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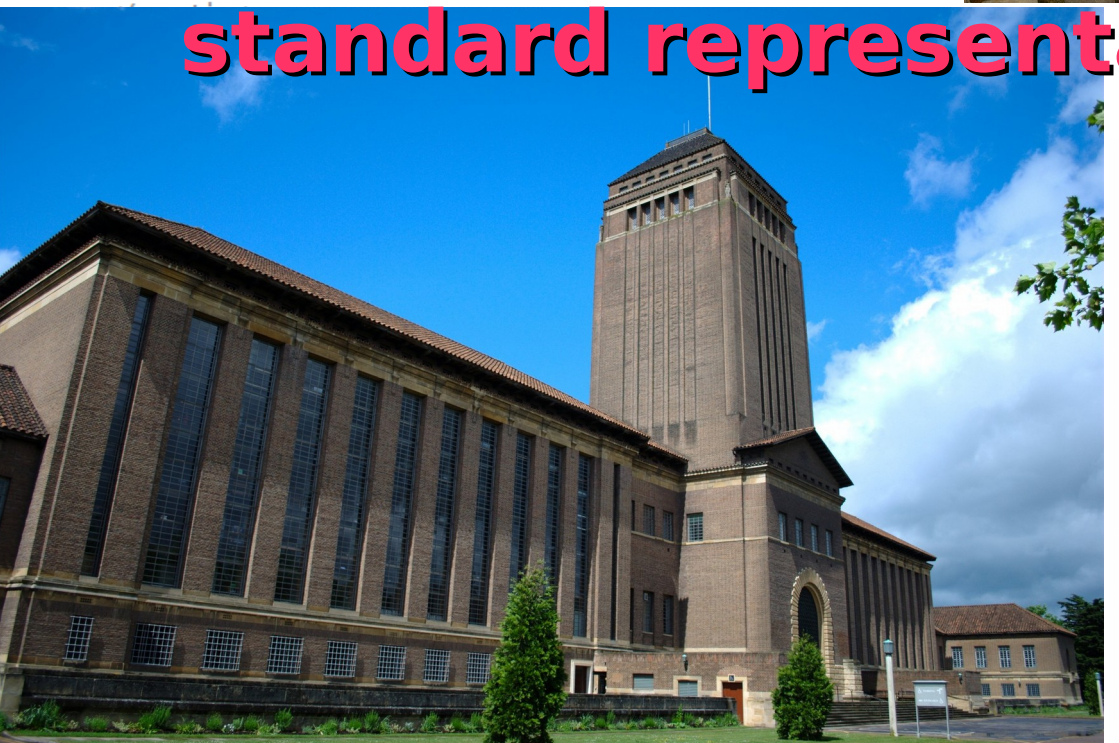
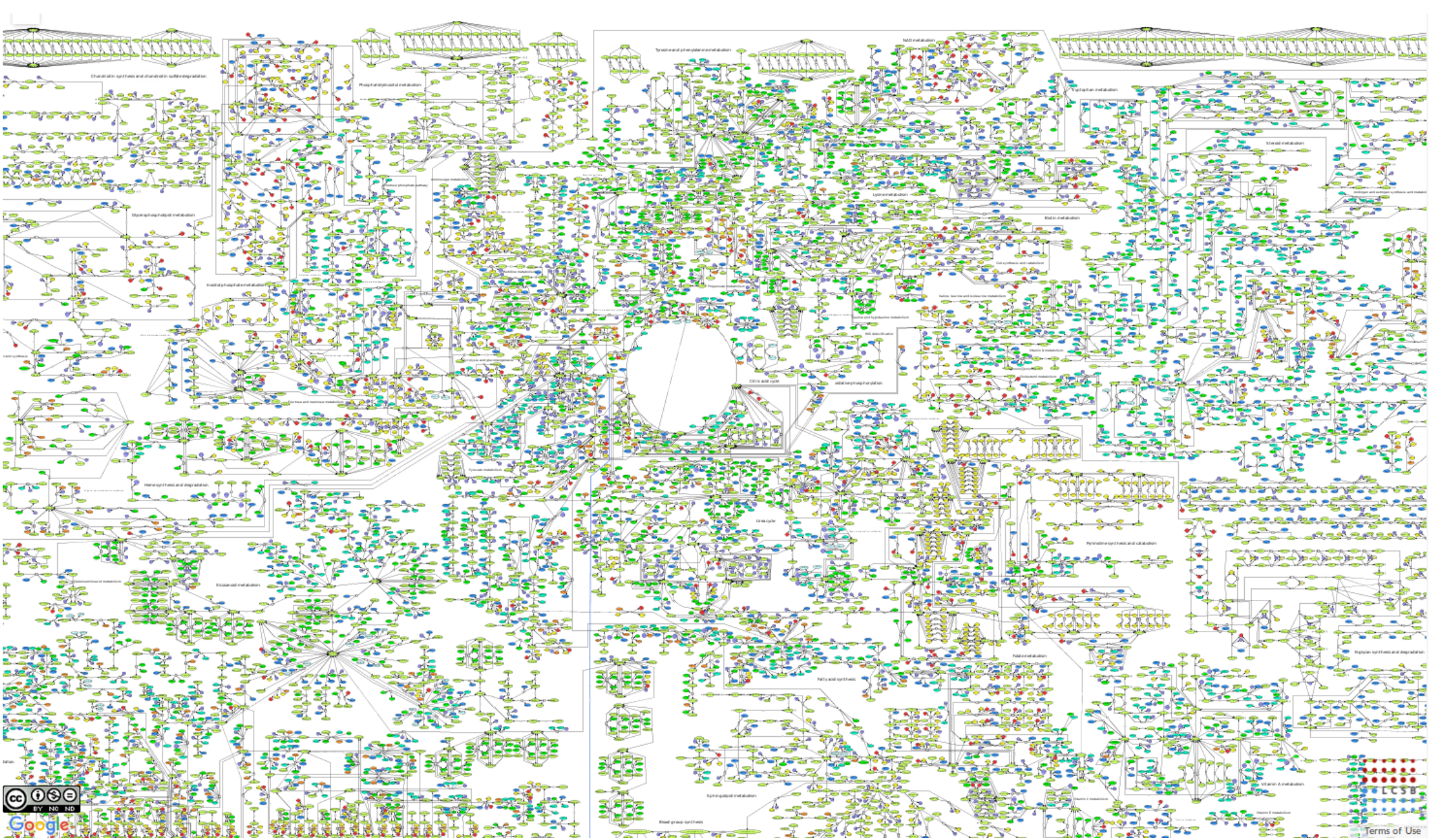
Building the biological Babylon Tower with standard representations of pathways



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



http://vmh.uni.lu

UNDERSTAND

Metabolic networks

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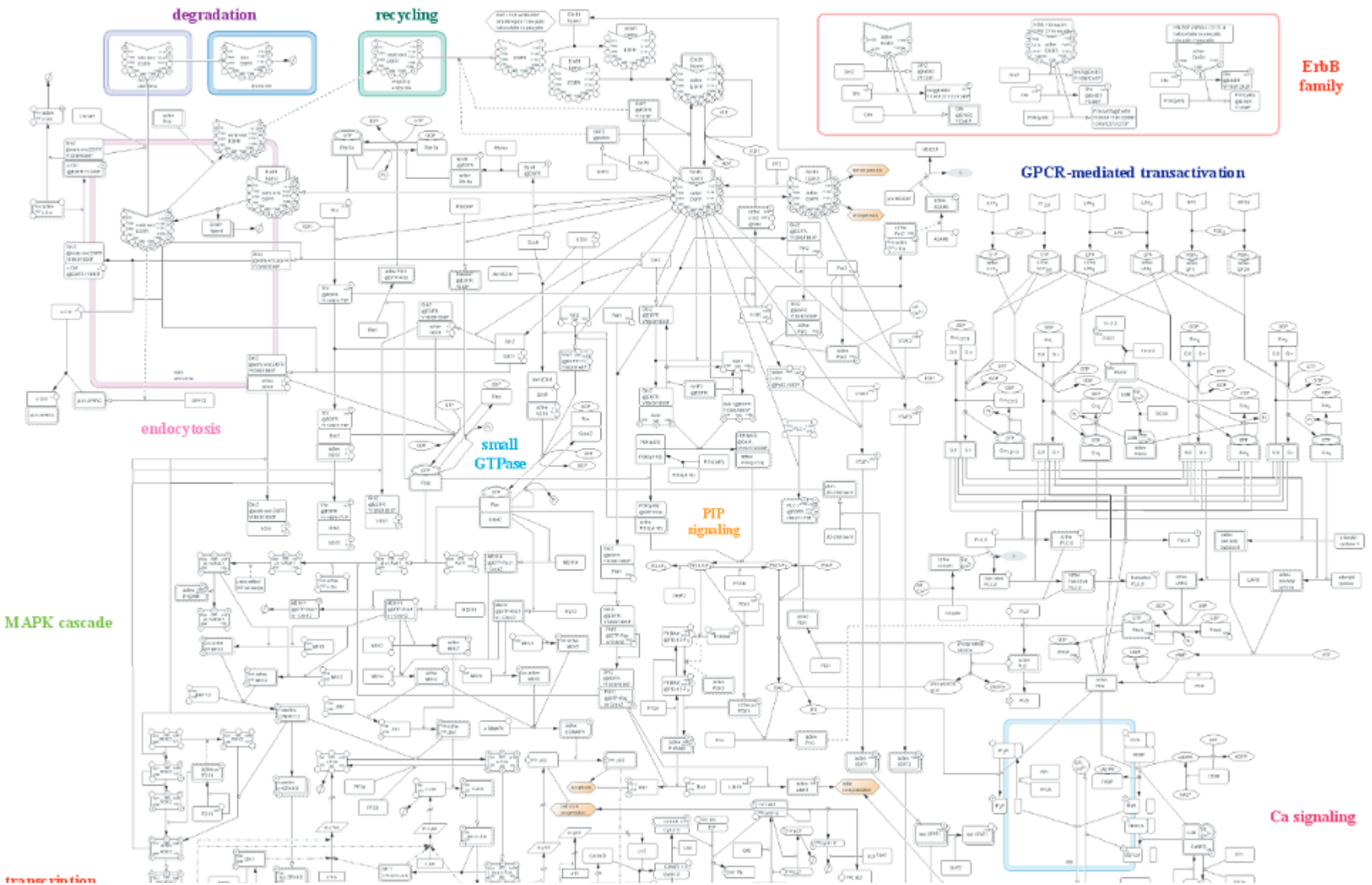

UNDERSTAND

Metabolic networks

Oda K. Mol Syst Biol. 2005;1:2005.0010.

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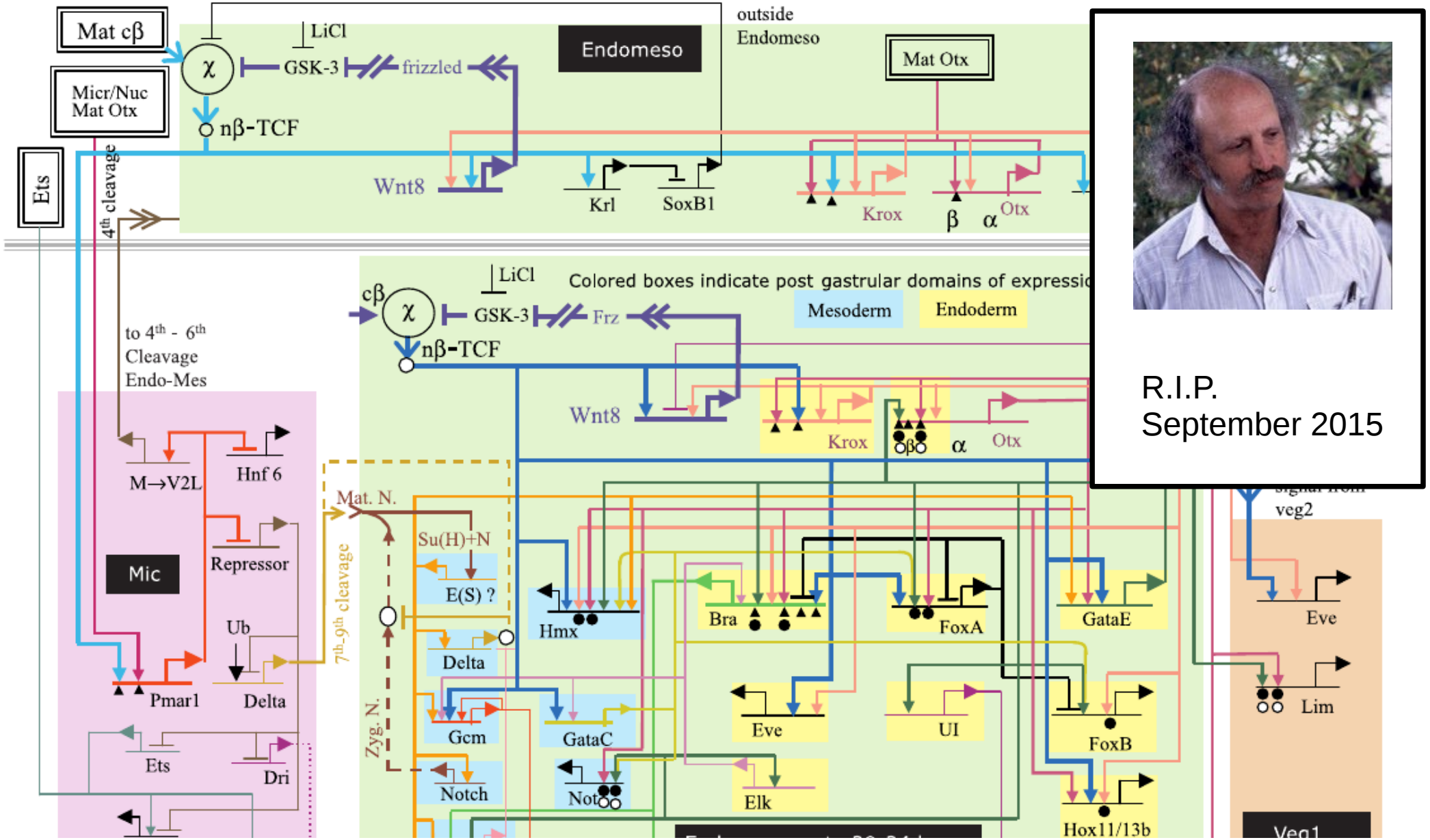
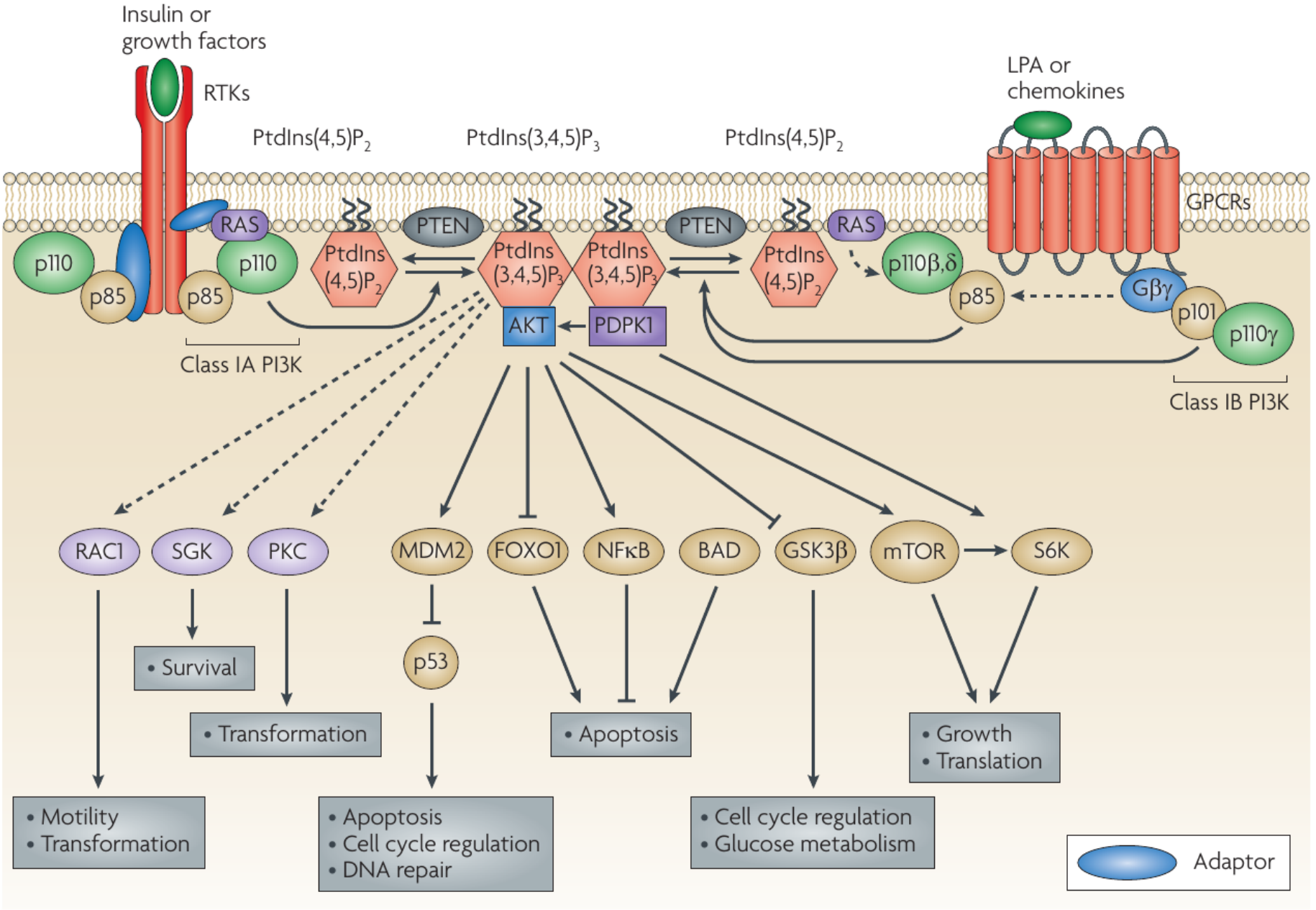


R.I.P.
September 2015

UNDERSTAND

Gene regulatory networks

Davidson *et al. Science (2002)*



CURE

Liu *et al* (2009) *Nat Rev Drug Discov*

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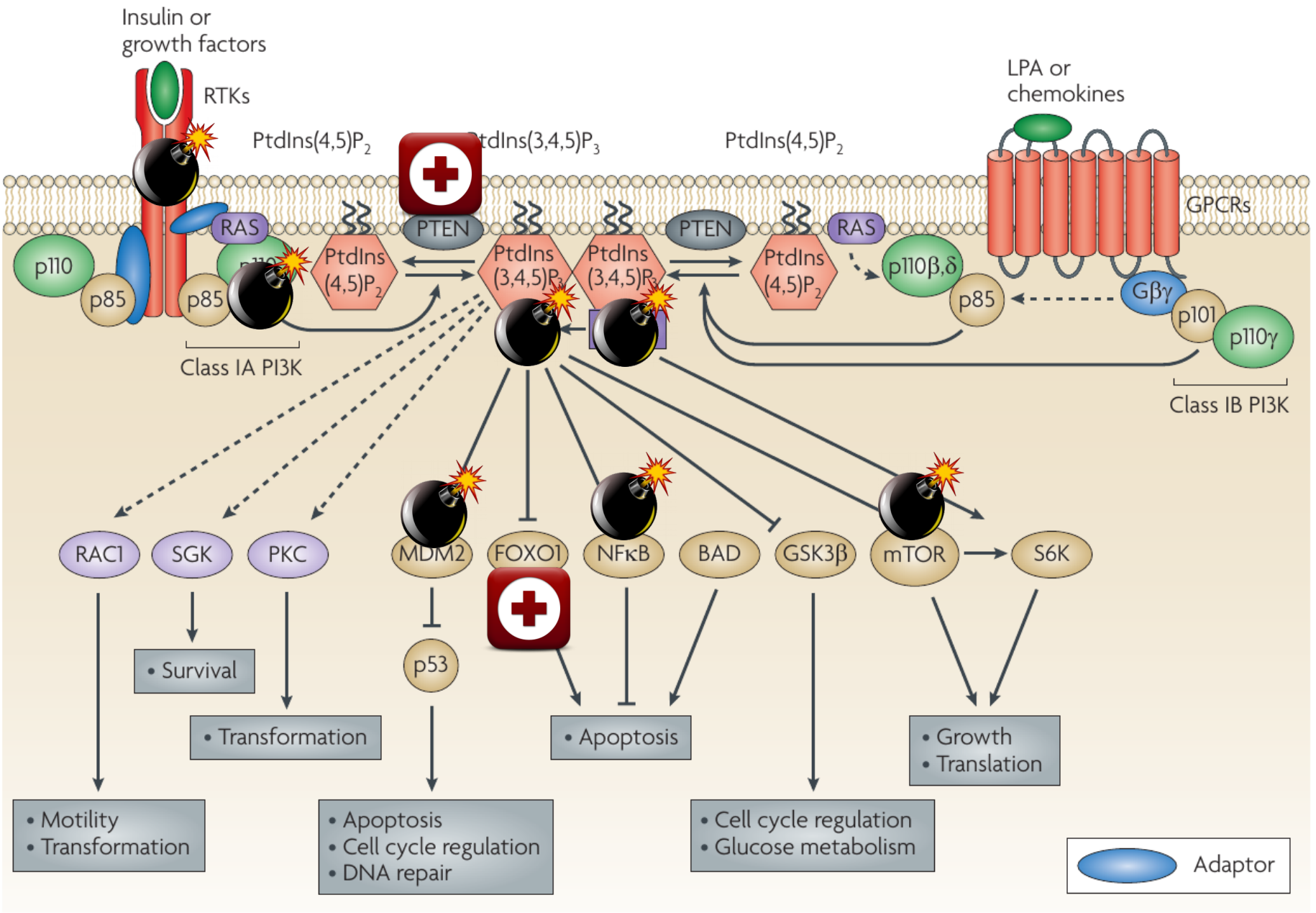
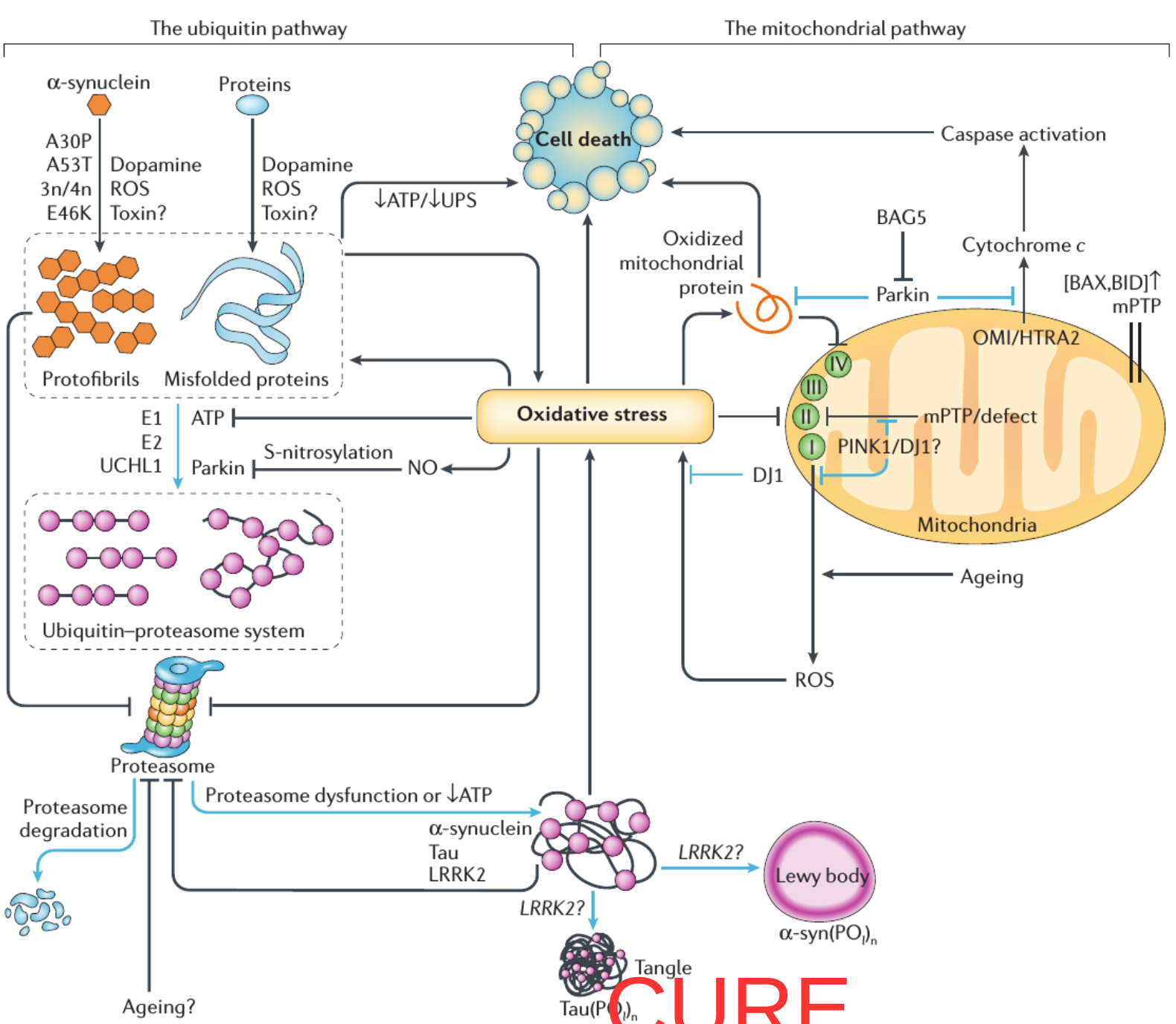


Liu *et al* (2009) *Nat Rev Drug Discov*

CURE

Breast cancer

Babraham Institute

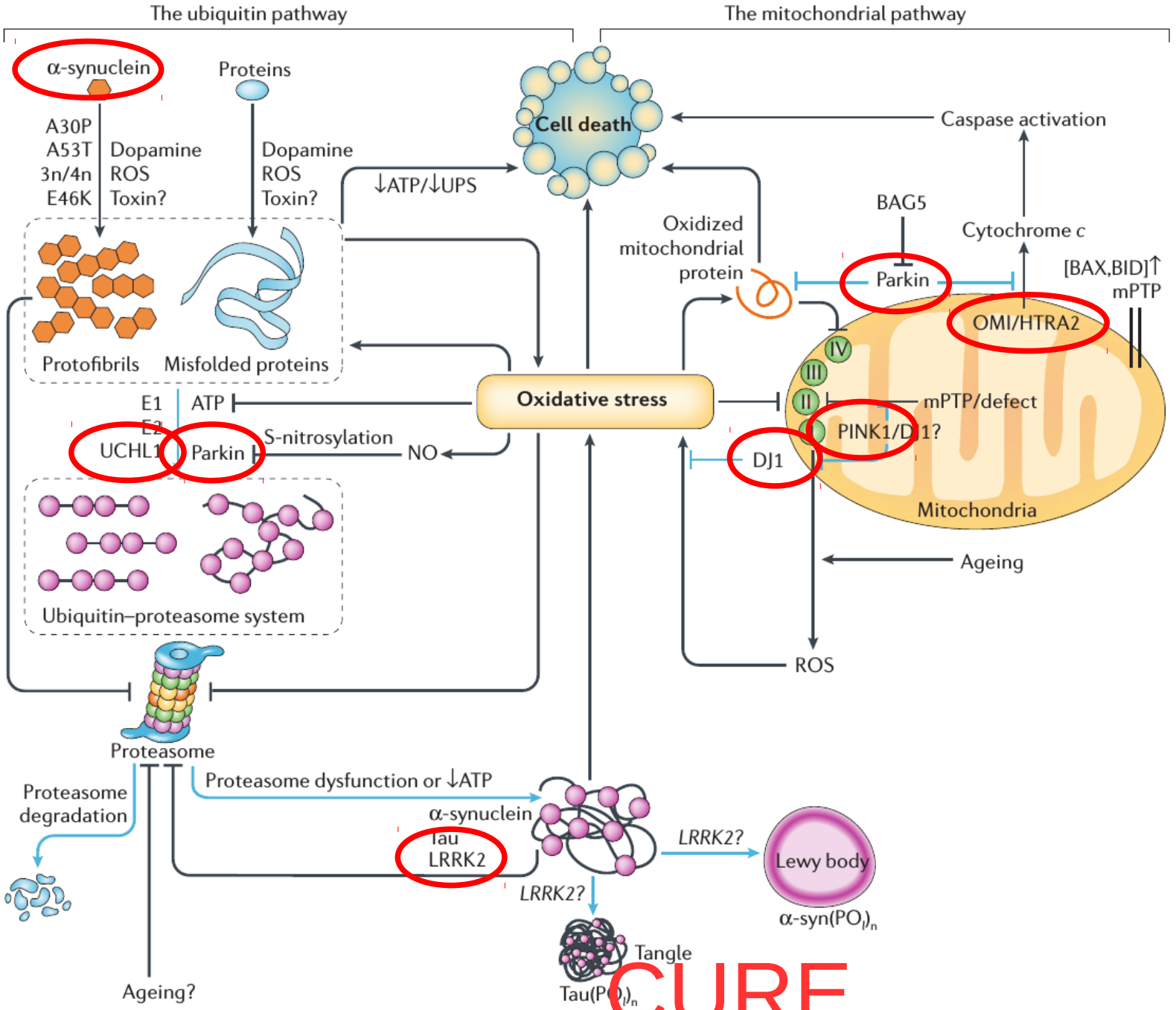


CURE

Parkinson's disease

Abou-Sleiman *et al* (2006) *Nat Rev Neurosci*

Babraham Institute

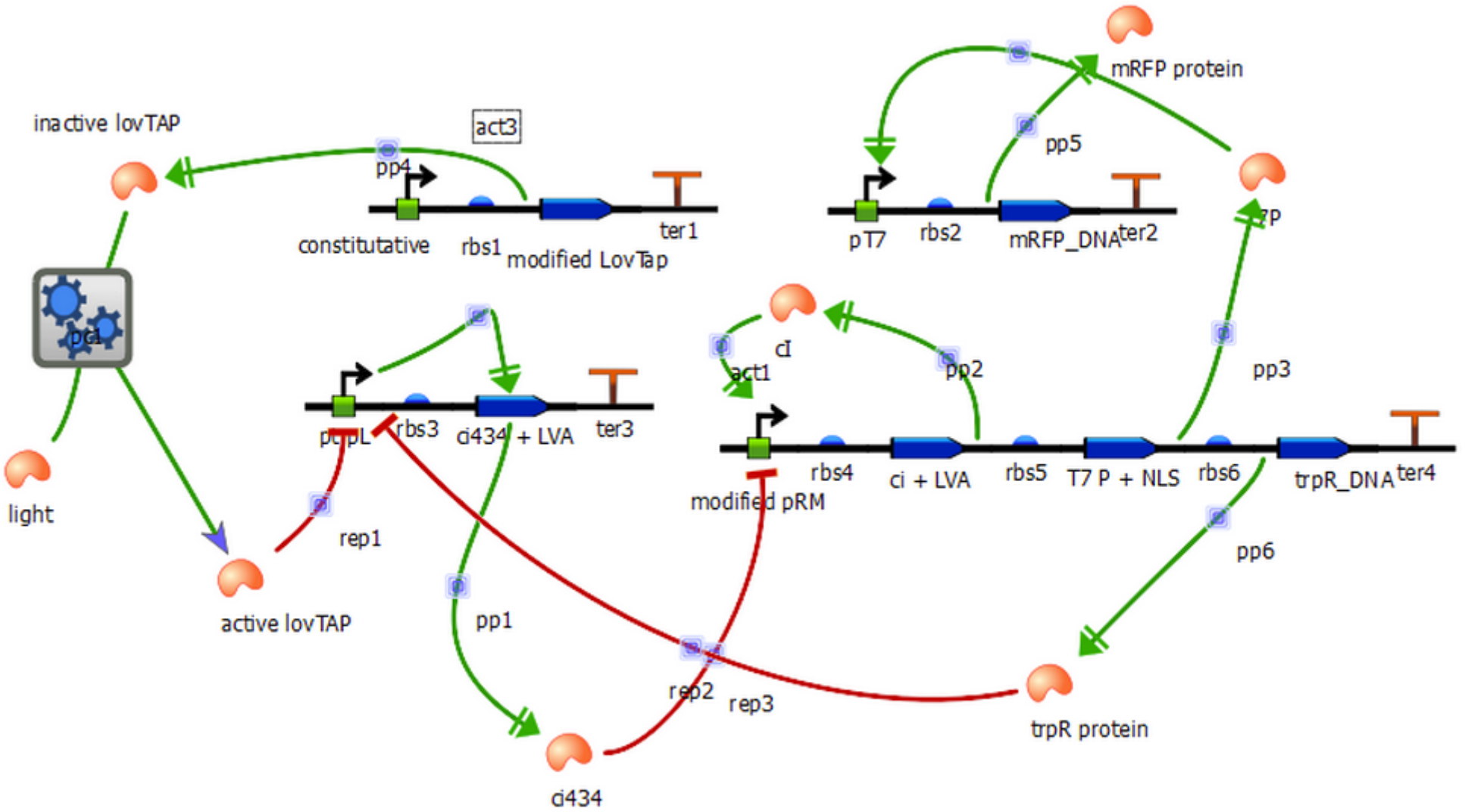


Abou-Sleiman *et al* (2006) *Nat Rev Neurosci*

CURE

Parkinson's disease

Babraham Institute



BUILD

Synthetic Biology

Team Nanjing, iGEM (2013)

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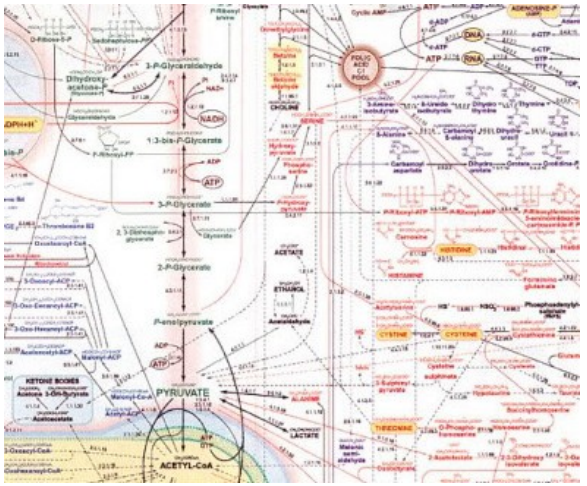
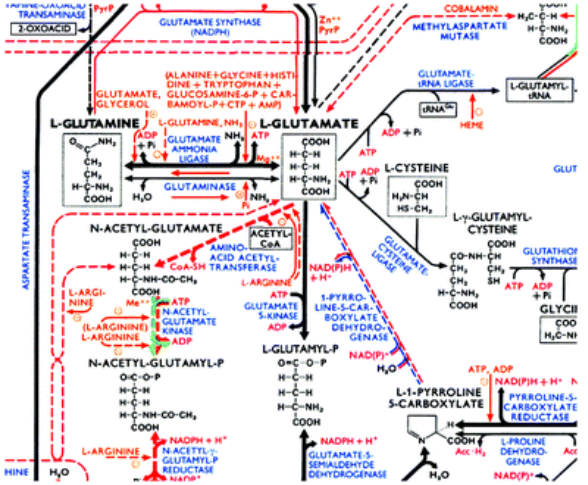
Biochemical pathways are old …

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



Michal (1984)



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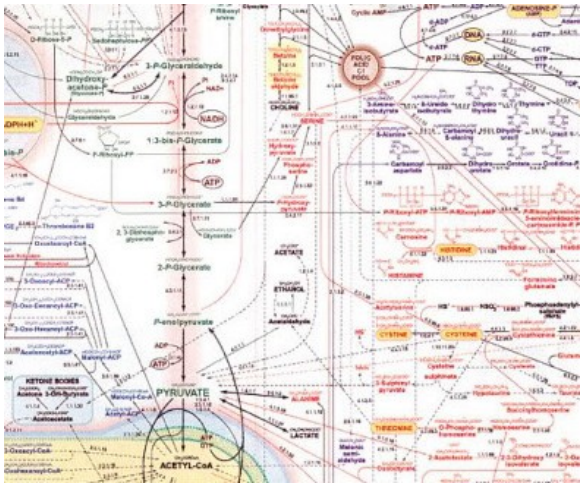
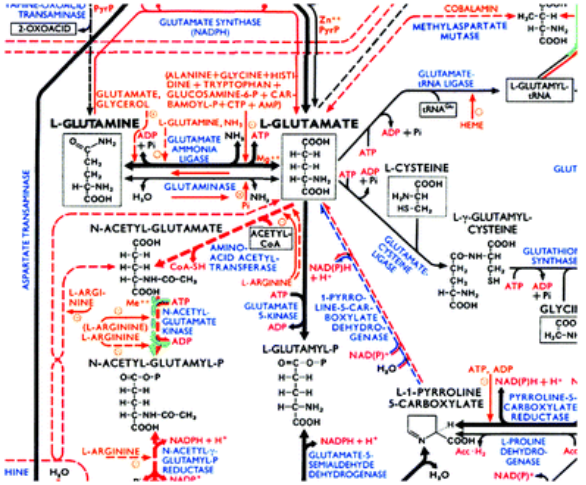
Biochemical pathways are old …

- 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

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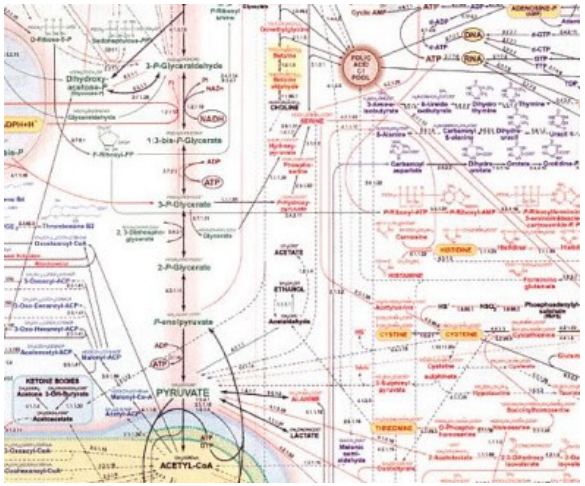
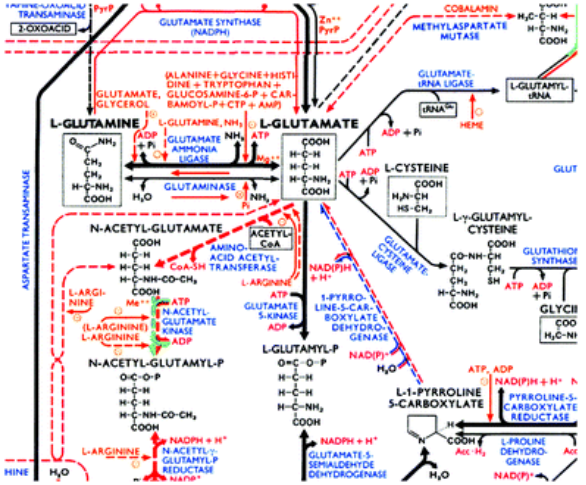
Biochemical pathways are old … or not so much

- 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: EcoCyc (1994), KEGG (1995), Reactome (2000)
- Formats: BioPAX (2000), SBML (2000), PSI-MI (2002)

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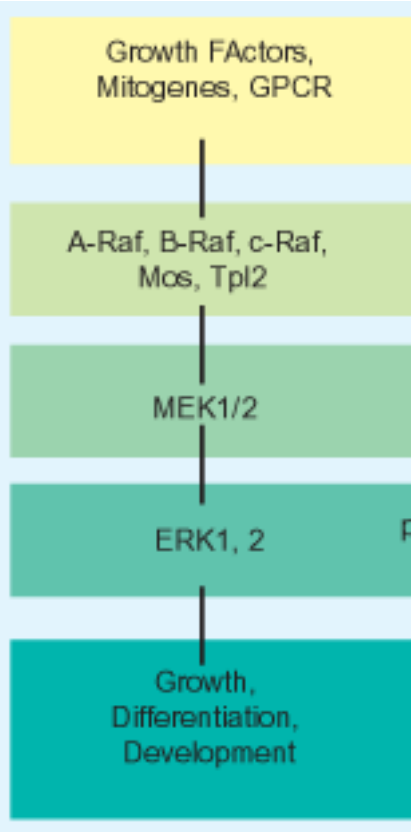
Different granularities of a pathway



- No temporal sequence
- No directionality
- No biochemical effects
- No mechanistic descriptions

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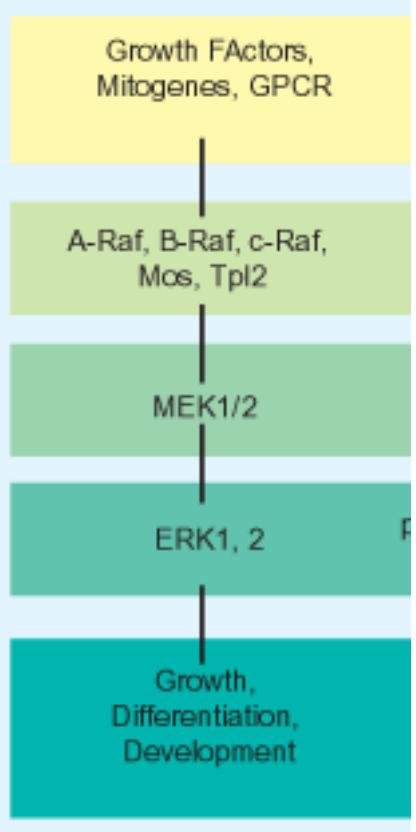
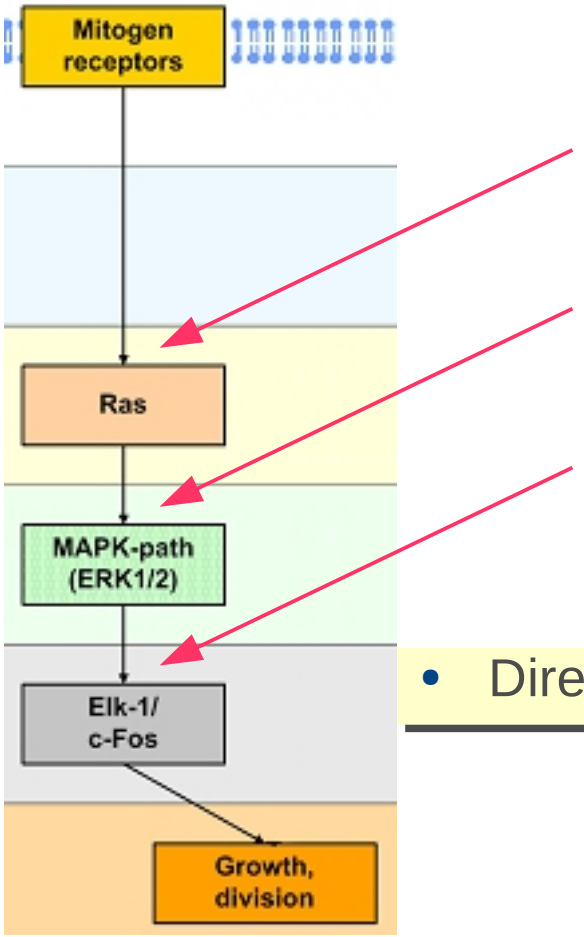
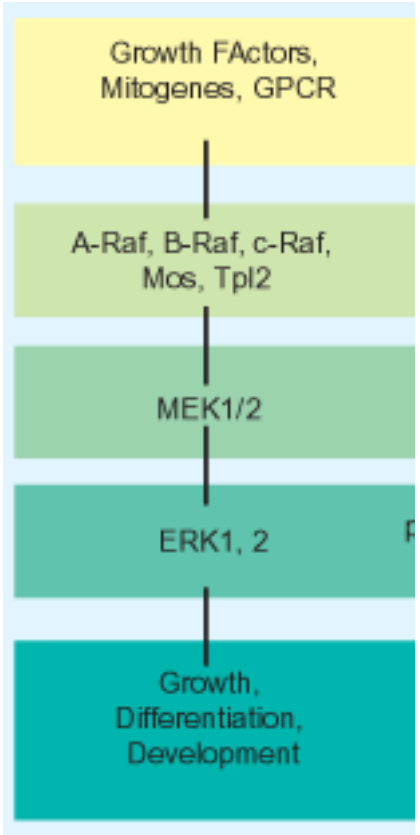
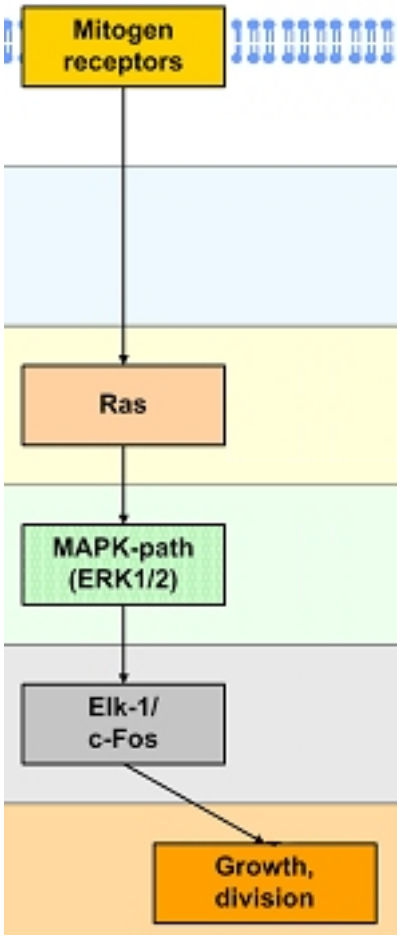
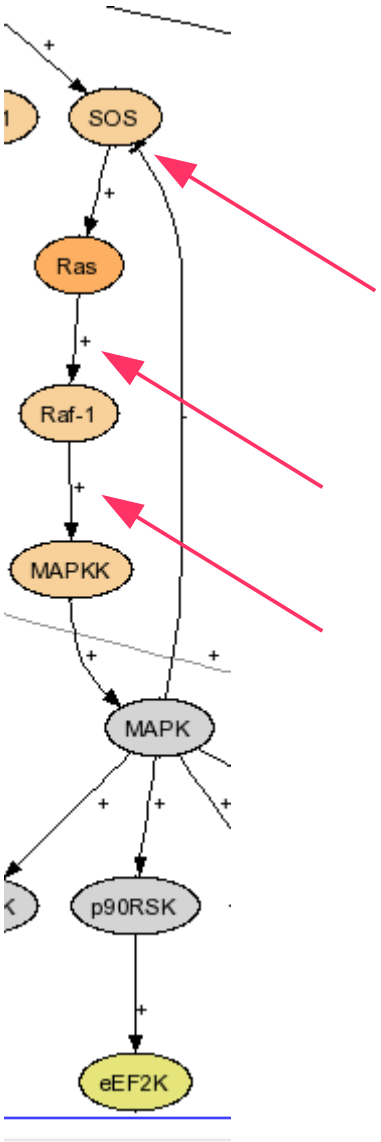




- Directionality of influence







- Directionality of influence
- Directionality of effect

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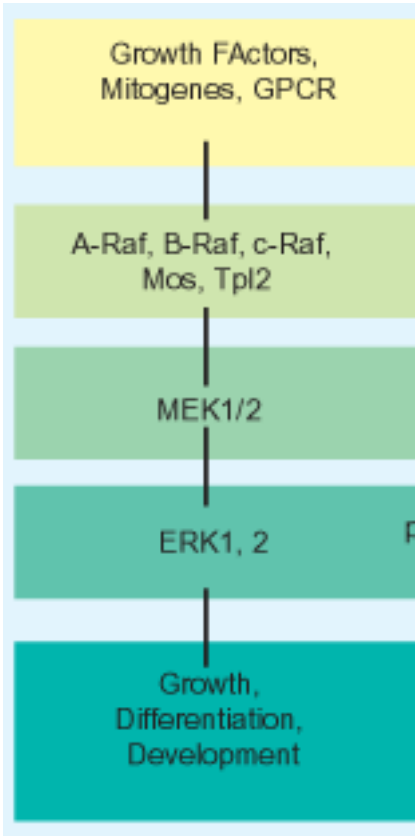
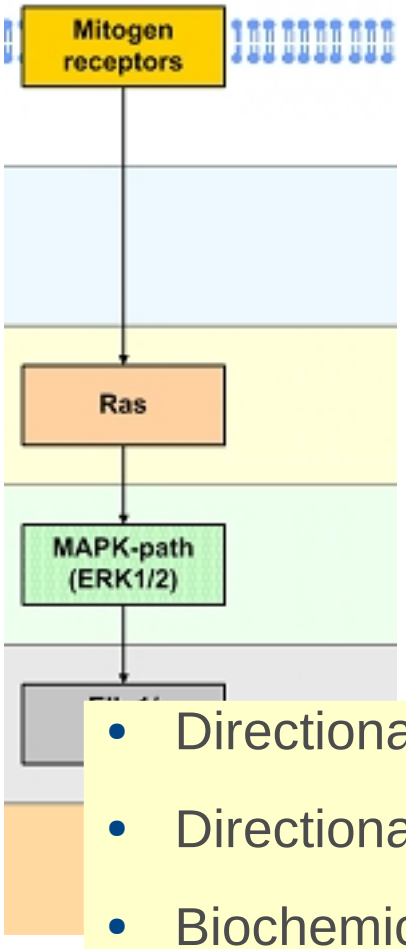
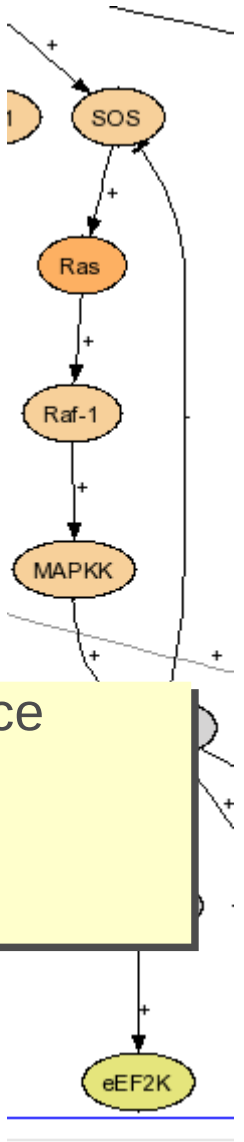
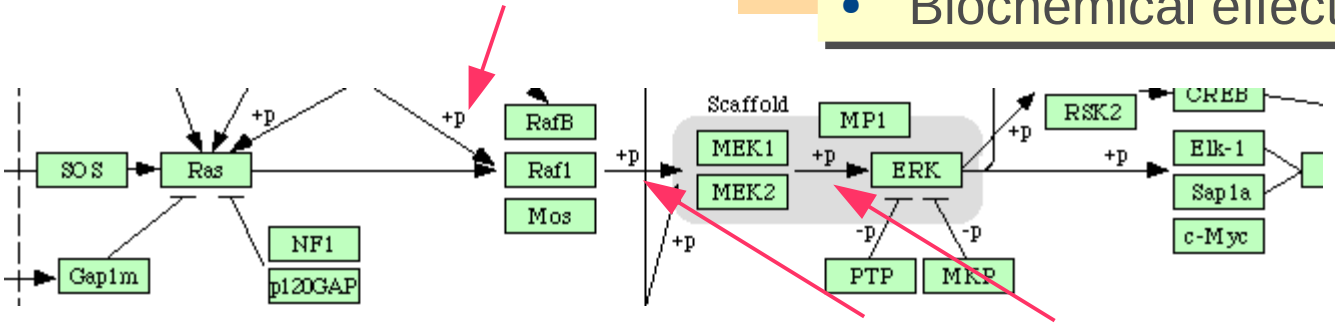




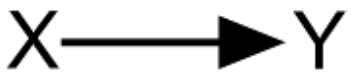


- Directionality of influence
- Directionality of effect
- Biochemical effect



Ambiguity of usual representations

Ambiguity of usual representations



is transformed into

translocates (X "=" Y)

is degraded into

associates into

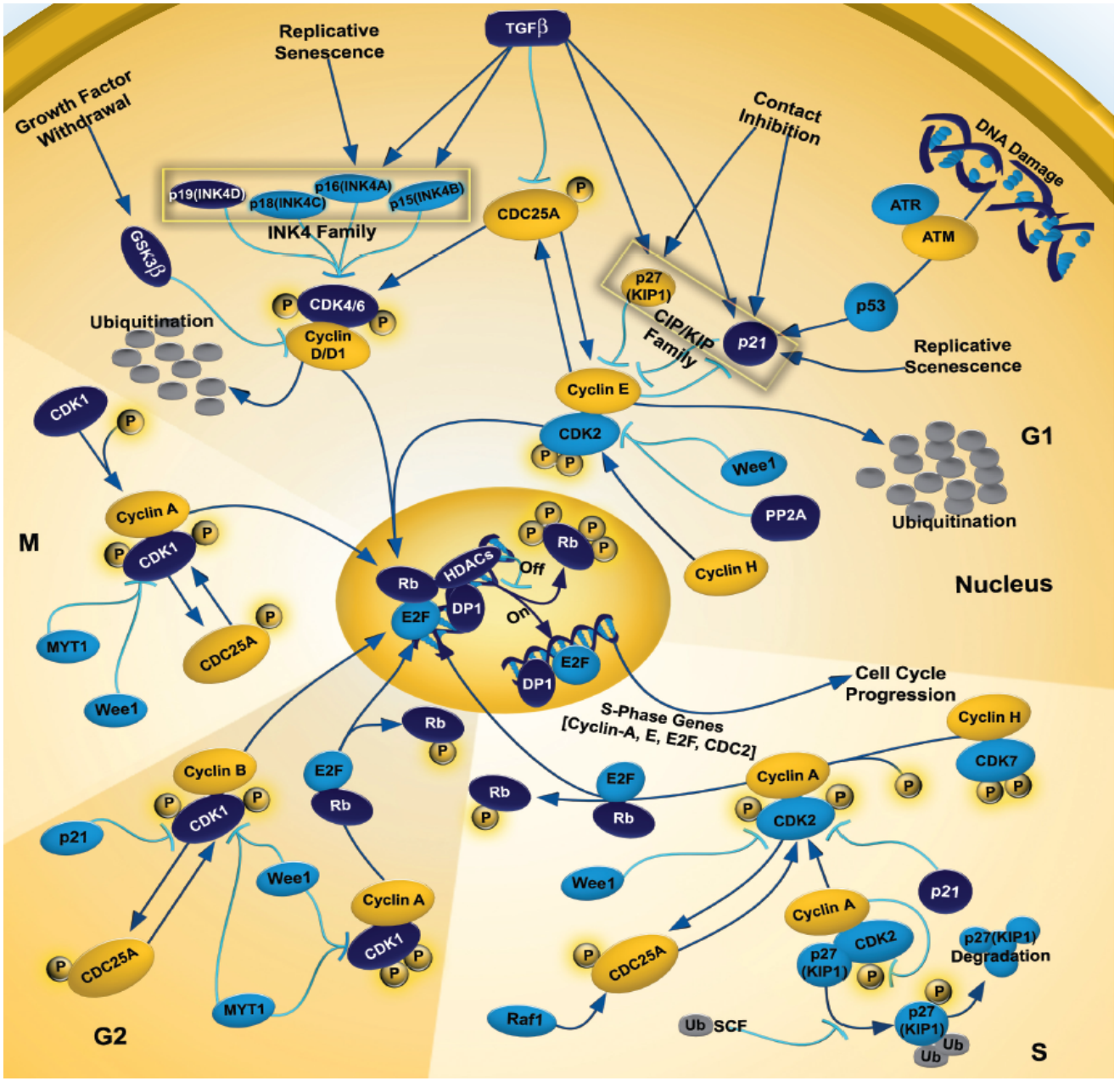
dissociates into

stimulates the activity of

stimulates the expression of

catalyses the formation of

Can-this be understood by biologists?



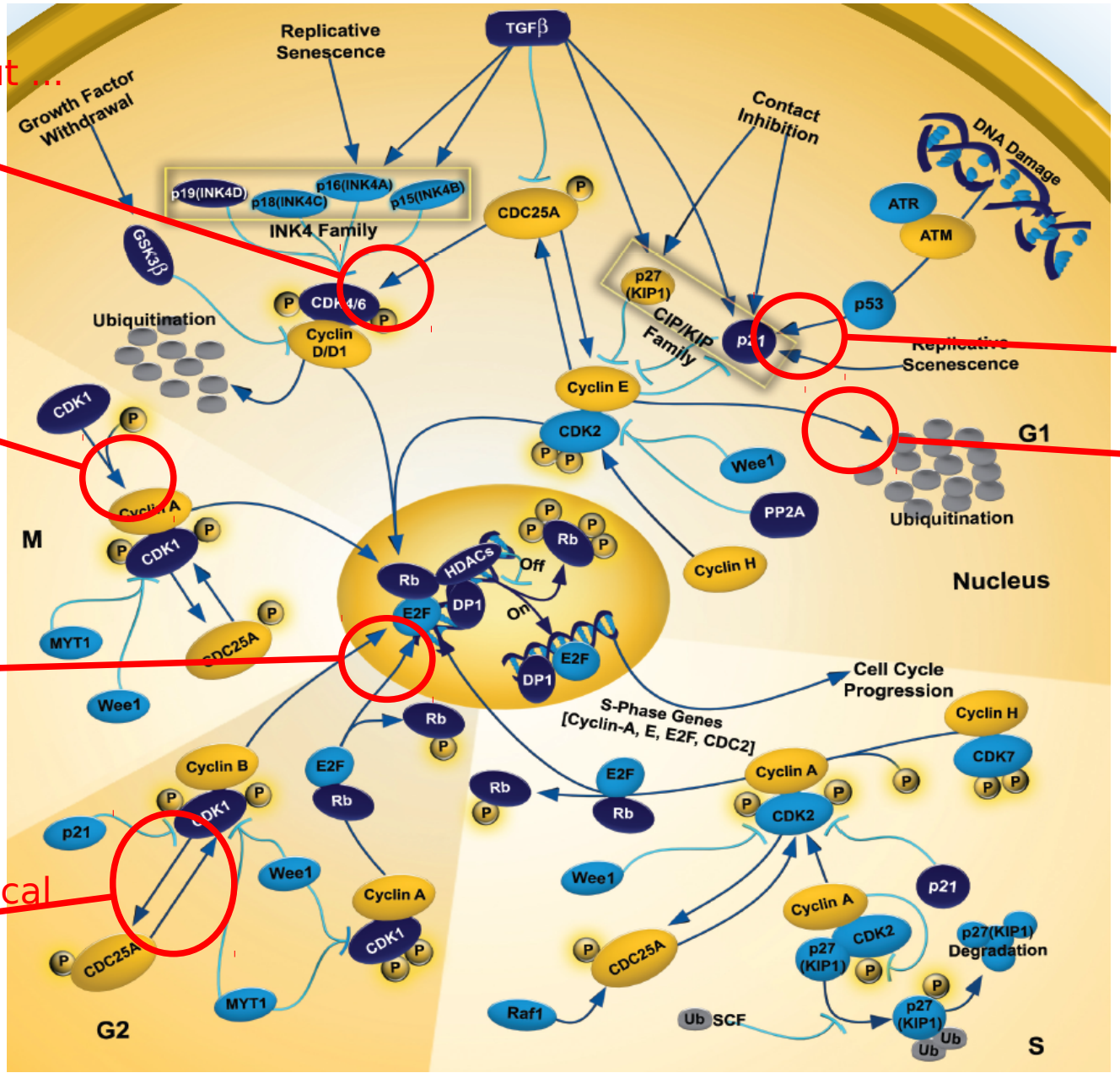
Can-this be understood by biologists?

Stimulates? but … what exactly?

Associates into?

Translocates?

No idea. Reciprocal stimulation?



Stimulates gene transcription?

Is degraded?

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Ambiguity of usual representations

X inhibits Y

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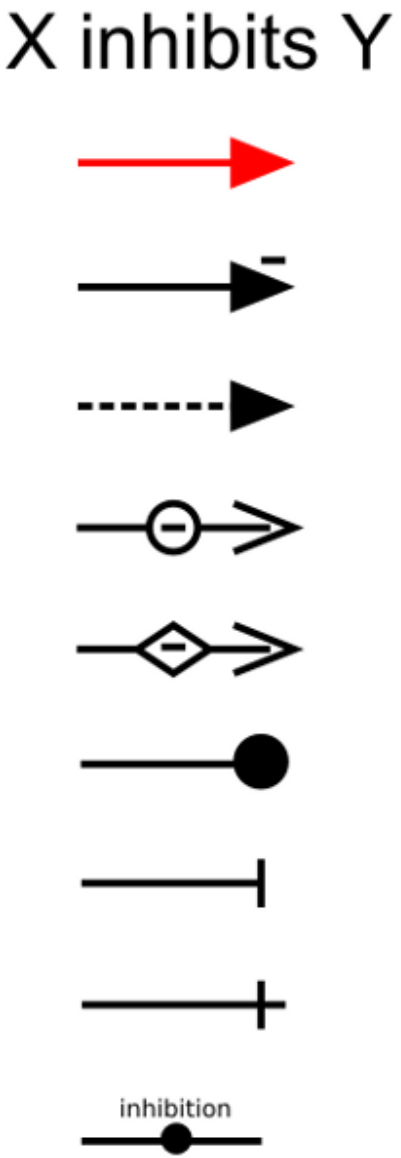
Ambiguity of usual representations



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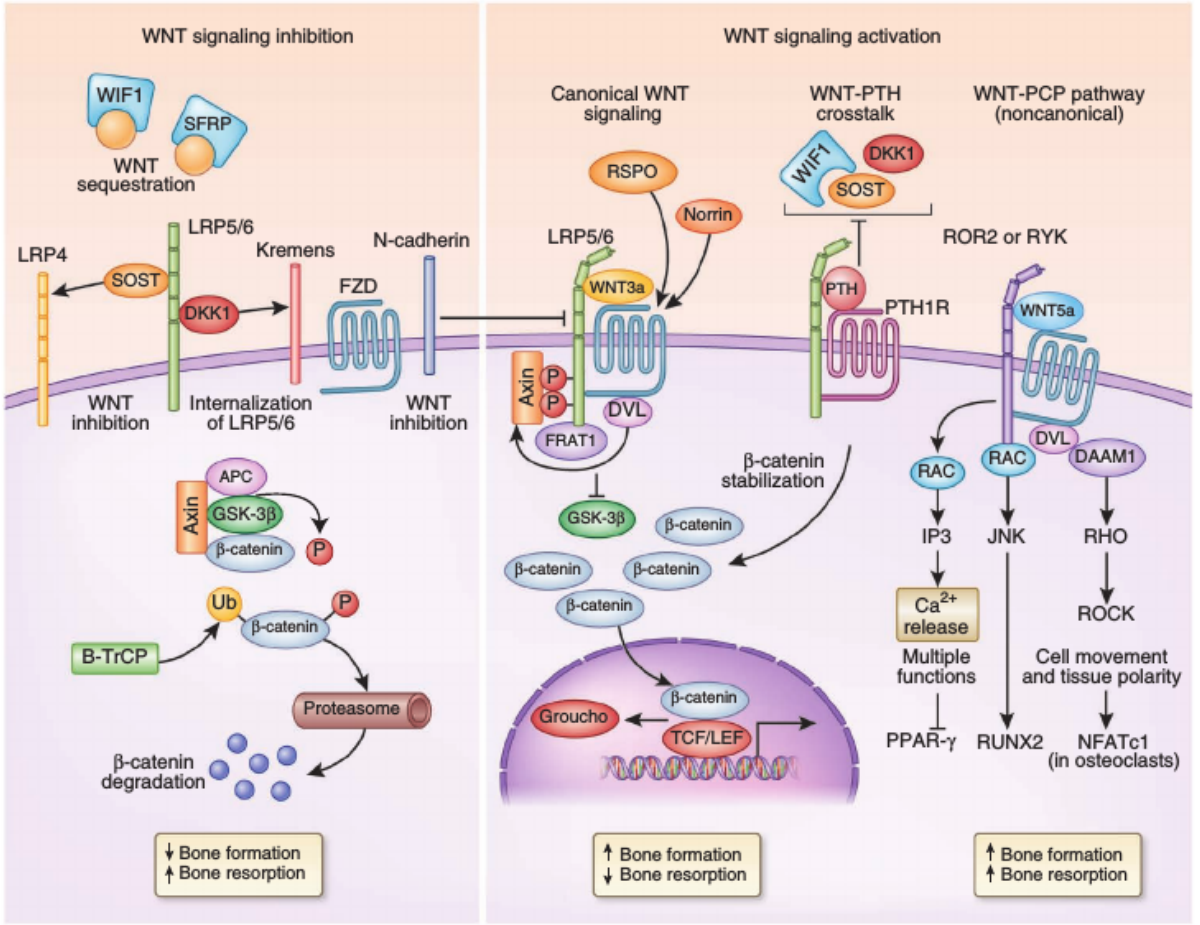
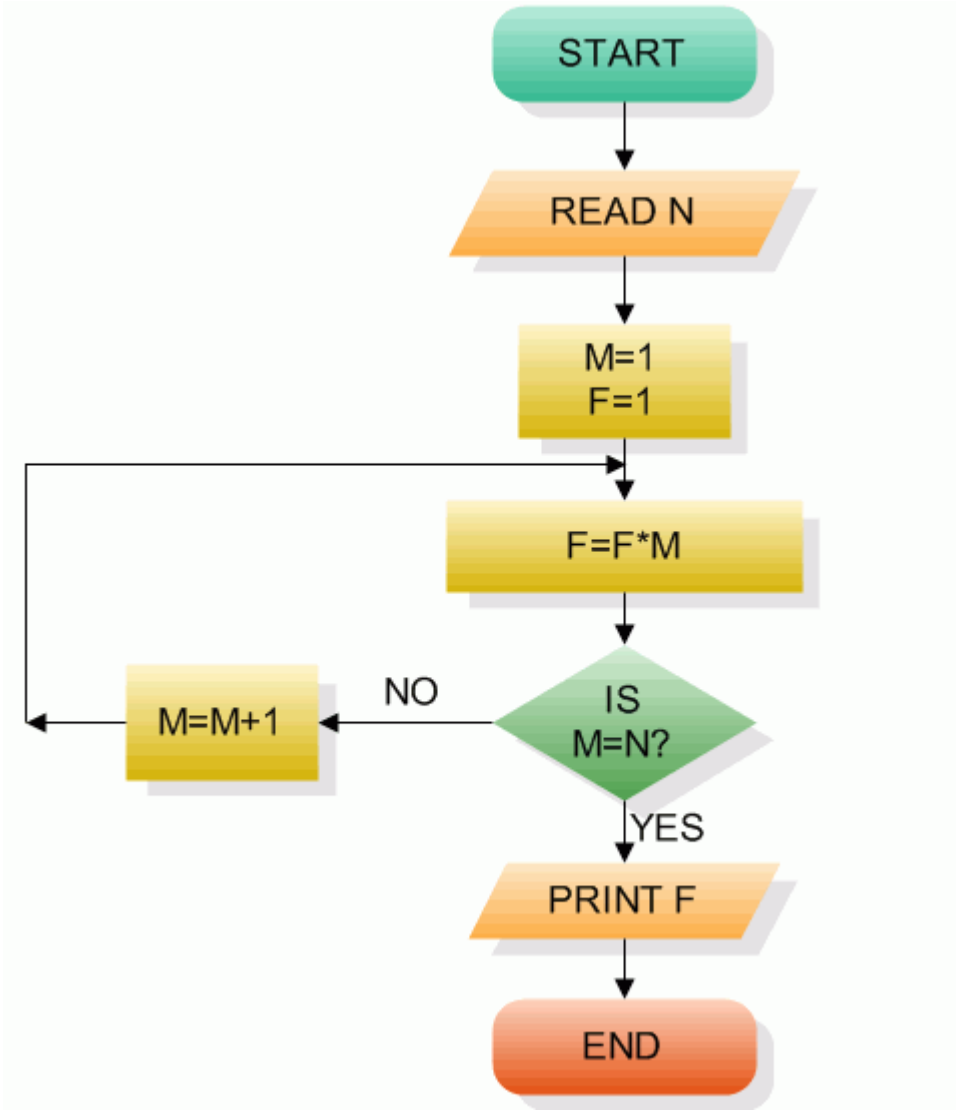
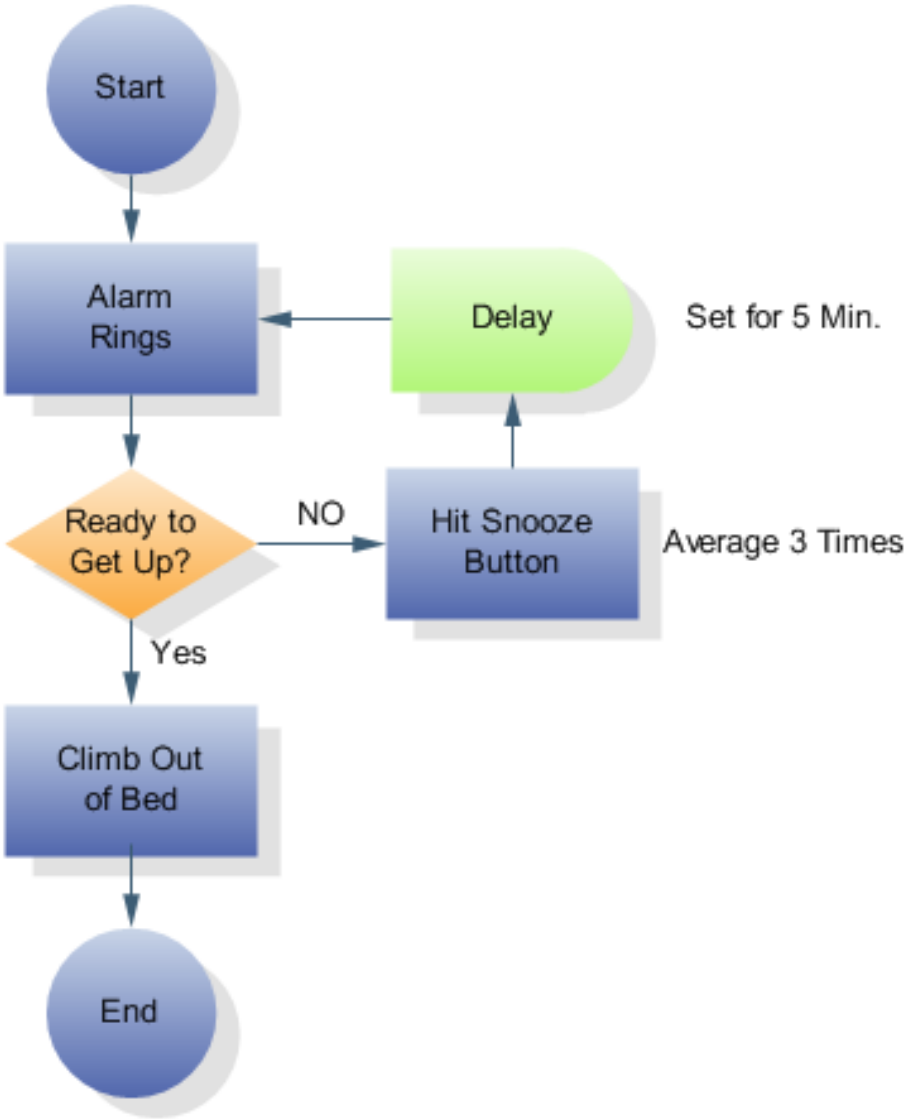


Figure 1 WNT signaling: a simplified view. In the absence of WNT, the amounts of β-catenin are low, except in adherens junctions, because of its constitutive targeting by a multiprotein destruction complex (left). The tumor suppressors axin and adenomatous polyposis (APC) bring β-catenin to GSK-3β and casein kinase 1 (CK1) (not shown), resulting in its phosphorylation (Ps in circles) at specific serine/threonine residues (left). Phosphorylated β-catenin is then targeted for polyubiquitination (Ub) (predominantly by the E3 ligase B-TrCP) and proteosomal destruction. T cell factor/lymphoid enhancer factor (TCF/LEF) transcription factors are repressed by Groucho in the nucleus. Binding of canonical WNT ligands to a dual receptor complex comprising the WNT co-receptors LRP5 or LRP6 (LRP5/6) and one of the seven transmembrane receptors of the FZD family (right) initiates WNT–β-catenin signaling. Axin moves to the LRP5/6 tail at the membrane through its interaction with dishevelled (DVL, also called DSH), which is recruited by FZD (right). This forms a complex that also includes FRAT1 and GSK-3β, which prevents phosphorylation of β-catenin and its proteosomal degradation. β-catenin accumulates in the cytoplasm and translocates into the nucleus, where it associates with members of the TCF/LEF transcription factors while displacing Groucho to control target gene transcription. WNT signaling is modulated not only through fine tuning by a large number of WNT ligands and RSPO proteins and norrin (right) but also by extracellular antagonists such as DKK1, SOST and Wise, which bind LRP5/6 (left). Their antagonism is mediated or enhanced by receptors such as Kremen proteins and LRP4. In addition to sequestering β-catenin, N-cadherin also inhibits WNT–β-catenin signaling by interacting with LRP5 (left to right). In contrast, secreted frizzled-related proteins (SFRPs) and WNT inhibitory factor 1 (WIF1), which have ligand specificity, inhibit WNT signaling by directly sequestering WNT ligands and inhibiting both canonical and noncanonical WNT signaling (left). The PTH1 receptor can also activate the pathway in the absence of WNT ligands by forming a complex with LRP5/6 after PTH binding (right). In the WNT-PCP pathway (right), WNT binding to FZD also recruits DVL, which forms a complex with dishevelled associated activator of morphogenesis 1 (DAAM1) to trigger activation of the small G protein RHO, which in turn activates RHO-associated kinase (ROCK). Alternatively, DVL forms a complex with RAC, resulting in Jun kinase (JNK) activity. The WNT-Ca^{2+} pathway is activated by WNT5a binding to FZD and receptor-tyrosine-kinase-like orphan receptor (ROR). Intracellular calcium concentrations increase after WNT-induced coupled G protein activation of phospholipase C (PLC), resulting in dystroglycan 1 (DAG) and inositol 1,4,5-trisphosphate, type 3 (IP3) generation and cyclic GMP (cGMP)-specific phosphodiesterase (PDE) decreasing the amount of cGMP. NFATc1, nuclear factor of activated T cells, cytoplasmic, calcineurin dependent 1; PPAR-γ, peroxisome proliferator activated receptor-γ.

Every computer scientist understands those





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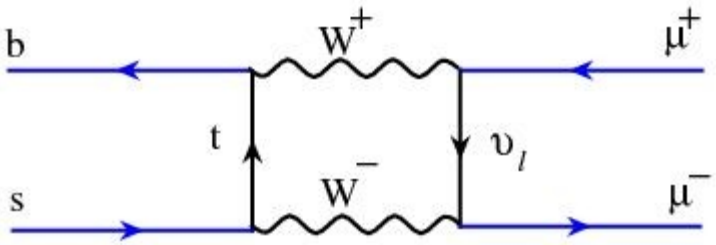
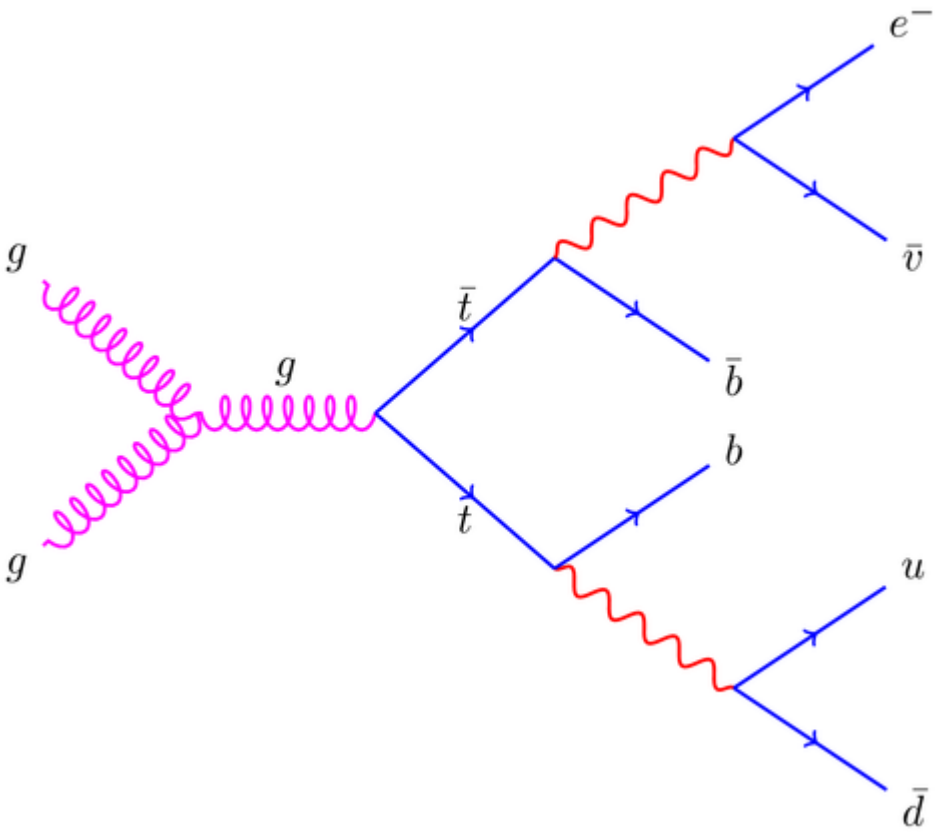
Every physicist understands those





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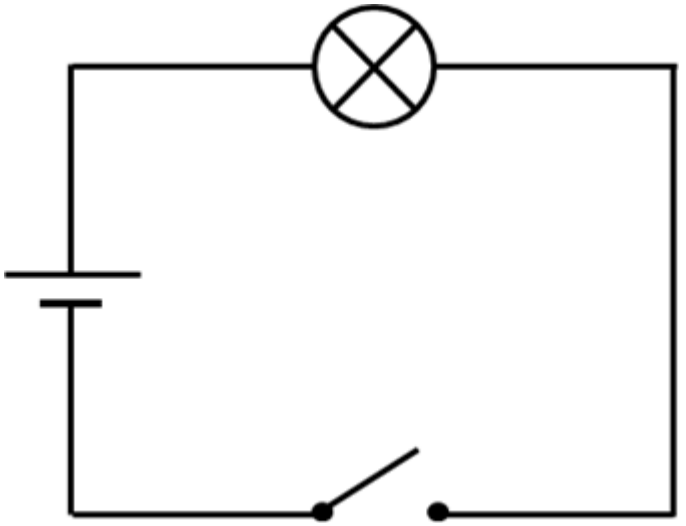
Every engineer understands that



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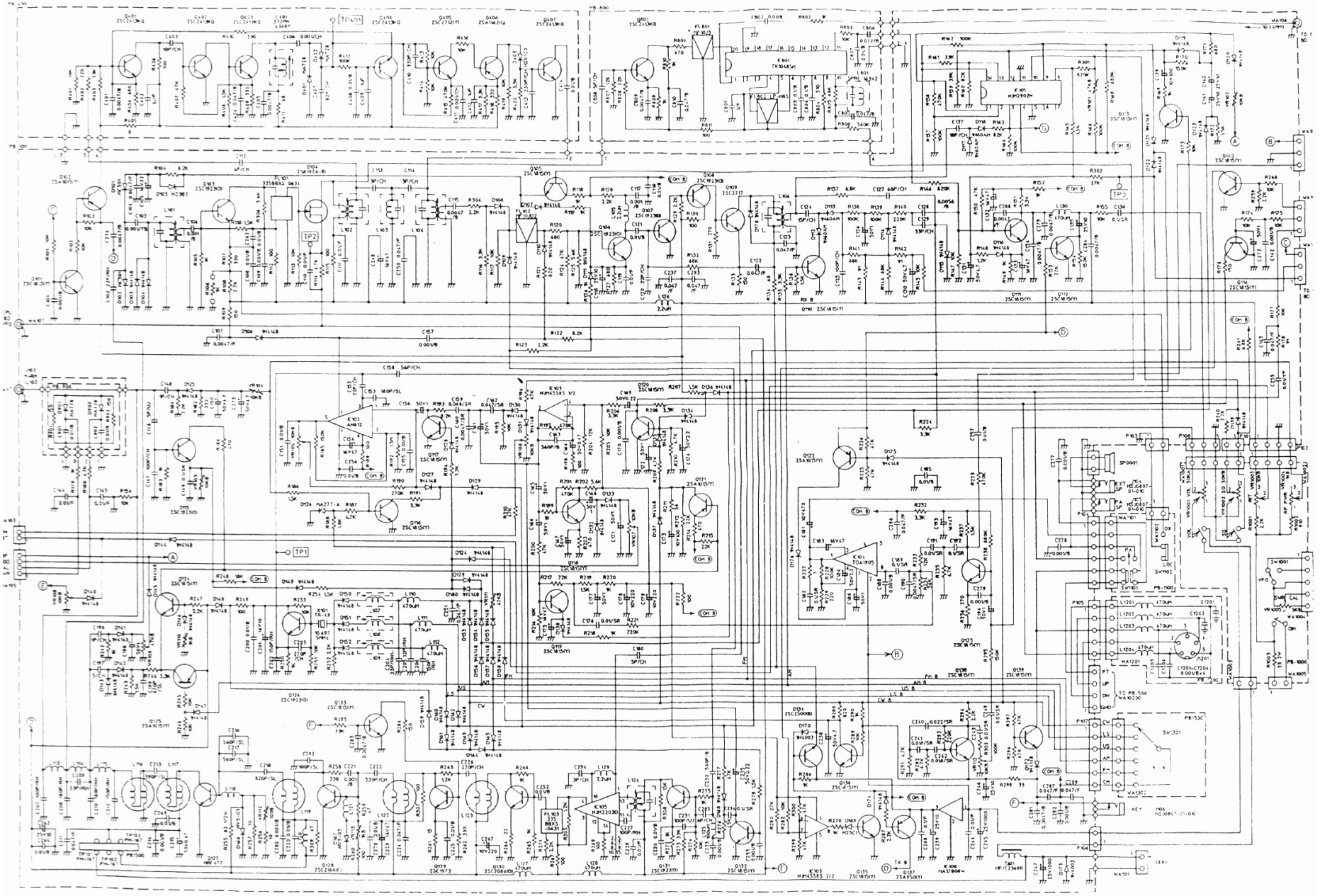

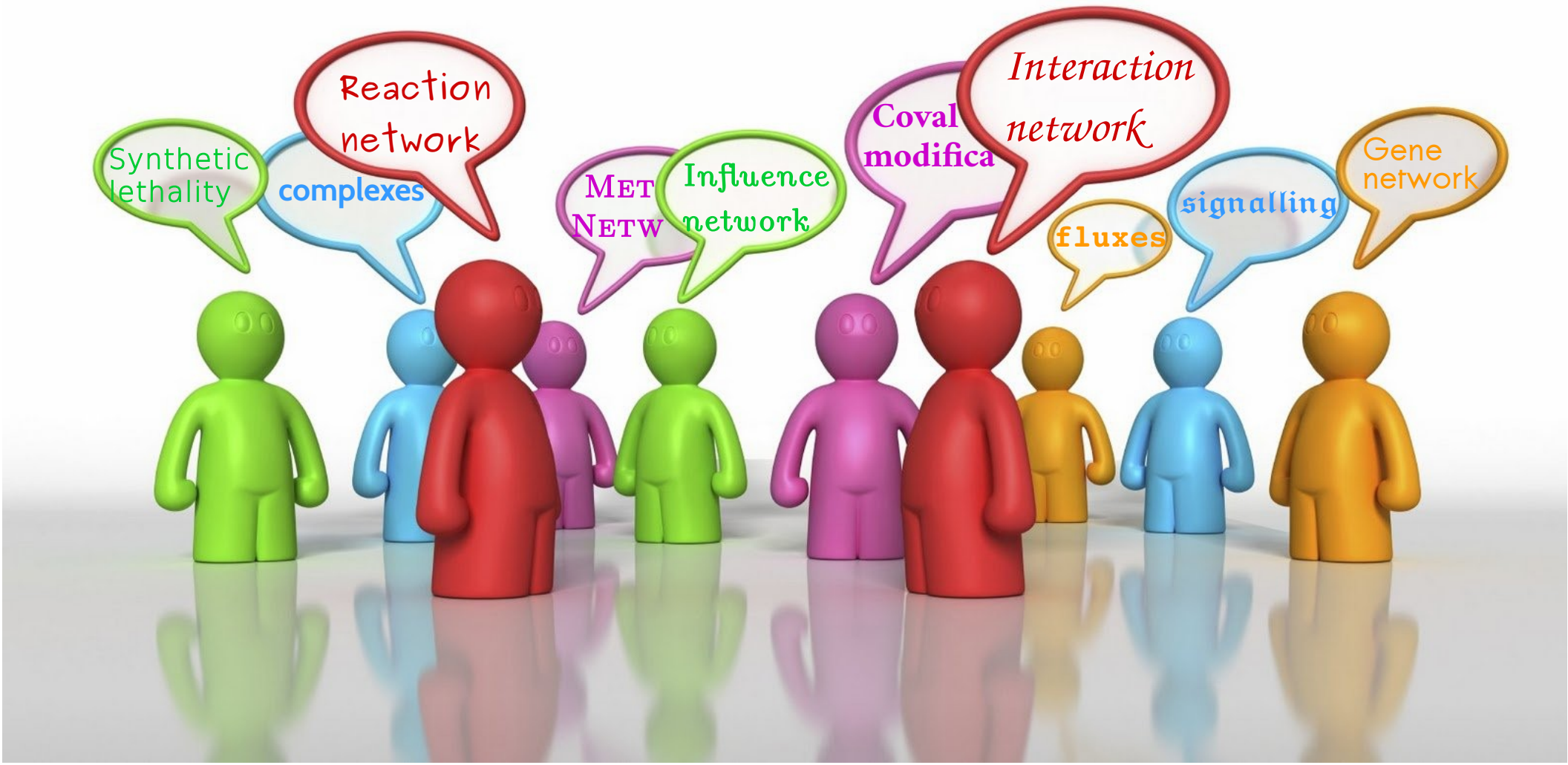

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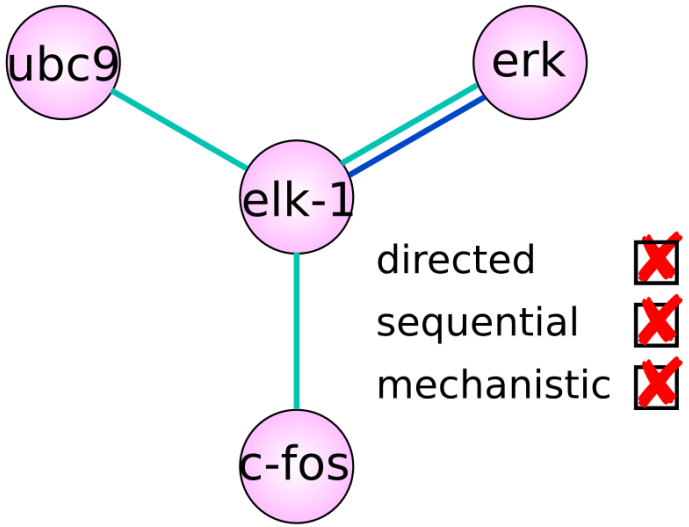
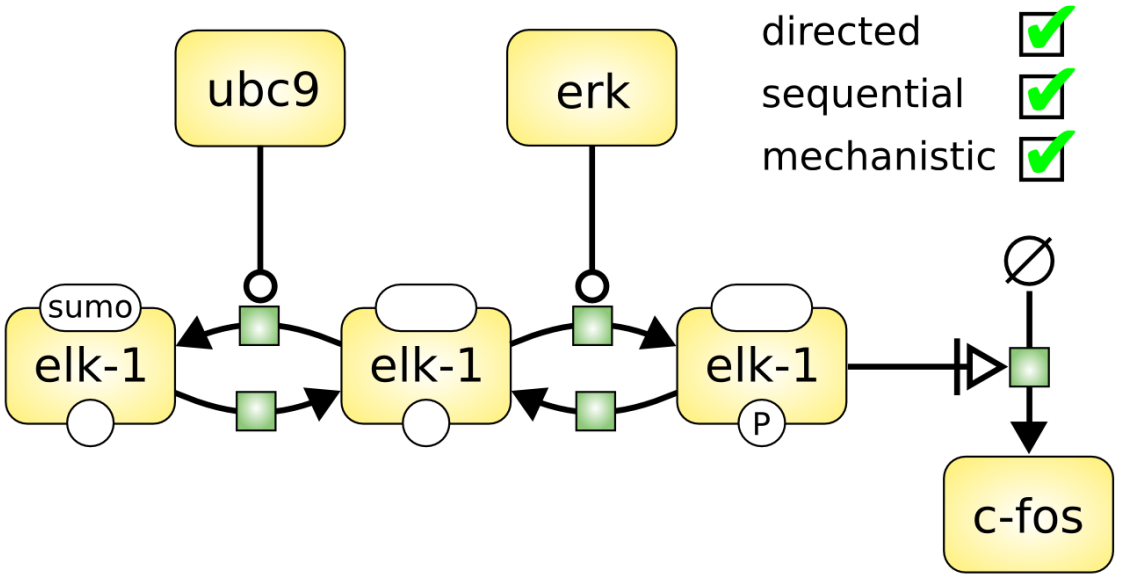
The four views of systems biology

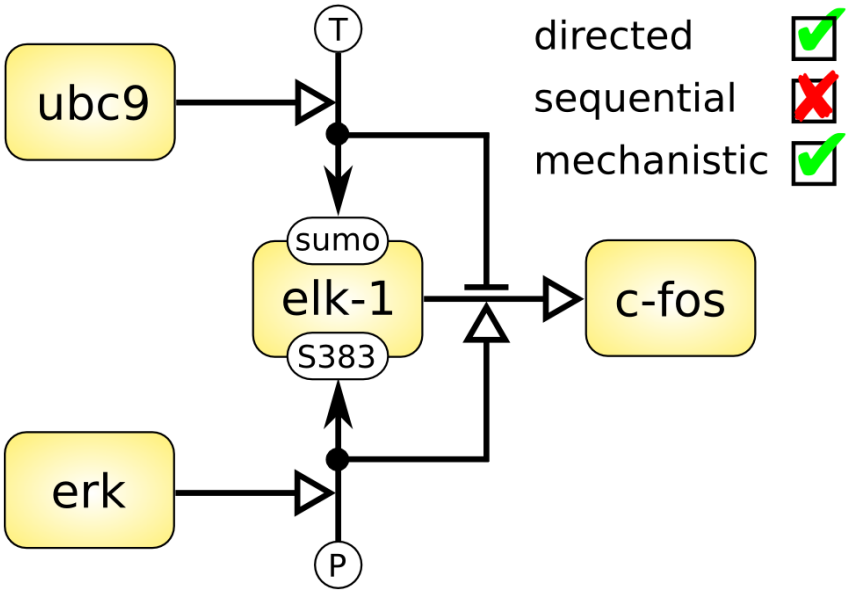
interaction network



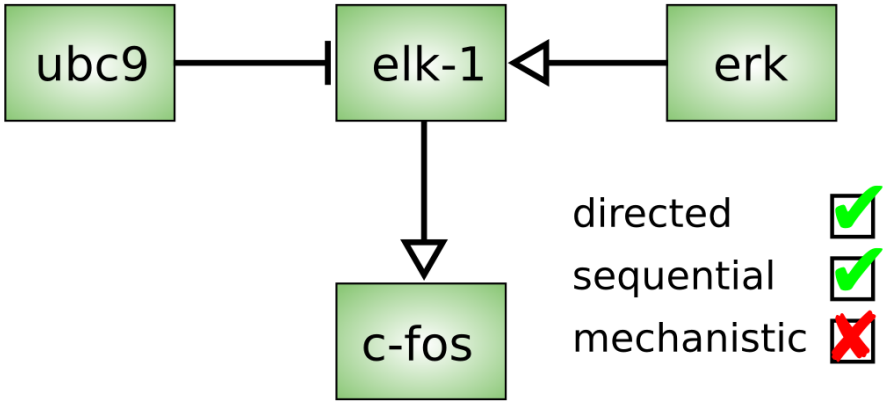
process descriptions

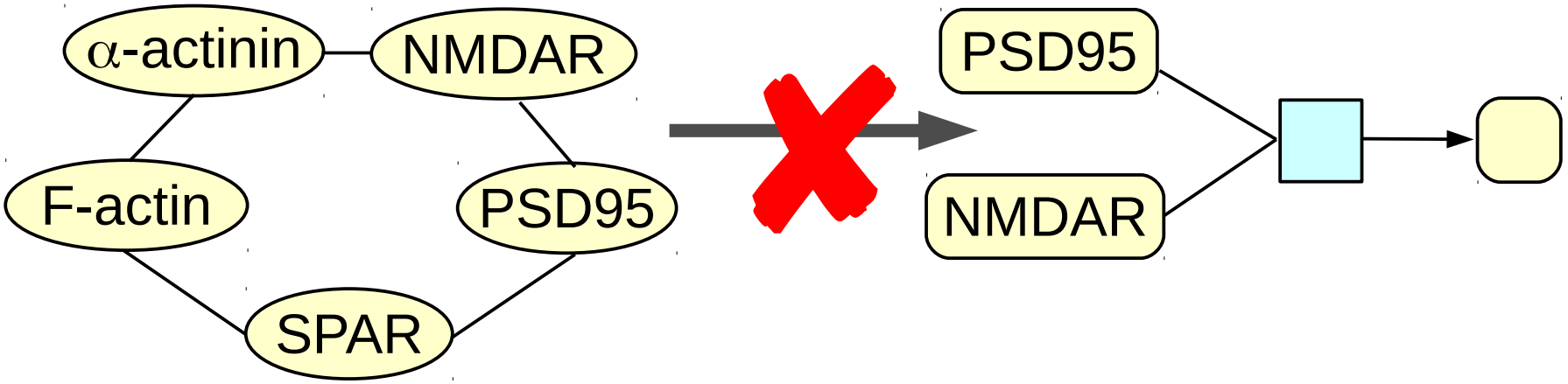


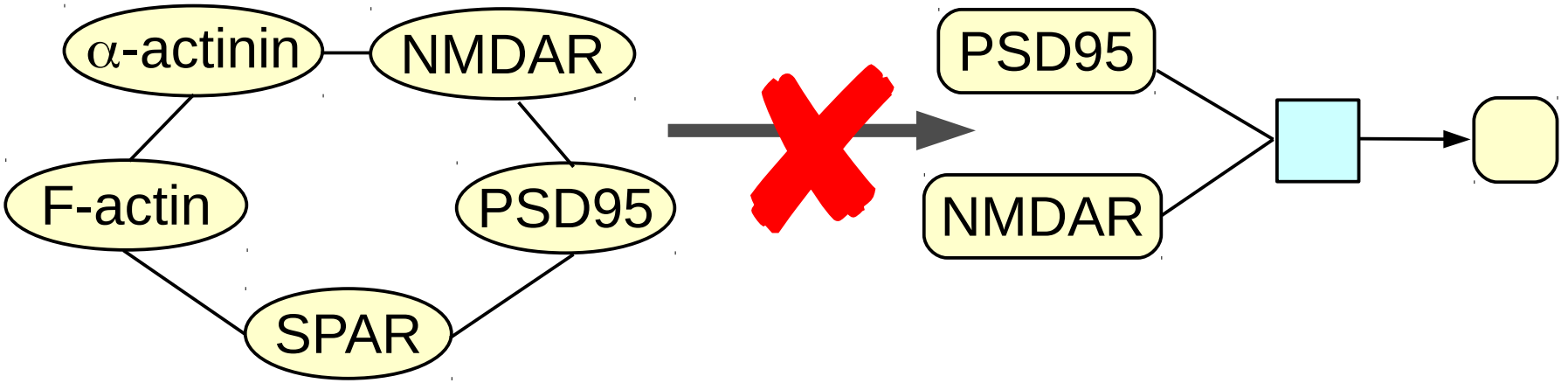
entity relationships

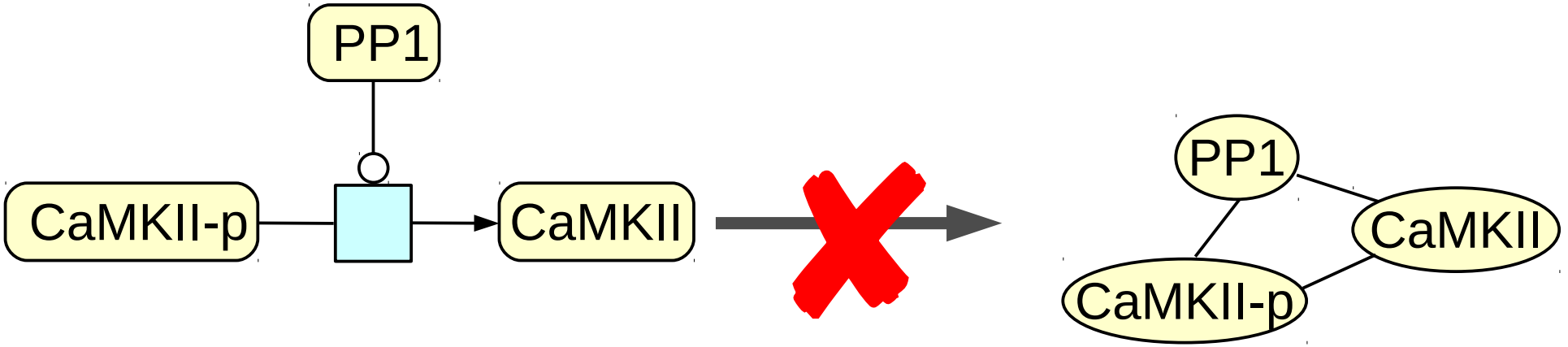


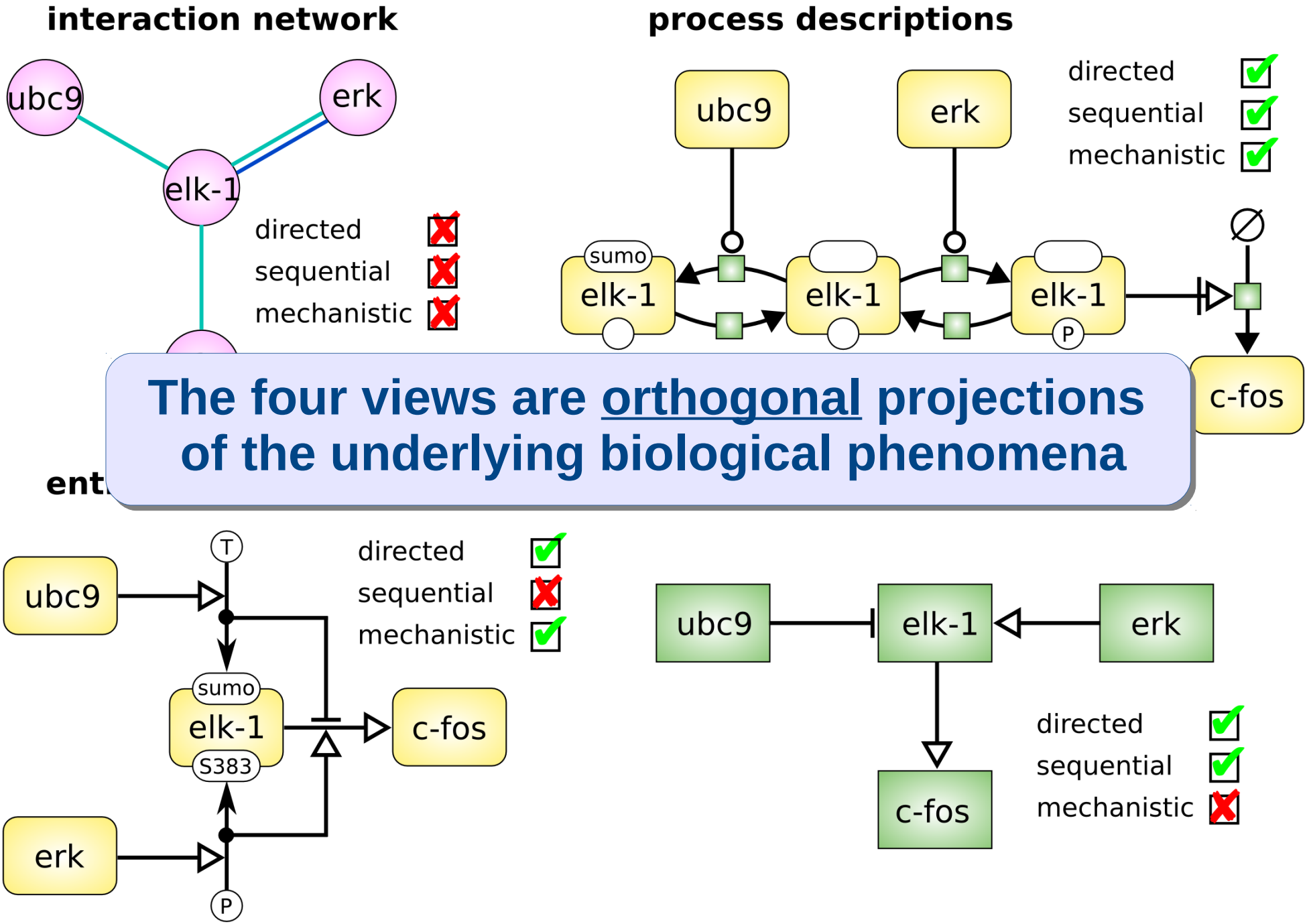
activity flows










interaction network
ubc9
erk
elk-1
directed
sequential
mechanistic
process descriptions
ubc9
erk
directed
sequential
mechanistic
sumo
elk-1
elk-1
elk-1
P
c-fos
The four views are orthogonal projections of the underlying biological phenomena
ubc9
T
directed
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mechanistic
sumo
elk-1
S383
c-fos
erk
P
ubc9
elk-1
erk
c-fos
directed
sequential
mechanistic

The Systems Biology Graphical Notation

http://sbgn.org/

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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.

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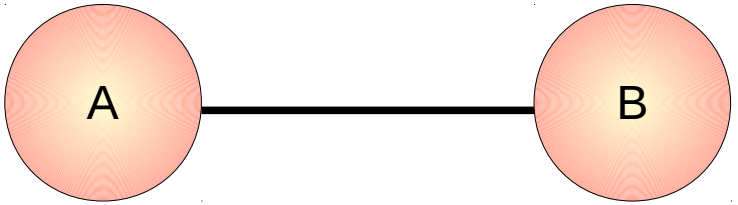
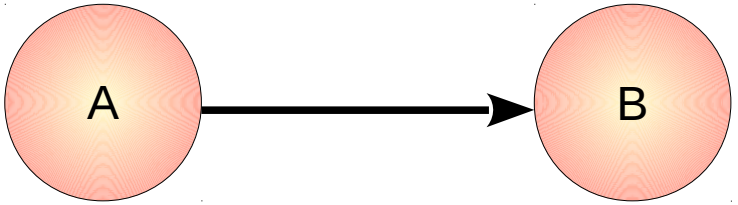
Undirected, directed, signed networks



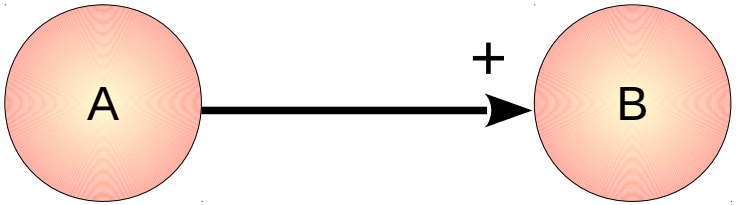
Undirected

"A interacts with B"



directed

"A influences B"



Signed

A influences positively B

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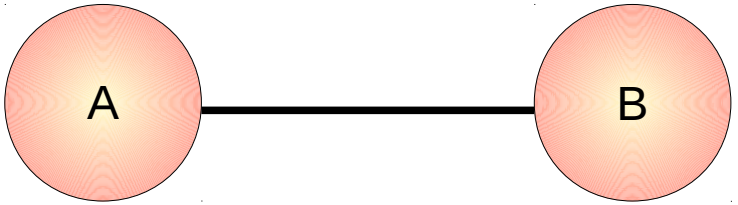
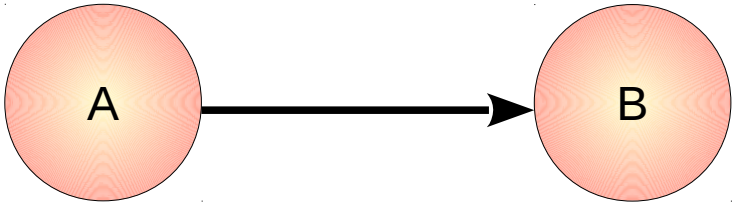
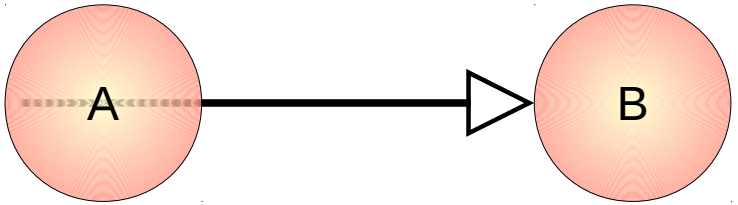
Undirected, directed, signed networks



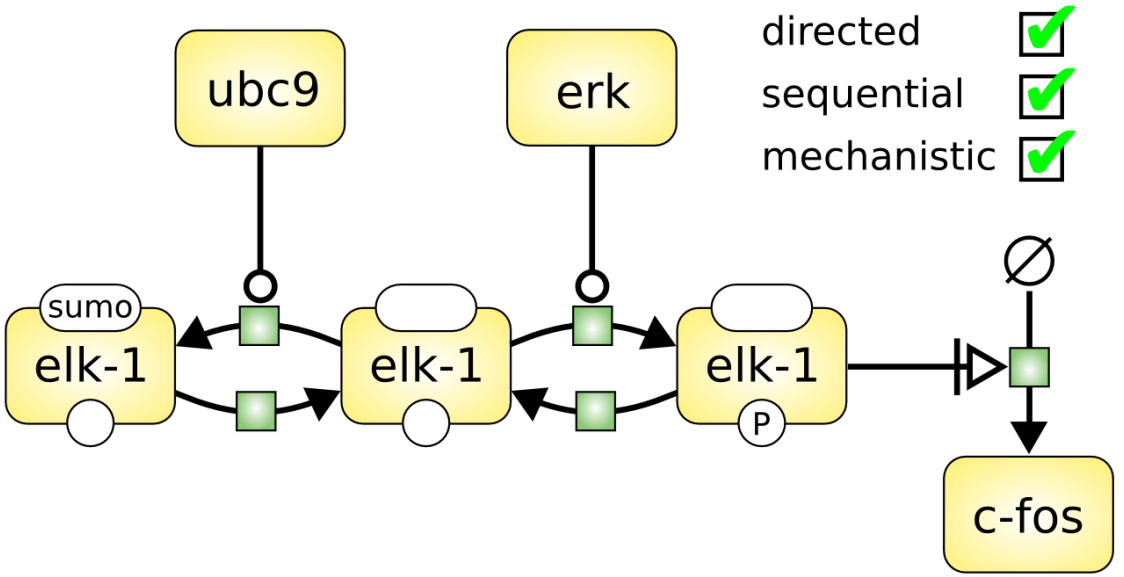




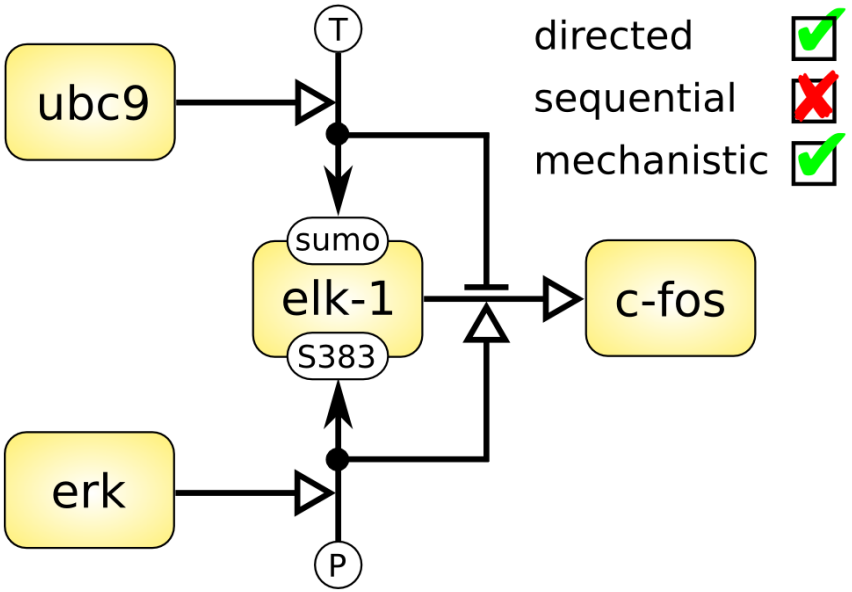
A signed interaction network
is equivalent to an activity flow

One notation – three languages

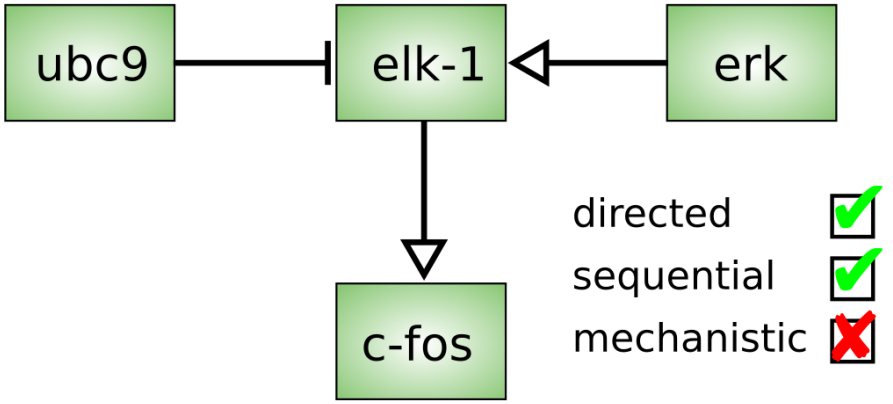
process descriptions



entity relationships

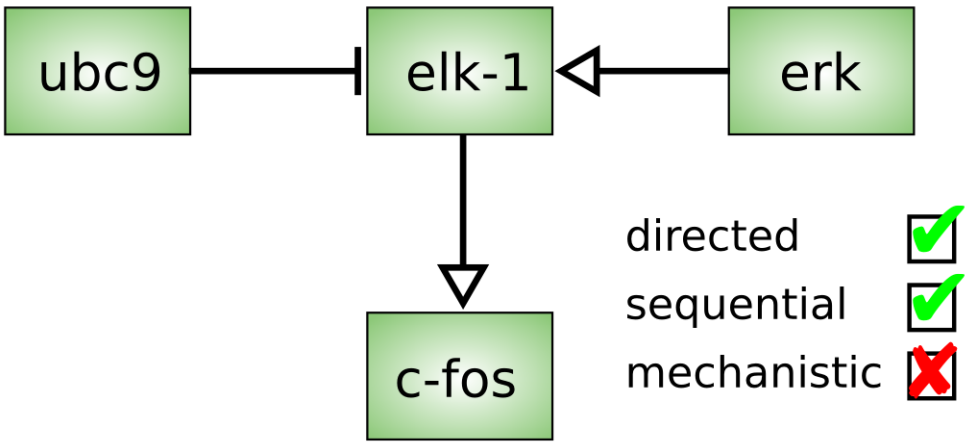


activity flows



Functional descriptions: the Activity Flows

- Logical modelling
- Signalling pathways, gene regulatory networks



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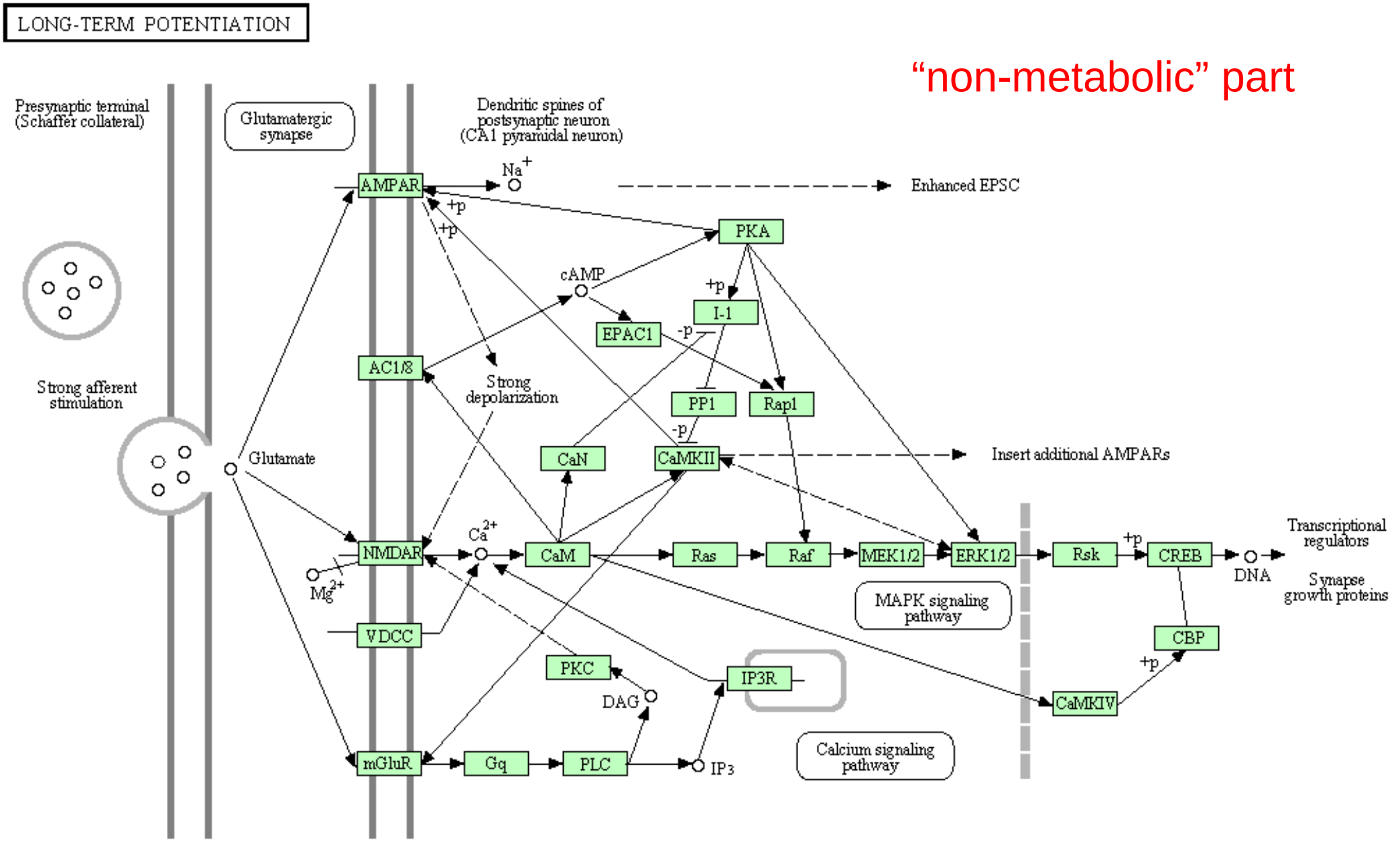
http://www.genome.jp/kegg/pathway.html



"non-metabolic" part

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

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Articles by Ma'ayan, A.
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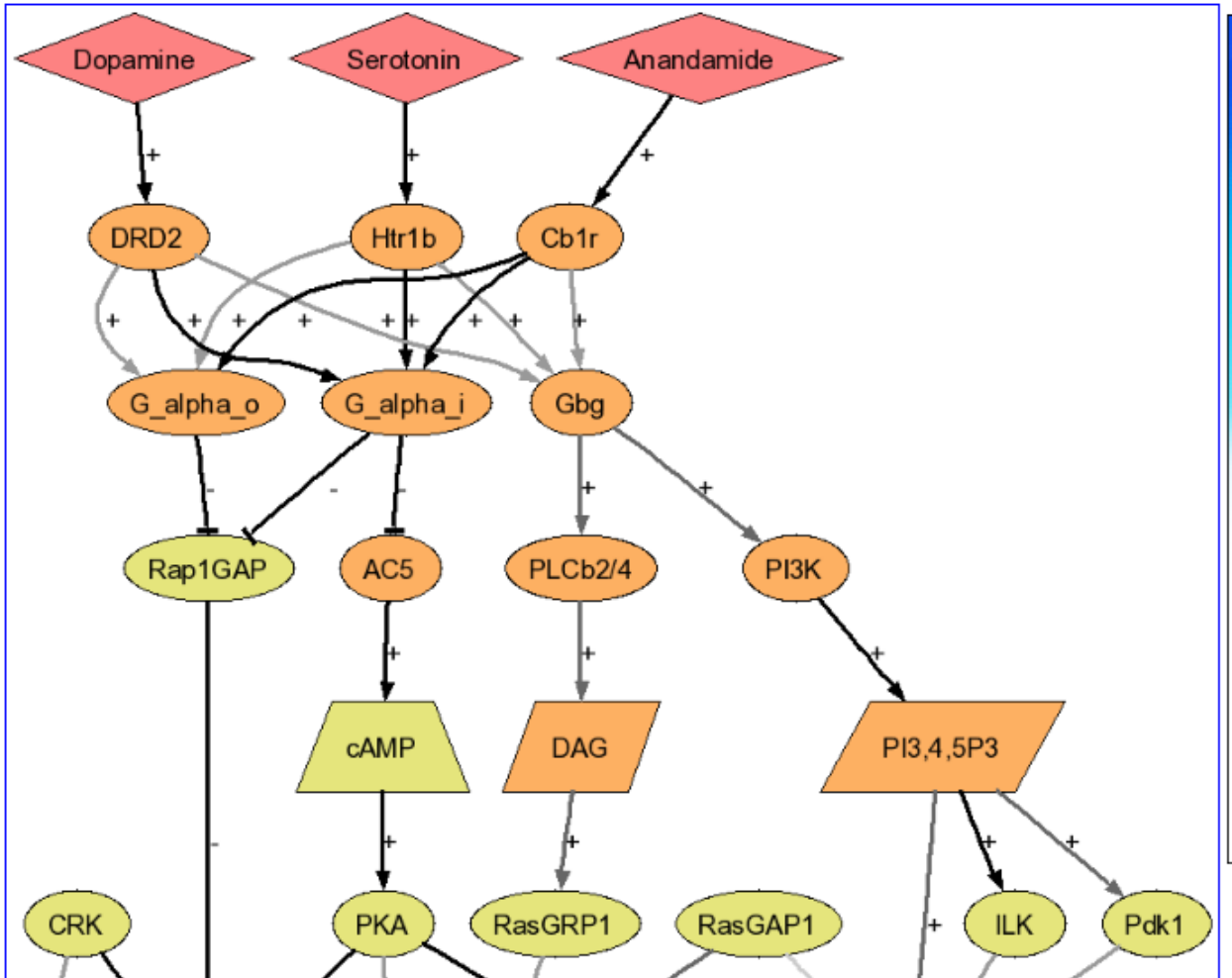
Help & Feedback
Database of Cell Signaling Help
Feedback
My Science Signaling
My Folders
My Alerts
My Display Settings
My Saved Searches
My Directory Information
Sign In

Pathway Information

Neuro2A Differentiation by G alpha i/o Pathway

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

Pathway
View Connections Map Legend
Get SVG Pathway Image



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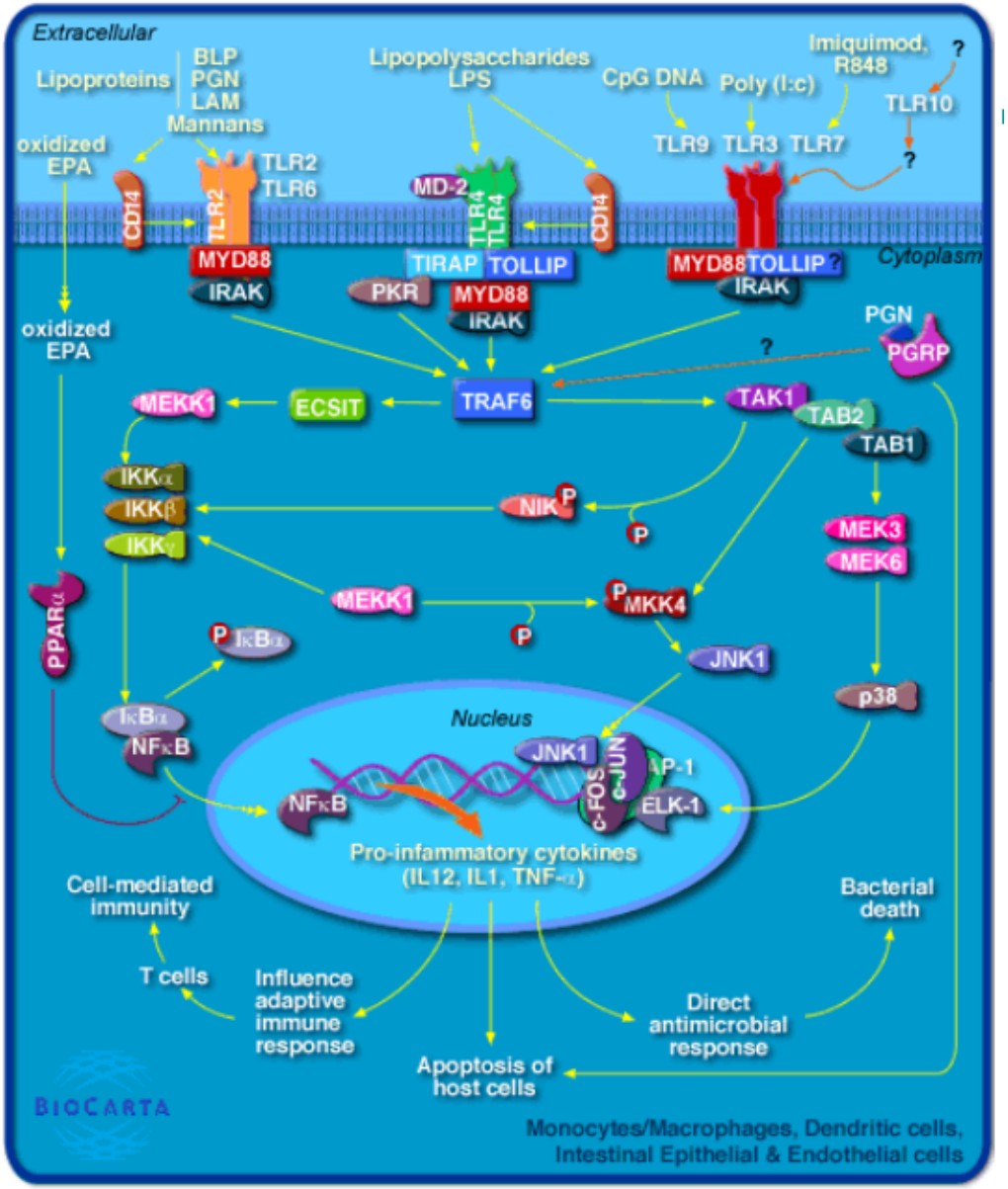
http://cgap.nci.nih.gov/Pathways/BioCarta.org



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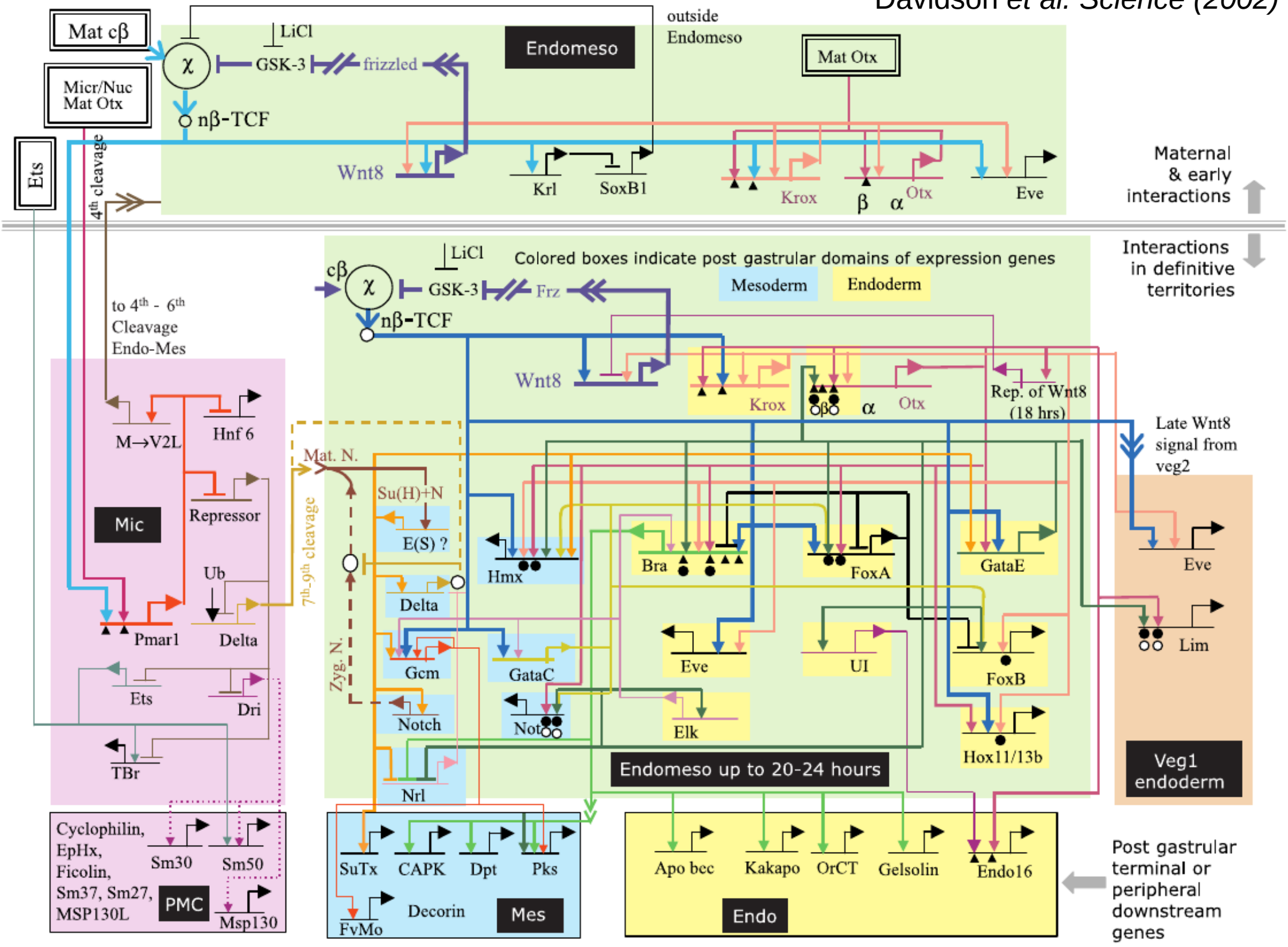
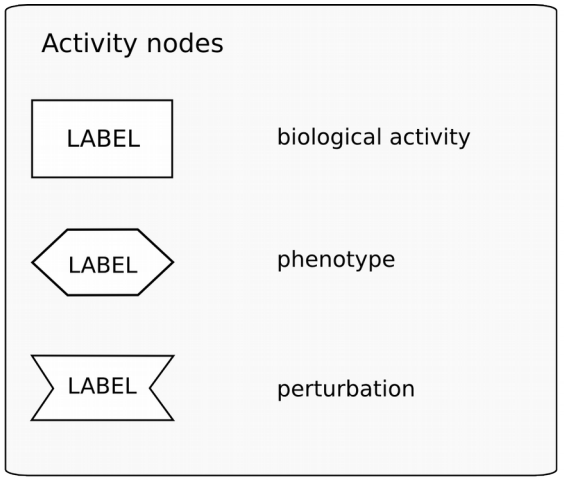
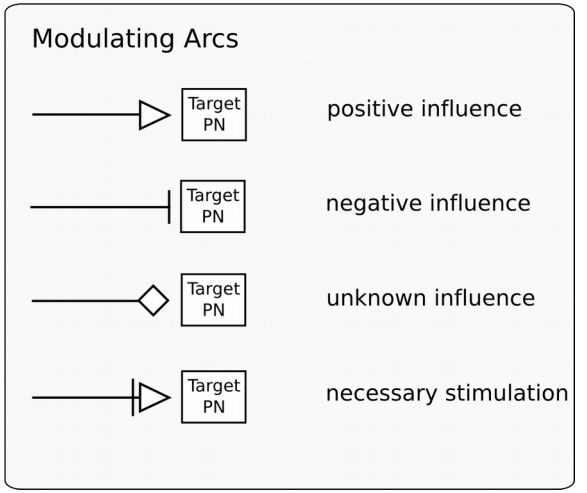
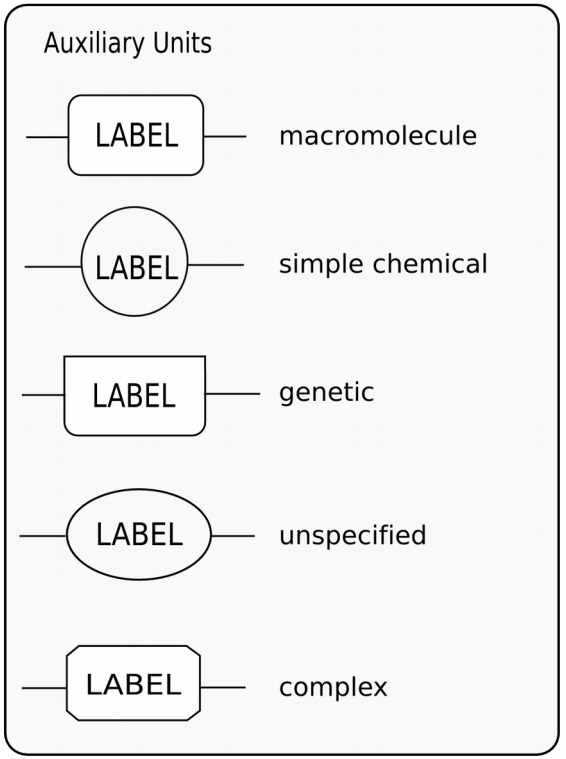
Davidson *et al. Science (2002)*

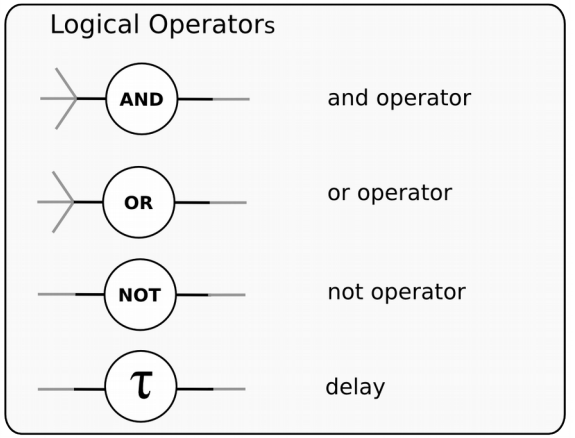


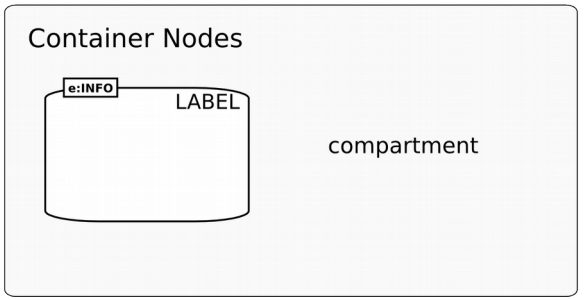
SBGN Activity Flows L1 reference card











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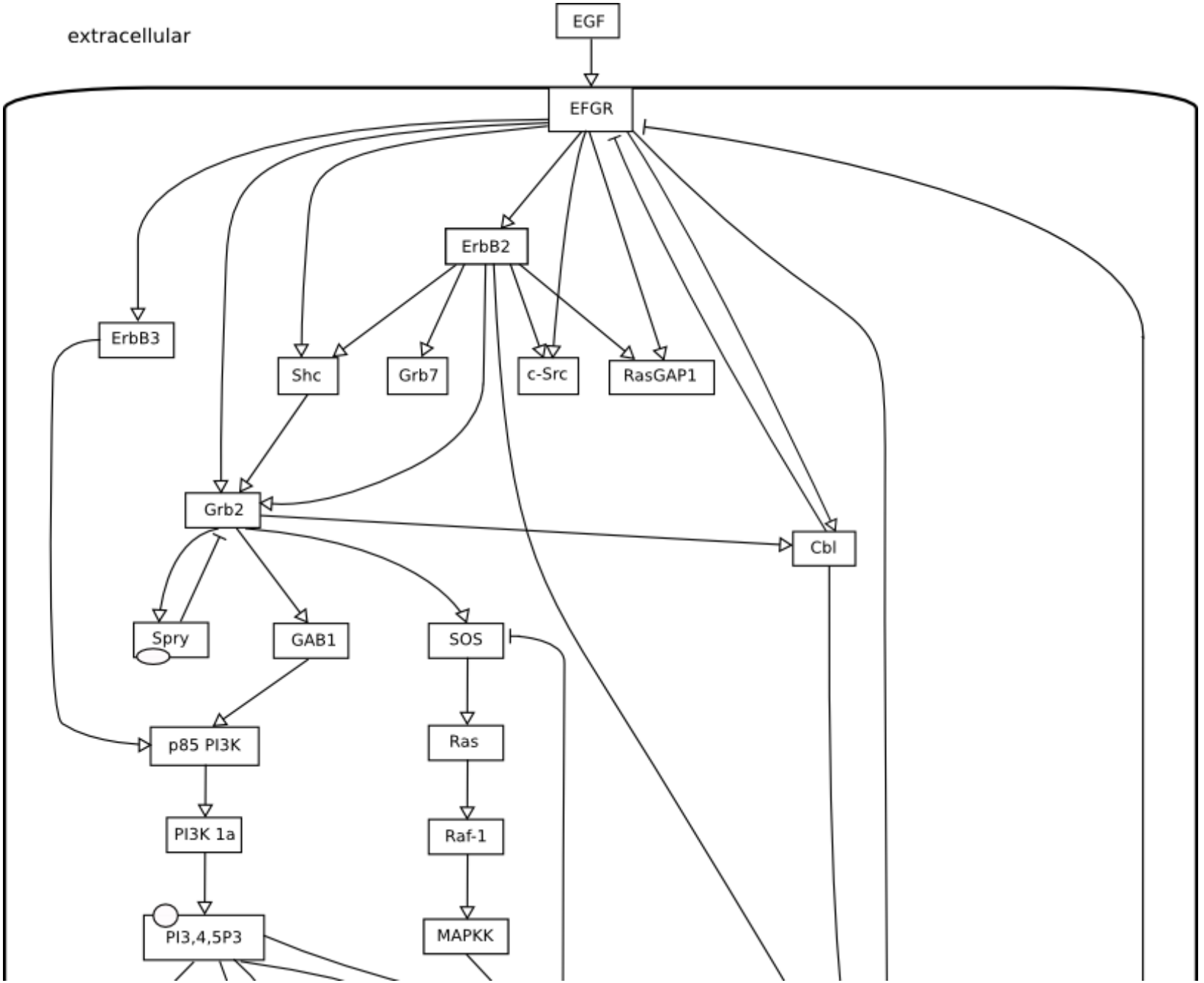
Example of Activity Flow map



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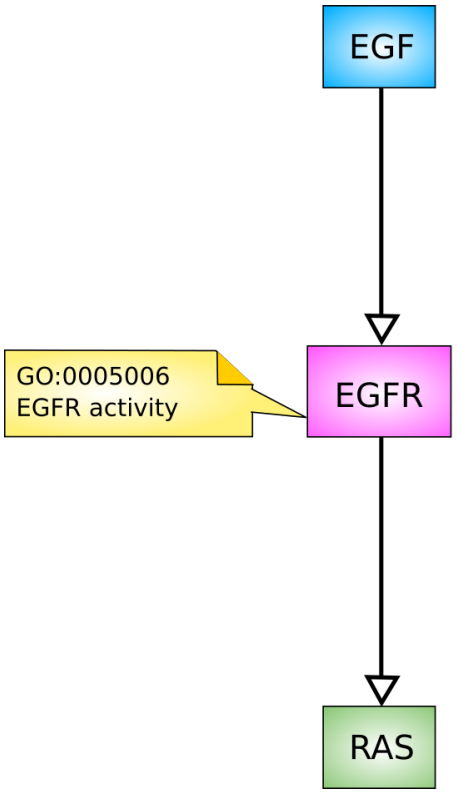
TIMTOWTDI
(There Is More Than One Way To Do It)



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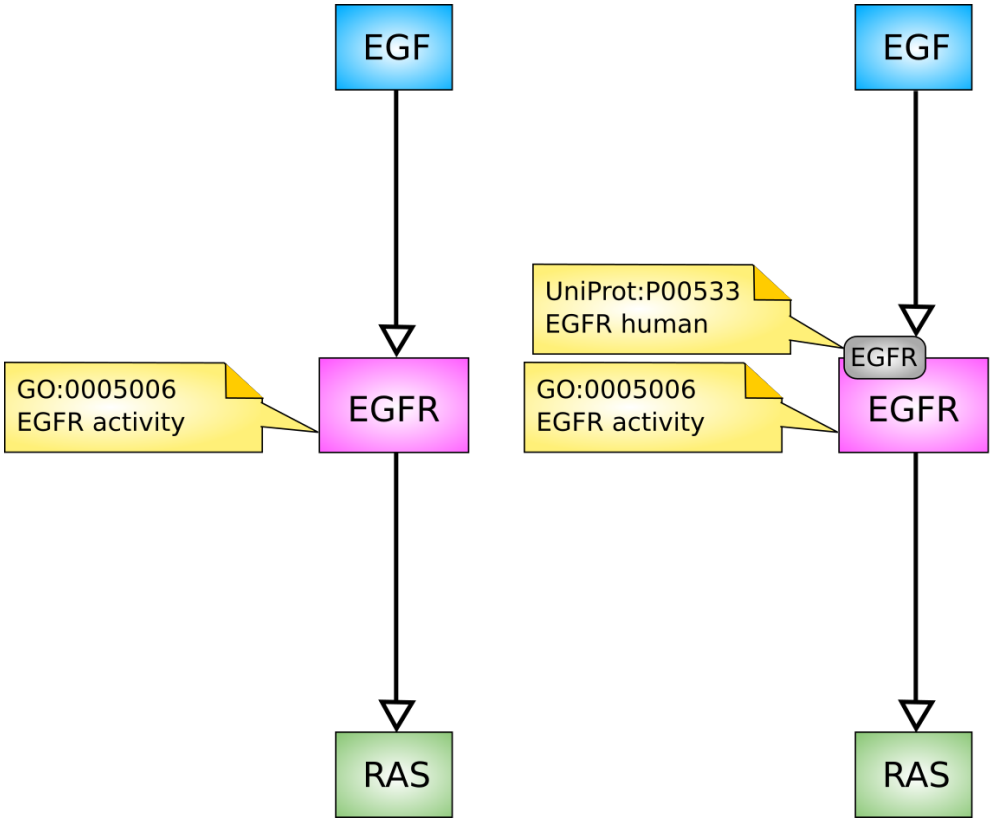

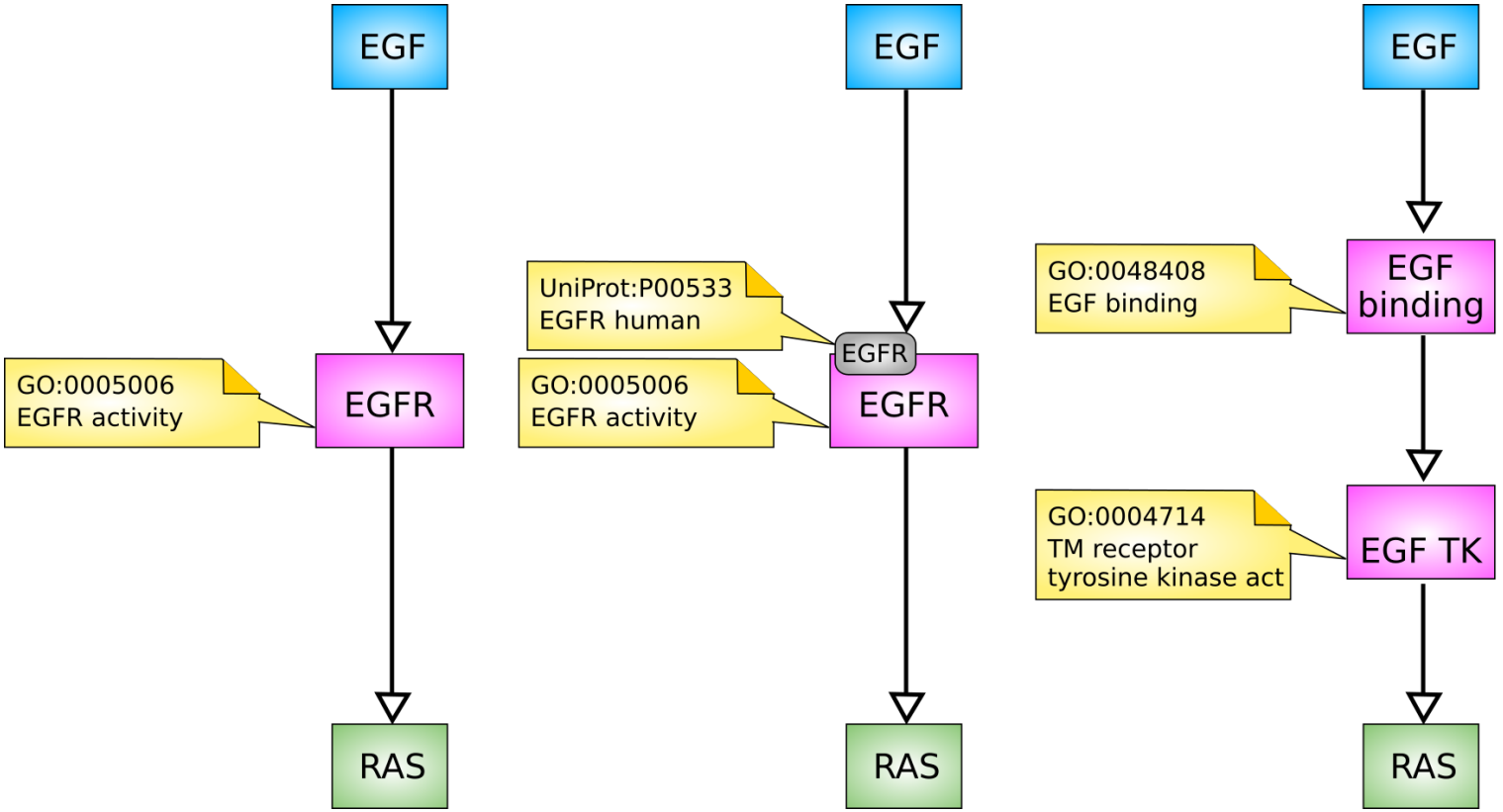

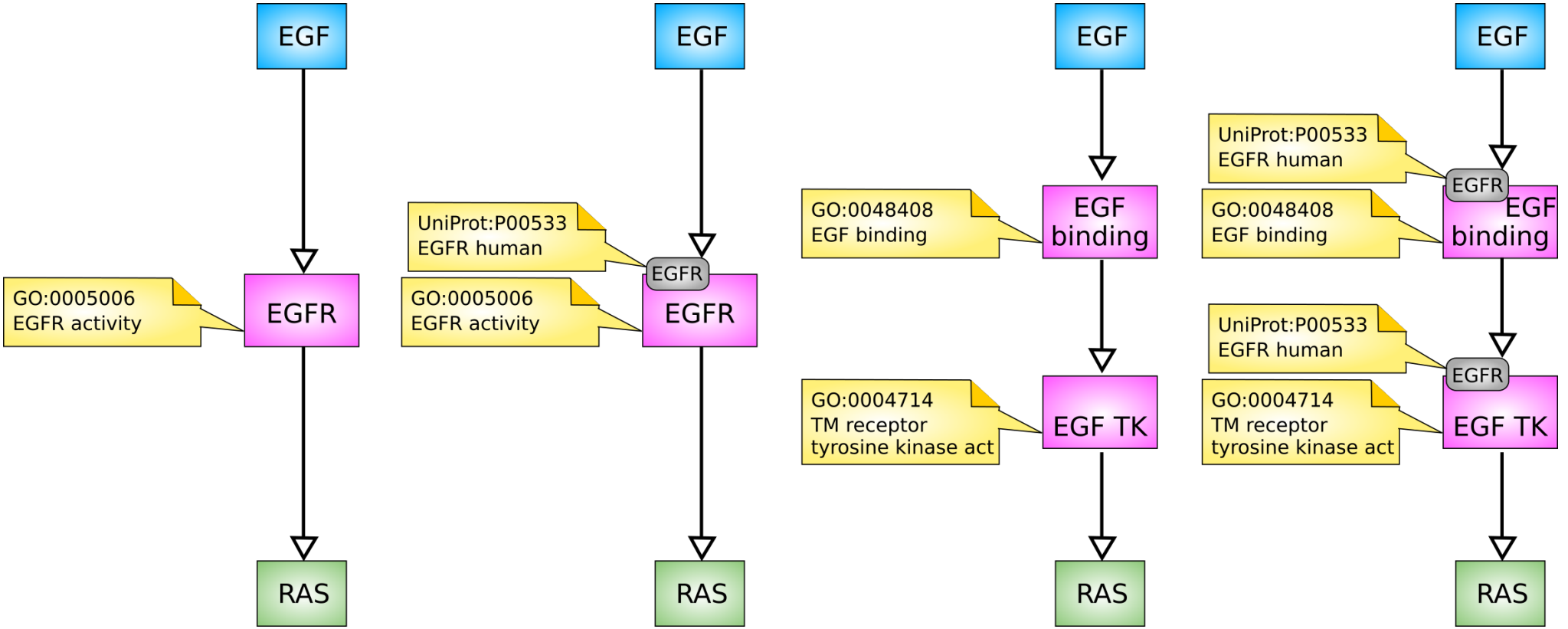

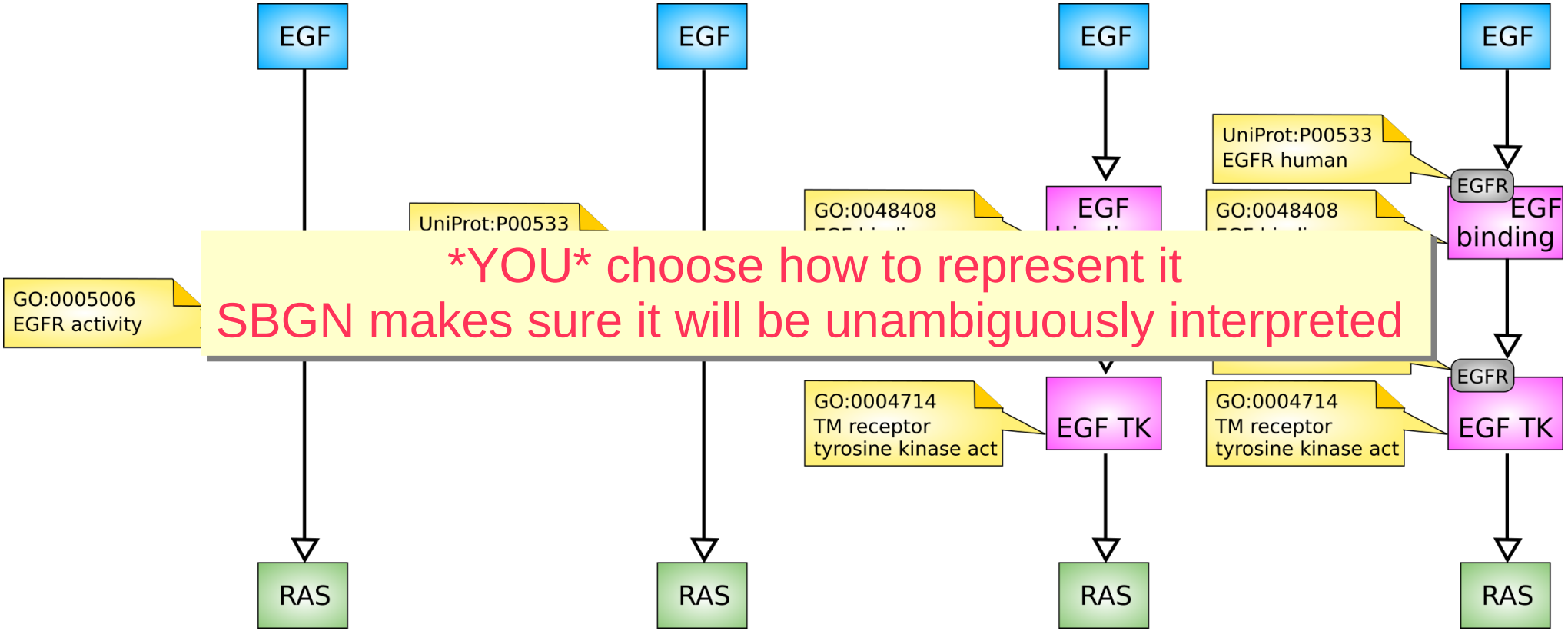

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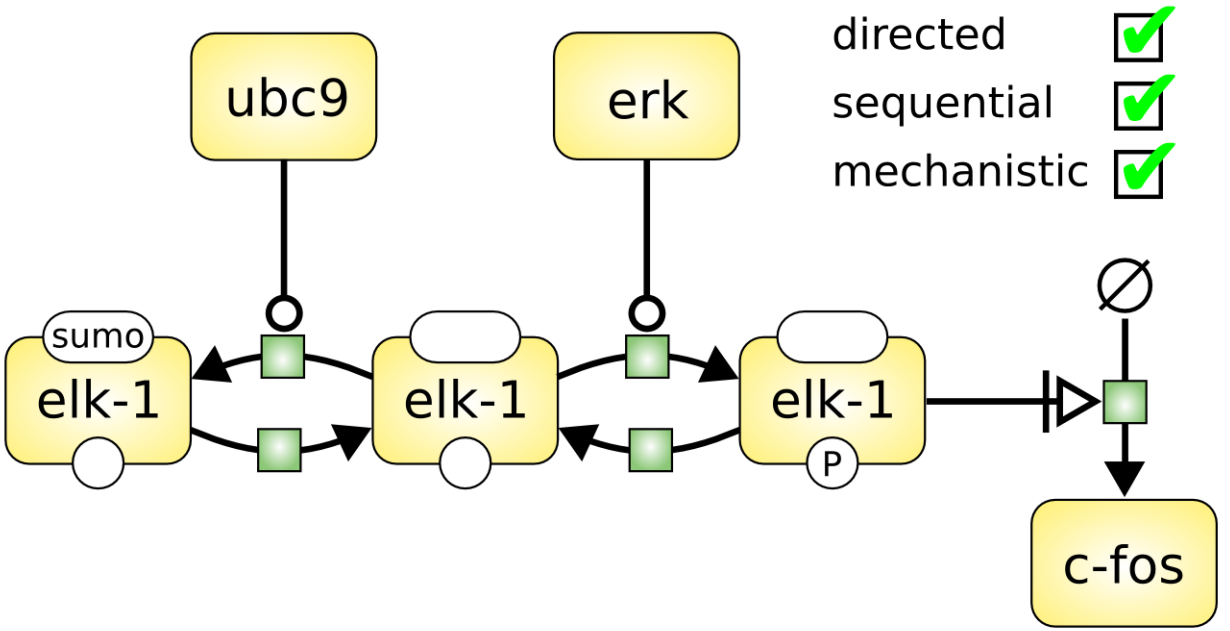
Puting in mechanisms: the Process Descriptions



- Process modelling
- Biochemistry, Metabolic networks
- Generally within "**closed world**"
- Subjected to combinatorial explosion

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Open world

Anything not explicitly stated is unknown

Failure to observe does not imply non-existence

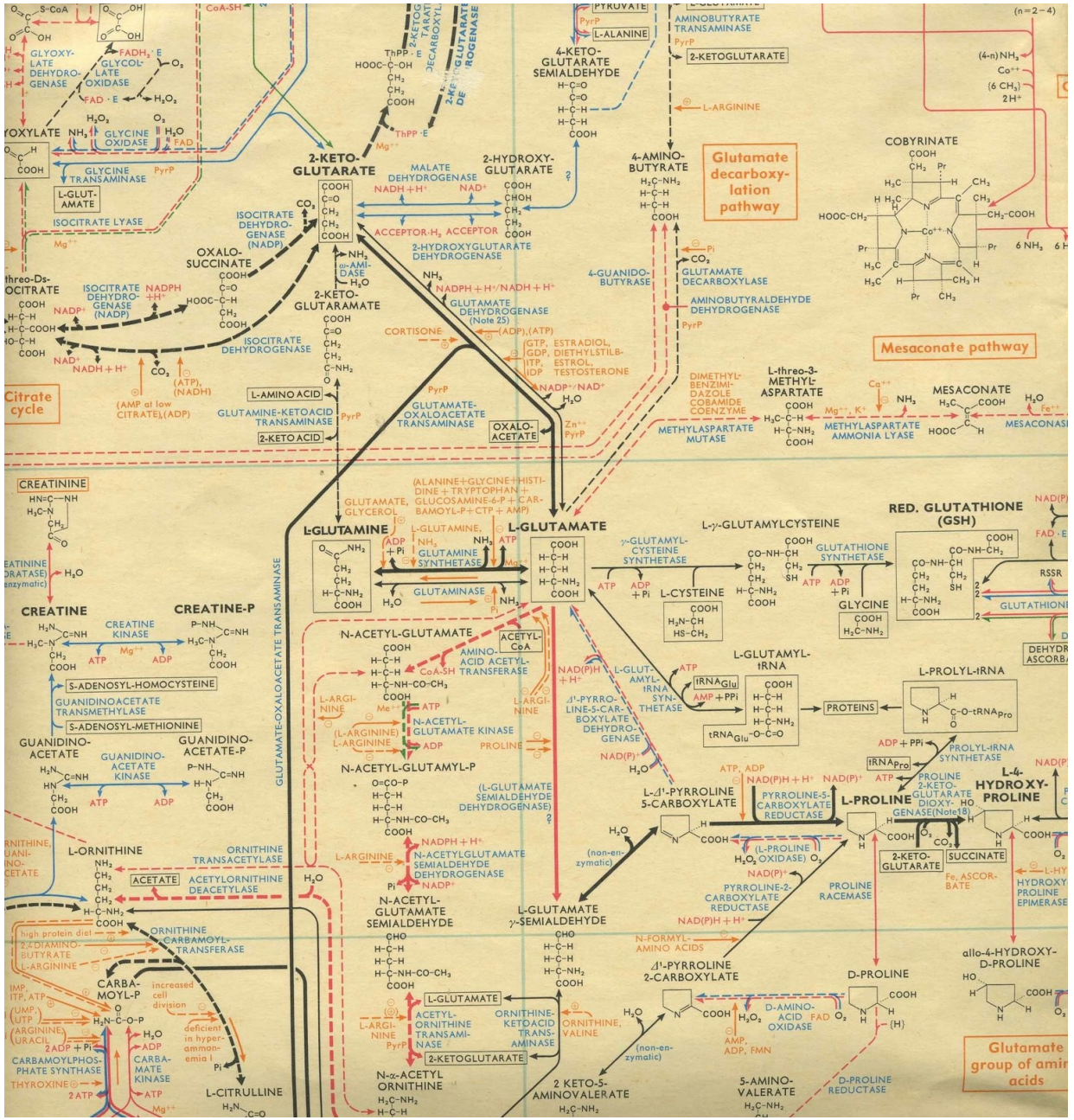
New pieces of knowledge do not affect prior pieces

Closed world

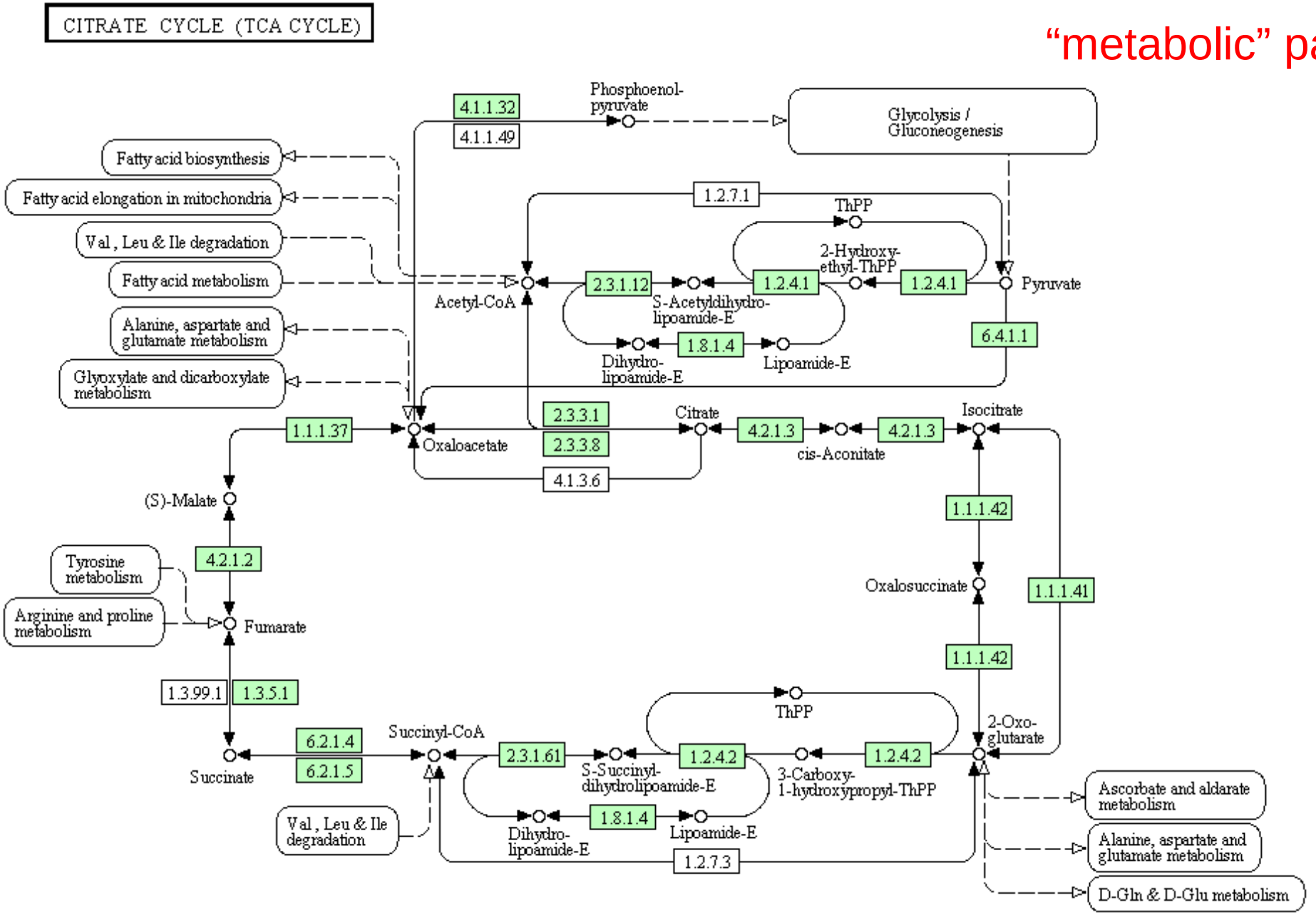
Anything not explicitly stated does not exist

Failure to observe implies non-existence

New pieces of knowledge might change the meaning of prior pieces


Citrate cycle
Glutamate decarboxylation pathway
Mesaconate pathway
Glutamate group of amino acids
2-KETO-GLUTARATE
L-GLUTAMINE
L-GLUTAMATE
N-ACETYL-GLUTAMATE
N-ACETYL-GLUTAMYL-P
N-ACETYL-GLUTAMATE SEMIALDEHYDE
L-GLUTAMATE γ-SEMIALDEHYDE
L-ORNITHINE
CARBAMOYL-P
L-CITRULLINE
CREATINE
CREATINE-P
CREATININE
GUANIDINOACETATE
GUANIDINOACETATE-P
L-GLUTAMYL-tRNA
PROTEINS
L-PROLYL-tRNA
L-Δ1-PYRROLINE 5-CARBOXYLATE
L-PROLINE
L-4-HYDROXYPROLINE
D-PROLINE
allo-4-HYDROXY-D-PROLINE
Δ1-PYRROLINE 2-CARBOXYLATE
5-AMINOVALERATE
2 KETO-5-AMINOVALERATE
N-α-ACETYL ORNITHINE
4-AMINOBUTYRATE
4-KETO-GLUTARATE SEMIALDEHYDE
2-HYDROXYGLUTARATE
OXALOACETATE
SUCCINATE
L-γ-GLUTAMYLCYSTEINE
RED. GLUTATHIONE (GSH)
L-CYSTEINE
GLYCINE
COBYRINATE
MESACONATE
L-threo-3-METHYLASPARTATE
PYRUVATE
2-KETOGLUTARATE
L-ALANINE
L-ARGININE
ACETATE
GLUTAMATE-OXALOACETATE TRANSAMINASE

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



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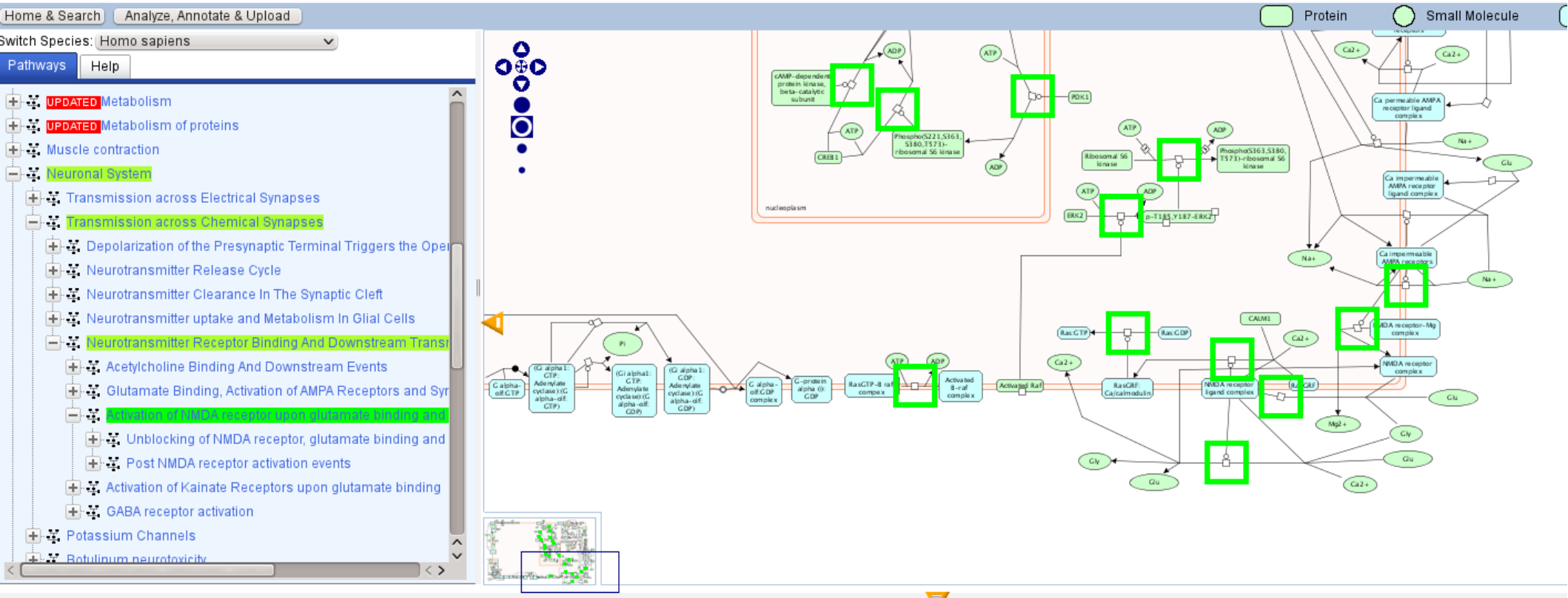
http://www.reactome.org



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.

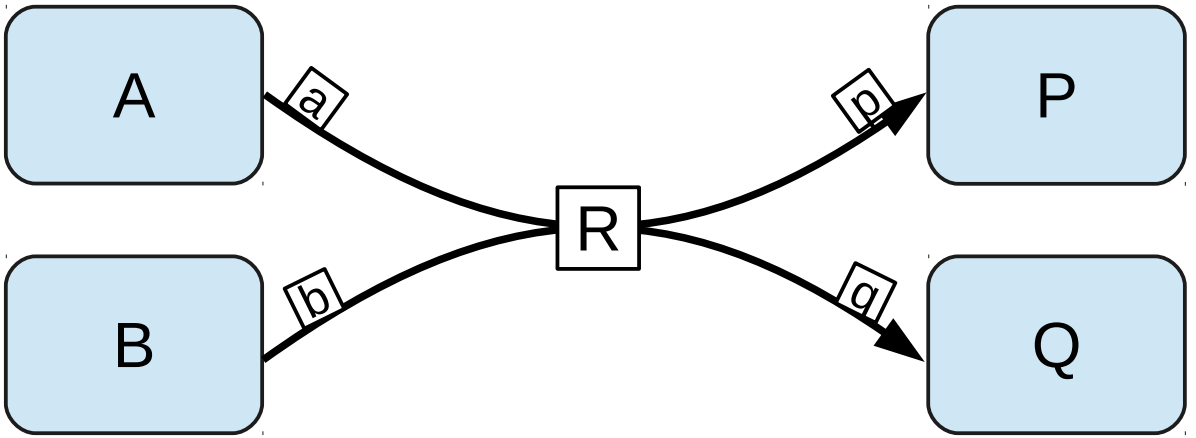
Organism	Homo sapiens
Cellular compartment	extracellular region GO plasma membrane GO cytoplasm GO nucleoplasm GO

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



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

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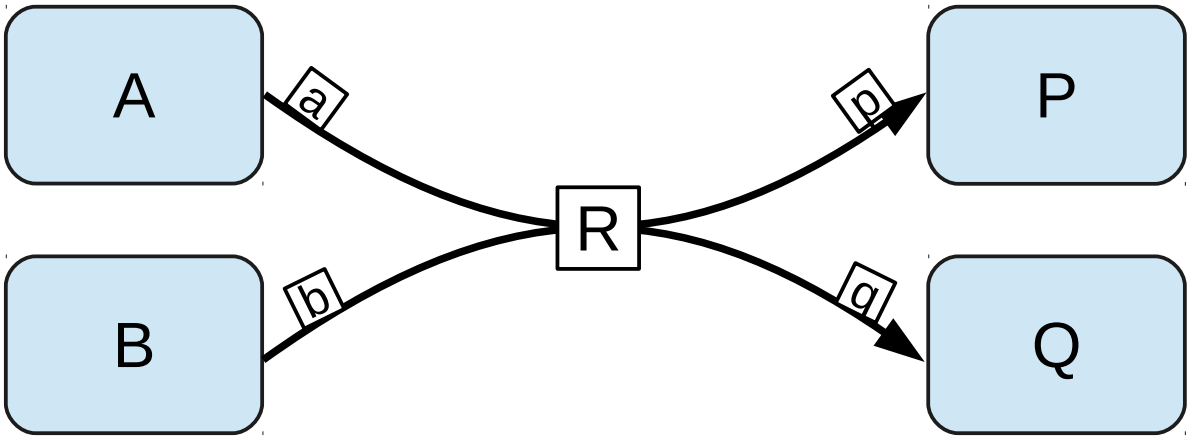
A biochemical reaction is a process



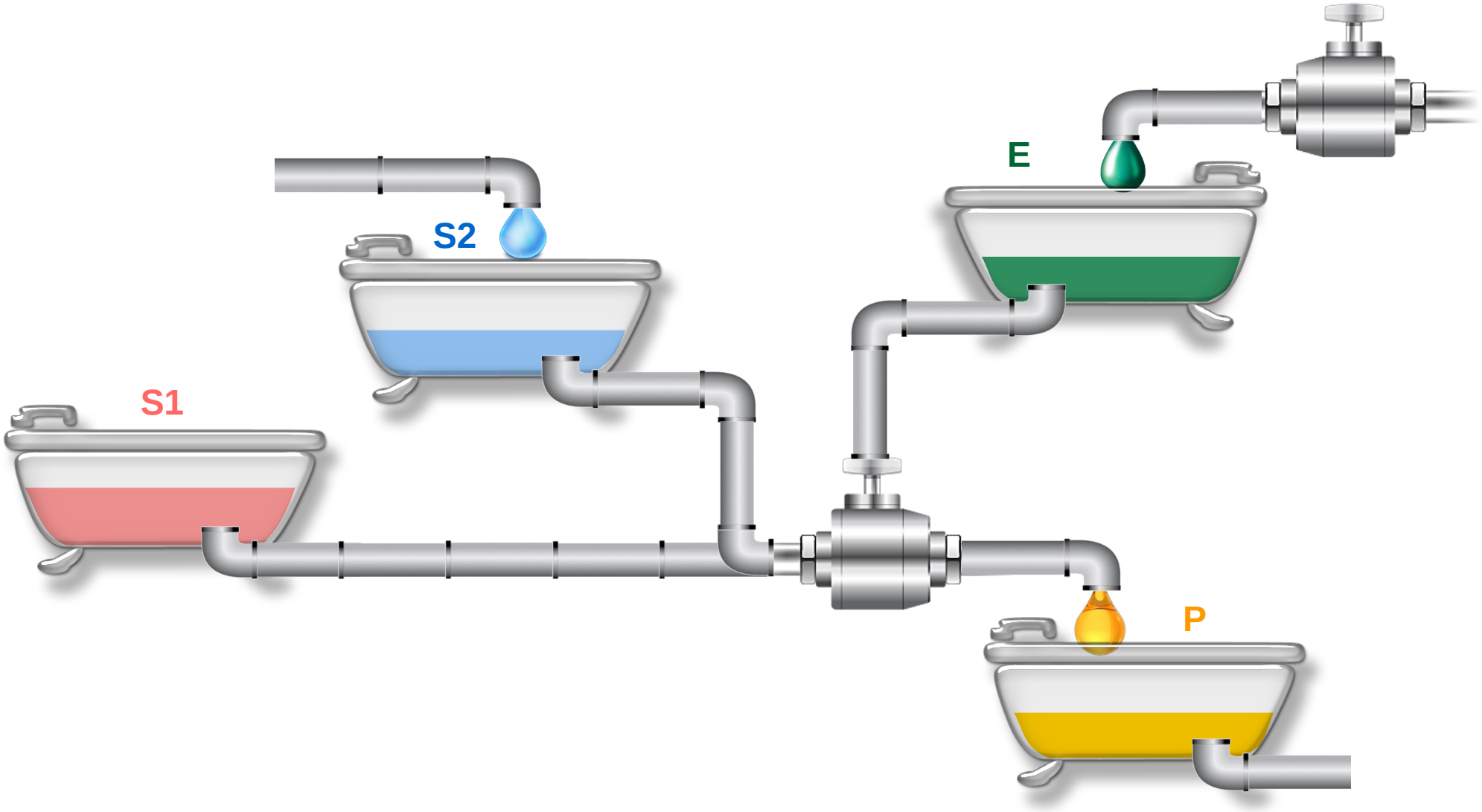
substances A and B are consumed by reaction R that produces substances P and Q

→ 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

Bipartite graphs: 2 kinds of nodes interacting through each other

Process Descriptions can be viewed as pipelines



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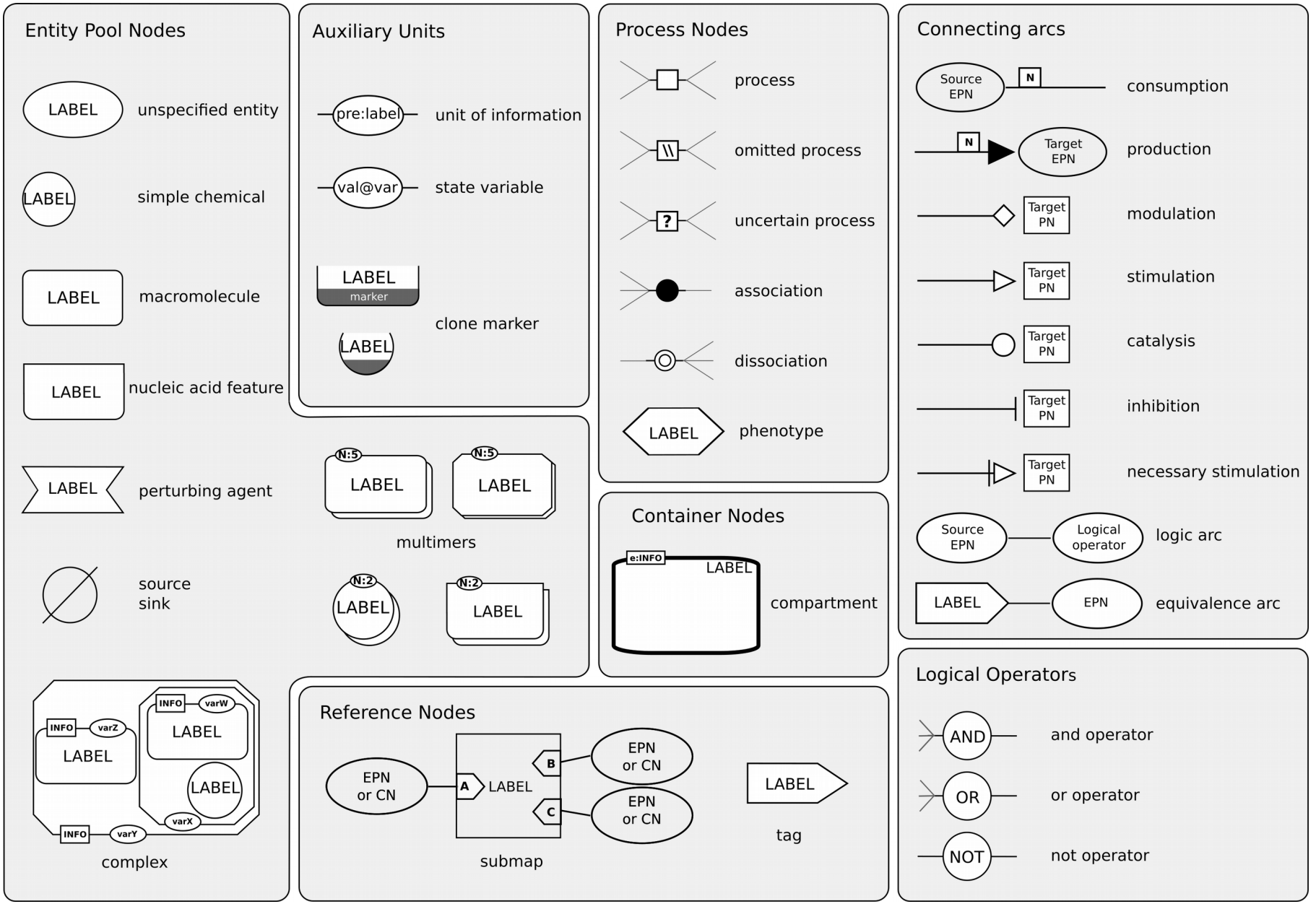
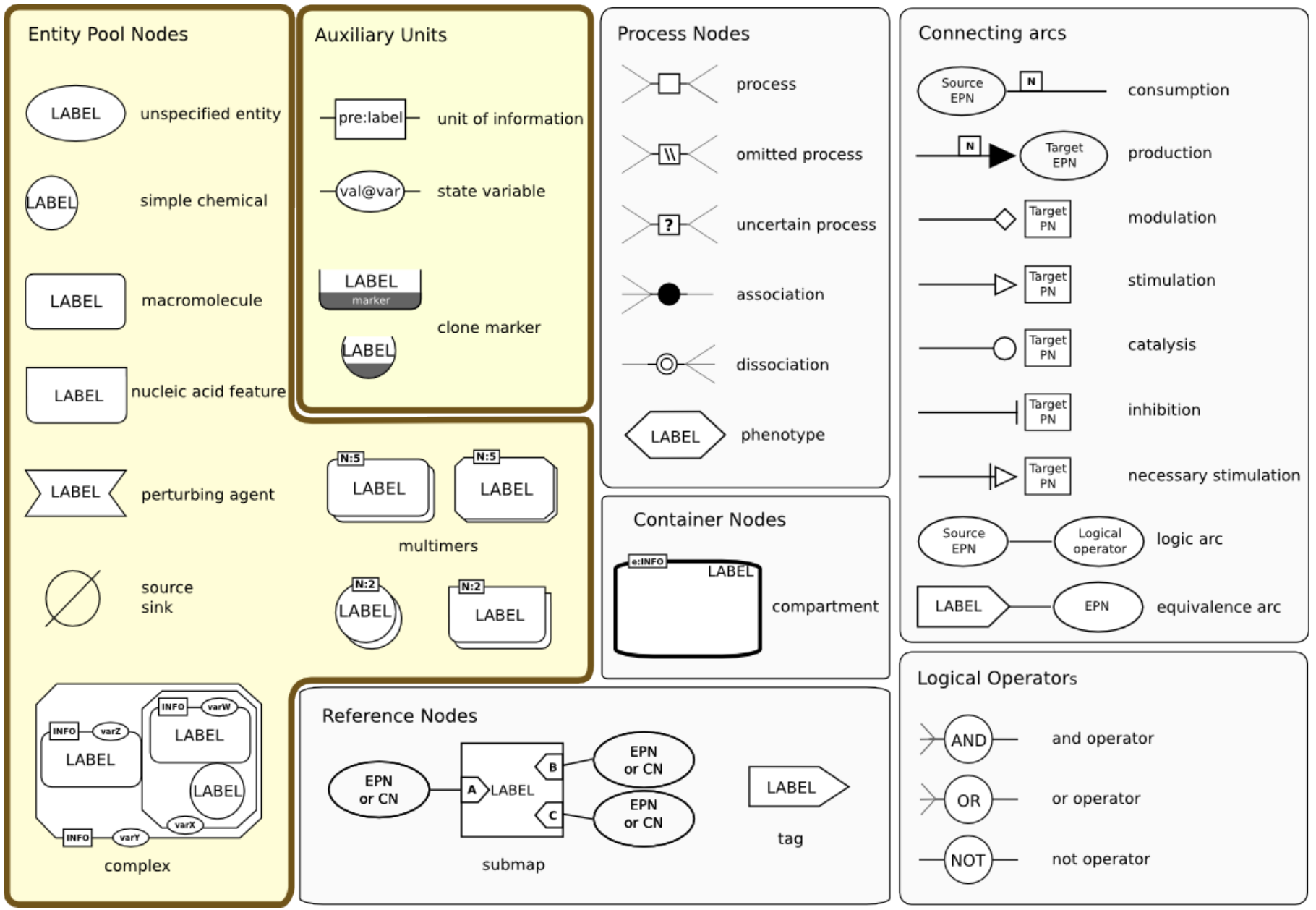
SBGN Process Diagram L1 reference card



Entity Pool Nodes



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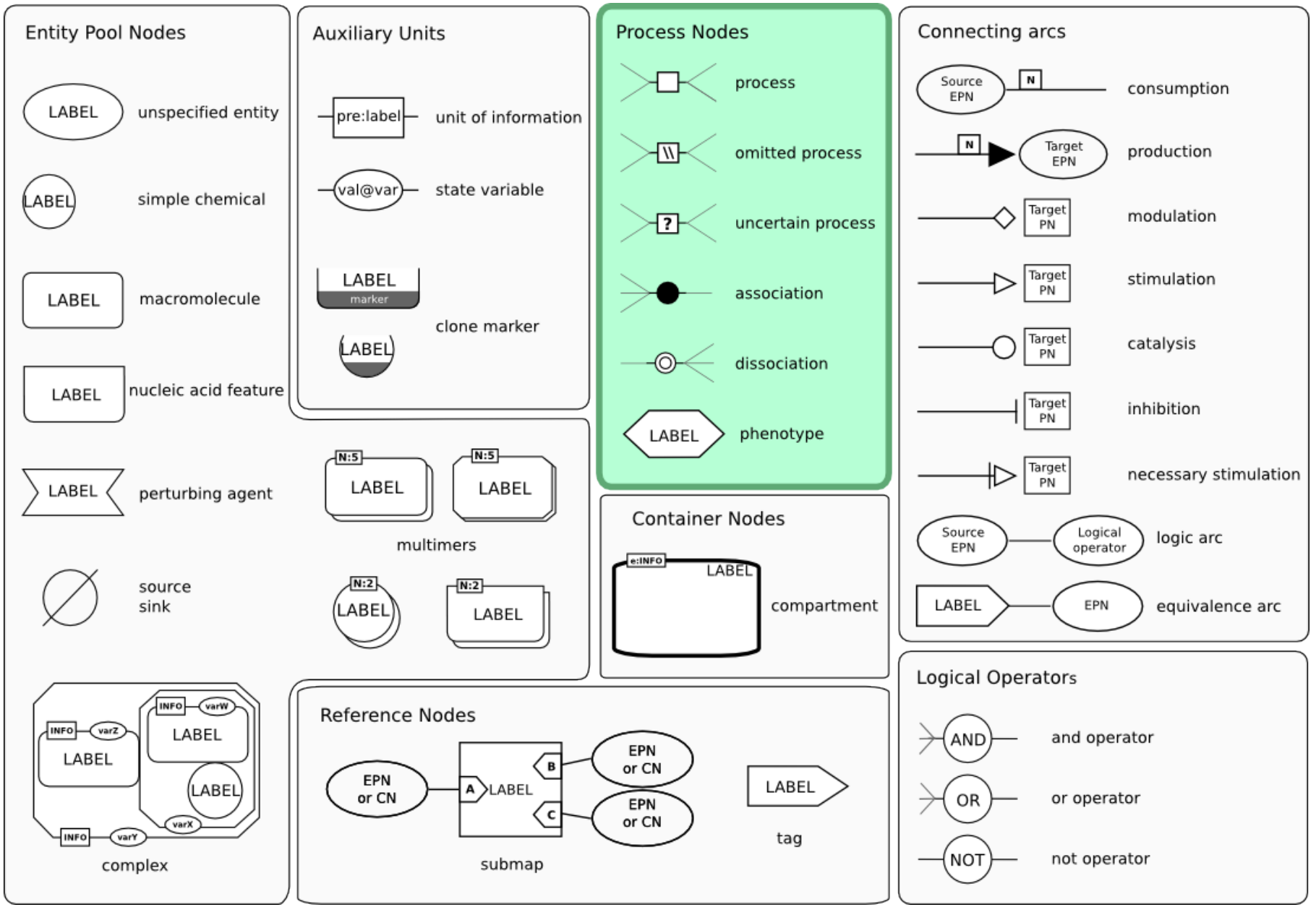
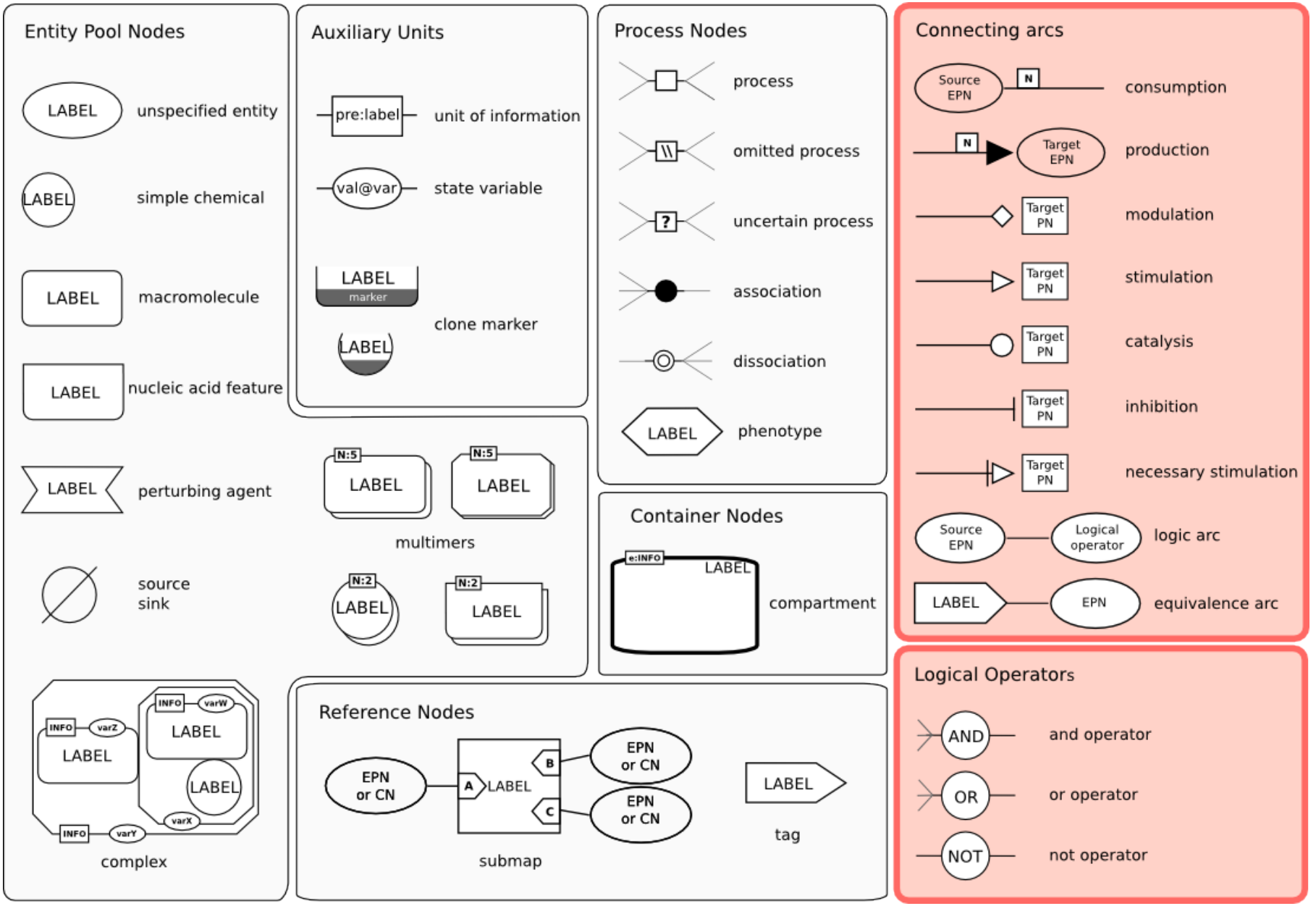
Process Nodes



Connecting arcs



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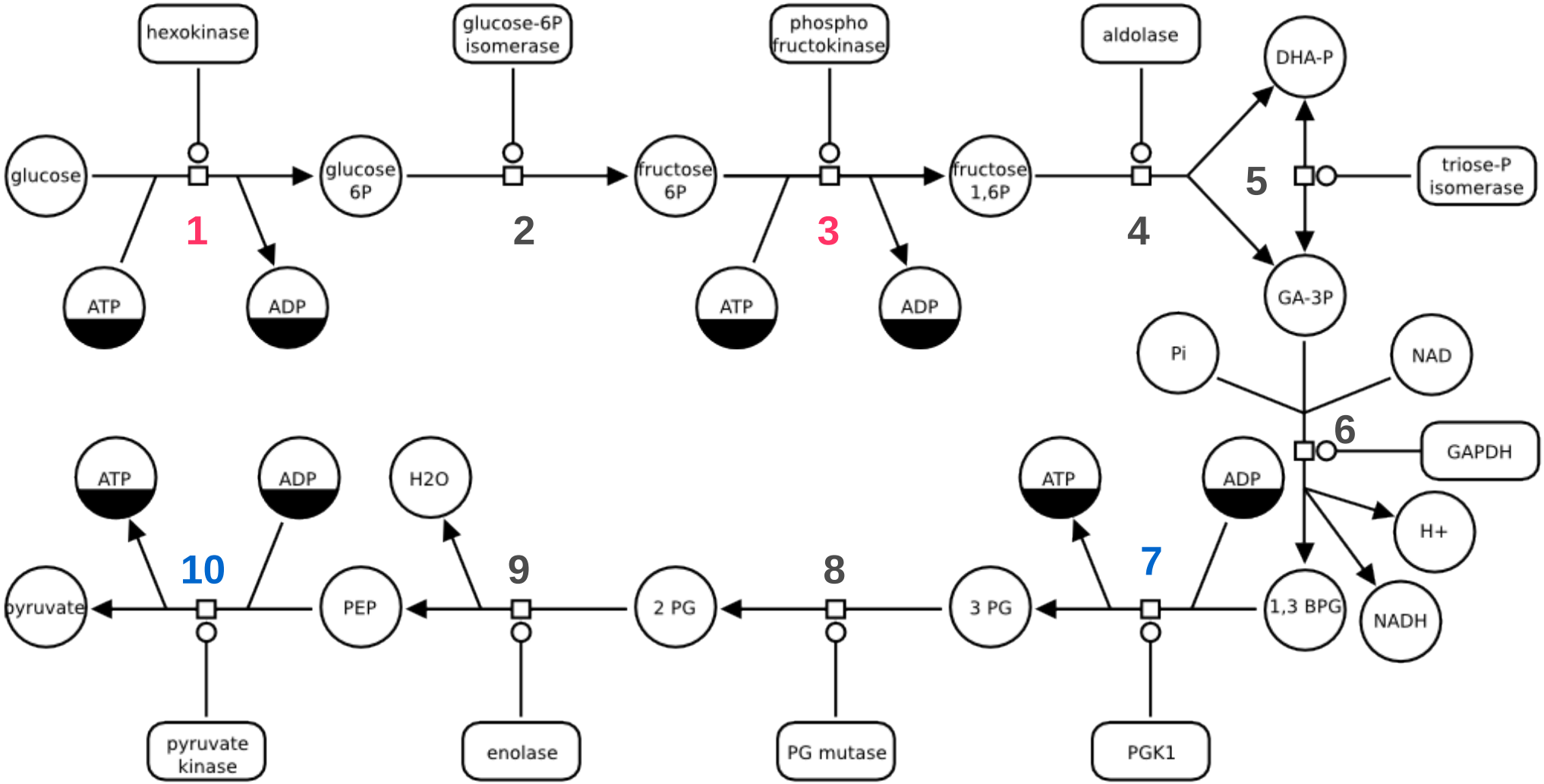

ATP is consumed by processes 1 and 3, and produced by processes 7 and 10

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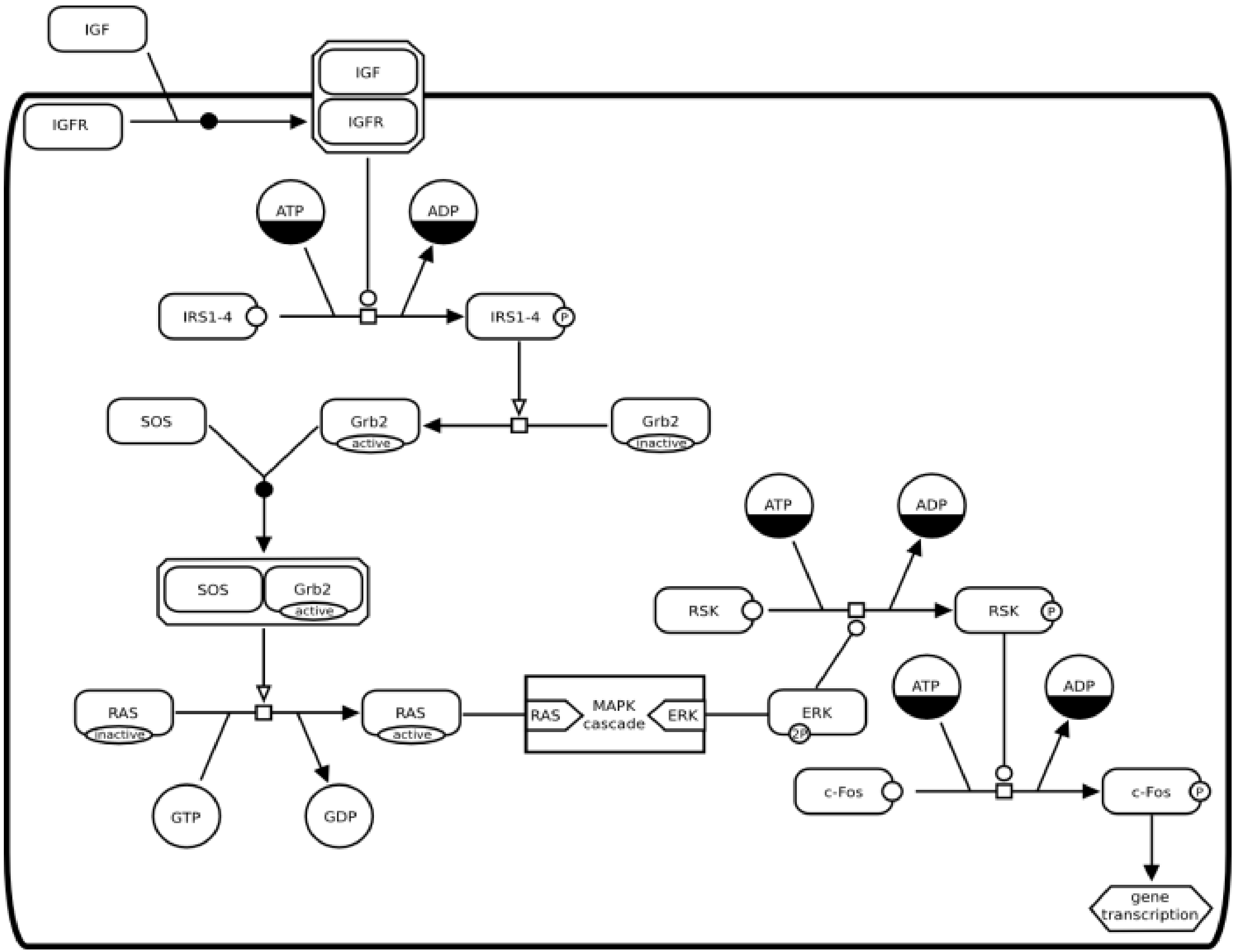
Signalling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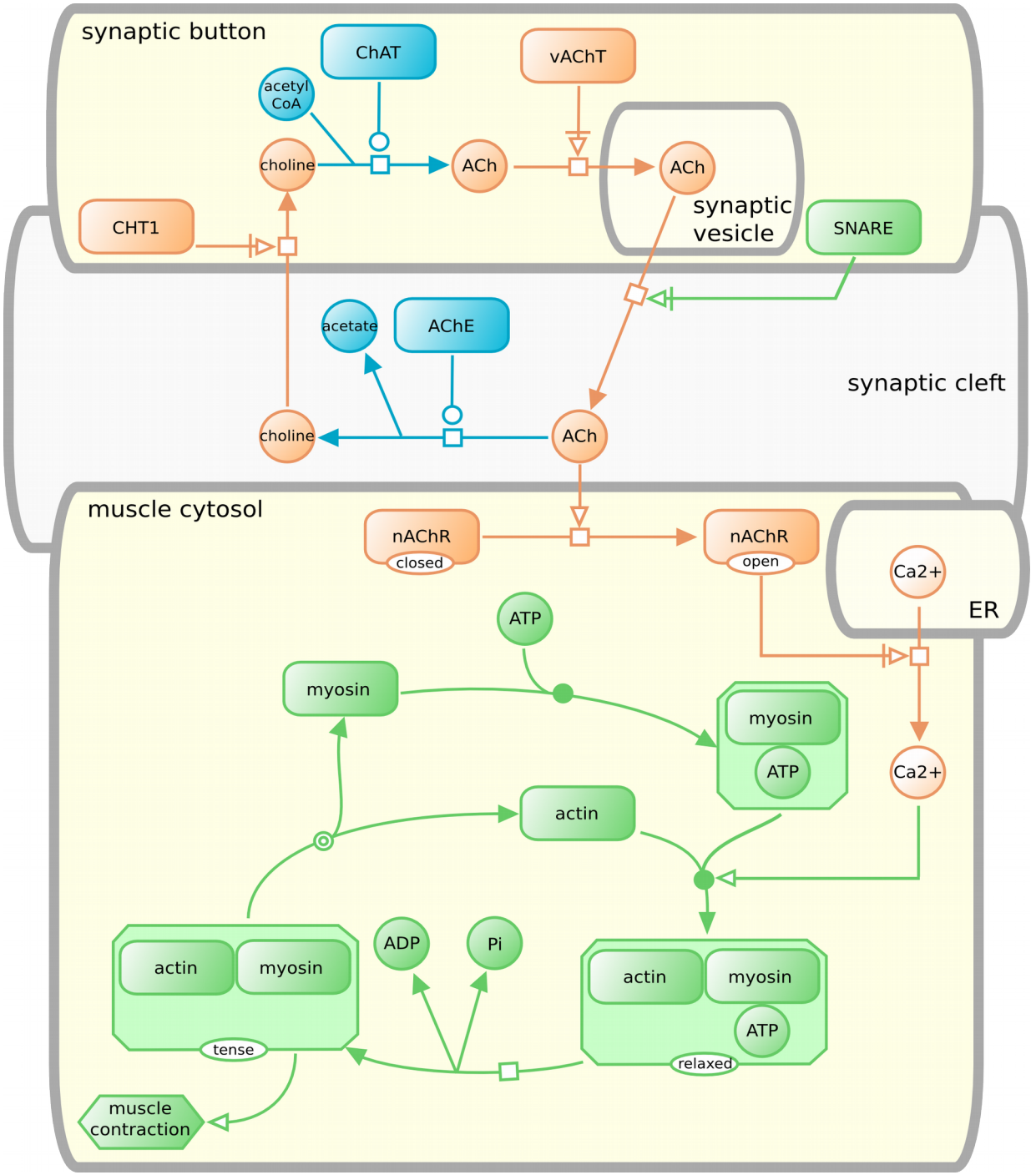
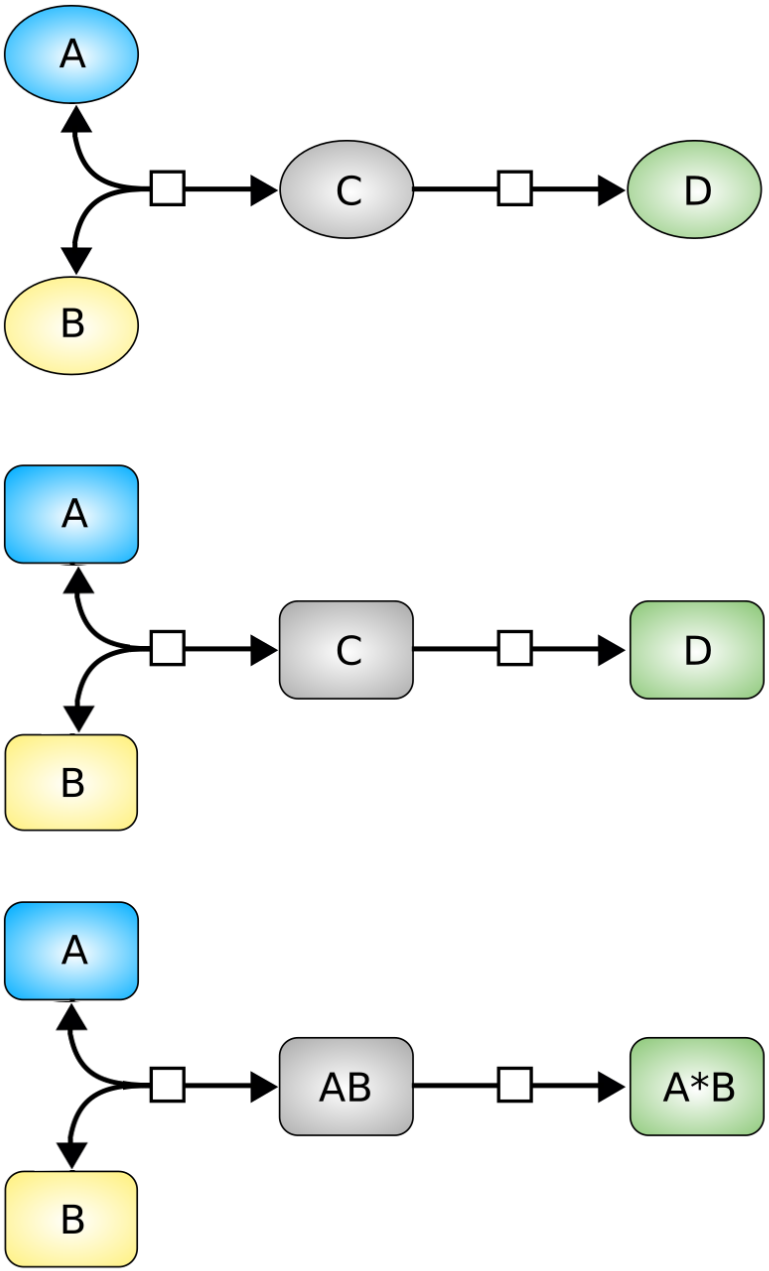
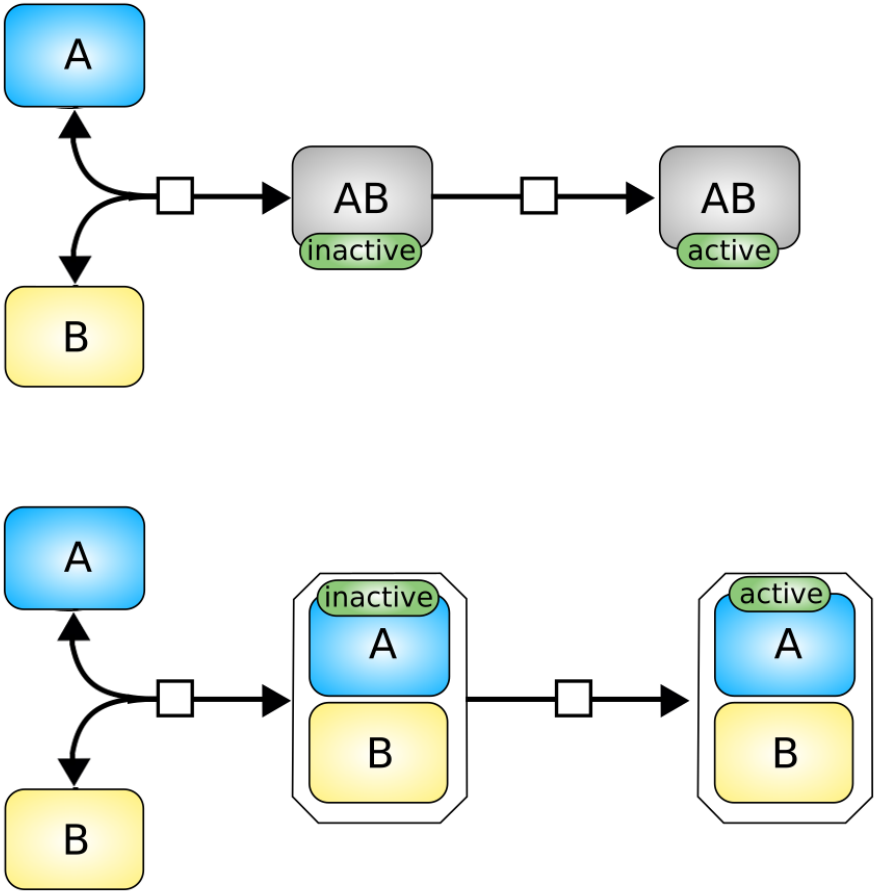
IGFR
IGF
IGFR
ATP
ADP
IRS1-4
IRS1-4
P
SOS
Grb2
active
Grb2
inactive
SOS
Grb2
active
ATP
ADP
RSK
RSK
P
RAS
inactive
RAS
active
RAS
MAPK
cascade
ERK
ERK
2P
ATP
ADP
c-Fos
c-Fos
P
GTP
GDP
gene
transcription

Multicellular



Variable granularity





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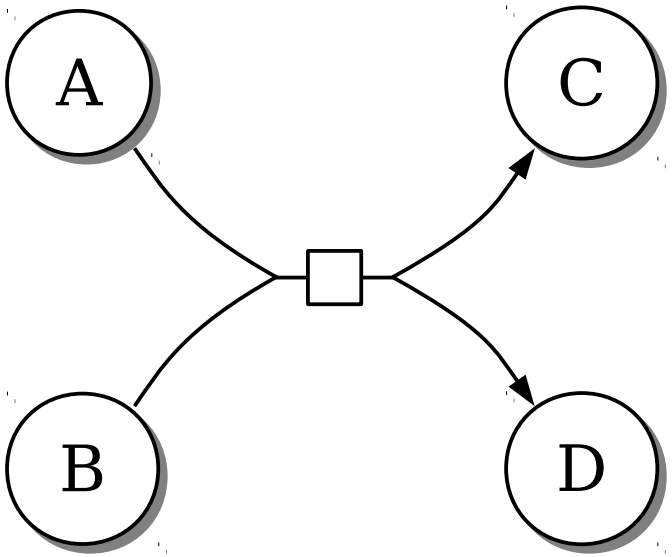
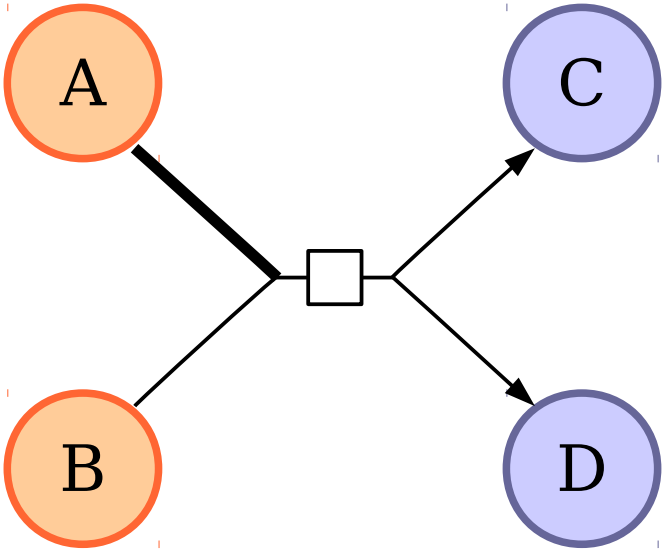
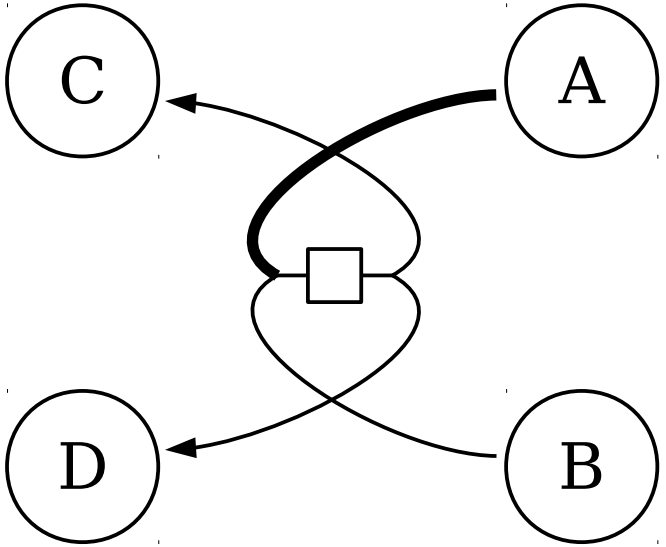
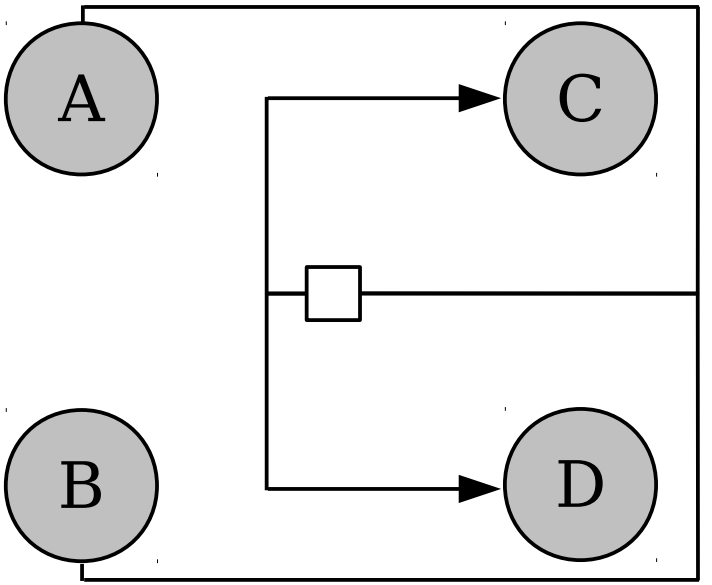
All those diagrams are identical









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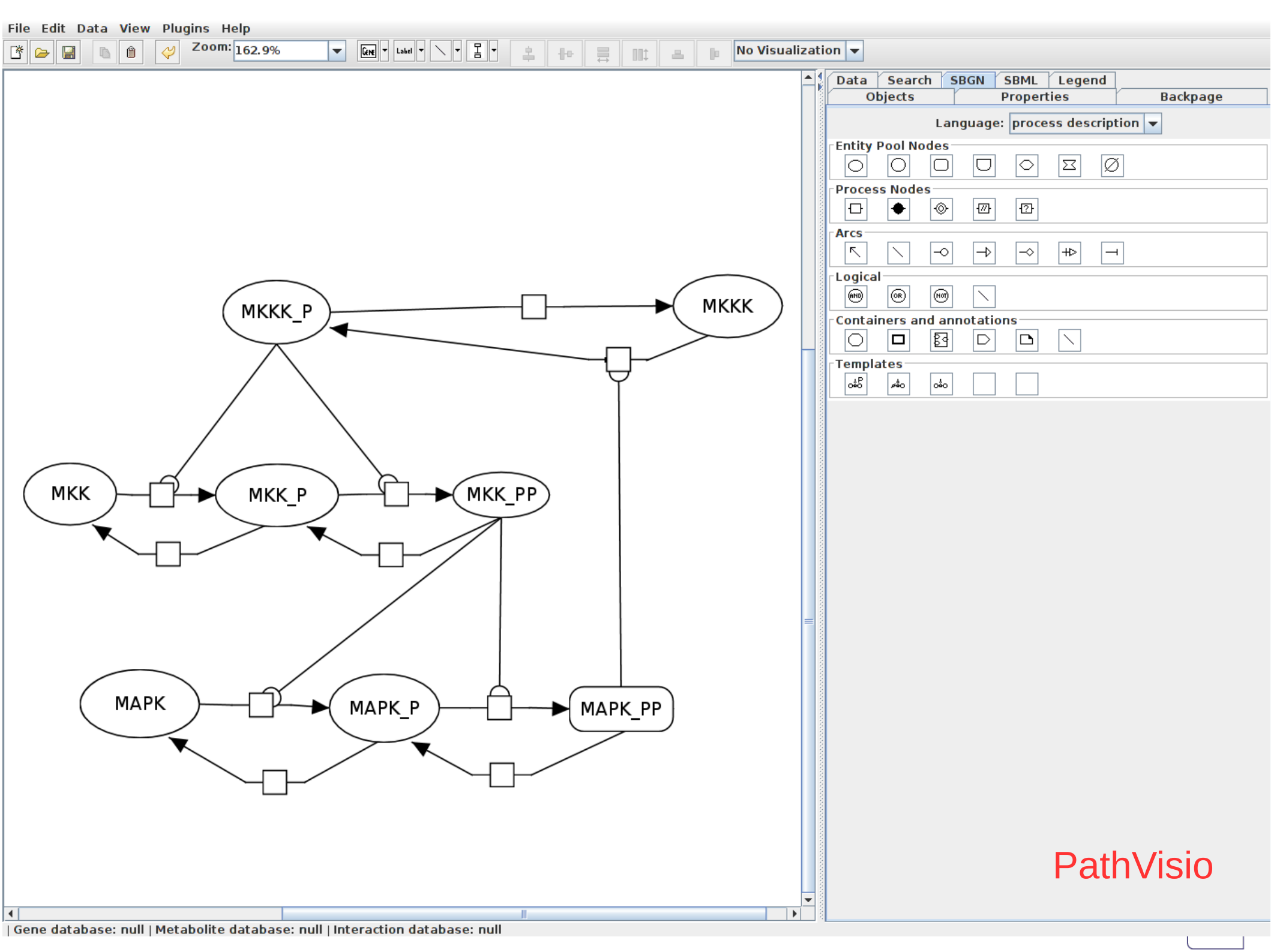
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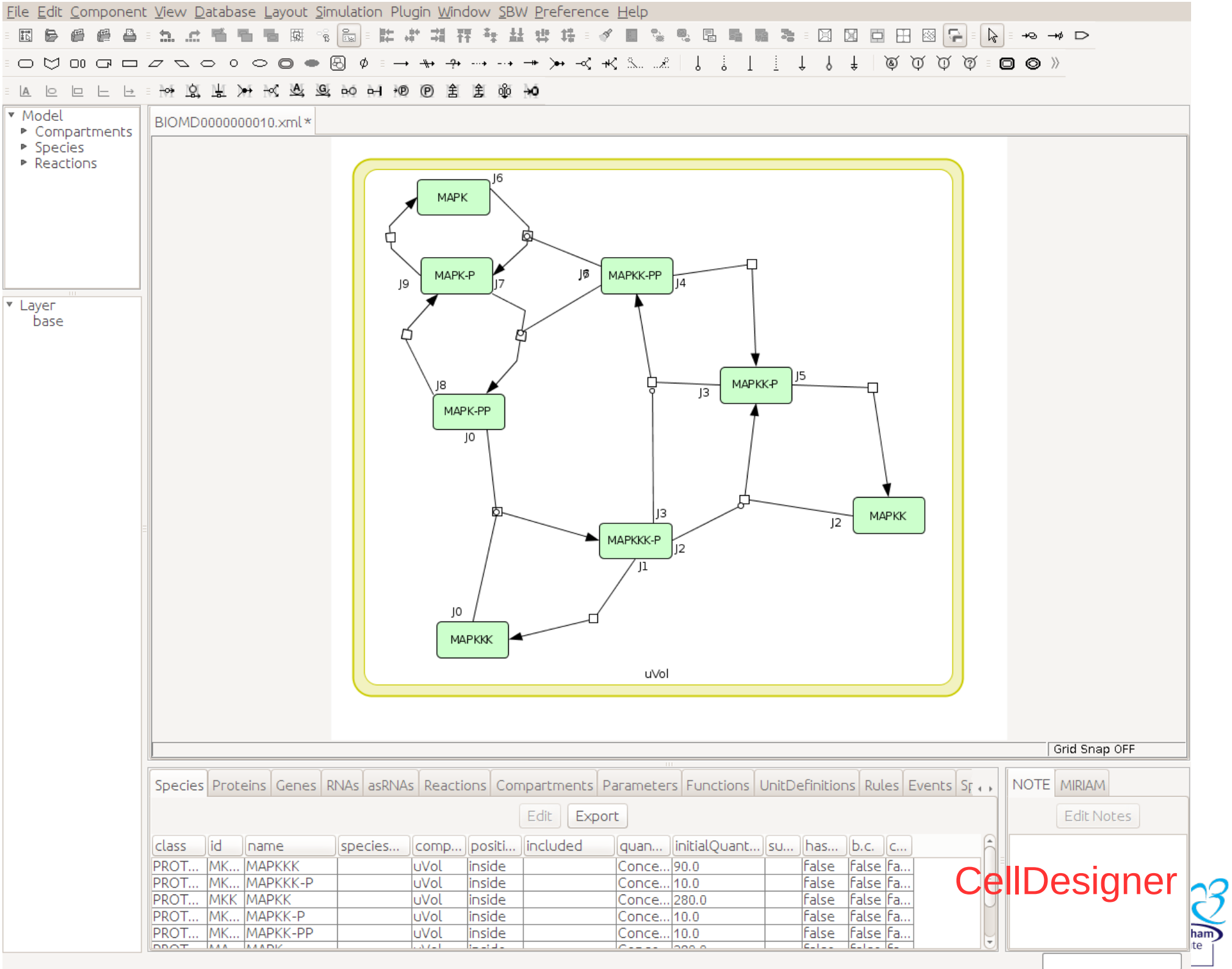
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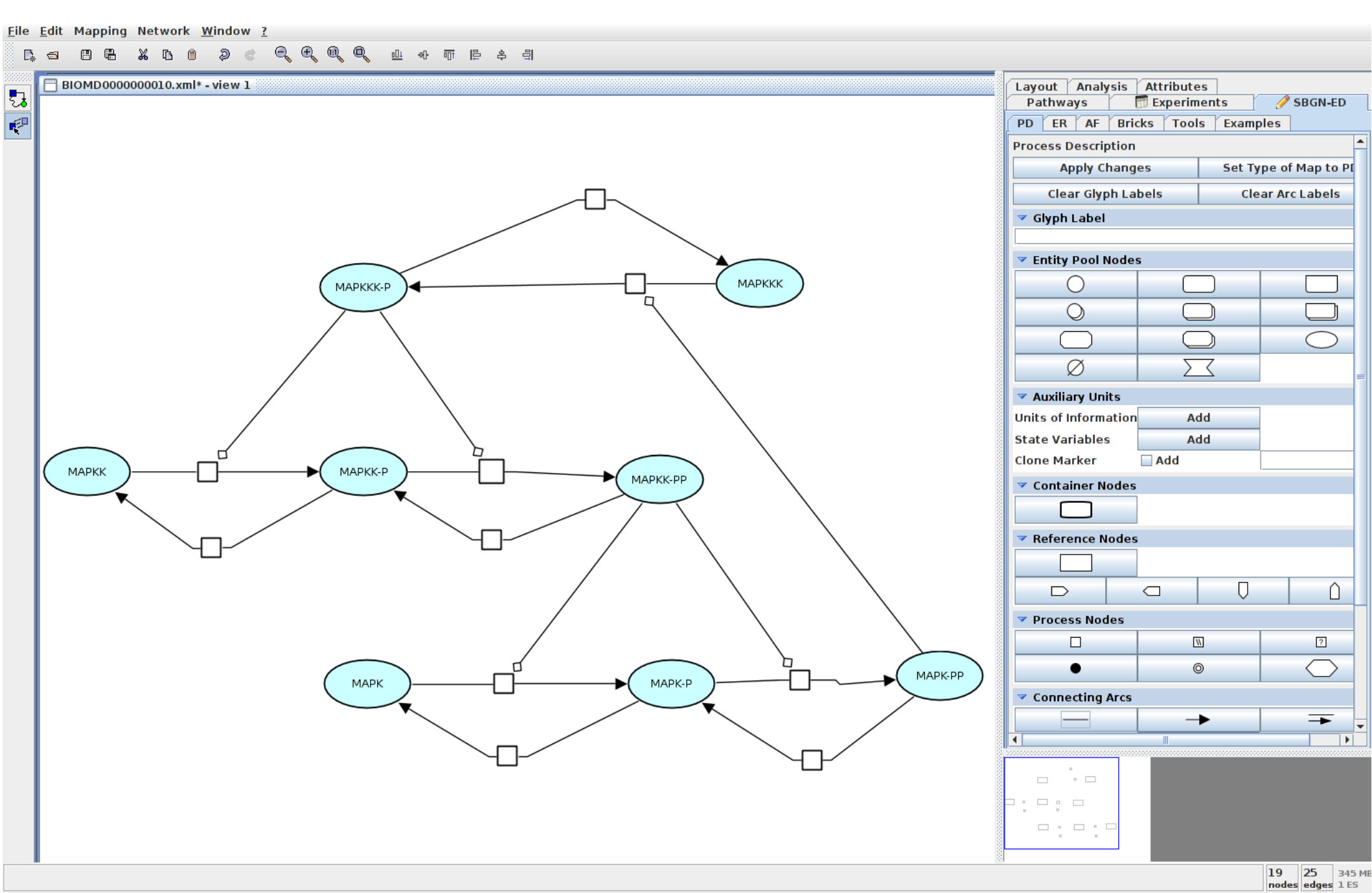
has...
b.c.
PROT... MK... MAPKKK uVol inside Conce... 90.0 false false
PROT... MK... MAPKKK-P uVol inside Conce... 10.0 false false
PROT... MKK MAPKK uVol inside Conce... 280.0 false false
PROT... MK... MAPKK-P uVol inside Conce... 10.0 false false
PROT... MK... MAPKK-PP uVol inside Conce... 10.0 false false
NOTE
MIRIAM
Edit Notes
CellDesigner



Vanted

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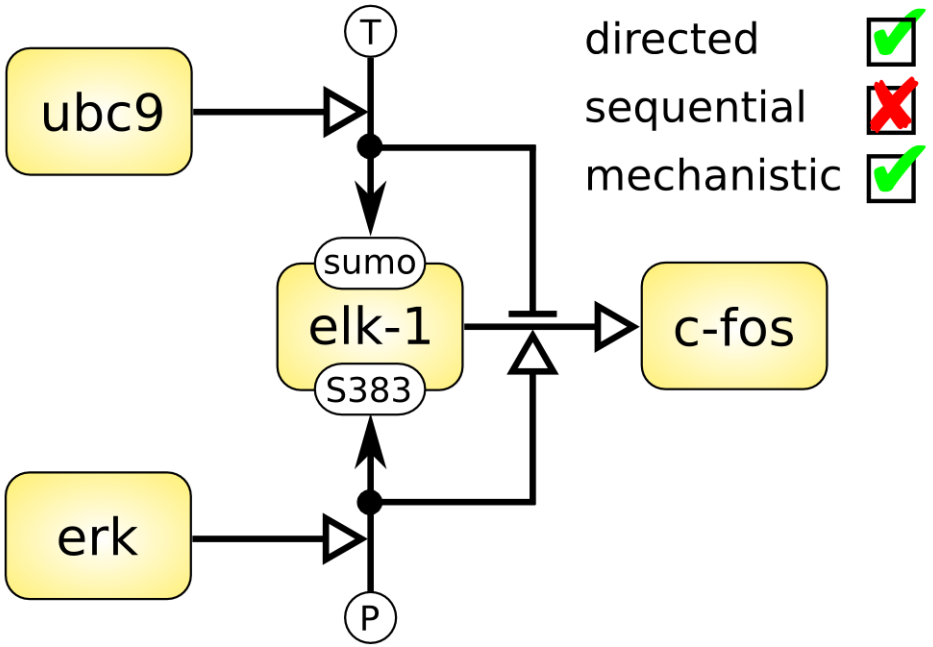
Entity Relationships



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

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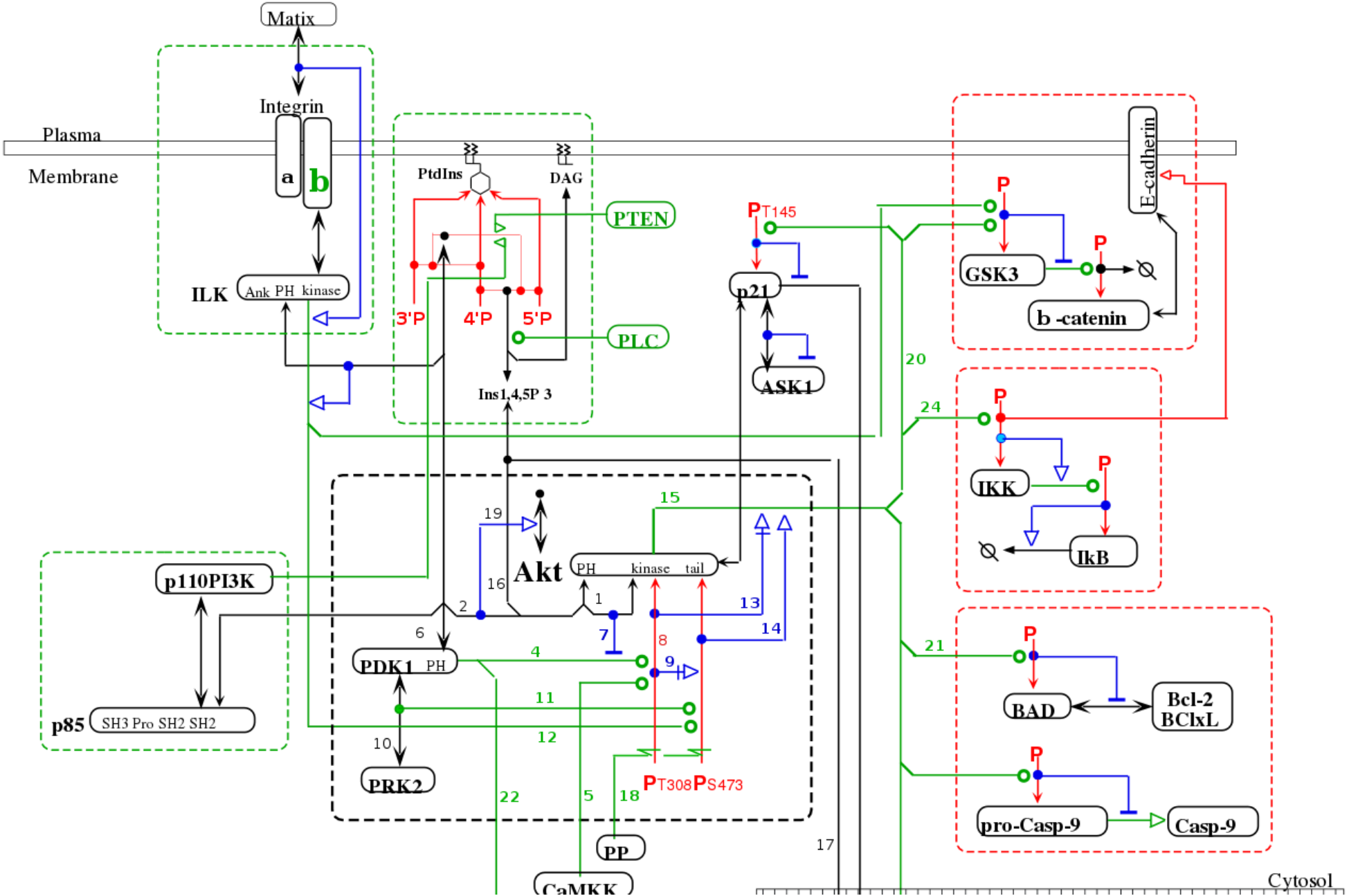
http://discover.nci.nih.gov/mim/

Map description

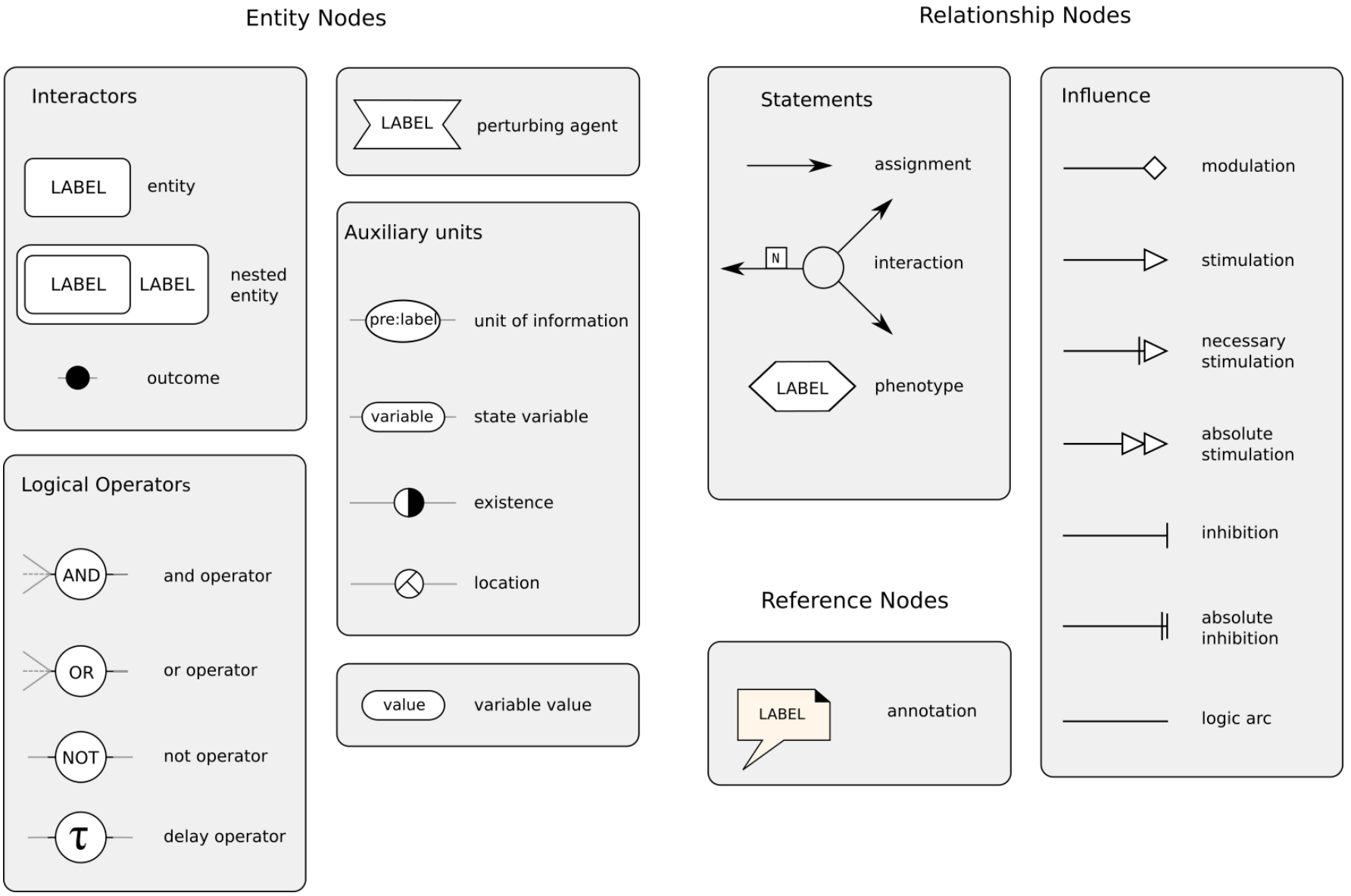
(see System Requirements)

AKT

Click here to return to original map size



SBGN Entity Relationships L1 reference card



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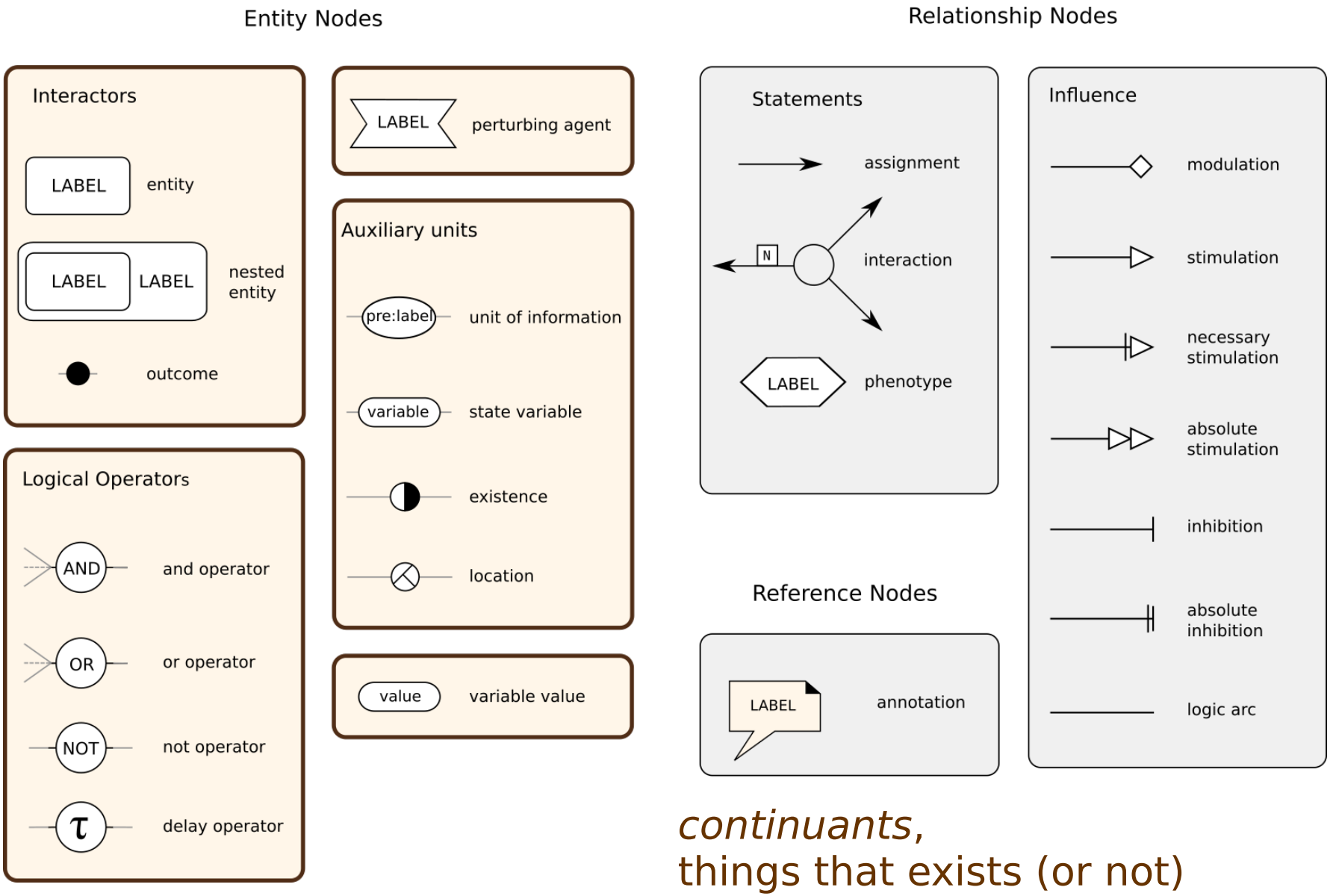
SBGN Entity Relationships L1 reference card



continuants,
things that exists (or not)

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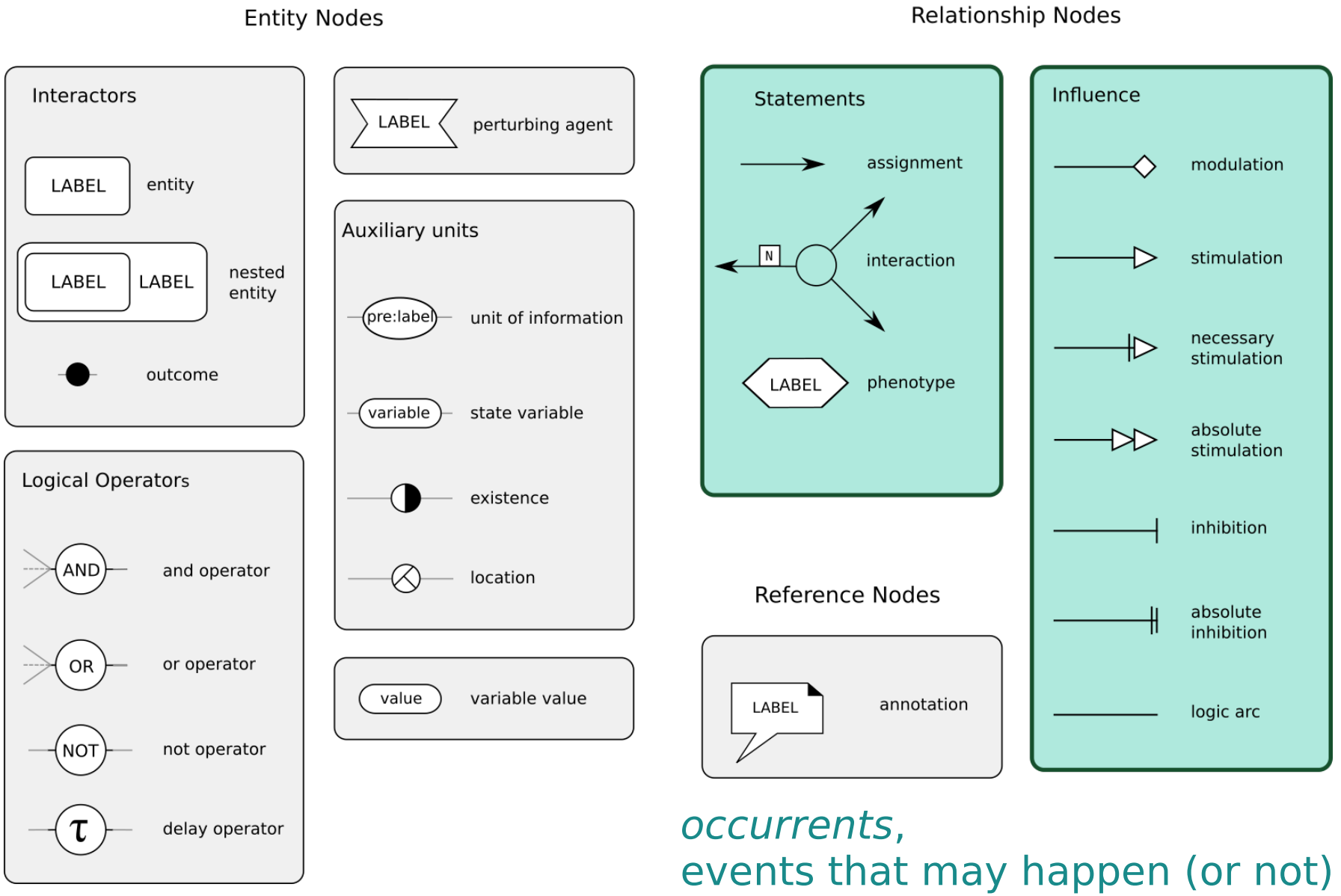
SBGN Entity Relationships L1 reference card



occurrents,
events that may happen (or not)

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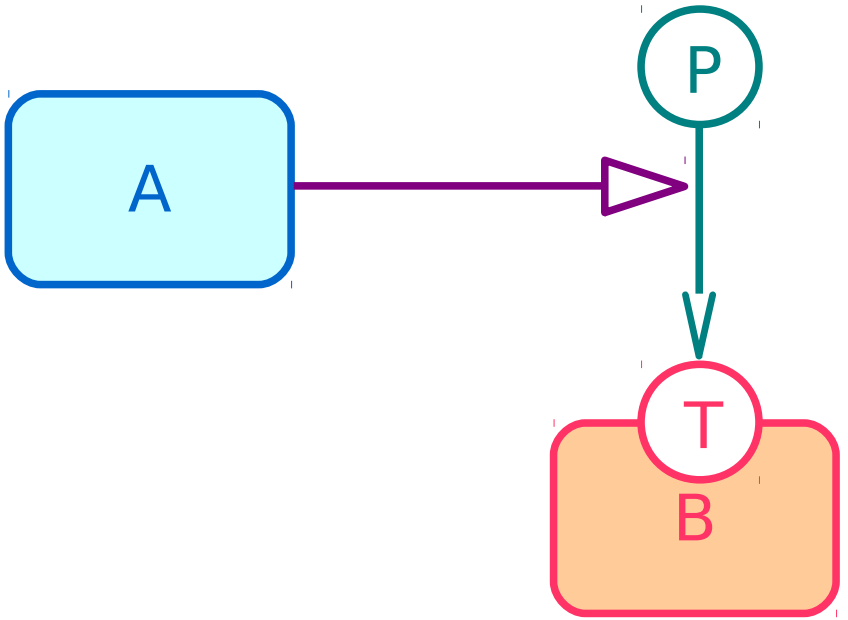
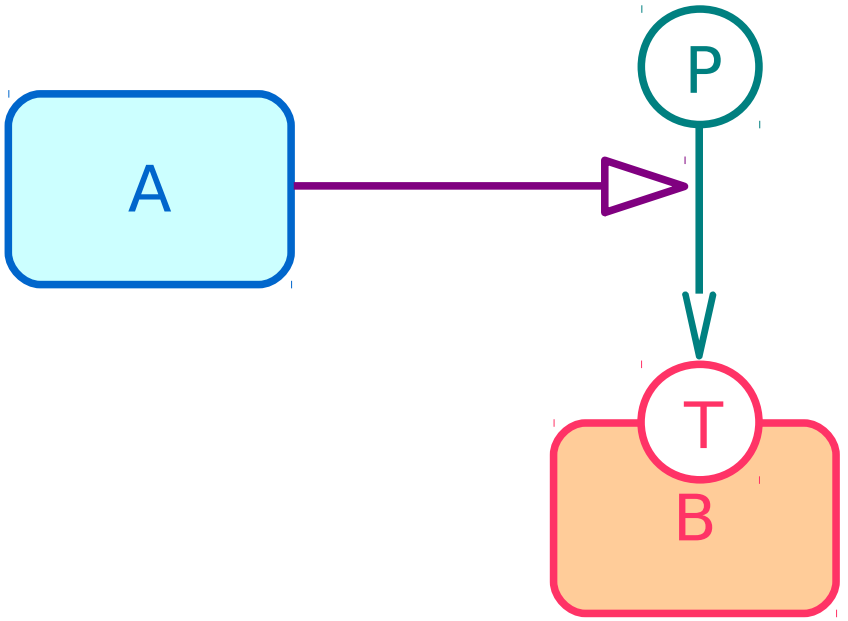
Entity Relationships can be viewed as rules



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

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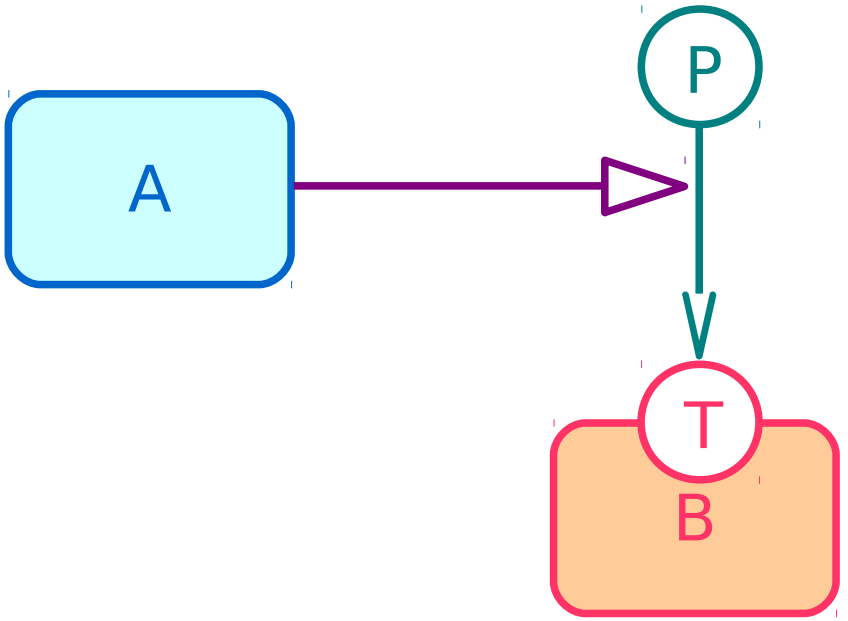
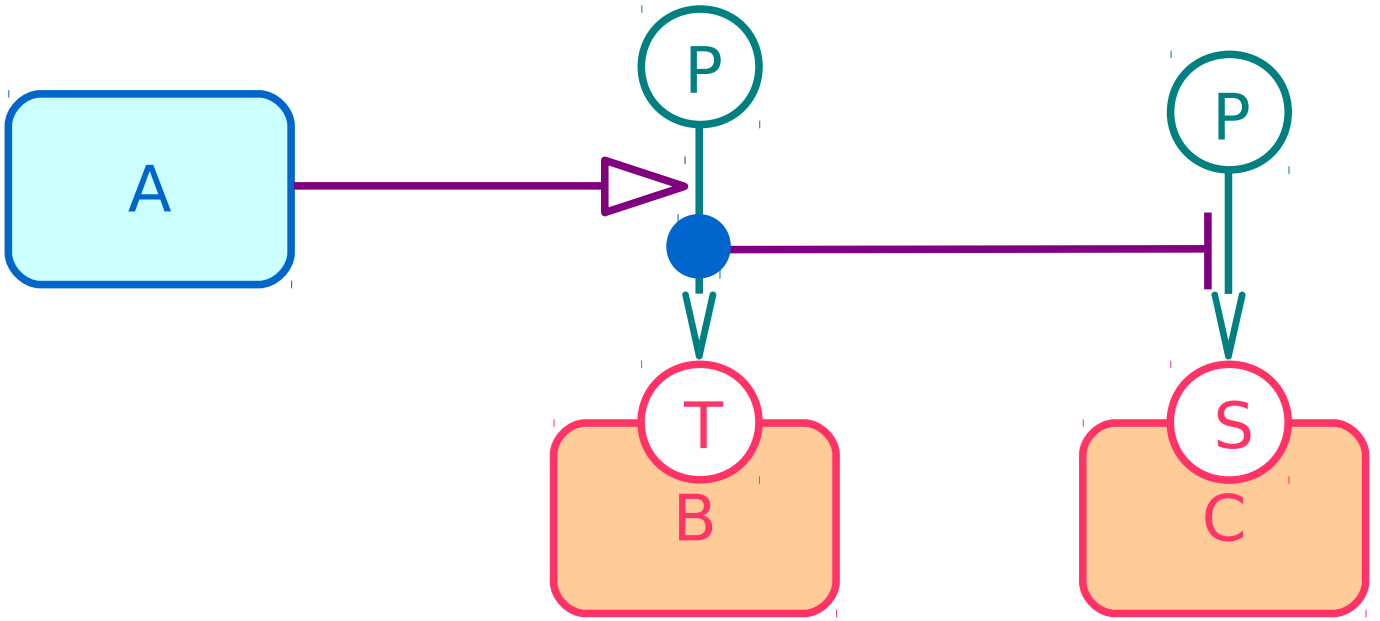
Entity Relationships can be viewed as rules



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)

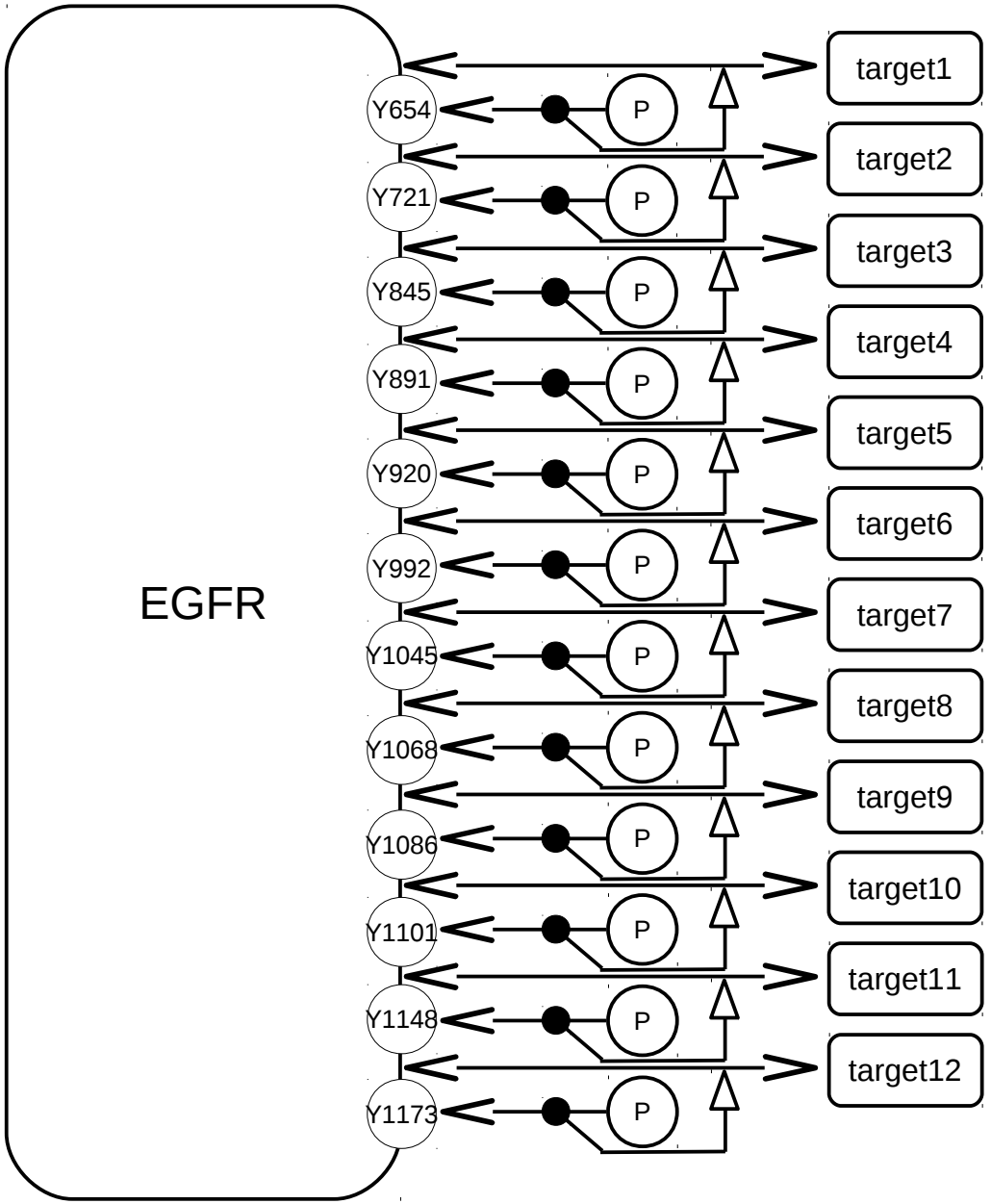
Entity Relationships can be viewed as rules



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

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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”

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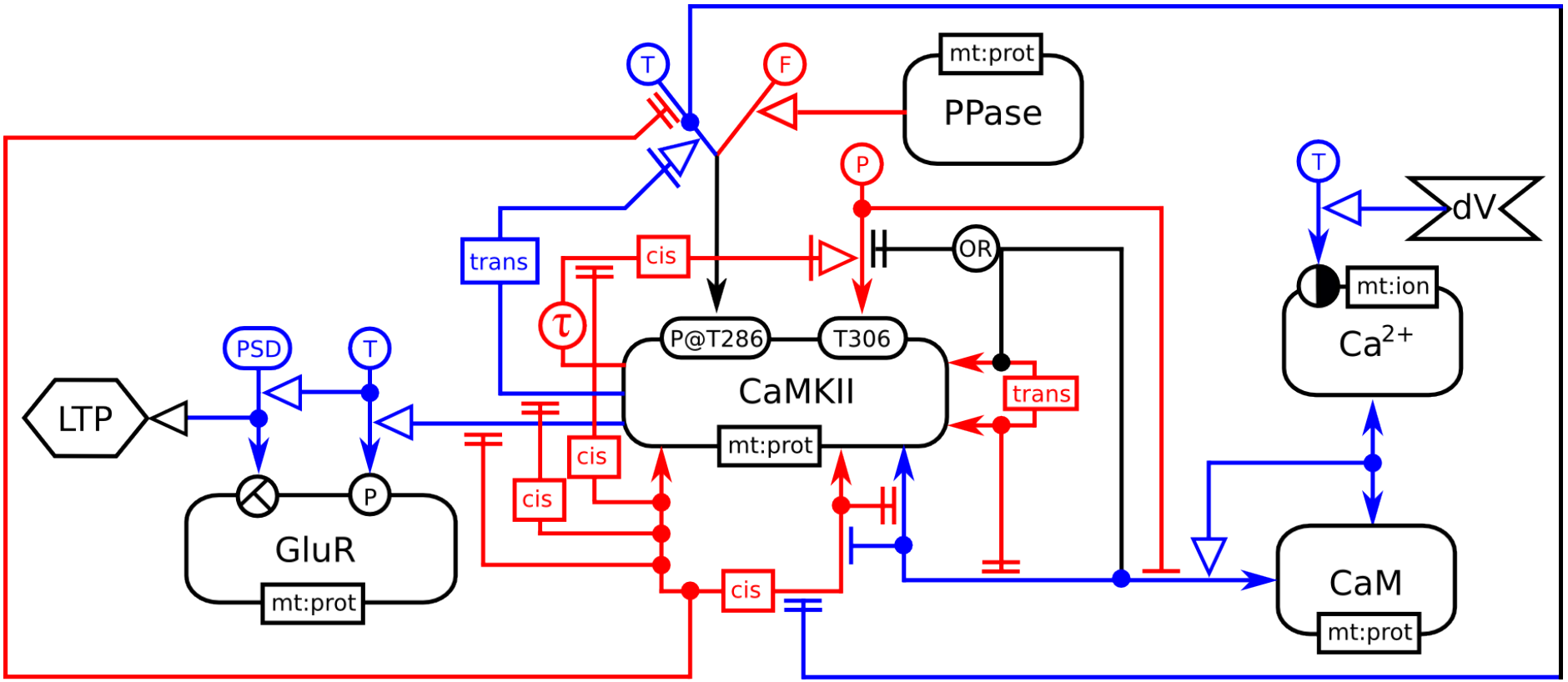
Regulation of synaptic plasticity by calcium



Systems Biology Graphical Notation: Activity Flow language Level 1

Version 1.2

Date: July 27, 2015

Editors:

Huaiyu Mi	*University of Southern California, USA*
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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-l1/.

Systems Biology Graphical Notation: Entity Relationship language Level 1

Version 2.0

Date: August 8, 2015

Editors:

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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*

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```xml
<?xml version="1.0" encoding="UTF-8"?>
<sbgn xmlns="http://sbgn.org/libsbgn/0.3">
  <map version="http://identifiers.org/combine.specifications/
  sbgn.pd.level-1.version-1.3" id="map1">
        <bbox x="0" y="0" w="363" h="253"/>
        <glyph class="simple chemical" id="glyph1">
              <label text="Ethanol"/> <!-- fontsize="" etc -->
              <!-- 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">
              <label text="Ethanal" />
              <bbox x="220" y="110" w="60" h="60"/>
        </glyph>
        <glyph class="macromolecule" id="glyph_adh1">
              <label text="ADH1" />
              <bbox x="106" y="20" w="108" h="60"/>
        </glyph>
        <glyph class="simple chemical" id="glyph_h">
              <label text="H+" />
              <bbox x="220" y="190" w="60" h="60"/>
        </glyph>
        <glyph class="simple chemical" id="glyph_nad">
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        </glyph>
        <glyph class="simple chemical" id="glyph_nadh">
              <label text="NADH" />
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        </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">
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        </arc>

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

        <arc class="catalysis" source="glyph_adh1" target="pn1"
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        </arc>

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        id="a04">
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        id="a05">
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```
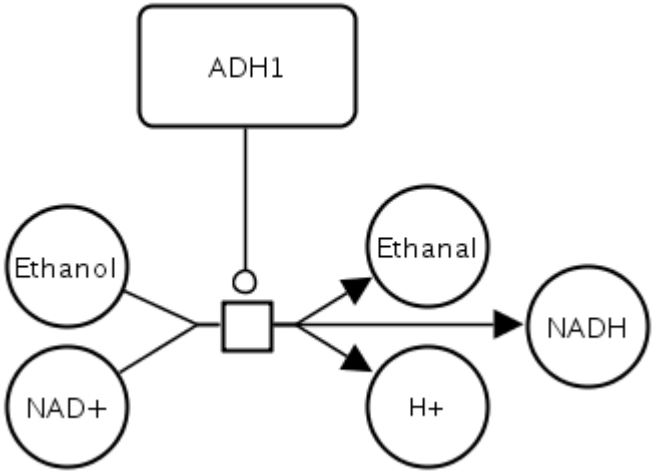

SBGN-ML and libSBGN



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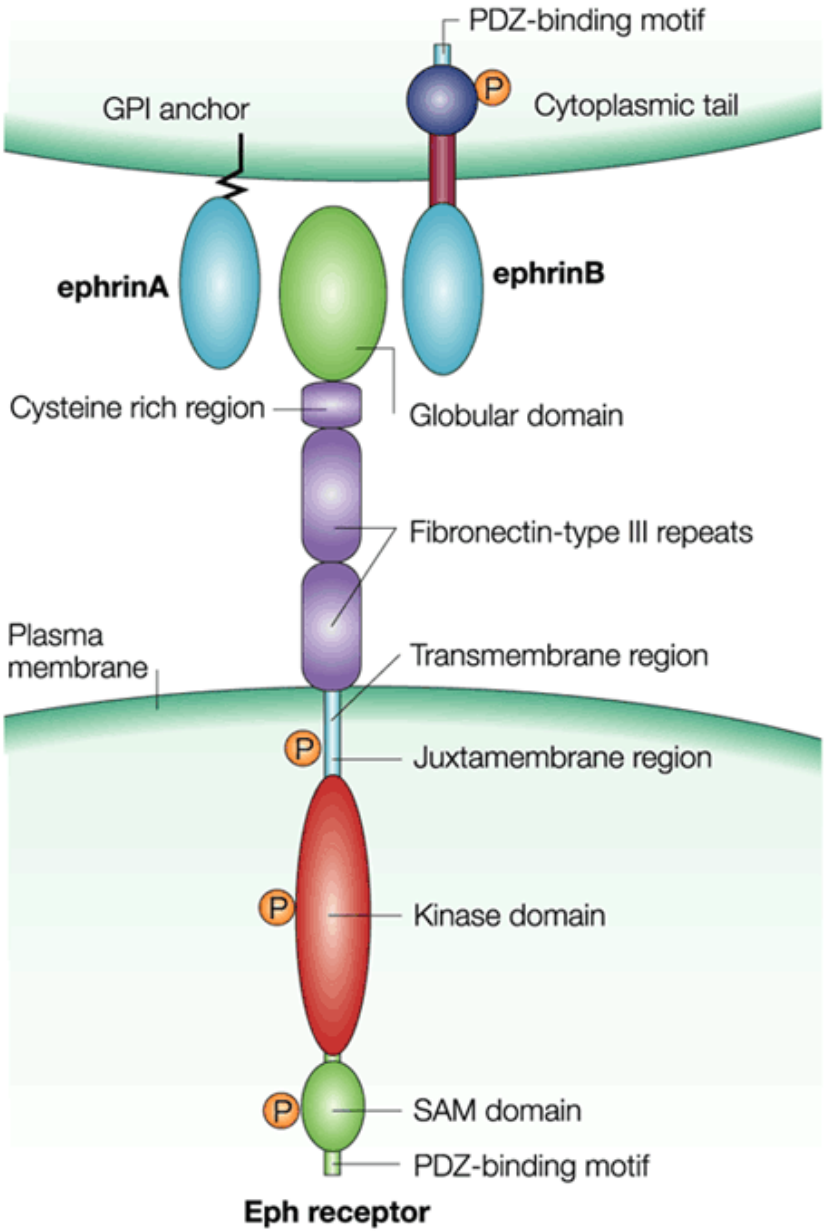
Are we done? Everything is solved right?

Multi-compartment entities



Nature Reviews | Molecular Cell Biology

Easy in ER

Tricky in AF

Impossible in PD

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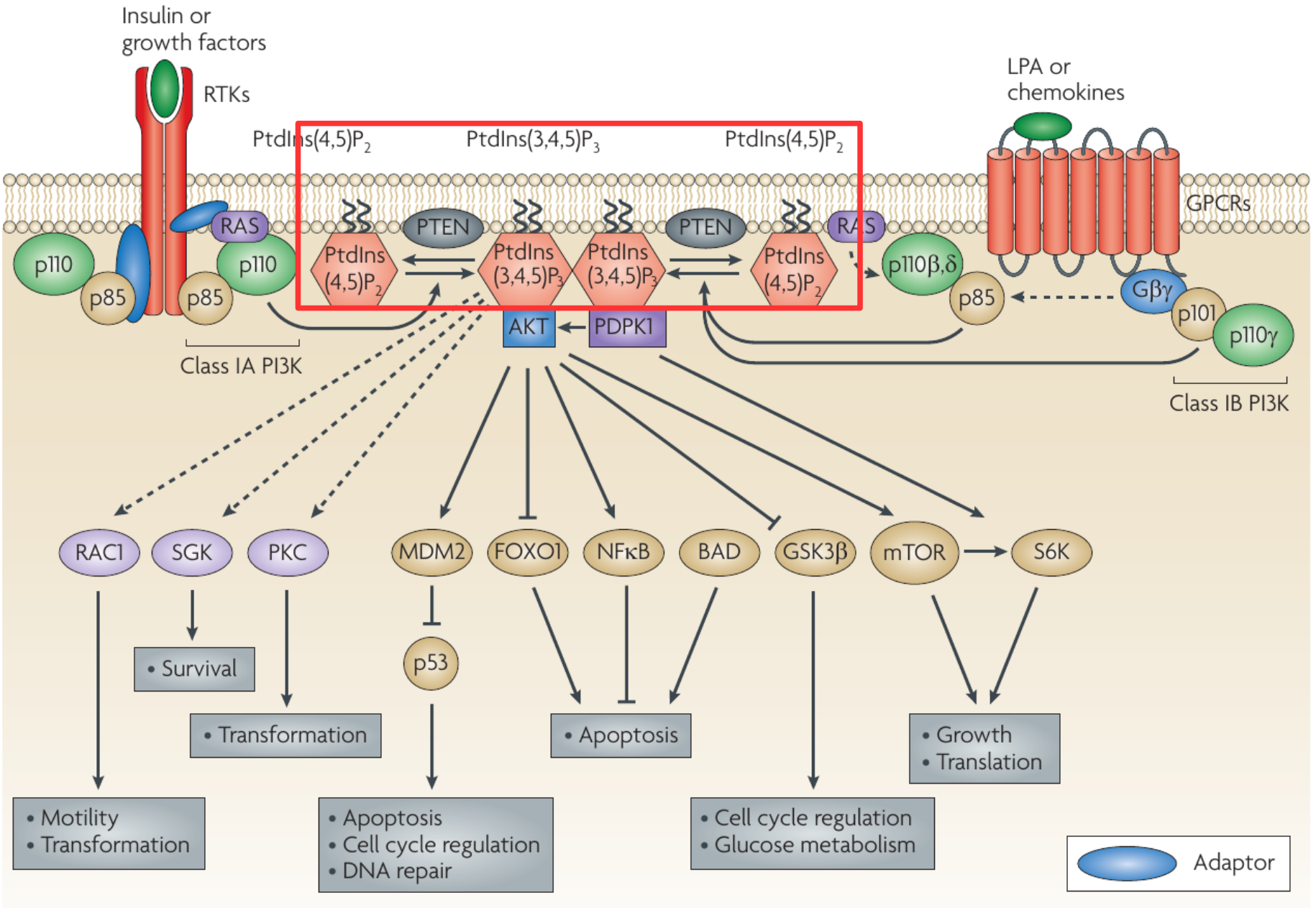
Hybrid maps



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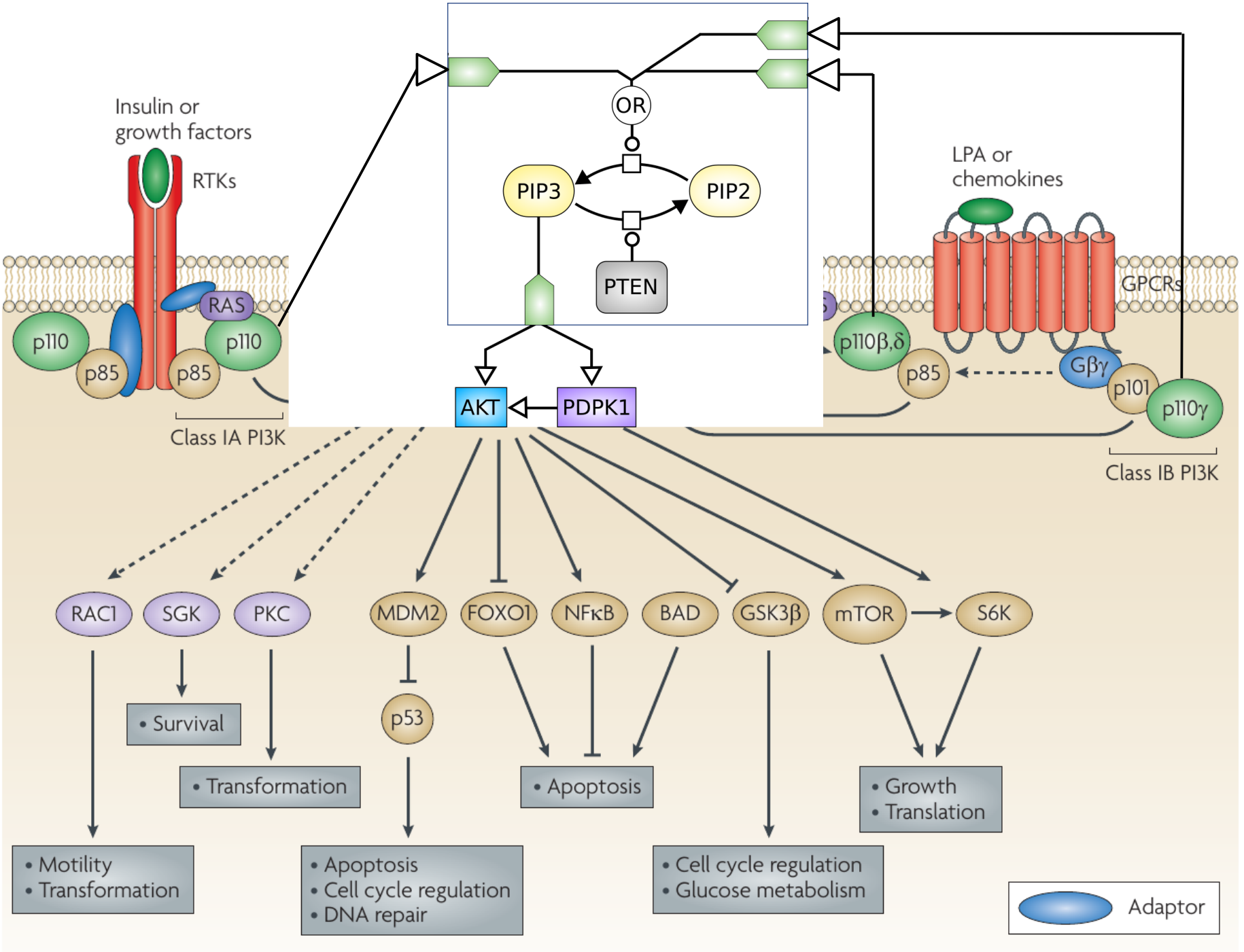
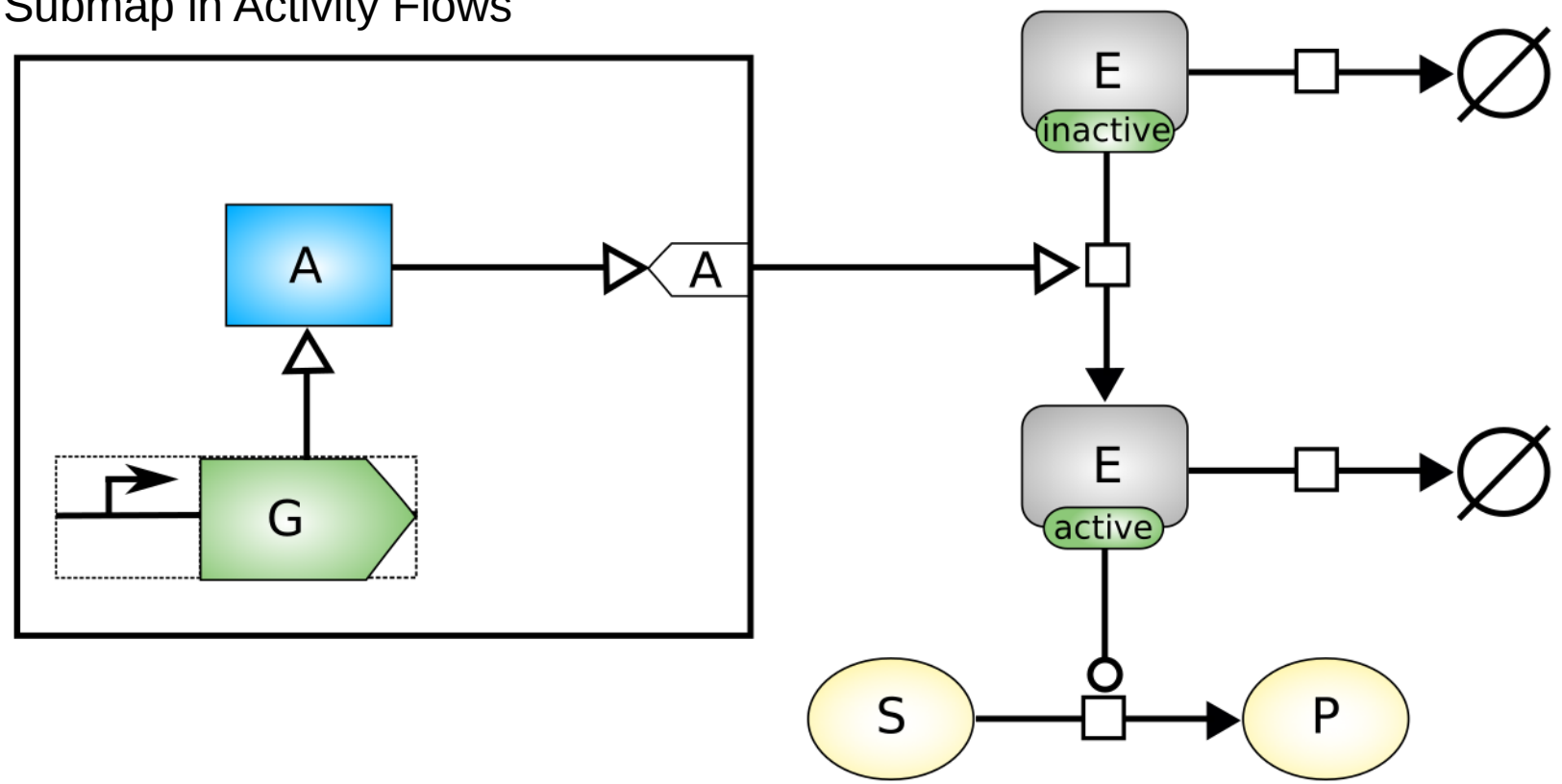
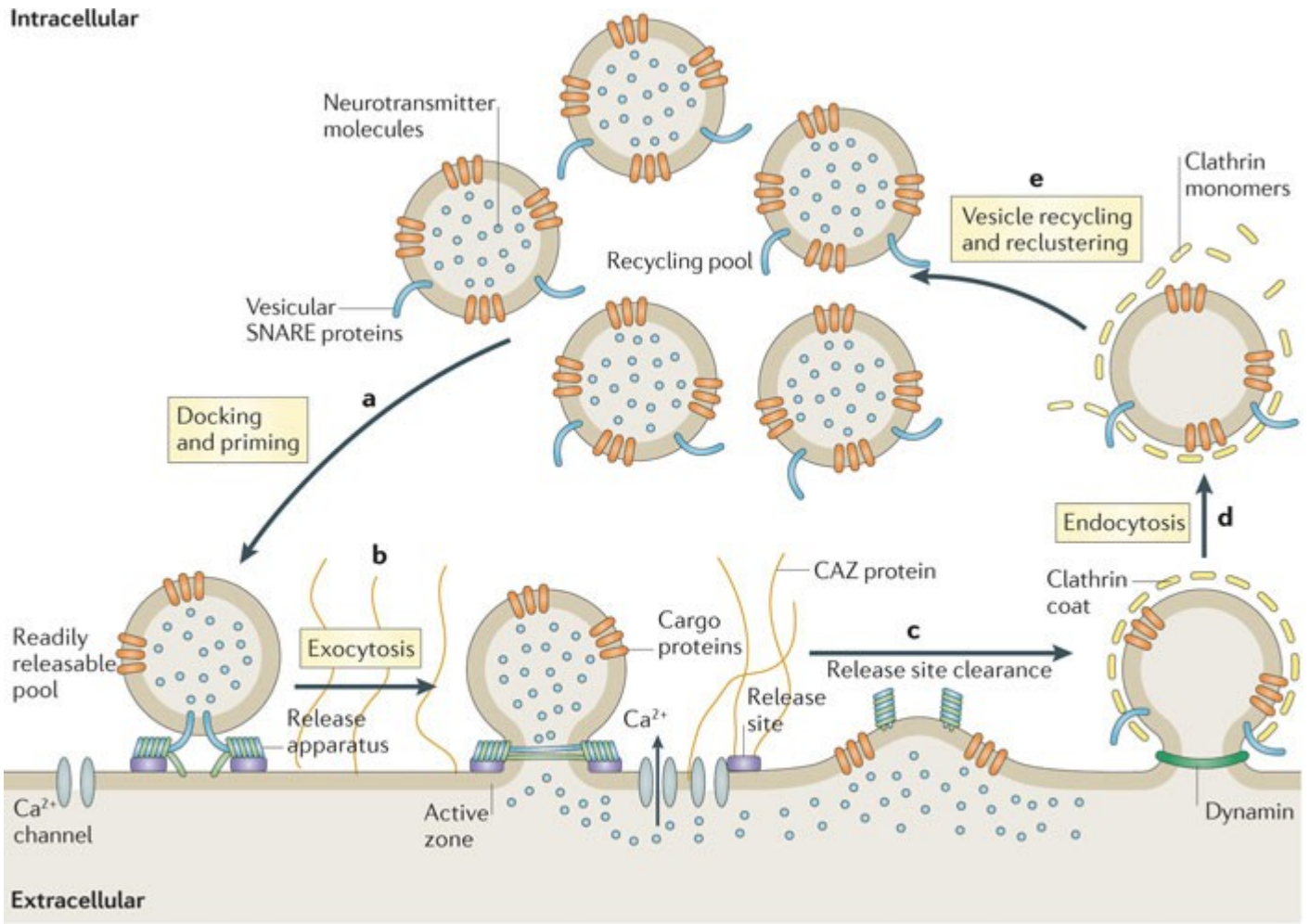


Main map in Process Descriptions

Submap in Activity Flows



Creation, movement, destruction



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Systems Biology Graphical Notation

http://sbgn.org

Join the conversation

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.

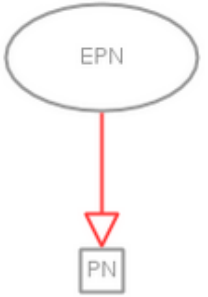
Quick start

Learn how to use SBGN

Get involved

Symbol Highlight

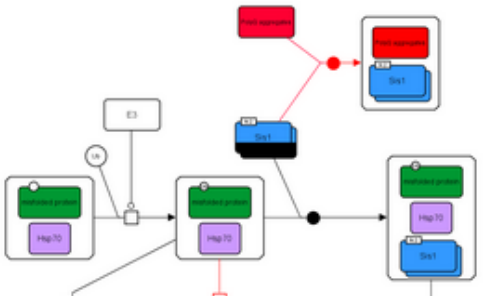
Stimulation



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.



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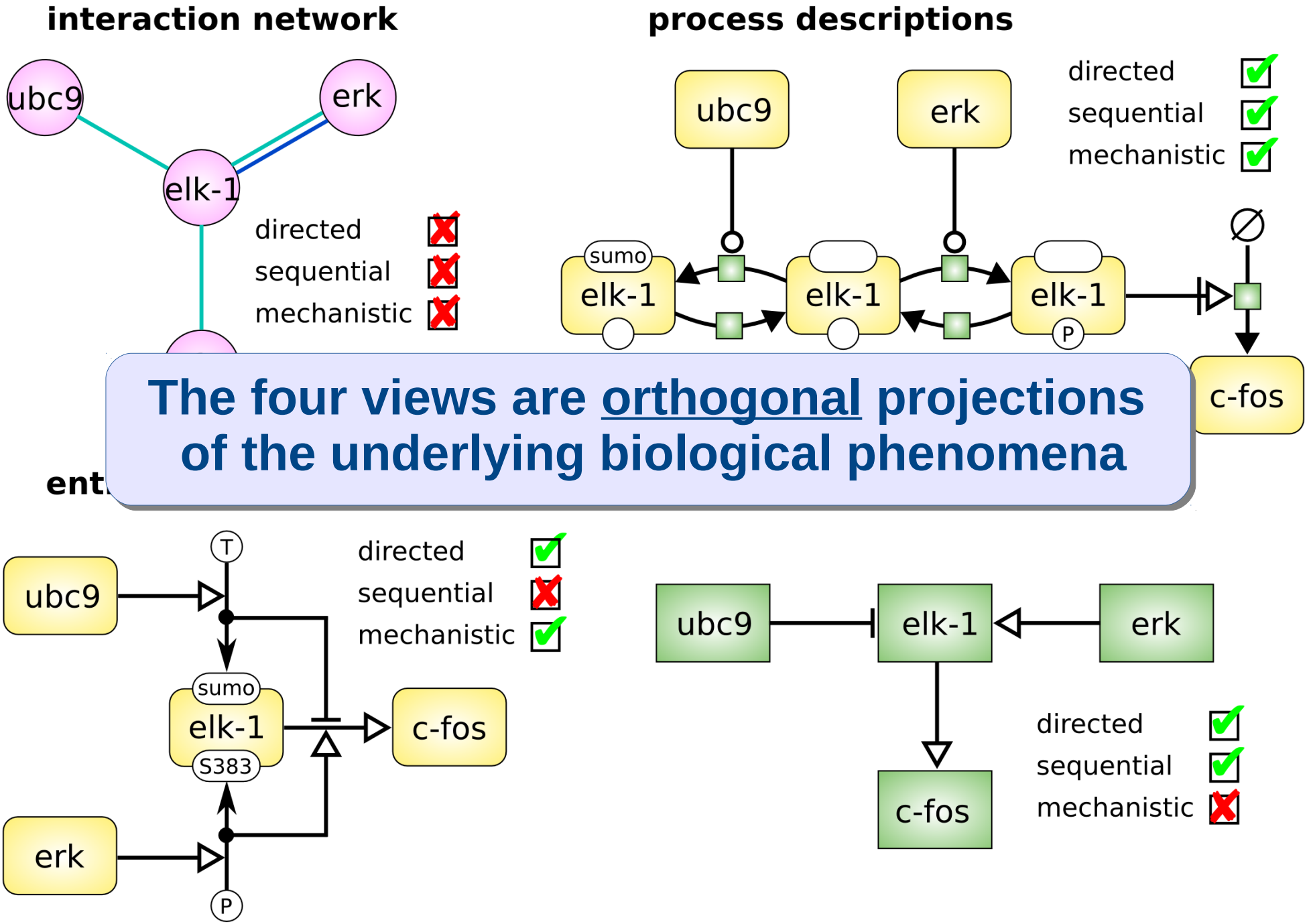
interaction network
ubc9
erk
elk-1
directed
sequential
mechanistic
process descriptions
ubc9
erk
directed
sequential
mechanistic
sumo
elk-1
elk-1
elk-1
P
c-fos
The four views are orthogonal projections of the underlying biological phenomena
ubc9
T
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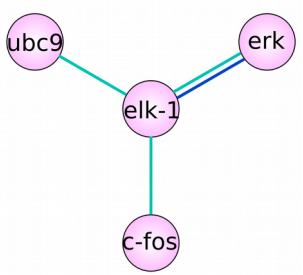
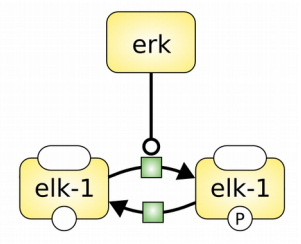


Interaction networks

PSI-MI

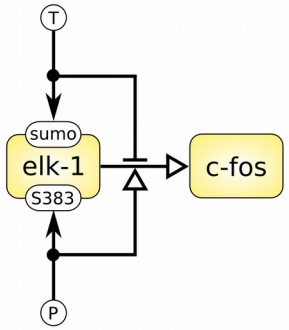


Process Descriptions

SBML Core

SBGN Process Description

Metabolism

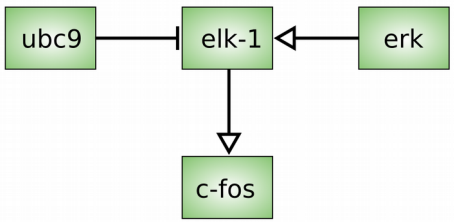


Entity relationships

SBML Multi

SBGN Entity Relationships

Signalling



Activity Flows

SBML Qual

SBGN Activity Flows

Signalling
Gene networks

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