

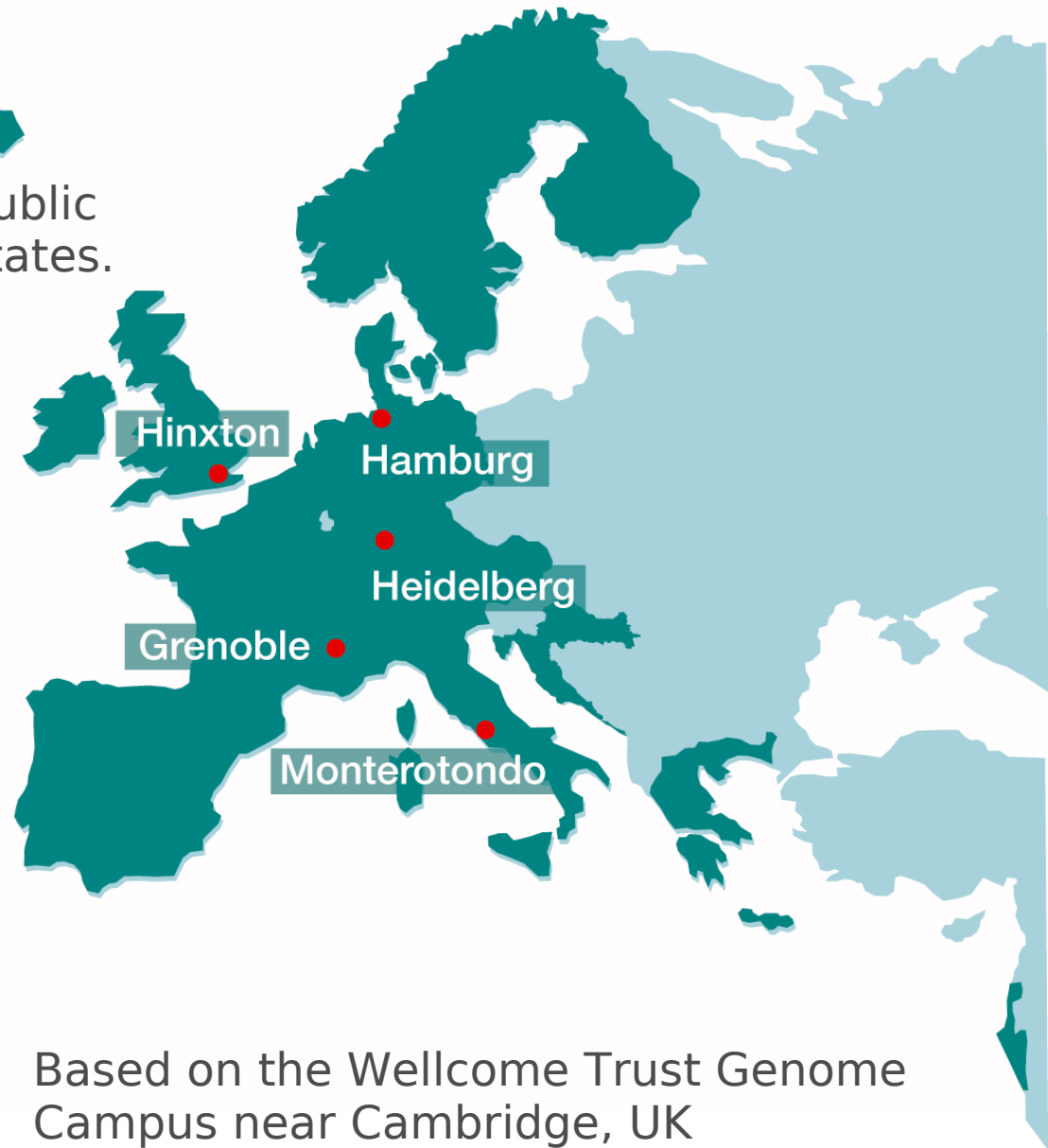


Nicolas Le Novère, EMBL-EBI



EBI is part of EMBL

- Non-profit organization
- Part of the European Molecular Biology Laboratory (EMBL), a basic research institute funded by public research monies from 19 member states.



- Based on the Wellcome Trust Genome Campus near Cambridge, UK



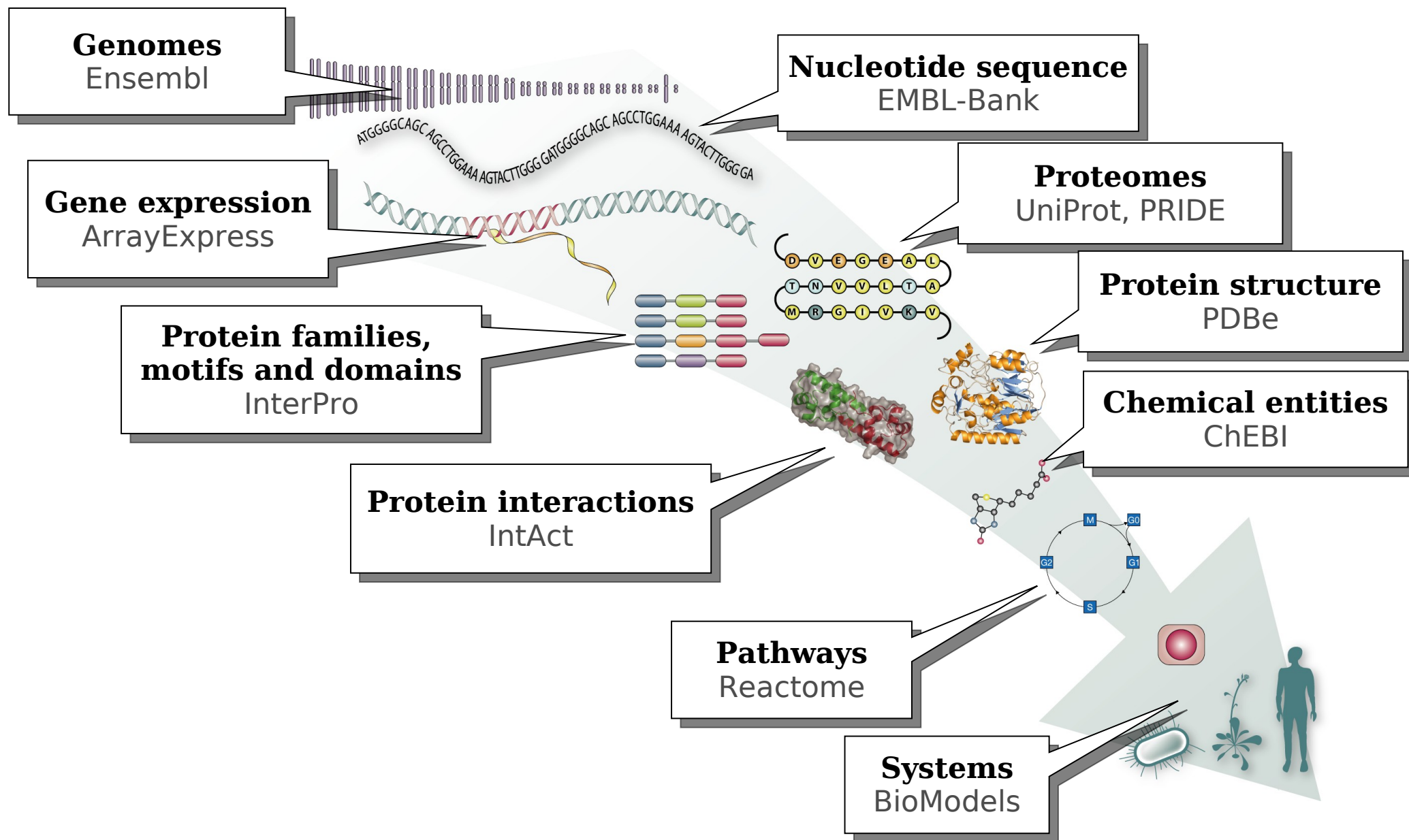
- To provide freely available **data** and bioinformatics **services** to all facets of the scientific community in ways that promote scientific progress
- To contribute to the advancement of biology through basic investigator-driven **research** in bioinformatics
- To provide advanced bioinformatics **training** to scientists at all levels, from PhD students to independent investigators
- To help disseminate cutting-edge technologies to **industry**



Principles of service provision

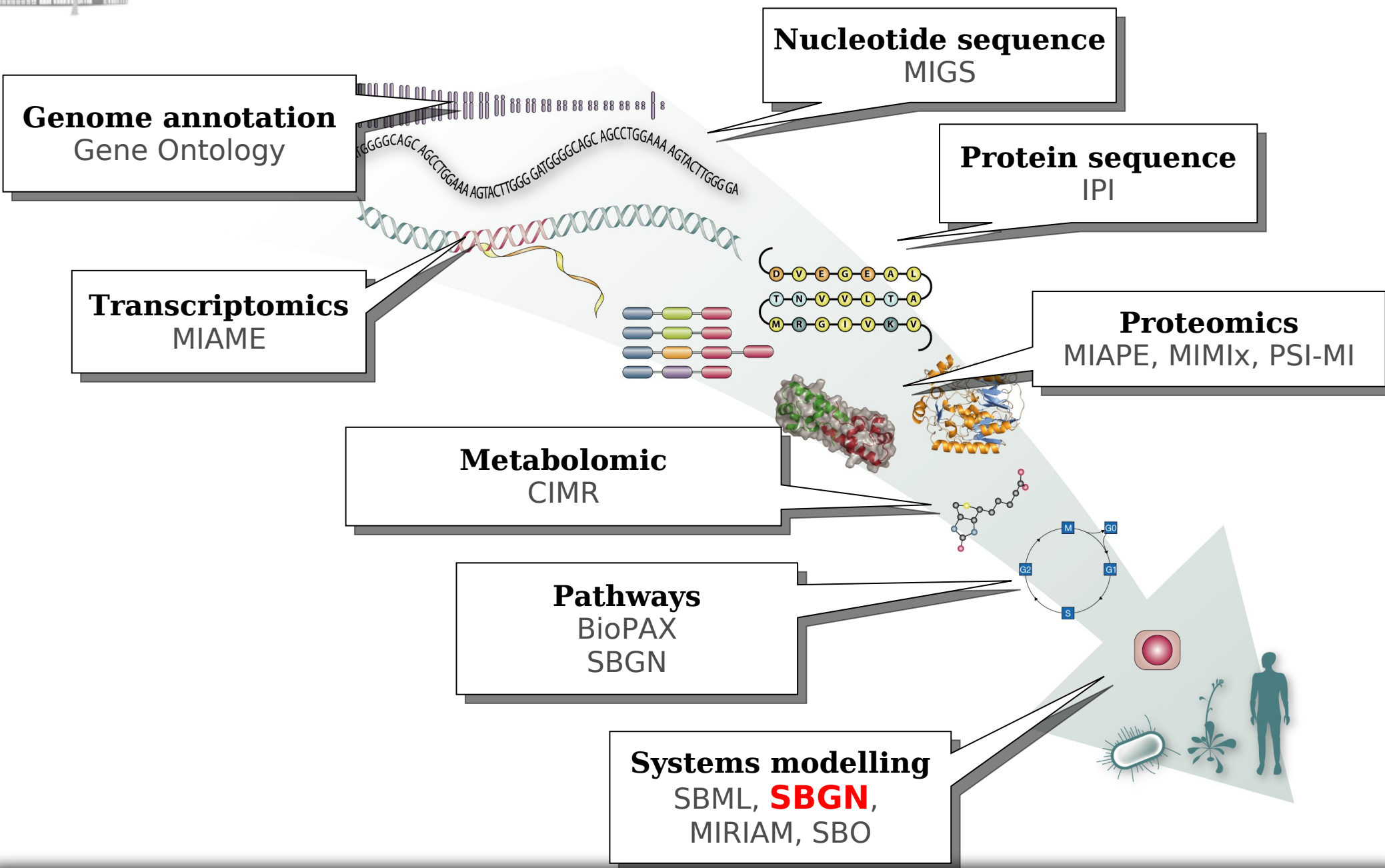
- **Accessibility** – all data and tools freely available without restriction
- **Compatibility** – we develop and promote the use of standards in bioinformatics
- **Comprehensive data sets** – agreements with other data providers ensure that our resources contain comprehensive and up-to-date data; agreements with publishers ensure that published data are placed in a public repository at the earliest opportunity
- **Portability** – data and software can be downloaded and installed locally
- **Quality** – Our databases are enhanced through annotation and cross-referencing

EBI Data resources: molecules to systems



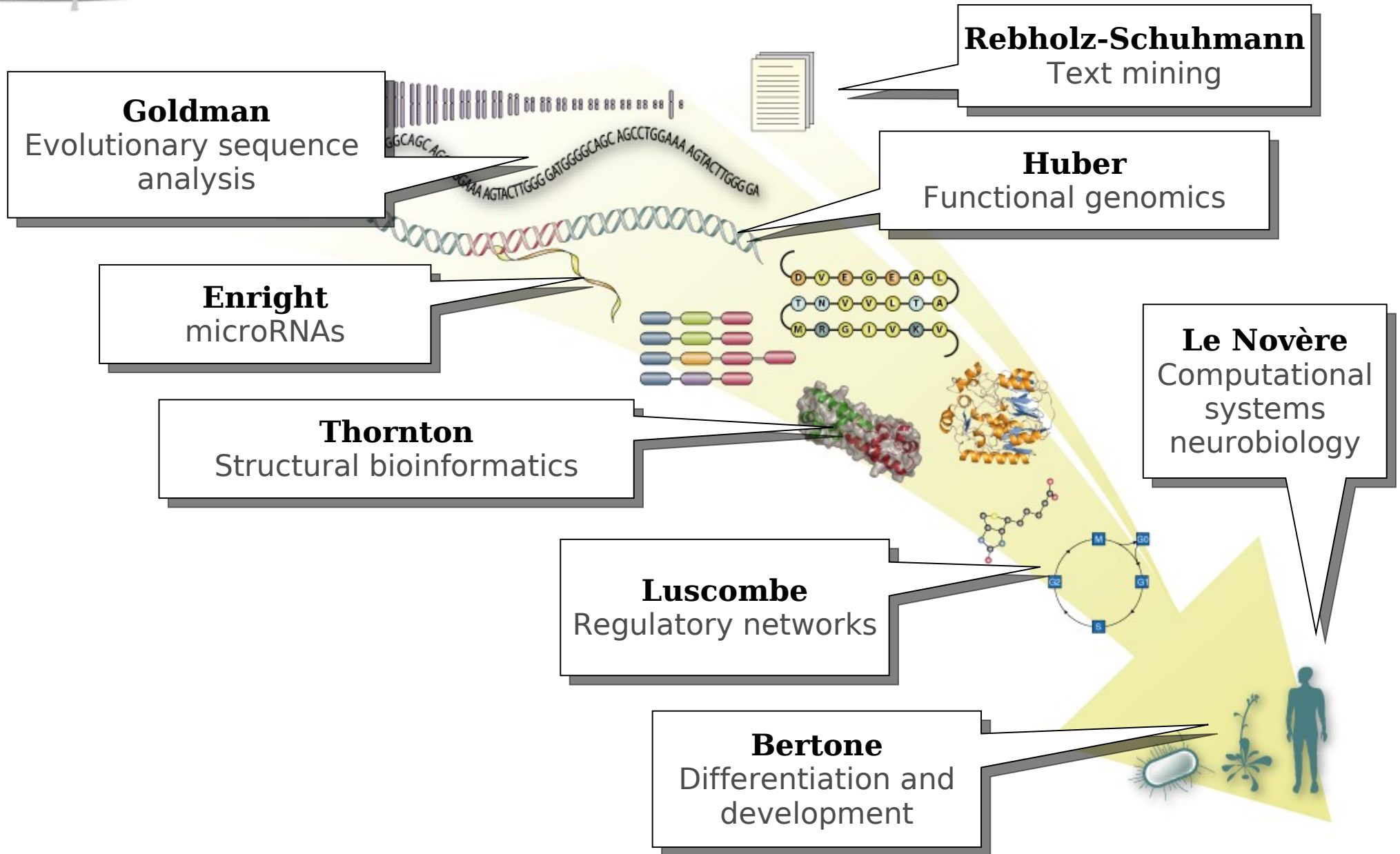


Standards development





Research groups



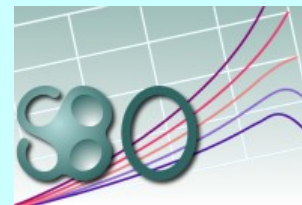
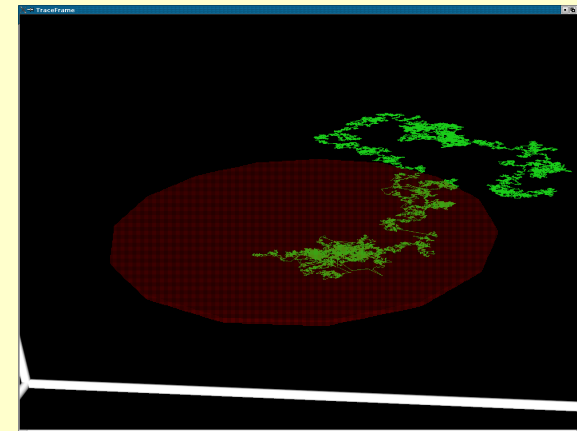
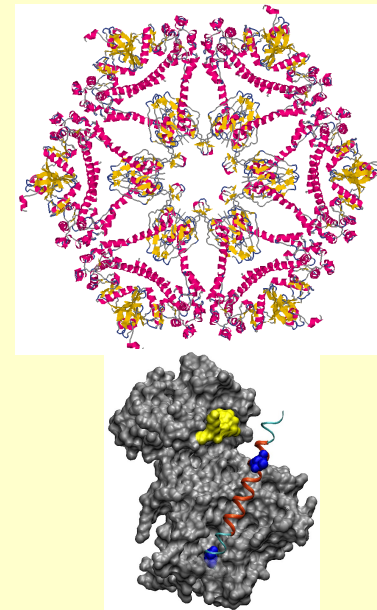
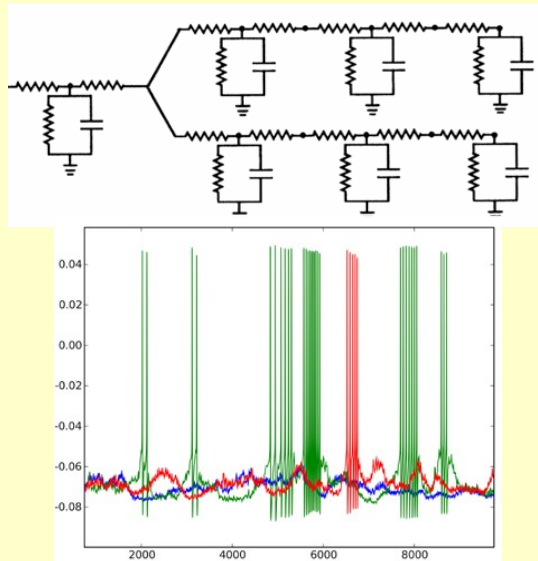
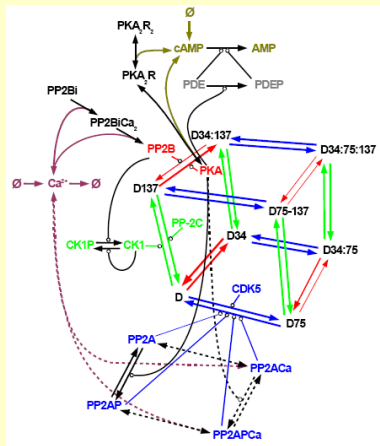


- >3 million web requests per day
- >300 000 unique hosts served per month
- ~5 million files downloaded per month
- ~173 TB data downloaded in 2008
(excluding data sync)
- Millions of cross-references
- 5 petabytes of storage
- > 1000 cores in clusters
- 1 million compute jobs per day

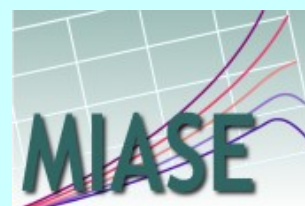
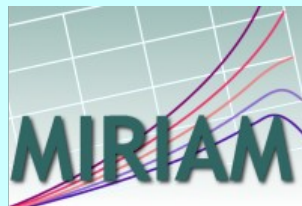


Group themes and projects

Computational Neurobiology



Systems Biology





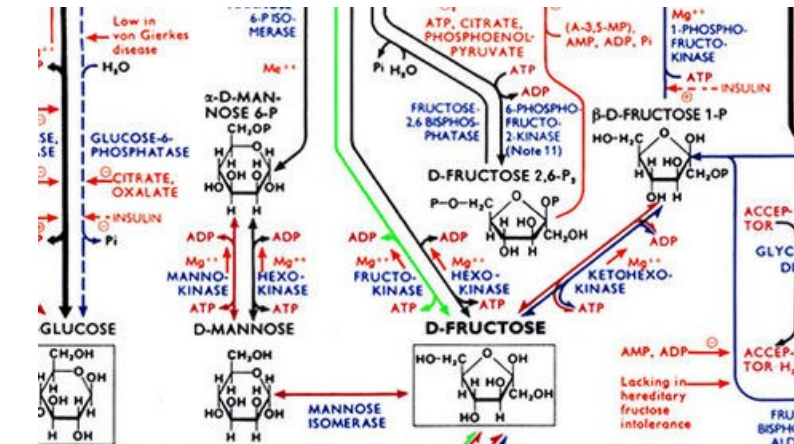
The Systems Biology Graphical Notation

Nicolas Le Novère, EMBL-EBI

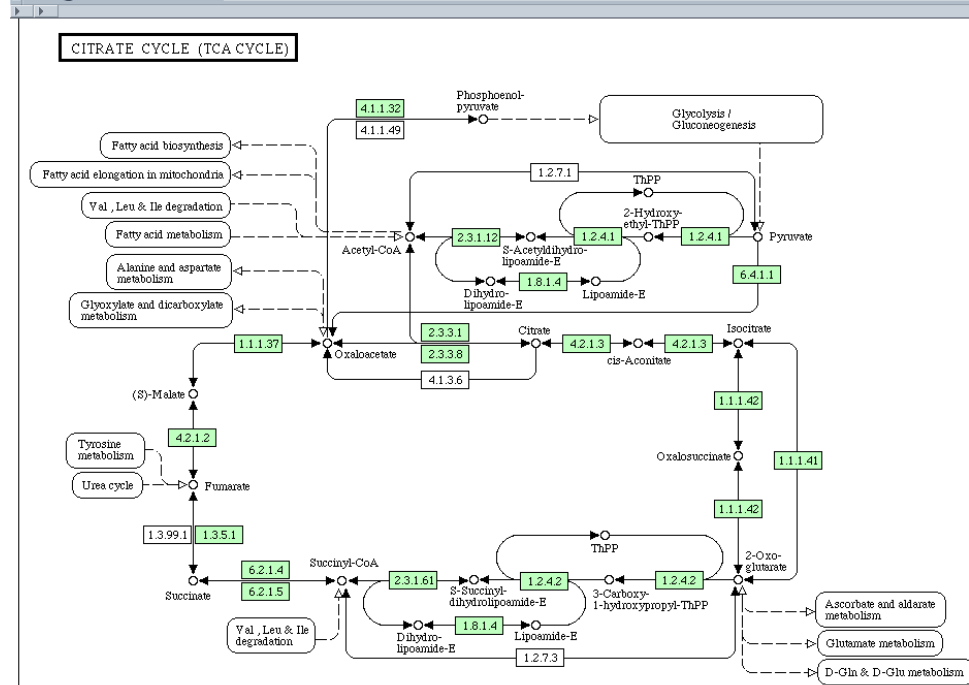
(on the behalf of SBGN editors, authors and contributors)



Graphs are everywhere in biology



KEGG PATHWAY: Citrate cycle (TCA cycle) - Homo sapiens (human) - SeaMonkey
http://www.genome.jp/dbget-bin/get_pathway?org_name=hsa&mapno=00020



00020 5/18/09
 (c) Kanehisa Laboratories

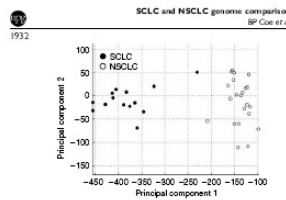
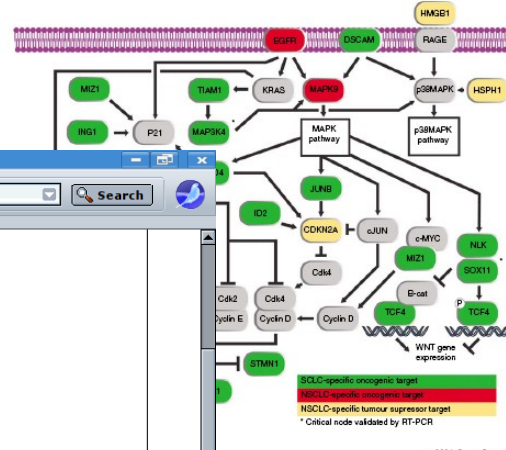


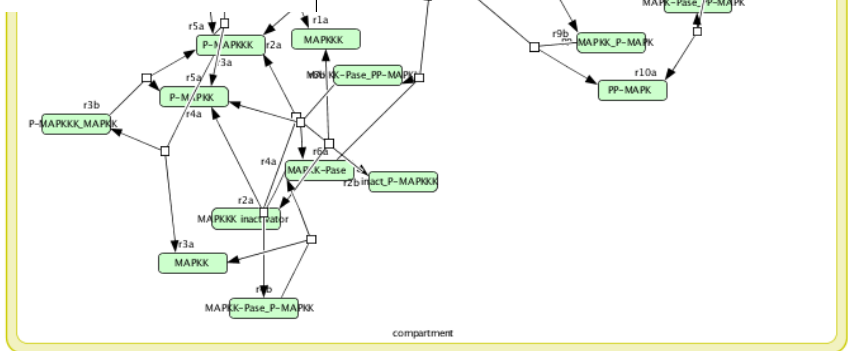
Figure 4. Contribution of copy number-induced gene expression differences to the SCLC and NSCLC phenotypes. Principal components analysis was performed using all 243 Affymetrix probe sets demonstrating expression differences as a result of copy number alterations. The SCLC samples are indicated by solid circles, while the NSCLC samples are indicated by open circles. Strong separation of the SCLC and NSCLC cell lines along principal component 1 demonstrates the contribution of these genes to the differential phenotypes.

amplification in the NSCLC samples as well suggests that this gene may play an essential role in the development of lung cancers (Garnis et al. 2006).
 It is noteworthy that a subset of the genomic similarities between the SCLC and NSCLC cell lines could be the result of adaptation to culturing conditions. Owing to this, the greatest insight into the biology of the clinical disease will be attainable through analysis of differences (rather than their similarities) in genomic alterations and gene regulation.

Regions of difference
 Through our analysis, numerous regions throughout the genome were determined to be differentially altered between the SCLC and NSCLC samples. This difference-based approach compensates for random cell culturing artifacts and should identify the regions most strongly linked to clinical disease. These regions ranged in size from whole chromosomes (chromosome 21) to discrete peaks, kilobases in size (3q27.1). Using our stringent, multiplex criteria (Fisher's exact test followed by additional thresholding), we detected several regions that differed strongly in their alteration status between the cell types; we refer to these as phenotype-specific copy number alterations (PSCNAs). These included 1p36.33-1p34.2,



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Grid Snap OFF



Ambiguity of usual representations

$X \longrightarrow Y$



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



Ambiguity of usual representations



X inhibits Y

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



Ambiguity of usual representations



is transformed into

translocates ($X \rightleftharpoons Y$)

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associates into

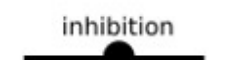
dissociates into

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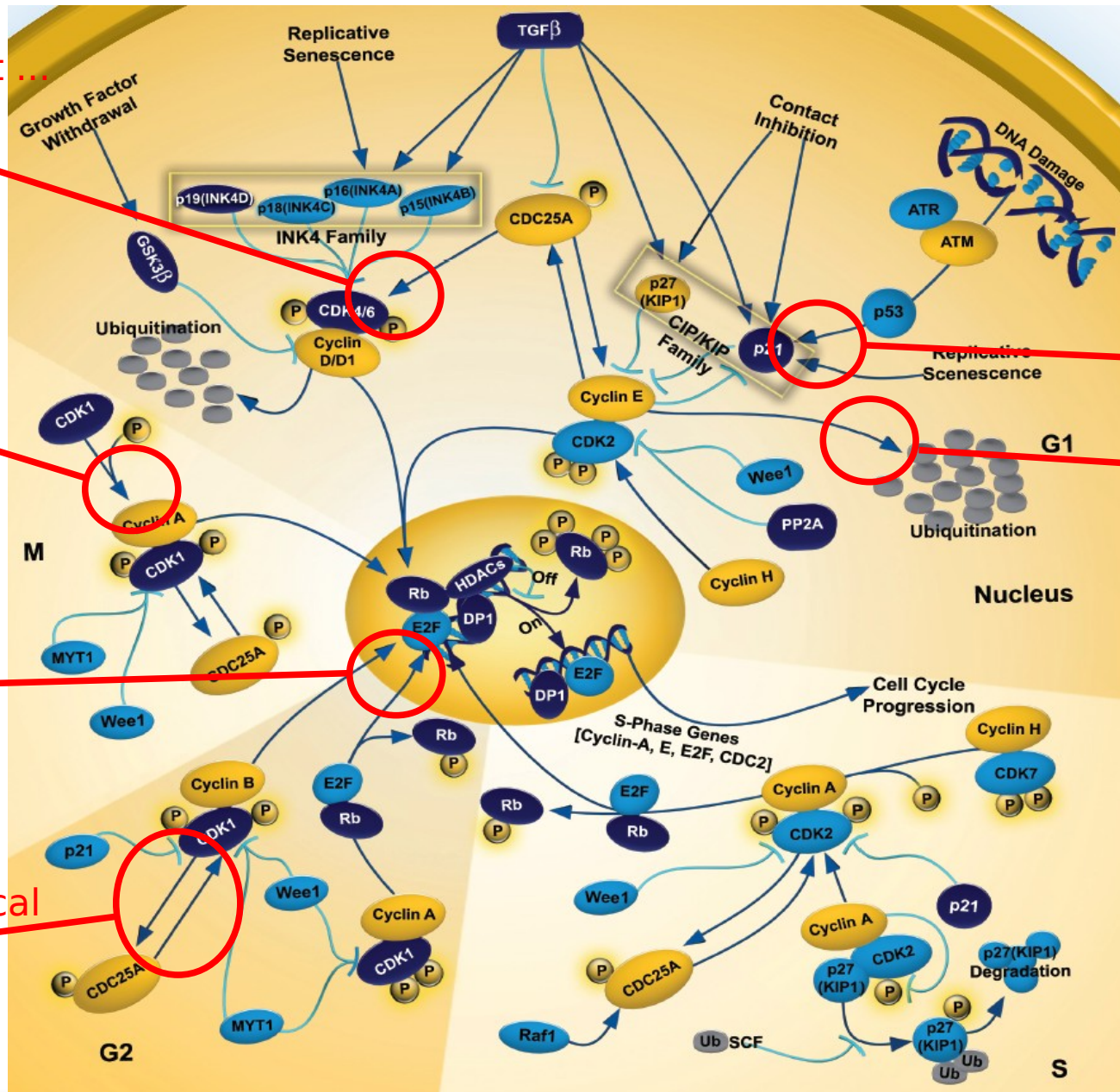
X inhibits Y





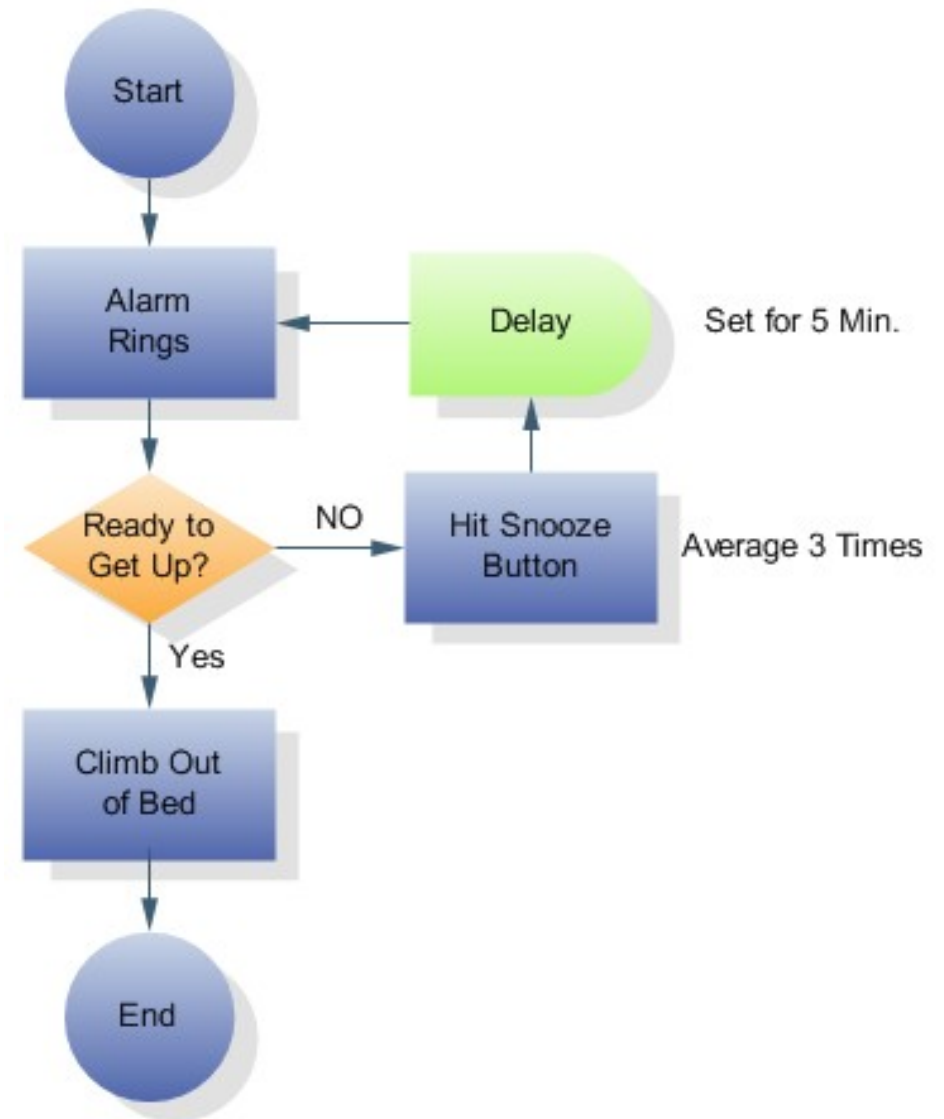
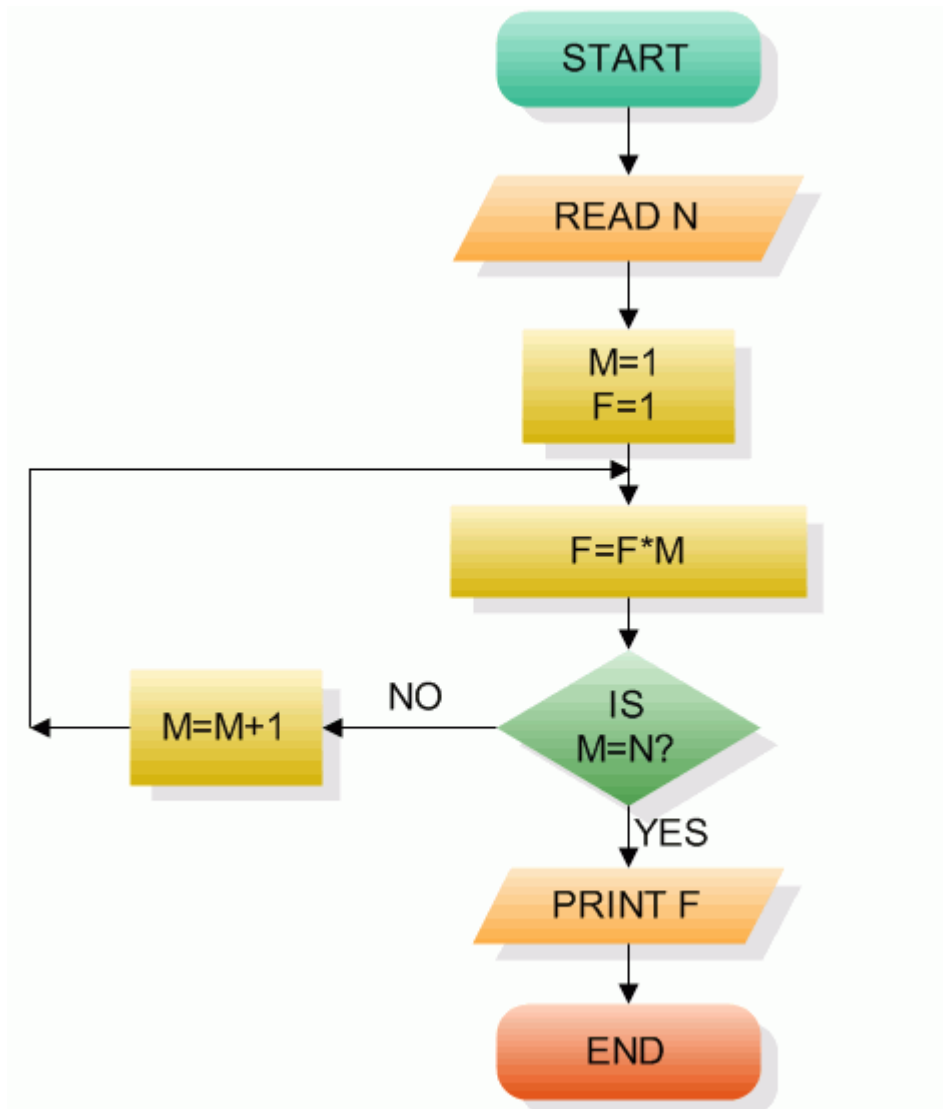


Can this be understood by biologists?



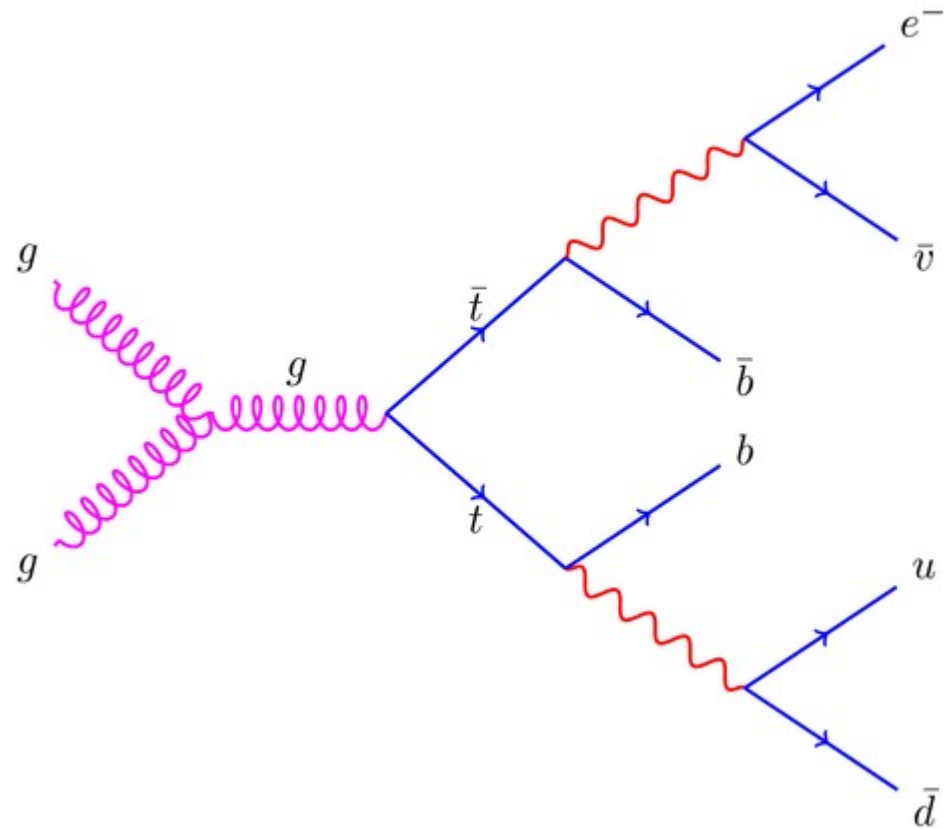
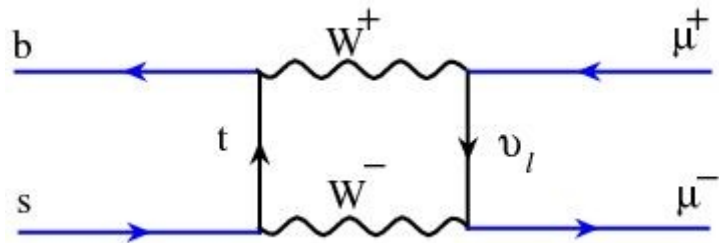


Every computer scientist understands those



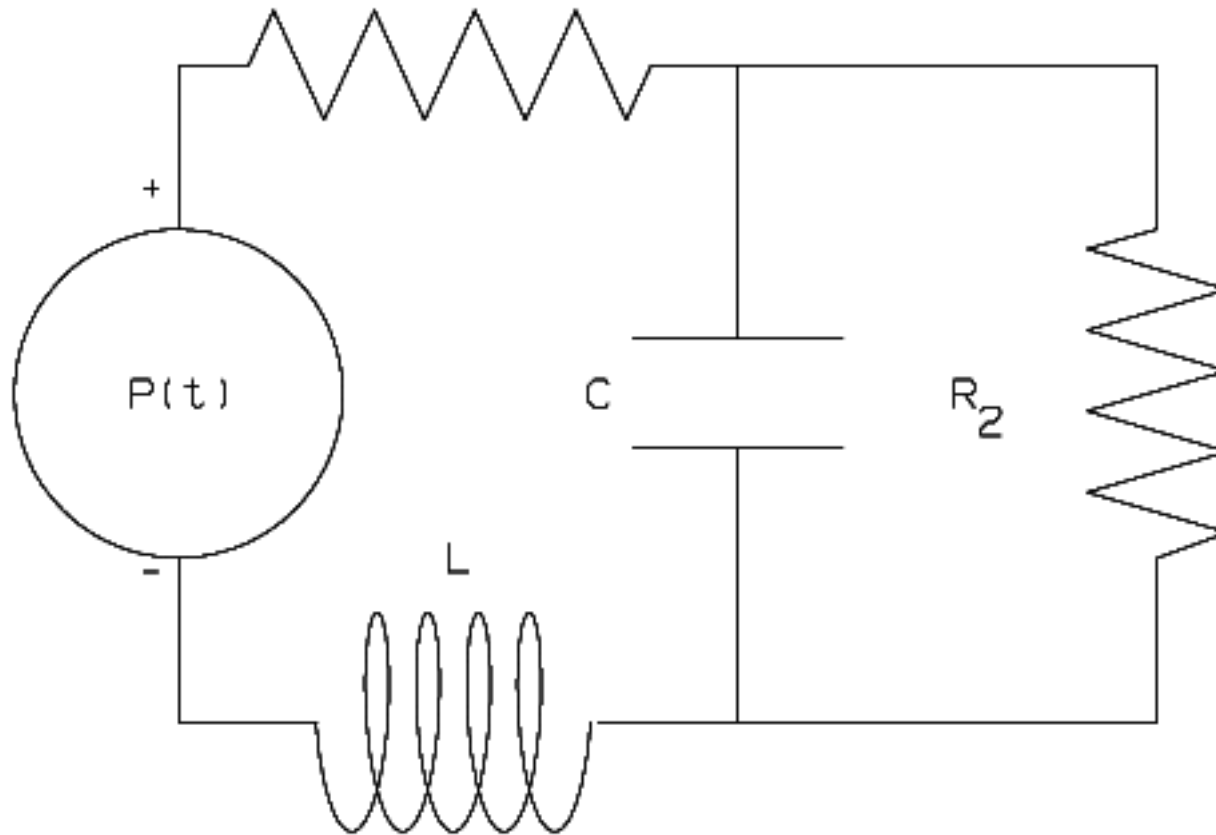


Every physicist understands those

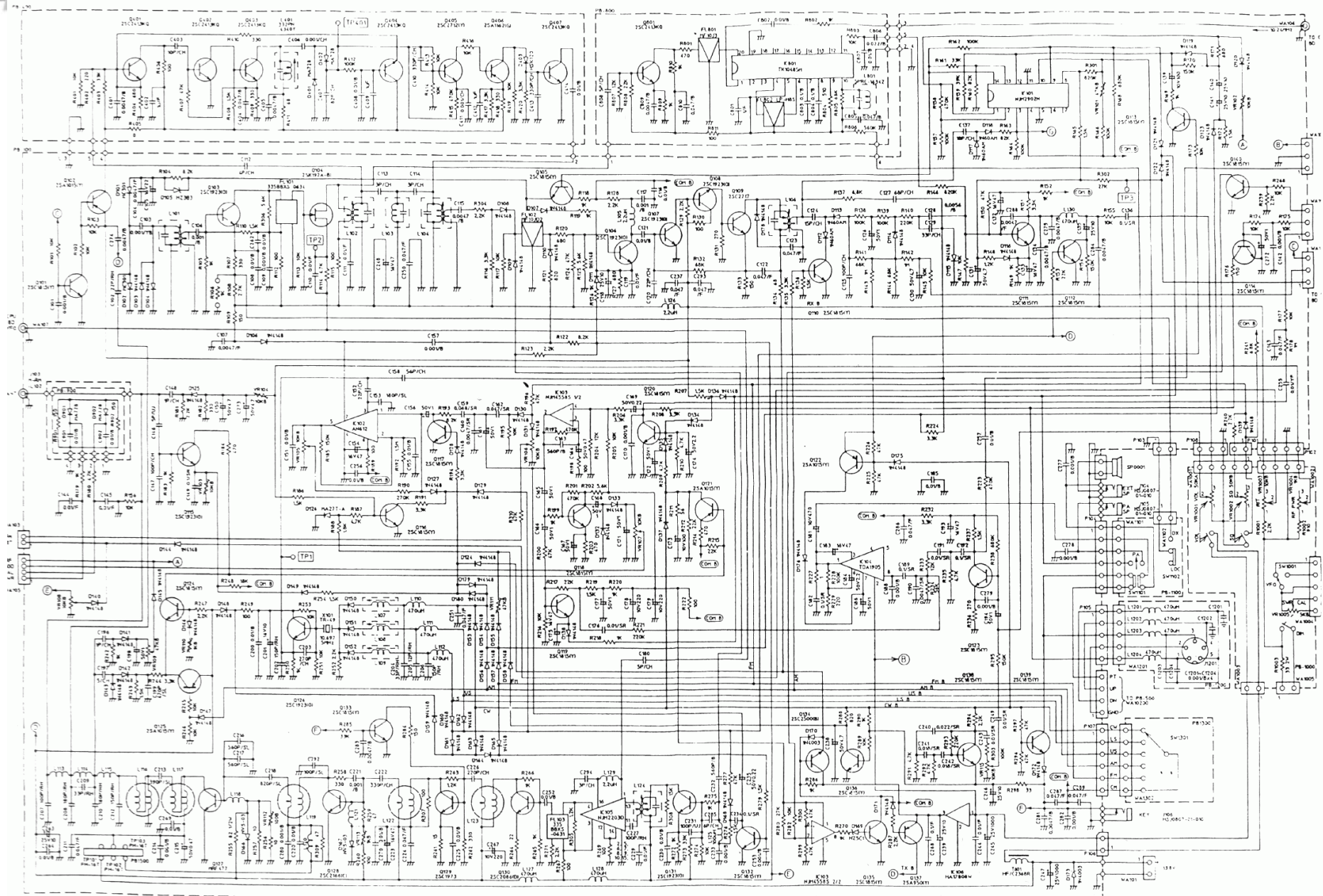




Every engineer understands that



Or that





What did those diagram bring?





What do-we expect in modern (future) life science

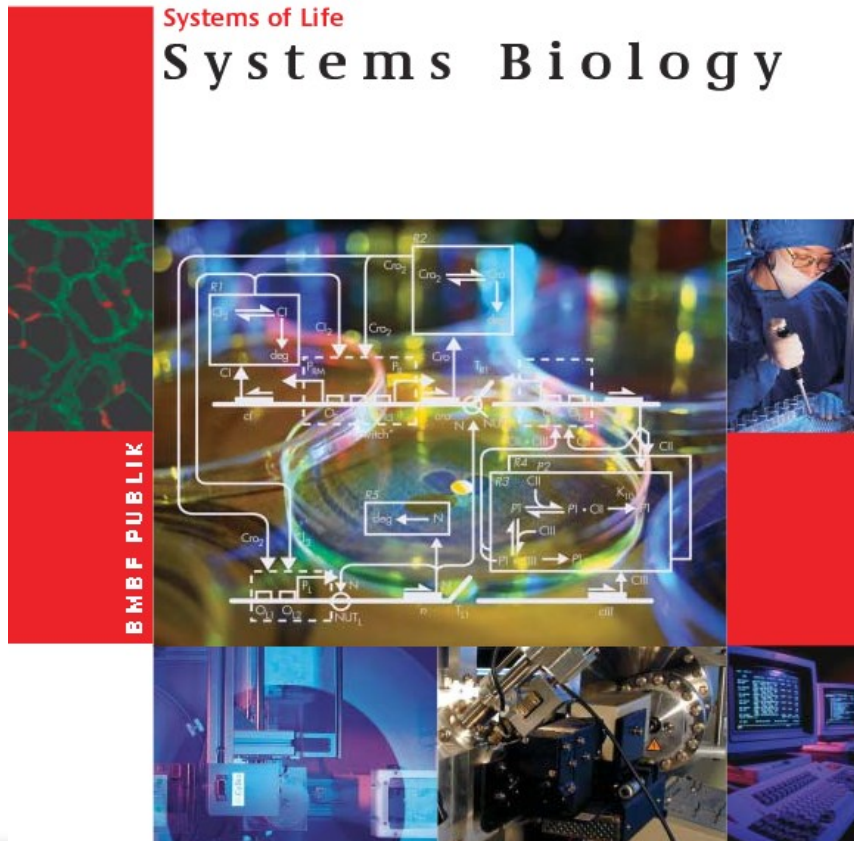


Federal Ministry
of Education
and Research

Basic science

Systems of Life

Systems Biology



Technology



EXTREME GENETIC ENGINEERING

An Introduction to Synthetic Biology

January 2007



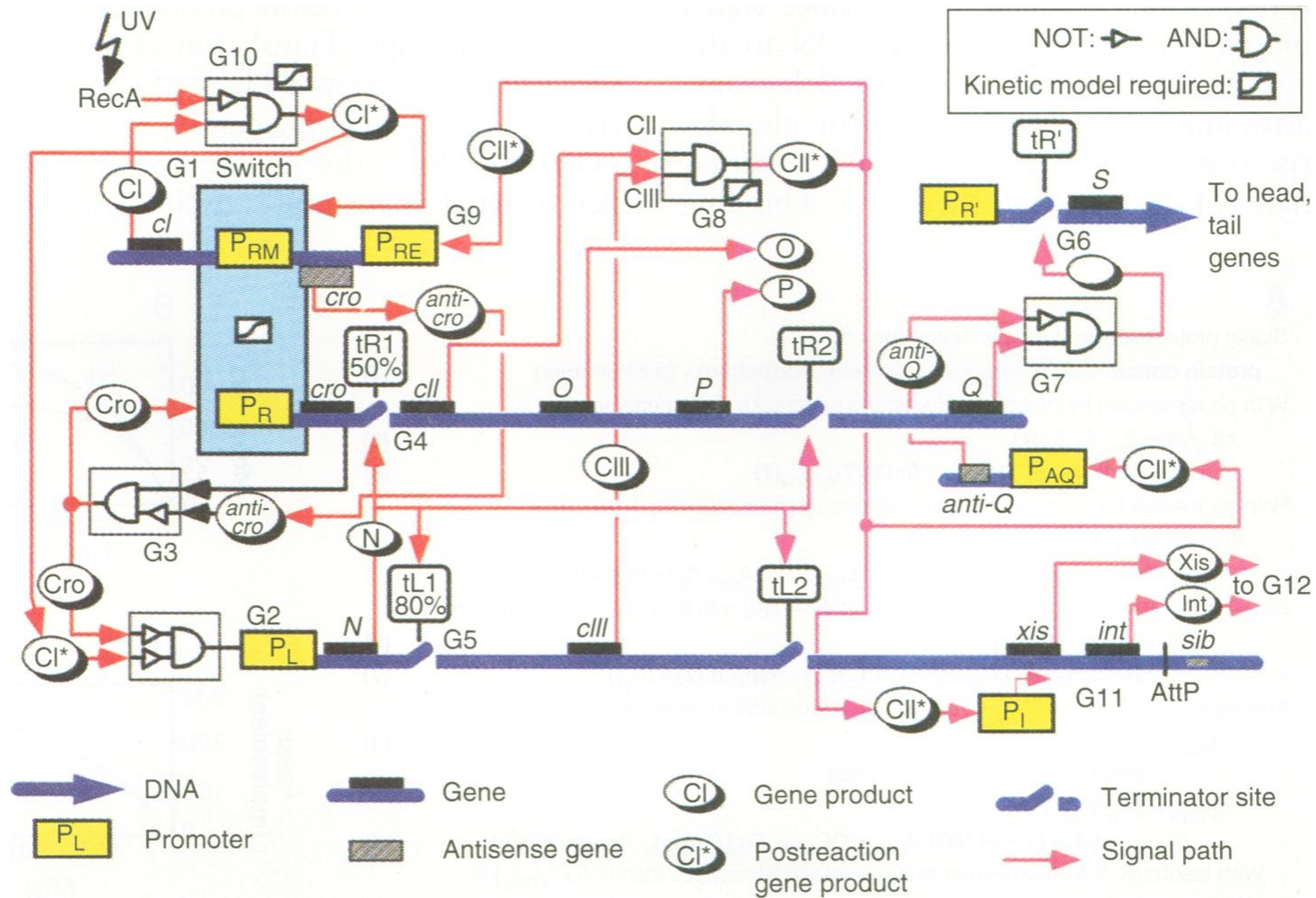


Why can-we understand electric diagrams?

- Standard symbols
 - Simple shapes, easily recognisable
 - Limited number of basic symbols (<70)
 - Similarity of shapes reflects similarity of functions
- Unambiguous interpretation of the circuits
- Endorsed by the community for practical reasons
 - End-users: manufacturers
 - Tool developers
 - Publishing industry
 - Teaching communities



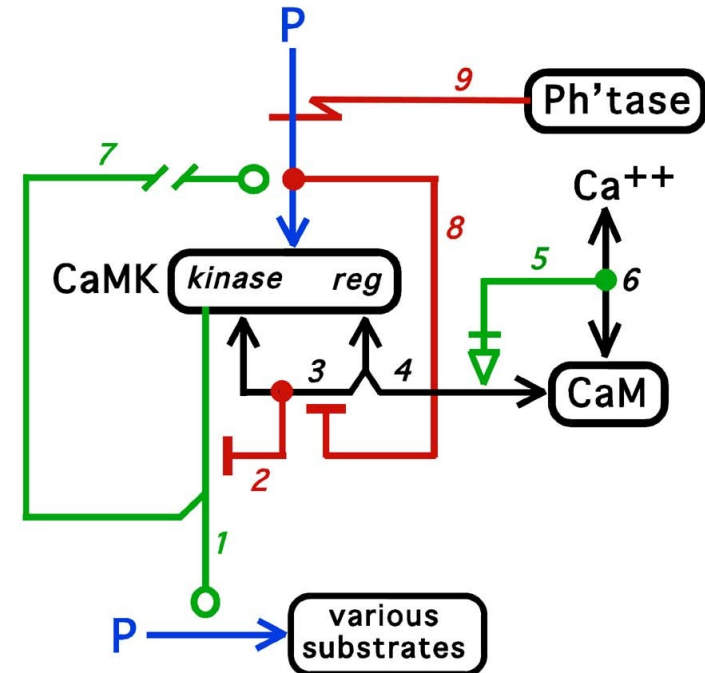
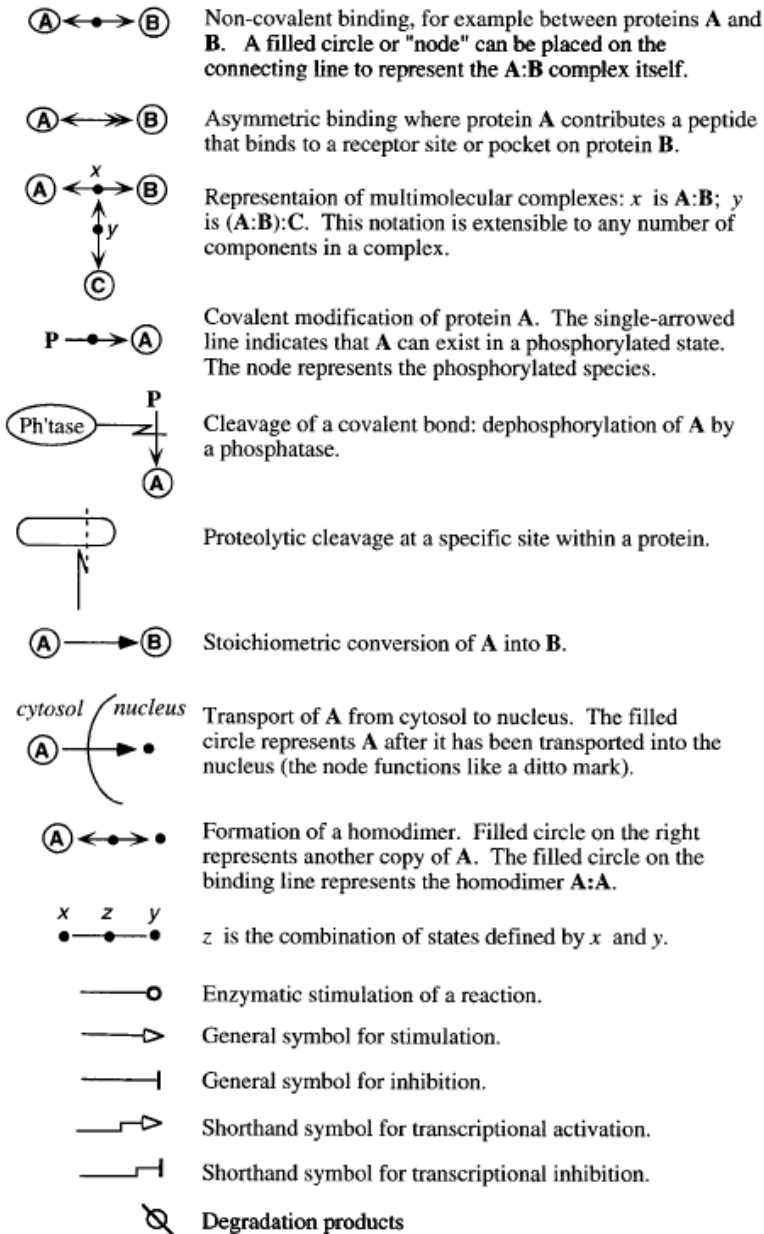
Using electrical diagrams



- McAdams and Shapiro (1995) Science, 269: 650-657



Kohn's Molecular Interaction Maps



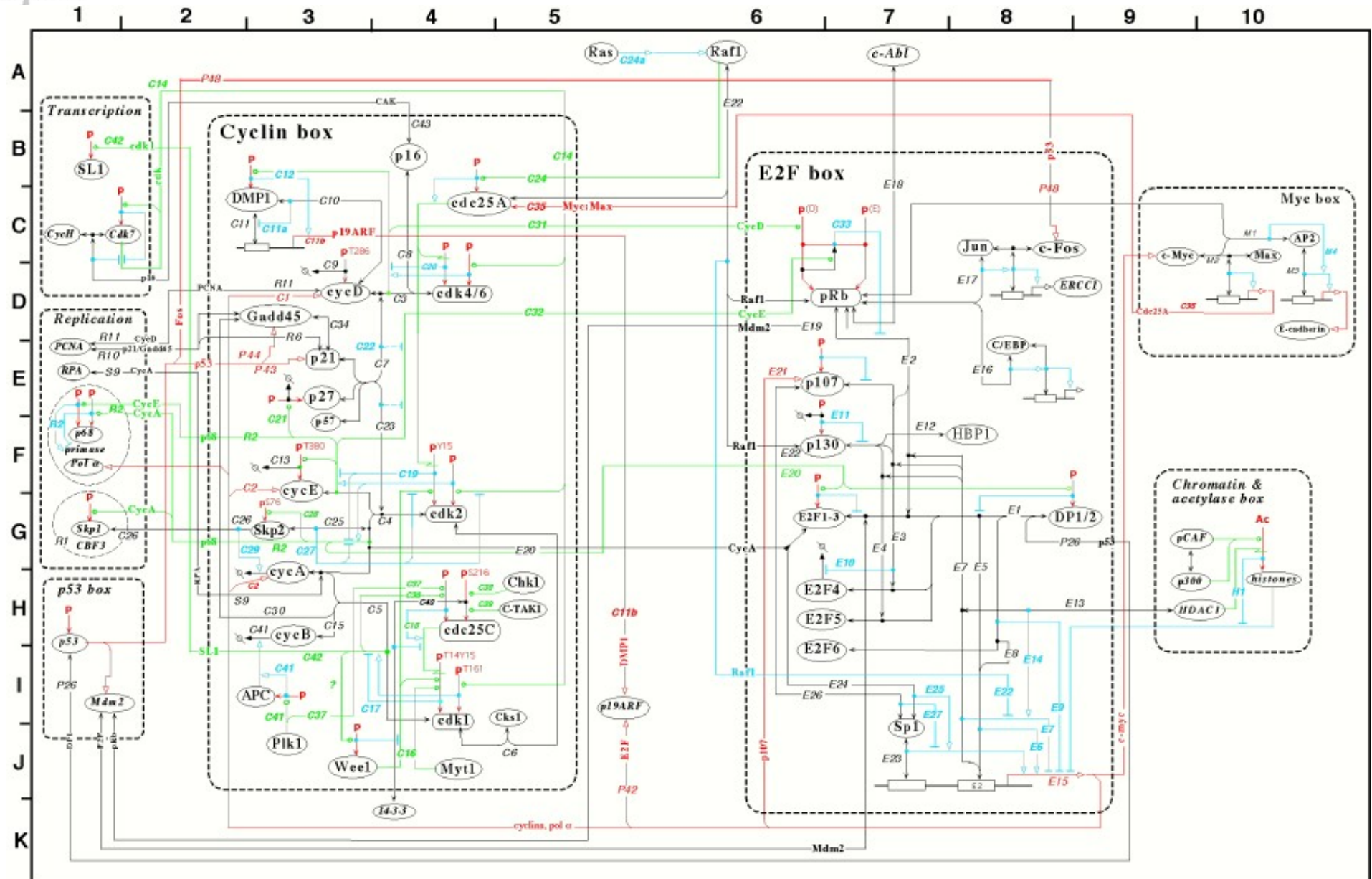
- Kurt W Kohn (1998)
Oncogene, 16: 1065-1075
- Kurt W. Kohn (1999)
Mol Biol Cell, 10(8):2703-2734





MIM are Entity Relationship diagrams

- Non-sequential interactions between entities
- Each *entity* appears only once
- Complexes are defined by interactions
- Modulations of relationships possible
- Order of interactions is meaningful (only binary ones)
- Angles between edges are meaningful
- ...
- Designed manually





Kitano's Notation

State node symbols

Protein	
Receptor	
Ion channel (closed)	
Ion channel (open)	
Truncated protein	
Gene	
RNA	
Anti-sense RNA	
Ion	
Simple molecule	
Unknown	
Phenotype	
Homodimer / N-mer with N stacked symbols	
Active protein	

Arc symbols (Transit node and edges)

State transition	
Known transition omitted	
Unknown transition	
Bidirectional transition	
Translocation	
Association	
Dissociation	
Truncation	
Promote transition	
Inhibit transition	
Add reactant	
Add product	
AND	
OR	

Reduced notation symbols

Category-I reduced notation

Degradation	
Transcription	
Translation	
Module	

Category-II reduced notation (viewer only)

Activation/inhibition/modification	
------------------------------------	--

Node structure

Residue modification	
Complex state node	
Promotor and coding structure for gene	
Exon structure for RNA	

- Kitano (2003)
Biosilico, 1: 169-170
- Kitano et al (2005)
Nat Biotech, 23: 961-966



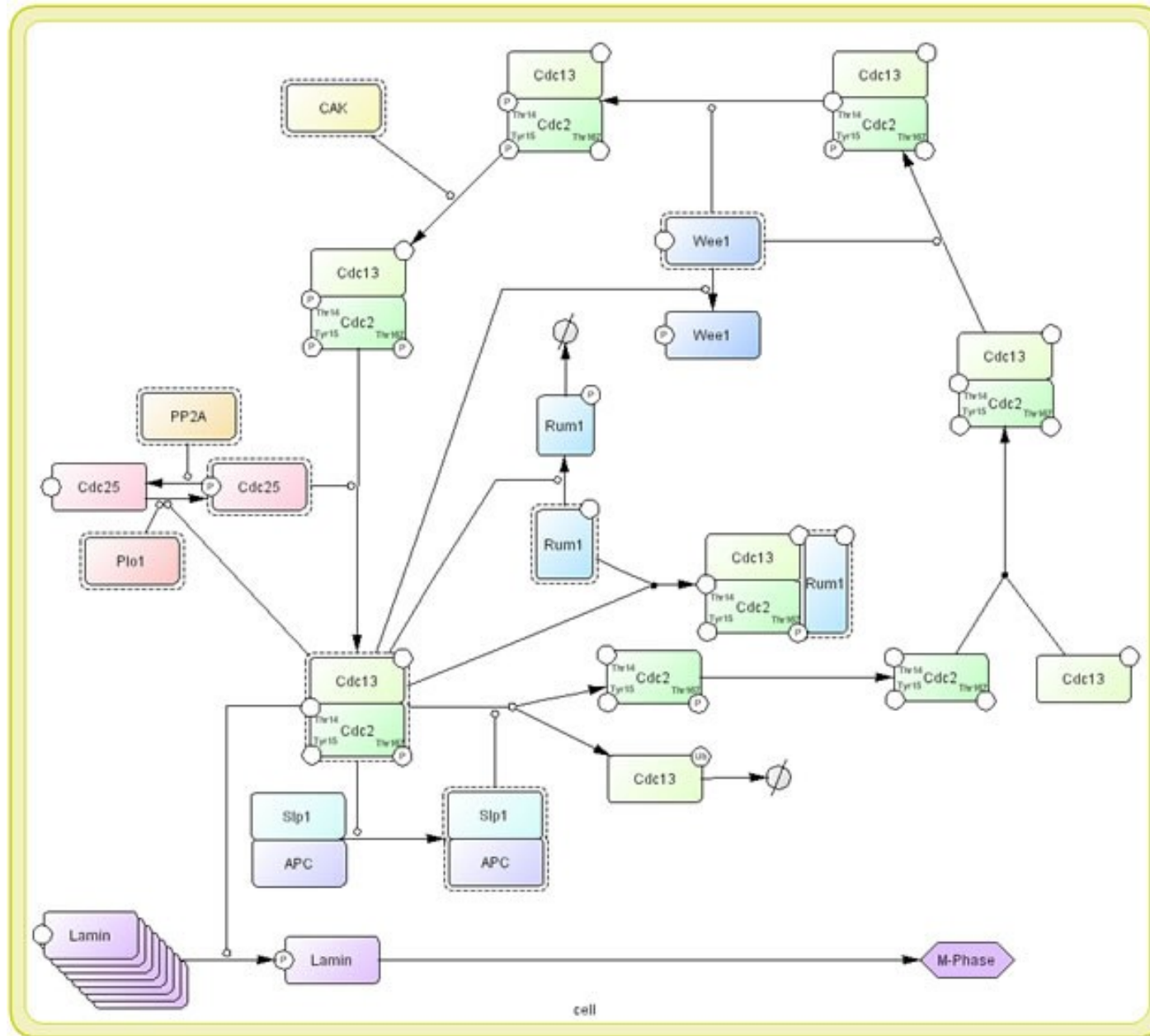


Kitano's graphs are Process Diagrams

- Causal sequence of molecular processes and their results
- Each *state* appears only once
- Complexes are defined as independent entity nodes
- Correspondence with *pathway* descriptions and reaction-based *models*
- Some software support (CellDesigner)



Cell Cycle in Kitano's Process Diagram







Why were those pioneer efforts not suitable?

- Somehow fuzzy semantics
 - No structured data model or ontology behind the notation
 - Overlapping concepts rather than sub-classing
 - Gaps in the coverage of biochemistry or modelling
 - Ambiguous interpretation of the graph
- Little software support (except CellDesigner for Kitano's Process Diagrams)
- No community involvement
 - No systematic bug tracking and consistency checking
 - No comprehensive coverage (focussed on some use-cases)
 - No endorsement by the tool developers or by the end-users



Enters The Systems Biology Markup Language



<http://www.sbgn.org/>



- A way to unambiguously describe biochemical and cellular events in graphs
- Limited amount of symbols ➡ Smooth learning curve
- Can graphically represent quantitative models, biochemical pathways, at different levels of granularity
- Developed over three years by a growing community



The Systems Biology Graphical Notation

¶

Nicolas Le Novère^{1*}, Michael Hucka^{2*}, Huaiyu Mi^{3*}, Stuart Moodie^{4*}, Falk Schreiber^{5,6*},
Anatoly Sorokin^{7*}, Emek Demir⁸, Katja Wegner⁹, Mirit Aladjem¹⁰, Sarala M
Wimalaratne¹¹, Frank T. Bergman¹², Ralph Gauges¹³, Peter Ghazal^{4,21}, Kawaji
Hideya¹⁴, Lu Li¹, Yukiko Matsuoka¹⁵, Alice Villéger^{16,17}, Sarah E. Boyd¹⁸, Laurence
Calzone¹⁹, Melanie Courtot²⁰, Ugur Dogrusoz²¹, Tom Freeman²², Akira Funahashi²³,
Samik Ghosh¹⁵, Akiya Jouraku²³, Sohyoung Kim¹⁰, Fedor Kolpakov²⁴, Augustin
Luna¹⁰, Sven Sahle²⁵, Esther Schmidt¹, Steven Watterson^{4,22}, Guanming Wu²⁶, Igor
Goryanin⁴, Douglas B. Kell^{17,27}, Chris Sander⁸, Herbert Sauro¹², Jacky L. Snoep²⁸, Kurt
Kohn¹⁰, Hiroaki Kitano^{15,29,30¶}

¶

39 authors, 30 affiliations

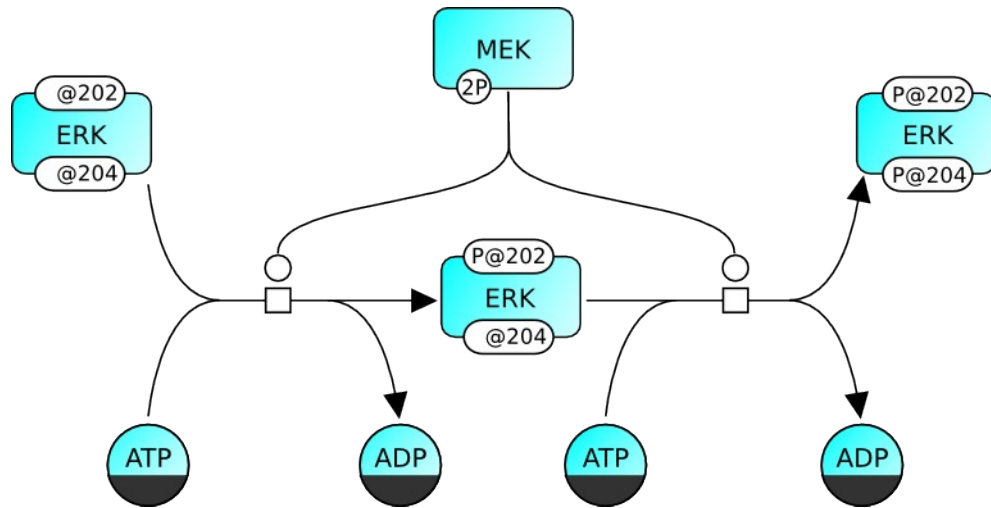


- A way to unambiguously describe biochemical and cellular events in graphs
- Limited amount of symbols ➡ Smooth learning curve
- Can graphically represent quantitative models, biochemical pathways, at different levels of granularity
- Developed over three years by a growing community
- Three languages
 - Process Diagrams ➡ one state = one glyph, biochemical level
 - Entity Relationships ➡ one entity = one glyph, biochemical level
 - Activity Flow ➡ conceptual level



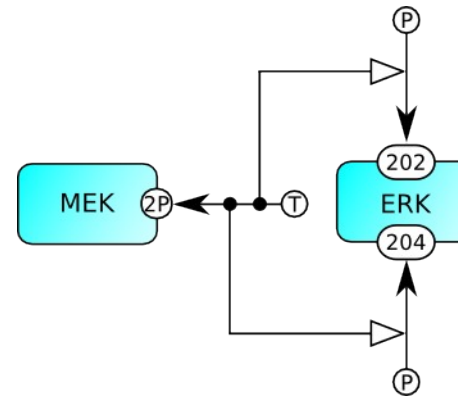
Graph trinity: three languages in one

Process diagrams



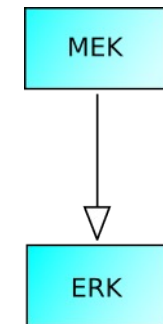
- Unambiguous
- Mechanistic
- Sequential
- Subject to combinatorial explosion

Entity Relationships
diagrams



- Unambiguous
- Mechanistic
- Non-sequential

Activity Flow
diagrams

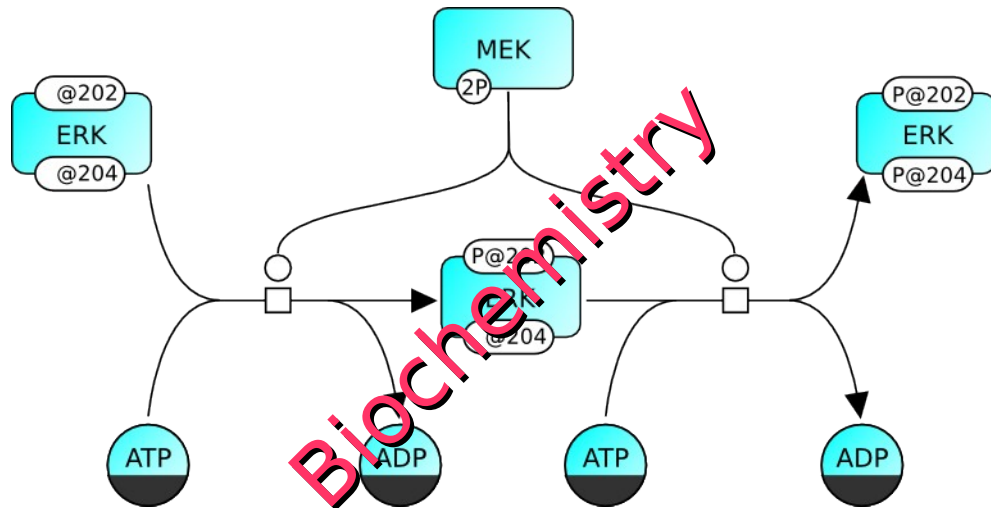


- Ambiguous
- Conceptual
- Sequential



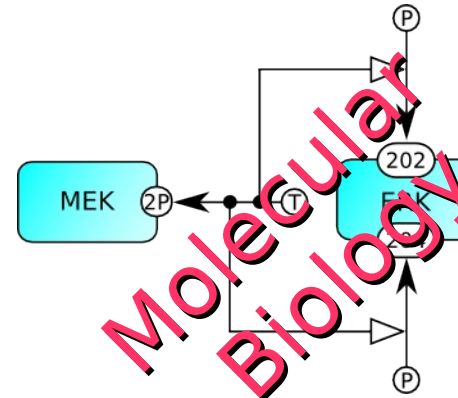
Graph trinity: three languages in one

Process diagrams



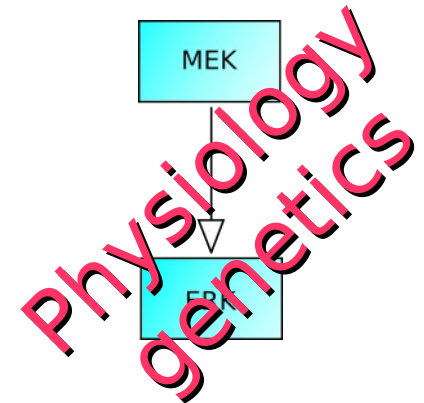
- Unambiguous
- Mechanistic
- Sequential
- Combinatorial explosion

Entity Relationships
diagrams



- Unambiguous
- Mechanistic
- Non-sequential
- Independence of relationships

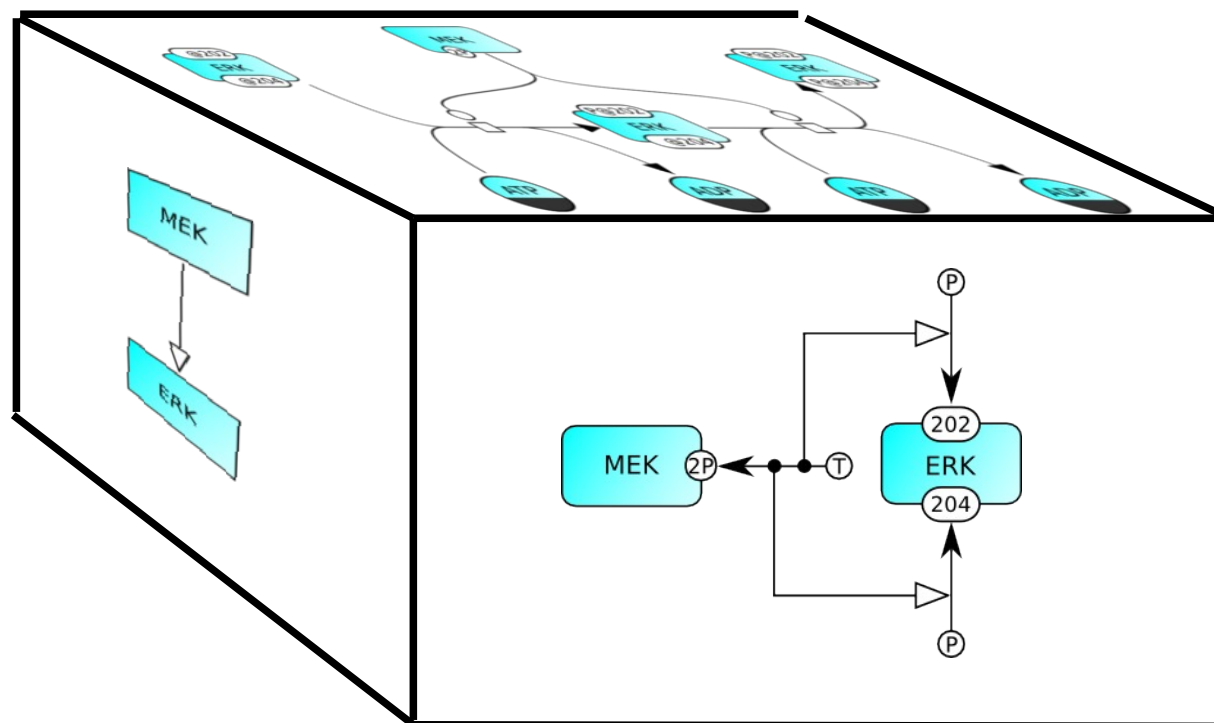
Activity Flow
diagrams



- Ambiguous
- Conceptual
- Sequential

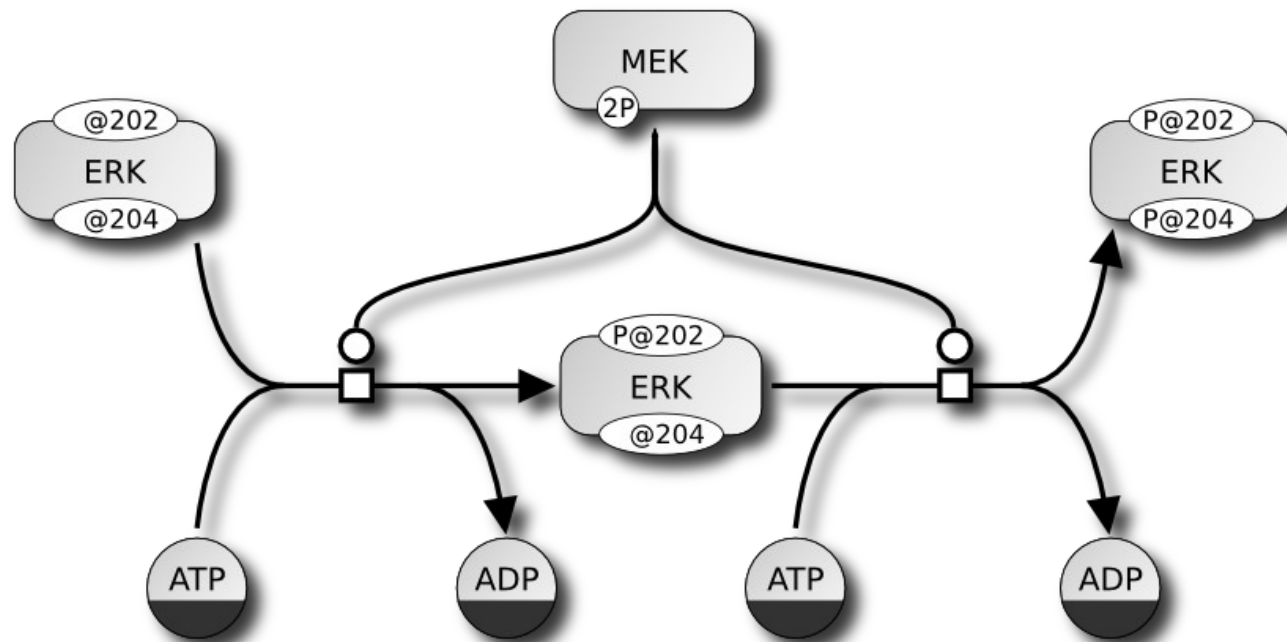


Three orthogonal projections of biology





SBGN Process Diagram Level 1

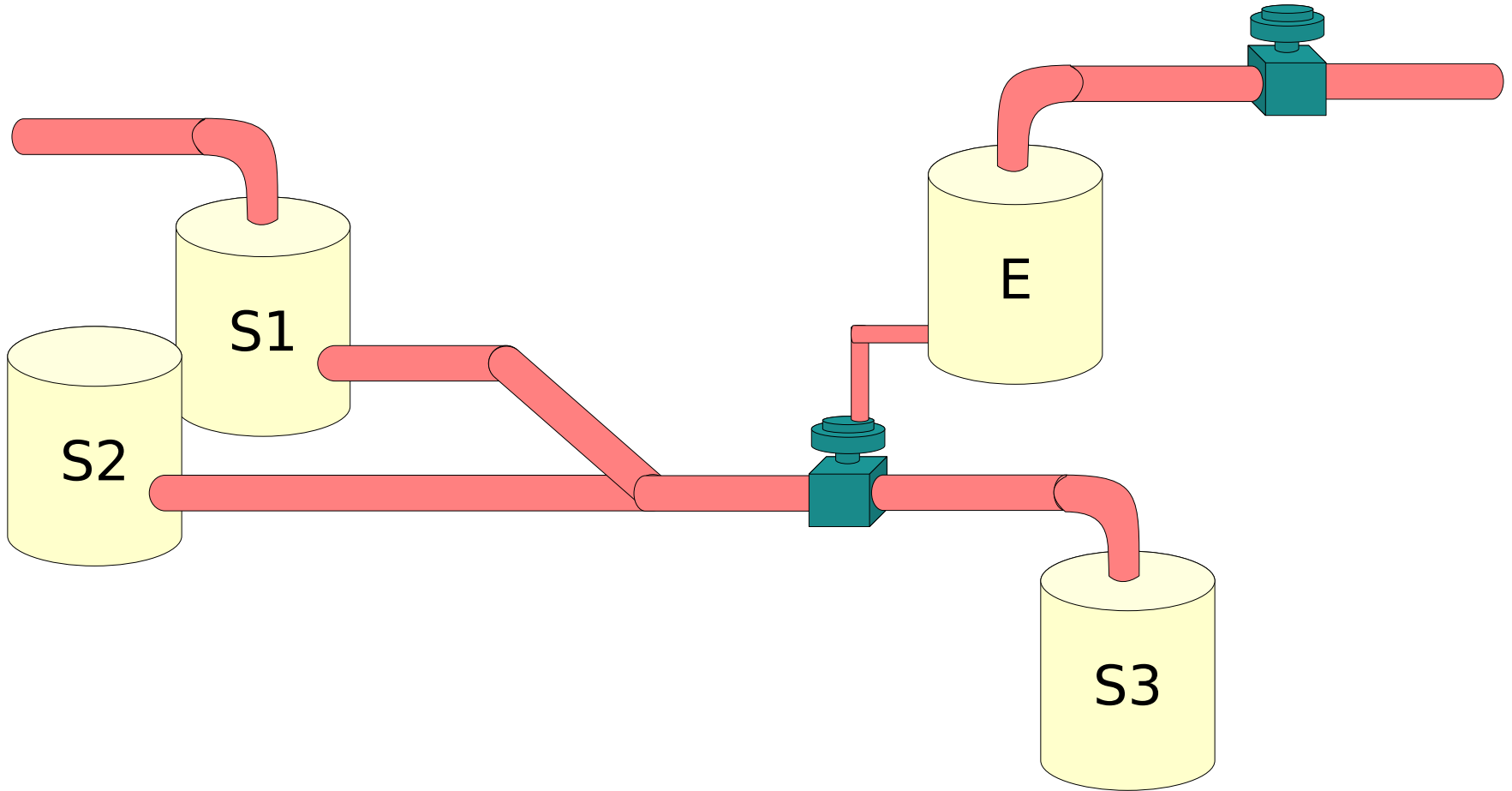


Le Novère, Moodie, Sorokin, Hucka, Schreiber, Demir, Mi, Matsuoka, Wegner, Kitano
Systems Biology Graphical Notation: Process Diagram Level 1 (2008)
Available from *Nature Precedings* <<http://hdl.handle.net/10101/npre.2008.2320.1>>



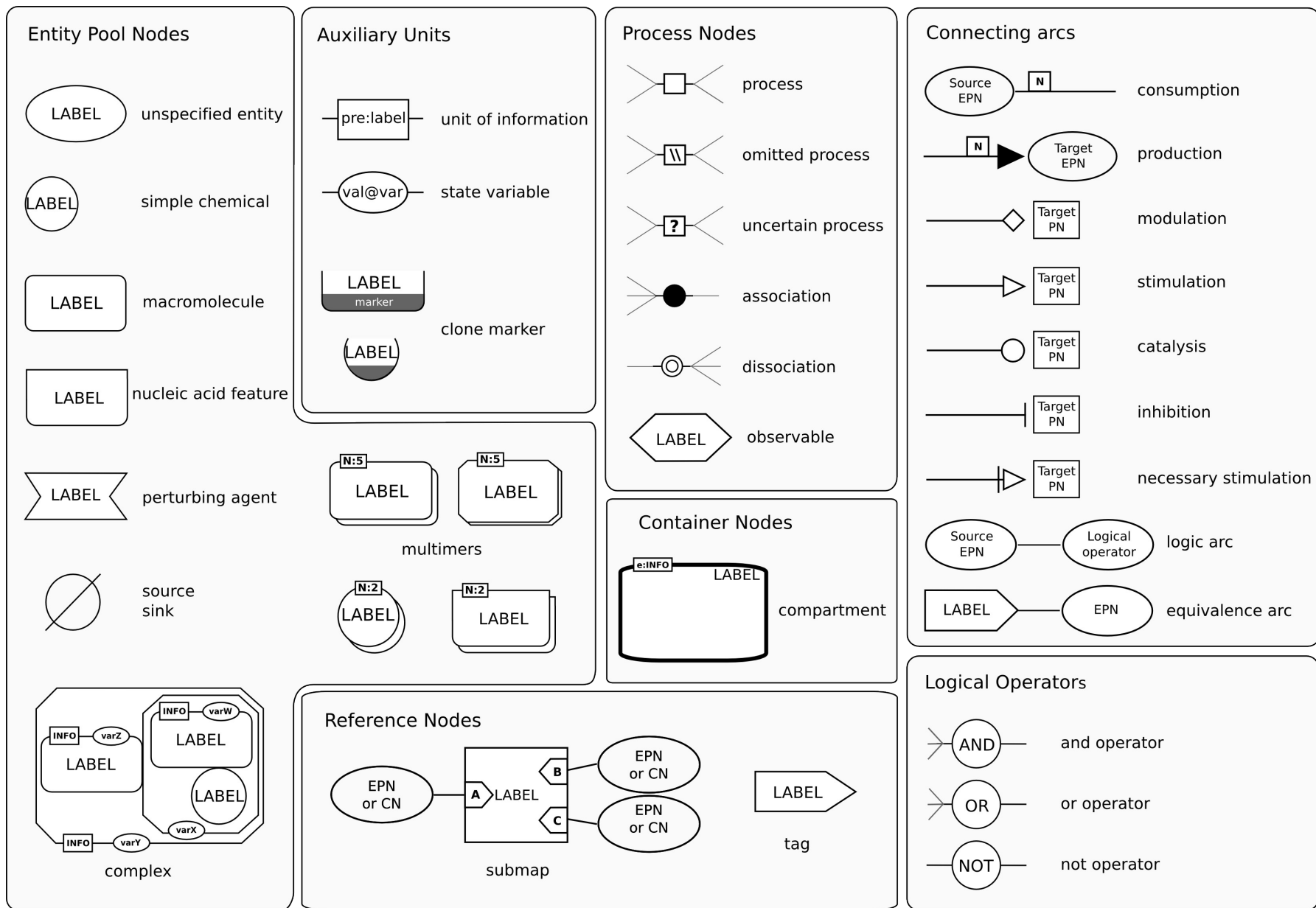


Process Diagrams can be viewed as pipelines



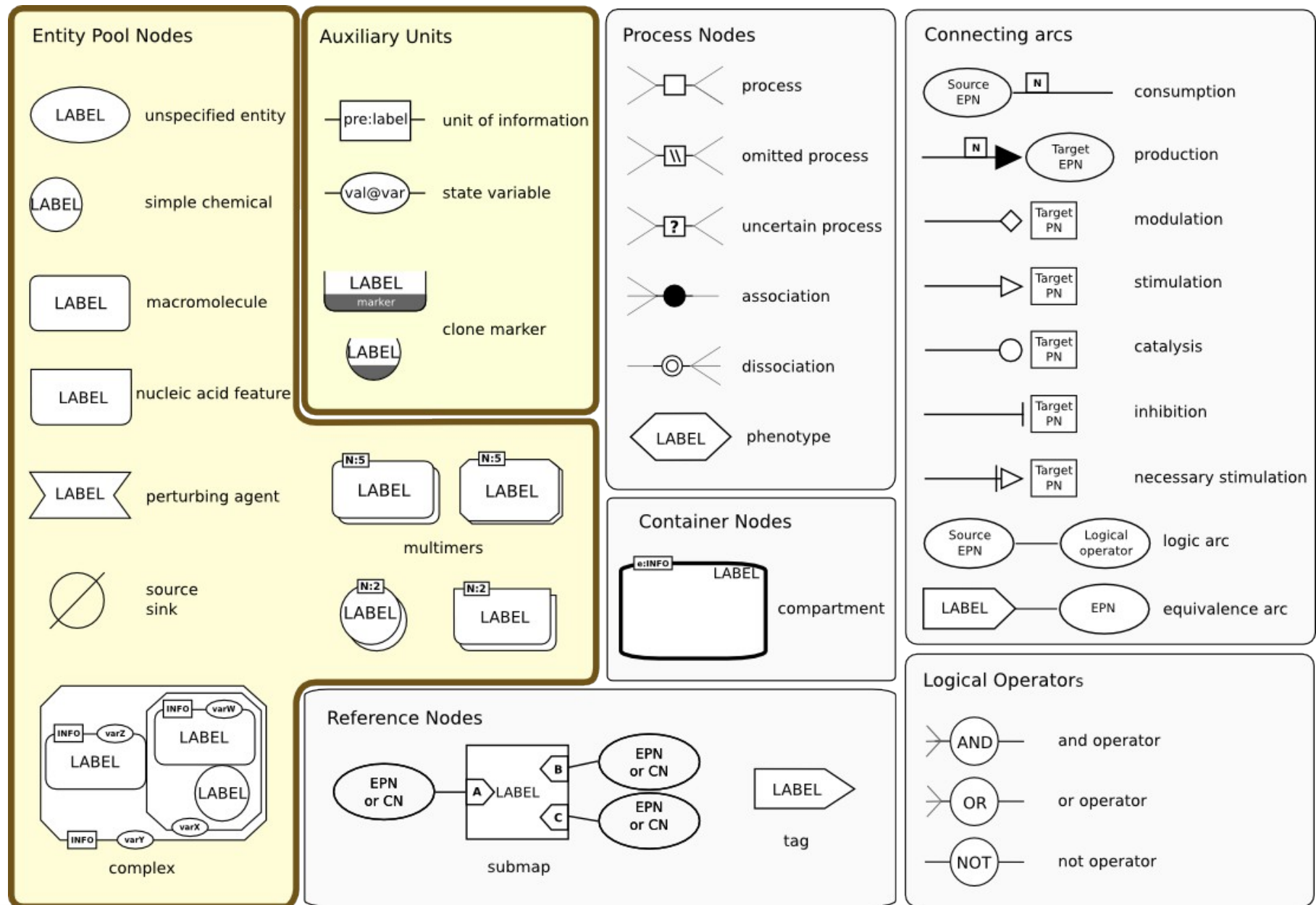


SBGN Process Diagram L1 reference card



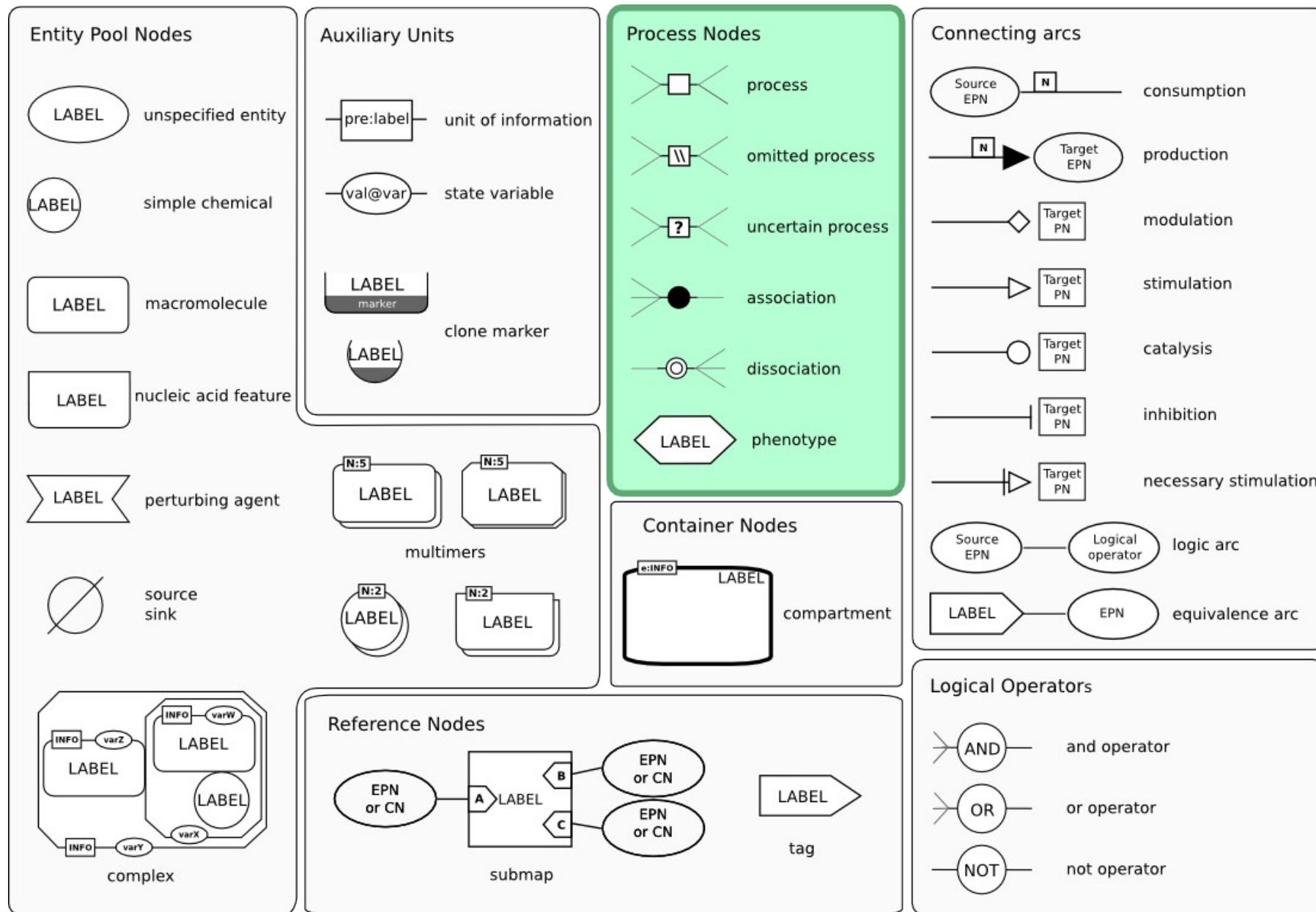


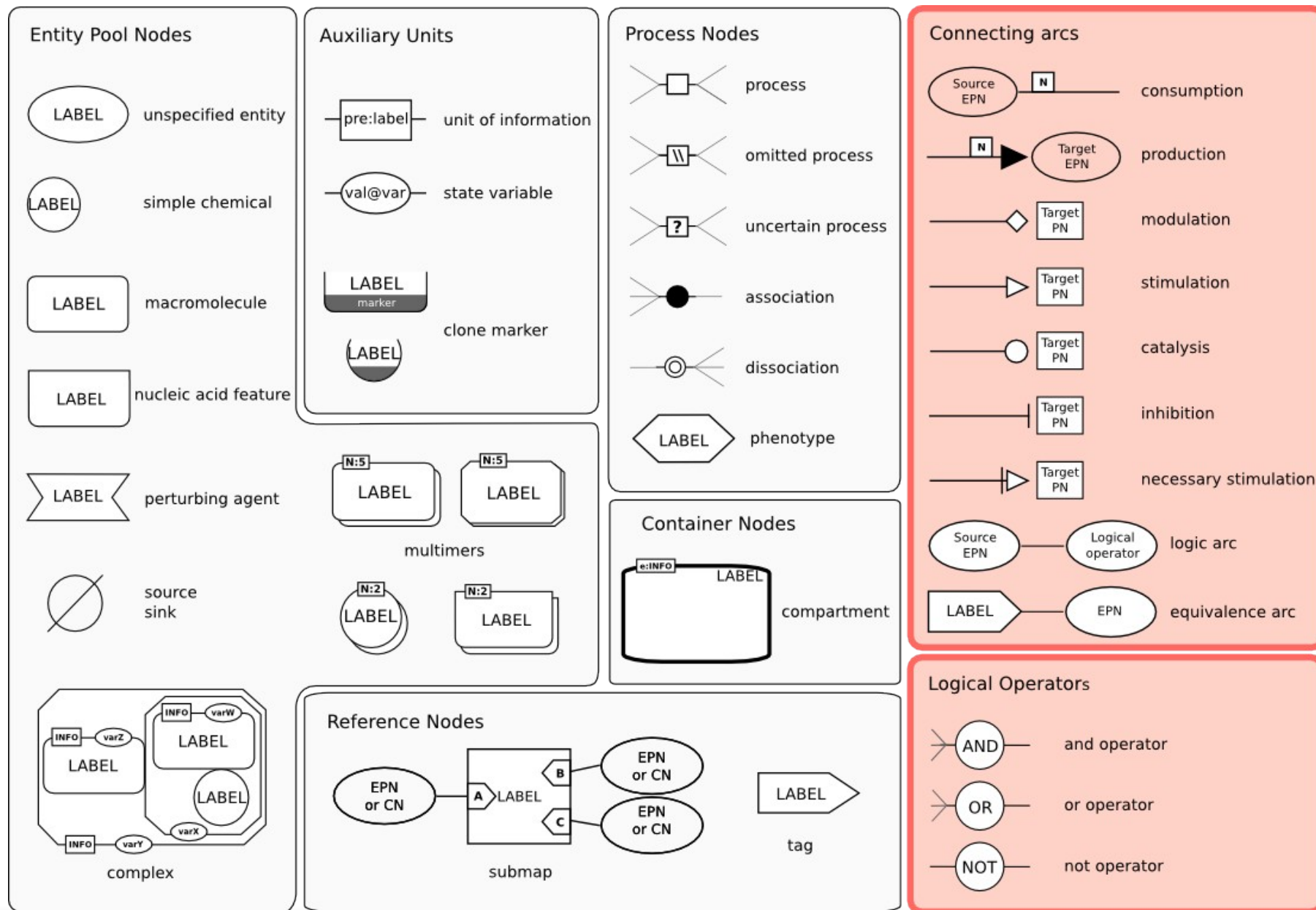
Entity Pool Nodes





Process Nodes



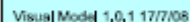




Syntax definition

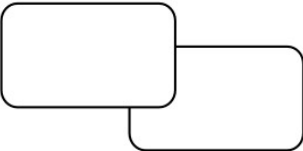
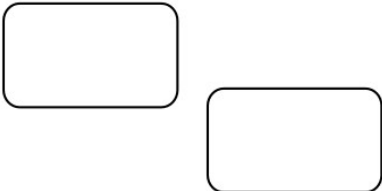
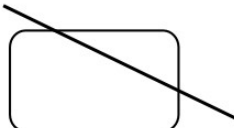
<i>Arc\EPN</i>	<i>macromolecule</i>	<i>simple chemical</i>	<i>unspecified entity</i>	<i>multimer</i>	<i>complex</i>	<i>nucleic acid feature</i>	<i>tag</i>	<i>source/sink</i>	<i>perturbation</i>	<i>observable</i>	<i>submap</i>
<i>consumption</i>	I	I	I	I	I	I		I			
<i>production</i>	O	O	O	O	O	O		O			
<i>modulation</i>	I	I	I	I	I	I			I	O	
<i>stimulation</i>	I	I	I	I	I	I			I	O	
<i>catalysis</i>	I	I	I	I	I				I	O	
<i>inhibition</i>	I	I	I	I	I	I			I	O	
<i>trigger</i>	I	I	I	I	I	I			I	O	
<i>logic arc</i>	I	I	I	I	I	I					
<i>equivalence arc</i>	I	I	I	I	I	I	O				O

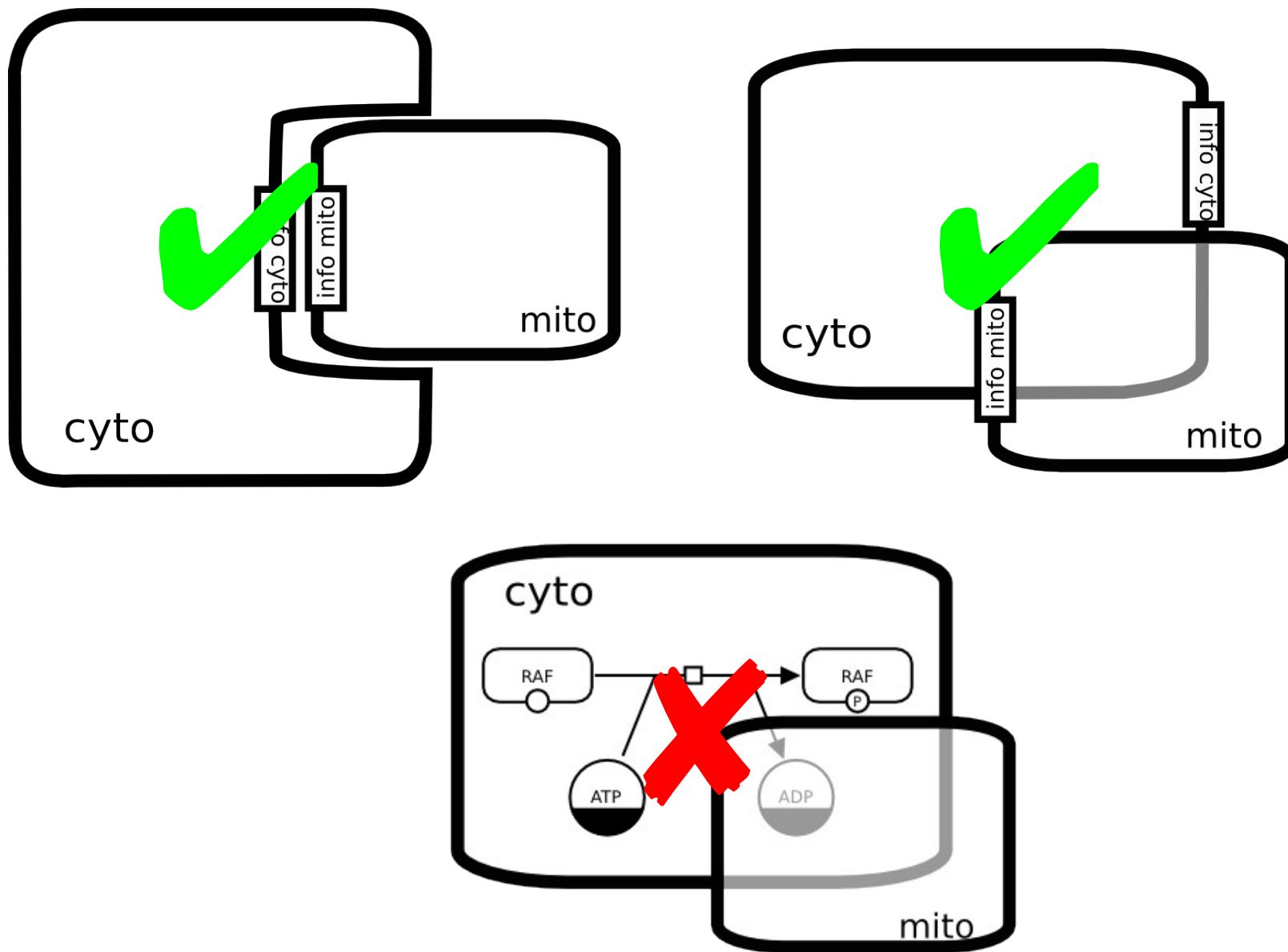
<i>Arc\PN</i>	<i>transition</i>	<i>omitted process</i>	<i>uncertain process</i>	<i>association</i>	<i>dissociation</i>	<i>and</i>	<i>or</i>	<i>not</i>
<i>consumption</i>	O	O	O	O	O(1)			
<i>production</i>	I	I	I	I(1)	I			
<i>modulation</i>	O	O	O			I(1)	I(1)	I(1)
<i>stimulation</i>	O	O	O			I(1)	I(1)	I(1)
<i>catalysis</i>	O	O	O			I(1)	I(1)	I(1)
<i>inhibition</i>	O	O	O			I(1)	I(1)	I(1)
<i>trigger</i>	O	O	O			I(1)	I(1)	I(1)
<i>logic arc</i>						O	O	O(1)
<i>equivalence arc</i>								





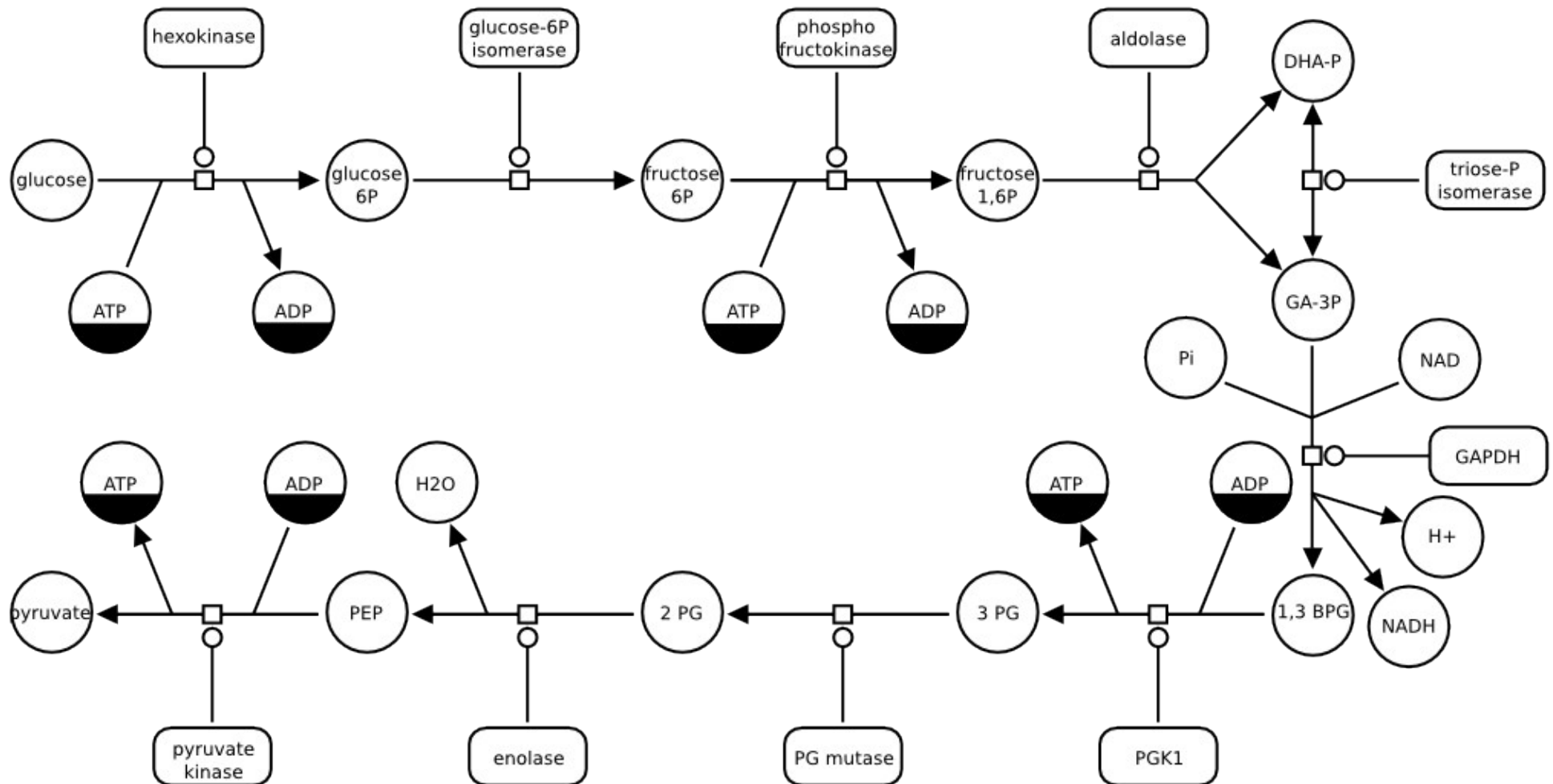
Layout constraints

 wrong	 correct	 wrong	 correct
 wrong	 correct	 better	
 wrong	 correct	 correct	
 wrong	 correct	 correct	



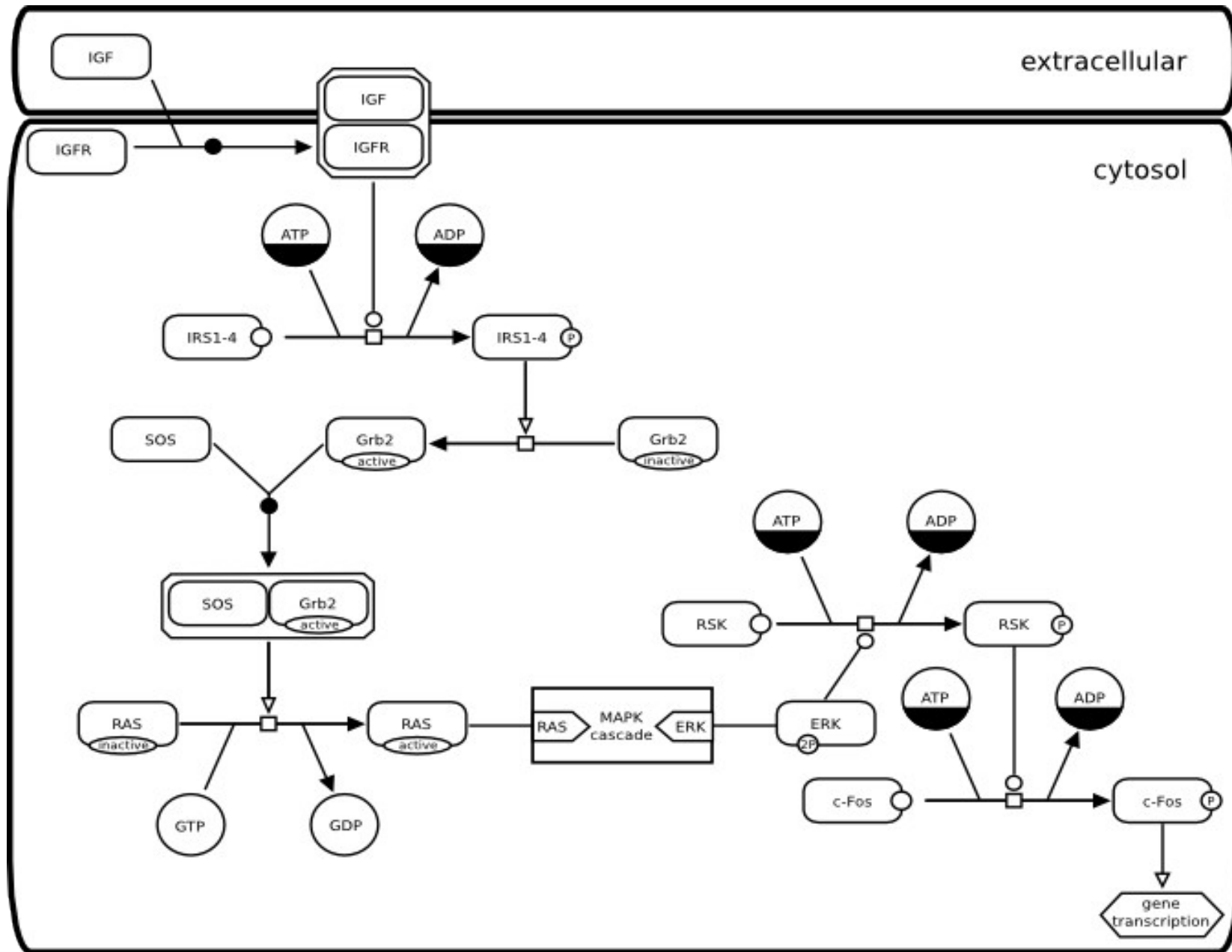


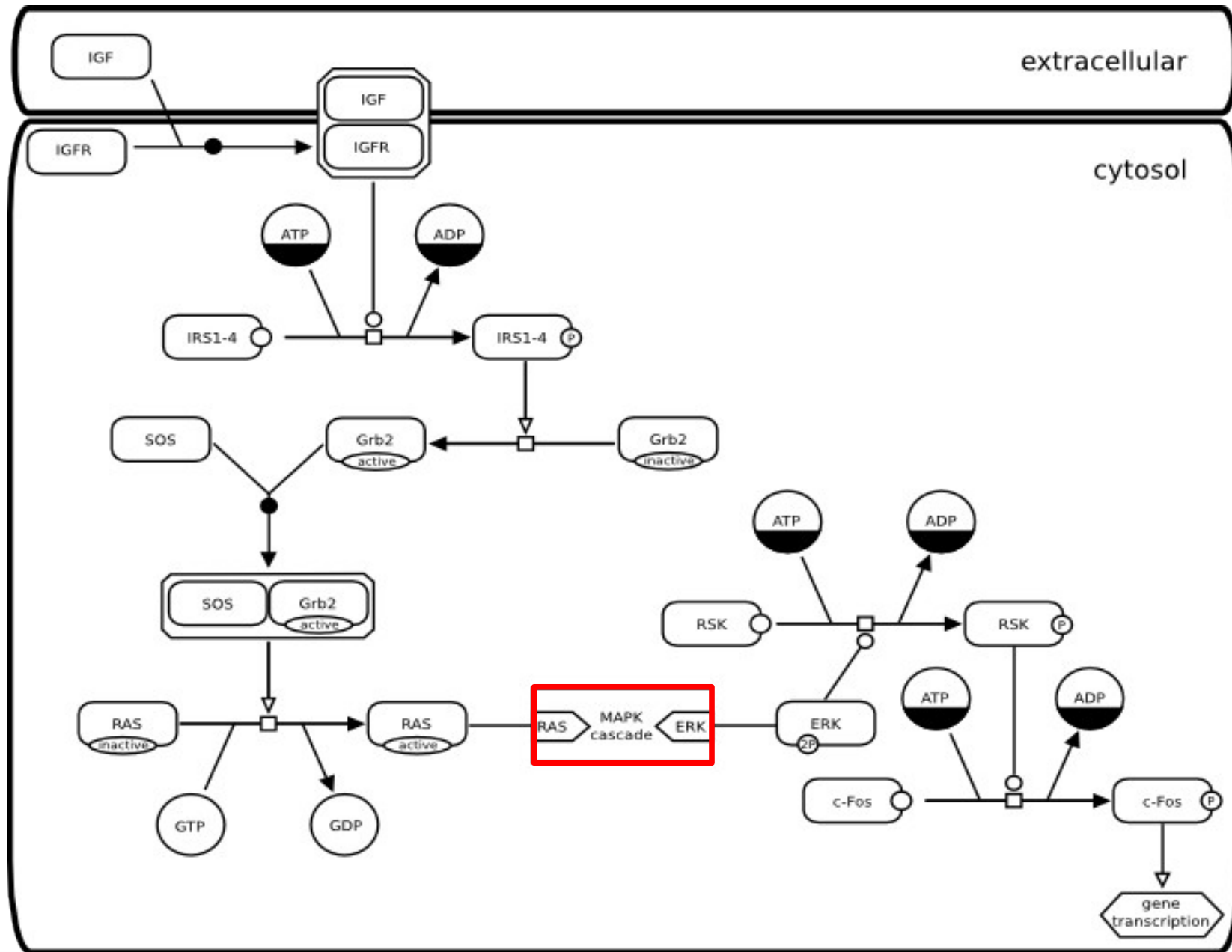
Metabolic network

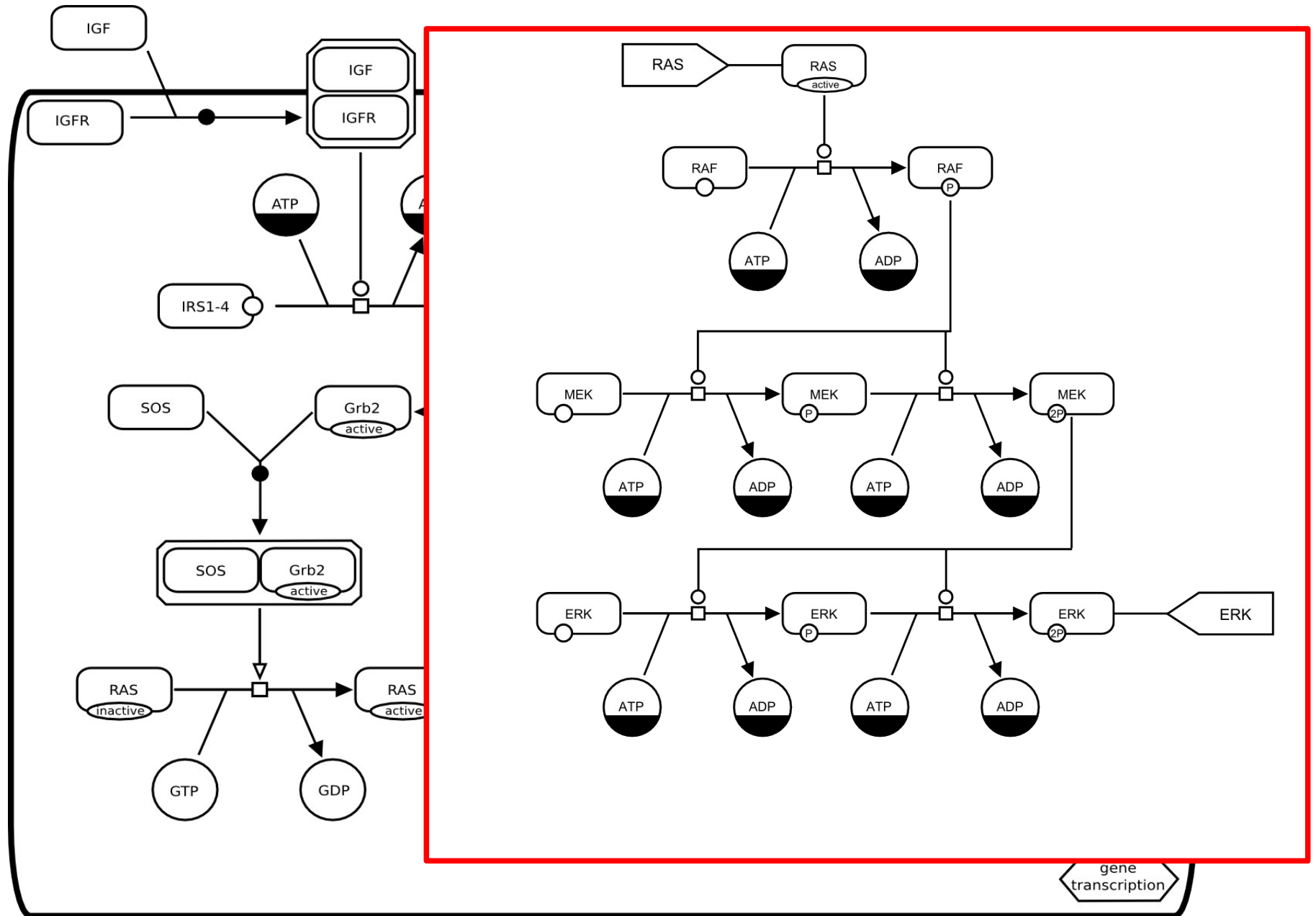




Signalling pathways

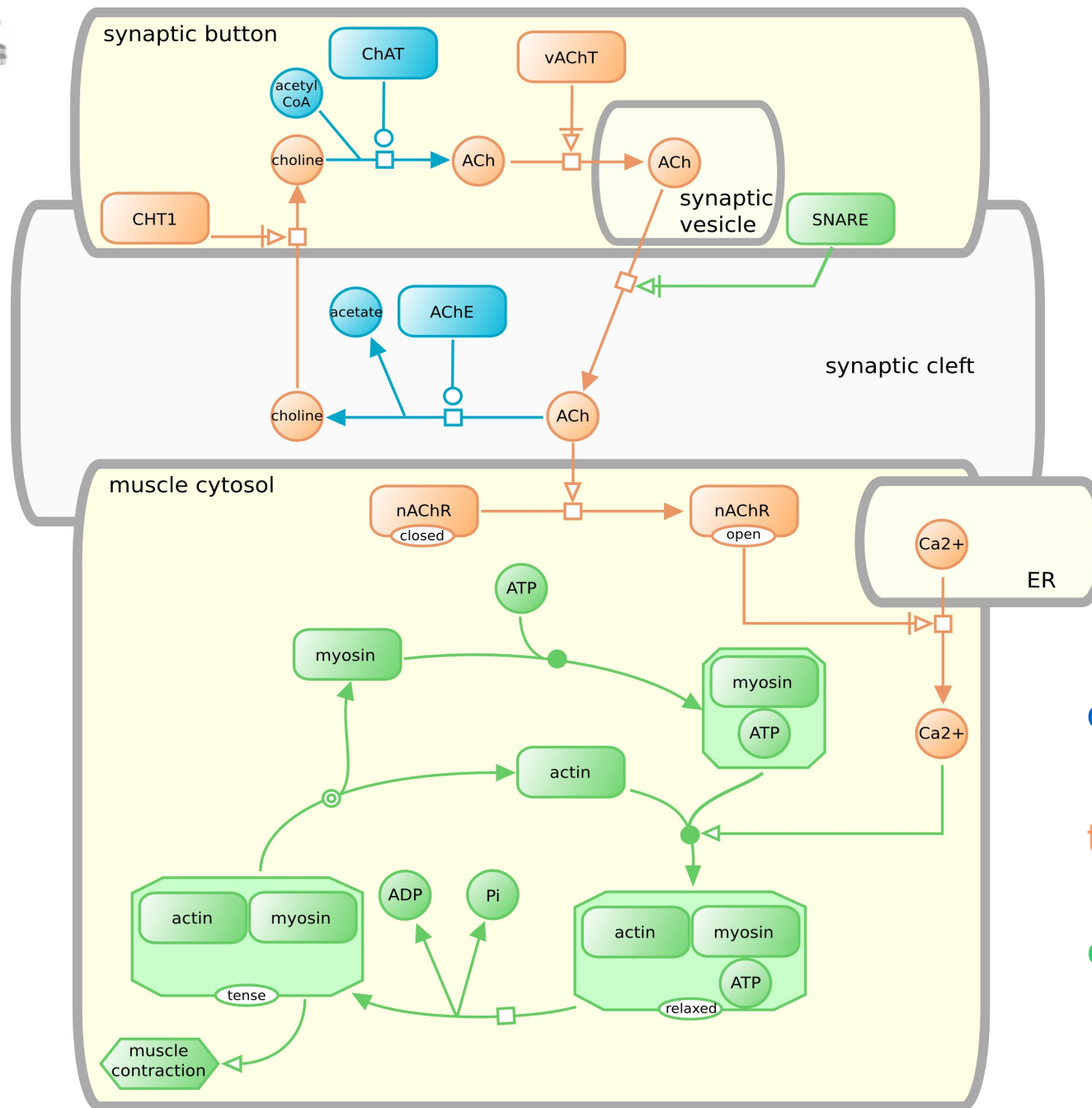








multi-cellular processes



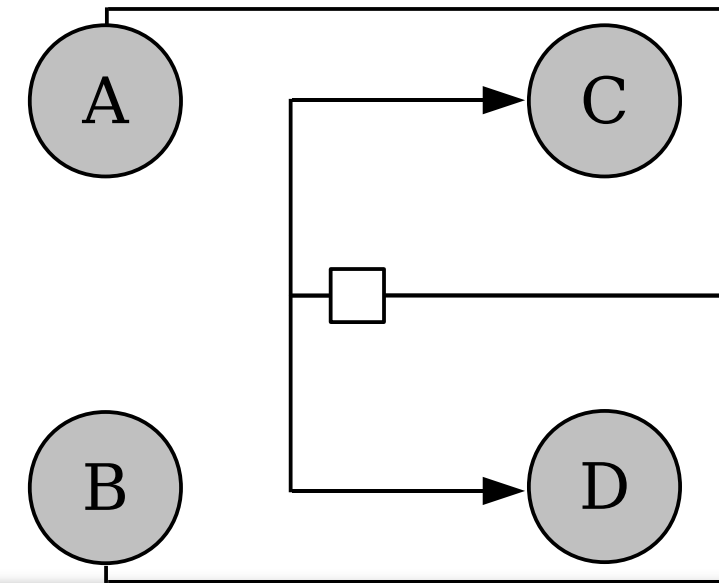
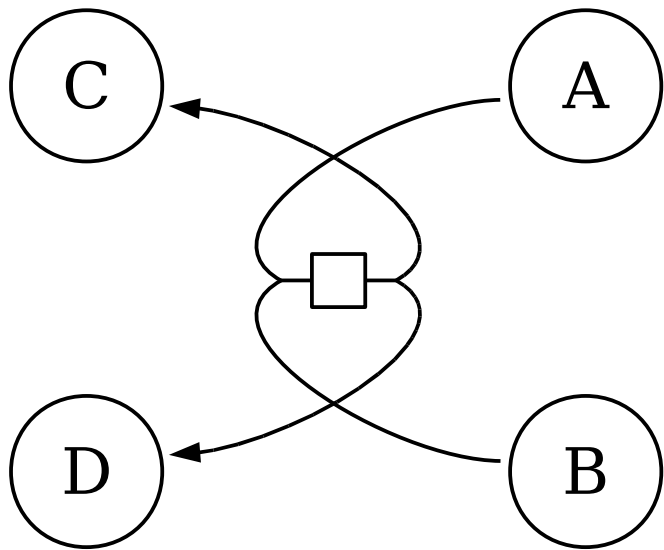
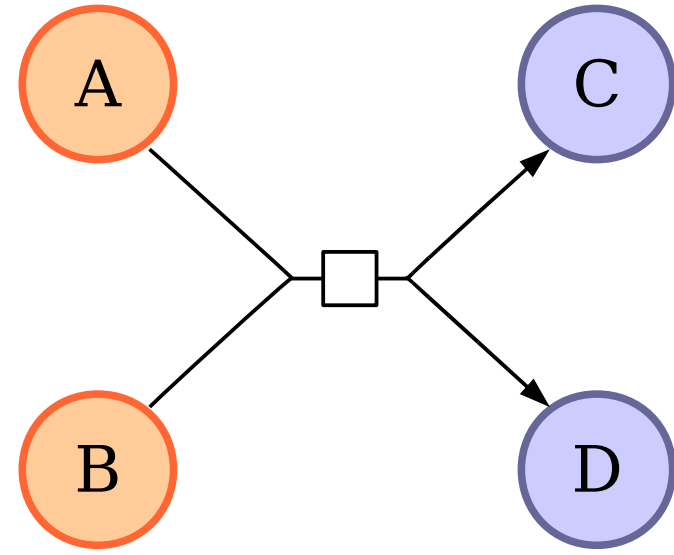
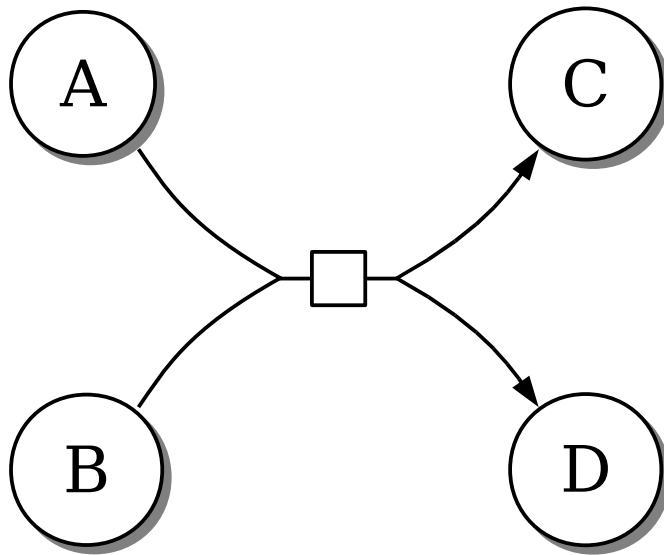
catalytic processes

transport processes

contractile proteins

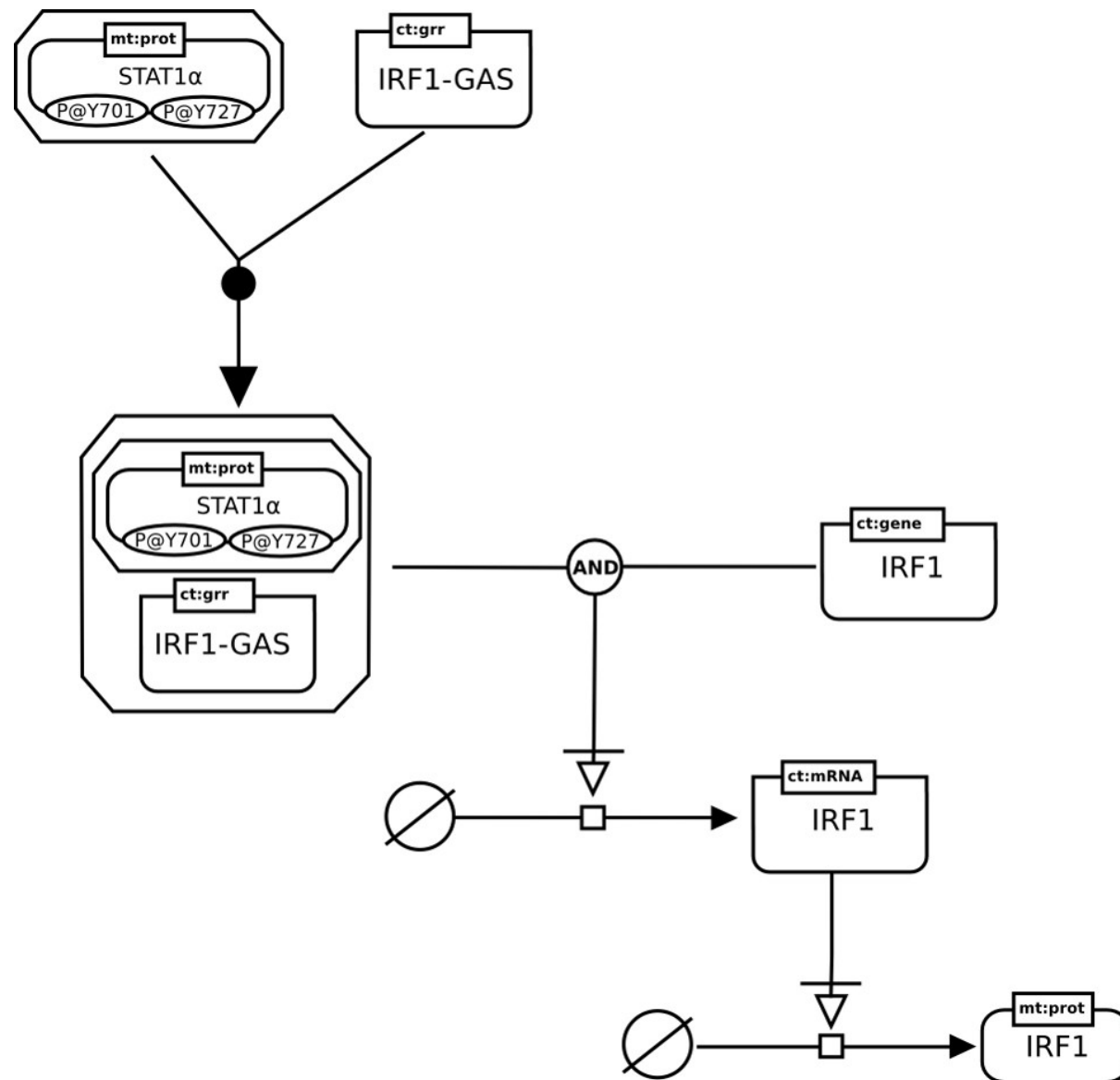


All those diagrams are identical





Genetic regulation





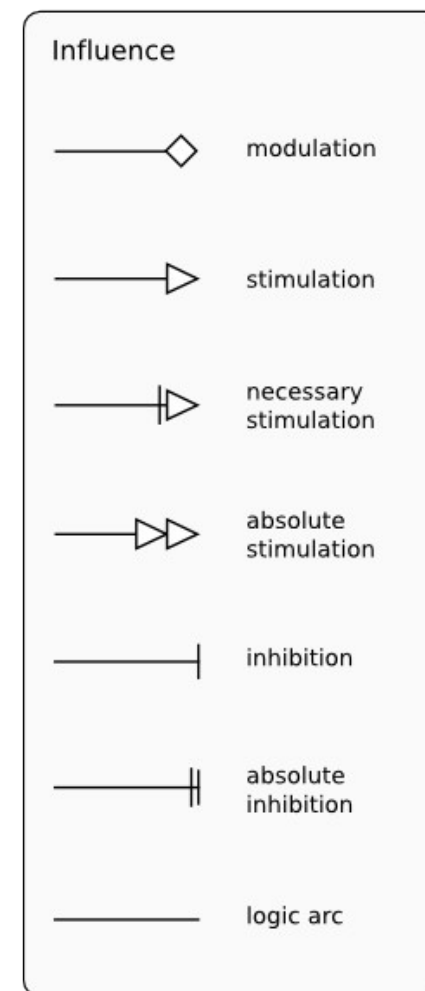
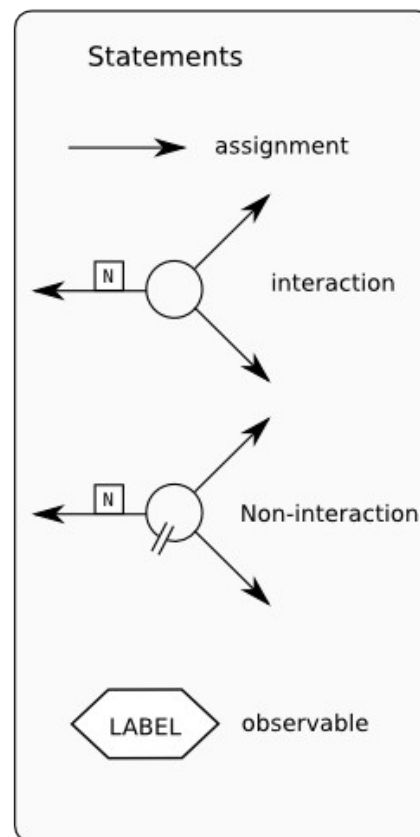
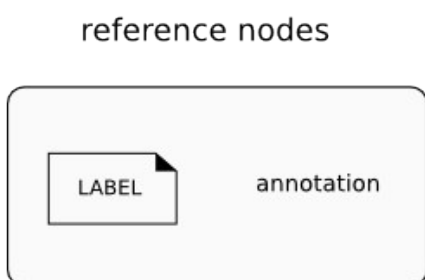
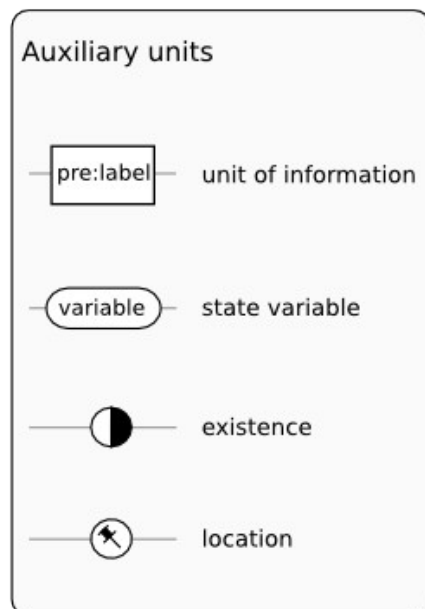
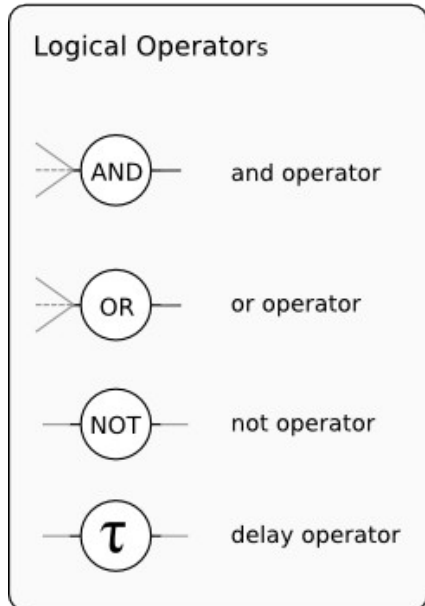
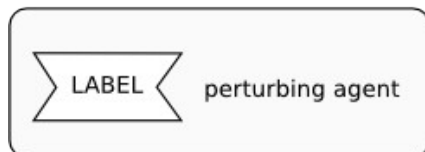
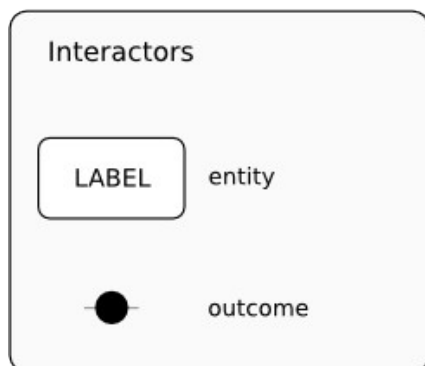
- Generics (entity pools representing several possible biochemical types)
- Trans-compartment (e.g. transmembrane) structures
- Logical combination of state-variable values (and close-world/open-world position)
- Moving and transforming compartments
- Non-chemical entity pool nodes (“voltage”, “pH” ...)



SBGN Entity Relationships L1 reference card

Entity Nodes

Relationship Nodes

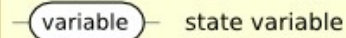
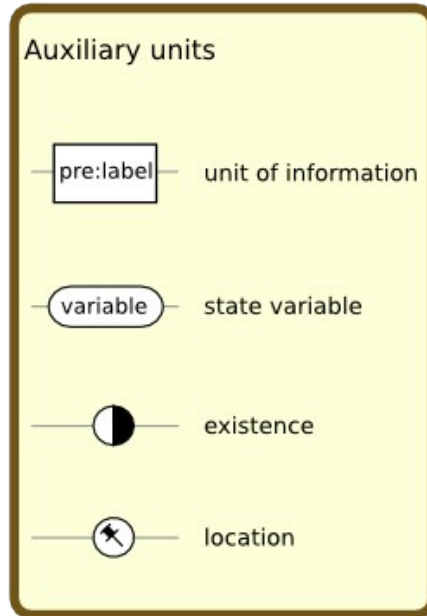
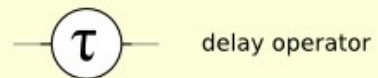
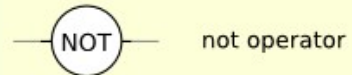
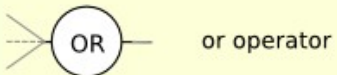
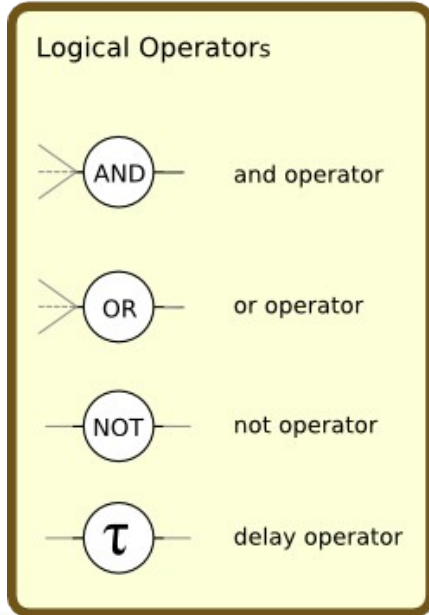
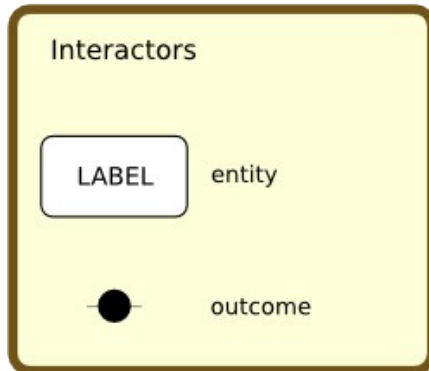




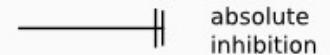
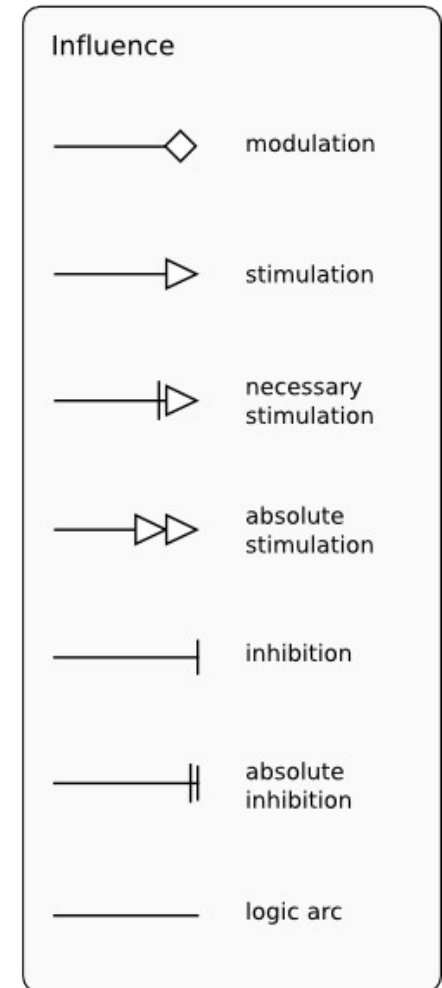
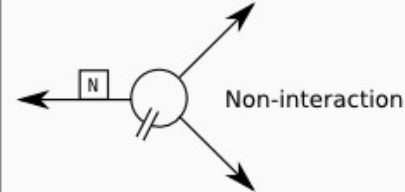
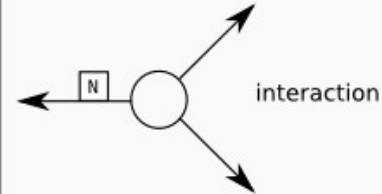
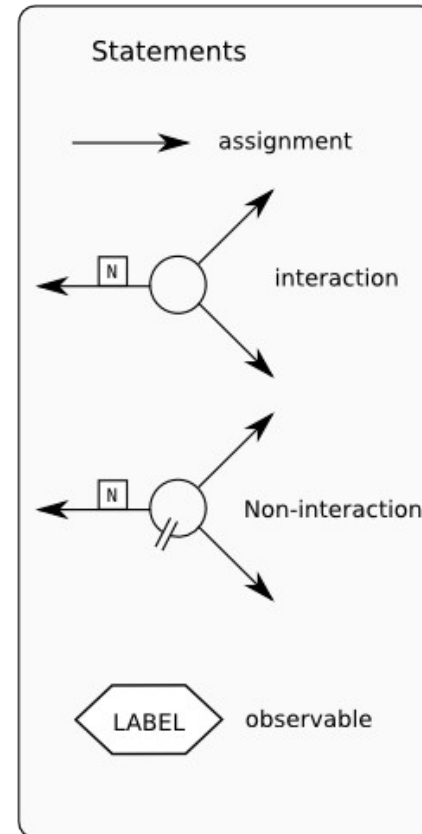
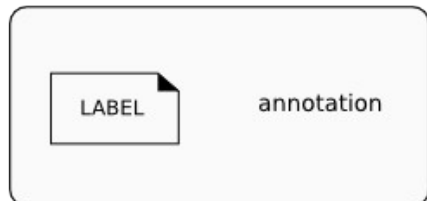
SBGN Entity Relationships L1 reference card

Entity Nodes

Relationship Nodes



reference nodes

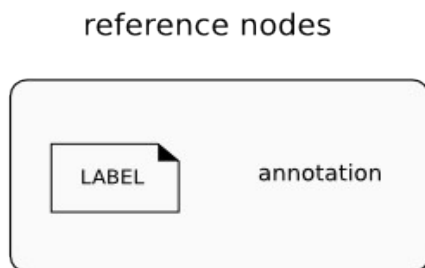
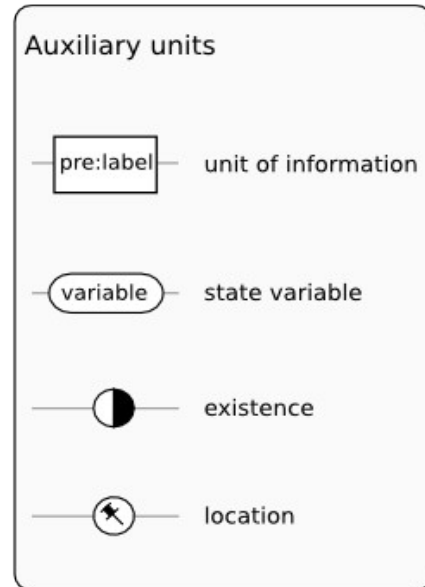
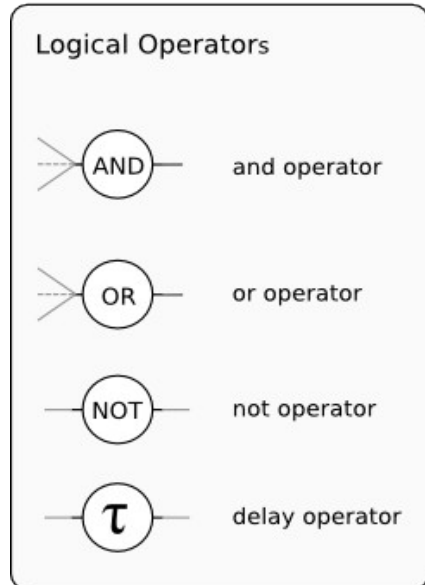
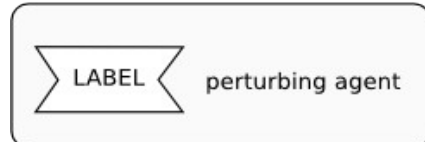
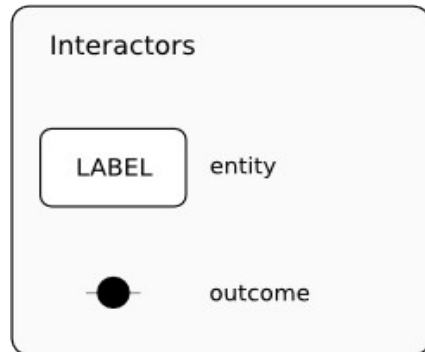


continuants,
things that exists (or not)

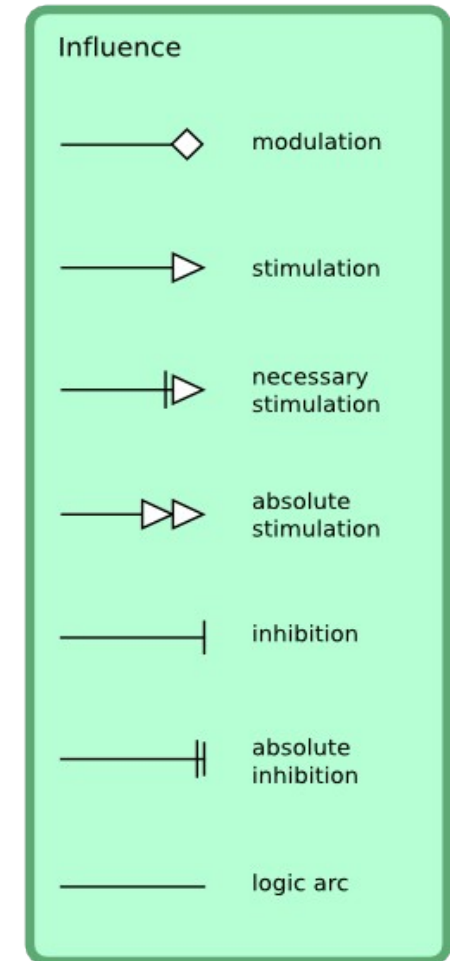
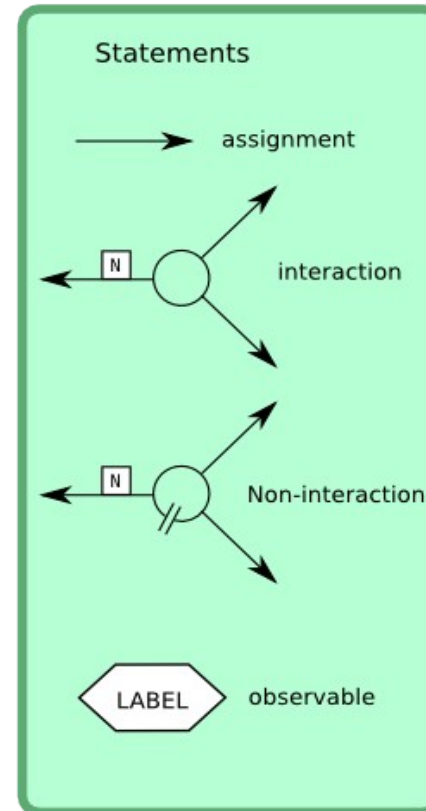


SBGN Entity Relationships L1 reference card

Entity Nodes



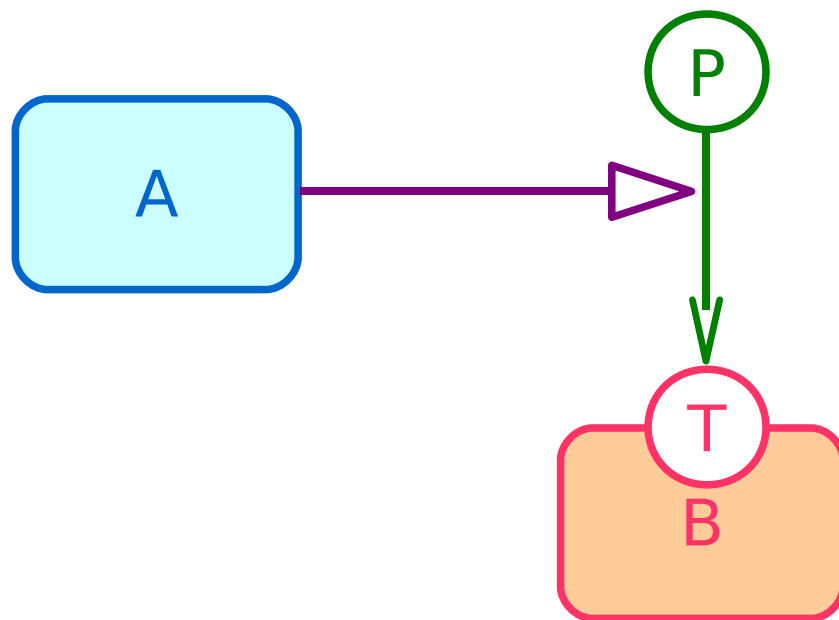
Relationship Nodes



occurents,
events that may happen (or not)

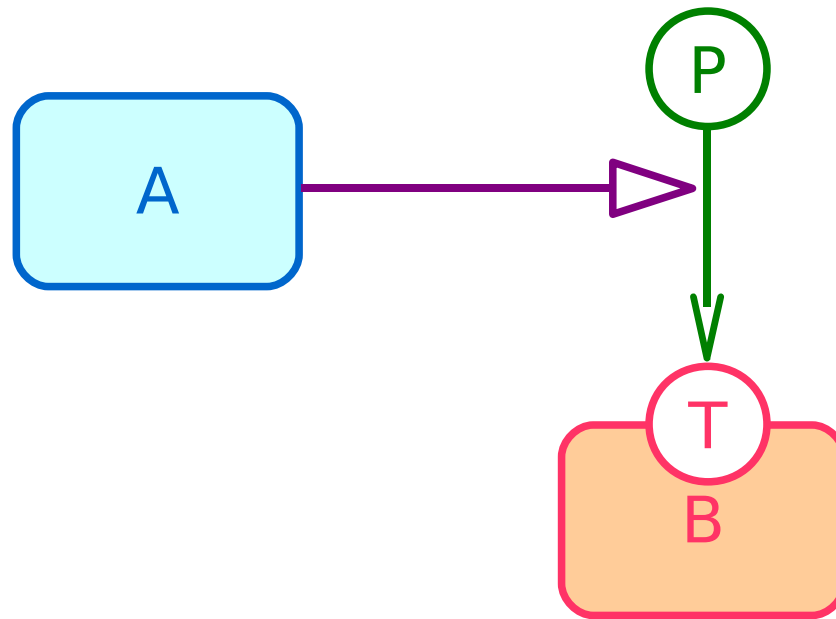


Entity Relationships can be viewed as rules





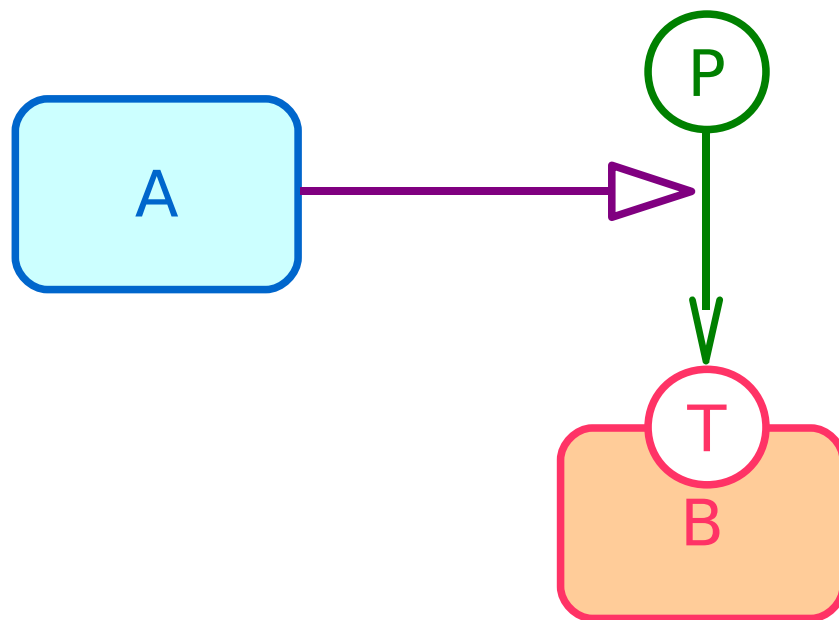
Entity Relationships can be viewed as rules



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

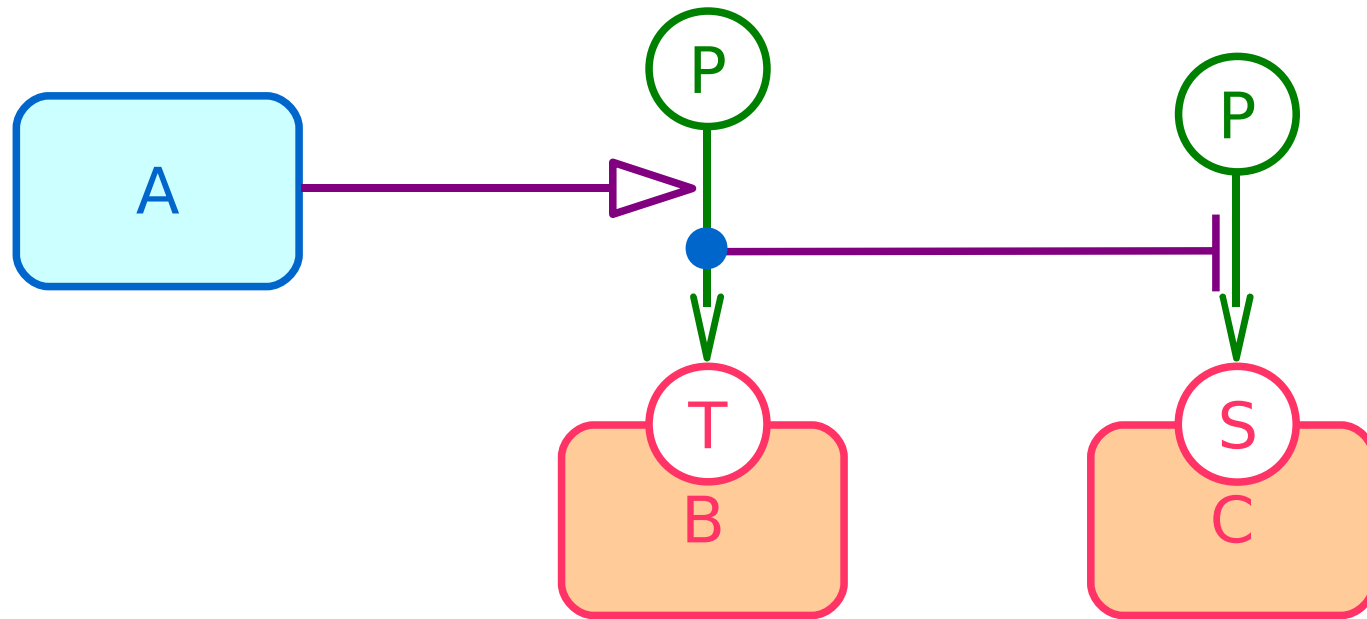


If **A** exists, the assignment of the value **P** to the state variable **T** of **B** is increased

(**A** stimulates the phosphorylation of **B** on the threonine)



Entity Relationships can be viewed as rules

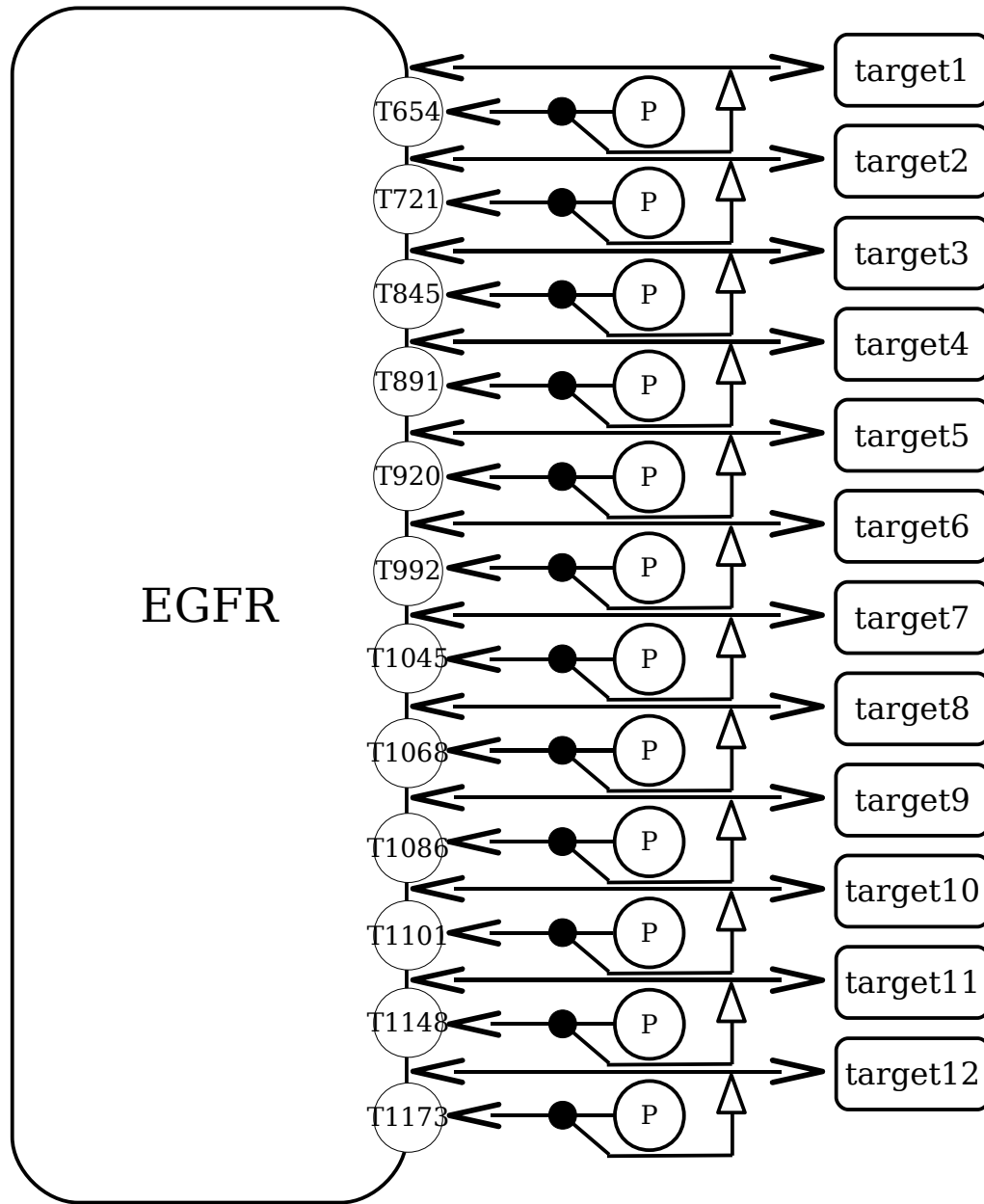


If **A exists**, the **assignment of the value P** to the **state variable T of B** is **increased**

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



Multistate and combinatorial explosion

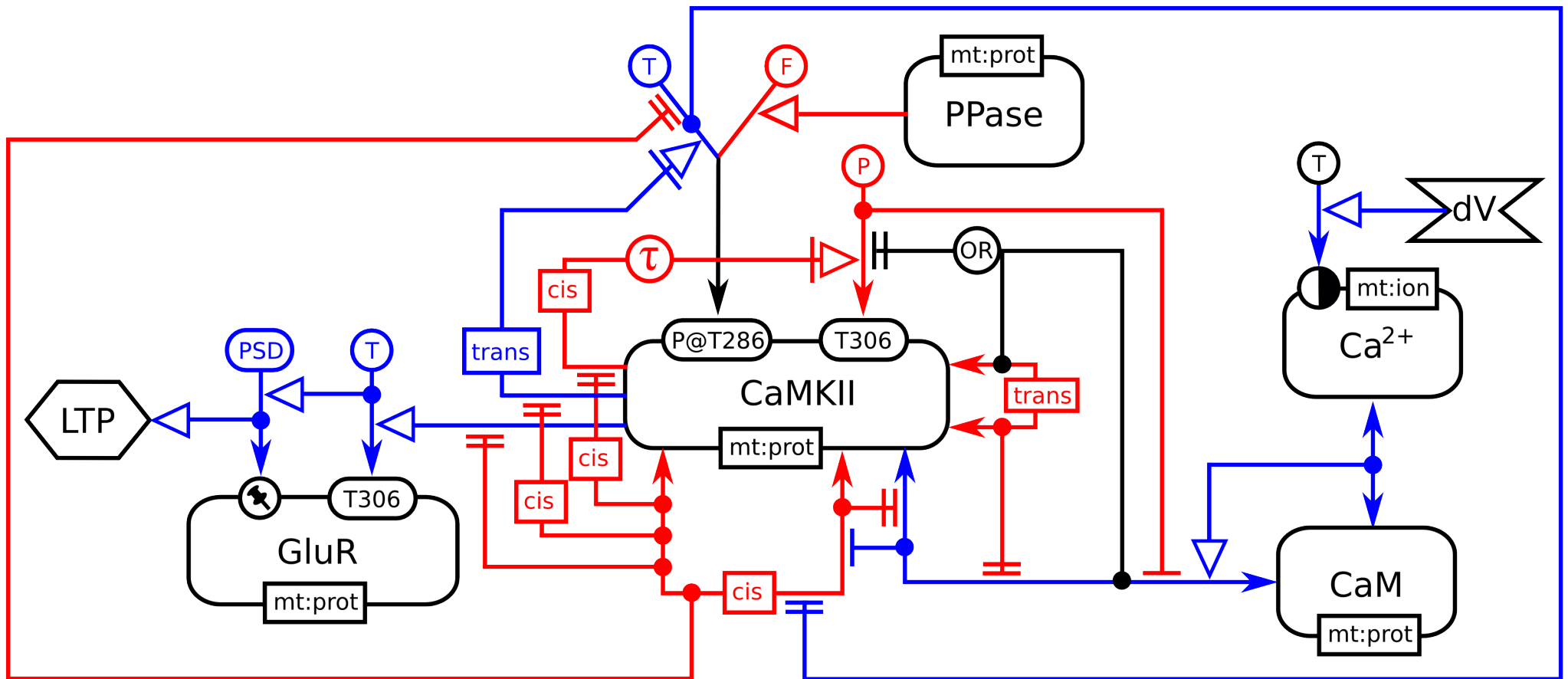


Process Diagram:
“once a state variable value,
always a state variable value”

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



Example of Entity Relationships map



increases synaptic weight

decreases synaptic weight

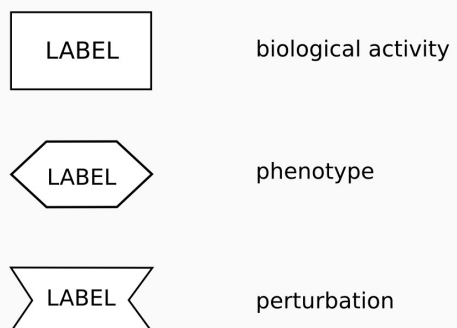


- Internal structure of entities (domains, sites, complexes)
- Identification of instances: How to differentiate between several instances of the same entity, differentially involved in a relationships?

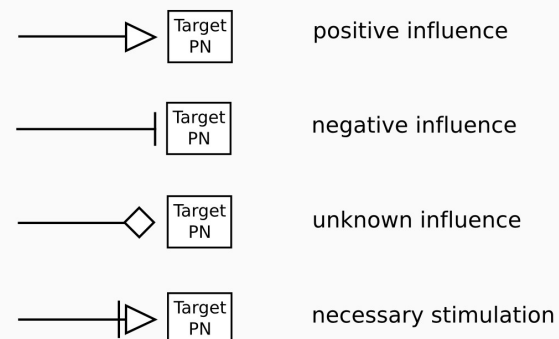


SBGN Activity Flow L1 reference card

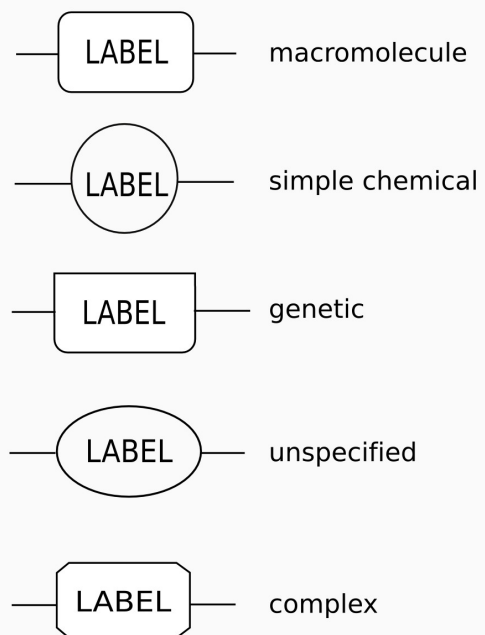
Activity nodes



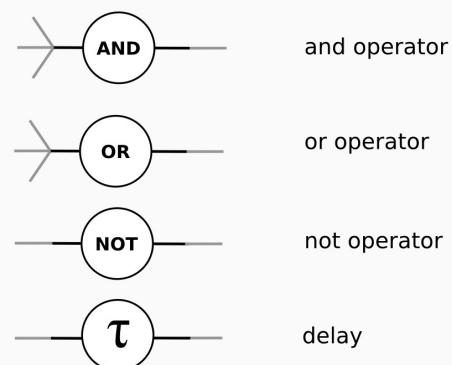
Modulating Arcs



Auxiliary Units



Logical Operators

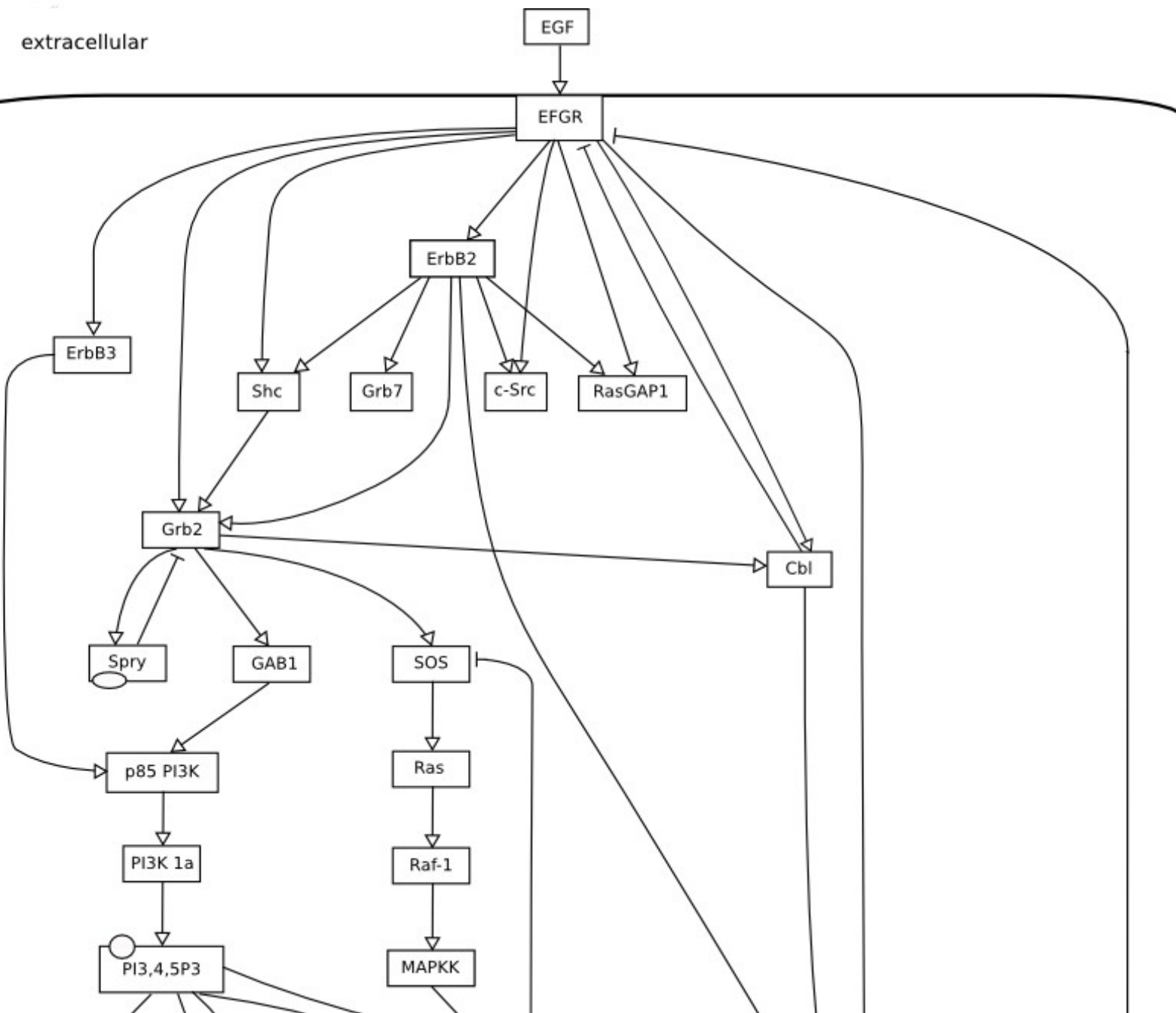


Container Nodes

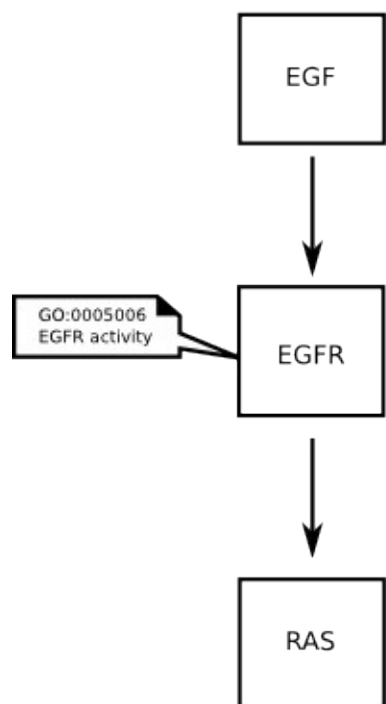


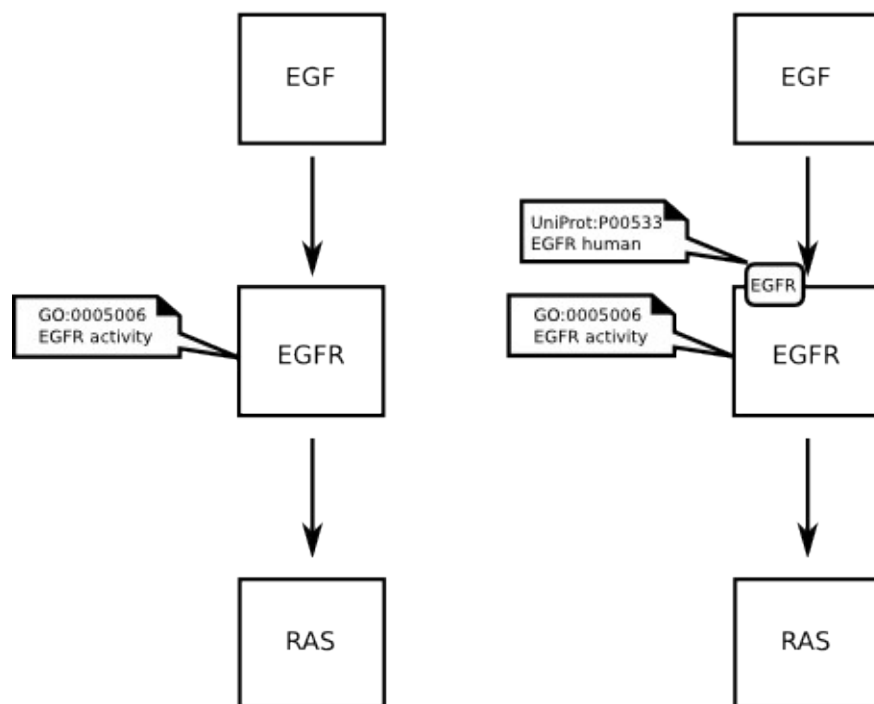
extracellular

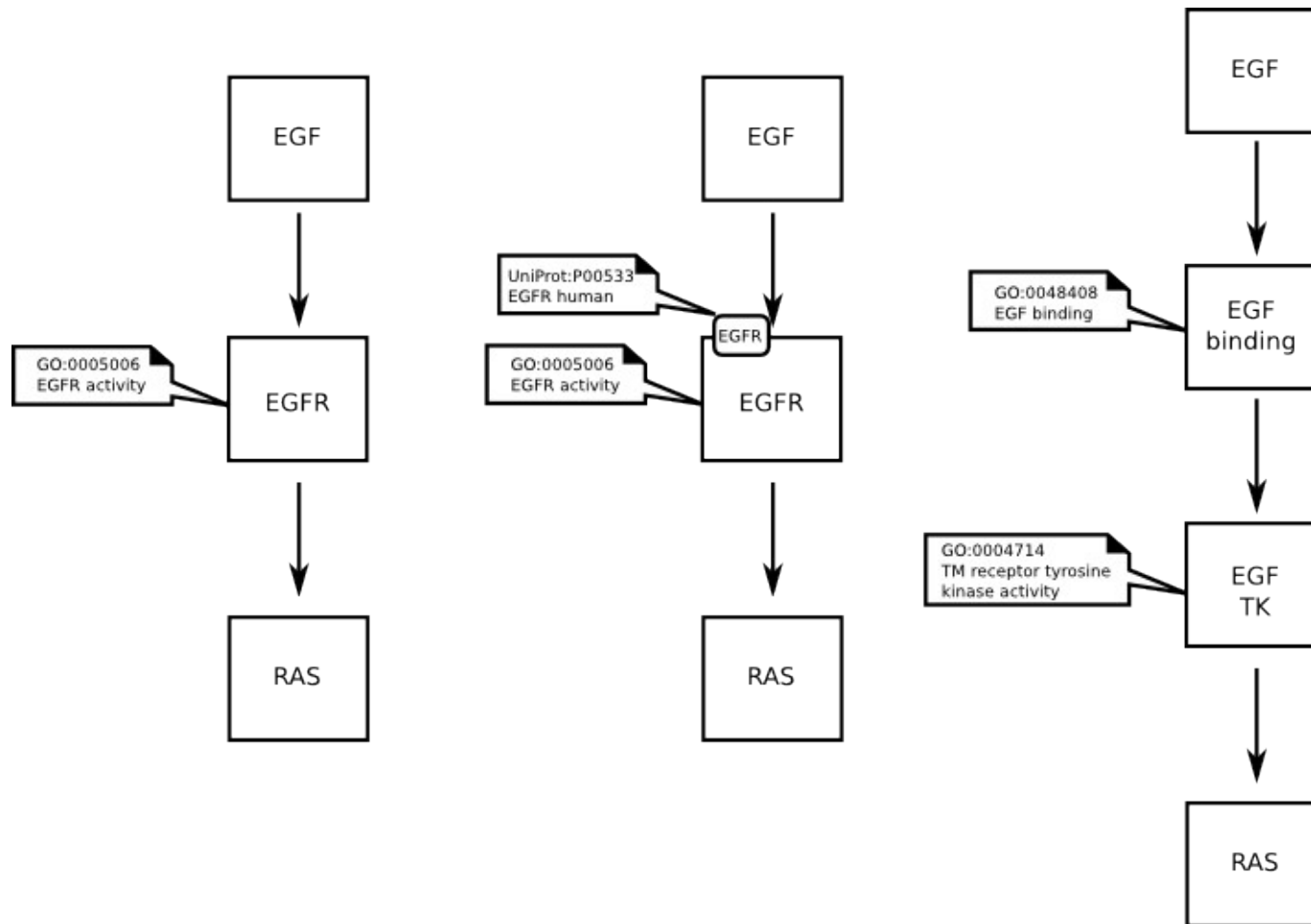
Example of Activity Flow map

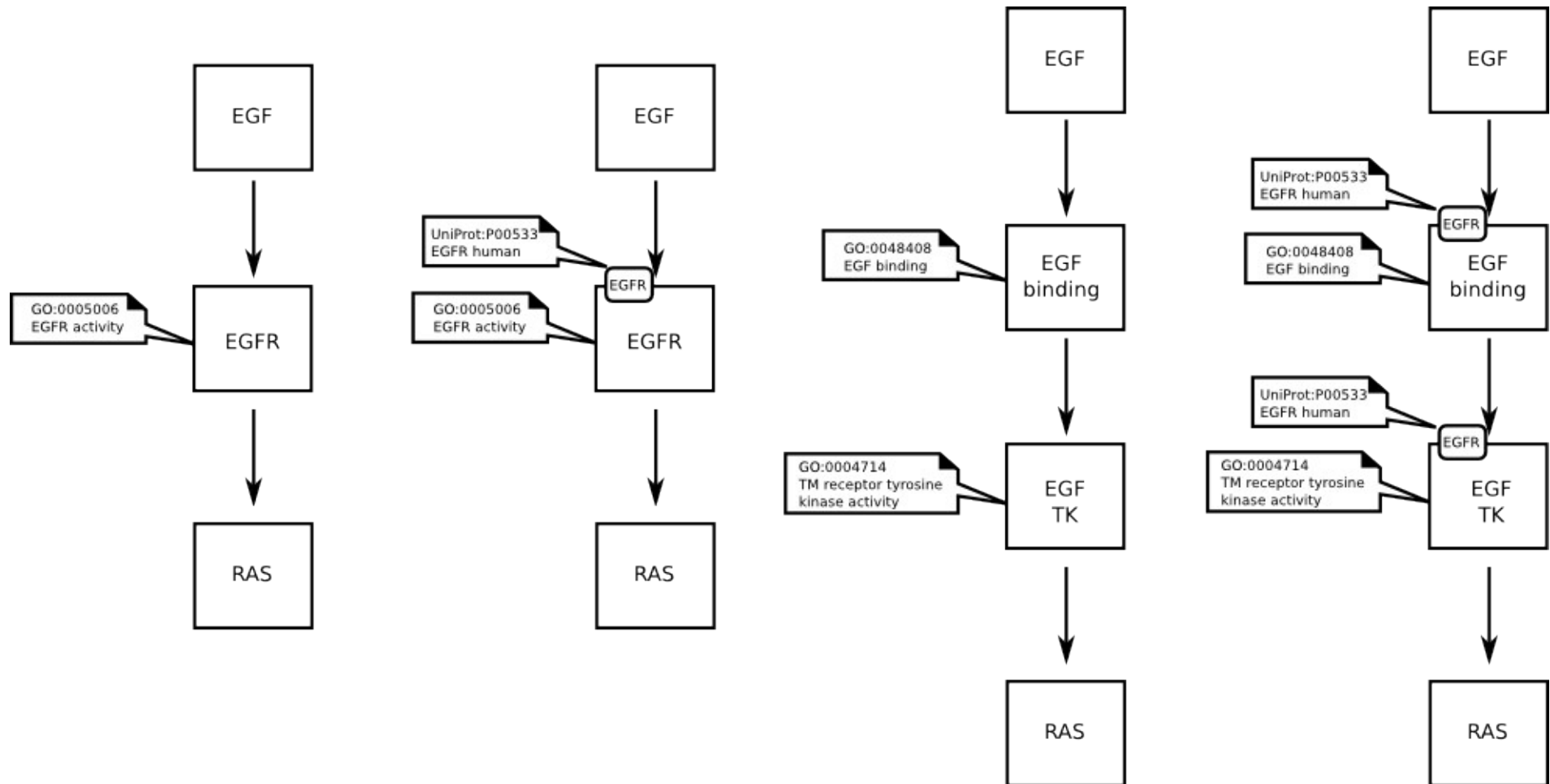








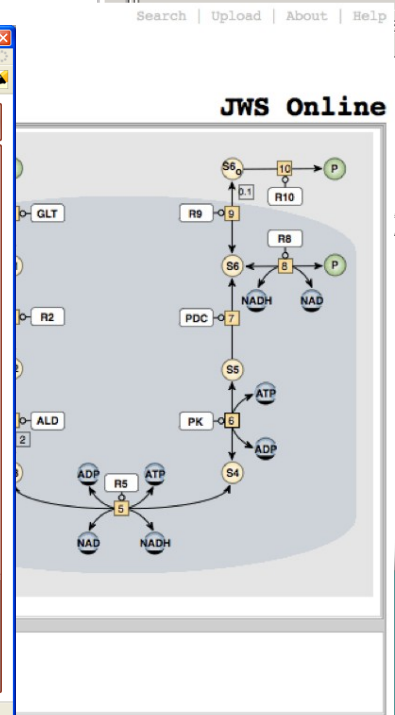
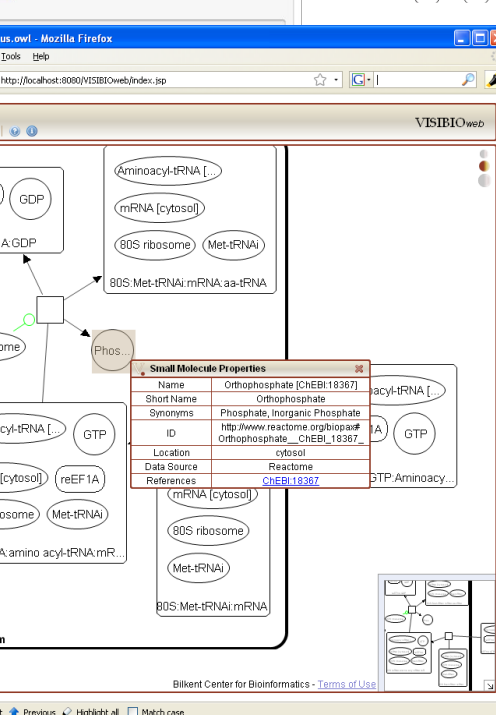
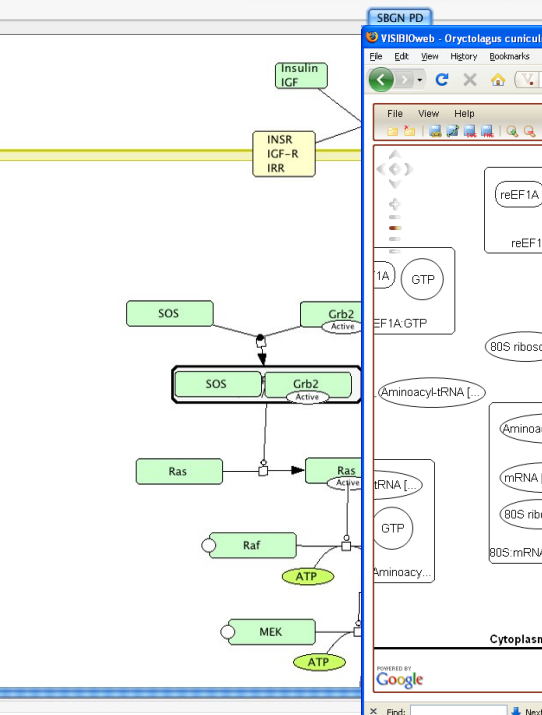
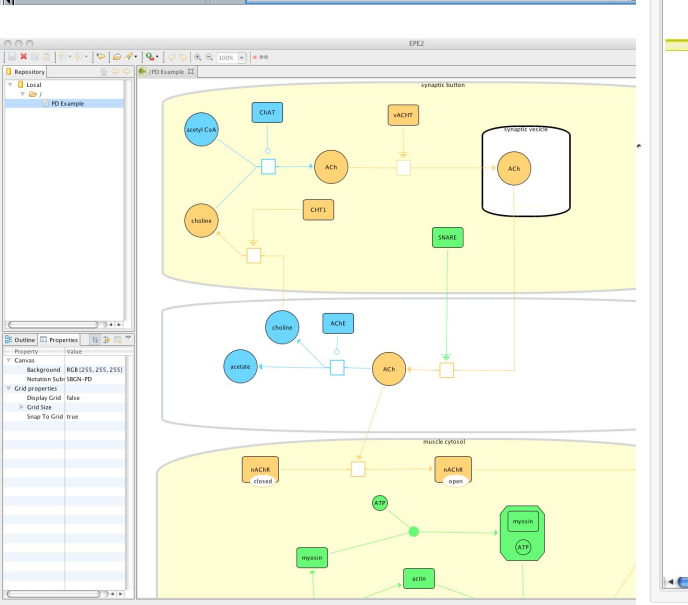
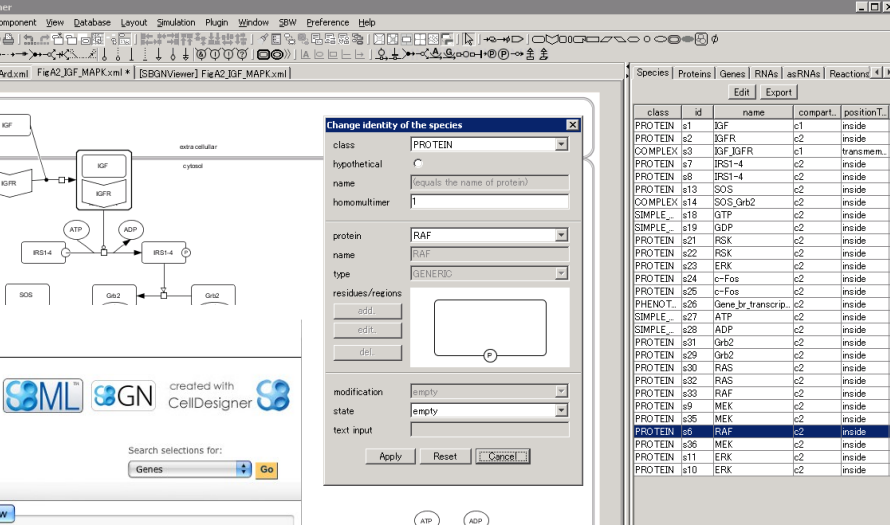
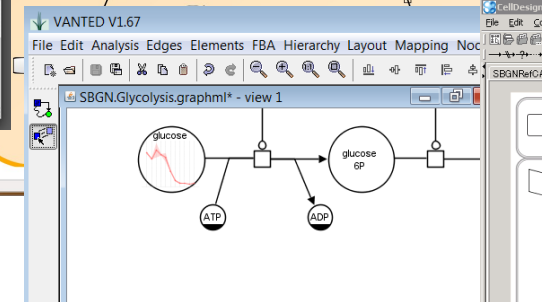
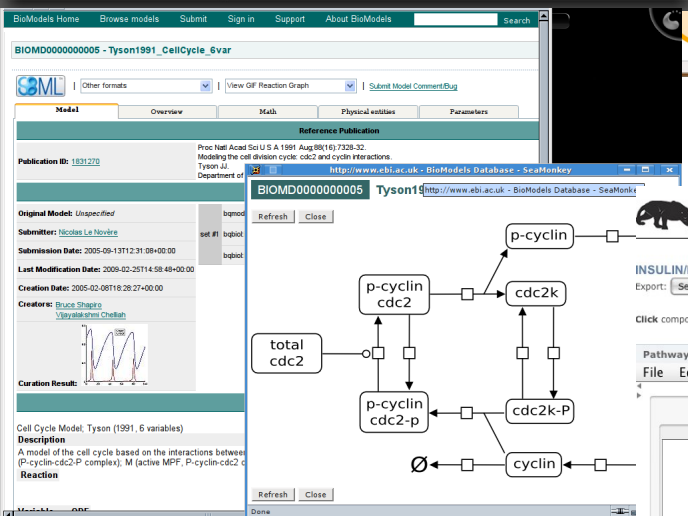
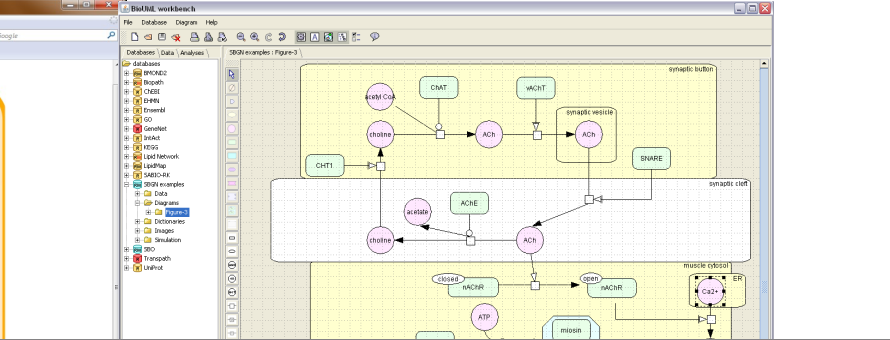
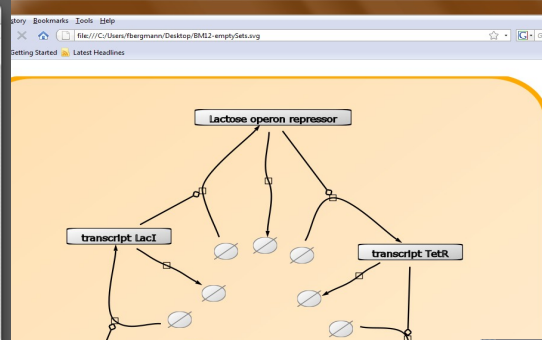
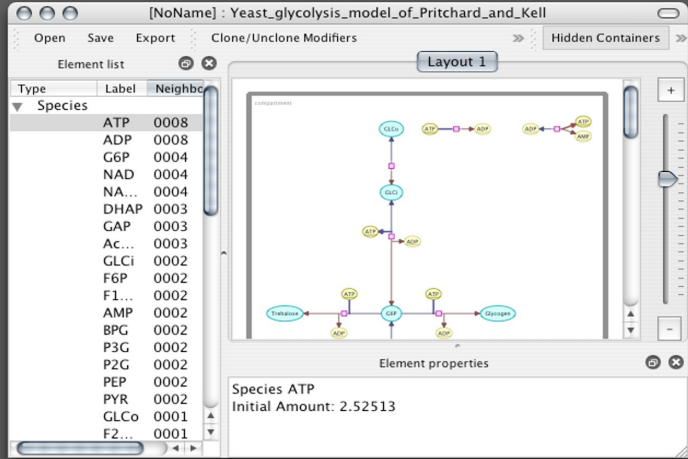






Software support for SBGN PD L1

- **Arcadia** (MCISB, Manchester, UK) <http://arcadiapathways.sourceforge.net/>
- **Athena** (Univ Washington, Seattle, US) <http://www.codeplex.com/athena/>
- **BioModels DB** (EMBL-EBI, UK) <http://www.ebi.ac.uk/biomodels/>
- **BioUML** (Inst Systems Biology, Novosibirsk, RU) <http://www.biouml.org/>
- **CellDesigner** (SBI, Tokyo, JP) <http://www.celldesigner.org/>
- **EPE** (CISBE, Edinburgh, UK) <http://www.bioinformatics.ed.ac.uk/epe/>
- **JWS Online** (Stellenbosh University, ZA) <http://jjj.biochem.sun.ac.za/>
- **NetBuilder** (Univ Hertfords, UK) <http://strc.herts.ac.uk/bio/maria/Apostrophe/>
- **PANTHER** (SRI international, USA) <http://www.pantherdb.org/pathway/>
- **Reactome** (EMBL-EBI, UK) <http://www.reactome.org/>
- **Vanted** (IPK Gatersleben, DE) <http://vanted.ipk-gatersleben.de/>
- **VISIOweb** (Bilkent Univ, Turkey) <http://www.bilkent.edu.tr/~bcbi/pvs.html>





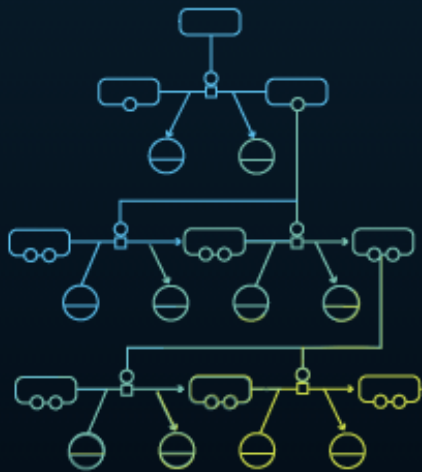
- SBGN Process Diagrams
 - Level 1 Version 1.0 release on August 23rd 2008
 - Level 1 Version 1.1 to be released over summer
 - Level 1 Version 2 to be finalised over summer
- SBGN Entity Relationships
 - Level 1 Version 1.0 to be released over summer
- SBGN Activity Flow
 - Level 1 Version 1.0 to be released over summer



Future SBGN meetings

- 5th SBGN forum
 - 02-03 September 2009,
 - San Francisco
 - “Satellite” of ICSB 2009
- 4rd SBGN hackathon (SBGN 5.5)
 - 21-23 April 2010
 - Wittenberg
- 6th SBGN forum (provisional)
 - October 2010
 - Edinburgh
 - Satellite of ICSB 2010
- 5rd SBGN hackathon (SBGN 6.5)
 - Spring 2011, Bethesda, USA





A Visual Notation for Network Diagrams in Biology

SBGN.org is 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 diagrams of biochemical and cellular processes studied in systems biology.

Standardizing the diagrammatic notation is crucial for more efficient and accurate transmission of biological knowledge between different research communities in the expanding field of systems biology. Notations traditionally used by researchers and software have been informal, idiosyncratic and highly variable. Until SBGN, there has been no standard agreed-upon convention defining precisely how to draw biochemical interaction diagrams in a regular and systematic way that helps readers interpret them consistently and unambiguously.

SBGN defines a comprehensive set of symbols with precise semantics, together with detailed syntactic rules defining their use and how diagrams are to be interpreted. By standardizing the visual notation, SBGN can serve as a bridge between different communities in research, education, publishing, and more. The real payoff will come when researchers are as familiar with the notation as electronics engineers are familiar with the notation of circuit schematics. If researchers are saved the time and effort required to familiarize themselves with different notations, they can spend more time thinking about the biology being depicted.

On this site, you can browse some [example diagrams](#) to get a feeling for SBGN, read the SBGN [specification documents](#), join [online discussions](#), see current working documents in the [SBGN wiki](#), and much more.

SBGN is the work of many people. It would not have been possible without the generous [support of multiple organizations](#) over the years, for which we are very thankful.

SBGN News

(23 Aug. '08) The first **SBGN Process Diagrams Level 1** specification is out! [Download the specification](#) and [tell us](#) what you think!



Acknowledgements

SBGN editors

- Nicolas Le Novère (UK)
- Stuart Moodie (UK)
- Anatoly Sorokin (UK)
- Michael Hucka (US)
- Falk Schreiber (DE)
- Huaiyu Mi (US)

Special contributors

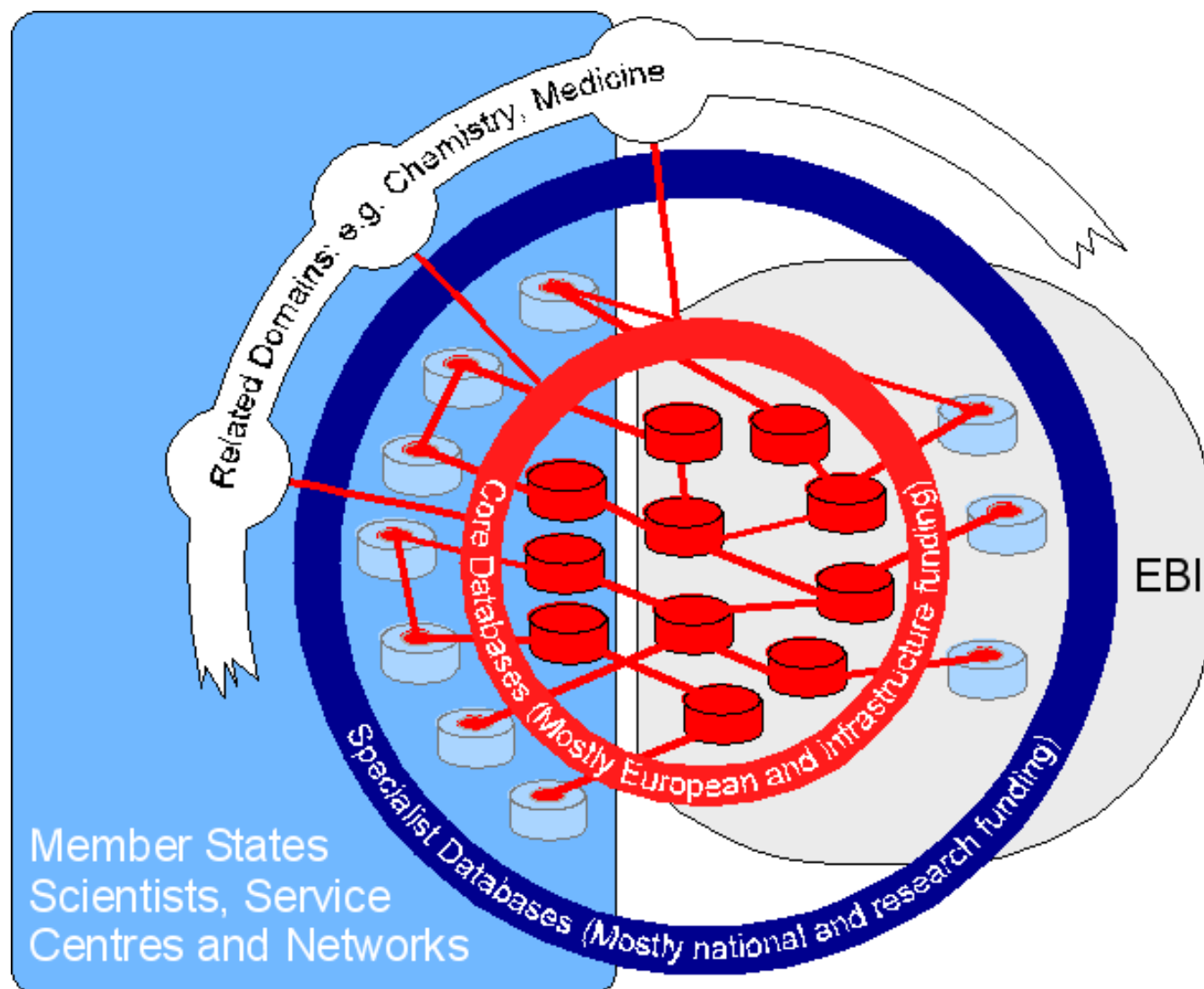
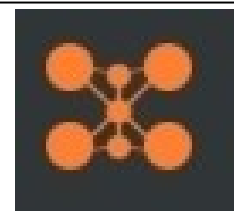
Emek Demir, Katja Wegner, Mirit Aladjem, Sarala Wimalaratne, Frank Bergman, Ralph Gauges, Peter Ghazal, Kawaji Hideya, Lu Li, Yukiko Matsuoka, Alice Villéger, Sarah Boyd, Laurence Calzone, Melanie Courtot, Ugur Dogrusoz, Akira Funahashi, Sohyoung Kim, Fedor Kolpakov, Augustin Luna, Sven Sahle, Douglas Kell, Kurt Kohn, Hiroaki Kitano

The whole community participating
to SBGN meetings, and mailing-lists



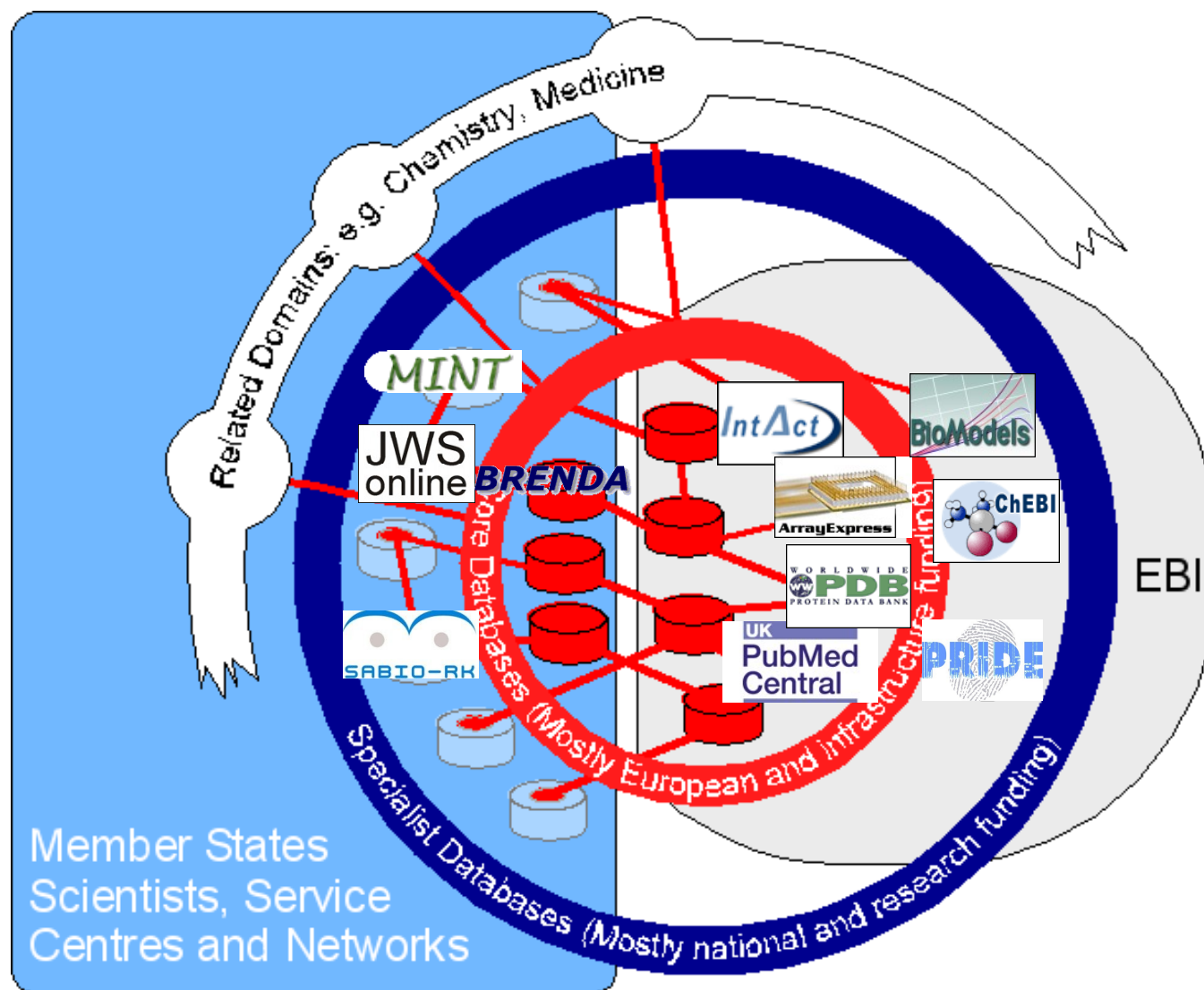
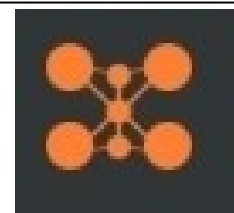


ELIXIR content



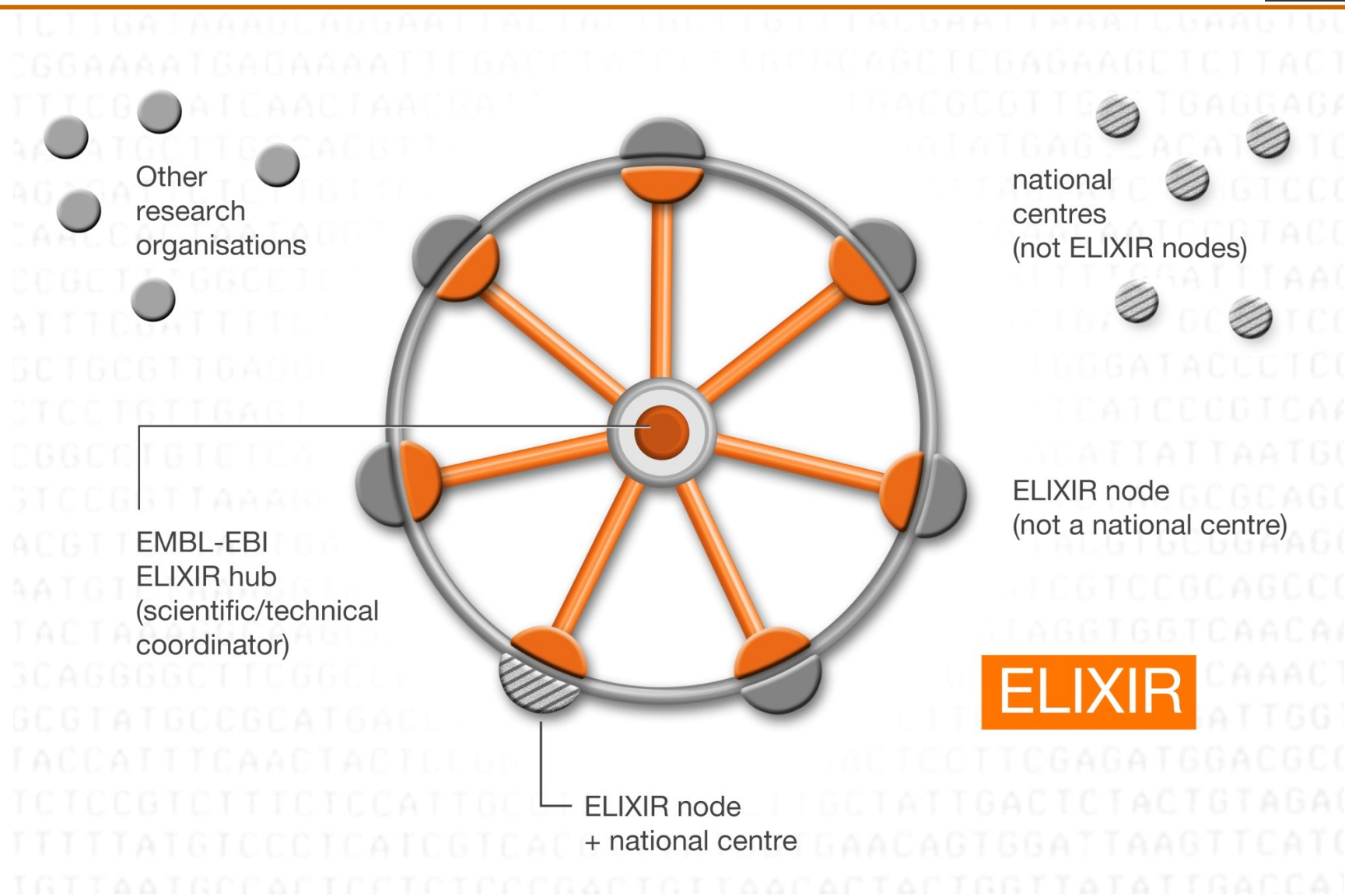
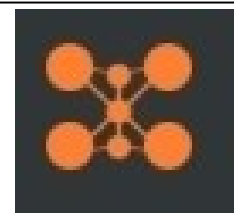
ELIXIR: a **sustainable** infrastructure for biological information in Europe.

ELIXIR content



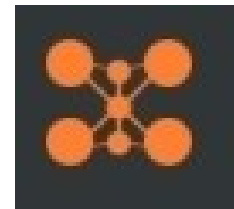
ELIXIR: a **sustainable** infrastructure for biological information in Europe.

ELIXIR Scientific and technical Structure



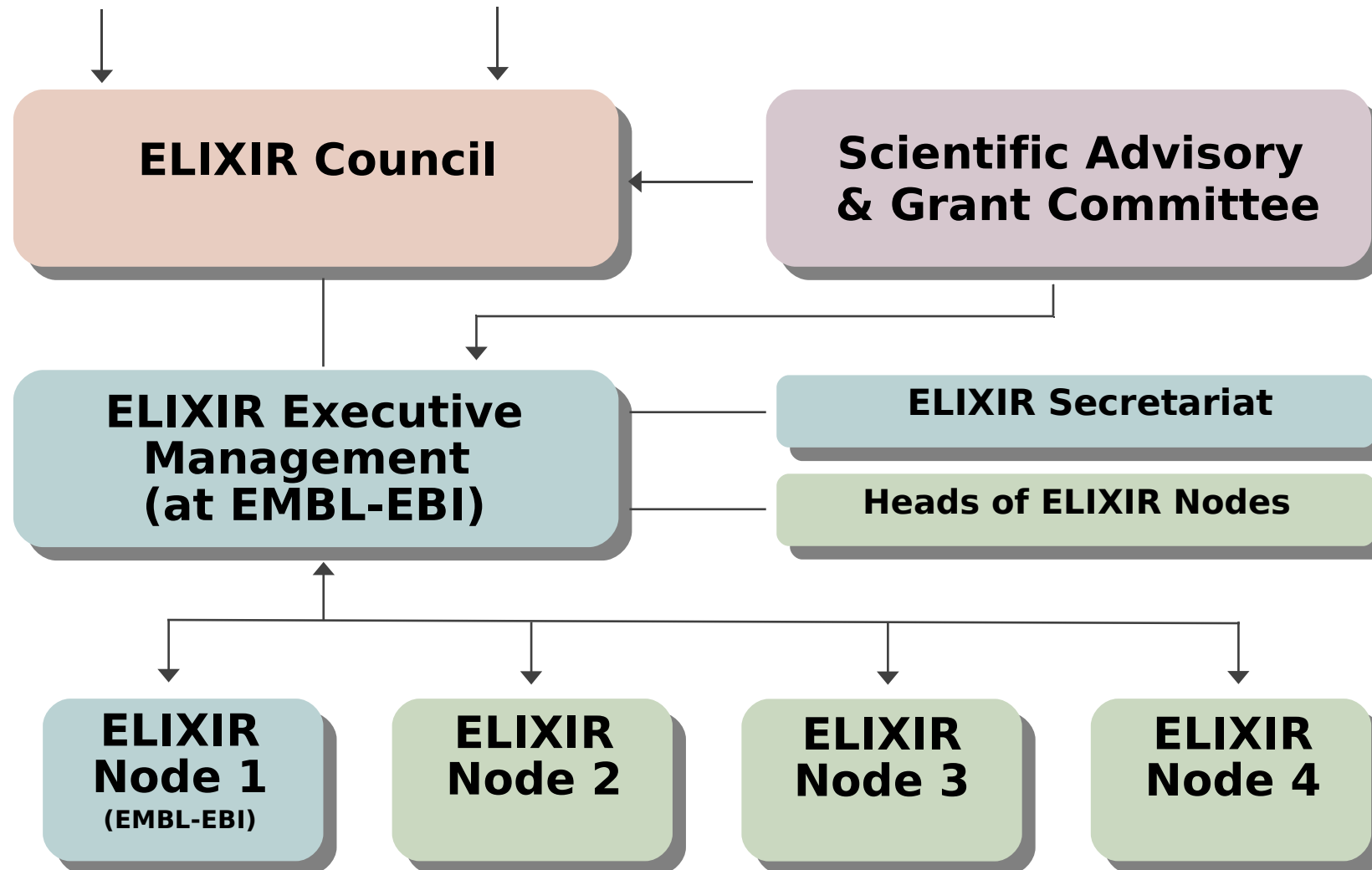
ELIXIR: a *sustainable* infrastructure for biological information in Europe.

ELIXIR Legal and Governance



ELIXIR
Member States

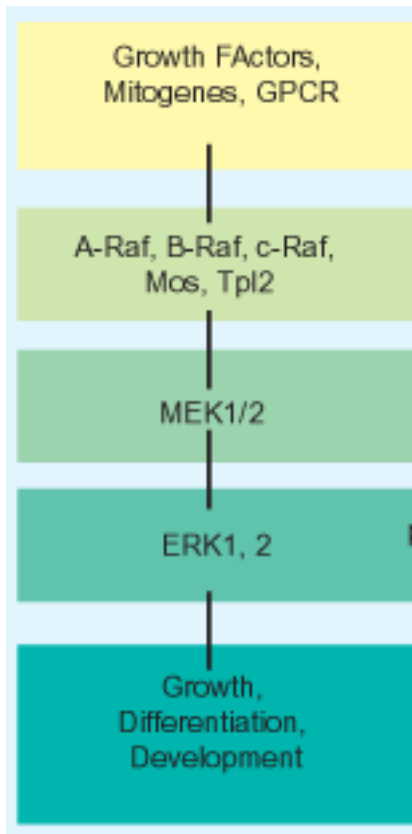
EMBL



ELIXIR: a *sustainable* infrastructure for biological information in Europe.



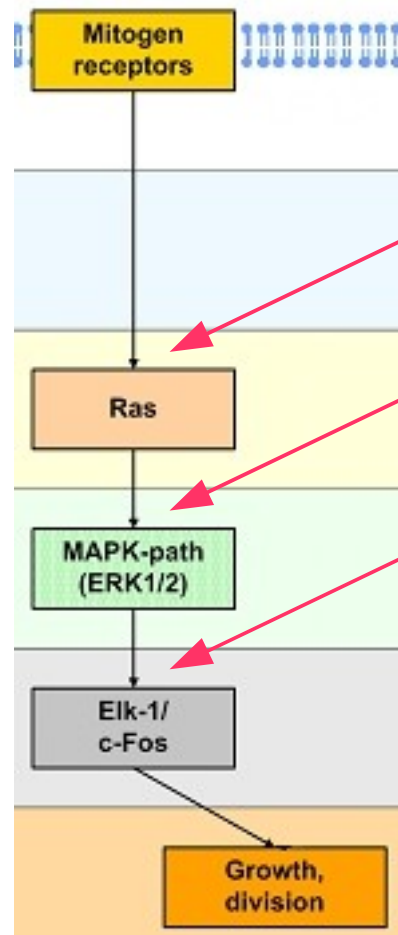
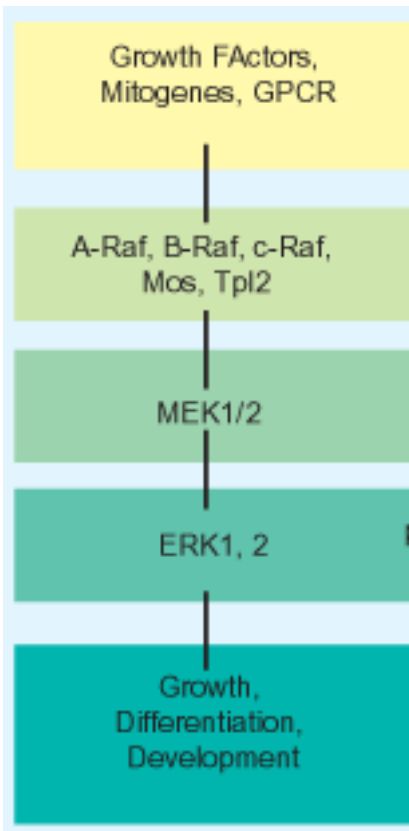
Different representations of a pathway



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



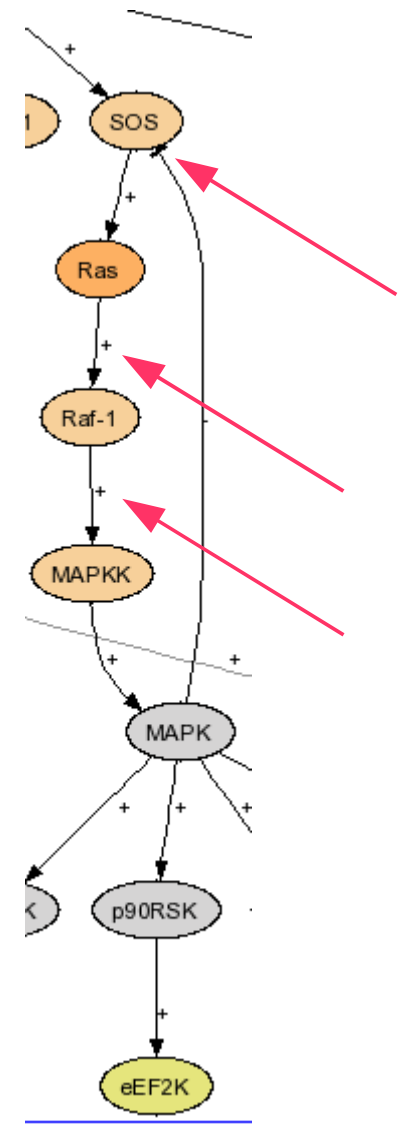
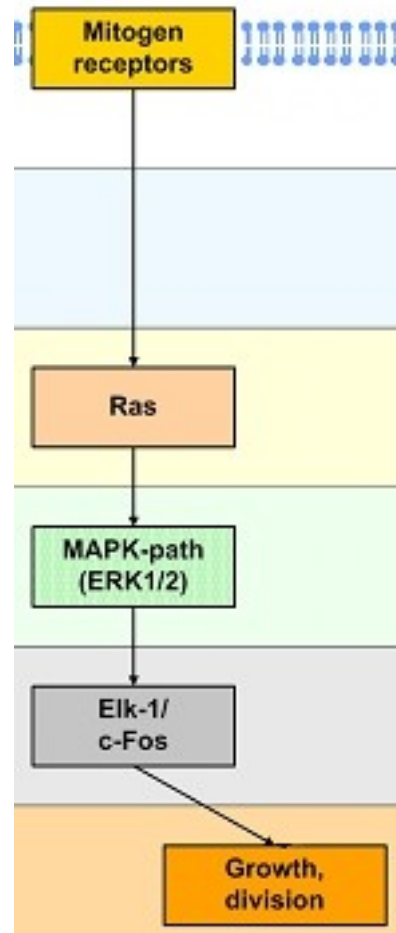
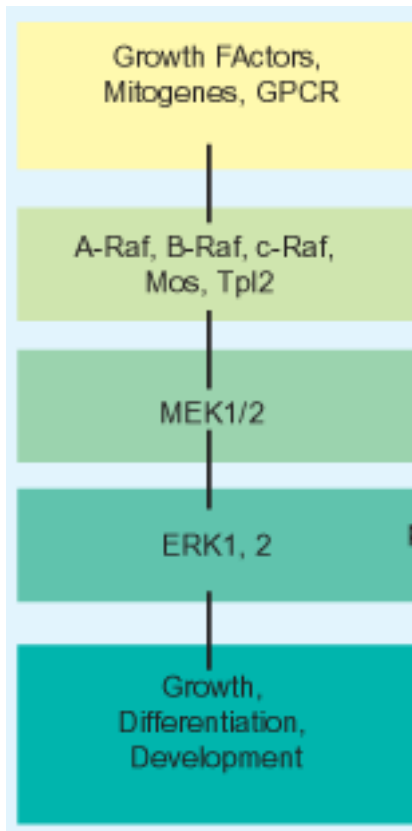
Different representations of a pathway



■ Directionality of influence



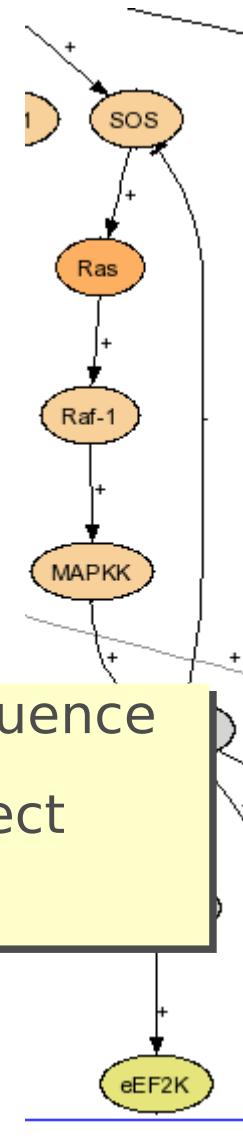
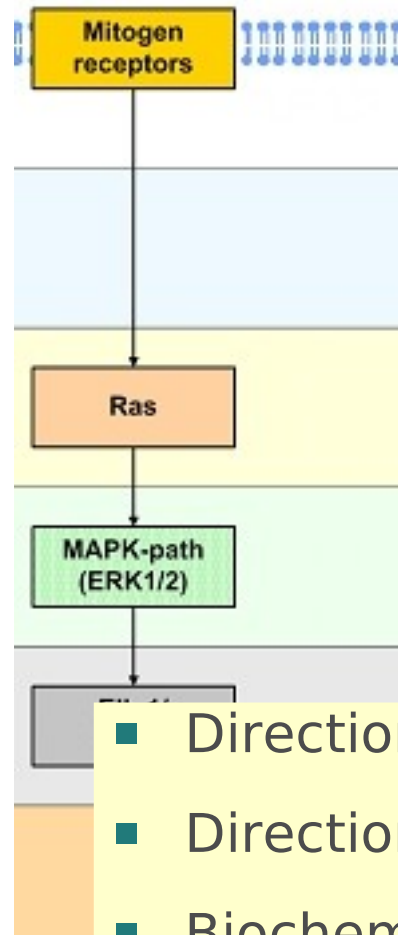
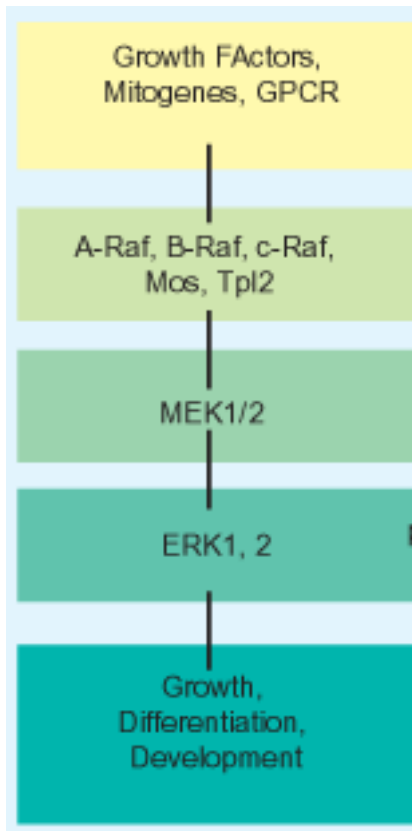
Different representations of a pathway



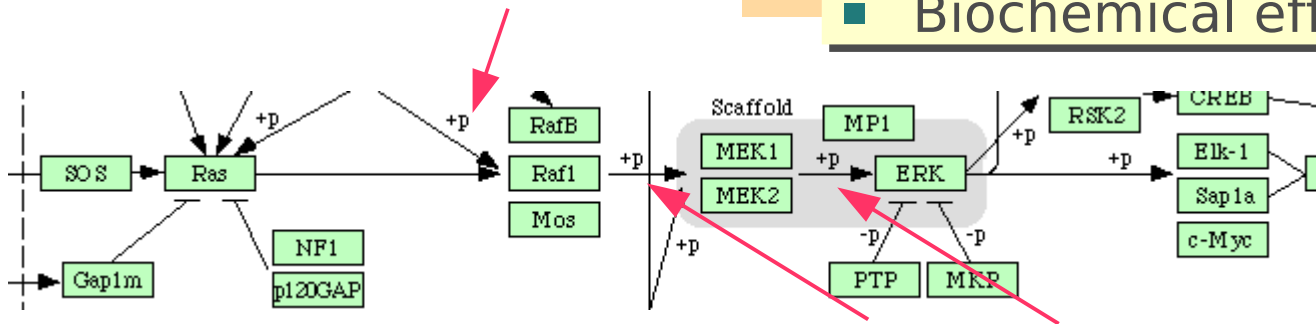
- Directionality of influence
- Directionality of effect



Different representations of a pathway

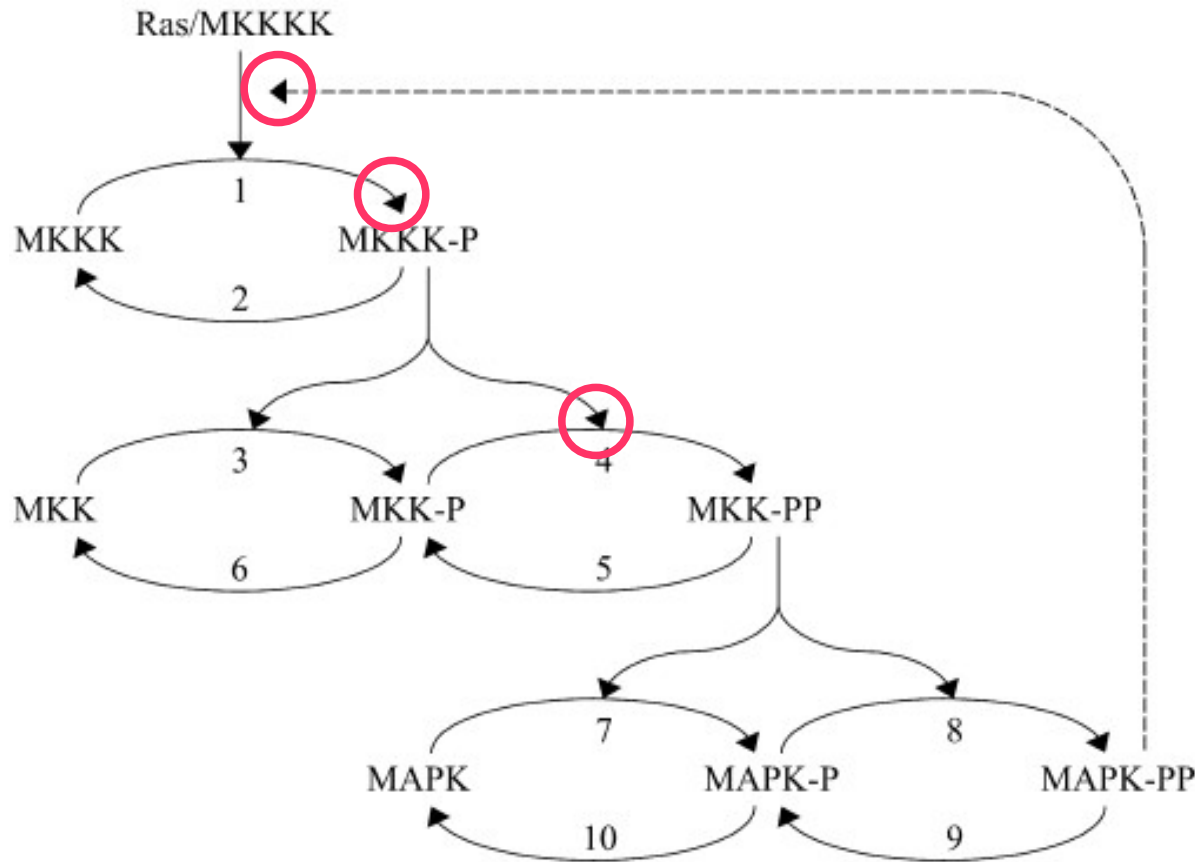


- Directionality of influence
- Directionality of effect
- Biochemical effect





Different representations of a pathway

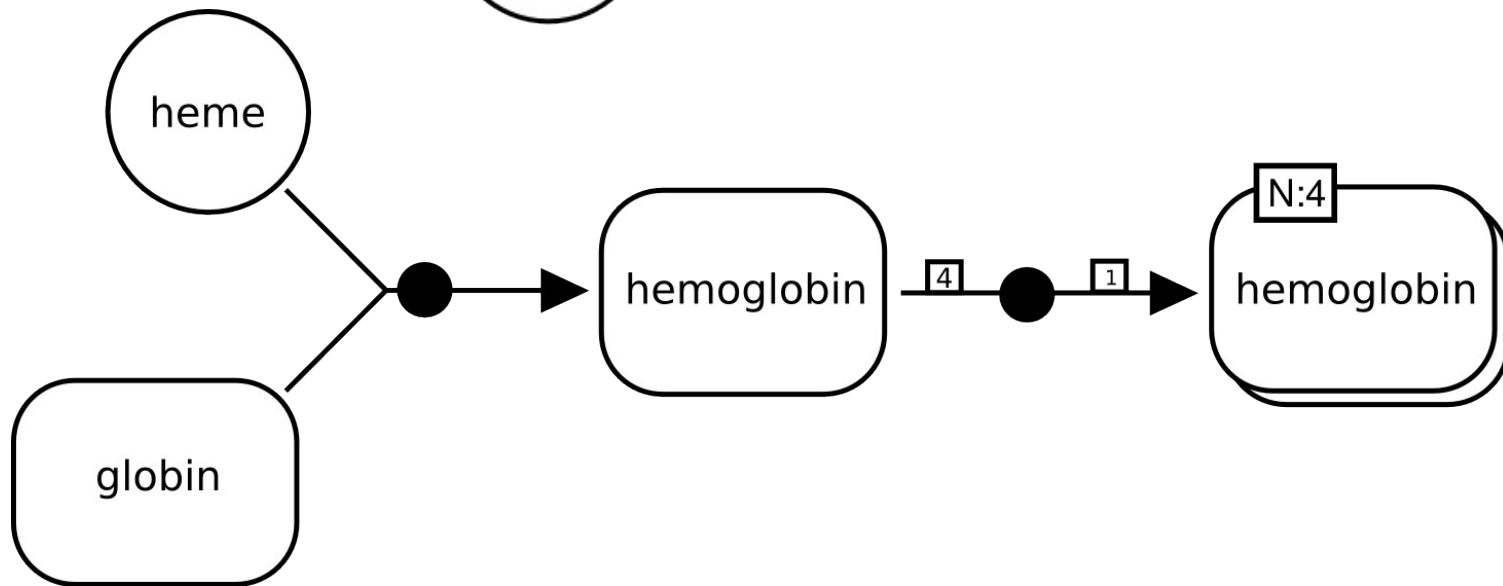
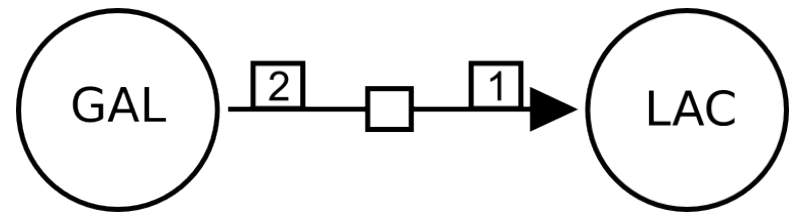
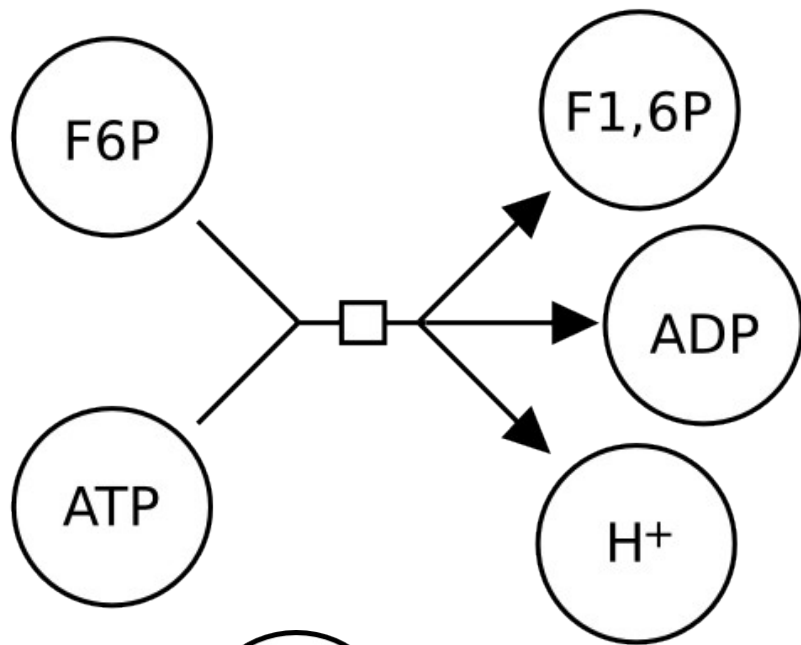


THREE *different* meanings
for ONE symbol!

- Transition
- catalysis
- inhibition

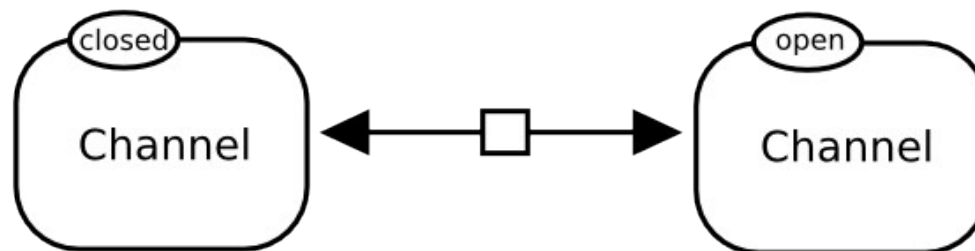
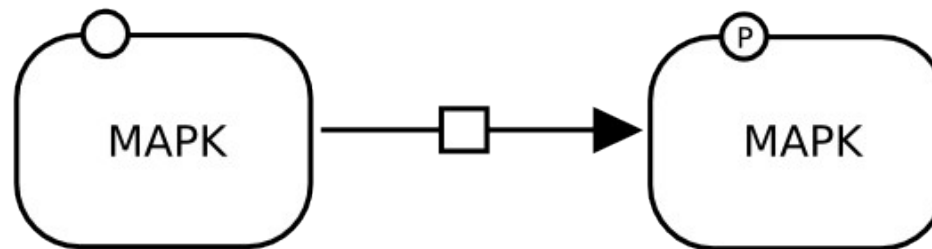


Examples of transitions



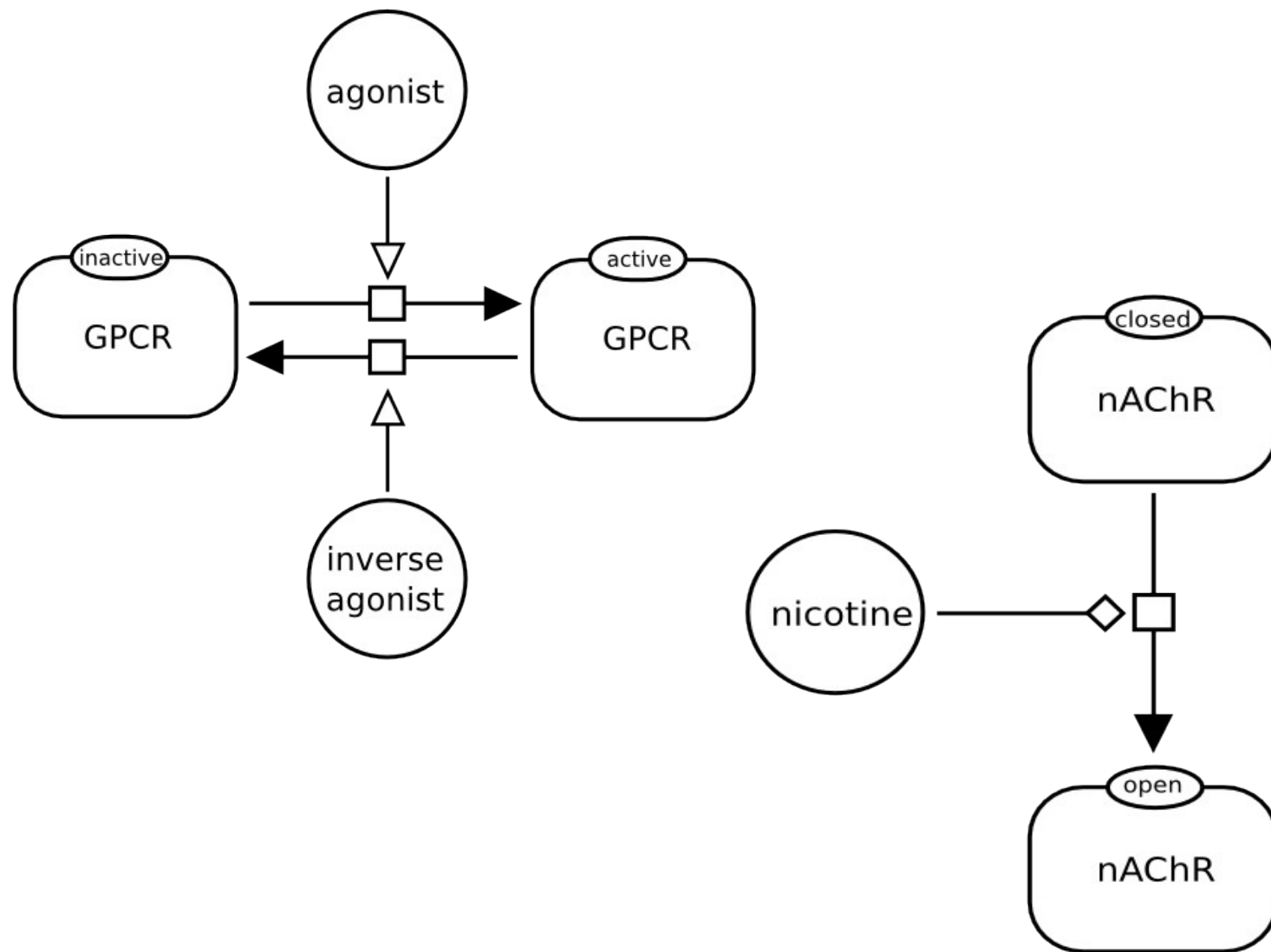


Transitions with state variables



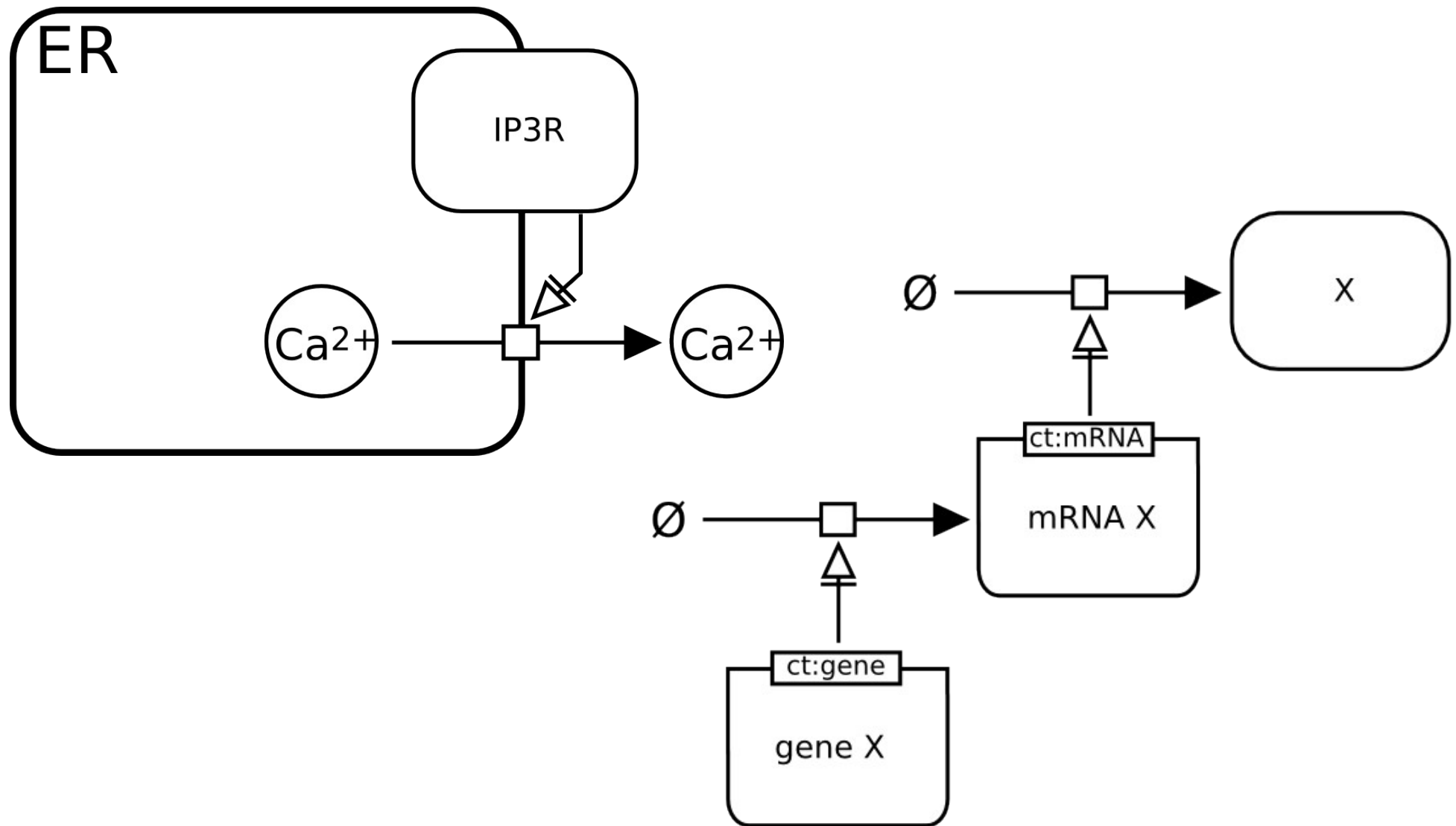


Transitions with modulations





Necessary stimulations





Use of logical operators

