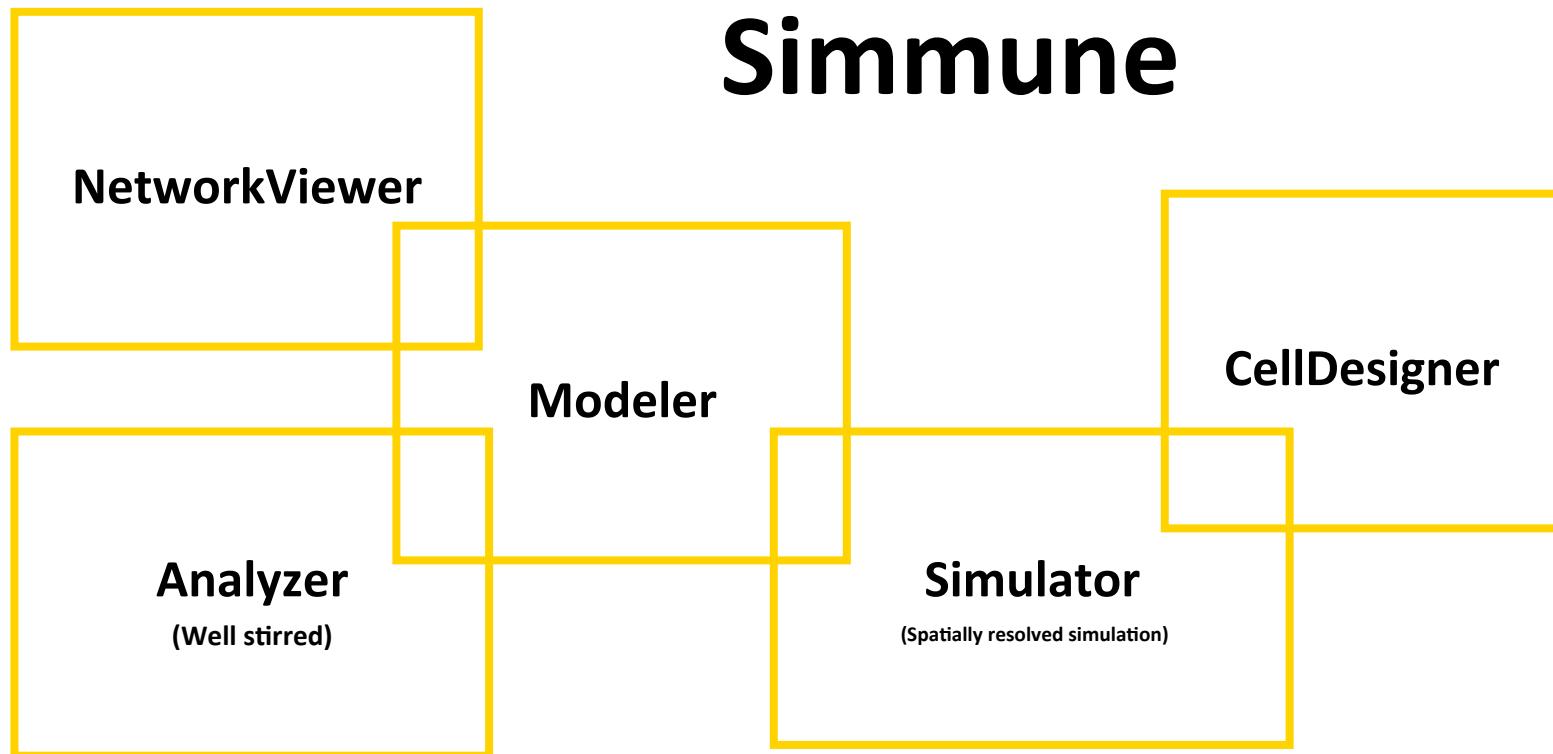


# **Build and View Rule-Based Models With Simmune Modeler and Network Viewer**

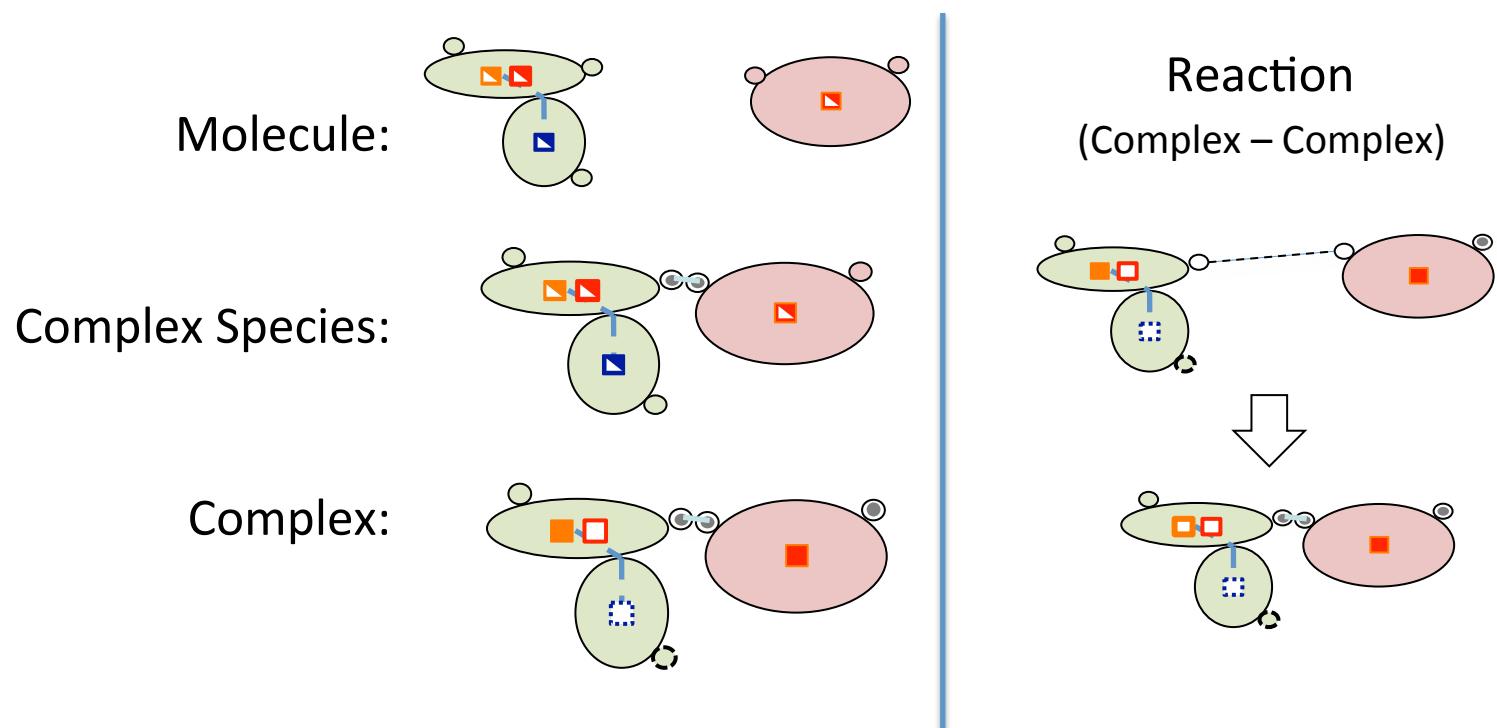
Fengkai Zhang\* , Hsueh-Chien Chen, Bastian Angermann, and Martin Meier-Schellersheim

Computational Biology Unit  
Laboratory of Systems Biology  
NIAID/NIH

# Simmune



# Simmune Model Graphical Language



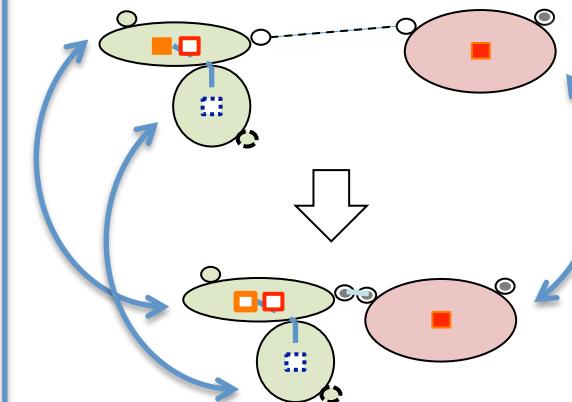
# Simmune Model Graphical Language

**Rule-based modeling**

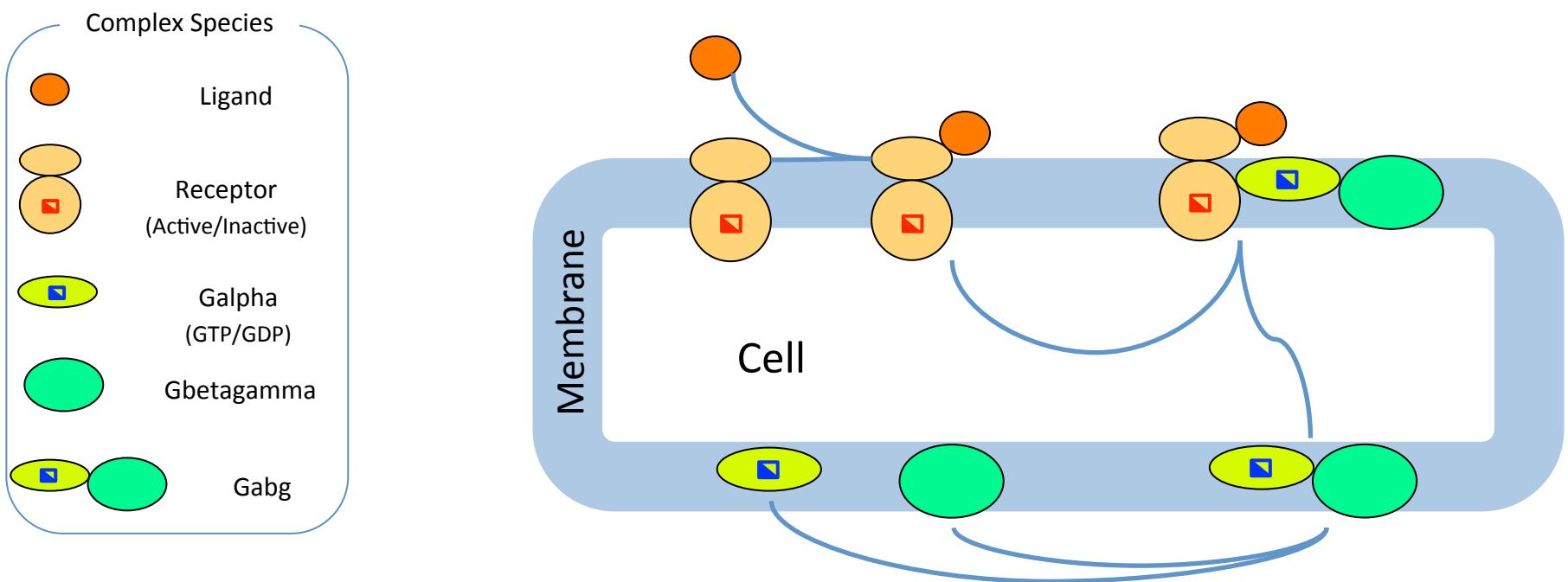
more specific:

**Domain-detailed reaction rule  
modeling**

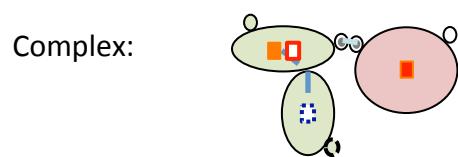
Reaction  
(Complex – Complex)



# G-proteins Model



# Build G-proteins Model with *Simmune Modeler*



**Molecule**

Save Clear Molecule Color Related Item(s) Delete

**Warning:**  
Related items found. Can NOT remove any molecule component or binding site. Can NOT add any new molecule component. But it is allowed to add a new feature or a new binding site to a molecule component.

**Molecule Composition**

Add Component Add Feature Add Binding Site Remove

Molecule: Receptor

- Molecule component 1: Intracellular Domain
  - Feature(s)  
phosphorlation
  - Binding Site(s)  
1: Receptor\_site\_1
- Molecule component 2: Extracellular Domain
  - Feature(s)
  - Binding Site(s)  
2: Receptor\_site\_2

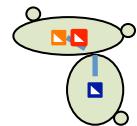
**Properties of Molecule**

Name: Receptor  
Type: Protein  
 Freely Diffusing  Membrane Associated  
Diff\_Coeff: 0.01 microns<sup>2</sup>/s  
Category: Receptor  
References: Add Remove

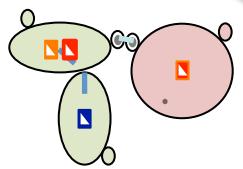
Type ID

Annotation:

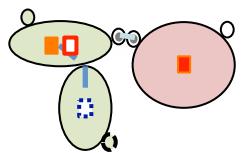
### Molecule:



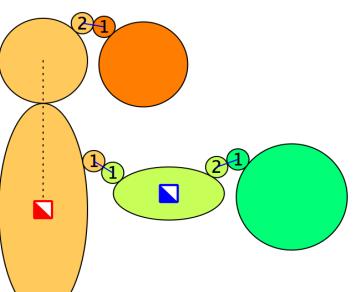
## Complex Species:



## Complex:



Complex Species



Composition      Binding Site Interactions

Complex Species

- Molecule 1: Receptor
  - Molecule component 1: Intracellular Domain
    - Feature(s)
      - phosphorylation
    - Binding Site(s)
      - 1: Receptor\_site\_1
  - Molecule component 2: Extracellular Domain
    - Feature(s)
      - Binding Site(s)
        - 1: Receptor\_site\_2
- Molecule 2: Ligand
  - Molecule component 1: Ligand\_component\_1
    - Feature(s)
      - Binding Site(s)
        - 1: Ligand\_site\_1

Edit Options

Move

Change Layout

Rotate +90°

Rotate -90°

Flip

Enable Editing

Properties of Complex Species

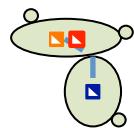
Name:

References:

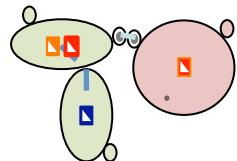
Type	ID

Annotation:

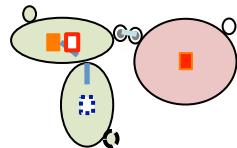
Molecule:



Complex Species:



Complex:



Complex

Complex Name: Ligated Receptor  
Species Name: Ligated Receptor  
 Display in Complex List  
Current complex is a "PATTERN" complex.

Save Back Delete

References

Add Remove

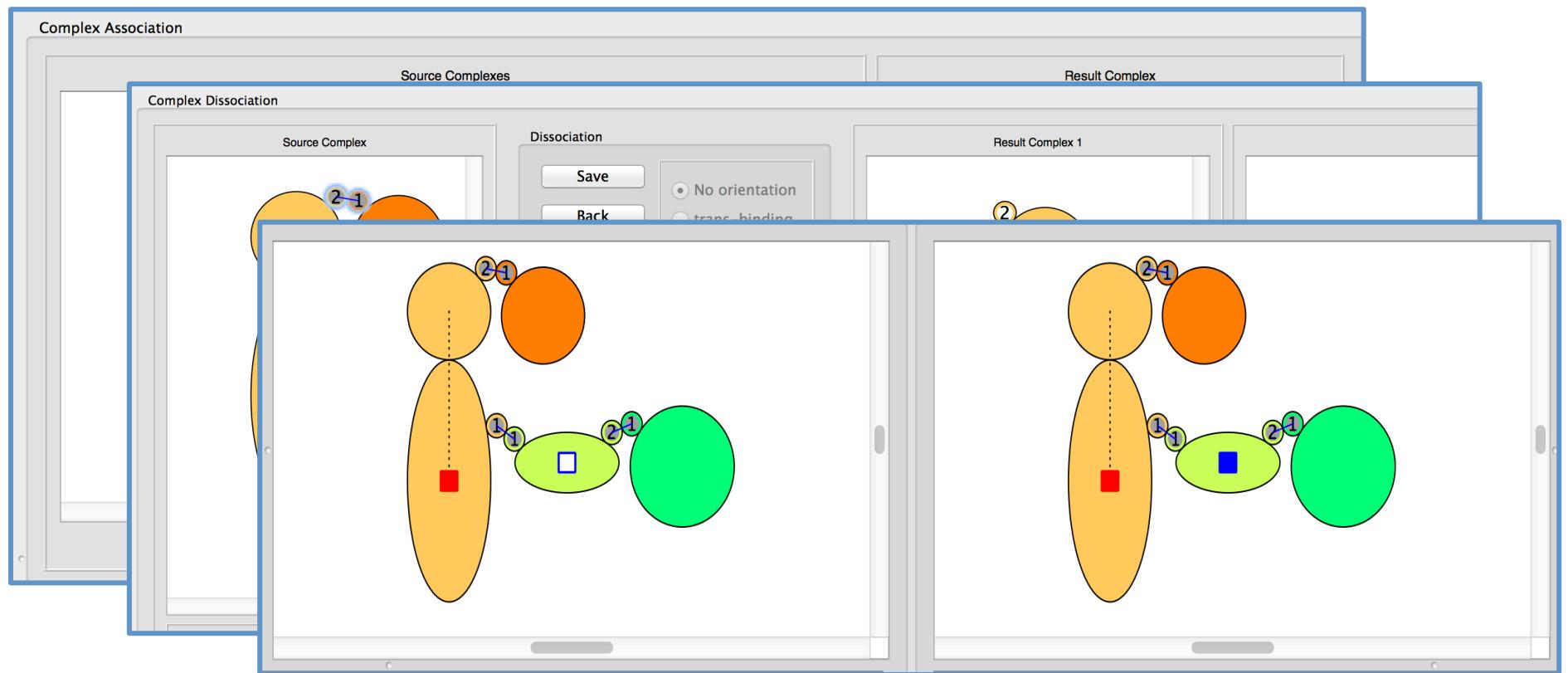
Type ID

Annotation

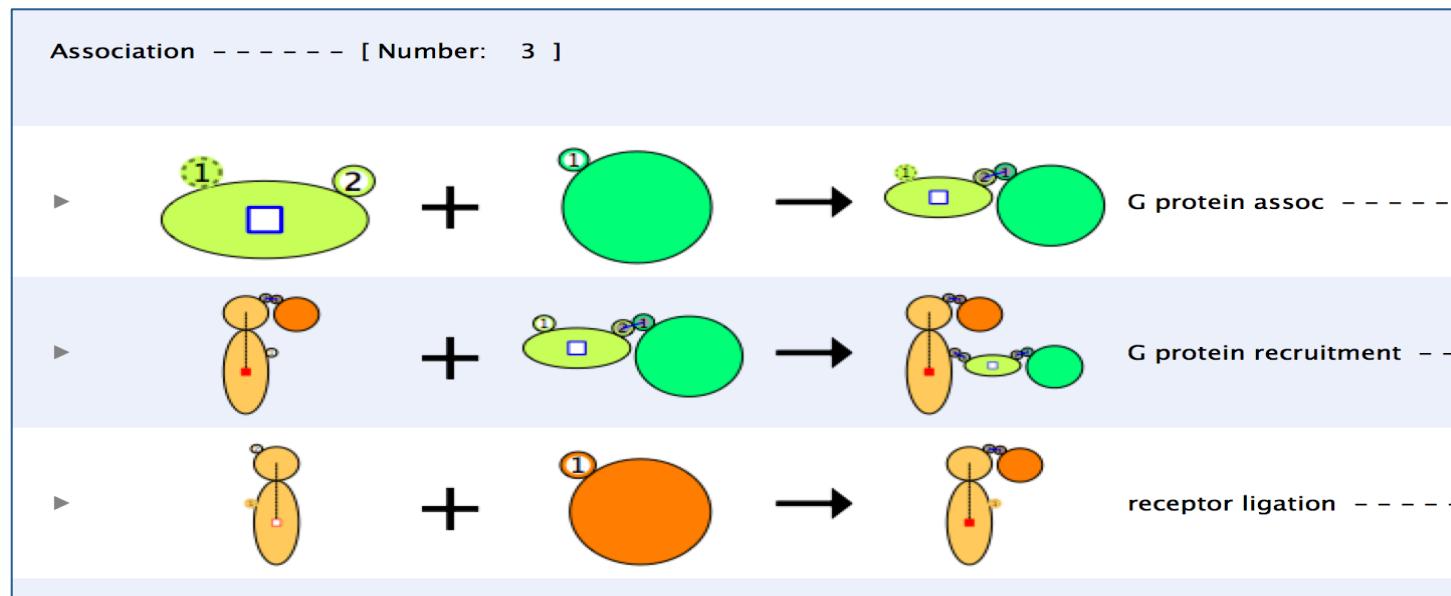
Molecule Component Tag States and Binding Status

Component	State
Complex	
Molecule 1: Receptor	
Molecule Component 1: Intracellular Domain	
Feature	
phosphorlation	On
Binding Site	
1: Receptor_site_1	Don't Care
Molecule Component 2: Extracellular Domain	
Binding Site	
2: Receptor_site_2	Bound
Molecule 2: Ligand	
Molecule Component 1: Ligand_component_1	
Binding Site	
1: Ligand_site_1	Bound

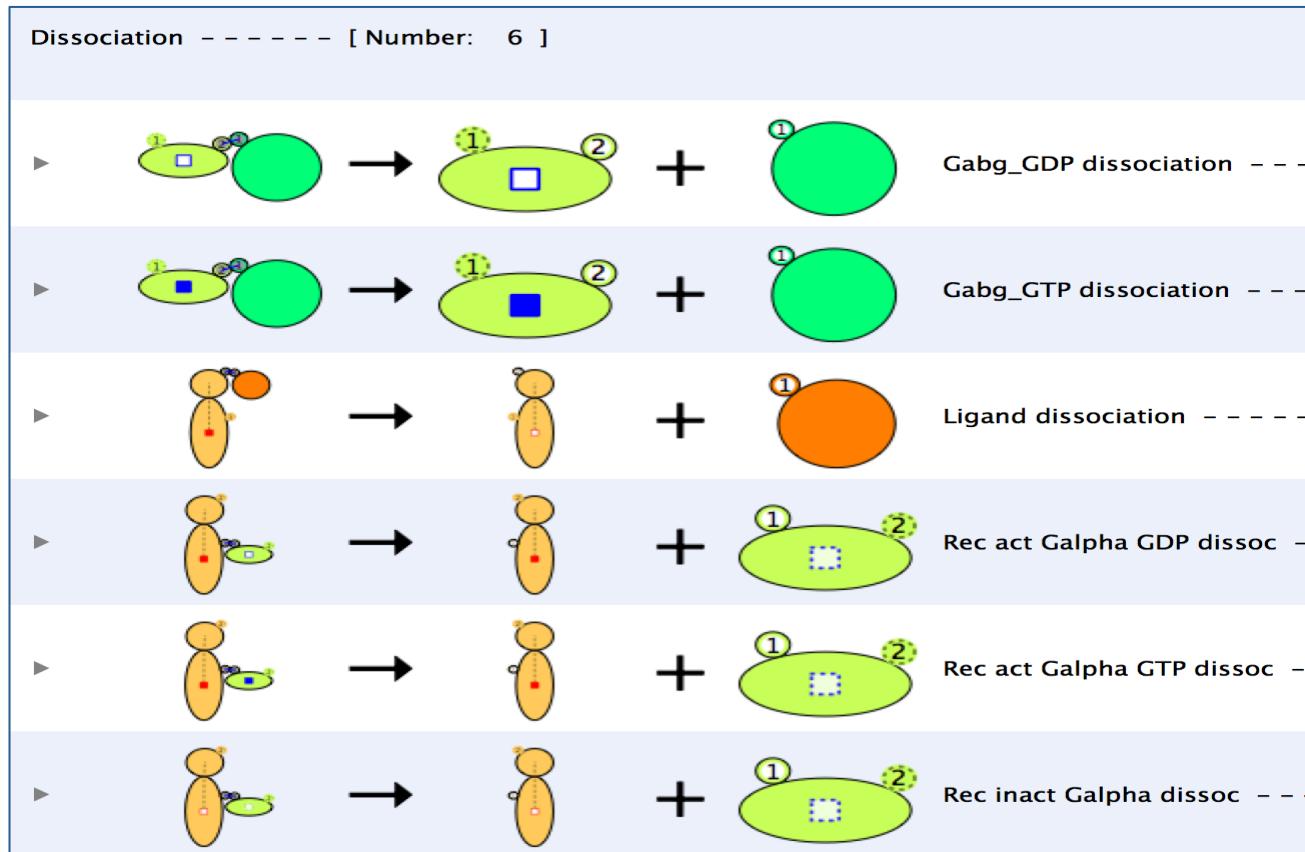
# Reactions (Complex – Complex)



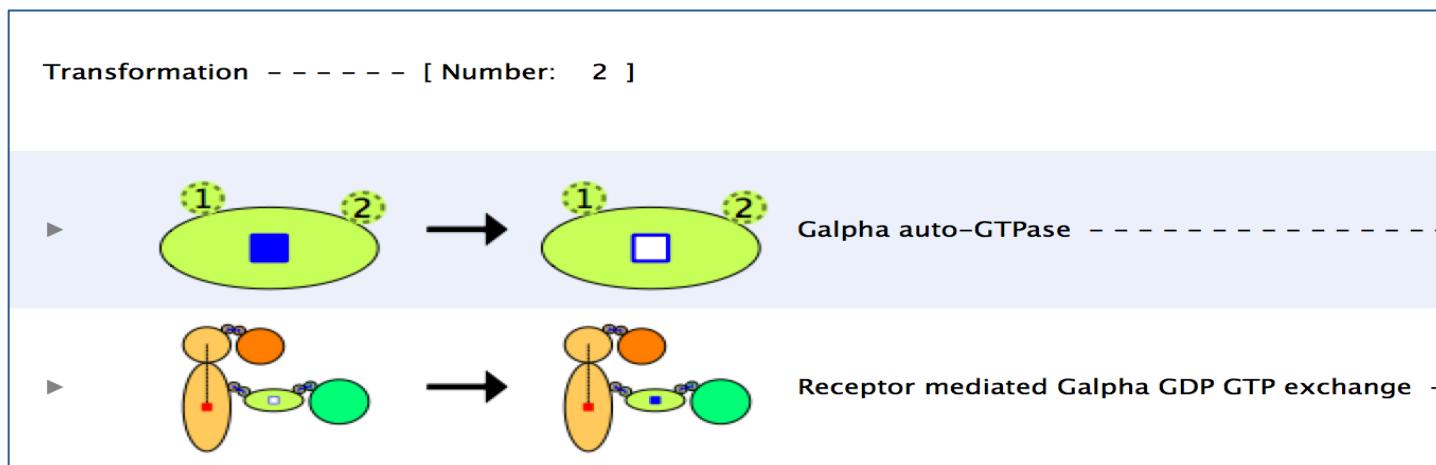
## G-proteins Model: Association Rules



# G-proteins Model: Dissociation Rules



## G-proteins Model: Transformation Rules



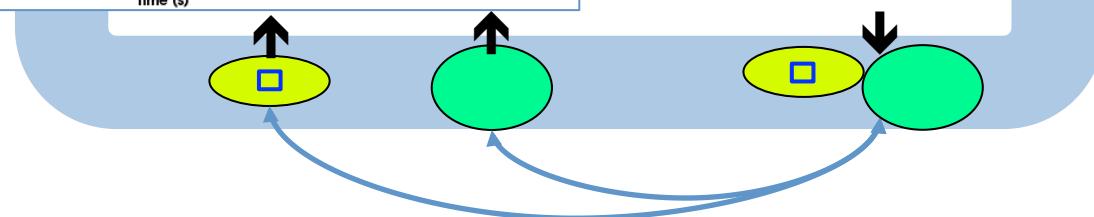
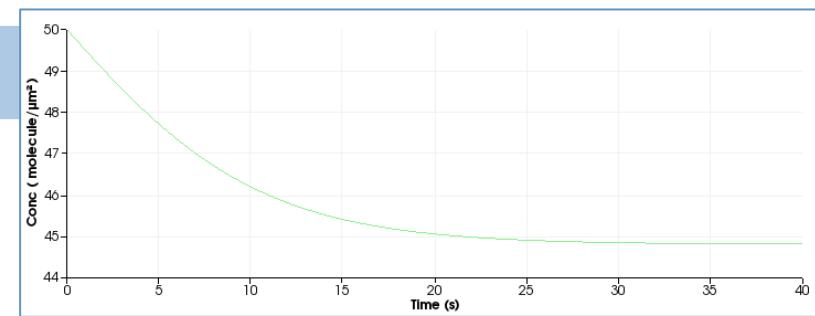
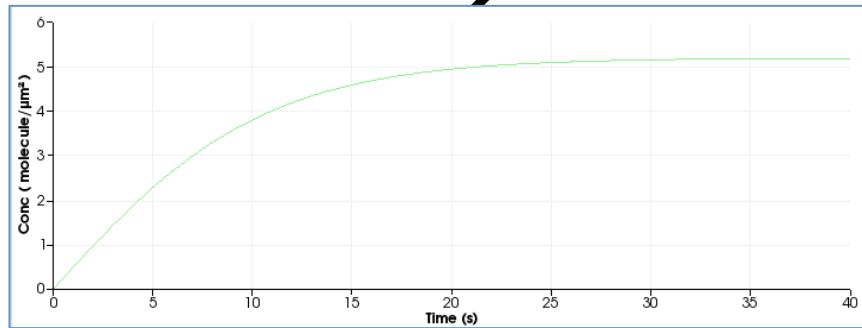
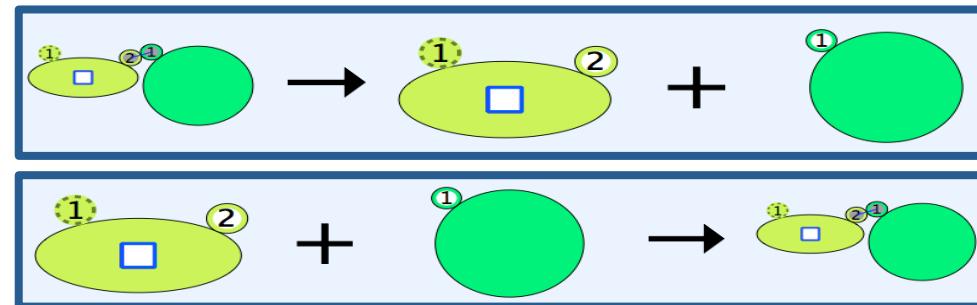
# Simulate G-proteins Model

## Initial condition



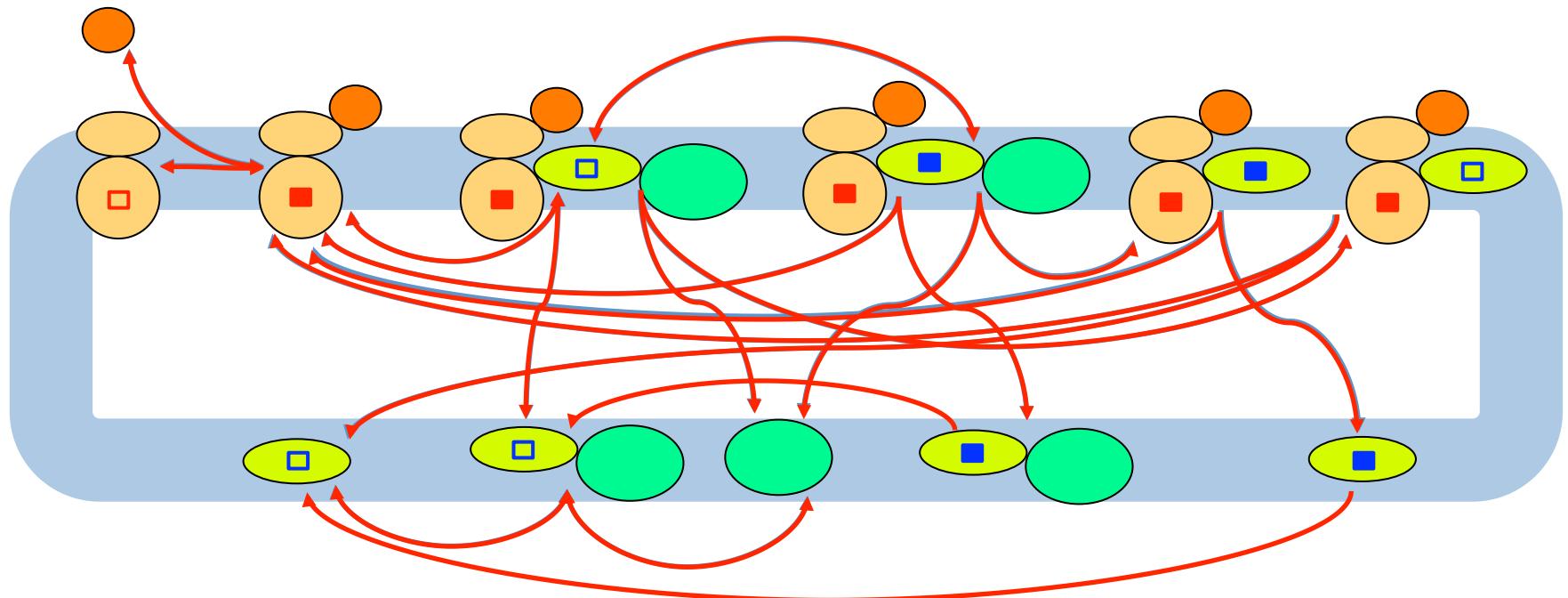
# Simulate G-proteins Model

Rules applied:

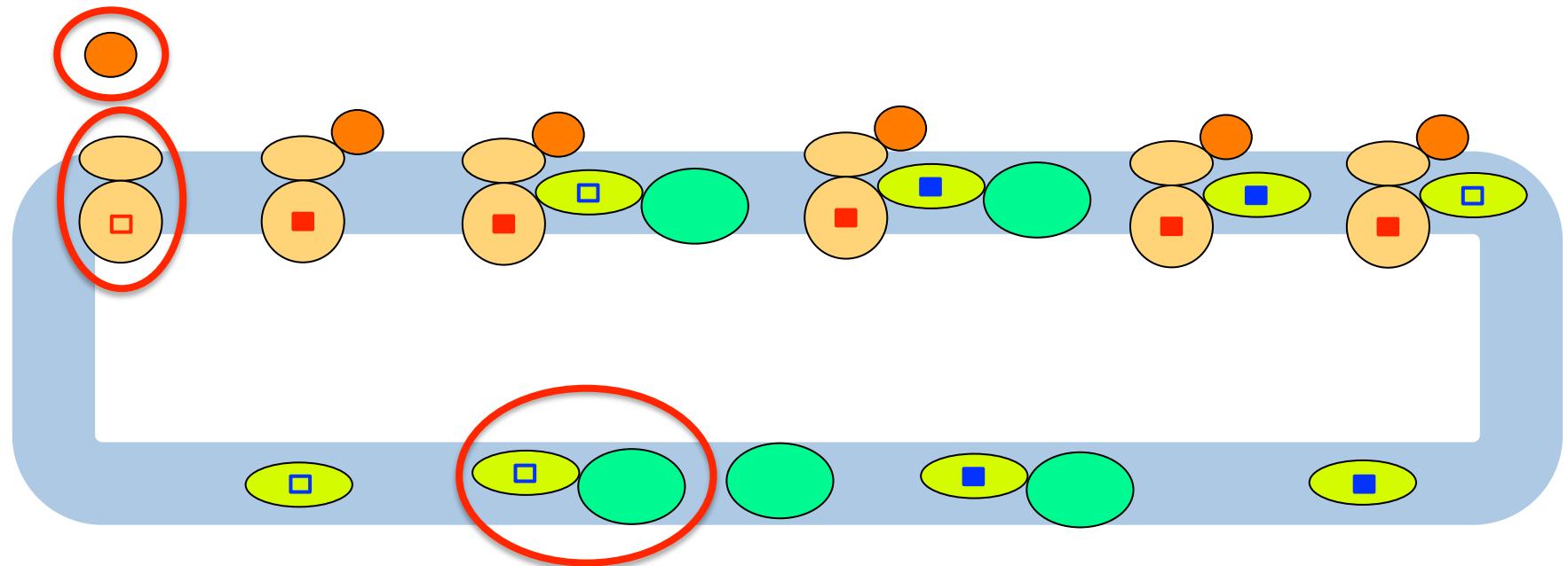


# Simulate G-proteins Model

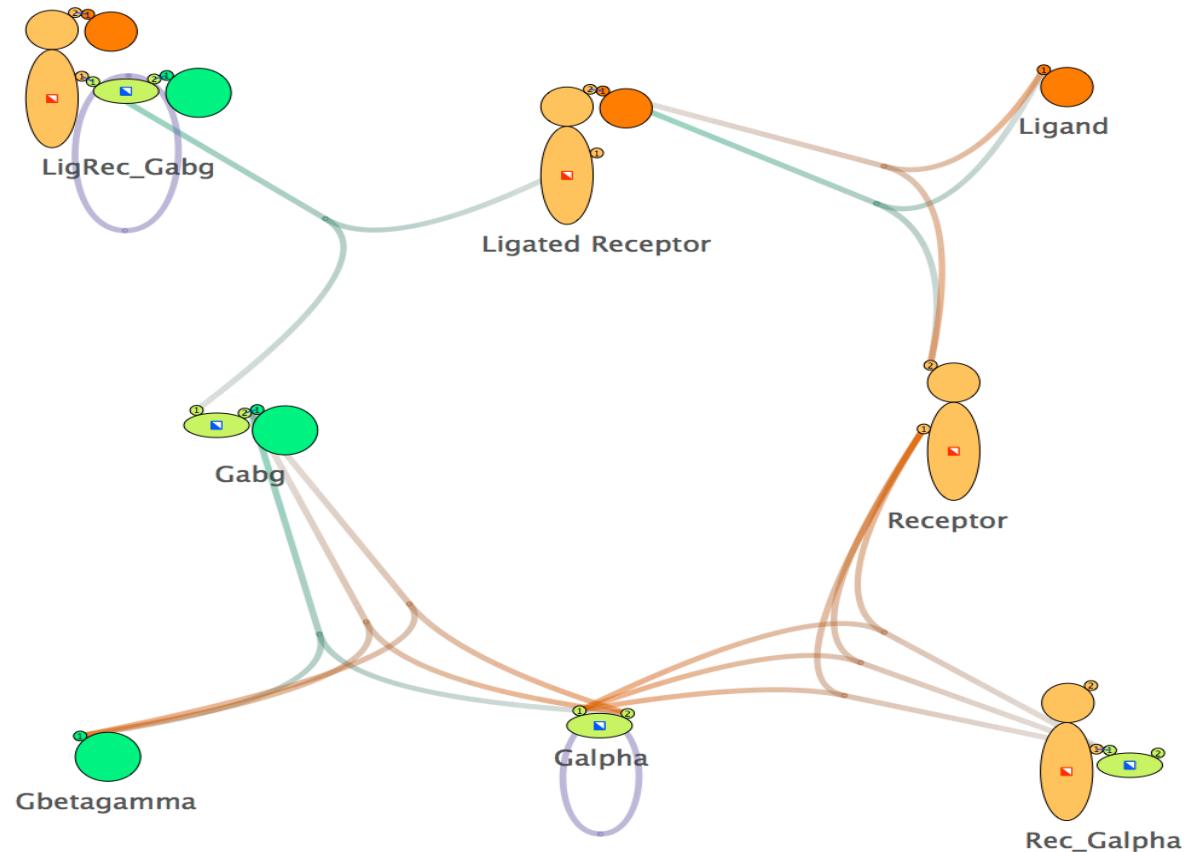
At 40 sec, add “Ligand”  to extracellular space  
Reactions are triggered by following the “**rules**”



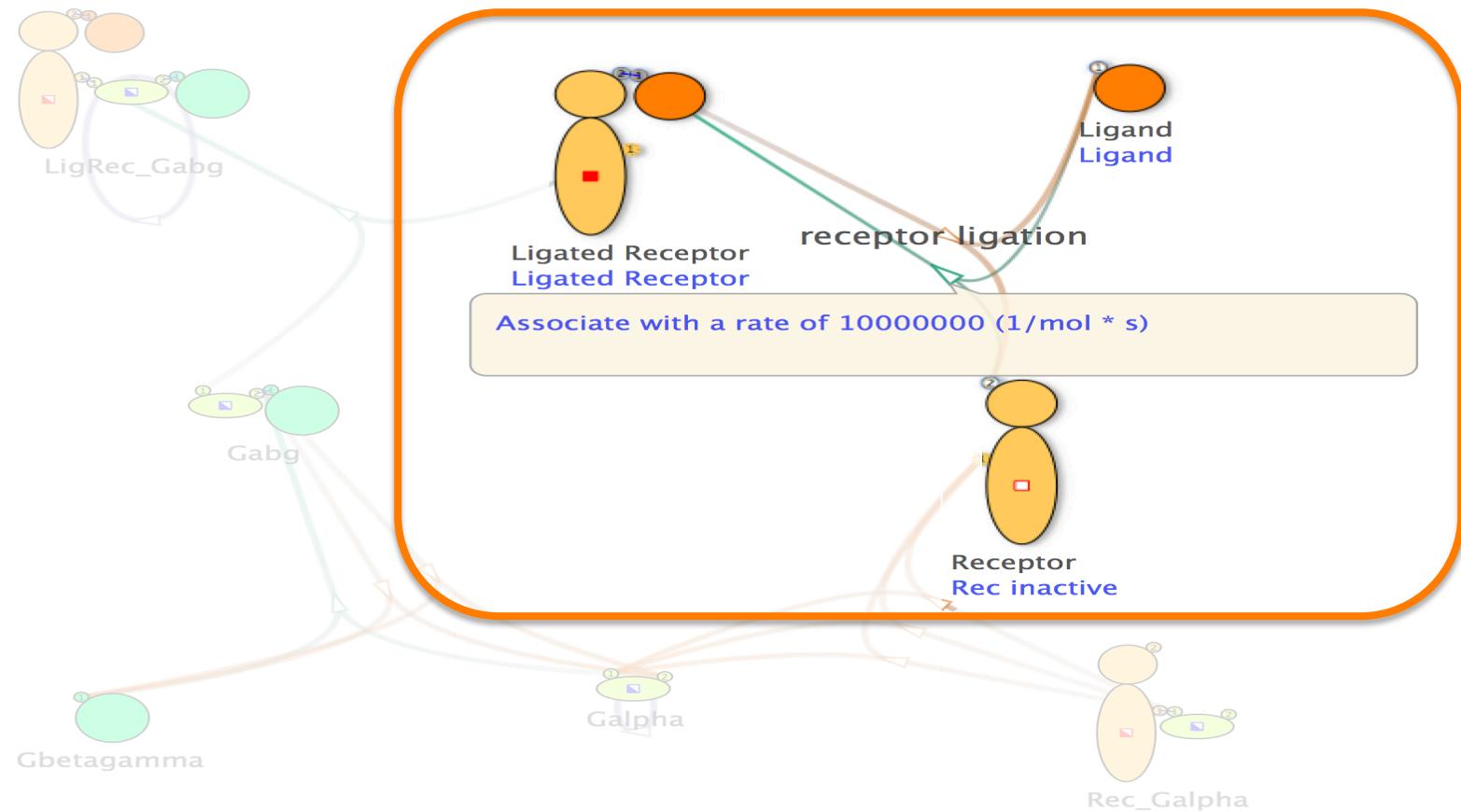
# Simulate G-proteins Model



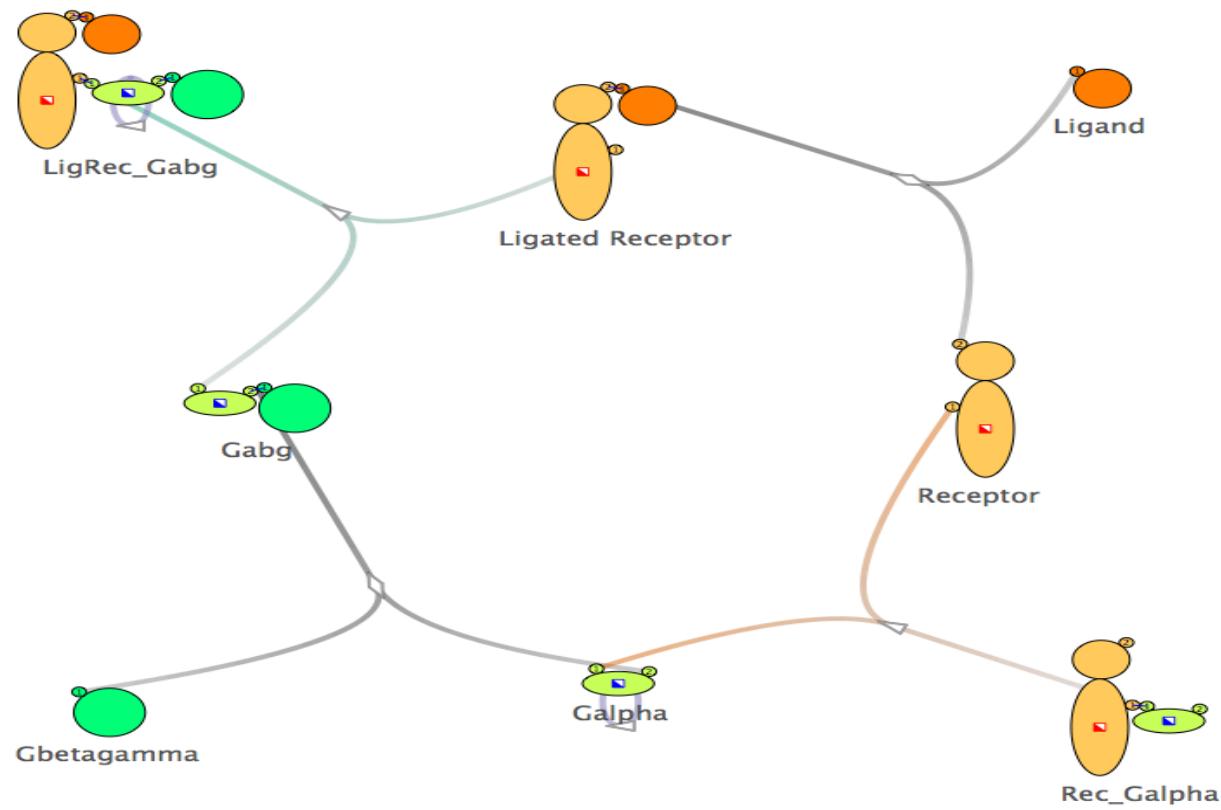
# Inspect G-proteins Model With NetworkViewer



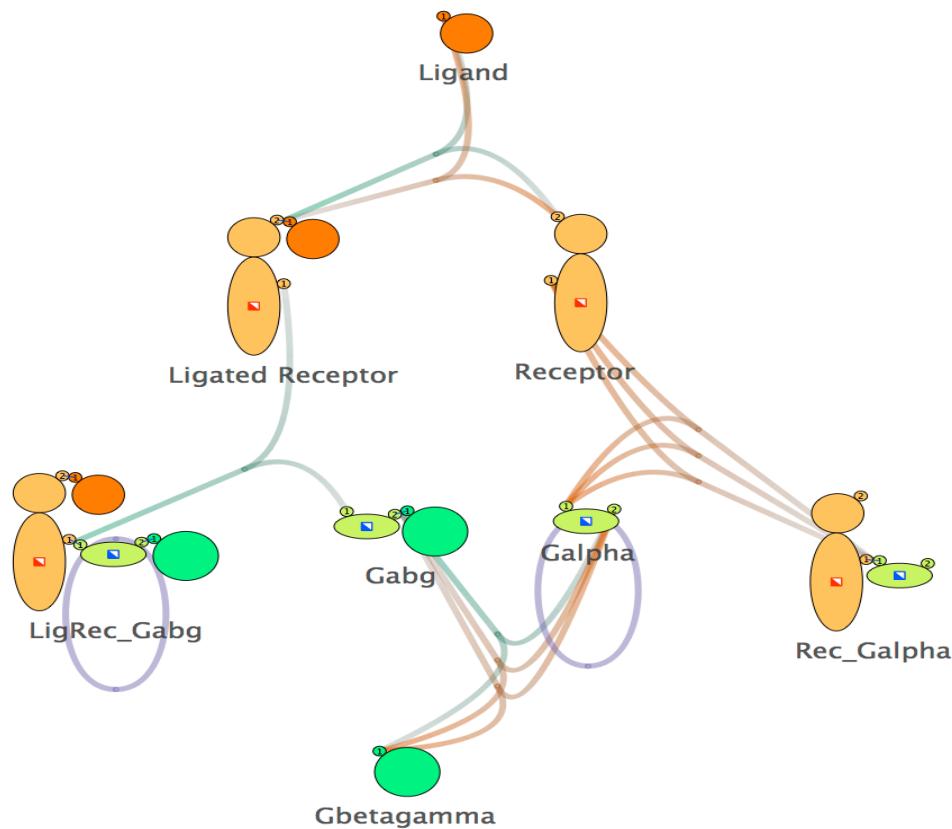
## Complex-Complex Reaction



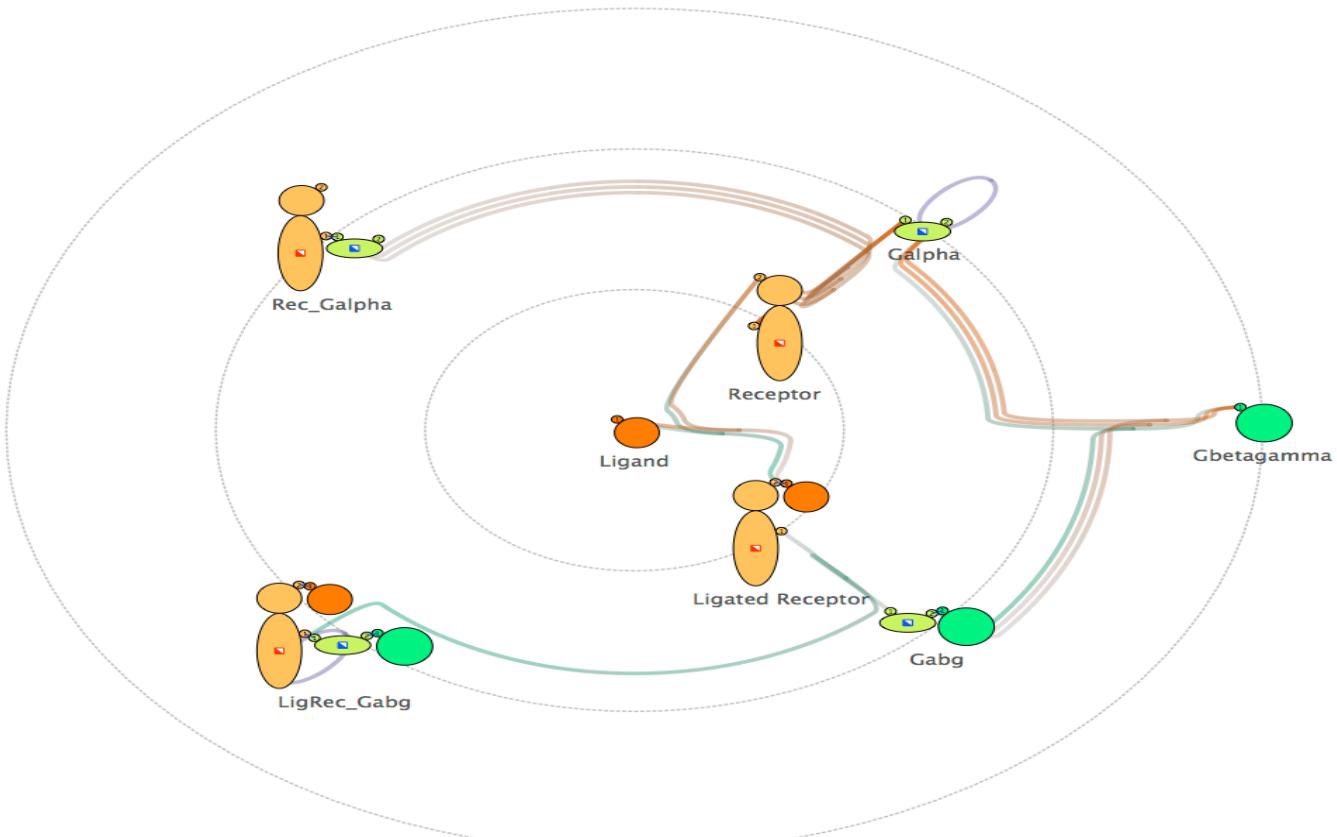
## Simple Connection



## “Level” Layout



# “Radial” Layout



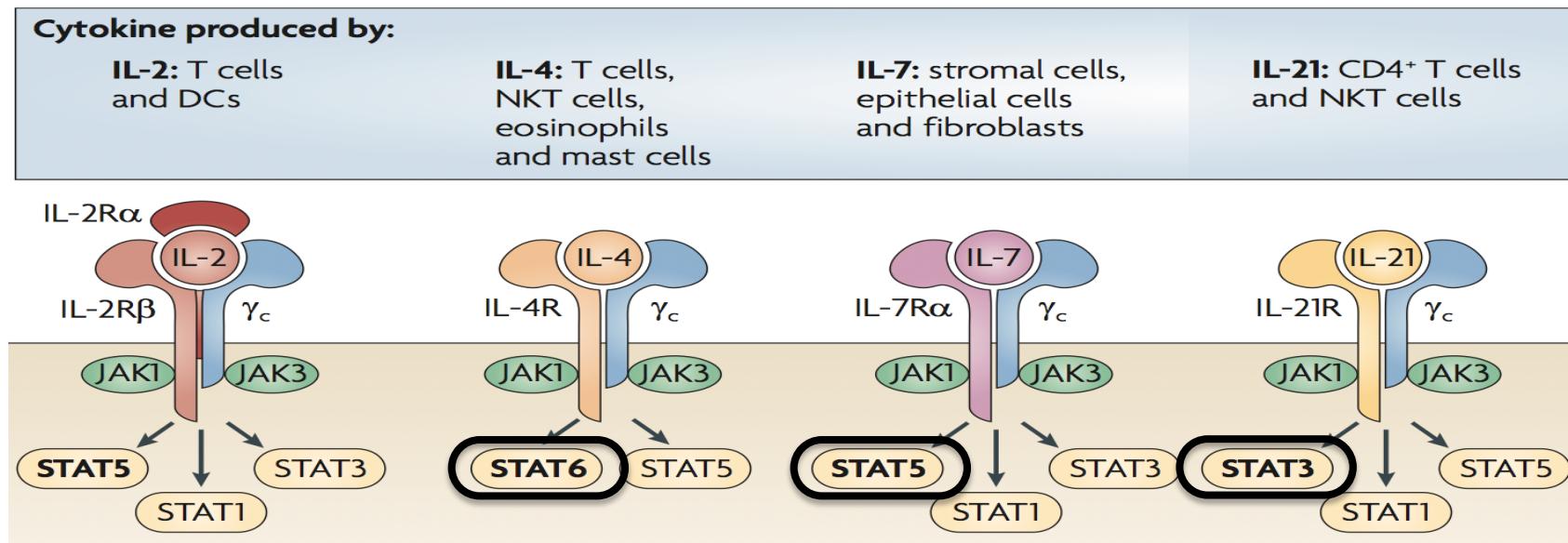
A combined experimental / computational approach to  
explore the crosstalk among cytokine receptors using the  
common  $\gamma$  chain

T-cell Biophysics Group  
Laboratory of Systems Biology



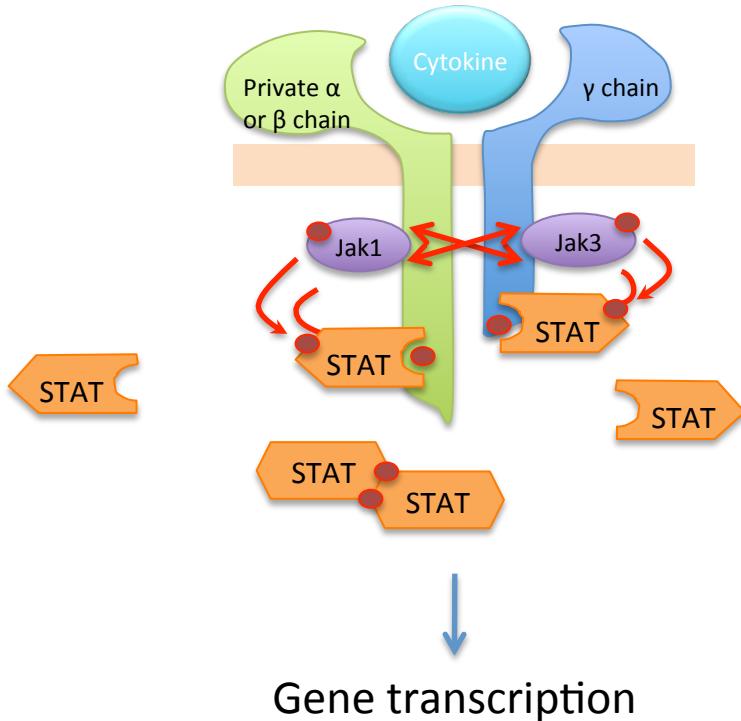
Pauline Gonnord   Rajat Varma

The common  $\gamma$  chain is shared among several cytokine signaling pathways that are essential for T cell ***survival*** and the diversity of T cell ***differentiation***.



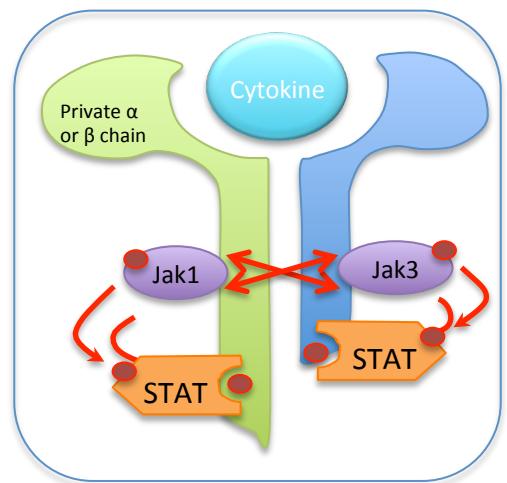
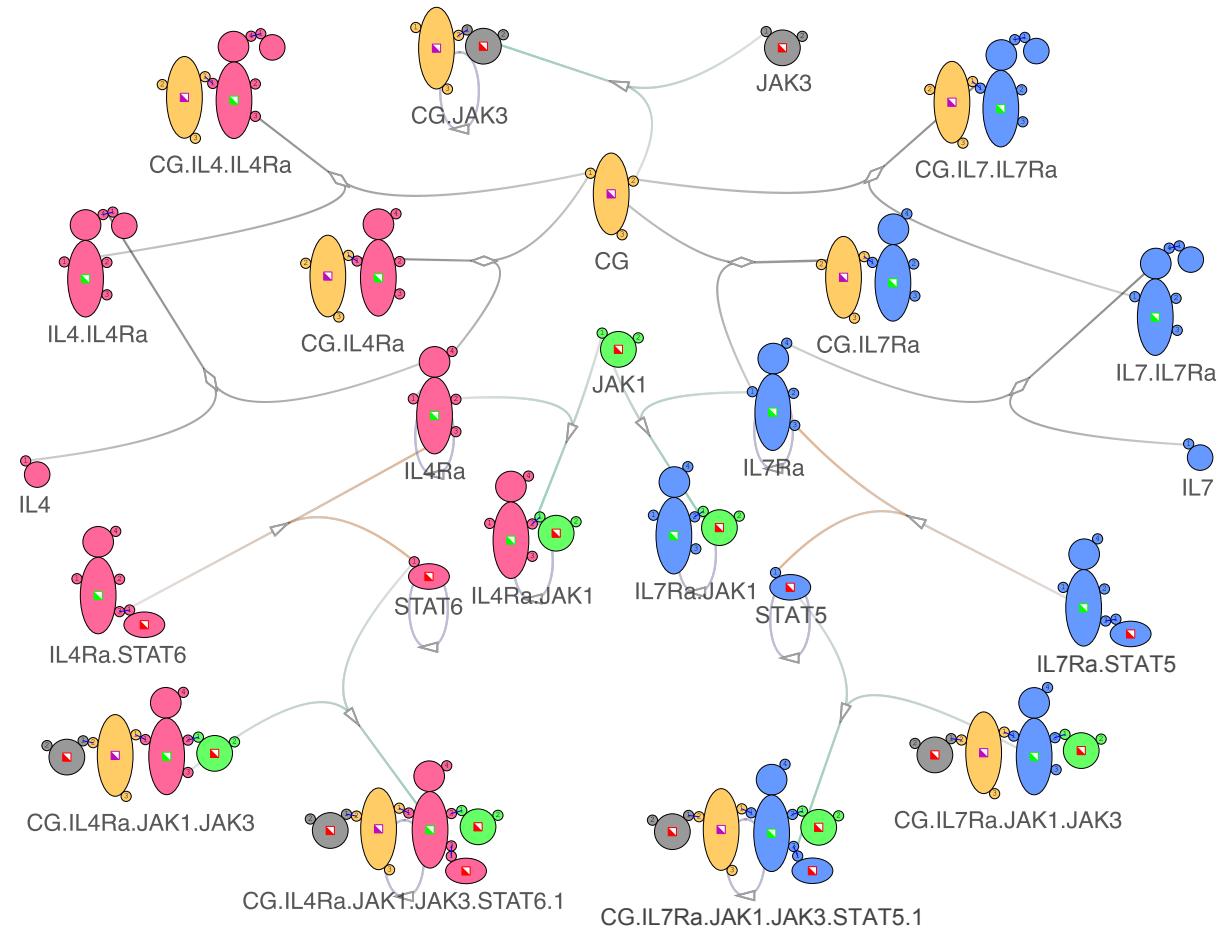
Rochman et al.  
Nat Rev Imm. 2009

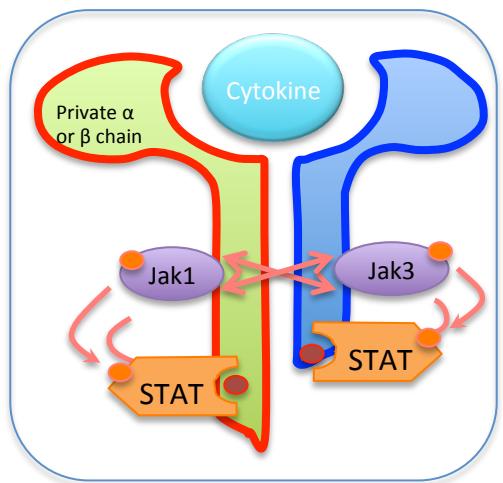
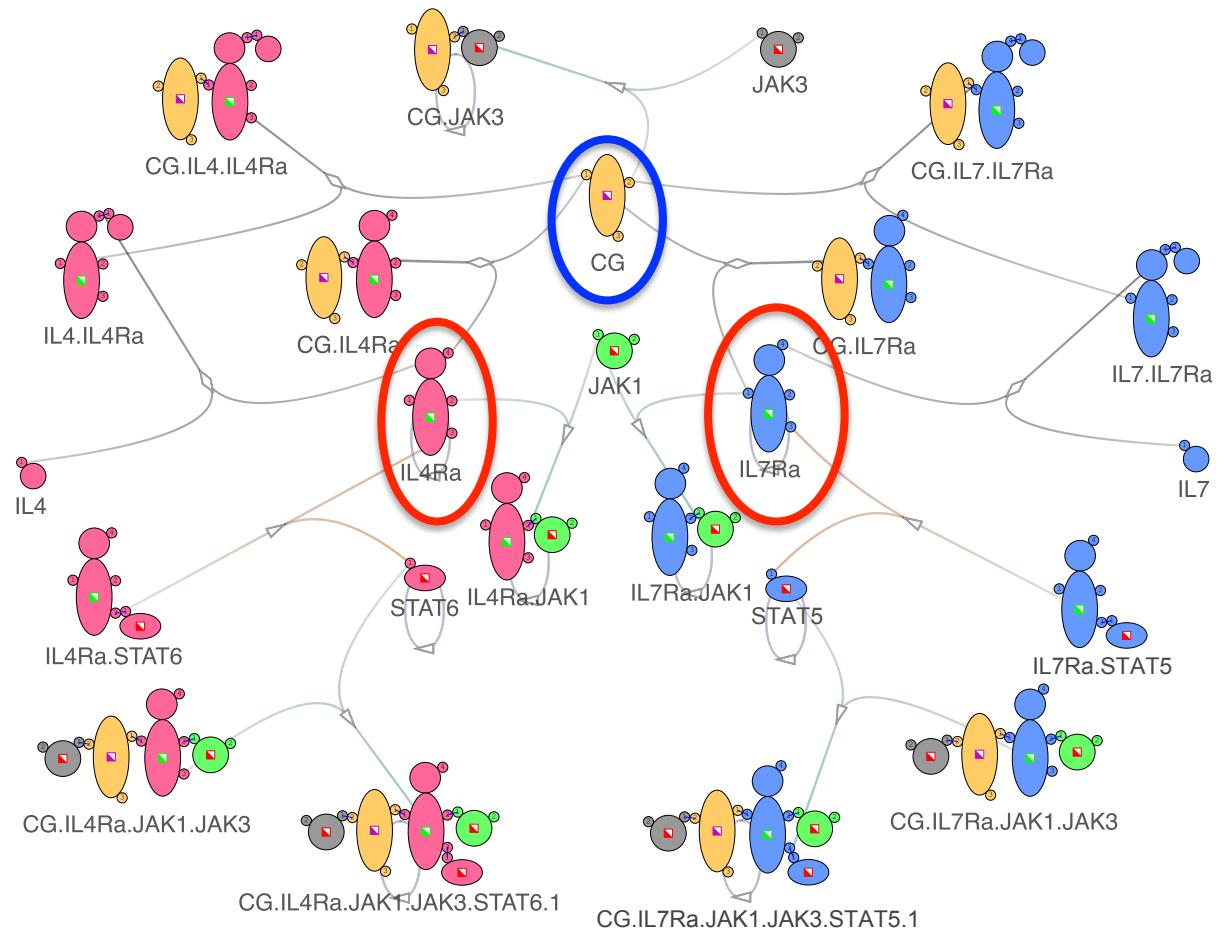
# Signaling through receptors using the Common Gamma chain

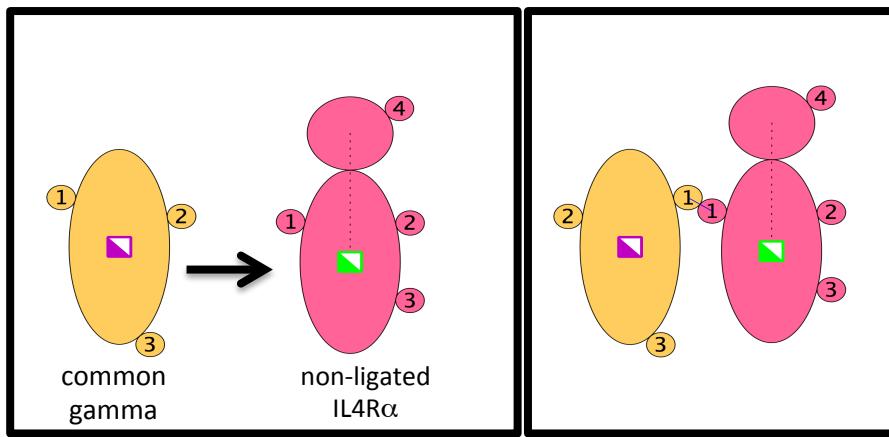


Assumptions :

- Jak1 and Jak3 are constitutively associated with the receptors
- STAT specificity is encoded in the private chain

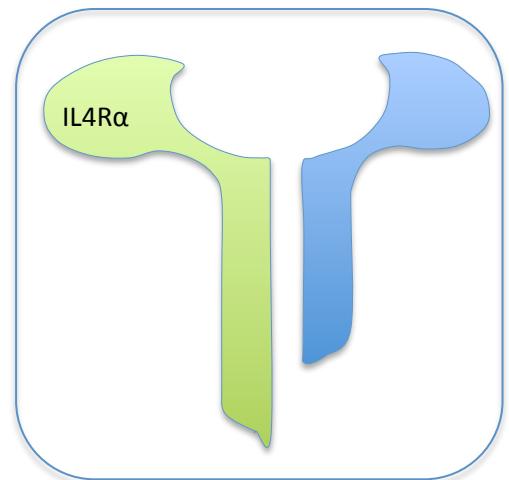


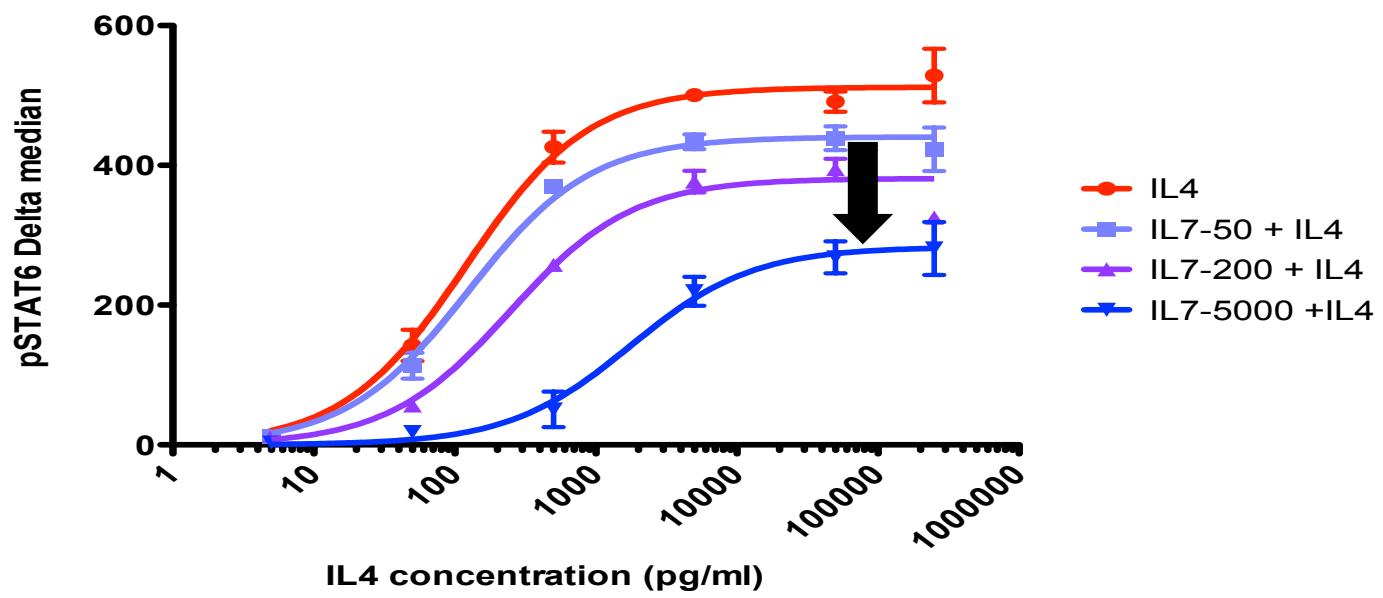




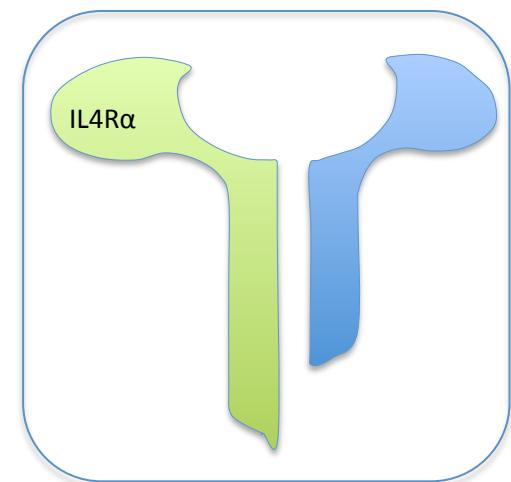
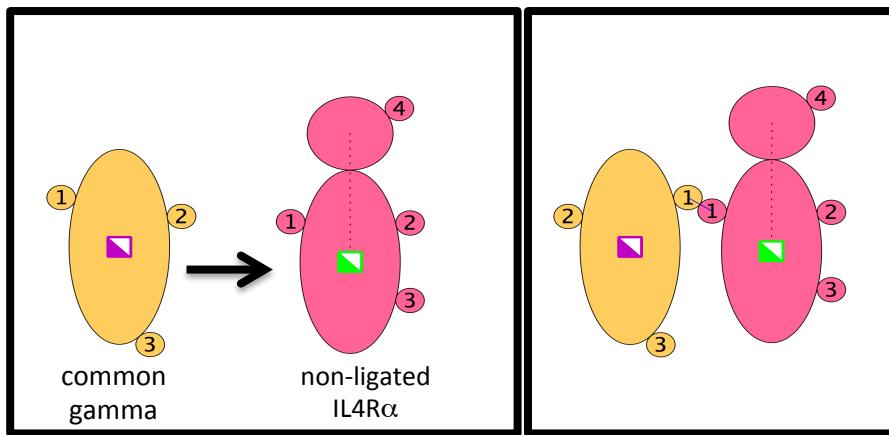
**Low** affinity recruitment

unstable dimeric complex





IL7-dose dependent suppression of pSTAT6 output



**Low** affinity recruitment

unstable dimeric complex

**Medium** affinity recruitment

somewhat stable dimeric complex

# Simmune and SBML Multi

Rule-based model (by other tools supporting SBML Multi)



Multi Model



Simmune Model



Inspect model with ***Simmune Modeler*** and ***NetworkView***

Simulate with ***Simmune Simulator*** and ***Analyzer***

## Acknowledgments

Martin Meier-Schellersheim	<b>Computational Biology Unit</b>
Hsueh-Chien Chen	
Bastian Angermann	
Rajat Varma	<b>T-cell Biophysics Group</b>
Pauline Gonnord	
Many other people	Lab of Systems Biology, SBML community

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