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    </listOfCompartments>
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    </listOfSpecies>
    <listOfParameters>
      <parameter id="k1" value="0.1"/>
    </listOfParameters>
    <listOfReactions>
      <reaction id="r1" reversible="false">
      <listOfReactants>
          <speciesReference species="A"/>
        </listOfReactants>
        <listOfProducts>
          <speciesReference species="B"/>
        </listOfProducts>
        <kineticLaw>
          <math xmlns="http://www.w3.org/1998/Math/MathML">
            <apply>
              <times/>
              <ci> cell </ci>
              <ci> k1 </ci>
              <ci> [illegible] </ci>
            </apply>
          </math>
        </kineticLaw>
```

Building the biological Babylon Tower with standard representations of pathways

Nicolas Le Novère
Babraham Institute,
n.lenovere@gmail.com

What is a “pathway”

Wikipedia (October 16th 2017): “In biochemistry, a metabolic pathway is a linked series of chemical reactions occurring within a cell.”

Different types: Signalling pathways, metabolic networks, gene regulatory networks ...

Many “pathway” databases:

Biocarta, Bio/MetaCyc, Ingenuity IPA, KEGG Pathway, Panther pathways, Reactome, STKE, Wikipathways etc.

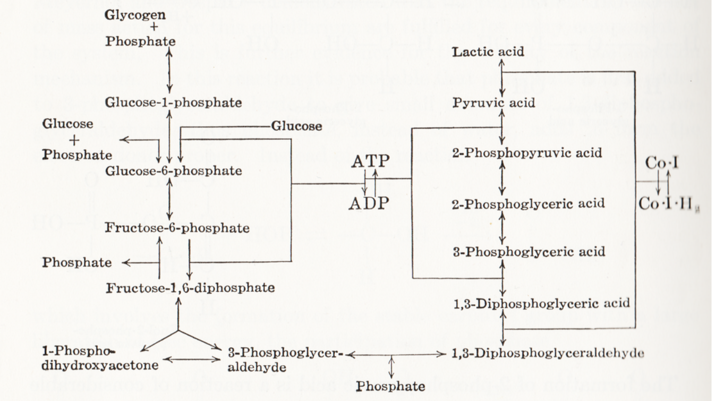
➜ Detailed representation of reality based on observation

OR

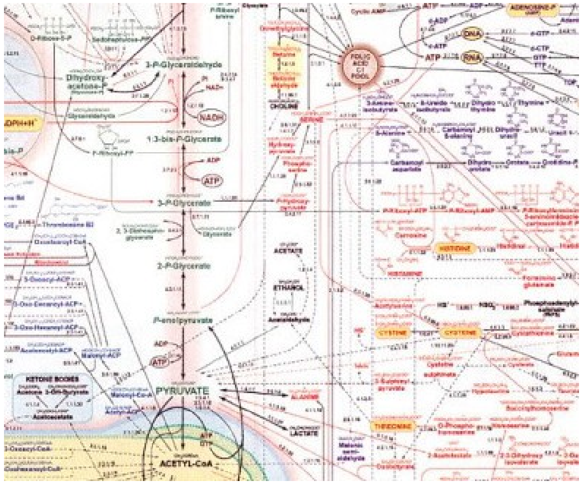
➜ Abstract representation of reality based on needs

Biochemical pathways are old …

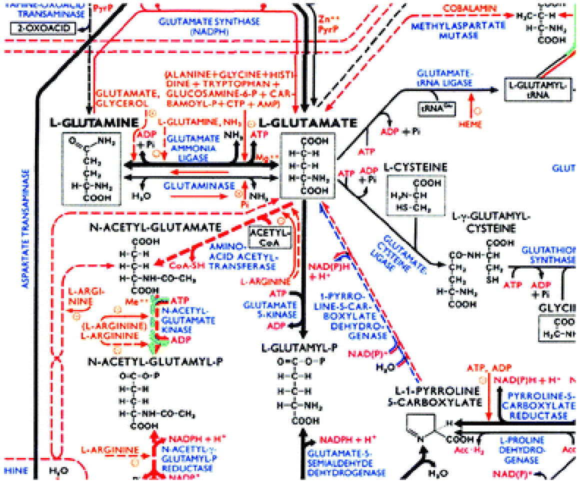
Gortner (1949)



Nicholson (1970)



Michal (1984)

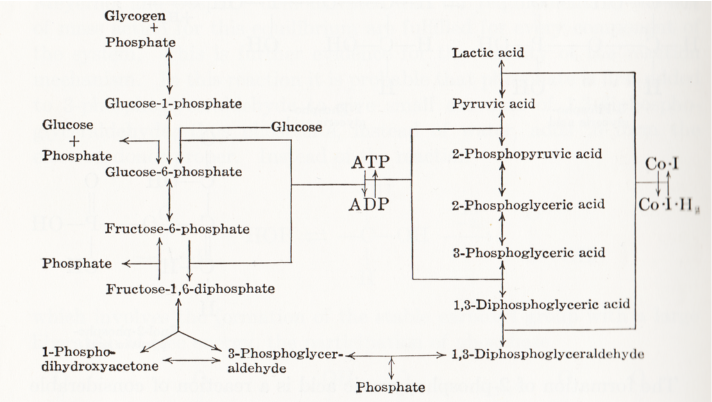


"Hand drawing" on paper

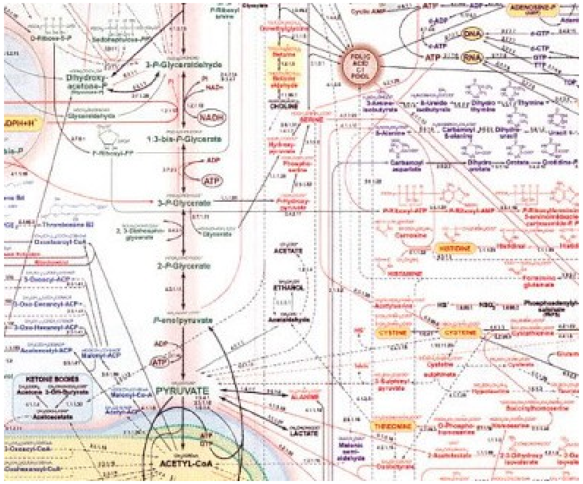
→ no software-based browsing, processing and analysis

Biochemical pathways are old … or not so much

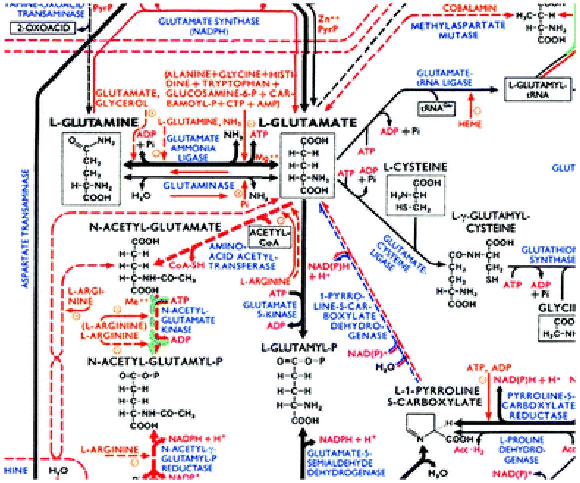
Gortner (1949)



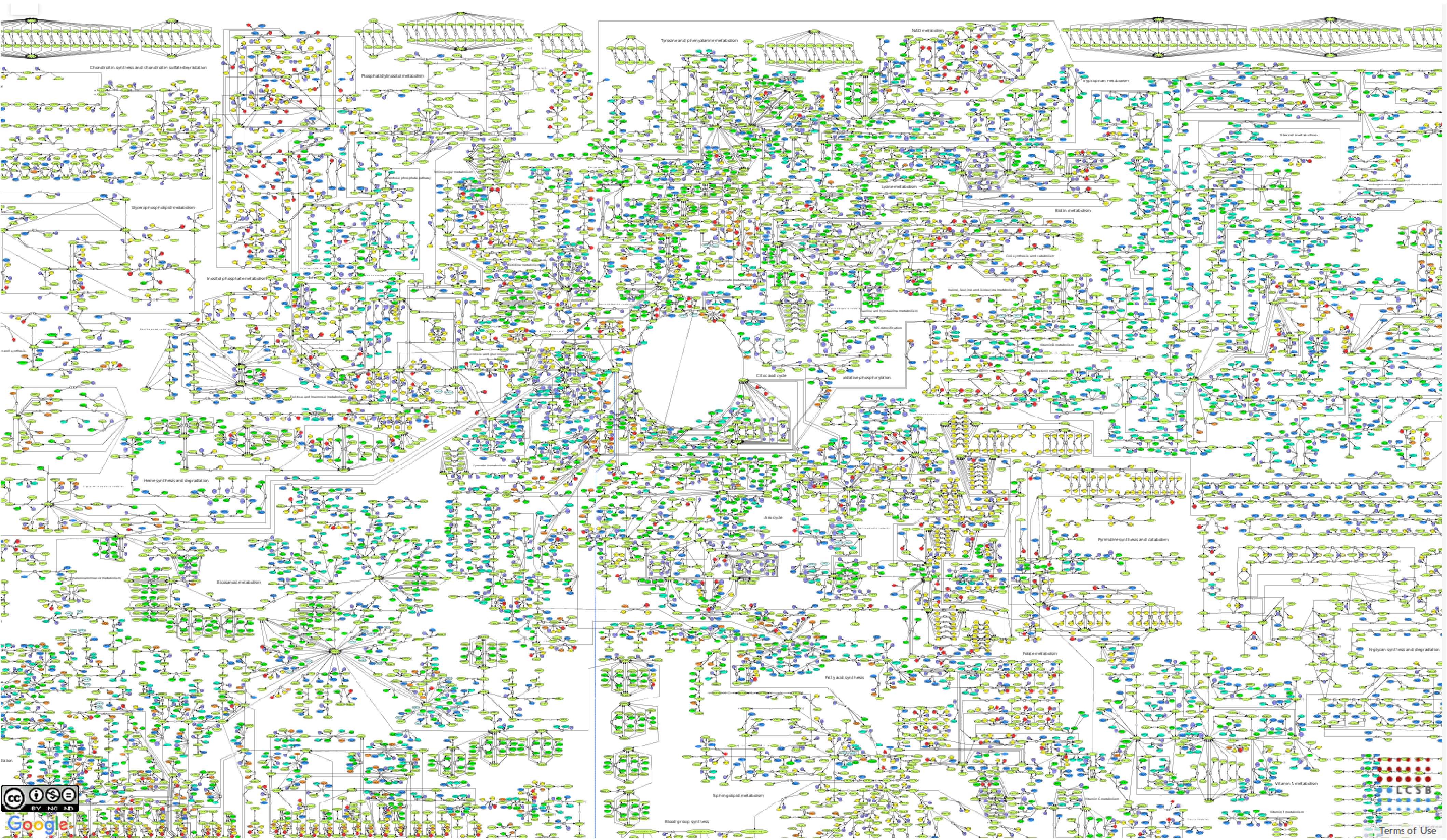
Nicholson (1970)



Michal (1984)



- 1990s: high-throughput data generation → Large amount of knowledge
  increase in computing power → automatic reconstruction, browsing and analysis
- Databases: EcoCyc (1994), KEGG (1995), Reactome (2000)
- Formats: BioPAX (2000), SBML (2000), PSI-MI (2002)



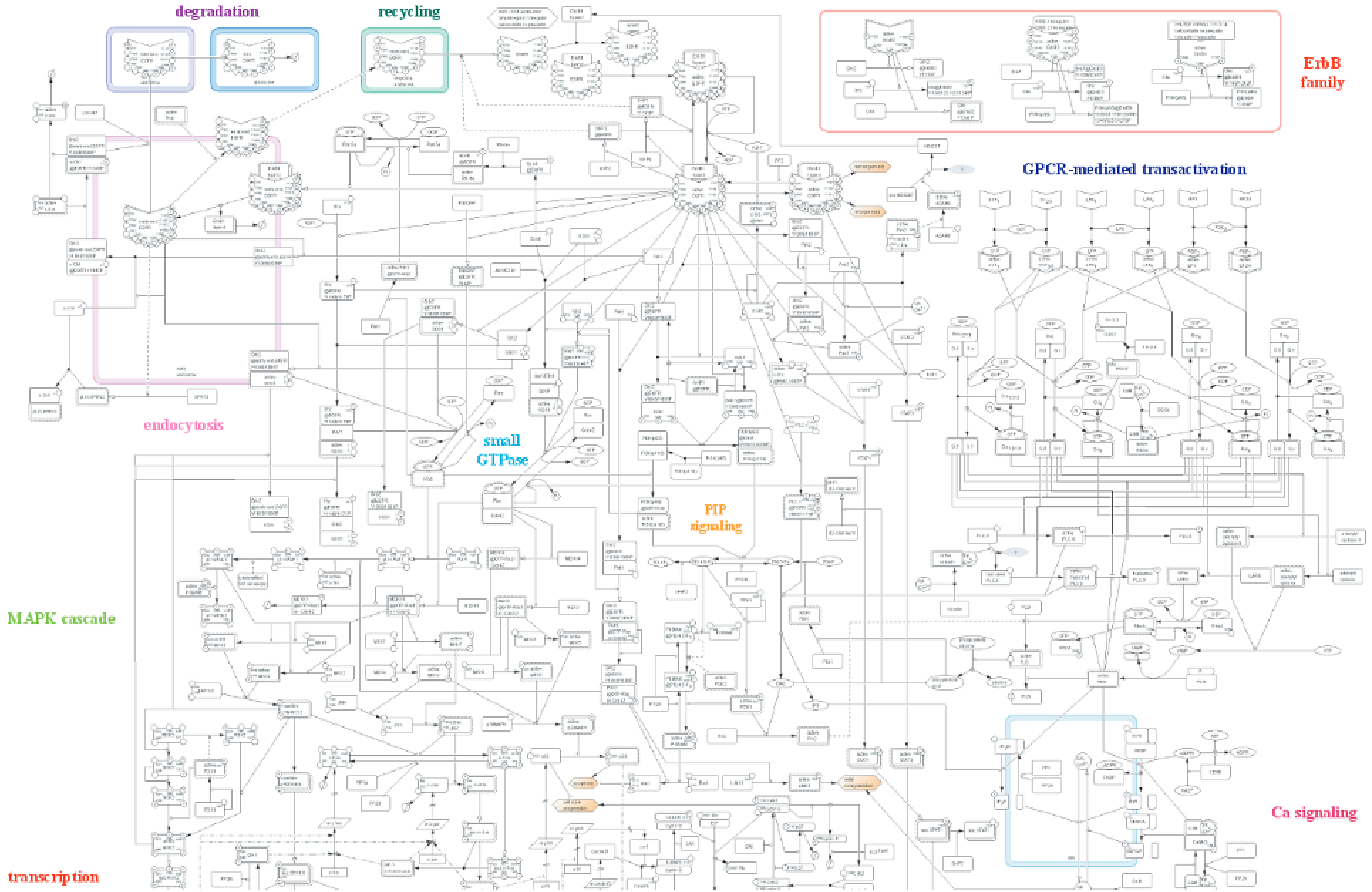
http://vmh.uni.lu

UNDERSTAND

Metabolic networks

part III Systems Biology, 17 October 2017

Babraham Institute

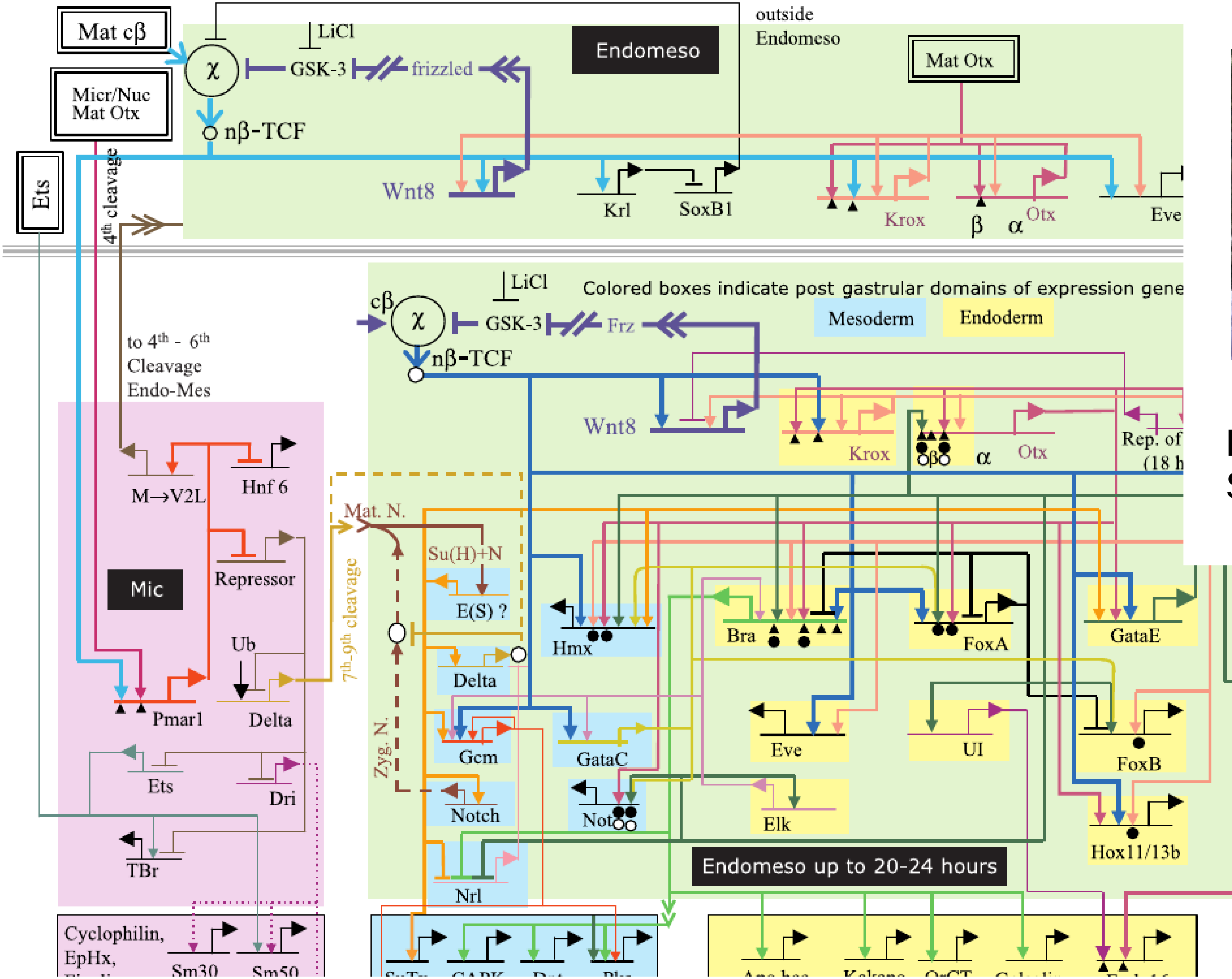


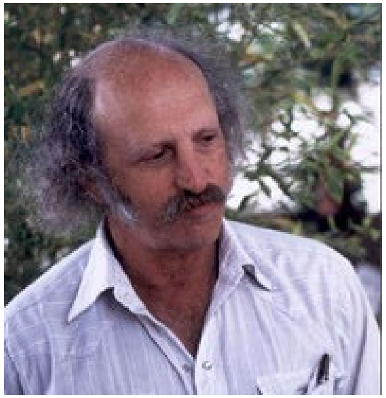
UNDERSTAND

Signalling pathways

Oda *et al*. *Mol Syst Biol*. 2005

part III Systems Biology, 17 October 2017



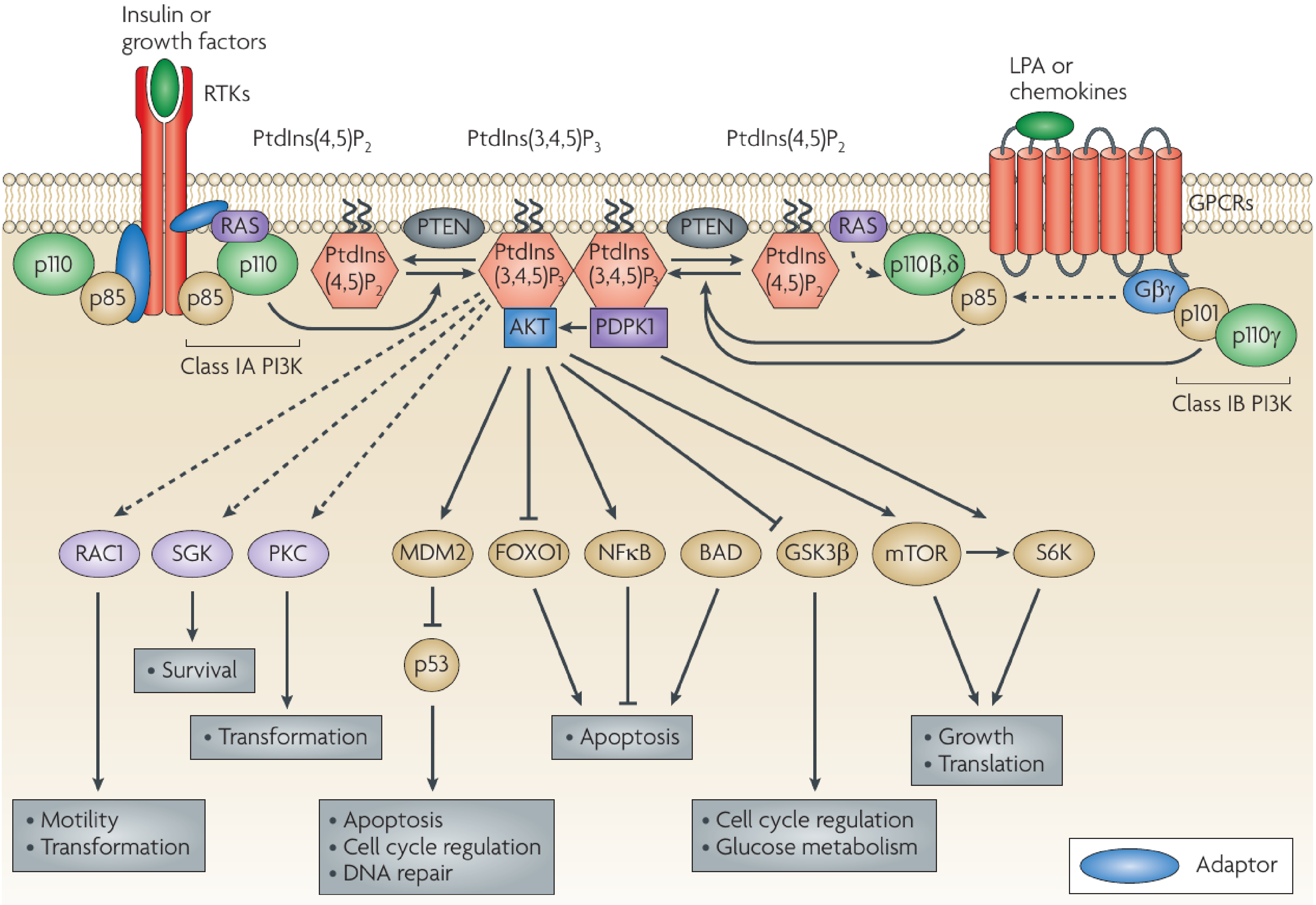


R.I.P.
September 2015

UNDERSTAND

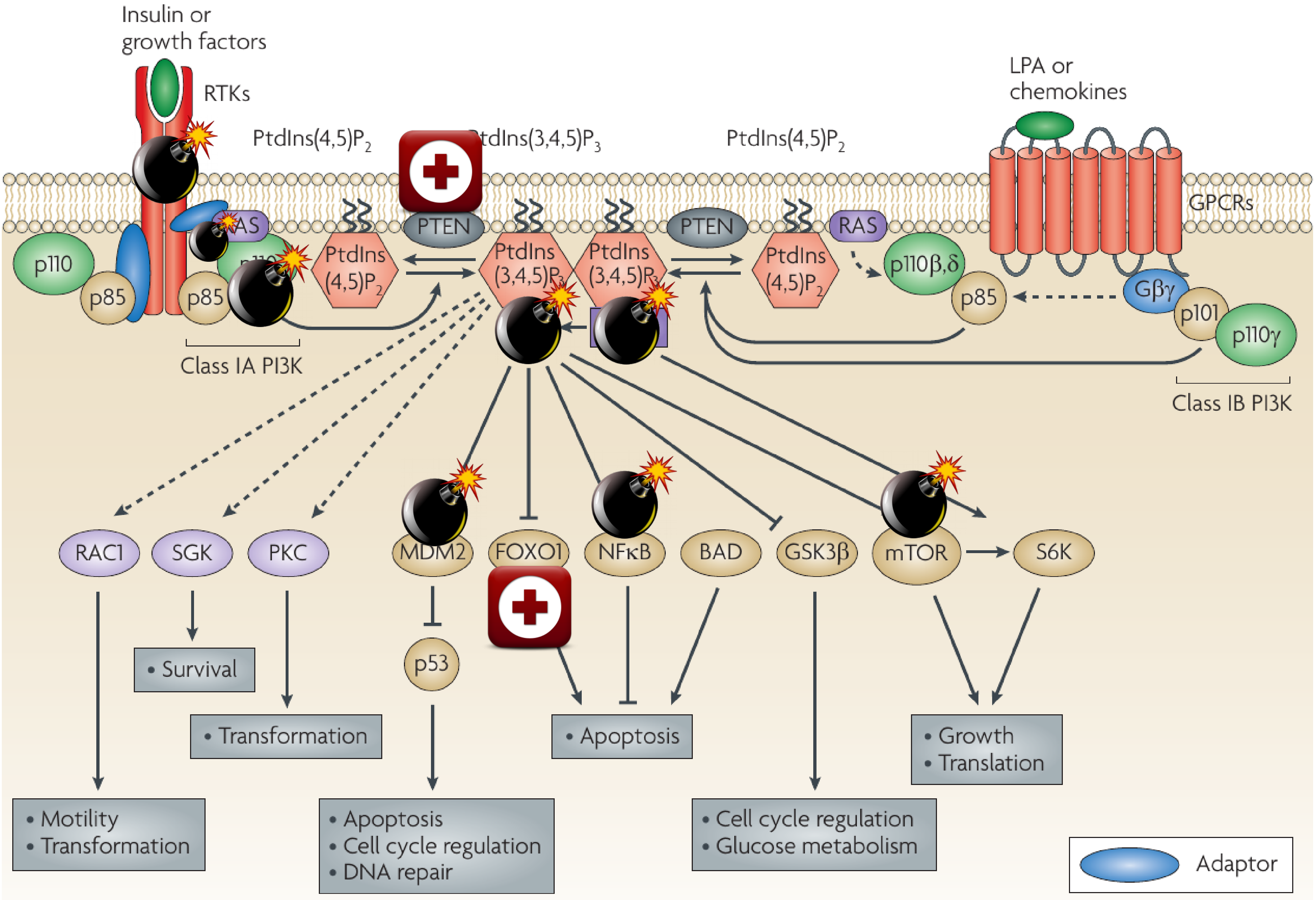
Gene regulatory networks

Davidson *et al. Science* 2002



CURE

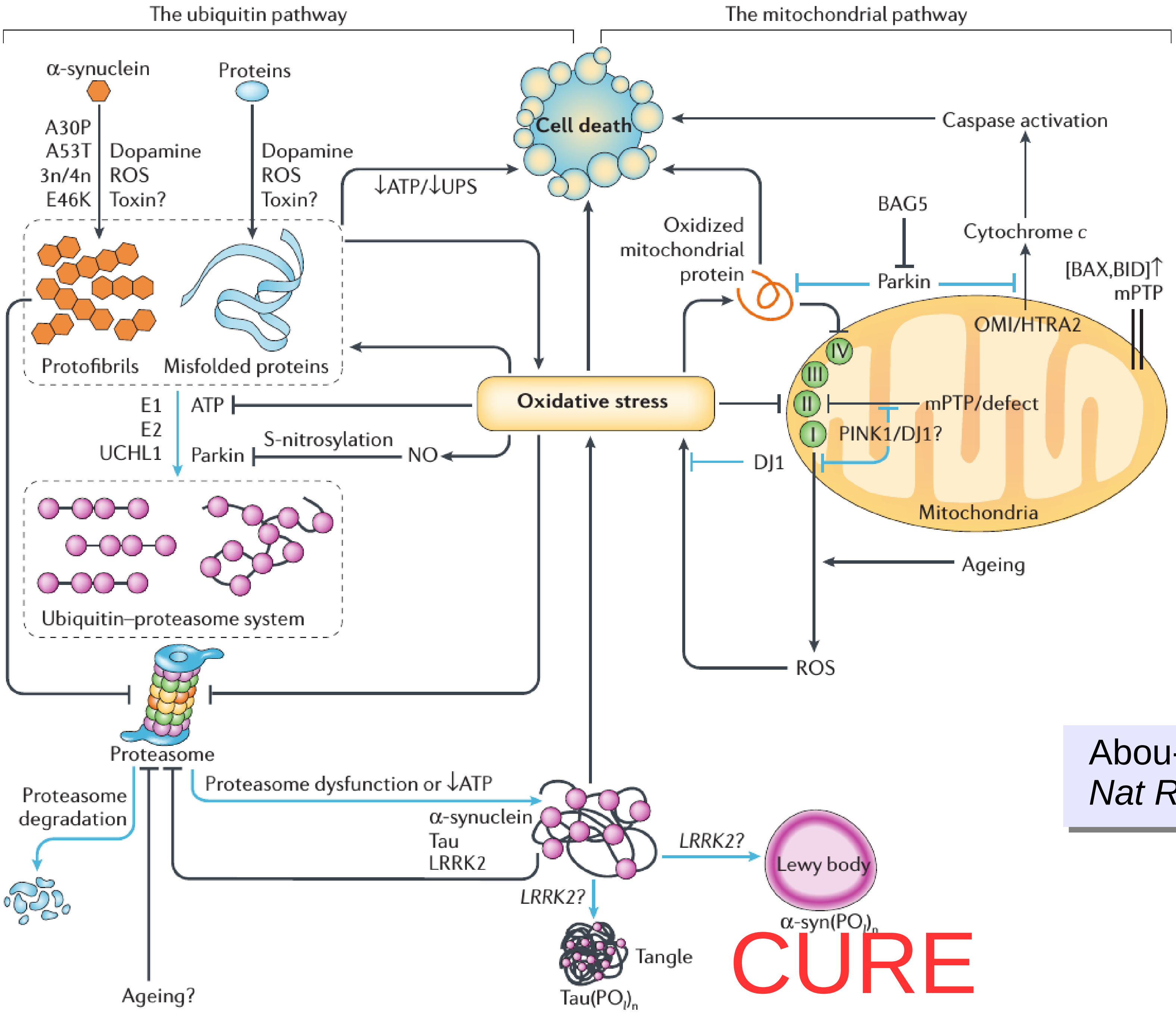
Liu *et al*. *Nat Rev Drug Discov* 2009



Liu *et al*. *Nat Rev Drug Discov* 2009

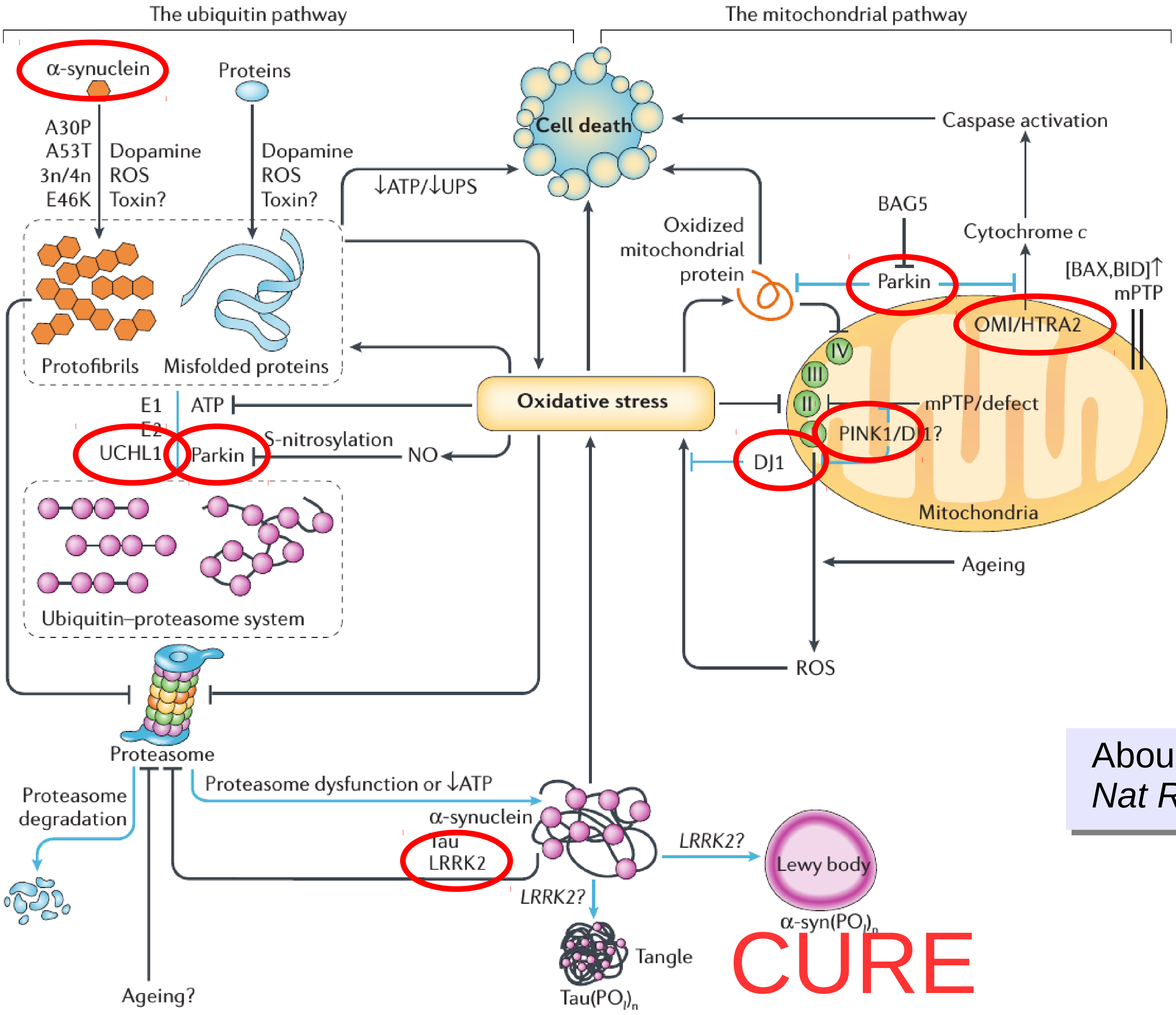
CURE

Breast cancer



Abou-Sleiman *et al.*
Nat Rev Neurosci 2006

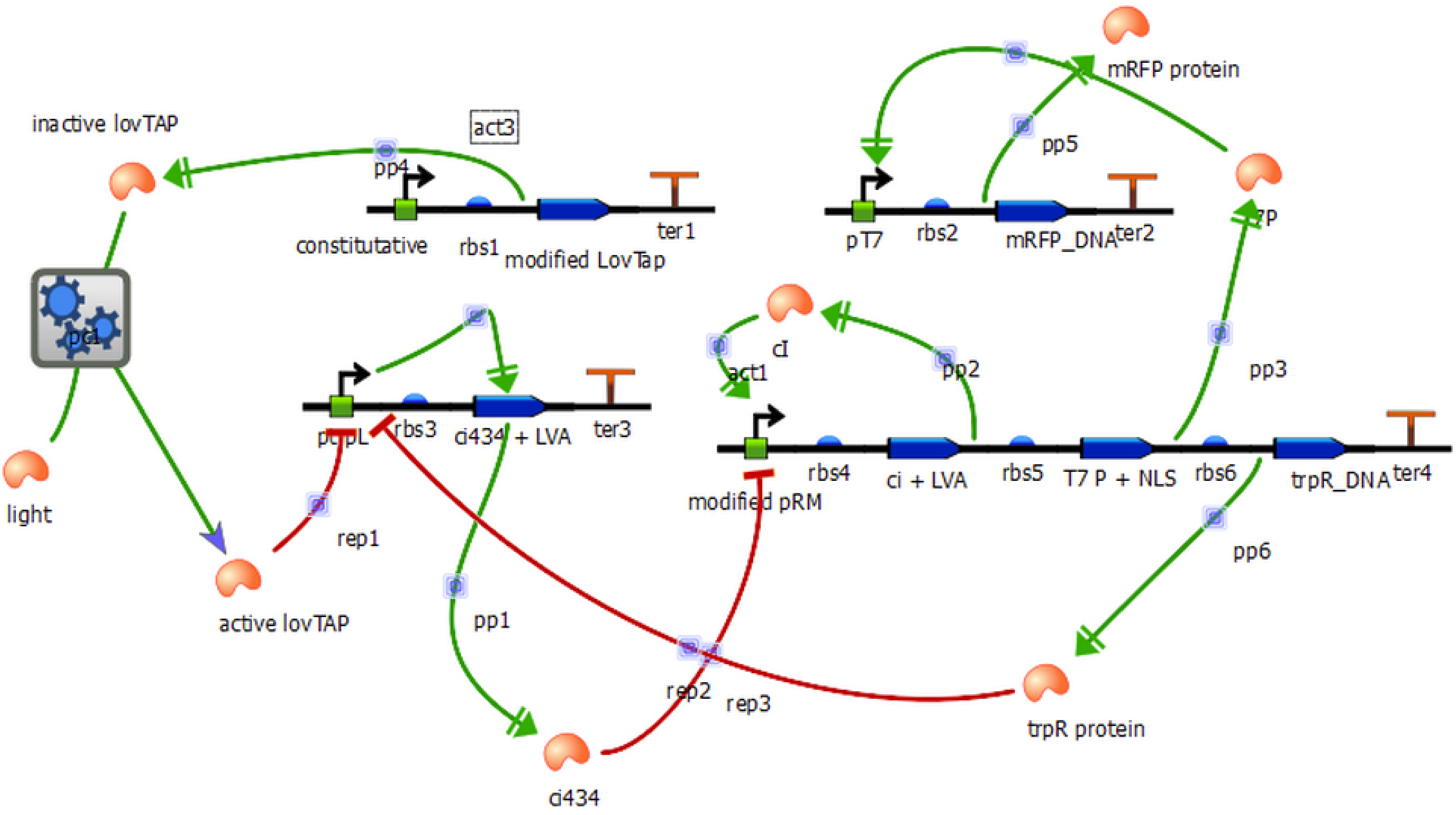
CURE
Parkinson’s disease



Abou-Sleiman *et al.*
Nat Rev Neurosci 2006

CURE

Parkinson’s disease



Team Nanjing, iGEM 2013

BUILD

Synthetic Biology

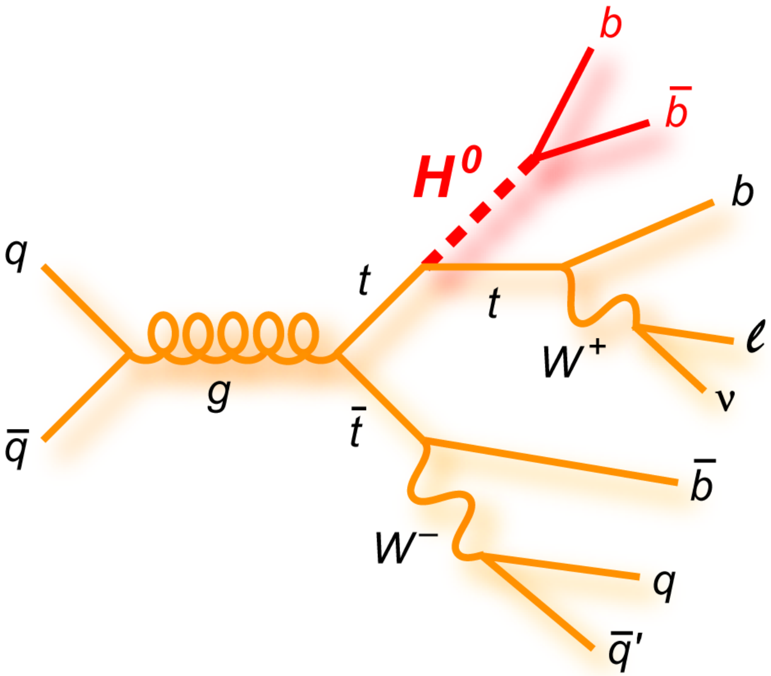
part III Systems Biology, 17 October 2017

What I cannot create,
I do not understand.

Richard Feynman

What I cannot create,
I do not understand

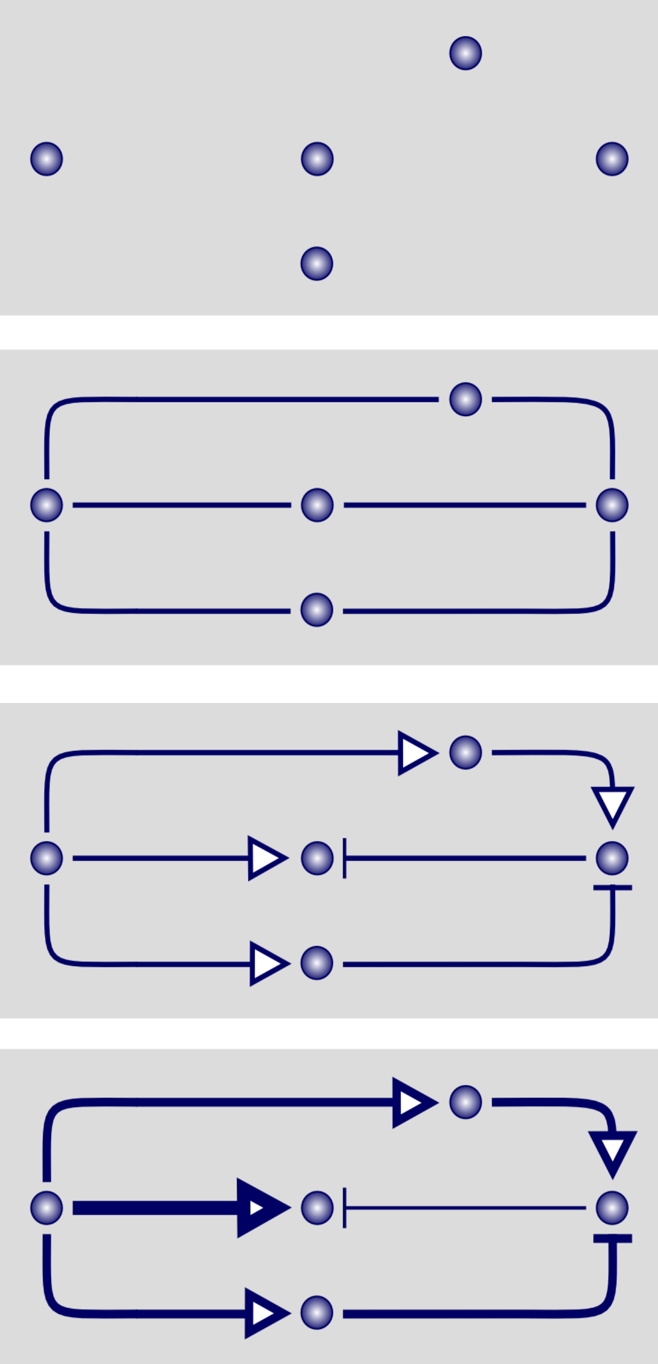
Richard Feynman



"If you cannot draw it,
you do not understand it"

Nicolas Le Novère, 2017

Layered approach for designing pathways



List of participants

Interactions between participants

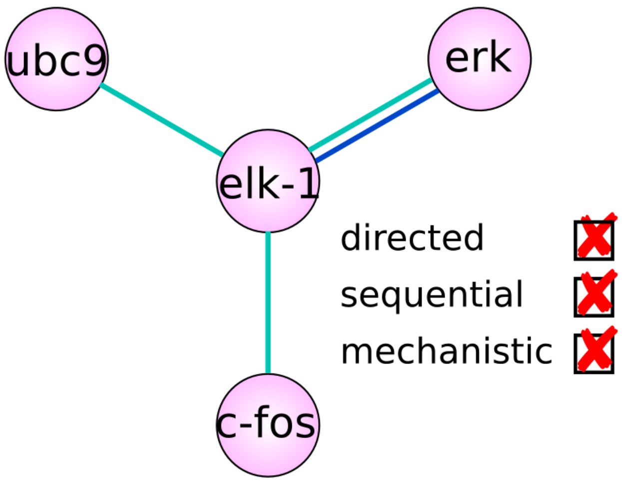
Influences of participants onto others

Quantitative relationships

Useful insights at each level

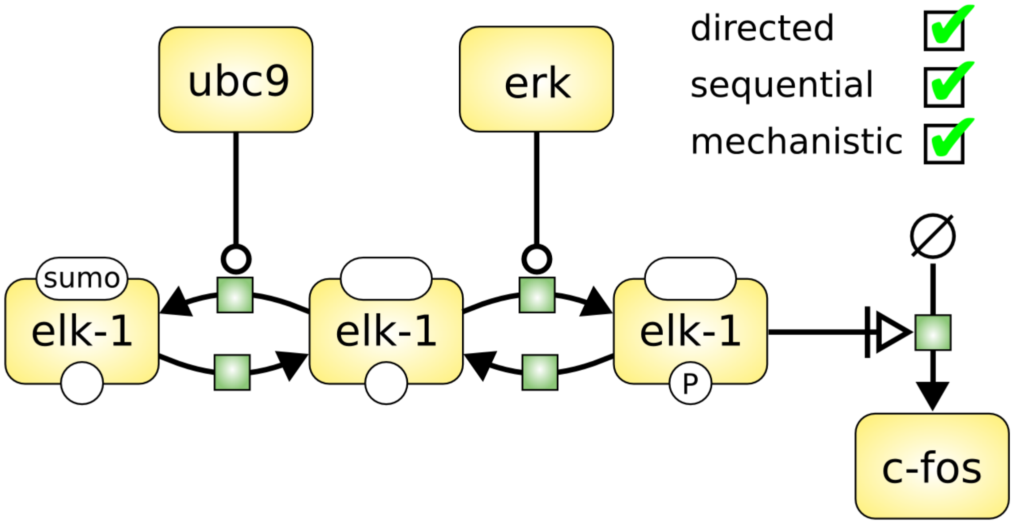
The four views of systems biology

interaction network



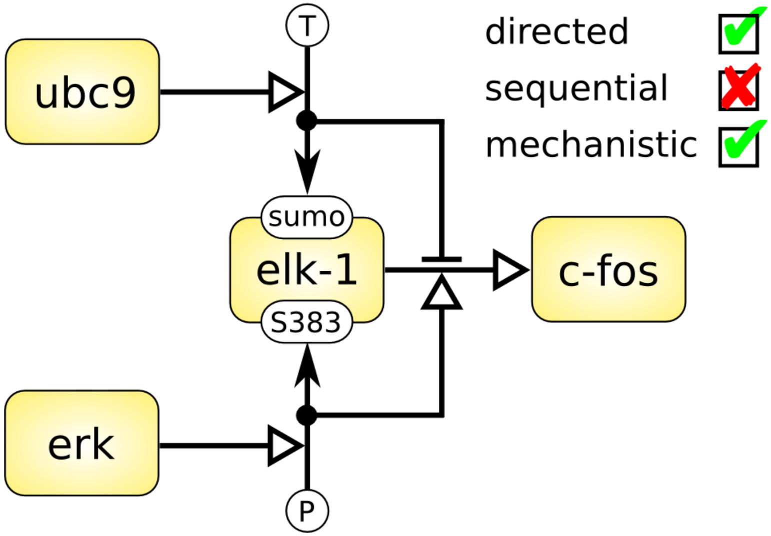
directed ☒
sequential ☒
mechanistic ☒

process descriptions



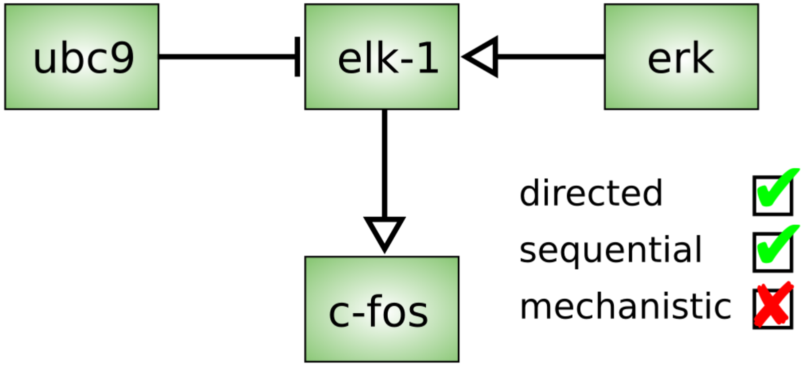
directed ☑
sequential ☑
mechanistic ☑

entity relationships



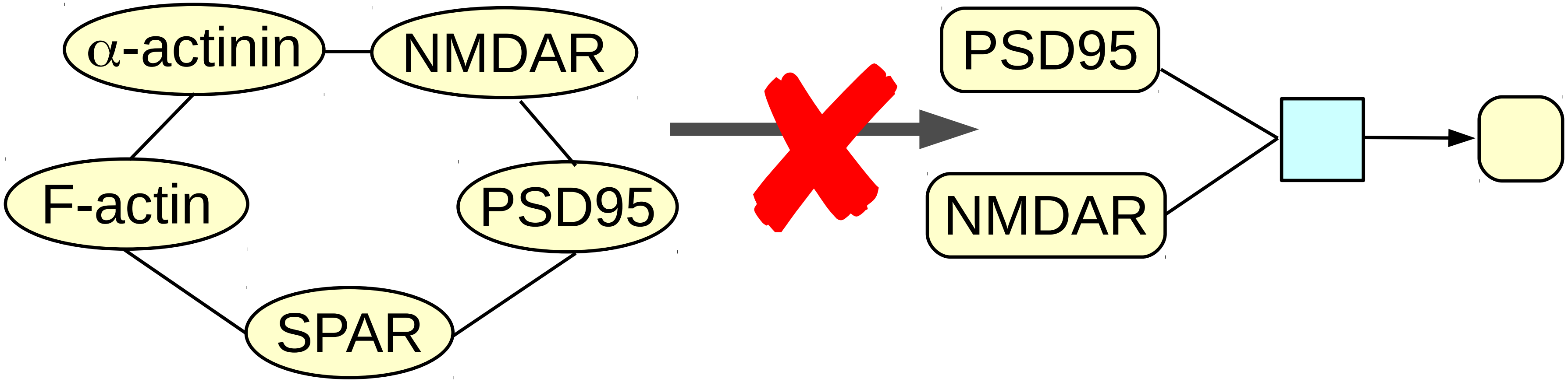
directed ☑
sequential ☒
mechanistic ☑

activity flows



directed ☑
sequential ☑
mechanistic ☒

Le Novère. *Nat Rev* Genet 2015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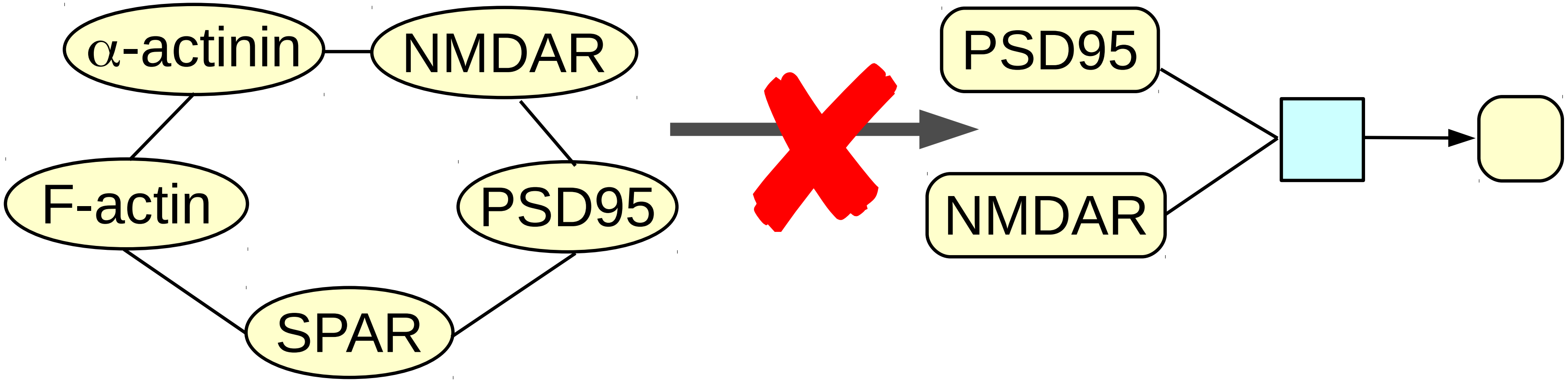
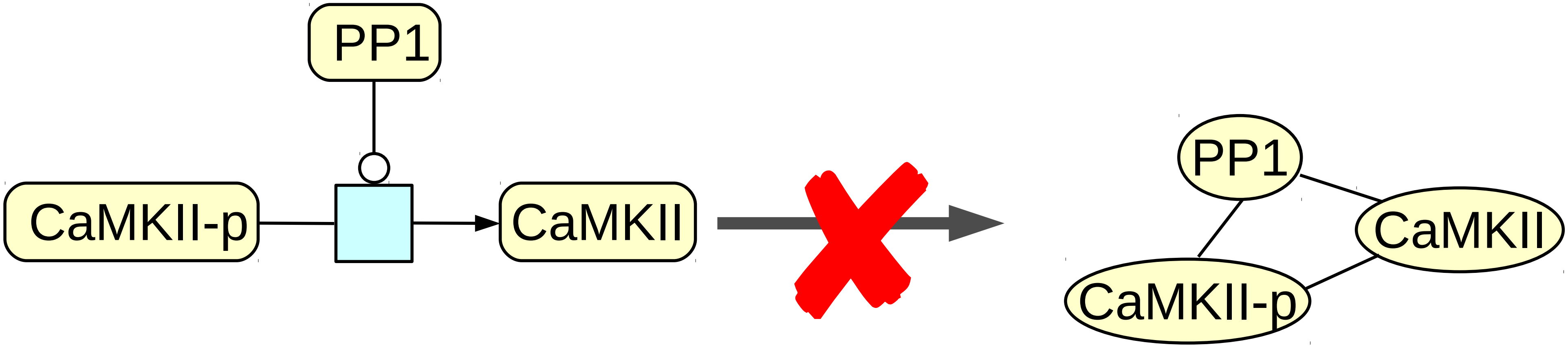
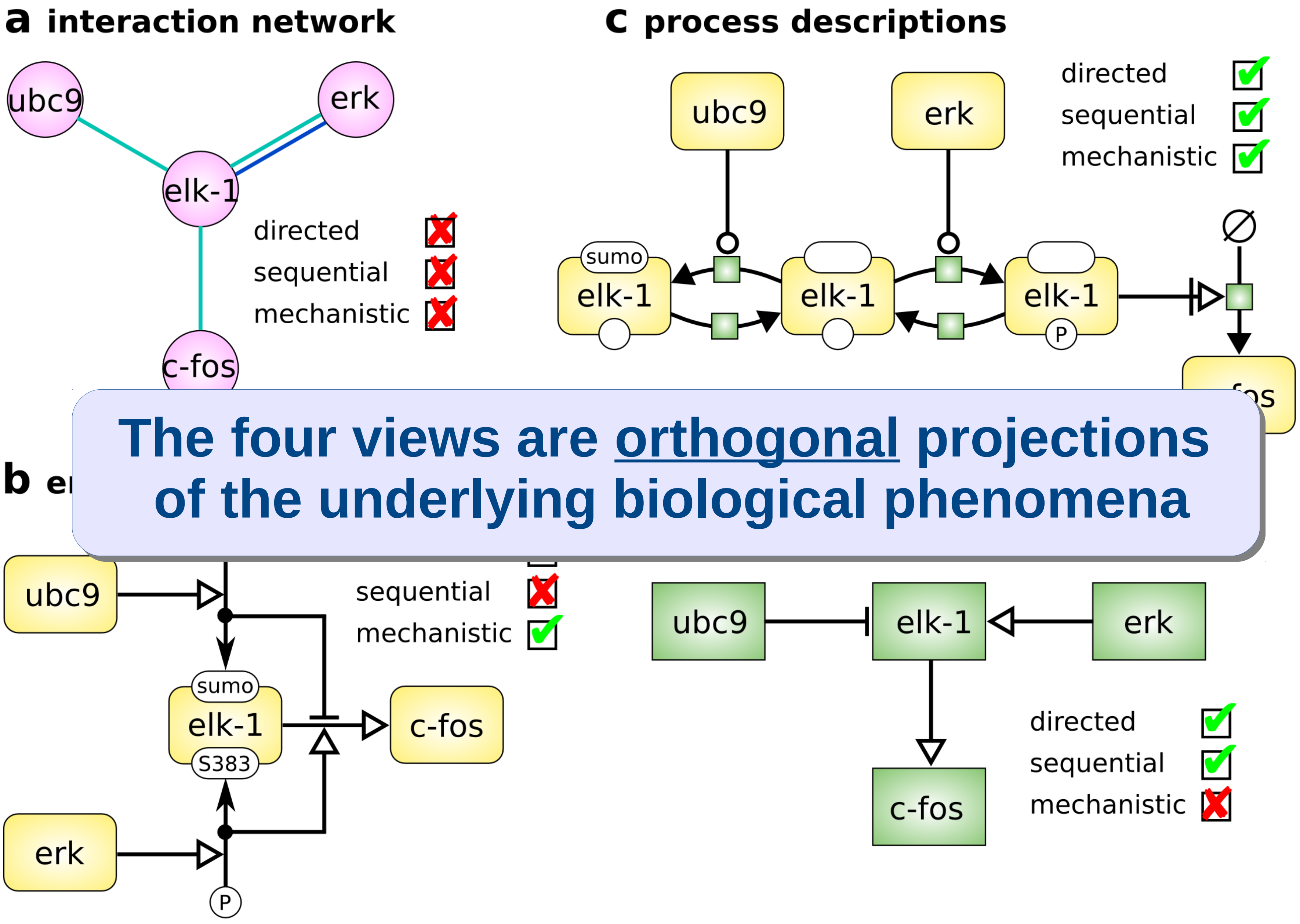
NMDAR
F-actin
PSD95
SPAR
PSD95
NMDAR

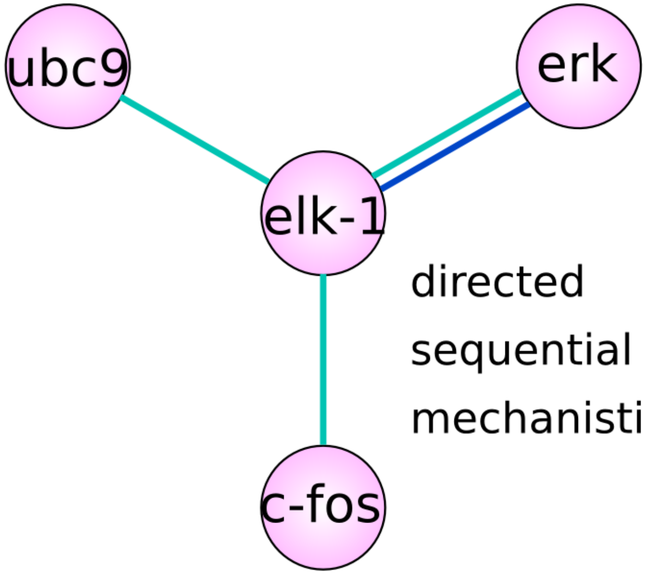

α-actinin
NMDAR
F-actin
PSD95
SPAR
PSD95
NMDAR


PP1
CaMKII-p
CaMKII
PP1
CaMKII
CaMKII-p



The four views are orthogonal projections of the underlying biological phenomena

Interaction networks



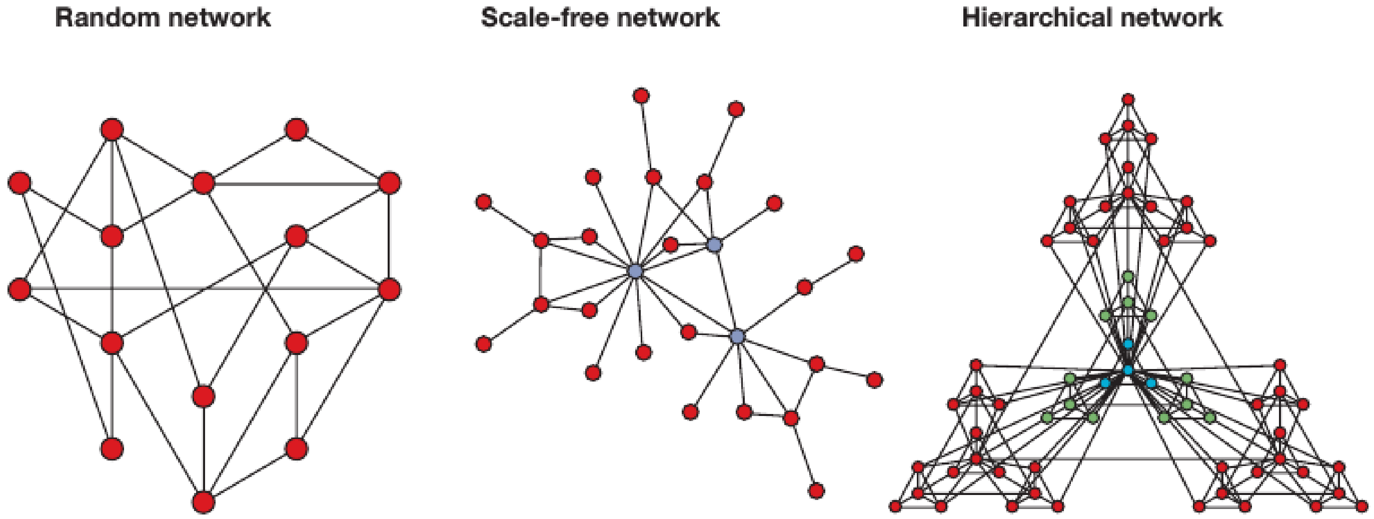
directed ☒
sequential ☒
mechanistic ☒

- Statistical modelling
- Functional genomics

What can we get from interaction networks

- Characteristics: degree of nodes (k) [k_{in}, k_{out} for directed networks], shortest and mean path lengths (l), clustering coefficient (C)

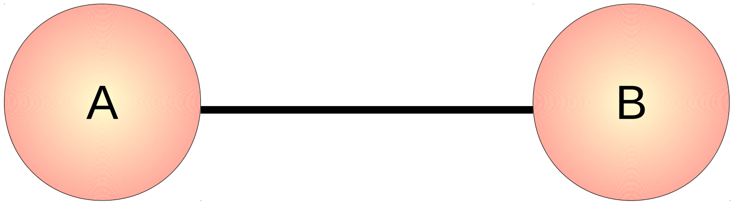
- Type of network



- Subgraphs, modules, motifs, motifs clusters …

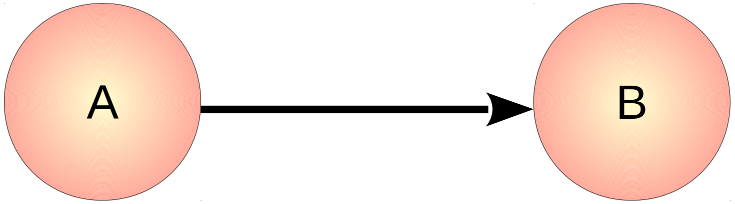
Barabasi *et al* (2004) *Nat Rev Genet*

Undirected, directed, signed



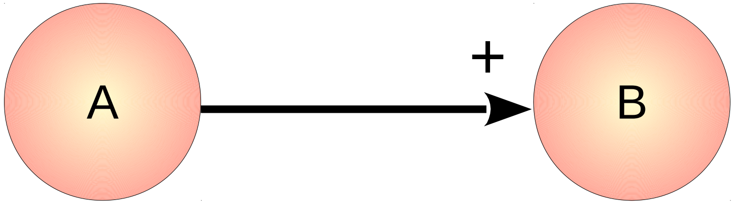
Undirected

“A interacts with B”



directed

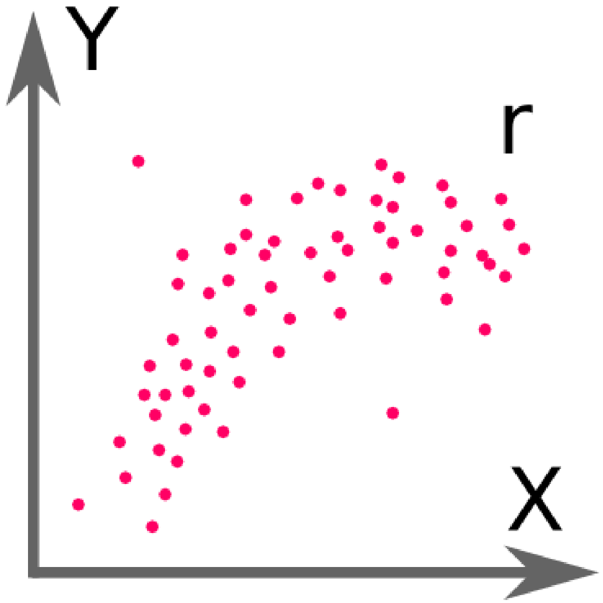
“A influences B”



Signed

A influences positively B

Network inference: Correlation



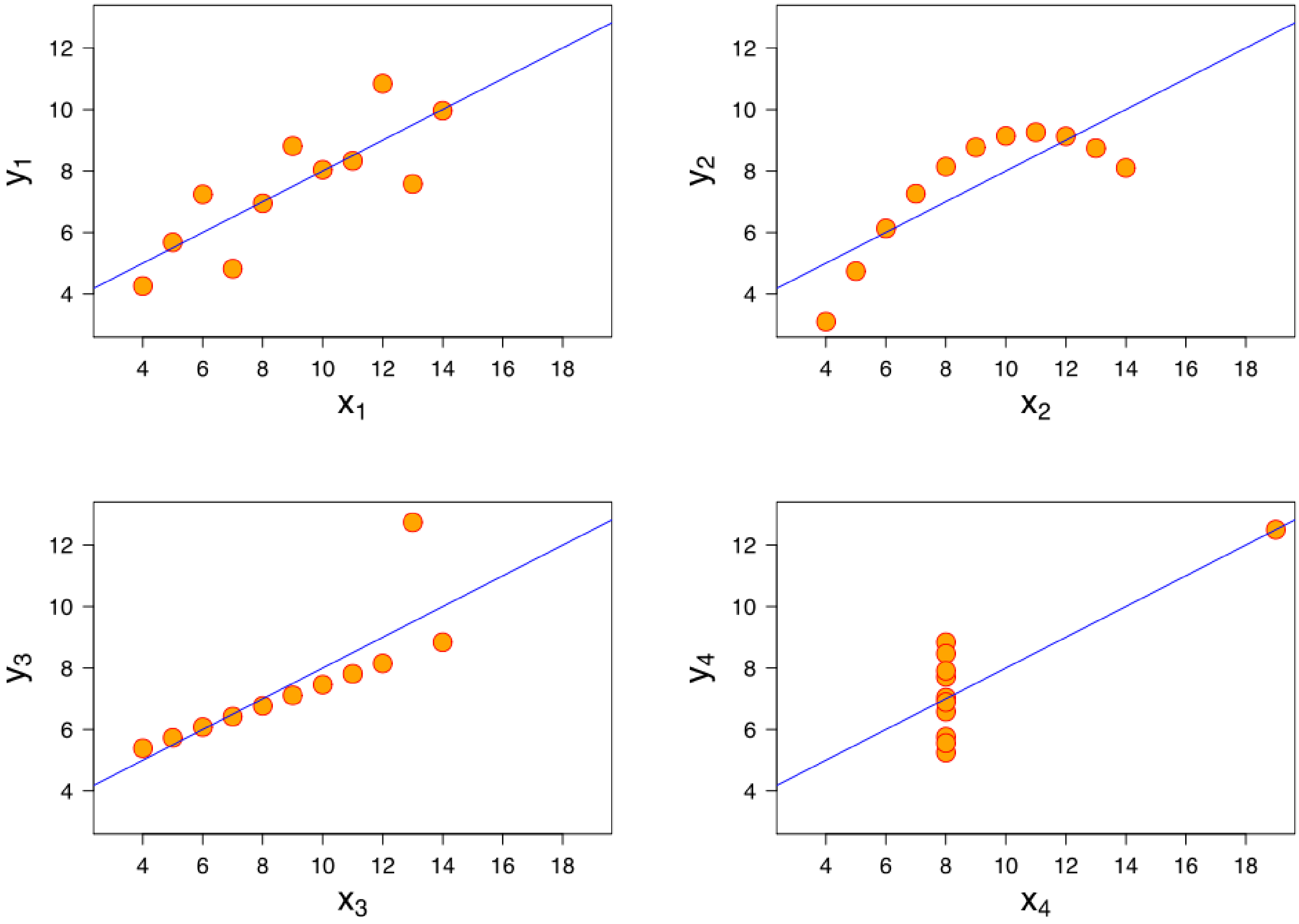
$$r = \frac{\sum_{i=1}^{n}(X_i - \bar{X})(Y_i - \bar{Y})}{\sqrt{\sum_{i=1}^{n}(X_i - \bar{X})^2}\sqrt{\sum_{i=1}^{n}(Y_i - \bar{Y})^2}}$$

Values of X are somewhat related to values of Y

Tools:

LASSO
WGCNA (R)
GENIE3 (R)
TIGRESS (MatLab)

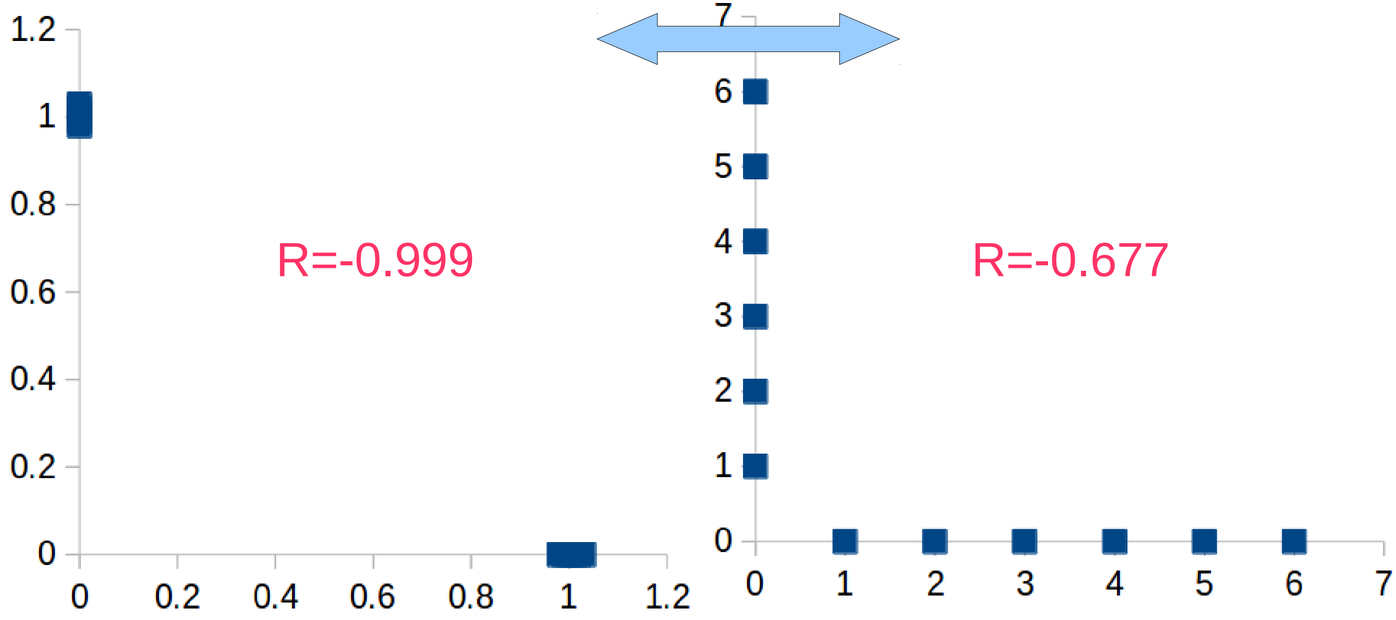
Warning: Correlation does not tell nature of relation



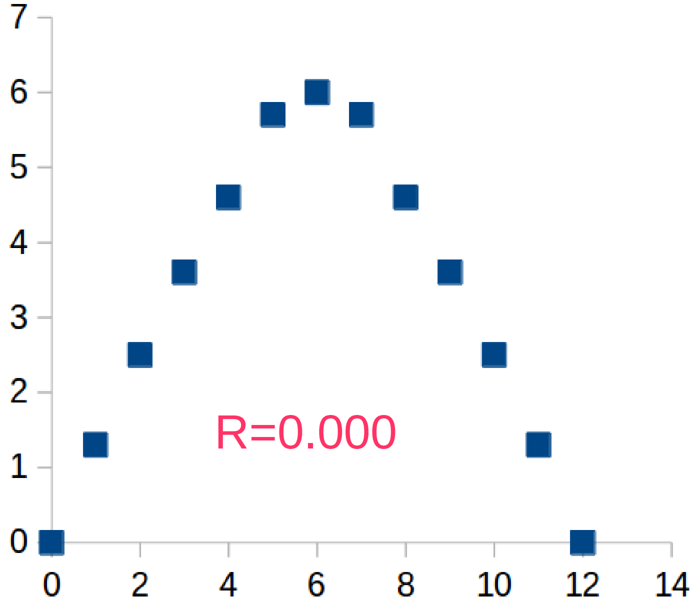
The four datasets have the same Pearson correlation

Correlations coefficients might be misleading

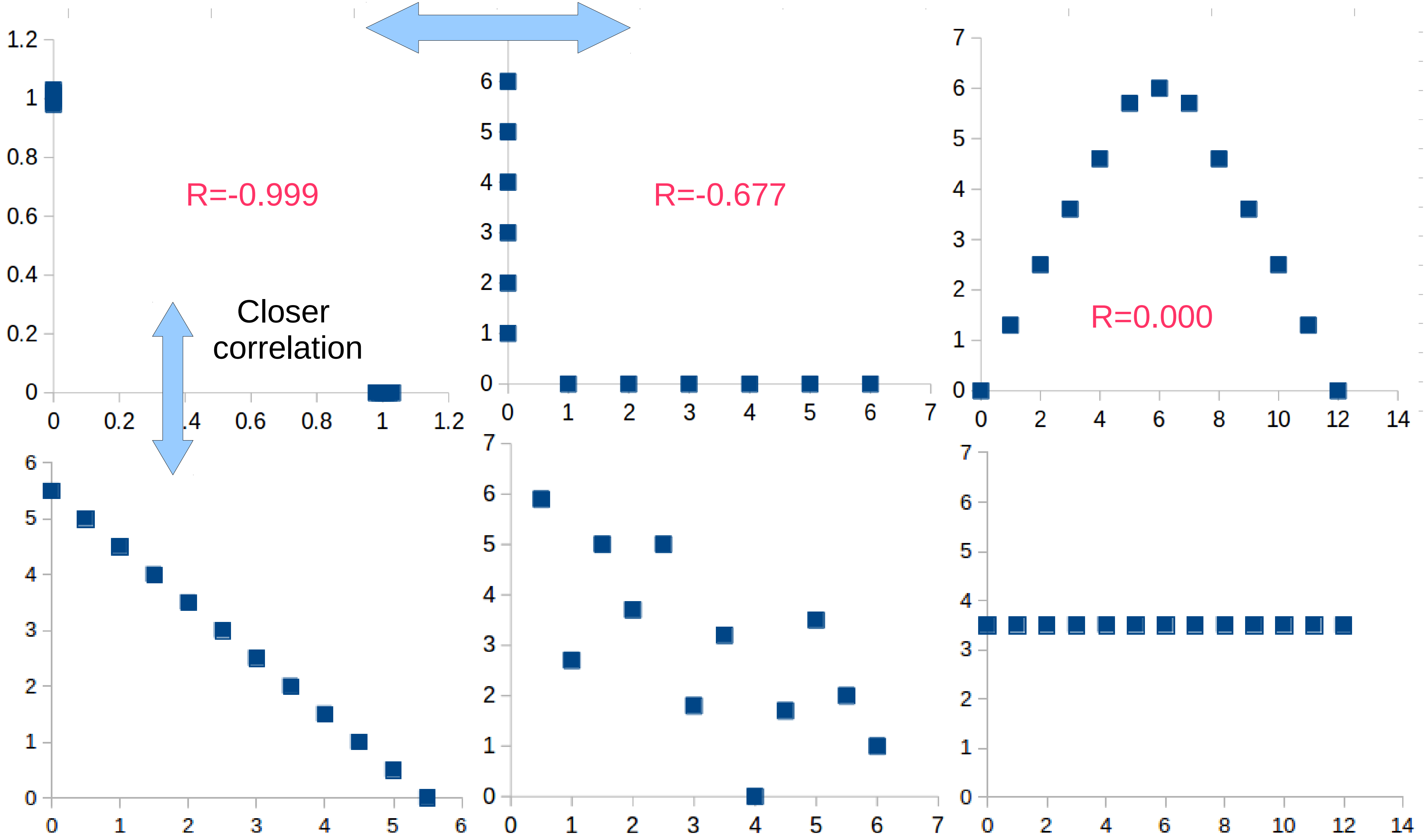
Different correlation,
same biological meaning



Undetected correlation



Correlations coefficients might be misleading



Closer biological meaning

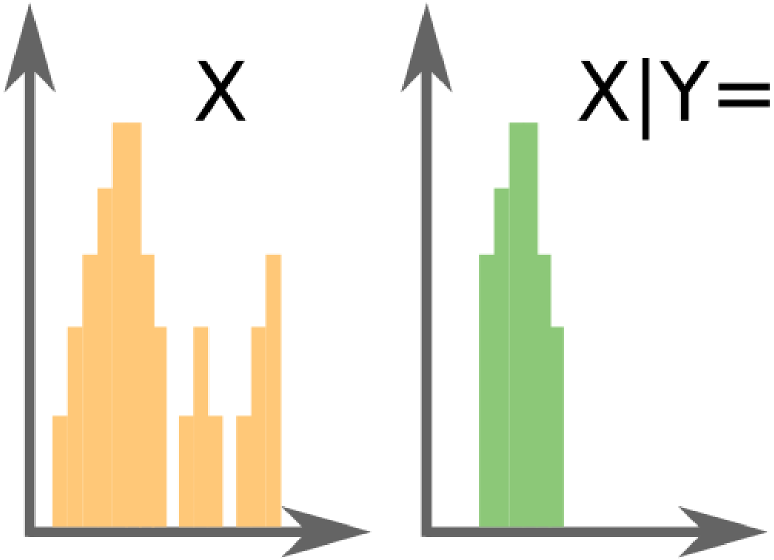
Closer correlation

R=-0.999

R=-0.677

R=0.000

Network inference: Information Theory



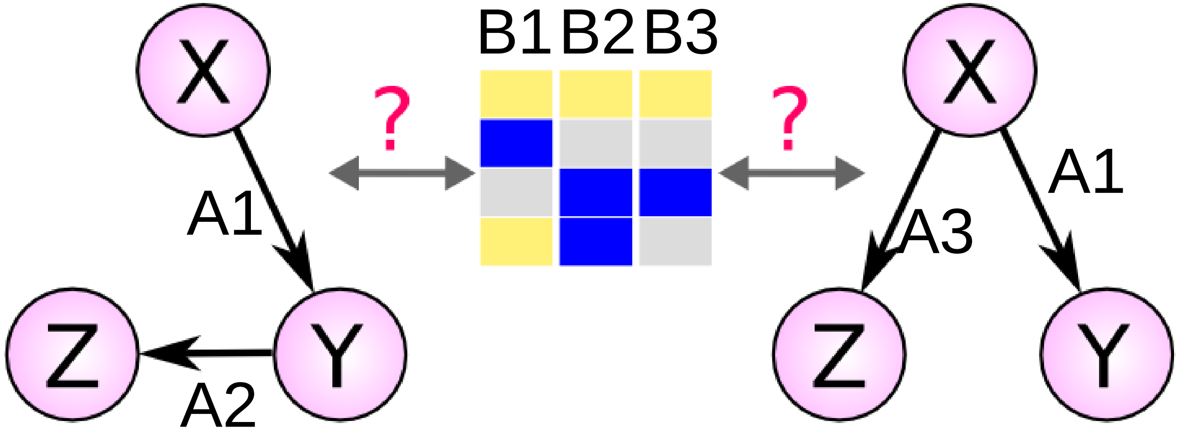
$$I(X,Y) = H(X) - H(X|Y)$$

E.g. mutual information:
knowledge of the value of Y reduces the uncertainty on the values of X

Tools:

ARACNE
CLR
(both in R package *minet*)

Network inference: Bayesian inference

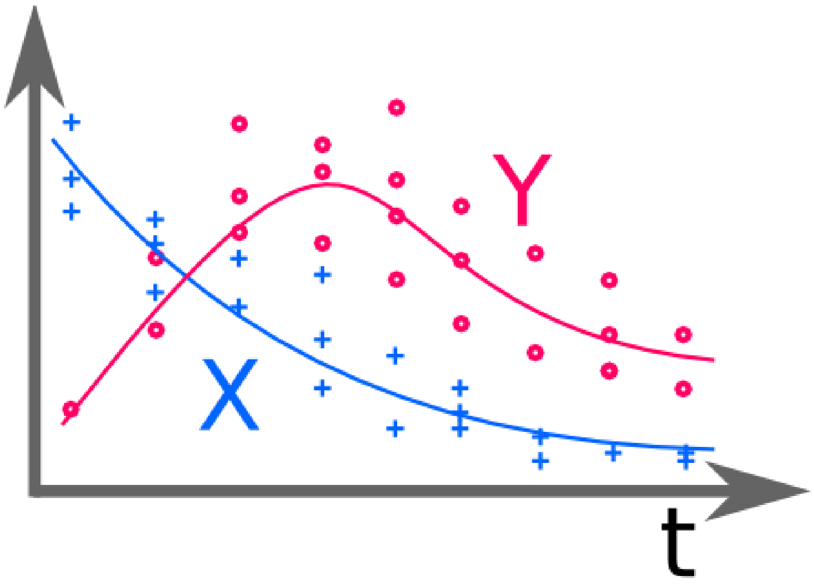


$$P(A|B) = \frac{P(B|A)P(A)}{P(B)}$$

Which network most probably generates this dataset?

Tools: BANJO (Java), catnet (R)

Network inference: ODEs



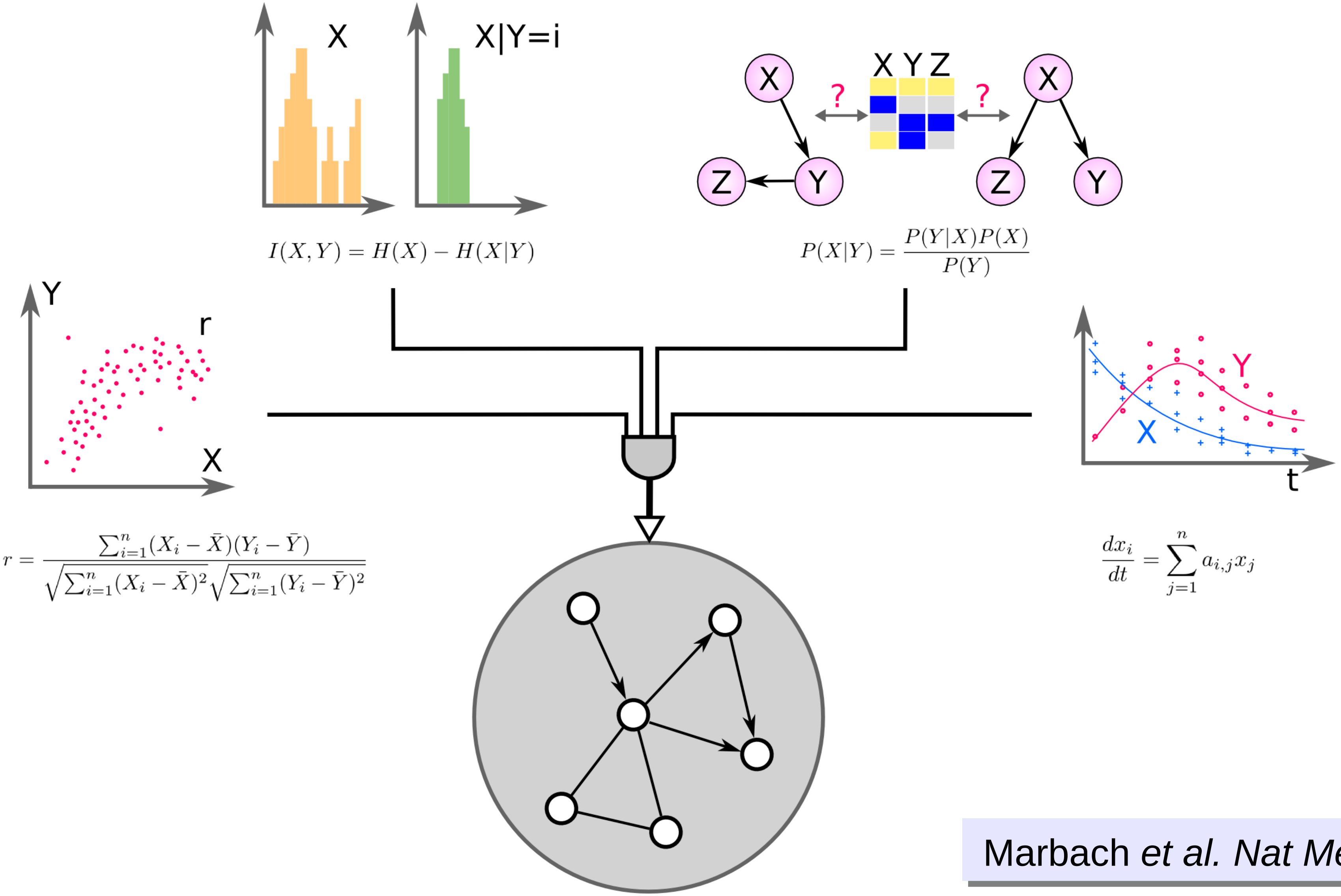
$$\frac{dx_i}{dt} = \sum_{j=1}^{n} a_{i,j} x_j$$

Equations describing time courses best

Tools:

Inferelator

As always: use several approaches



$$I(X,Y) = H(X) - H(X|Y)$$

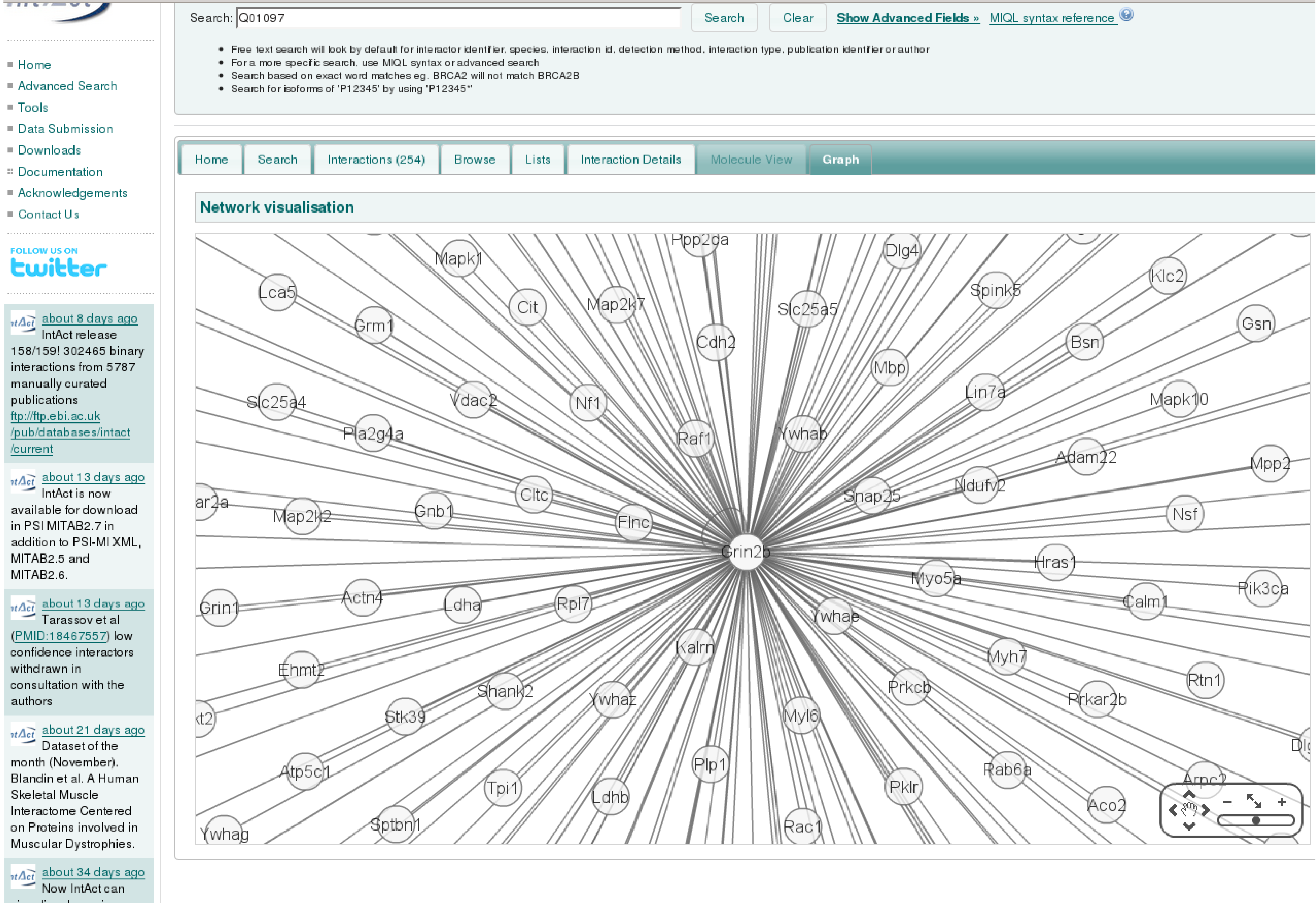
$$P(X|Y) = \frac{P(Y|X)P(X)}{P(Y)}$$

$$r = \frac{\sum_{i=1}^{n}(X_i - \bar{X})(Y_i - \bar{Y})}{\sqrt{\sum_{i=1}^{n}(X_i - \bar{X})^2}\sqrt{\sum_{i=1}^{n}(Y_i - \bar{Y})^2}}$$

$$\frac{dx_i}{dt} = \sum_{j=1}^{n} a_{i,j}x_j$$

Marbach *et al. Nat Meth* 2012

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



Search: Q01097

- Free text search will look by default for interactor identifier, species, interaction id, detection method, interaction type, publication identifier or author
- For a more specific search, use MIQL syntax or advanced search
- Search based on exact word matches eg. BRCA2 will not match BRCA2B
- Search for isoforms of 'P12345' by using 'P12345*'

about 8 days ago IntAct release 158/159! 302465 binary interactions from 5787 manually curated publications ftp://ftp.ebi.ac.uk/pub/databases/intact/current

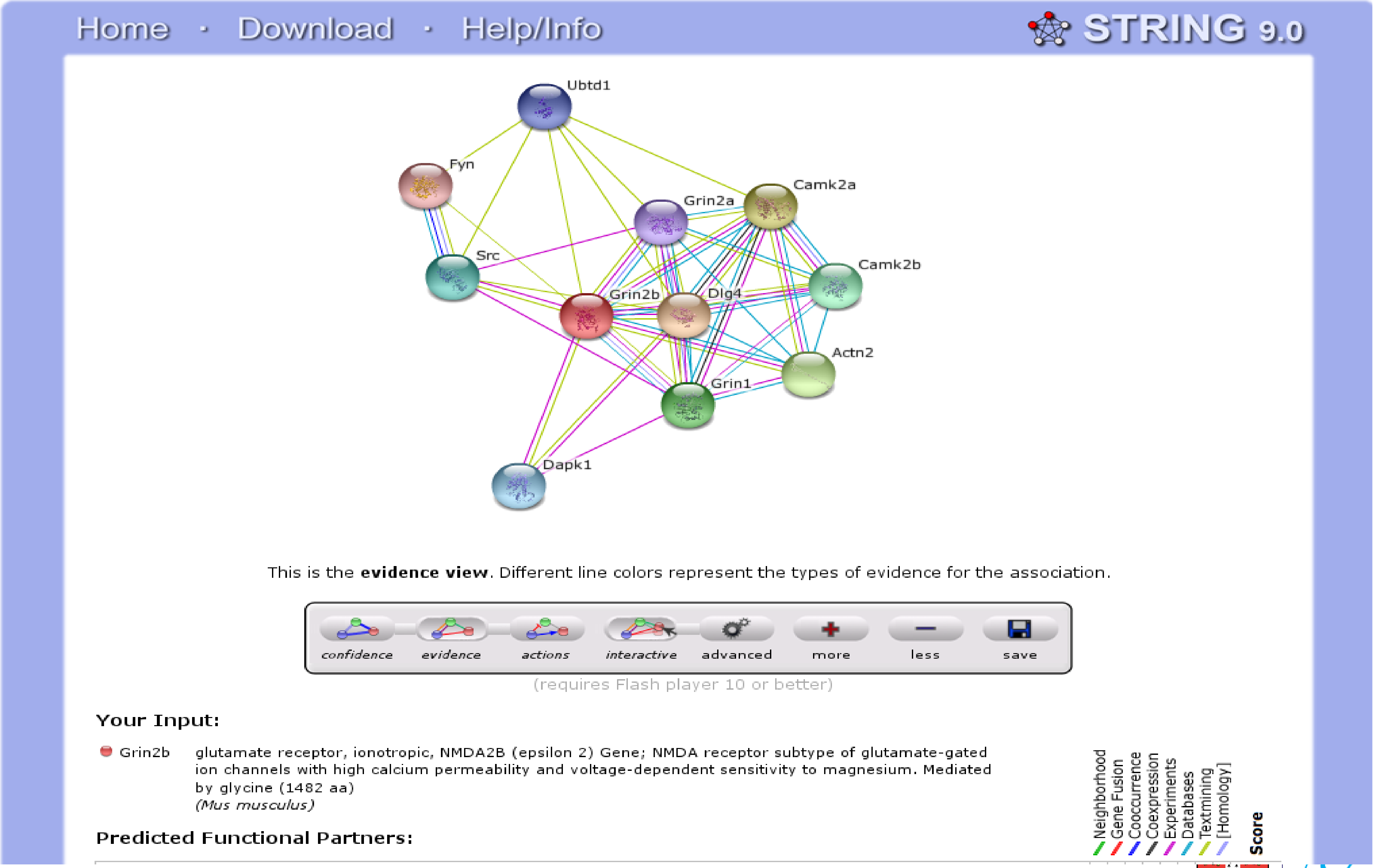
about 13 days ago IntAct is now available for download in PSI MITAB2.7 in addition to PSI-MI XML, MITAB2.5 and MITAB2.6.

about 13 days ago Tarassov et al (PMID:18467557) low confidence interactors withdrawn in consultation with the authors

about 21 days ago Dataset of the month (November). Blandin et al. A Human Skeletal Muscle Interactome Centered on Proteins involved in Muscular Dystrophies.

about 34 days ago Now IntAct can

http://string-db.org/



This is the **evidence view**. Different line colors represent the types of evidence for the association.

(requires Flash player 10 or better)

Your Input:

● Grin2b glutamate receptor, ionotropic, NMDA2B (epsilon 2) Gene; NMDA receptor subtype of glutamate-gated ion channels with high calcium permeability and voltage-dependent sensitivity to magnesium. Mediated by glycine (1482 aa)
(Mus musculus)

Predicted Functional Partners:

The Systems Biology Graphical Notation

Le Novère *et al. Nat Biotechnol* (2009)

Unambiguous consensual visual notation

- An unambiguous way of graphically describing and interpreting biochemical and cellular events
- Limited amount of symbols
  Re-use existing symbols
  ☞ Smooth learning curve
- Can represent logical or mechanistic models, biochemical pathways, at different levels of granularity
- Detailed technical specification, precise data-models, standard API and growing software support
- Developed over ten years by a diverse community, including biologists, modellers, computer scientists etc.

Systems Biology Graphical Notation: Activity Flow language Level 1

Version 1.2

Date: July 27, 2015

Editors:

Huaiyu Mi	*University of Southern California, USA*
Falk Schreiber	*Monash University, Australia & MLU Halle, Germany*
Stuart Moodie	*Eight Pillars Ltd, UK*
Tobias Czauderna	*Monash University, Australia*
Emek Demir	*Memorial Sloan-Kettering Institute, USA*
Robin Haw	*Ontario Institute for Cancer Research, Canada*
Augustin Luna	*Memorial Sloan-Kettering Institute, USA*
Nicolas Le Novère	*Babraham Institute, UK*
Anatoly Sorokin	*Institute of Cell Biophysics RAS, RU*
Alice Villéger	*Freelance IT Consultant, UK*

To discuss any aspect of SBGN, please send your messages to the mailing list `sbgn-discuss@caltech.edu`. *To get subscribed to the mailing list or to contact us directly, please write to* `sbgn-editors@lists.sourceforge.net`. *Bug reports and specific comments about the specification should be entered in the issue tracker* `http://sf.net/p/sbgn/sbgn-af-11/`.

SBGN

Systems Biology Graphical Notation: Entity Relationship language Level 1

Version 2.0

Date: August 8, 2015

Editors:

Anatoly Sorokin	*Institute of Cell Biophysics RAS, RU*
Nicolas Le Novère	*Babraham Institute, UK*
Augustin Luna	*Memorial Sloan-Kettering Institute, USA*
Tobias Czauderna	*Monash University, Australia*
Emek Demir	*Memorial Sloan-Kettering Institute, USA*
Robin Haw	*Ontario Institute for Cancer Research, Canada*
Huaiyu Mi	*University of Southern California, USA*
Stuart Moodie	*Eight Pillars Ltd, UK*
Falk Schreiber	*Monash University, Australia & MLU Halle, Germany*
Alice Villéger	*Freelance IT Consultant, UK*

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SBGN

Systems Biology Graphical Notation: Process Description language Level 1

Version 1.3

14 February, 2010

Editors:

Stuart Moodie	*University of Edinburgh, UK*
Nicolas Le Novère	*EMBL European Bioinformatics Institute, UK*
Emek Demir	*Sloan-Kettering Institute, USA*
Huaiyu Mi	*University of Southern California, USA*
Alice Villéger	*University of Manchester, UK*

To discuss any aspect of SBGN, please send your messages to the mailing list `sbgn-discuss@sbgn.org`. *To get subscribed to the mailing list or to contact us directly, please write to* `sbgn-editors@lists.sourceforge.net`. *Bug reports and specific comments about the specification should be entered in the issue tracker* `http://p.sf.net/sbgn/pd_tracker`.

SBGN

SBGN-ML

```
<?xml version="1.0" encoding="UTF-8"?>
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                <!-- Line breaks are allowed in the text attribute -->
                <bbox x="40" y="120" w="60" h="60"/>
        </glyph>
        <glyph class="simple chemical" id="glyph_ethanal">
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        </glyph>
        <glyph class="macromolecule" id="glyph_adh1">
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                <bbox x="106" y="20" w="108" h="60"/>
        </glyph>
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        <glyph class="simple chemical" id="glyph_nadh">
                <label text="NADH" />
                <bbox x="300" y="150" w="60" h="60"/>
        </glyph>

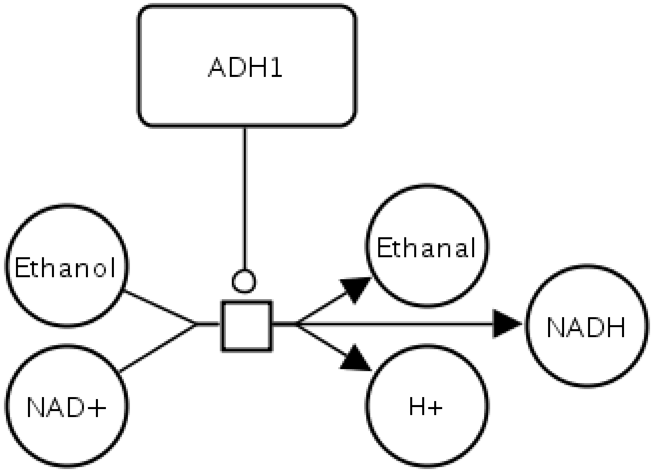
        <glyph class="process" orientation="horizontal" id="pn1">
                <bbox x="148" y="168" w="24" h="24"/>
                <port x="136" y="180" id="pn1.1"/>
                <port x="184" y="180" id="pn1.2"/>
        </glyph>

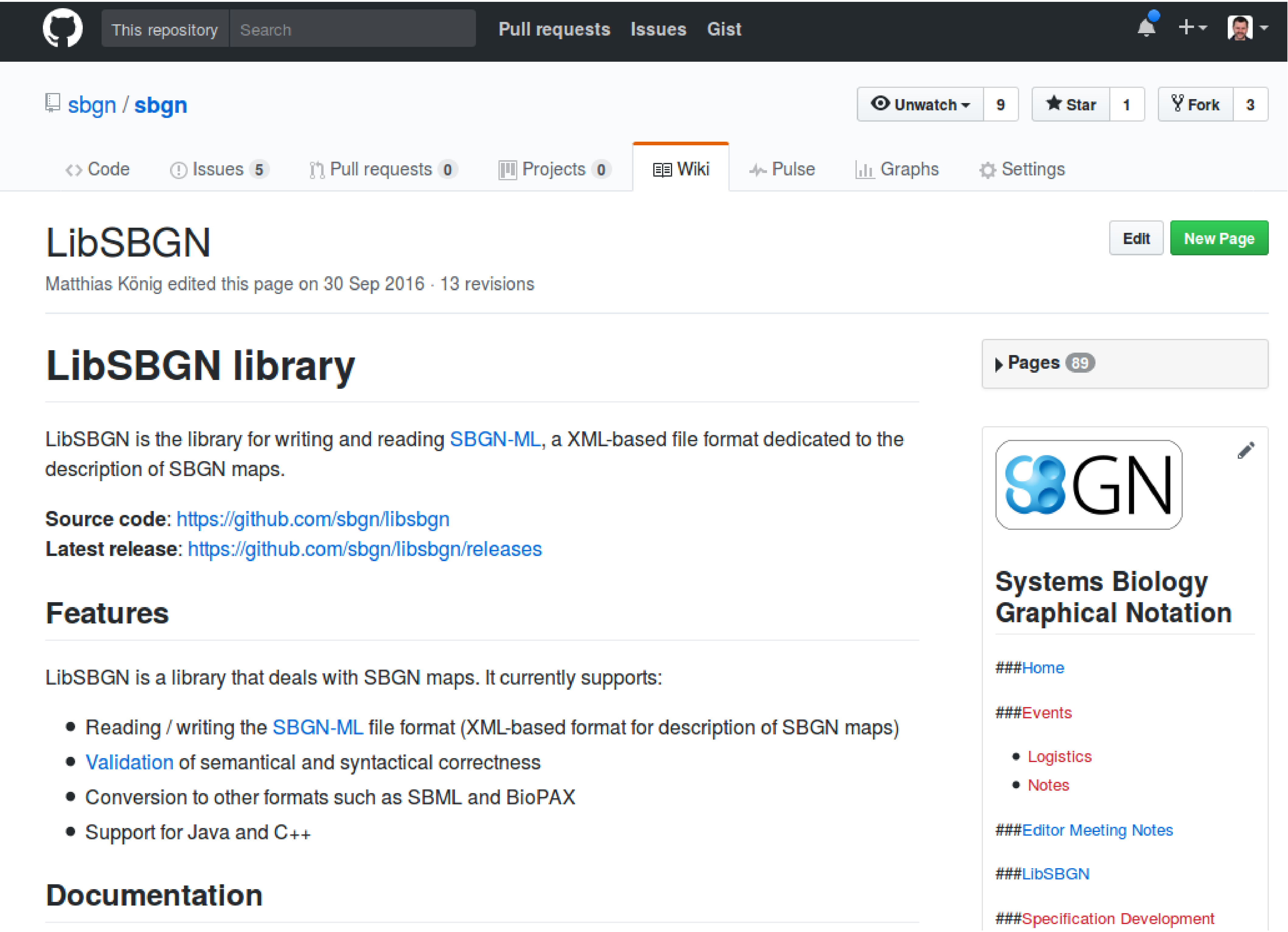
        <arc class="consumption" source="glyph1" target="pn1.1"
        id="a01">
                <start x="98" y="160" />
                <end x="136" y="180" />
        </arc>

        <arc class="production" source="pn1.2" target="glyph_nadh"
        id="a02">
                <start x="184" y="180" />
                <end x="300" y="180" />
        </arc>

        <arc class="catalysis" source="glyph_adh1" target="pn1"
        id="a03">
                <start x="160" y="80" />
                <end x="160" y="168" />
        </arc>

        <arc class="production" source="pn1.2" target="glyph_h"
        id="a04">
                <start x="184" y="180" />
                <end x="224" y="202" />
        </arc>
        <arc class="production" source="pn1.2" target="glyph_ethanal"
        id="a05">
                <start x="184" y="180" />
                <end x="224" y="154" />
```





LibSBGN

Matthias König edited this page on 30 Sep 2016 · 13 revisions

LibSBGN library

LibSBGN is the library for writing and reading SBGN-ML, a XML-based file format dedicated to the description of SBGN maps.

Source code: https://github.com/sbgn/libsbgn
Latest release: https://github.com/sbgn/libsbgn/releases

Features

LibSBGN is a library that deals with SBGN maps. It currently supports:

- Reading / writing the SBGN-ML file format (XML-based format for description of SBGN maps)
- Validation of semantical and syntactical correctness
- Conversion to other formats such as SBML and BioPAX
- Support for Java and C++

Documentation

Systems Biology Graphical Notation

###Home

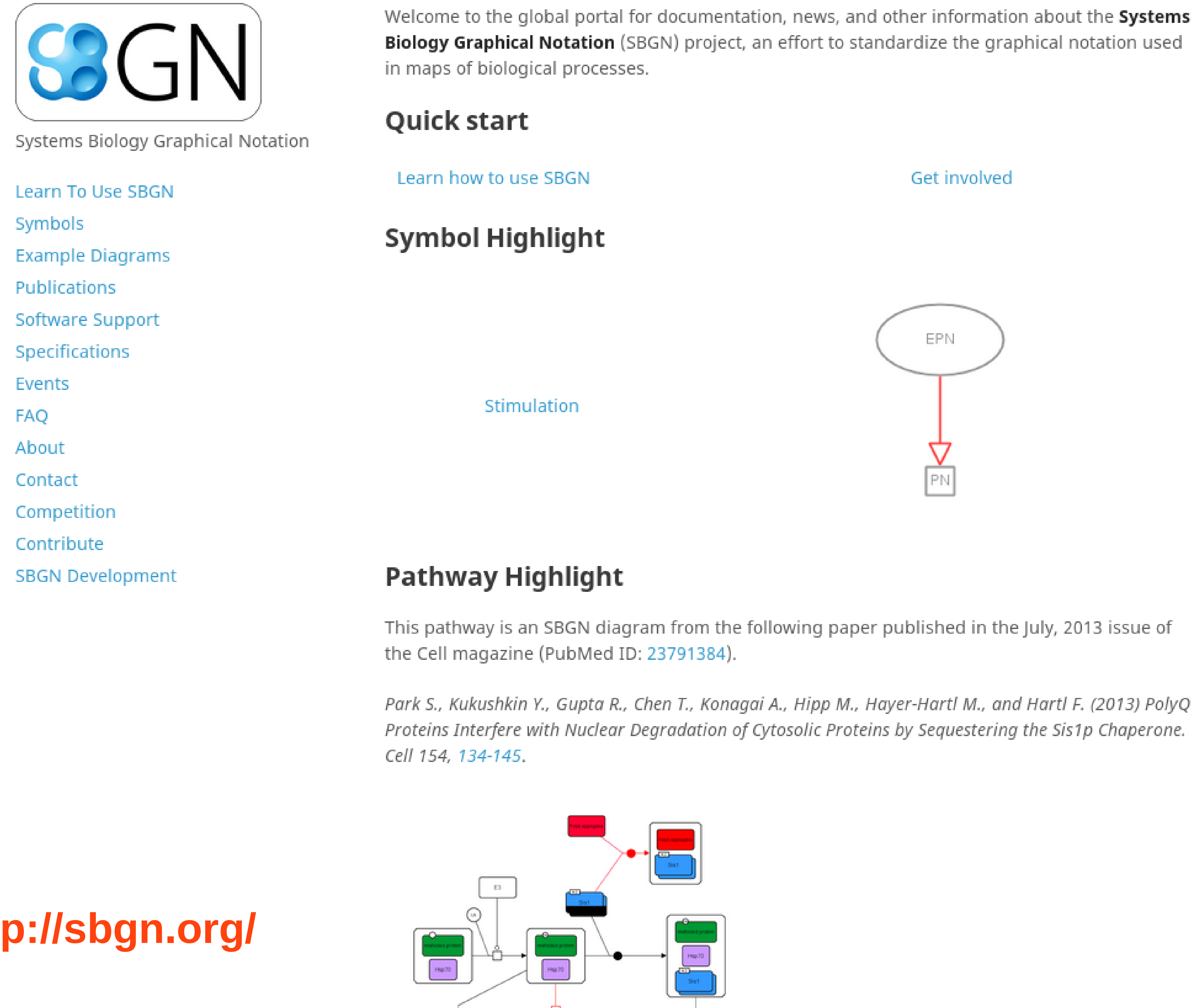
###Events

- Logistics
- Notes

###Editor Meeting Notes

###LibSBGN

###Specification Development



Systems Biology Graphical Notation

- Learn To Use SBGN
- Symbols
- Example Diagrams
- Publications
- Software Support
- Specifications
- Events
- FAQ
- About
- Contact
- Competition
- Contribute
- SBGN Development

Welcome to the global portal for documentation, news, and other information about the **Systems Biology Graphical Notation** (SBGN) project, an effort to standardize the graphical notation used in maps of biological processes.

Quick start

Learn how to use SBGN

Get involved

Symbol Highlight

Stimulation

Pathway Highlight

This pathway is an SBGN diagram from the following paper published in the July, 2013 issue of the Cell magazine (PubMed ID: 23791384).

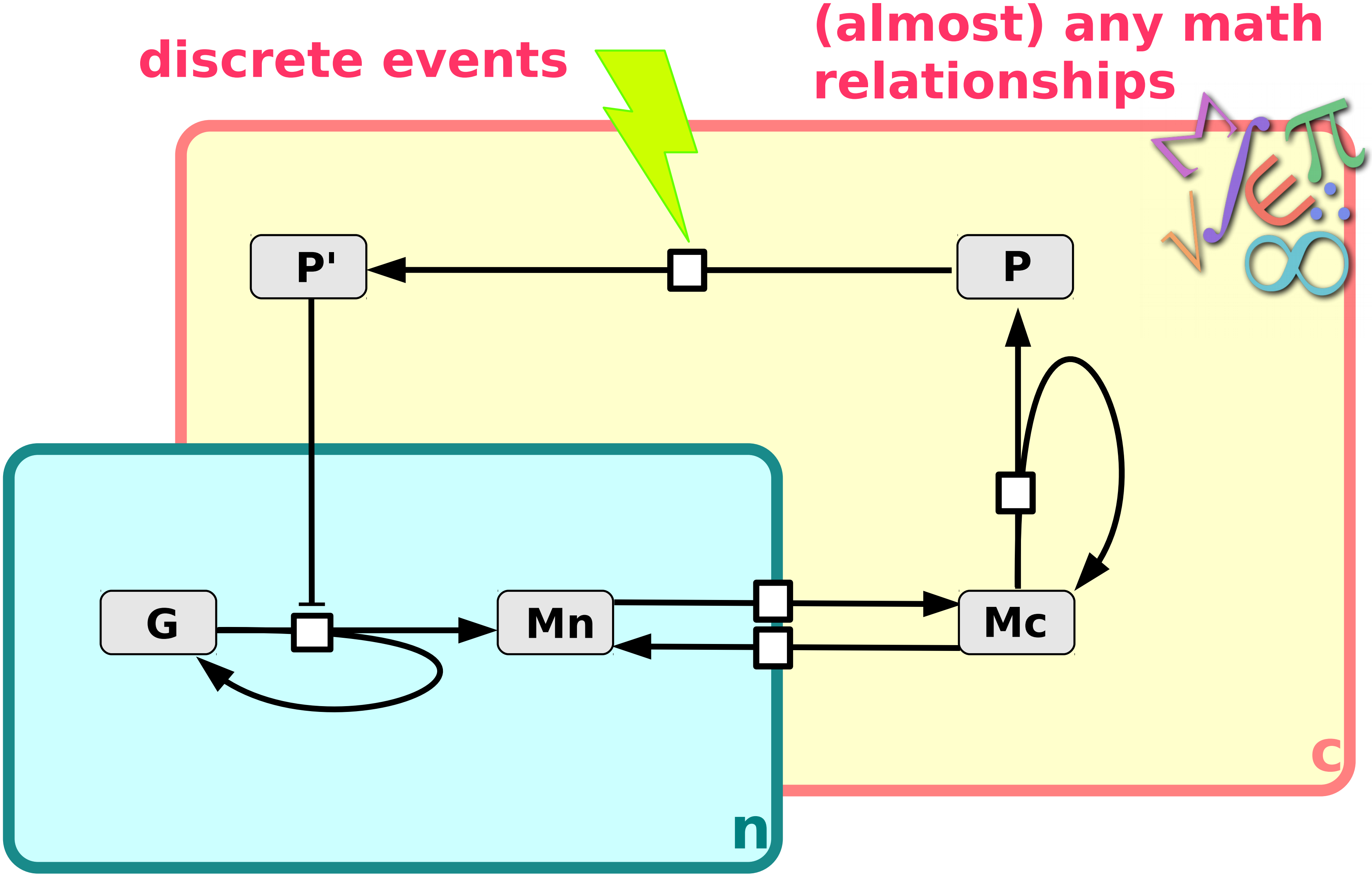
Park S., Kukushkin Y., Gupta R., Chen T., Konagai A., Hipp M., Hayer-Hartl M., and Hartl F. (2013) PolyQ Proteins Interfere with Nuclear Degradation of Cytosolic Proteins by Sequestering the Sis1p Chaperone. Cell 154, 134-145.

http://sbgn.org/

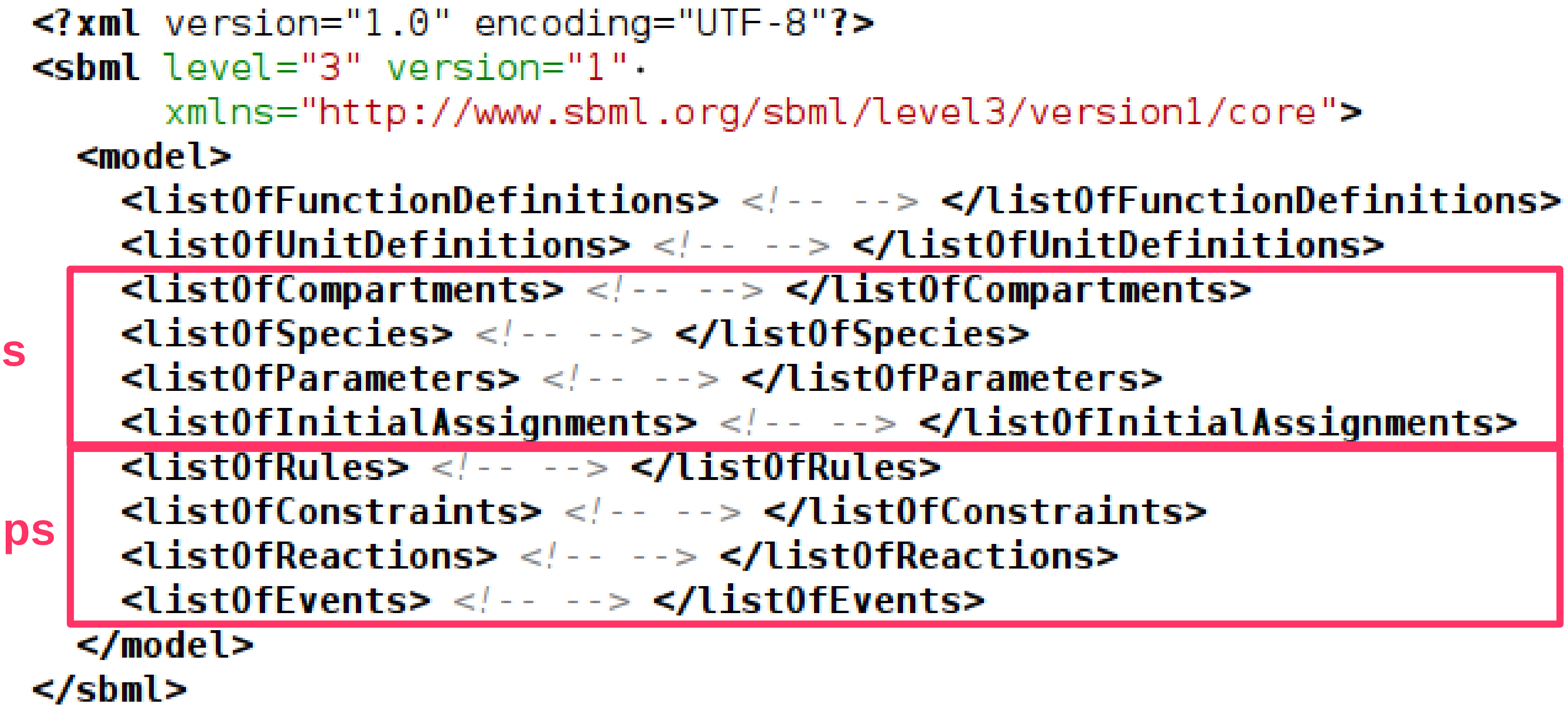
The Systems Biology Markup Language

Hucka *et al. Bioinformatics* (2003)

What can we encode in SBML (core)?



Structure of SBML (core)



variables

relationships

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml level="3" version="1"·
      xmlns="http://www.sbml.org/sbml/level3/version1/core">
  <model>
    <listOfFunctionDefinitions> <!-- --> </listOfFunctionDefinitions>
    <listOfUnitDefinitions> <!-- --> </listOfUnitDefinitions>
    <listOfCompartments> <!-- --> </listOfCompartments>
    <listOfSpecies> <!-- --> </listOfSpecies>
    <listOfParameters> <!-- --> </listOfParameters>
    <listOfInitialAssignments> <!-- --> </listOfInitialAssignments>
    <listOfRules> <!-- --> </listOfRules>
    <listOfConstraints> <!-- --> </listOfConstraints>
    <listOfReactions> <!-- --> </listOfReactions>
    <listOfEvents> <!-- --> </listOfEvents>
  </model>
</sbml>
```

SBML Level 3 is modular

- Core package – public specification → Process Descriptions
- Flux balance constraint – public specification
- Qualitative models – public specification → Activity Flows
- Model composition – public specification
- Graph Layout – public specification
- Complex species – public specification → Entity Relationships
- Groups – public specification
- Graph rendering – specification finalised
- Spatial diffusion – specification finalised
- Distributions and ranges - specification under discussion
- Enhanced metadata – specification proposed
- Arrays and sets – specification proposed
- Dynamic structures - discussed

SBML supporting tools

- LibSBML: free, open-source programming library to help you read, write, manipulate, translate, and validate SBML files. Written in C++, with bindings for: c#, Python, Java, Perl, Ruby, MatLab, Octave
- JSBML: free, open-source, pure Java library for reading, writing, and manipulating SBML files (validation done via libSBML)
- SBML converters: Converter from and to SBML, including Octave, XPP, BioPAX, dot, SVG, MDL
- Software guide: >250 software, including modelling and simulation environment, databases, model processing

Parent pages: **SBML.org**

SBML Software Guide

The following pages describe SBML-compatible software packages known to us. We offer different ways of viewing the information, all drawn from the same underlying data collected from the systems' developers via our **software survey**. The *Matrix* provides a table listing all known software and a variety of their features; the *Summary* provides general descriptions of most of the software; and the *Showcase* provides a sequential slideshow of a subset of the software.

Number of software packages listed in the matrix today: **283**.

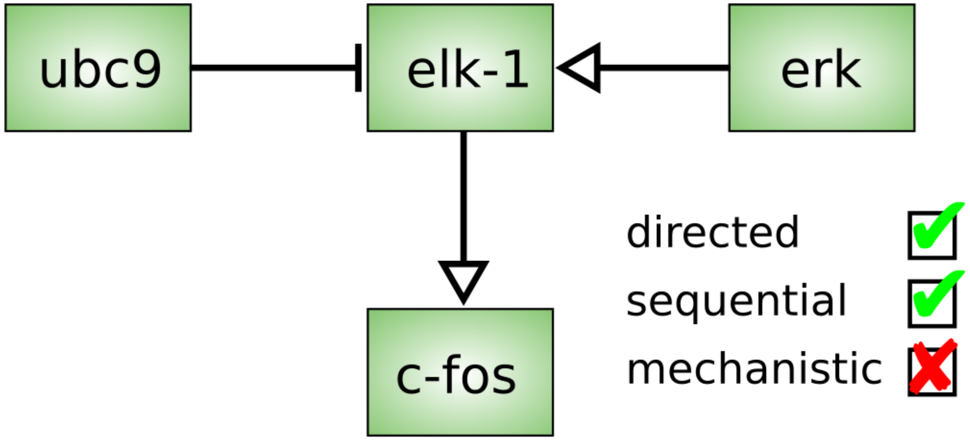
Please **tell us about additions and updates**.

Historical trend

The following graph shows the total number of known SBML-compatible software packages each year, as counted by the SBML Team. The counts shown are for approximately the middle of each year.

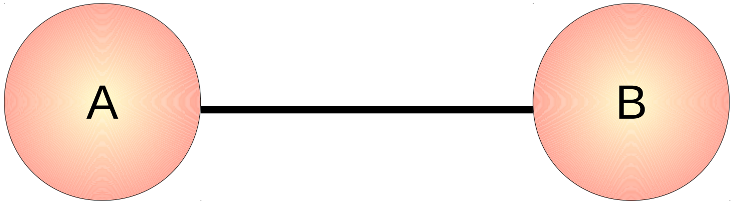
Activity Flows

- Logical modelling
- Signalling pathways, gene regulatory networks



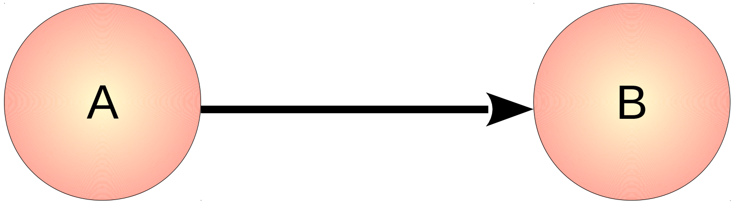
directed ☑
sequential ☑
mechanistic ☒

Undirected, directed, signed



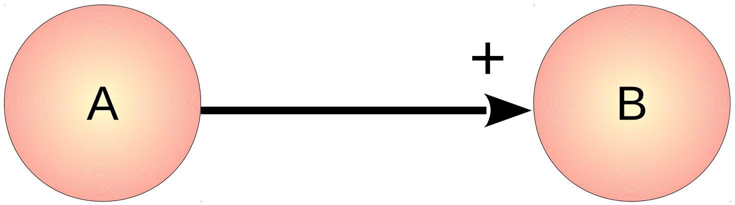
Undirected

“A interacts with B”



directed

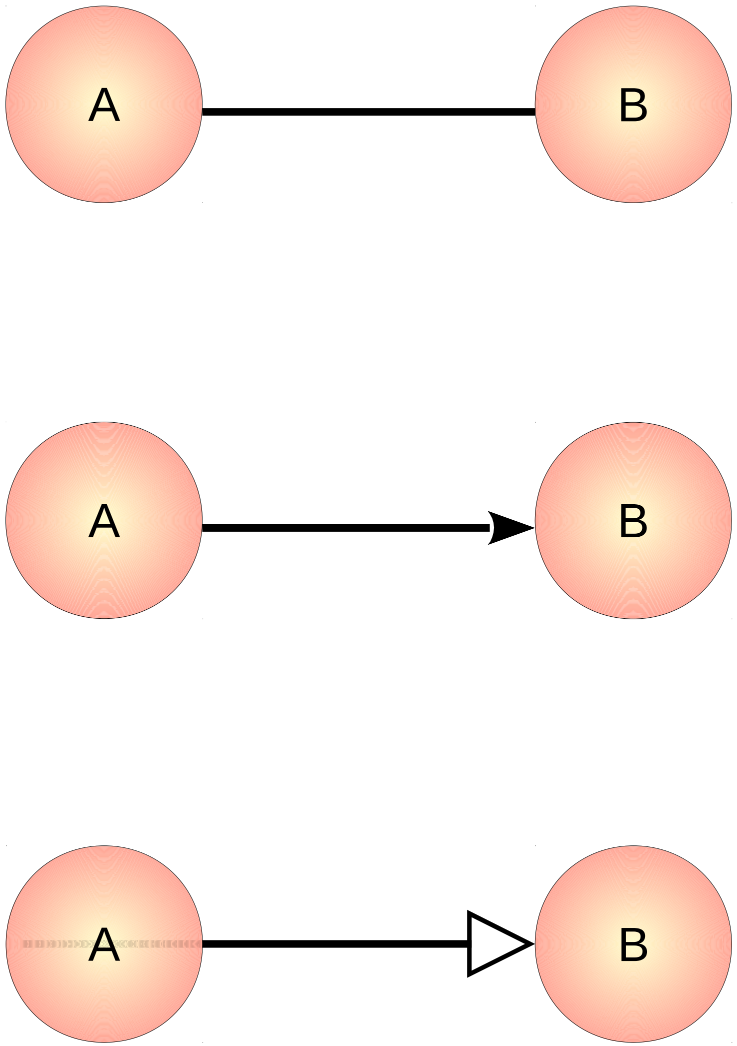
“A influences B”



Signed

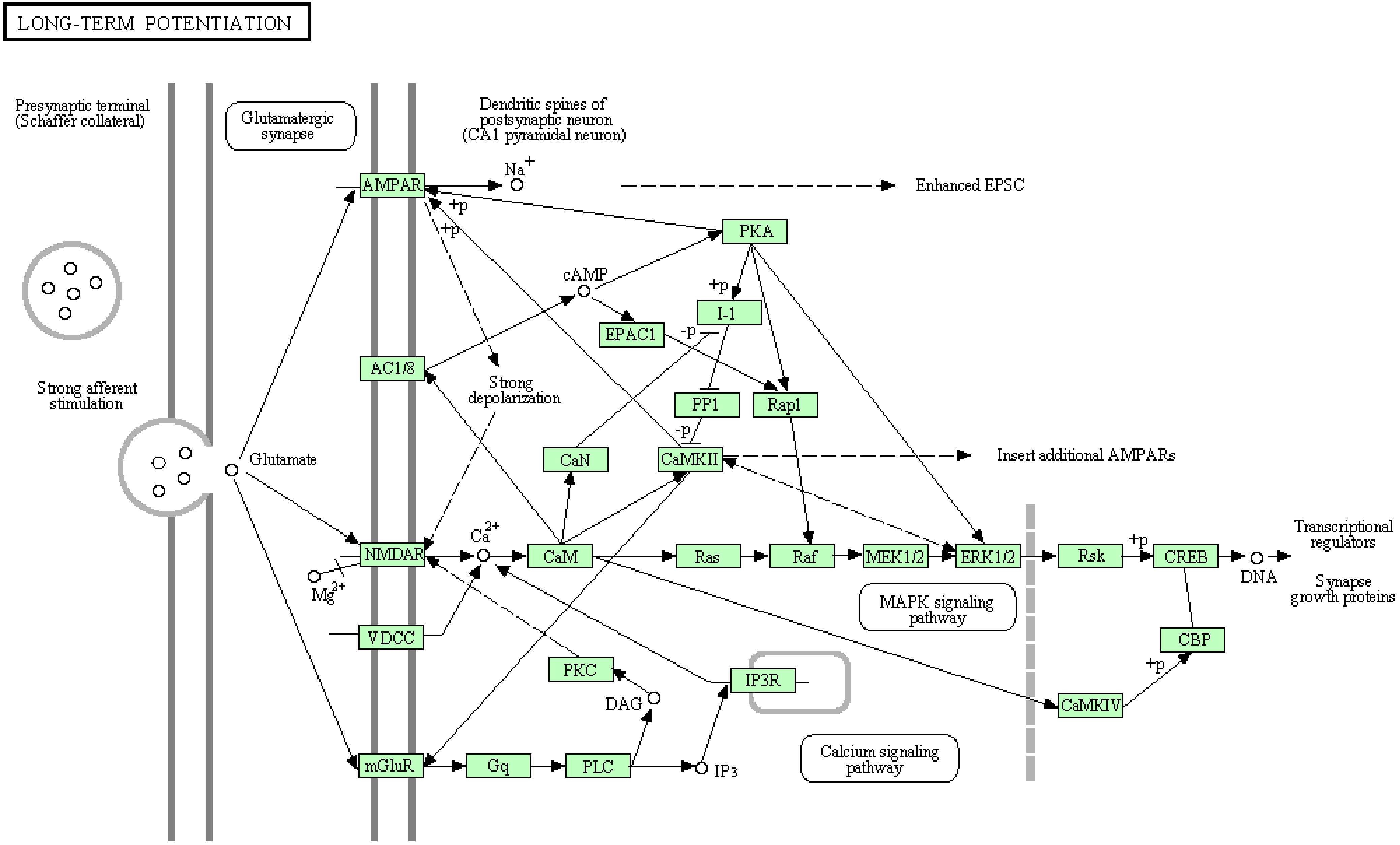
A influences positively B

Undirected, directed, signed

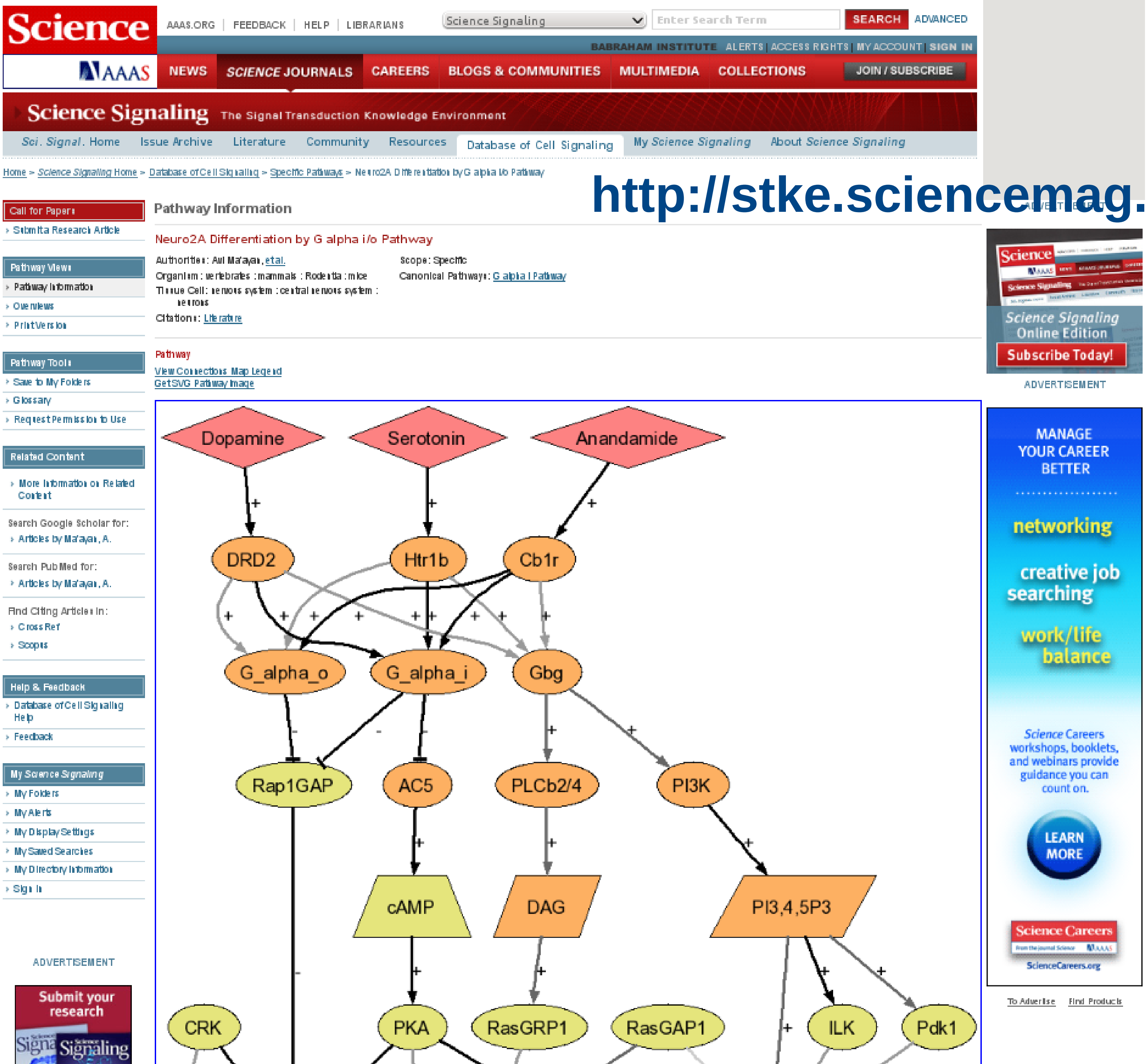


A signed interaction network
is equivalent to an activity flow

http://www.genome.jp/kegg/pathway.html



http://stke.sciencemag.org/cm/



Pathway Information

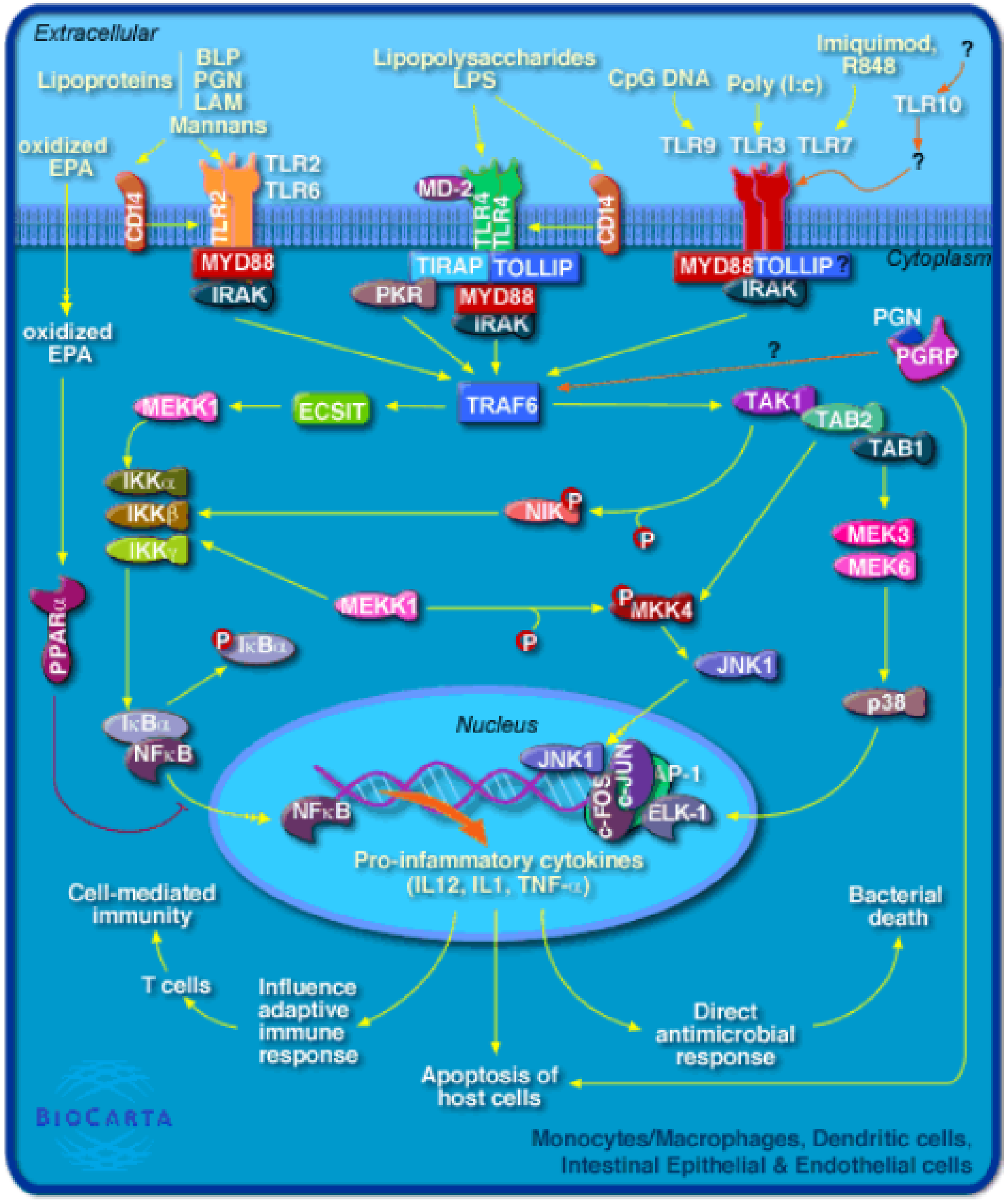
Neuro2A Differentiation by G alpha i/o Pathway

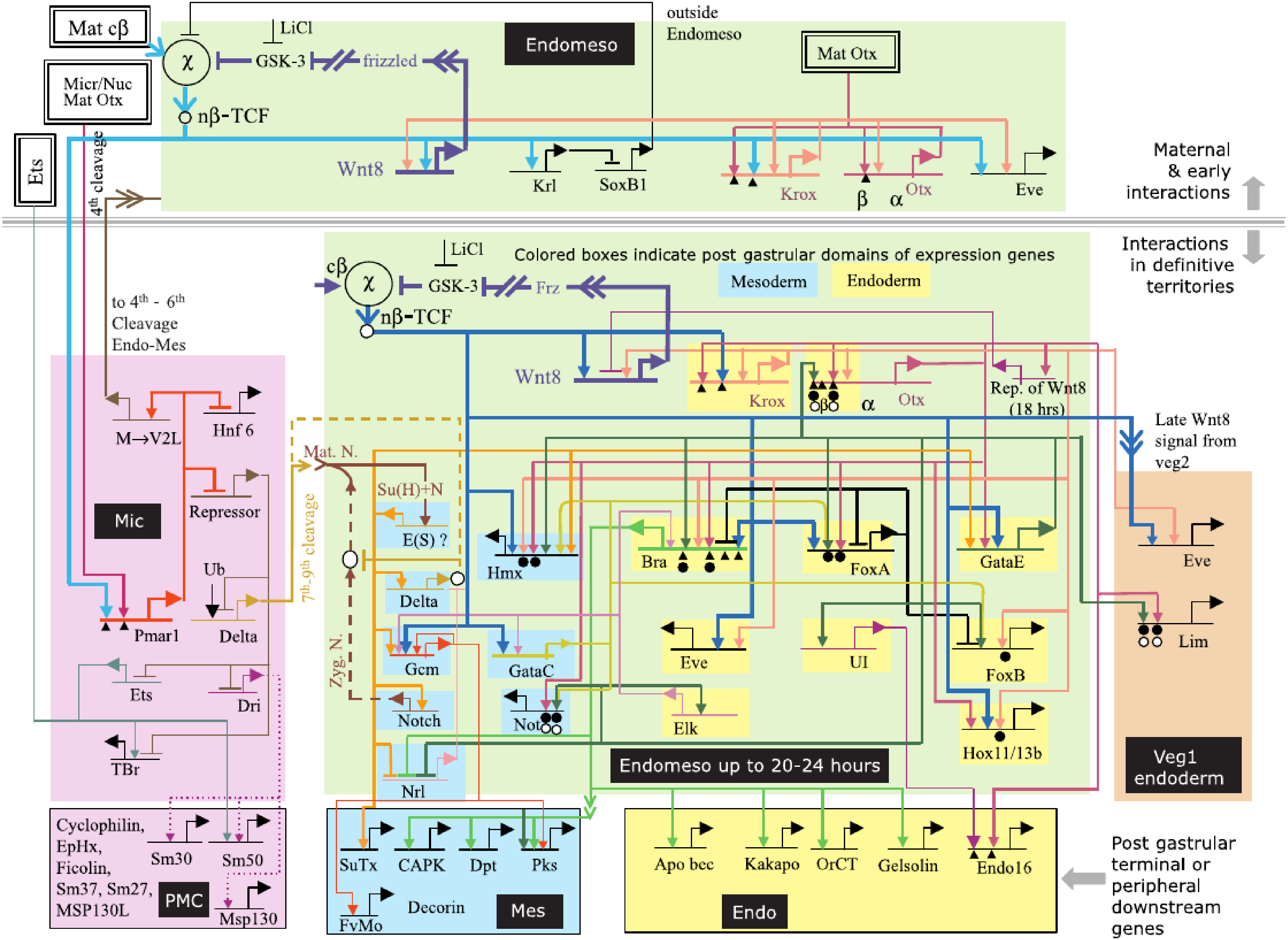
Authorities: Avi Ma'ayan, et al.
Scope: Specific
Organism: vertebrates : mammals : Rodentia : mice
Canonical Pathways: G alpha i Pathway
Tissue Cell: nervous system : central nervous system : neurons
Citations: Literature

Pathway

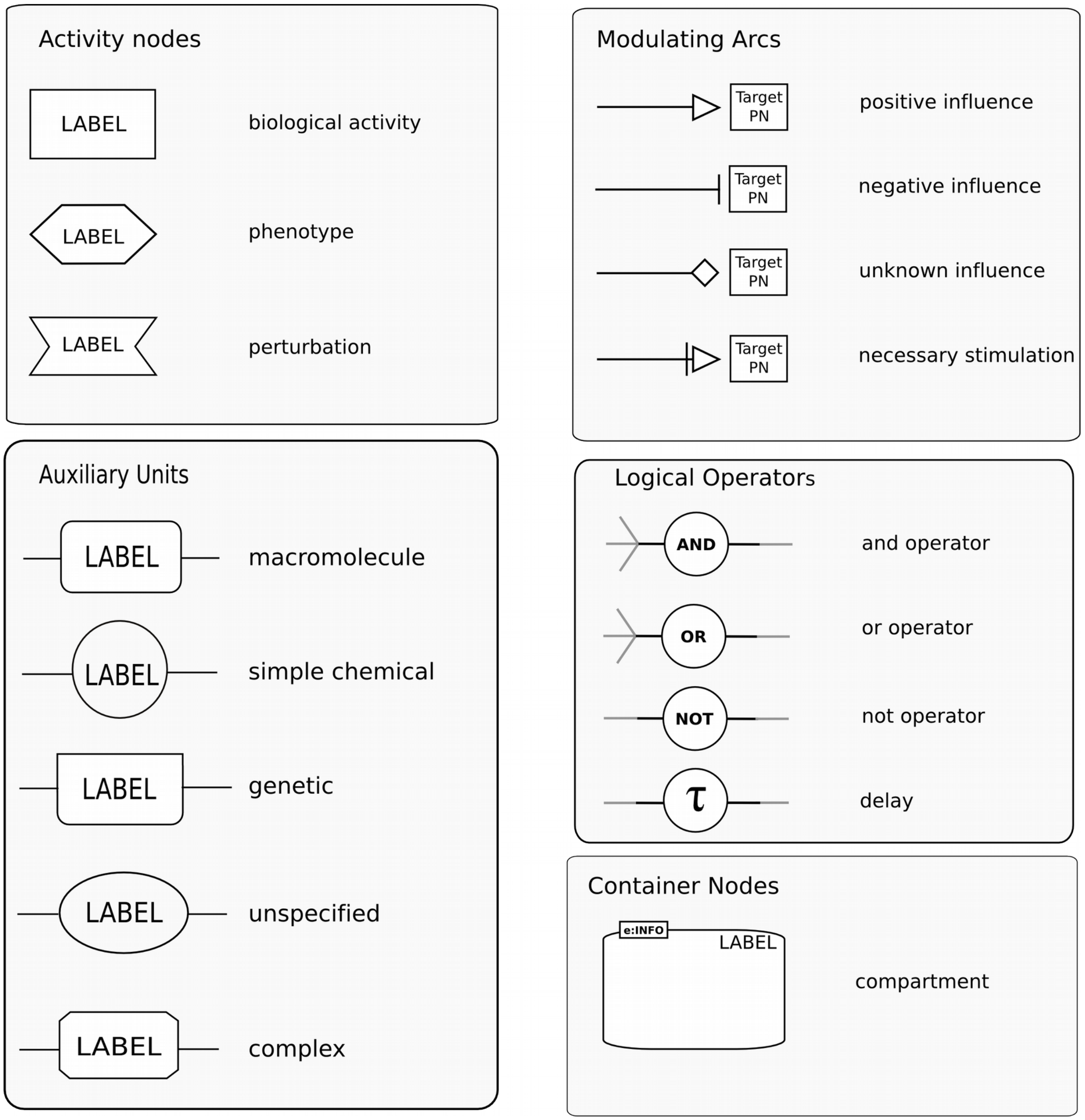
View Connections Map Legend
Get SVG Pathway Image

http://cgap.nci.nih.gov/Pathways/BioCarta.org




Mat cβ
Micr/Nuc Mat Otx
Ets
4th cleavage
χ
LiCl
GSK-3
frizzled
nβ-TCF
Endomeso
outside Endomeso
Mat Otx
Wnt8
Krl
SoxB1
Krox
β
α
Otx
Eve
Maternal & early interactions
Interactions in definitive territories
to 4th - 6th Cleavage Endo-Mes
cβ
χ
LiCl
GSK-3
Frz
nβ-TCF
Colored boxes indicate post gastrular domains of expression genes
Mesoderm
Endoderm
Wnt8
Krox
βγ
α
Otx
Rep. of Wnt8 (18 hrs)
Late Wnt8 signal from veg2
M→V2L
Hnf 6
Repressor
Mic
Ub
Pmar1
Delta
Ets
Dri
TBr
Mat. N.
Su(H)+N
E(S) ?
7th-9th cleavage
Delta
Zyg. N.
Gcm
GataC
Notch
Nrl
Hmx
Bra
FoxA
GataE
Eve
Lim
Eve
UI
FoxB
Not
Elk
Hox11/13b
Endomeso up to 20-24 hours
Veg1 endoderm
Cyclophilin, EpHx, Ficolin, Sm37, Sm27, MSP130L
Sm30
Sm50
PMC
Msp130
SuTx
CAPK
Dpt
Pks
FvMo
Decorin
Mes
Apo bec
Kakapo
OrCT
Gelsolin
Endo16
Endo
Post gastrular terminal or peripheral downstream genes

SBGN Activity Flows L1 reference card



Activity nodes

- biological activity
- phenotype
- perturbation

Modulating Arcs

- positive influence
- negative influence
- unknown influence
- necessary stimulation

Auxiliary Units

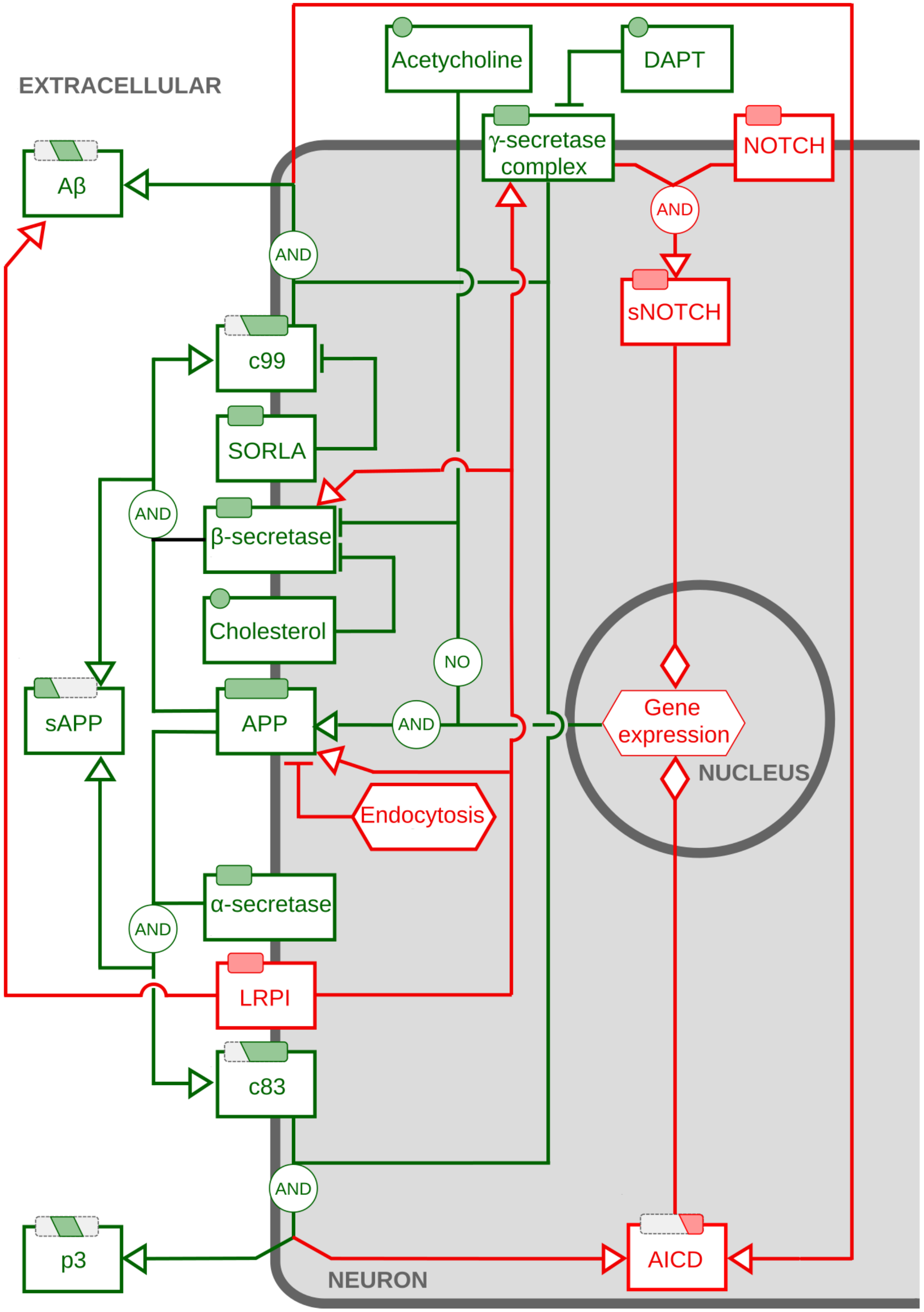
- macromolecule
- simple chemical
- genetic
- unspecified
- complex

Logical Operators

- and operator
- or operator
- not operator
- delay

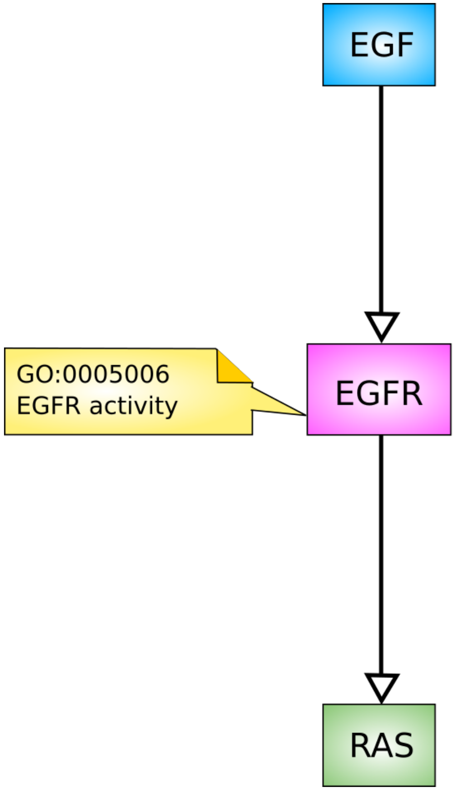
Container Nodes

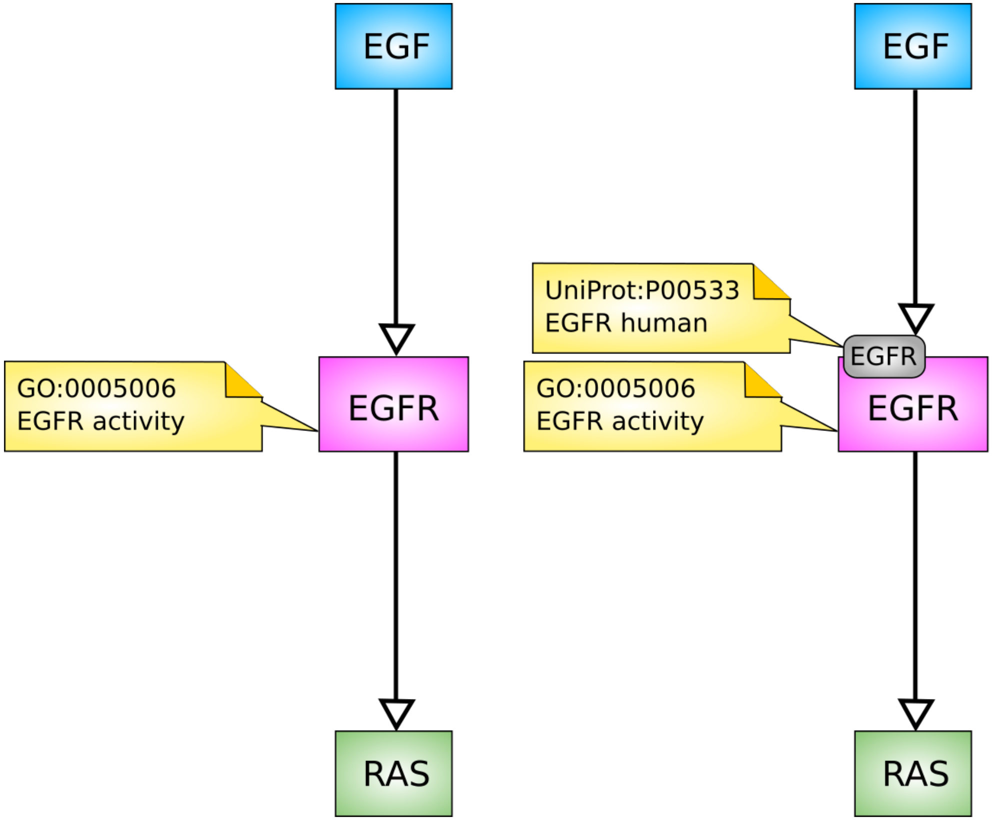
- compartment

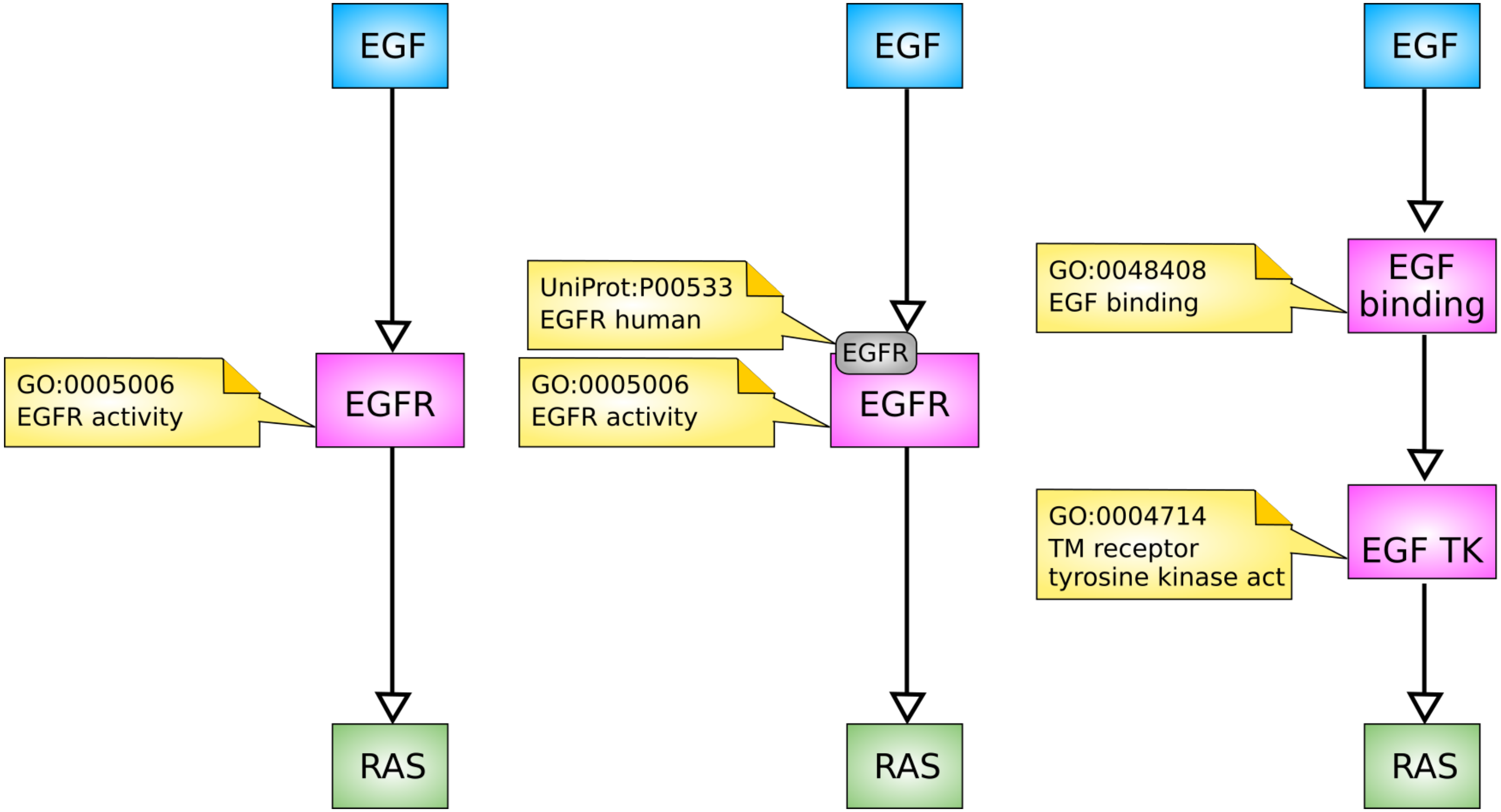


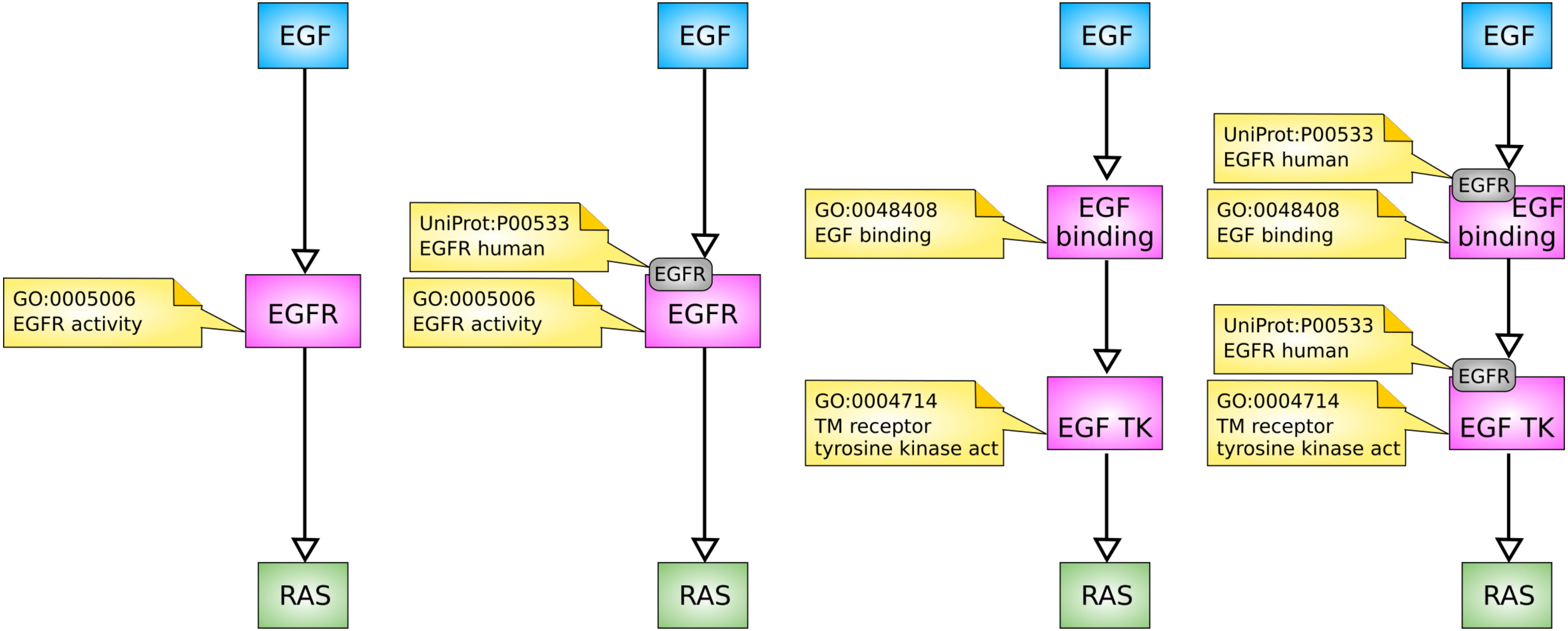
Lloret i Villas *et al.*
CPT: Pharm. Syst. Pharmacol.
(2016)

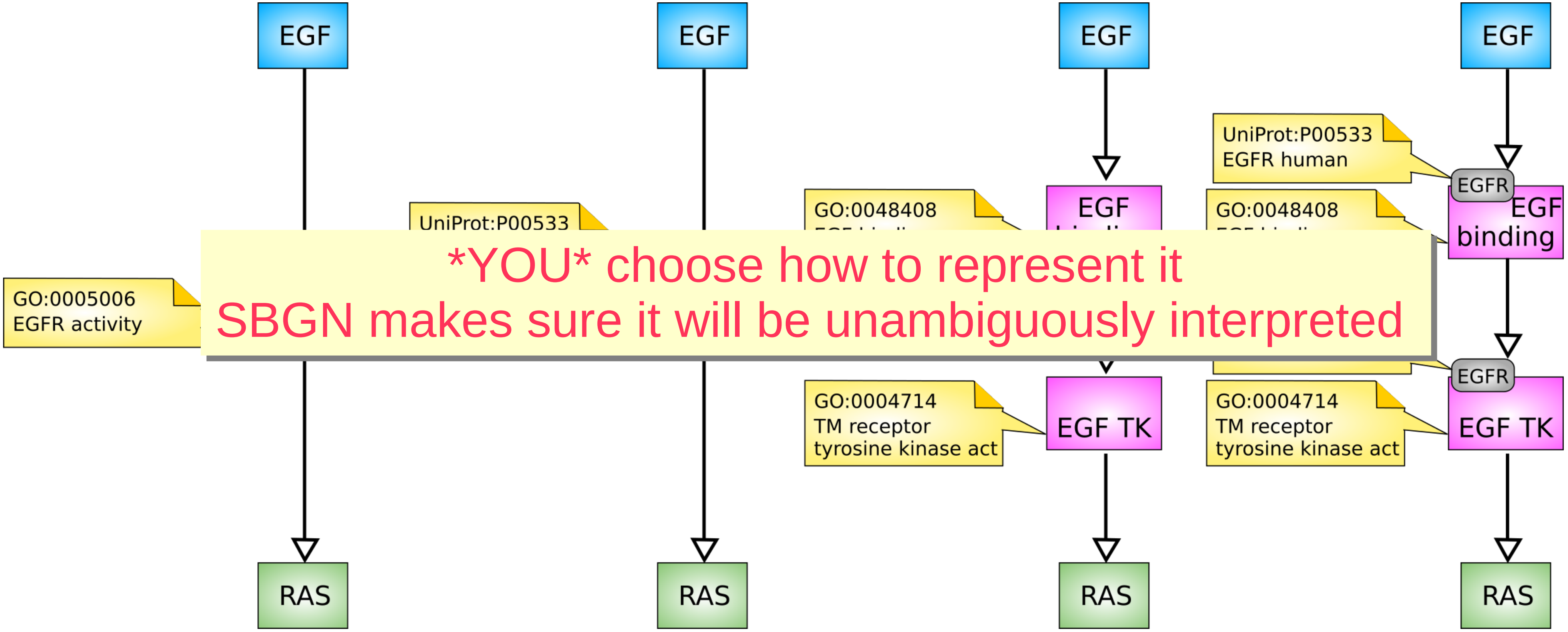
TIMTOWTDI
(There Is More Than One Way To Do It)




EGF
GO:0005006
EGFR activity
EGFR
RAS
EGF
UniProt:P00533
EGFR human
EGFR
GO:0005006
EGFR activity
EGFR
RAS

 EGF
GO:0005006
EGFR activity
EGFR
RAS
EGF
UniProt:P00533
EGFR human
EGFR
GO:0005006
EGFR activity
EGFR
RAS
EGF
GO:0048408
EGF binding
EGF binding
GO:0004714
TM receptor
tyrosine kinase act
EGF TK
RAS


EGF
GO:0005006
EGFR activity
EGFR
RAS
EGF
UniProt:P00533
EGFR human
EGFR
GO:0005006
EGFR activity
EGFR
RAS
EGF
GO:0048408
EGF binding
EGF binding
GO:0004714
TM receptor
tyrosine kinase act
EGF TK
RAS
EGF
UniProt:P00533
EGFR human
EGFR
GO:0048408
EGF binding
EGF binding
UniProt:P00533
EGFR human
EGFR
GO:0004714
TM receptor
tyrosine kinase act
EGF TK
RAS

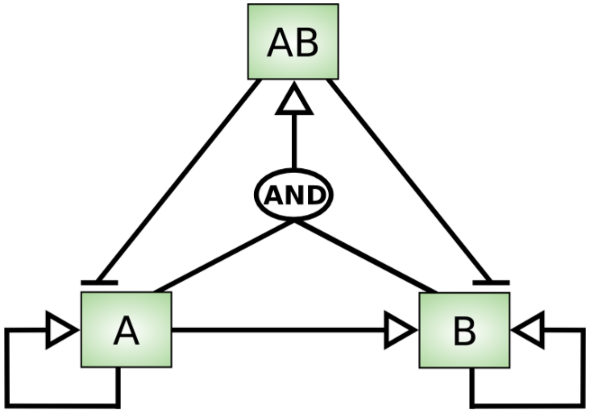


YOU choose how to represent it

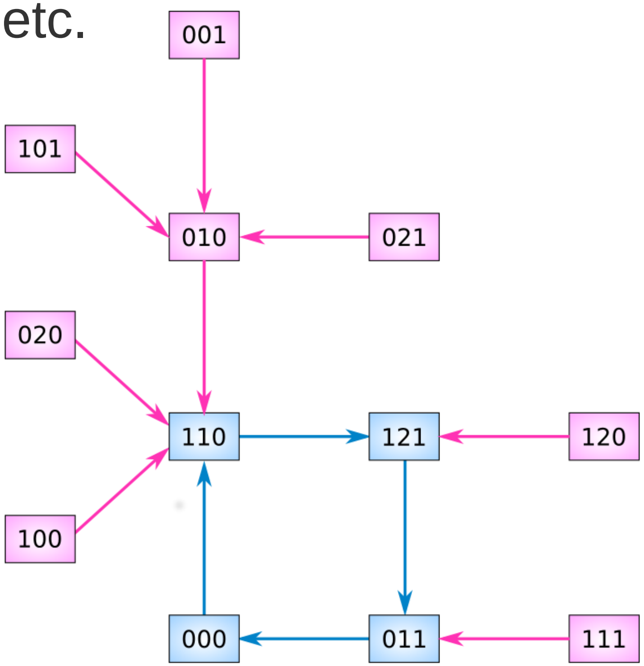
SBGN makes sure it will be unambiguously interpreted

Logic models

- Variables can take a discrete number of values, at least 2
- Transitions of output are expressed as logical combinations of input values
- Simulations can be:
  - synchronous: all the nodes are updated at once
  - asynchronous: nodes are updated one after the other
- One can add delays, inputs etc.



Influence diagram



state diagram

SBML Qual

Logic model with SBML Qual

```
<?xml version='1.0' encoding='UTF-8' standalone='no'?>
<sbml xmlns="http://www.sbml.org/sbml/level3/version1/core" level="3" qual:required="true" version="1" xmlns:qual="http://www
version1/qual/version1">
  <model id="model_id">

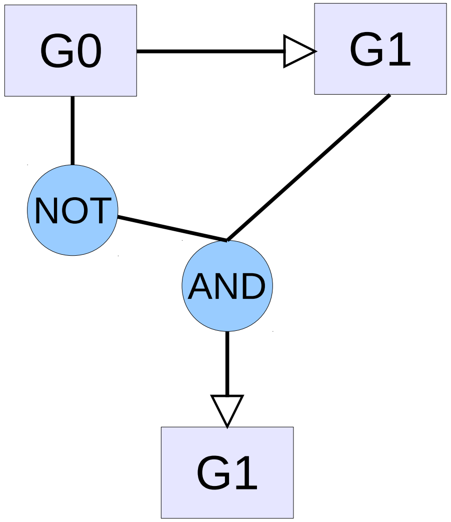
    <qual:listOfQualitativeSpecies xmlns:qual="http://www.sbml.org/sbml/level3/version1/qual/version1">
      <qual:qualitativeSpecies qual:maxLevel="1" qual:compartment="comp1" qual:constant="true" qual:id="G0"/>
      <qual:qualitativeSpecies qual:maxLevel="1" qual:compartment="comp1" qual:constant="false" qual:id="G1"/>
      <qual:qualitativeSpecies qual:maxLevel="1" qual:compartment="comp1" qual:constant="false" qual:id="G2"/>
    </qual:listOfQualitativeSpecies>

    <qual:listOfTransitions xmlns:qual="http://www.sbml.org/sbml/level3/version1/qual/version1">
      <qual:transition qual:id="tr_G1">
      <qual:transition qual:id="tr_G2">
        <qual:listOfInputs>
          <qual:input qual:qualitativeSpecies="G0" qual:transitionEffect="none" qual:sign="negative" qual:id="tr_G2_in_0"/>
          <qual:input qual:qualitativeSpecies="G1" qual:transitionEffect="none" qual:sign="positive" qual:id="tr_G2_in_1"/>
        </qual:listOfInputs>
        <qual:listOfOutputs>
          <qual:output qual:qualitativeSpecies="G2" qual:transitionEffect="assignmentLevel" qual:id="tr_G2_out"/>
        </qual:listOfOutputs>
        <qual:listOfFunctionTerms>
          <qual:defaultTerm qual:resultLevel="0">
          </qual:defaultTerm>
          <qual:functionTerm qual:resultLevel="1">
            <math xmlns="http://www.w3.org/1998/Math/MathML">
              <apply>
                <and/>
                <apply>
                  <eq/>
                  <ci> G0 </ci>
                  <cn type="integer"> 0 </cn>
                </apply>
                <apply>
                  <eq/>
                  <ci> G1 </ci>
                  <cn type="integer"> 1 </cn>
                </apply>
              </apply>
            </math>
          </qual:functionTerm>
        </qual:listOfFunctionTerms>
      </qual:transition>
    </qual:listOfTransitions>

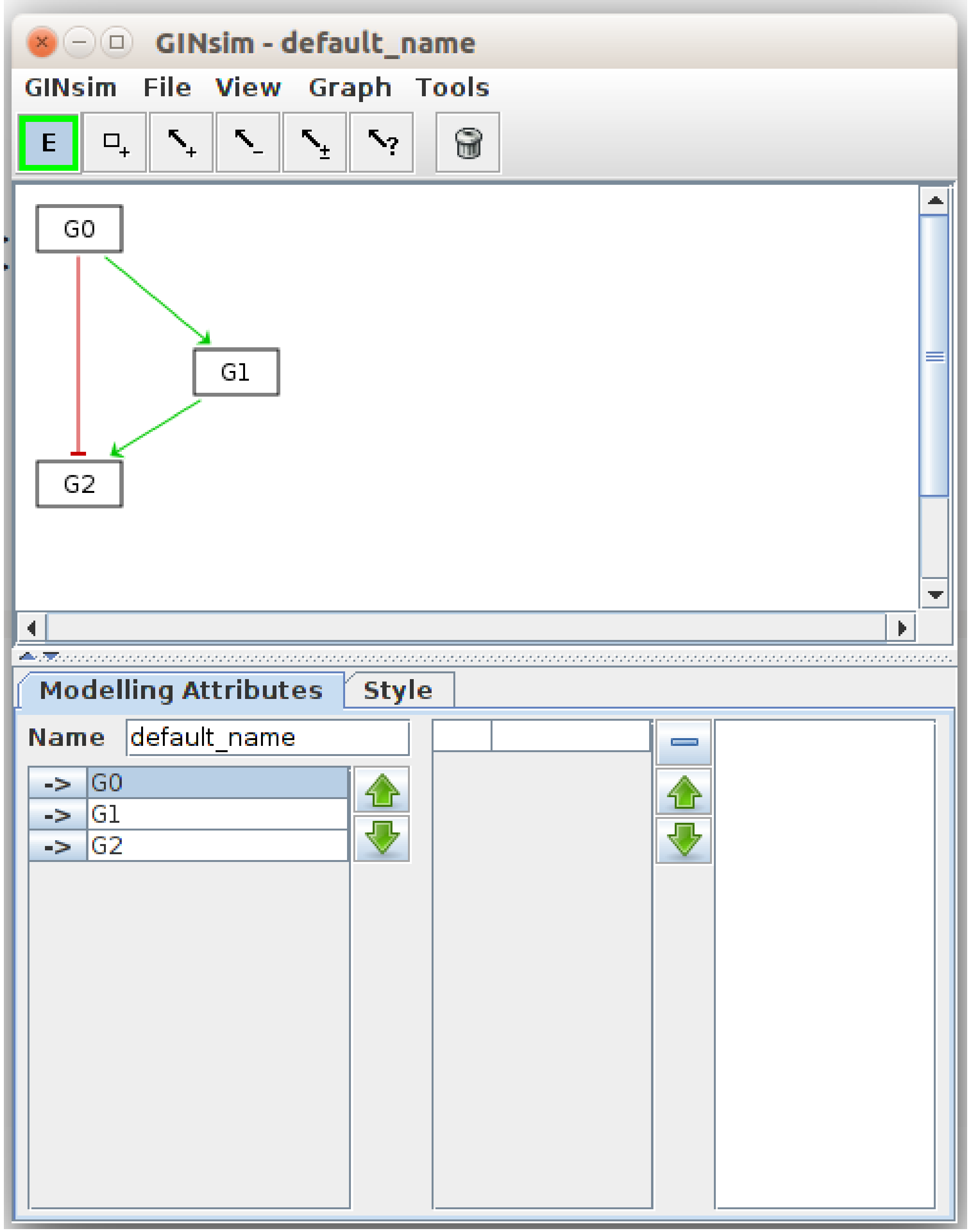
    <listOfCompartments>
      <compartment constant="true" id="comp1"/>
    </listOfCompartments>
```

$$G0 \geqslant 1 \Rightarrow G1 = 1$$

$$\left.\begin{array}{l} G0 = 0 \\ G1 = 1 \end{array}\right\} \Rightarrow G2 = 1$$

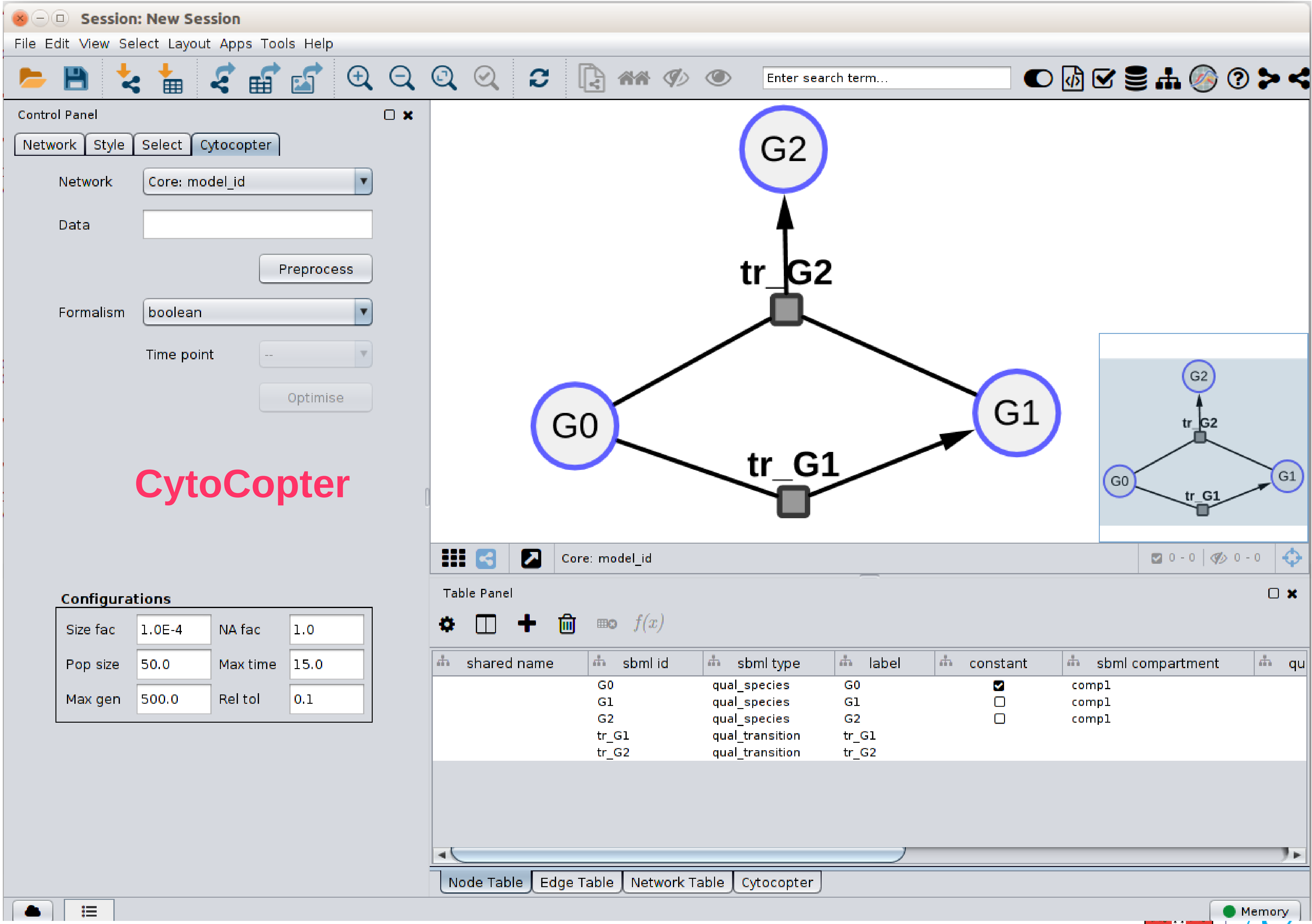


GINsim



default_name

->	G0
->	G1
->	G2



Network: Core: model_id

Data:

Formalism: boolean

Time point: --

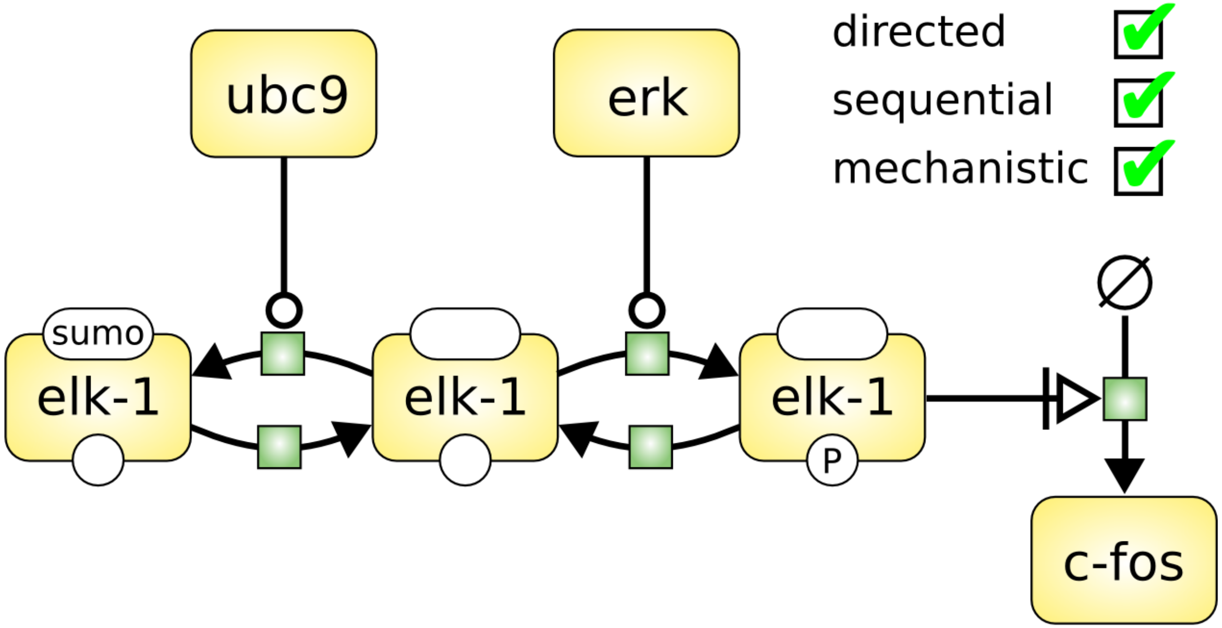
CytoCopter

Configurations

Size fac	1.0E-4	NA fac	1.0
Pop size	50.0	Max time	15.0
Max gen	500.0	Rel tol	0.1

shared name	sbml id	sbml type	label	constant	sbml compartment	qu
	G0	qual_species	G0	☑	comp1	
	G1	qual_species	G1	☐	comp1	
	G2	qual_species	G2	☐	comp1	
	tr_G1	qual_transition	tr_G1			
	tr_G2	qual_transition	tr_G2			

Process Descriptions



- Process modelling
- Biochemistry, Metabolic networks
- Generally within “closed world”
- Subjected to combinatorial explosion

Open world

Anything not explicitly stated is unknown

Failure to observe does not imply non-existence

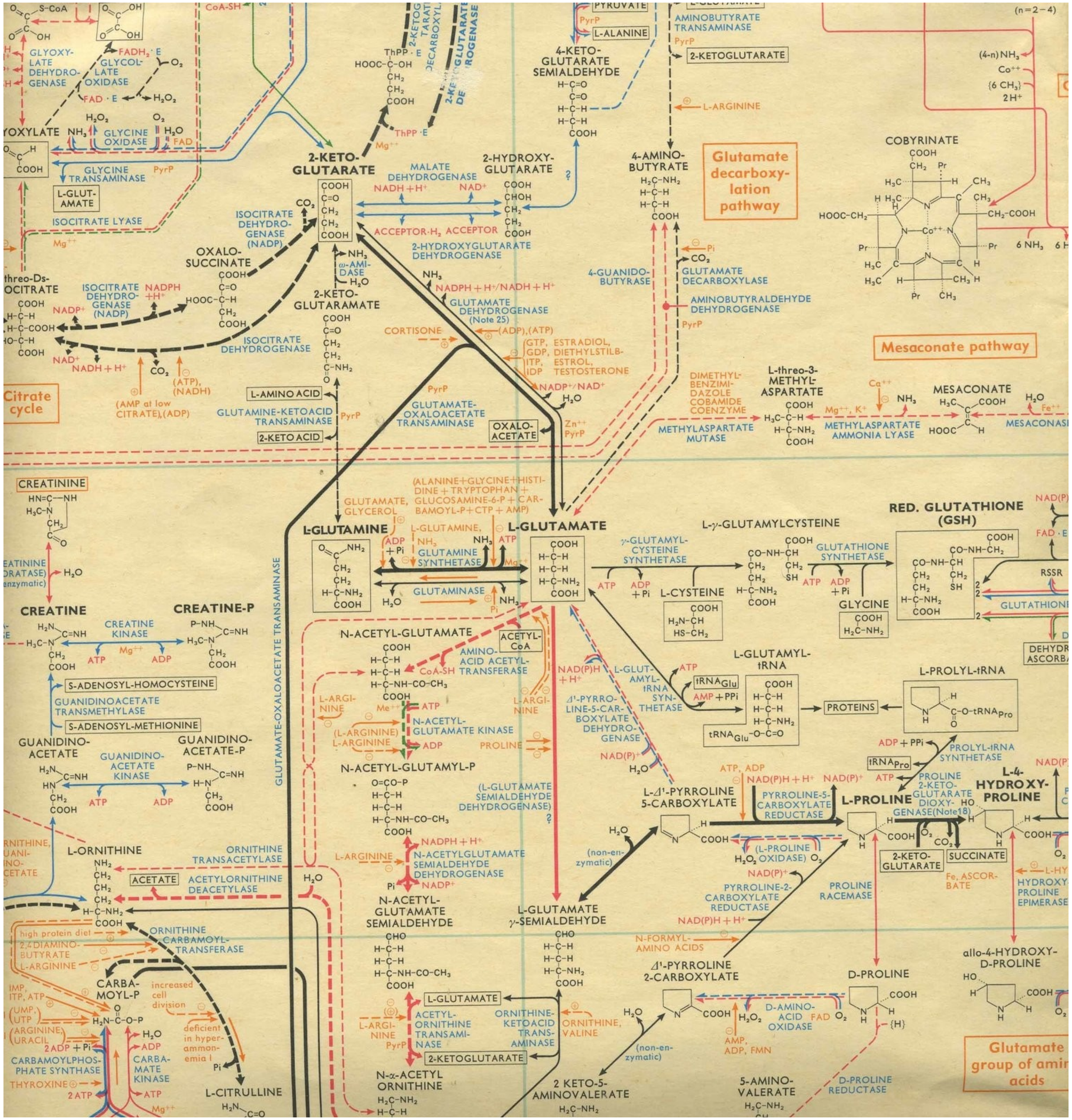
New pieces of knowledge do not affect prior pieces

Closed world

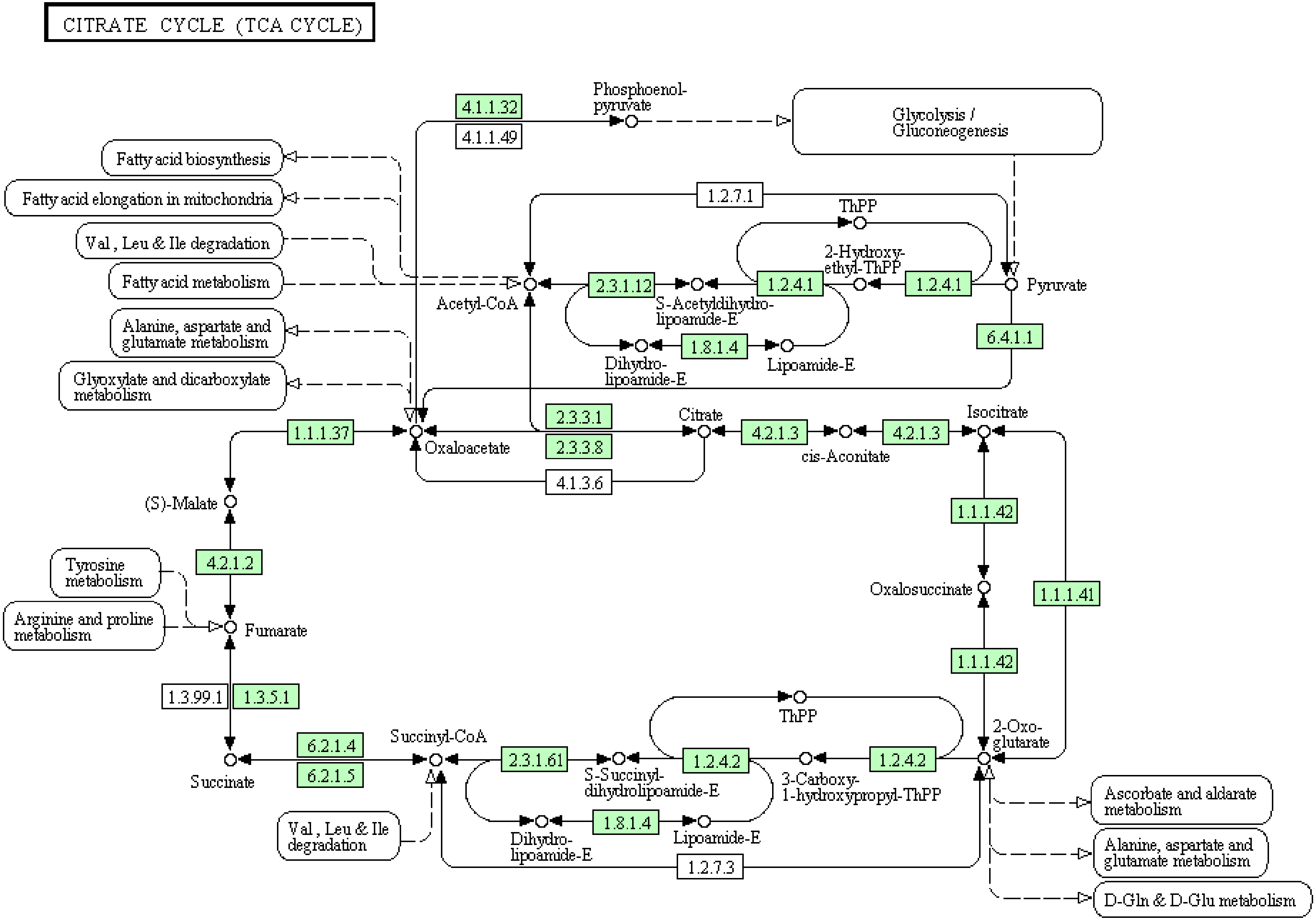
Anything not explicitly stated does not exist

Failure to observe implies non-existence

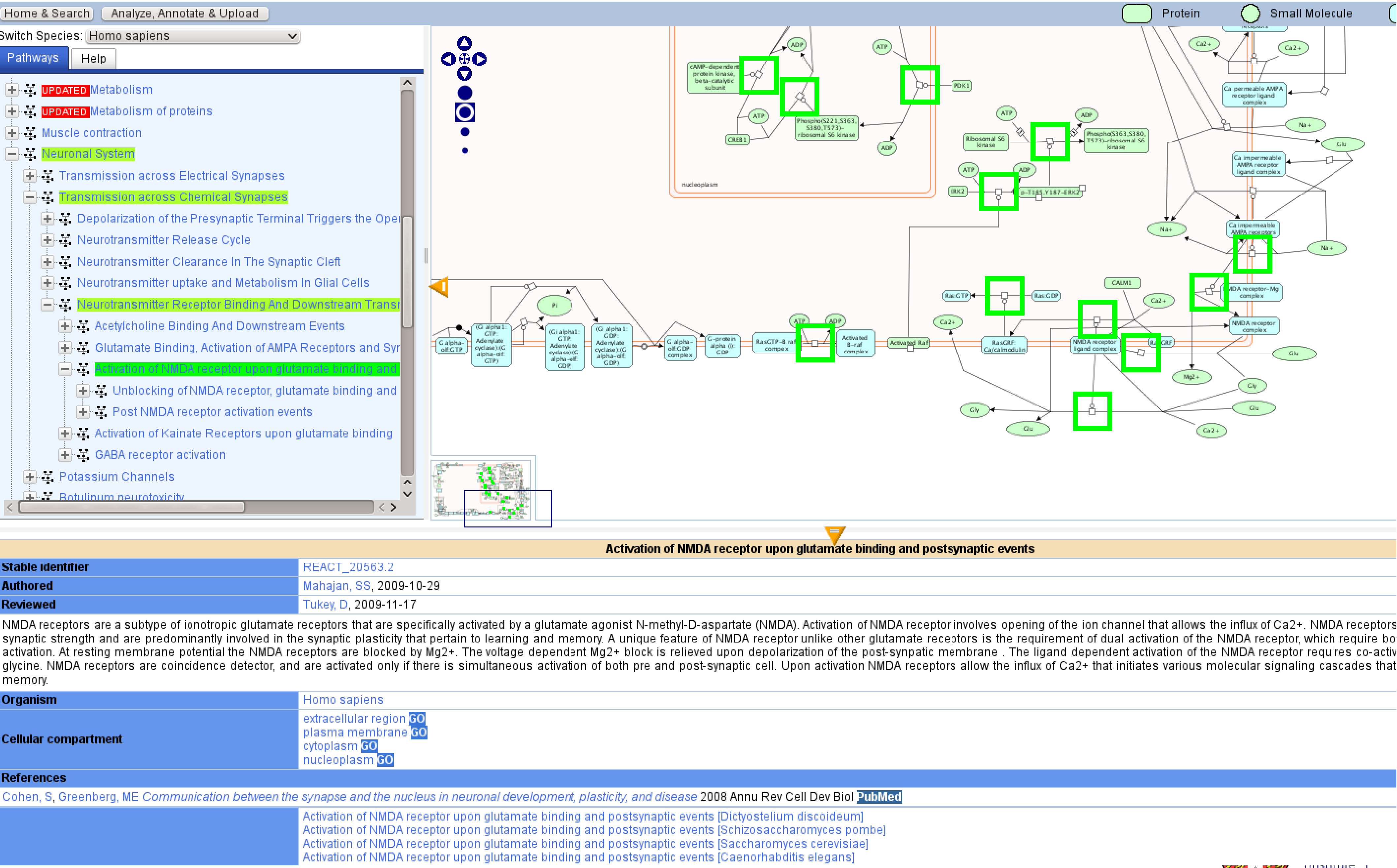
New pieces of knowledge might change the meaning of prior pieces


Glutamate decarboxylation pathway
Mesaconate pathway
Citrate cycle
Glutamate group of amino acids
2-KETOGLUTARATE
MALATE DEHYDROGENASE
2-HYDROXYGLUTARATE
2-HYDROXYGLUTARATE DEHYDROGENASE
ISOCITRATE DEHYDROGENASE (NADP)
OXALOSUCCINATE
threo-Ds-ISOCITRATE
ISOCITRATE LYASE
GLYOXYLATE
GLYCOLLATE OXIDASE
GLYCINE OXIDASE
GLYCINE TRANSAMINASE
L-GLUTAMATE
ω-AMIDASE
2-KETOGLUTARAMATE
GLUTAMATE DEHYDROGENASE (Note 25)
CORTISONE
GTP, ESTRADIOL, GDP, DIETHYLSTILBESTROL, ITP, ESTROL, IDP, TESTOSTERONE
GLUTAMINE-KETOACID TRANSAMINASE
L-AMINO ACID
2-KETO ACID
GLUTAMATE-OXALOACETATE TRANSAMINASE
OXALOACETATE
4-KETOGLUTARATE SEMIALDEHYDE
PYRUVATE
L-ALANINE
AMINOBUTYRATE TRANSAMINASE
2-KETOGLUTARATE
L-ARGININE
4-AMINOBUTYRATE
4-GUANIDOBUTYRATE
GLUTAMATE DECARBOXYLASE
AMINOBUTYRALDEHYDE DEHYDROGENASE
DIMETHYLBENZIMIDAZOLE COBAMIDE COENZYME
METHYLASPARTATE MUTASE
L-threo-3-METHYLASPARTATE
METHYLASPARTATE AMMONIA LYASE
MESACONATE
MESACONASE
COBYRINATE
CREATININE
CREATININE DEHYDRATASE (non-enzymatic)
CREATINE
CREATINE-P
CREATINE KINASE
S-ADENOSYL-HOMOCYSTEINE
GUANIDINOACETATE TRANSMETHYLASE
S-ADENOSYL-METHIONINE
GUANIDINOACETATE
GUANIDINOACETATE-P
GUANIDINOACETATE KINASE
GLUTAMATE-OXALOACETATE TRANSAMINASE
L-GLUTAMINE
L-GLUTAMATE
GLUTAMINE SYNTHETASE
GLUTAMINASE
(ALANINE + GLYCINE + HISTIDINE + TRYPTOPHAN + GLUCOSAMINE-6-P + CARBAMOYL-P + CTP + AMP)
GLUTAMATE, GLYCEROL
N-ACETYL-GLUTAMATE
ACETYL-CoA
AMINO-ACID ACETYLTRANSFERASE
N-ACETYLGLUTAMATE KINASE
N-ACETYL-GLUTAMYL-P
(L-GLUTAMATE SEMIALDEHYDE DEHYDROGENASE)
N-ACETYLGLUTAMATE SEMIALDEHYDE DEHYDROGENASE
N-ACETYL-GLUTAMATE SEMIALDEHYDE
ACETYL-ORNITHINE TRANSAMINASE
N-α-ACETYL ORNITHINE
L-GLUTAMATE γ-SEMIALDEHYDE
ORNITHINE-KETOACID TRANSAMINASE
2 KETO-5-AMINOVALERATE
L-ORNITHINE
ORNITHINE TRANSACETYLASE
ACETATE
ACETYLORNITHINE DEACETYLASE
ORNITHINE CARBAMOYLTRANSFERASE
CARBAMOYL-P
CARBAMOYLPHOSPHATE SYNTHASE
CARBAMATE KINASE
THYROXINE
L-CITRULLINE
high protein diet
increased cell division
deficient in hyperammonemia I
L-γ-GLUTAMYLCYSTEINE
γ-GLUTAMYLCYSTEINE SYNTHETASE
L-CYSTEINE
GLUTATHIONE SYNTHETASE
GLYCINE
RED. GLUTATHIONE (GSH)
L-GLUTAMYL-tRNA
L-GLUTAMYL-tRNA SYNTHETASE
PROTEINS
L-PROLYL-tRNA
PROLYL-tRNA SYNTHETASE
Δ1-PYRROLINE-5-CARBOXYLATE DEHYDROGENASE
L-Δ1-PYRROLINE 5-CARBOXYLATE
PYRROLINE-5-CARBOXYLATE REDUCTASE
L-PROLINE
PROLINE 2-KETOGLUTARATE DIOXYGENASE (Note 18)
L-4-HYDROXYPROLINE
SUCCINATE
(L-PROLINE OXIDASE)
PYRROLINE-2-CARBOXYLATE REDUCTASE
PROLINE RACEMASE
HYDROXYPROLINE EPIMERASE
N-FORMYL-AMINO ACIDS
Δ1-PYRROLINE 2-CARBOXYLATE
D-PROLINE
D-AMINO-ACID OXIDASE
allo-4-HYDROXY-D-PROLINE
5-AMINOVALERATE
D-PROLINE REDUCTASE
(non-enzymatic)

http://www.genome.jp/kegg/pathway.html



http://www.reactome.org



- UPDATED Metabolism
- UPDATED Metabolism of proteins
- Muscle contraction
- Neuronal System
  - Transmission across Electrical Synapses
  - Transmission across Chemical Synapses
    - Depolarization of the Presynaptic Terminal Triggers the Oper
    - Neurotransmitter Release Cycle
    - Neurotransmitter Clearance In The Synaptic Cleft
    - Neurotransmitter uptake and Metabolism In Glial Cells
    - Neurotransmitter Receptor Binding And Downstream Transr
      - Acetylcholine Binding And Downstream Events
      - Glutamate Binding, Activation of AMPA Receptors and Syr
      - Activation of NMDA receptor upon glutamate binding and
        - Unblocking of NMDA receptor, glutamate binding and
        - Post NMDA receptor activation events
      - Activation of Kainate Receptors upon glutamate binding
      - GABA receptor activation
  - Potassium Channels
  - Botulinum neurotoxicity

Activation of NMDA receptor upon glutamate binding and postsynaptic events

Stable identifier	REACT_20563.2
Authored	Mahajan, SS, 2009-10-29
Reviewed	Tukey, D, 2009-11-17

NMDA receptors are a subtype of ionotropic glutamate receptors that are specifically activated by a glutamate agonist N-methyl-D-aspartate (NMDA). Activation of NMDA receptor involves opening of the ion channel that allows the influx of Ca2+. NMDA receptors
synaptic strength and are predominantly involved in the synaptic plasticity that pertain to learning and memory. A unique feature of NMDA receptor unlike other glutamate receptors is the requirement of dual activation of the NMDA receptor, which require bo
activation. At resting membrane potential the NMDA receptors are blocked by Mg2+. The voltage dependent Mg2+ block is relieved upon depolarization of the post-synpatic membrane . The ligand dependent activation of the NMDA receptor requires co-activ
glycine. NMDA receptors are coincidence detector, and are activated only if there is simultaneous activation of both pre and post-synaptic cell. Upon activation NMDA receptors allow the influx of Ca2+ that initiates various molecular signaling cascades that
memory.

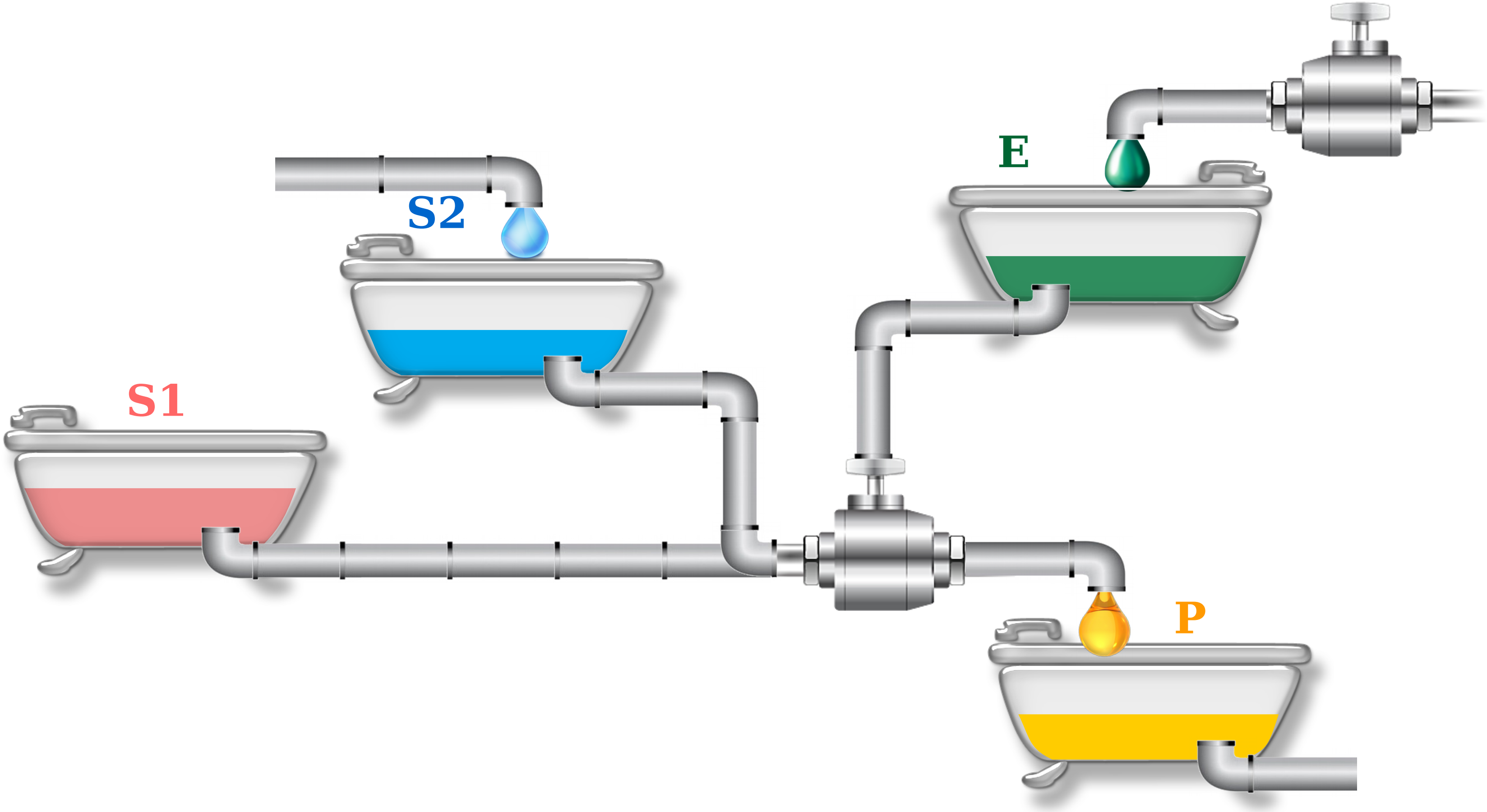
Organism	Homo sapiens
Cellular compartment	extracellular region GO plasma membrane GO cytoplasm GO nucleoplasm GO

References

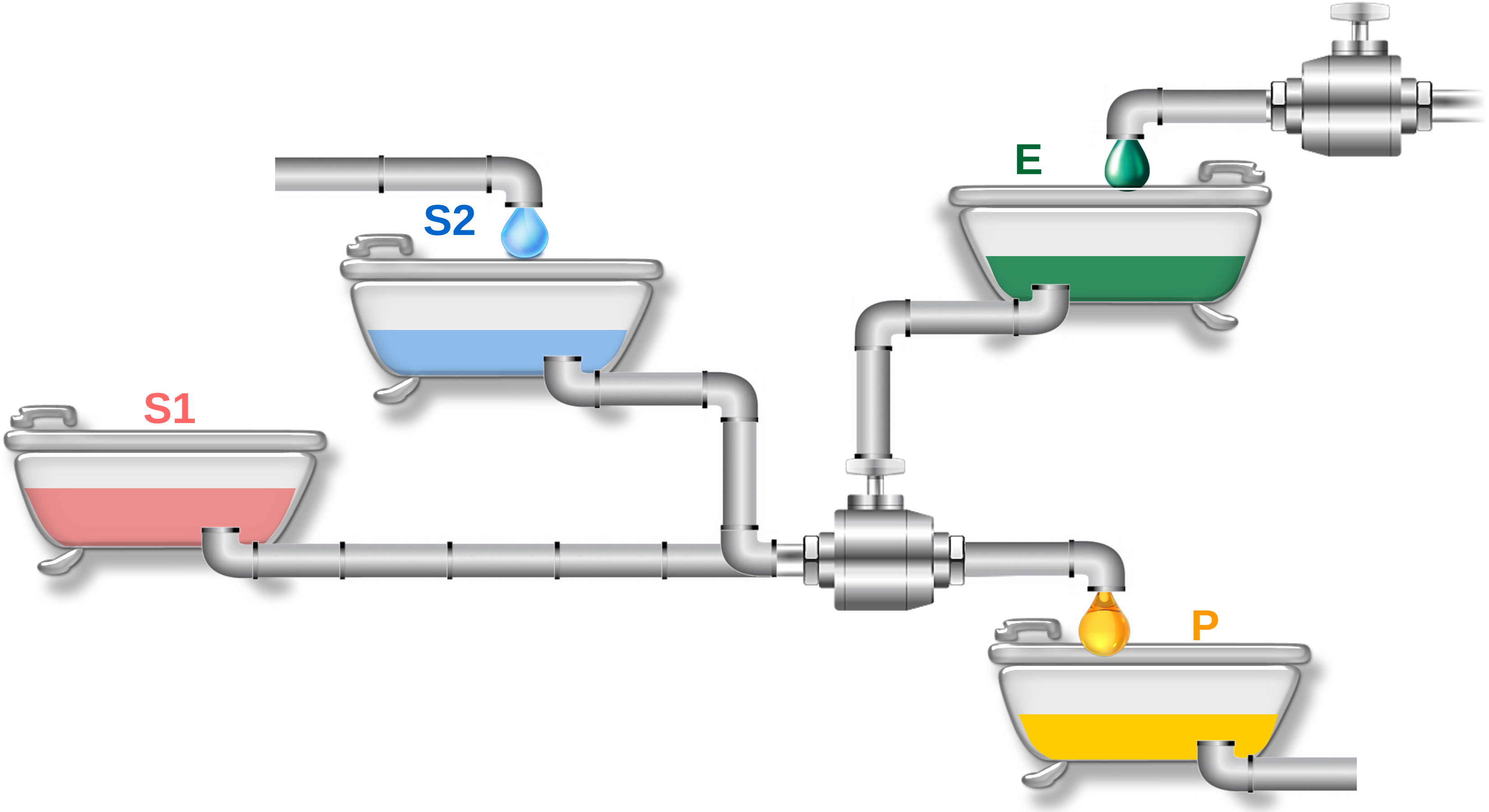
Cohen, S, Greenberg, ME *Communication between the synapse and the nucleus in neuronal development, plasticity, and disease* 2008 Annu Rev Cell Dev Biol PubMed

Activation of NMDA receptor upon glutamate binding and postsynaptic events [Dictyostelium discoideum]
Activation of NMDA receptor upon glutamate binding and postsynaptic events [Schizosaccharomyces pombe]
Activation of NMDA receptor upon glutamate binding and postsynaptic events [Saccharomyces cerevisiae]
Activation of NMDA receptor upon glutamate binding and postsynaptic events [Caenorhabditis elegans]

A biochemical reaction is a process

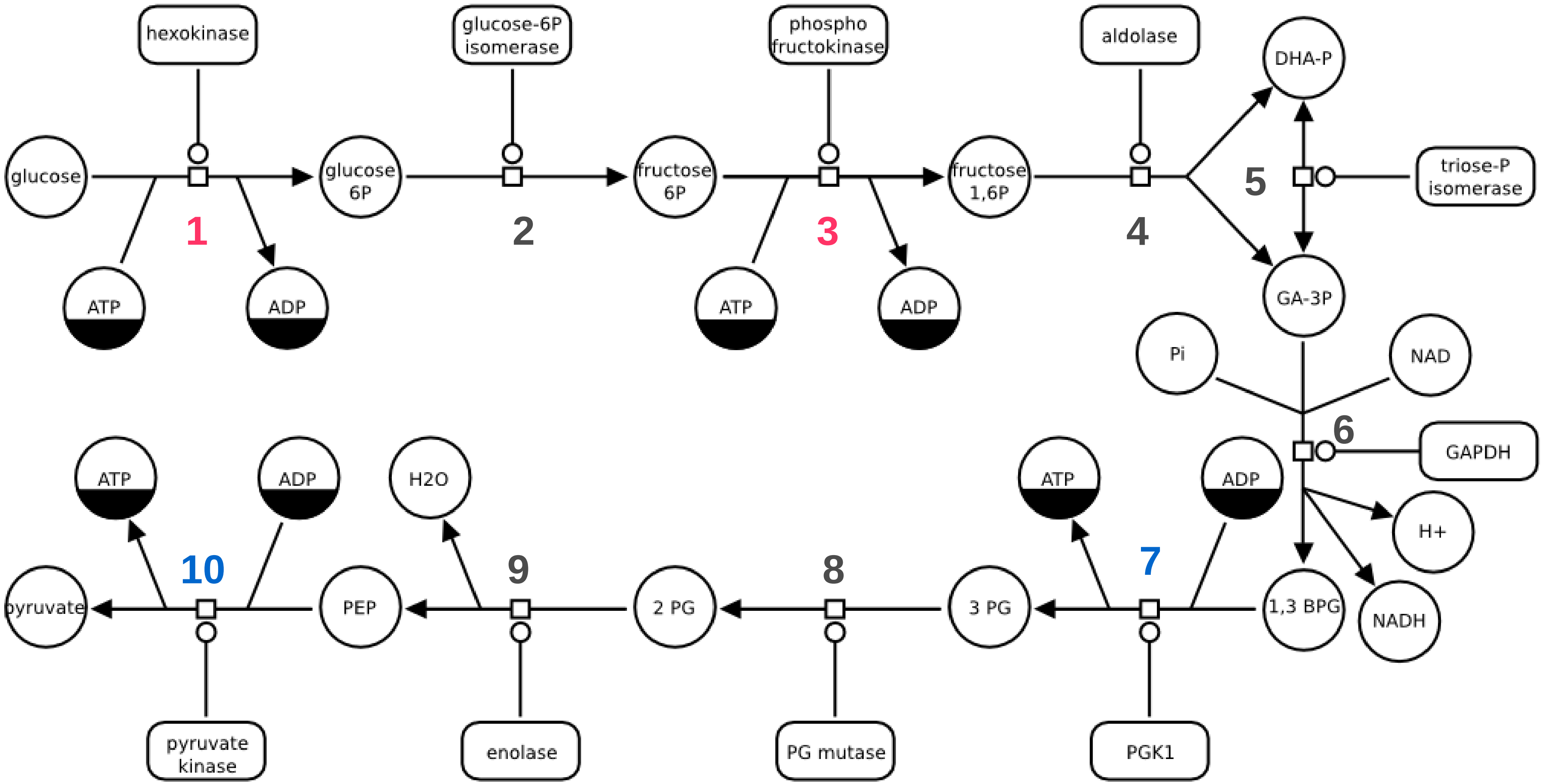


A biochemical reaction is a process



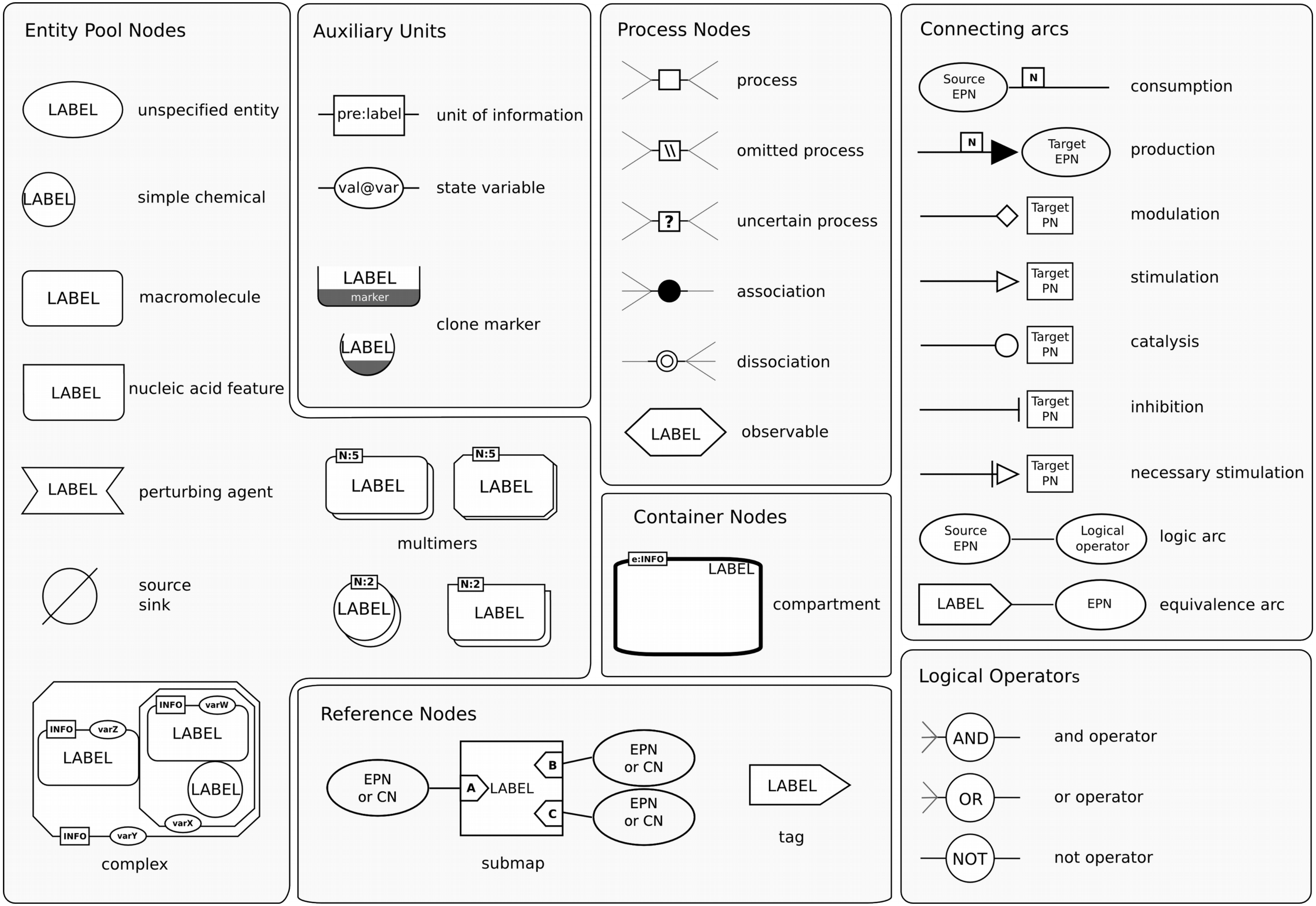
→ Reconstruction of state variable evolution from process descriptions:

- Processes can be combined in ODEs (for deterministic simulations); transformed in propensities (for stochastic simulations)
- Systems can be reconfigured quickly by adding or removing a process



ATP is consumed by processes 1 and 3, and produced by processes 7 and 10

SBGN Process Diagram L1 reference card



Entity Pool Nodes

- unspecified entity
- simple chemical
- macromolecule
- nucleic acid feature
- perturbing agent
- source
  sink
- complex

Auxiliary Units

- unit of information
- state variable
- clone marker
- multimers

Process Nodes

- process
- omitted process
- uncertain process
- association
- dissociation
- observable

Container Nodes

- compartment

Reference Nodes

- submap
- tag

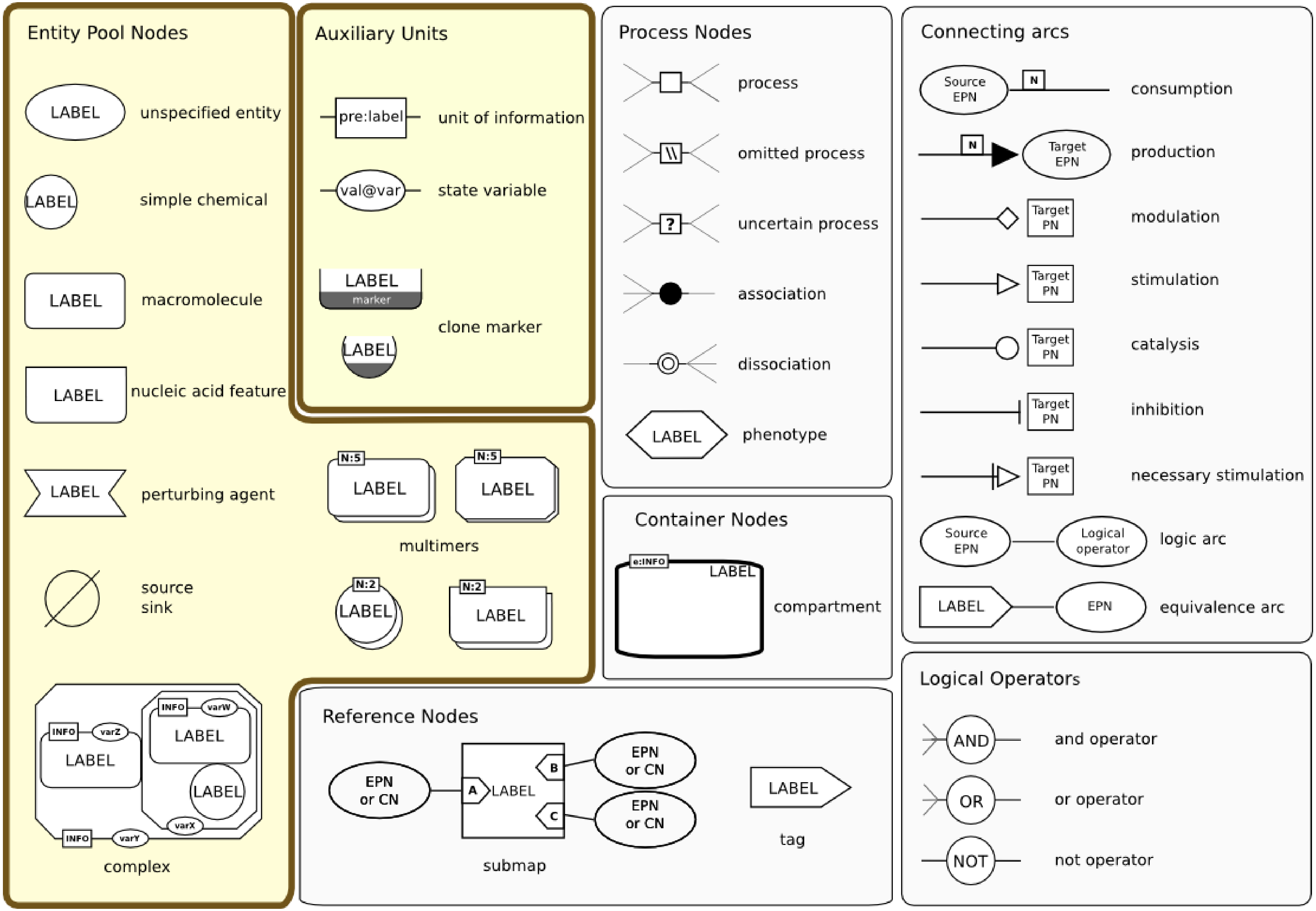
Connecting arcs

- consumption
- production
- modulation
- stimulation
- catalysis
- inhibition
- necessary stimulation
- logic arc
- equivalence arc

Logical Operators

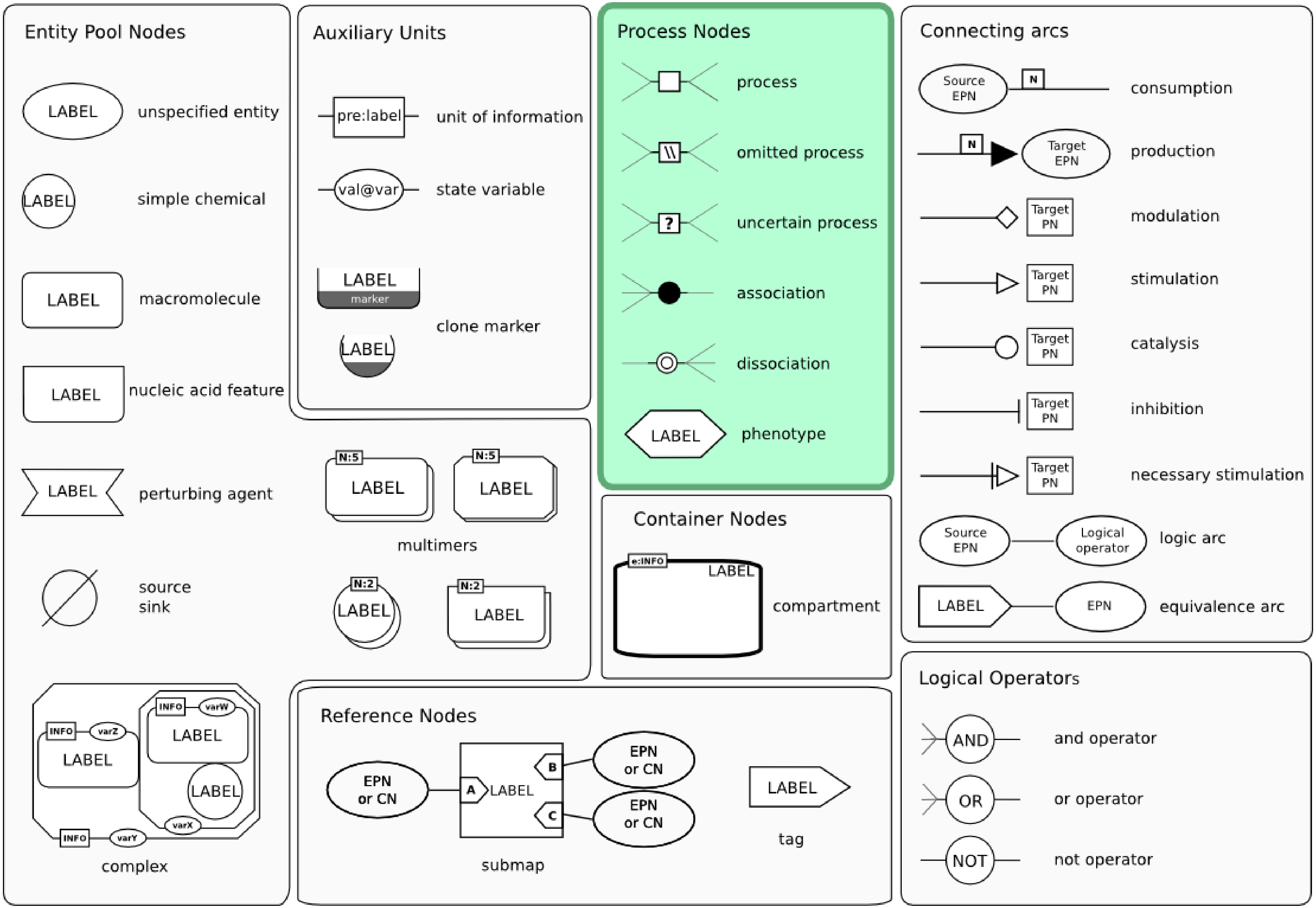
- and operator
- or operator
- not operator

Entity Pool Nodes

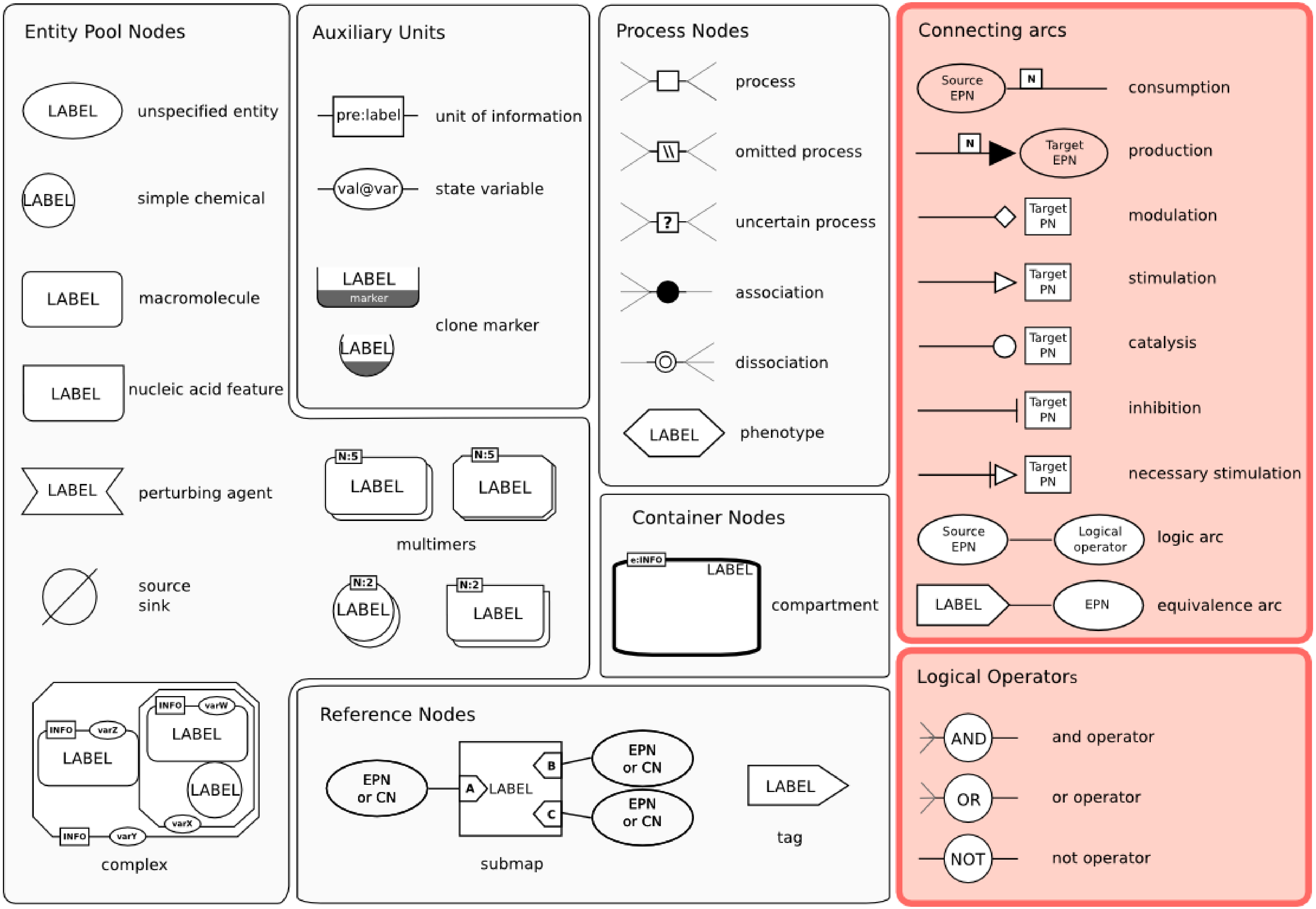


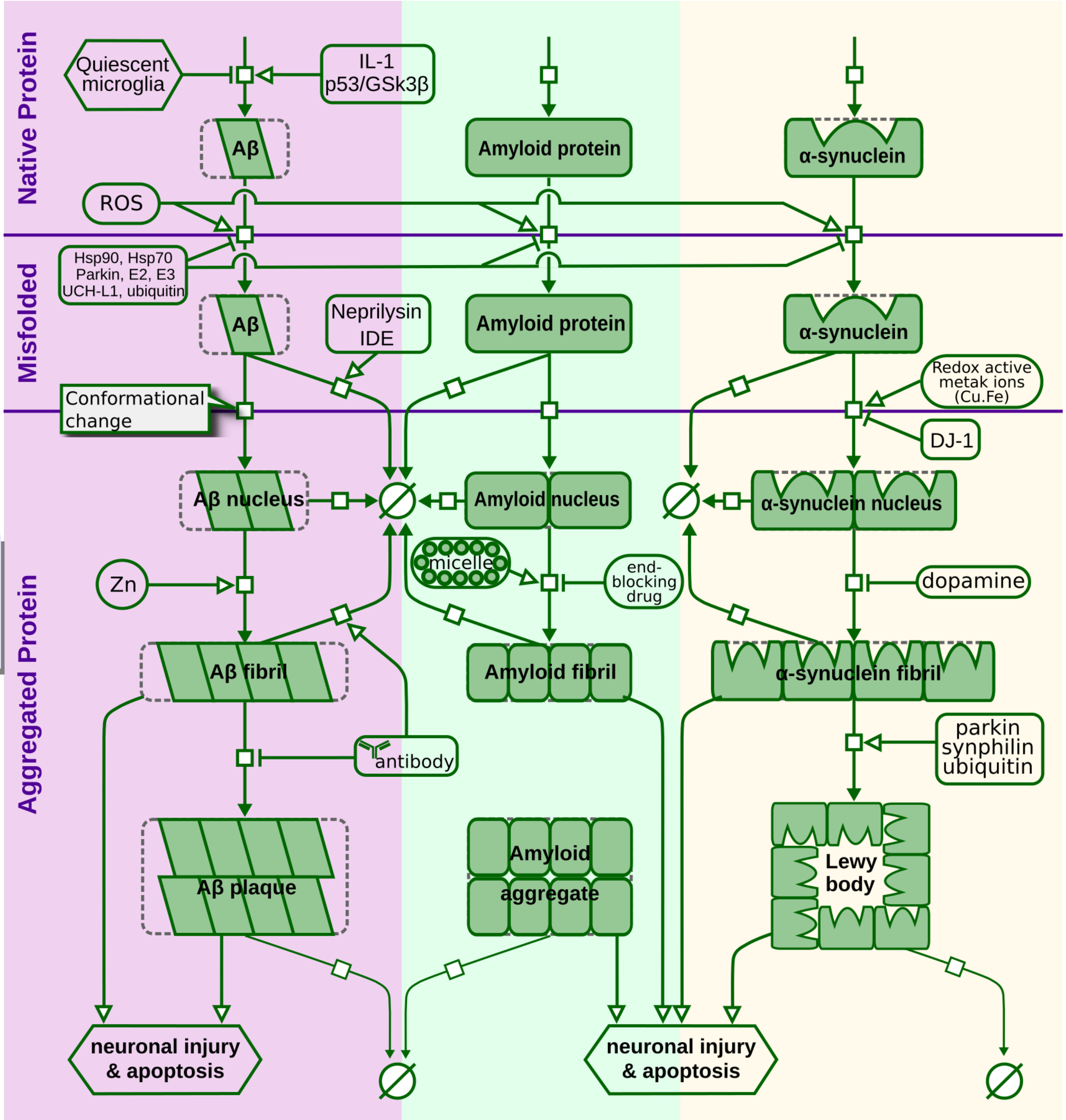
part III Systems Biology, 17 October 2017

Process Nodes



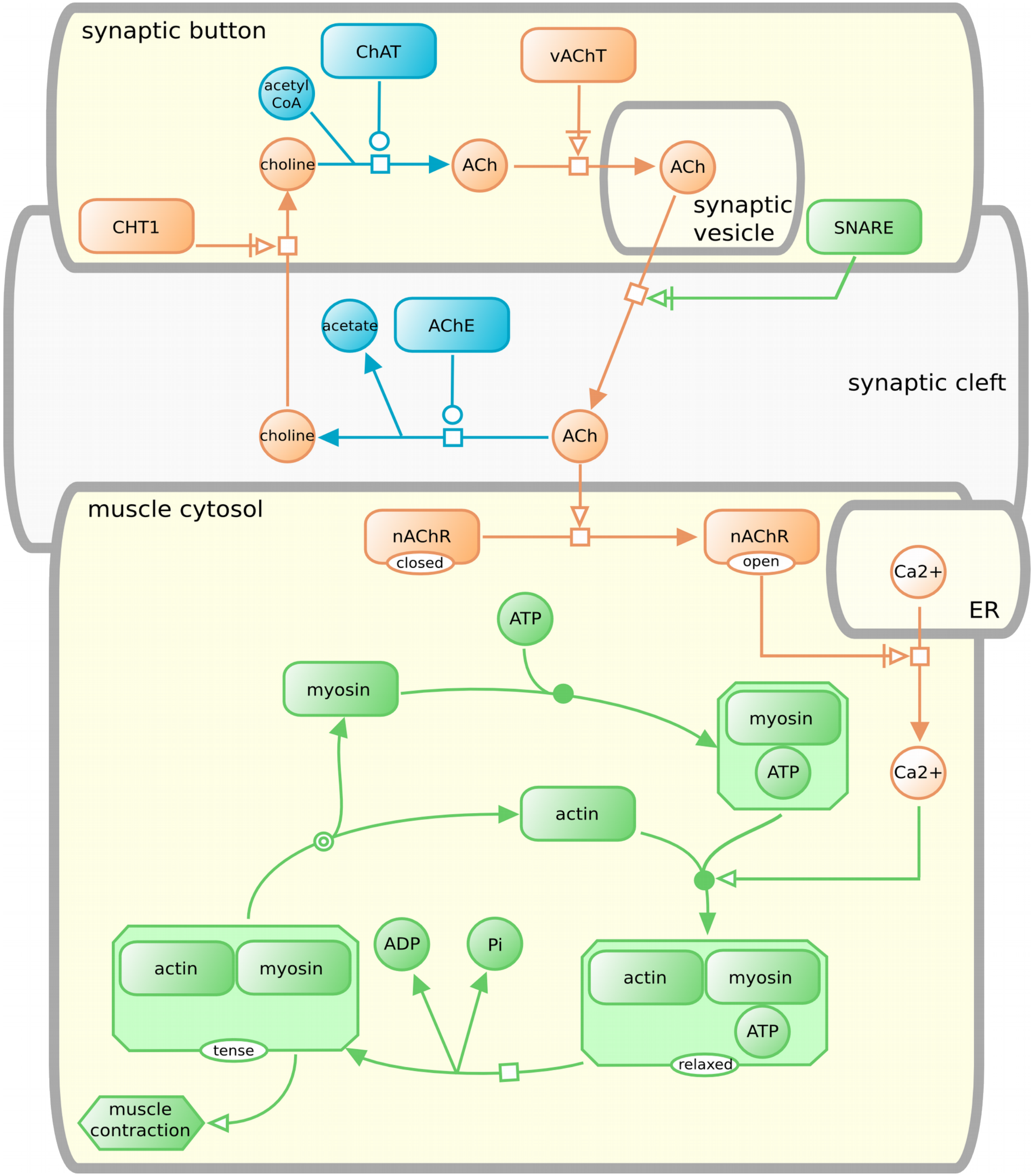
Connecting arcs



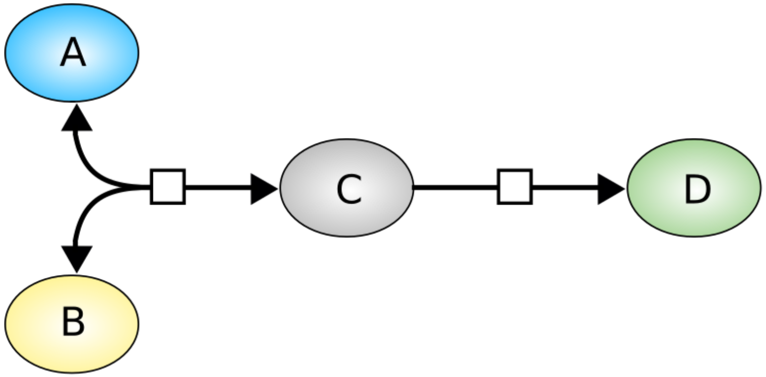


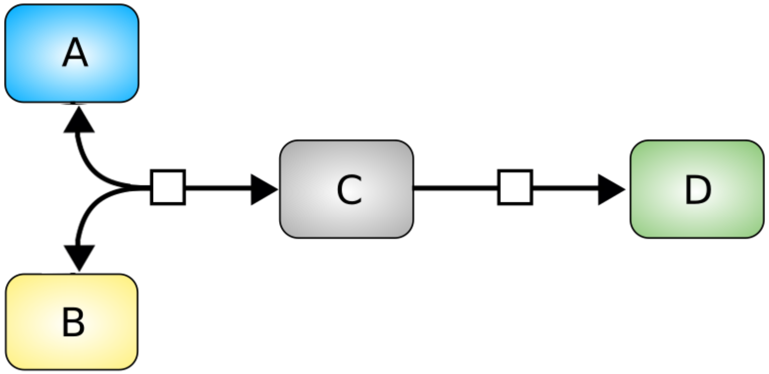
Lloret i Villas*et al.*
CPT: Pharm. Syst. Pharmacol.
(2016)

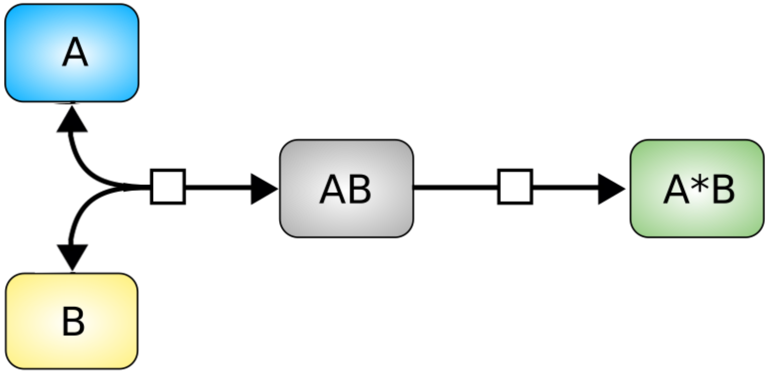
Multicellular

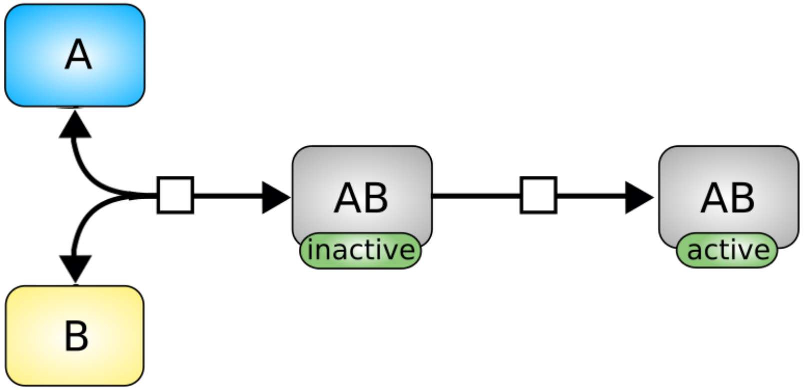


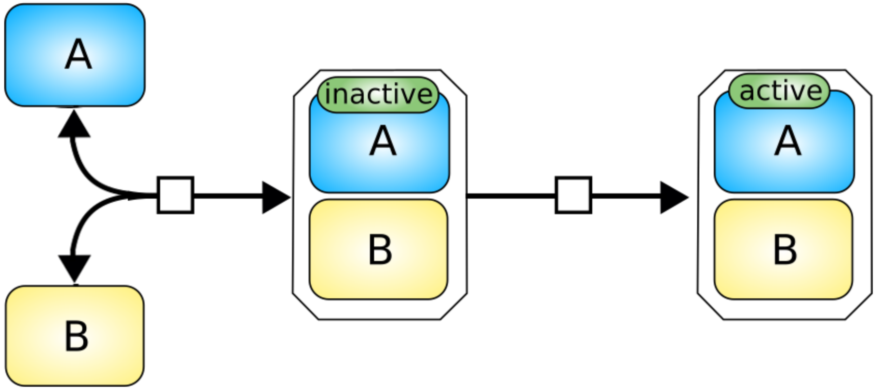
Variable granularity

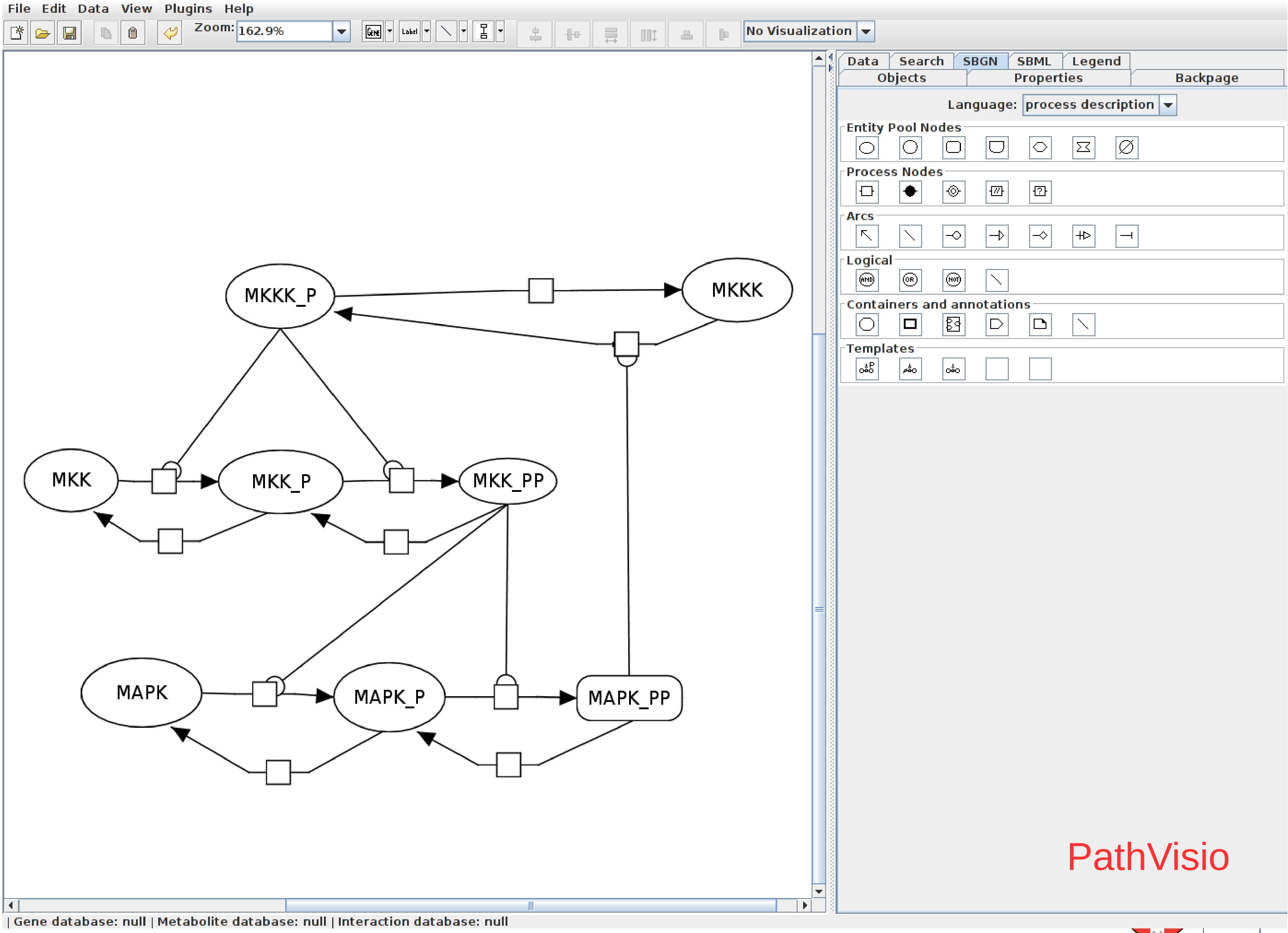










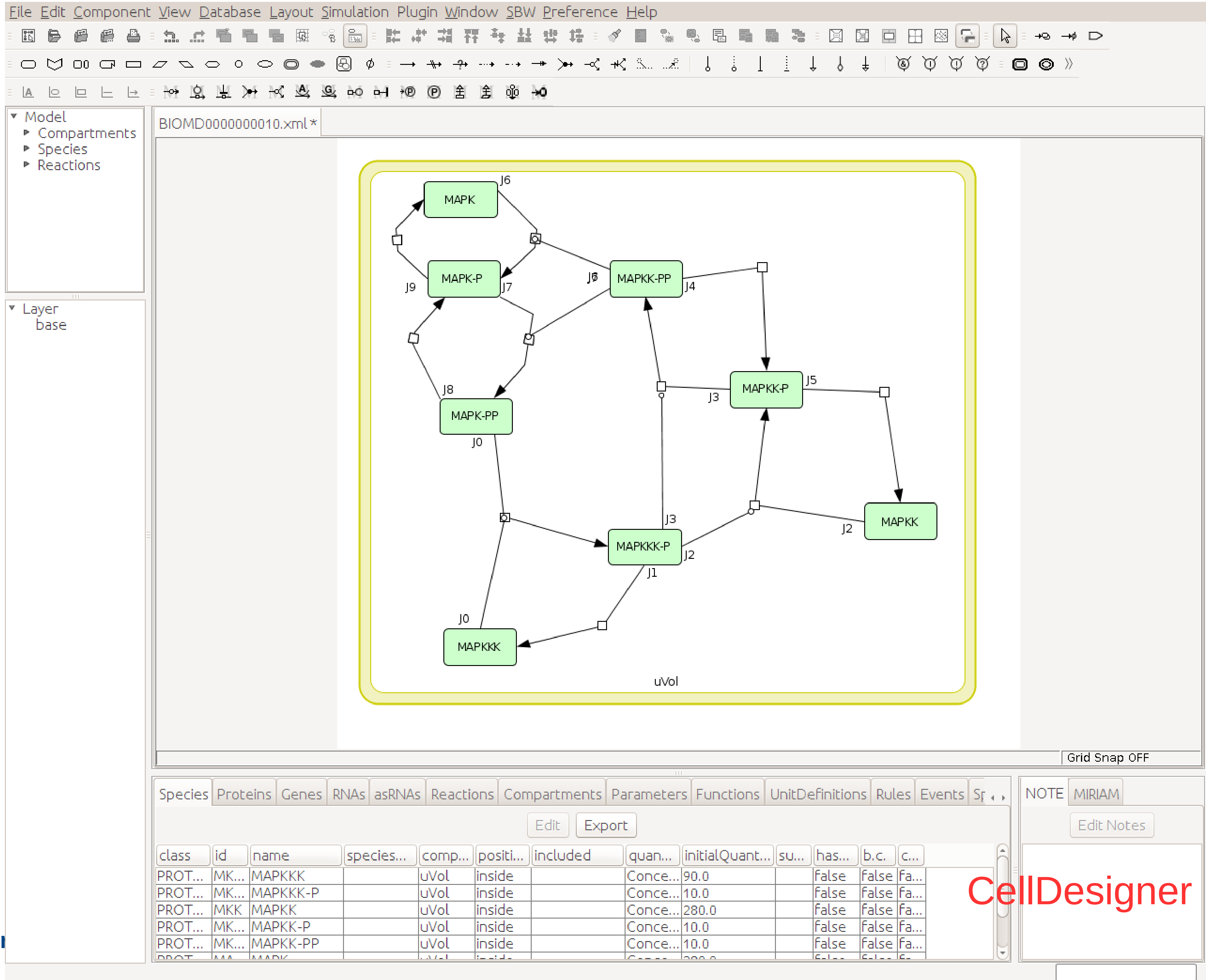


Zoom: 162.9%

Language: process description

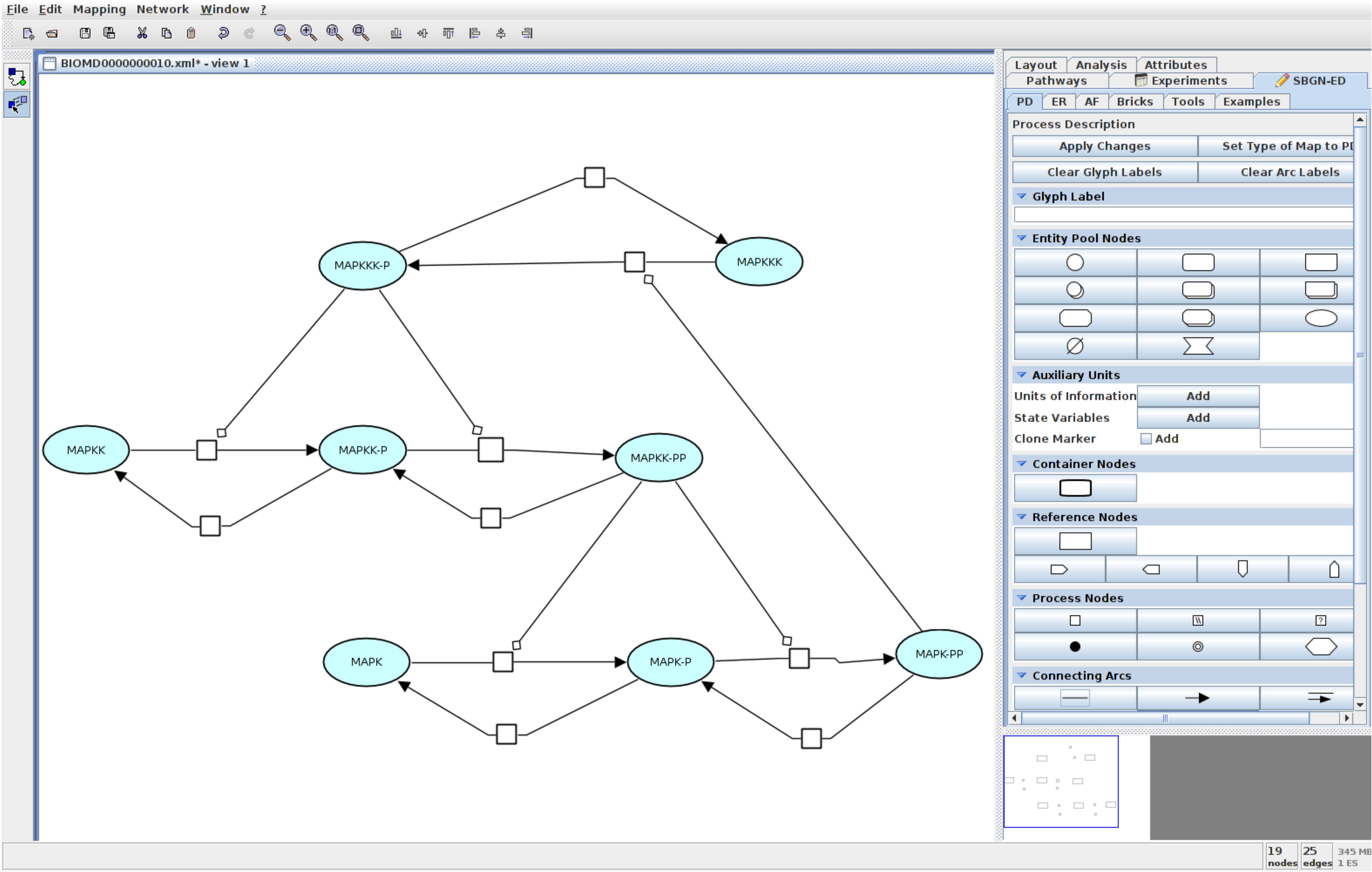
| Gene database: null | Metabolite database: null | Interaction database: null

PathVisio

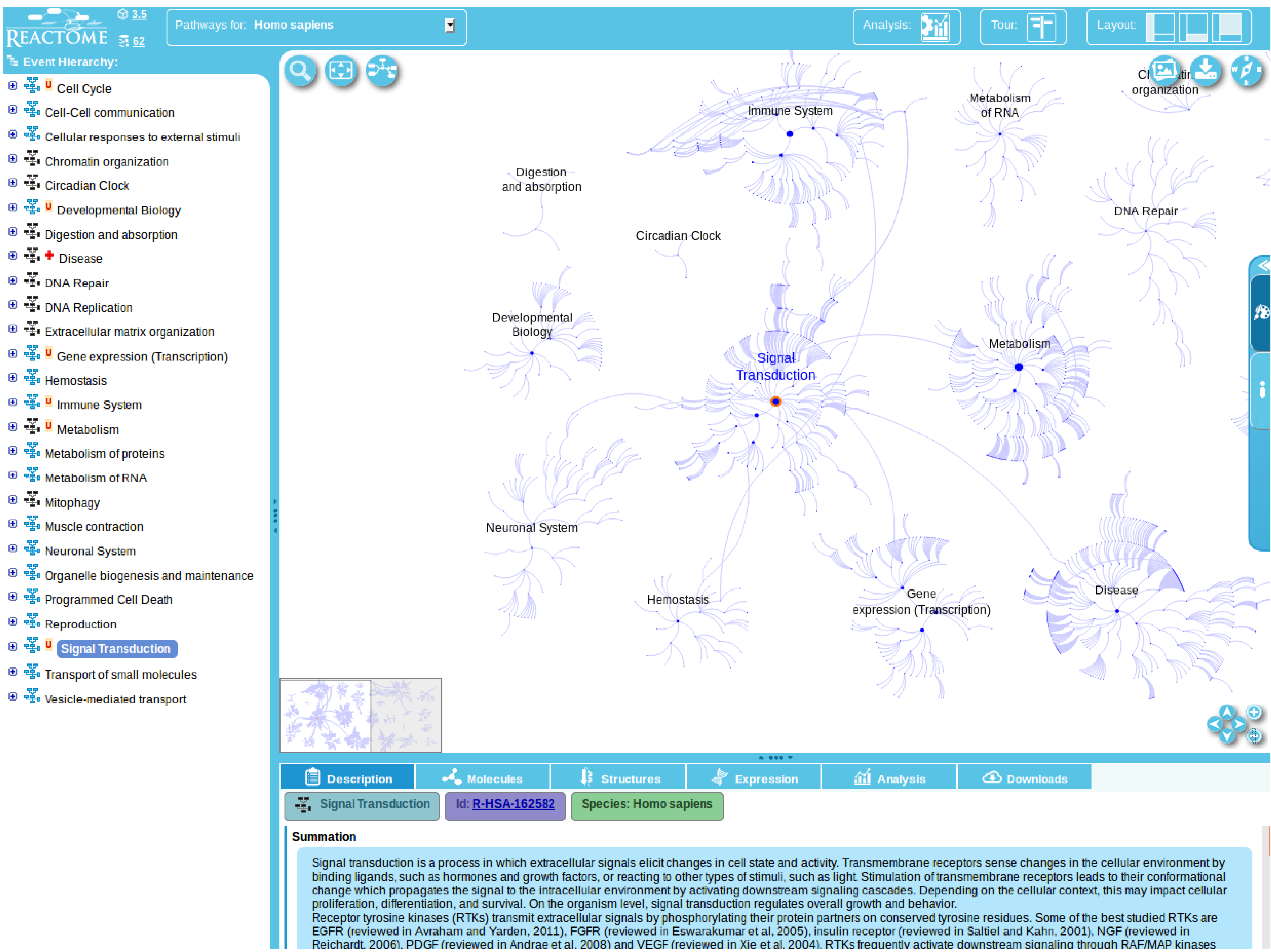


class	id	name	species...	comp...	positi...	included	quan...	initialQuant...	su...	has...	b.c.	c...
PROT...	MK...	MAPKKK		uVol	inside		Conce...	90.0		false	false	fa...
PROT...	MK...	MAPKKK-P		uVol	inside		Conce...	10.0		false	false	fa...
PROT...	MKK	MAPKK		uVol	inside		Conce...	280.0		false	false	fa...
PROT...	MK...	MAPKK-P		uVol	inside		Conce...	10.0		false	false	fa...
PROT...	MK...	MAPKK-PP		uVol	inside		Conce...	10.0		false	false	fa...

CellDesigner

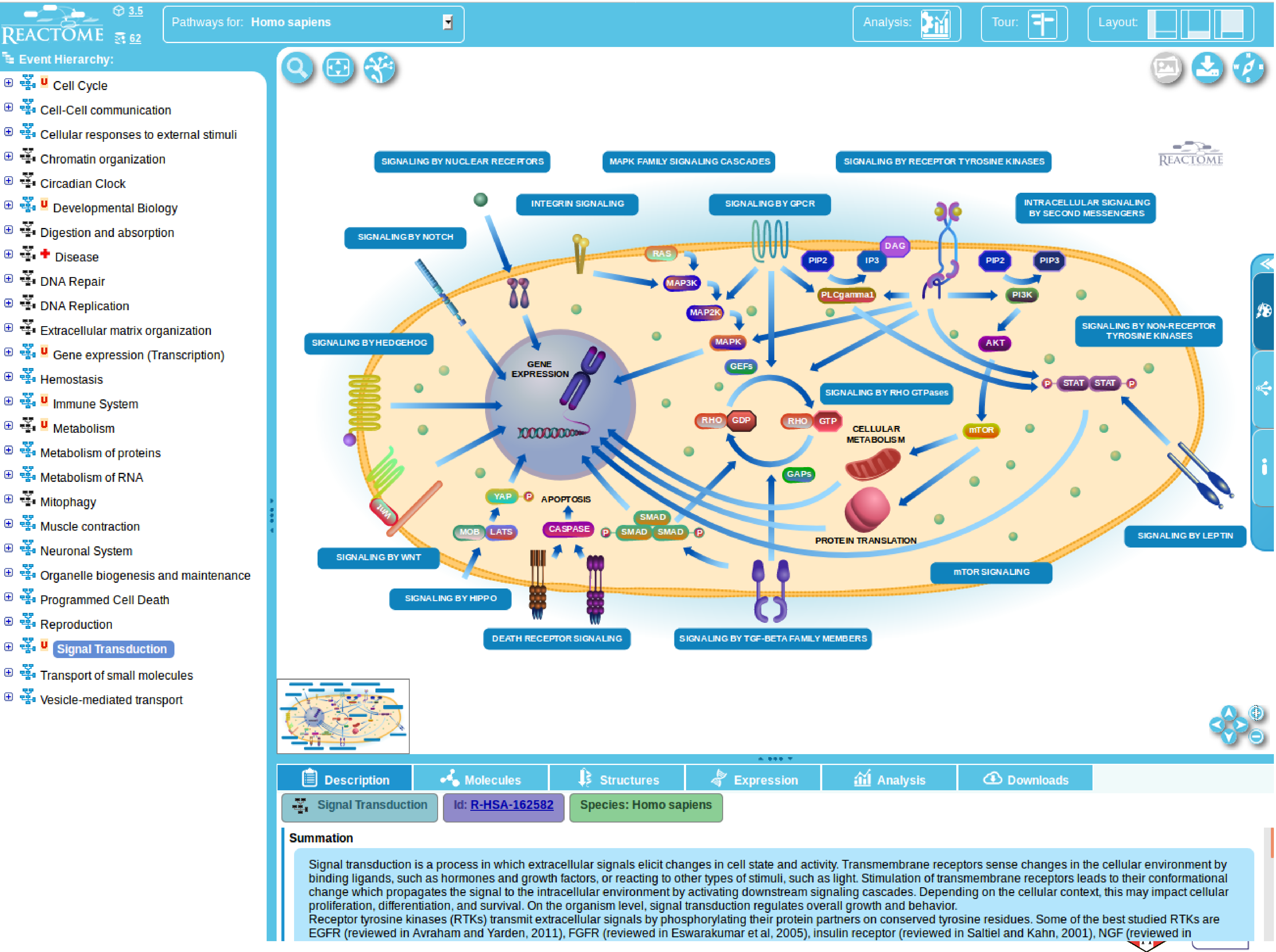

File
Edit
Mapping
Network
Window
?
BIOMD0000000010.xml* - view 1
MAPKKK-P
MAPKKK
MAPKK
MAPKK-P
MAPKK-PP
MAPK
MAPK-P
MAPK-PP
Layout
Analysis
Attributes
Pathways
Experiments
SBGN-ED
PD
ER
AF
Bricks
Tools
Examples
Process Description
Apply Changes
Set Type of Map to PD
Clear Glyph Labels
Clear Arc Labels
Glyph Label
Entity Pool Nodes
Auxiliary Units
Units of Information
Add
State Variables
Add
Clone Marker
Add
Container Nodes
Reference Nodes
Process Nodes
Connecting Arcs
19 nodes
25 edges
345 MB
1 ES

Vanted



Summation

Signal transduction is a process in which extracellular signals elicit changes in cell state and activity. Transmembrane receptors sense changes in the cellular environment by binding ligands, such as hormones and growth factors, or reacting to other types of stimuli, such as light. Stimulation of transmembrane receptors leads to their conformational change which propagates the signal to the intracellular environment by activating downstream signaling cascades. Depending on the cellular context, this may impact cellular proliferation, differentiation, and survival. On the organism level, signal transduction regulates overall growth and behavior.
Receptor tyrosine kinases (RTKs) transmit extracellular signals by phosphorylating their protein partners on conserved tyrosine residues. Some of the best studied RTKs are EGFR (reviewed in Avraham and Yarden, 2011), FGFR (reviewed in Eswarakumar et al, 2005), insulin receptor (reviewed in Saltiel and Kahn, 2001), NGF (reviewed in Reichardt, 2006), PDGF (reviewed in Andrae et al, 2008) and VEGF (reviewed in Xie et al, 2004). RTKs frequently activate downstream signaling through RAF/MAP kinases



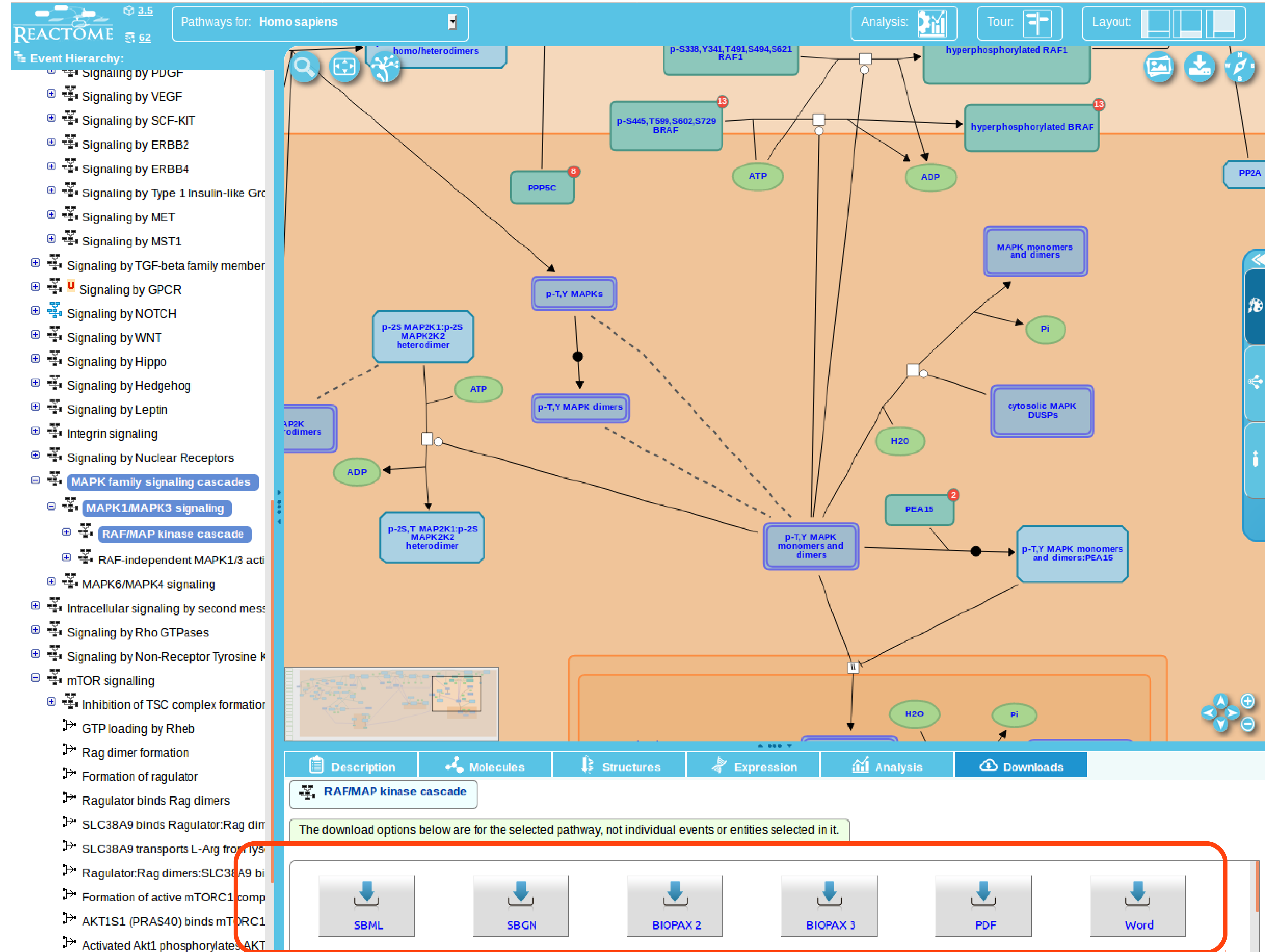
Signal Transduction

Id: R-HSA-162582

Species: Homo sapiens

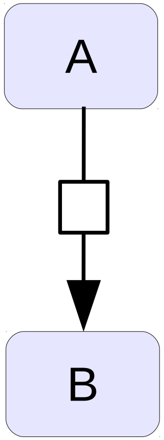
Summation

Signal transduction is a process in which extracellular signals elicit changes in cell state and activity. Transmembrane receptors sense changes in the cellular environment by binding ligands, such as hormones and growth factors, or reacting to other types of stimuli, such as light. Stimulation of transmembrane receptors leads to their conformational change which propagates the signal to the intracellular environment by activating downstream signaling cascades. Depending on the cellular context, this may impact cellular proliferation, differentiation, and survival. On the organism level, signal transduction regulates overall growth and behavior.
Receptor tyrosine kinases (RTKs) transmit extracellular signals by phosphorylating their protein partners on conserved tyrosine residues. Some of the best studied RTKs are EGFR (reviewed in Avraham and Yarden, 2011), FGFR (reviewed in Eswarakumar et al, 2005), insulin receptor (reviewed in Saltiel and Kahn, 2001), NGF (reviewed in



The download options below are for the selected pathway, not individual events or entities selected in it.

A very simple Process with SBML



$$\frac{d[B]}{dt} = k \times [A]$$

```xml
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              <times/>
              <ci> cell </ci>
              <ci> k1 </ci>
              <ci> A </ci>
            </apply>
          </math>
        </kineticLaw>
      </reaction>
    </listOfReactions>
  </model>
</sbml>
```
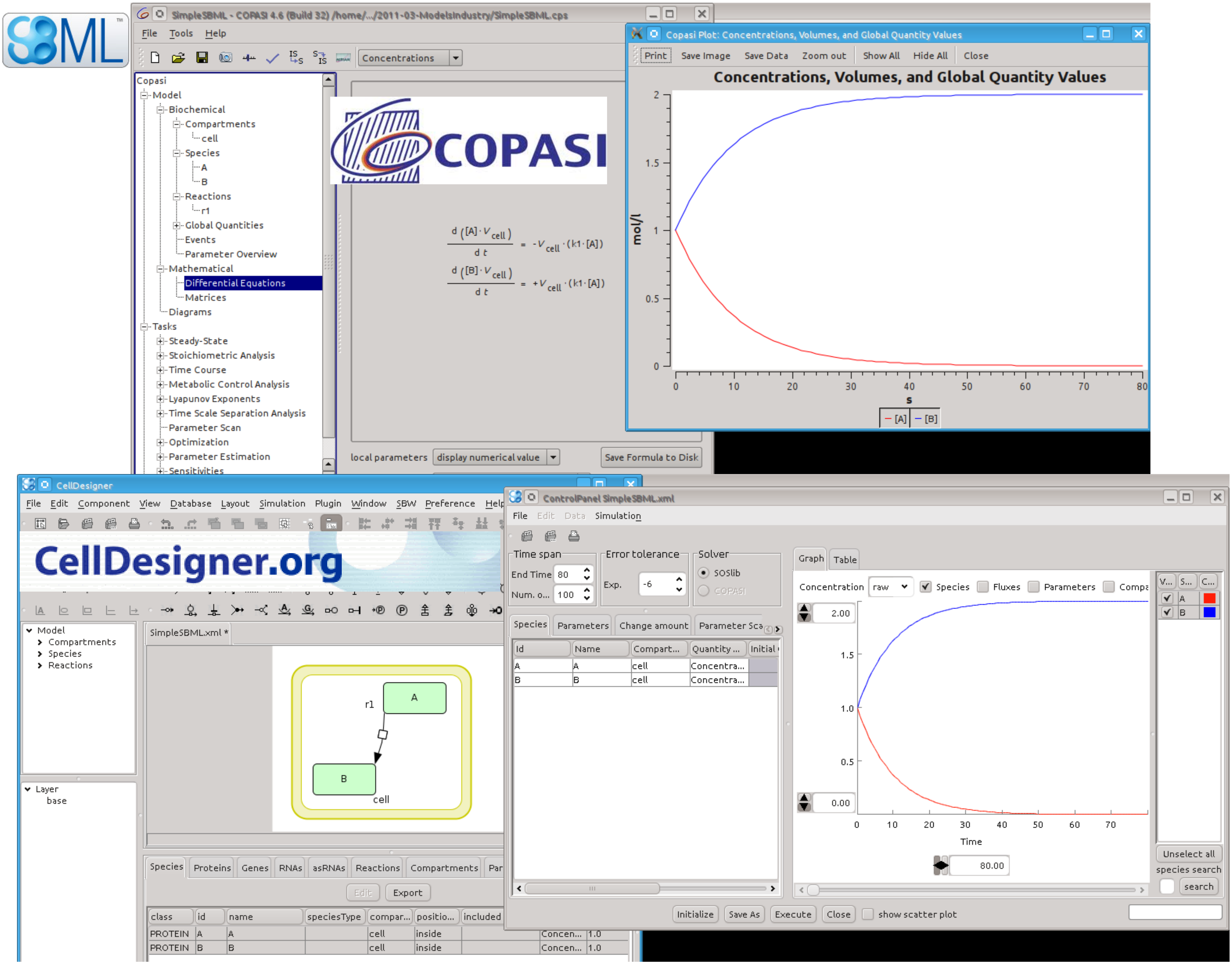

http://sbml.org



SimpleSBML - COPASI 4.6 (Build 32) /home/.../2011-03-ModelsIndustry/SimpleSBML.cps

$$\frac{d\,([A]\cdot V_{cell})}{d\,t} = -V_{cell}\cdot(k1\cdot[A])$$

$$\frac{d\,([B]\cdot V_{cell})}{d\,t} = +V_{cell}\cdot(k1\cdot[A])$$

local parameters: display numerical value

Copasi Plot: Concentrations, Volumes, and Global Quantity Values

CellDesigner

ControlPanel SimpleSBML.xml

Time span: End Time 80; Num. o... 100

Error tolerance: Exp. -6

Solver: ● SOSlib ○ COPASI

Id	Name	Compart...	Quantity ...	Initial
A	A	cell	Concentra...	
B	B	cell	Concentra...	

Concentration: raw ☑ Species ☐ Fluxes ☐ Parameters ☐ Compa

class	id	name	speciesType	compar...	positio...	included		
PROTEIN	A	A		cell	inside		Concen...	1.0
PROTEIN	B	B		cell	inside		Concen...	1.0

A not so simple SBML file (Recon2)

_computational BIOLOGY

RESOURCE

A community-driven global reconstruction of human metabolism

Ines Thiele[1,2,37], Neil Swainston[3,4,37], Ronan M T Fleming[1,5], Andreas Hoppe[6], Swagatika Sahoo[1], Maike K Aurich[1], Hulda Haraldsdottir[1], Monica L Mo[7], Ottar Rolfsson[1], Miranda D Stobbe[8,9], Stefan G Thorleifsson[1], Rasmus Agren[10], Christian Bölling[6], Sergio Bordel[10], Arvind K Chavali[11], Paul Dobson[12], Warwick B Dunn[3,13], Lukas Endler[14], David Hala[15], Michael Hucka[16], Duncan Hull[4], Daniel Jameson[3,4], Neema Jamshidi[7], Jon J Jonsson[5], Nick Juty[17], Sarah Keating[17], Intawat Nookaew[10], Nicolas Le Novère[17,18], Naglis Malys[3,19,20], Alexander Mazein[21], Jason A Papin[11], Nathan D Price[22], Evgeni Selkov, Sr[23], Martin I Sigurdsson[1], Evangelos Simeonidis[22,24], Nikolaus Sonnenschein[25], Kieran Smallbone[3,26], Anatoly Sorokin[21,27], Johannes H G M van Beek[28–30], Dieter Weichart[3,31], Igor Goryanin[21,32], Jens Nielsen[10], Hans V Westerhoff[3,28,33,34], Douglas B Kell[3,35], Pedro Mendes[3,4,36] & Bernhard Ø Palsson[1,7]

Multiple models of human metabolism have been reconstructed, but each represents only a subset of our knowledge. Here we describe Recon 2, a community-driven, consensus 'metabolic reconstruction', which is the most comprehensive representation of human metabolism that is applicable to computational modeling. Compared with its predecessors, the reconstruction has improved topological and functional features, including ~2× more reactions and ~1.7× more unique metabolites. Using Recon 2 we predicted changes in metabolite biomarkers for 49 inborn errors of metabolism with 77% accuracy when compared to experimental data. Mapping metabolomic data and drug information onto Recon 2 demonstrates its potential for integrating and analyzing diverse data types. Using protein expression data, we automatically generated a compendium of 65 cell type–specific models, providing a basis for manual curation or investigation of cell-specific metabolic properties. Recon 2 will facilitate many future biomedical studies and is freely available at http://humanmetabolism.org/.

An understanding of metabolism is fundamental to comprehending the phenotypic behavior of all living organisms, including humans, where metabolism is integral to health and is involved in much of human disease. High quality, genome-scale 'metabolic reconstructions' are at the heart of bottom-up systems biology analyses and represent the entire network of metabolic reactions that a given organism is known to exhibit[1]. The metabolic-network reconstruction procedure is now well-established[2] and has been applied to a growing number of model organisms[3]. Metabolic reconstructions allow for the conversion of biological knowledge into a mathematical format and the subsequent computation of physiological states[1,4,5] to address a variety of scientific and applied questions[3,6]. Reconstructions enable network-wide mechanistic investigations of the genotype-phenotype relationship. A high-quality reconstruction of the metabolic network is thus

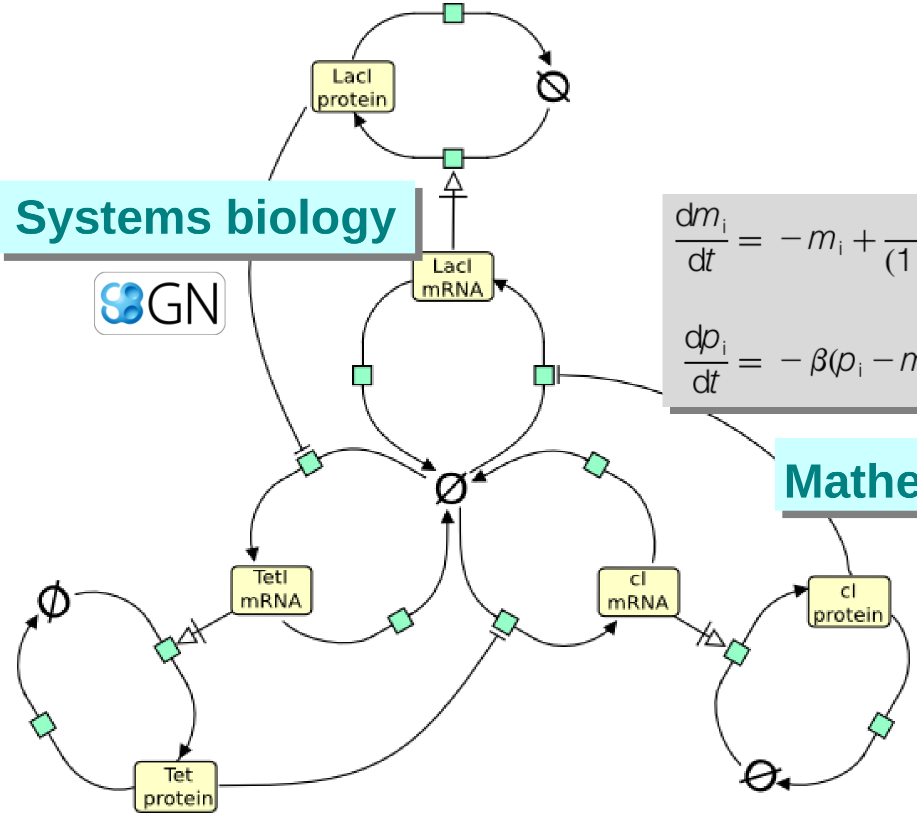
- 8 compartments
- 5 063 metabolites
- 2 194 proteins
- 7 440 reactions

MODEL1109130000

BioModels Database – http://www.ebi.ac.uk/biomodels

Systems biology

SBGN



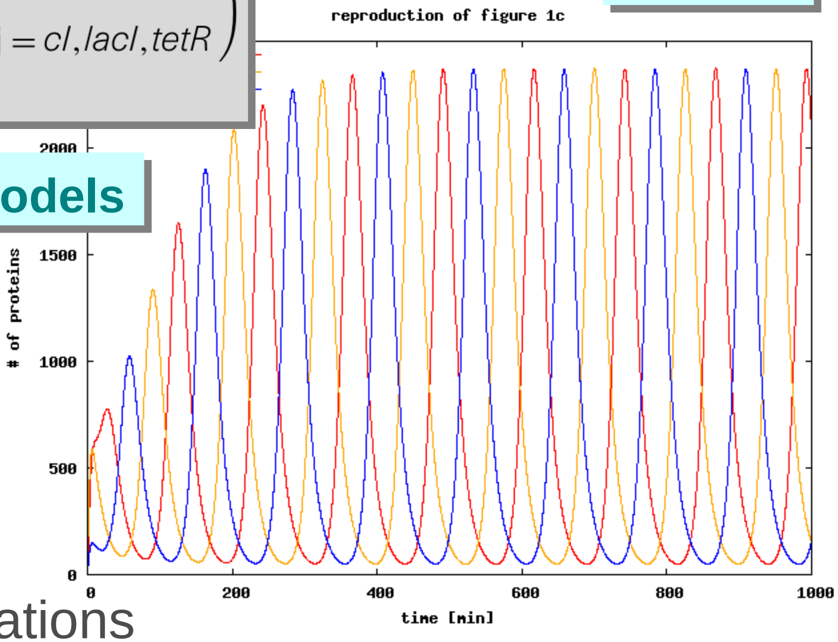
$$\frac{dm_i}{dt} = -m_i + \frac{\alpha}{(1+p_j^n)} + \alpha_0 \qquad \begin{pmatrix} i = lacI, tetR, cI \\ j = cI, lacI, tetR \end{pmatrix}$$

$$\frac{dp_i}{dt} = -\beta(p_i - m_i)$$

Mathematical models

SBML

curated

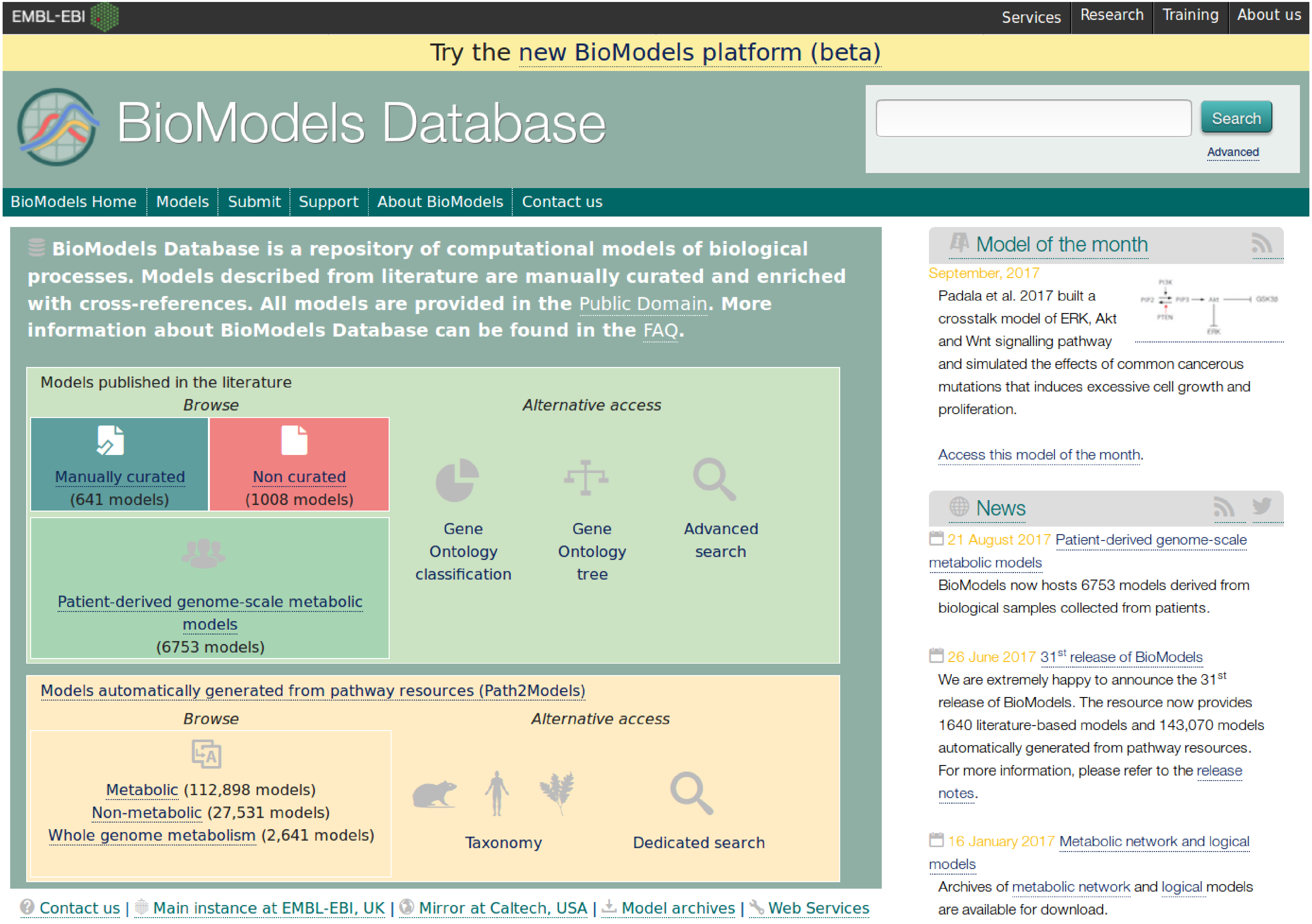


>140 000 models, >10 millions mathematical relations

Deposition advised by >300 journals, database > 600 citations

1.5 million page requests per year

Submission in SBML and CellML; Export in SBML, CellML, XPP, SciLab, BioPAX, Octave, PDF, VCML, SBGN



Try the new BioModels platform (beta)

BioModels Database

BioModels Database is a repository of computational models of biological processes. Models described from literature are manually curated and enriched with cross-references. All models are provided in the Public Domain. More information about BioModels Database can be found in the FAQ.

Models published in the literature

Browse

Manually curated
(641 models)

Non curated
(1008 models)

Patient-derived genome-scale metabolic models
(6753 models)

Alternative access

Gene Ontology classification

Gene Ontology tree

Advanced search

Models automatically generated from pathway resources (Path2Models)

Browse

Metabolic (112,898 models)
Non-metabolic (27,531 models)
Whole genome metabolism (2,641 models)

Alternative access

Taxonomy

Dedicated search

Contact us | Main instance at EMBL-EBI, UK | Mirror at Caltech, USA | Model archives | Web Services

Model of the month

September, 2017

Padala et al. 2017 built a crosstalk model of ERK, Akt and Wnt signalling pathway and simulated the effects of common cancerous mutations that induces excessive cell growth and proliferation.

Access this model of the month.

News

21 August 2017 Patient-derived genome-scale metabolic models

BioModels now hosts 6753 models derived from biological samples collected from patients.

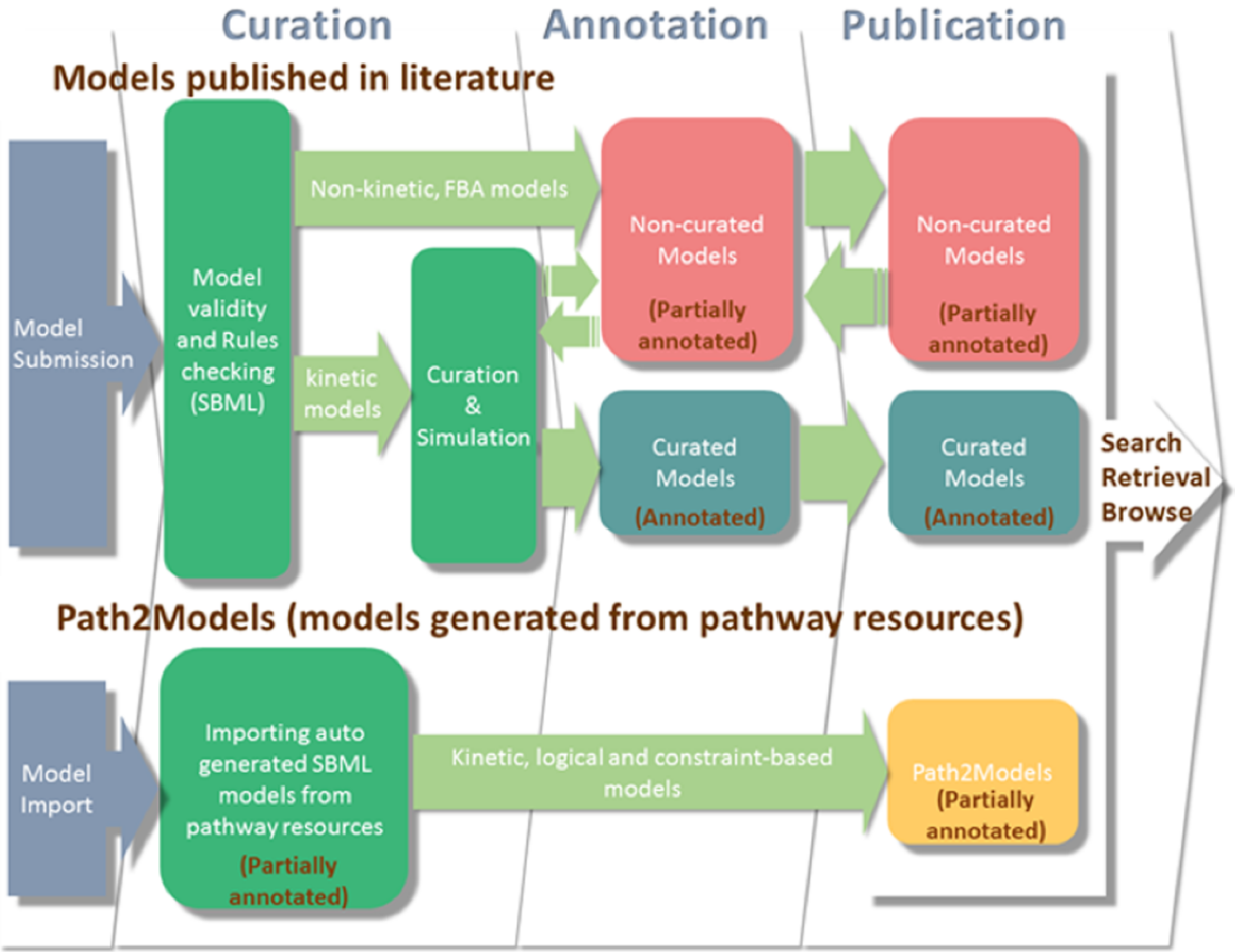
26 June 2017 31^{st} release of BioModels

We are extremely happy to announce the 31^{st} release of BioModels. The resource now provides 1640 literature-based models and 143,070 models automatically generated from pathway resources. For more information, please refer to the release notes.

16 January 2017 Metabolic network and logical models

Archives of metabolic network and logical models are available for download.

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



Curation

Annotation

Publication

Models published in literature

Model Submission

Model validity and Rules checking (SBML)

Non-kinetic, FBA models

kinetic models

Curation & Simulation

Non-curated Models

(Partially annotated)

Non-curated Models

(Partially annotated)

Curated Models

(Annotated)

Curated Models

(Annotated)

Search Retrieval Browse

Path2Models (models generated from pathway resources)

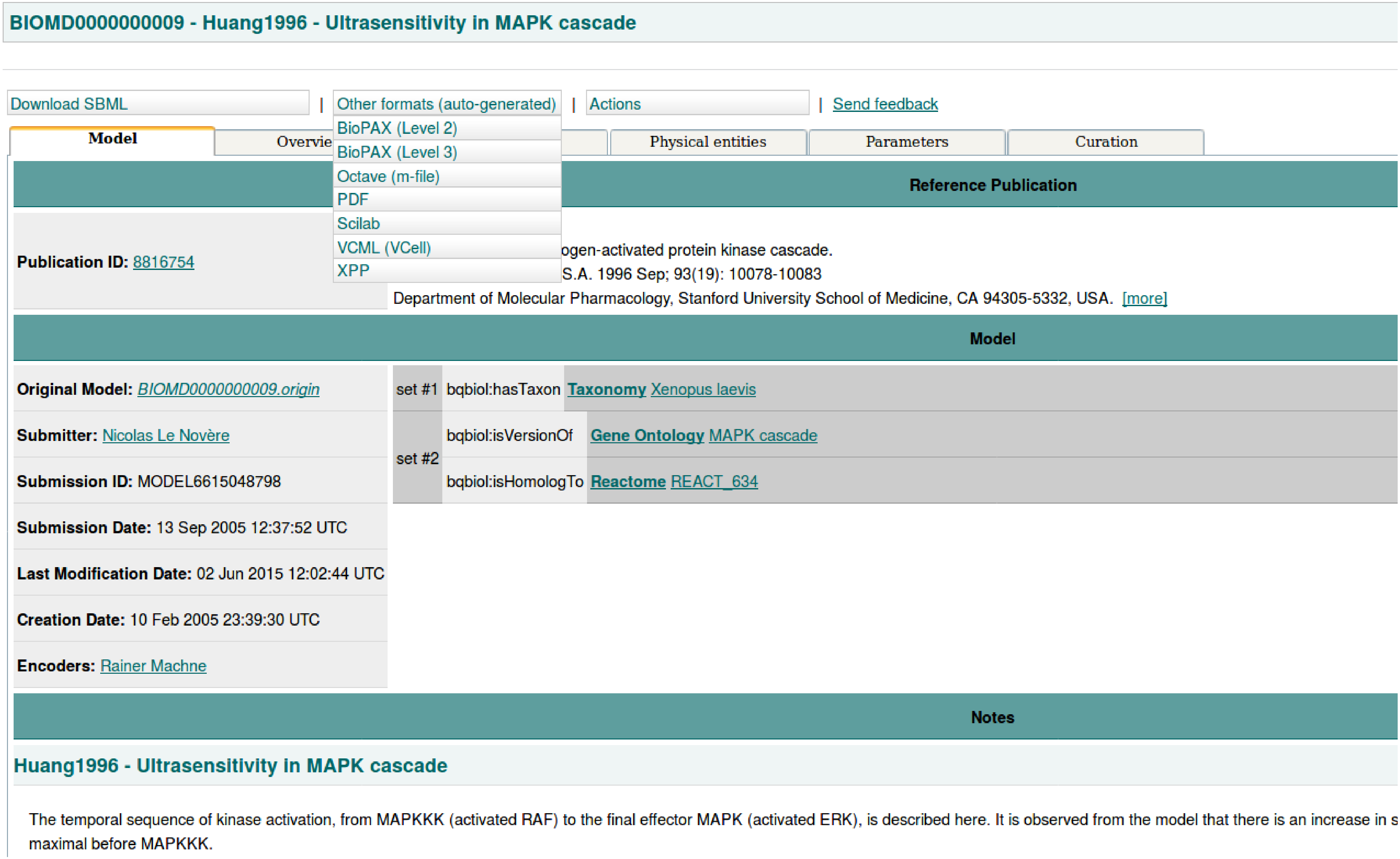
Model Import

Importing auto generated SBML models from pathway resources

(Partially annotated)

Kinetic, logical and constraint-based models

Path2Models (Partially annotated)



BIOMD0000000009 - Huang1996 - Ultrasensitivity in MAPK cascade

Reference Publication

Publication ID: 8816754

ogen-activated protein kinase cascade.

S.A. 1996 Sep; 93(19): 10078-10083

Department of Molecular Pharmacology, Stanford University School of Medicine, CA 94305-5332, USA. [more]

Model

Original Model: *BIOMD0000000009.origin*

Submitter: Nicolas Le Novère

Submission ID: MODEL6615048798

Submission Date: 13 Sep 2005 12:37:52 UTC

Last Modification Date: 02 Jun 2015 12:02:44 UTC

Creation Date: 10 Feb 2005 23:39:30 UTC

Encoders: Rainer Machne

set #1	bqbiol:hasTaxon	**Taxonomy** Xenopus laevis
set #2	bqbiol:isVersionOf	**Gene Ontology** MAPK cascade
	bqbiol:isHomologTo	**Reactome** REACT_634

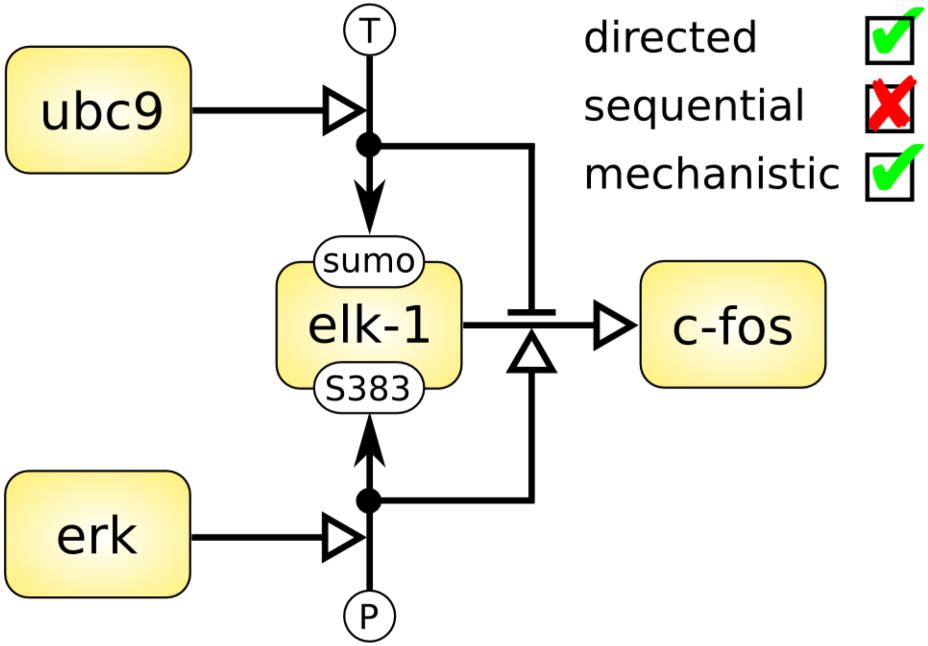
Notes

Huang1996 - Ultrasensitivity in MAPK cascade

The temporal sequence of kinase activation, from MAPKKK (activated RAF) to the final effector MAPK (activated ERK), is described here. It is observed from the model that there is an increase in s

maximal before MAPKKK.

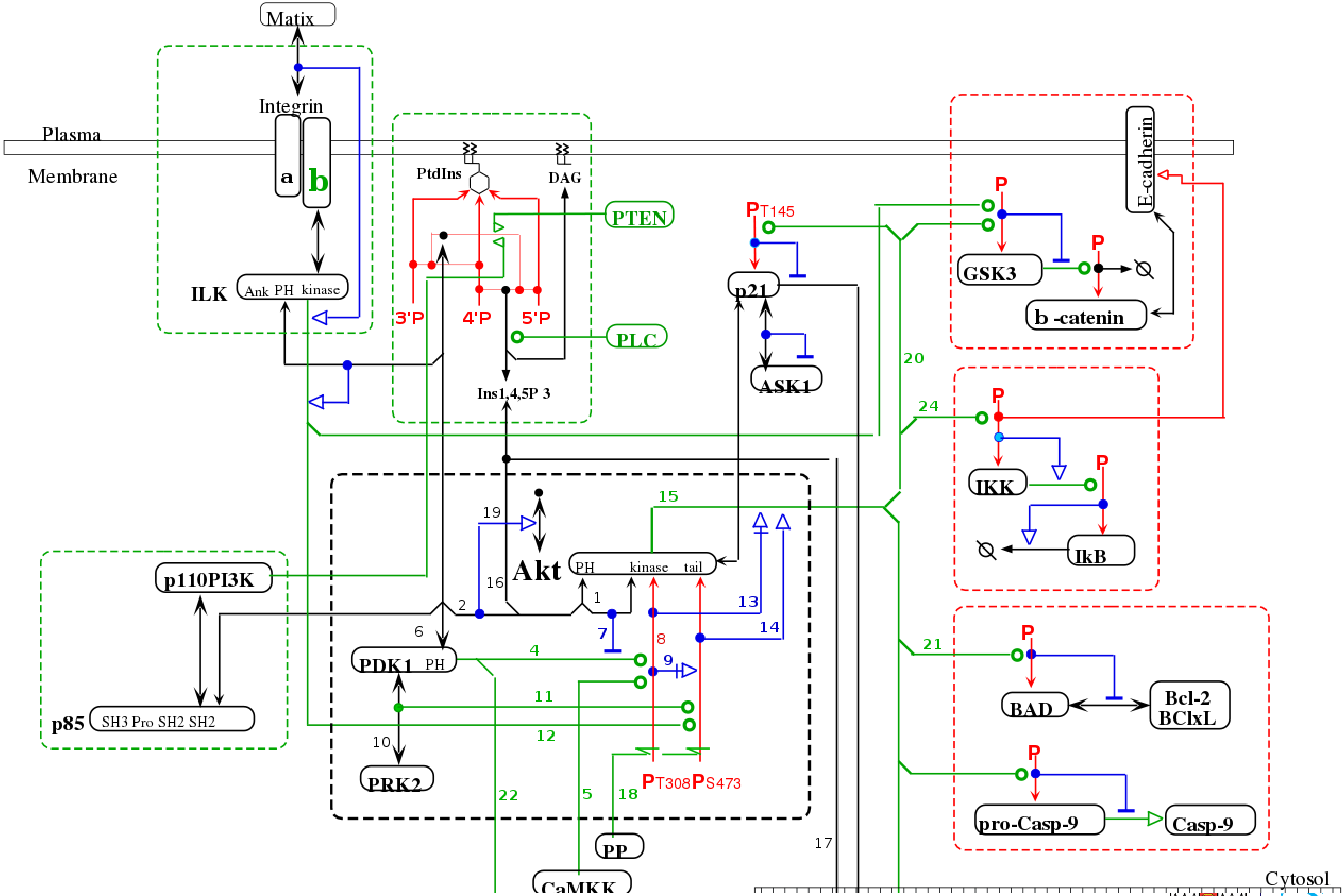
Entity Relationships



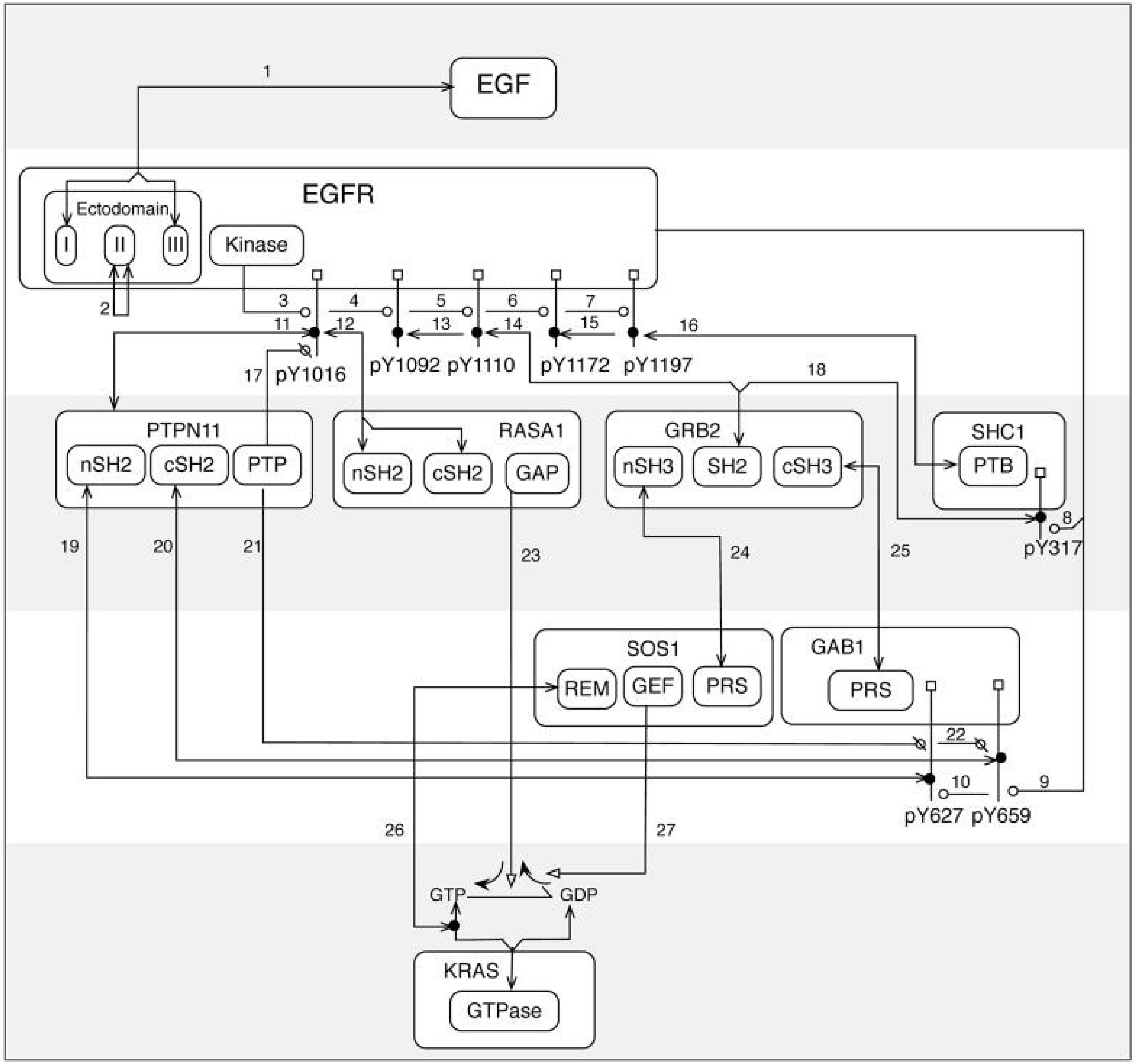
directed ☑
sequential ☒
mechanistic ☑

- Rule-based modelling
- Molecular Biology
- “Open world”
- Independent rules: no explosion

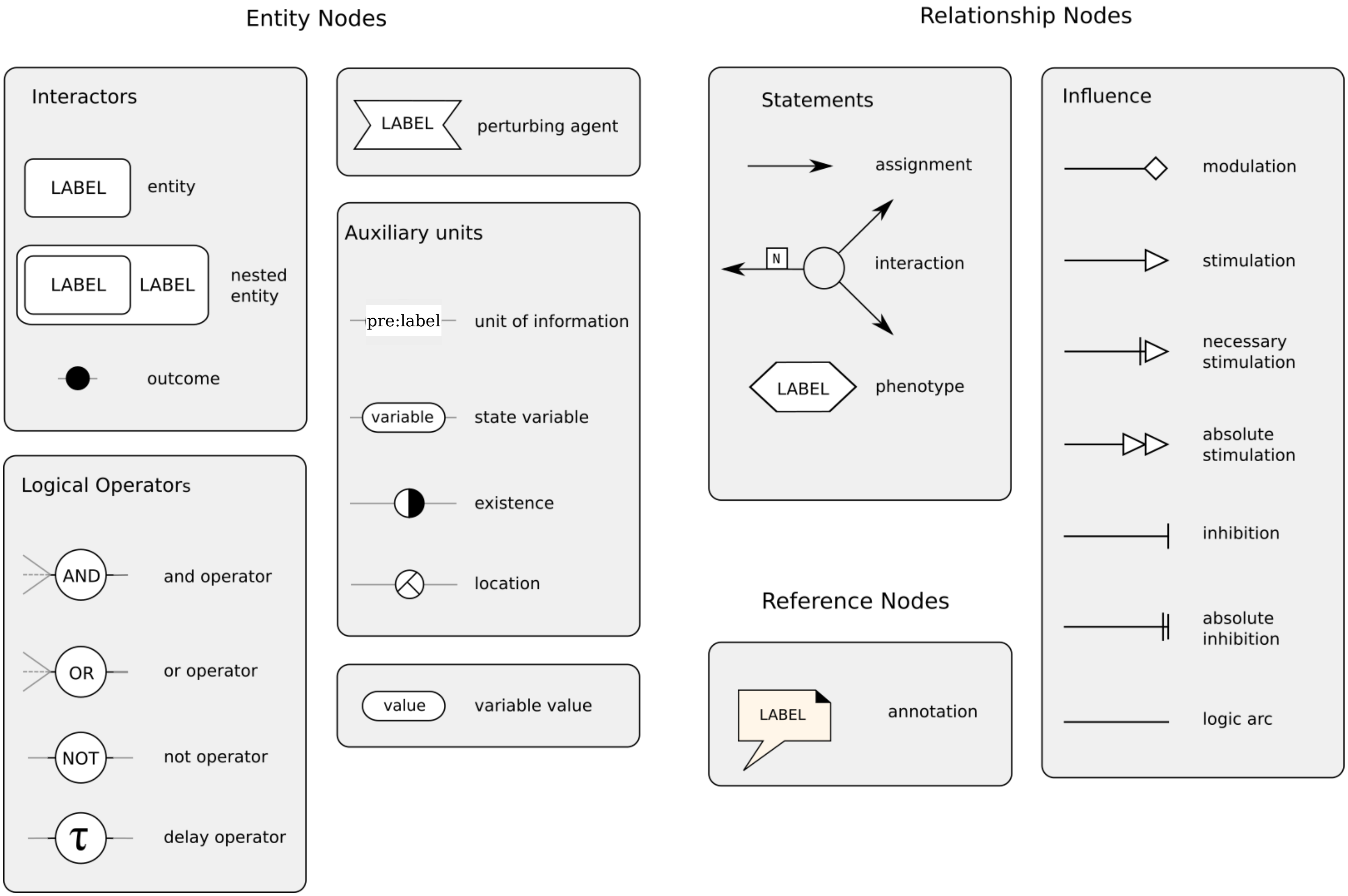
Molecular Interaction Maps



Extended Contact Maps



SBGN Entity Relationships L1 reference card



Entity Nodes

Interactors

entity

nested entity

outcome

perturbing agent

Auxiliary units

unit of information

state variable

existence

location

variable value

Logical Operators

and operator

or operator

not operator

delay operator

Relationship Nodes

Statements

assignment

interaction

phenotype

Influence

modulation

stimulation

necessary stimulation

absolute stimulation

inhibition

absolute inhibition

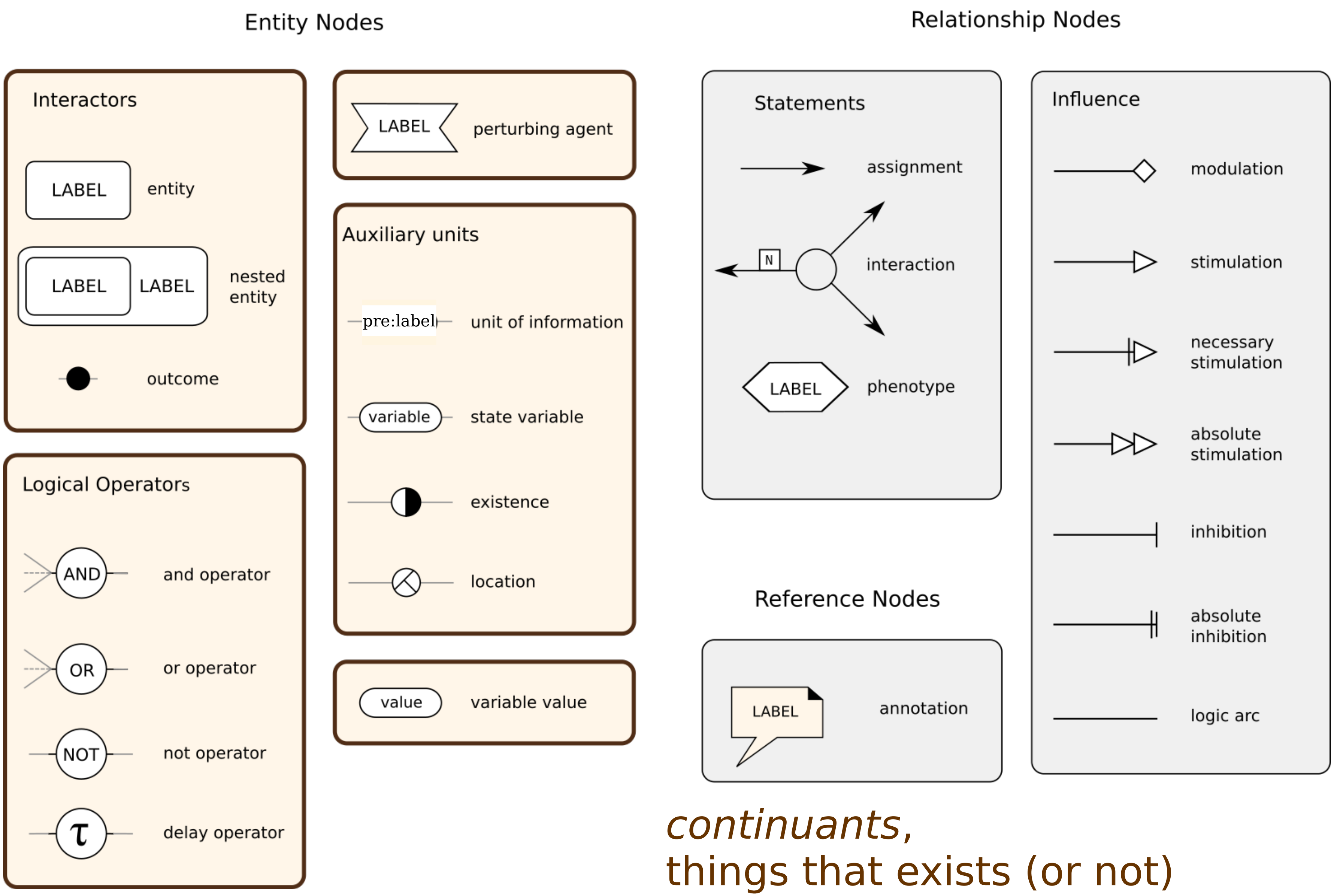
logic arc

Reference Nodes

annotation

Babraham Institute

SBGN Entity Relationships L1 reference card



Entity Nodes

Interactors

- entity
- nested entity
- outcome

- perturbing agent

Auxiliary units

- unit of information
- state variable
- existence
- location

- variable value

Logical Operators

- and operator
- or operator
- not operator
- delay operator

Relationship Nodes

Statements

- assignment
- interaction
- phenotype

Influence

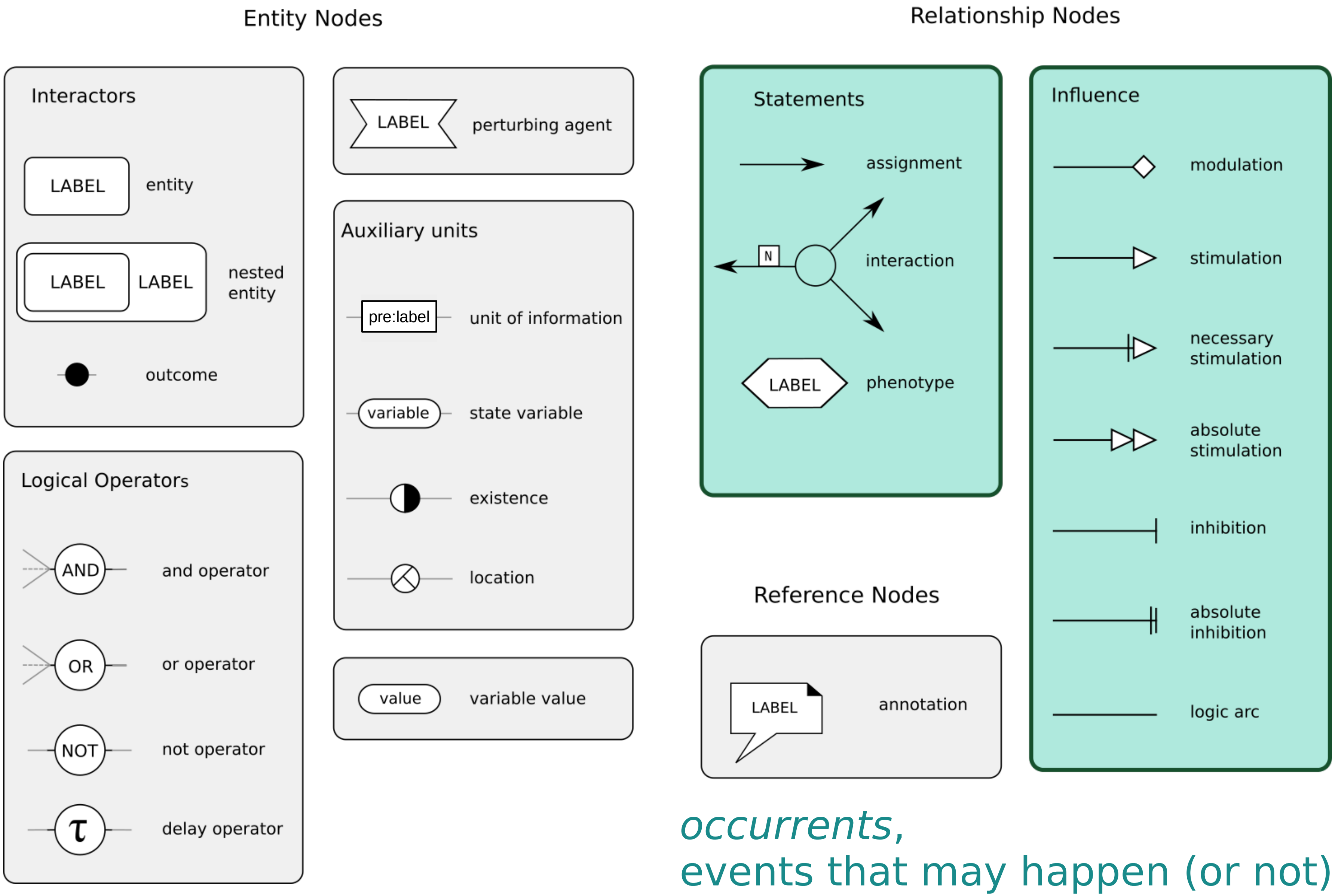
- modulation
- stimulation
- necessary stimulation
- absolute stimulation
- inhibition
- absolute inhibition
- logic arc

Reference Nodes

- annotation

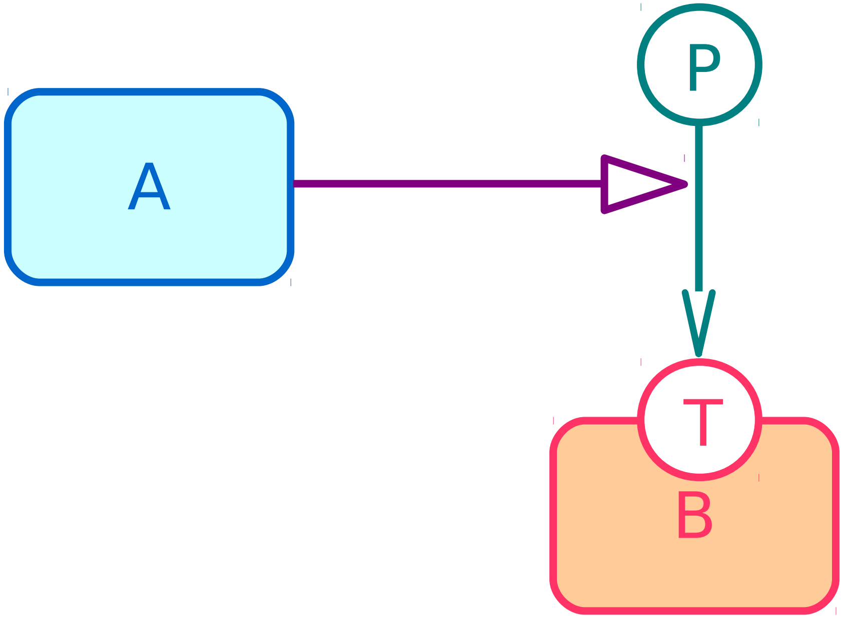
continuants,
things that exists (or not)

SBGN Entity Relationships L1 reference card

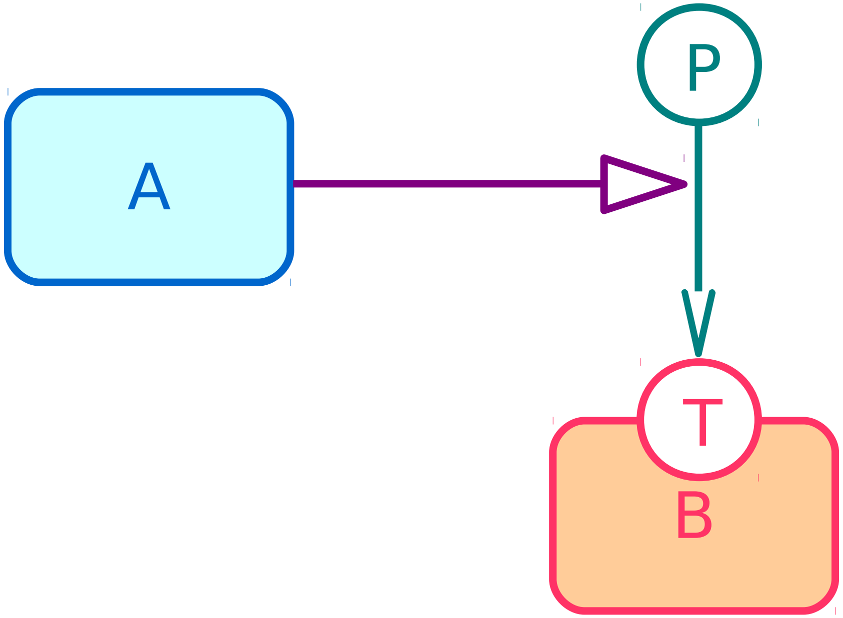


occurrents,
events that may happen (or not)

Entity Relationships can be viewed as rules

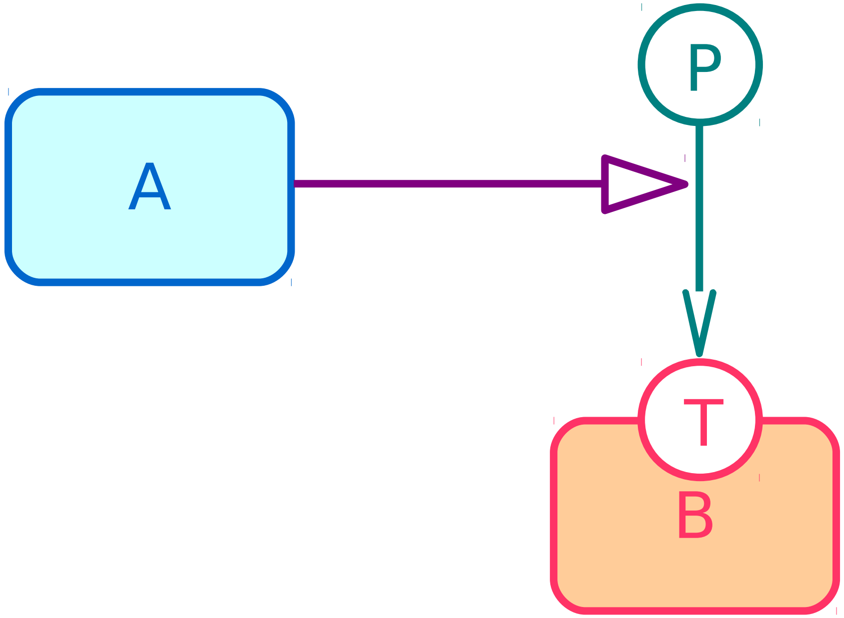


Entity Relationships can be viewed as rules



If A exists, the assignment of the value P to the state variable T of B is increased

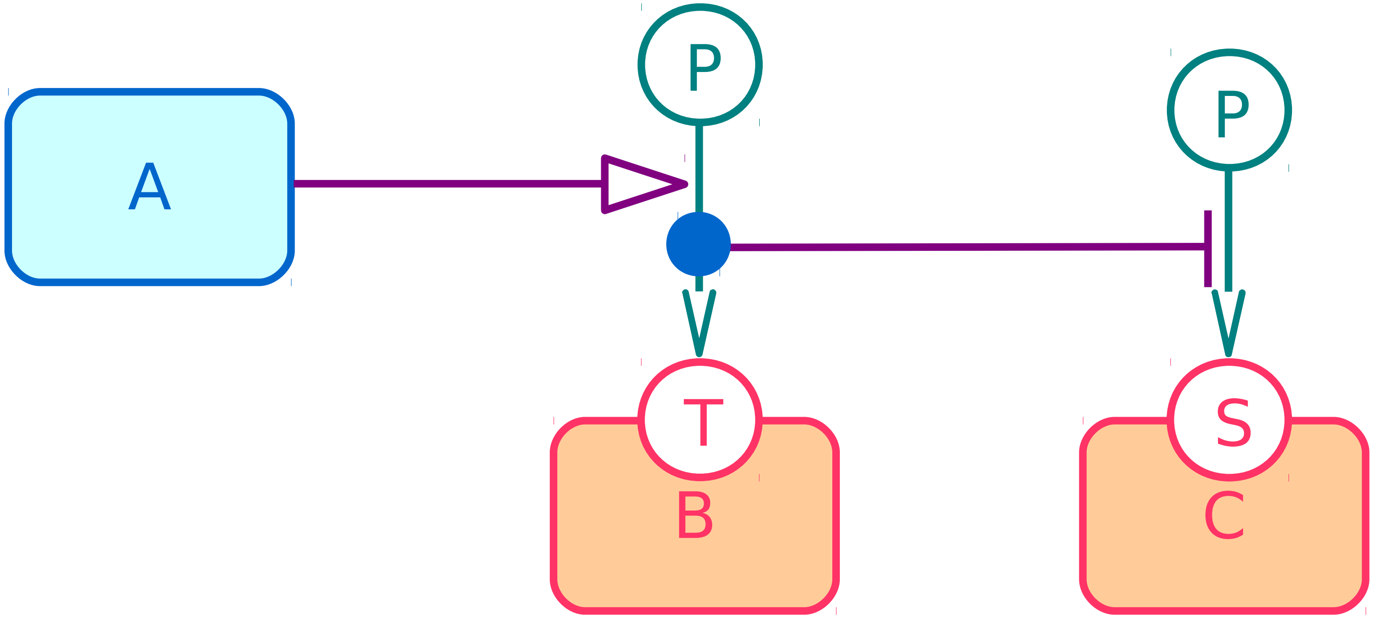
Entity Relationships can be viewed as rules



If A exists, the assignment of the value P to the state variable T of B is increased

(A stimulates the phosphorylation of B on the threonine)

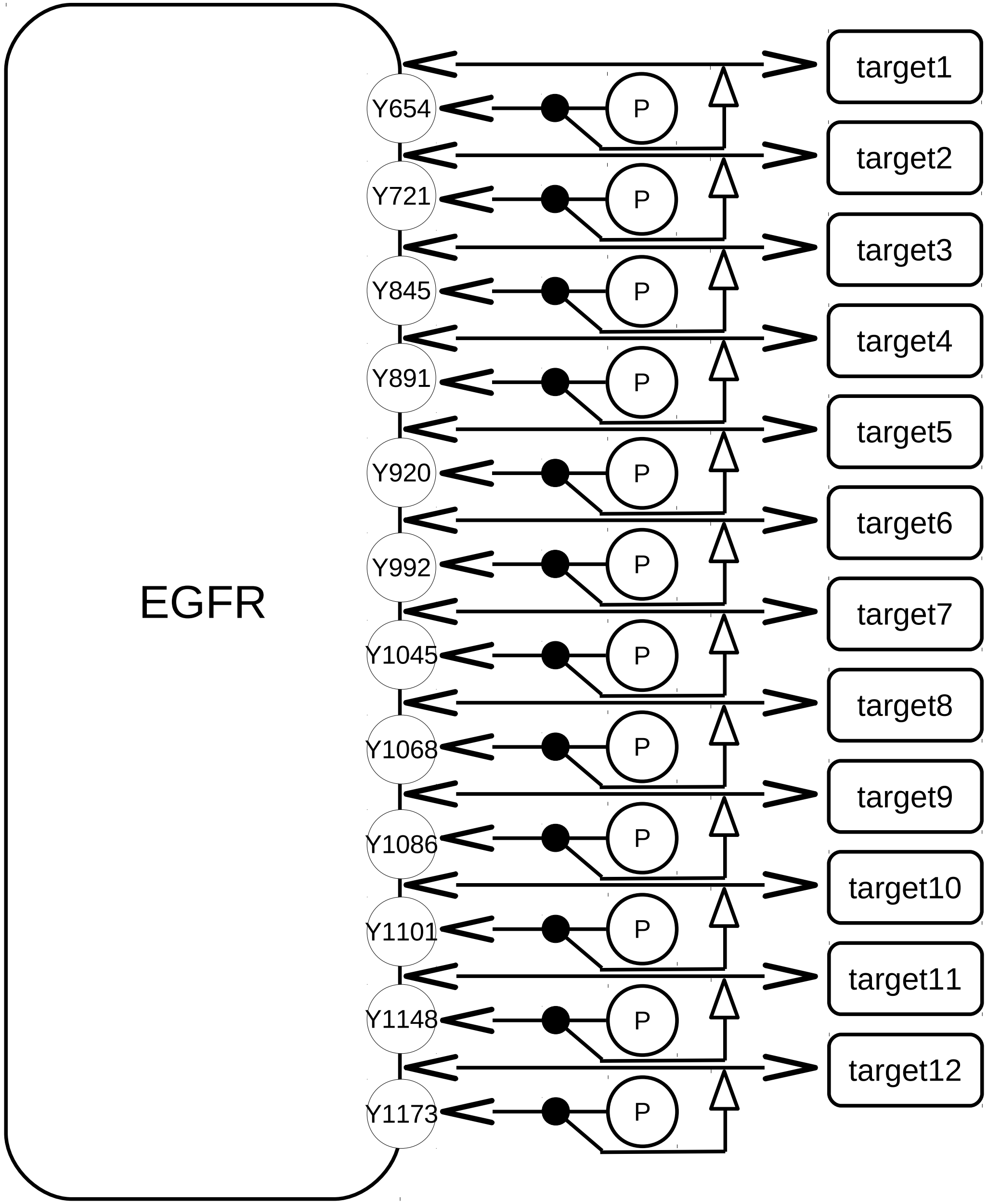
Entity Relationships can be viewed as rules



If A exists, the assignment of the value P to the state variable T of B is increased

If P is assigned to the state variable T of B, the assignment of the value P to the state variable S of B is decreased

Multistate and combinatorial explosion



Process Descriptions:
“once a state variable value,
always a state variable value”

2^{12} = 4096 states
(i.e. EPN glyphs) for EGFR
and 4096 complexes between
EGFR and targets

Rule-based modelling

- Kappa http://www.kappalanguage.org/

  Kappa: A(Site1~u),B(Site1) -> A(Site1~u!1),B(Site1!1)

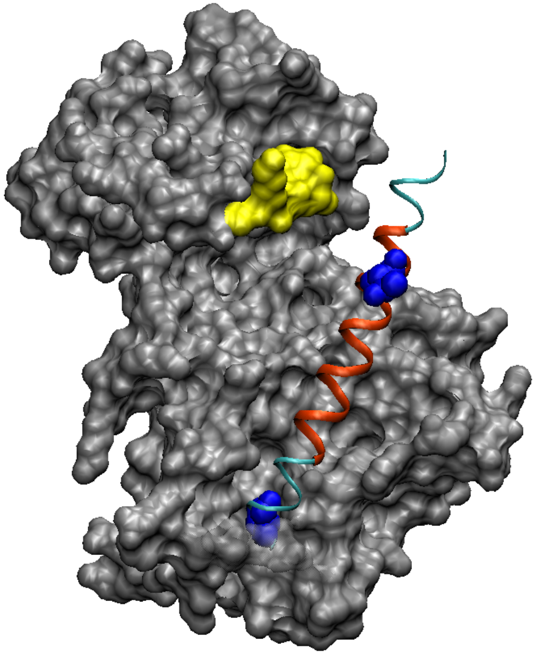
  English: "Unphosphorylated Site1 of A binds to Site1 of B"

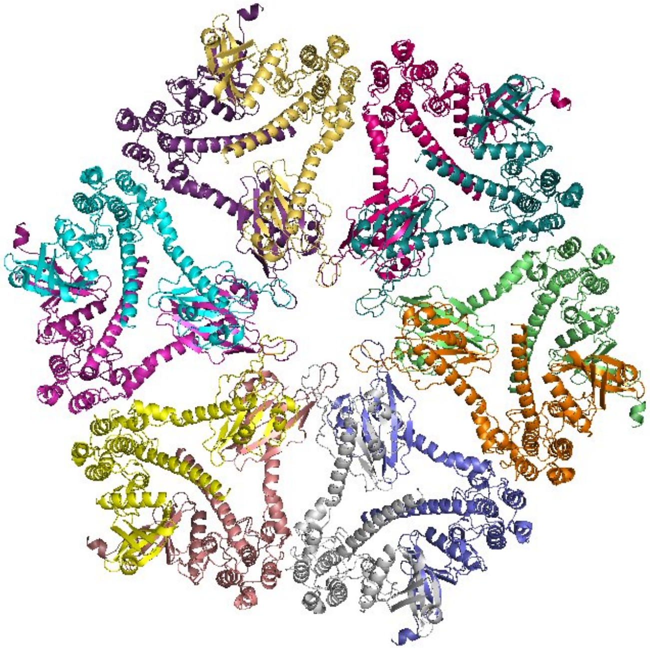
- BioNetGen http://bionetgen.org/

  EGF(R) + EGFR(L) <-> EGF(R!1).EGFR(L!1) kp1, km1

  English: “unbound EGF receptor site binds to unbound receptor ligand site”

Multi-state nature of CaMKII and rule-based modelling





12 monomers

5 binary state variables

Open/Closed
T286 P/nonP
T306 P/nonP
CaM on low affinity
CaM on high affinity

2^{60} states = 1 billions of billions

$$???0??? \xrightarrow{p_{base}} ???1???$$

$$0??0??? \xrightarrow{p_{base} \times p_{rel(0,0)}} 0??1???$$

$$1??0??? \xrightarrow{p_{base} \times p_{rel(0,1)}} 1??1???$$

Flags '?' do not affect the reaction

4 species are necessary and not 128

2 reactions are necessary and not 64

Simulation with StochSim

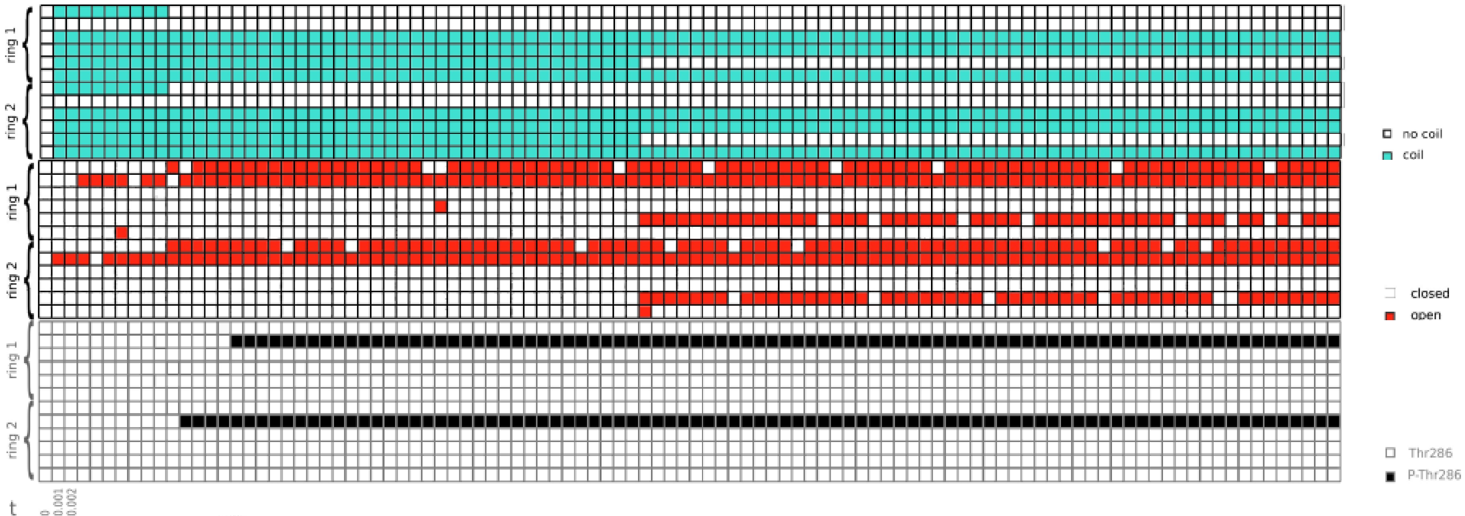
time

single
oligomer

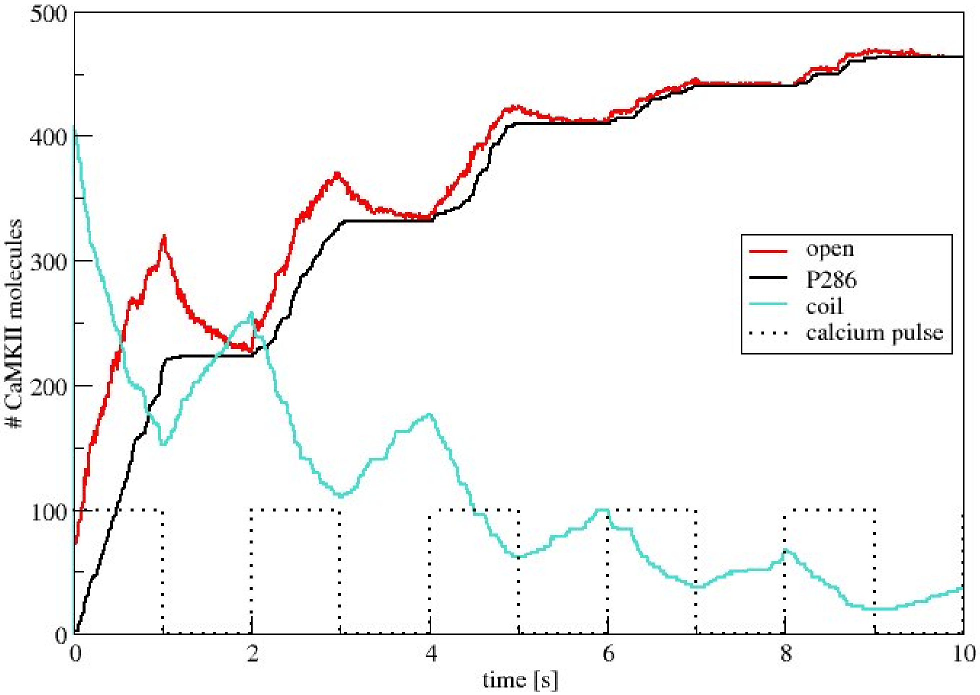
dimer
coil

open

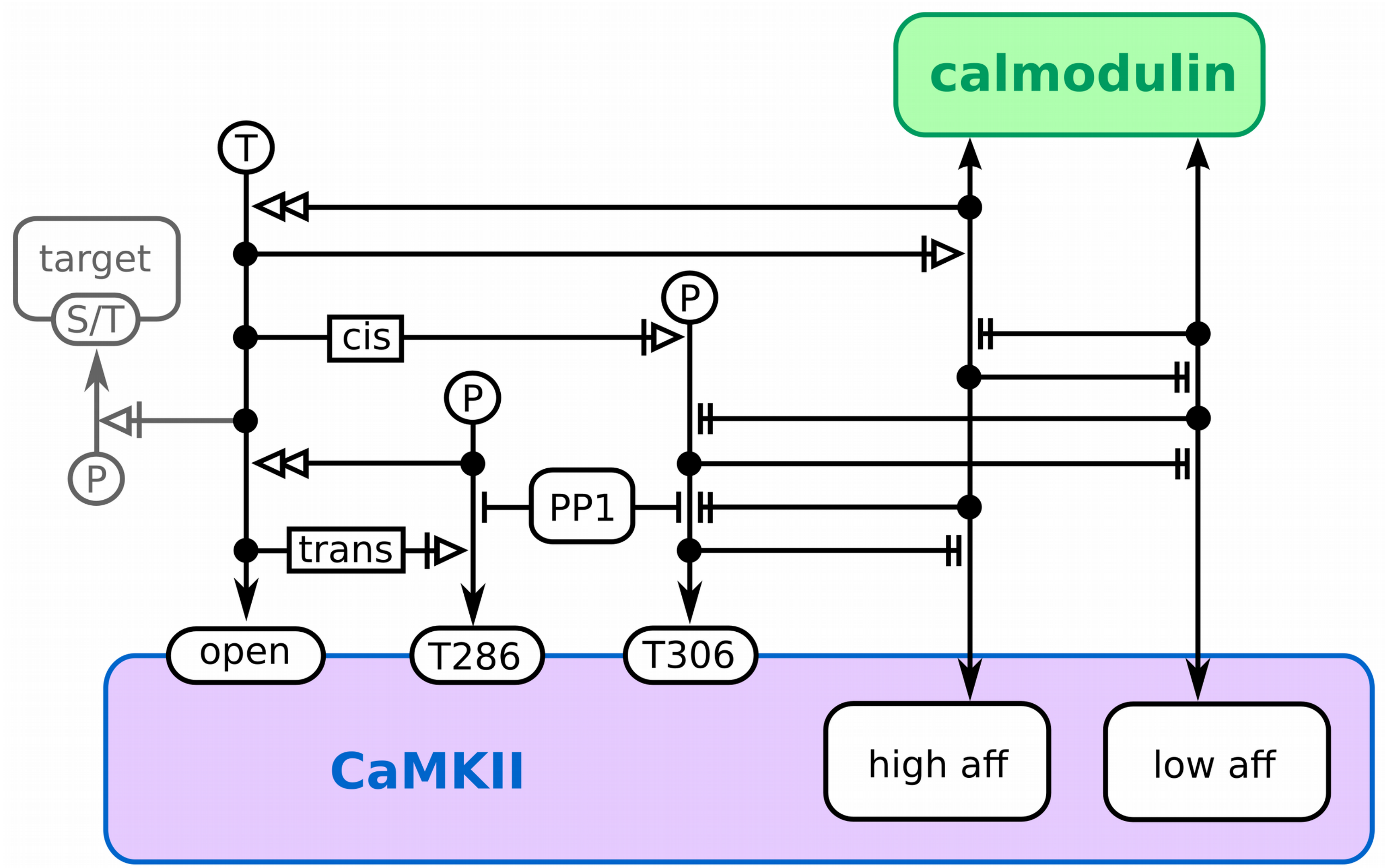
T286P



population
of multimers



Regulation of synaptic plasticity by calcium



Stefan *et al. PloS ONE* (2012)

Biological Pathway Exchange format

BioPAX

http://biopax.org/

Demir *et al* (2010)

BioPAX is a data format and an ontology

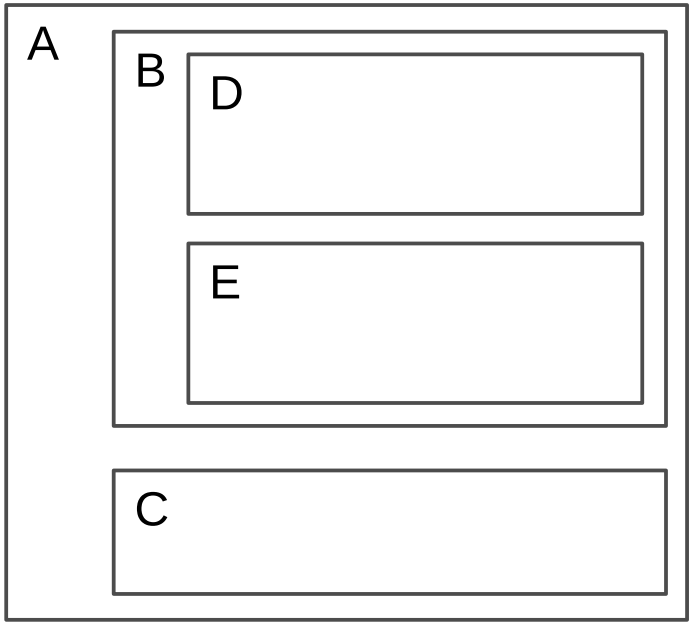
- **RDF/OWL**-based language to represent biological pathways at the molecular and cellular level
- Covers molecular and genetic interactions, metabolic network, signalling pathways, gene regulatory networks
- **Interactions**: Control (Catalysis, Modulation, TemplateReactionRegulation), Conversion (BiochemicalReaction, ComplexAssembly, Degradation, Transport, TransportWithBiochemicalReaction), GeneticInteraction, MolecularInteraction, TemplateReaction
- **Physical entities**: Complex, DNA, DNARegion, Protein, RNA, RNARegion, SmallMolecule
- **Utility classes**: BioSource, ChemicalStructure, ControlledVocabulary, DeltaG, EntityFeature, EntityReference, Evidence, ExperimentalForm, kPrime, PathwayStep, Provenance, Score, SequenceLocation, Stoichiometry, Xref

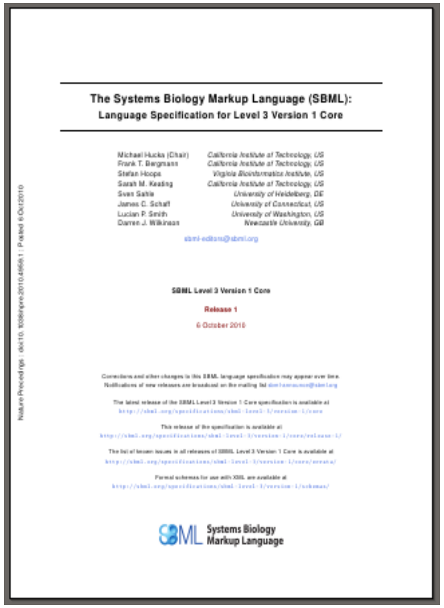
Resource Description Framework - RDF

- Language of the semantic web; allow distributed semantic queries
- Semantic entirely embedded in the language (does not require external schemas and specifications)
- Series of statements

Subject	**Predicate**	**Object**
EGFR	*located_in*	plasma membrane
P00533	OBO_REL:0000008	GO:0005886
(UniProt)	(OBO Relation ontology)	(Gene Ontology)

“XML” Vs RDF





The Systems Biology Markup Language (SBML):
Language Specification for Level 3 Version 1 Core

Michael Hucka (Chair)	*California Institute of Technology, US*
Frank T. Bergmann	*California Institute of Technology, US*
Stefan Hoops	*Virginia Bioinformatics Institute, US*
Sarah M. Keating	*California Institute of Technology, US*
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sbml-editors@sbml.org

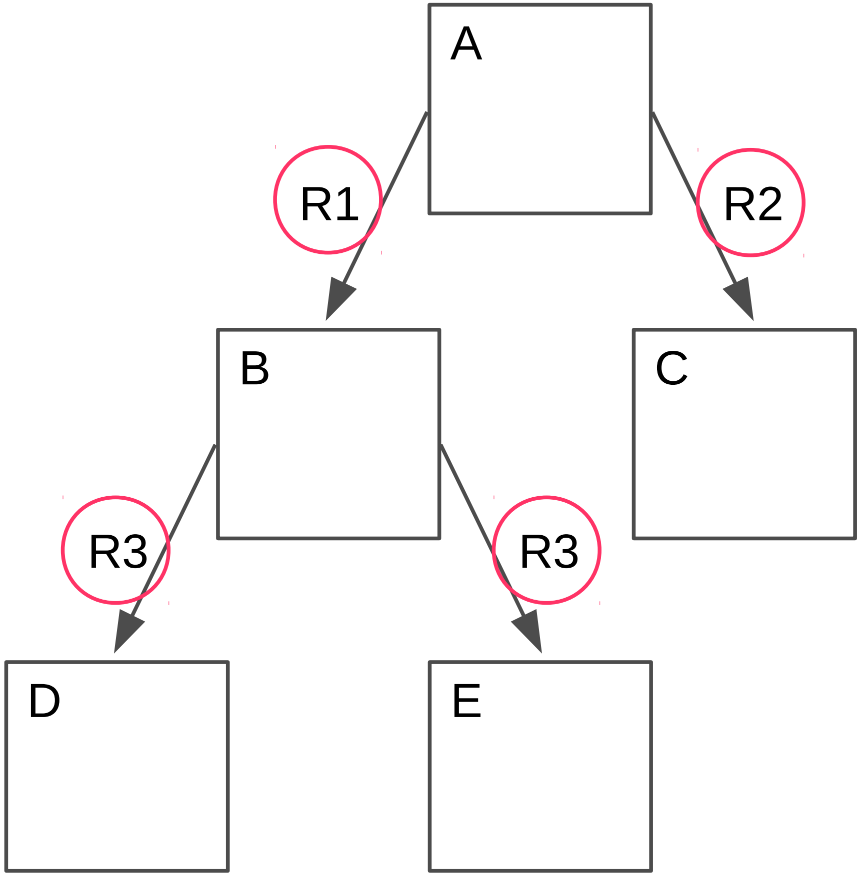
SBML Level 3 Version 1 Core

Release 1

6 October 2010

Systems Biology Markup Language

Relationships defined in another document

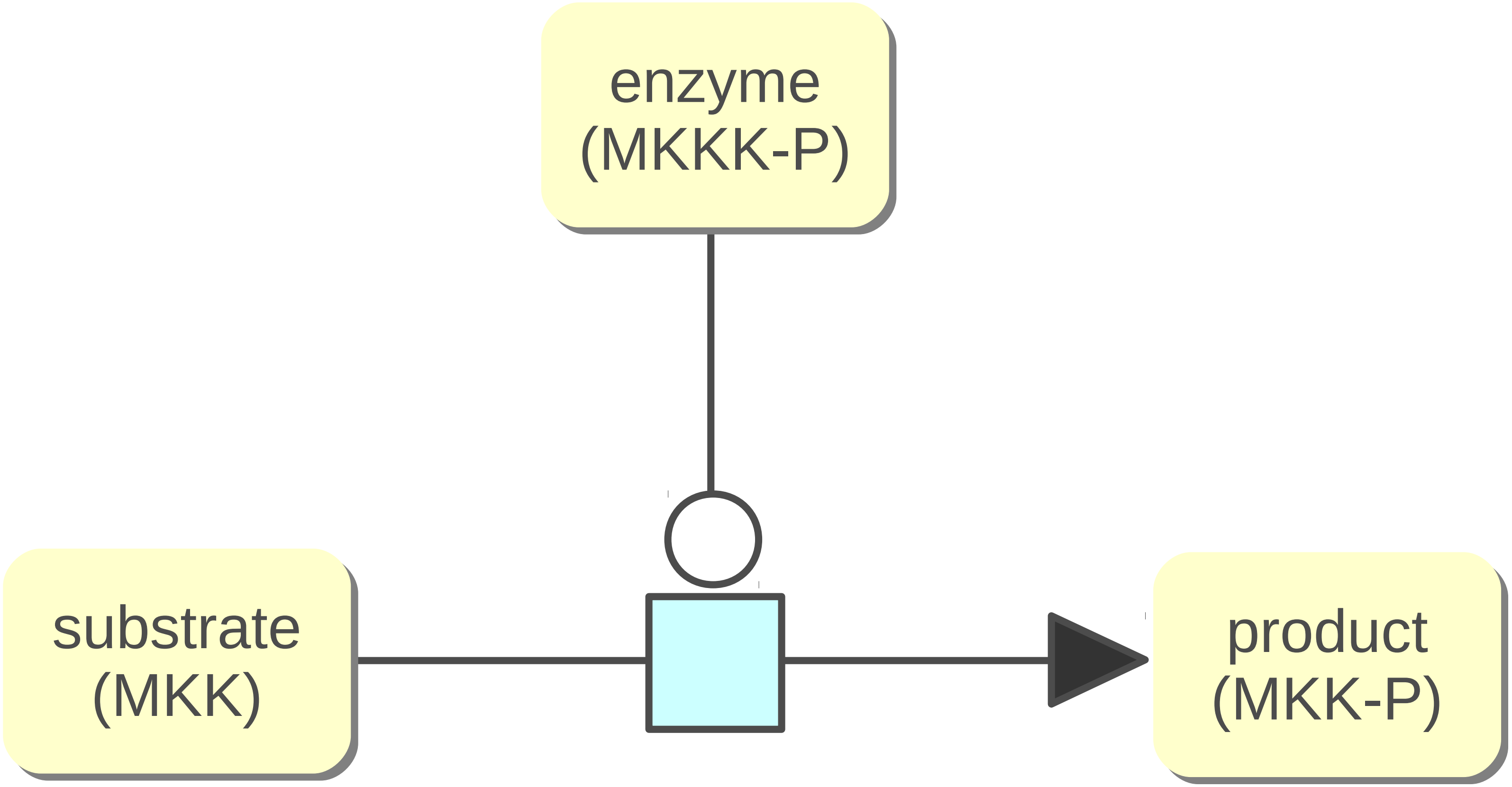


Relationships defined in the pathway

Web Ontology Language - OWL

- BioPAX contains classes, relations and properties, constraints, objects, values.
- Classes are arranged in a specialisation hierarchy. E.g. a “protein” is a “physical entity”
- Classes may have properties of specific types. The types are linked to other classes by relations. E.g. “reaction X” has *participant* “protein P”. An attribute is a property that has a simple type.
- Constraints define allowable values and connexions. E.g. “MOLECULAR_WT” must be a positive real number
- Objects are instances of classes.

A catalysis in BioPAX



enzyme
(MKKK-P)

substrate
(MKK)

product
(MKK-P)

A catalysis in BioPAX (L3)

```
<!-- The catalytic reaction -->

<bp:BiochemicalReaction rdf:about="conversion_J2">
  <bp:left rdf:resource="LEFT_0_conversion_J2_MKK" />
  <bp:right rdf:resource="RIGHT_0_conversion_J2_MKK_P" />
</bp:BiochemicalReaction>

<bp:Control rdf:about="control_J2_MKKK_P_0">
 <bp:controlled rdf:resource="conversion_J2" />
 <bp:controlType rdf:datatype="http://www.w3.org/2001/XMLSchema#string">
   ACTIVATION</bp:controlType>
 <bp:controller rdf:resource="PEP0_control_J2MKKK_P" />
</bp:Control>
```

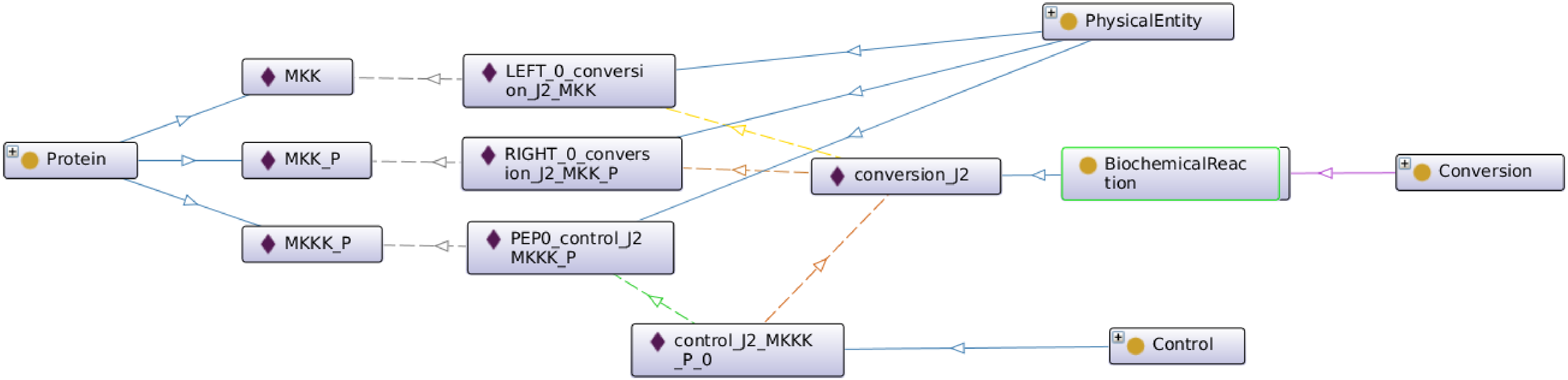
A catalysis in BioPAX (L3)

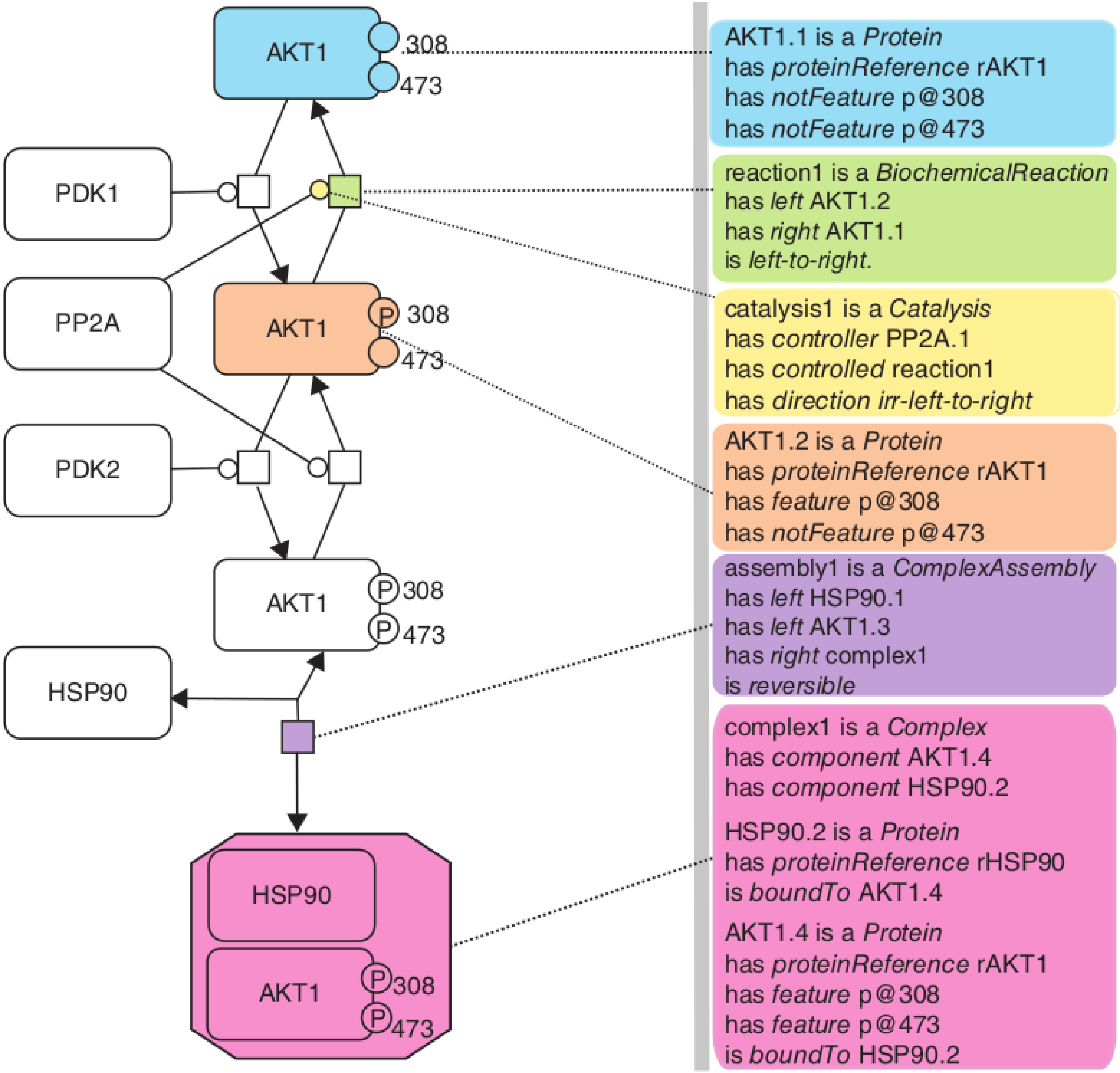
```
<!-- The participants -->

<bp:PhysicalEntity rdf:about="RIGHT_0_conversion_J2_MKK_P">
  <bp:displayName rdf:datatype="http://www.w3.org/2001/XMLSchema#string">
  MKK_P</bp:displayName>
  <bp:memberPhysicalEntity rdf:resource="MKK_P" />
</bp:PhysicalEntity>

<bp:PhysicalEntity rdf:about="LEFT_0_conversion_J2_MKK">
  <bp:displayName rdf:datatype="http://www.w3.org/2001/XMLSchema#string">
  MKK</bp:displayName>
  <bp:memberPhysicalEntity rdf:resource="MKK" />
</bp:PhysicalEntity>

<bp:PhysicalEntity rdf:about="PEP0_control_J2MKKK_P">
  <bp:displayName rdf:datatype="http://www.w3.org/2001/XMLSchema#string">
  MKKK_P</bp:displayName>
  <bp:memberPhysicalEntity rdf:resource="MKKK_P" />
</bp:PhysicalEntity>
```

A catalysis in BioPAX (L3)

```
<!-- Proteins -->

<bp:Protein rdf:about="MKKK_P">
 <bp:displayName rdf:datatype="http://www.w3.org/2001/XMLSchema#string">
   Mos-P</bp:displayName>
</bp:Protein>

<bp:Protein rdf:about="MKK">
 <bp:displayName rdf:datatype="http://www.w3.org/2001/XMLSchema#string">
   Mek1</bp:displayName>
</bp:Protein>

<bp:Protein rdf:about="MKK_P">
 <bp:displayName rdf:datatype="http://www.w3.org/2001/XMLSchema#string">
   Mek1-P</bp:displayName>
</bp:Protein>
```

RDF graph (Protégé, http://protege.stanford.edu/)





AKT1.1 is a *Protein*
has *proteinReference* rAKT1
has *notFeature* p@308
has *notFeature* p@473

reaction1 is a *BiochemicalReaction*
has *left* AKT1.2
has *right* AKT1.1
is *left-to-right.*

catalysis1 is a *Catalysis*
has *controller* PP2A.1
has *controlled* reaction1
has *direction irr-left-to-right*

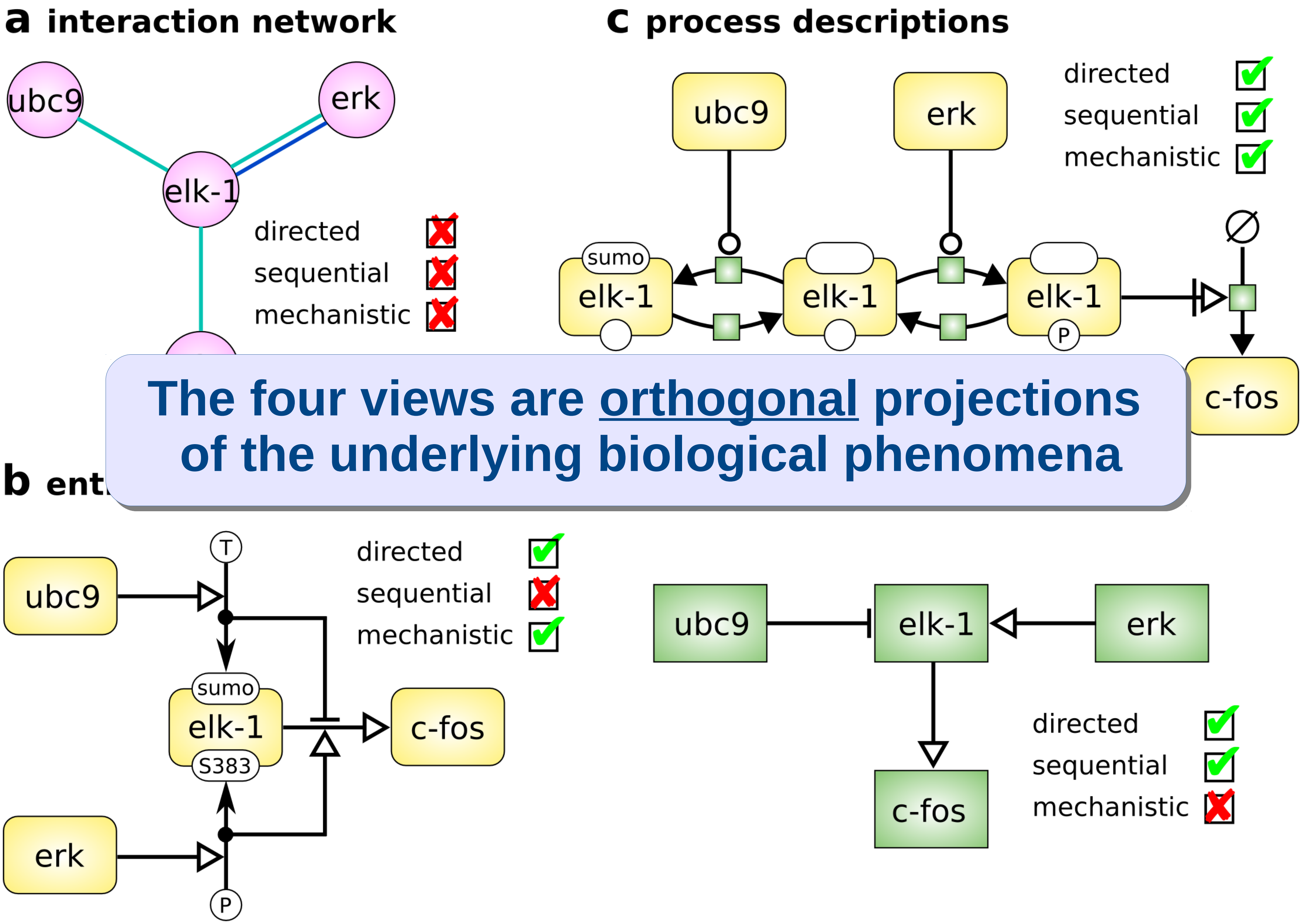
AKT1.2 is a *Protein*
has *proteinReference* rAKT1
has *feature* p@308
has *notFeature* p@473

assembly1 is a *ComplexAssembly*
has *left* HSP90.1
has *left* AKT1.3
has *right* complex1
is *reversible*

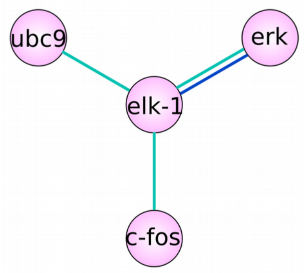
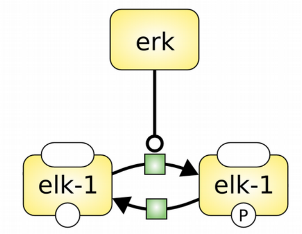
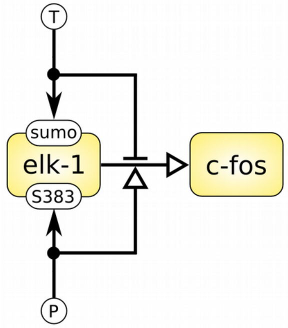
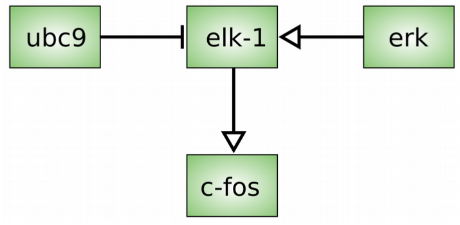
complex1 is a *Complex*
has *component* AKT1.4
has *component* HSP90.2

HSP90.2 is a *Protein*
has *proteinReference* rHSP90
is *boundTo* AKT1.4

AKT1.4 is a *Protein*
has *proteinReference* rAKT1
has *feature* p@308
has *feature* p@473
is *boundTo* HSP90.2



The four views are <u>orthogonal</u> projections of the underlying biological phenomena

	Interaction networks	PSI-MI		
	Process Descriptions	SBML Core	SBGN Process Description	Metabolism
	Entity relationships	SBML Multi	SBGN Entity Relationships	Signalling
	Activity Flows	SBML Qual	SBGN Activity Flows	Signalling Gene networks

Practical, Friday

Lu Li