

Biochemical pathways

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What is a “pathway”

Wikipedia (October 20th 2016): “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.

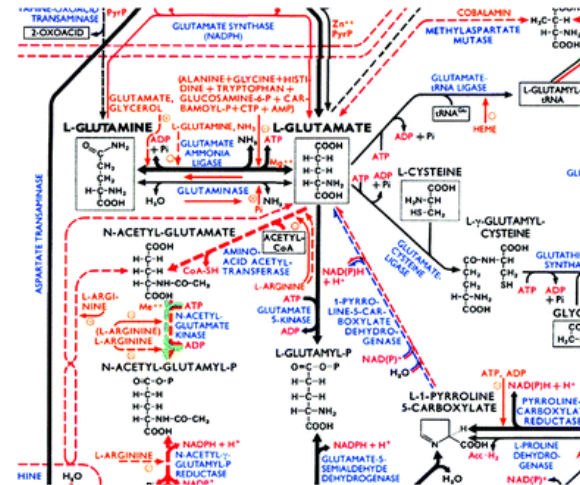
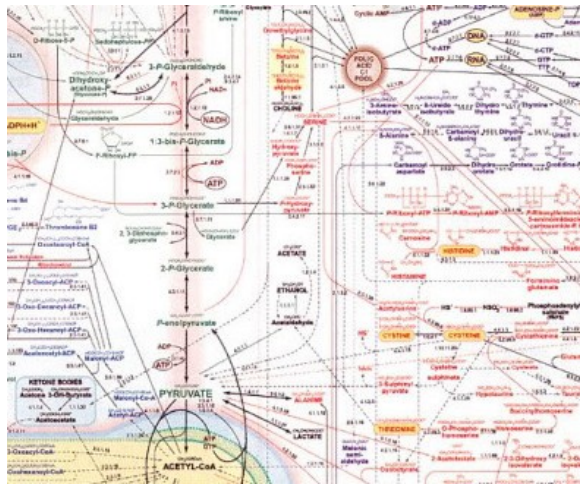
→ Detailed representation of reality based on observation

OR

→ Abstract representation of reality based on needs

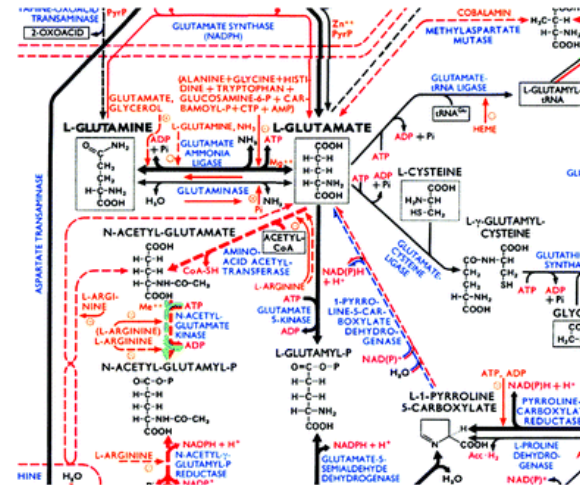
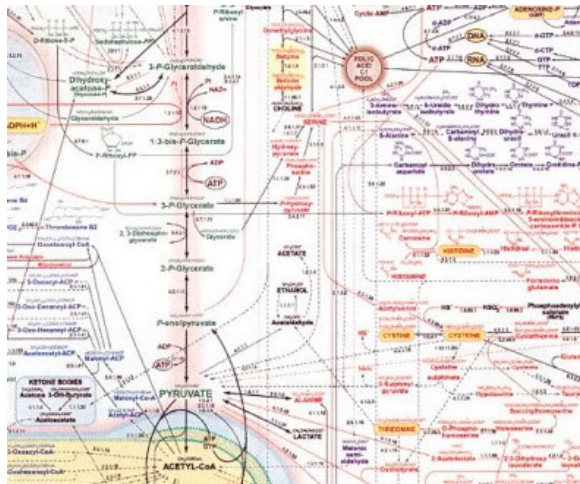
Biochemical pathways are old ...

- Gortner, R.A. *Outlines of Biochemistry* (Wiley, New York, 1949)
- Nicholson (1970)
- Michal (1984)



Biochemical pathways are old ...

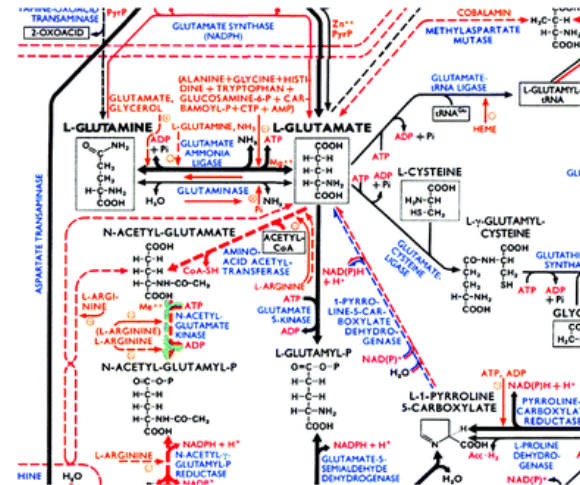
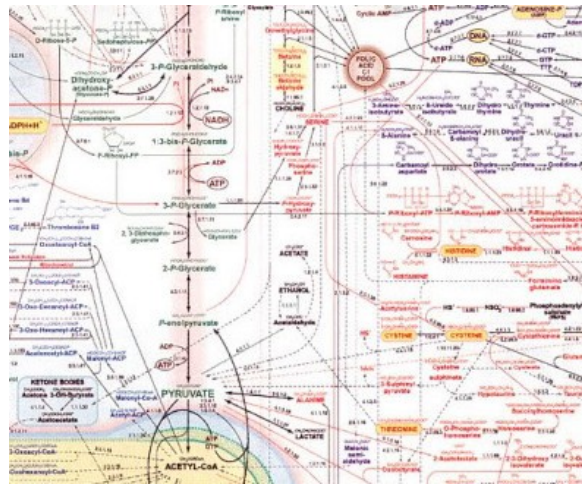
- Gortner, R.A. *Outlines of Biochemistry* (Wiley, New York, 1949)
- Nicholson (1970) Michal (1984)



“Hand drawing” on paper
→ no software-based browsing, processing and analysis

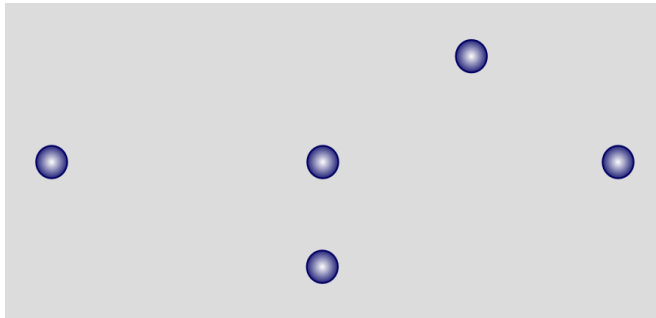
Biochemical pathways are old ... or not so much

- Gortner, R.A. *Outlines of Biochemistry* (Wiley, New York, 1949)
- Nicholson (1970)
- Michal (1984)

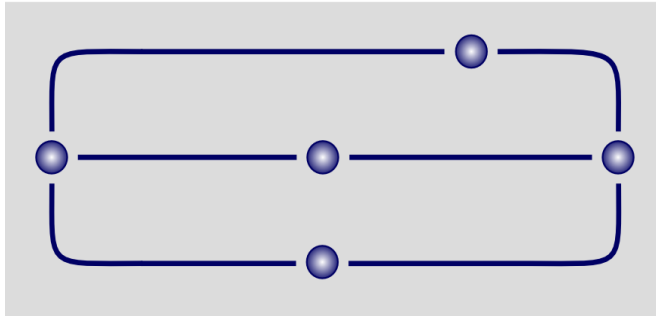


- 1990s: high-throughput data generation → Large amount of knowledge increase in computing power → automatic reconstruction, browsing and analysis
- Databases: KEGG (1995), EcoCyc (1994), Reactome (2000)
- Formats: BioPAX (2000), SBML (2000), PSI-MI (2002)

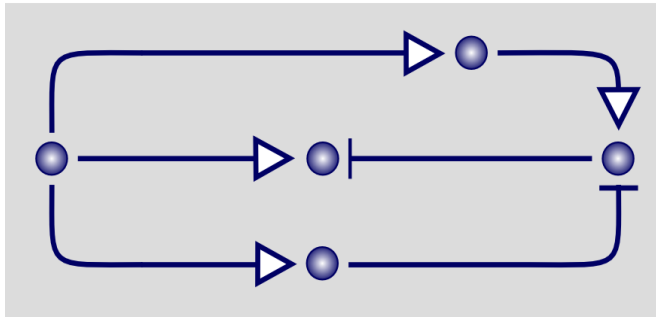
Layered approach for designing pathways



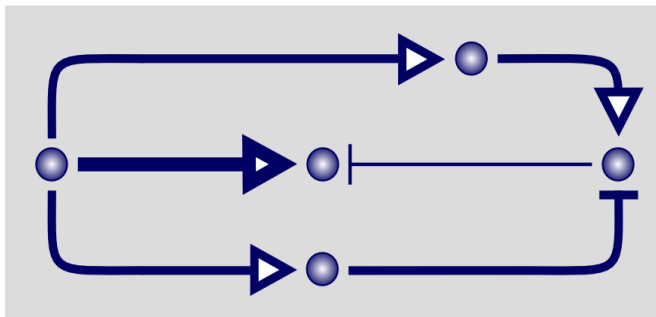
List of participants



Interactions between participants



Influences of participants onto others

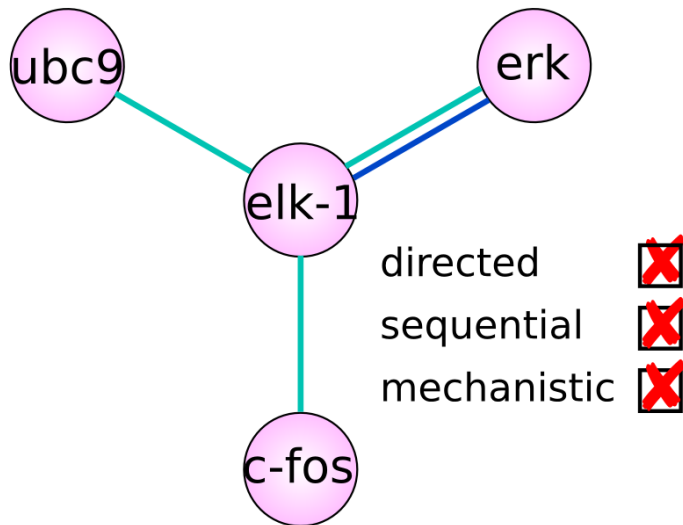


Quantitative relationships

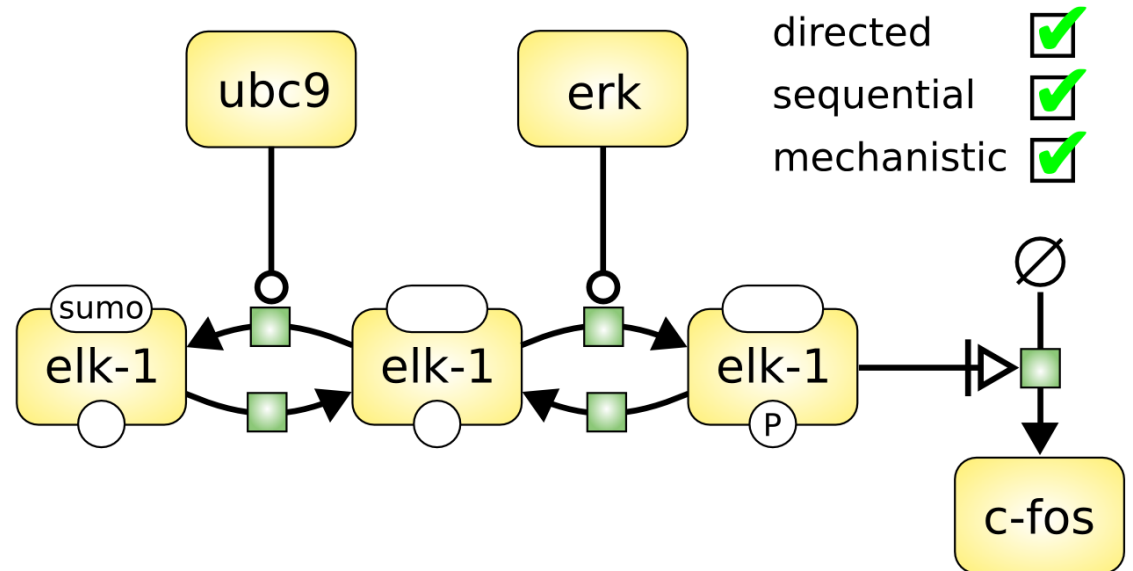
Useful insights at each level

The four views of systems biology

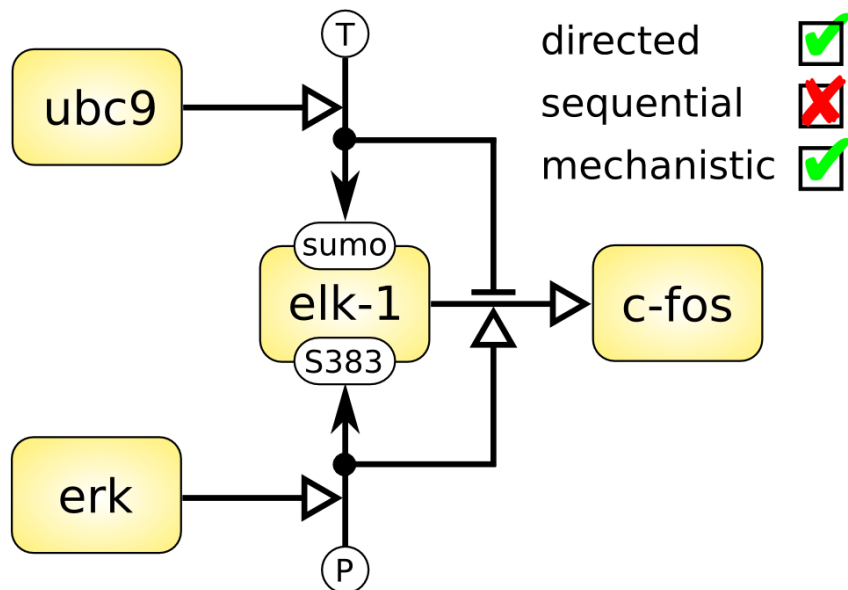
a interaction network



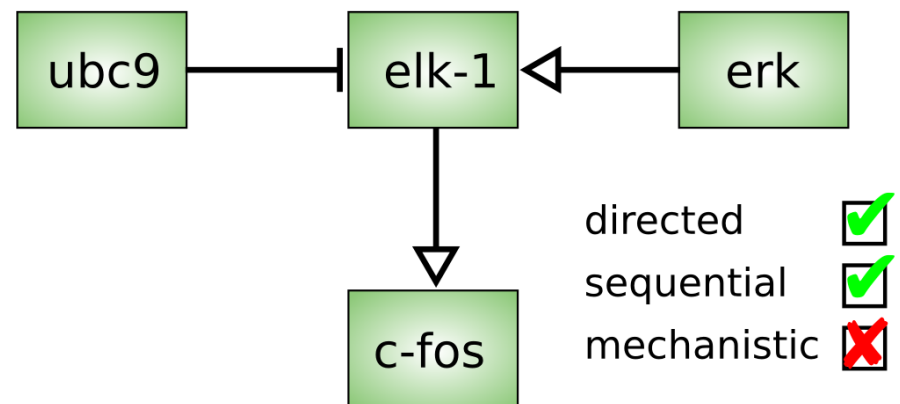
c process descriptions

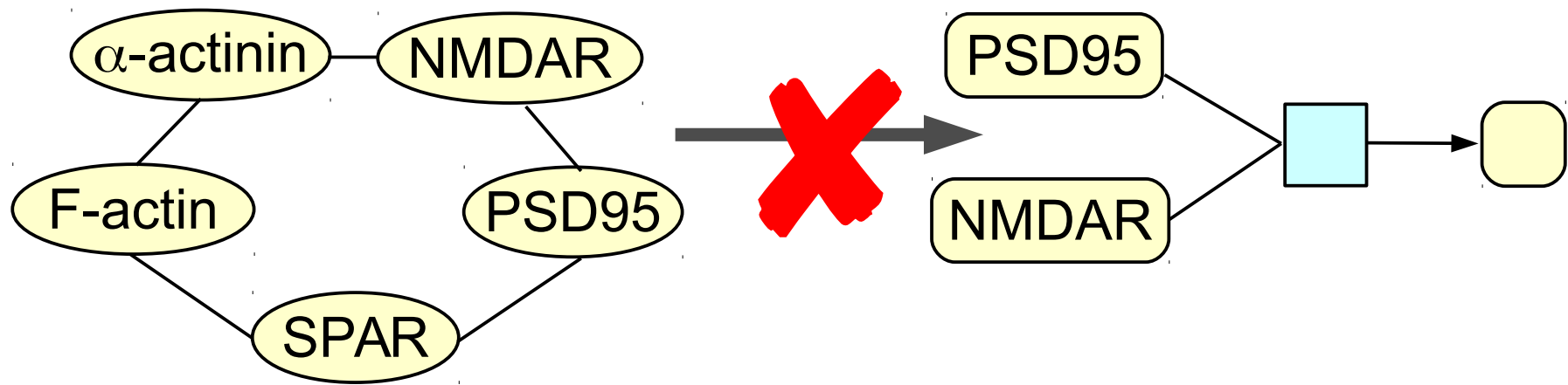


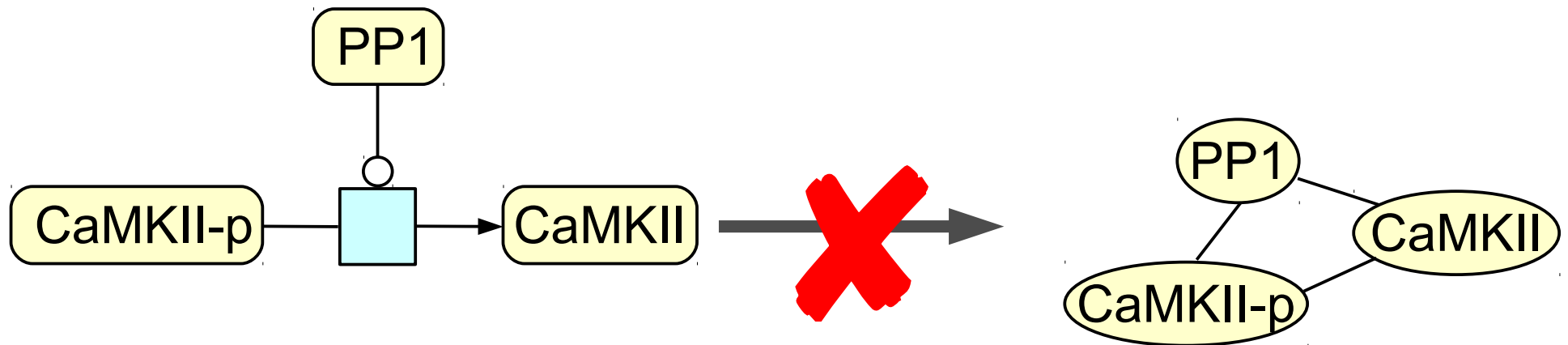
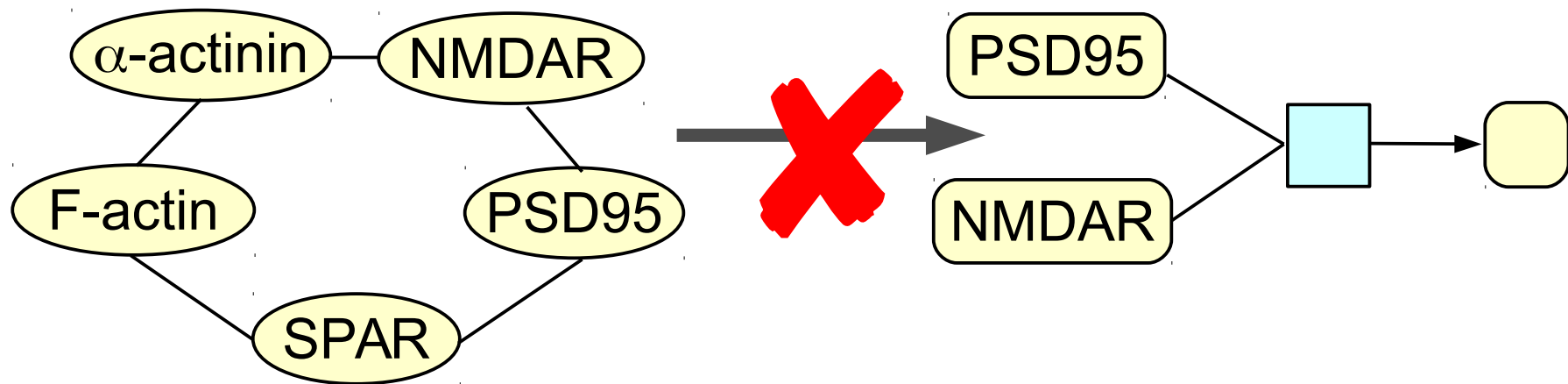
b entity relationships



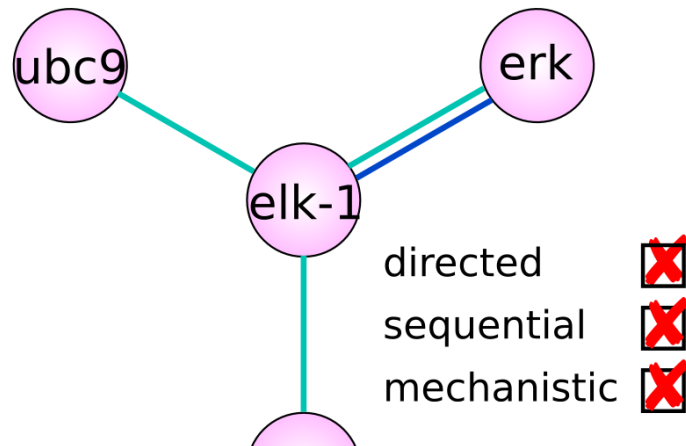
d activity flows



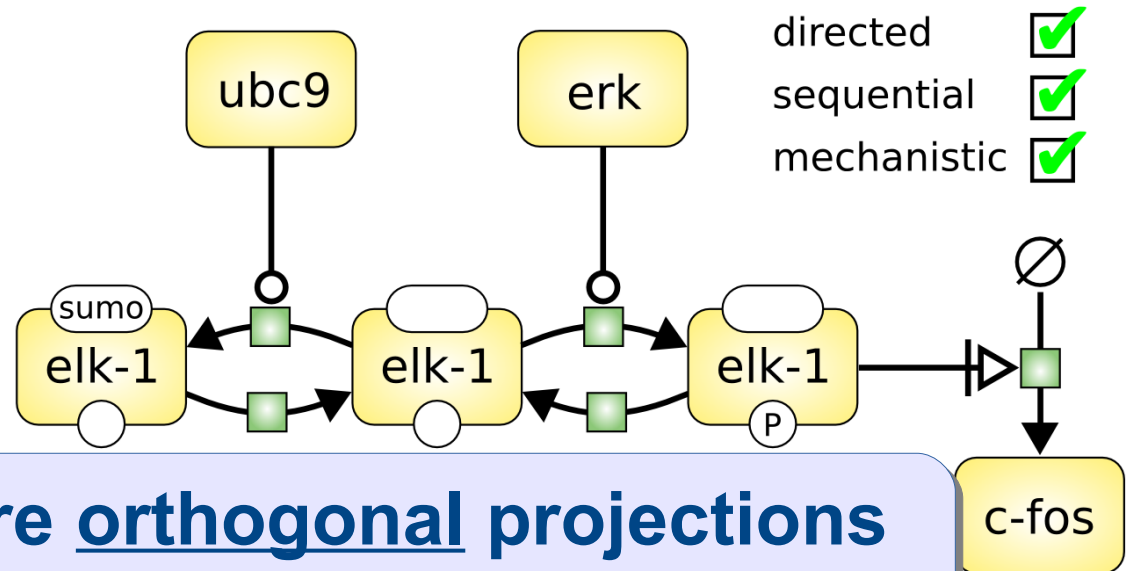




a interaction network

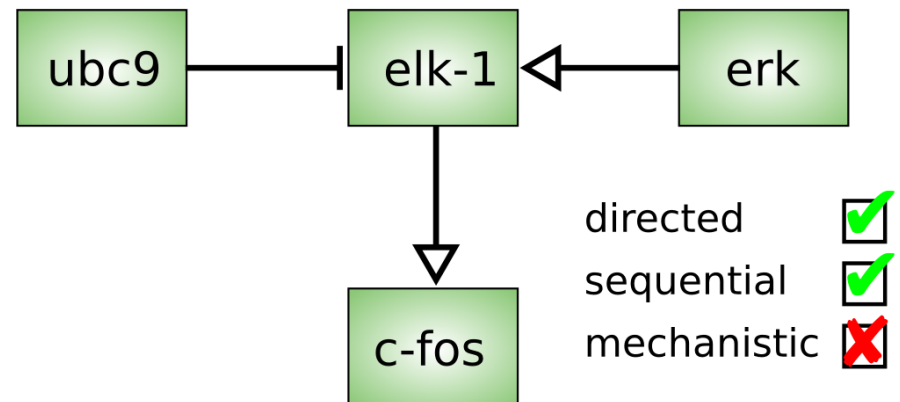
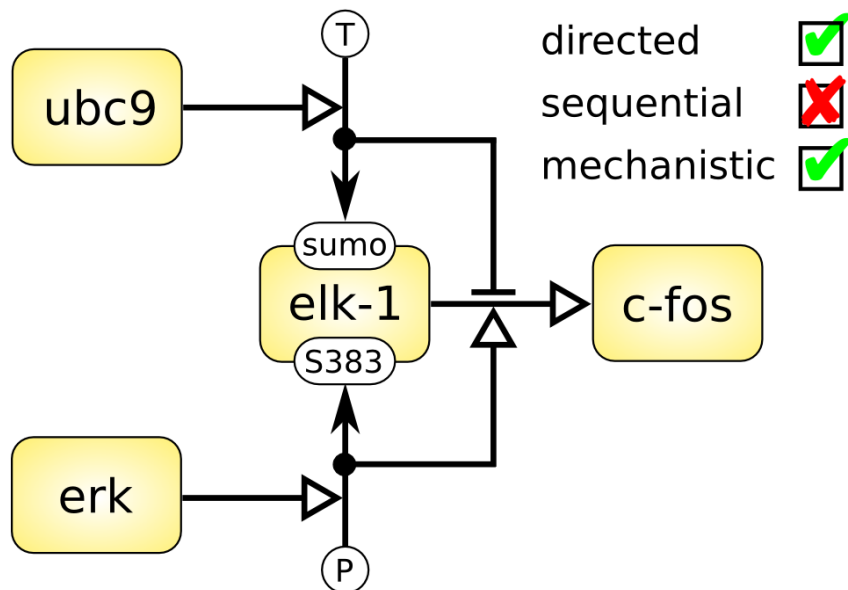


c process descriptions

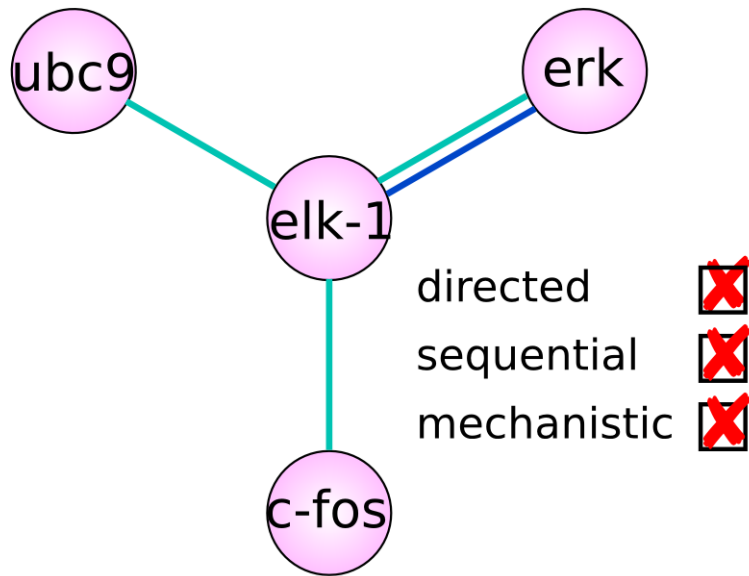


The four views are orthogonal projections of the underlying biological phenomena

b ent



Interaction networks

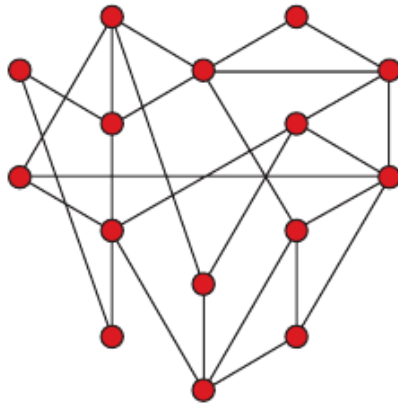


- Statistical modelling
- Functional genomics

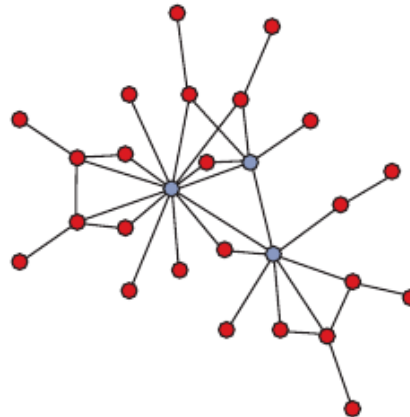
What can we get from interaction networks

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

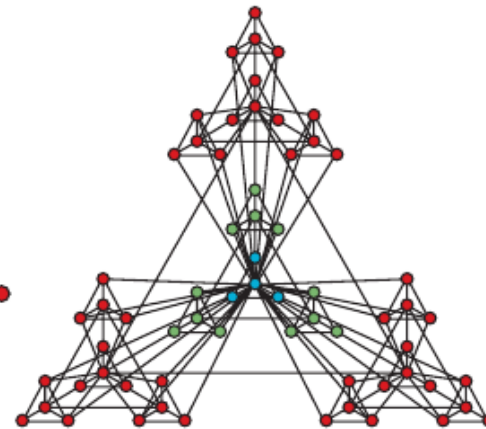
Random network



Scale-free network



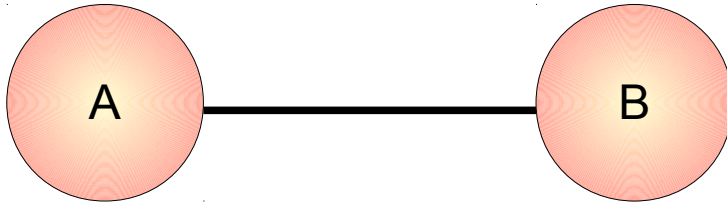
Hierarchical network



- Subgraphs, modules, motifs, motifs clusters ...

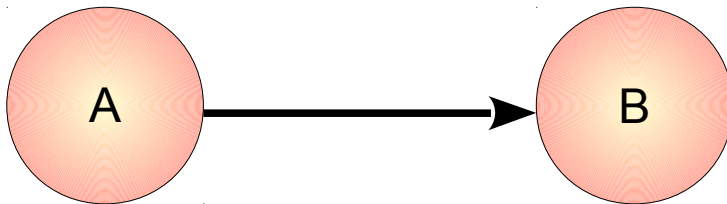
Barabasi *et al* (2004)

Undirected, directed, signed



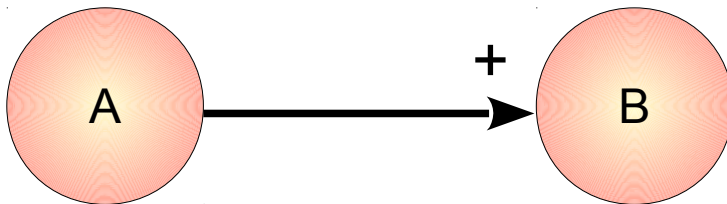
Undirected

“A interacts with B”



directed

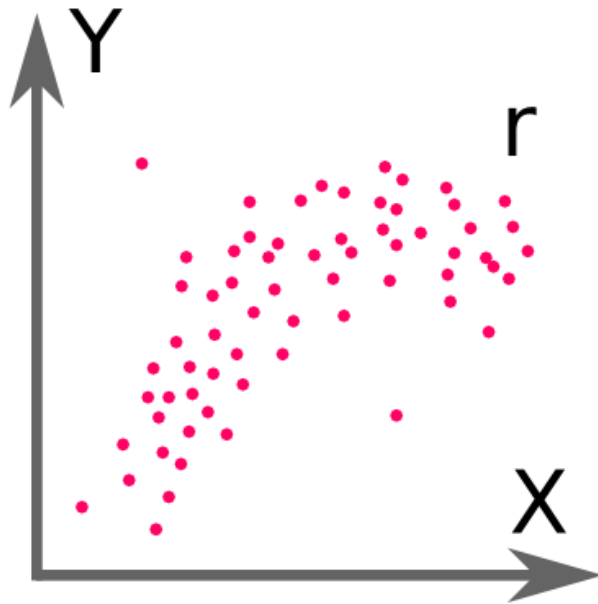
“A influences B”



Signed

A influences positively B

Network inference: Correlation



Values of X are somewhat related to values of Y

Tools:

LASSO

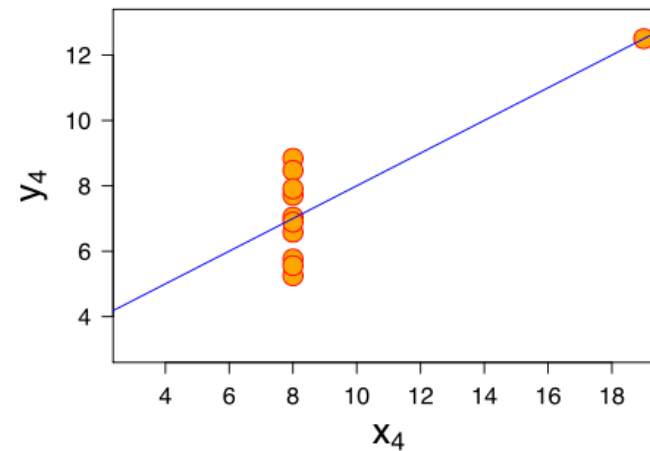
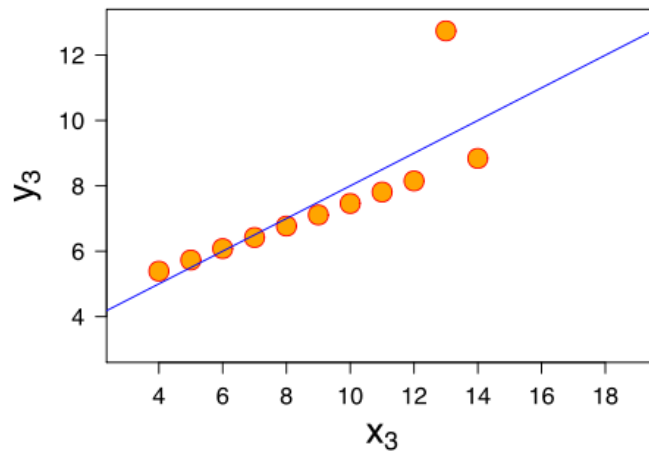
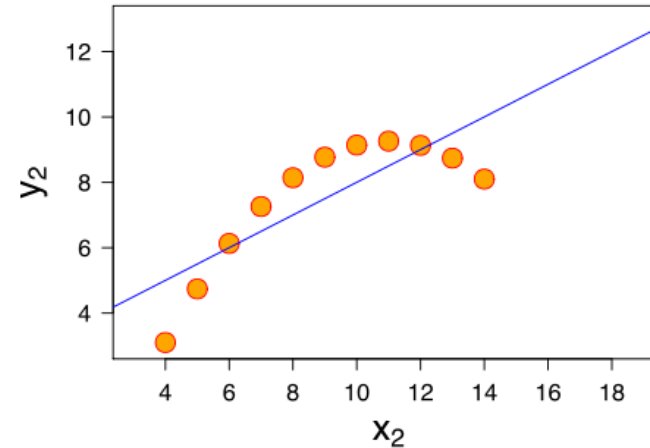
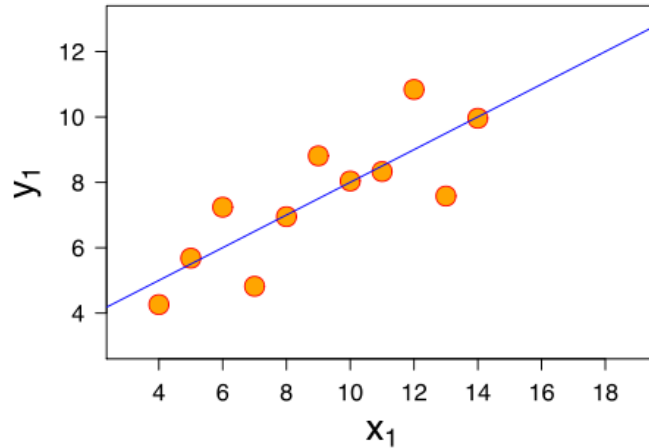
WGCNA (R)

TIGRESS (MatLab)

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

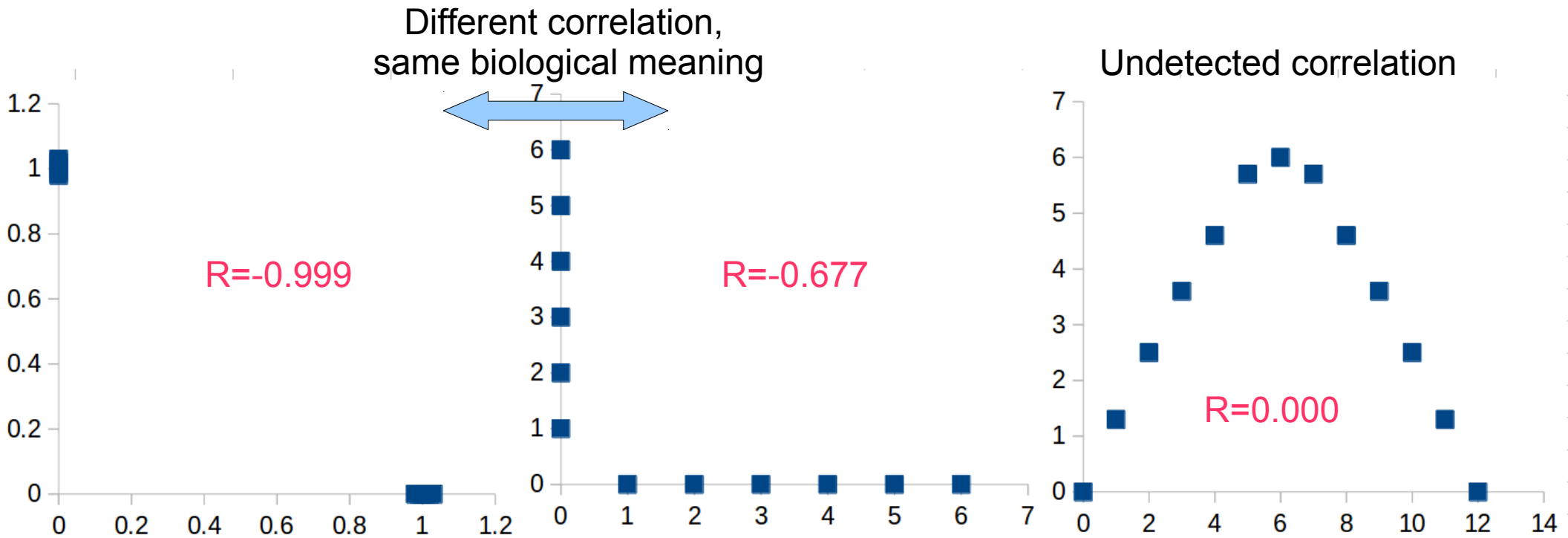
Marbach *et al* (2012)
Villaverde *et al* (2014)

Warning: Correlation does not tell nature or relation

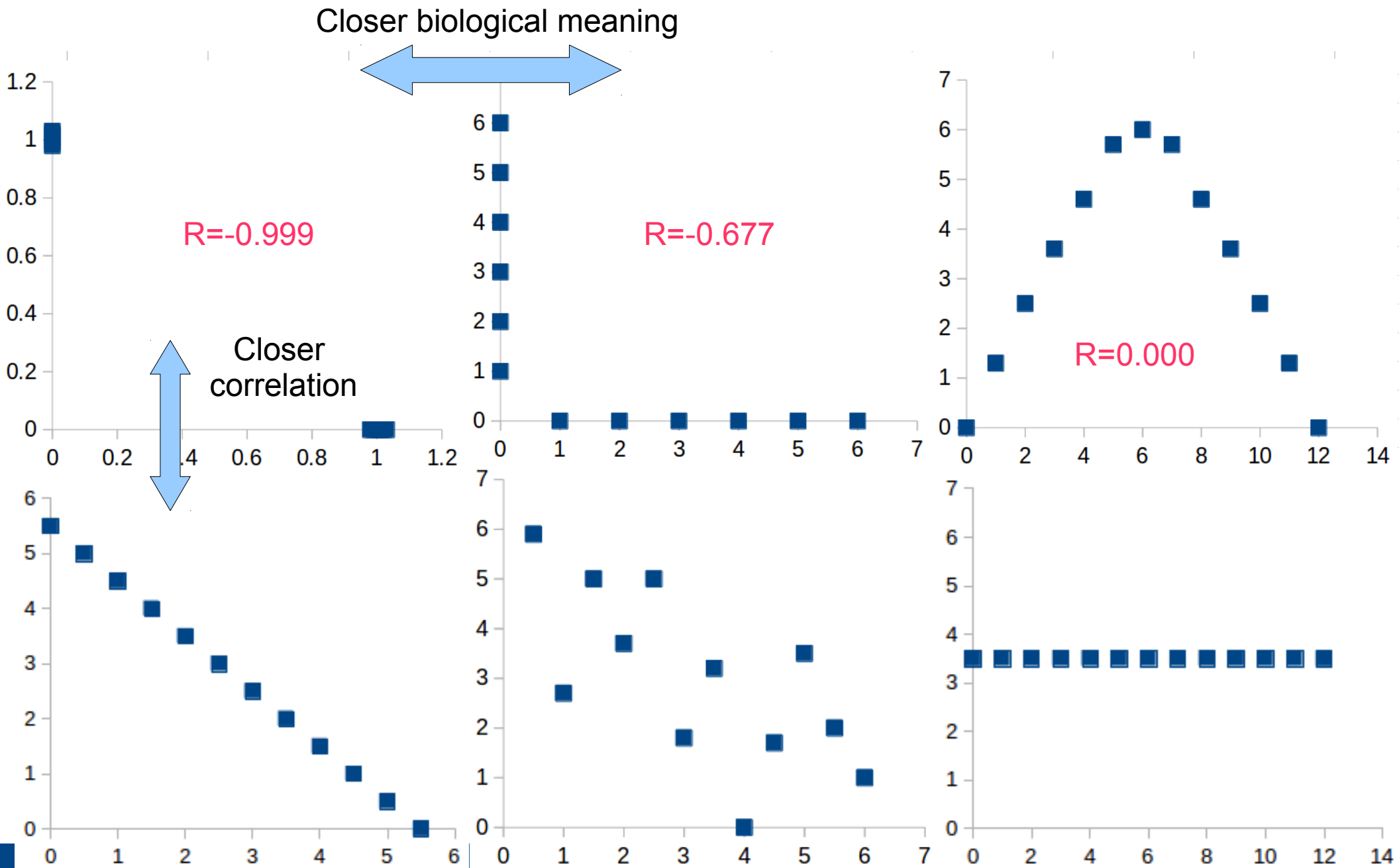


The four datasets have the same Pearson correlation

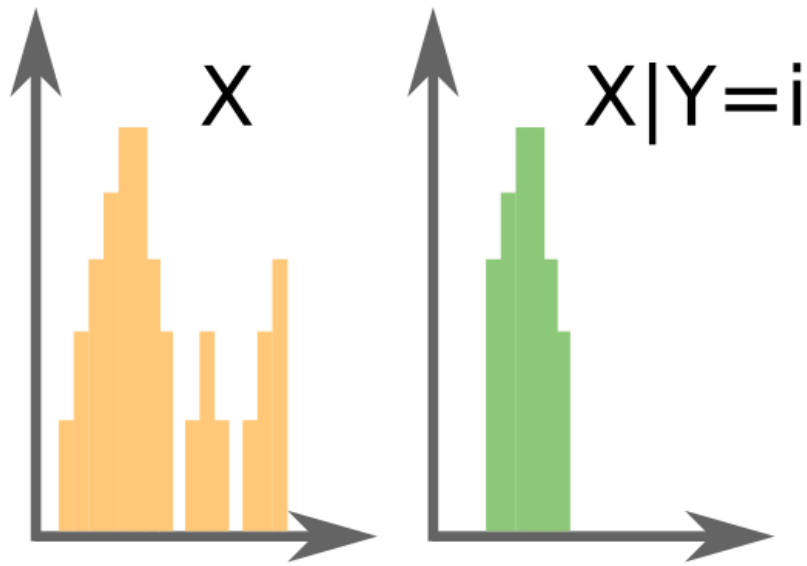
Correlations coefficients might be misleading



Correlations coefficients might be misleading



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

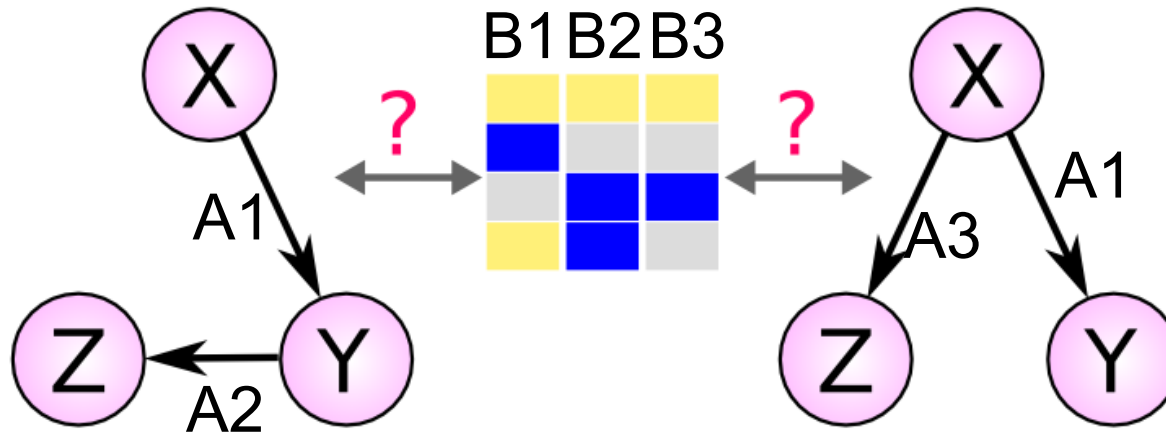
Tools:

ARACNE

CLR

(both in R package *minet*)

Network inference: Bayesian inference

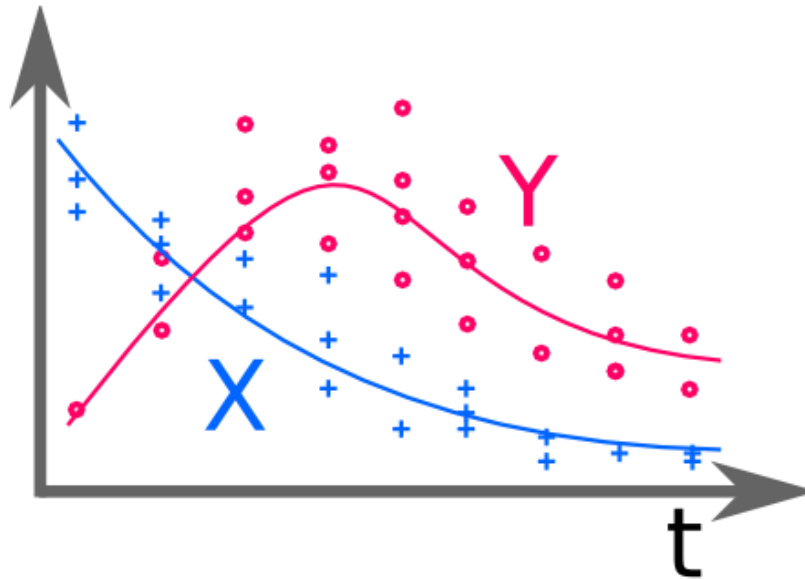


$$P(A|B) = \frac{P(B|A)P(A)}{P(B)}$$

Which network most probably generates this dataset?

Tools: BANJO (Java), catnet (R)

Network inference: ODEs



Equations describing
time courses best

Tools:

Inferelator

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

Search: Q01097

Search

Clear

[Show Advanced Fields »](#) [MIQL syntax reference](#)

- 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'

Home

Search

Interactions (254)

Browse

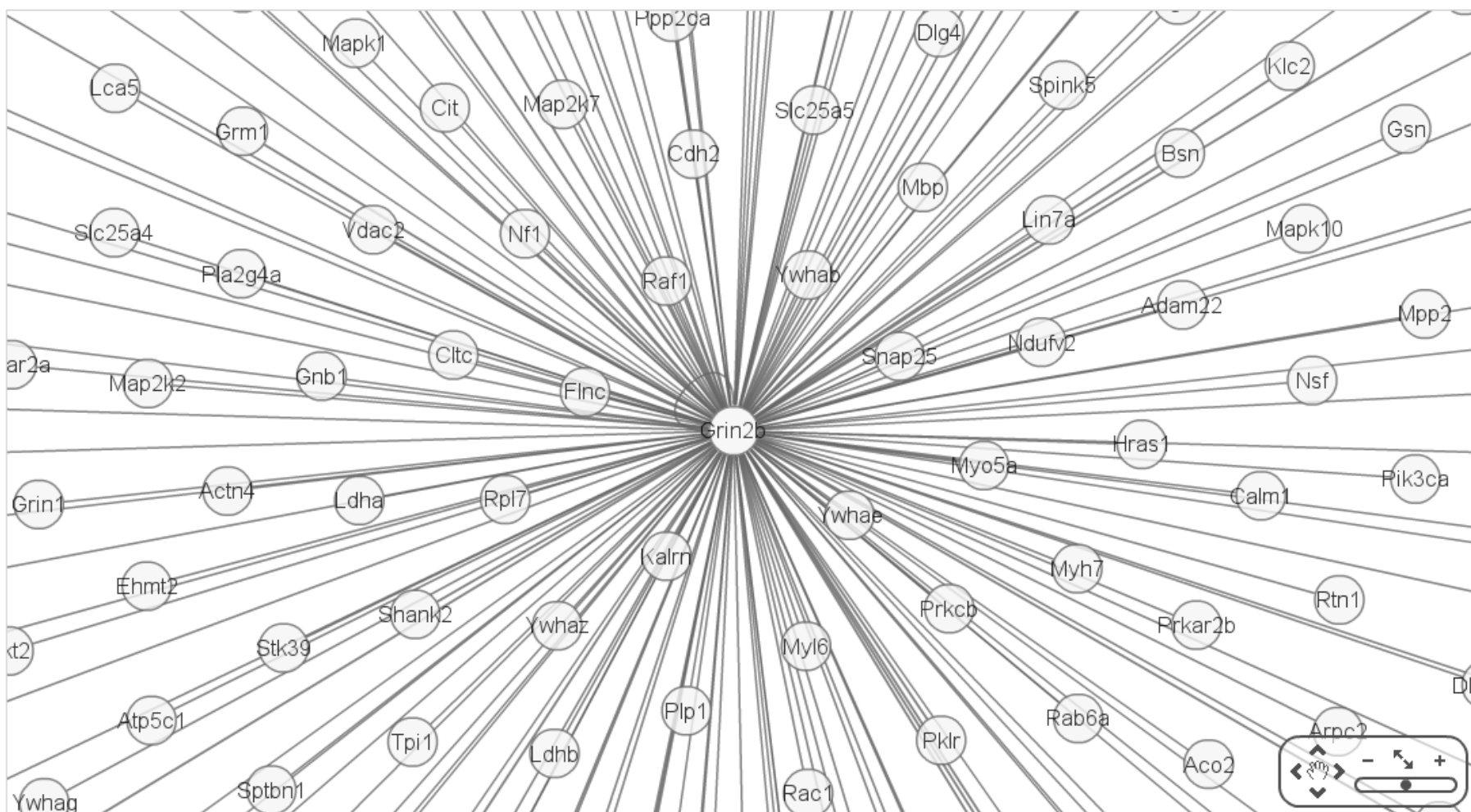
Lists

Interaction Details

Molecule View

Graph

Network visualisation



- Home
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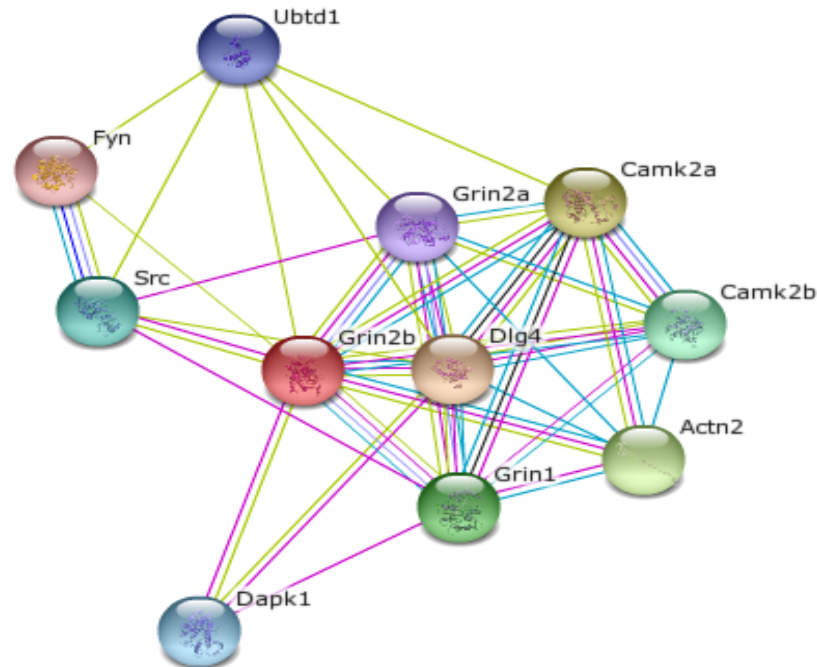
[IntAct release](#)
about 8 days ago
158/159! 302465 binary
interactions from 5787
manually curated
publications
<http://ftp.ebi.ac.uk/pub/databases/intact/current>

[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 13 days ago

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

[Now IntAct can visualise dynamic](#)
about 34 days ago



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:

Neighborhood
Gene Fusion
Cooccurrence
Coexpression
Experiments
Databases
Textmining
[Homology]
Score

The Systems Biology Graphical Notation



<http://sbgn.org/>

Le Novère *et al* (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

[Learn To Use SBGN](#)

[Symbols](#)

[Example Diagrams](#)

[Publications](#)

[Software Support](#)

[Specifications](#)

[Events](#)

[FAQ](#)

[About](#)

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[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

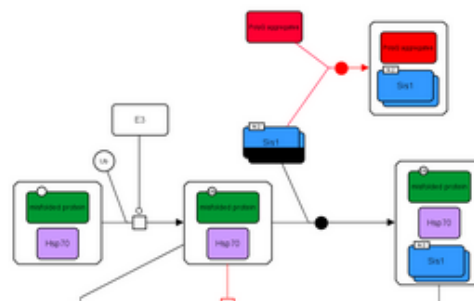
[Stimulation](#)



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.



The Systems Biology Markup Language



<http://sbml.org/>

Hucka *et al* (2003)

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

- 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
- Graph rendering – specification finalised
- Complex species – specification finalised → Entity Relationships
- Groups - specification finalised
- Spatial diffusion – specification under discussion
- Distributions and ranges - specification under discussion
- Enhanced metadata – specification proposed
- Arrays and sets – specification proposed
- Dynamic structures - discussed

**SBML Level 3
is modular**

Welcome to the portal for the **Systems Biology Markup Language (SBML)**, a free and open interchange format for computer models of biological processes. SBML is useful for models of metabolism, cell signaling, and more. It **continues to be evolved and expanded** by an international community.



For the curious

What is SBML? Read our [introduction](#), then perhaps browse the [mailing lists](#), the [FAQ](#), and look at the [SBML Level 3 package activities](#) to glimpse what's happening with SBML today.



For modelers

Looking for software that supports SBML? Our [software guide](#) lists over 250 systems. Are you instead looking for models? Visit [BioModels Database](#), where you can find hundreds!



For software developers

Want to support SBML in your software? Read our [intro](#) and then the [specifications](#) to understand SBML in depth, then check our [libraries](#), [test resources](#), and also [3rd-party software](#).

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

SBML would not have been possible without support from [multiple agencies and organizations](#), as well as intellectual contributions from many motivated individuals, including the [major contributors](#) who are shaping SBML Level 3.

SBML News

SBML Layout spec. released

(14 Aug.'13) The SBML Level 3 Layout V.1 specification has been finalized and released.



COMBINE 2013

(28 Jul.'13) Registration and a preliminary agenda for the September event are now available.



SBML Test Runner 3.0

(6 Jun.'13) A new version of the standalone Test Runner for the SBML Test Suite is now available.



[Older news ...](#)

Community News

SBML2GPML

(12 Sep.'13) This new PathVisio plugin allows SBML models to be imported.



CellNOpt 1.7.7

(12 Aug.'13) This logic-based modeling software system now supports SBML Level 3 Qualitative Models.



iNA 0.4.2 released

(11 Jun.'13) The new release offers a new plot editor and supports multi-core computations on MacOS.



[Older news](#)

Parent pages: [SBML.org](#)

SBML Software Guide

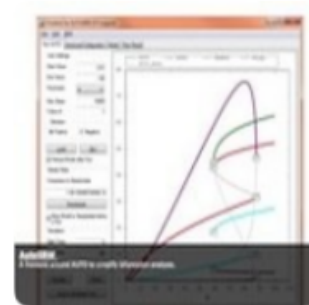
The following pages describe SBML-compatible software packages known to us. We offer different ways of viewing the information, all drawn from the same underlying data collected from the systems' developers via our [software survey](#). The *Matrix* provides a table listing all known software and a variety 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**.

Go to the SBML
Software Matrix

Go to the SBML
Software Summary

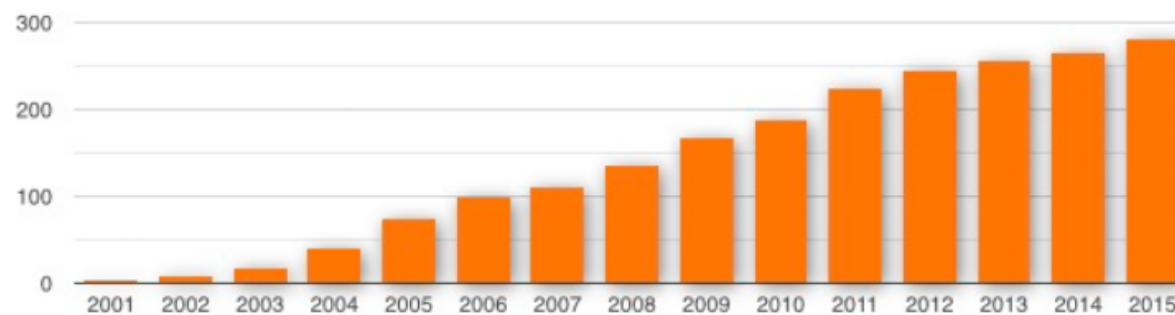
Go to the SBML
Software Showcase



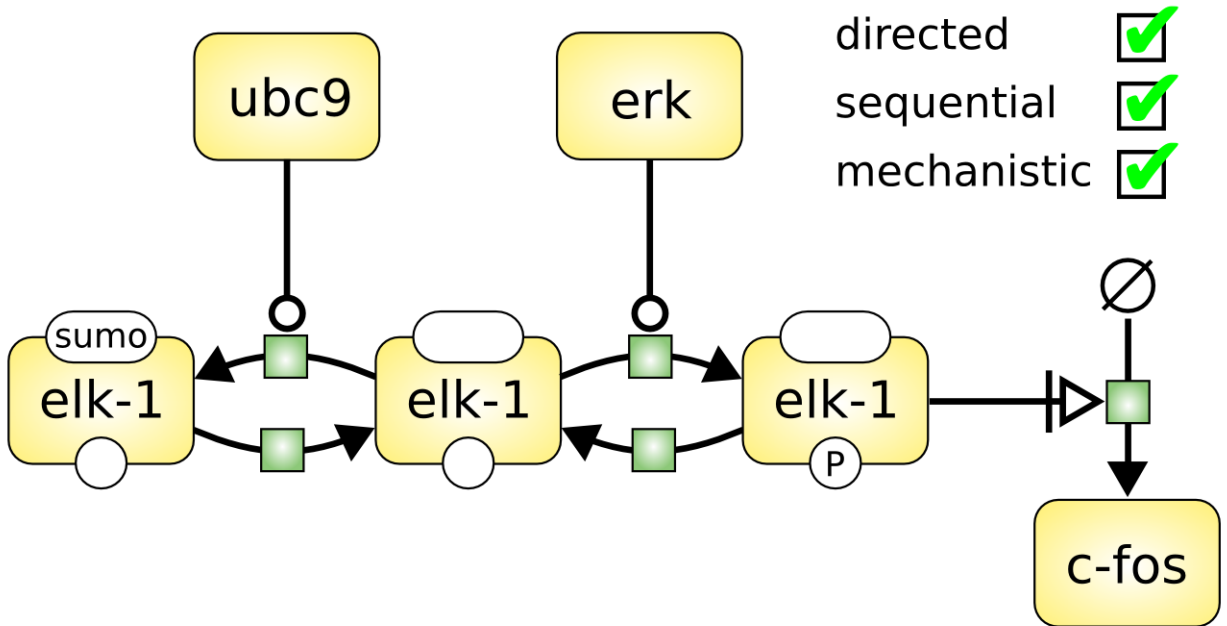
Please [tell us about additions and updates](#).

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.



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

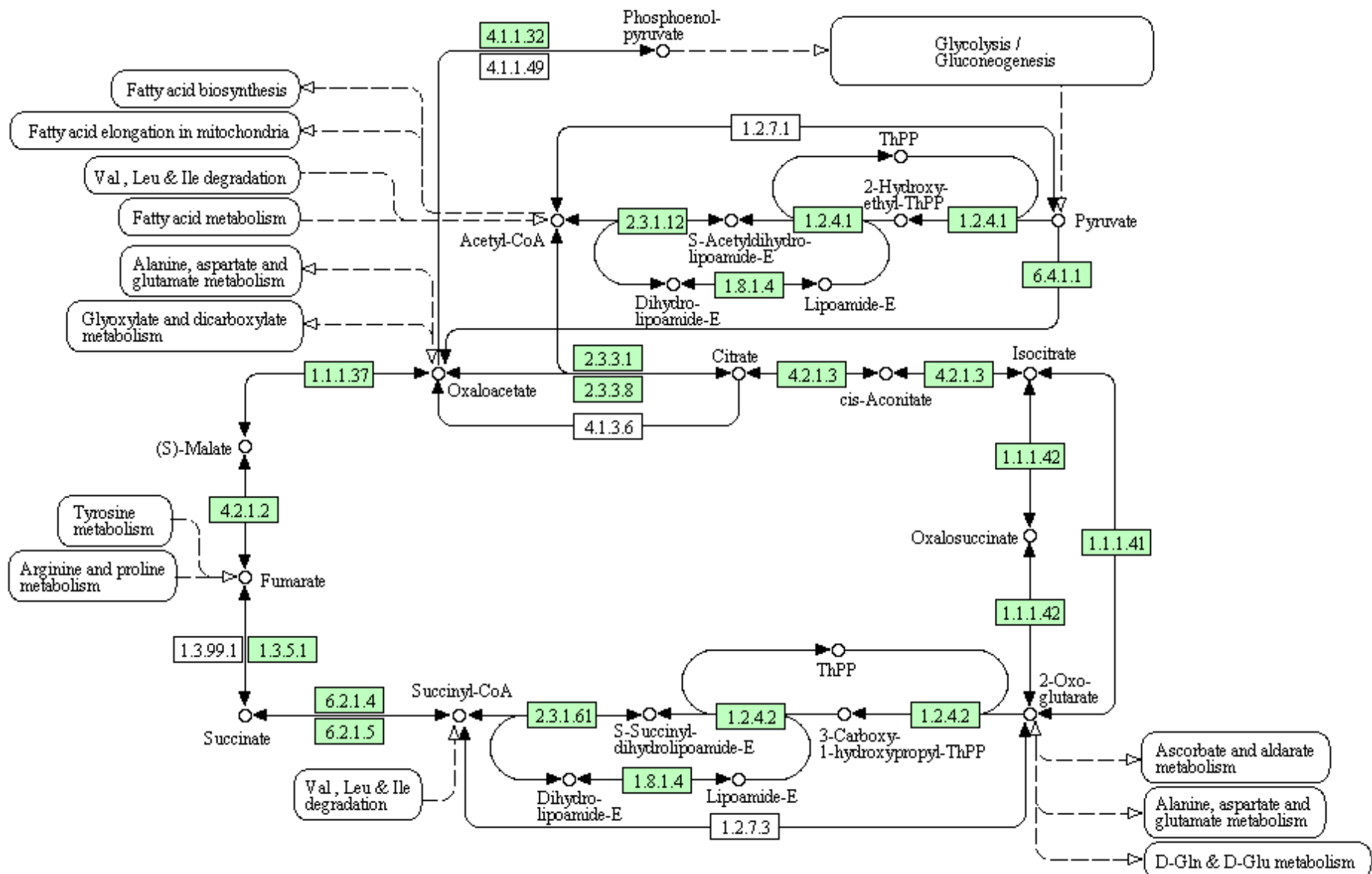
Closed world

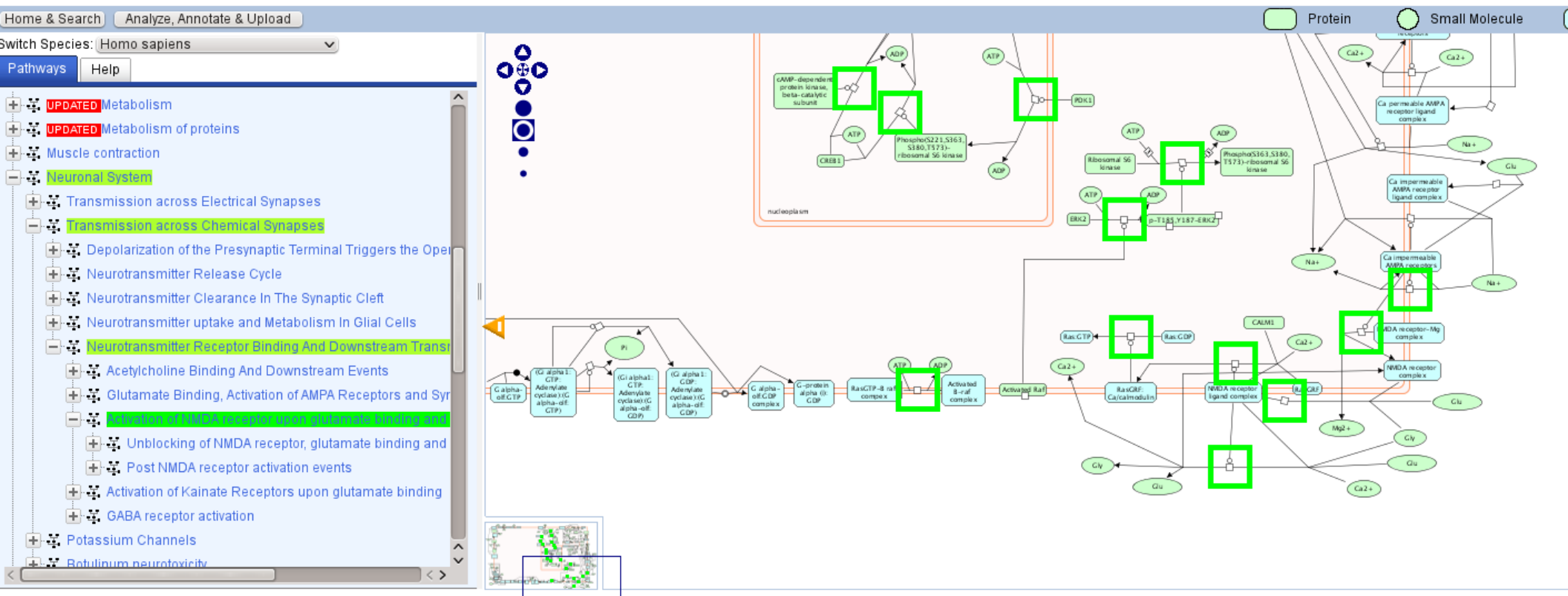
Anything not explicitly stated does not exist

Failure to observe implies non-existence

New pieces of knowledge might change the meaning of prior pieces

CITRATE CYCLE (TCA CYCLE)





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 Ca^{2+} . 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 both glutamate and glycine for activation. At resting membrane potential the NMDA receptors are blocked by Mg^{2+} . The voltage dependent Mg^{2+} block is relieved upon depolarization of the post-synaptic membrane. The ligand dependent activation of the NMDA receptor requires co-activation by glutamate and 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 Ca^{2+} that initiates various molecular signaling cascades that lead to changes in synaptic strength and memory.

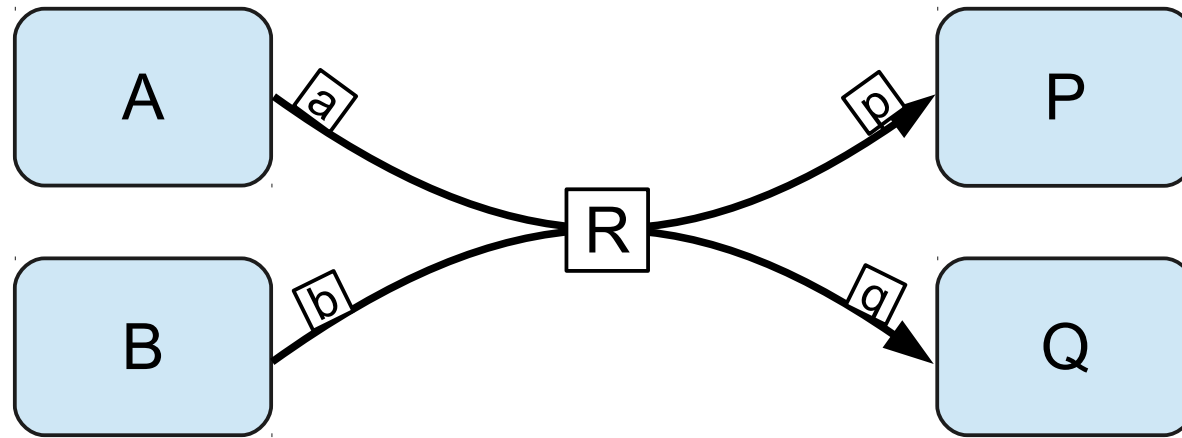
Organism	Homo sapiens
Cellular compartment	extracellular region GO plasma membrane GO cytoplasm GO nucleoplasm GO

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

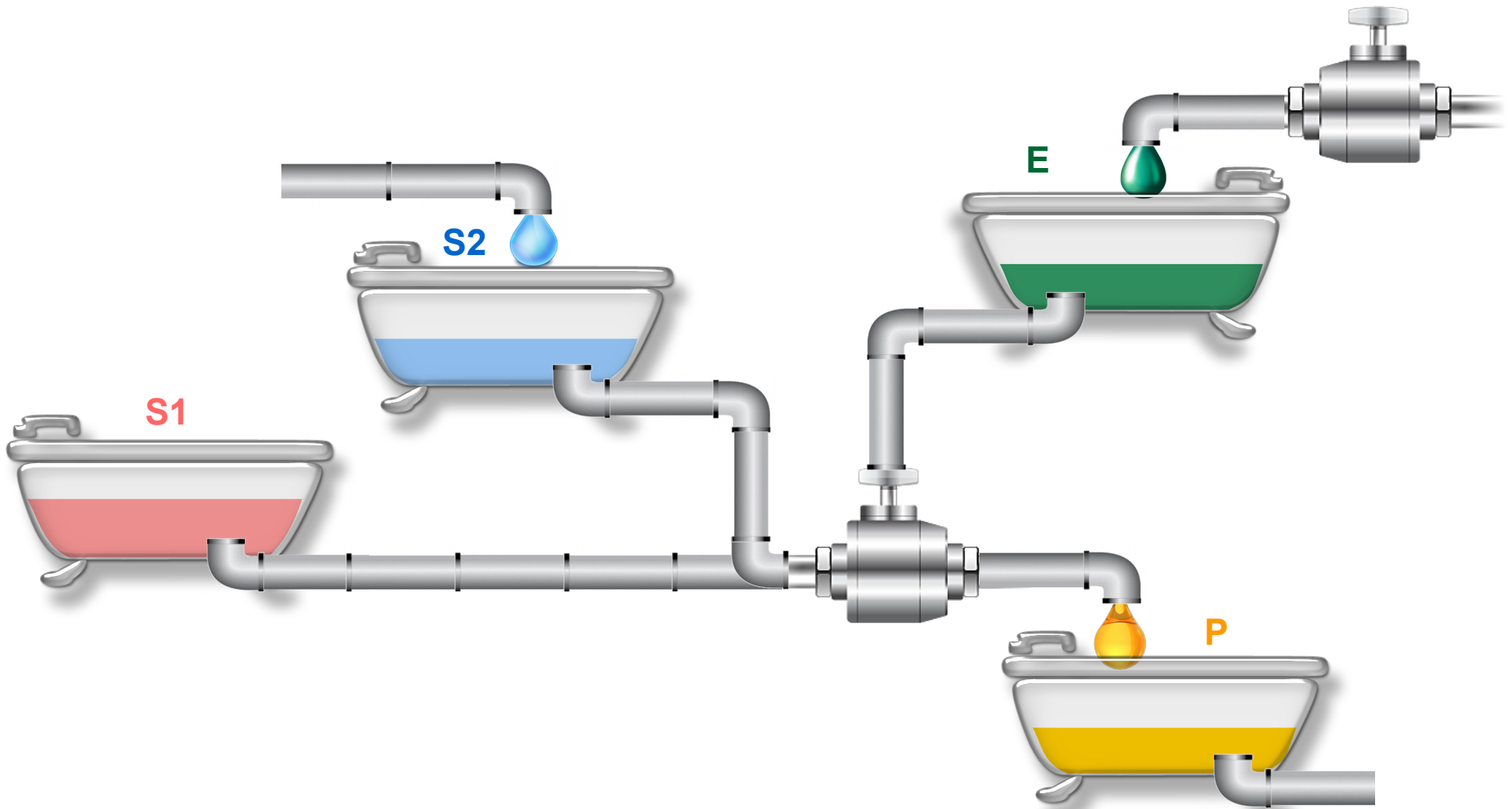


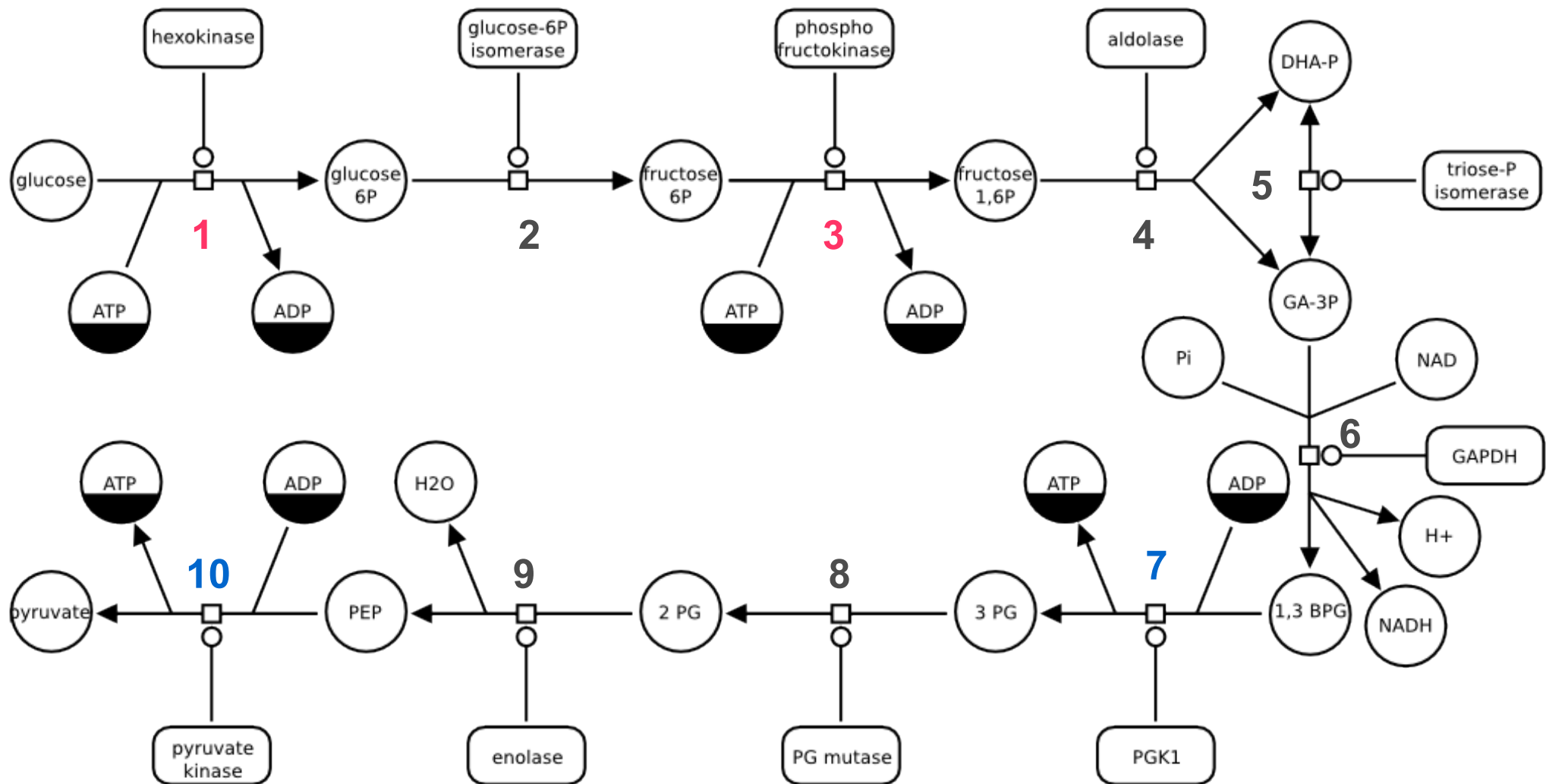
substances A and B are consumed by reaction R that produces substances P and Q

→ 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

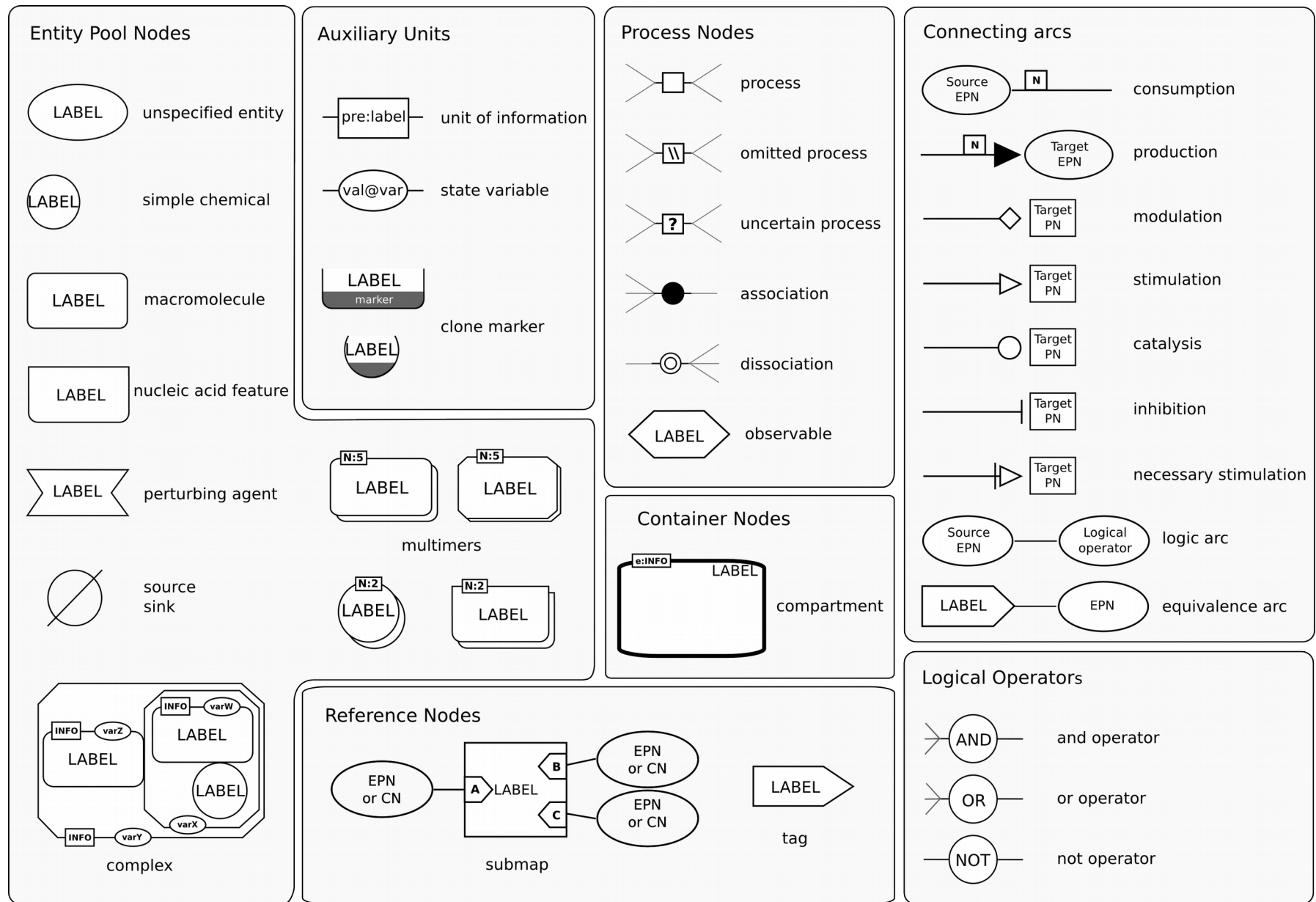
Process Descriptions can be viewed as pipelines



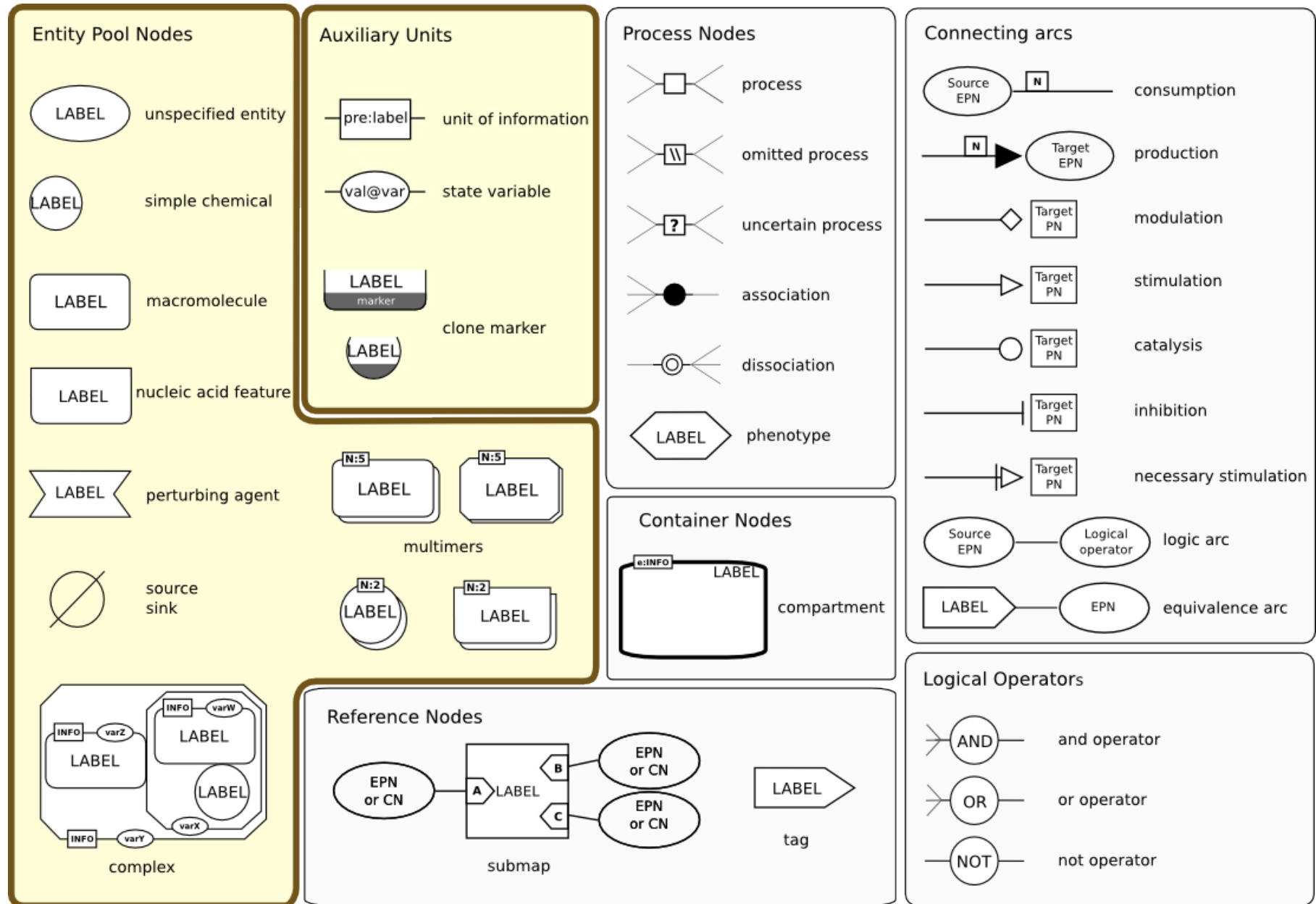


ATP is consumed by processes 1 and 3, and produced by processes 7 and 10

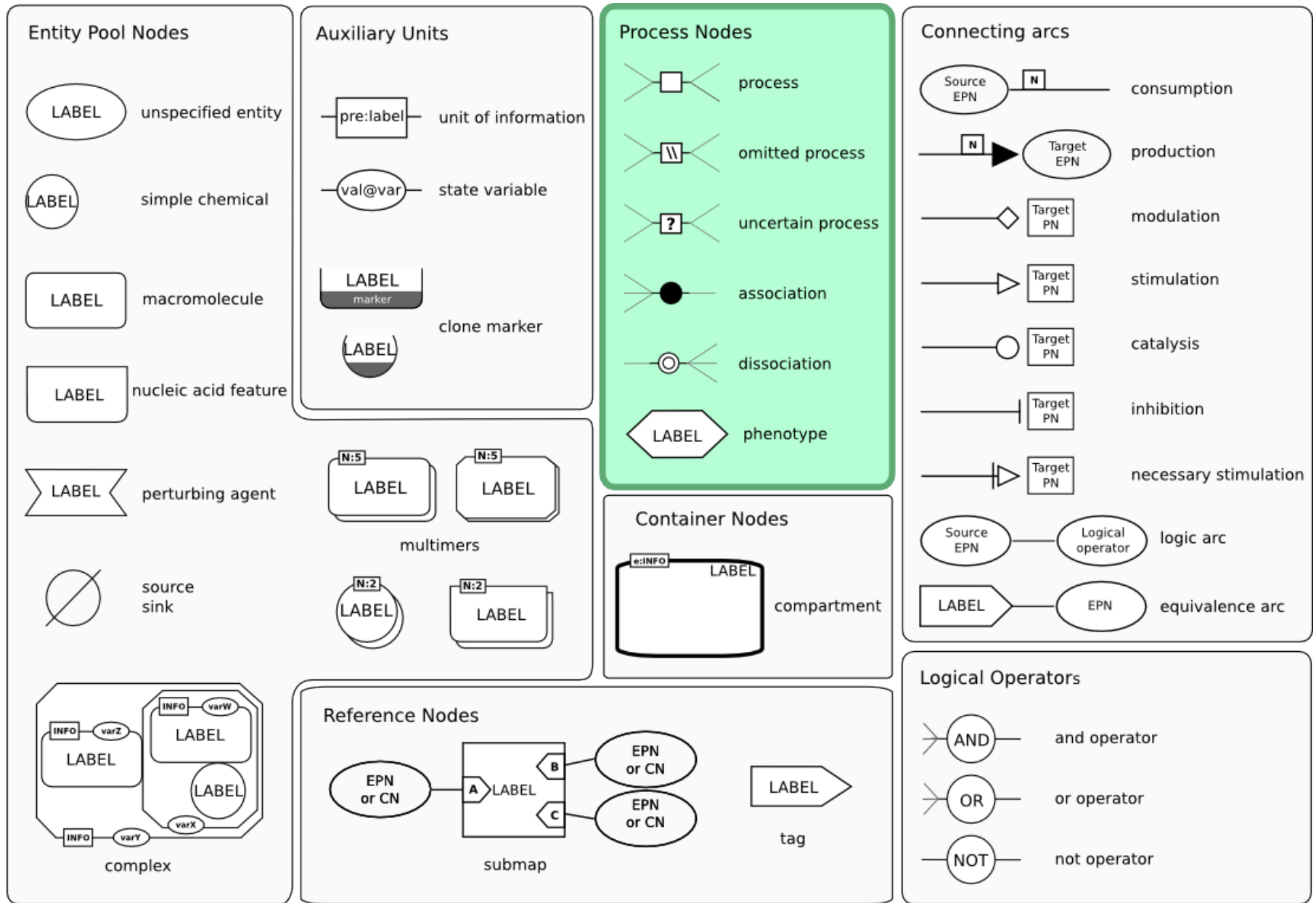
SBGN Process Diagram L1 reference card



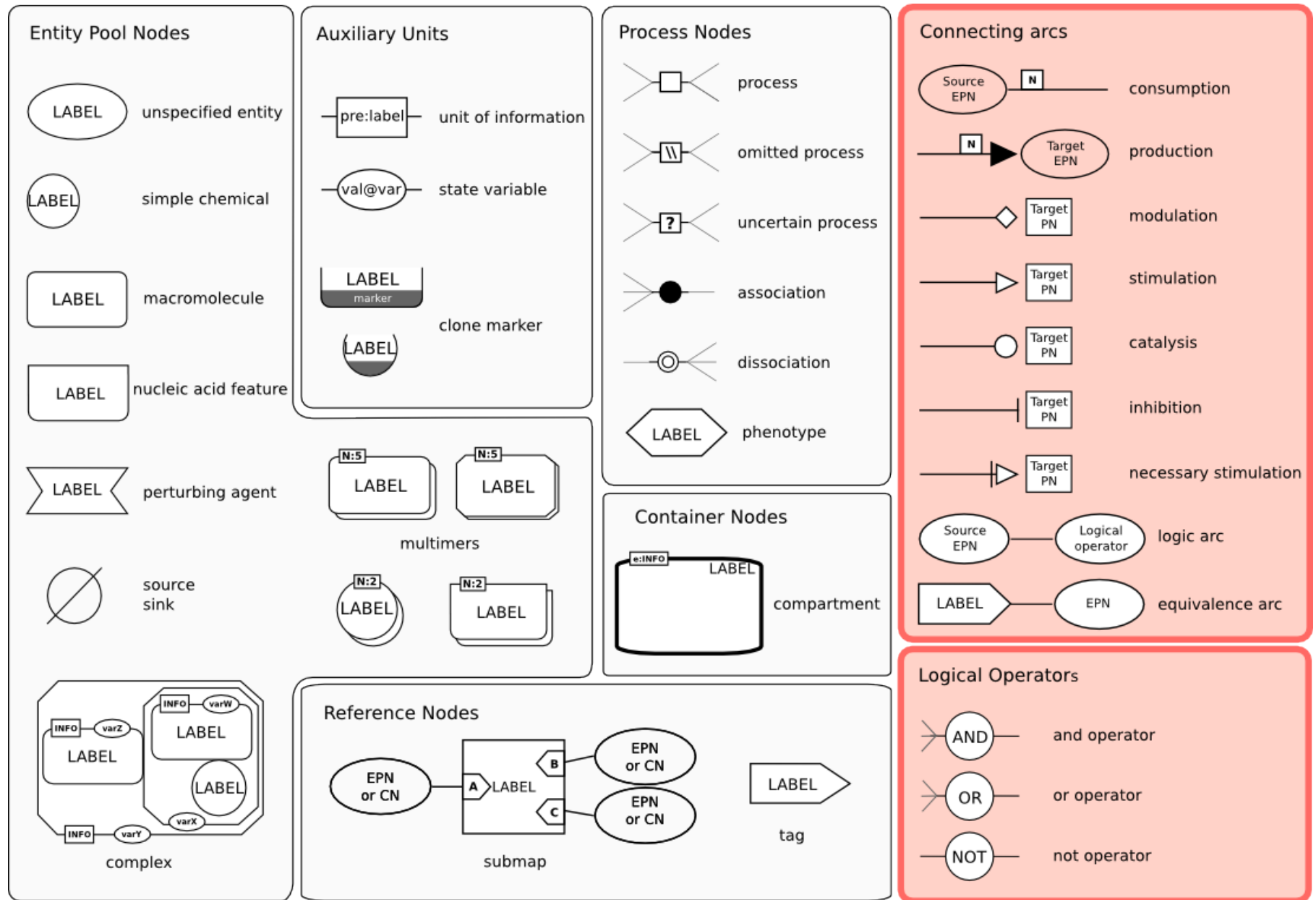
Entity Pool Nodes



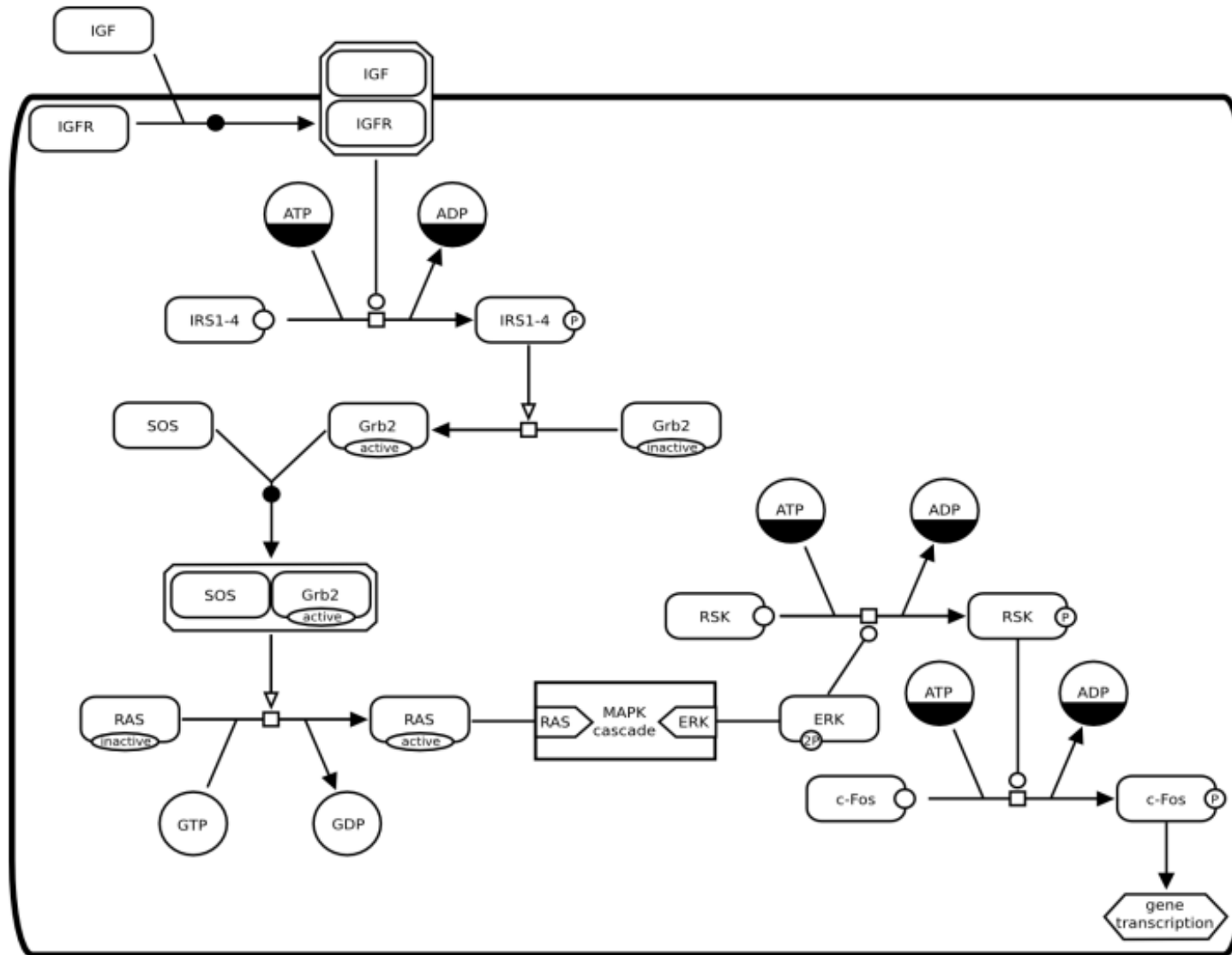
Process Nodes



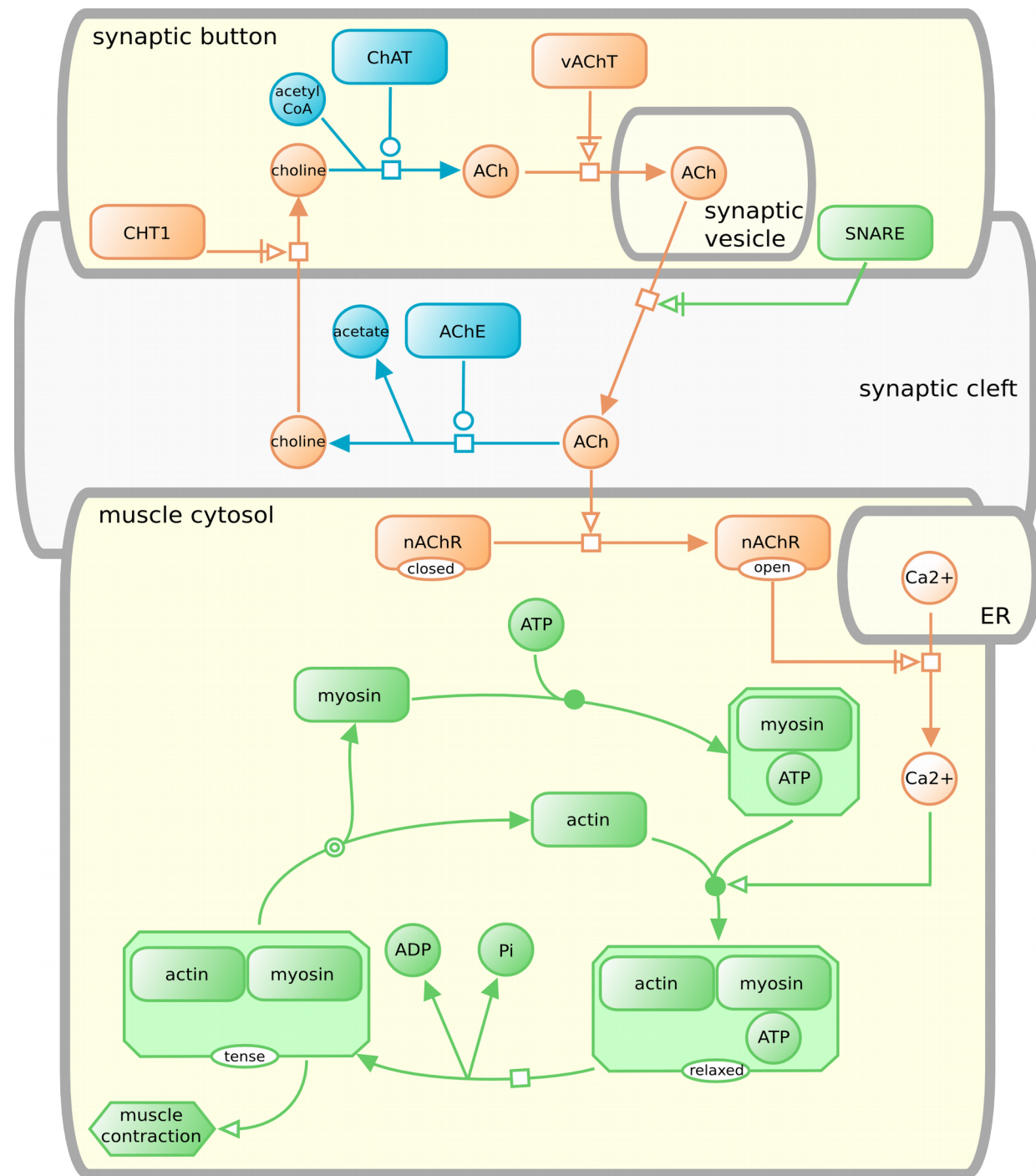
Connecting arcs

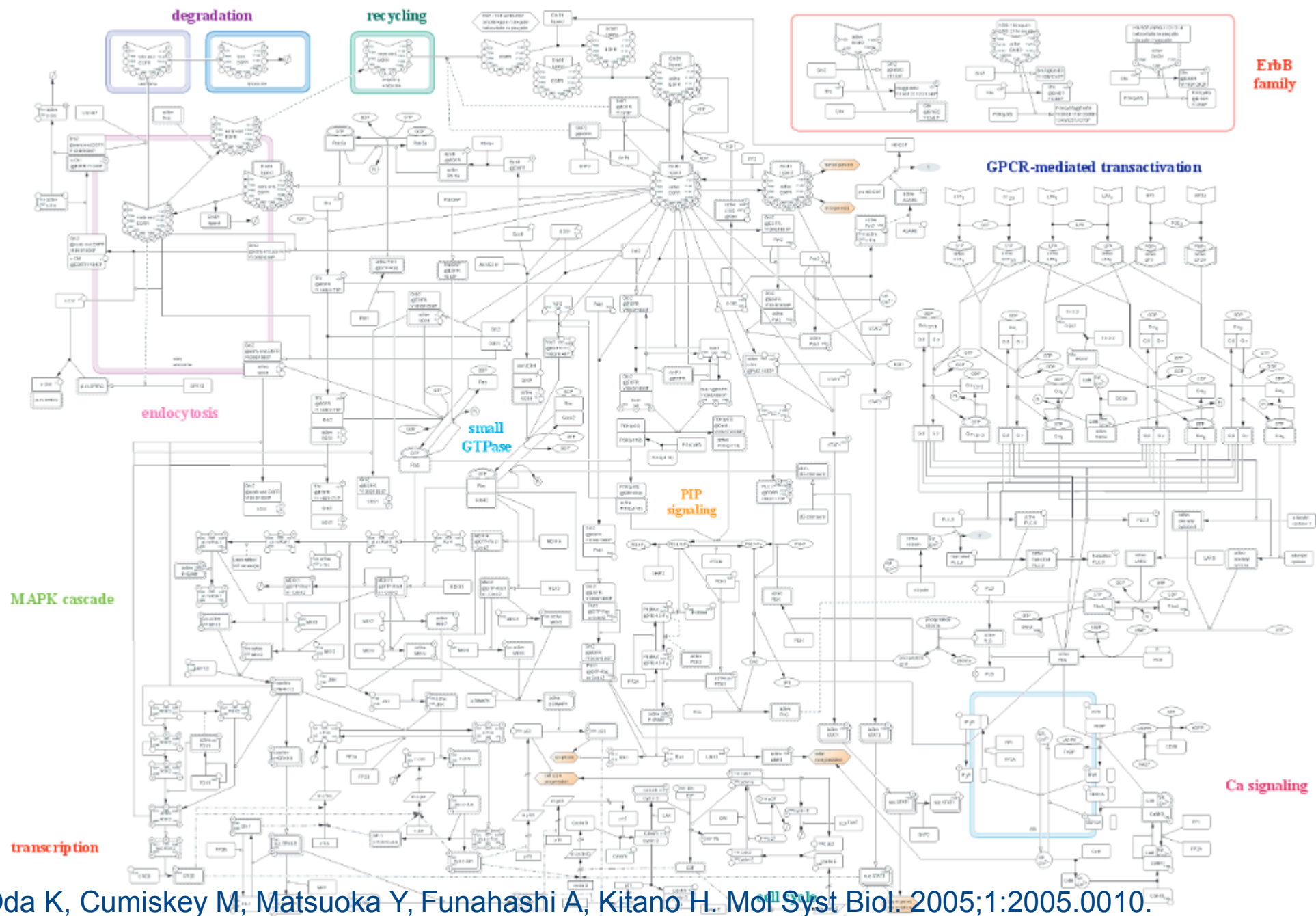


Signalling

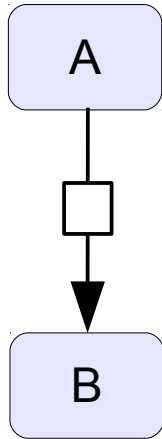


Multicellular





Oda K, Cumiskey M, Matsuoka Y, Funahashi A, Kitano H. Mol Syst Biol. 2005;1:2005.0010.



```

<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns="http://www.sbml.org/sbml/level2/version4" level="2" version="4">
  <model name="Simple Model">
    <listOfCompartments>
      <compartment id="cell" size="1" />
    </listOfCompartments>
    <listOfSpecies>
      <species id="A" compartment="cell" initialConcentration="1"/>
      <species id="B" compartment="cell" initialConcentration="1"/>
    </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> A </ci>
            </apply>
          </math>
        </kineticLaw>
      </reaction>
    </listOfReactions>
  </model>
</sbml>

```

**A very simple
SBML file**

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

<http://sbml.org>



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

File Tools Help

Concentrations

- Copasi
 - Model
 - Biochemical
 - Compartments
 - cell
 - Species
 - A
 - B
 - Reactions
 - r1
 - Global Quantities
 - Events
 - Parameter Overview
 - Mathematical
 - Differential Equations
 - Matrices
 - Diagrams
 - Tasks
 - Steady-State
 - Stoichiometric Analysis
 - Time Course
 - Metabolic Control Analysis
 - Lyapunov Exponents
 - Time Scale Separation Analysis
 - Parameter Scan
 - Optimization
 - Parameter Estimation
 - Sensitivities



$$\frac{d([A] \cdot V_{\text{cell}})}{dt} = -V_{\text{cell}} \cdot (k_1 \cdot [A])$$

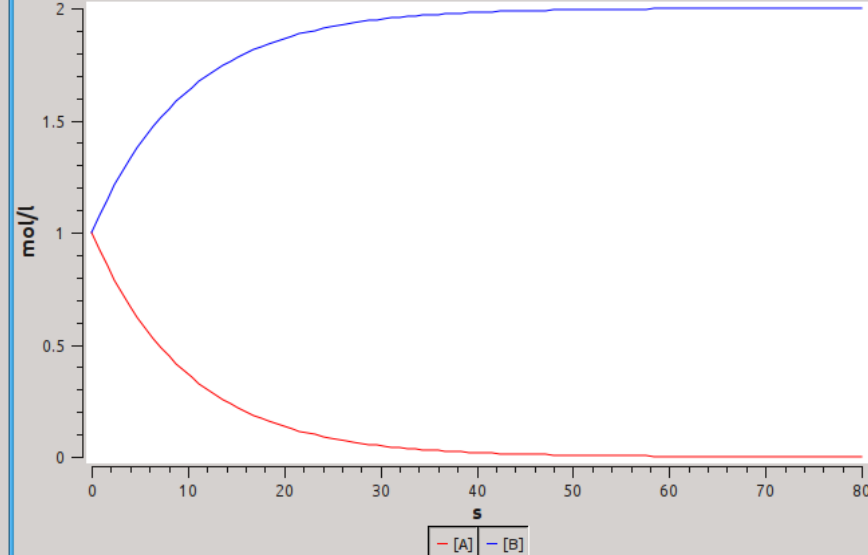
$$\frac{d([B] \cdot V_{\text{cell}})}{dt} = +V_{\text{cell}} \cdot (k_1 \cdot [A])$$

local parameters display numerical value Save Formula to Disk

Copasi Plot: Concentrations, Volumes, and Global Quantity Values

Print Save Image Save Data Zoom out Show All Hide All Close

Concentrations, Volumes, and Global Quantity Values



CellDesigner

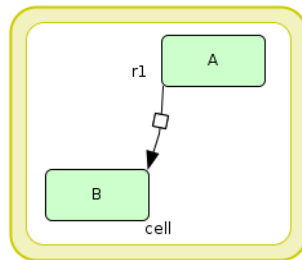
File Edit Component View Database Layout Simulation Plugin Window SBW Preference Help

CellDesigner.org

- Model
 - Compartments
 - Species
 - Reactions

Layer base

SimpleSBML.xml *



Species Proteins Genes RNAs asRNAs Reactions Compartments Par

Edit Export

class	id	name	speciesType	compart...	positio...	included
PROTEIN	A	A		cell	inside	
PROTEIN	B	B		cell	inside	

ControlPanel SimpleSBML.xml

File Edit Data Simulation

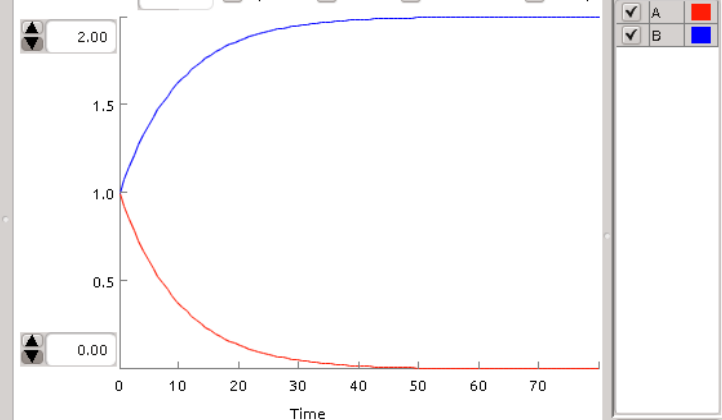
Time span End Time 80 Num. o... 100 Error tolerance Exp. -6 Solver SOSlib COPASI

Species Parameters Change amount Parameter Scan

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

Graph Table

Concentration raw Species Fluxes Parameters Compe



Initialize Save As Execute Close show scatter plot

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 Hoppe⁶, Swagatika Sahoo¹, Maike K Aurich¹, Hulda Haraldsdottir¹, Monica L Mo⁷, Ottar Rolfsson¹, Miranda D Stobbe^{8,9}, Stefan G Thorleifsson¹, Rasmus Agren¹⁰, Christian Bölling⁶, Sergio Bordel¹⁰, Arvind K Chavali¹¹, Paul Dobson¹², Warwick B Dunn^{3,13}, Lukas Endler¹⁴, David Hala¹⁵, Michael Hucka¹⁶, Duncan Hull⁴, Daniel Jameson^{3,4}, Neema Jamshidi⁷, Jon J Jonsson⁵, Nick Judy¹⁷, Sarah Keating¹⁷, Intawat Nookaew¹⁰, Nicolas Le Novère^{17,18}, Naglis Malys^{3,19,20}, Alexander Mazein²¹, Jason A Papin¹¹, Nathan D Price²², Evgeni Selkov, Sr²³, Martin I Sigurdsson¹, Evangelos Simeonidis^{22,24}, Nikolaus Sonnenschein²⁵, Kieran Smallbone^{3,26}, Anatoly Sorokin^{21,27}, Johannes H G M van Beek²⁸⁻³⁰, Dieter Weichart^{3,31}, Igor Goryanin^{21,32}, Jens Nielsen¹⁰, 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 exhibit¹. The metabolic-network reconstruction procedure

is now well-established² and has been applied to a growing number of model organisms³. 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

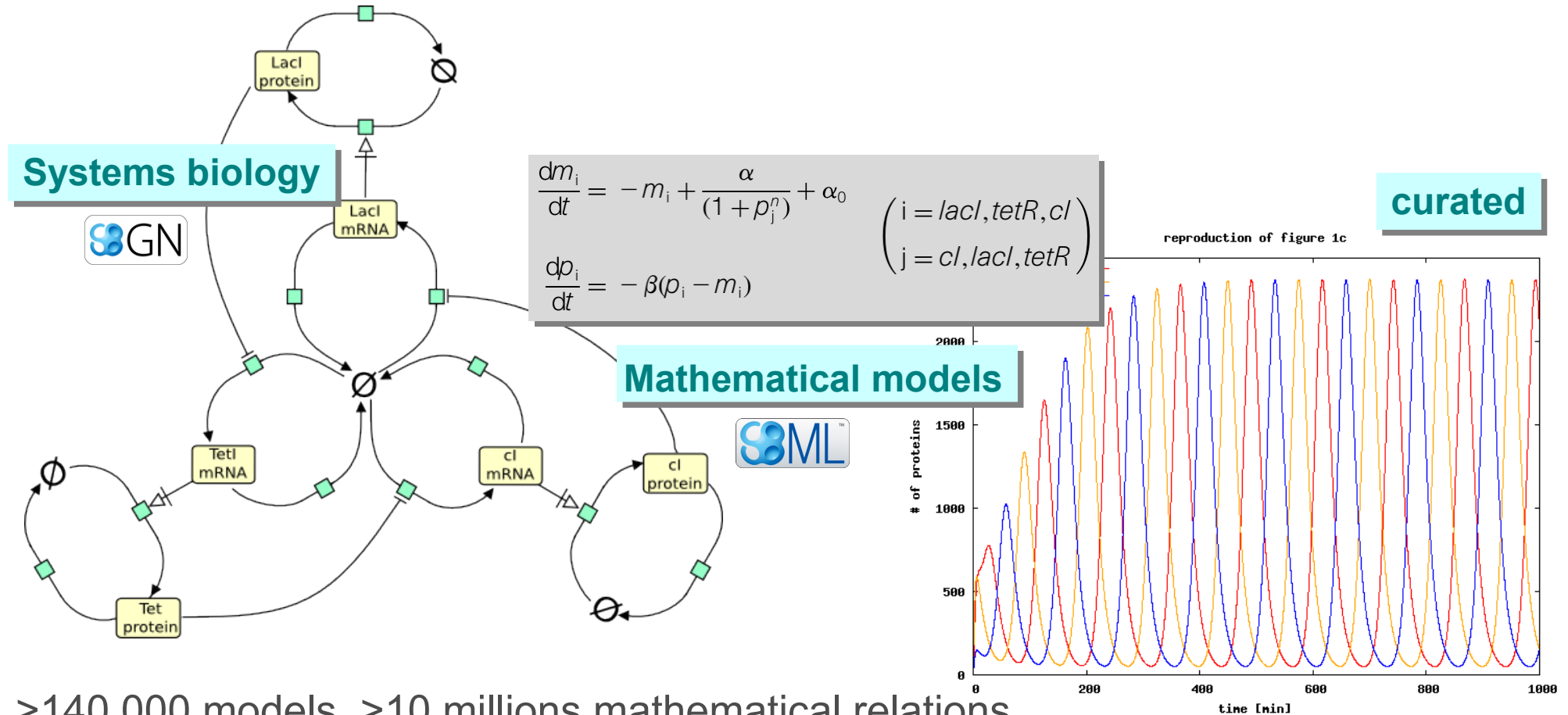
A not so simple SBML file (Recon2)

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



MODEL1109130000

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



>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



BioModels Database

Search

Advanced

[BioModels Home](#) [Models](#) [Submit](#) [Support](#) [About BioModels](#) [Contact us](#)

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

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

Models published in the literature

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

Browse the models in the curated branch. These models have been thoroughly curated, and model elements have been annotated with terms from controlled vocabularies as well as links to relevant data resources.

Path2Models

Submit a model

Links

- [Main instance at EMBL-EBI, UK](#)
- [Mirror at Caltech, USA](#)
- [Project on SourceForge](#)
- [Web Services](#)
- [Download archived models](#)

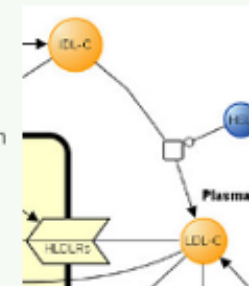
<http://www.ebi.ac.uk/biomodels>

Model of the month

October, 2013

Why LDL-C rises with age? The model presented here demonstrates that mechanistic changes to cholesterol absorption and LDL-C removal from the plasma with age, can result in a significant rise in LDL-C.

[Please read more...](#)



News [Follow us on Twitter](#)

8 October 2013 **SPARQL endpoint available**

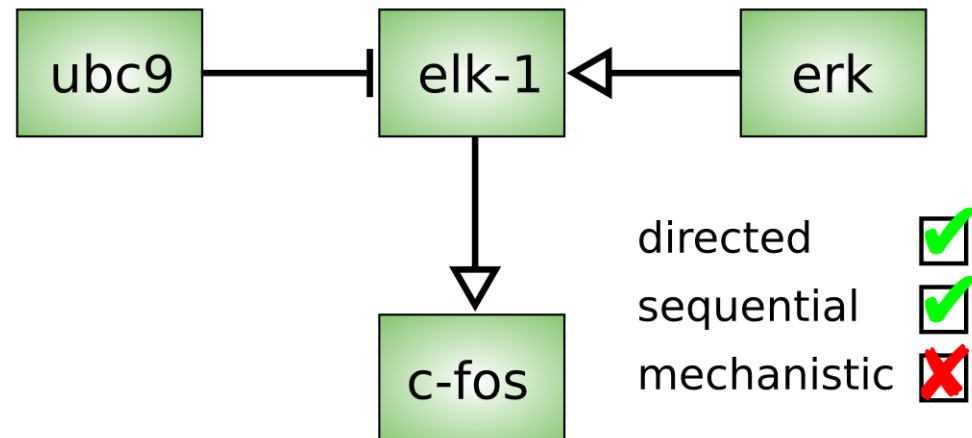
The EBI launched a RDF platform. This provides access to various bioinformatics resources (including BioModels Database) using Semantic Web technologies (SPARQL endpoints and RDF dumps are available). [Read more about this news.](#)

18 June 2013 **25th release**

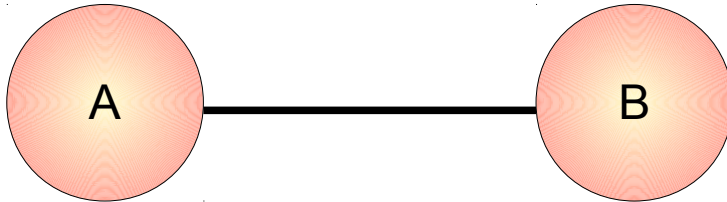
We are pleased to announce the [twenty-fifth release of BioModels Database](#)! The resource now publicly provides 143013 models. Numerous new models have been made available, several have been updated and various new features have been unveiled.

Activity Flows

- Logical modelling
- Signalling pathways, gene regulatory networks

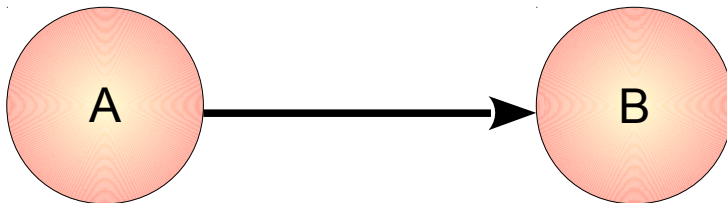


Undirected, directed, signed



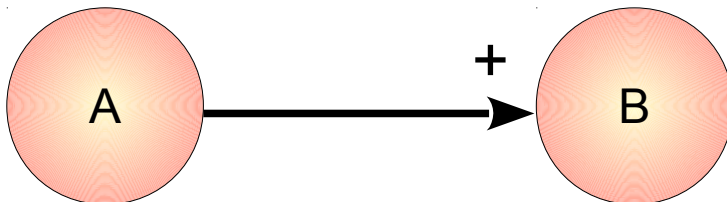
Undirected

“A interacts with B”



directed

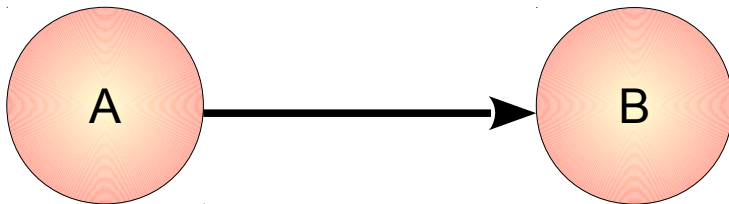
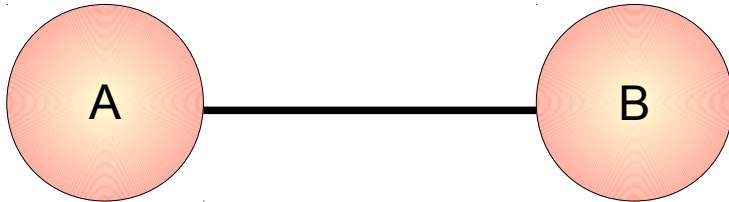
“A influences B”



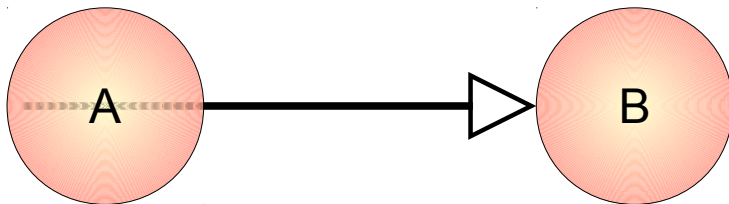
Signed

A influences positively B

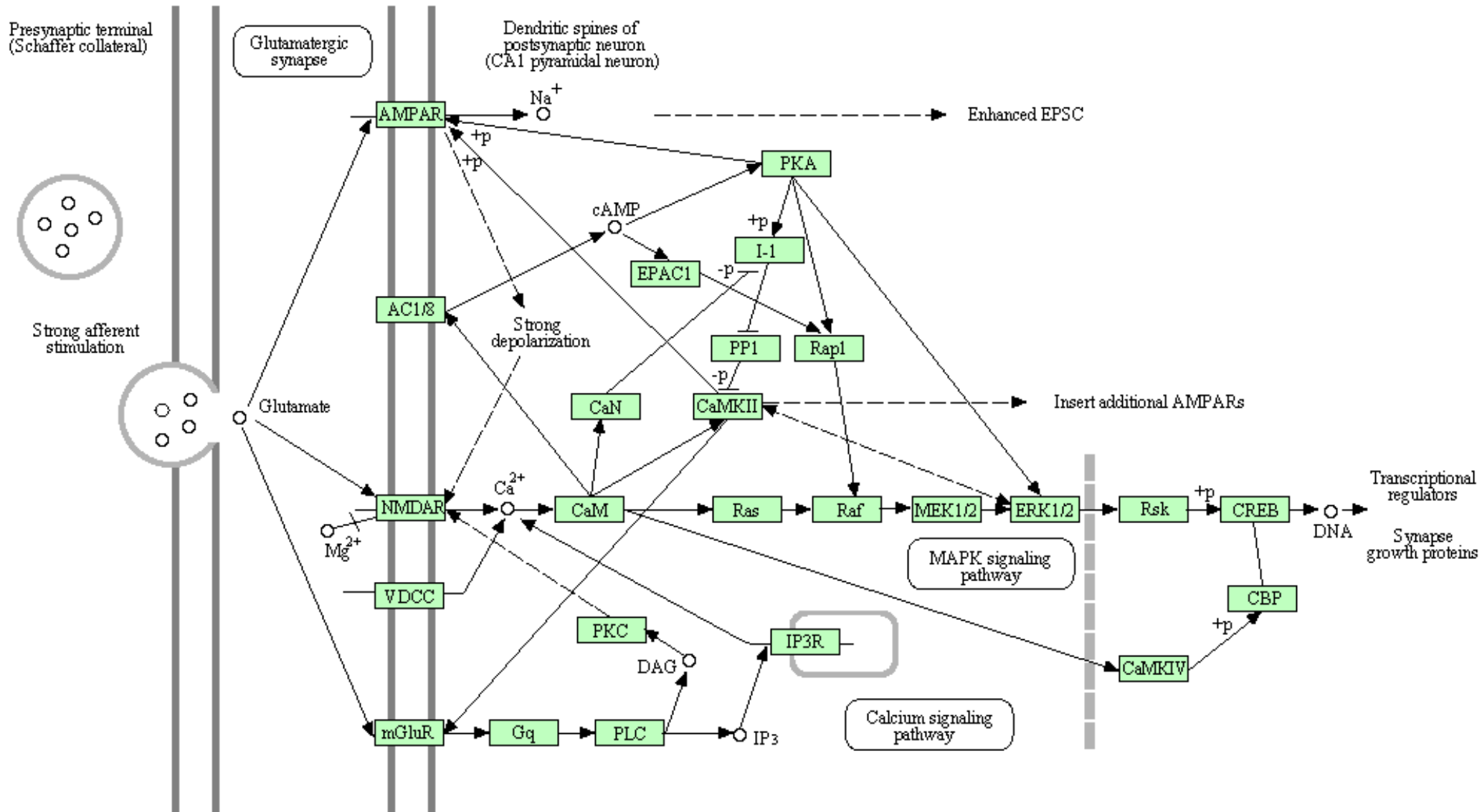
Undirected, directed, signed



A signed interaction network is equivalent to an activity flow



LONG-TERM POTENTIATION



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

Call for Papers
 Submit a Research Article
 Pathway Views
 Pathway Information
 Overview
 Print Version

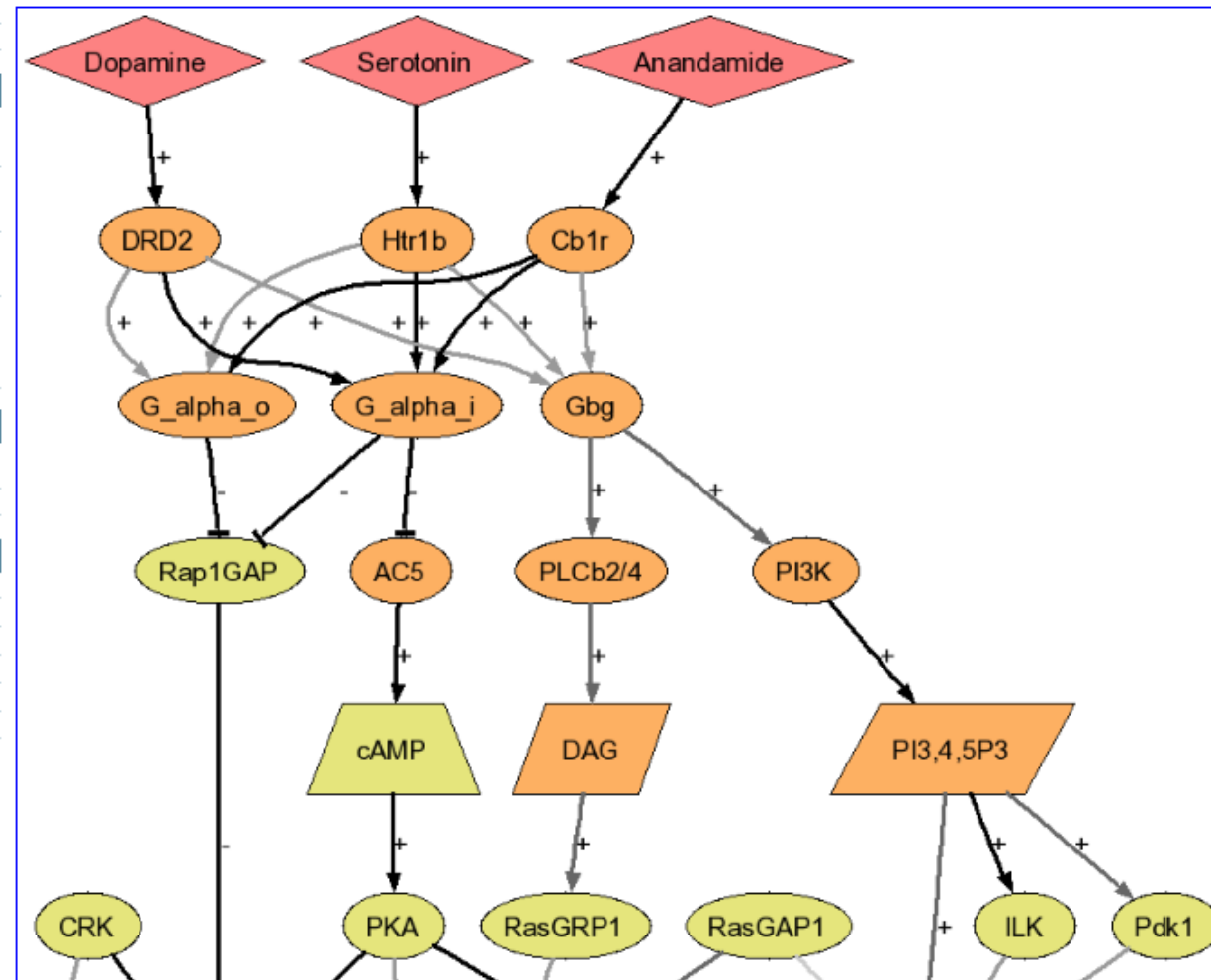
Pathway Information

Neuro2A Differentiation by G alpha i/o Pathway

Author(s): Aul, Mayana, et al.
 Organism: vertebrates : mammals : Rodentia : mouse
 Tissue/Cell: nervous system : central nervous system : neurons
 Citation: [Literature](#)
 Scopes: Specific
 Canonical Pathways: [G alpha i Pathway](#)

Pathway

[View Connections](#) [Map Legend](#)
[Get SVG Pathway Image](#)



ADVERTISEMENT

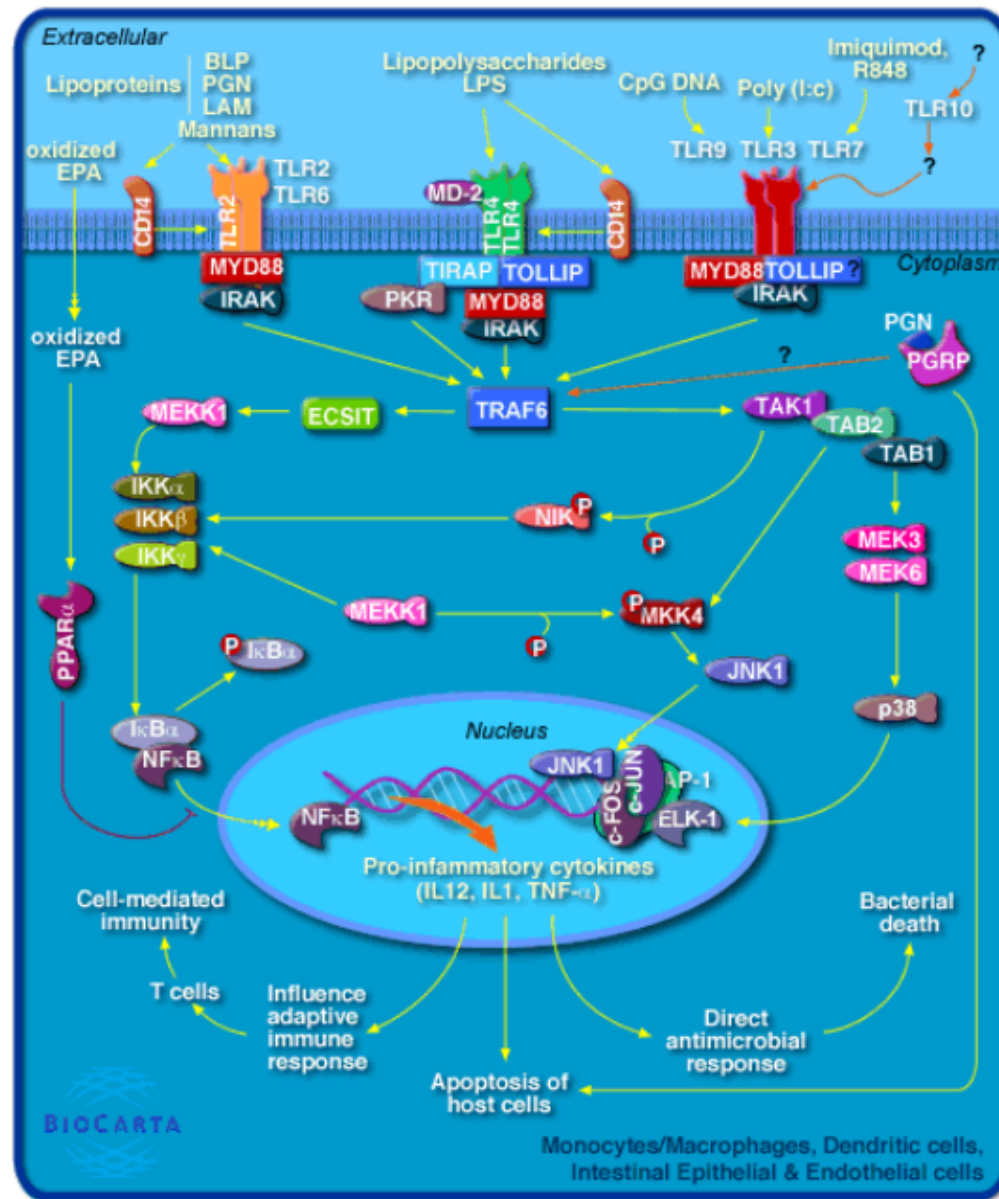
MANAGE
YOUR CAREER
BETTER

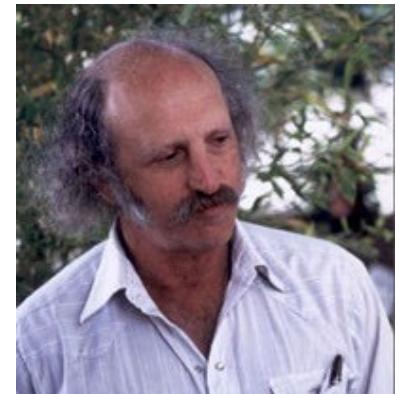
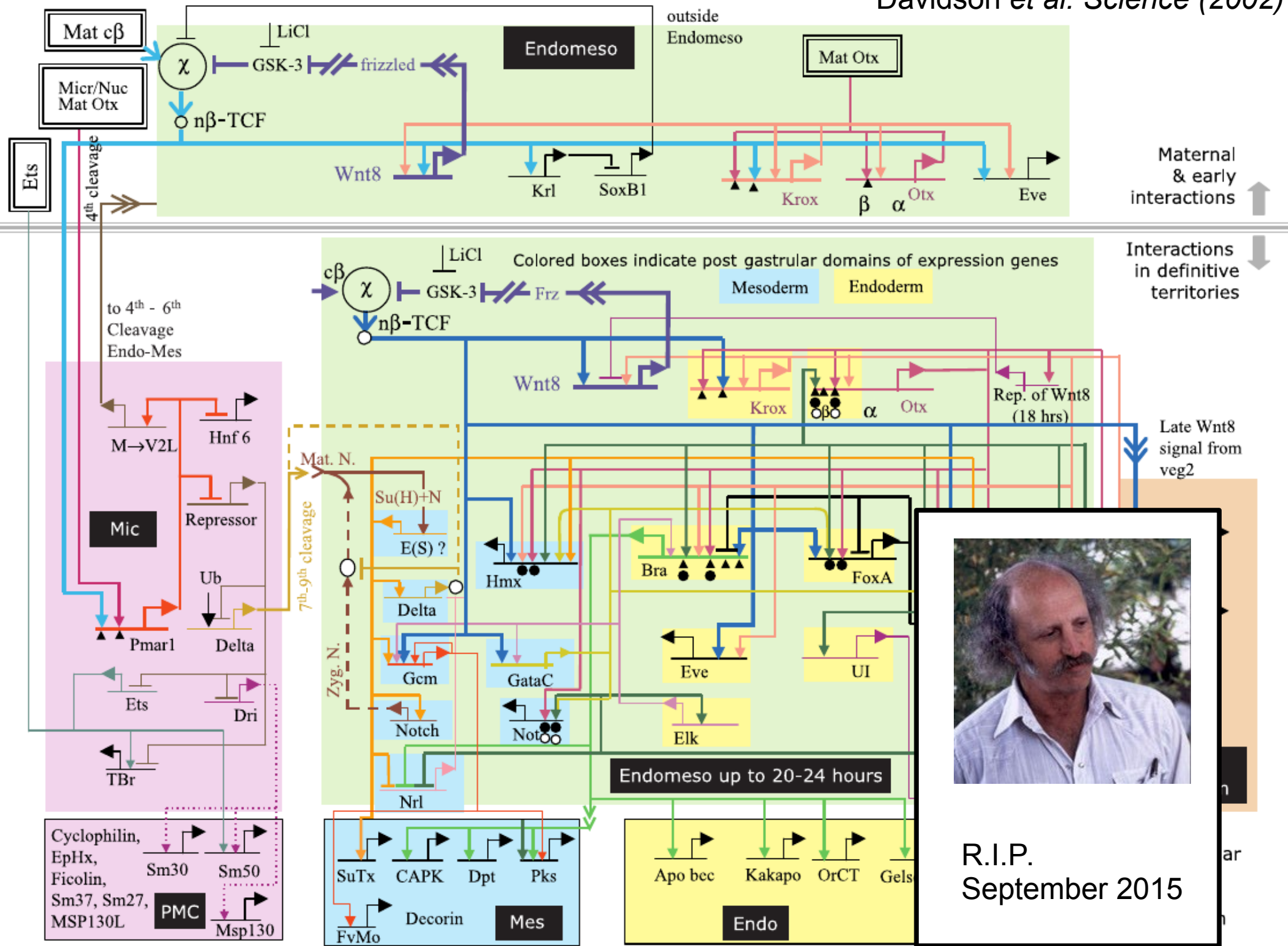
networking
 creative job
searching
 work/life
balance
 Science Careers
workshops, booklets,
and webinars provide
guidance you can
count on.
**LEARN
MORE**
 Science Careers
From the journal Science AAAS
ScienceCareers.org

To Advertise Find Products

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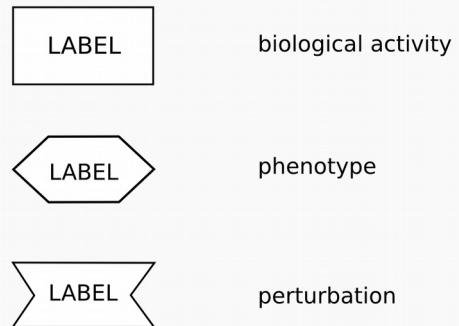




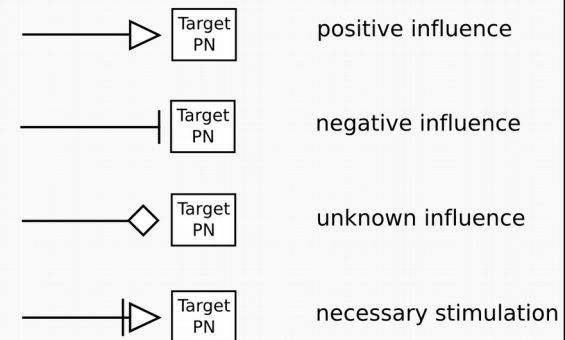
R.I.P.
September 2015

SBGN Activity Flows L1 reference card

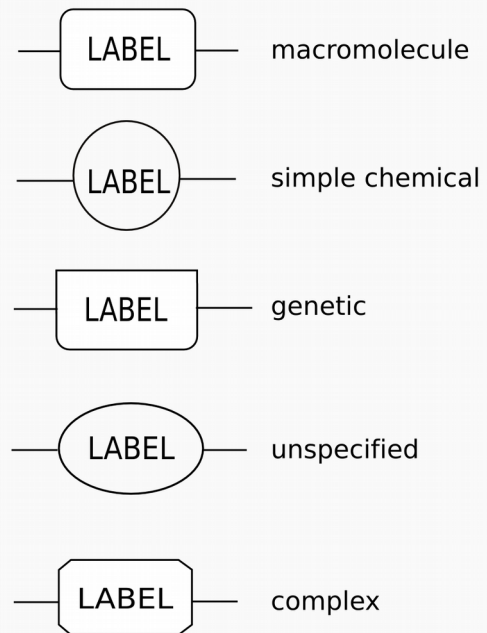
Activity nodes



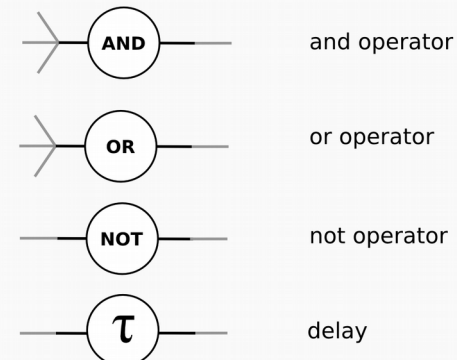
Modulating Arcs



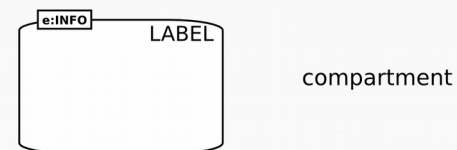
Auxiliary Units



Logical Operators

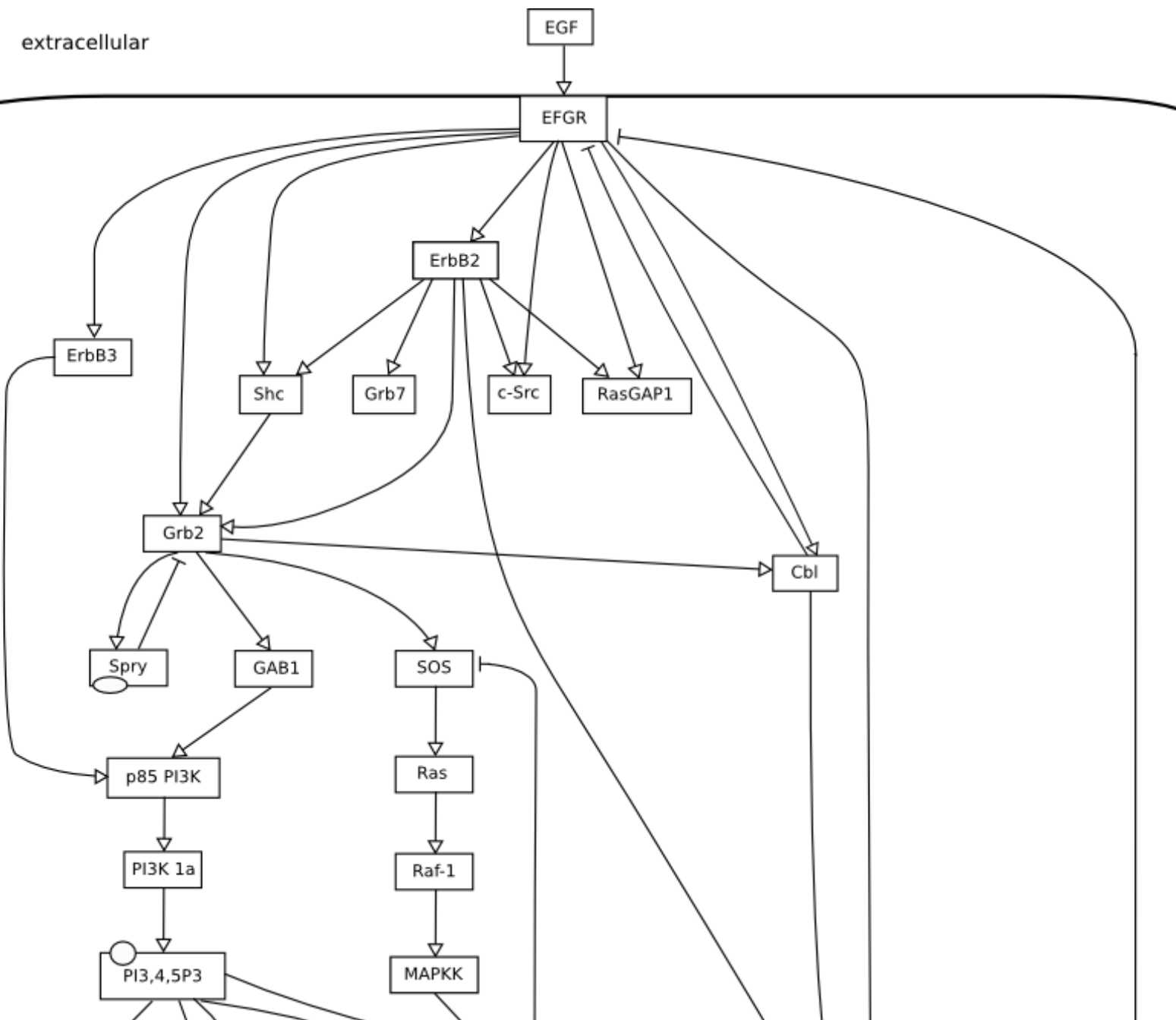


Container Nodes



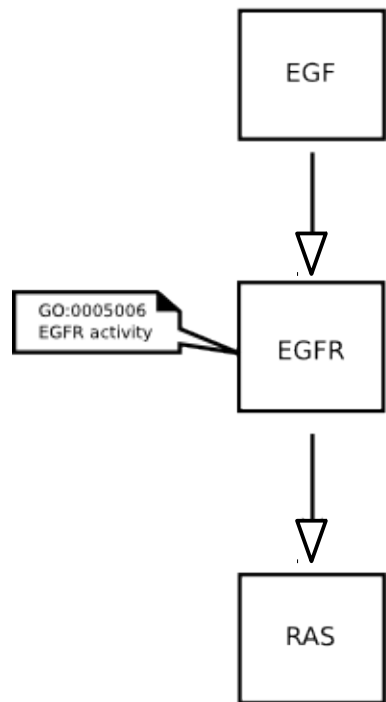
extracellular

Example of Activity Flow map

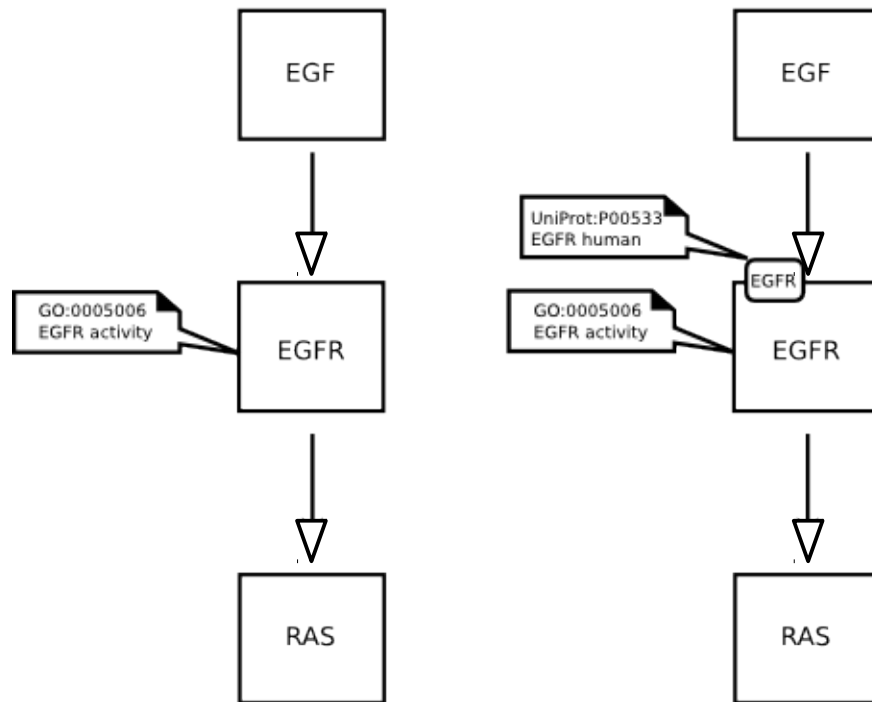


TIMTOWTDI

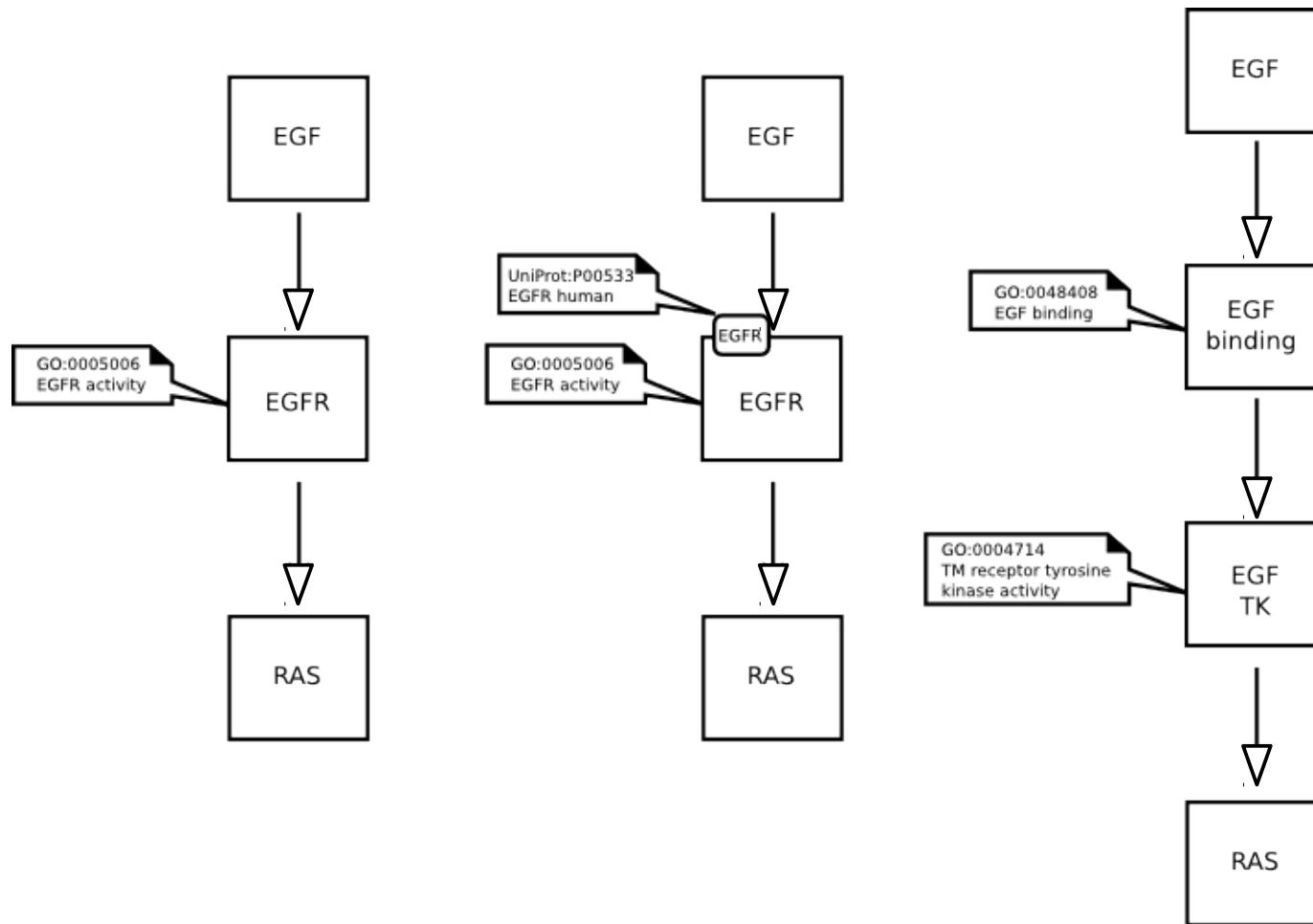
(There Is More Than One Way To Do It)



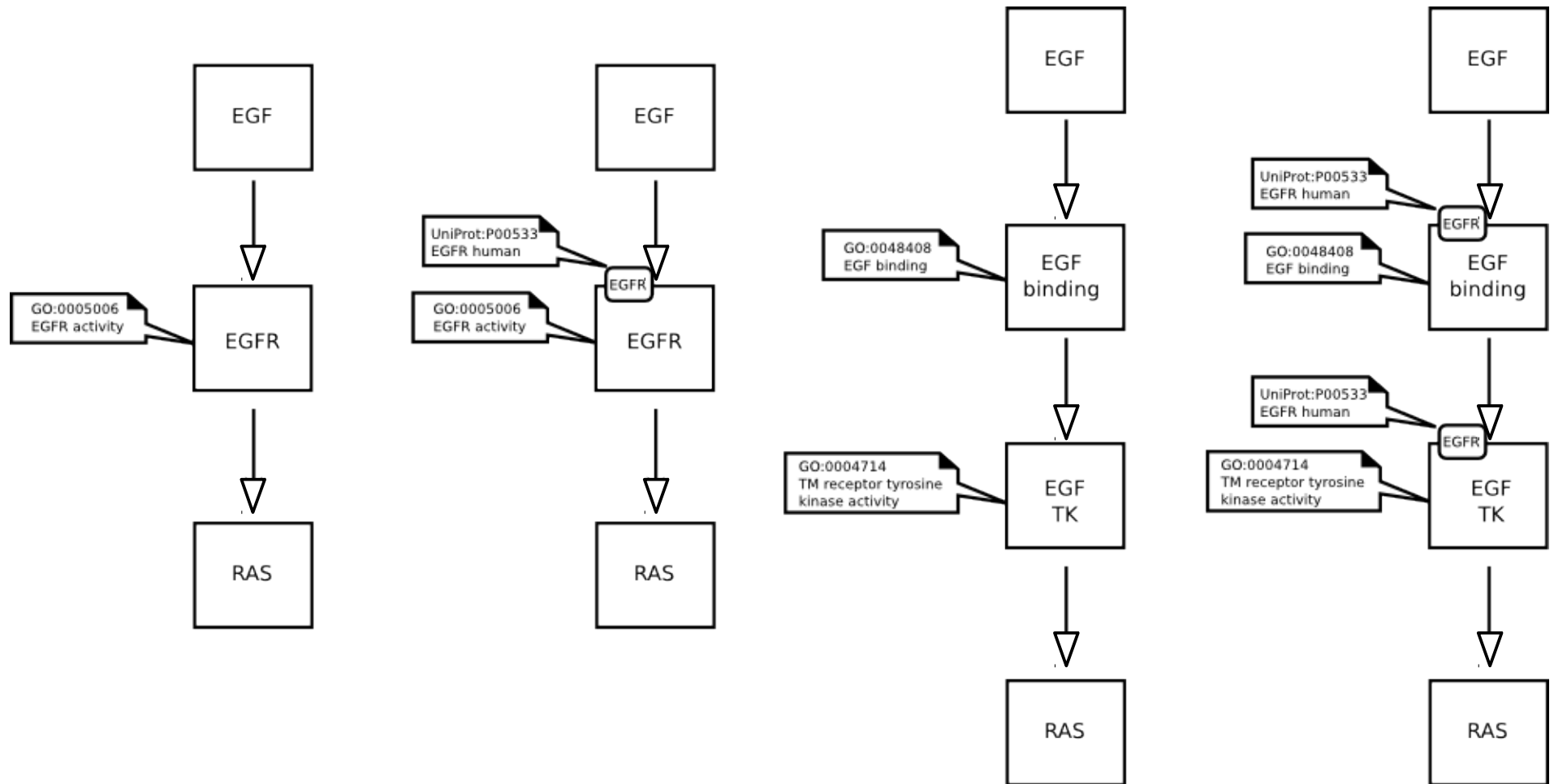
TIMTOWTDI



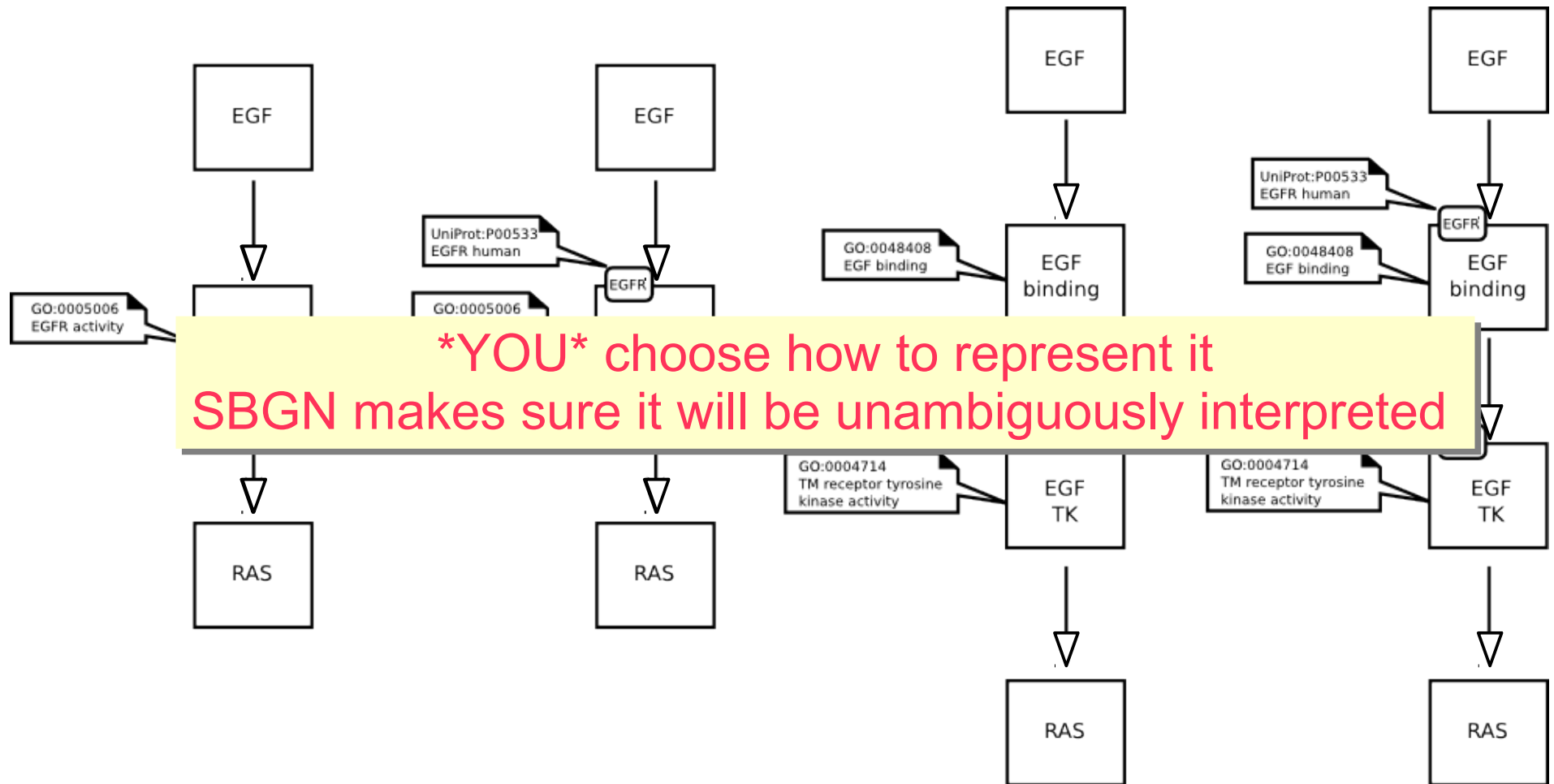
TIMTOWTDI



TIMTOWTDI

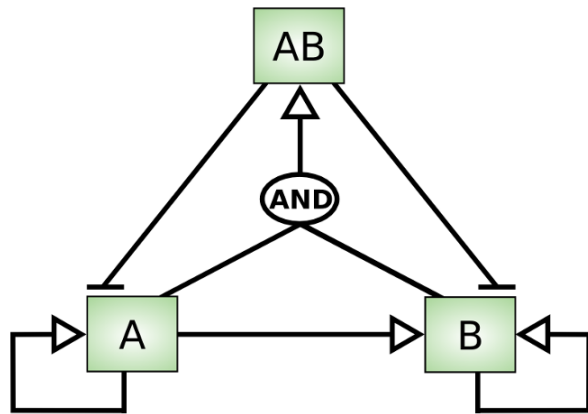


TIMTOWTDI

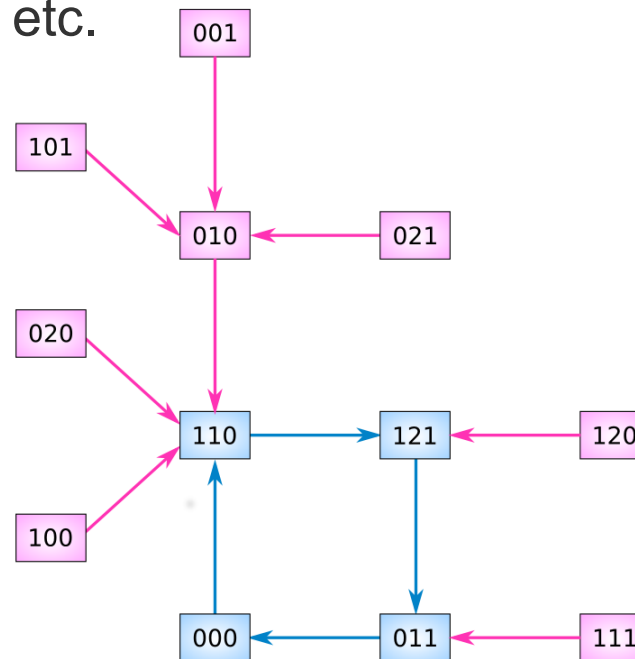


Logic models

- 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.



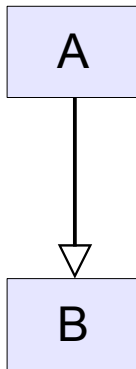
Influence diagram



state diagram



Qual



$$A \geq 1 \Rightarrow B = 1$$

Logical model with SBML Qual

```

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      xmlns:qual="http://www.sbml.org/sbml/level3/version1/qual/version1" qual:required="true":
  <model id="example">
    <listOfCompartments>
      <compartment id="cytosol" name="cytosol" constant="true"/>
    </listOfCompartments>
    <qual:listOfQualitativeSpecies>
      <qual:qualitativeSpecies qual:compartment="cytosol" qual:constant="false"
                              qual:id="A" qual:maxLevel="2"/>
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                              qual:id="B" qual:maxLevel="1"/>
    </qual:listOfQualitativeSpecies>
    <qual:listOfTransitions>
      <qual:transition qual:id="tr_B">
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          <qual:input qual:id="theta_B_A" qual:qualitativeSpecies="A" qual:sign="positive"
                     qual:thresholdLevel="1" qual:transitionEffect="none"/>
        </qual:listOfInputs>
        <qual:listOfOutputs>
          <qual:output qual:transitionEffect="assignmentLevel" qual:qualitativeSpecies="B"/>
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          <qual:functionTerm qual:resultLevel="1">
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                <geq/>
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                <ci>theta_B_A</ci>
              </apply>
            </math>
          </qual:functionTerm>
          <qual:defaultTerm qual:resultLevel="0"/>
        </qual:listOfFunctionTerms>
      </qual:transition>
    </qual:listOfTransitions>
  </model>
</sbml>
  
```

Session: New Session

File Edit View Select Layout Apps Tools Help

Control Panel

Network Style Select Cytocopter

Network ToyModelPB

Data

Preprocess

Formalism boolean

Time point --

Optimise

CytoCopter

Configurations

Size fac	1.0E-4	NA fac	1.0
Pop size	50.0	P mutation	50.0
Max time	15.0	Max gen	500.0
Stall gen max	100.0	Sel press	1.2
Elistism	5.0	Rel tol	0.1

qual

```

graph TD
    A[A] --> B[B]
  
```

Table Panel

qual

shared name	shared interaction	name	interaction
A (1) B	1	A (1) B	1

Node Table Edge Table Network Table Cytocopter

Memory: OK

Cytoscape Desktop (New Session)

File Edit View Select Layout Plugins Help

Control Panel

Network VizMapper™ Filter

Network

No...	Ed...
BIOMD0000000012	18(0) 18(...)

BIOMD0000000012

Results Panel

CySBML

BIOMD0000000012

- Compartments
- Species
 - LacI protein
 - TetR protein
 - ci protein
 - LacI mRNA
 - TetR mRNA
 - ci mRNA
- Reactions
 - degradation of LacI transcripts
 - degradation of TetR transcripts
 - degradation of Ci transcripts
 - translation of LacI

CySBML

CySBML - Cytoscape SBML Support

The main functionality of cySBML is accessible via the Cytoscape menu bar.

- SBML Import** Load SBML files via the File Import Dialogue. To import multiple files select multiple files.
- BioModel Import** SBML files from BioModels can be loaded via the BioModel Import Dialogue.
- SBML** Imported SBML files can be validated against the

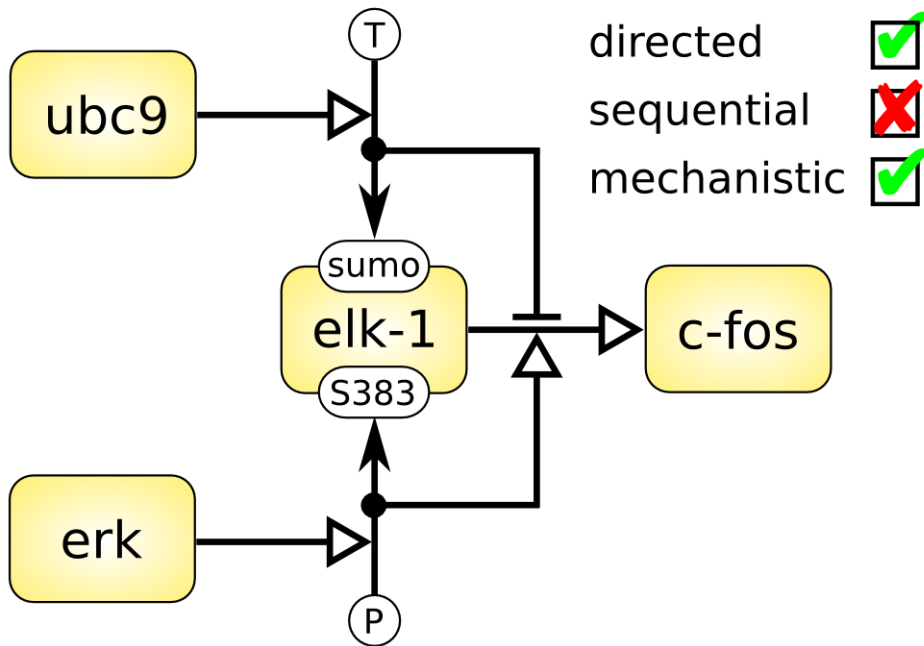
Data Panel

ID	sbml type	sbml name	sbml compartment	sbml metaId	sbml sbo

Node Attribute Browser Edge Attribute Browser Network Attribute Browser

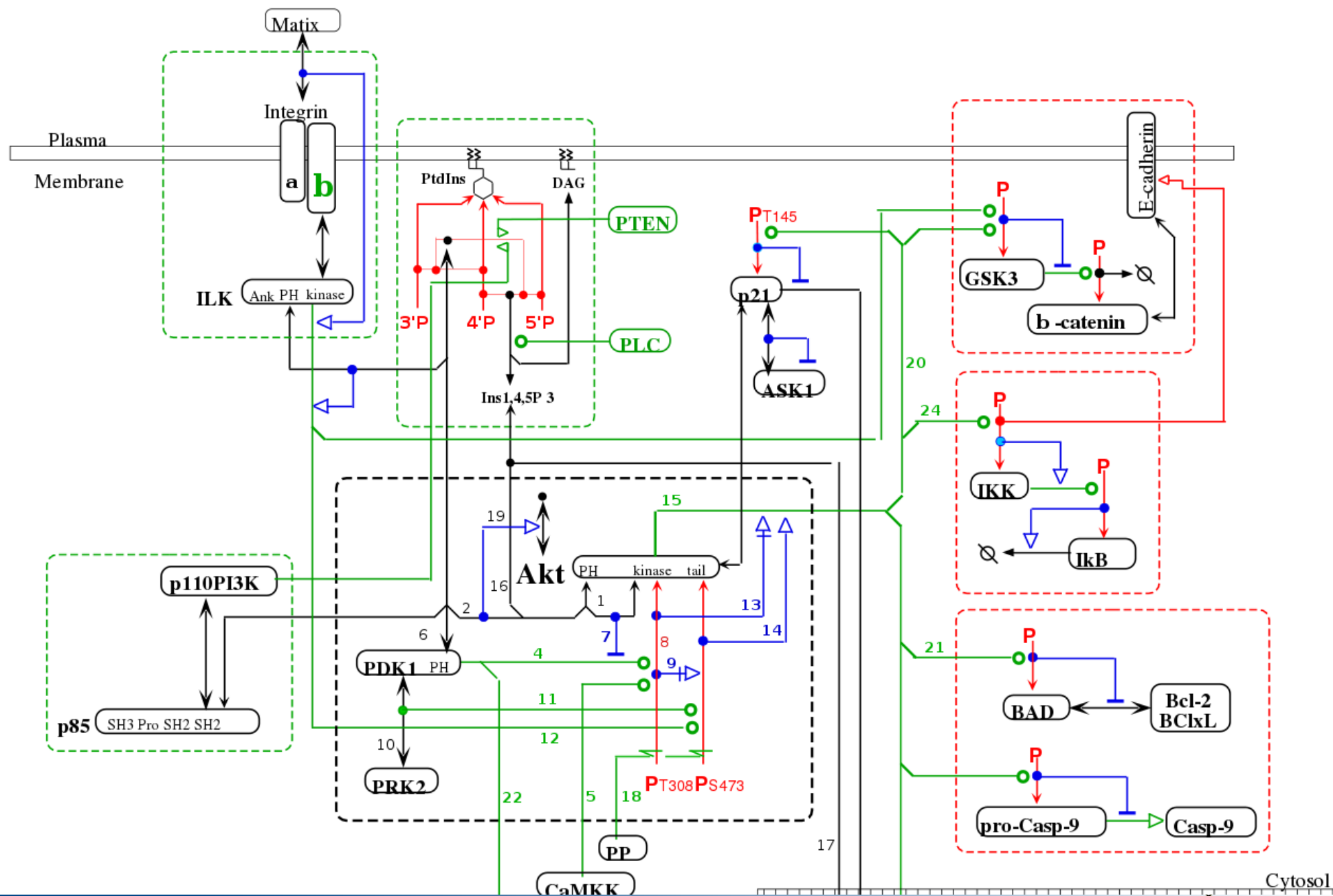
Entity Relationships

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



AKT

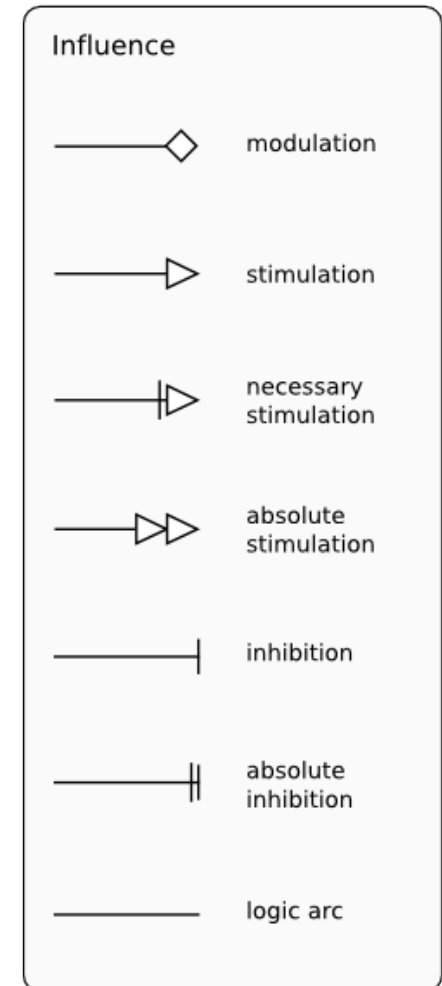
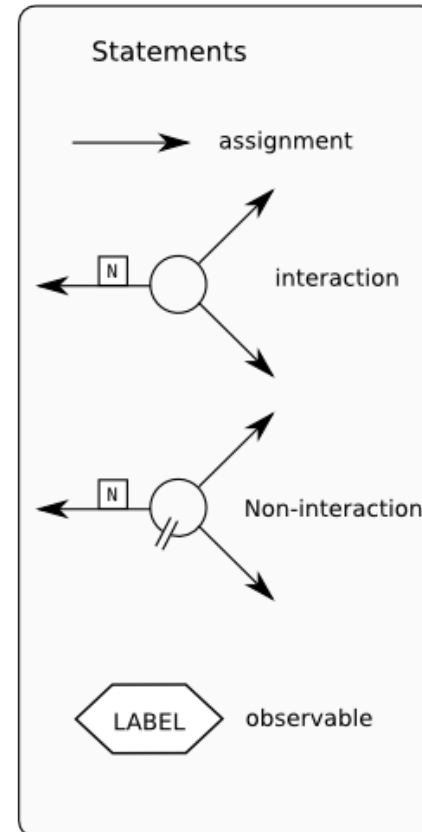
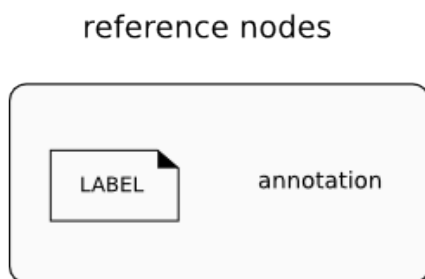
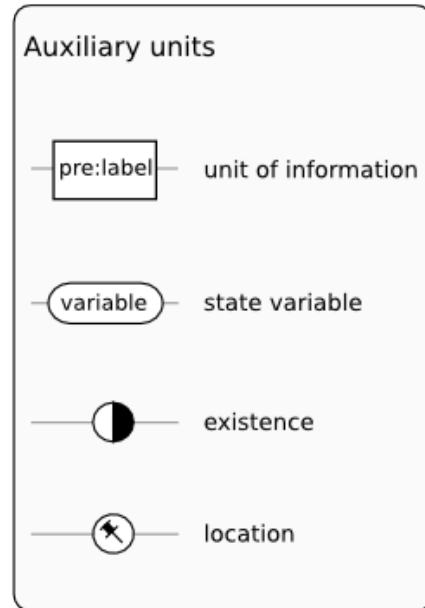
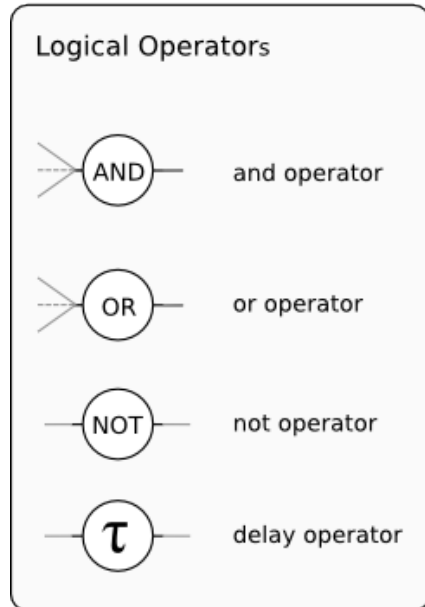
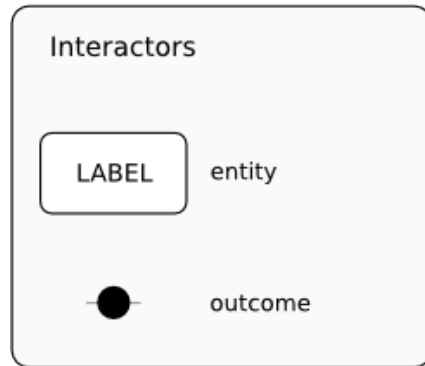
Click [here](#) to return to original map size



SBGN Entity Relationships L1 reference card

Entity Nodes

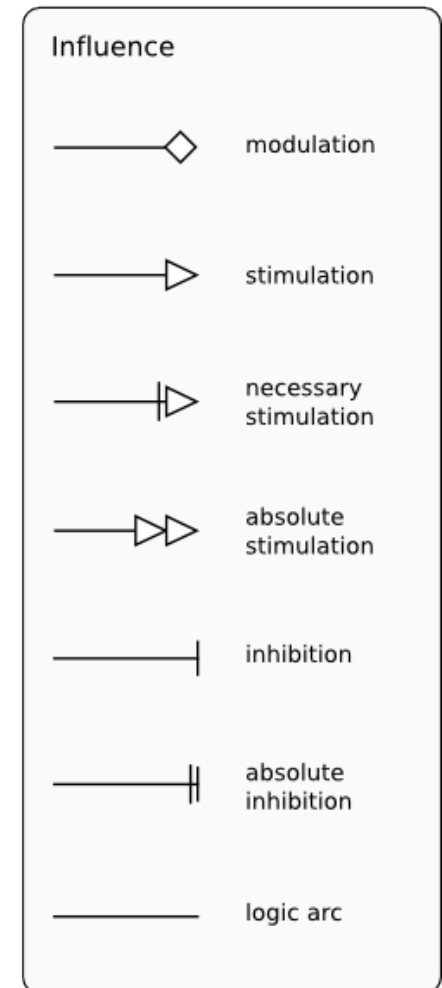
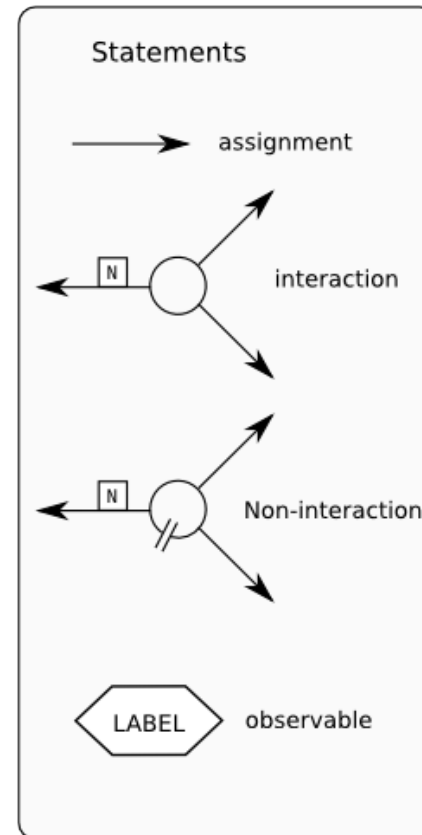
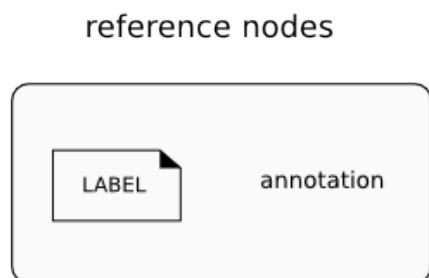
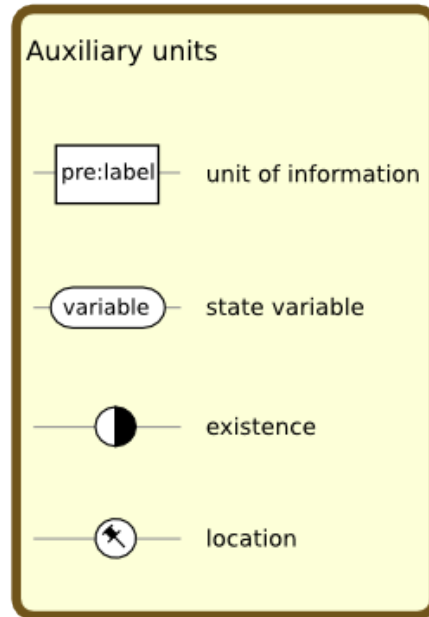
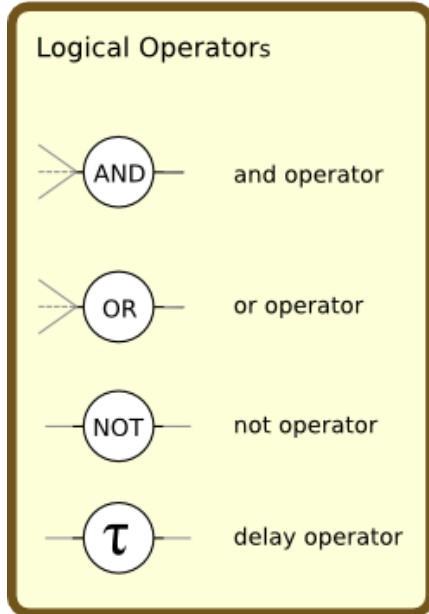
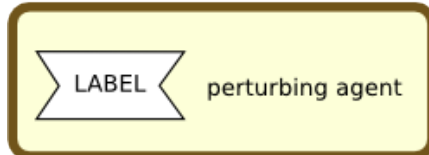
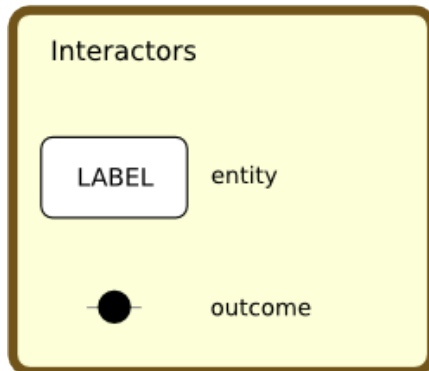
Relationship Nodes



SBGN Entity Relationships L1 reference card

Entity Nodes

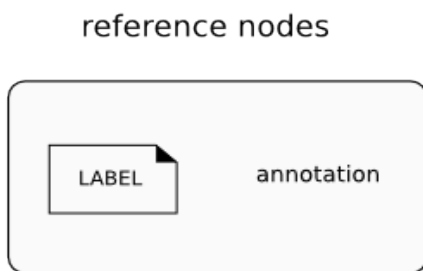
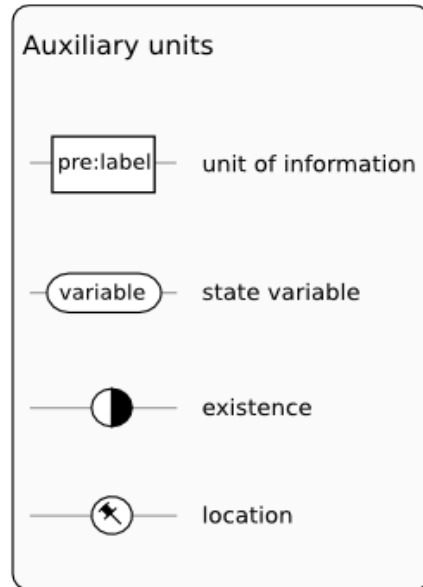
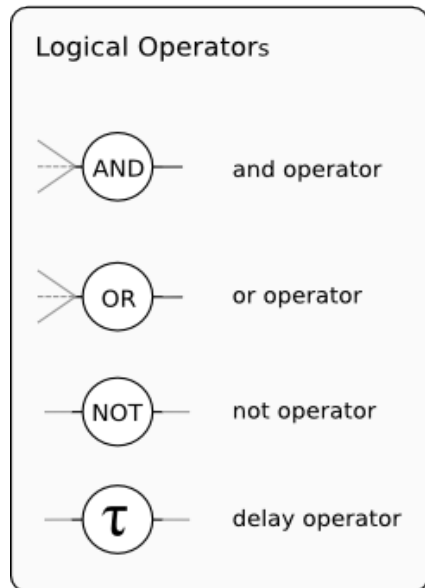
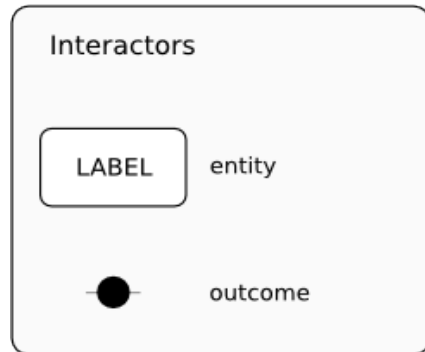
Relationship Nodes



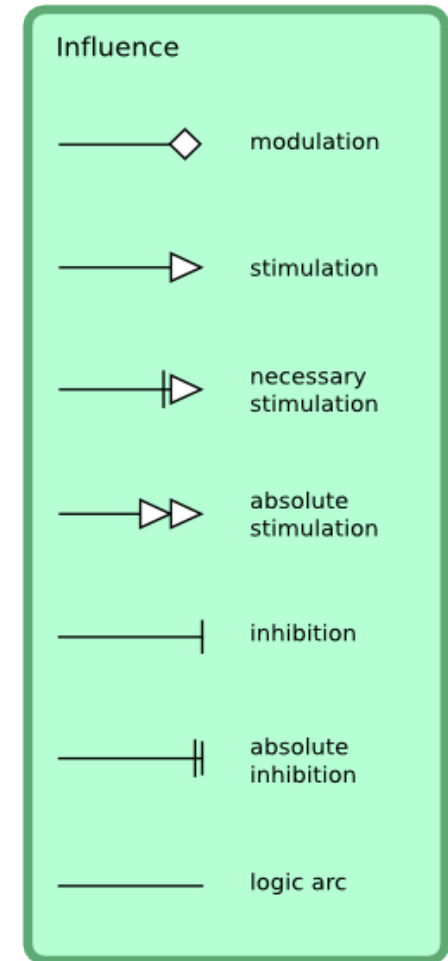
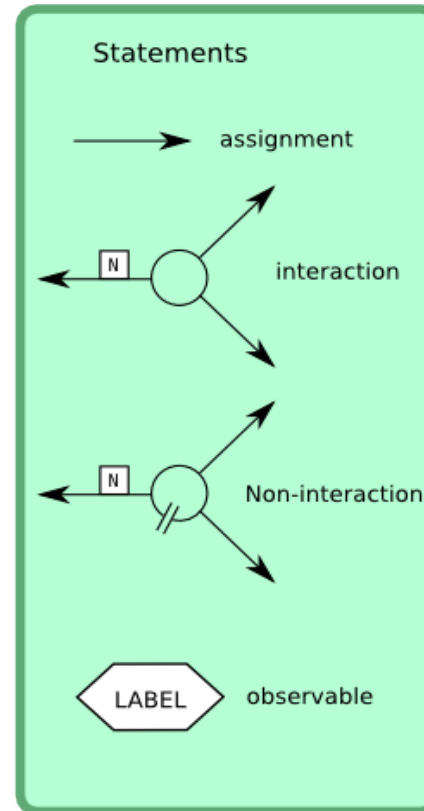
continuants,
things that exists (or not)

SBGN Entity Relationships L1 reference card

Entity Nodes

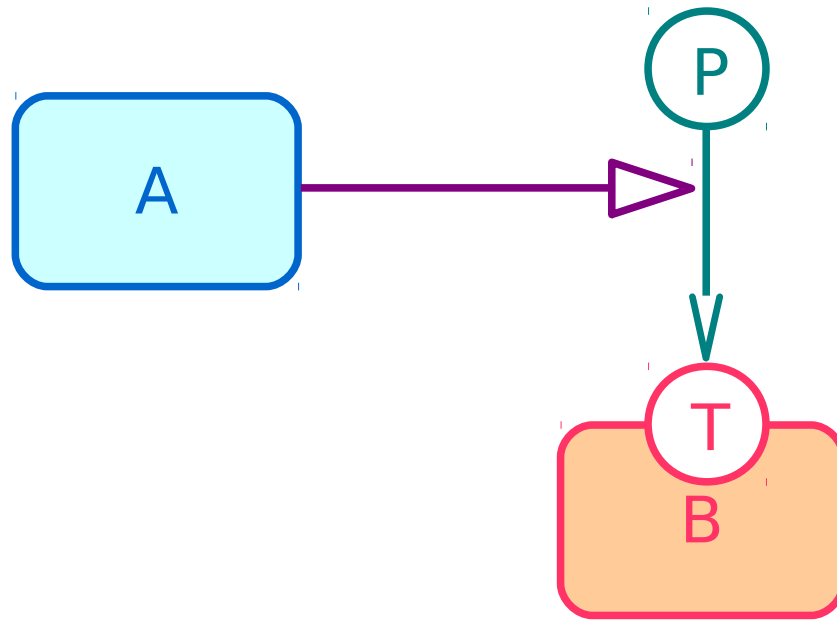


Relationship Nodes

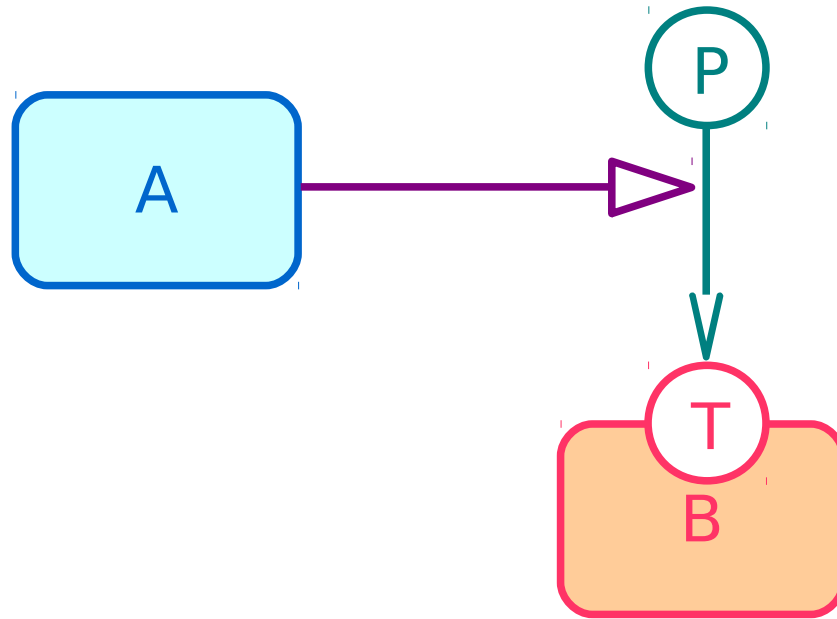


occurents,
events that may happen (or not)

Entity Relationships can be viewed as rules

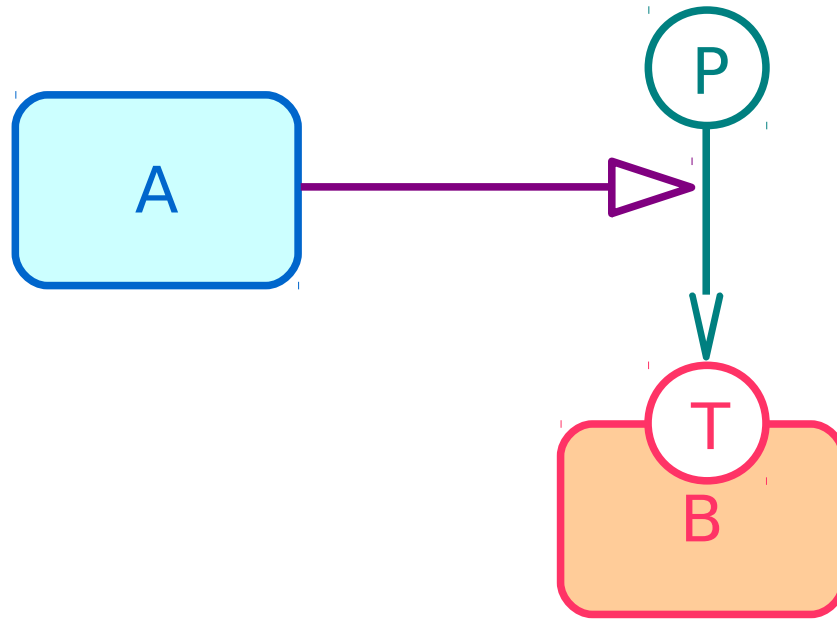


Entity Relationships can be viewed as rules



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

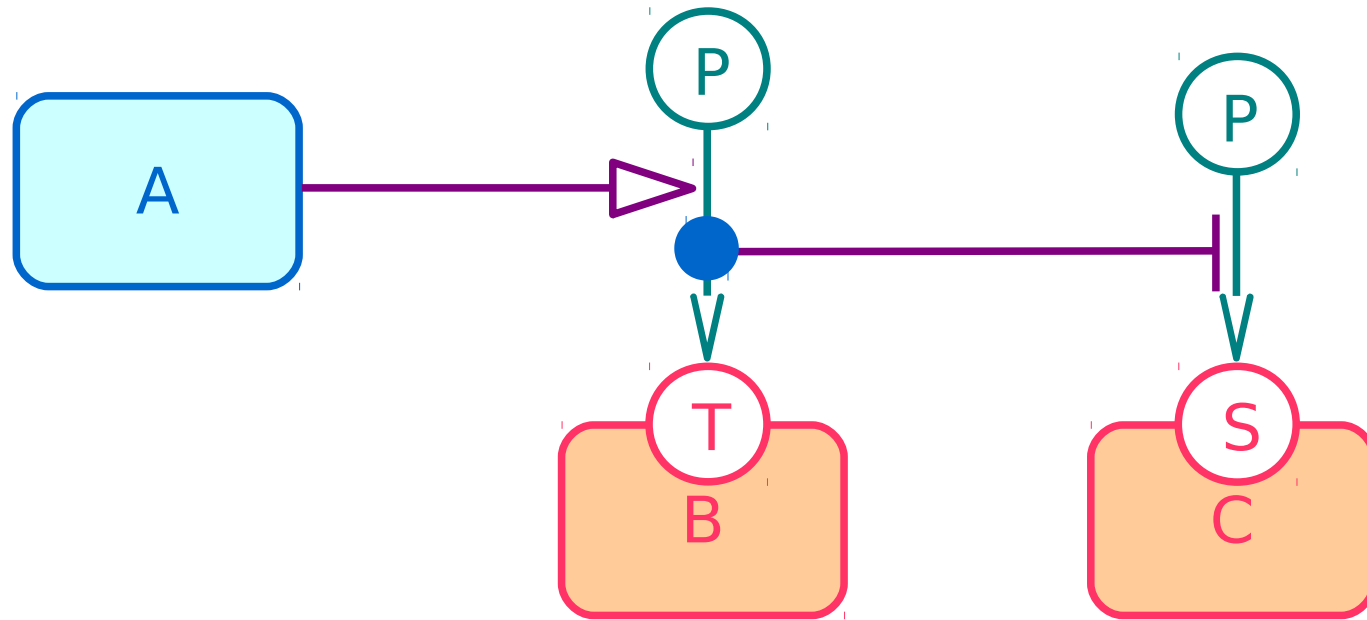
Entity Relationships can be viewed as rules



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**)

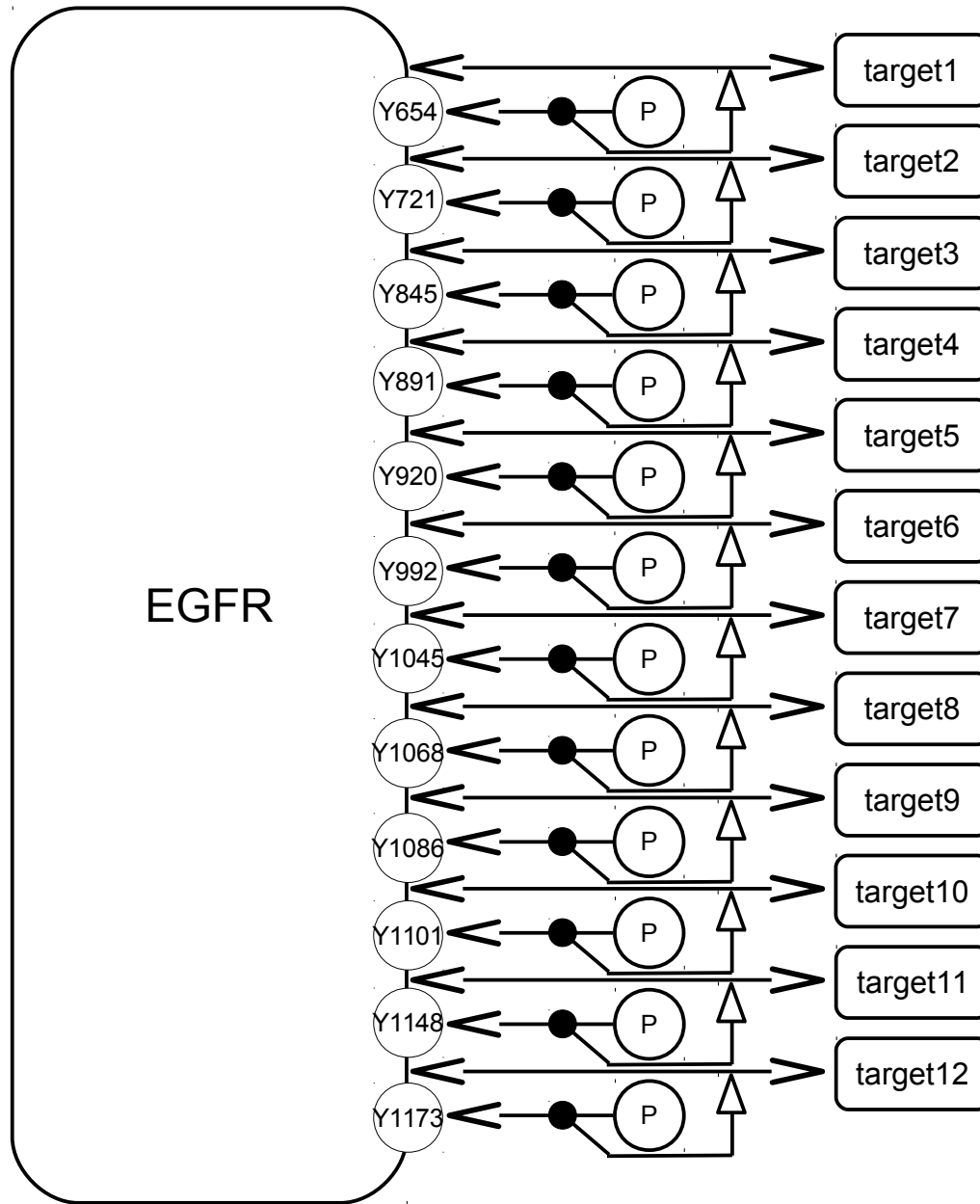
Entity Relationships can be viewed as rules



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 C 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: $A(\text{Site1} \sim u), B(\text{Site1}) \rightarrow A(\text{Site1} \sim u!1), B(\text{Site1}!1)$

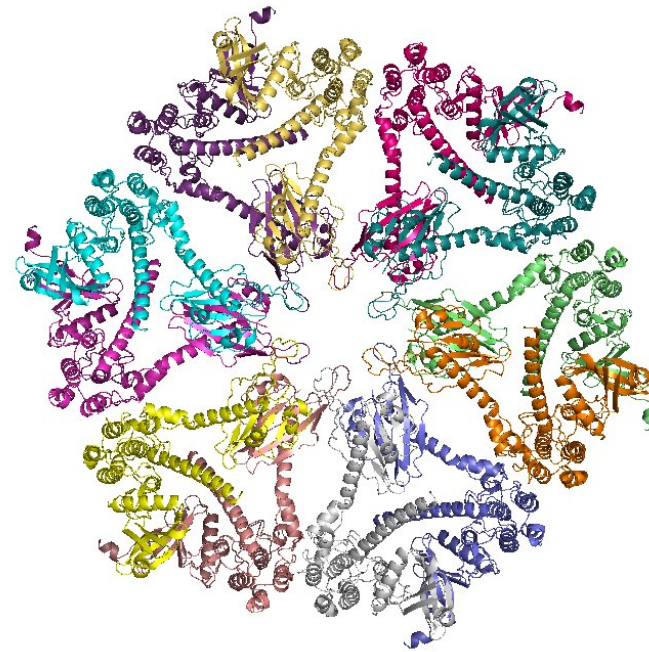
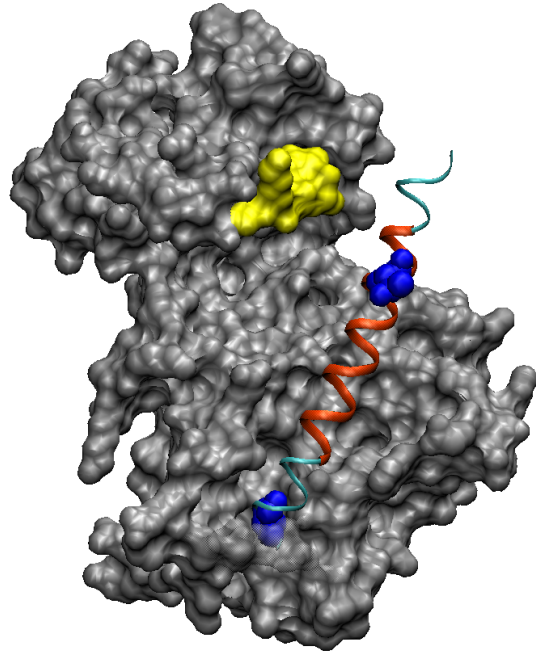
English: "Unphosphorylated Site1 of A binds to Site1 of B"

- **BioNetGen** <http://bionetgen.org/>

EGF(R) + EGFR(L) $\leftrightarrow$ 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

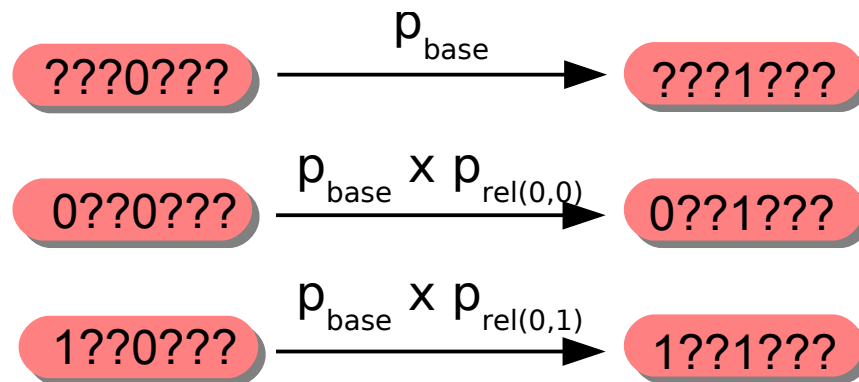


12 monomers

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

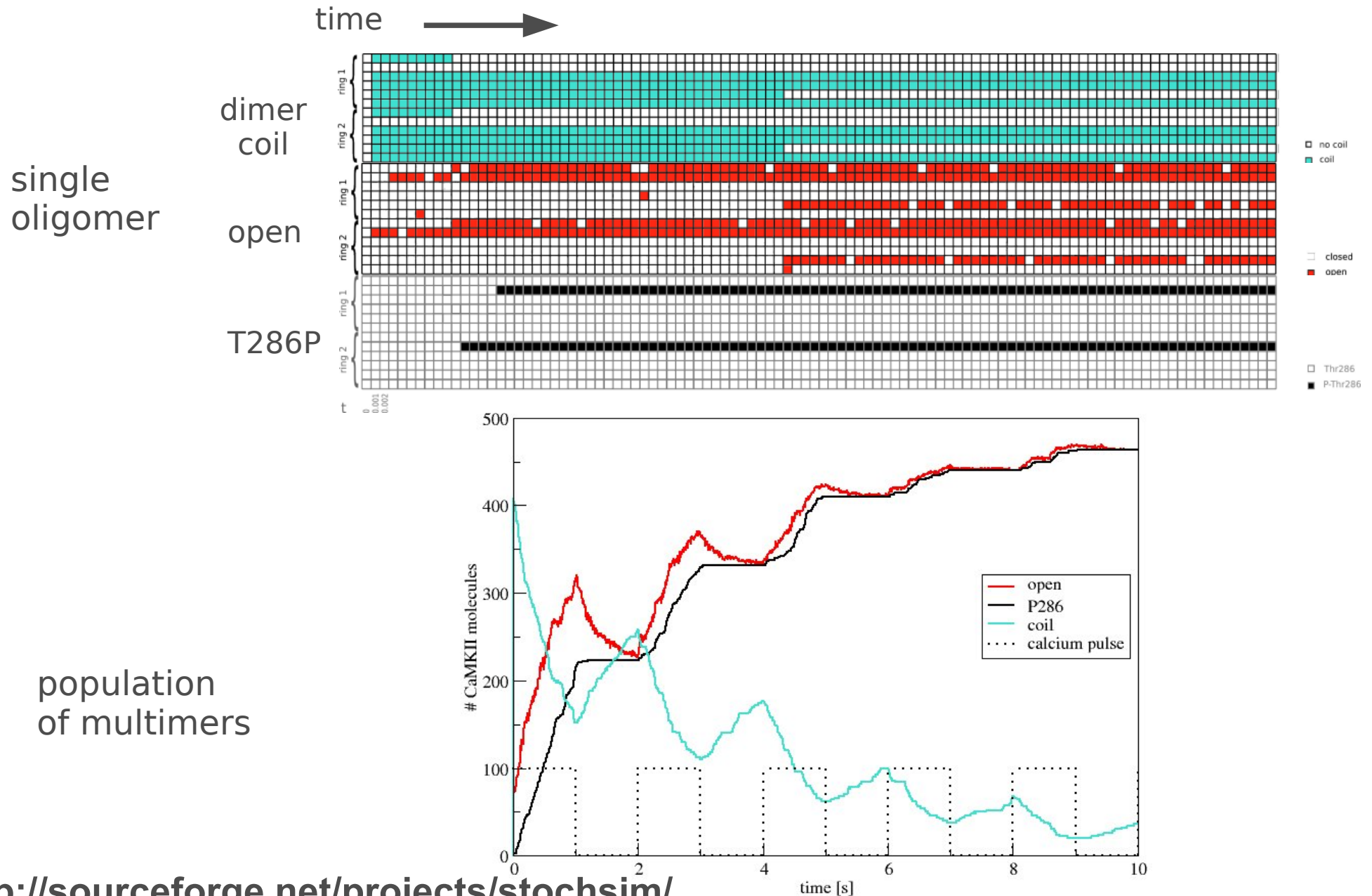


Flags '?' do not affect the reaction

4 species are necessary and not 128

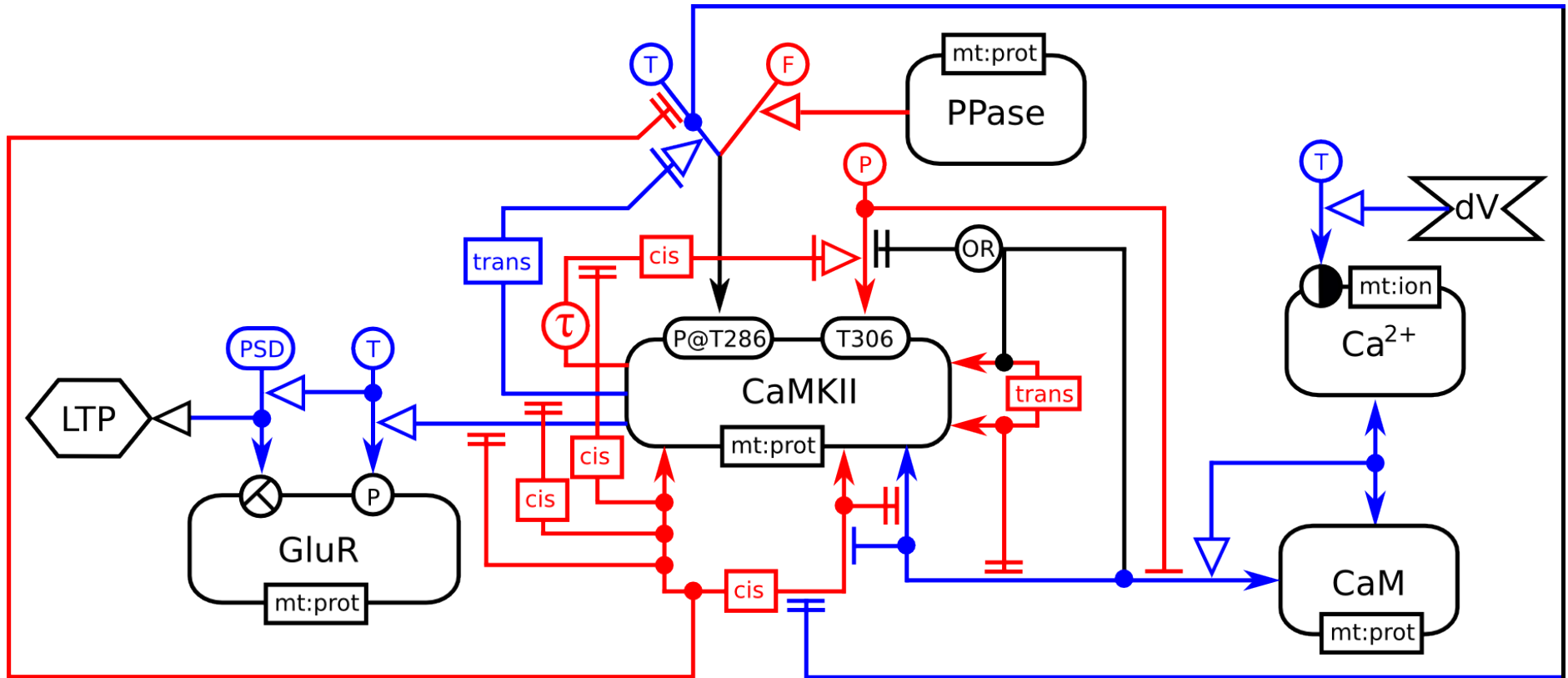
2 reactions are necessary and not 64

Simulation with StochSim

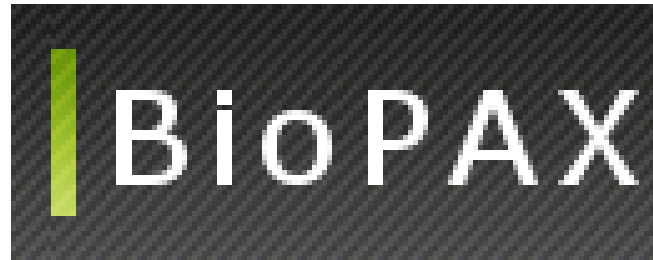


<http://sourceforge.net/projects/stochsim/>

Regulation of synaptic plasticity by calcium



Biological Pathway Exchange format



<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)

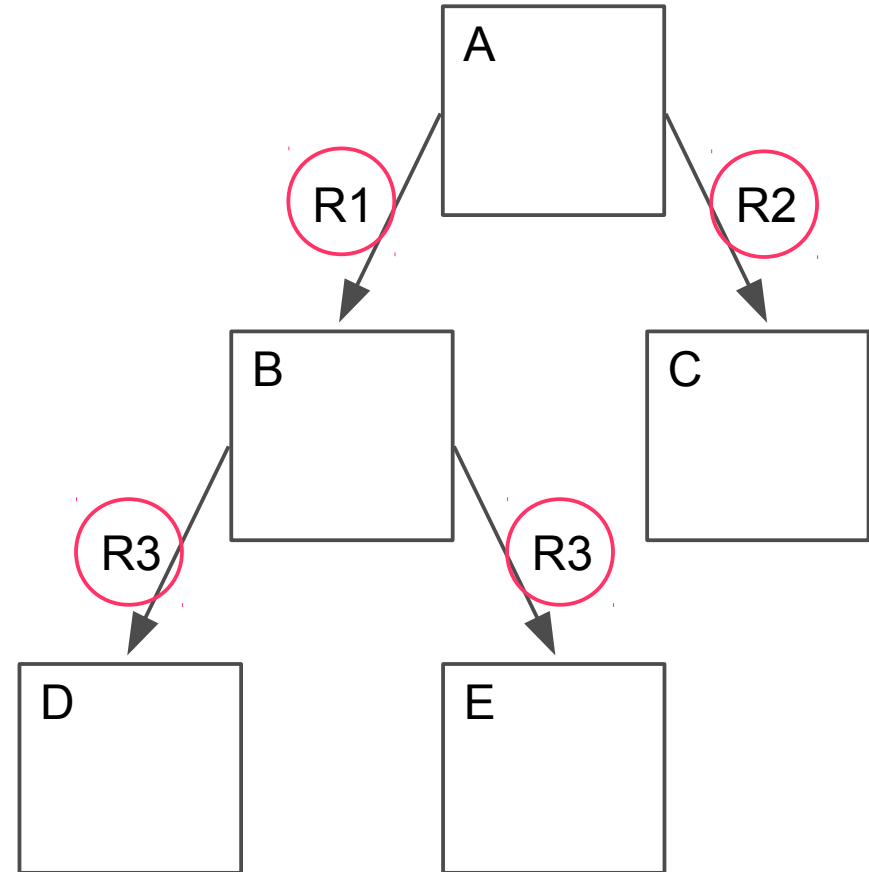
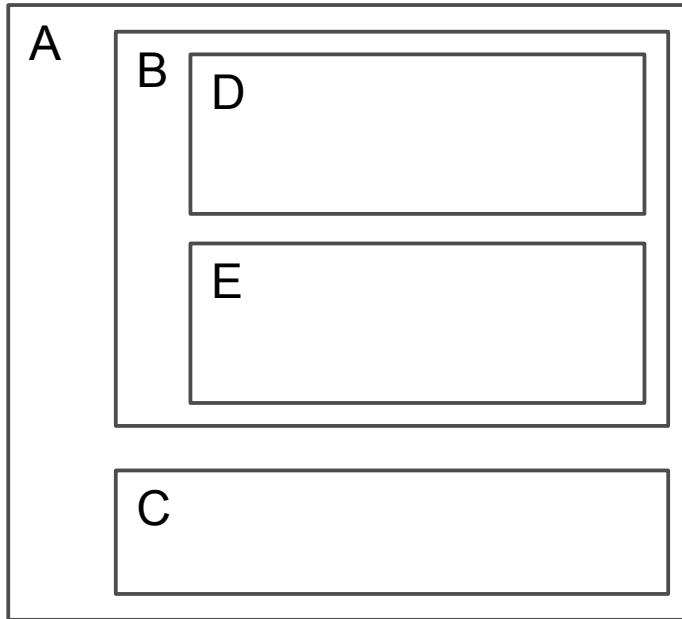
(OBO Relation ontology)

(Gene Ontology)

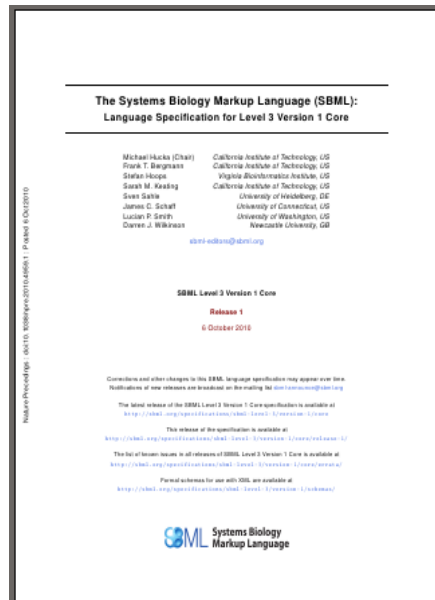
“XML”

Vs

RDF



Relationships
defined in another
document

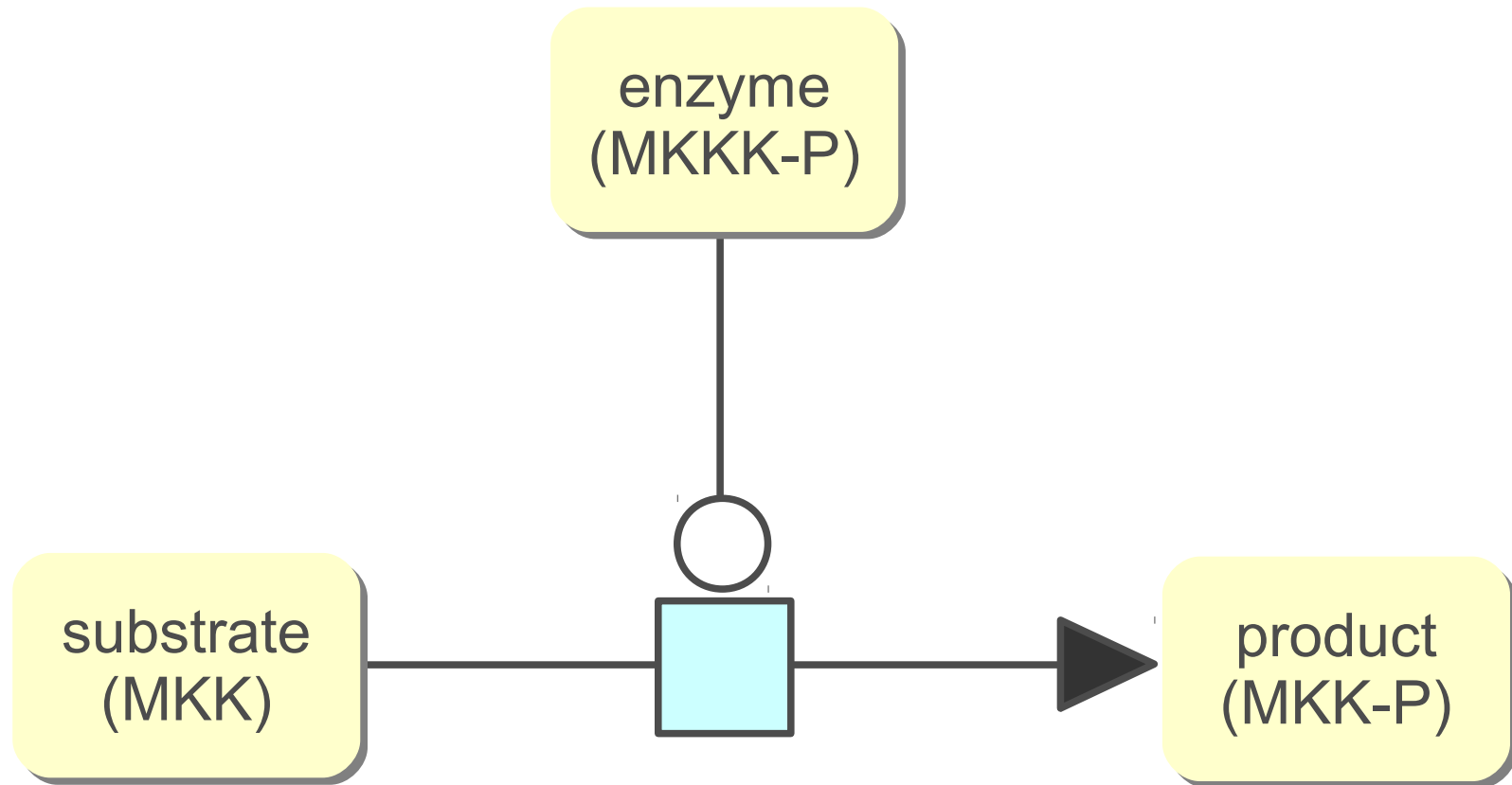


Relationships
defined in the pathway

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

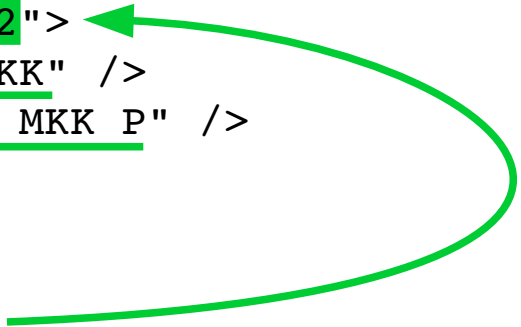


A catalysis in BioPAX (L3)

<!-- 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)

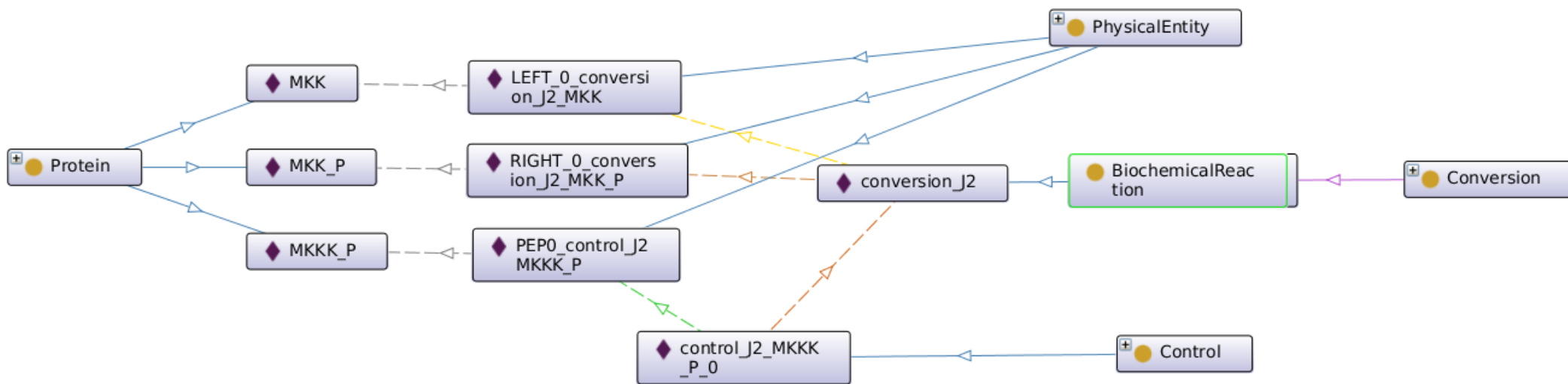
```
<!-- Proteins -->
```

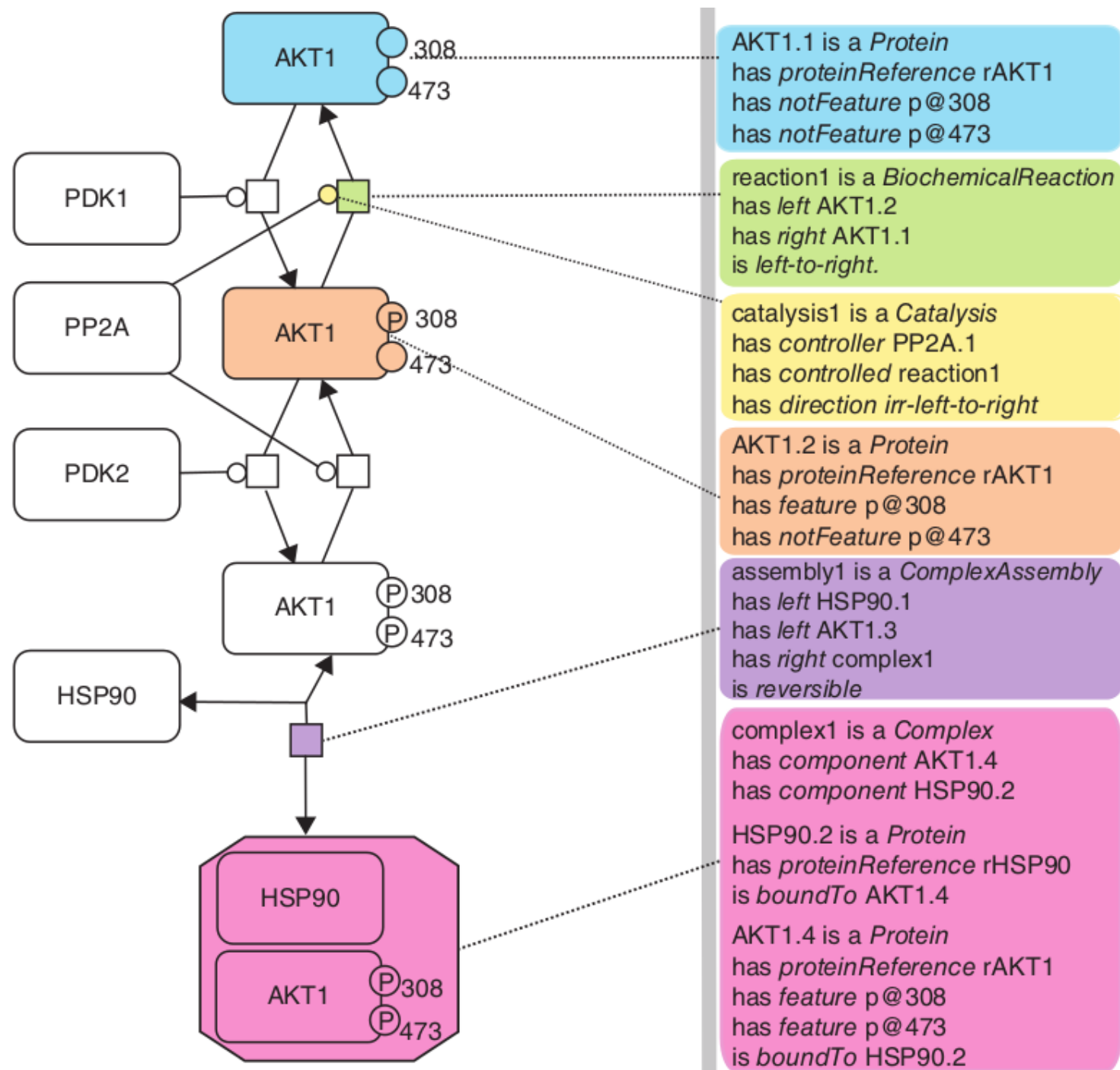
```
<bp:Protein rdf:about="MKKK_P">  
  <bp:displayName rdf:datatype="http://www.w3.org/2001/XMLSchema#string">  
    Mos-P</bp:displayName>  
</bp:Protein>
```

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

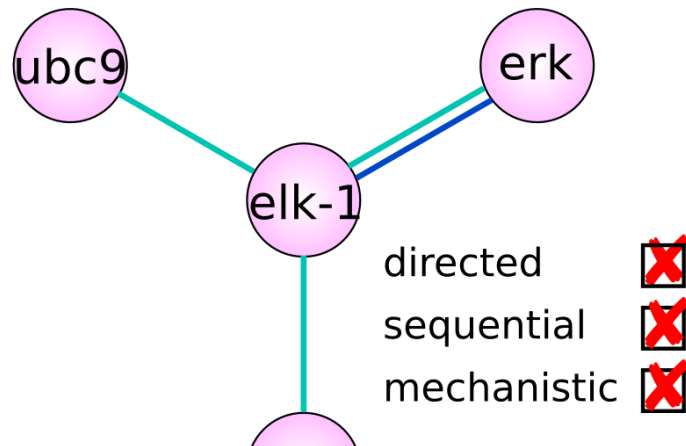
```
<bp:Protein rdf:about="MKK_P">  
  <bp:displayName rdf:datatype="http://www.w3.org/2001/XMLSchema#string">  
    Mek1-P</bp:displayName>  
</bp:Protein>
```

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

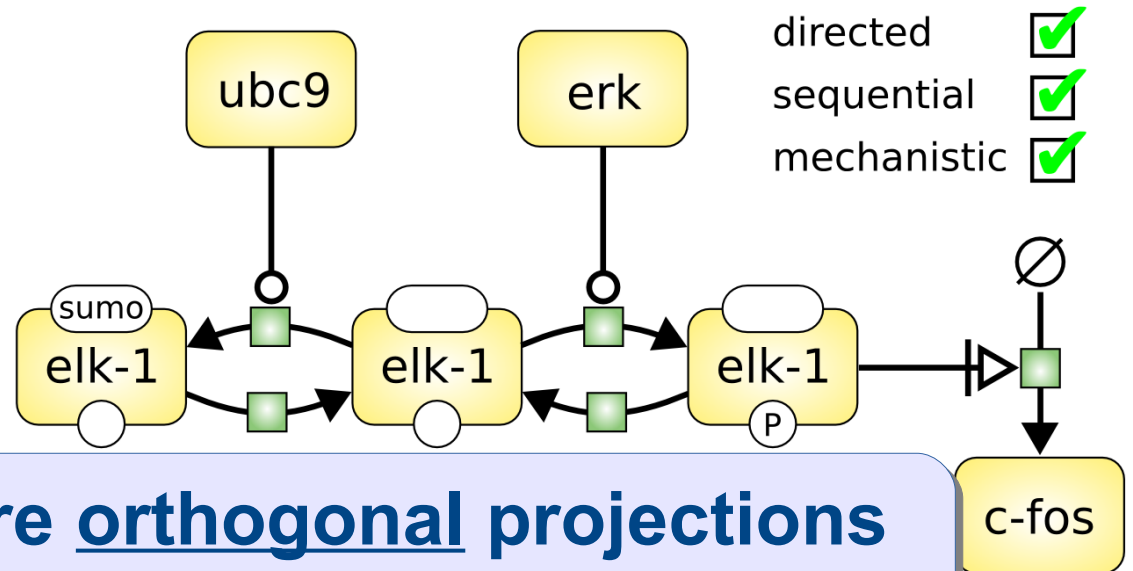




a interaction network

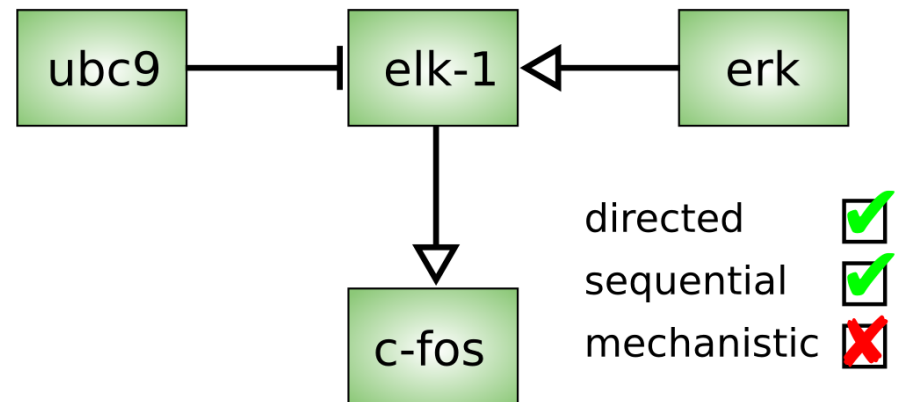
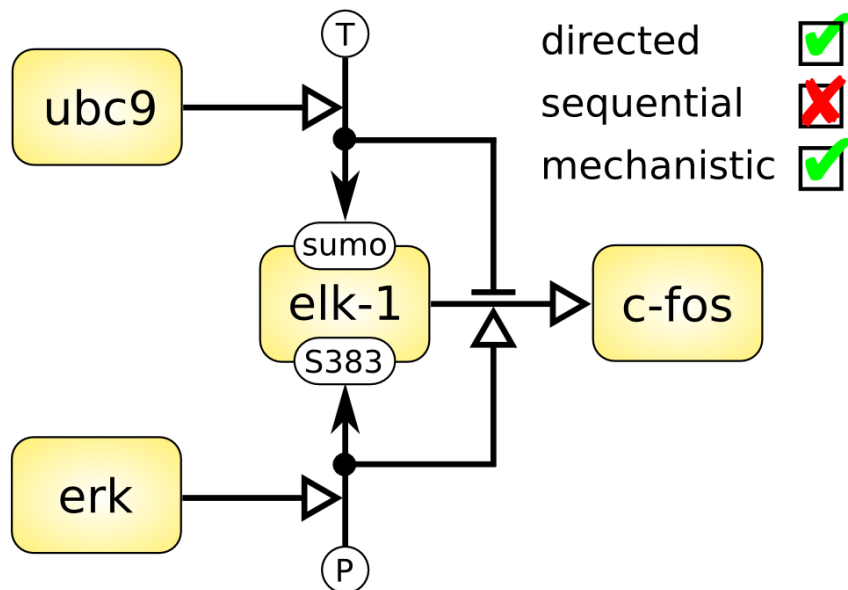


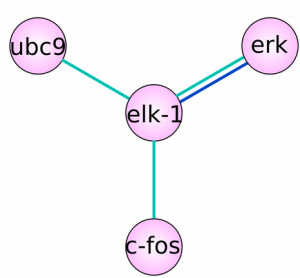
c process descriptions



The four views are orthogonal projections of the underlying biological phenomena

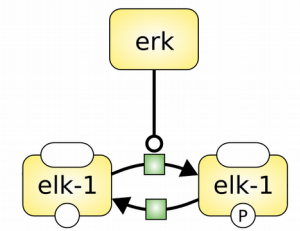
b ent





Interaction
networks

PSI-MI

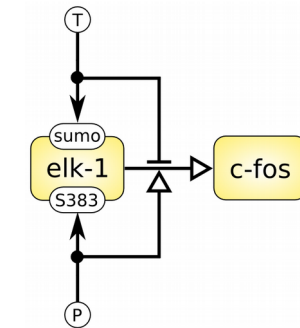


Process
Descriptions

SBML Core

SBGN Process
Description

Metabolism

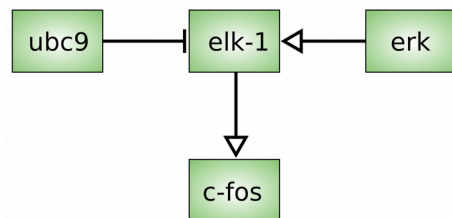


Entity
relationships

SBML Multi

SBGN Entity
Relationships

Signalling



Activity Flows

SBML Qual

SBGN Activity
Flows

Signalling
Gene networks

Practical, tomorrow



Lu Li



Bhupinder Virk

