

# SBGN-AF UPDATE

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# Road Map of SBGN-AF

- Level 1 Version 1.0 – released in Sept. 2009.
- Level 1 Version 1.2
  - draft will be available after COMBINE for feedback
  - release at the end of October

# Activity nodes



Biological activity



Phenotype

# Auxiliary unit

**A**



**B**



**C**



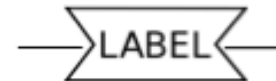
**D**



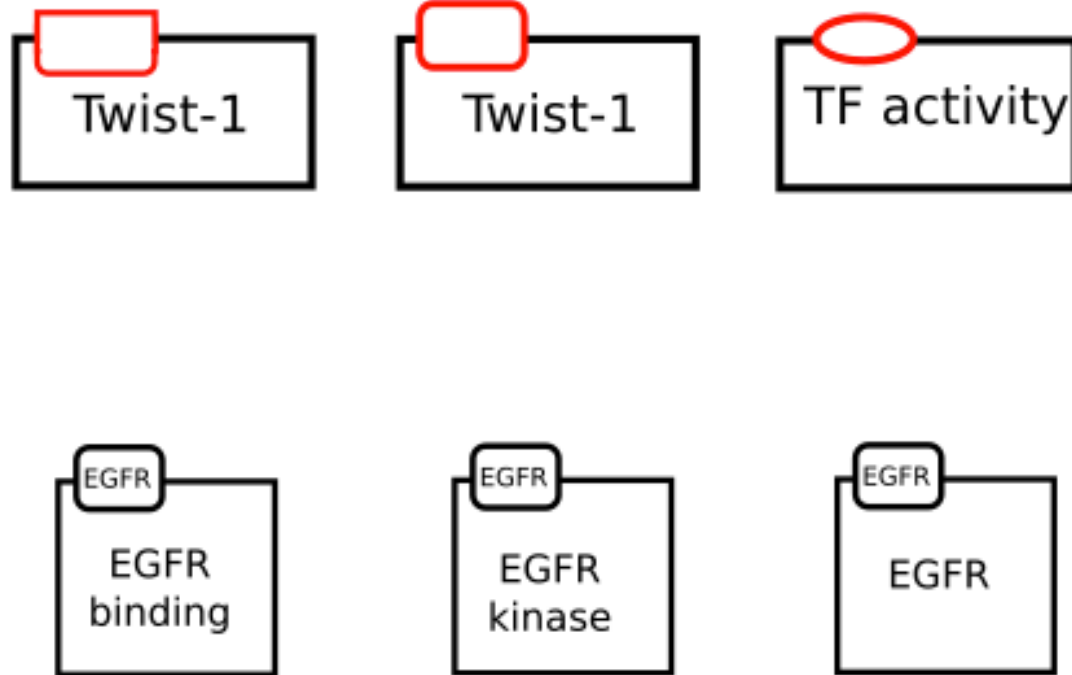
**E**



**F**



# Auxiliary unit



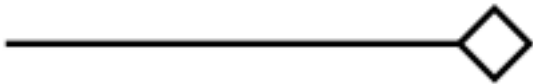
# Modulation arcs



Positive influence



Negative influence



Unknown influence

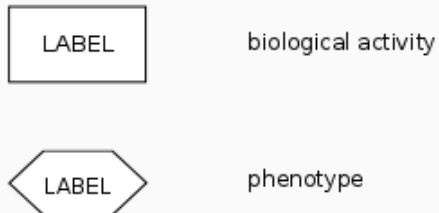


Necessary stimulation

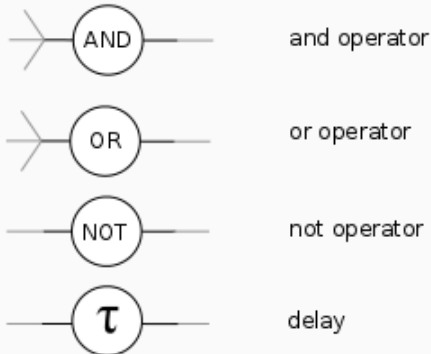
# SBGN AF L1 reference card

SYSTEMS BIOLOGY GRAPHICAL NOTATION ACTIVITY FLOW DIAGRAM REFERENCE CARD

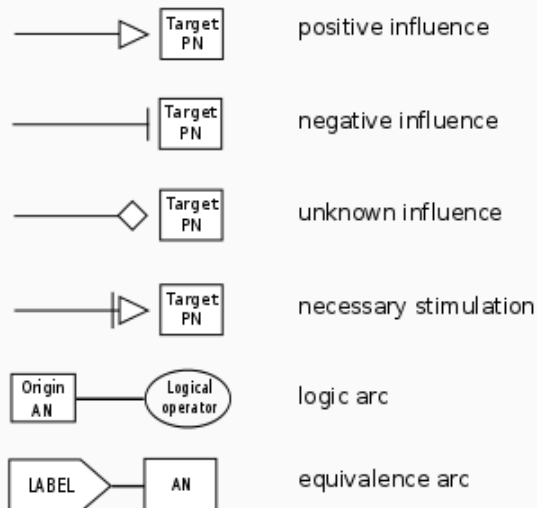
## Activity Nodes



## Logical Operators



## Modulating Arcs

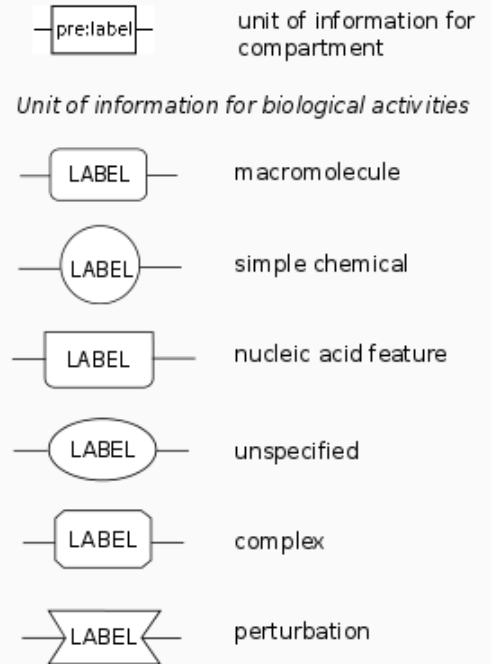


## Reference Node

### Submap



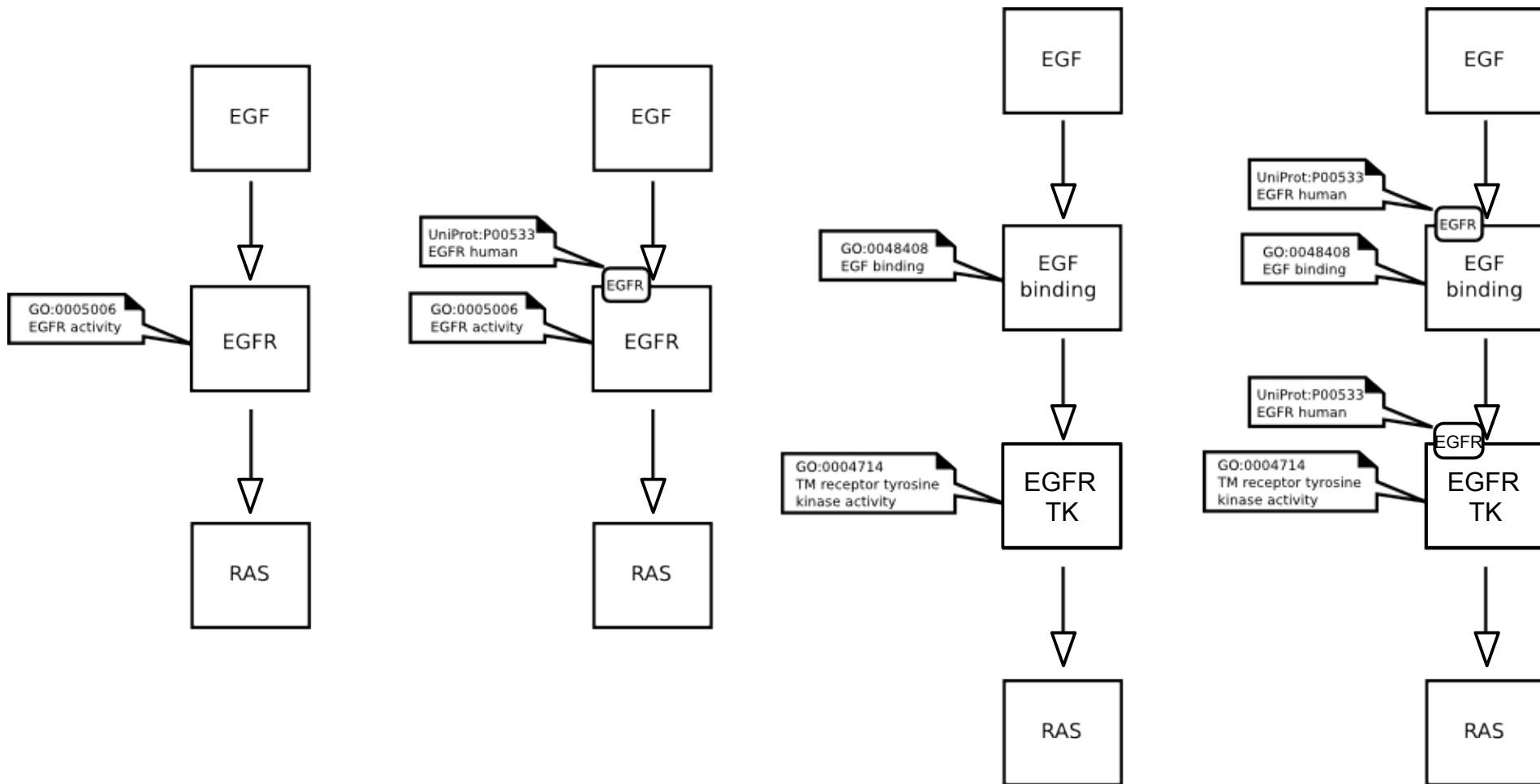
## Auxiliary Units



## Container Nodes

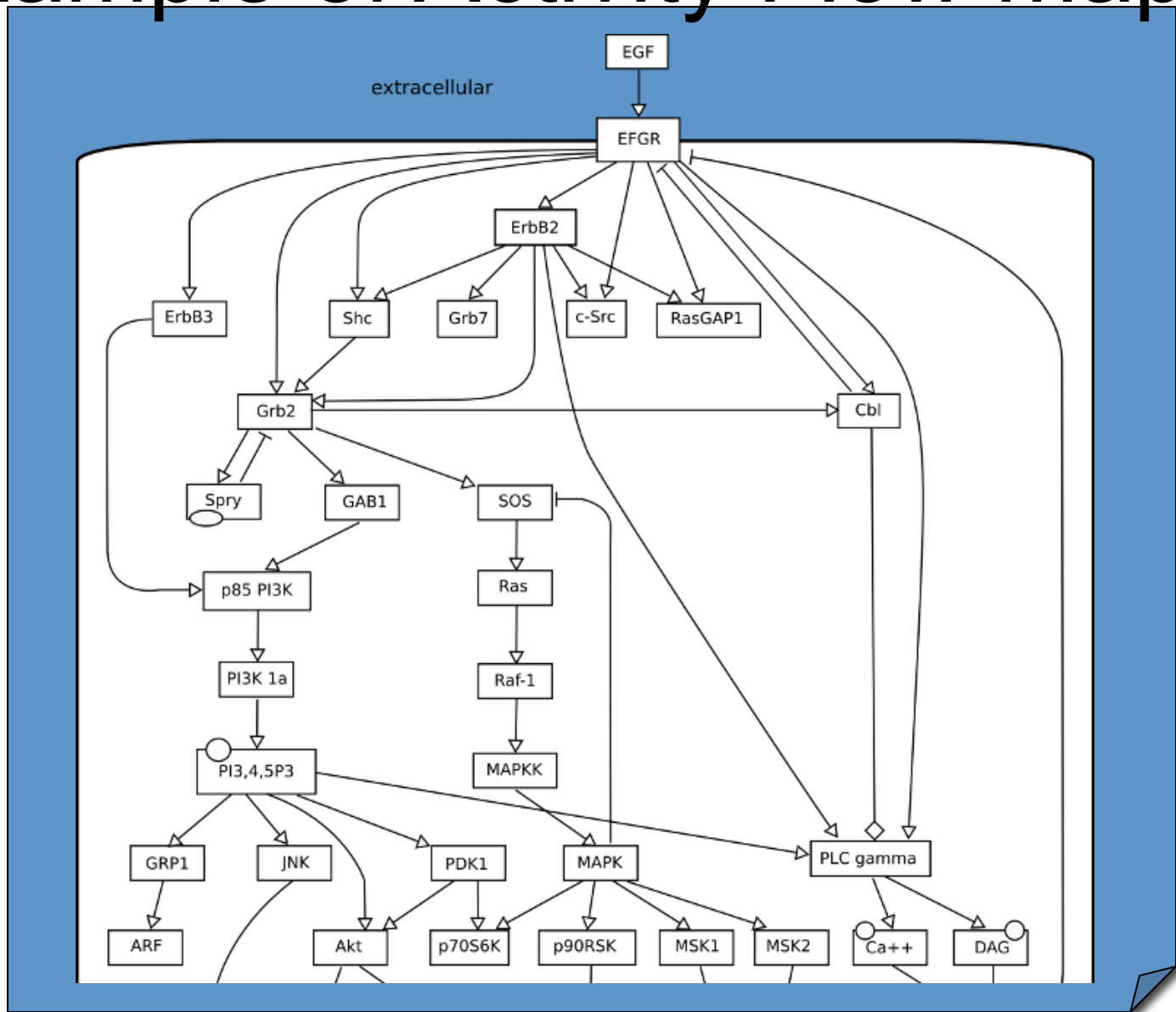


# SBGN AF - multiple ways to do it



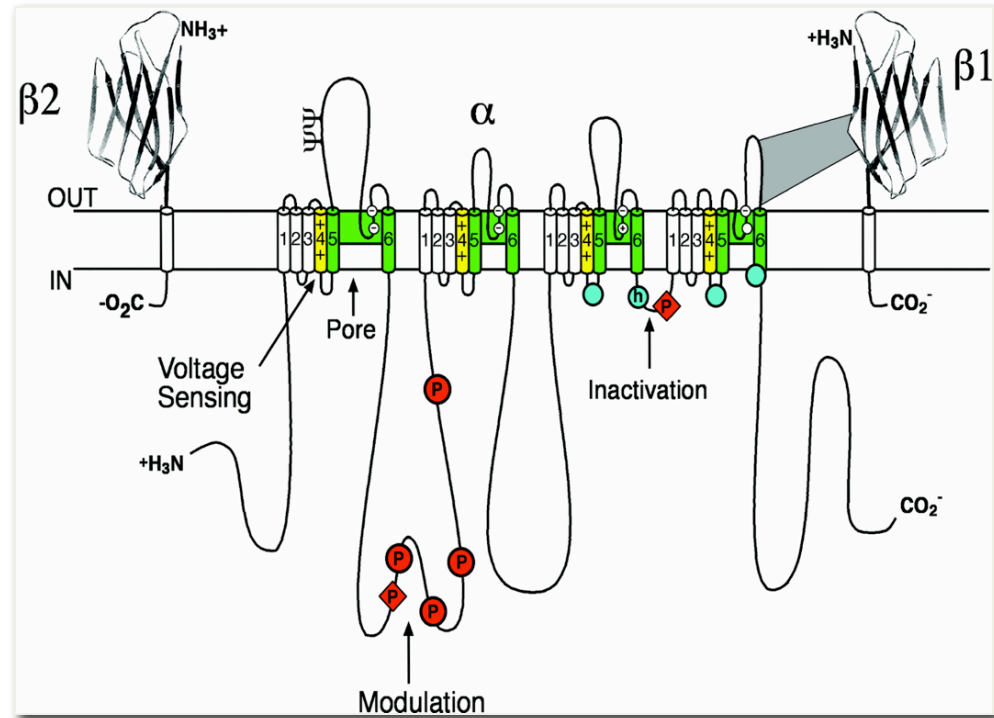
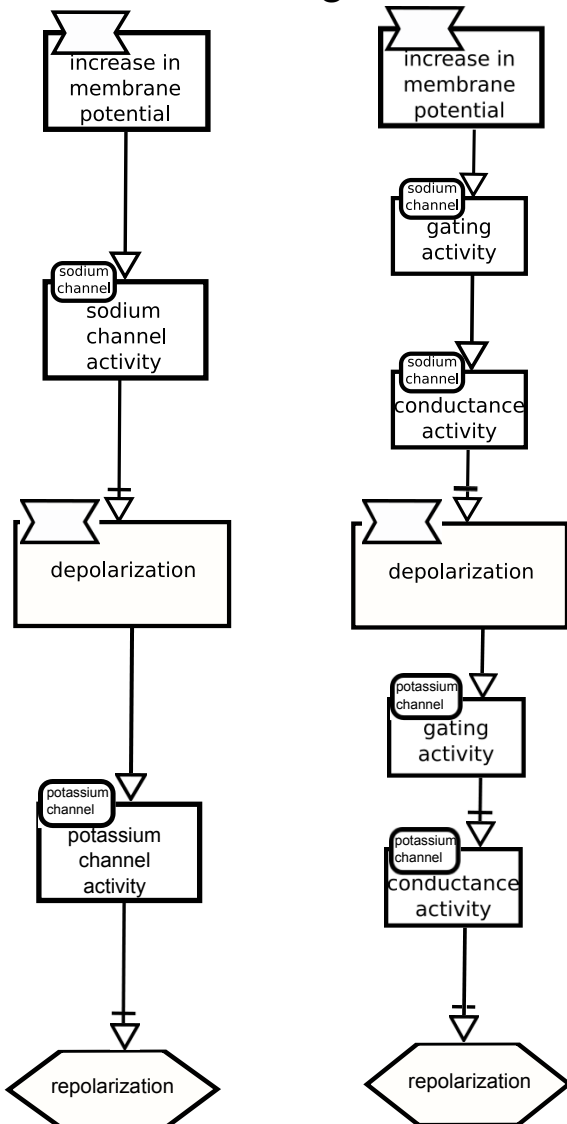


# Example of Activity Flow map

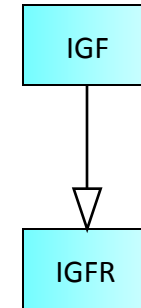
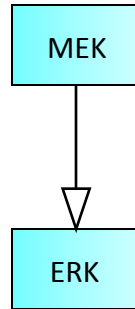


# Example of AF Map

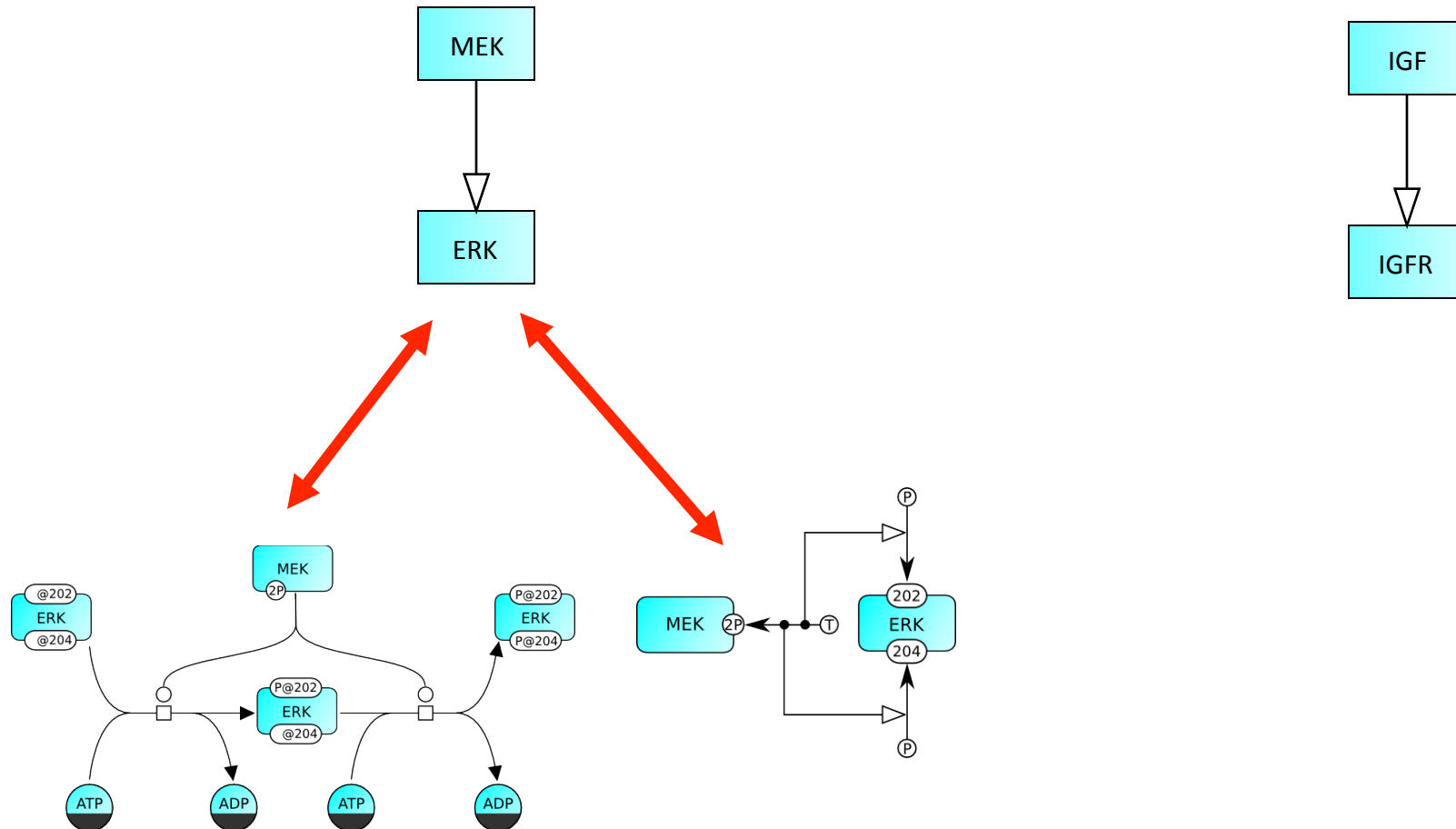
## ■ Gating mechanism of voltage-dependent sodium channel



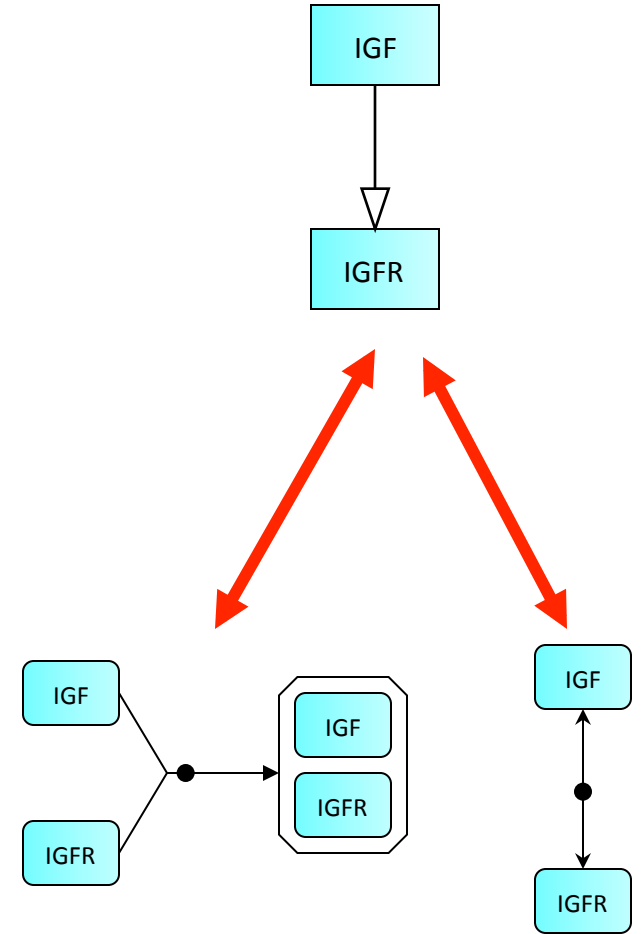
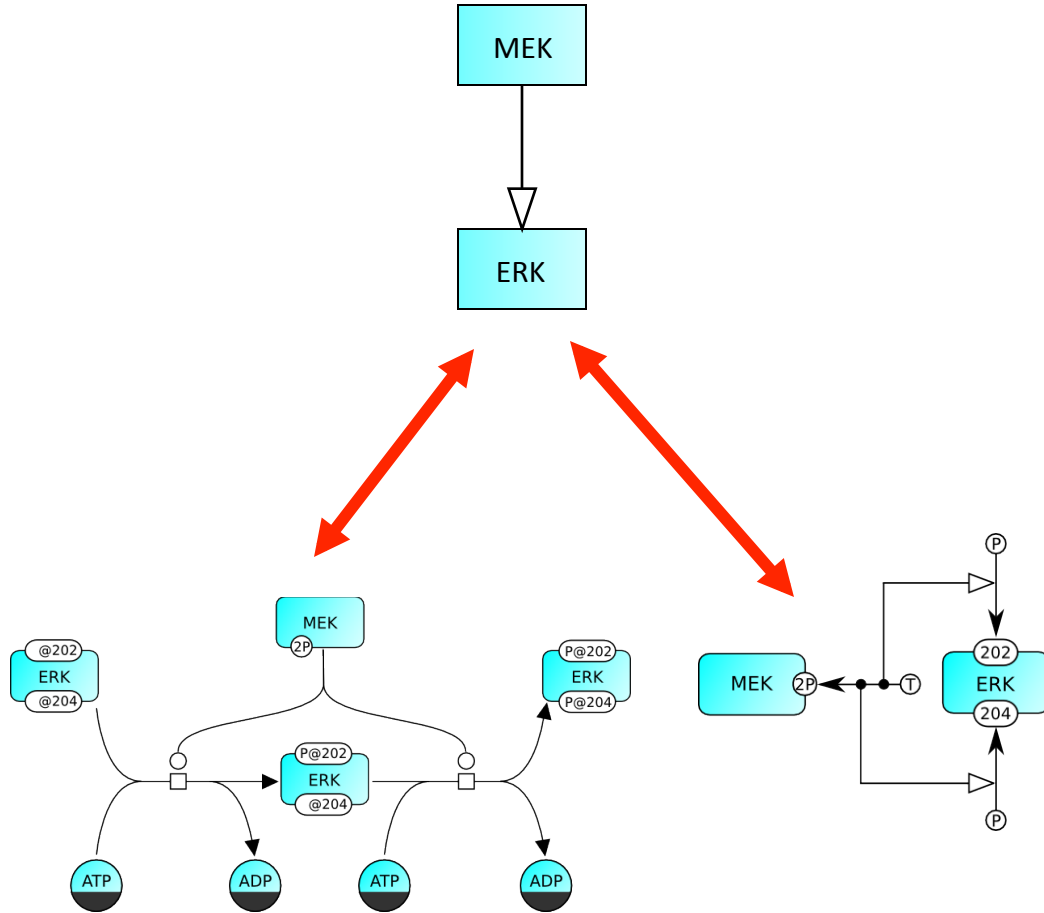
# Activity Flow map is ambiguous



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# LEGO PROJECT

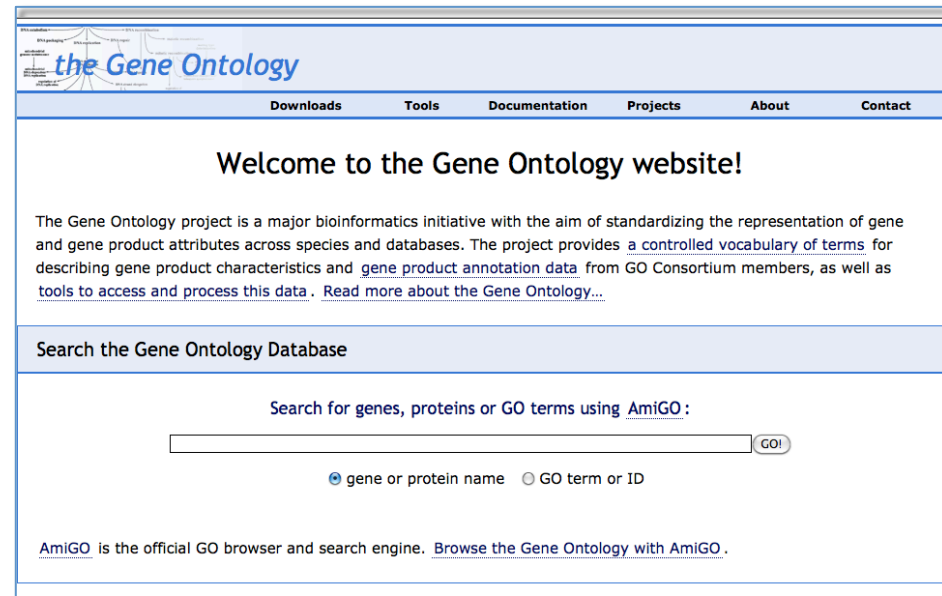
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# What is LEGO Project?

- LEGO is a new development under the Gene Ontology project.
- It is an extension of the existing GO by capturing relationships among various GO terms during the curation of genes.
- LEGO will enable curators to use the GO to express rich biological statements from the literature
  - Maximize biological knowledge captured by curator
  - Represent complex biology in an accurate, computable manner
  - Prevent
    - “kludges” that use existing terms misleadingly or inconsistently
    - Combinatorial explosion of GO terms

# Gene Ontology

- The first ontology that was designed as a formal representation of biological knowledge
- Three knowledge domains:
  - molecular function
  - biological process
  - cellular component.



EGFR (MGI:95294)

Molecular function: GO:0005006: epidermal growth factor-activated receptor activity

Biological process: GO:0007173: epidermal growth factor receptor signaling pathway

Cellular component: GO:0016021 integral component of membrane

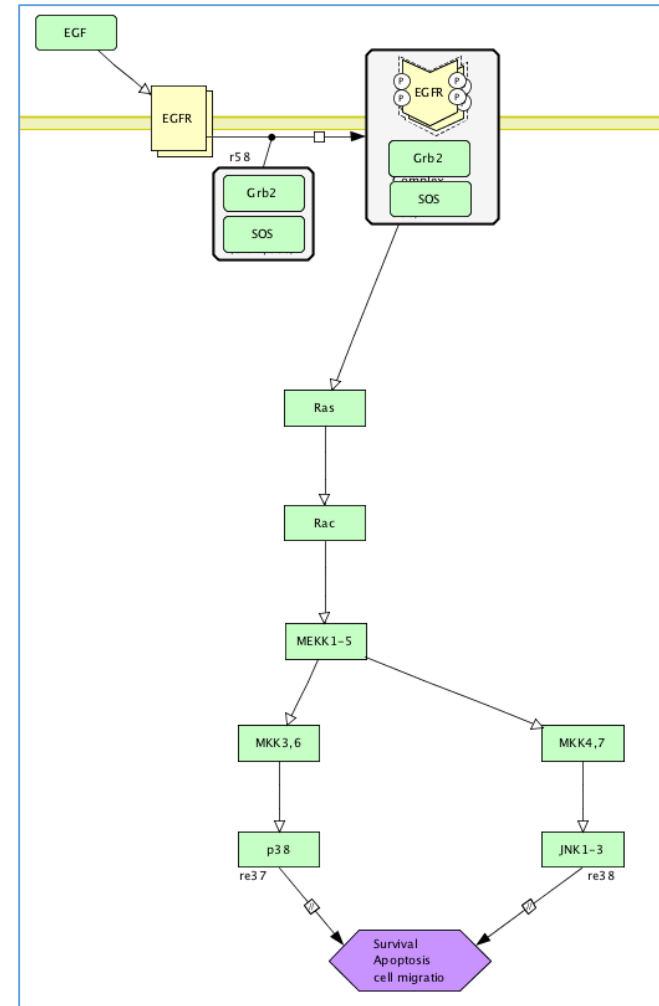
Ashburner, M. et al. (2000) Gene ontology: tool for the unification of biology. The Gene Ontology Consortium. *Nat Genet.* **25**: p. 25-9.

The Gene Ontology Consortium (2012) The Gene Ontology: enhancements for 2011. *Nucleic Acids Res.* 40:D559



# EGFR signaling

- GO annotation is gene-centric.
- The current ontology is not able to capture the relationship of GO terms between two different entities.



# LEGO is an *extension* of GO

- Currently, GPs have separate MF, CC, BP annotations
  - In LEGO, a particular GP executes a particular MF in a particular CC as part of\* a particular BP
  - LEGO is backwards compatible with current annotations
    - Current annotations are incomplete
      - E.g. an MF annotation states that a particular GP executes a particular MF in some CC as part of some BP

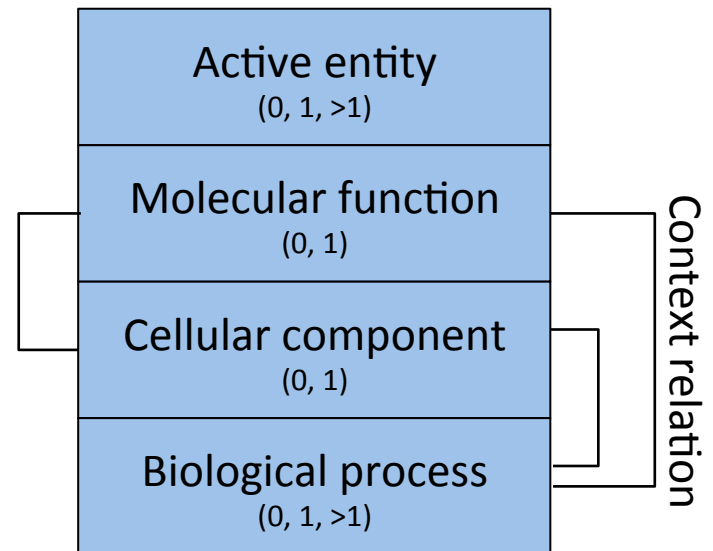
# LEGO formalism

Annoton – the annotation unit in LEGO



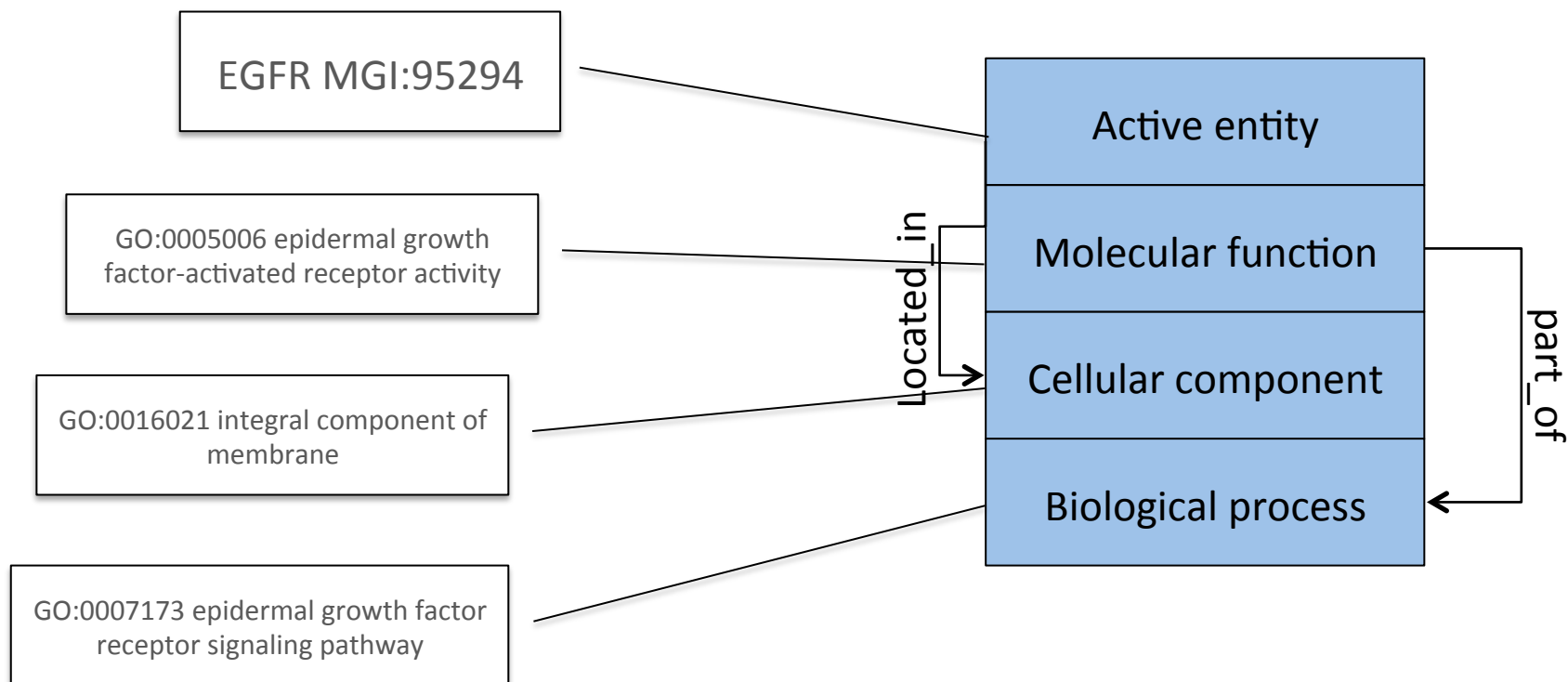
# Molecular Activity

- A molecular activity is defined as the molecular function that an entity is capable of performing, via a particular biochemical mechanism, in a specific cellular location, as part of a biological process.



# Molecular Activity

## -EGFR

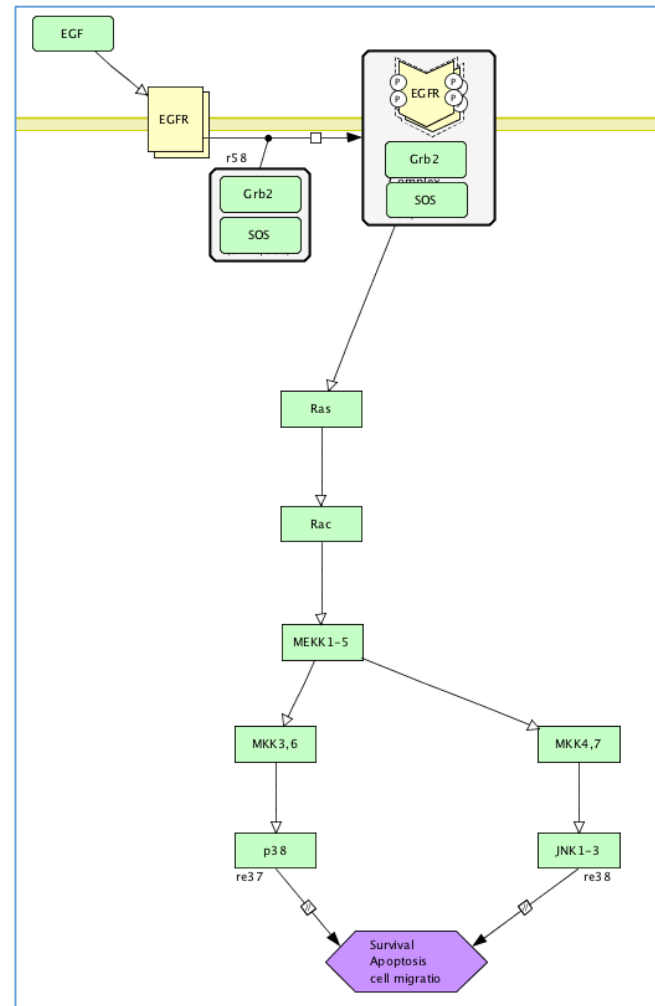


# Molecular Activity

## -Rasa1

MGI:97860

<input type="checkbox"/>	Rasa1	RAS p21 protein activator 1	protein binding		MGI	Mus musculus	IPI
<input type="checkbox"/>	Rasa1	RAS p21 protein activator 1	protein binding		MGI	Mus musculus	IPI
<input type="checkbox"/>	Rasa1	RAS p21 protein activator 1	Ras GTPase activator activity		MGI	Mus musculus	IBA
<input type="checkbox"/>	Rasa1	RAS p21 protein activator 1	positive regulation of Ras GTPase activity		MGI	Mus musculus	IBA
<input type="checkbox"/>	Rasa1	RAS p21 protein activator 1	negative regulation of Ras protein signal transduction		MGI	Mus musculus	IBA
<input type="checkbox"/>	Rasa1	RAS p21 protein activator 1	plasma membrane	part_of bone marrow part_of macrophage	MGI	Mus musculus	IDA
<input type="checkbox"/>	Rasa1	RAS p21 protein activator 1	intrinsic component of the cytoplasmic side of the plasma membrane		MGI	Mus musculus	IBA
<input type="checkbox"/>	Rasa1	RAS p21 protein activator 1	cytoplasm		MGI	Mus musculus	IBA

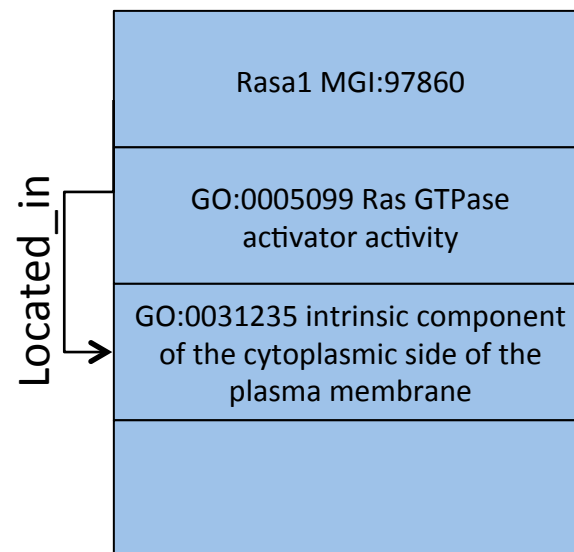


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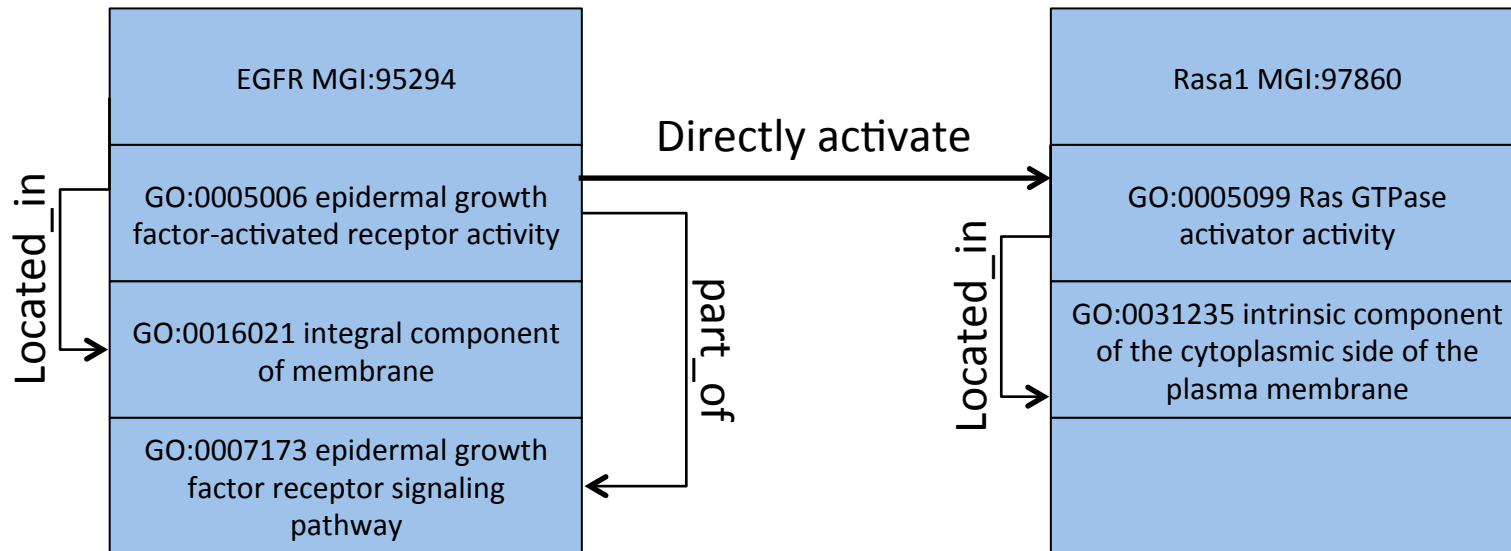


# Effect Relation

- The *effect relation* describes the effects exerted by one *molecular activity* unit to the other.
  - Directly activate
  - Directly inhibit
  - Positively influence
  - Negatively influence
  - Regulate
  - Upstream



# LEGO Model

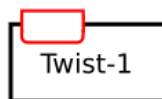


Epidermal growth factor-activated receptor activity from mouse **EGFR**, which is an integral component of membrane and is involved in epidermal growth factor receptor signaling pathway, directly activates the Ras GTPase activator activity of mouse **Rasa1** that is located in the intrinsic component of the cytoplasmic side of the plasma membrane.

# SBGN-AF can be used as graphical representations of LEGO Models

## SBGN

Unit of information



Biological activity



Compartment



Submap



Phenotype (when MF=0)



## LEGO

Active entity

Molecular function

Cellular component

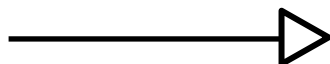
Biological process

Context relation

# Representing LEGO Model in SBGN-AF (cont.)

## SBGN

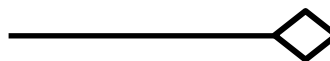
Positive influence



Negative influence



Unknown influence



## LEGO

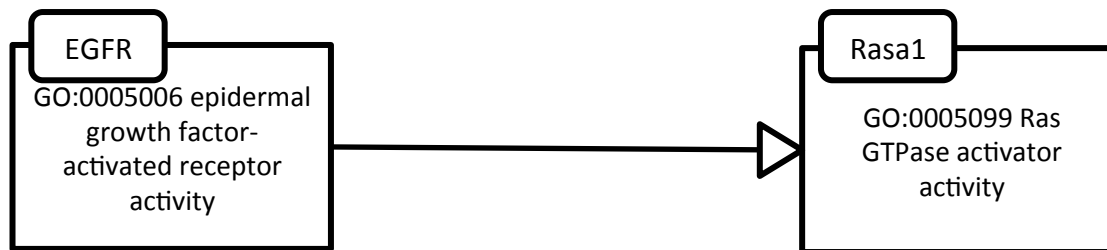
Directly activate  
Positively influence

Directly inhibit  
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Regulate  
Upstream

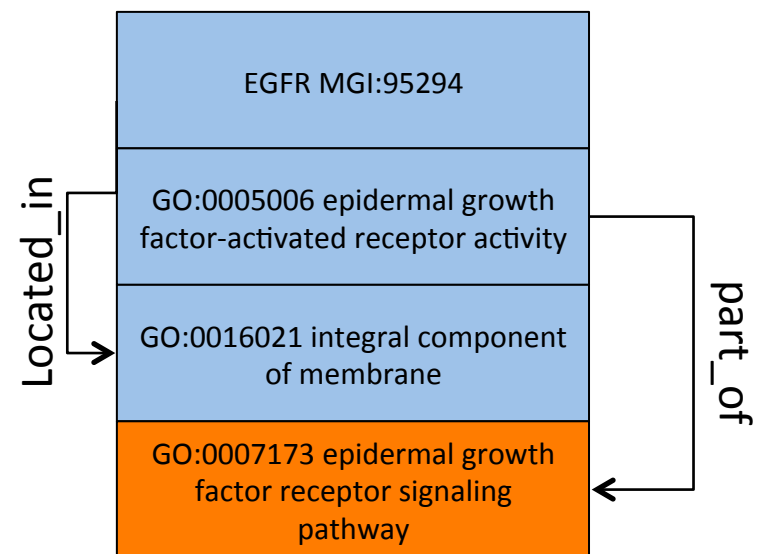
# SBGN-AF Representation

## -activation of Rasa1 by EGFR



# Issues

- Context relation between MF and BP.
  - The BP annotation here is to show the context relationship between the MF and BP.
  - The current LEGO spec does not require that the BP annotations be consistent throughout the model.
  - Submap may not be an option because it will make the map look really bad



# Issues

- Context relation between MF and BP.
  - The BP annotation here is to show the context relationship between the MF and BP.
  - The current spec does not require that the BP annotations be consistent throughout the model.
  - Submap may not be an option because it will make the map look really bad
- Effect relations
  - “Directly ....” have implications of direct interaction between the affect and effect proteins. SBGN-AF does not differentiate whether the influence is direct or indirect.
  - Upstream has no regulation or influence implication.

# LEGO annotation tool

- **Launch page**
  - <http://noctua.berkeleybop.org>
- **Examples**
  - **Single paper curation**
    - <http://www.ncbi.nlm.nih.gov/pubmed/?term=17996703>
    - [http://go-genkisugi.rhcloud.com/seed/model/gomodel:goa\\_human-5323da180000002](http://go-genkisugi.rhcloud.com/seed/model/gomodel:goa_human-5323da180000002)
  - **Seeding**
    - <http://go-genkisugi.rhcloud.com/seed/model/gomodel:pombase-GO-0051306>

# LEGO team

- Lawrence Berkeley Lab
  - Seth Carbon
  - Chris Mungall
  - Heiko Dietze
  - Suzi Lewis
- USC
  - Anushya Muruganujan
  - Huaiyu Mi
  - Paul Thomas



# Acknowledgements

- Editors
  - Tobias Czauderna
  - Stuart Moodie
  - Falk Screiber
  - Anatoly Sorokin
- Past editors
  - Emek Demir
  - Nicolas Le Novere
  - Alice Villeger
- Community members
  - Michael Blinov
  - Robin Haw
  - Augustine Luna
  - Alex Mazein
  - Anushya Muruganujan
  - Jacqueline Quinn
  - Katja Wengler
  - Many more .....
- COMBINE community