

An update on Systems Biology Graphical Notation

SBGN Community

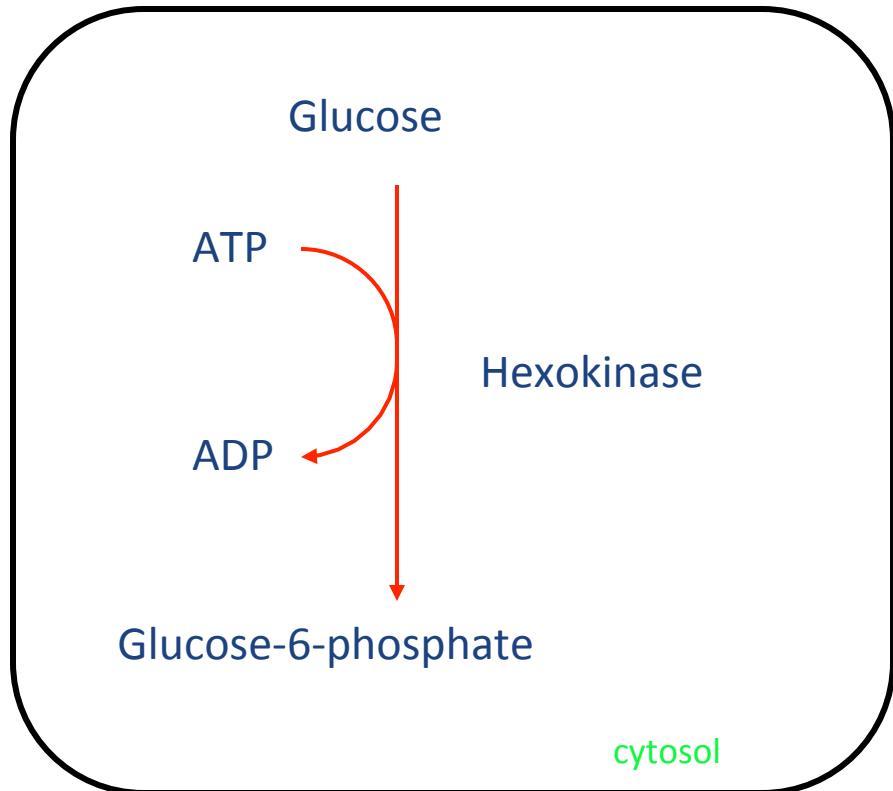
Outline

- Motivation
- Specification development
- Software support

MOTIVATIONS

Pathway Network Diagram

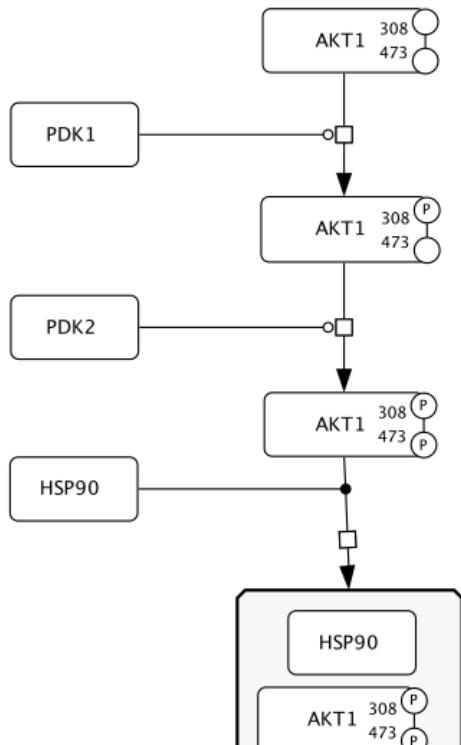
— An easy way to read biological knowledge



- Glucose is converted to glucose -6-phosphate with the consumption of ATP and production of ADP. The process is catalyzed by hexokinase. The reaction occurs in the cytosol of a cell.

Pathway Network Diagram

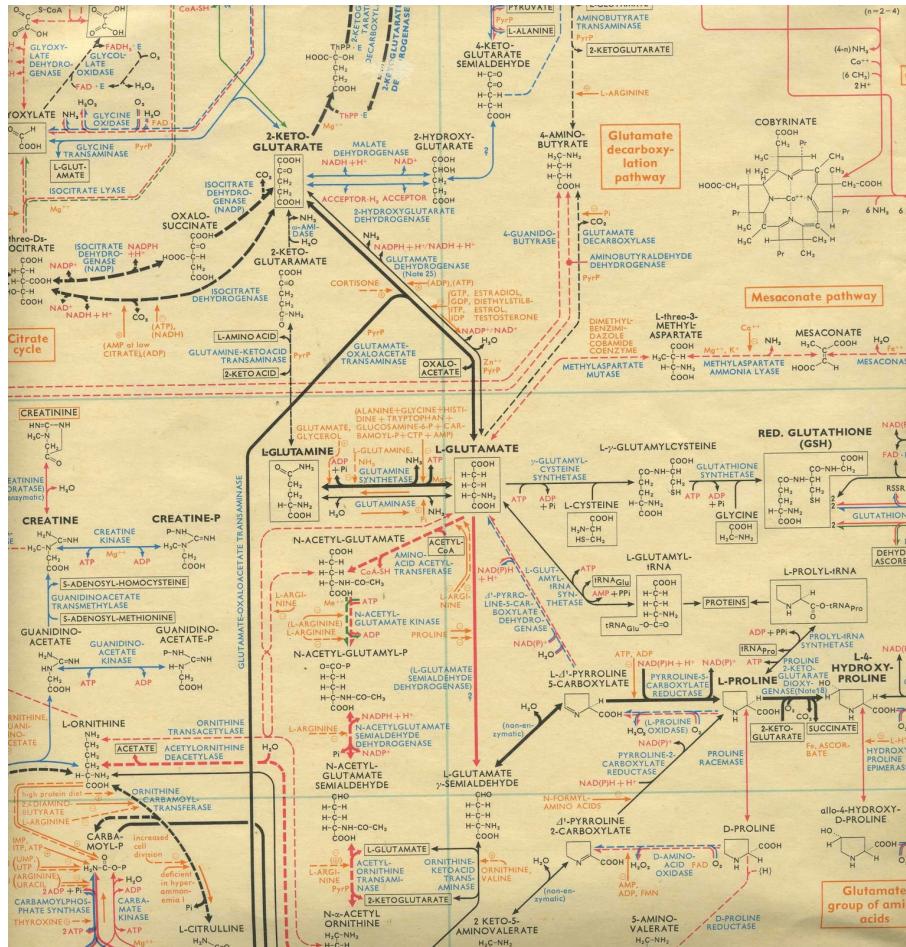
— An easy way to read biological knowledge



cytosol

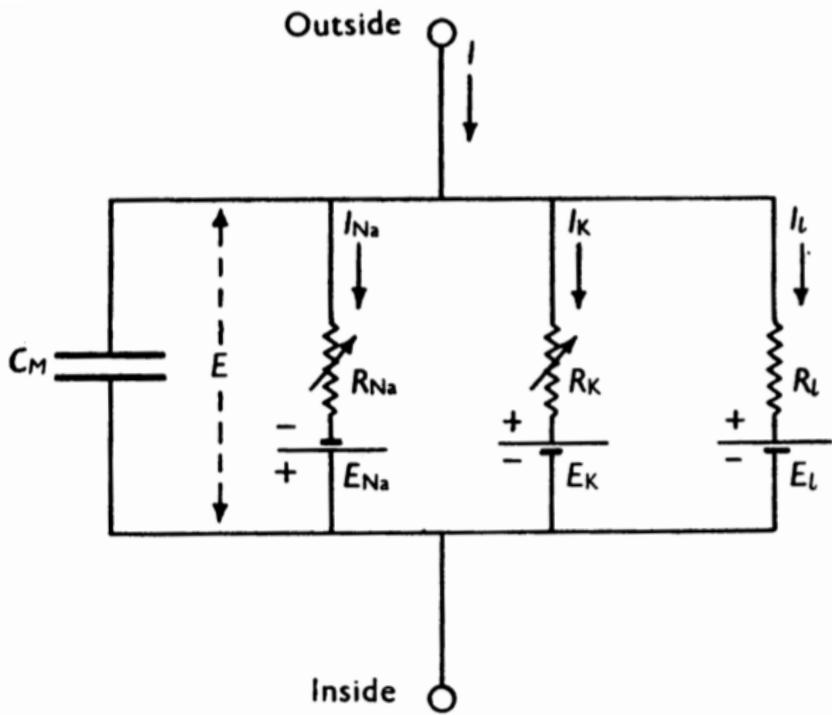
AKT1 is phosphorylated at residue 308 by PDK1. The phosphorylated AKT is then phosphorylated at residue of 473 by PDK2. The second phosphorylation reaction does not happen until the first residue (308) is phosphorylated. When both sites are phosphorylate. All the reactions occur in cytosol.

Pathway diagram has been used a long time ago



A metabolic pathway diagram

From the wall chart of *Biochemical Pathways* created by Gerhard Michal (1968)



Electrical circuit diagram
representing cell membrane.

From Hodgkin A.L. and Huxley A.F. (1952) A quantitative description of membrane current and its application to conduction and excitation in nerve. *J. Physiol.* 117:500-544

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Volume 159, Issue 2, p281–294, 9 October 2014

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Article

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γCaMKII Shuttles Ca²⁺/CaM to the Nucleus to Trigger CREB Phosphorylation and Gene Expression

Huan Ma  , Rachel D. Groth, Samuel M. Cohen, John F. Emery, Boxing Li, Esthelle Hoedt, Guoan Zhang, Thomas A. Neubert, Richard W. Tsien  

DOI: <http://dx.doi.org/10.1016/j.cell.2014.09.019> | 

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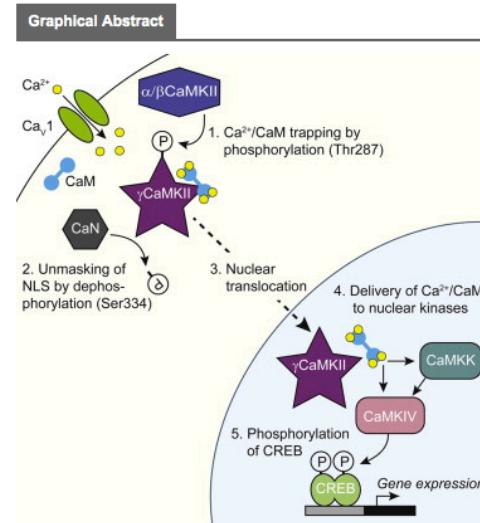
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Highlights

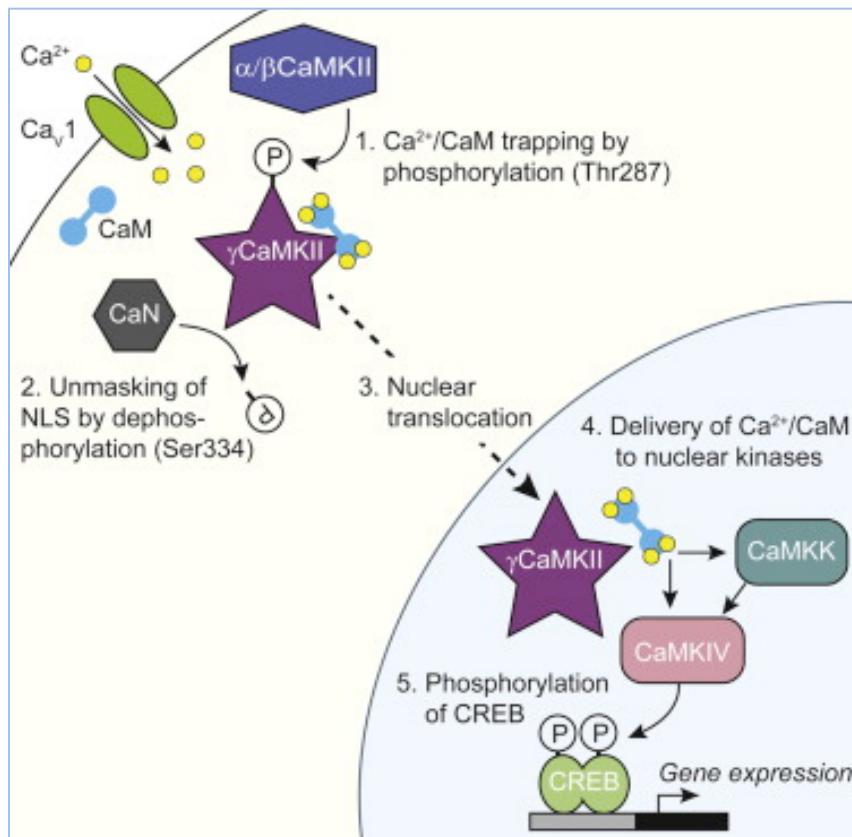
- Ca²⁺/CaM near Ca_{v1} channels is delivered into the nucleus by γCaMKII
- Ca²⁺/CaM provides the crucial signal to activate transcription factor CREB
- βCaMKII phosphorylates γCaMKII at Thr287 to protect the Ca²⁺/CaM signal
- CaN dephosphorylates γCaMKII at Ser334 to trigger γCaMKII nuclear translocation

Summary

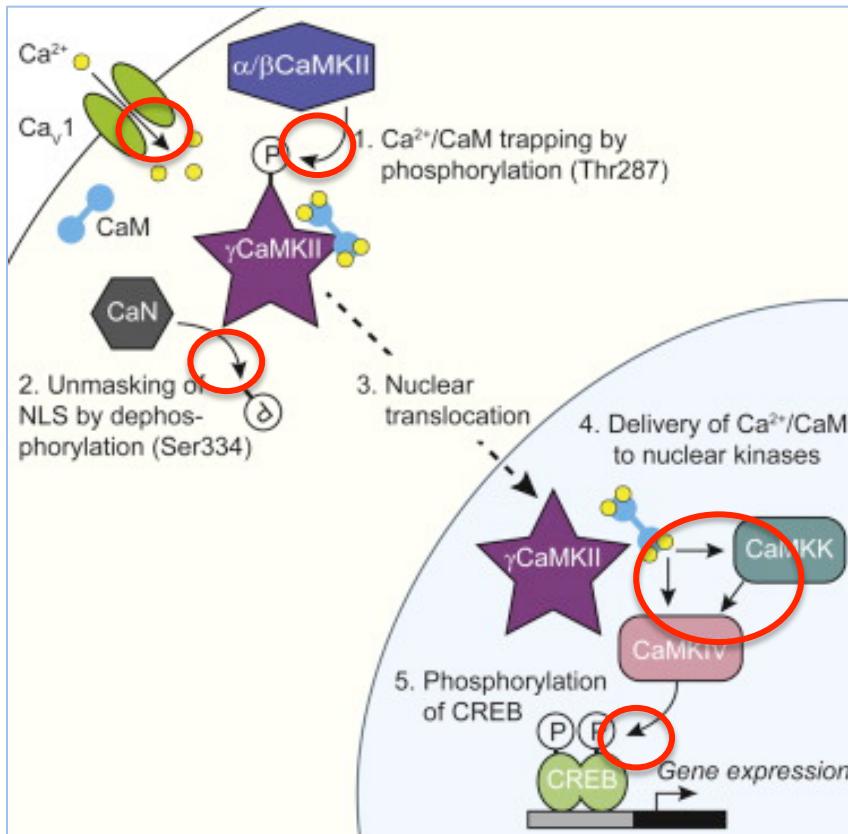
Activity-dependent CREB phosphorylation and gene expression are critical for long-term neuronal plasticity. Local signaling at Ca_{v1} channels triggers these events, but how information is relayed onward to the nucleus remains unclear. Here, we report a mechanism that mediates long-distance communication within cells: a shuttle that transports Ca²⁺/calmodulin from the surface membrane to the nucleus. We show that the shuttle protein is γCaMKII, its phosphorylation at Thr287 by βCaMKII protects the Ca²⁺/CaM signal, and CaN triggers its nuclear translocation. Both βCaMKII and CaN act in close proximity to Ca_{v1} channels, supporting their dominance, whereas γCaMKII operates as a carrier, not as a kinase. Upon arrival within the nucleus, Ca²⁺/CaM activates CaMKK and its substrate CaMKIV, the CREB kinase. This mechanism resolves long-standing puzzles about CaM/CaMK-dependent signaling to the nucleus. The significance of the mechanism is emphasized by dysregulation of Ca_{v1}, γCaMKII, βCaMKII, and CaN in multiple neuropsychiatric disorders.



What are the problems?



What are the problems?



- Graphically ambiguous
 - Glyphs are not defined.
 - It is difficult to interpret the meaning of the diagram without referring to the text.

Ambiguity in Conventional Representation

X → Y

Ambiguity in Conventional Representation

X → 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

X inhibits Y

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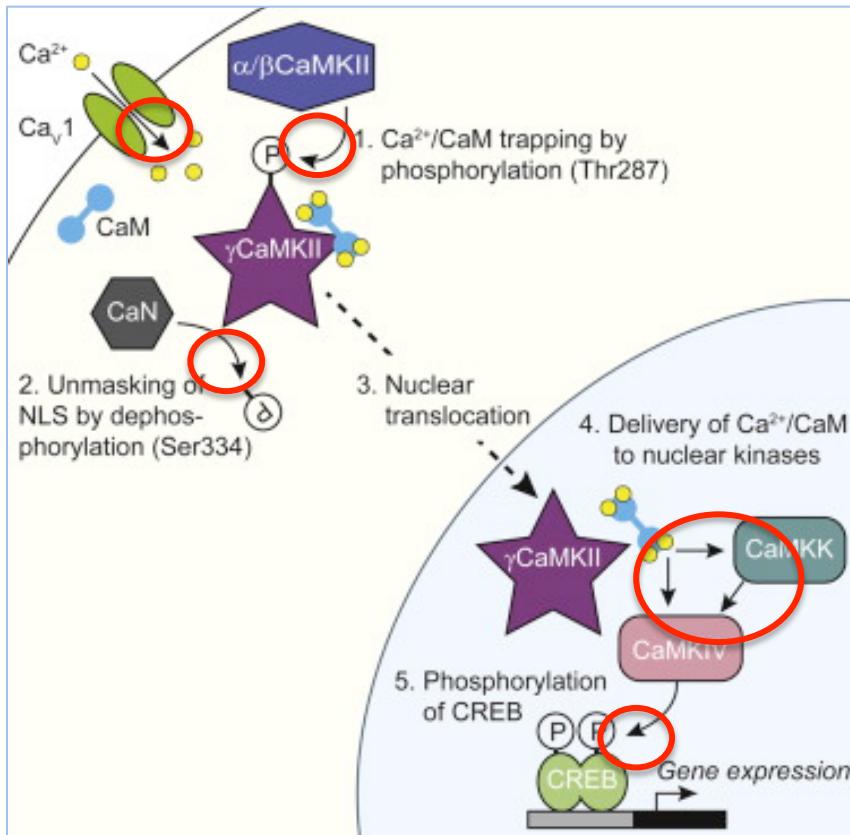
catalyses the formation of



inhibition



What are the problems?



- Graphically ambiguous
 - Glyphs are not defined.
 - It is difficult to interpret the meaning of the diagram without referring to the text.
- Not in computer-readable format

Here comes

The Systems Biology Graphical Notation



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

History of SBGN

- The SBGN effort was initiated by Professor Hiroaki Kitano.
- The inaugural SBGN workshop was held in Tokyo in February 2006.





The Systems Biology Graphical Notation

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¹⁸Manchester Interdisciplinary Biocentre, Manchester, UK. ¹⁹Clayton School of Information Technology, Faculty of Information Technology, Monash University, Melbourne, Victoria, Australia. ²⁰U900 INSERM, Paris Mines Tech, Institut Curie, Paris, France. ²¹Terry Fox Laboratory, British Columbia Cancer Research Center, Vancouver, British Columbia, Canada. ²²Bilkent Center for Bioinformatics, Bilkent University, Ankara, Turkey. ²³The Roslin Institute, University of Edinburgh, Midlothian, UK. ²⁴Department of Biosciences and Informatics, Keio University, Hiyoshi, Kouhoku-ku, Yokohama, Japan. ²⁵Institute of Systems Biology, Novosibirsk, Russia. ²⁶Design Technological Institute of Digital Techniques SB RAS, Novosibirsk, Russia. ²⁷Ontario Institute for Cancer Research, Toronto, Ontario, Canada. ²⁸School of Chemistry, University of Manchester, Manchester, UK. ²⁹Department of Biochemistry, Stellenbosch University, Matieland, South Africa. ³⁰Sony Computer Science Laboratories, Tokyo, Japan. ³¹Okinawa Institute of Science and Technology, Okinawa, Japan. Correspondence should be addressed to N.L.N. (lenov@ebi.ac.uk).

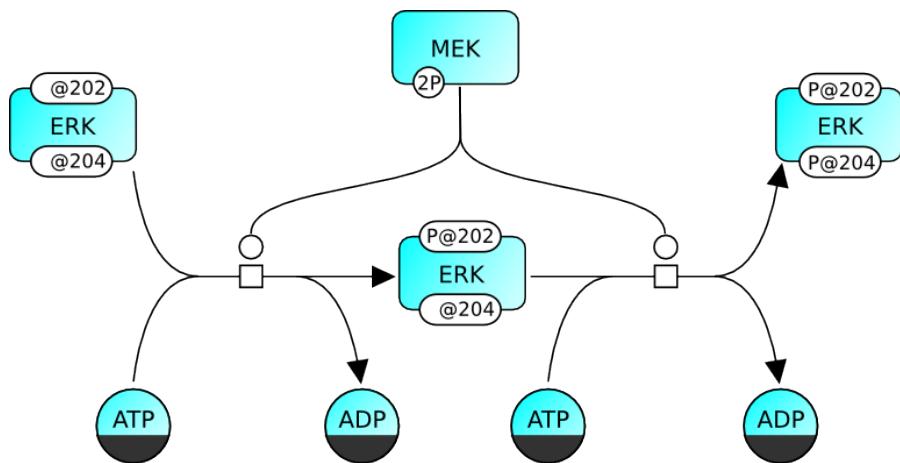
39 authors, 31 affiliations

¹⁷ SBGN is being developed by a large user community

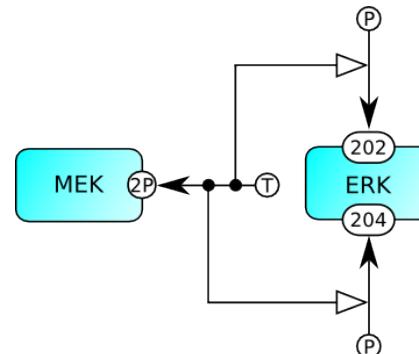
SPECIFICATION DEVELOPMENT

Three Languages in One Notation

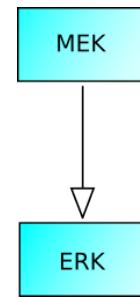
Process Descriptions



Entity Relationships



Activity Flows



SBGN Specifications

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

The screenshot shows the SBGN.org website with a dark blue header. The header features the SBGN logo (blue stylized letters S and G followed by the word "GN") and the text "Systems Biology Graphical Notation". To the right, it says "Parent pages: [SBGN.org](#) / [Documents](#)". Below the header is a navigation bar with links: Home, News, Documents (highlighted in yellow), Software, Community, Events, About, and a search bar labeled "Google Site Search...".

SPECIFICATIONS

This page provides a summary of the state of the **public specifications**. You can also access [all specifications](#). More details are available elsewhere about the [nomenclature of SBGN](#). All documents and source files are available in the [Subversion repository for SBGN on Sourceforge.net](#).

Process Description language (formerly Process Diagram language)

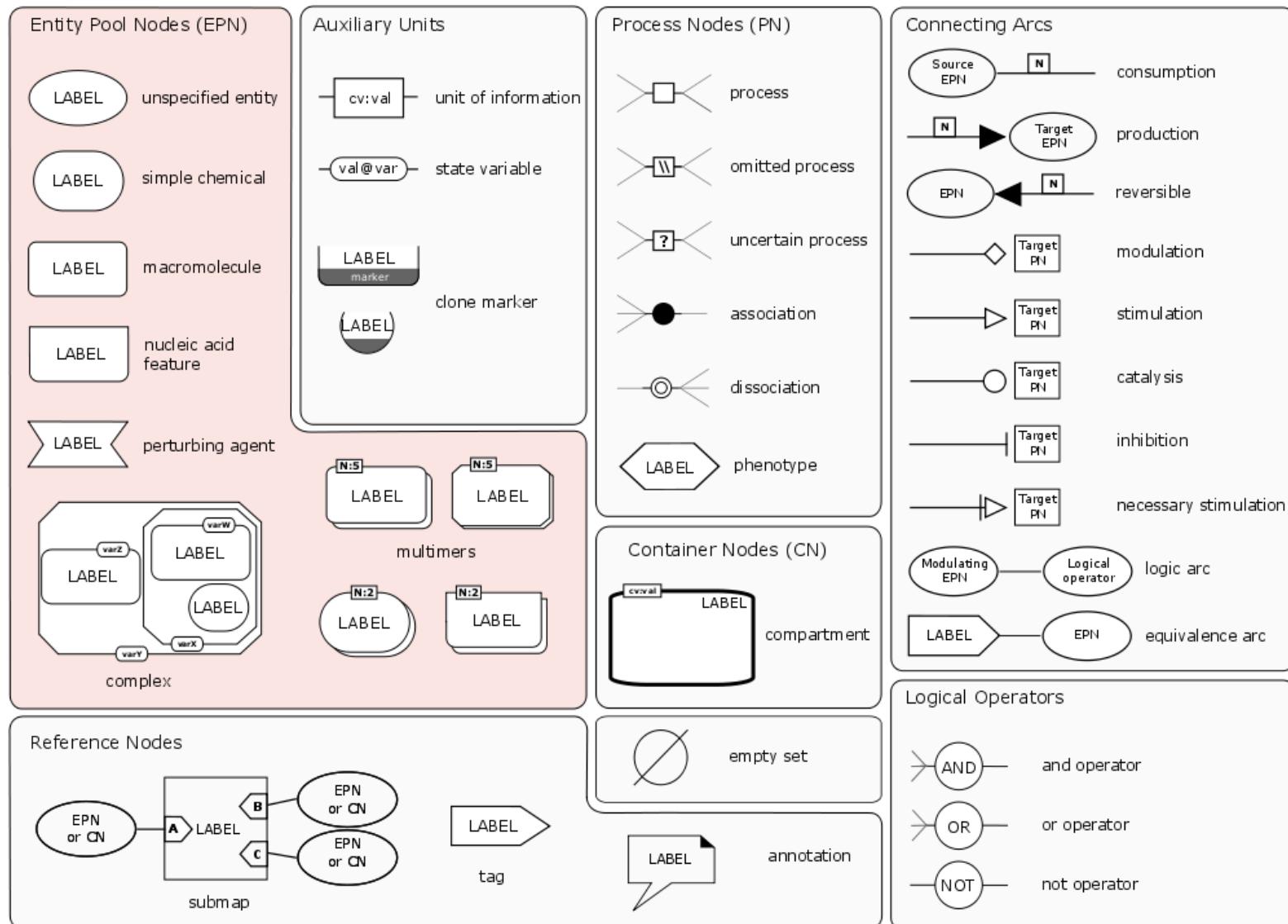
The SBGN *Process Description* (PD) language shows the temporal courses of biochemical interactions in a network. It can be used to show all the molecular interactions taking place in a network of biochemical entities, with the same entity appearing multiple times in the same diagram.

The public specification for SBGN Process Description language Level 1 Version 1.3 can be accessed through Nature Precedings: [doi:10.1038/npre.2011.3721.4](https://doi.org/10.1038/npre.2011.3721.4).

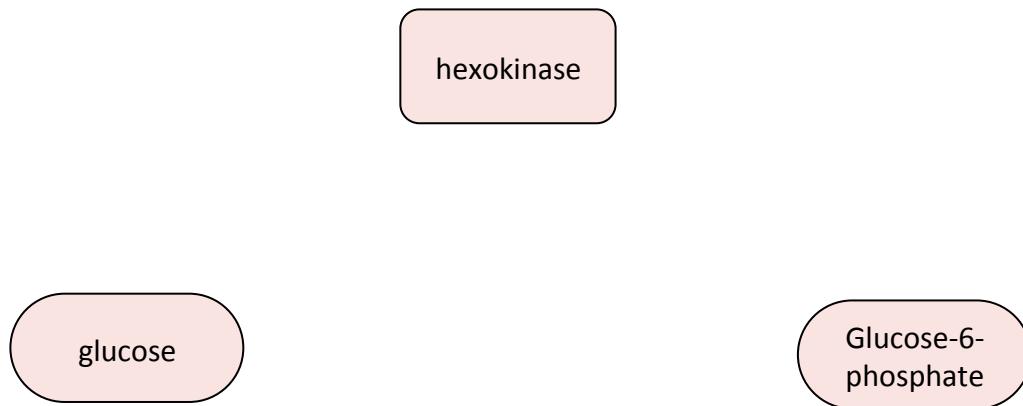
For end-users more than software developers a [user manual](#) is also available.

To report an error or to comment on the SBGN Process Description specification, please use the [dedicated PD L1 tracker](#)

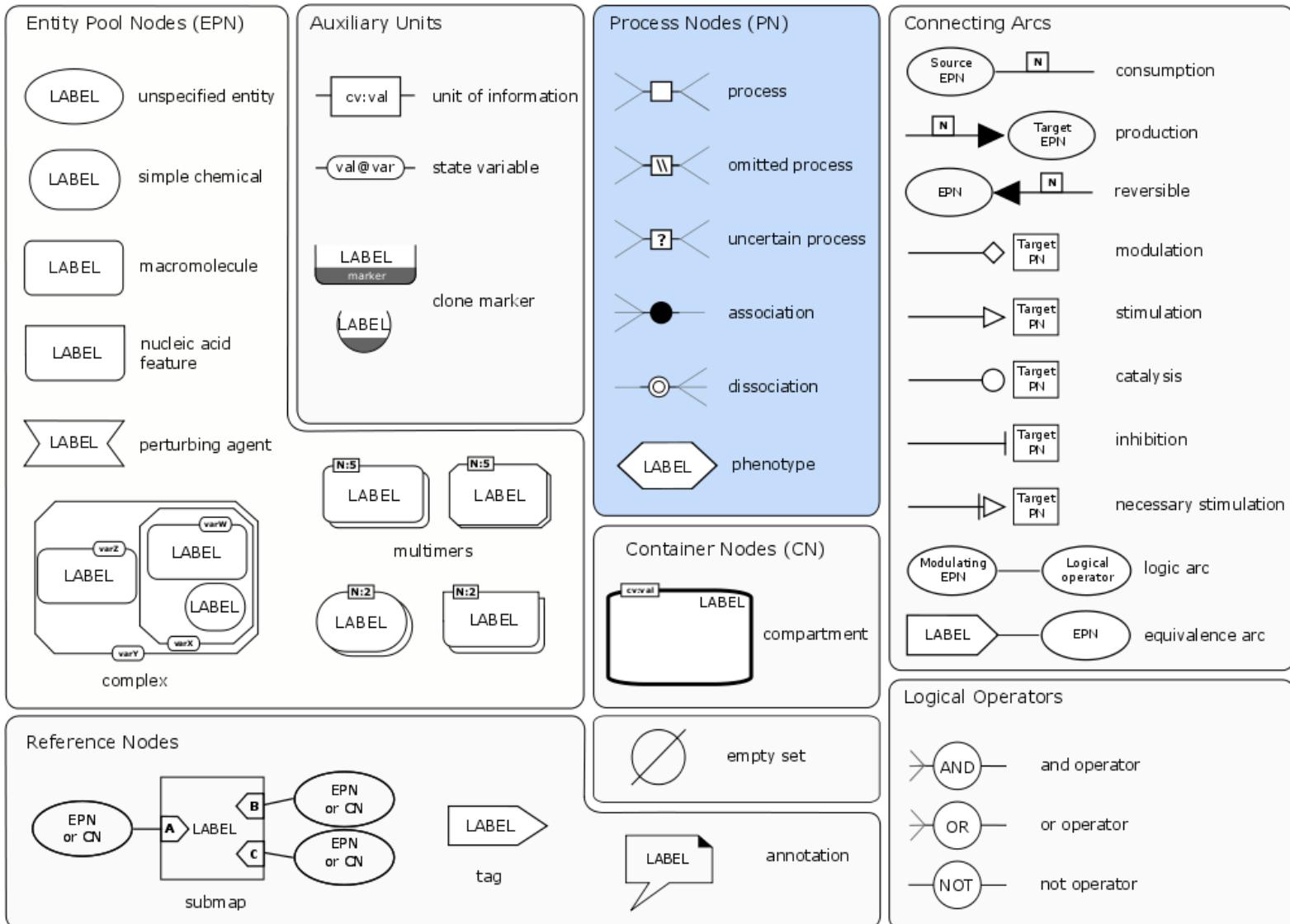
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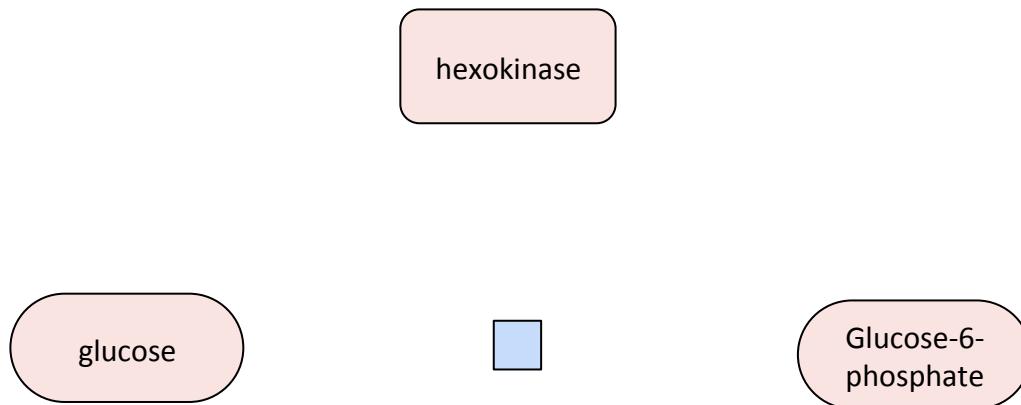
SBGN Process Description



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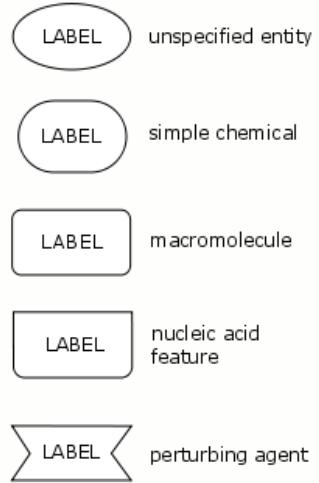


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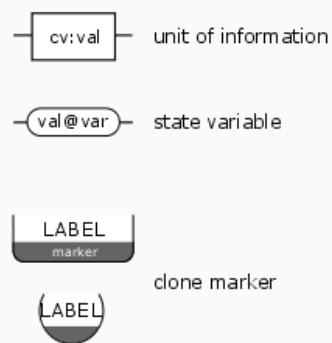


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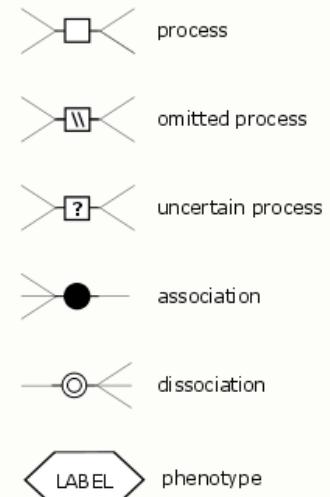
Entity Pool Nodes (EPN)



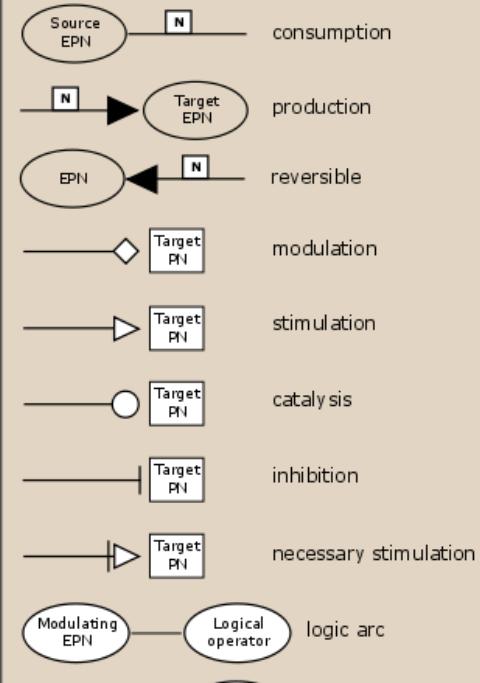
Auxiliary Units



Process Nodes (PN)



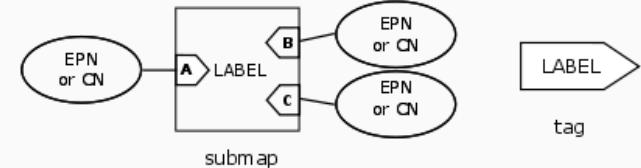
Connecting Arcs



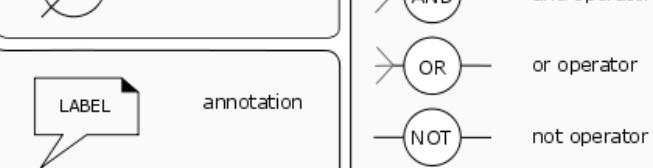
Container Nodes (CN)



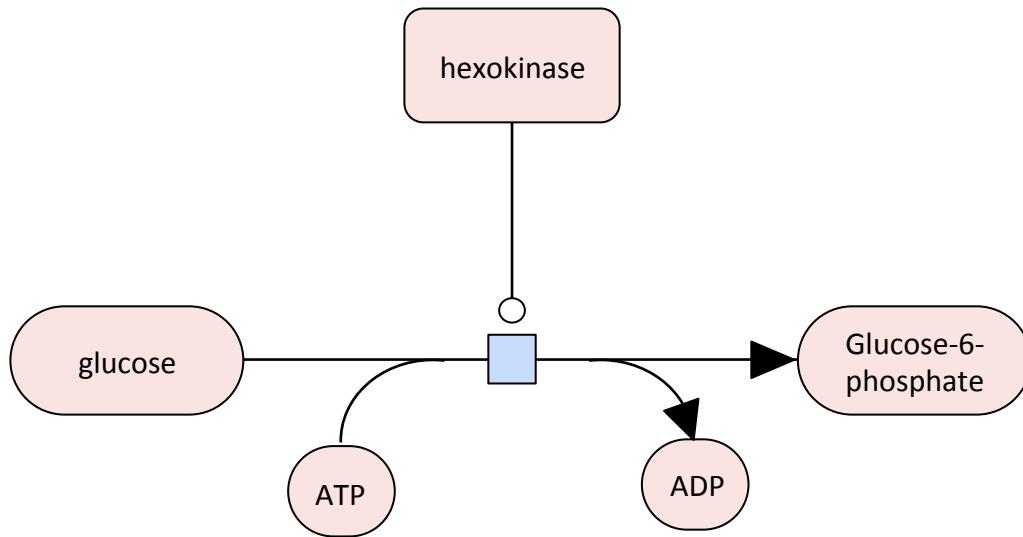
Reference Nodes



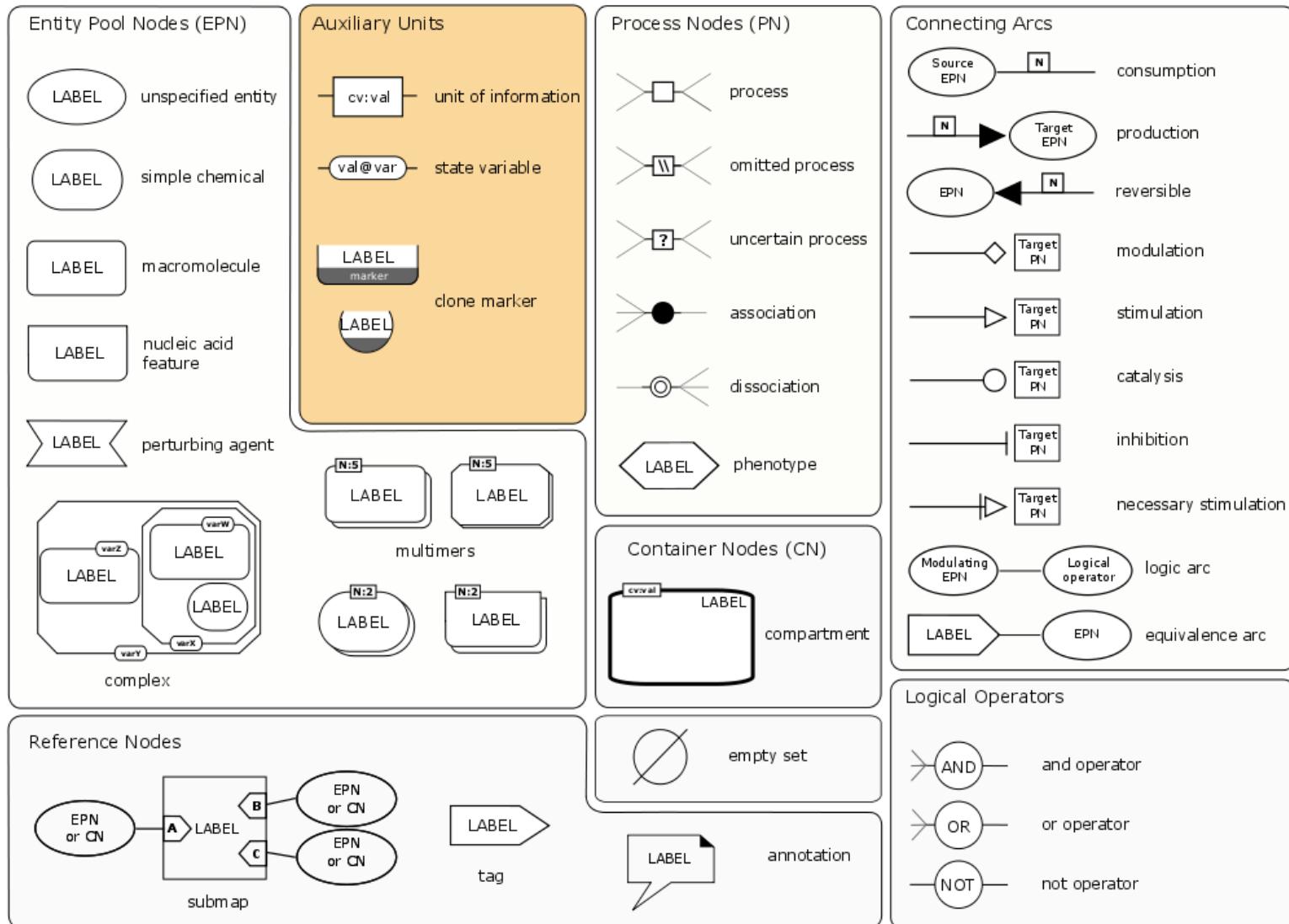
Logical Operators



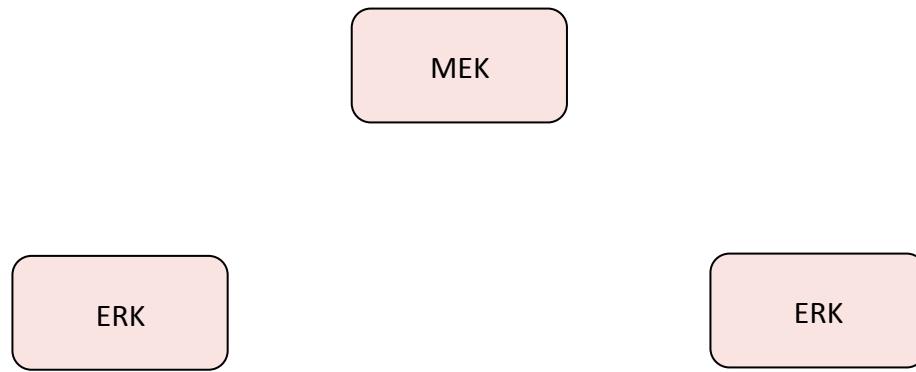
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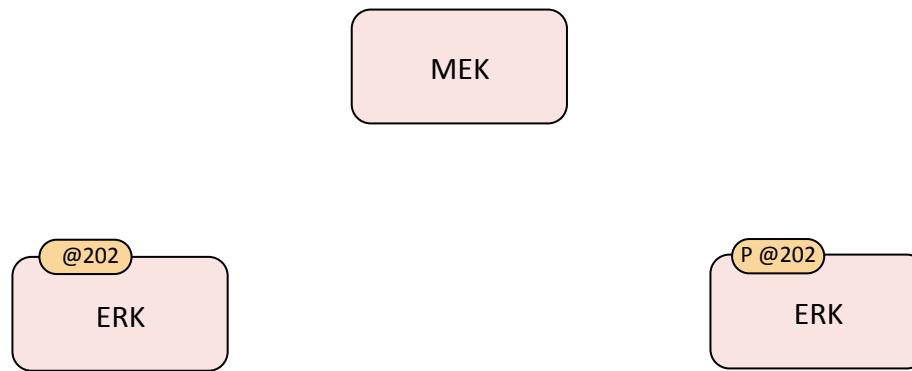
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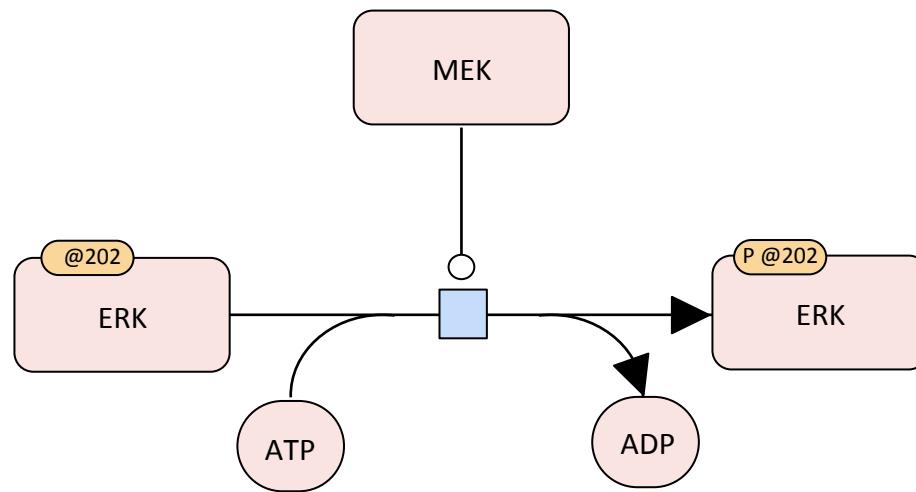
SBGN Process Description



SBGN Process Description



SBGN Process Description



PD Example

γ CaMKII Shuttles Ca^{2+} /CaM to the Nucleus to Trigger CREB Phosphorylation and Gene Expression

Huan Ma,^{1,*} Rachel D. Groth,³ Samuel M. Cohen,¹ John F. Emery,¹ Boxing Li,¹ Estelle Hoedt,² Guoan Zhang,² Thomas A. Neubert,² and Richard W. Tsien^{1,*}

¹Department of Neuroscience and Physiology, Neuroscience Institute, NYU Langone Medical Center, New York, NY 10016, USA

²Department of Biochemistry and Molecular Pharmacology and Skirball Institute, NYU Langone Medical Center, New York, NY 10016, USA

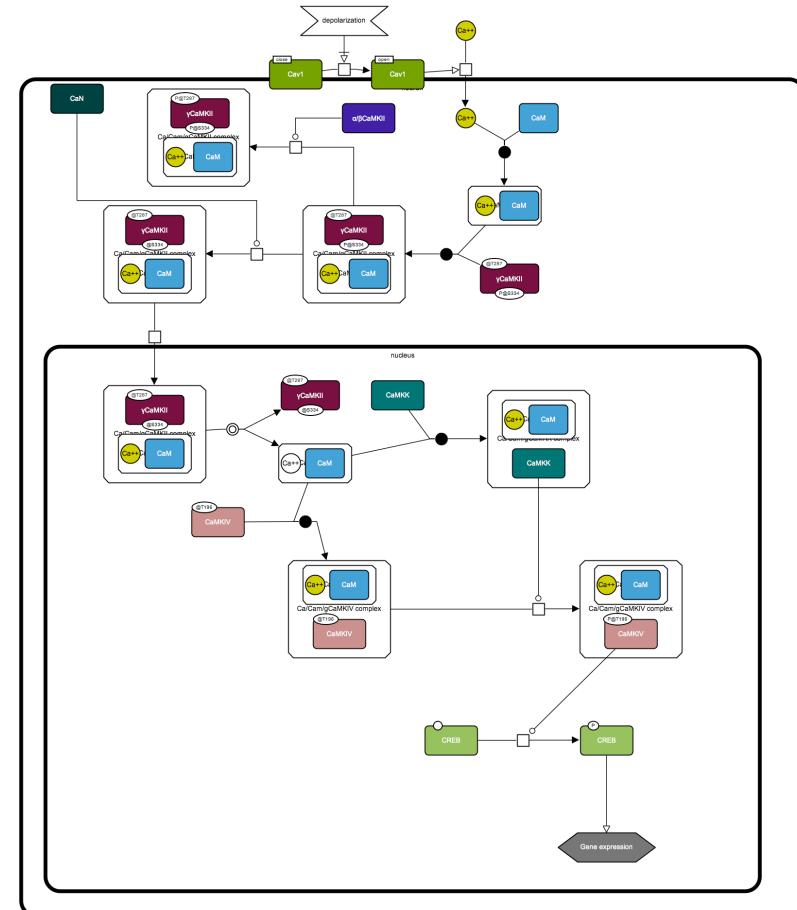
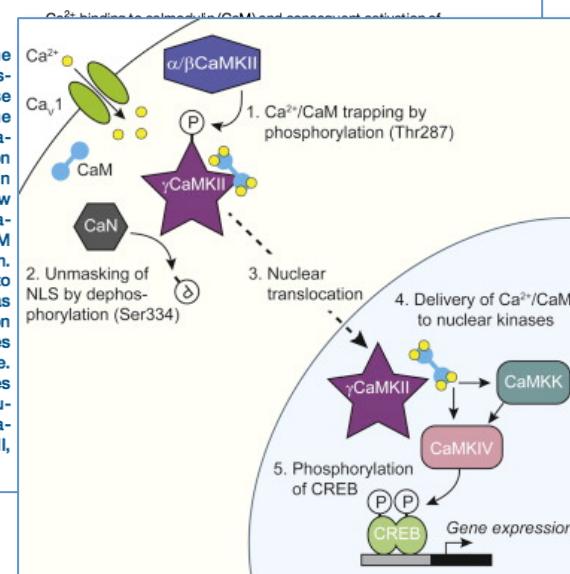
³Centers for Therapeutic Innovation, Pfizer, 1700 Owens Street, San Francisco, CA 94158, USA

*Correspondence: mahuhan@gmail.com (H.M.), richard.tsien@nyumc.org (R.W.T.)

<http://dx.doi.org/10.1016/j.jcell.2014.09.019>

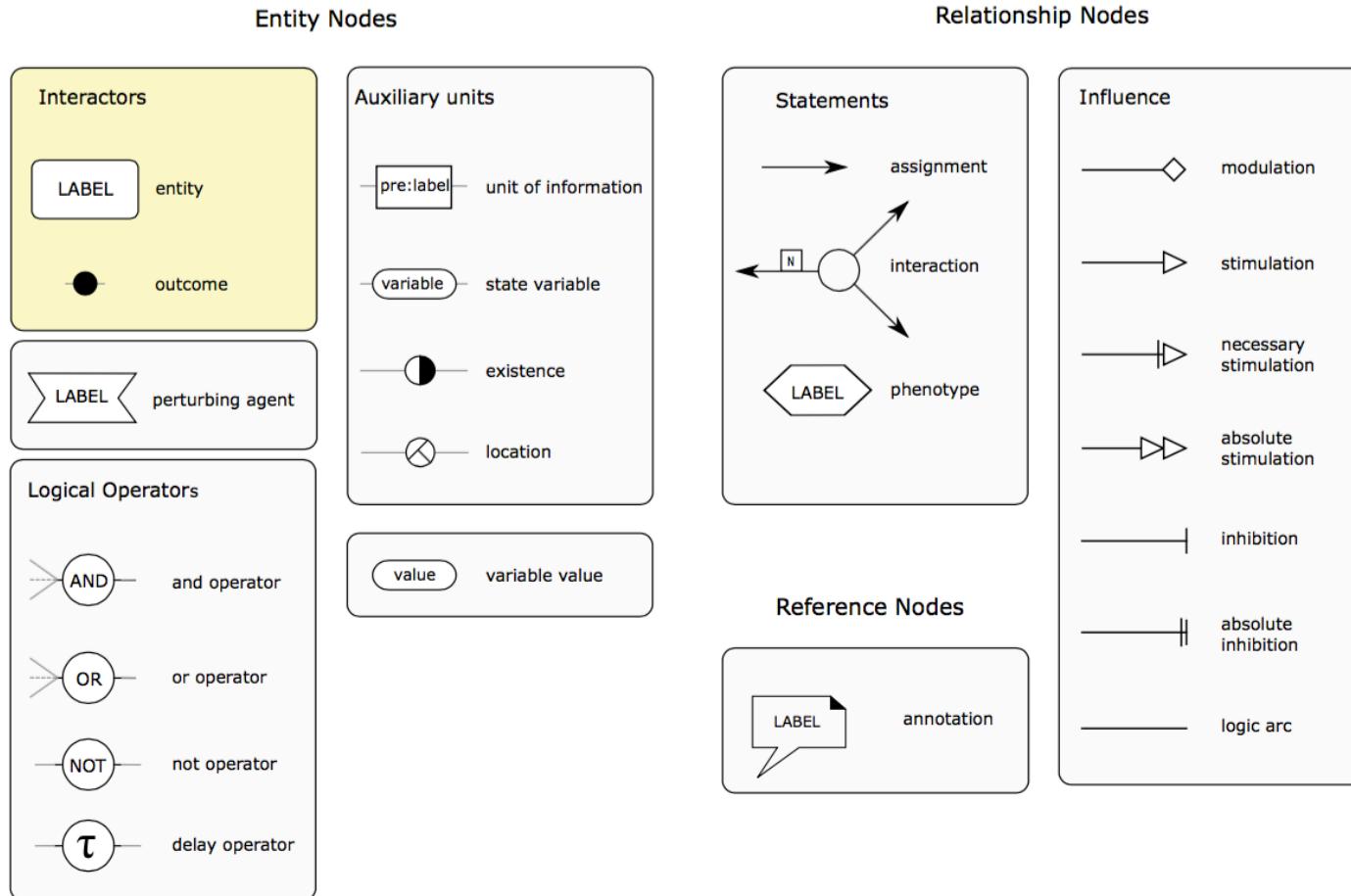
SUMMARY

Activity-dependent CREB phosphorylation and gene expression are critical for long-term neuronal plasticity. Local signaling at Ca_v1 channels triggers these events, but how information is relayed onward to the nucleus remains unclear. Here, we report a mechanism that mediates long-distance communication within cells: a shuttle that transports Ca^{2+} /calmodulin from the surface membrane to the nucleus. We show that the shuttle protein is γ CaMKII, its phosphorylation at Thr287 by β CaMKII protects the Ca^{2+} /CaM signal, and CaN triggers its nuclear translocation. Both β CaMKII and CaN act in close proximity to Ca_v1 channels, supporting their dominance, whereas γ CaMKII operates as a carrier, not as a kinase. Upon arrival within the nucleus, Ca^{2+} /CaM activates CaMKK and its substrate CaMKIV, the CREB kinase. This mechanism resolves long-standing puzzles about CaM/CaMK-dependent signaling to the nucleus. The significance of the mechanism is emphasized by dysregulation of Ca_v1 , γ CaMKII, β CaMKII, and CaN in multiple neuropsychiatric disorders.

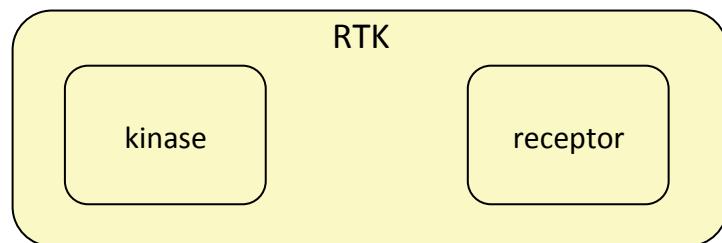
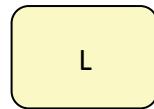


SBGN-PD

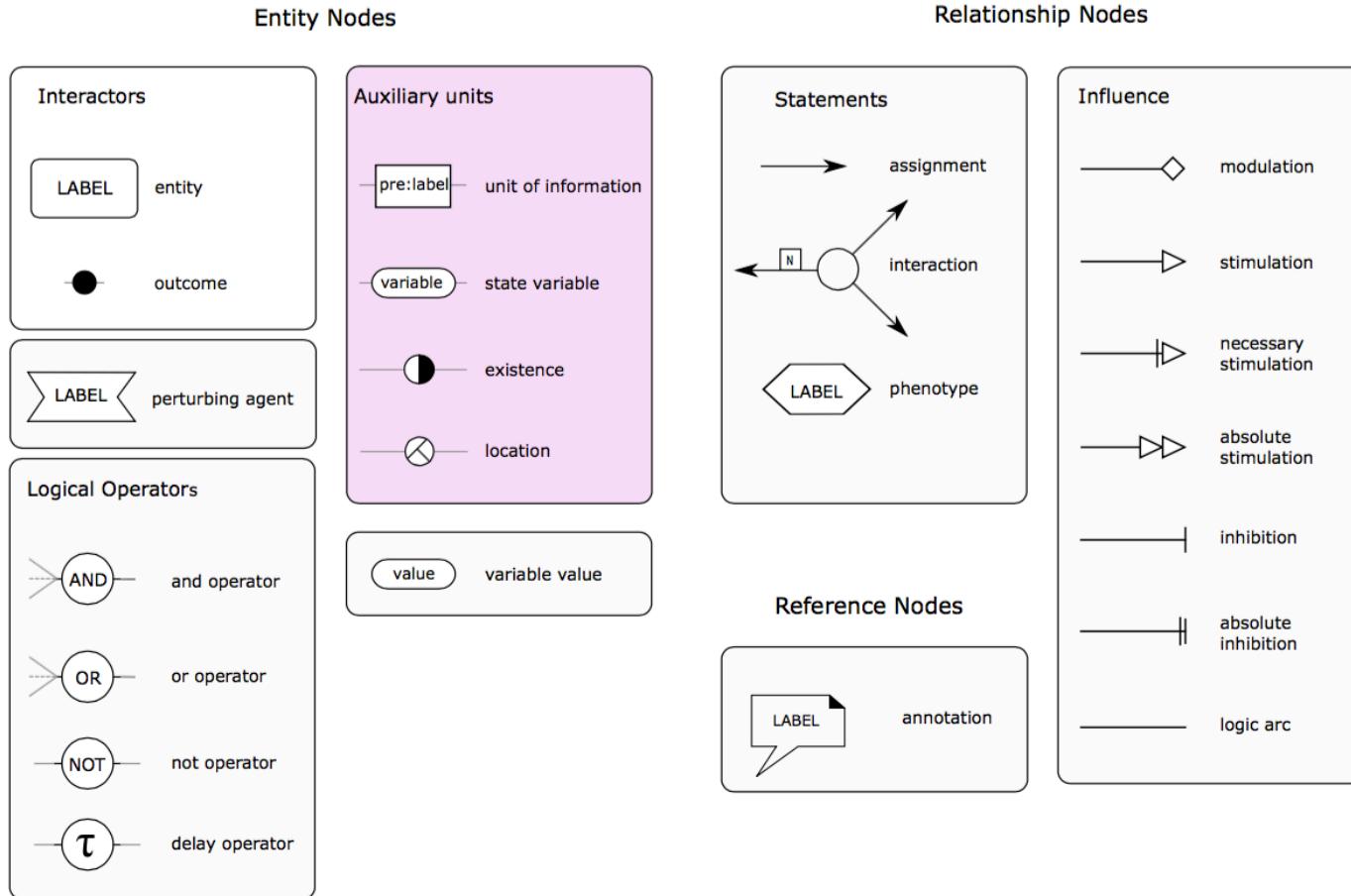
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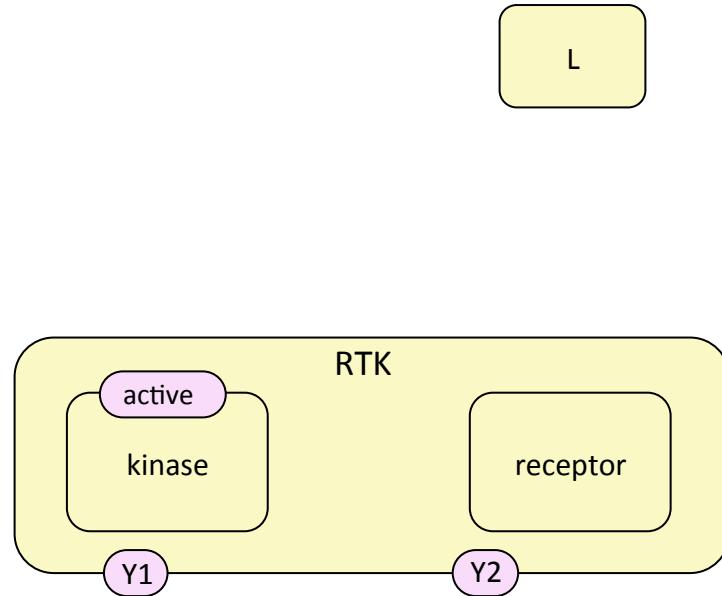
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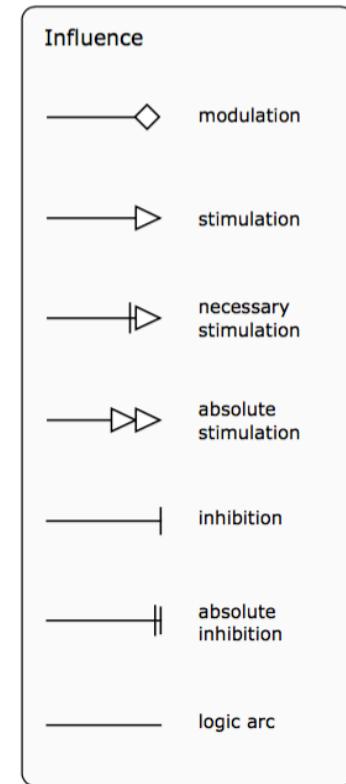
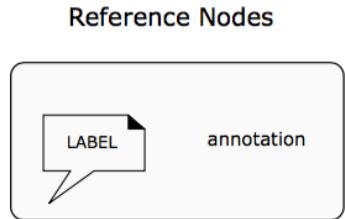
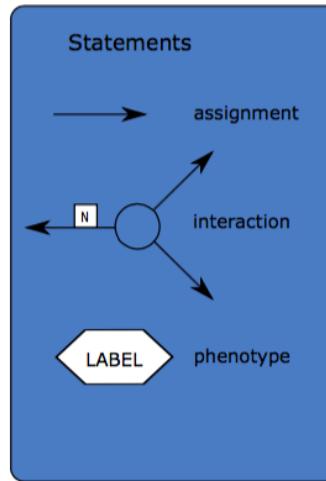
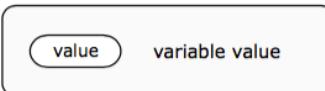
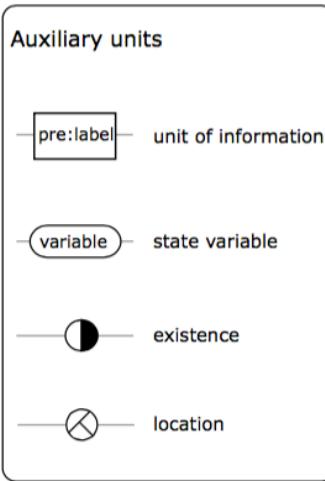
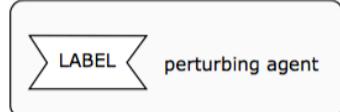
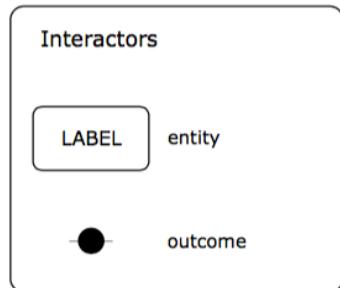
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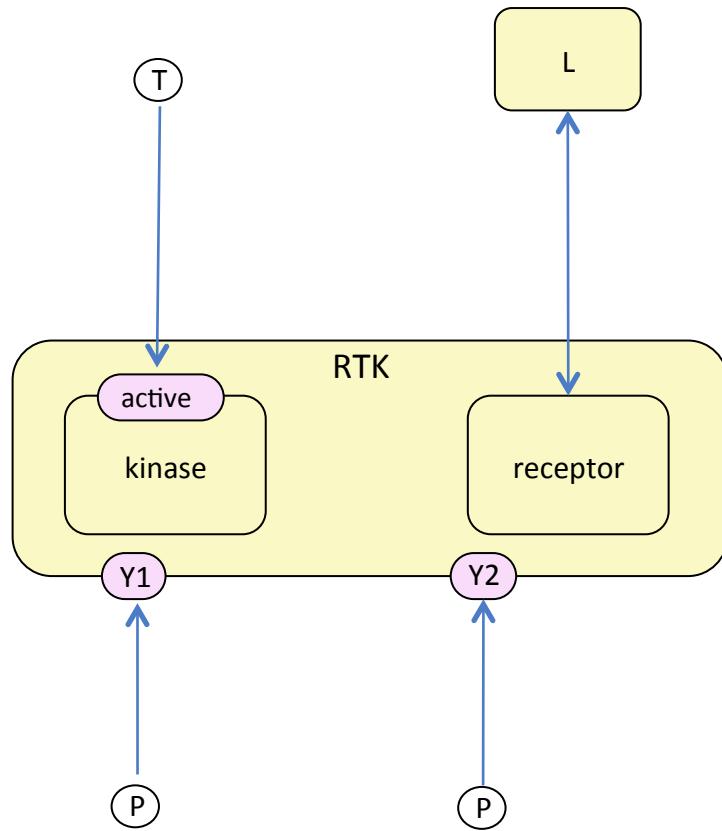
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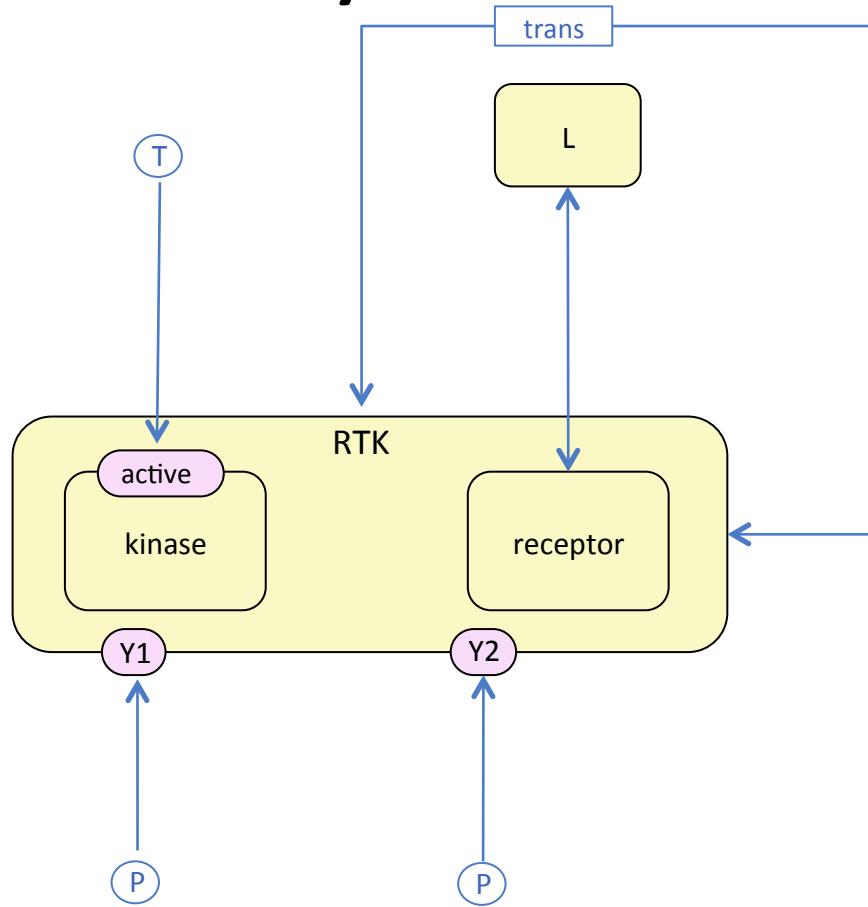
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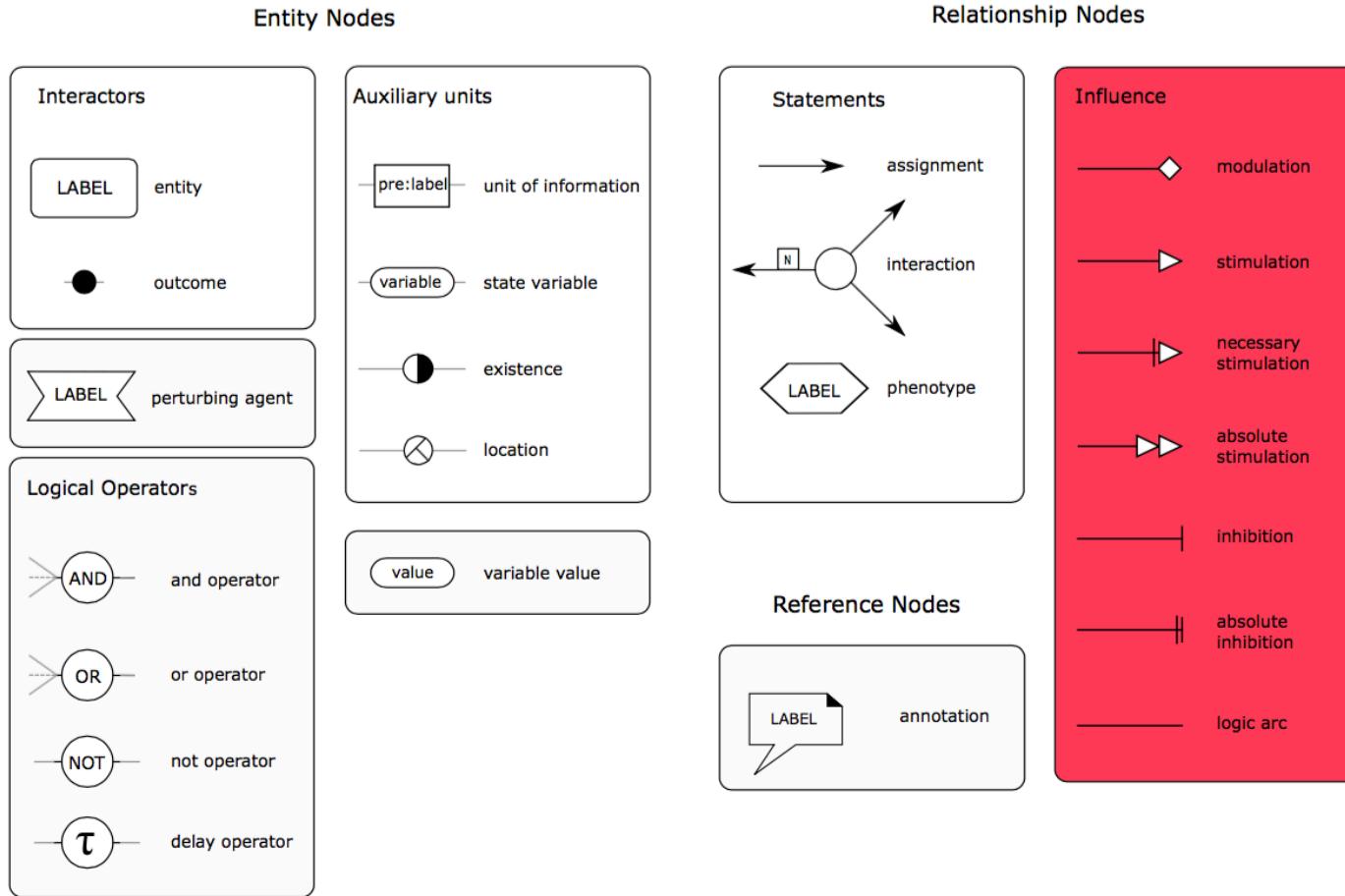
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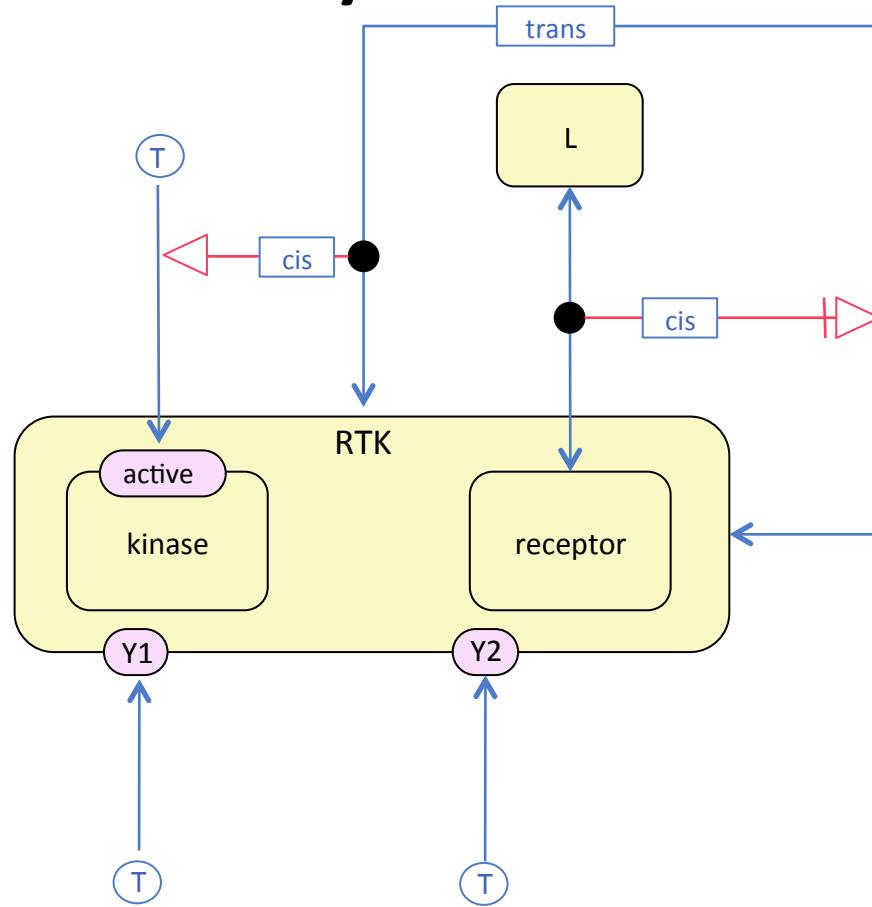
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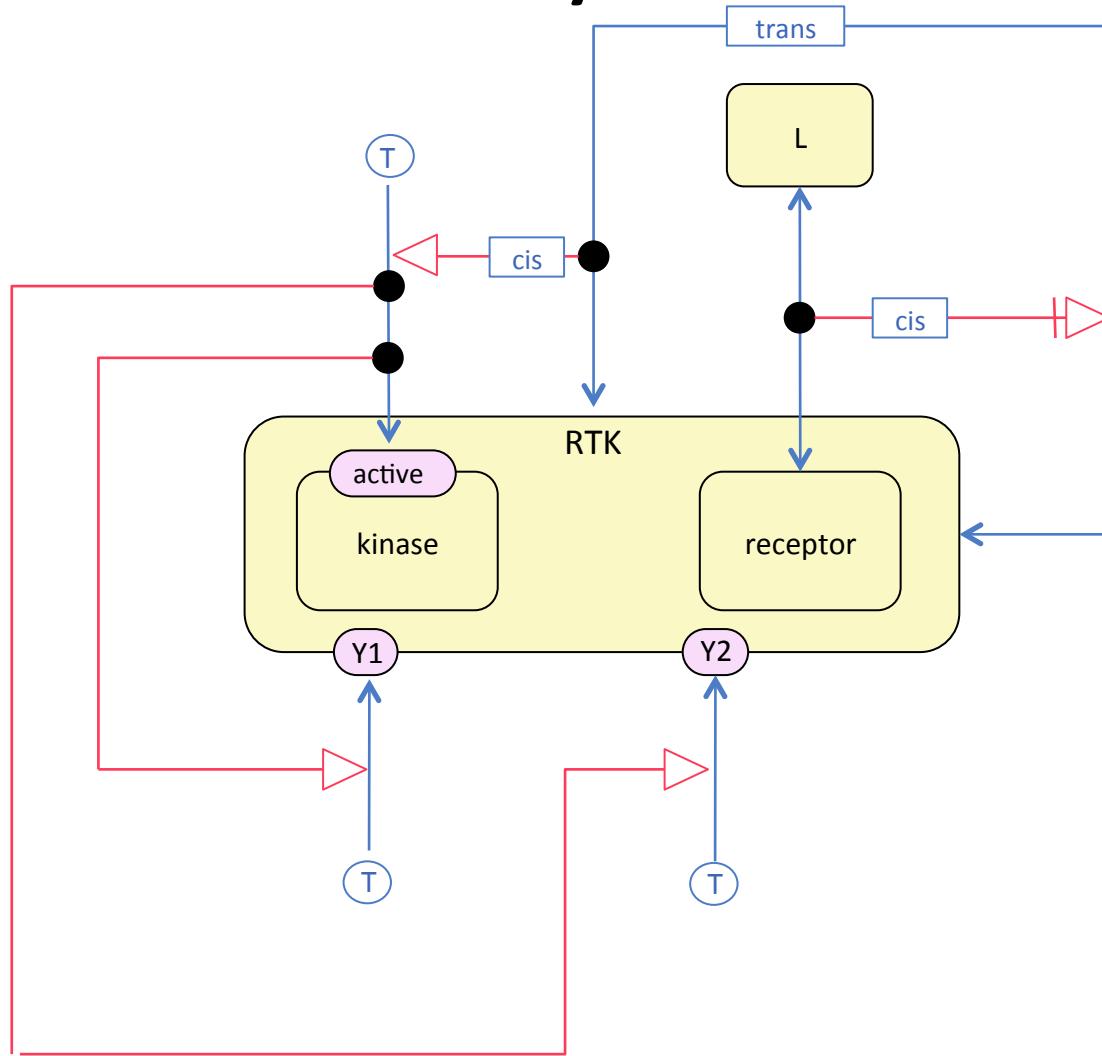
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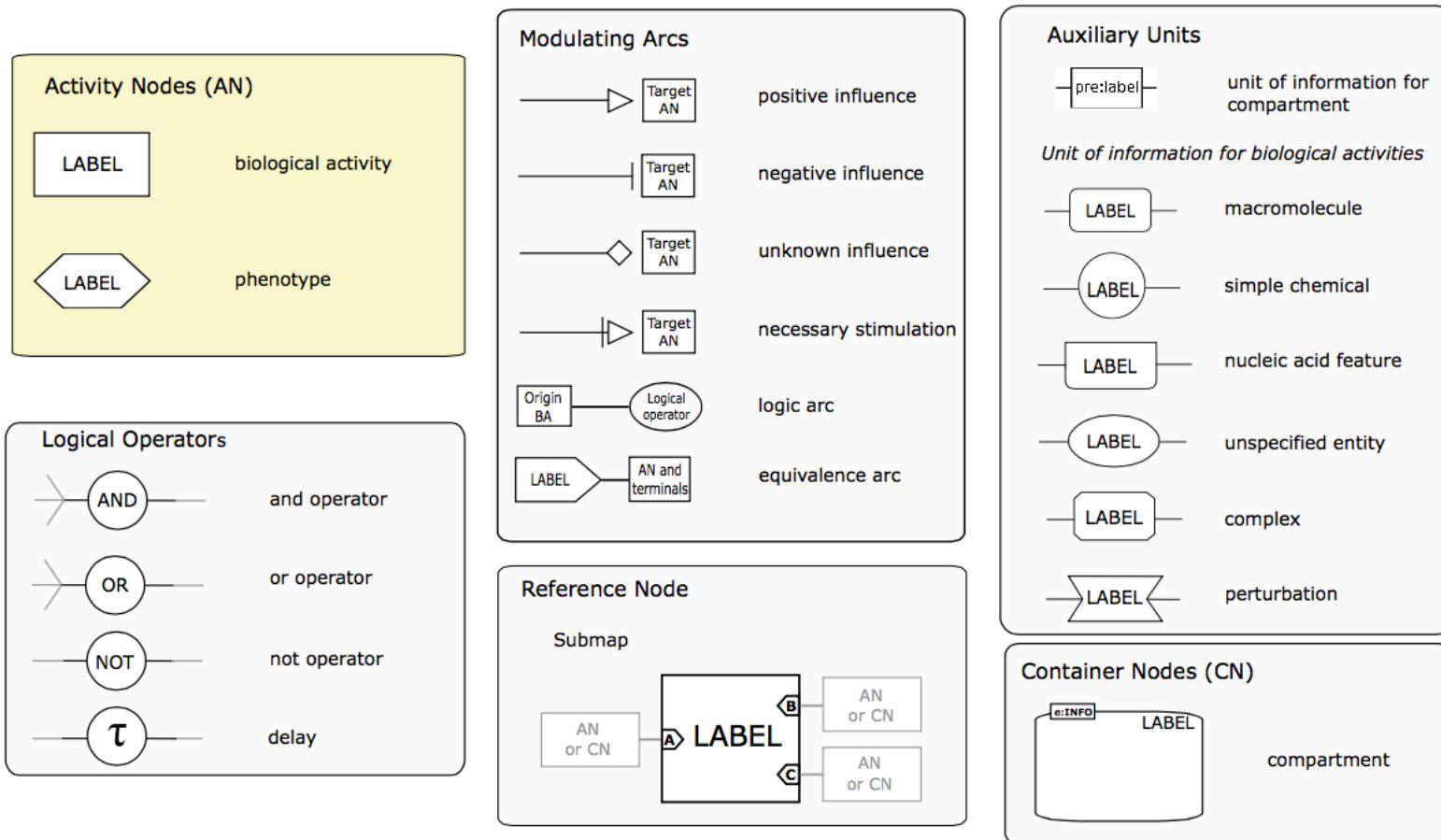
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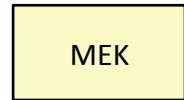
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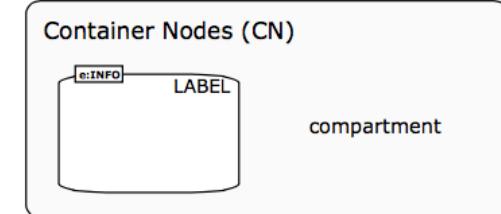
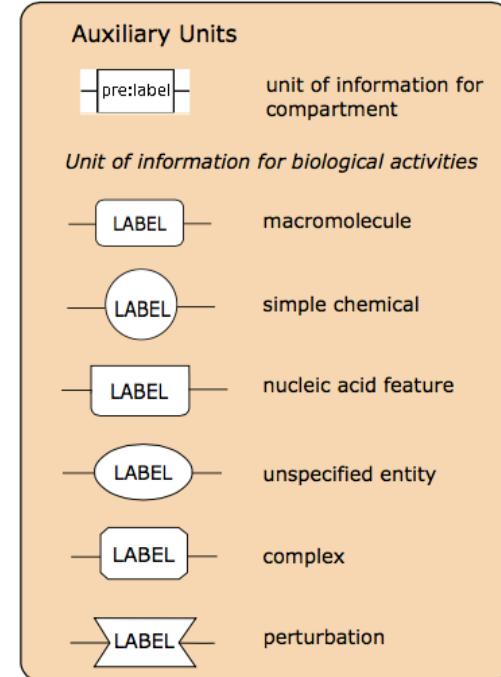
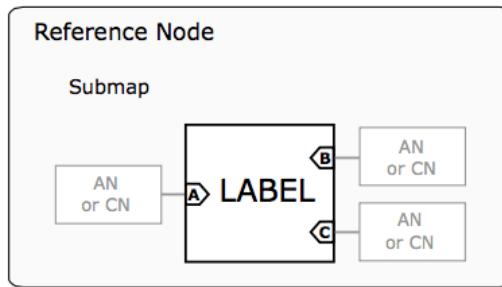
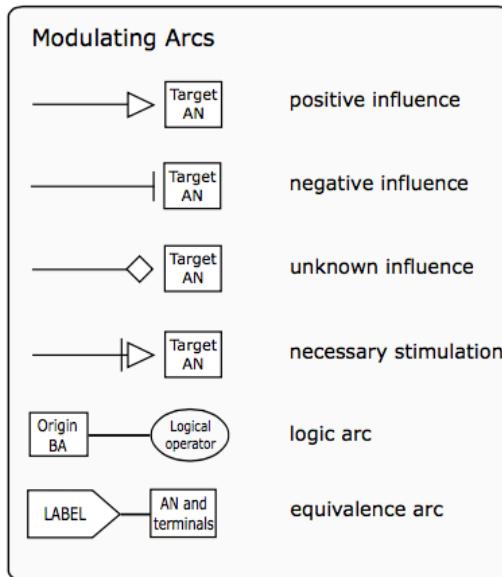
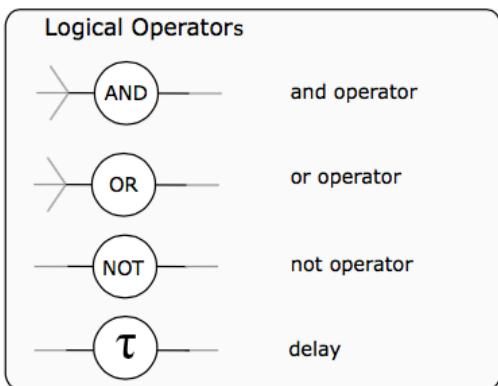
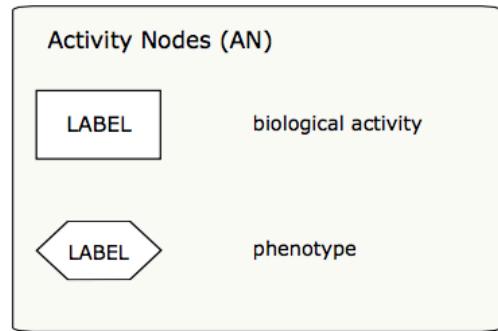
Activity Flow Reference Card



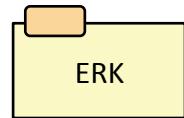
SBGN Activity Flow



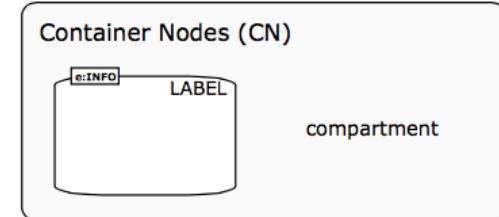
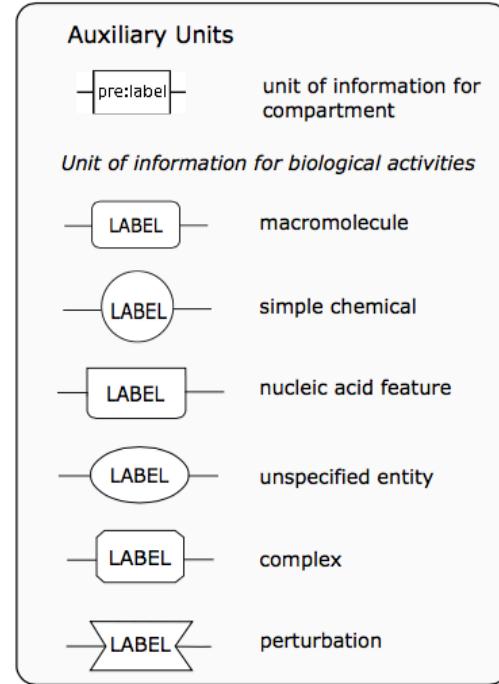
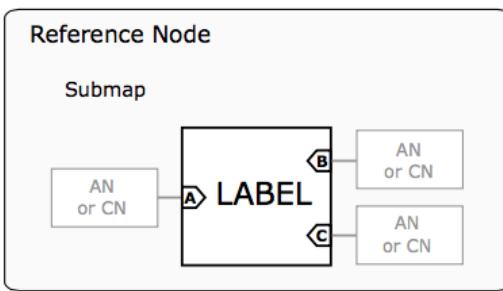
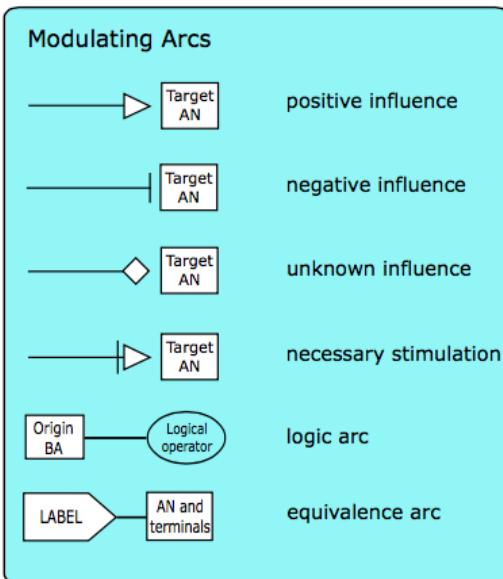
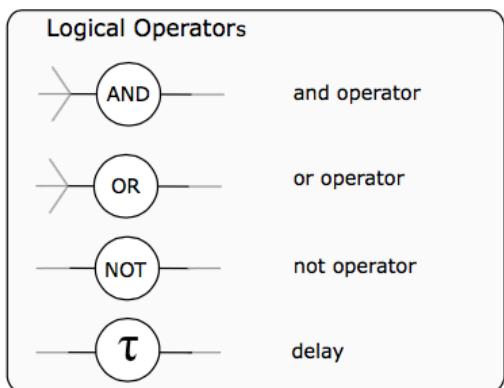
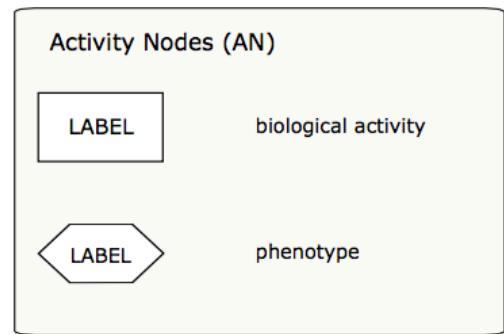
Activity Flow Reference Card



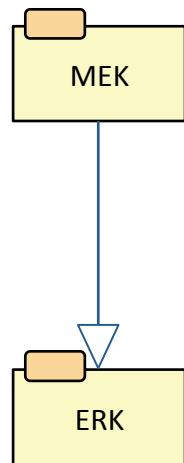
SBGN Activity Flow



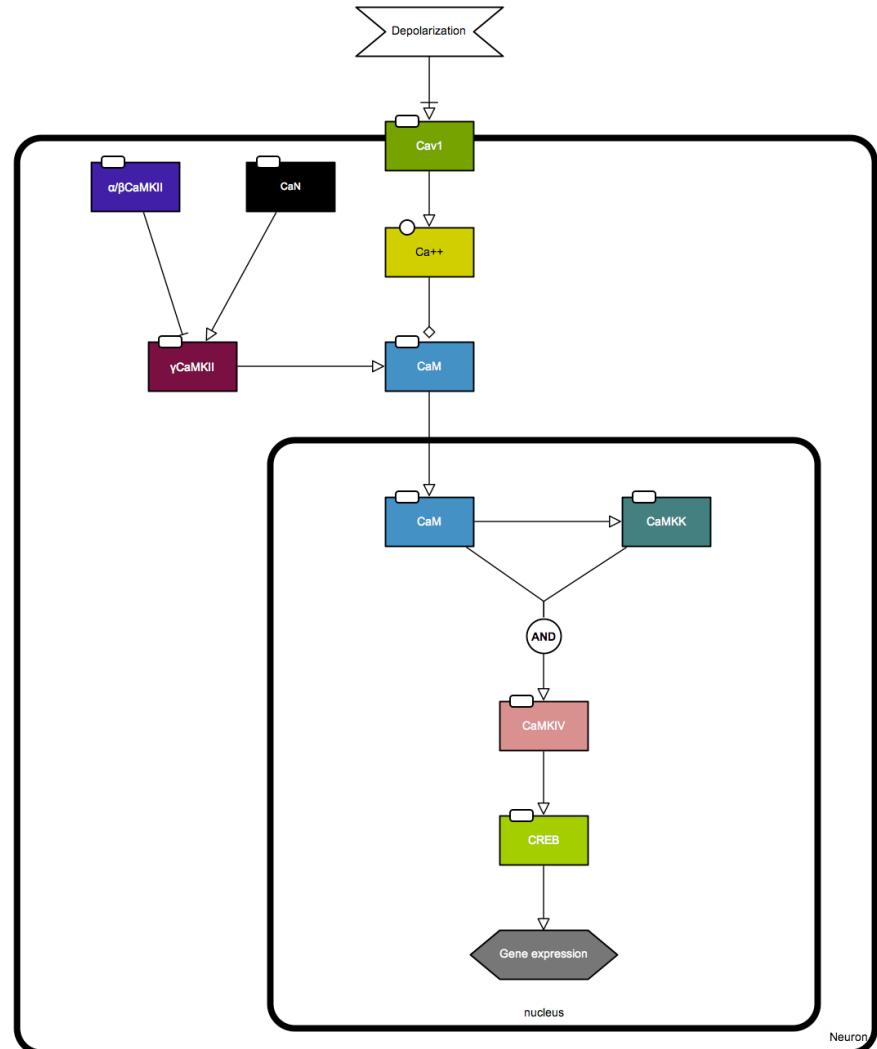
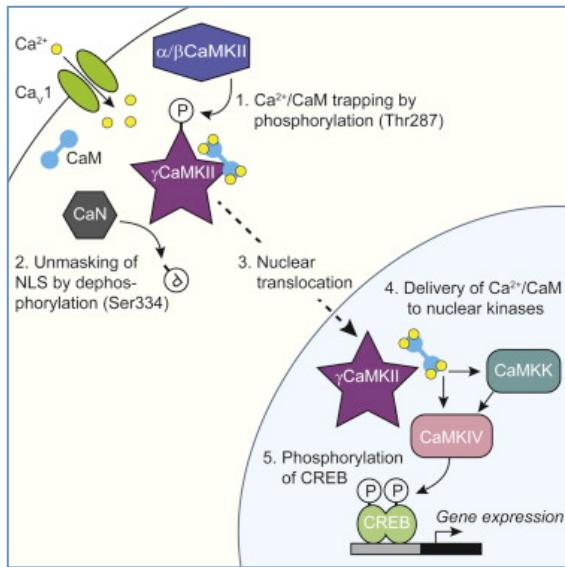
Activity Flow Reference Card



SBGN Activity Flow



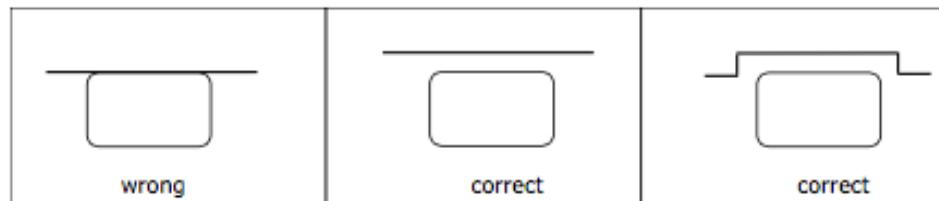
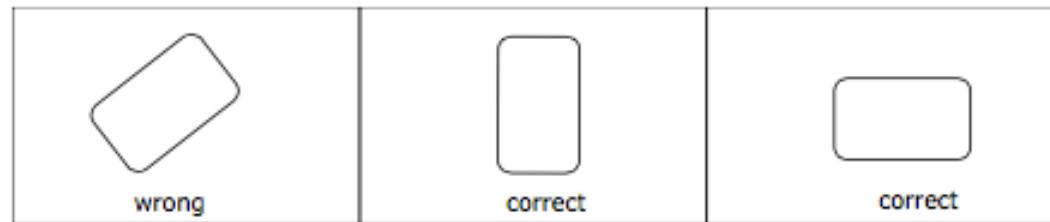
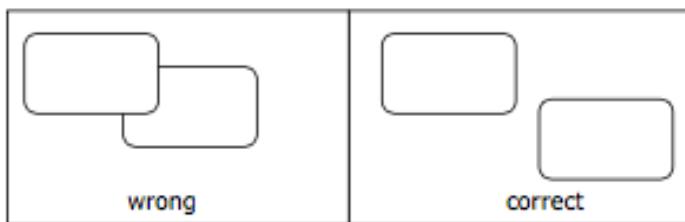
AF Example



SBGN-AF

Semantics and Layout Rules

- All SBGN concepts are mapped to Systems Biology Ontology (SBO) terms.
- Layout rules



Current Status

- SBGN-PD
 - Current release: Level 1 Version 1.3
 - Candidate release: Level 1 Version 2 (end of 2015)
- SBGN-ER
 - Current release: Level 1 Version 2
- SBGN-AF
 - Current release: Level 1 Version 1.2

SOFTWARE SUPPORT

SBGN SOFTWARE

This page summarizes what we know about software support for SBGN languages. This knowledge comes from a variety of sources, and is necessarily incomplete. If your software is not listed below, or if you know of another effort, please post a message to sbgn-discuss@sbgn.org.

Software tool assisting in supporting SBGN

The implementation of SBGN support in software tools may be facilitated by the use of an XML exchange format: [SBGN-ML](#). SBGN-ML can be processed and generated by a standard library: *LibSBGN*. LibSBGN is a [community project](#) and everyone is welcome to participate. For a very brief introduction to LibSBGN, check: [SBGN Software/LibSBGN](#)

Discussions around SBGN-ML and LibSBGN take place on [sbgn-libsbgn-discuss](#)

One can compare the rendering of SBGN-ML by the different software using the [LibSBGN Render Comparison](#) site or [Frank Bergmann's Render Comparison](#) site.

Software providing support for SBGN

The following is a list of software packages known to provide (or have started to develop) support for SBGN notations. As the list grows, we envision more sophisticated way of recording support, but we hope this will be useful nevertheless. The webpages and e-mail addresses (remove spaces) were correct at the time of recording.

- [Arcadia](#) - Contact: alice . villeger @ manchester . ac . uk
- [Athena](#) - Contact: fbergman @ u . washington . edu
- [Biological Connection Markup Language \(BCML\)](#) -

Contact: duccio . cavalieri @ unifi . it

- [Biographer and jSBGN](#) - Contact: biographer @ googlegroups . com
- [BiNoM](#) - Contact: laurence . calzone @ curie . fr

http://www.sbgn.org/SBGN_Software

lists . sourceforge . net

- [BioPAX-SBGN Mapping](#) - Contact: demir @ cbio . mskcc . org
- [BioUML](#) - Contact: fedor @ developmentontheedge . com

SBGN-ML and LibSBGN

BIOINFORMATICS ORIGINAL PAPER

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Systems Biology

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Software support for SBGN maps: SBGN-ML and LibSBGN

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Associate Editor: Trey Ideker

ABSTRACT

Motivation: LibSBGN is a software library for reading, writing and manipulating Systems Biology Graphical Notation (SBGN) maps stored using the recently developed SBGN-ML file format. The library (available in C++ and Java) makes it easy for developers to add SBGN support to their tools, whereas the file format facilitates the exchange of maps between compatible software applications. The library also supports validation of maps, which simplifies the task of ensuring compliance with the detailed SBGN specifications. With this effort we hope to increase the adoption of SBGN in bioinformatics tools, ultimately enabling more researchers to visualize biological knowledge in a precise and unambiguous manner.

Availability and implementation: Milestone 2 was released in December 2011. Source code, example files and binaries are freely available under the terms of either the LGPL v2.1+ or Apache v2.0 open source licenses from <http://libsbgn.sourceforge.net>.

Contact: sbgn-lsbsgn@lists.sourceforge.net

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1 INTRODUCTION

The Systems Biology Graphical Notation (SBGN, Le Novère *et al.*, 2009) facilitates the representation and exchange of complex biological knowledge in a concise and unambiguous manner: as standardized pathway maps. It has been developed and supported by a vibrant community of biologists, biochemists, software developers, bioinformaticians and pathway databases experts.

SBGN is described in detail in the online specifications ([see http://sbgn.org/Documents/Specifications](http://sbgn.org/Documents/Specifications)). Here we summarize its concepts only briefly. SBGN defines three orthogonal visual languages: Process Description (PD), Entity Relationship (ER) and Activity Flow (AF). SBGN maps must follow the visual vocabulary, syntax and layout rules of one of these languages. The choice of language depends on the type of pathway or process being depicted and the amount of available information. The PD language, which originates from Kitano's Process Diagrams (Kitano *et al.*, 2005) and the related CellDesigner tool (Funahashi *et al.*, 2008), is equivalent to a bipartite graph (with a few exceptions) with one type of nodes representing pools of biological entities, and a second type of nodes representing biological processes such as biochemical reactions, transport, binding and degradation. Arcs represent consumption, production or control, and can only connect nodes of differing types. The PD language is very suitable for metabolic pathways, but struggles to concisely depict the combinatorial complexity of certain proteins with many phosphorylation states. The ER language, on the other hand, is inspired by Kohn's Molecular Interaction Maps (Kohn *et al.*, 2006), and describes relations between biomolecules. In ER, two entities can be linked with an interaction arc. The outcome of an interaction (for example, a protein complex), is considered an entity in itself, represented by a black dot, which can engage in further interactions. Thus ER represents dependencies between interactions, or putting it differently, it can represent which interaction is necessary for another one to take place. Interactions are possible between two or more entities, which make ER maps roughly equivalent to a hypergraph in which an arc can connect more than two nodes. ER is more concise than PD when it comes to representing protein modifications and protein interactions, although it is less capable when it comes to presenting biochemical reactions. Finally, the third language in the SBGN family is AF, which

*To whom correspondence should be addressed.

- Community project started in 2009
 - facilitate development of SBGN supporting tools
 - increase interoperability between these tools
- Electronic implementation of SBGN
 - exchange format for SBGN maps: **SBGN-ML**
 - XML schema based
 - express semantics, relationships and geometry
 - software library to interact with SBGN maps: **LibSBGN**
 - object model and API (C++, C#, Java)
 - key features: reading, writing, validation
 - libSBGN python was released recently after the HOARMONY 2015

SBGN-ML and LibSBGN

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

SourceForge project <http://sourceforge.net/projects/libsbgn/>

Mailing list sbgn-libsbgn@lists.sourceforge.net

Tools supporting SBGN-ML

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

Databases supporting SBGN-ML

Path2Models, PANTHER Pathway, Reactome, MetaCrop

Rendering comparison pipeline

http://libsbgn.sourceforge.net/render_comparison/

libSBGN python

<https://github.com/matthiaskoenig/libsbgn-python>

SBGN-ED

BIOINFORMATICS APPLICATIONS NOTE

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Systems biology

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Editing, validating and translating of SBGN maps

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Associate Editor: Trey Ideker

ABSTRACT

Motivation: The recently proposed Systems Biology Graphical Notation (SBGN) provides a standard for the visual representation of biochemical and cellular processes. It aims to support more efficient and accurate communication of biological knowledge between different research communities in the life sciences. However, to increase the use of SBGN, tools for editing, validating and translating SBGN maps are desirable.

Results: We present SBGN-ED, a tool which allows the creation of all three types of SBGN maps from scratch or the editing of existing maps, the validation of these maps for syntactical and semantical correctness, the translation of networks from the KEGG and MetaCrop databases into SBGN and the export of SBGN maps into several file and image formats.

Availability: SBGN-ED is freely available from <http://vanted.ipk-gatersleben.de/addons/sbgn-ed>. The web site contains also tutorials and example files.

Contact: schreibe@ipk-gatersleben.de

Received on March 16, 2010; revised on June 18, 2010; accepted on July 6, 2010

1 INTRODUCTION

The Systems Biology Graphical Notation (SBGN; <http://sbgn.org>) (Le Novère *et al.*, 2009) is an emerging standard for the visual representation of biological networks. This standardization aims to improve information exchange and to support the collaborative creation of large maps based on individual modules. Such unified graphical representation should overcome the current situation in which many different styles of networks are used in biochemical, biological and medical books, articles and online resources. Especially in the growing field of systems biology, where increasingly complex and large networks have to be investigated, SBGN offers a promising approach for creating more intuitive and unambiguous visualizations.

Three different views of biological processes cover different levels of detail:

- (1) *Process Description* (PD), which shows the temporal dependencies of biological interactions in a network in detail;
- (2) *Entity Relationship* (ER), which displays the relationships in which a given entity participates in a network (without consideration of temporal aspects); and
- (3) *Activity Flow* (AF), which shows the flow of information between biological entities in a network in an abstract way.

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Drawing large interaction maps is a time-consuming task. To enhance the usability of SBGN, tool support for creating, editing and validating such maps is required. Currently, several tools support or have started to consider SBGN, for an overview see http://sbgn.org/SBGN_Software.

Here we present SBGN-ED, a Vanted (Junker *et al.*, 2006) add-on for editing, validating and translating of SBGN maps. SBGN-ED contains a unique combination of features from SBGN map creation and editing to syntactic and semantic validation of SBGN maps, to automatic translation of existing non-SBGN networks from KEGG (Kanehisa *et al.*, 2010) and MetaCrop (Grafahrend-Belau *et al.*, 2008) into SBGN, and to the export of SBGN maps in different file and image formats. Furthermore, all methods of the Vanted system for integration and network-based analysis of high-throughput data, data visualization and network layout as well as constraint-based model simulation are fully accessible to the SBGN maps. The Vanted system and the SBGN-ED add-on form a comprehensive platform for SBGN-supported analysis and visualization of biological networks.

2 METHODS

SBGN-ED is an add-on for Vanted (Junker *et al.*, 2006). Vanted is an open source software that offers the loading and editing of networks, allows the integration of different *omics data and provides a variety of functions for data mapping and processing, statistical analysis and visualization. The main functions of SBGN-ED are:

- (1) SBGN map creation and editing;
- (2) SBGN map validation; and
- (3) the translation of networks into SBGN.

These SBGN maps can then be exported into different file and image formats such as GML, GraphML, PDF, SVG, PNG, PNG/HTML image maps and JPG. The following subsections describe the methodology of important functions such as validation and translation.

2.1 Editing

SBGN maps can be created from scratch or loaded from files. The relevant functionality for editing such maps is similar to well-established editing methods for networks (see typical network analysis and graph drawing tools) and allows the addition, removal and alteration of SBGN symbols (nodes and edges), the alteration of the size, color, label and other attributes of map elements, and the alteration of the layout of the map manually or automatically.

Following the SBGN specification, SBGN-ED supports all SBGN symbols (nodes and edges) as well as special connectors defined within glyphs (e.g. ports sticking out of process nodes). These connectors are dynamically adapted during the drawing of a map according to user interaction. For each SBGN language (PD, ER and AF), a side panel contains

- editing, validating and translating of SBGN maps
- add-on for VANTED
- supports all three SBGN languages
- supports SBGN-ML
- <http://www.sbgn-ed.org>

SBGN-ED

SBGN-ED

Editing, Translating and
Validating of SBGN Maps

Overview

Download & Installation

Tutorials

Example Files

Copyright & Contact

Overview

The Systems Biology Graphical Notation (SBGN, <http://sbgn.org>) is an emerging standard for graphical representations of biochemical and cellular processes studied in systems biology. This standardisation helps to communicate biological knowledge more efficient and accurate between different research communities in the life sciences. However, to support SBGN, tools for editing, validating and translating of SBGN maps are necessary.

We present SBGN-ED, a VANTED add-on which allows to create and edit all three types of SBGN maps, that is Process Description, Entity Relationship and Activity Flow, to validate these maps according to the SBGN [specifications](#), to translate maps from the KEGG pathway database into SBGN, and to export SBGN maps into several file and image formats.

The **VANTED** system (**V**isualisation and **A**nalysis of **N**eutral **E**xperimental **D**ata) is an open source software that offers the possibility to load and edit graphs, which may represent biological pathways or functional hierarchies. It allows to integrate different *omics data into the functional context and provides a variety of functions for data mapping and processing, statistical analysis, and visualisation. With the VANTED Add-on interface it is easily possible to extend the functionality of the software.

News

31/08/2015 - SBGN-ED 1.5.1 released

- compatible with [VANTED 2.5](#)
- bug fixes

24/10/2013 - SBGN-ED 1.5 released

- SBGN Process Description (PD) to SBGN Activity Flow (AF) translation added
- bug fixes

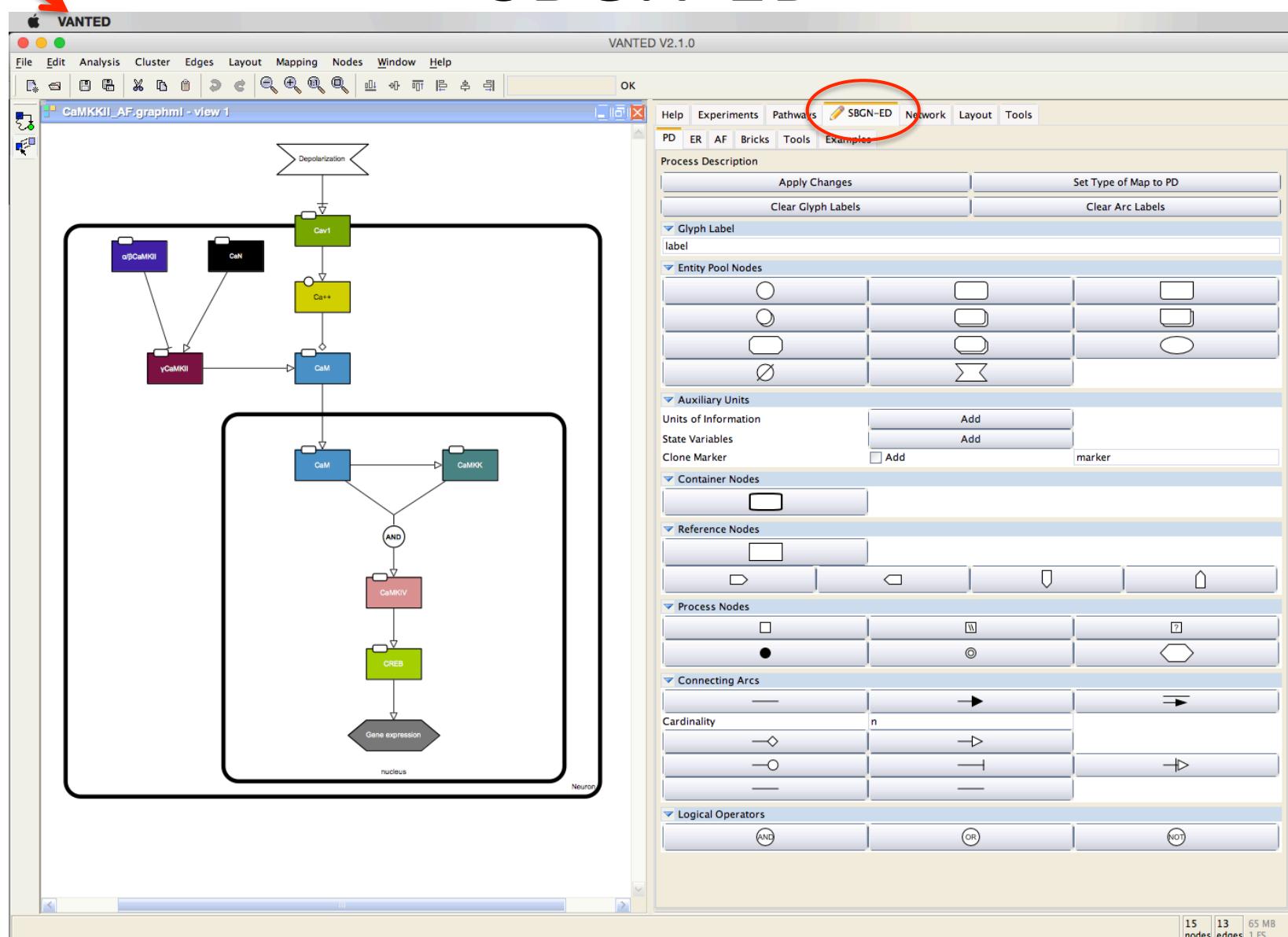
16/08/2013 - SBGN-ED 1.4 released

- KEGG to SBGN translation with Constraint Layout added
- [SBGN bricks](#) added
- simple SBML to SBGN translation added
- bug fixes

07/08/2012 - SBGN-ED 1.3 released

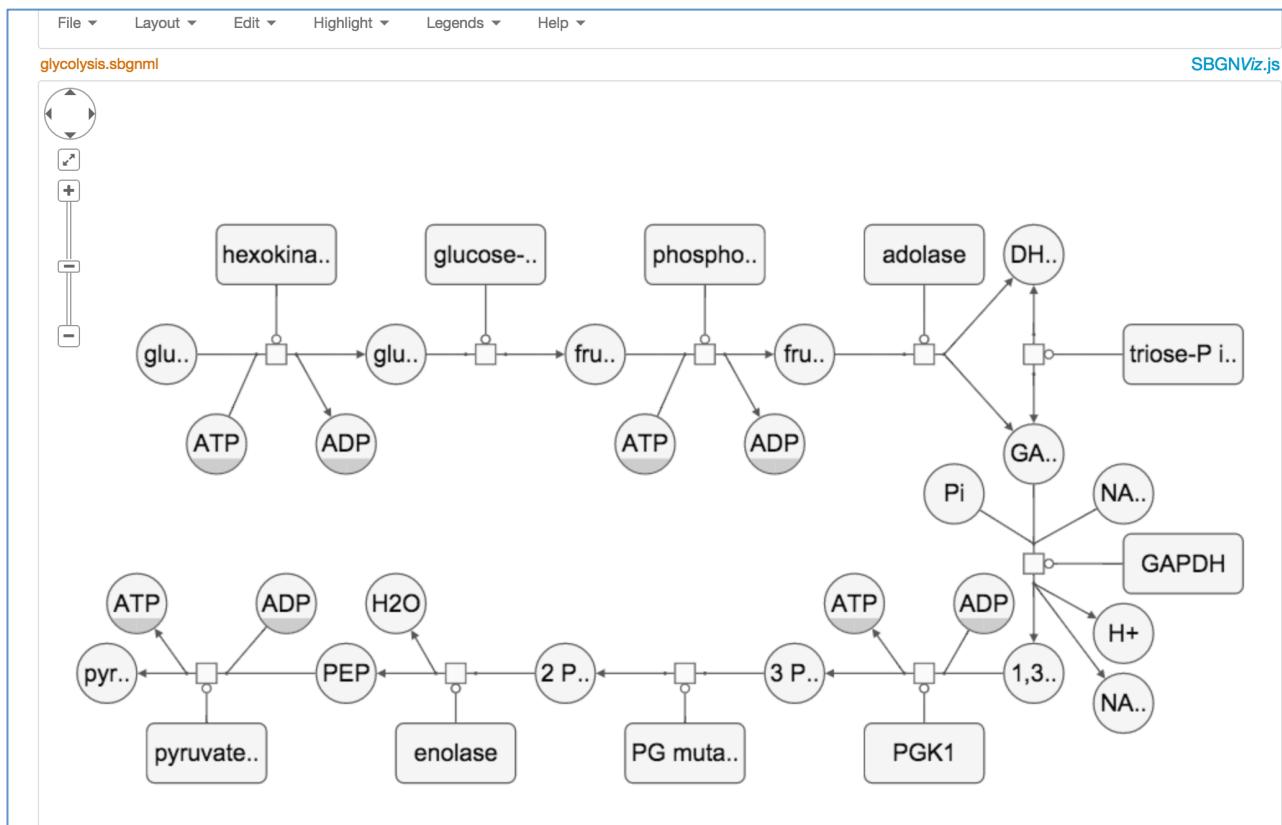
- compatible with [VANTED 2.1.0](#)
- bug fixes

SBGN-ED



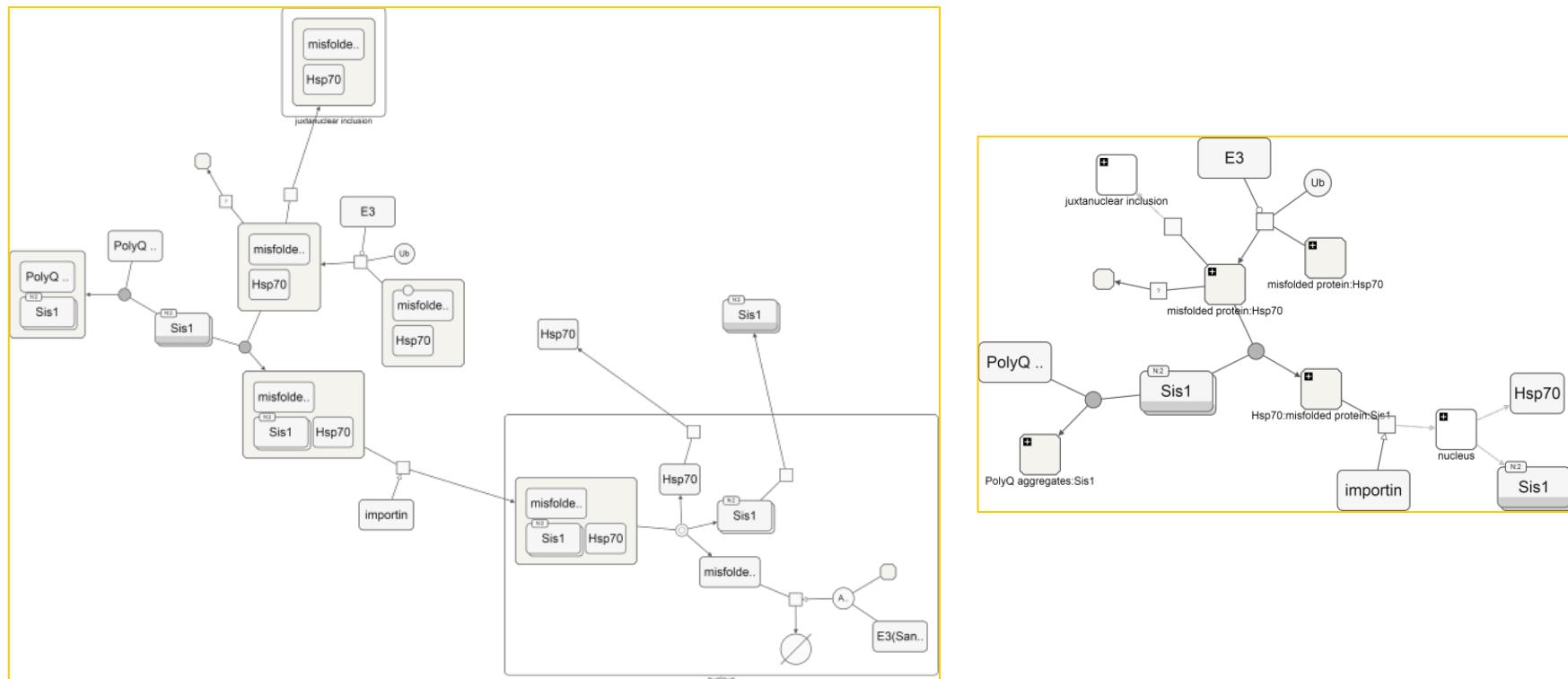
SBGNViz: a web based SBGN viewer

- Read/write SBGN-ML, display in SBGN-PD
- Full support for compound structures including auto-layout
- Save as static images
- Code URL: <https://github.com/PathwayCommons/sbgnviz-js>



SBGNViz: a web based SBGN viewer

- Complexity management operations to show/hide selected and collapse/expand compound structures



What's next?

- Continue to support the community to incorporate SBGN functionality.
 - Level 2 specification - easier support of a diverse community.
 - Community support – SBOL, Gene Ontology, etc.
 - Software support
 - Community outreach
 - Funding

Acknowledgements

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