Graphical Notations to Represent System Biology

Stuart Moodie

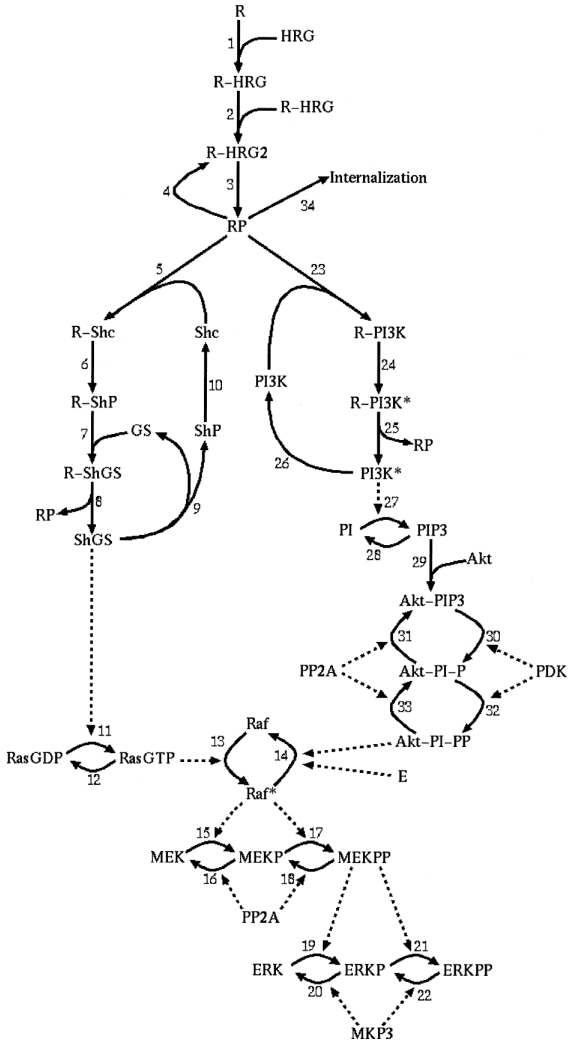
Overview

- Background on Graphical Notations
- Overview of previous notations
- SBGN

Graphical Representations - Why?

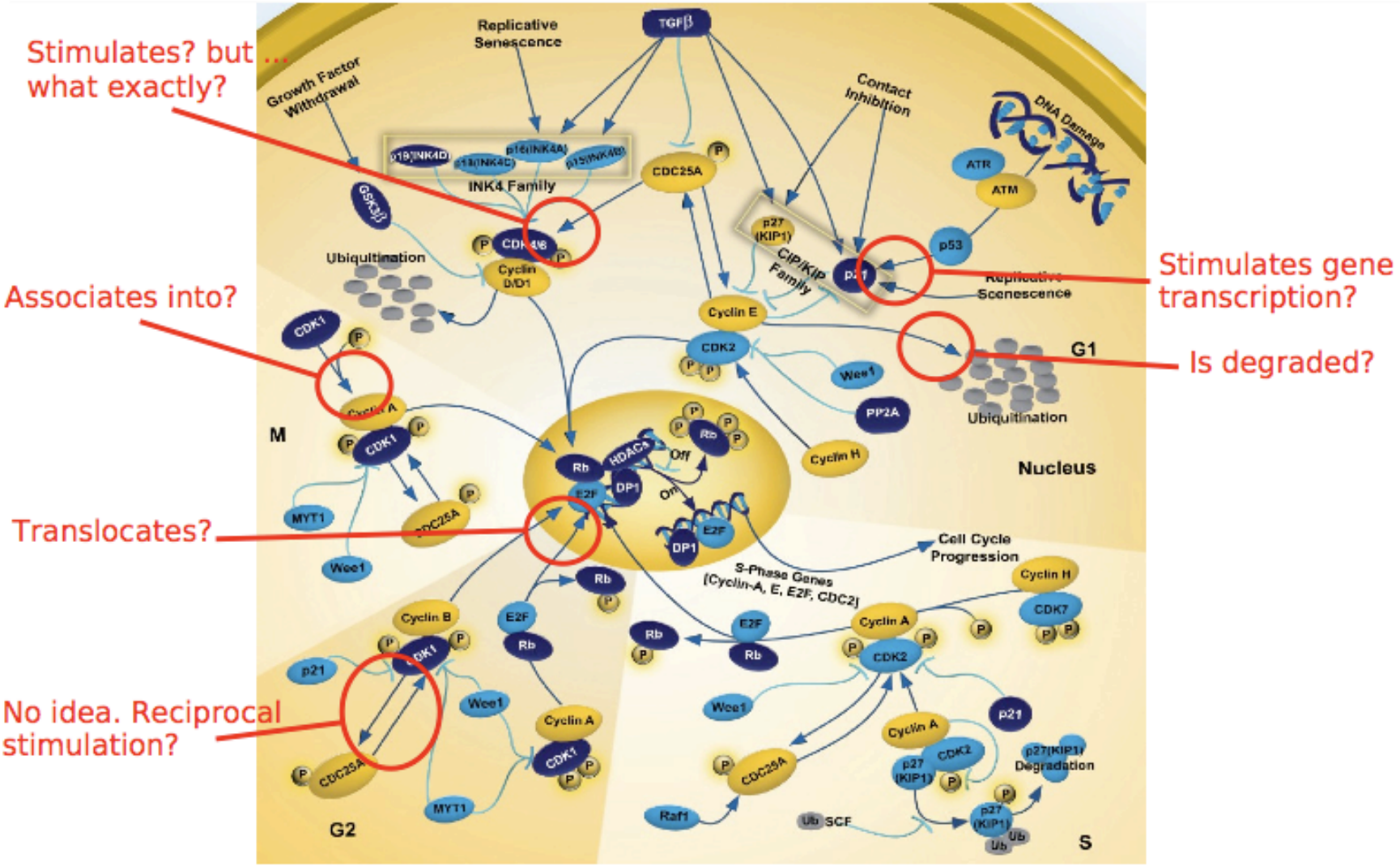
- Summarise information
- Networks easier to understand visually

Reaction number	Rate equation
1	$k_1[R][HRG] - k_{-1}[R\text{-}HRG]$
2	$k_2[R\text{-}HRG]^2 - k_{-2}[R\text{-}HRG2]$
3	$k_3[R\text{-}HRG2] - k_{-3}[RP]$
4	$V_4[RP]/(K_4 + [RP])$
5	$k_5[RP][Shc] - k_{-5}[R\text{-}Shc]$
6	$k_6[R\text{-}Shc] - k_{-6}[R\text{-}ShP]$
7	$k_7[R\text{-}ShP][GS] - k_{-7}[R\text{-}ShGS]$
8	$k_8[R\text{-}ShGS] - k_{-8}[ShGS][RP]$
9	$k_9[ShGS] - k_{-9}[GS][ShP]$
10	$V_{10}[ShP]/(K_{10} + [ShP])$
11	$k_{11}[ShGS][RasGDP]/(K_{11} + [RasGDP])$
12	$V_{12}[RasGTP]/(K_{12} + [RasGTP])$
13	$k_{13}[RasGTP][Raf]/(K_{13} + [Raf])$
14	$k_{14}([Akt\text{-}PI\text{-}PP] + [E])[Raf^*]/(K_{14} + [Raf^*])$
15	$k_{15}[Raf^*][MEK]\Big/\left[K_{15}\left(1 + \frac{[MEKP]}{K_{15}}\right) + [MEK]\right]$
16	$k_{16}[PP2A][MEKP]\Big/\left[K_{16}\left(1 + \frac{[MEKP]}{K_{16}} + \frac{[Akt\text{-}PI\text{-}P]}{K_{17}} + \frac{[Akt\text{-}PI\text{-}PP]}{K_{18}}\right) + [MEKP]\right]$
17	$k_{17}[Raf^*][MEKP]\Big/\left[K_{17}\left(1 + \frac{[MEKP]}{K_{17}}\right) + [MEKP]\right]$
18	$k_{18}[PP2A][MEKPP]\Big/\left[K_{19}\left(1 + \frac{[MEKP]}{K_{19}} + \frac{[Akt\text{-}P\text{-}P]}{K_{20}} + \frac{[Akt\text{-}P\text{-}PP]}{K_{21}}\right) + [MEKPP]\right]$
19	$k_{19}[MEKPP][ERK]\Big/\left[K_{19}\left(1 + \frac{[ERKP]}{K_{19}}\right) + [ERK]\right]$
20	$k_{20}[MKP3][ERKP]\Big/\left[K_{20}\left(1 + \frac{[ERKP]}{K_{20}}\right) + [ERKP]\right]$
21	$k_{21}[MEKPP][ERKP]\Big/\left[K_{21}\left(1 + \frac{[ERKP]}{K_{21}}\right) + [ERKP]\right]$
22	$k_{22}[MKP3][ERKPP]\Big/\left[K_{22}\left(1 + \frac{[ERKP]}{K_{22}}\right) + [ERKPP]\right]$
23	$k_{23}[RP][PI3K] - k_{-23}[R\text{-}PI\text{-}3K]$
24	$k_{24}[R\text{-}PI3K] - k_{-24}[R\text{-}PI\text{-}3K^*]$
25	$k_{25}[R\text{-}PI3K^*] - k_{-25}[RP][PI\text{-}3K^*]$
26	$V_{26}[PI3K^*]/(K_{26} + [PI\text{-}3K^*])$
27	$k_{27}[PI3K^*][PI]/(K_{27} + [PI])$
28	$V_{28}[PIP_3]/(K_{28} + [PIP_3])$
29	$k_{29}[PIP_3][Akt] - k_{-29}[Akt\text{-}PIP_3]$
30	$V_{30}[Akt\text{-}PIP_3]\Big/\left[K_{30}\left(1 + \frac{[Akt\text{-}P\text{-}P]}{K_{30}}\right) + [Akt\text{-}PIP_3]\right]$
31	$k_{31}[PP2A][Akt\text{-}PI\text{-}P]\Big/\left[K_{31}\left(1 + \frac{[MEKP]}{K_{31}} + \frac{[Akt\text{-}P\text{-}P]}{K_{32}} + \frac{[Akt\text{-}PI\text{-}PP]}{K_{33}}\right) + [Akt\text{-}PI\text{-}P]\right]$
32	$V_{32}[Akt\text{-}PI\text{-}P]\Big/\left[K_{32}\left(1 + \frac{[Akt\text{-}P]}{K_{32}}\right) + [Akt\text{-}PI\text{-}P]\right]$
33	$k_{33}[PP2A][Akt\text{-}PI\text{-}PP]\Big/\left[K_{33}\left(1 + \frac{[MEKP]}{K_{33}} + \frac{[Akt\text{-}P\text{-}P]}{K_{34}} + \frac{[Akt\text{-}PI\text{-}P]}{K_{34}}\right) + [Akt\text{-}PI\text{-}P]\right]$
34	$k_{34}[RP] - k_{-34}[\text{internalization}]$

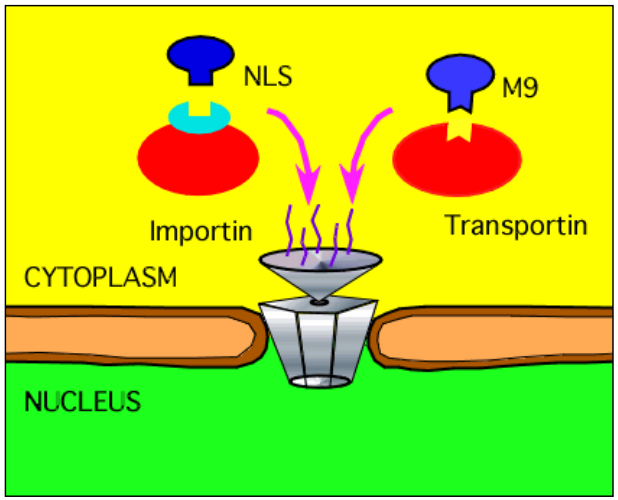


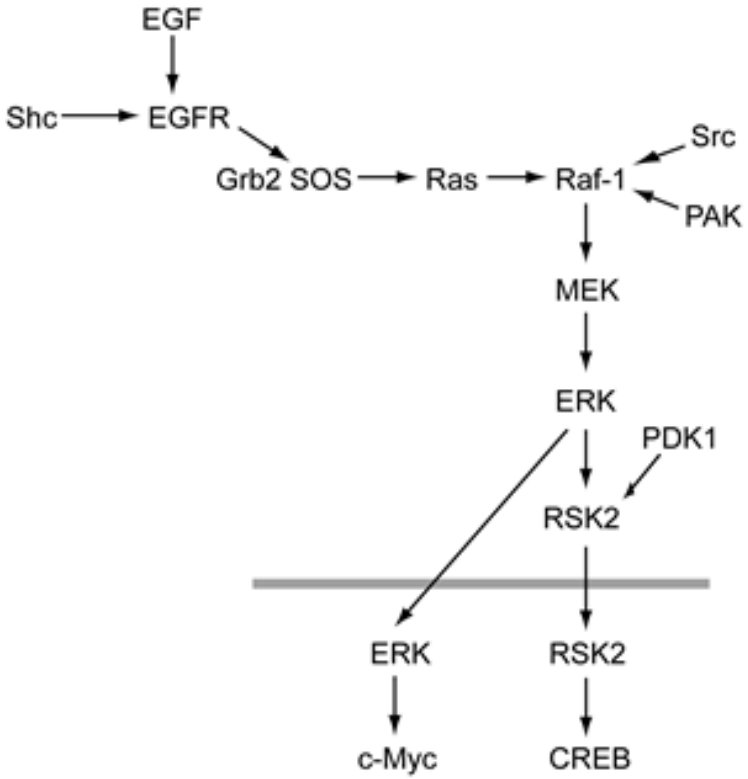
from Hatakeyma *et al.* Biochem J. (2003) 373. 451-463.

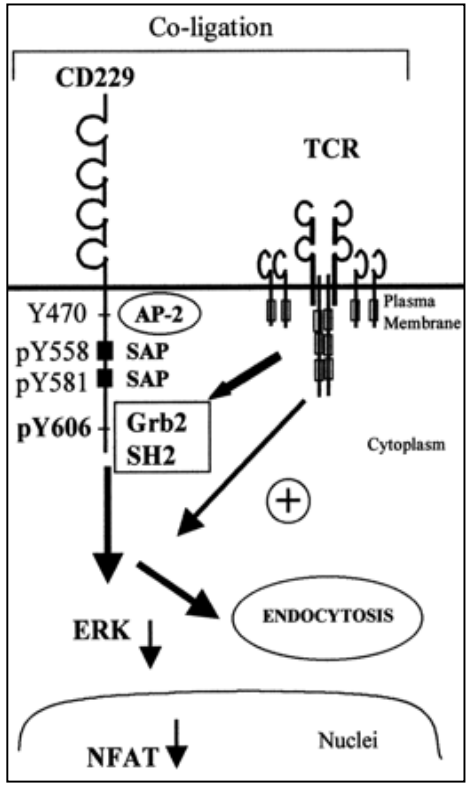
Can this be understood by a Biologist?



Graphical Representations - Why Not?





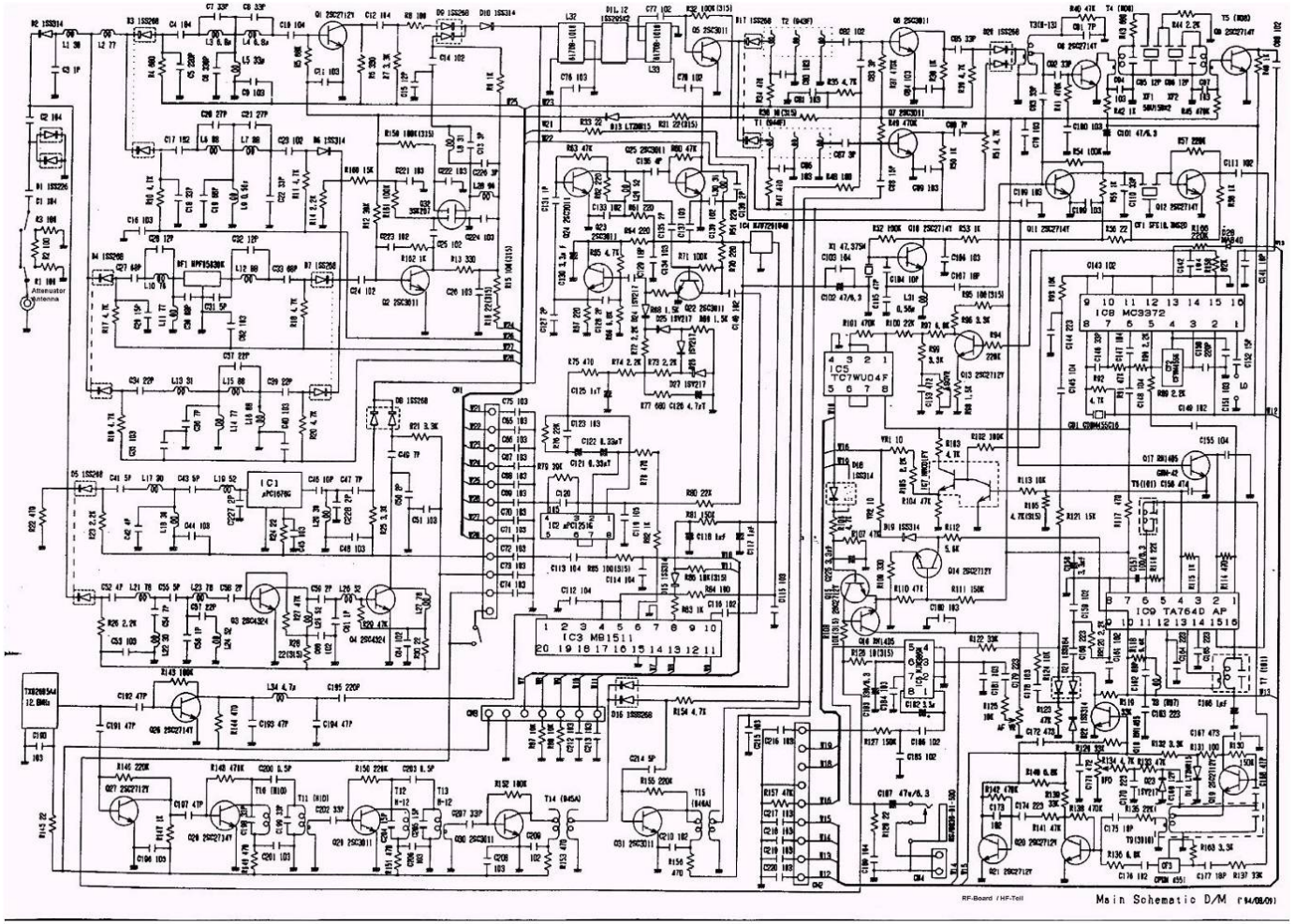


- Ambiguous
- Not amenable to computational analysis

Graphical Notations: "Formalised" Pictures

- Visual Language
- Rules and guidelines ensure:
  - reader can unambiguously understand what writer meant
  - amenable to computation manipulation/ analysis

Classic Example



Pathways are not Electronic Circuits

- Circuits designed by humans
  - –Follow a defined set of rules
  - –Boundaries well defined

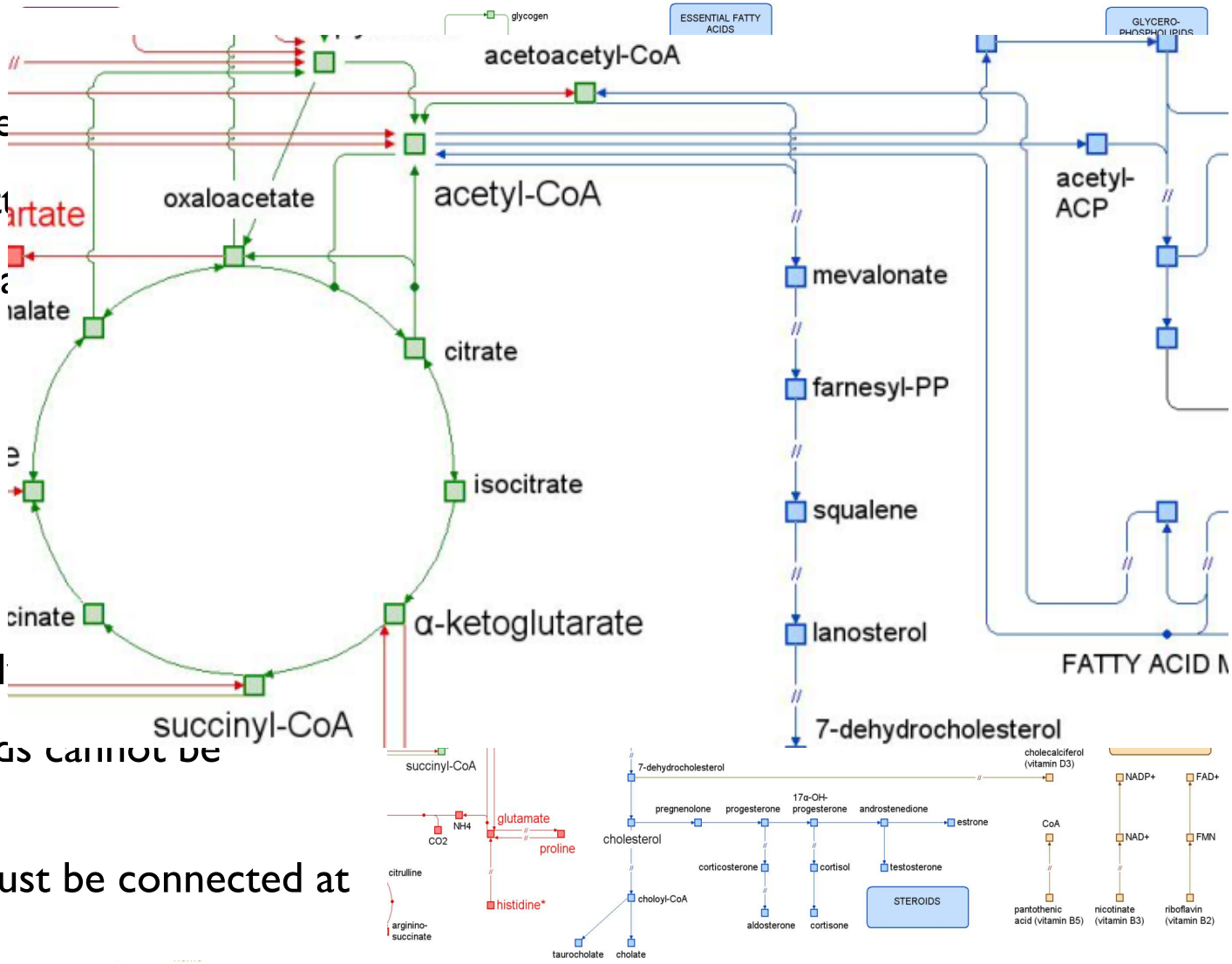
- Pathways
  - –Don’t know all the “rules”
  - –Boundaries not clear
  - –Knowledge often incomplete

Graphical Notation

- Has an underlying conceptual abstraction
  - a model of its world
- Visual Language
  - vocabulary (symbols/**glyphs**)
  - **syntax** (basic assembly or glyphs)
  - grammar (rules based on meaning - **semantics**)

Notation Example

- Abstraction
  - biochemical re
  - enzymes omitt
  - net flow of rea
- Language
  - Symbols
  - Syntax
  - Semantics
    - Names onl
    - Compounds cannot be orphaned
    - Arrows must be connected at both ends

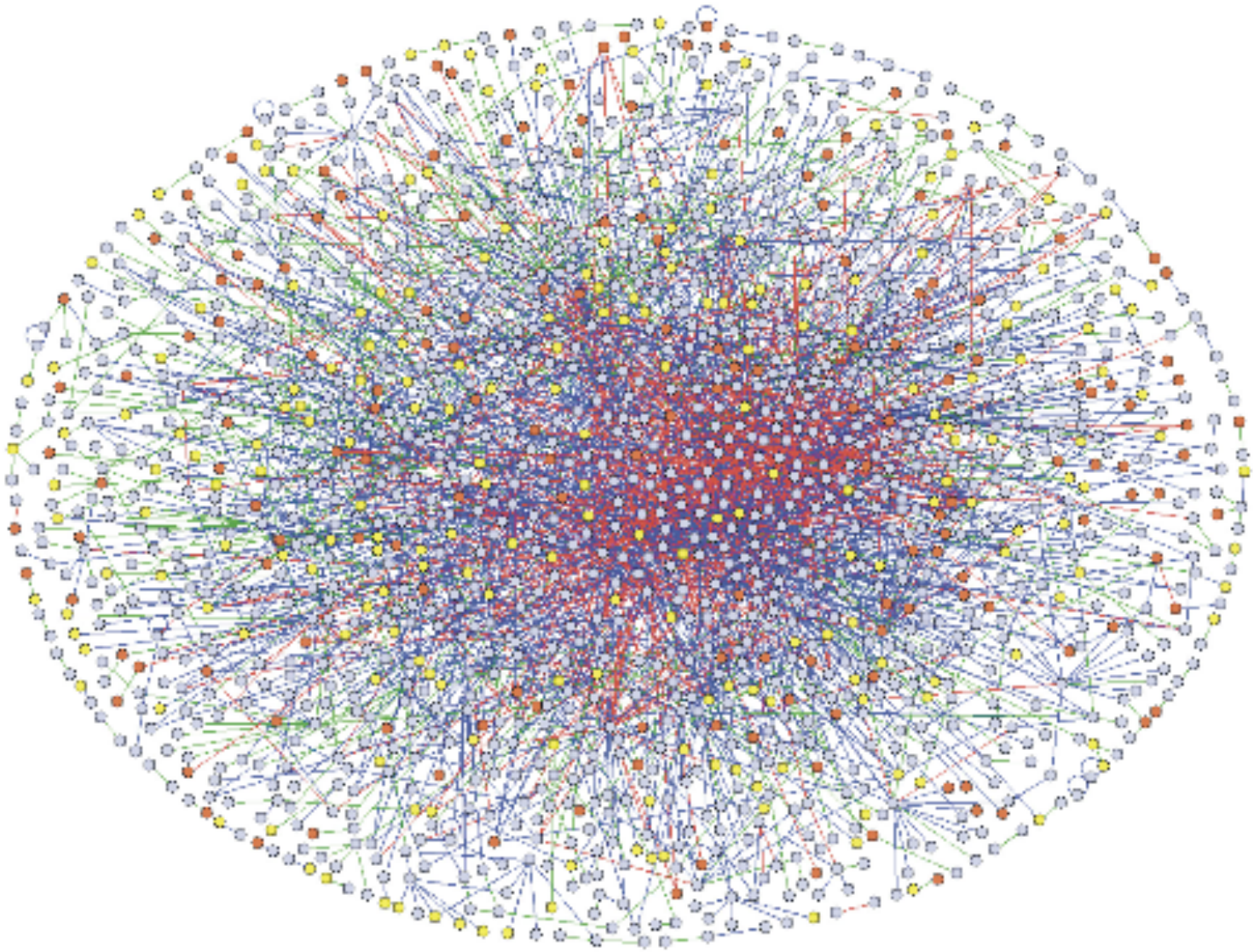


Types of Graphical Notation

- Entity Relationship
  - –Protein Interaction Diagrams
  - –MIM (Kohn)
  - –SBGN-ER
- State Transition/Process
  - –EPN
  - –PDN (Kitano)
  - –SBGN-PD

Overview of Pre-SBGN Notation

Entity Relationship View



MIMs

- Inspired by circuit diagrams
- Invented by Kurt Kohn, NIH
- First published 1999
- Presented to SBGN by Marit Aladjem

- Slides taken from Aladjem presentation at SBGN-1

Molecular Biology of the Cell
Vol. 17, 1–13, January 2006

Essay

Molecular Interaction Maps of Bioregulatory Networks: A General Rubric for Systems Biology

Kurt W. Kohn, Mirit I. Aladjem, John N. Weinstein, and Yves Pommier

Laboratory of Molecular Pharmacology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892

Submitted September 1, 2005; Accepted October 21, 2005
Monitoring Editor: Gerard Evan

Molecular Systems Biology (2006) doi:10.1038/msb4100088
© 2006 EMBO and Nature Publishing Group All rights reserved 1744-4292/06
www.nature.com/msb
Article number: 51

REVIEW

Depicting combinatorial complexity with the molecular interaction map notation

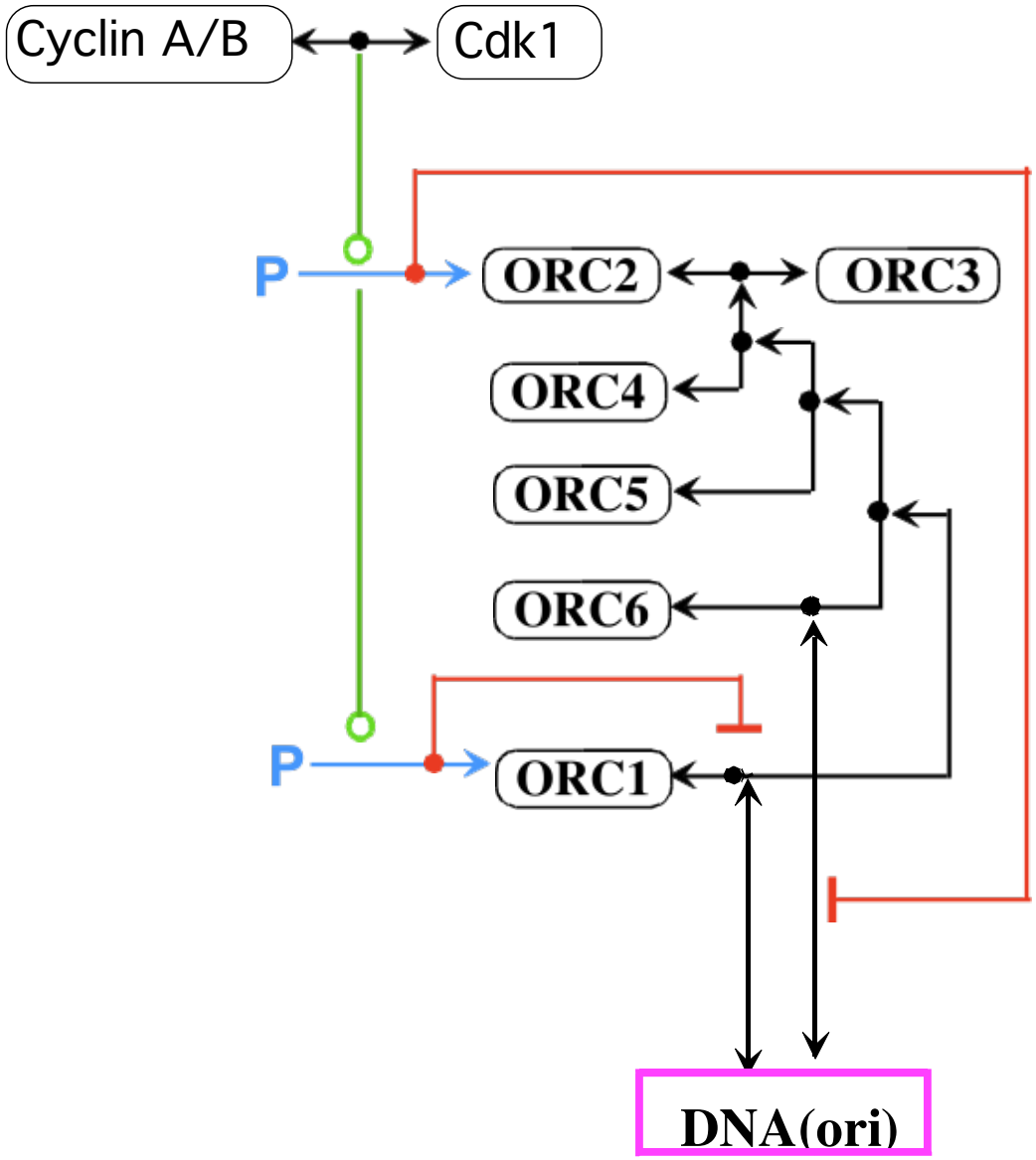
Kurt W Kohn*, Mirit I Aladjem, Sohyoung Kim, John N Weinstein and Yves Pommier

Laboratory of Molecular Pharmacology, Center for Cancer Research, National Cancer Institute, NIH, Bethesda, MD, USA
* Corresponding author. Laboratory of Molecular Pharmacology, Center for Cancer Research, National Cancer Institute, Building 37, Room 5068, NIH, Bethesda, MD 20892, USA. Tel.: +1 301 496 2769; Fax: +1 301 402 0752; E-mail: kohnk@dc37a.nci.nih.gov

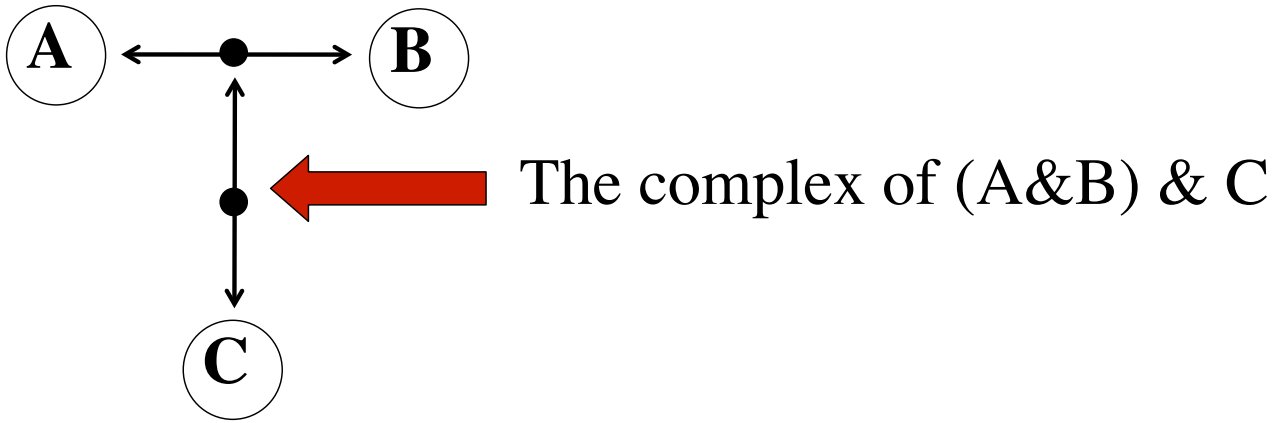
Received 2.1.06; accepted 2.1.06

Two of the best developed notations are the molecular interaction maps (MIMs) that we have described (Kohn, 1999, 2001; Kohn *et al*, 2006) and the 'process diagrams' described by Kitano *et al* (Kitano, 2003; Kitano *et al*, 2005). We recently discussed the strengths and weaknesses of the various notations that have been proposed (Kohn *et al*, 2006). These include, in addition to the MIM and process diagram notations, the computer-aided design (CAD)-like diagrams produced by CellDesigner (Funahashi *et al*, 2003), a software suite called CADLIVE (Kurata *et al*, 2005), the automated diagrams of Cook *et al* (2001), and BIOCARTA's connection diagrams

Assembly of a multimolecular complex: ORC, the origin recognition complex (involved in cell cycle regulation)

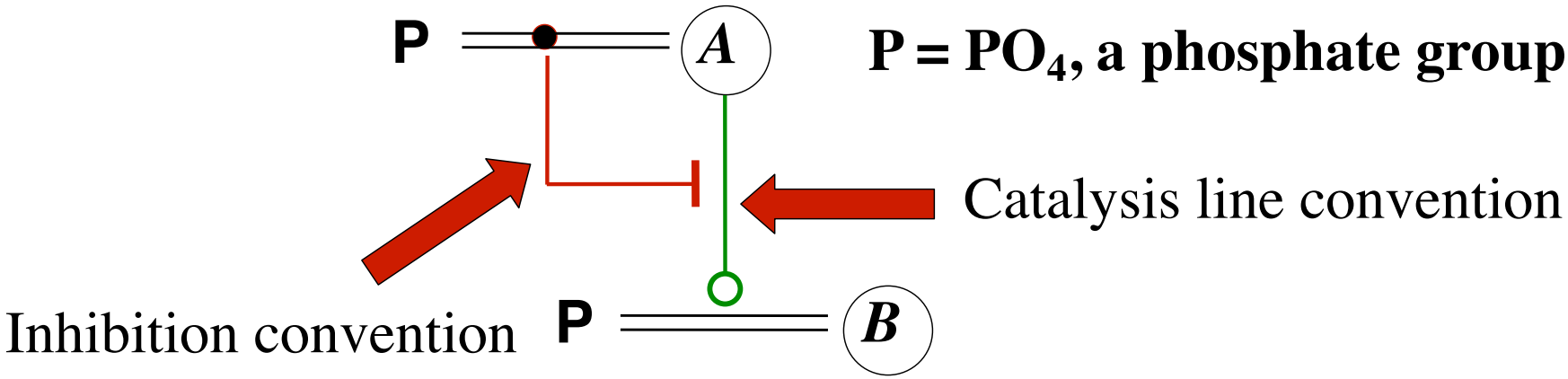


Multi-protein complexes



Each molecule appears only once per diagram. Interaction outcomes - complexes or modified molecules - are depicted as nodes on the interaction lines.

Covalent modification (e.g., protein phosphorylation)



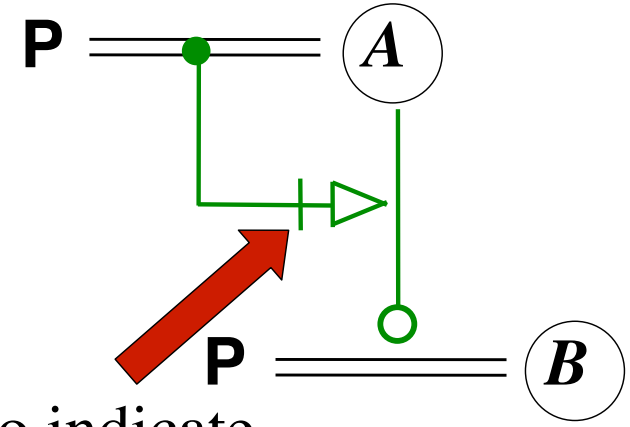
P = PO_4, a phosphate group

Catalysis line convention

Inhibitory phosphorylation:

Phosphorylation of *A* blocks the kinase activity of *A*.

Activating phosphorylation:
The phosphorylated form of kinase ***A*** is the active form, phosphorylates ***B***



Bar added to indicate obligatory requirement

Reactions

Binding (non-covalent)

Covalent Modification
(e.g. phosphorylation)

Bond cleavage
(e.g. Phosphatase)

A → B Stochiometric Conversion (A to B)

→ ∅ Degradation

Transcription/translation

A ↔ ● Dimerization

A → | → ● Transport

Contingencies

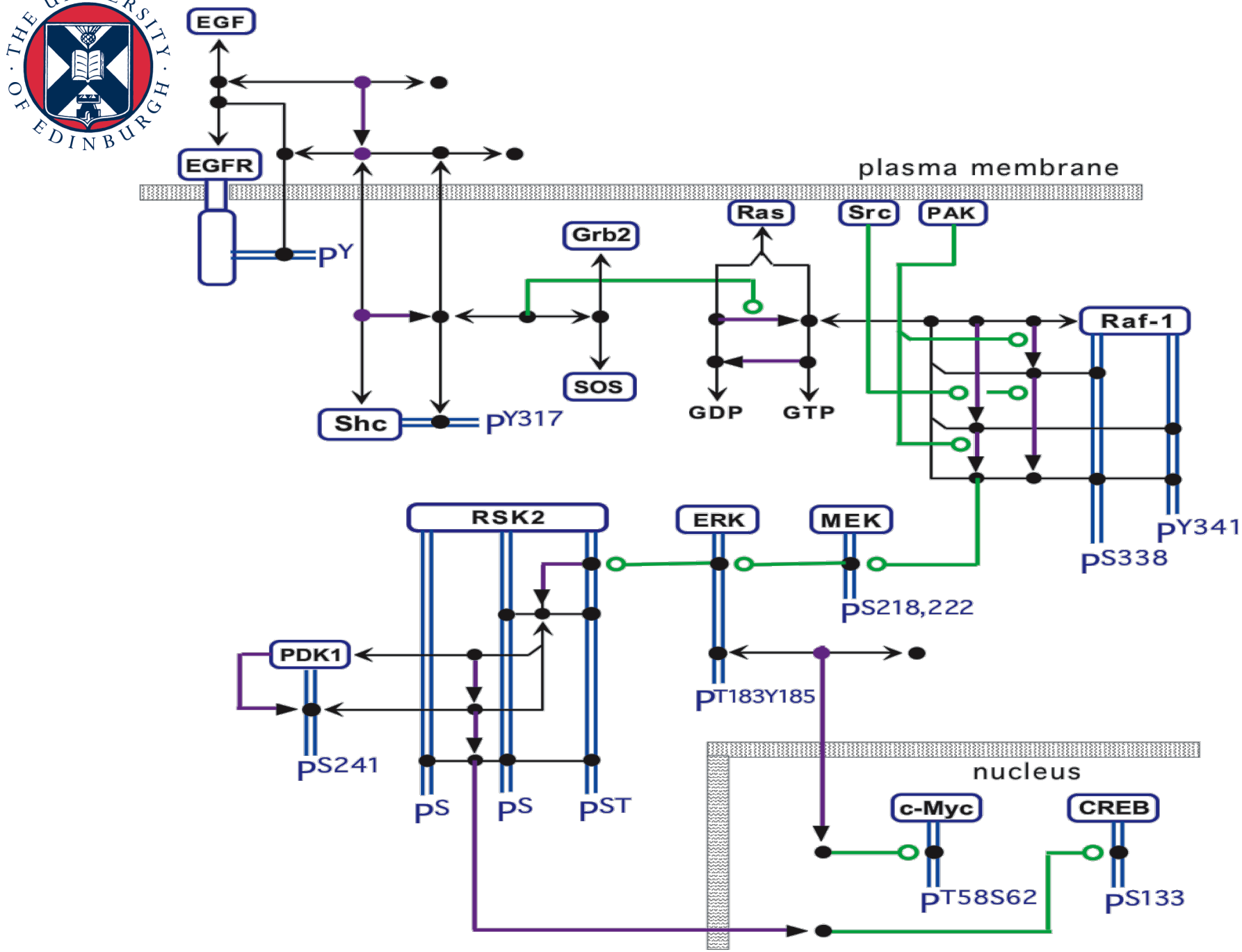
Catalysis

Stimulation

Stimulation required

Inhibition

Reactions operate on molecular species; contingencies operate on reactions, or on other contingencies; reaction outcomes (nodes) are treated as molecular species.


EGF
EGFR
plasma membrane
PY
Grb2
SOS
Shc
PY317
Ras
GDP
GTP
Src
PAK
Raf-1
PS338
PY341
RSK2
ERK
MEK
PS218,222
PDK1
PS241
PS
PS
PST
PT183Y185
nucleus
c-Myc
PT58S62
CREB
PS133

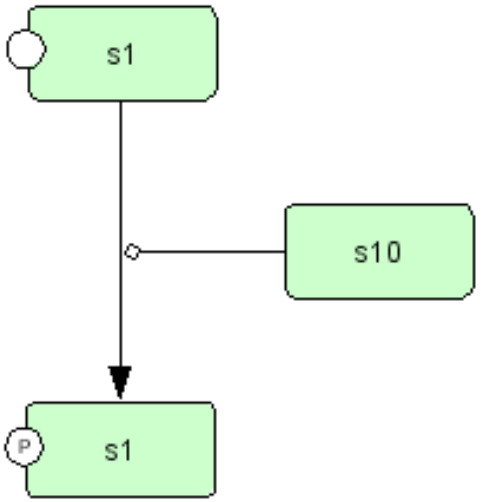
MIMs

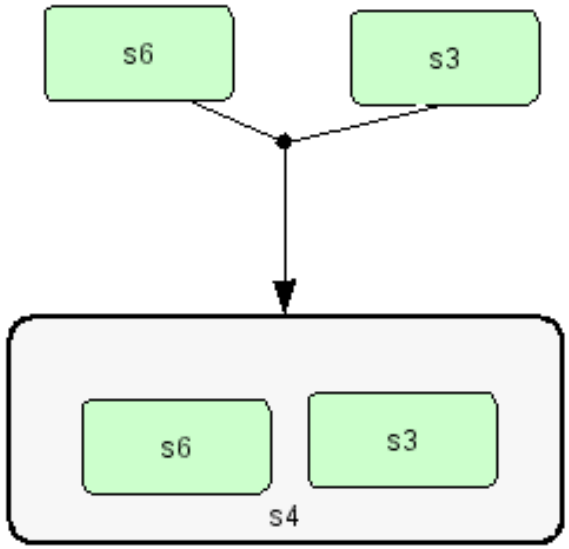
- Benefits
  - –Compact
  - –Established
  - –Useful to biologists
- Drawbacks
  - –Learning curve
  - –No tool support

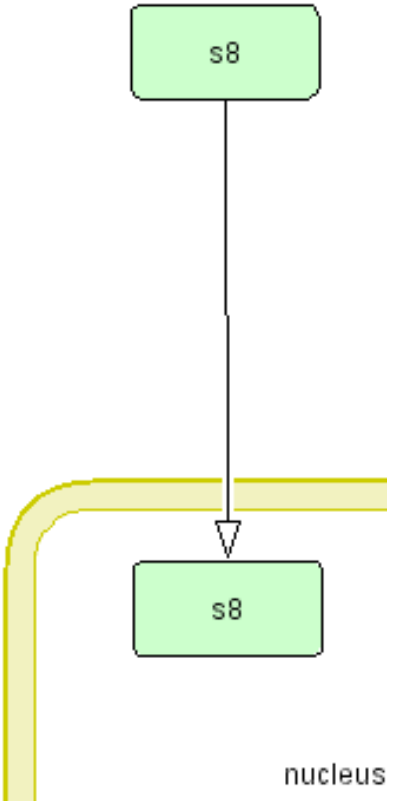
State Transition Diagrams

- PDN & EPN

State Transition/Process Diagrams

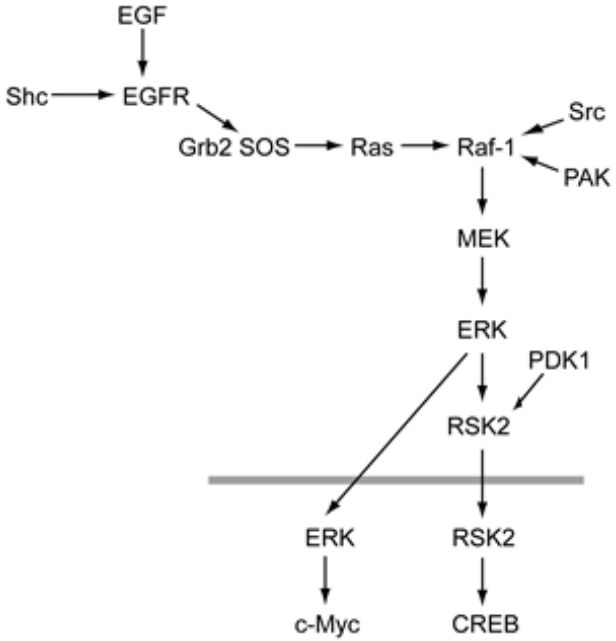


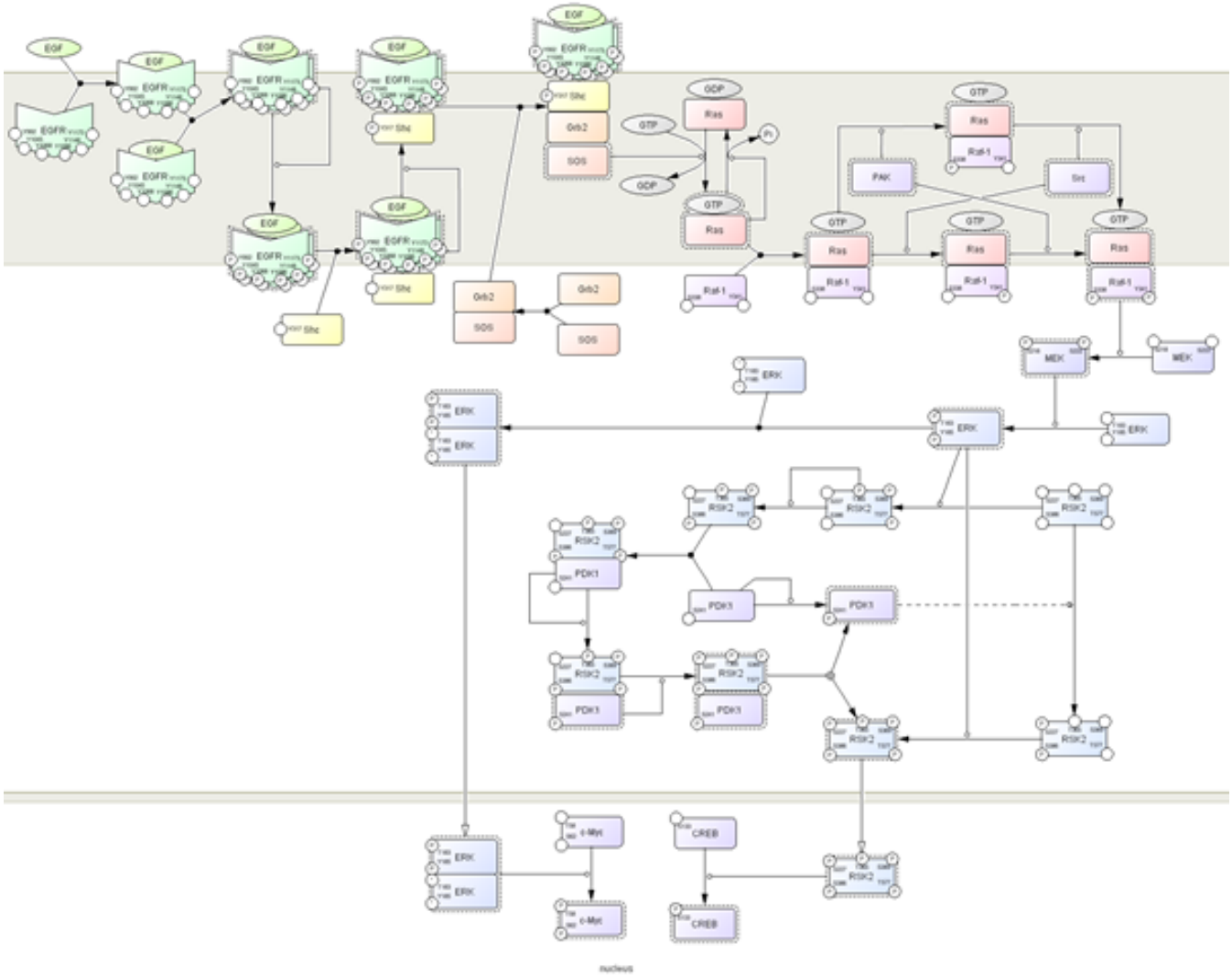




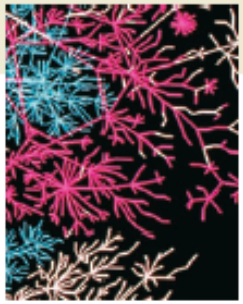
- Slides taken from Kitano presentation at SBGN-1

PDN (Kitano Notation)





http://www.nature.com/nbt/journal/v23/n8/abs/nbt1111.html



_computational BIOLOGY

PERSPECTIVE

Group http://www.nature.com/naturebiotechnology

Using process diagrams for the graphical representation of biological networks

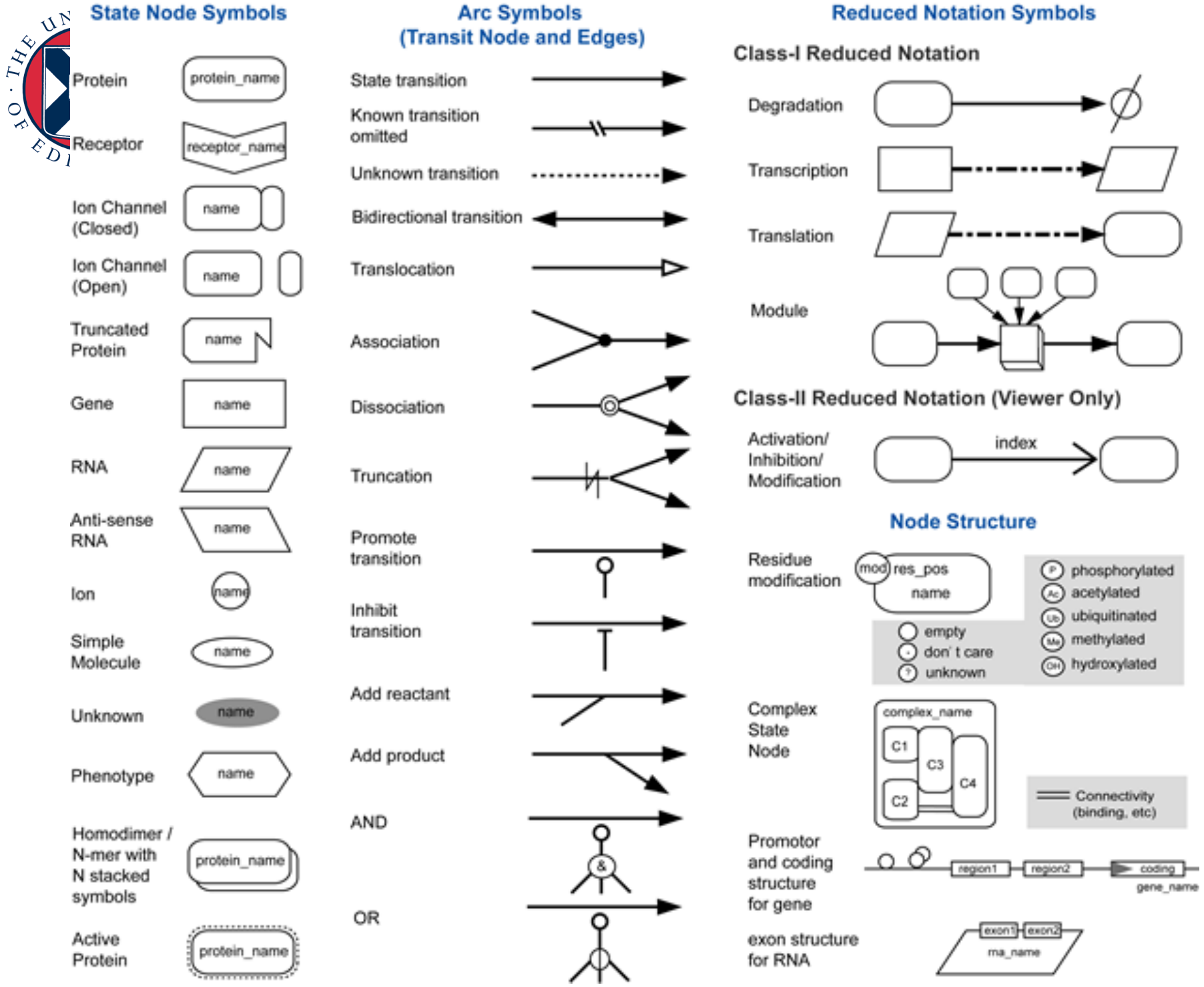
Hiroaki Kitano[1–4], Akira Funahashi[1,3,4], Yukiko Matsuoka[1,3] & Kanae Oda[1,4]

With the increased interest in understanding biological networks, such as protein-protein interaction networks and gene regulatory networks, methods for representing and communicating such networks in both human- and machine-readable form have become increasingly important. Although there has been significant progress in machine-readable representation of networks, as exemplified by the Systems Biology Mark-up Language (SBML) (http://www.sbml.org) issues in human-readable representation have been largely ignored. This article discusses human-readable diagrammatic representations and

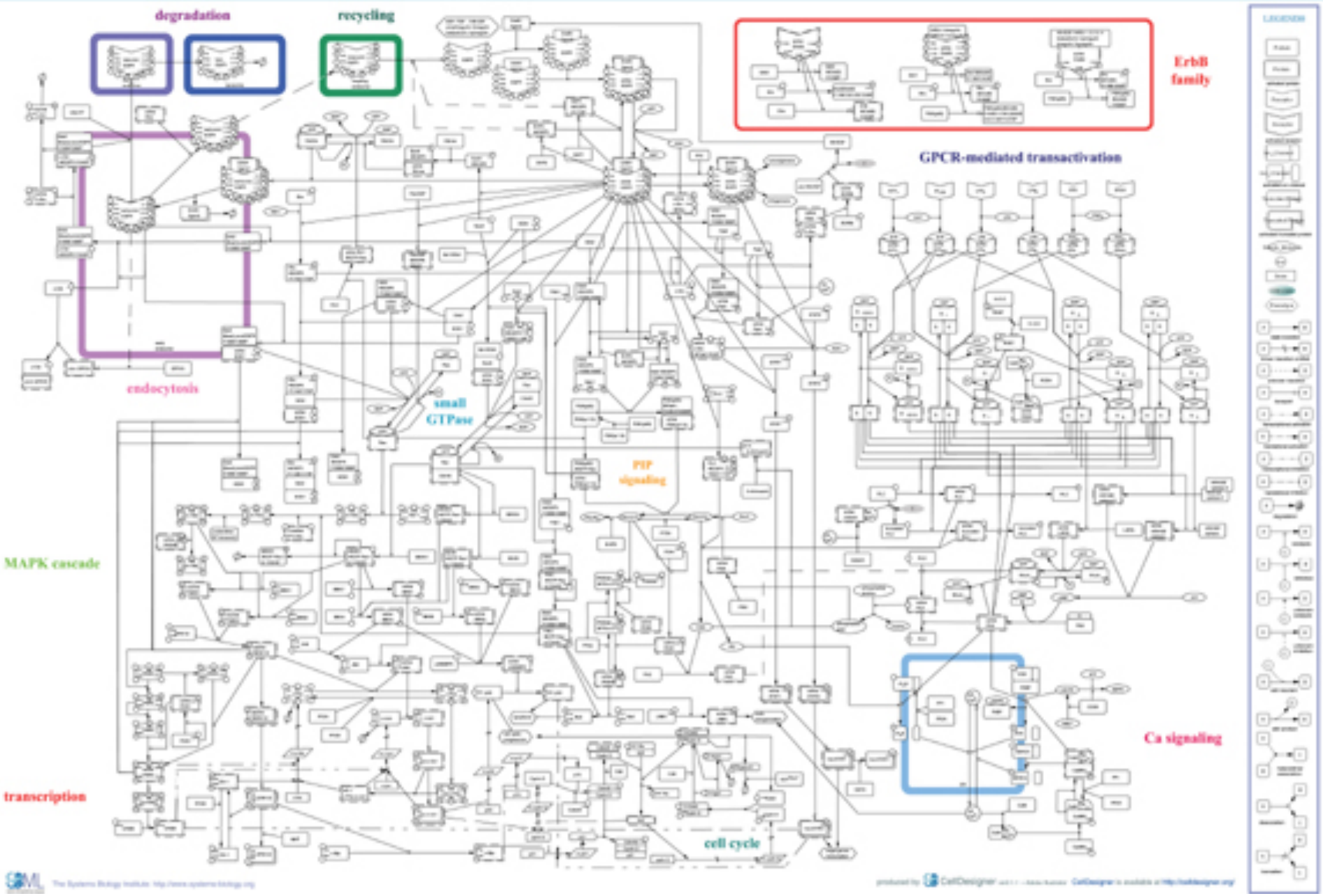
when representing interactions within larger networks. Therefore, there is a need for diagrams that contain unambiguous process information in the symbols used and that can be transferred to standard machine-readable codes such as SBML for computational analysis[1].

Circuit schematic diagrams used in electronics are ideal examples of a graphical diagram. Engineers can reproduce the circuits drawn in the schematic diagrams without substantial additional information, because the diagrams are unambiguously defined, contain sufficient information and are based on well-accepted standards.

Kurt Kohn was the first to produce canonical representations for


State Node Symbols
Protein
protein_name
Receptor
receptor_name
Ion Channel (Closed)
name
Ion Channel (Open)
name
Truncated Protein
name
Gene
name
RNA
name
Anti-sense RNA
name
Ion
name
Simple Molecule
name
Unknown
name
Phenotype
name
Homodimer / N-mer with N stacked symbols
protein_name
Active Protein
protein_name
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
Class-I Reduced Notation
Degradation
Transcription
Translation
Module
Class-II Reduced Notation (Viewer Only)
Activation/ Inhibition/ Modification
index
Node Structure
Residue modification
mod
res_pos
name
empty
don' t care
unknown
phosphorylated
acetylated
ubiquitinated
methylated
hydroxylated
Complex State Node
complex_name
C1
C2
C3
C4
Connectivity (binding, etc)
Promotor and coding structure for gene
region1
region2
coding
gene_name
exon structure for RNA
exon1
exon2
rna_name

EGF Receptor Cascade

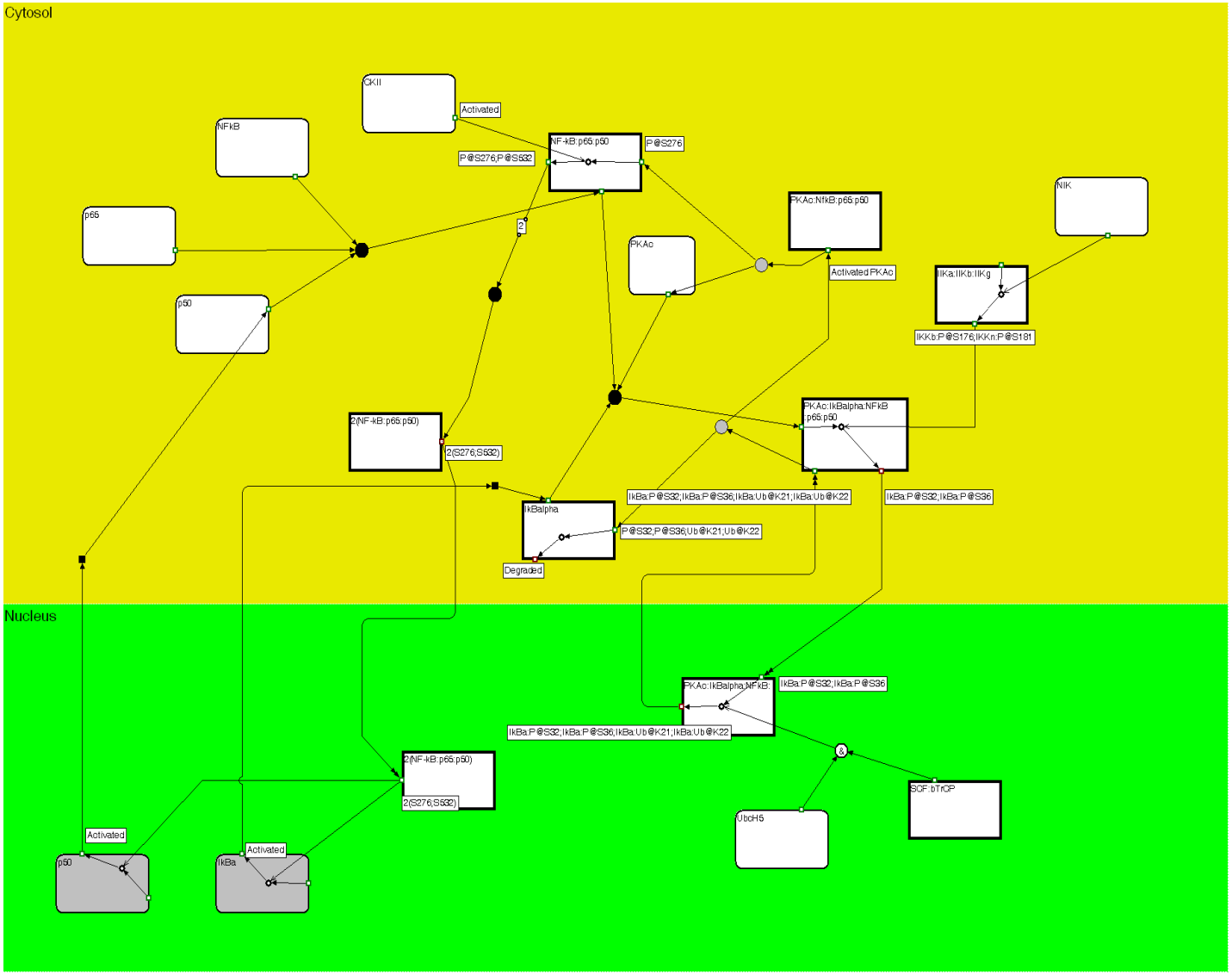


Oda, et al. Molecular Systems Biology, 2005

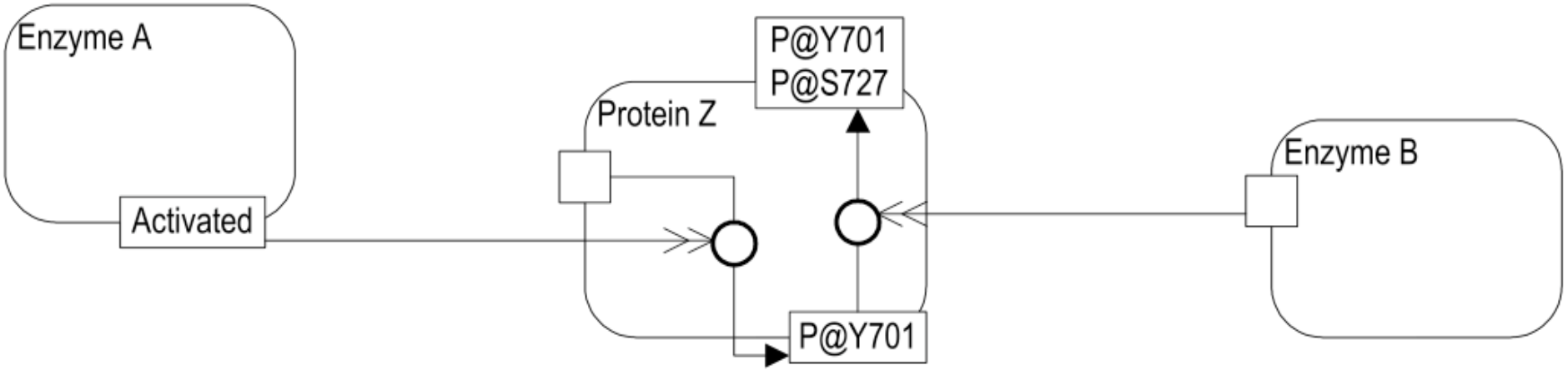
PDN (Kitano) Notation

- Benefits
  - Simple – easy to learn
  - Maps easily to SBML
  - Established
  - Tool support (CellDesigner, EPE)
- Drawbacks
  - Verbose (takes up a lot of space)
  - Need to know pathway in detail

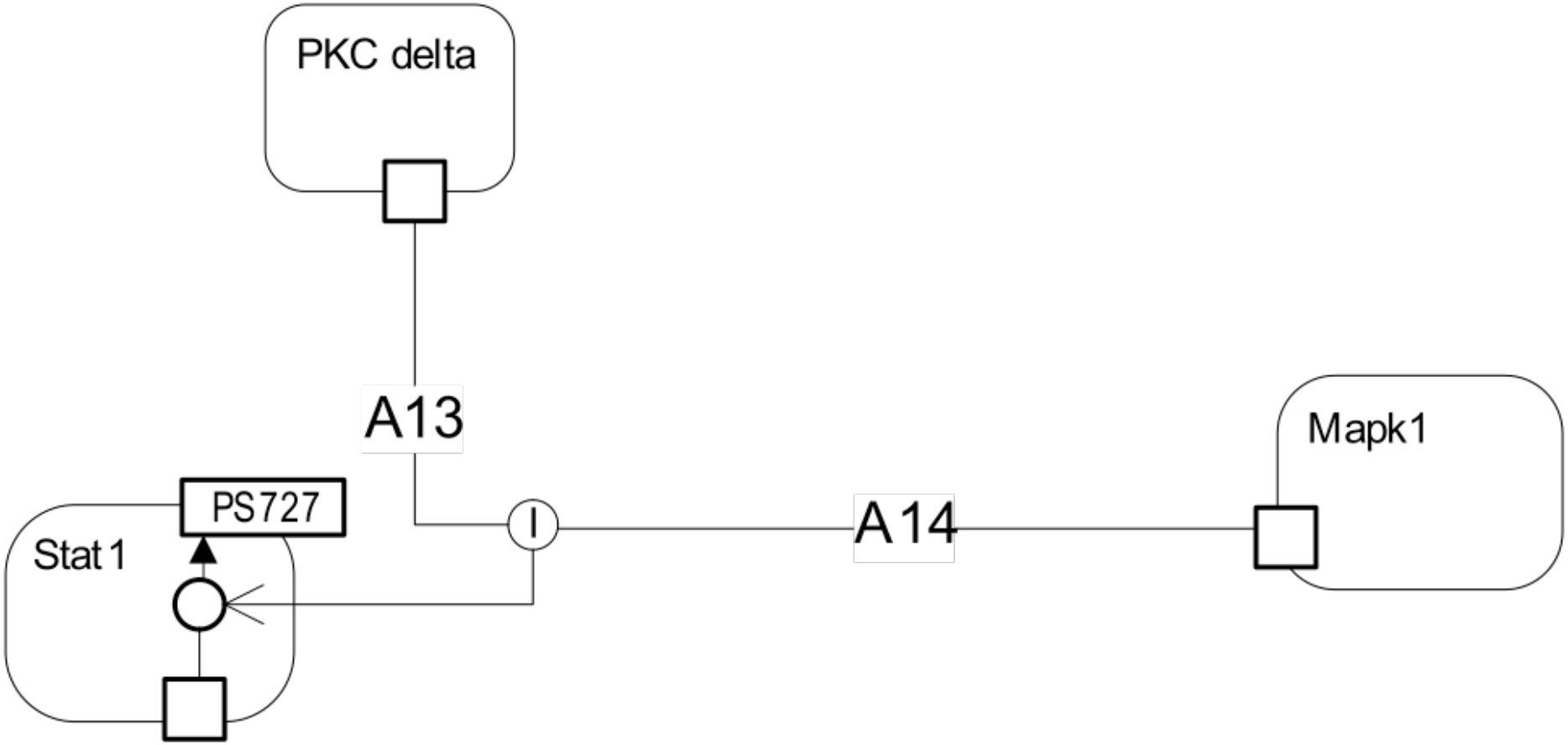
Edinburgh Pathway Notation (EPN)



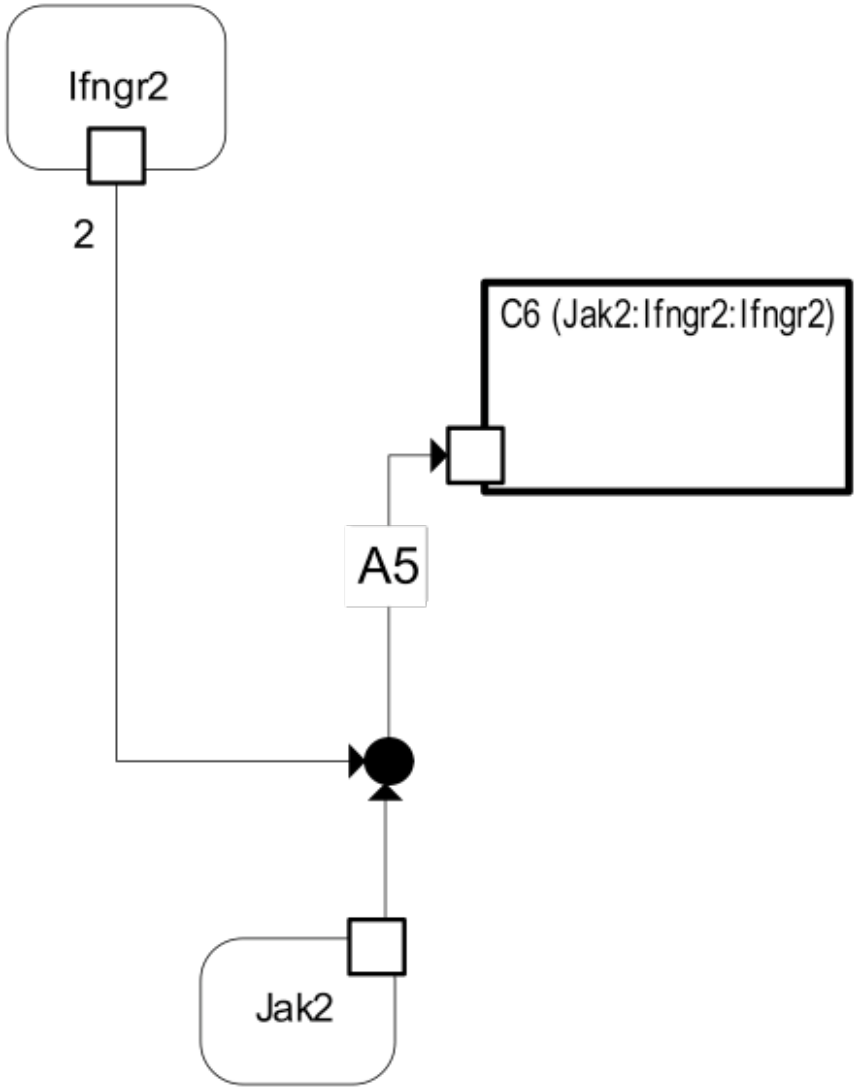
State Transition/ Activation



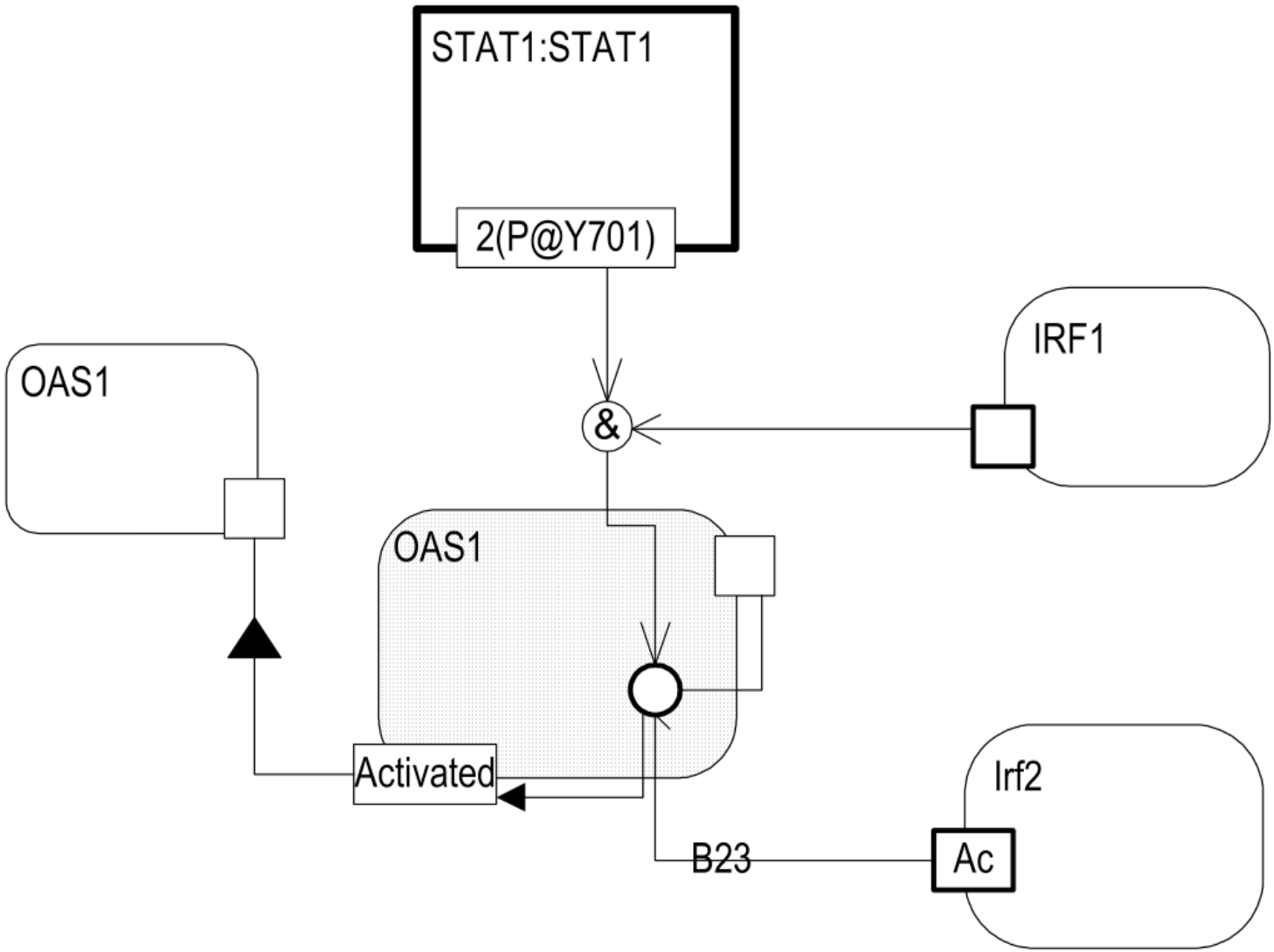
Logic Gates



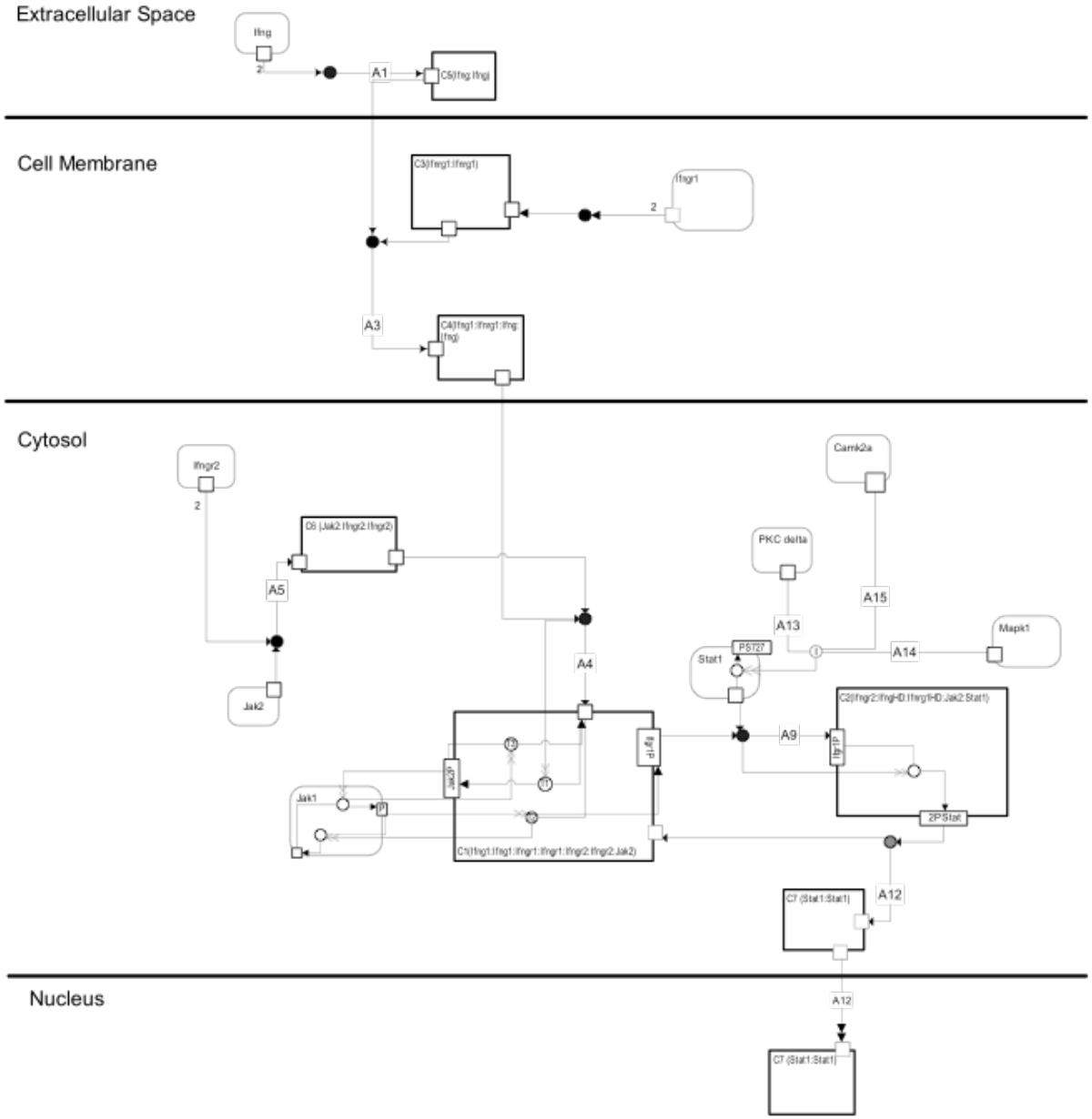
Complex Formation



Gene Regulation



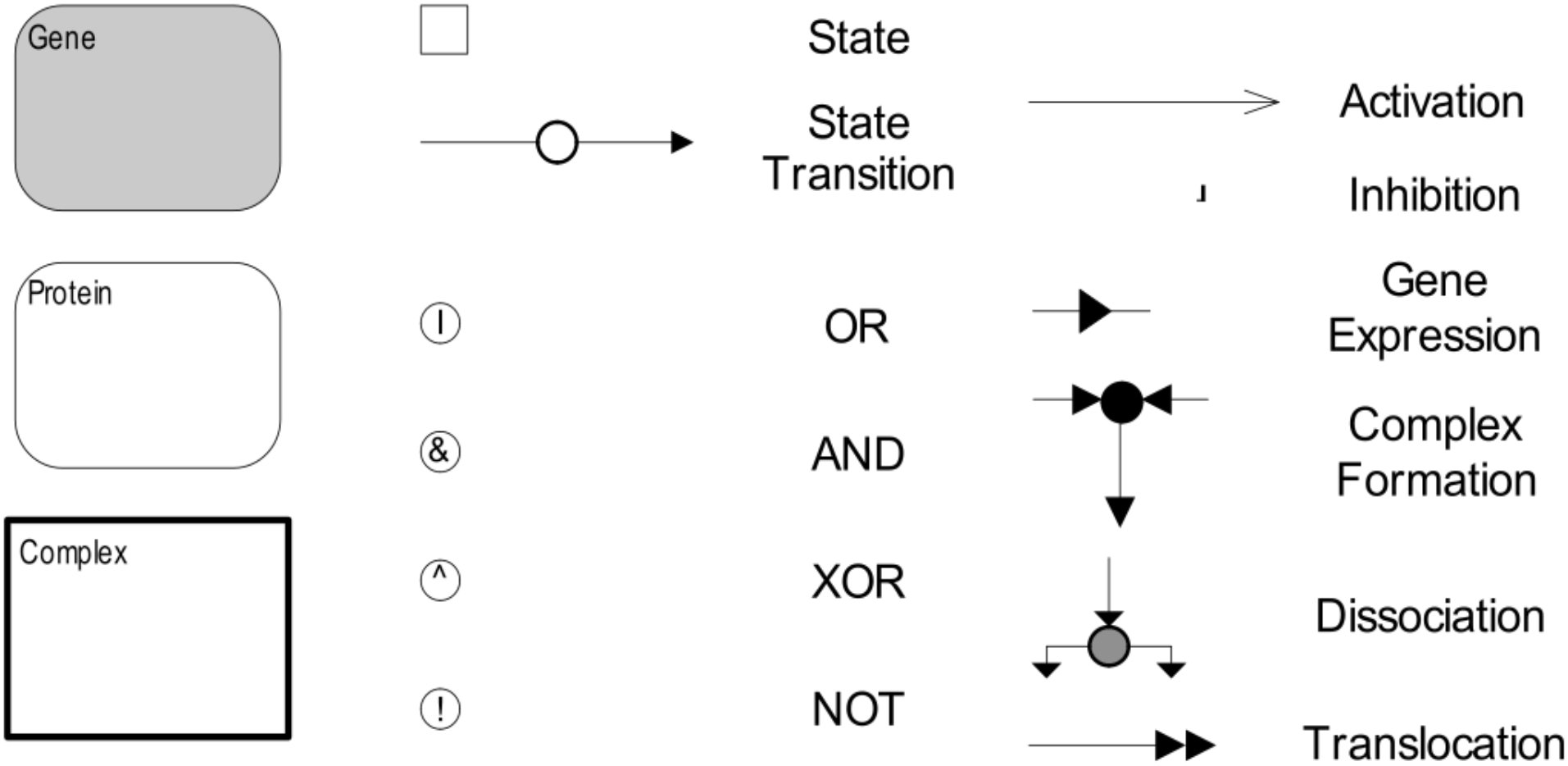
Localisation



Outside

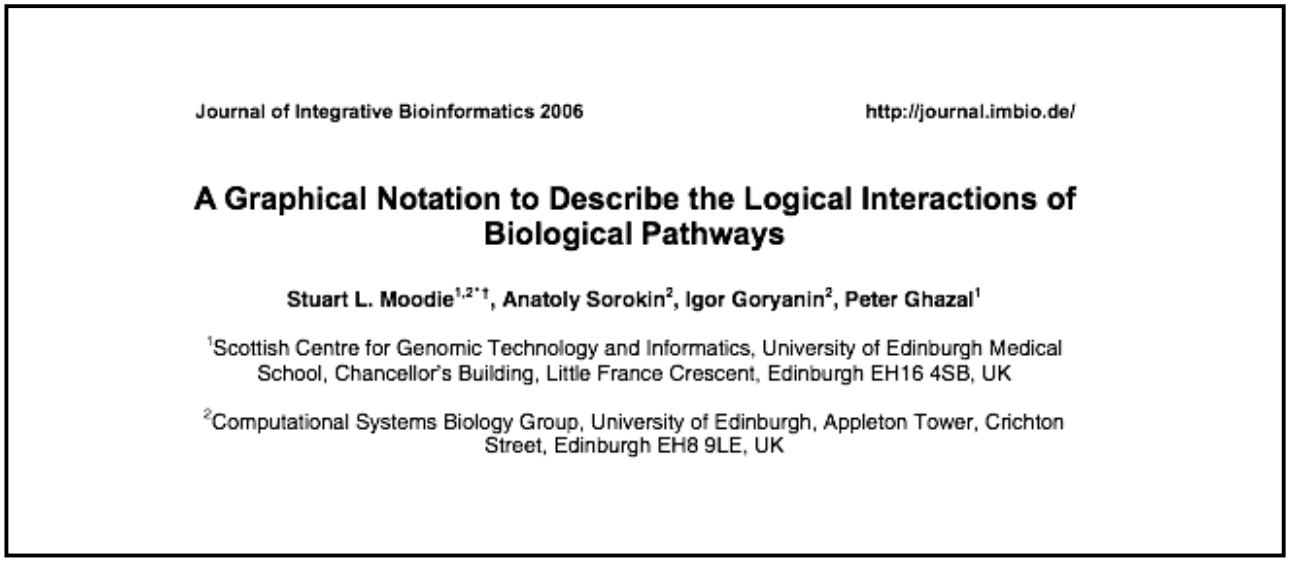
Inside

Symbols


Gene
Protein
Complex
State
State Transition
OR
AND
XOR
NOT
Activation
Inhibition
Gene Expression
Complex Formation
Dissociation
Translocation

Innovations

- Permitted arbitrary “logical states”
- Comprehensive use of logic gates
- Workable description of gene regulation
- Use of state description language: P@S727



Journal of Integrative Bioinformatics 2006 http://journal.imbio.de/

A Graphical Notation to Describe the Logical Interactions of Biological Pathways

Stuart L. Moodie[1,2*†], Anatoly Sorokin[2], Igor Goryanin[2], Peter Ghazal[1]

[1]Scottish Centre for Genomic Technology and Informatics, University of Edinburgh Medical School, Chancellor's Building, Little France Crescent, Edinburgh EH16 4SB, UK

[2]Computational Systems Biology Group, University of Edinburgh, Appleton Tower, Crichton Street, Edinburgh EH8 9LE, UK

www.sbgn.org

SYSTEMS BIOLOGY GRAPHICAL NOTATION

SBGN (www.sbgn.org)

- Aims
  - Agree a standard set of graphical notations for systems biology
  - Encourage tool support for SBGN
  - Encourage community usage
- Initiated by:
  - Kitano, SBI
  - Le Novere, EBI

SBGN Governance

- 5 Editors who write the specs and coordinate
  - Nicolas Le Novere (EBI)
  - Huaiyu Mi (SRI)
  - Stuart Moodie (UofE)
  - Falk Schreiber (MLU Halle-Wittenberg)
  - Emek Demir (MSKCC)
- 5 Member Scientific Committee

Annual Hackathon (Spring 2010 in Germany)

Annual Forum Meeting (Edinburgh Oct 2010)

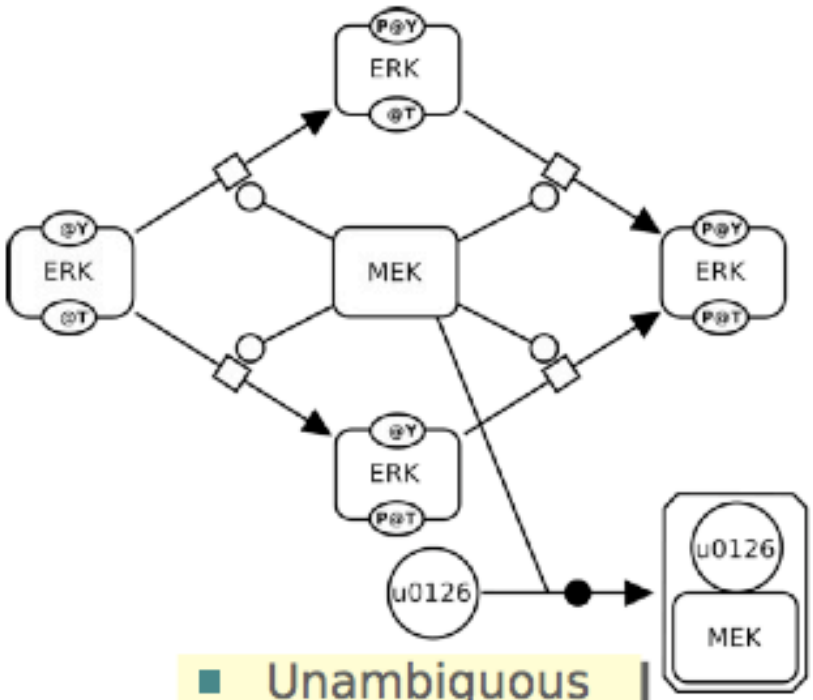
A Systems Biology Graphical Notation

Desirable Properties

1. Unambiguous
2. Parsimonious (NL)
3. Computationally tractable
4. Can be hand drawn
5. Follows accepted conventions where-ever possible
6. Can be printed and reproduced in black and white
7. Allows for incomplete information

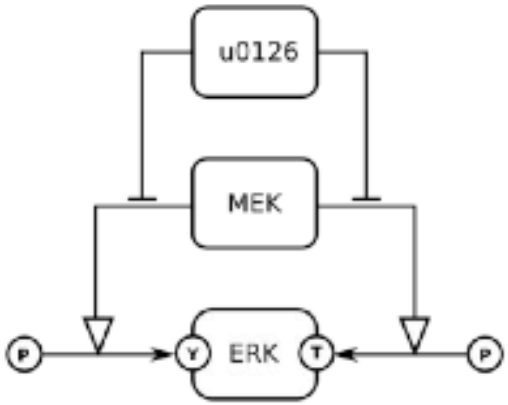
SBGN 3 Languages

Process diagrams



- Unambiguous
- Mechanistic
- Sequential
- Combinatorial explosion

Entity Relationships diagrams



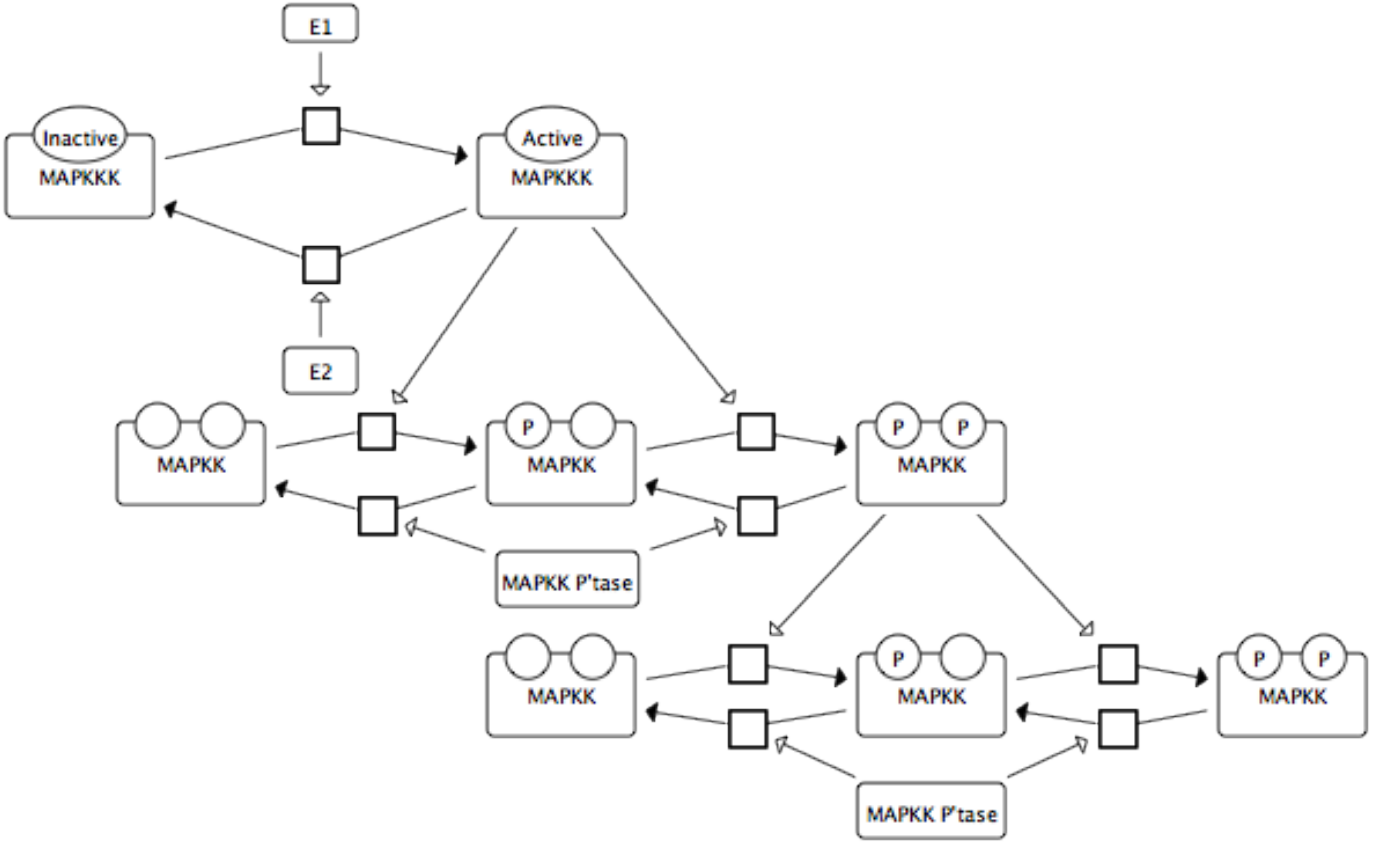
- Unambiguous
- Mechanistic
- Non-sequential

Activity Flow diagrams

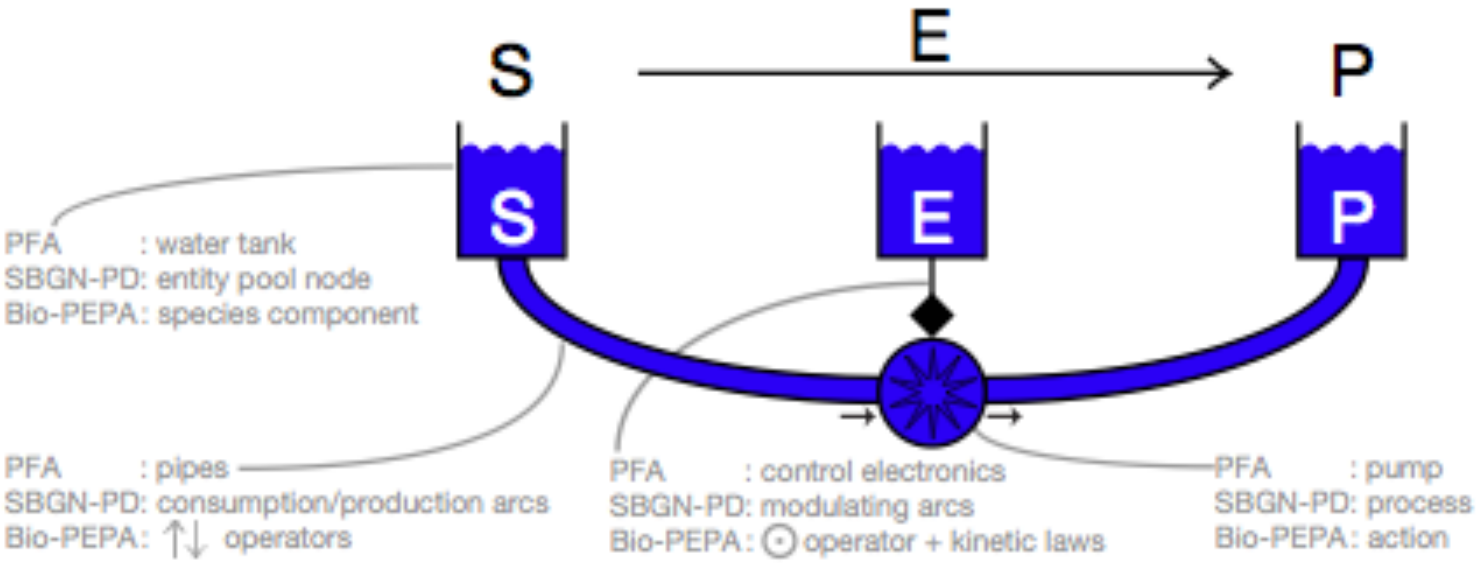
activity influence

- Ambiguous
- Conceptual
- Sequential

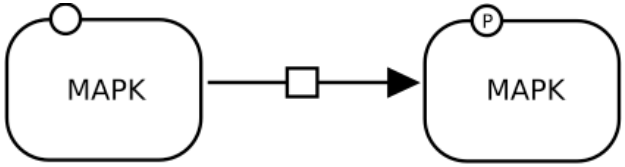
SBGN: Process Description

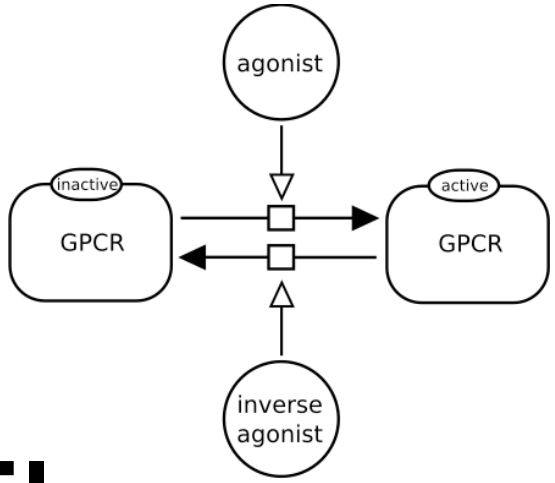

E1
Inactive
MAPKKK
Active
MAPKKK
E2
MAPKK
P
MAPKK
P
P
MAPKK
MAPKK P'tase
MAPKK
P
MAPKK
P
P
MAPKK
MAPKK P'tase

Process-flow abstraction

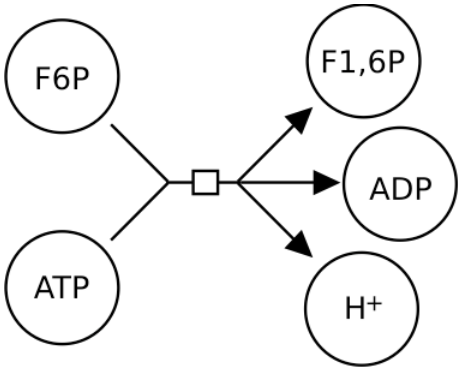


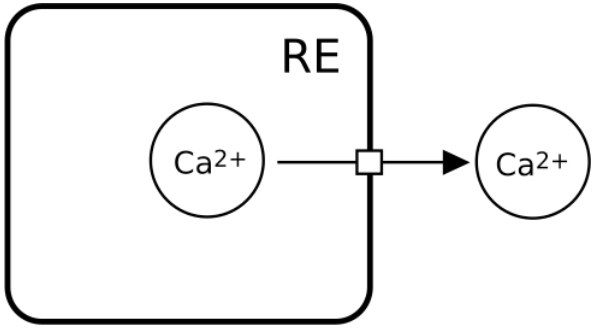
from Loewe, Moodie & Hilston CompMod 2009.

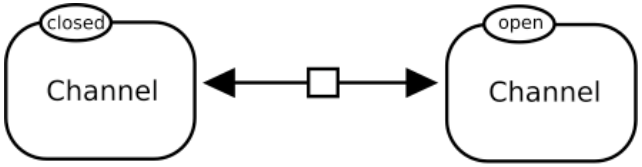


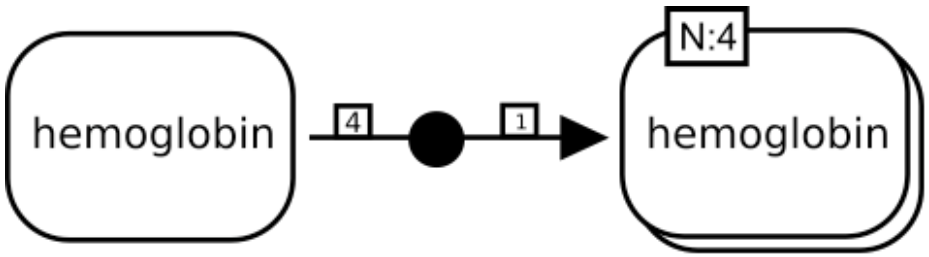


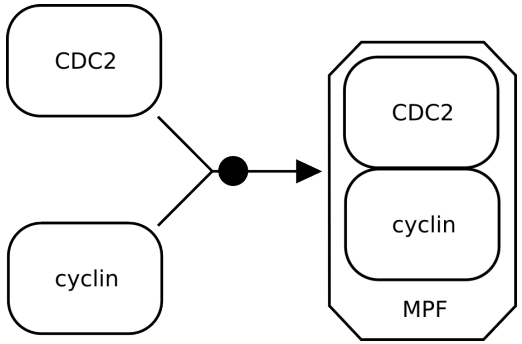
Process Flow

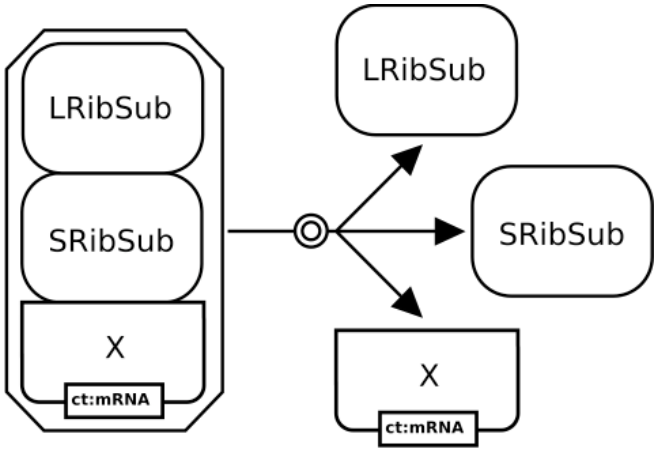


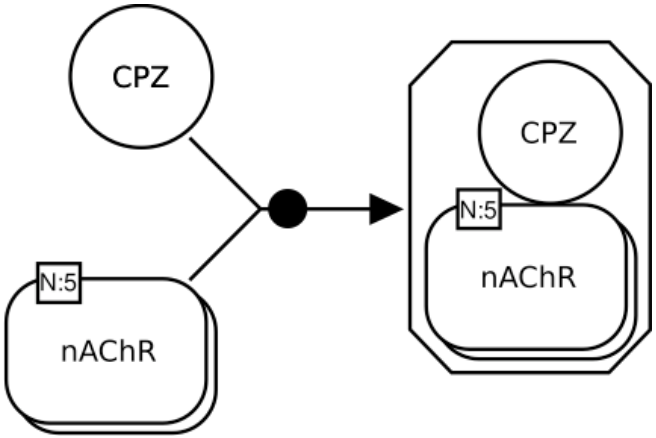




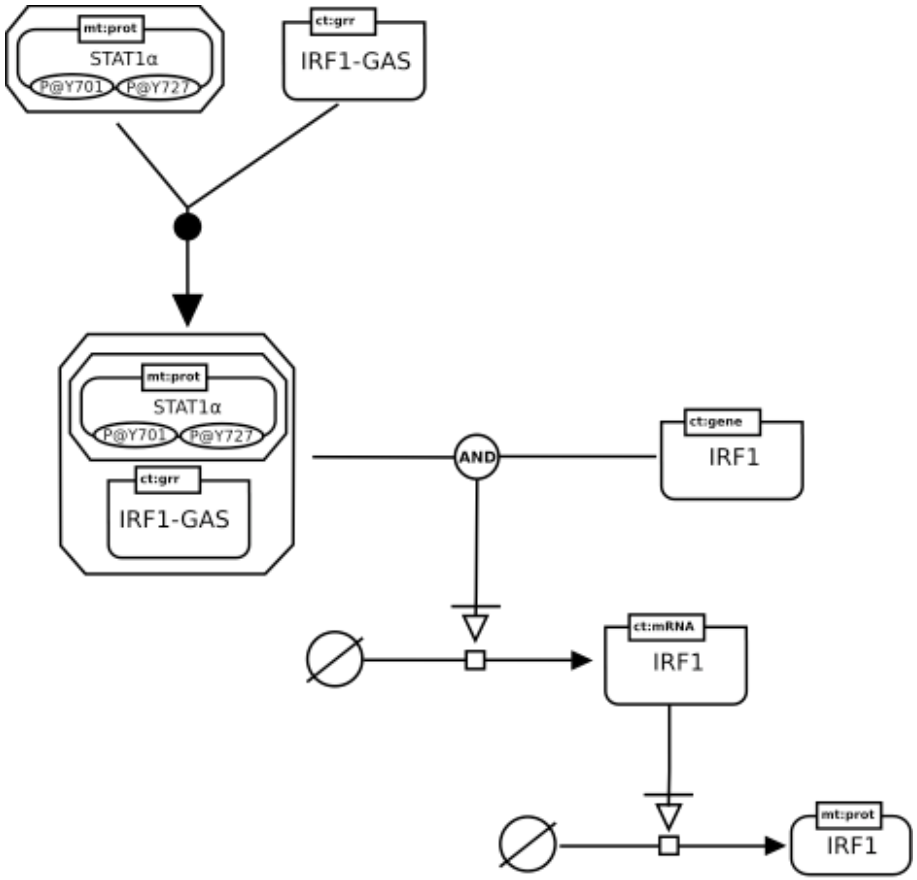




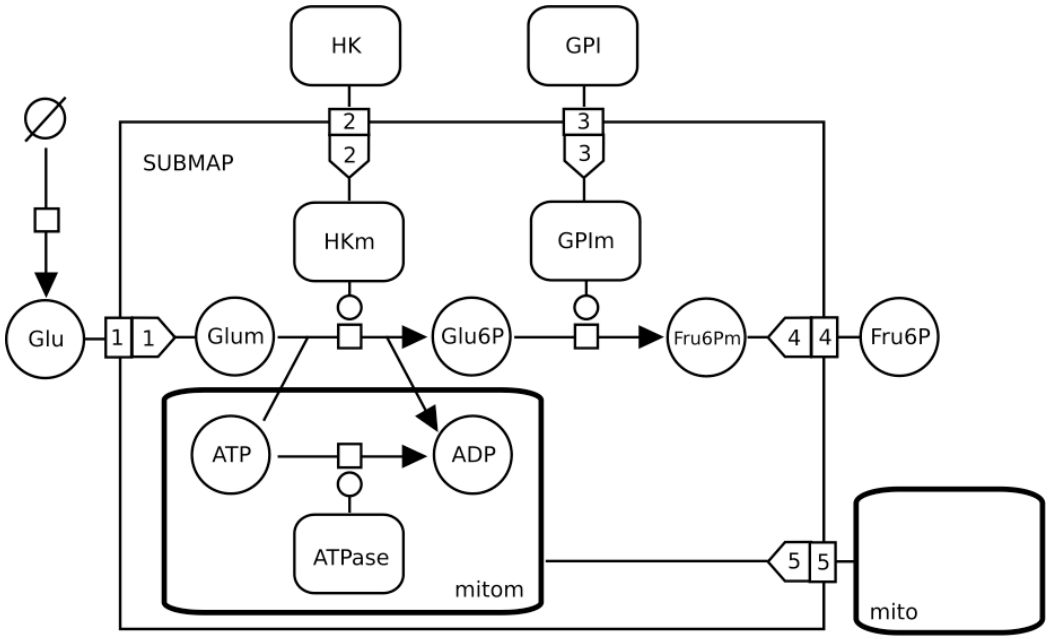


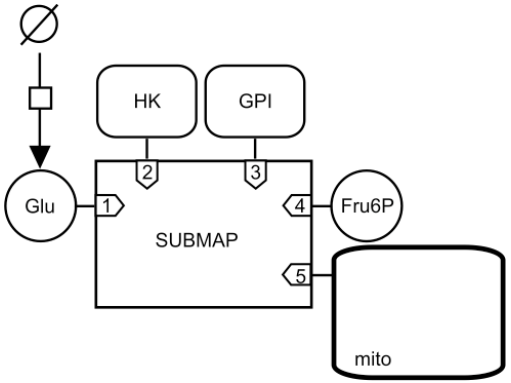


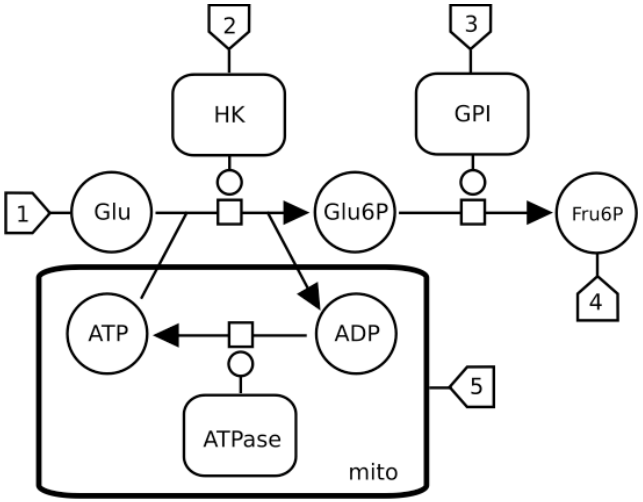
Complex Formation



Summarising information: Logic gates

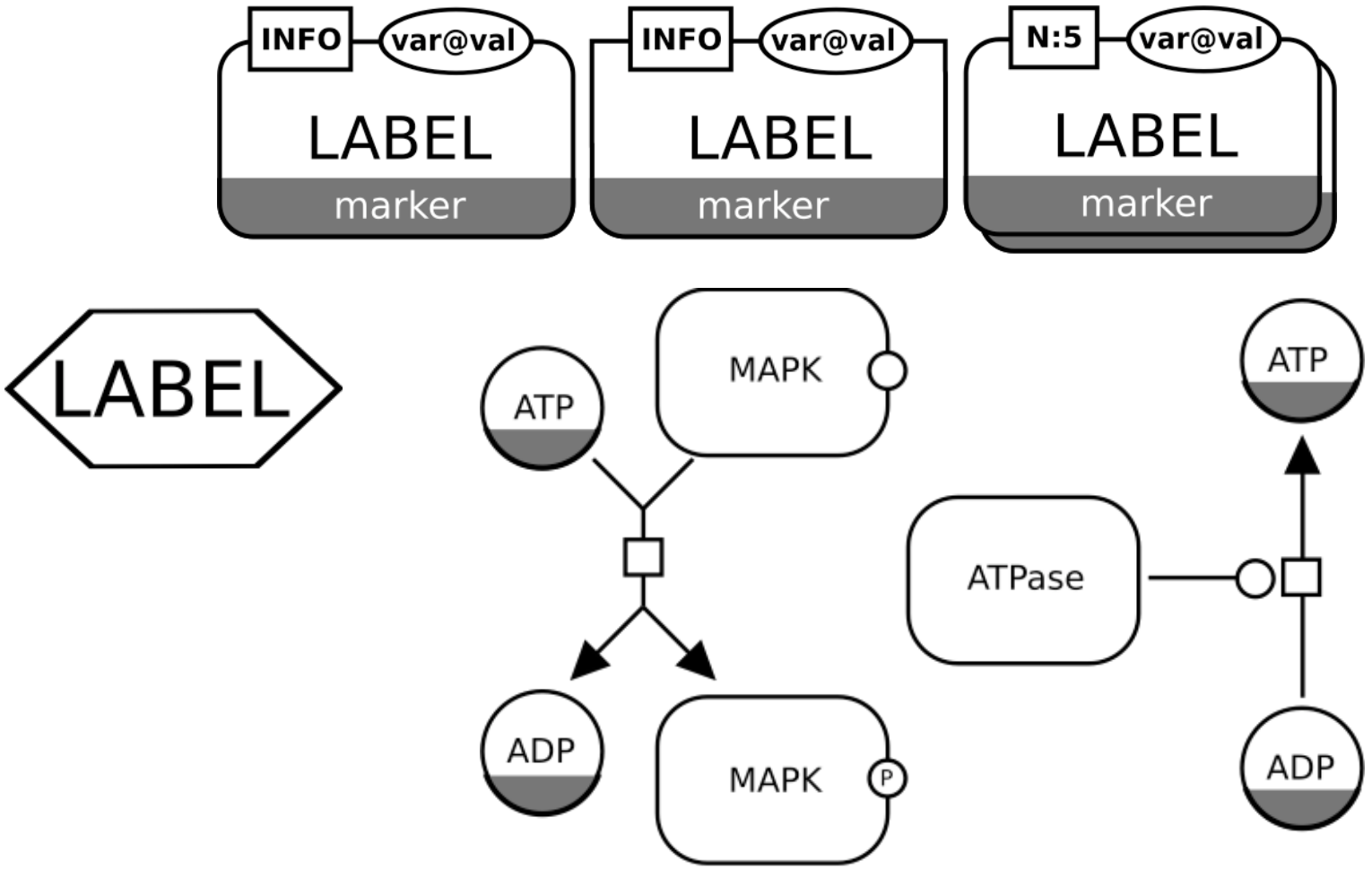




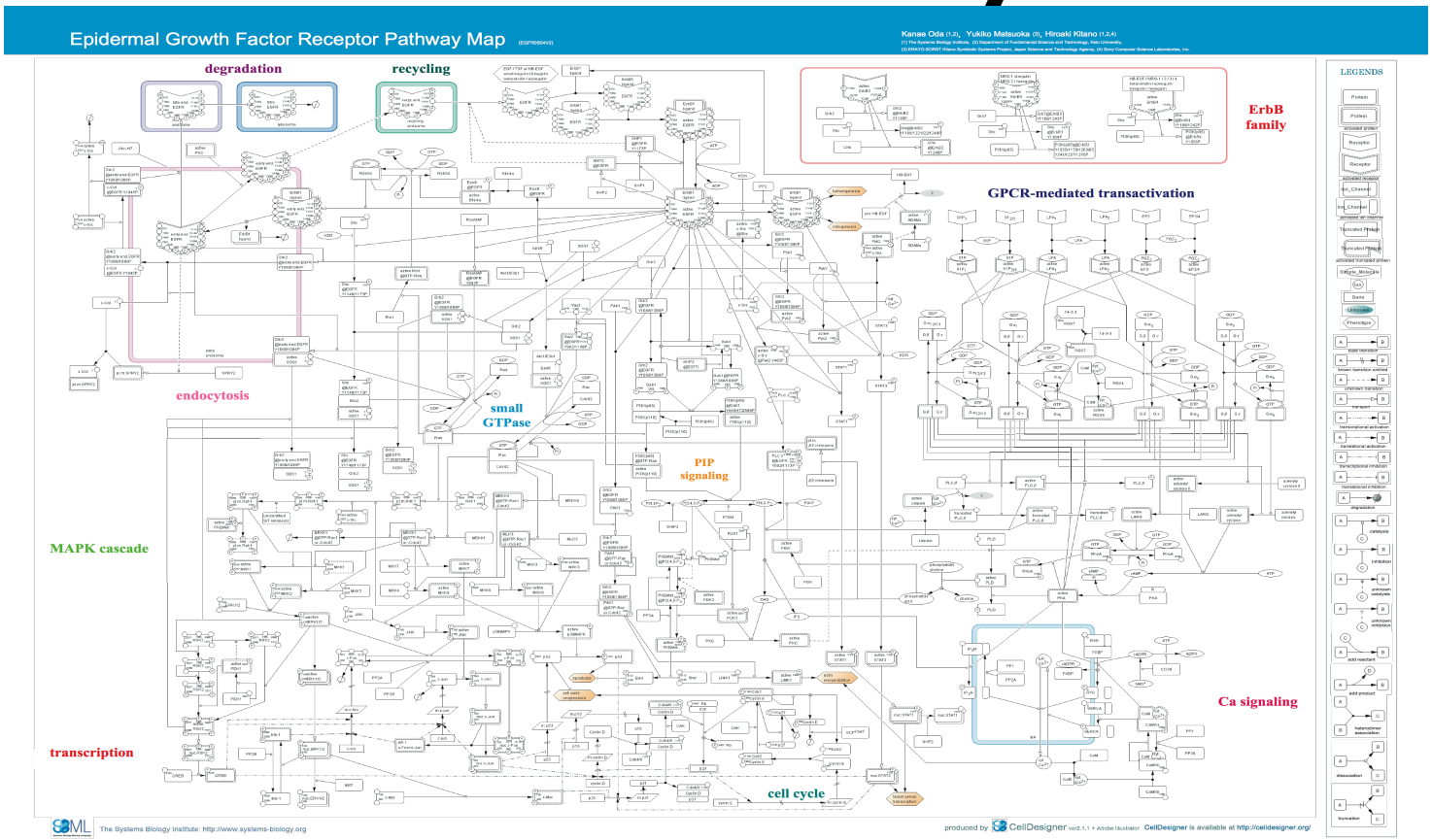


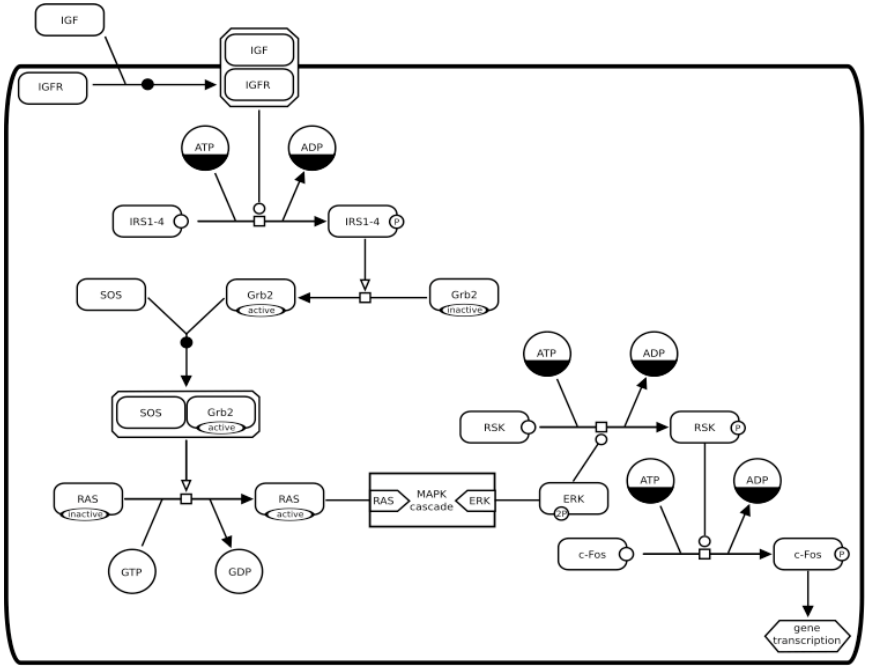
Reducing complexity: Sub-Maps

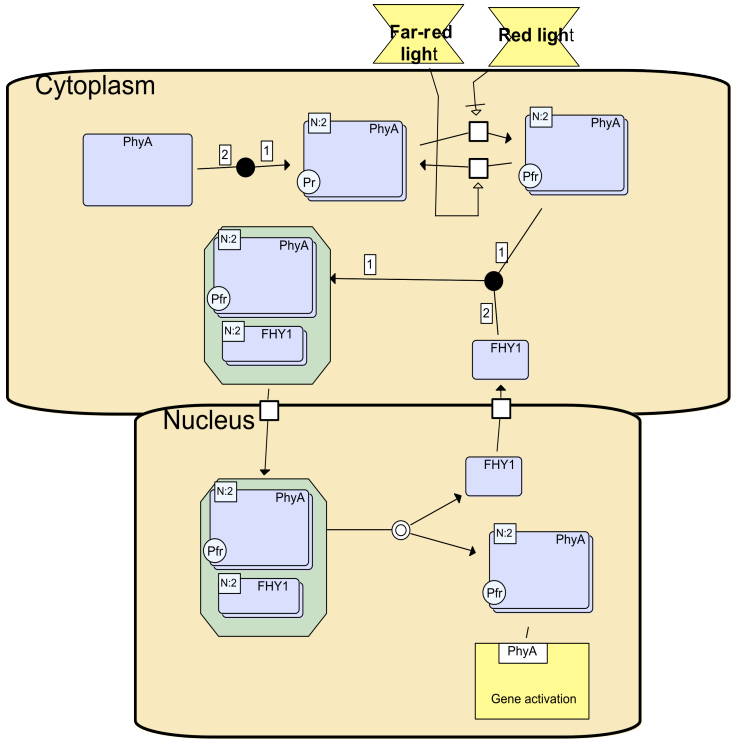
Redundant EPNS: Cloning



Why Cloning is Necessary

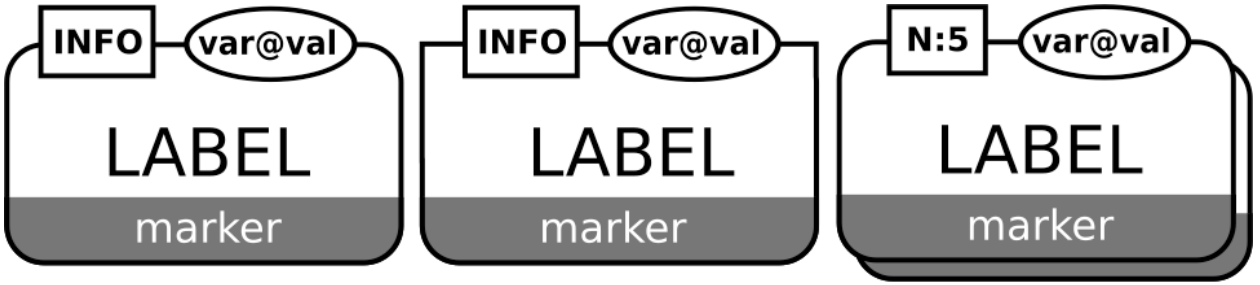


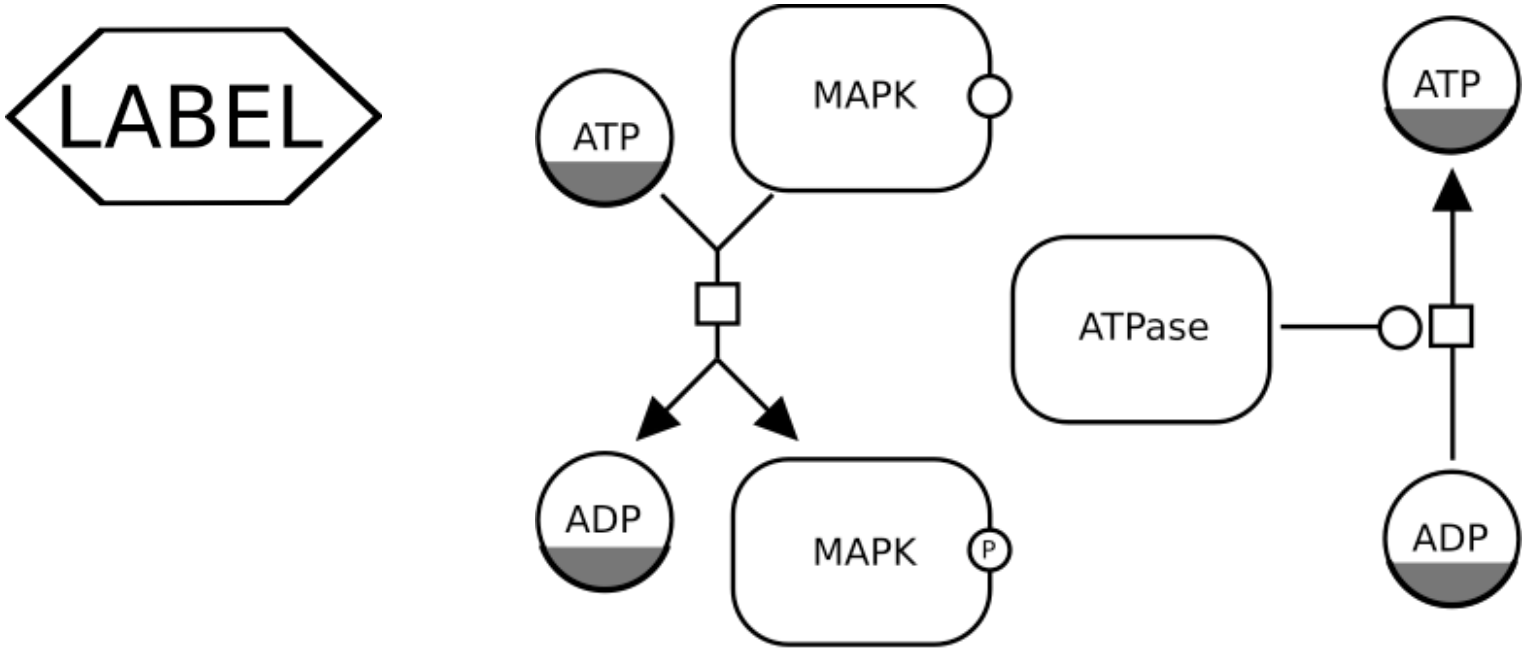


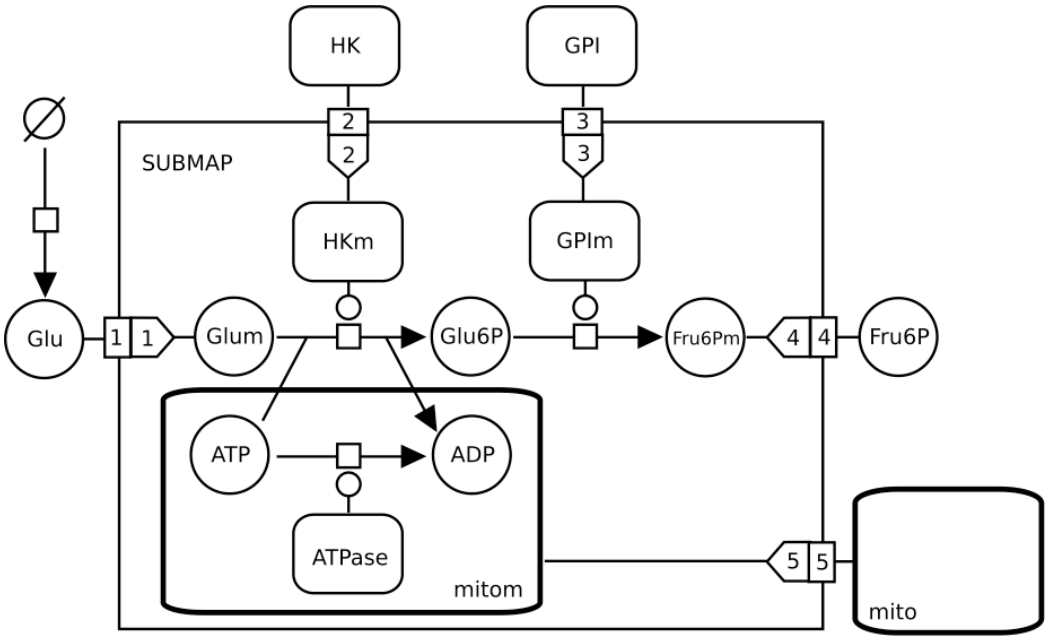


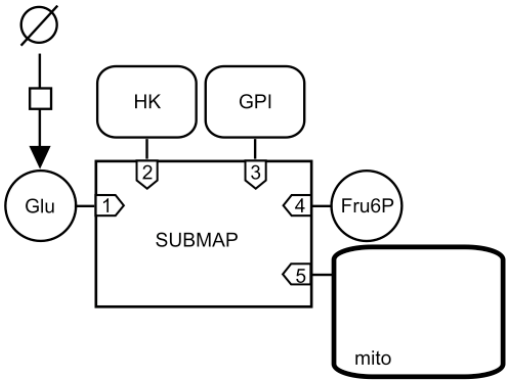
Relating to the "Outside World": Perturbation/Observable

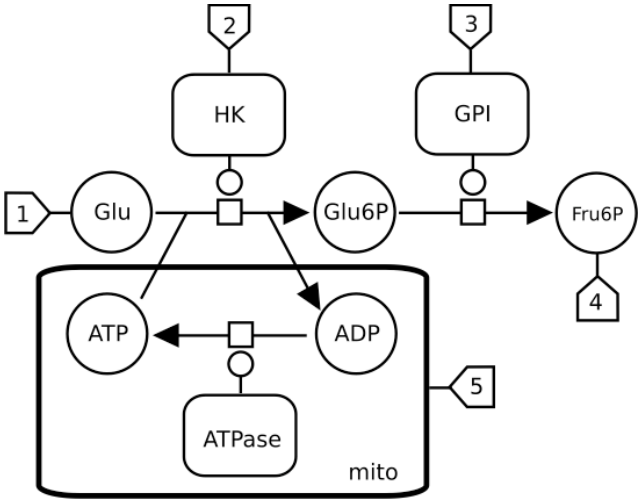
Redundant EPNS: Cloning





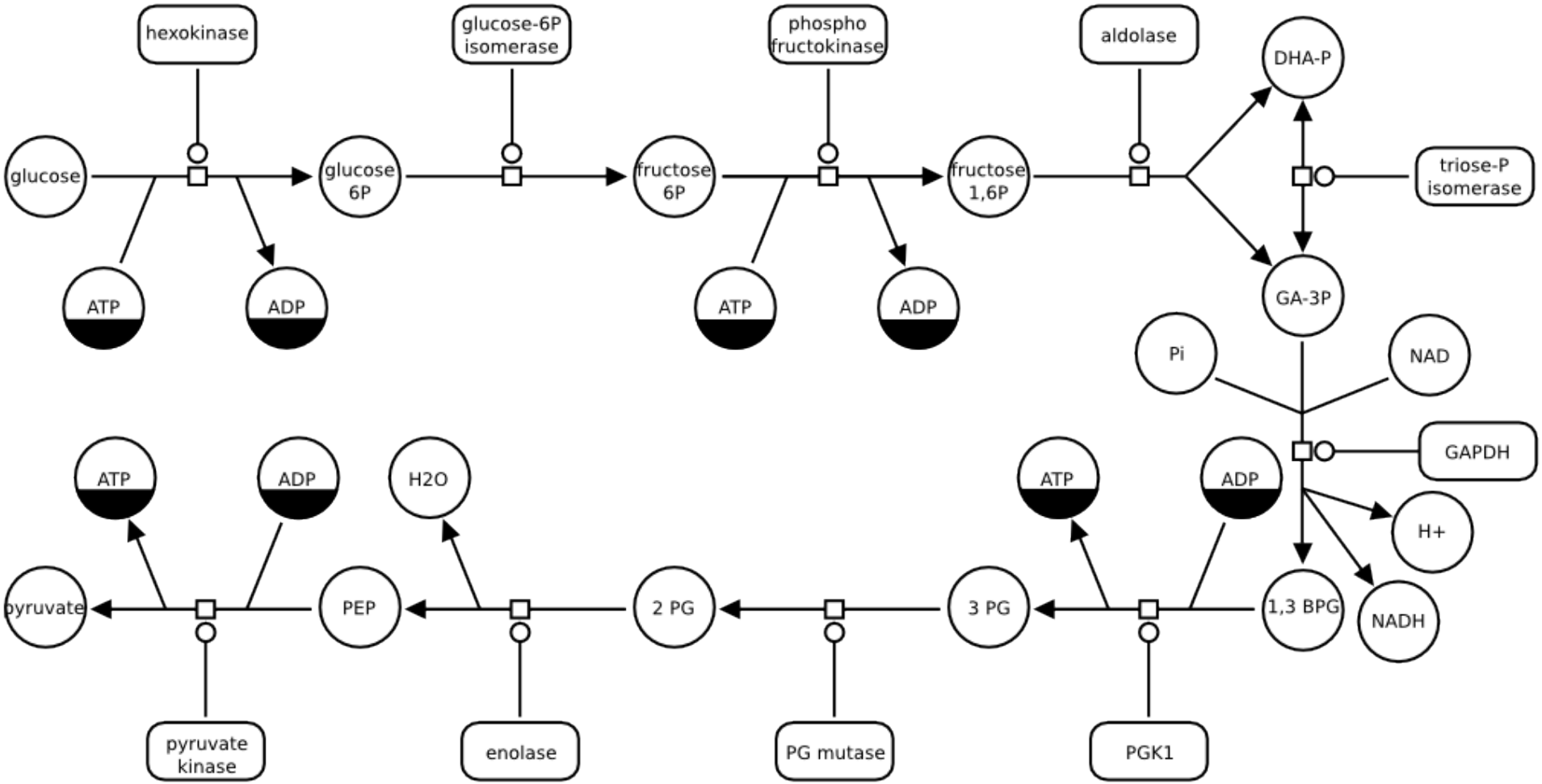




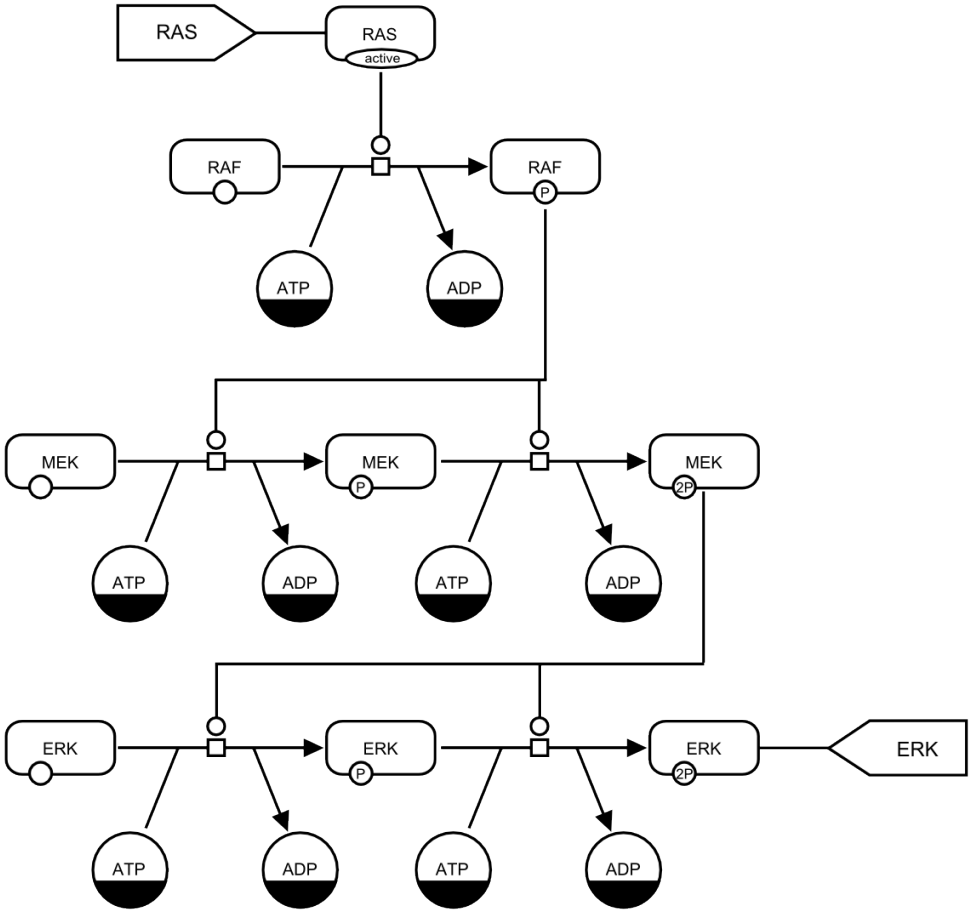


Reducing complexity: Sub-Maps

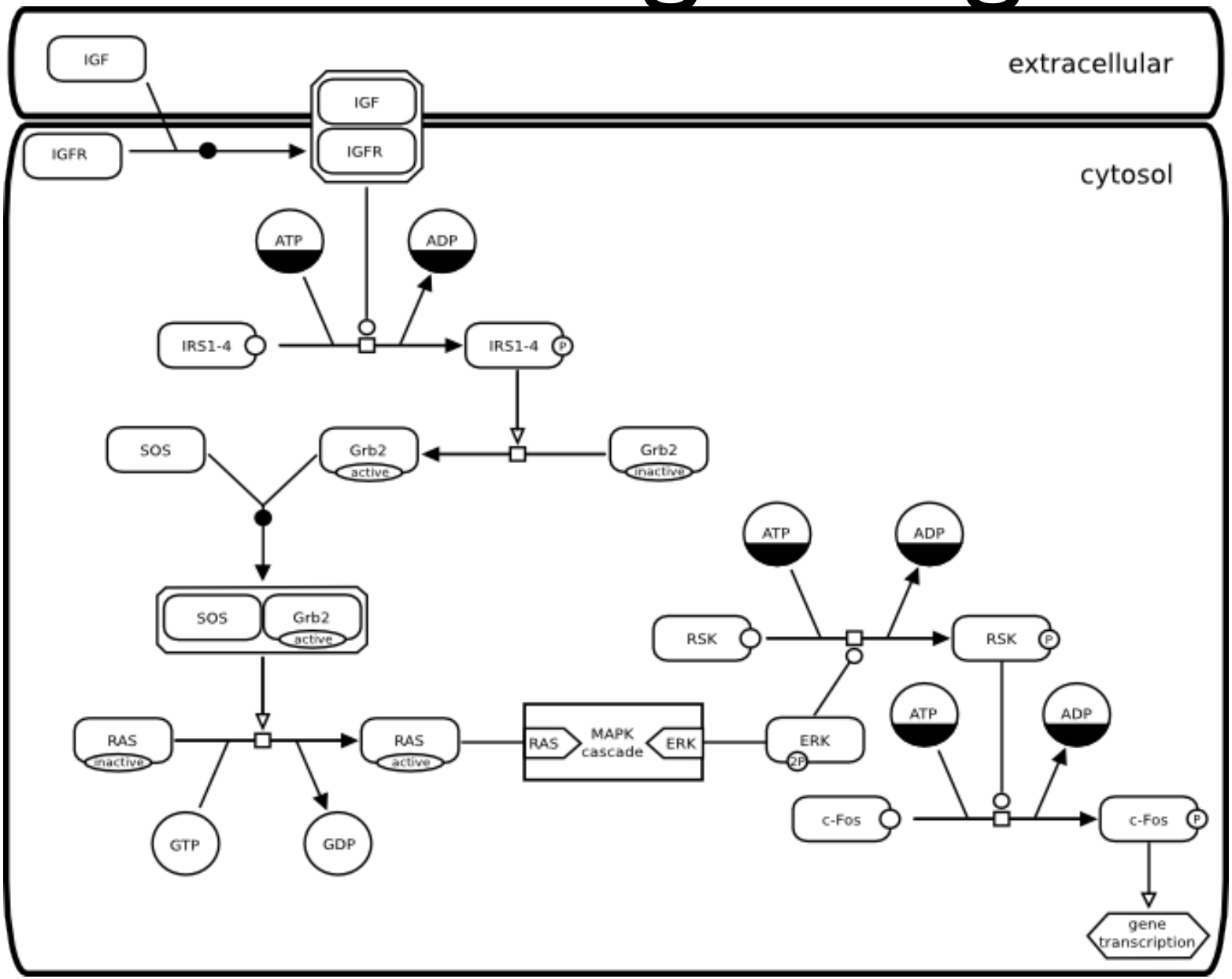
Process Diagram Examples



MAPK


RAS
RAS
active
RAF
RAF
P
ATP
ADP
MEK
MEK
P
MEK
2P
ATP
ADP
ATP
ADP
ERK
ERK
P
ERK
2P
ERK
ATP
ADP
ATP
ADP

Insulin Signalling



SYSTEMS BIOLOGY GRAPHICAL NOTATION REFERENCE CARD (PD Level 1 R1.1)

Entity Pool Nodes

unspecified entity

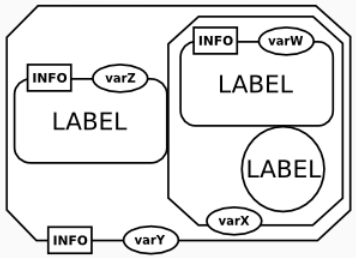
simple chemical

macromolecule

nucleic acid feature

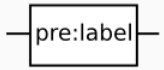
perturbation


source
sink



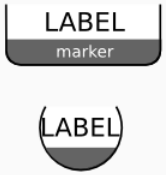
complex

Auxiliary Units

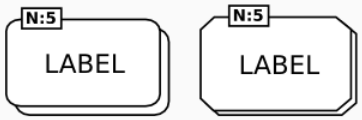


unit of information

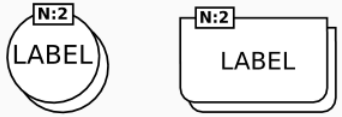
state variable



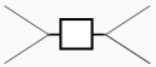
clone marker



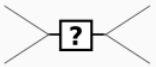
multimers



Process Nodes

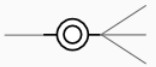

process


omitted process



uncertain process


association

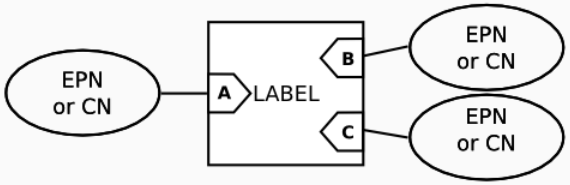

dissociation

observable

Compartment Nodes

compartment

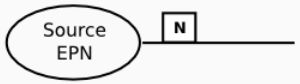
Reference Nodes



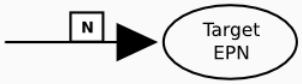
submap

tag

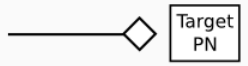
Arcs



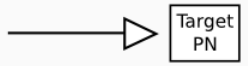
consumption



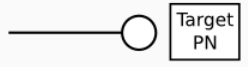
production



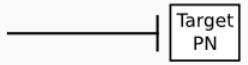
modulation



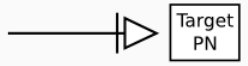
stimulation



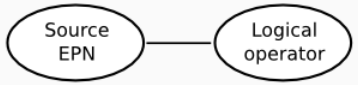
catalysis



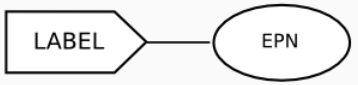
inhibition



necessary stimulation



logic arc



equivalence arc

Logical Operators

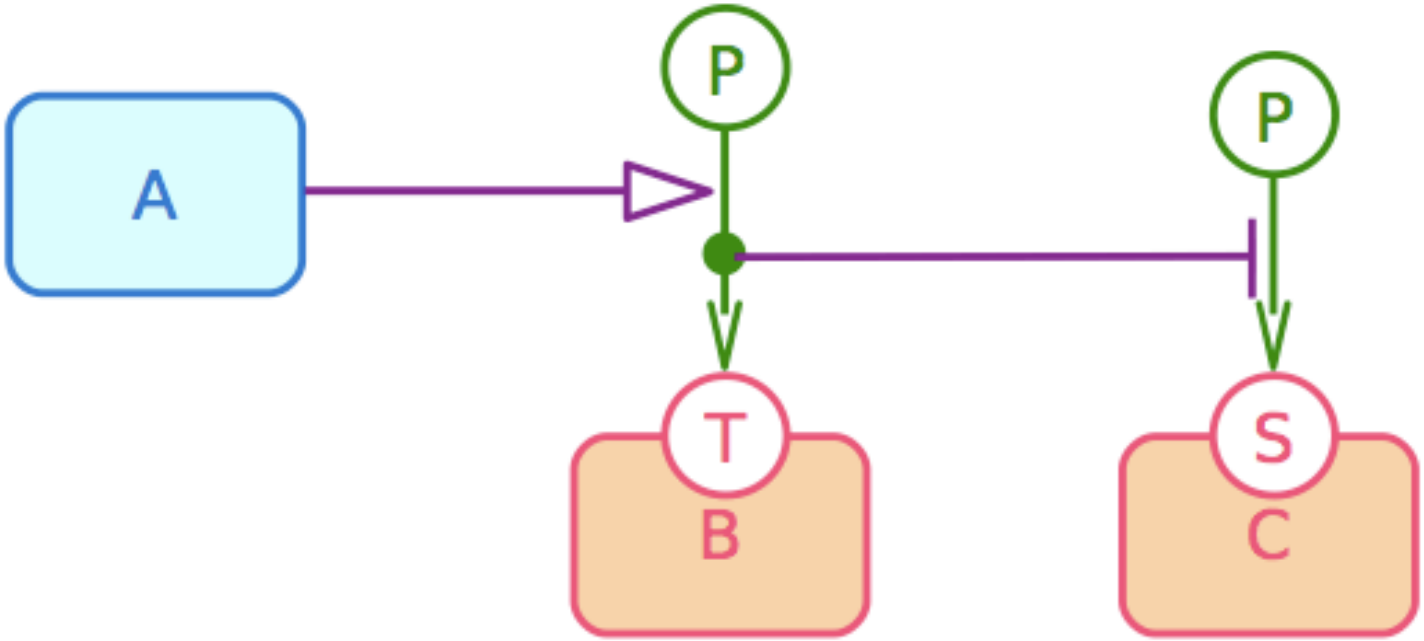
and operator

or operator

not operator

SBGN-Entity Relationship Diagram

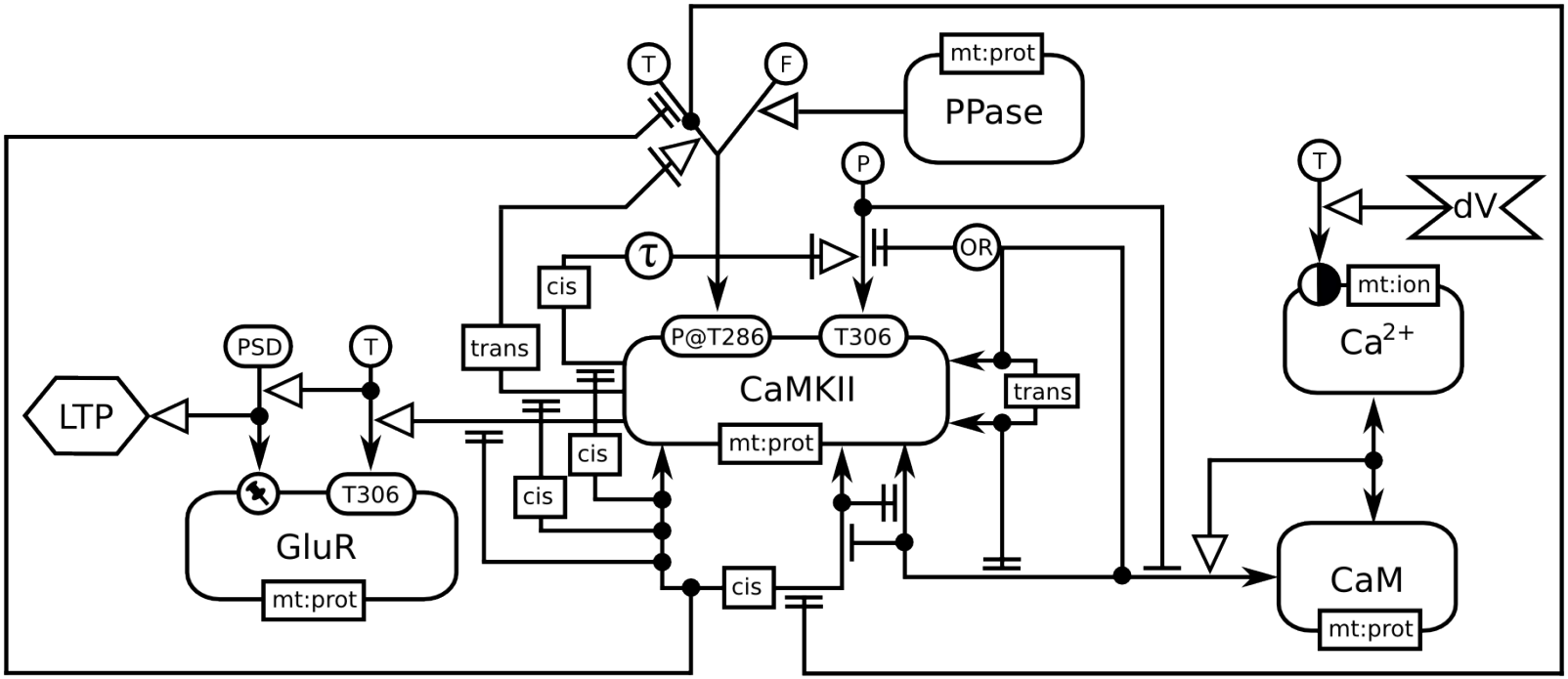
A Simple Example



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

ER Example


T
F
mt:prot
PPase
P
T
dV
τ
OR
cis
mt:ion
Ca2+
PSD
T
trans
P@T286
T306
CaMKII
trans
LTP
cis
mt:prot
cis
T306
GluR
cis
CaM
mt:prot

SYSTEMS BIOLOGY GRAPHICAL NOTATION ENTITY RELATIONSHIP REFERENCE CARD

Entity Nodes

Interactors

entity

outcome

perturbing agent

Logical Operators

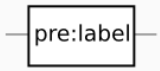
and operator

or operator

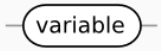
not operator

delay operator

Auxiliary units



unit of information



state variable

existence

location

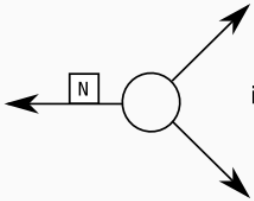
Containers

submap

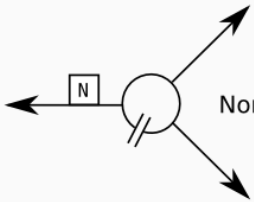
Relationship Nodes

Statements

assignment



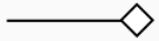
interaction



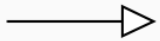
Non-interaction

observable

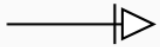
Influence



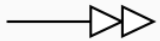
modulation



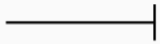
stimulation



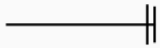
necessary stimulation



absolute stimulation



inhibition



absolute inhibition

logic arc

Cell

From Cell 137, p. 87-p. 98, April 3, 2009

A Mutant-p53/Smad Complex Opposes p63 to Empower TGFβ-Induced Metastasis

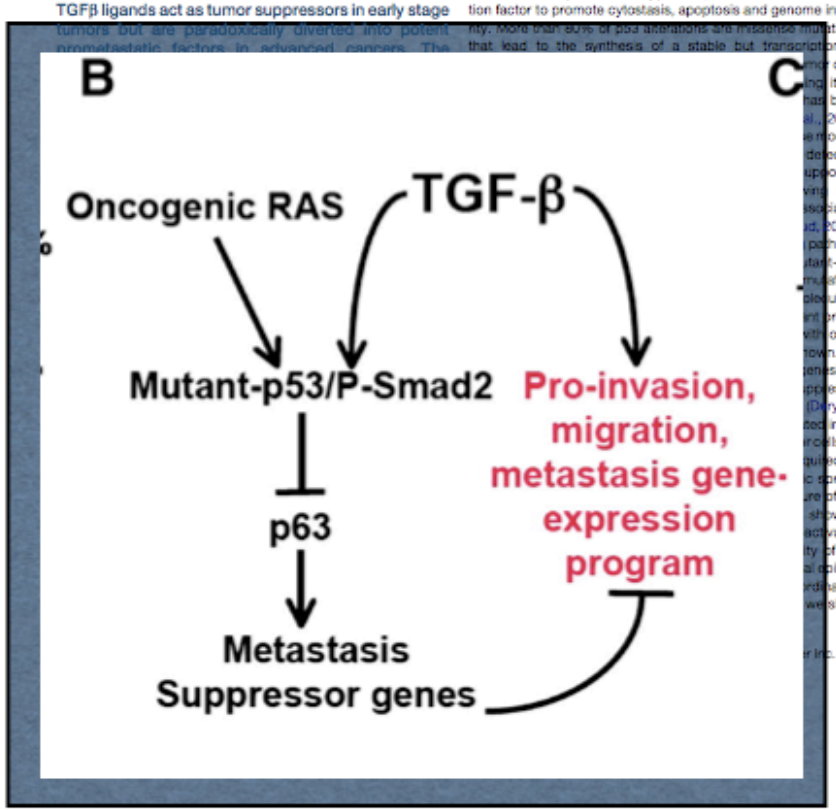
Maddalena Adorno,[1,8] Michelangelo Cordenonsi,[1,8] Marco Montagner,[1] Sirio Dupont,[1] Christine Wong,[2] Byron Hann,[2] Aldo Solari,[3] Sara Bobisse,[4] Maria Beatrice Rondina,[4] Vincenza Guzzardo,[5] Anna R. Parenti,[5] Antonio Rosato,[4,6] Silvio Bicciato,[6,7] Allan Balmain,[2] and Stefano Piccolo[1,*]

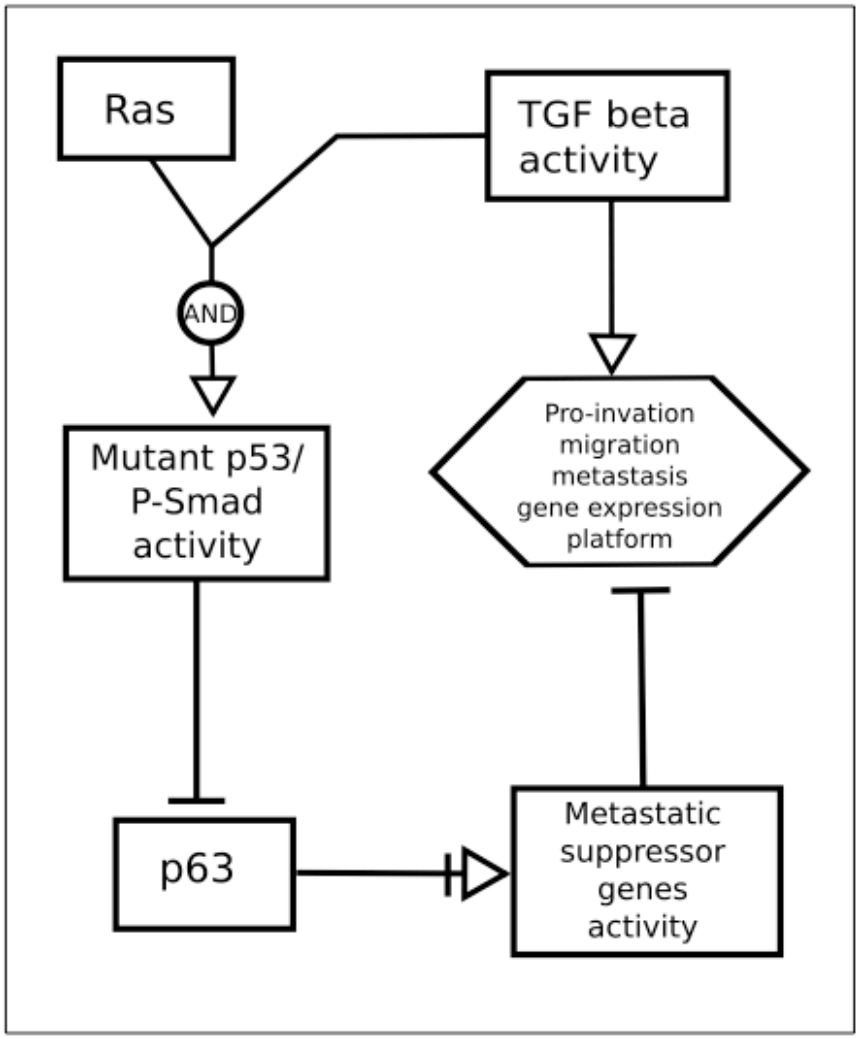
[1]Department of Histology, Microbiology and Medical Biotechnologies, University of Padua School of Medicine, viale Colombo 3, 35100 Padua, Italy
[2]Cancer Research Institute, University of California, San Francisco, 2340 Sutter Street, San Francisco, CA 94115, USA
[3]Department of Chemical Engineering Processes, University of Padua, via F. Marzolo 9, 35131, Padua, Italy
[4]Department of Oncology and Surgical Sciences and Istituto Oncologico Veneto, University of Padua, via Gattamelata 64, 35126 Padua, Italy
[5]Department of Medical Diagnostic Science and Special Therapies, Section of Pathology, University of Padua, viale Gabelli 2, 35126 Padua, Italy
[6]Istituto Oncologico Veneto, via Gattamelata 64, 35126 Padua, Italy
[7]Department of Biomedical Sciences, University of Modena and Reggio Emilia, via G. Campi 287, 41100, Modena, Italy
[8]These authors contributed equally to the work
*Correspondence: piccolo@civ.bio.unipd.it
DOI 10.1016/j.cell.2009.01.039

SUMMARY

TGFβ ligands act as tumor suppressors in early stage tumors but are paradoxically diverted into potent pro-metastatic factors in advanced cancers. The

One of the most frequent genetic lesions in human tumors is mutation of the p53 tumor suppressor, which acts as transcription factor to promote cytostasis, apoptosis and genome integ-rity. More than 80% of p53 alterations are missense mutations that lead to the synthesis of a stable but transcriptionally





Activity Node (AN)
-Biological activity

- Each node represents an activity, but not the entity.
- Multiple ANs can be used to represent activities from one entity, e.g., receptor protein kinase, and ligand gated ion channel.
- One AN can be used to represent activities from a group of entities (e.g., a complex).

SYSTEMS BIOLOGY GRAPHICAL NOTATION
ACTIVITY FLOW DIAGRAM REFERENCE CARD

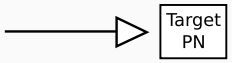
Activity nodes

biological activity

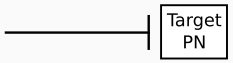
observable

perturbation

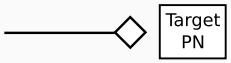
Modulating Arcs



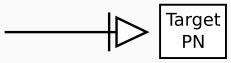
positive influence



negative influence



unknown influence



necessary stimulation

Auxiliary Units

macromolecule

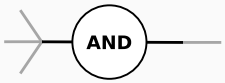
simple chemical

genetic

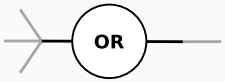
unspecified

complex

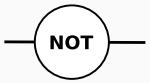
Logical Operators



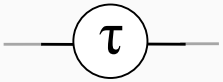
and operator



or operator

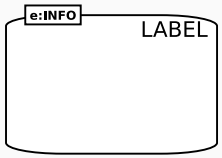


not operator



delay

Container Nodes



compartment

Current Status

- 5 workshops since Feb 2006
- Specification for Process Notation Level1:
  - Released Level 1 in August at ICSB 2008
- ER Level 1 Specification
  - Sep 2009
- AF Level 1 Specification
  - Sep 2009

References

General overview of the standard:

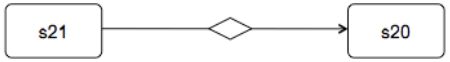
Nat Biotechnol. 2009 27(8):735-41 (http://www.nature.com/nbt/journal/v27/n8/abs/nbt.1558.html)

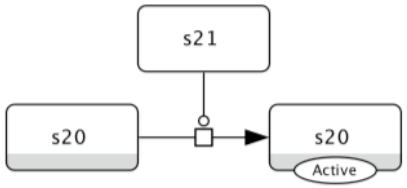
Specification documents:

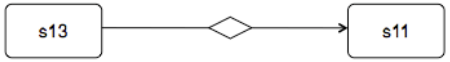
- PD: doi:10.1038/npre.2009.3721.1 (http://precedings.nature.com/documents/3721/version/1)
- ER: doi:10.1038/npre.2009.3719.1 (http://precedings.nature.com/documents/3719/version/1)
- AF: doi:10.1038/npre.2009.3724.1 (http://precedings.nature.com/documents/3724/version/1)

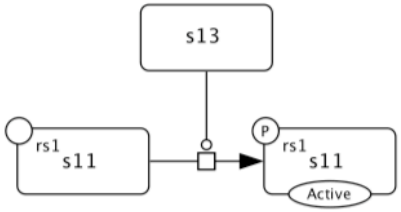
Activity Flow

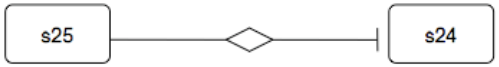
- Describes changes in “activity”
- Good providing overview
- “Lossy”

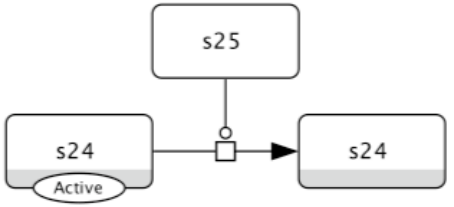

s21
s20

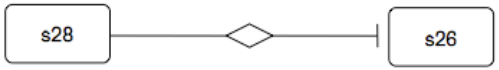

s21
s20
s20
Active

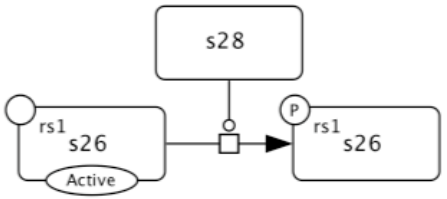

s13
s11


s13
rs1
s11
P
rs1
s11
Active


s25
s24


s25
s24
Active
s24


s28
s26


s28
rs1
s26
Active
P
rs1
s26

Example