SBML Multi - From Specification to Application
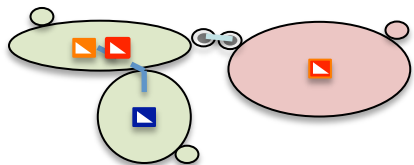
Fengkai Zhang*,[1] , Jose Juan Tapia Valenzuela[2], and Martin Meier-Schellersheim[1]

1: Computational Biology Unit, Laboratory of Systems Biology, NIAID/NIH
2: University of Pittsburgh

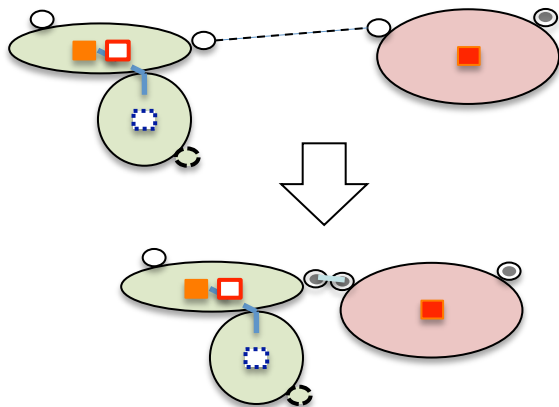# Modeling: Rule-Based, Domain Detailed

Complex Species:

Molecule type:

EGFR(L, CR1, Y1068~U~P)

Association (complex-complex):
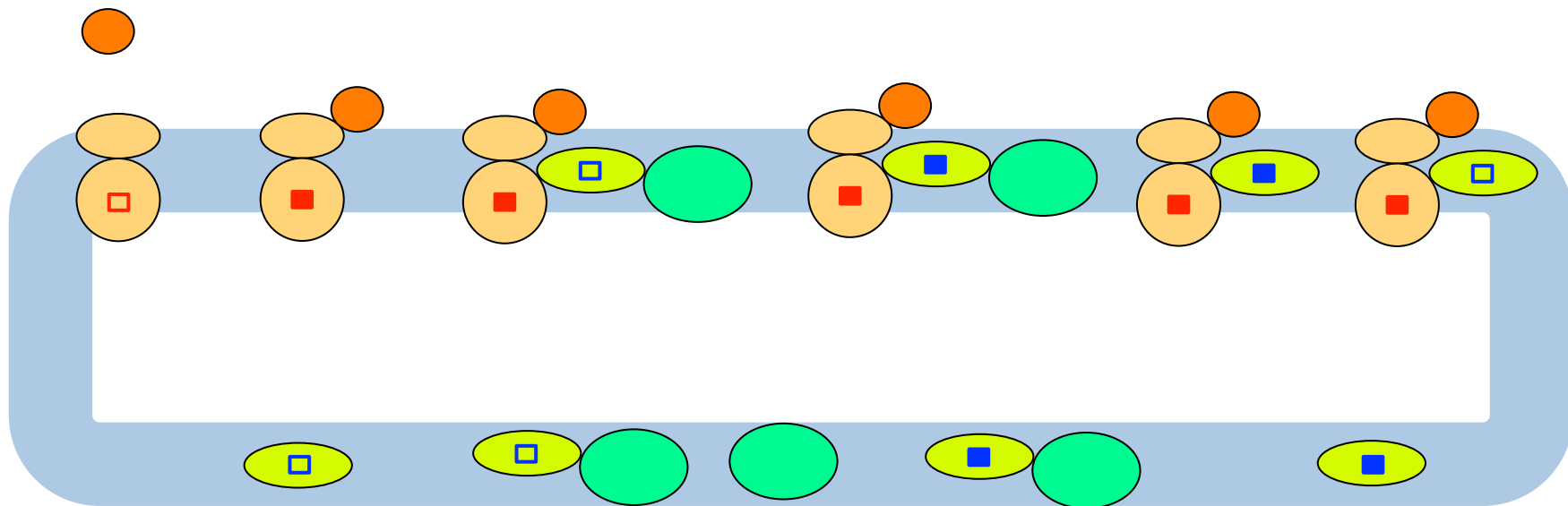

Transformation (Phosphorylation)

EGFR(CR1!+,Y1068~U)

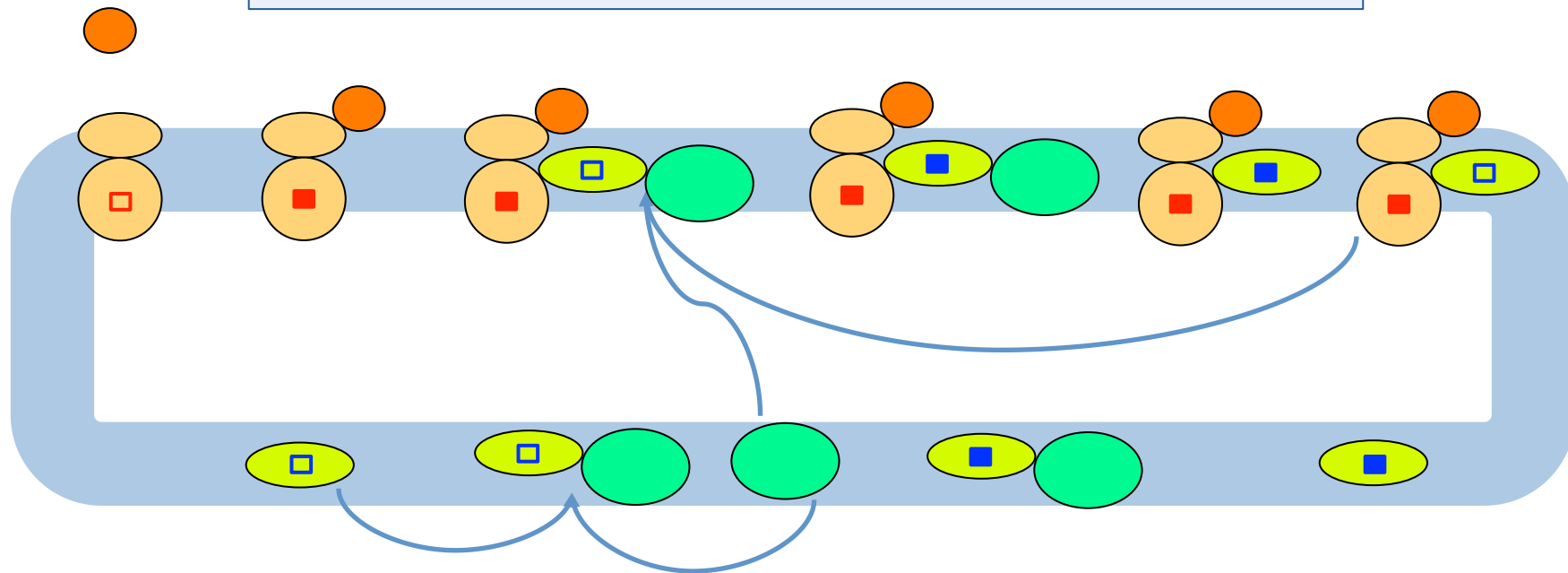EGFR(CR1!+,Y1068~P)

Example: Applying Reaction Rules

Model Rules: Associations, Dissociations, Transformations

Example: Applying Reaction Rules
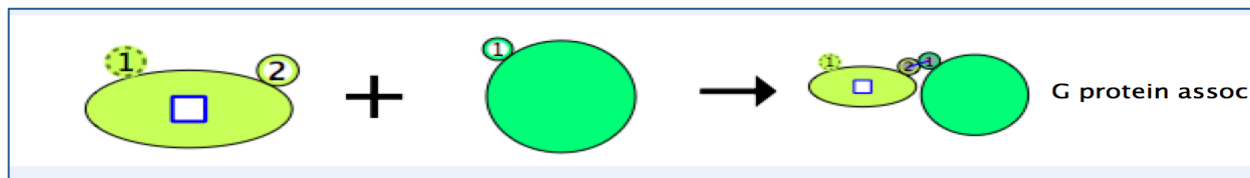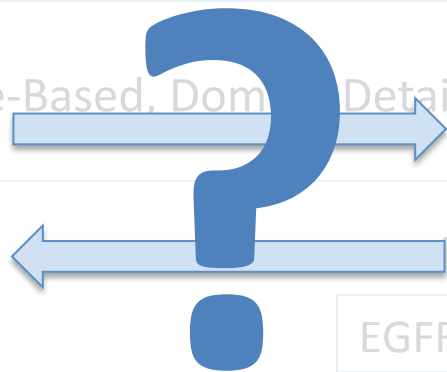
SBML Multi Package

Multistate, Multicomponent and Multicompartment Species Package for SBML Level 3

How *Multi* features extend *SBML L3 Core*
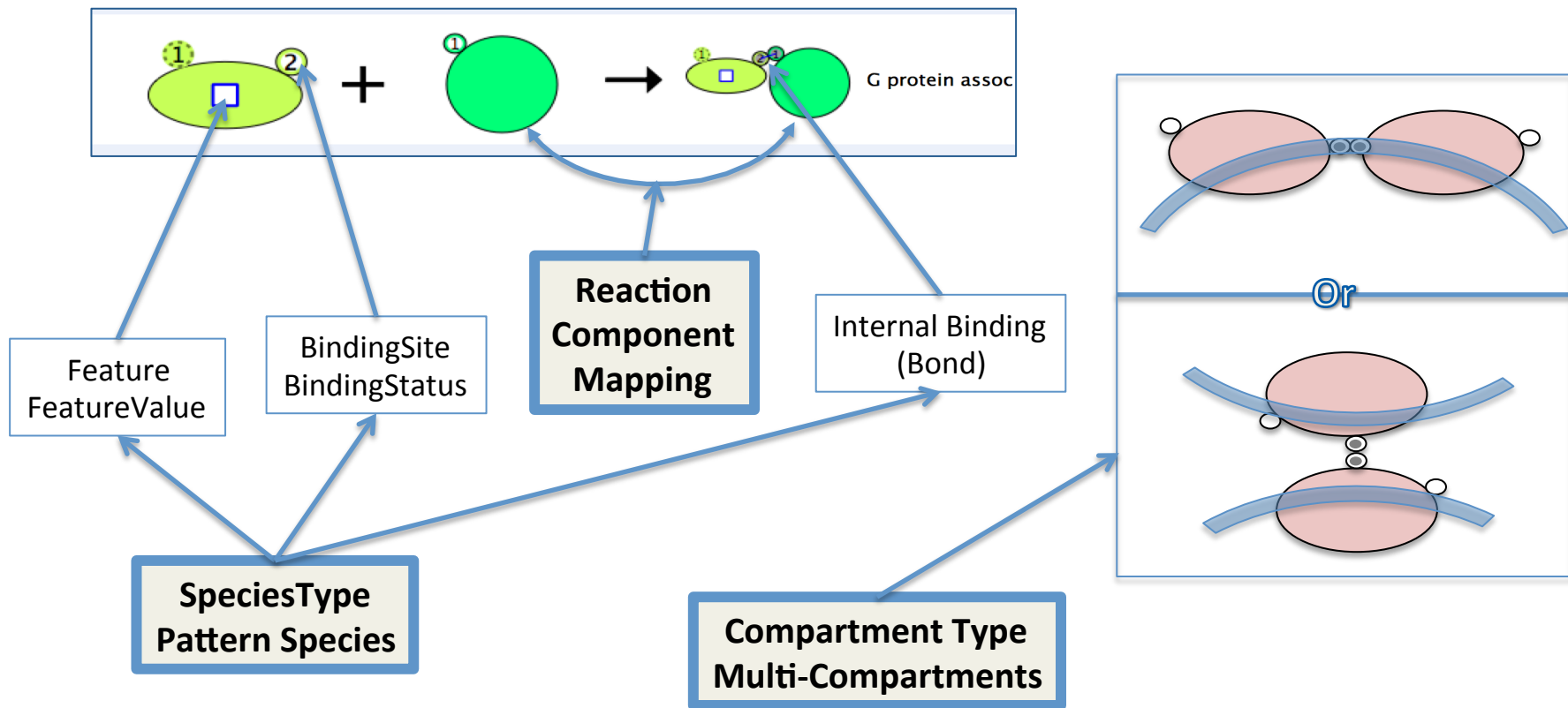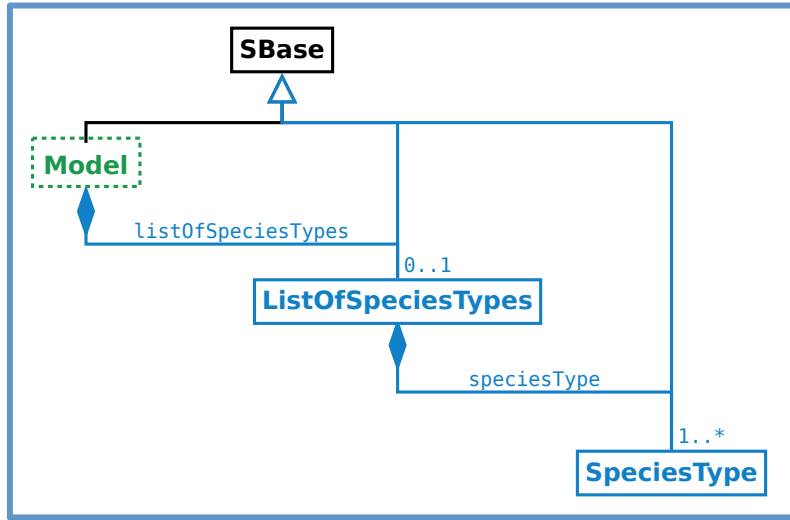
SBML Multi Specification (V 1.0.7)

SBML Multi Specification (V 1.0.7)

COMBINE 2016

SBML Multi Specification (V 1.0.7)

COMBINE 2016

SBML Multi Specification (V 1.0.7)

SBase

Model

SBase

SpeciesType
id: SId
name: string {use="optional"}
compartment: SIdRef {use="optio...

SBase

listO

listO

listOfSp

list

SBase

SimpleSpeciesReference
compartmentReference: SIdRef {use="optional"}

SpeciesReference

listOfSpeciesTypeComponentMapsInProduct

0..1

ListOfSpeciesTypeComponentMapsInProduct

speciesTypeComponentMapInProduct

1..*

SpeciesTypeComponentMapInProduct
reactant: SIdRef
reactantComponent: SIdRef
productComponent: SIdRef

SBML Multi Specification (V 1.0.7)

SBase

Model

SBase

SpeciesType
- id: SId
- name: string {use="optional"}
- compartment: SIdRef {use="optio...

SBase

SBase

SBase

Compartment
- compartmentType: SIdRef {use="optional"}
- isType: boolean

listOfCompartmentReferences

0..1

ListOfCompartmentReferences

compartmentReference 1..*

CompartmentReference
- id: SId {use="optional"}
- name: string {use="optional"}
- compartment: SIdRef

...apInProduct

1..*

TypeComponentMapInProduct
- SIdRef
- omponent: SIdRef
- omponent: SIdRef

SBML Multi

Proposal ✔

Specification
(Draft, Stable ✔)

libsbml-multi
(Experimental v1.0.7) **?**

libsbml-multi

- Extended (plugins)
  Model, Compartment, Species, Reaction, SpeciesReference, SimpleSpeciesReference, AST

- Multi Specific
  SpeciesType, SpeciesFeatureType, InSpeciesTypeBond, SpeciesTypeComponentMapInProduct ... (14 new classes)

- Validation
  155 validation rules

- Bindings
  swig: *Python*, *Java*, *Javascript*...

SBML Multi
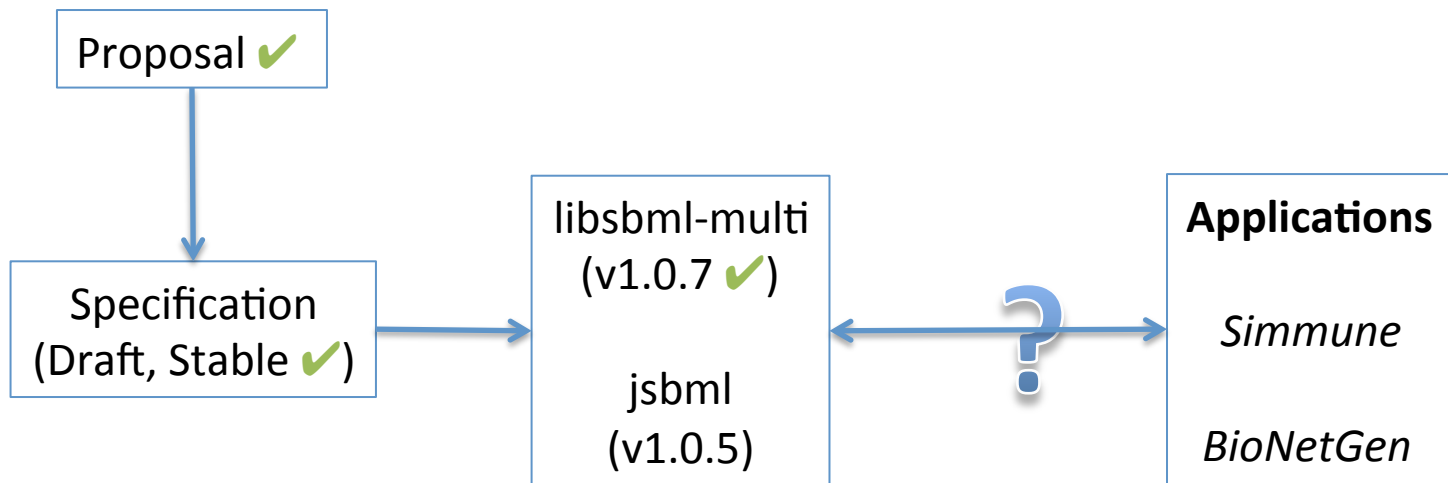
Applications Supporting SBML-Multi

- ***Simmune***
  Export and Import

- ***BioNetGen***
  Export

- Examples:
  - Simmune → Multi → Simmune
  - BioNetGen → Multi → Simmune

Simmune – Multi – Simmune (G Proteins)
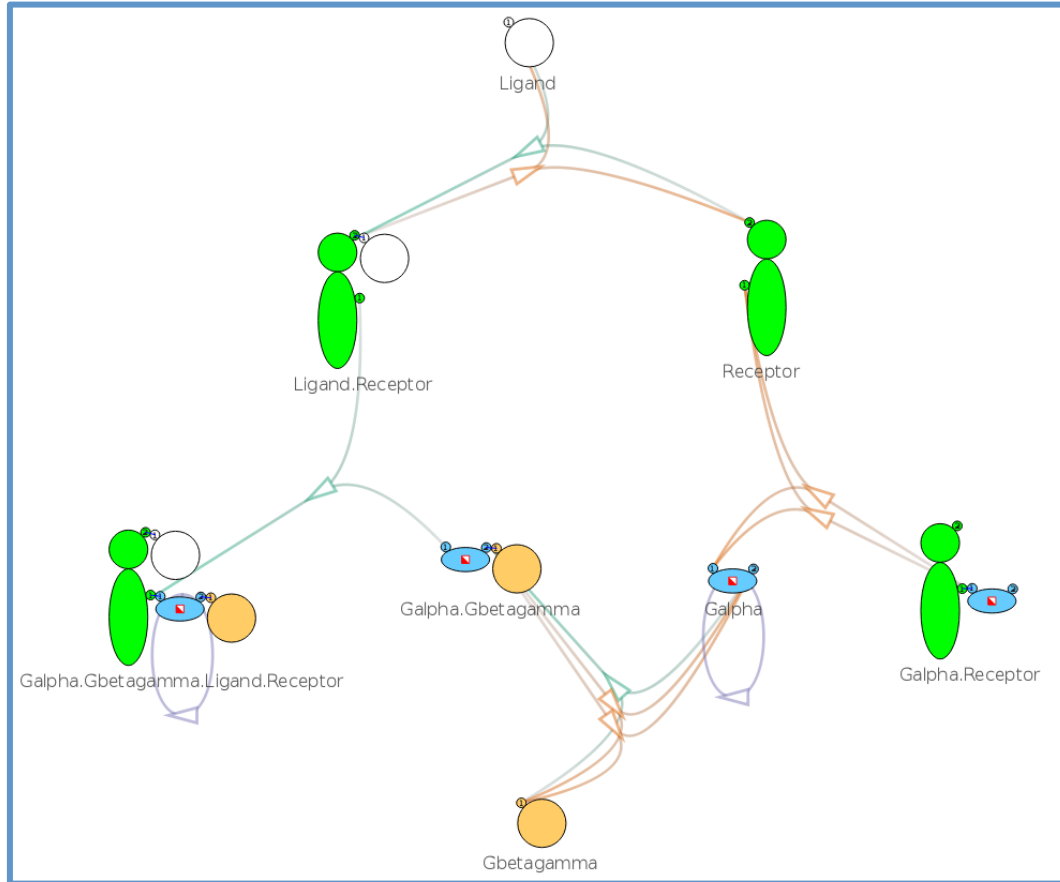
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    <listOfUnitDefinitions>
    <listOfCompartments>
    <listOfSpecies>
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      <species id="sp_cpx_000005" name="Ligand_1" compartment="any" hasOnlySubstanceUnits="true" boundaryCondition="true" constant="false" multi:species
      <species id="sp_cpx_000006" name="Ligand.Receptor_1" compartment="any" hasOnlySubstanceUnits="true" boundaryCondition="true" constant="false" mult
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      <species id="sp_cpx_000008" name="Gbetagamma_1" compartment="any" hasOnlySubstanceUnits="true" boundaryCondition="true" constant="false" multi:spe
      <species id="sp_cpx_000009" name="Galpha.Gbetagamma_1" compartment="any" hasOnlySubstanceUnits="true" boundaryCondition="true" constant="false" mu
      <species id="sp_cpx_000010" name="Galpha_2" compartment="any" hasOnlySubstanceUnits="true" boundaryCondition="true" constant="false" multi:mu
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      <species id="sp_cpx_000016" name="Galpha.Receptor_1" compartment="any" hasOnlySubstanceUnits="true" boundaryCondition="true" constant="false" mult
      <species id="sp_cpx_000017" name="Receptor_2" compartment="any" hasOnlySubstanceUnits="true" boundaryCondition="true" constant="false" multi:speci
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      <multi:bindingSiteSpeciesType multi:id="st_bst_000001" multi:name="G protein recruitment site"/>
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```
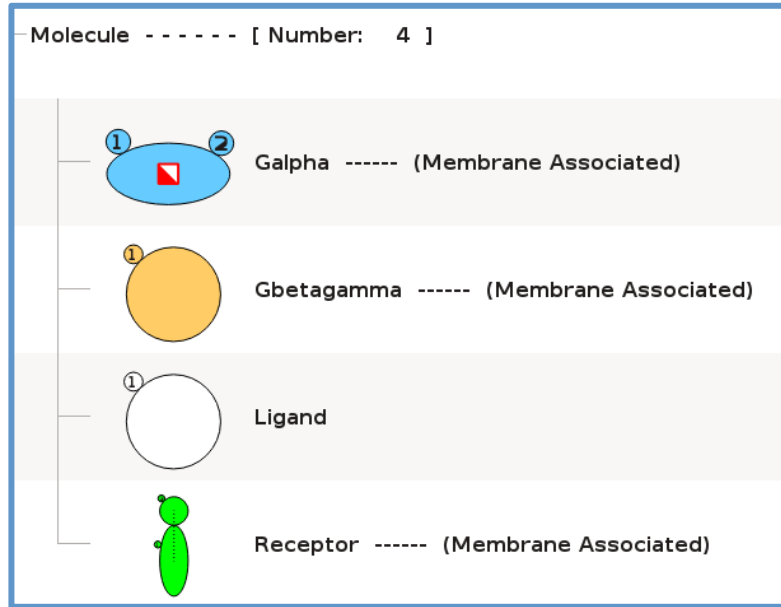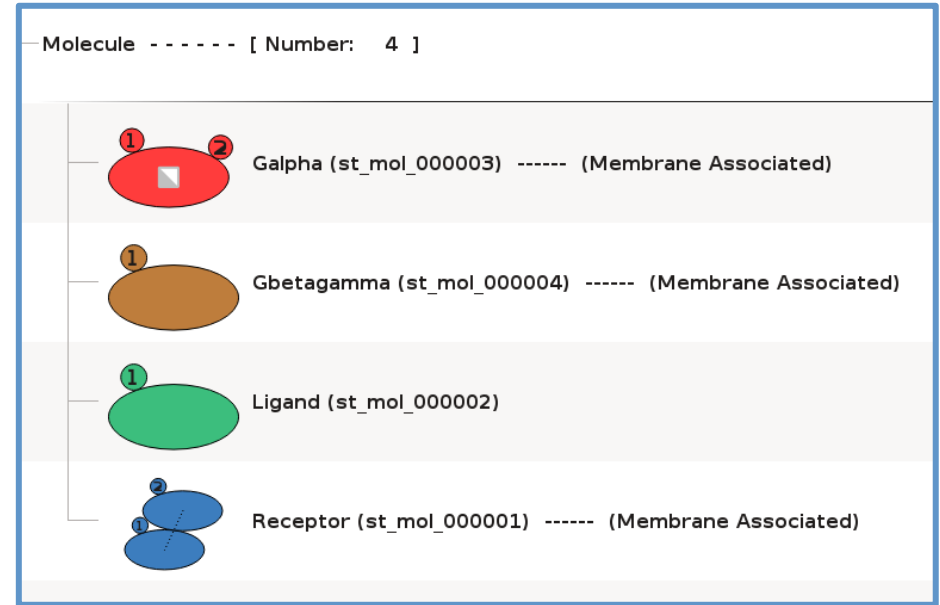
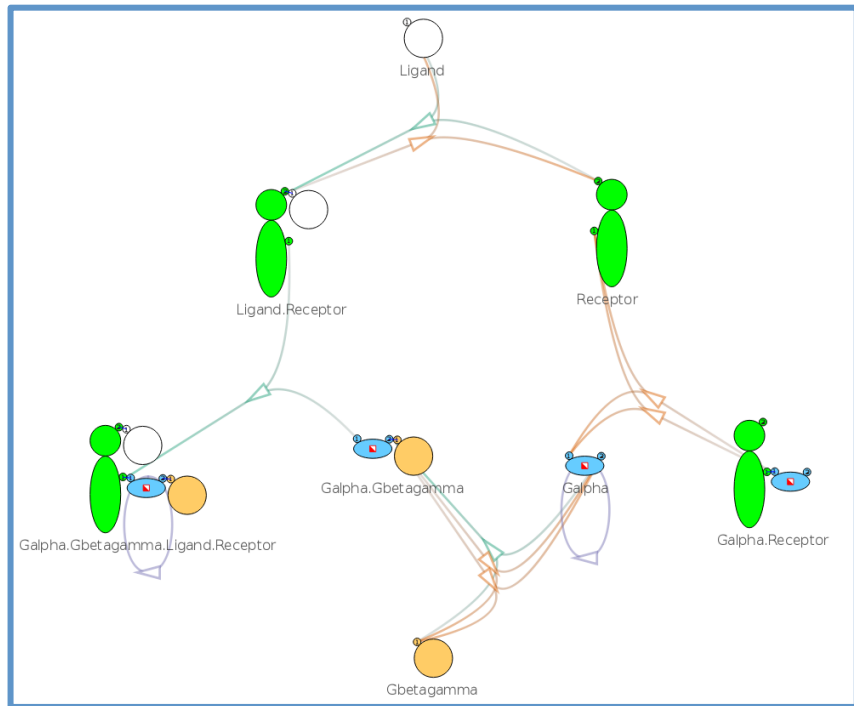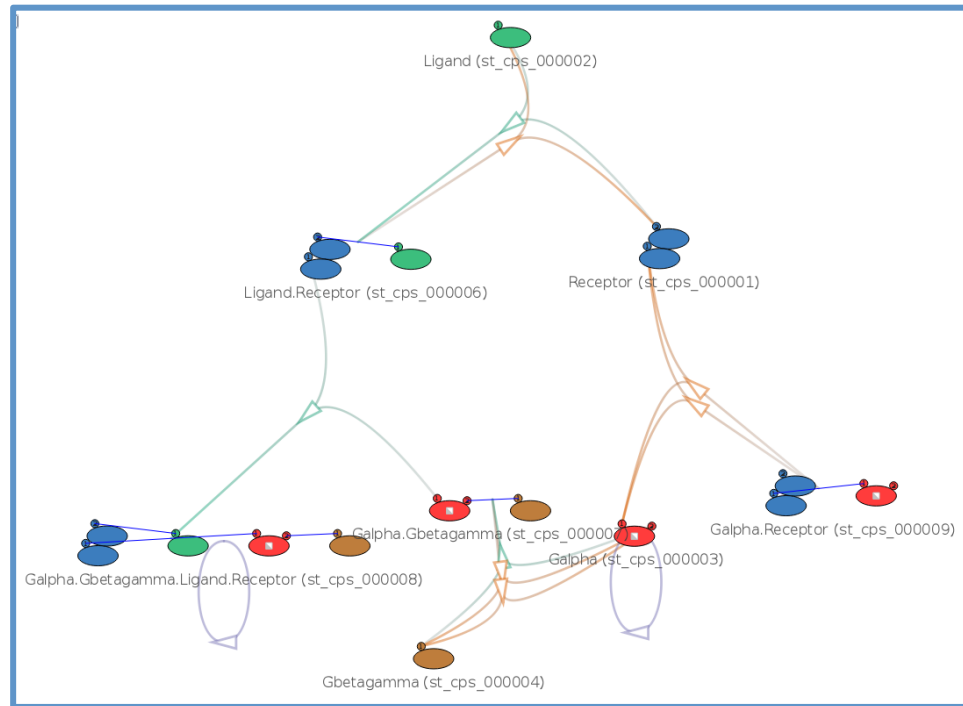# Example: Simmune – SBML Multi – Simmune

Original

Imported

Simmune – Multi – Simmune (G Proteins)

Original

Imported

Example: BioNetGen – Multi – Simmune

Simple EGFR BioNetGen Model

```
1  begin model
2  begin parameters
3
4      NA 6.02e23    # Avogadro's number (molecues/mol)
5      f  1          # Fraction of the cell to simulate
6      Vo f*1e-10    # Extracellular volume=1/cell_density (L)
7      V  f*3e-12    # Cytoplasmic volume (L)
8      # Inital amount of ligand (20 nM)
9      EGF_init 20*1e-9*NA*Vo # convert to copies per cell
10     # Initial amounts of cellular components (copies per cell)
11     EGFR_init f*1.8e5
12     Grb2_init f*1.5e5
13     Sos1_init f*6.2e4
14     # Rate constants
15     # Divide by NA*V to convert bimolecular rate constants
16     # from /M/sec to /(molecule/cell)/sec
17     kp1 9.0e7/(NA*Vo) # ligand-monomer binding
18     km1 0.06          # ligand-monomer dissociation
19     kp2 1.0e7/(NA*V)  # aggregation of bound monomers
20     km2 0.1           # dissociation of bound monomers
21     kp3 0.5           # dimer transphosphorylation
22     km3 4.505         # dimer dephosphorylation
23     kp4 1.5e6/(NA*V)  # binding of Grb2 to receptor
24     km4 0.05          # dissociation of Grb2 from receptor
25     kp5 1.0e7/(NA*V)  # binding of Grb2 to Sos1
26     km5 0.06          # dissociation of Grb2 from Sos1
27     deg 0.01          # degradation of receptor dimers
28
29  end parameters
30
31  begin molecule types
32
33     EGF(R)
34     EGFR(L,CR1,Y1068~U~P)
35     Grb2(SH2,SH3)
36     Sos1(PxxP)
37
38  end molecule types
```
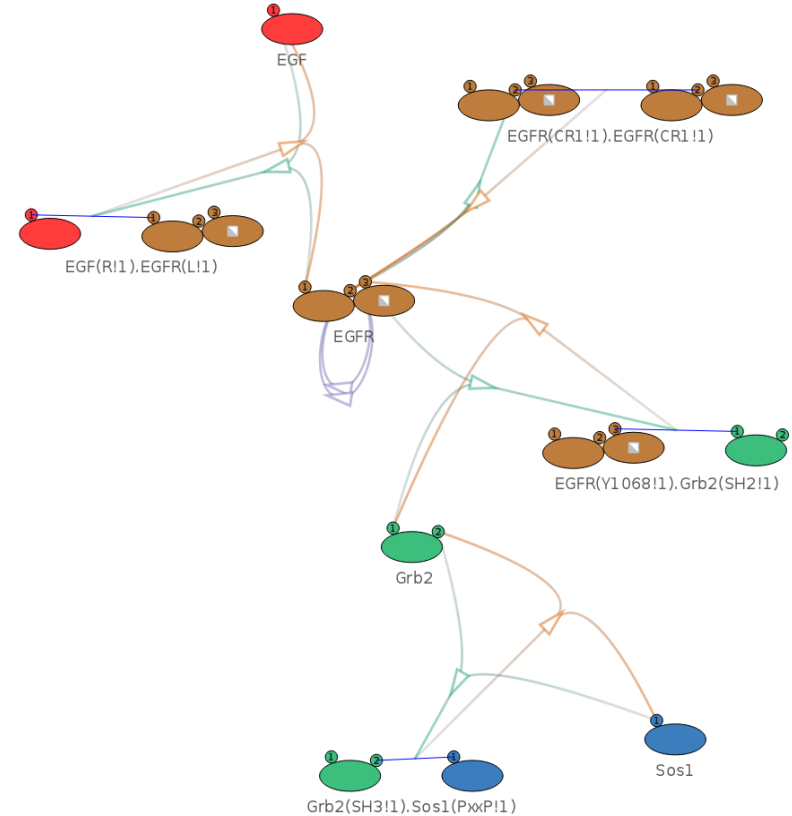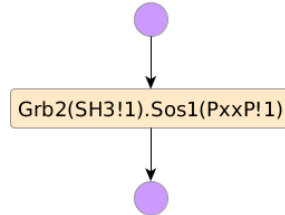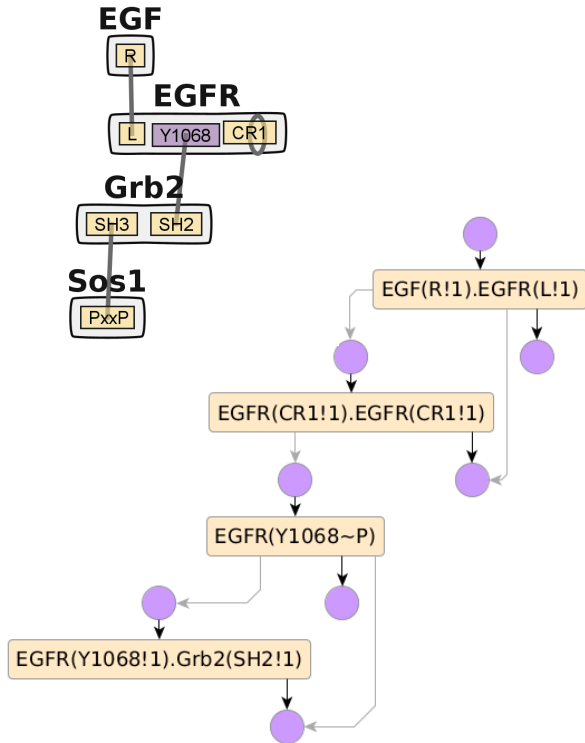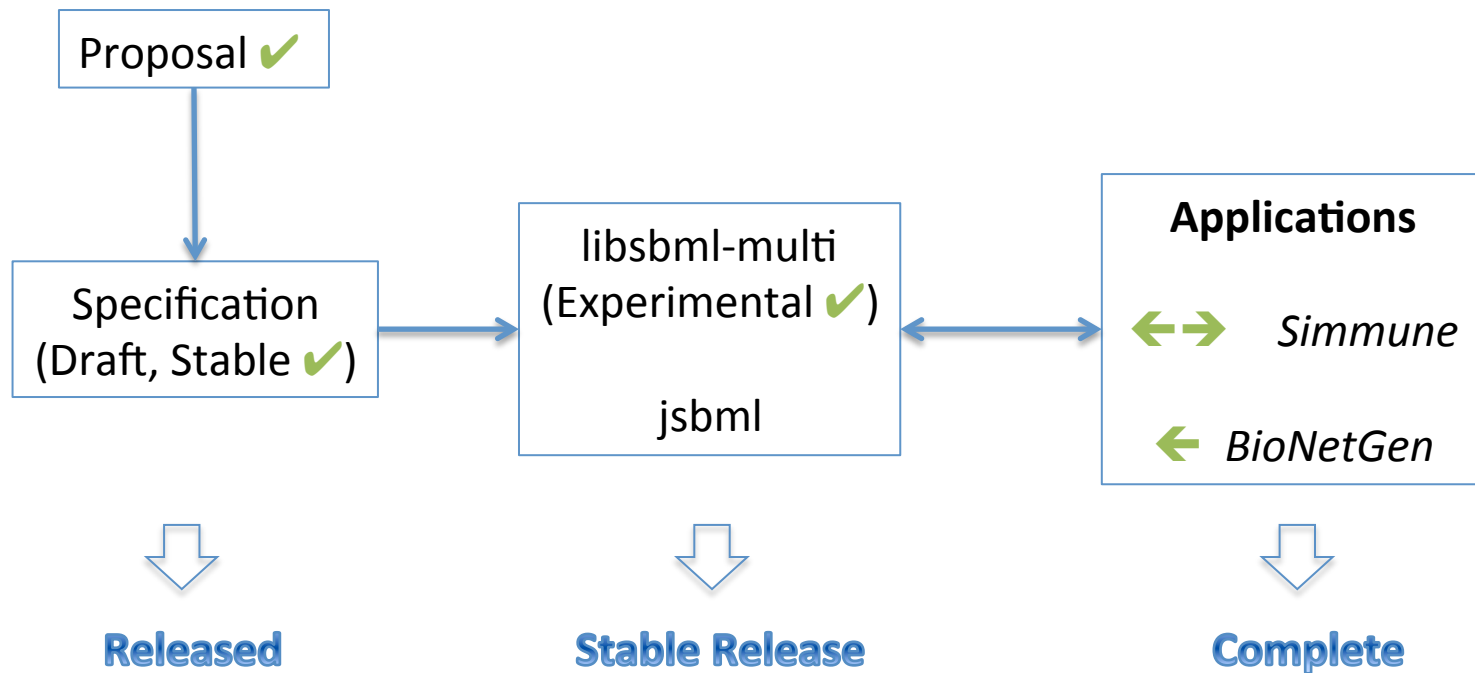
```
40  begin seed species
41
42     EGF(R)               0
43     EGFR(L,CR1,Y1068~U) EGFR_init
44     Grb2(SH2,SH3)        Grb2_init
45     Sos1(PxxP)           Sos1_init
46
47  end seed species
48
49  begin observables
50
51     O1: Molecules EGFR_tot  EGFR()
52     O2: Molecules Lig_free  EGF(R)
53     O3: Species   Dim       EGFR(CR1!+)
54     O4: Molecules RP         EGFR(Y1068~P!?)
55     O5: Molecules Grb2_Sos1 Grb2(SH2,SH3!1).Sos1(PxxP!1) # Cytosolic Grb2-Sos1
56     O6: Molecules Sos1_act  EGFR(Y1068!1).Grb2(SH2!1,SH3!2).Sos1(PxxP!2)
57
58  end observables
59
60  begin reaction rules
61
62     # Ligand-receptor binding
63     R1: EGFR(L,CR1) + EGF(R) <-> EGFR(L!1,CR1).EGF(R!1) kp1,km1
64     # Receptor-aggregation
65     R2: EGFR(L!+,CR1) + EGFR(L!+,CR1) <-> EGFR(L!+,CR1!1).EGFR(L!+,CR1!1) kp2,km2
66     # Transphosphorylation of EGFR by RTK
67     R3: EGFR(CR1!+,Y1068~U) -> EGFR(CR1!+,Y1068~P) kp3
68     # Dephosphorylation
69     R4: EGFR(Y1068~P) -> EGFR(Y1068~U) km3
70     # Grb2 binding to pY1068
71     R5: EGFR(Y1068~P) + Grb2(SH2) <-> EGFR(Y1068~P!1).Grb2(SH2!1) kp4,km4
72     # Grb2 binding to Sos1
73     R6: Grb2(SH3) + Sos1(PxxP) <-> Grb2(SH3!1).Sos1(PxxP!1) kp5,km5
74     # Receptor dimer internalization/degradation
75     #R7: EGF(R!1).EGF(R!2).EGFR(L!1,CR1!3,Y1068).EGFR(L!2,CR1!3,Y1068) -> 0 deg DeleteMole
76
77  end reaction rules
78  end model
```

BioNetGen – Multi – Simmune (Simple EGRR)

Next

Proposal ✔

Specification
(Draft, Stable ✔)

libsbml-multi
(Experimental ✔)

jsbml

Applications

← → *Simmune*

← *BioNetGen*

Released

Stable Release

Complete

Resources and References

- SBML Multi Package
  - SBML Multi website: http://sbml.org/Documents/Specifications/SBML_Level_3/Packages/multi
  - Current specification: https://sourceforge.net/p/sbml/code/HEAD/tree/trunk/specifications/sbml-level-3/version-1/multi/spec/sbml-multi_spec_1.0.7.pdf
- libsbml-multi
  - https://sourceforge.net/projects/sbml/files/libsbml/5.14.0-experimental/
- Simmune
  - Simmune project: https://www.niaid.nih.gov/research/simmune-project
  - SimModeler: "The Simmune Modeler visual interface for creating signaling networks based on bi-molecular interactions." *Bioinformatics*. 29(9): 1229-1230, 2013
  - NetworkViewer: "Network Viewer: Visualizing biochemical reaction networks with on-demand detailed rendering of user-selected sub-networks." *BMC Systems Biology*. 8:70, 2014
- BioNetGen
  - BioNetGen: http://bionetgen.org
  - Visualization: http://biorxiv.org/content/early/2016/09/09/074138

Acknowledgments

- Martin Meier-Schellersheim
- Jose Juan Tapia Valenzuela (BioNetGen SBML-Multi exporter)
- Libsbml-multi
    - Sarah Keating
    - Frank Bergmann
- SBML Multi Spec and Proposal
    - Lucian Smith
    - Nicolas Le Novère and Anika Oellrich
- SBML Multi Development
    - Michael Hucka
    - jsbml team
    - SBML Multi community (SBML Multi mailing list)
    - NIH/NIAID/LSB

Thank You!