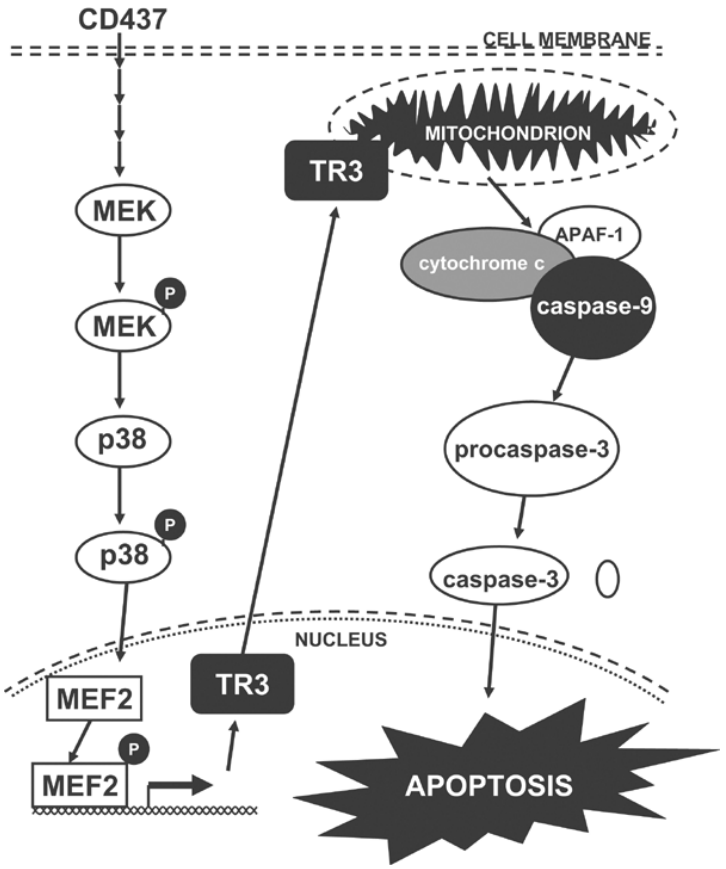
Tutorial ICSB 2013
Modelling and Simulation of Quantitative Biological Models

A (brief) introduction to the Systems Biology Graphical Notation

Tobias Czauderna
04/09/2013

Biological networks

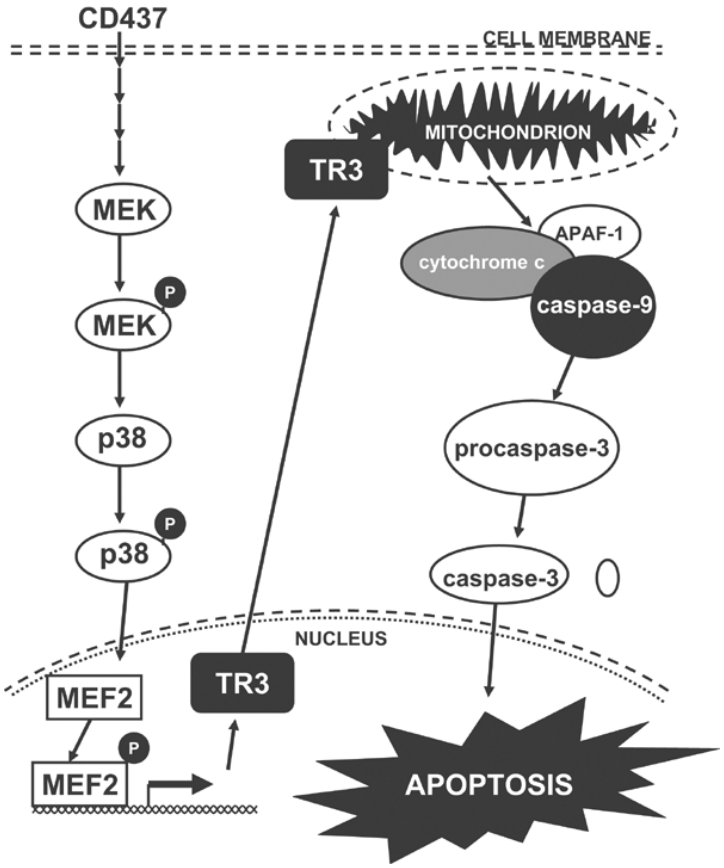


A model for CD437-induced MAP kinase pathway activation and apoptosis in ovarian carcinoma cells. Our previous findings (Holmes et al., 2002) combined with the findings presented here help to define the molecular pathway, depicted in the model, activated by CD437 treatment to induce apoptosis in the CA-OV-3 ovarian carcinoma cell line. CD437 treatment is able to induce the activation of MEK. The activation of MEK is able to induce a cascade of events that include p38 MAP kinase and MEF2 activation resulting in the transcription of TR3. TR3 translocates to the cytoplasm and associates with the mitochondrial membrane inducing its depolarization. Depolarization of the mitochondrial membrane causes the release of caspase-9, cytochrome c, and APAF-1. These three proteins associate and induce activation of caspase-9. Casape-9 activates casape-3 leading to the final stages of apoptosis, such as PARP cleavage. CD437 is able to induce this molecular mechanism in the CA-OV-3 ovarian carcinoma cell line and this mechanism may be a model for future targets of cancer treatment. The early molecular events, described in this report, occur in both the CA-OV-3 and the CA-CD437R cell lines. The CA-CD437R cell line does respond to the apoptosis-inducing agent 4-HPR by depolarization of the mitochondrial membrane, activation of caspase-9, activation of caspase-3, and subsequent apoptosis but this does not occur in response to CD437 treatment. This indicates that, although TR3 associates with the mitochondria, the defect that results in resistance of the CA-CD437R cells maps to CD437-induced mitochondrial membrane depolarization

From Holmes *et al.*, Early events in the induction of apoptosis in ovarian carcinoma cells by CD437: activation of the p38 MAP kinase signal pathway, *Oncogene* 22 (2003)

Can this diagram easily be understood?

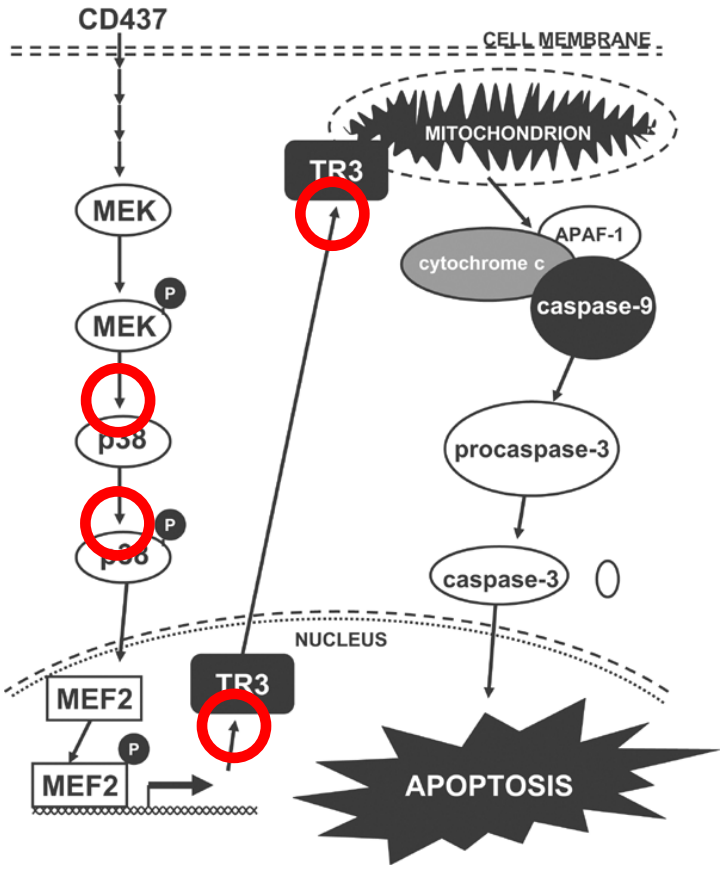
"A picture is worth a thousand words“ …



From Holmes *et al.*, Early events in the induction of apoptosis in ovarian carcinoma cells by CD437: activation of the p38 MAP kinase signal pathway, *Oncogene* 22 (2003)

Can this diagram easily be understood?

Do these arrows have the same meaning?



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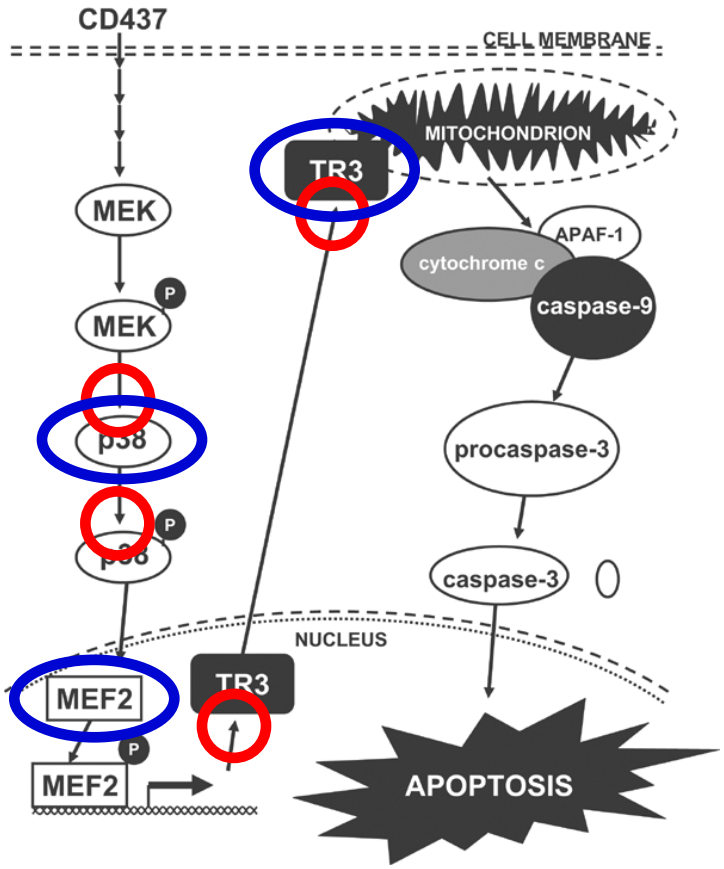
Can this diagram easily be understood?

Do these arrows have the same meaning?

Are these different types of entities?



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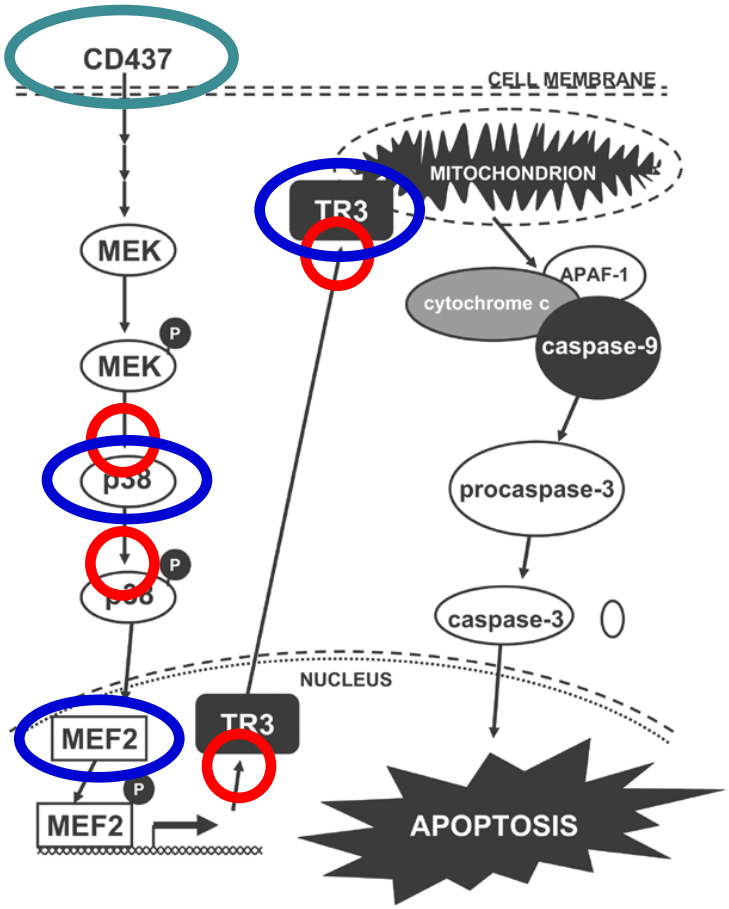
Can this diagram easily be understood?

What is this?

Do these arrows have the same meaning?

Are these different types of entities?



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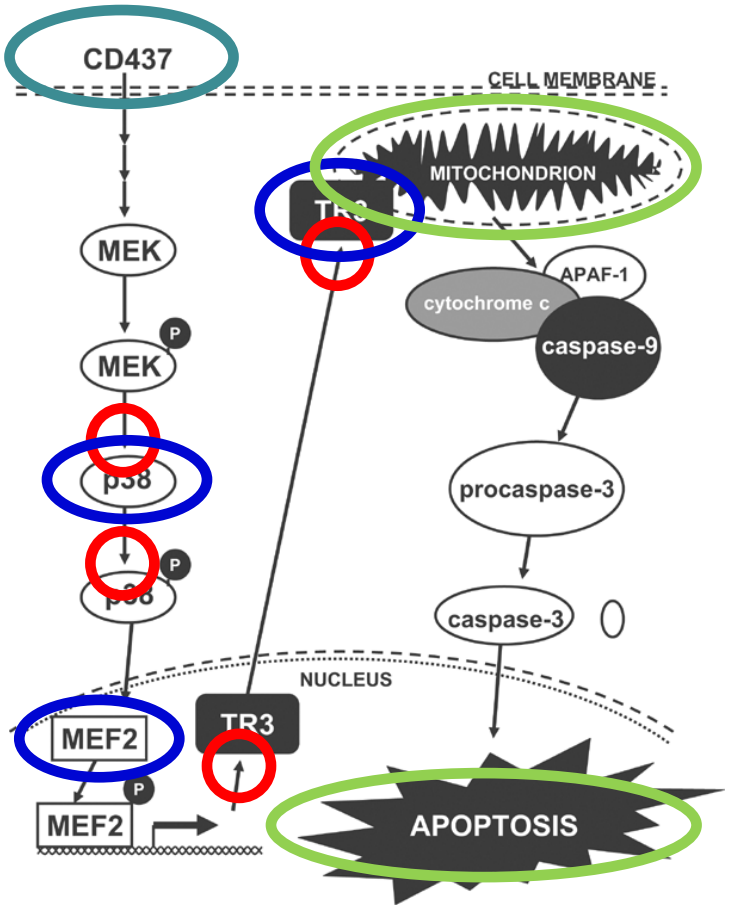
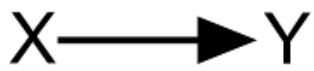


How about these?

From Holmes *et al.*, Early events in the induction of apoptosis in ovarian carcinoma cells by CD437: activation of the p38 MAP kinase signal pathway, *Oncogene* 22 (2003)

Ambiguity in conventional representation

Ambiguity in conventional representation



is transformed into

translocates (X "=" Y)

is degraded into

associates into

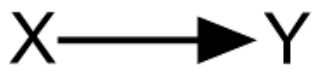
dissociates into

stimulates the activity of

stimulates the expression of

catalyses the formation of

Ambiguity in conventional representation



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 in conventional representation

X ⟶ Y

is transformed into

translocates (X "=" Y)

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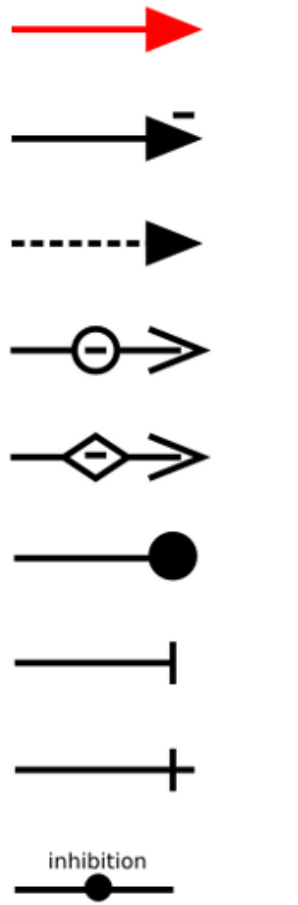


Standardised symbols are important

Most English speaking countries

Quebec

Iran

China

Israel

Singapore

Norway

Poland

USA and Canada

SBGN – Systems Biology Graphical Notation

- An unambiguous way of graphically describing and interpreting biochemical and cellular events
- Visualisation and exchange of biological knowledge
- Limited amount of symbols

  Re-use of existing symbols
- Can graphically represent biochemical pathways, regulatory networks and more at different levels of granularity
- Developed over seven years by a diverse community, including biologists, modellers, computer scientists, etc.

Le Novère *et al.*, The Systems Biology Graphical Notation, *Nature Biotechnology* 27 (2009)

SBGN

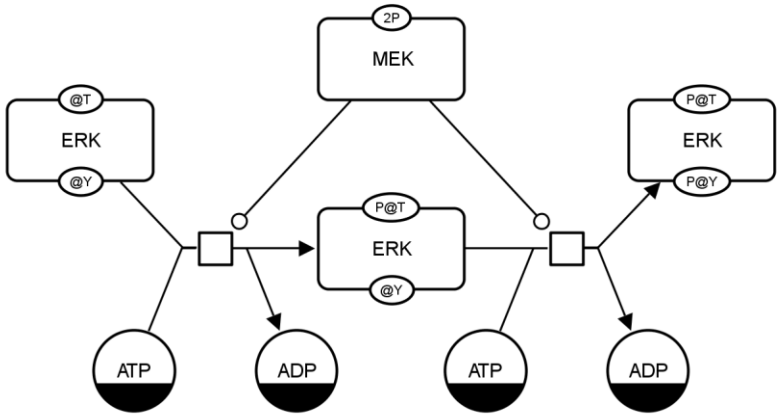
- Three languages
  - Process Description (PD) → one state = one glyph
  - Entity Relationship (ER) → one entity = one glyph
  - Activity Flow (AF) → conceptual level

- Colour has no meaning
  Size has no meaning

- Meaning should be conserved upon
  - Scaling
  - Resolution
  - Re-layout

Le Novère *et al.*, The Systems Biology Graphical Notation, *Nature Biotechnology* 27 (2009)

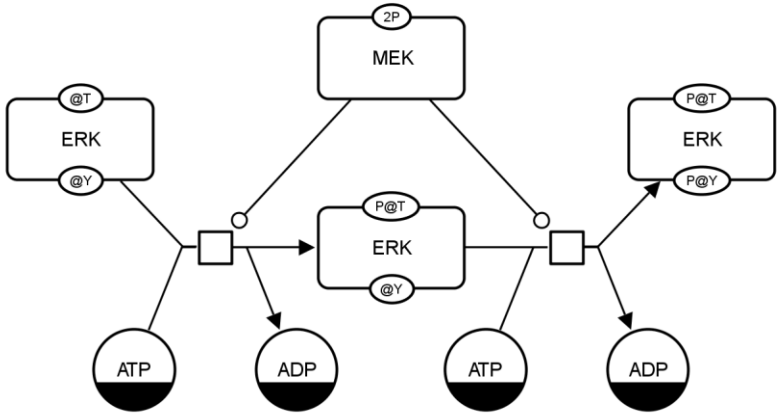
SBGN – Process Description (PD)



- Unambiguous
- Directional
- Sequential
- Mechanistic
- Subjected to combinatorial explosion

- Biochemistry
- Metabolic networks
- Regulatory networks

SBGN – Process Description (PD)



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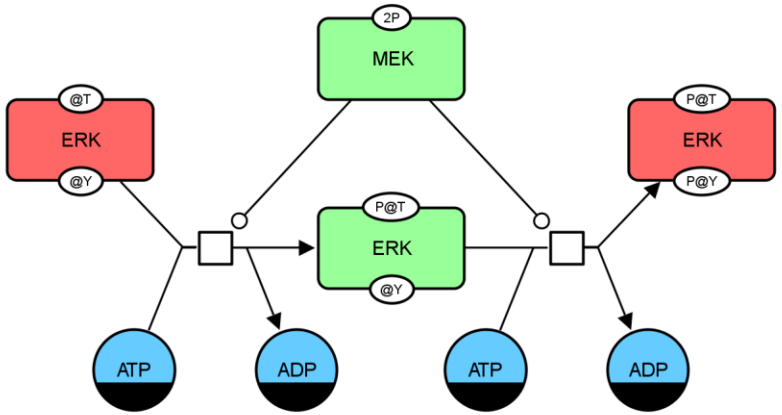

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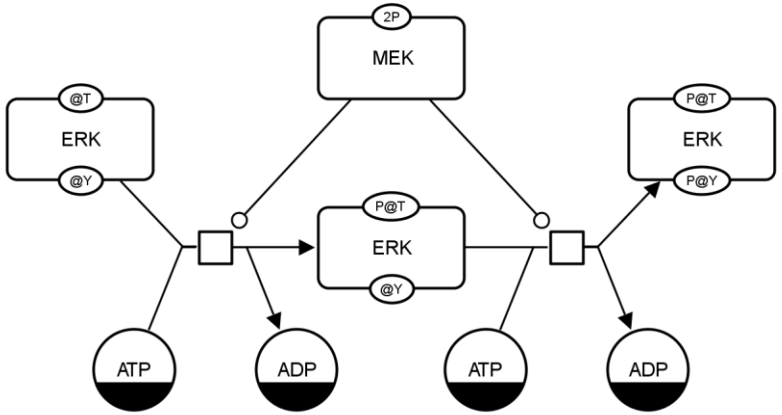

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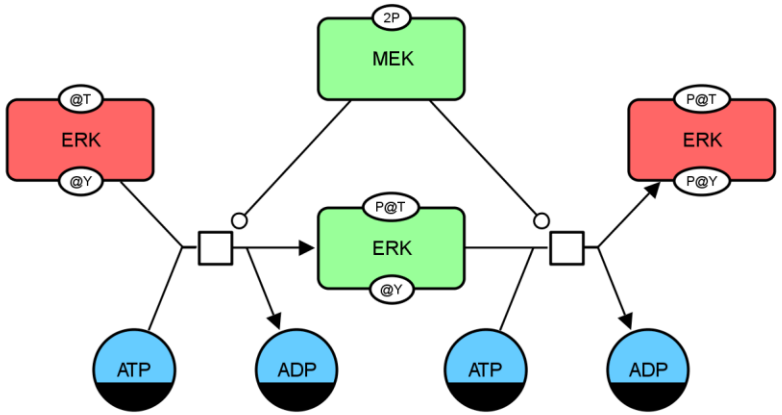

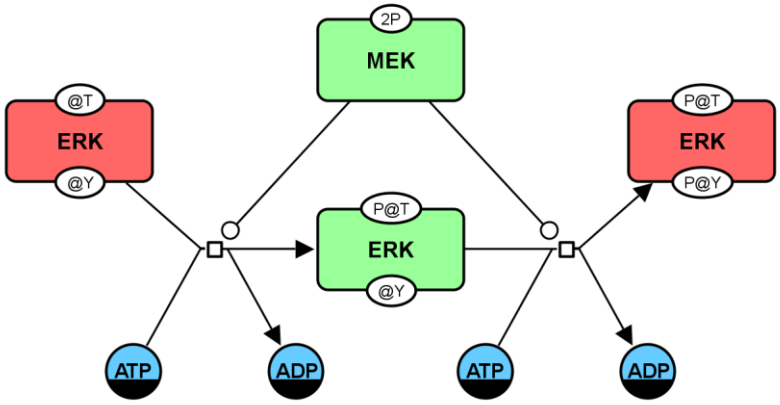

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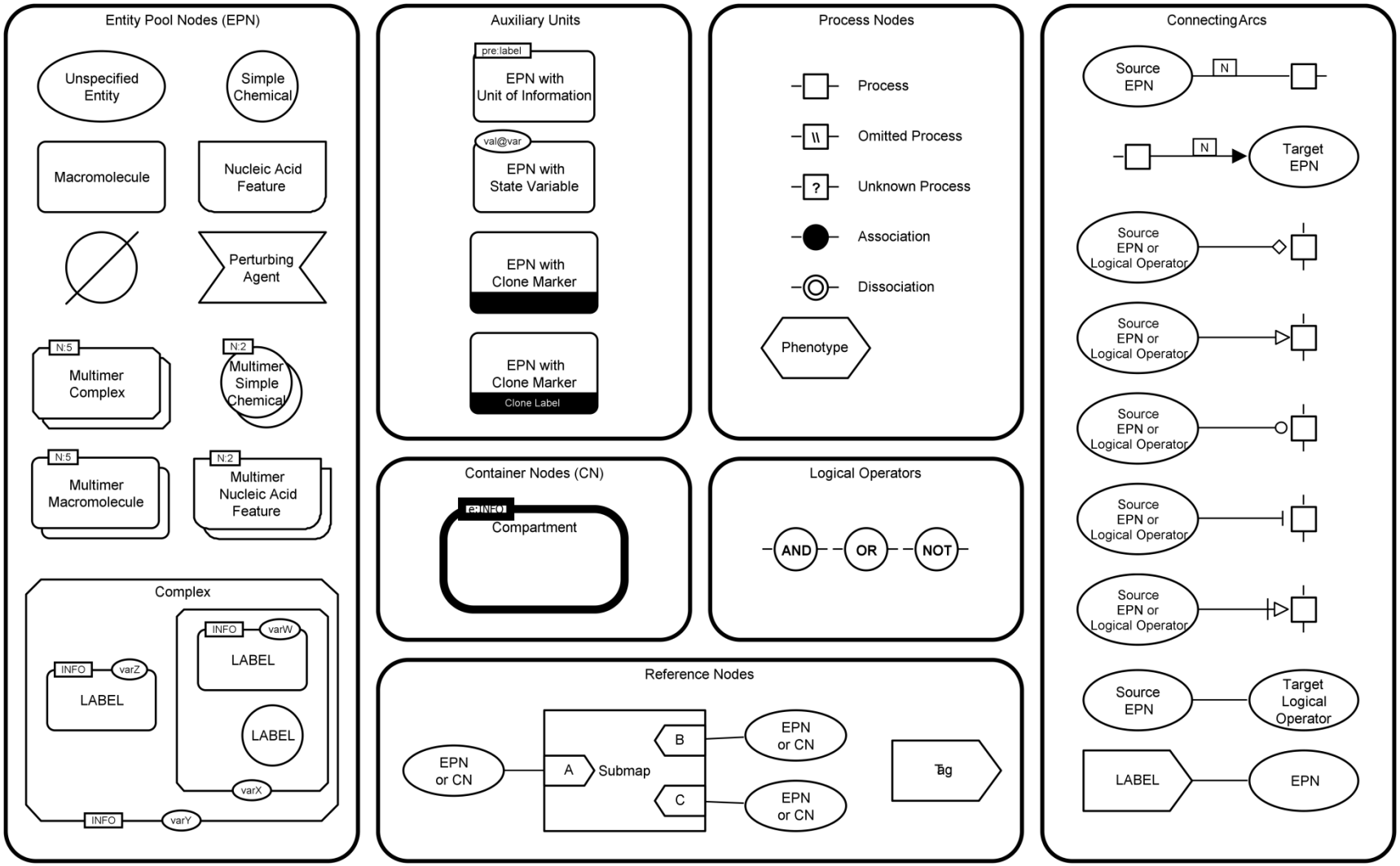
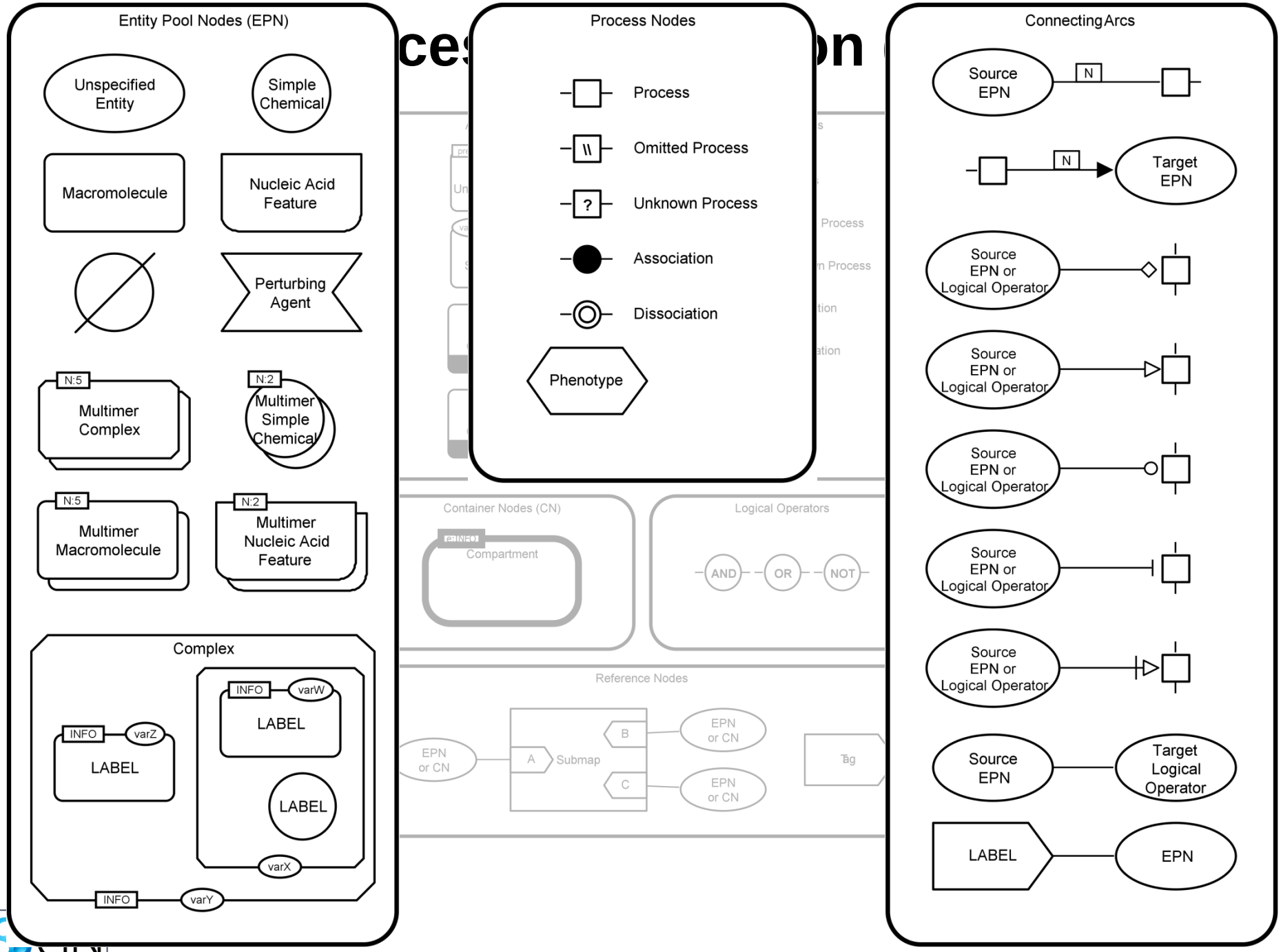
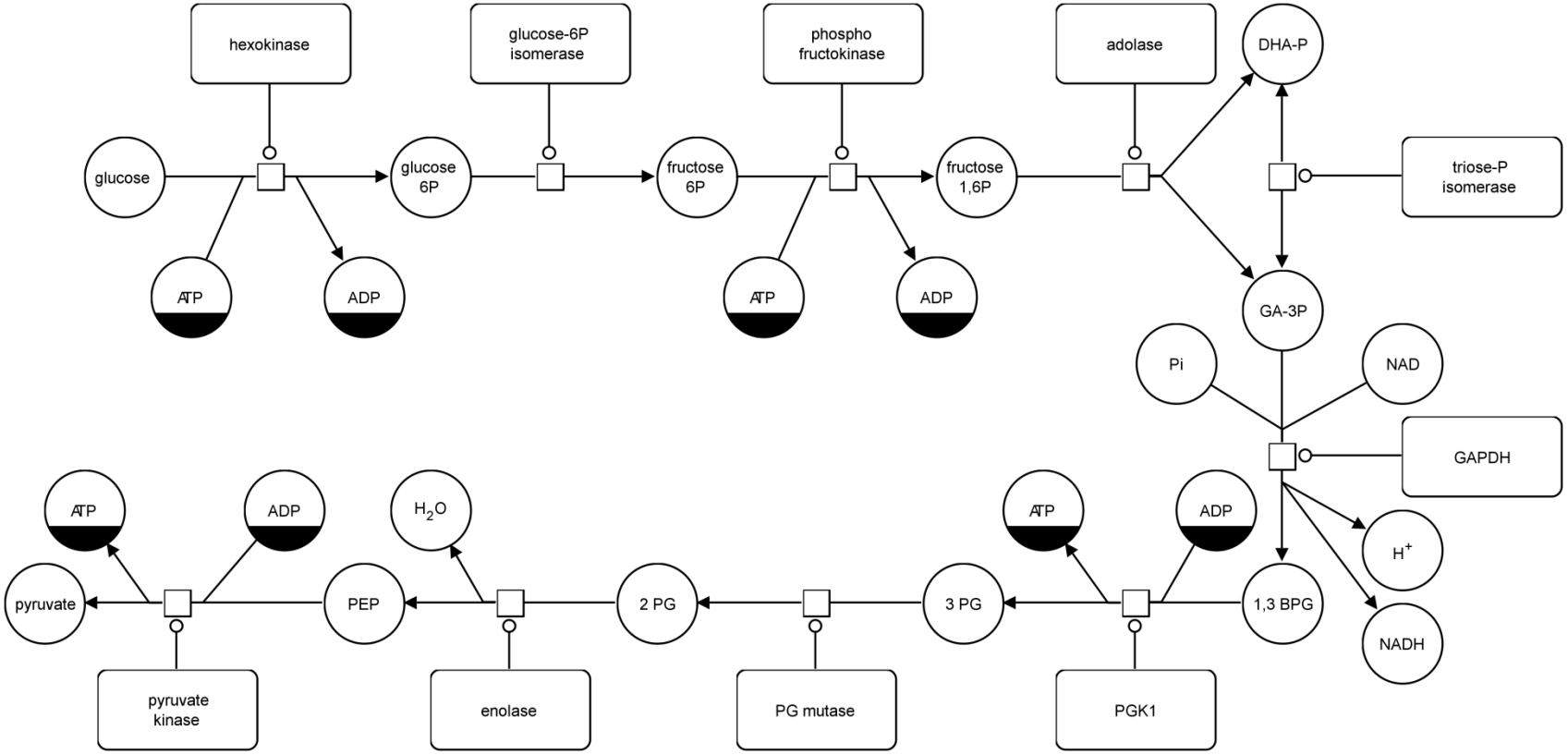
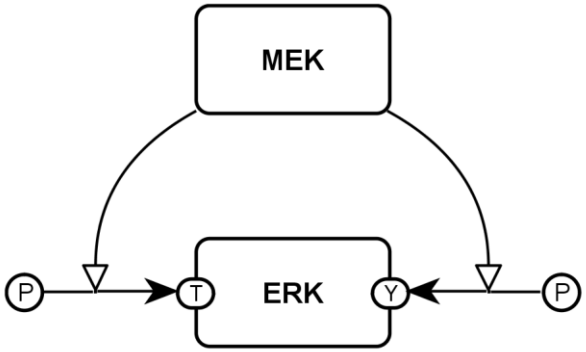



Entity Pool Nodes (EPN)
Unspecified Entity
Simple Chemical
Macromolecule
Nucleic Acid Feature
Perturbing Agent
N:5
Multimer Complex
N:2
Multimer Simple Chemical
N:5
Multimer Macromolecule
N:2
Multimer Nucleic Acid Feature
Complex
INFO
varZ
LABEL
INFO
varW
LABEL
LABEL
varX
INFO
varY
Process Nodes
Process
Omitted Process
Unknown Process
Association
Dissociation
Phenotype
Container Nodes (CN)
INFO
Compartment
Logical Operators
AND
OR
NOT
Reference Nodes
EPN or CN
A
Submap
B
C
EPN or CN
EPN or CN
Tag
Connecting Arcs
Source EPN
N
N
Target EPN
Source EPN or Logical Operator
Source EPN or Logical Operator
Source EPN or Logical Operator
Source EPN or Logical Operator
Source EPN or Logical Operator
Source EPN
Target Logical Operator
LABEL
EPN

SBGN – Process Description (PD)



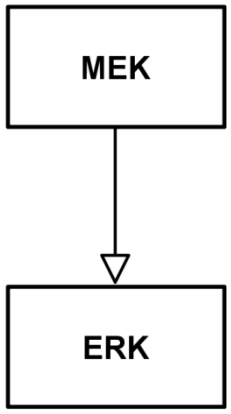
SBGN – Entity Relationship (ER)



- Unambiguous
- Directional
- Non-Sequential
- Mechanistic

- Molecular Biology
- Protein-Protein-Interaction networks
- Signal transduction networks

SBGN – Activity Flow (AF)

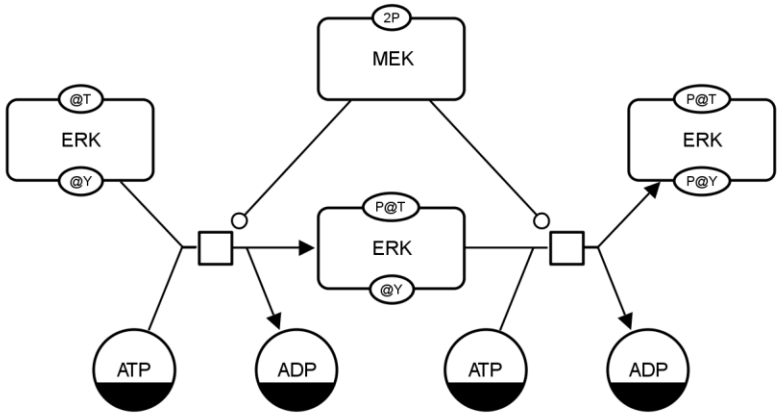


- Ambiguous (in sense of mechanism)
- Directional
- Conceptual
- Sequential
- Non-mechanistic

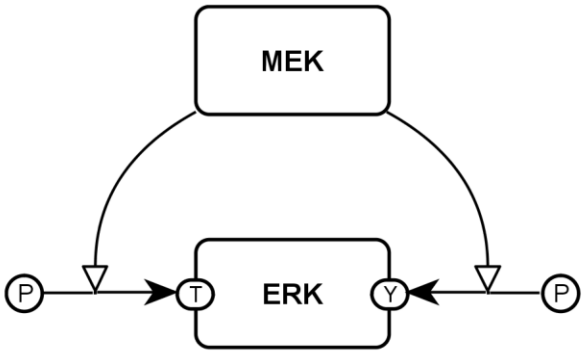
- Physiology
- Signalling pathways
- Gene regulatory networks

SBGN – Orthogonal projections of of the underlying biological phenomena

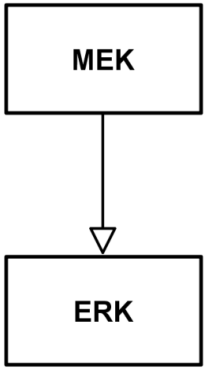
Process Description



Entity Relationship



Activity Flow



Resources

- Main source of information: http://sbgn.org/
  - Specifications, templates, examples
  - Meeting discussions, votes and their results
  - List of software supporting SBGN
- How to participate
  - Mailing list sbgn-discuss@caltech.edu
  - Bug tracker on Sourceforge
- Meetings
  - COMBINE, HARMONY, dedicated editor meetings

- LibSBGN: http://www.sbgn.org/LibSBGN
  - Electronic implementation of SBGN
    - Increase interoperability between software
    - Exchange format for SBGN maps: SBGN-ML

Governance

- Editorial board


Stuart Moodie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- Scientific committee


Gary Bader


Igor Goryanin


Michael Hucka

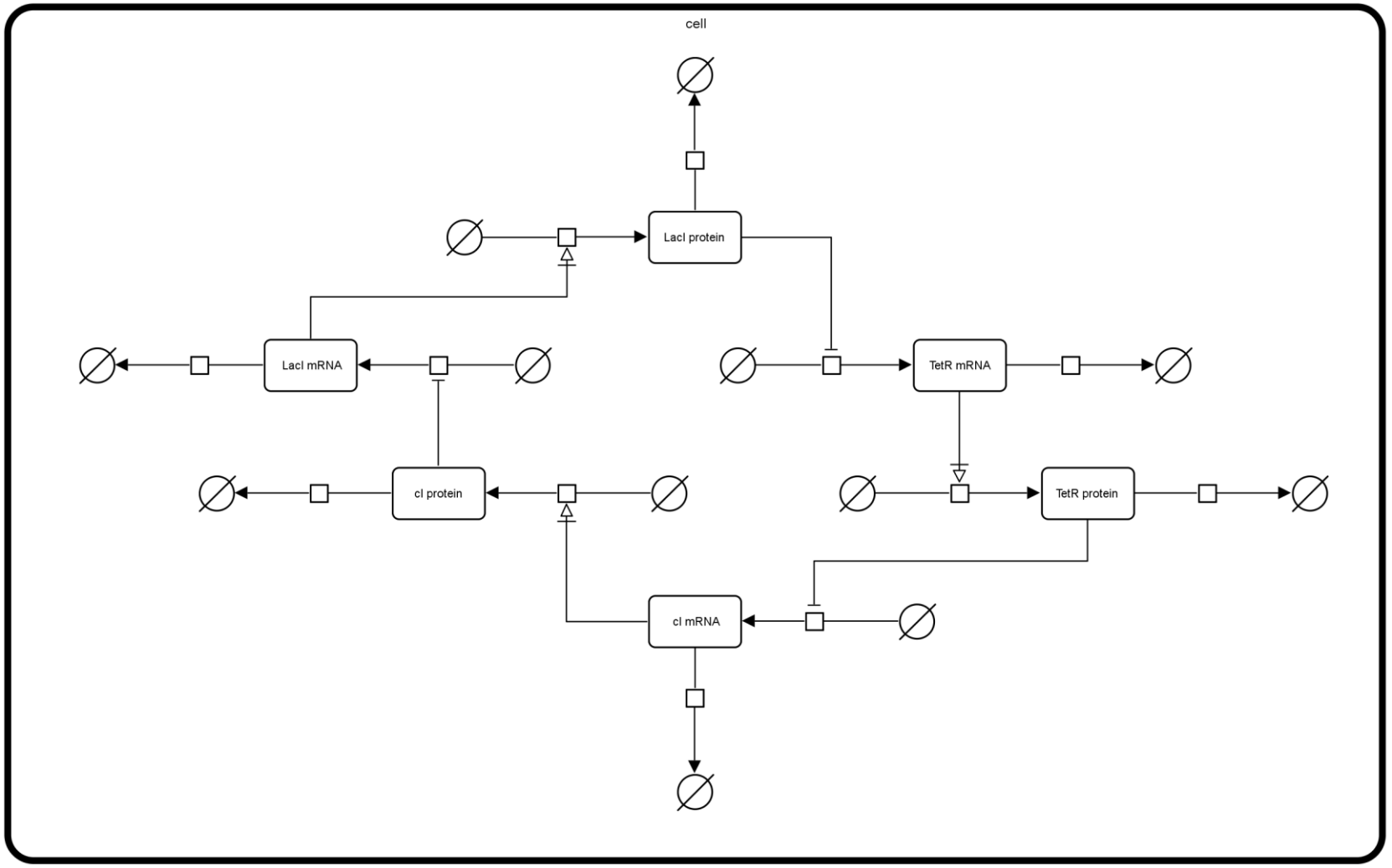

Hiroaki Kitano


Paul Thomas


Falk Schreiber


Nicolas Le Novère

SBML modell visualised in SBGN



BioModels Database
BIOMD0000000012

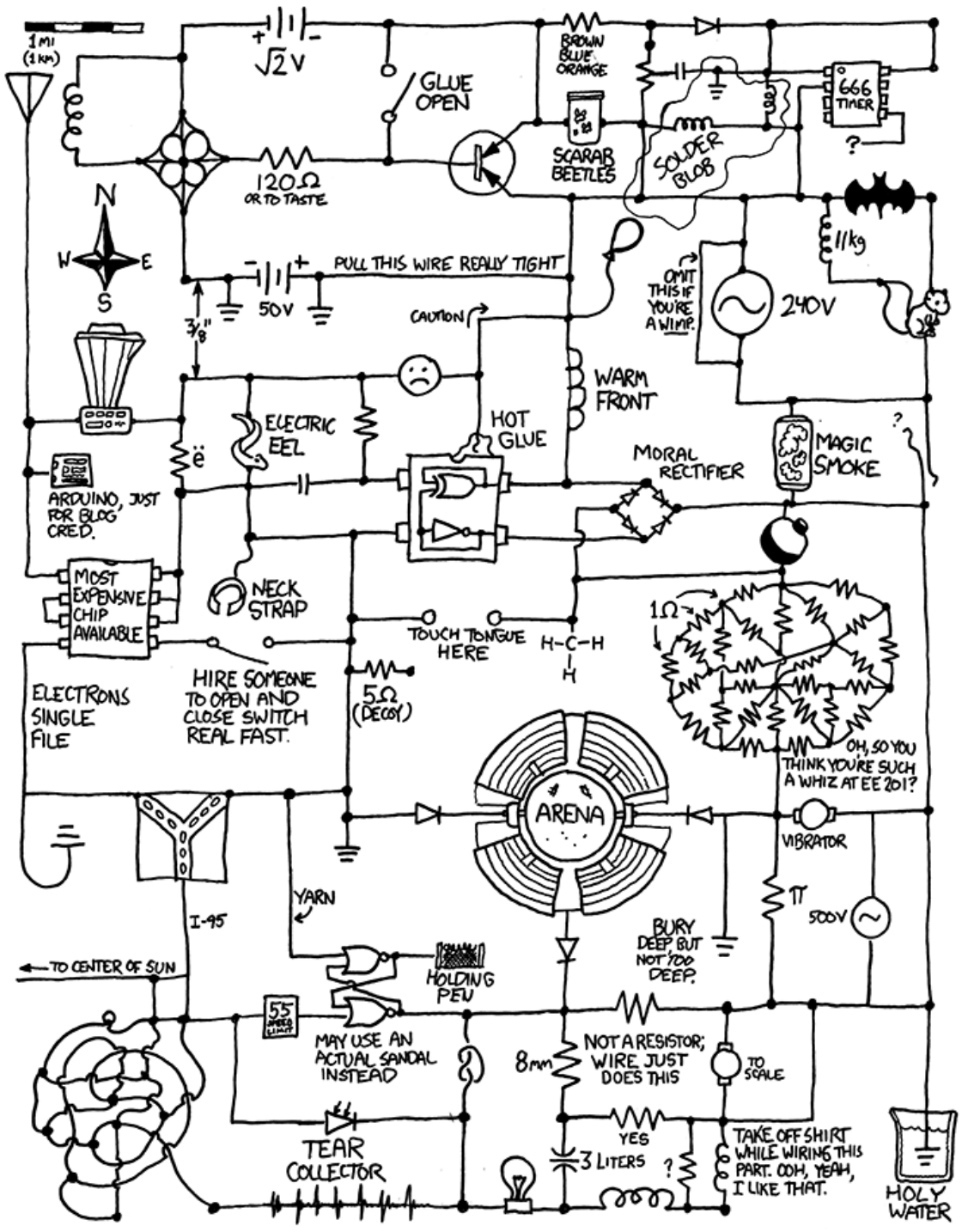
Elowitz MB, Leibler S
A synthetic oscillatory network of transcriptional regulators

Thank you for your attention!

Are there questions?

What circuit diagrams probably would look like without standardisation.

https://www.xkcd.com/730/



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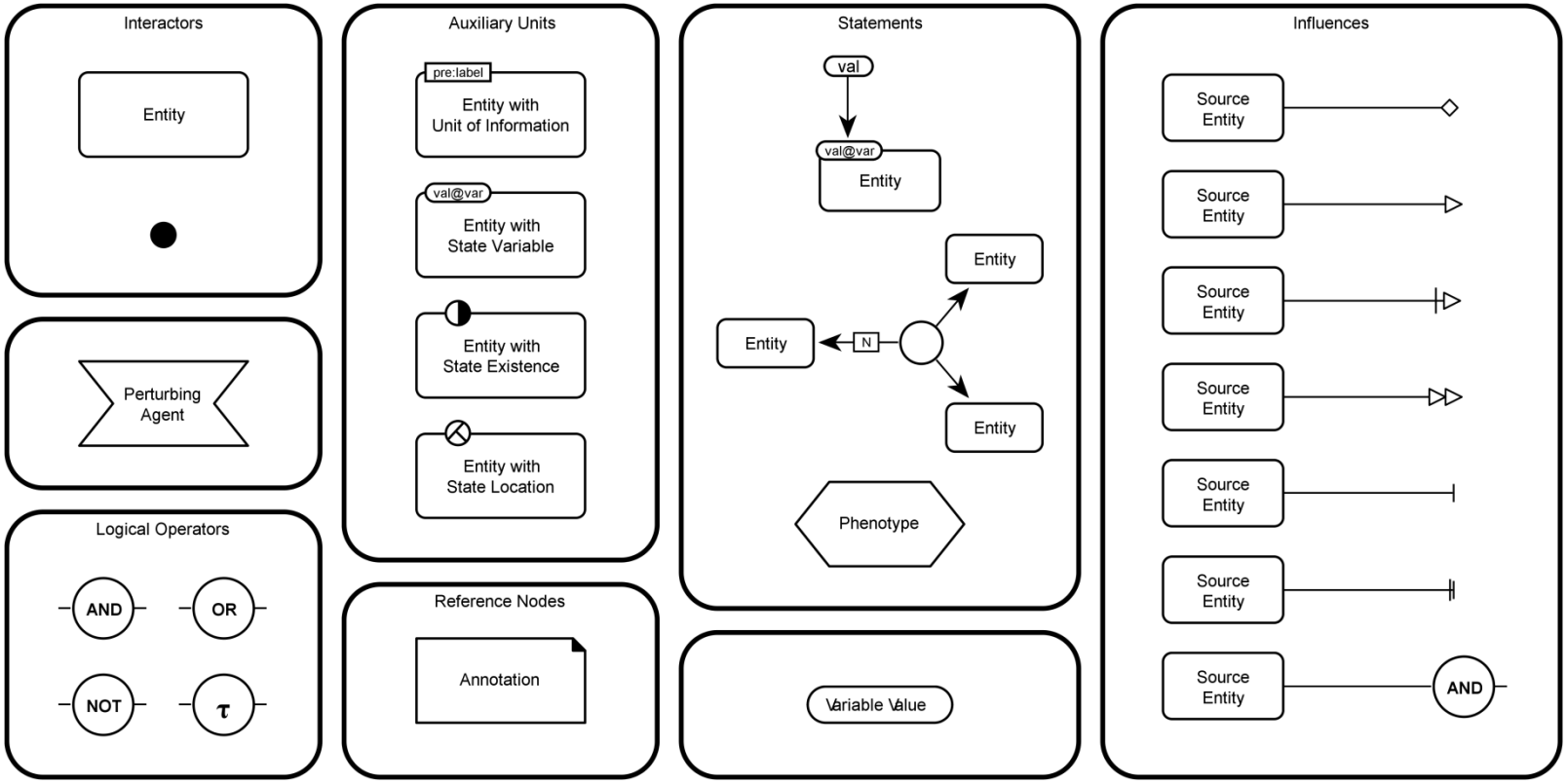

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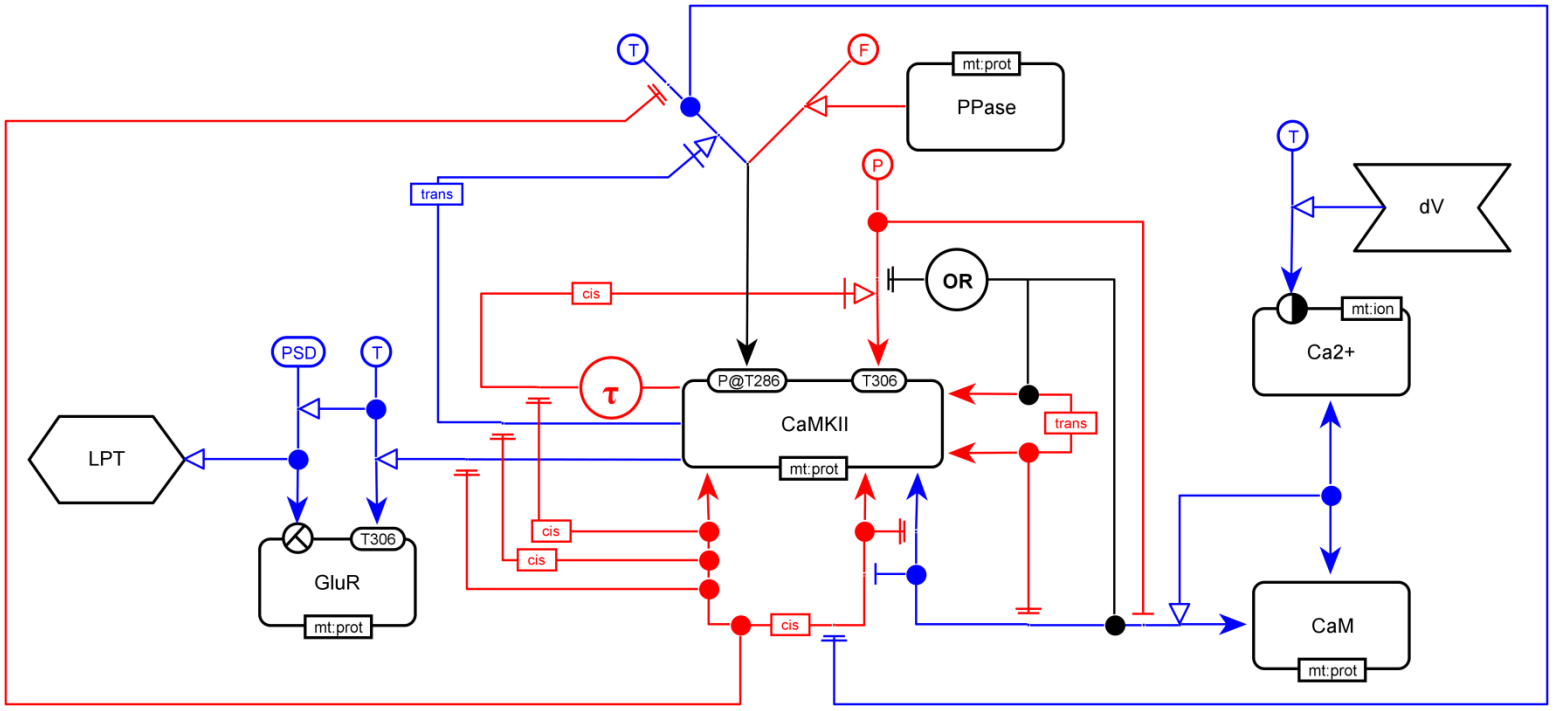
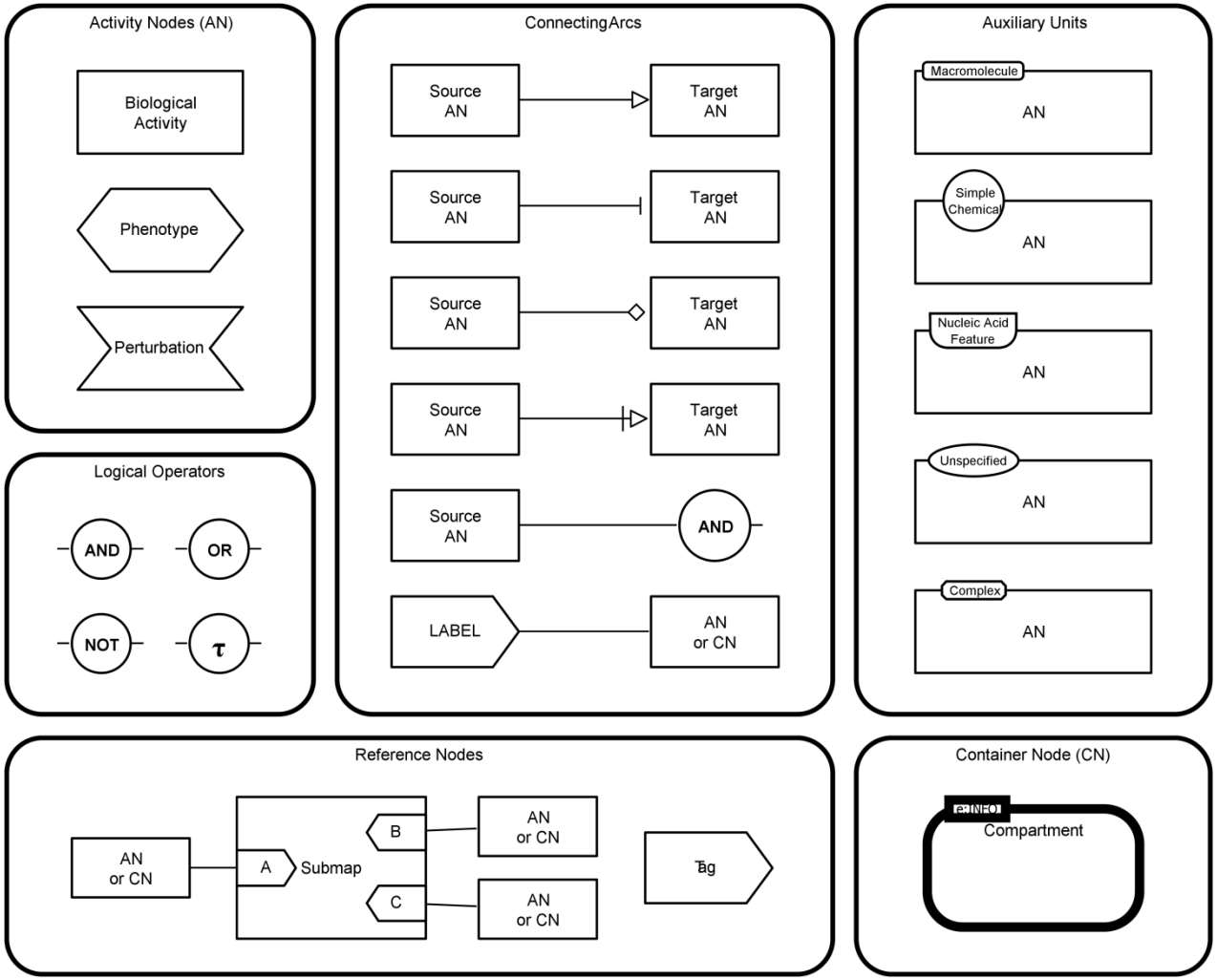


Regulation of calcium / calmoduline kinase II effect on synaptic plasticity

SBGN – Activity Flow (AF)



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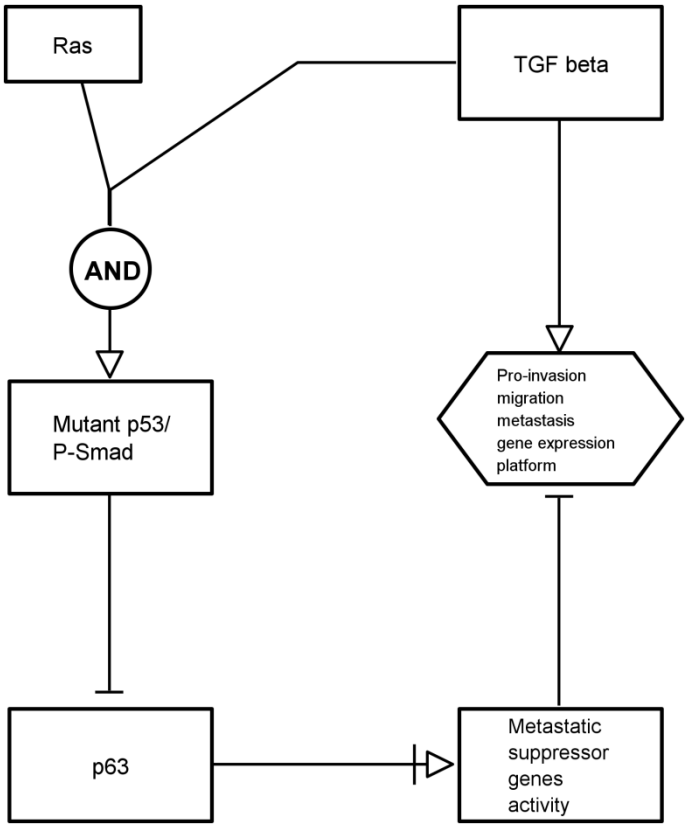

Regulation of TGFβ-induced metastasis