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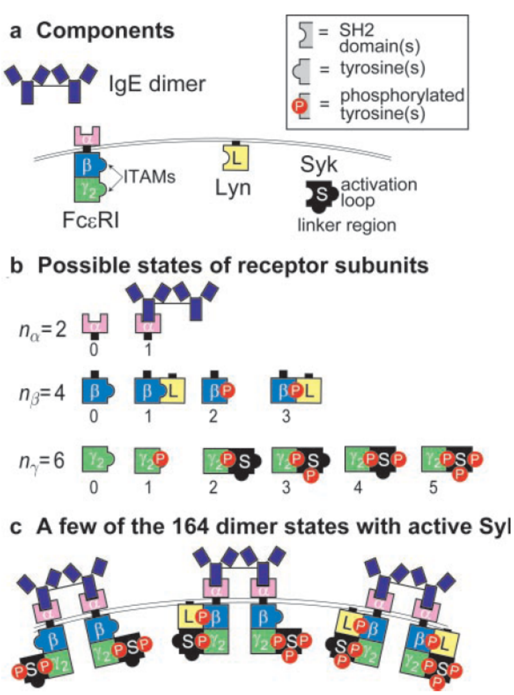
SBML L3: features necessary for description of rule-based modeling

1 Introduction

This document describes proposed features for inclusion in Systems Biology Markup Language (SBML) Level 3 that will enable the description of large chemical entities that are composed from other chemical entities and rule-based operations on such entities.

This document is not a complete proposal of SBML Level 3, but it presents features that are necessary for rule-based modeling specification and that should be incorporated into SBML Level 3, namely multi-state multi-component species located in several compartments that undergo modifications of different components and bind multiple binding partners in multiple compartments. We will discuss how to encode in SBML:

1. (1) Multi-state multi-component species expressed as typed graphs with explicit representation of the connectivity of species' components.
2. (2) Reactions in the form of graph transformations.
3. (3) Patterns that select groups of species having user-specified properties.
4. (4) Rules that define transformations of sets of species selected by some pattern.



In what follows we will consider a model for the early events in Fc_RI signaling induced by a bivalent ligand (Goldstein et al, 2002 and Faeder et al., 2003) *(a)* The bivalent ligand shown is a covalently cross-linked IgE dimer. The tetrameric form of FceRI, the high affinity receptor for IgE, consists of an alpha subunit that binds IgE, a beta subunit, and a disulfide-linked dimer of gamma subunits. The alpha and beta subunits contain ITAMs that become phosphorylated on tyrosine residues. The membrane-associated kinase Lyn can associate with the unphosphorylated or phosphorylated beta subunit. The cytosolic kinase Syk associates with a doubly phosphorylated gamma ITAM. On the representations of the kinases, notches indicate SH2 domains. The tandem SH2 domains of Syk are lumped together in the representation. On beta, gamma, and Syk, bumps represent groups of tyrosines that are lumped in the model as single targets for phosphorylation. On Syk, the model distinguishes tyrosines in the linker region, which are phosphorylated by Lyn, and those in the activation loop, which are phosphorylated by Syk. (*b*) The alpha subunit can be bound to ligand or unbound (two states of alpha). The beta subunit can be unphosphorylated or phosphorylated, with or without associated Lyn (four states of beta). The gamma dimer can be unphosphorylated or phosphorylated, and the phosphorylated form can be bound to Syk in any of four states of phosphorylation (six states of gamma). (*c*) There are 300 possible states for crosslinked FceRI dimers, of which 164 contain autophosphorylated Syk. Three of these states containing active Syk are shown.

2 New data needed for rule-based specification of multi-state multi-component species

Below we specify blocks in SBML specification that need to be added or modified in order to specify a rule-based model of FceRI (Faeder et al., 2003):

- **componentTypes – new feature (optional)**. They serve as “minimal” indivisible elements, construction blocks for species.
- **physicalEntities – new feature (optional)**. The name is chosen to be consistent with the term in BioPAX ontology. They serve as a higher hierarchical level of construction blocks for species.
- **SpeciesTypes – modified**. In addition to current use as a selector of species located in multiple compartments, it is used as pattern that selects any arbitrary user-specified sets of species. In particular, all physicalEntities are now speciesTypes.
- **Species – modified**. As before, species are uniquely defined entities. Species have the same use as in SBML L2: specify initial concentrations and be referenced as reactants or products in reactions. New feature is that each species has an internal structure consisting of physicalEntities connected either directly or through bonds between components. Each species may be of several speciesTypes.
- **Reactions – modified**. SpeciesReference may be replaced with speciesTypeReference, then reaction operates on the set of species and effectively becomes a reaction rule (although no special tag for reaction rule is introduced). Depending on whether reactants or products are uniquely defined species; it can be a regular reaction or a reaction rule.

3 componentTypes

A component represents an independent module of a chemical species and is capable of assuming one of any number of user-enumerated states. A common use of the component construct might be to define a prototypical phosphorylation site:

```
<componentType id="p-site" name="site_of_phosphorylation">
    <listOfComponentTypeStates>
        <componentTypeState id="u" name="unphosphorylated" default="true"/>
        <componentTypeState id="p" name="phosphorylated"/>
    </listOfComponentTypeStates>
</componentType>
```

The component above, "p-site", is capable of assuming one of two states, an “unphosphorylated” state, and a "phosphorylated" state. Any species whose definition includes this component will have its state space doubled in that all other states of the species may occur with either the unphosphorylated or phosphorylated component.

componentType
id : SId name : string {use="optional"} state: state [0..*] {use="optional"} compartment

maxExternalBonds: [0..*] {use="optional"; default="1"}
maxInternalBonds: [0..*] {use="optional"; default="0"}
externalConnectivity: "unspecified" , , “bound”, “unbound”
{ use="optional"; default="unbound"}
internalConnectivity: "unspecified" , “bound”, “unbound”
{ use="optional"; default="unbound"}

For the model of interest, the list of components will look as follows:

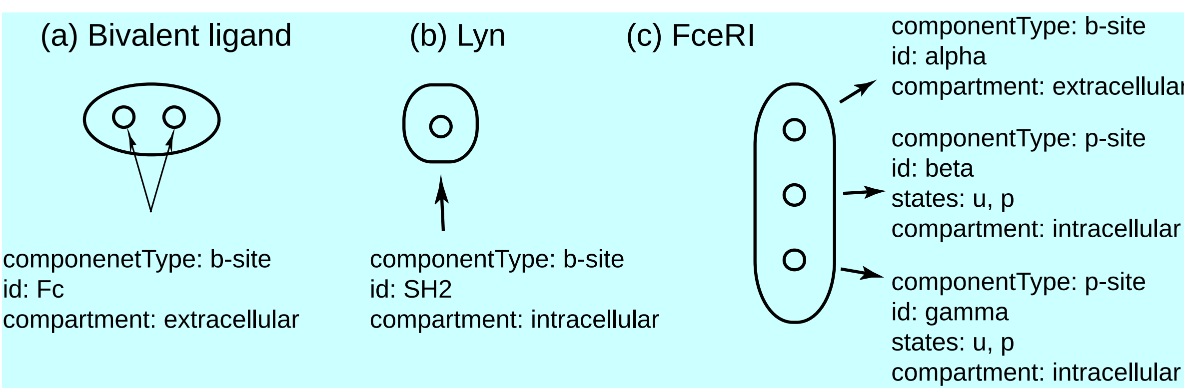
```
<listOfComponentTypes>
  <componentType id="b-site" name="site_of_binding"/>
  <componentType id="p-site" name="site_of_phosphorylation">
     <listOfStates>
        <state id="u" name="unphosphorylated" default="true"/>
        <state id="p" name="phosphorylated" />
      </listOfStates>
  </componentType>
</listOfComponentTypes>
```

NB:

1. state has an attribute default, which specifies which value of state is used when not explicitly declared in species description.
2. We keep this list as simple as possible, all searchable information will go into annotations.

4 physicalEntities

A physicalEntity is an optional feature that specifies the first level in hierarchy of speciesTypes.

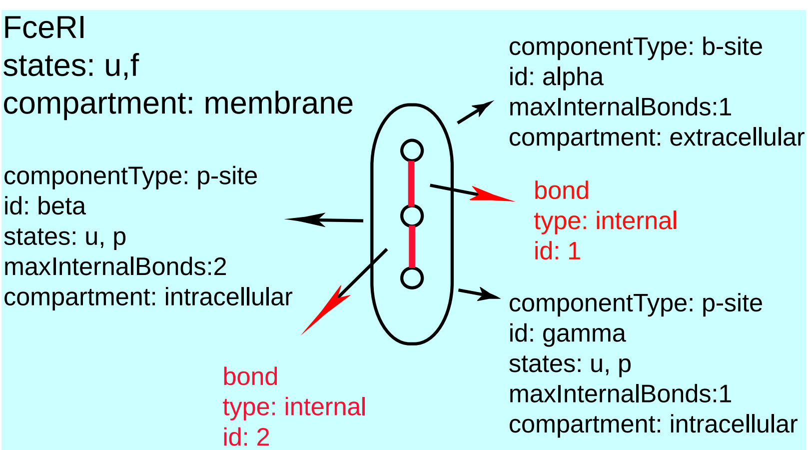



```
<physicalEntity id="Lig">
   <listOfComponents>
      <component id="Fc" componentType="b-site" multiplicity="2" compartment="extracellular"/>
   </listOfComponents>
</physicalEntity>

<physicalEntity id="Lin">
   <listOfComponents>
```

```
      <component id="SH2" componentType="p-site" compartment="intracellular"/>
   </listOfComponents>
</physicalEntity>

<physicalEntity id="FceRI">
   <listOfComponents>
      <component id="alpha" componentType="b-site" compartment="extracellular"/>
      <component id="beta" componentType="p-site" compartment="intracellular"/>
      <component id="gamma" componentType="p-site" compartment="intracellular"/>
   </listOfComponents>
</physicalEntity>
```

Note that
(1) Component may have an optional attribute “multiplicity” – the number of identical components within physical entity.
(2) Component may have an optional attribute “compartment” - restricting binding partners of this component to only those located within this compartment.

Components may have a scope which may either be global or constrained to within a specific molecular context. Global components are defined under a listOfComponentTypes element which occurs as a direct descendant of the sbml model element. In the example below, internal bonds are allowed and components within physical entity are connected. In addition, one more component state for gamma is included. PhysicalEntities itself may have states and compartment. Compartment for physicalEntity restricts only direct interactions of this physicalEntity, but not interactions of its components.




```
<physicalEntity id="FceRI" compartment=="membrane">
    <listOfStates>
          <state id="u" name="unfolded" />
           <state id="f" name="folded" />
   </listOfStates>
   <listOfComponents>
      <component id="alpha" componentType="b-site" compartment="extracellular"
maxInternalBonds ="1" internalConnectivity ="bound">
            <listOfBondReferences>
```

```
            <bondReference bond="1"/>
        </listOfBondReferences>
    </component>
    <component id="beta" componentType="p-site" compartment="intracellular"
maxInternalBonds ="2" internalConnectivity ="bound">
        <listOfBondReferences>
            <bondReference bond="1"/>
            <bond Reference bond="2"/>
        </listOfBondReferences>
    </component>
    <component id="gamma" componentType="p-site" compartment="intracellular"
maxInternalBonds ="1" internalConnectivity ="bound">
         <listOfStates>
              <state id="u" name="unphosphorylated" />
              <state id="p" name="phosphorylated" />
              <state id="m" name="modified" />
         </listOfStates>
        <listOfBondReferences>
            <bondReference bond="2"/>
        </listOfBondReferences>
    </component>
  </listOfComponents>
  <listOfBonds>
      <bond id="1" type=="internal" />
      <bond id="2" type=="internal" />
  </listOfBonds>
</physicalEntity>
```

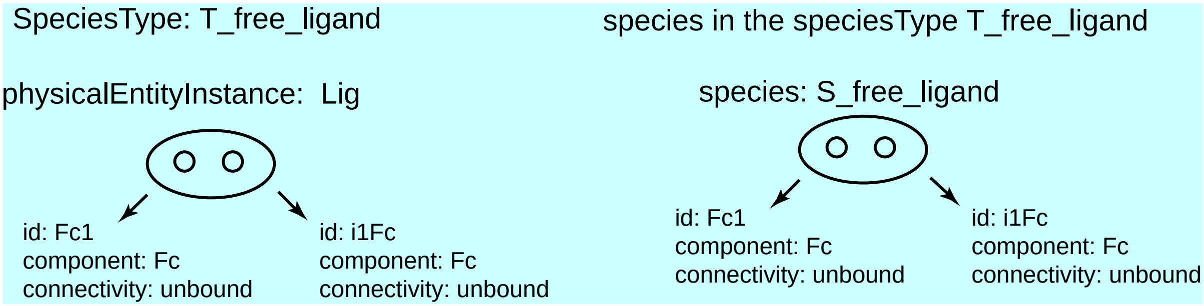
5 speciesType and species

<u>Species</u> are similar to SBML L2 – uniquely defined objects that may have location, initial amount, boundary condition etc. However, now species have internal structure – they consist of fully defined physical entities or species types. Species can be viewed as graphs with all participating physical entities and their components being fully defined. All unspecified connectivities having value ”unbound", all unspecified states having default value.

<u>speciesType</u> is a key feature of this SBML Level 3 proposal. It extends the speciesType of SBML L2 and defines a set of chemical species with specified shared features. SpeciesType can be declared as sub-graph consisting of either physicalEntities, or of another speciesTypes (that in turn consist of physicalEntities). SpeciesTypes are specified independently of compartments. The only reference to compartments is through components.

5.1 speciesType declared by a single physicalEntitiy and including a single species

The speciesType “T_free_ligand” includes a physical entity Lig with all components being unbound.




```
<speciesType id="T_free_ligand">
    <listOfPhysicalEntitiyInstances>
        <physicalEntityInstance physicalEntity="Lig" id="iLig">
            <listOfComponentInstances>
                <componentInstance id="i1Fc" component="Fc" connectivity="unbound"/>
                <componentInstance id="i2Fc" component="Fc" connectivity="unbound"/>
            </listOfComponentInstances>
        </ physicalEntity Instance>
    </listOfPhysicalEntityInstances>
</speciesType>
```

The speciesType “T_free_ligand” includes a single species, physicalEntity Lig, because all potential binding sites are declared unbound.

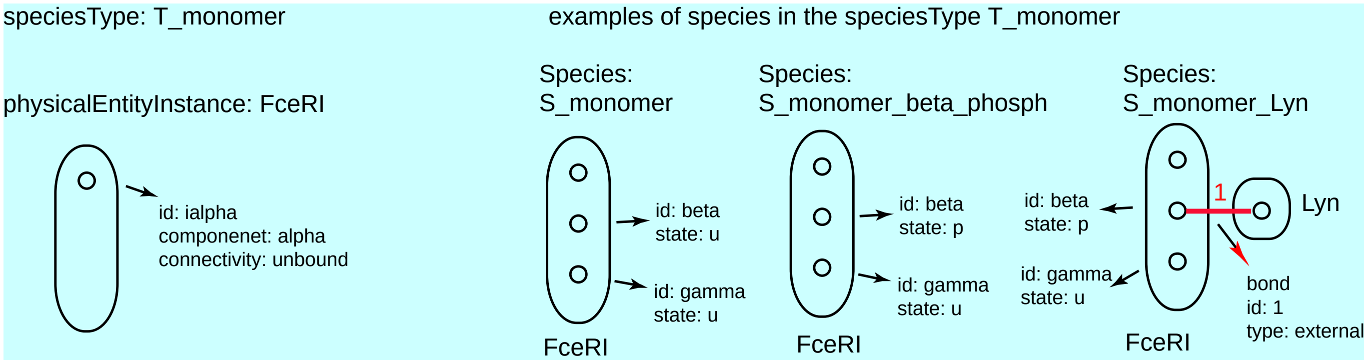
Please note that if we can specify direct binding to physicalEntity Lig, this spesiesType may consist of more than one species (direct binding to physicalEntity and not component is allowable, very much like states can be assigned not only to components but to any physical entity or species type).

There are two ways to declare a species: as a reference to physical entity or to a species type:

```
<species id="S_free_ligand">
    <listOfSpeciesTypeInstances>
        <speciesTypeInstance speciesType="T_free_ligand" id="iLig">
    </listOfSpeciesTypeInstances>
</speciesType>
```

```
<species id="S_free_ligand">
    <listOfPhysicalEntityInstances>
        <physicalEntityInstance physicalEntity="Lig" id="iLig">
    </listOfPhysicalEntity Instances>
</speciesType>
```

5.2 speciesType declared by a single physicalEntitiy but including multiple species



The speciesType T_monomer includes all species containing FceRI. The common among all these species that FceRI is not attached to ligand. If dimerization is only ligand-induced, then it means that all species in this speciesType are monomeric species. Meanwhile, any combination of states for beta and gamma components are allowed, and all species that involve other physicalEntities connected through beta or gamma components or through direct binding to FceRI are included in this speciesType.

```
<speciesType id="T_monomer">
    <listOfPhysicalEntityInstances>
        < physicalEntityInstance physicalEntity="FceRI" id="iFceRI">
            <listOfComponentInstances>
                <componentInstance id="ialpha" component="alpha" connectivity="unbound"/>
            </listOfComponentInstances>
        </ physicalEntityInstance>
    </listOfPhysicalEntityInstances>
</speciesType>
```

Below are some species that belong to the speciesType T_monomer, for example, a species that is a physical entity FceRI in default state (beta and gamma components have state p, all components are unbound):

```
  <species id="S_ monomer">
     <listOfSpeciesTypeInstances>
        <speciesTypeInstance speciesType="monomer" id="iFceRI"/>
    </listOfSpeciesTypeInstances>
</species>
```

More complicated example involves a physicalEntity FceRI with some states of components being overridden:

```
<species id=" S_monomer_beta_phosph">
     <listOfSpeciesTypeInstances>
        <speciesTypeInstance speciesType="T_monomer" id="iFceRI">
            <listOfComponentInstances>
                <componentInstance id="ibeta" component="beta" state="p"/>
            </listOfComponentInstances>
        </speciesTypeInstance>
    </listOfSpeciesTypeInstances>
```

```
</species>
```

Let’s note that although a speciesType includes a single physicalEntity, species in this type may include multiple physicalEntities:

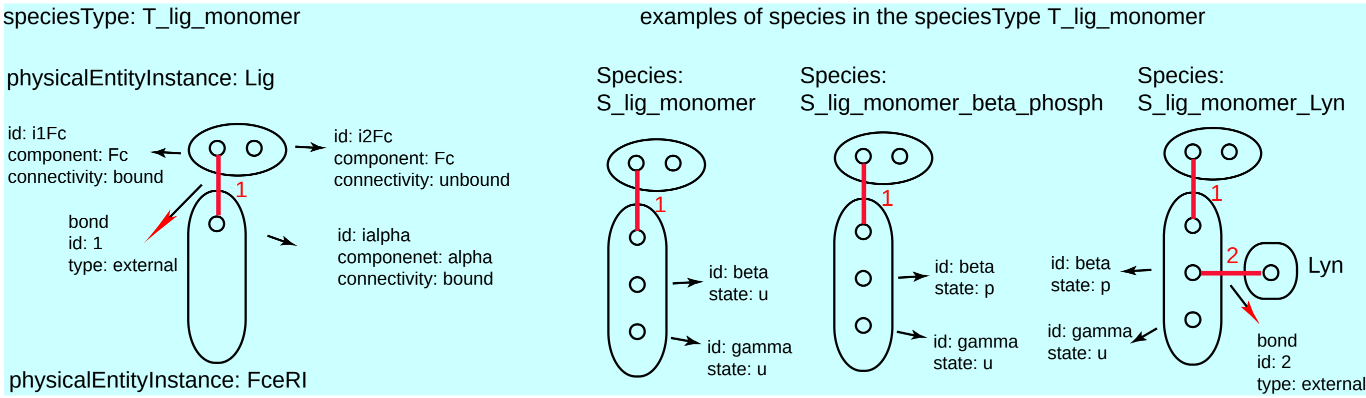
```
  <species id="S_monomer_Lyn" >
     <listOfPhysicalEntityInstances>
        < physicalEntityInstance physicalEntity="Lyn" id="iLyn">
             <listOfComponentInstances>
                 <componentInstance id="iSH2" component="SH2" connectivity="bound"/>
                    <listOfBondReferences>
                           <bondReference bond="1"/>
                    </listOfBondReferences>
            </listOfComponentInstances>
        </ physicalEntityInstance>
        < physicalEntityInstance physicalEntity="FcERI" id="iFceRI">
             <listOfComponentInstances>
                 <componentInstance id="ibeta" component="beta" state="p" connectivity="bound"/>
                    <listOfBondReferences>
                           <bondRreference bond="1"/>
                    </listOfBondReferences>
            </listOfComponentInstances>
        </ physicalEntityInstance>
    </listOfPhysicalEntityInstances>
     <listOfBonds>
          <bond id="1" type="external"/>
     </listOfBonds>
</species>
```

NB: It is very important to notice that each species may belong to multiple speciesTypes! Say, S_monomer_Lyn belongs to both T_monomer speciesType and to T_Lyn speciesType, defined below:

```
<speciesType id="T_Lyn">
    <listOfPhysicalEntityInstances>
        < physicalEntityInstance physicalEntity="Lyn" id="iLyn"/>
    </listOfPhysicalEntityInstances>
</speciesType>
```

This speciesType includes all species that include a physicalEntity Lyn.

5.3 speciesType declared by multiple physicalEntities



The speciesType “ligand-receptor” includes all species that include FceRI and ligand connected through binding of Fc component of ligand to alpha component of FceRI. However, the second Fc component of ligand is unbound. If dimerization is only ligand-induced, then it means that are monomeric species. Meanwhile, any combination of states for beta and gamma components are allowed, and all species that involve other physicalEntities connected through beta or gamma components or through direct binding to FceRI are included in this speciesType.

```
<speciesType id="T_lig_monomer ">
    <listOfPhysicalEntityInstances>
        < physicalEntityInstance physicalEntity="Lig" id="iLig">
            <listOfComponentInstances>
                <componentInstance id="i1Fc" component="Fc" connectivity="bound"/>
                    <listOfBondReferences>
                            <bondReference bond="1"/>
                    </listOfBondReferences>
                </componentInstance>
                <componentInstance id="i2Fc" component="Fc" connectivity="unbound"/>
            </listOfComponentInstances>
        </ physicalEntityInstance>
        < physicalEntityInstance physicalEntity="FcERI" id="iFceRI">
            <listOfComponentInstances>
                <componentInstance id="ialpha" component="alpha" connectivity="bound"/>
                    <listOfBondReferences>
                            <bondReference bond="1"/>
                    </listOfBondReferences>
                </componentInstance>
            </listOfComponentInstances>
        </ physicalEntityInstance>
    </listOfPhysicalEntityInstances>
    <listOfBonds>
          <bond id="1" type=="external"/>
    </listOfBonds>
</speciesType>
```

Below is an example of species of speciesType T_lig_monomer that involves a physicalEntity Lyn bound to beta component. First, we specify it without reference to speciesType:

```
<species id="S_lig_monomer_Lyn ">
    <listOfPhysicalEntityInstances>
        <physicalEntityInstance physicalEntity="Lig" id="iLig">
             <listOfComponentInstances>
                 <componentInstance id="i1Fc" component="Fc" connectivity="bound"/>
                    <listOfBondReferences>
                           <bondReference bond="1"/>
                    </listOfBondReferences>
                 </componentInstance>
                 <componentInstance id="i2Fc" component="Fc" connectivity="unbound"/>
            </listOfComponentInstances>
        </physicalEntityInstance>
        <physicalEntityInstance physicalEntity="FcERI" id="iFceRI">
             <listOfComponentInstances>
                 <componentInstance id="ialpha" component="alpha" connectivity="bound"/>
                    <listOfBondReferences>
                           <bondReference bond="1"/>
                    </listOfBondReferences>
                 </componentInstance>
                 <componentInstance id="ibeta" component="beta" state="p" connectivity="bound"/>
                    <listOfBondReferences>
                           <bondReference bond="2"/>
                    </listOfBondReferences>
                 </componentInstance>
            </listOfComponentInstances>
        </physicalEntityInstance>
        <physicalEntityInstance physicalEntity="Lyn" id="iLyn">
             <listOfComponentInstances>
                 <componentInstance id="iSH2" component="SH2" connectivity="bound"/>
                    <listOfBondReferences>
                           <bondReference bond="2"/>
                    </listOfBondReferences>
                 </componentInstance>
            </listOfComponentInstances>
        </physicalEntityInstance>
    </listOfPhysicalEntityInstances>
    <listOfBonds>
          <bond id="1" type=="external"/>
          <bond id="2" type=="external"/>
    </listOfBonds>
</speciesType>
```

The same species can be declared as a reference to speciesType, and then all id’s are inherited from this speciesType**.**

```
<species id="S_lig_monomer ">
    <listOfSpeciesTypeInstances>
        <speciesTypeInstance speciesType="T_lig_monomer" id="iT_lig_monomer">
             <listOfComponentInstances>
                 <componentInstance id="ibeta" component="beta" state="p" connectivity="bound"/>
```

```
                <listOfBondReferences>
                    <bondReference bond="2"/>
                </listOfBondReferences>
            </componentInstance>
        </listOfComponentInstances>
    </speciesTypeInstance>
  </listOfSpeciesTypeInstances>
  <listOfPhysicalEntityTypeInstances>
    <physicalEntityInstance physicalEntity="Lyn" id="iLyn">
        <listOfComponentInstances>
            <componentInstance id="iSH2" component="SH2" connectivity="bound"/>
                <listOfBondReferences>
                    <bondReference bond="2"/>
                </listOfBondReferences>
            </componentInstance>
        </listOfComponentInstances>
    </physicalEntityInstance>
  </listOfPhysicalEntityTypeInstances>
  <listOfBonds>
      <bond id="2" type=="external"/>
  </listOfBonds>
</speciesType>
```

5.4 Hierarchical speciesType consisting of multiple speciesTypes

SpeciesTypes can refer to previously specified speciesTypes, with all previously non-speciefied components being specified. Here, id’s are inherited from speciesType description.

```
<speciesType id="T_ligand-receptor-beta-phosph">
  <listOfSpeciesTypeInstances>
    <speciesTypeInstance speciesType="ligand-receptor" id="iligand-receptor-beta-phosph">
        <listOfComponentInstances>
            <componentInstance id="ibeta" component="beta" state="p"/>
        </listOfComponentInstances>
    </speciesTypeInstance>
</speciesType>
```

Similarly, species can refer to previously specified speciesTypes.

```
<species id=" S_ligand-receptor-beta-phosph " >
  <listOfSpeciesTypeInstances>
    <speciesTypeInstance="ligand-receptor-beta-phosph">
        <listOfComponentInstances>
            <componentInstance id="ibeta" component="beta" state="p"/>
        </listOfComponentInstances>
    </speciesTypeInstance>
</species>
```

6 Specification of observables

Sometimes multiple species and speciesTypes correspond to a specific experimental observable. For example, to measure total phosphorylation of FceRI, we have to some up all species that have either beta or gamma or both chains phosphorylated. It is done through observable:

```
<observable id="Receptor-phosph">
  <listOfSpecies>
    <speciesReference species="S1 "/>
    <speciesReference species="S2"/>
  </listOfSpecie>
  <listOfSpeciesTypes>
    <speciesTypeReference speciesType="Receptor-beta-phosph"/>
    <speciesTypeReference speciesType="Receptor-gamma-phosph"/>
  </listOfSpeciesTypes>
</observable>
```

7 Specification of reactions

Reaction rules are used to generate chemical reactions from a list of chemical species by identifying sets of reactants and products.

Applying a reaction to a set of chemical species consists of the following steps:

- identify the group of species corresponding to each reactant in speciesType;
- for each combination of reactant species drawn from these groups, the rule is applied by replacing states, connectivities and bonds in reactant species with the corresponding states, connectivities and bonds in product species to define the products. In carrying out this replacement, states, connectivities and bonds that are not specified are inherited in product species from reactant species.
- the product species are then checked against the current list of chemical species and added to the list if they are not already present. The generated reaction can also be checked against the list of previously generated reactions to prevent duplication of reactions or to identify overlap between rules.

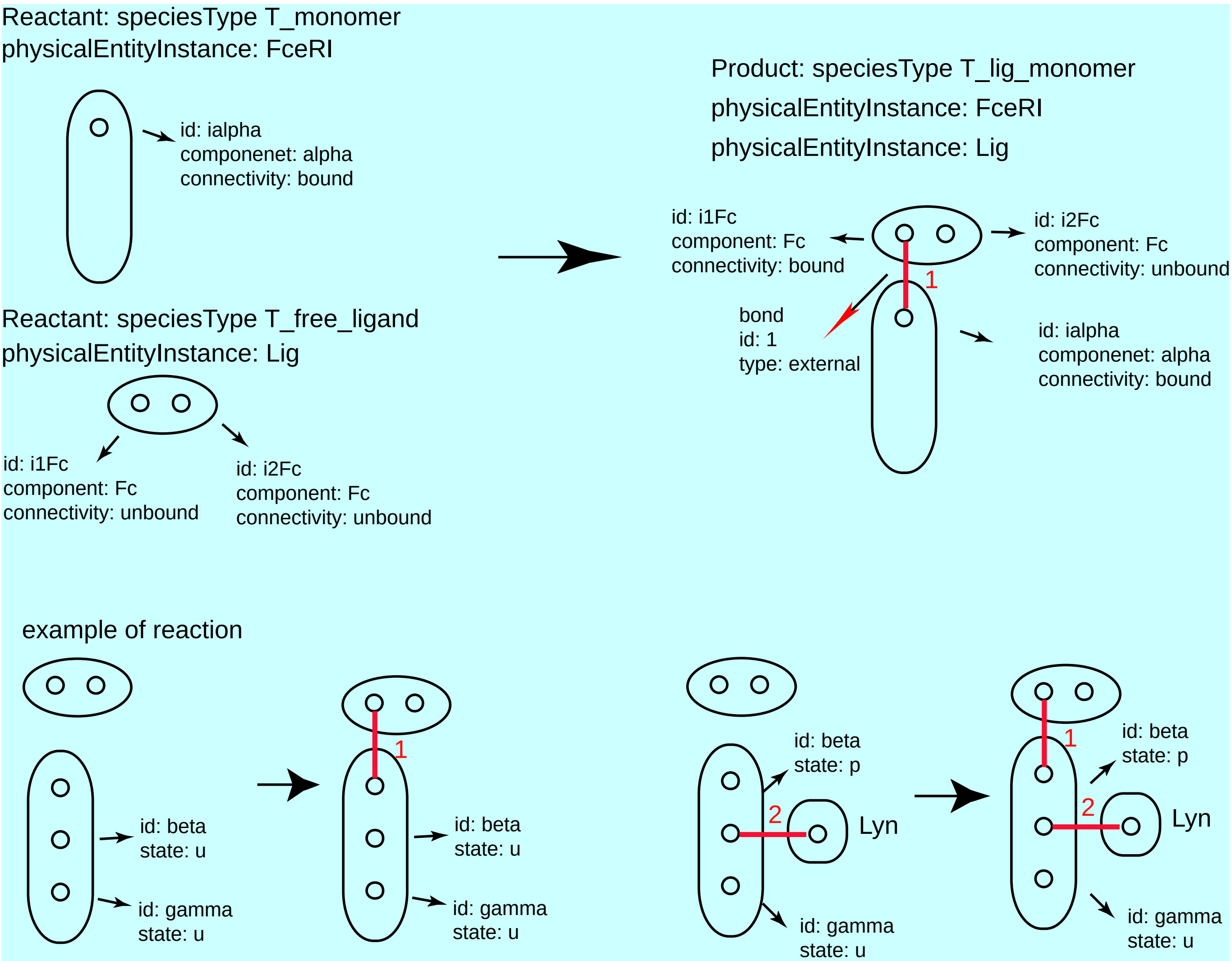
<u>*The main change: reactants and products are selected not as speciesReference, but as speciesTypeReference*</u>. Thus, if a reaction includes speciesTypereference in place of speciesReference, it is automatically a rule. Note that if a speciesTypeReference selects a single species, then the containing reaction is as in SBML L2.

If speciesTypes T_monomer, T_free_ligand" and T_lig_monomer are previously defined, ligand-binding reaction may be written in the following form (for clarity of XML examples, we describe only listOfReactants and listOfProducts; kineticLaw is omitted and will be considered later):

```
<reaction id="Ligand_bind" reversible="true">
    <listOfReactants>
        <speciesTypeReference speciesType="T_monomer"/>
        <speciesTypeReference species="T_free_ligand"/>
    </listOfReactants>
    <listOfProducts>
        <speciesTypeReference speciesType="T_lig_monomer"/>
```

</listOfProducts>
</reactionRule>

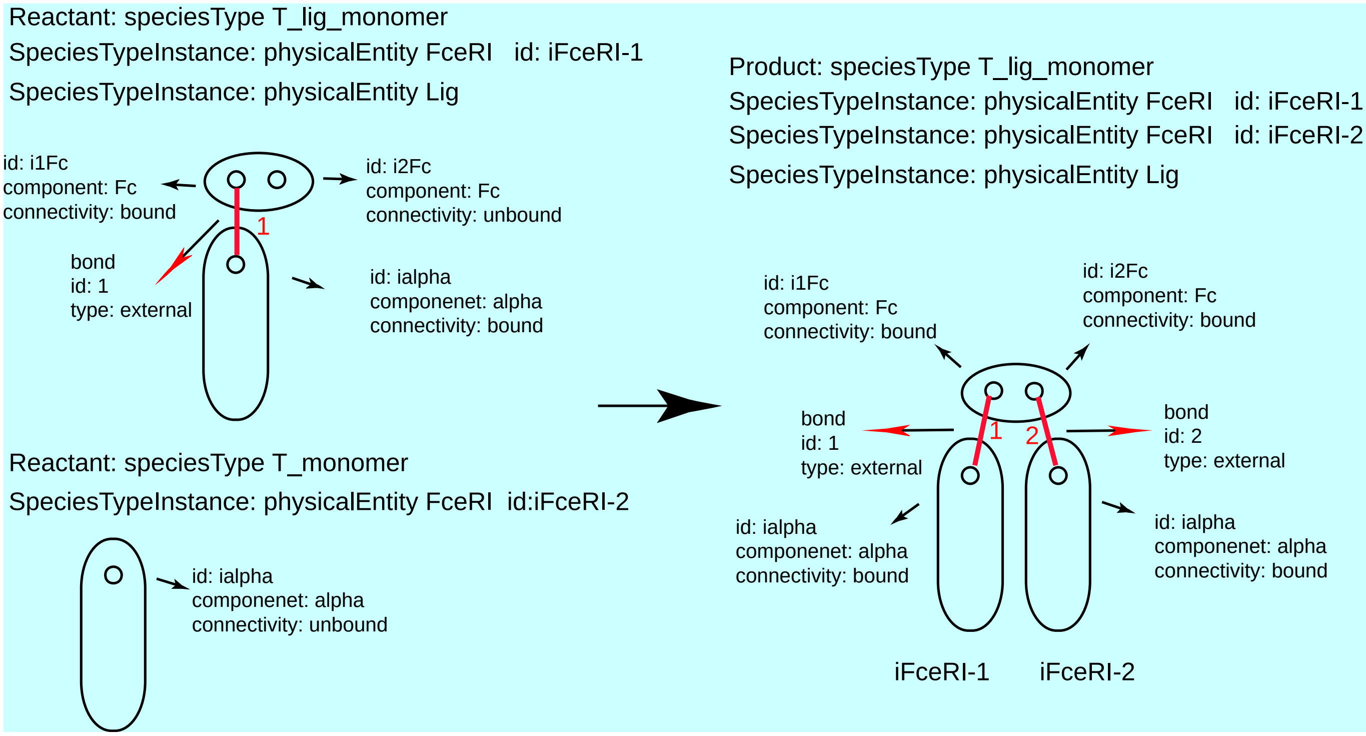
When we recall definition of these speciesTypes, we’ll see that reaction is uniquely recovered. However, in some cases, when components id’s are not unique, correspondence between components of reactants and products is difficult to recover. Thus, it is necessary to re-declare each speciesType implicitly with id's of reactants components inherited by products.



<reaction id="Ligand_bind" reversible="true">
<listOfReactants>
<speciesTypeReference speciesType="T_monomer">
<listOfPhysicalEntityInstances>
<physicalEntityInstance physicalEntity="FcERI" id="iFceRI">
<listOfComponentInstances>
<componentInstance id="ialpha" component="alpha" connectivity="unbound"/>
</listOfComponentInstances>
</physicalEntityInstance>
</listOfPhysicalEntityInstances>

```
          </speciesTypeReference>
          <speciesTypeReference speciesType="T_free_ligand">
            <listOfPhysicalEntityInstances>
              <physicalEntityInstance physicalEntity="Lig" id="iLig">
                <listOfComponentInstances>
                  <componentInstance id="i1Fc" component="Fc" connectivity="unbound"/>
                  <componentInstance id="i2Fc" component="Fc" connectivity="unbound"/>
                </listOfComponentInstances>
              </physicalEntityInstance>
            </listOfPhysicalEntityInstances>
          </speciesTypeReference>
      </listOfReactants>
      <listOfProducts>
        <speciesTypeReference speciesType="T_lig_monomer">
          <listOfPhysicalEntityInstances>
            <physicalEntityInstance physicalEntity="Lig" id="iLig">
              <listOfComponentInstances>
                <componentInstance id="i1Fc" component="Fc" connectivity="bound">
                  <listOfBondReferences>
                    <bondReference bond="1">
                  </listOfBondReferences>
                </componentInstance>
                <componentInstance id="i2Fc" component="Fc" connectivity="unbound"/>
              </listOfComponentInstances>
            </physicalEntityInstance>
            <physicalEntityInstance physicalEntity="FcERI" id="iFceRI">
              <listOfComponentInstances>
                <componentInstance id="ialpha" component="alpha" connectivity="bound">
                  <listOfBondReferences>
                    <bondReference id="1">
                  </listOfBondReferences>
                </componentInstance>
              </listOfComponentInstances>
            </physicalEntityInstance>
          </listOfPhysicalEntityInstances>
          <listOfBonds>
            <bond id="1" type="external">
          </listOfBonds>
        </speciesTypeReference>
    </listOfProducts>
</reactionRule>
```

The next is an example of ligand-induced dimerization reaction:




```
<reaction id="Dimerization" reversible="true">
    <listOfReactants>
        <speciesTypeReference speciesType="T_lig_monomer"/>
          <listOfPhysicalEntityInstances>
              <physicalEntityInstance physicalEntity="Lig" id="iLig">
                  <listOfComponentInstances>
                      <componentInstance id="i1Fc" component="Fc" connectivity="bound"/>
                          <listOfBondReferences>
                              <bondReference bond="1">
                          </listOfBondReferences>
                      <componentInstance id="i2Fc" component="Fc" connectivity="unbound"/>
                  </listOfComponentInstances>
              </physicalEntityInstance>
              <physicalEntityInstance physicalEntity="FcERI" id="iFceRI-1">
                  <listOfComponentInstances>
                      <componentInstance id="ialpha" component="alpha" connectivity="bound"/>
                          <listOfBondReferences>
                              <bondReference bond="1">
                          </listOfBondReferences>
                  </listOfComponentInstances>
              </physicalEntityInstance>
          </listOfPhysicalEntityInstances>
          <listOfBonds>
              <bond id="1" type="external">
          </listOfBonds>
```

```xml
        </speciesTypeReference>
        <speciesTypeReference speciesType="free-monomer">
            <listOfPhysicalEntityInstances>
                <physicalEntityInstance physicalEntity="FcERI" id="iFceRI-2">
                  <listOfComponentInstances>
                    <componentInstance id="ialpha" component="alpha" connectivity="unbound"/>
                  </listOfComponentInstances>
                </physicalEntityInstance>
            </listOfPhysicalEntityInstances>
          <physicalEntityReference/>
      </listOfReactants>
      <listOfProducts>
          <speciesTypeReference speciesType="bound-monomer"/>
            <listOfPhysicalEntityInstances>
                <physicalEntityInstance physicalEntity="Lig" id="iLig">
                    <listOfComponentInstances>
                        <componentInstance id="i1Fc" component="Fc" connectivity="bound"/>
                               <listOfBondReferences>
                                  <bondReference bond="1">
                               </listOfBondReferences>
                        <componentInstance id="i2Fc" component="Fc" connectivity="bound"/>
                               <listOfBondReferences>
                                  <bondReference bond="2">
                               </listOfBondReferences>
                    </listOfComponentInstances>
                 </physicalEntityInstance>
                 <physicalEntityInstance physicalEntity="FcERI" id="iFceRI-1">
                    <listOfComponentInstances>
                       <componentInstance id="ialpha" component="alpha" connectivity="bound"/>
                               <listOfBondReferences>
                                  <bondReference bond="1">
                               </listOfBondReferences>
                    </listOfComponentInstances>
                 </physicalEntityInstance>
                 <physicalEntityInstance physicalEntity="FcERI" id="iFceRI-2">
                    <listOfComponentInstances>
                       <componentInstance id="ialpha" component="alpha" connectivity="bound"/>
                               <listOfBondReferences>
                                  <bondReference bond="2">
                               </listOfBondReferences>
                    </listOfComponentInstances>
                 </physicalEntityInstance>
               </listOfPhysicalEntityInstances>
               <listOfBonds>
                   <bond id="1" type="external">
                   <bond id="2" type="external">
               </listOfBonds>
        </speciesTypeReference>
    </listOfProducts>
</reactionRule>
```

Not all bonds have to be completely defined. The example below illustrates how Lyn kinase associated with un-phosphorylated beta-chain transphosphorylates a receptor beta-chain in a complex. The exact mechanism of how two receptors are associated is not specified, but both extracellular domains of receptors are bound, that implies ligand-induced association.

```
<reaction id="beta-transphorylation" reversible="true">
  <listOfReactants>
    <speciesTypeReference speciesType="Receptor-Lyn-complex"/>
      <listOfPhysicalEntityInstances>
        <physicalEntityInstance physicalEntity="Lyn" id="iLyn">
          <listOfComponentInstances>
            <componentInstance id="iSH2" component="SH2" connectivity="bound"/>
                <listOfBondEnds>
                  <bondEnd id="1">
                </listOfBondEnds>
          </listOfComponentInstances>
        </physicalEntityInstance>
        <physicalEntityInstance physicalEntity="FcERI" id="iFceRI-1">
          <listOfComponentInstances>
            <componentInstance id="ibeta" component="beta" state="u" connectivity="bound"/>
                <listOfBondEnds>
                  <bondEnd id="1">
                </listOfBondEnds>
          </listOfComponentInstances>
        </physicalEntityInstance>
      </listOfPhysicalEntityInstances>
    </speciesReference>
    <speciesReference speciesType="receptor-in-complex">
      <listOfPhysicalEntityInstances>
        <physicalEntityInstance physicalEntity="FcERI" id="iFceRI-2">
          <listOfComponentInstances>
            <componentInstance id="ialpha" component="alpha" connectivity="bound"/>
            <componentInstance id="ibeta" component="beta" state="u"/>
          </listOfComponentInstances>
        </physicalEntityInstance>
      </listOfPhysicalEntityInstances>
    <speciesReference/>
  </listOfReactants>
  <listOfProducts>
    <speciesReference speciesType="Receptor-Lyn-complex"/>
      <listOfPhysicalEntityInstances>
        <physicalEntityInstance physicalEntity="Lyn" id="iLyn">
          <listOfComponentInstances>
            <componentInstance id="iSH2" component="SH2" connectivity="bound"/>
              <listOfBondEnds>
                <bondEnd id="1">
              </listOfBondEnds>
          </listOfComponentInstances>
        </physicalEntityInstance>
        <physicalEntityInstance physicalEntity="FcERI" id="iFceRI-1">
```

```
                    <listOfComponentInstances>
                      <componentInstance id="ibeta" component="beta" state="u" connectivity="bound"/>
                                <listOfBondEnds>
                                    <bondEnd id="1">
                                 </listOfBondEnds>
                     </listOfComponentInstances>
                  </physicalEntityInstance>
               </listOfPhysicalEntityInstances>
        </speciesReference>
        <speciesReference speciesType="receptor-in-complex">
            <listOfSpeciesTypeInstances>
               <speciesTypeInstance physicalEntity="FcERI" id="iFceRI-2">
                 <listOfComponentInstances>
                   <componentInstance id="ialpha" component="alpha" connectivity="bound"/>
                   <componentInstance id="ibeta" component="beta" state="p"/>
                </listOfComponentInstances>
               </speciesTypeInstance>
            </listOfSpeciesTypeInstances>
          <speciesReference/>
      </listOfProducts>
</reactionRule>
```

In the example below but both extracellular domains of receptors are bound.

8 Possible extension: logic and range

It would be useful to introduce boolean symbols (AND/OR/NOT) or declaration of a range for some states:

```
<speciesType id="A">
    <listOfMoleculesIncluded>
    <moleculeIncluded molecule="A1" id="a1">
        <listOfComponentsIncluded>
        <componentIncluded component="S1" componentState=NOT "phosph"/>
        <componentIncluded component="S2" componentState="phosph1" OR "phosph" />
        <componentIncluded component="S3" componentState=["state1",...,"state10"]/>
        </listOfComponentsIncluded>
    </moleculeIncluded>
    </listOfMoleculesIncluded>
</speciesType>
```