resource: PubMed

Resource ID: BIND

Resource ID: BIND

Resource ID: BIND

Compose by: and or

Search Reset

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Search **Models**

The search returned **6** models.

New Search

BioModels ID	Name	PubMed Id	Last Modified	
BIOMD0000000003	Goldbeter1991_MinMitOscil	1833774	2005-03-23T16:36:25	SBML
BIOMD0000000004	Goldbeter1991_MinMitOscil_ExplInact	1833774	2005-03-23T16:39:59	SBML
BIOMD0000000005	Tyson1991_CellCycle_6var	1831270	2005-03-23T16:42:49	SBML
BIOMD0000000006	Tyson1991_CellCycle_2var	1831270	2005-03-21T17:41:01	SBML
BIOMD0000000007	Novak1997_CellCycle_13var	9256450	2005-03-23T17:07:12	SBML
BIOMD0000000008	Gardner1998_CellCycle_Goldbeter	9826676	2005-03-23T17:09:08	SBML

New Search

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Computational Neurobiology

BIOMD0000000007 **Novak1997_CellCycle_13var**

Download SBML

Reference Publication

PubMed ID: 9256450

Proc Natl Acad Sci U S A. 1997 Aug 19;94(17):9147-52.
Modeling the control of DNA replication in fission yeast.
Novak B, Tyson JJ.

Model

Submitter: Nicolas Le Novère

Submission Date: 2005-02-09T13:27:02

Last Modification Date: 2005-04-01T23:58:07

Creators: Bruce Shapiro

Gene Ontology	GO:0000278 GO:0007049
KEGG Pathway	sce04110
Taxonomy	4896
Reactome	69278

Compartments (1)

Species (14)

Reactions (33)

Reaction1
Reactants: EmptySet
Products: mass
Modifiers:

Reaction2
Reactants: EmptySet
Products: G2K
Modifiers:

Reactome 68910 69282

Reaction3
Reactants: G2K
Products: EmptySet

Gene Ontology GO:0008054

Novak and Tyson Cell Cycle Model (1997)

Citation

Novak B, tyson JJ (1997) Modeling the control of DNA replication in fission yeast, PNAS, USA, 94:9147-9152. http://www.pnas.org/cgi/content/abstract/ 94/17/9147

Description

A cell cycle model with 13 dynamic variables (Cdc25,G1K,G1R=[Cig2/Cdc2/Rum1],G2K=[Cdc13/Cdc2],G2R=[Cdc13/Cdc2/Rum1],IE=[Intermediary enzyme],mass,PG2=[Cdc13/P-Cdc2],PG2R=[Cdc13/P-Cdc2/Rum1],R=[Rum1],UbE,UbE2, Wee1} and two auxilllary variables MPF = G2K+ beta*PG2, SPF=MPF+alpha*G1K+Cig1, (alpha, beta, Cig1 constants) . NOTE: The following switches in the published model are NOT described by the SBML: "Switches(i) When SPF crosses 0.1 from below, S phase is initiated (Start).(ii) When UbE crosses 0.1 from above, the cell divides functionally (mass->mass/2), although visible cytokinesis may be delayed.(iii) 60 min after Start,kp is divided by 2, and at cell division kp is multiplied by 2." (from Table 1 of the cited reference).

Rate constant	Reaction
0	G1R -> R
0.00175	EmptySet -> G1K
0.00495*mass[t]	EmptySet -> mass
0.0075*(1 - UbE[t]) + 0.25*UbE[t]	G2K -> EmptySet
0.0075*(1 - UbE[t]) + 0.25*UbE[t]	PG2 -> EmptySet
0.015	EmptySet -> G2K
0.025*(1 - Cdc25[t]) + 0.5*Cdc25[t]	PG2 -> G2K
0.035*(1 - Wee1[t]) + 0.35*Wee1[t]	G2K -> PG2
0.0375*(1 - UbE2[t]) + 7.5*UbE2[t]	G1K -> EmptySet
0.05 + 0.0075*(1 - UbE[t]) + 0.25*UbE[t]	G2R -> R
0.05 + 0.0075*(1 - UbE[t]) + 0.25*UbE[t]	PG2R -> R
0.09375	EmptySet -> R
0.1	G1R -> G1K + R
0.1	G2R -> G2K + R
0.1	PG2R -> PG2 + R
0.1875	G1R -> G1K

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Reactome 68910 69282

Reaction3
Reactants: G2K
Products: EmptySet

Gene Ontology GO:0008054

1: Proc Natl Acad Sci U S A. 1997 Aug 19;94(17):9147-52.

Modeling the control of DNA replication in fission yeast.

Novak B, Tyson JJ.

Department of Agricultural Chemical Technology, Technical University of Budapest, 1521 Budapest, St. Gellert ter 4, Hungary.

A central event in the eukaryotic cell cycle is the decision to commence DNA replication (S phase). Strict controls normally operate to prevent repeated rounds of DNA replication without intervening mitoses ("endoreplication") or initiation of mitosis before DNA is fully replicated ("mitotic catastrophe"). Some of the genetic interactions involved in these controls have recently been identified in yeast. From this evidence we propose a molecular mechanism of "Start" control in Schizosaccharomyces pombe. Using established principles of biochemical kinetics, we compare the properties of this model in detail with the observed behavior of various mutant strains of fission yeast: wee1(-) (size control at Start), cdc13Delta and rum1(OP) (endoreplication), and wee1(-) rum1Delta (rapid division cycles of diminishing cell size). We discuss essential features of the mechanism that are responsible for characteristic properties of Start control in fission yeast, to expose our proposal to crucial experimental tests.

PMID: 9256450 [PubMed - indexed for MEDLINE]

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Reactome	68910 69282

Reaction3
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Gene Ontology	GO:0008054

Reactome: Formation of CyclinA/B:Cdc2 complexes - Mozilla

File Edit View Go Bookmarks Tools Window Help

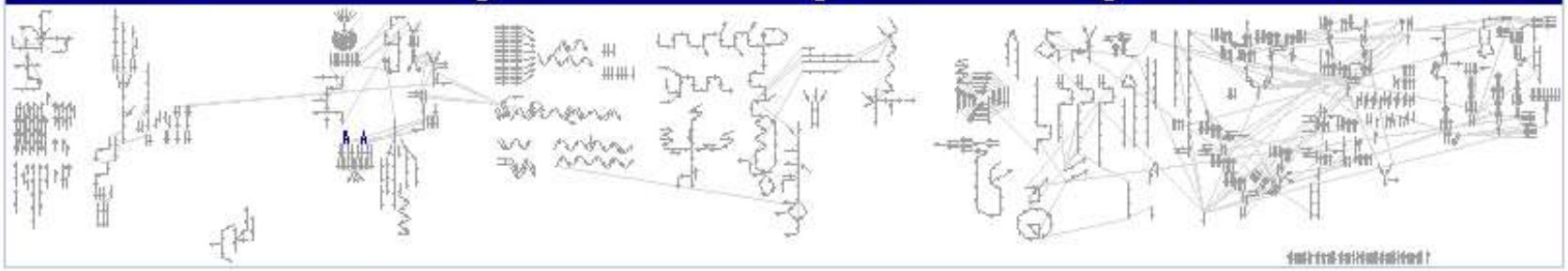
http://www.reactome.org/cgi-bin/eventbrowser?DB=gk_current&ID=68910

Search

About | TOC | User Guide | Data Model | Schema | Extended search | PathFinder | SkyPainter | Download | Linking | Citing

Find everything with ALL of the words in Homo sapiens Go!

Click on the map: shifts focus zooms in zooms out



[Reactome Home]

+ Cell Cycle, Mitotic

+ G2/M Transition

+ Cyclin A/B associated events during G2/M transition

- **Formation of CyclinA/B:Cdc2 complexes [Homo sapiens]**

Formation of Cyclin B2:Cdc2 complexes

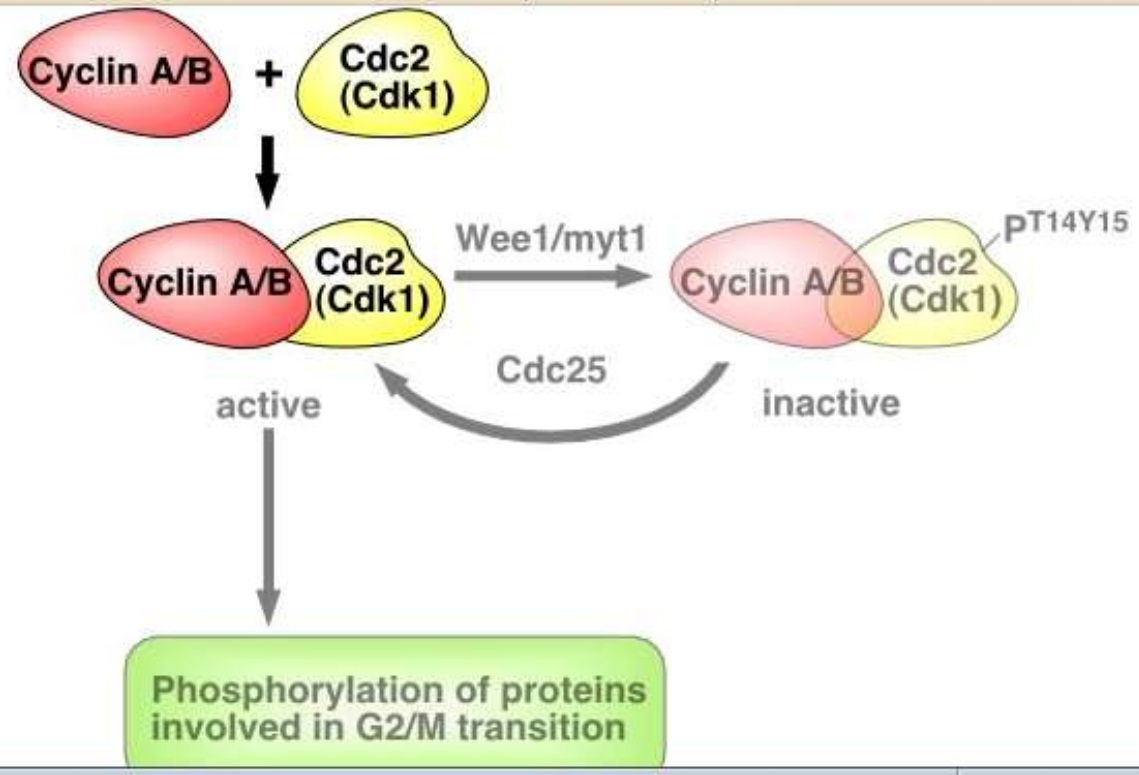
Formation of Cyclin B1:Cdc2 complexes

Formation of Cyclin A2:Cdc2 complexes

Formation of Cyclin A1:Cdc2 complexes

Show hierarchy types

Formation of CyclinA/B:Cdc2 complexes



Done

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Products: G2K
Modifiers:

Reactome	68910 69282

Reaction3
Reactants: G2K
Products: EmptySet

Gene Ontology	GO:0008054

```
      <reaction id="Reaction6" metaid="_000005" reversible="false">
        <annotation>
          <rdf:RDF xmlns:dc="http://purl.org/dc/elements/1.1/" xmlns:dcterms="http://purl.org/dc/terms/" xmlns:rdf="http://www.w3.org/1999/02/
            <rdf:Description rdf:about="#_000005">
                  <dc:relation>
                    <rdf:Bag>
                      <rdf:li rdf:resource="http://www.reactome.org/#69260"/>
                    <rdf:li rdf:resource="http://www.geneontology.org/#GO:0045736"/>
</rdf:Bag>
                  </dc:relation>
            </rdf:Description>
          </rdf:RDF>
        </annotation>
        <listOfReactants>
          <speciesReference species="G2K"/>
        </listOfReactants>
        <listOfProducts>
          <speciesReference species="PG2"/>
        </listOfProducts>
        <listOfModifiers>
          <modifierSpeciesReference species="Weel"/>
        </listOfModifiers>
        <kineticLaw>
          <math xmlns="http://www.w3.org/1998/Math/MathML">
            <apply>
              <times/>
              <ci> G2K </ci>
              <apply>
                <plus/>
                <apply>
                  <times/>
                  <ci> Vwp </ci>
                  <apply>
                    <minus/>
                    <cn type="integer"> 1 </cn>
                    <ci> Weel </ci>
                  </apply>
                </apply>
                <apply>
                  <times/>
                  <ci> Vw </ci>
                  <ci> Weel </ci>
                </apply>
              </apply>
            </apply>
          </math>
```

COPASI (4.0 Build 12 test version)

rxvt <2>

File Tools Help

- Copasi
  - Model
  - Tasks
    - Steady-State
    - Stoichiometry
    - Time Course
      - Result
    - Metabolic Control Analysis
  - Output
    - Plots
      - ConcentrationPlot
    - Reports
  - Functions

Task Name: Trajectory Task — Task Executable

Start Time: 0 — End Time: 400

Interval size: 4 — Intervals: 100

store time series in memory

Method: Deterministic (LSODA)

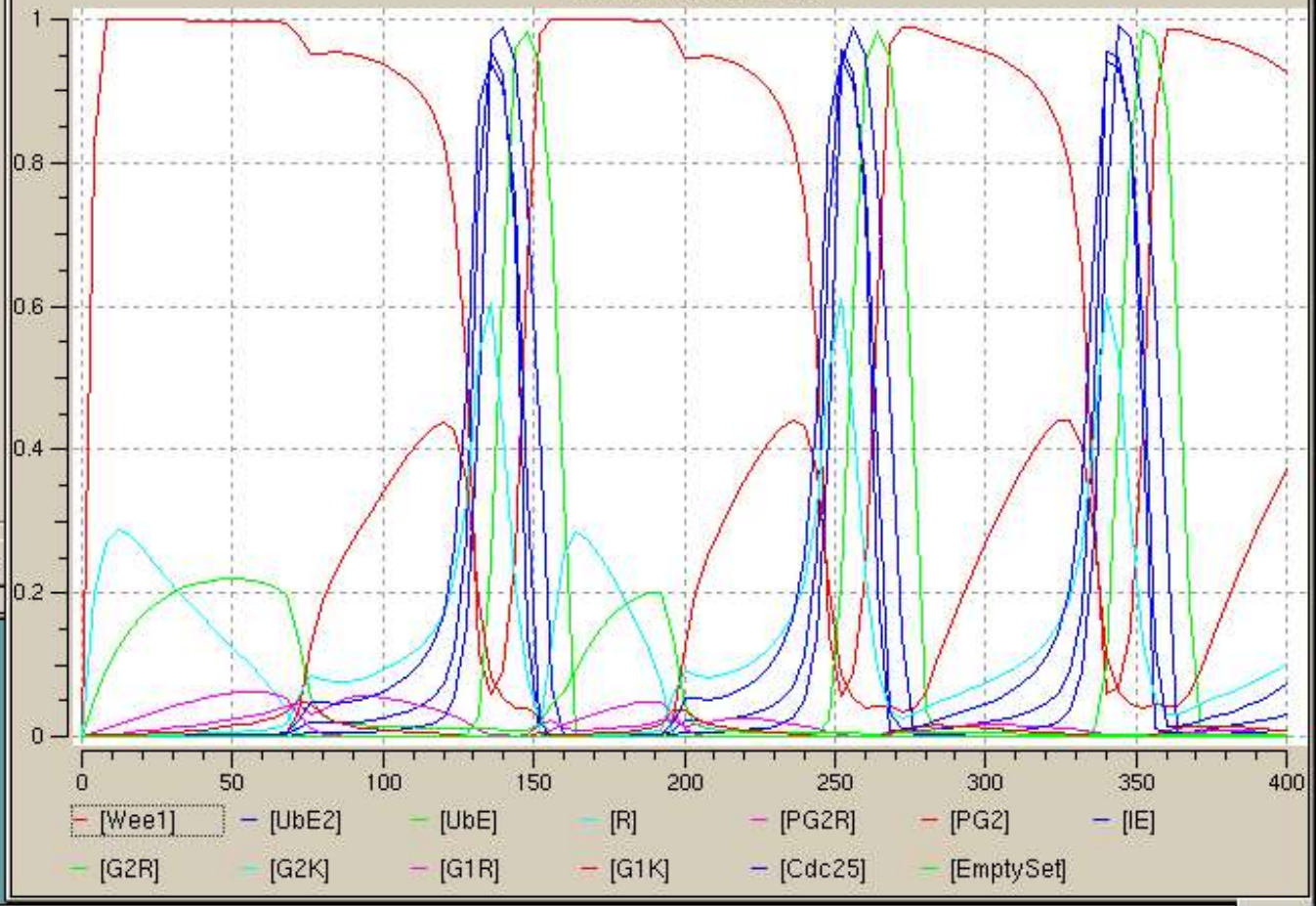
Parameter value

	Value
LSODA.RelativeTolerance	1e-06

Run

Copasi Plot: ConcentrationPlot

Zoom Print




```
PlotItem_0
** compiling a CModel is requested.
PlotItem_0
** compiling a CModel is requested.
PlotItem_0
** compiling a CModel is requested.
PlotItem_0
** compiling a CModel is requested.
PlotItem_0
```

Bottleneck: Few models are directly usable

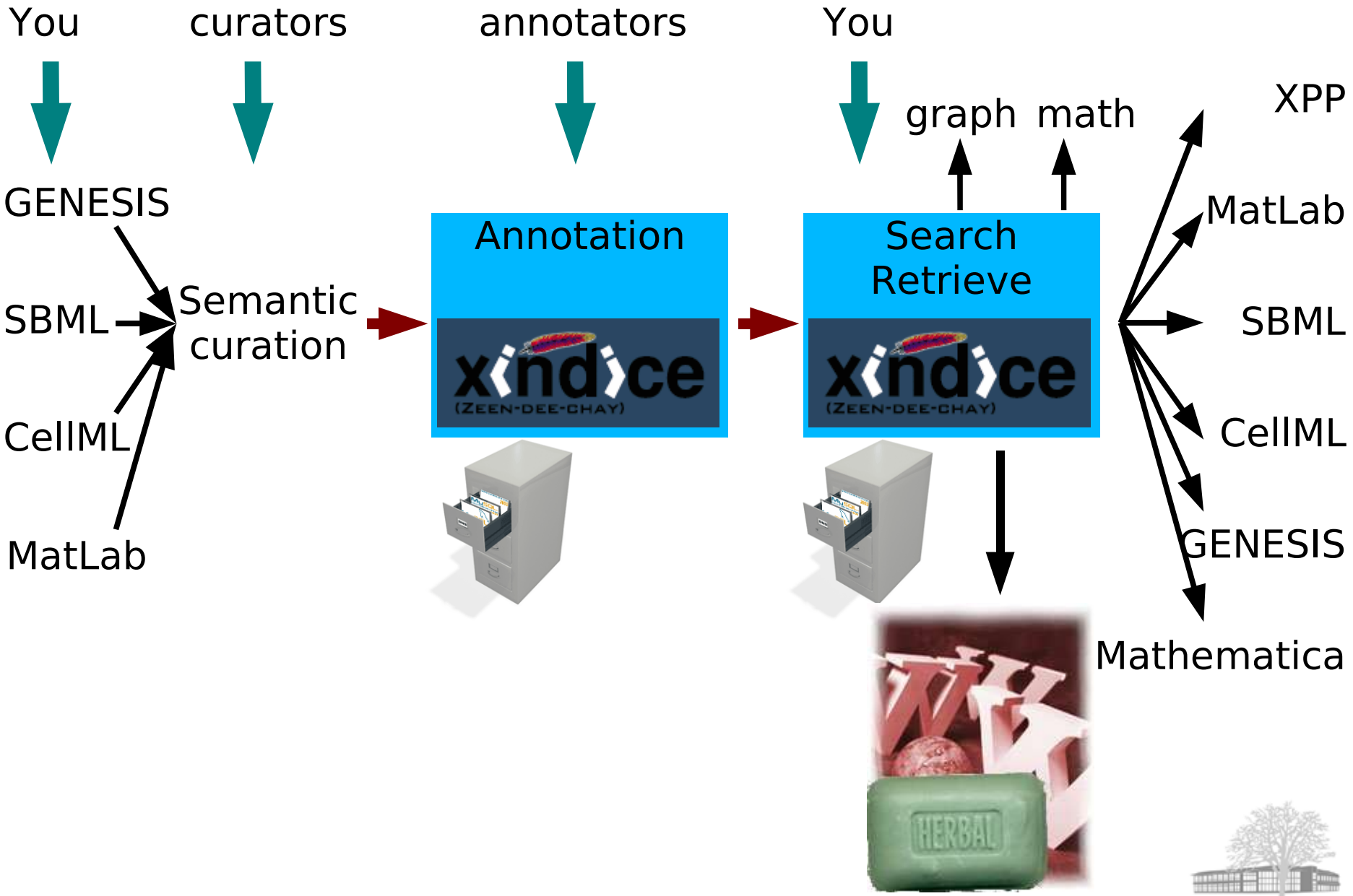
- syntactically wrong (incorrect SBML)
  - typos in the elements and attributes
  - invalid default: e.g. “constant” parameter fixed by a rule
- semantically wrong (correct SBML but make no sense)
  - wrong species: misunderstanding of “constant” and “boundaryCondition”
  - wrong initialconditions: everything zeroed, would not start
  - wrong reaction: the rate law produces concentrations rather than amounts
- bad correspondance with the article
  - wrong units: built-in are not redefined, resulting in M instead of μM
  - wrong compartments: only one compartment represents nucleus+cytoplasm
  - wrong formalism: Michaelis-Menten instead of elementary reactions
  - everything is fine but does not produce the same results than in paper ...

1st release: April 1? 2005

- 21 models [20]
- 383 species (0 – 86) [607]
- 689 reactions (0 – 300) [539]
- 1047 annotations
- Cell Cycle: 6 [1]
- MAPK cascade: 5 [4]
- Circadian clock: 2 [6]

- JWS online: 33 models
- CellML repository: 306 models
- DOQCS: 195 “pathways”

Let's move forward



An international collaboration

SBML developement

- Michael Hucka
- Andrew Finney
- Herbert Sauro
- Hamid Bolouri
- Ben Bornstein
- Nicolas Le Novère
- Pedro Mendes
- Martin Ginkel
- Kouichi Takahashi
- Takeshi Sakurada
- Jim Schaff
- John Wagner
- Jorg Stelling
- Poul Nielsen
- Hiroaki Kitano
- Bruce Shapiro
- Eric Mjolness

- Victoria Gor
- Jonathan Webb
- Igor Goryanin
- Jorg Weimar
- Stefan Hoops
- Akira Funahashi
- Sven Sahle
- Ralf Gauges
- Hugh Spencer
- Wayne Rindone
- Fabien Campagne
- Maria Schilstra
- Vijay Saraswat
- Ed Frank
- Ben Kovitz
- Jeremy Zucker
- ...
- ...

BioModel.net

- EBI
  - Nicolas Le Novère
  - Marco Donizelli
  - Alexander Broicher
- SBML team
  - Michael Hucka
  - Andrew Finney
  - Bruce Shapiro
  - Maria Schilstra
  - Sarah Keating
- Keck Graduate Institute
  - Herbert Sauro
  - Harish Dharuri
- Systems Biology Institute
  - Hiroaki Kitano
  - Akira Funahashi
- Stellenbosh University
  - Jacky Snoep
- External contributors
  - Upinder Bhalla
  - Rainer Machné
  - Marc Poolman
  - Tomas Radivoyevitch

The EBI team







```
<compneur>
  <member name=”Nicolas Le Novère” role=”leader”/>
  <member name=”Alexander Broicher” role=”trainee”/>
  <member name=”Mélanie Courtot” role=”developer”/>
  <member name=”Marco Donizelli” role=”developer”>
  <member name=”Éric Fernandez” role=”post-doc”/>
  <member name=”Nicolas Rodriguez” role=”developer”/>”
  <member name=”Dominic Tölle” role=”PhD student”/>
</compneur>
```