Features for an SBML L3 extension that enable

- the description of complex chemical entities that can have multiple functional states and/or are composed from other chemical entities, and
- rule-based operations on such entities.

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Today's goal

- List all possible features that are desirable to support
- Discuss the maximal set that includes features required for each tool.
- Discuss which features are critically needed to each tool.
- Discuss the minimal set that needs to be supported by all tools.

Essential features

- Objects
  - Have multiple states
  - Consist of other objects, that may have multiple states
  - May be connected with each other via different bonds
  - (Located in multiple compartments, with two objects within the third can be in three different compartments)
- Rules:
  - Select sets of objects with common properties
  - Transform sets of objects into another sets of objects

Other issues

- Objects specification (compatible with BioPAX)
  - Introduce logic and range for states
- Representational issues (compatible with SBGN)
  - Superset of rules for contact map and MIM
  - Inhibition/stimulation reactions
- Rules application (some hints from a tool to tool):
  - Rules priority, score, confidence
  - Restrictions on the number of applications
- Numerics:
  - Assigning of kinetics law within the rule
  - Using the right stoichiometry
  - Tracking mass and number of molecules
  - Tracking shape

Two approaches to define “a superset of features”

- Graph-based approach with the fixed hierarchy (BNG, kappa, hopefully Simmune, StochSim, Moleculizer, MIM, others?)
- Graph-based approach with an arbitrary level of hierarchy (…)
- Start with the simplest

Components

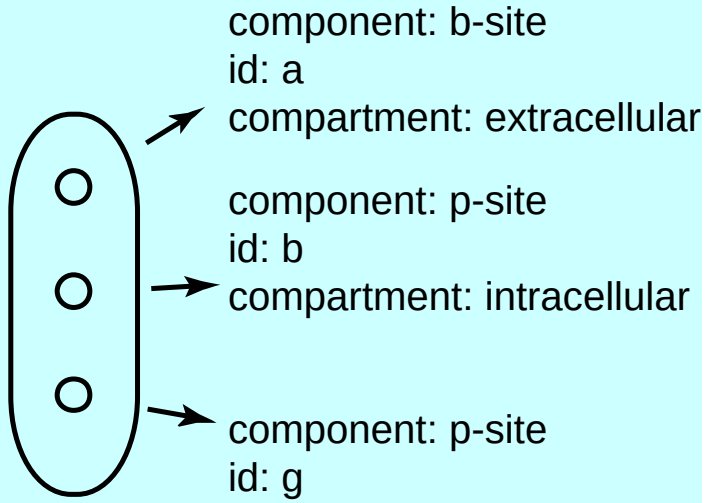
id : SId
name : string {use="optional"}
componentTypeState: string [0..*] {use="optional"}
compartment: Sid {use="optional"}

```
<componentType id="p-site" name="phosphosite" defaultStateValue="u" >
        <listOfComponentTypeStates>
            <componentTypeState value="u" name="unphosphor"/>
            <componentTypeState value="p" name="phosphor"/>
        </listOfComponentTypeStates>
</componentType>
<componentType id=“b-site" name=“binding site">
```

physical entities

R(a,b~u~p,g~u~p)

physicalEntity
id: R
states: u,f
compartment: membrane

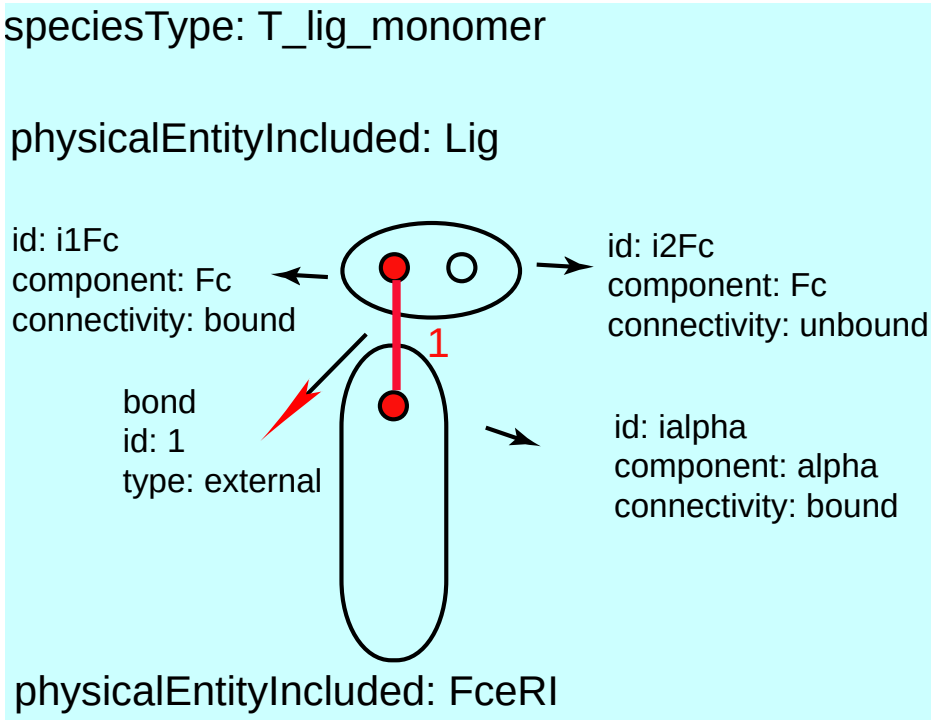



```
<physicalEntity id="R" compartment="m"/>
   <listOfStates>
      <state value="u" name="unfolded"/>
      <state value="f" name="folded"/>
   </listOfStates>
   <listOfComponents>
      <component id="a" componentType="b-site"/>
      <component id="b" componentType="p-site"/>
      <component id="g" componentType="p-site" compartment="ic"/>
   </listOfComponents>
</physicalEntity>
```

R(a[ec],b~u~p[ic],g~u~p[ic])~u~f[m]

speciesType

```
<speciesType id="T_L_monomer">
    <listOfPhysicalEntitiesIncluded>
        ....
        <listOfComponentInstances>
            ....
            <listOfBondReferences>
              ...
    <listOfBonds>
        ....
</speciesType>
```



R(a!1).L(Fc!1,Fc)

physicalEntity

id : SId
name : string {use="optional"}
State: state[0..*] {use="optional"}
components: component[0..*] {use="optional"}
compartment: Sid {use="optional"}

speciesType

id : SId
name : string {use="optional"}
physicalEntityIncluded: physicalEntity[0..*]
compartment: Sid {use="optional"}

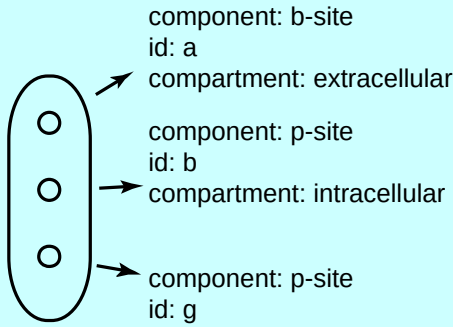
physicalEntityIncluded

physicalEntityValue: string {use="optional"}
componentInstance: string {use="optional"}
multiplicity: int {use="optional" default="1"}

componentInstance

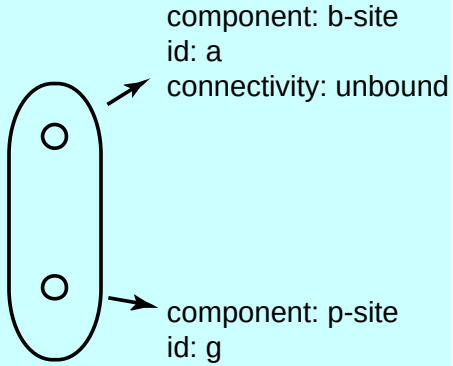
componentValue: string {use="optional"}
connectivity: {“bound" “unbound" “either“ (default)}

physicalEntity
id: R
states: u,f
compartment: membrane



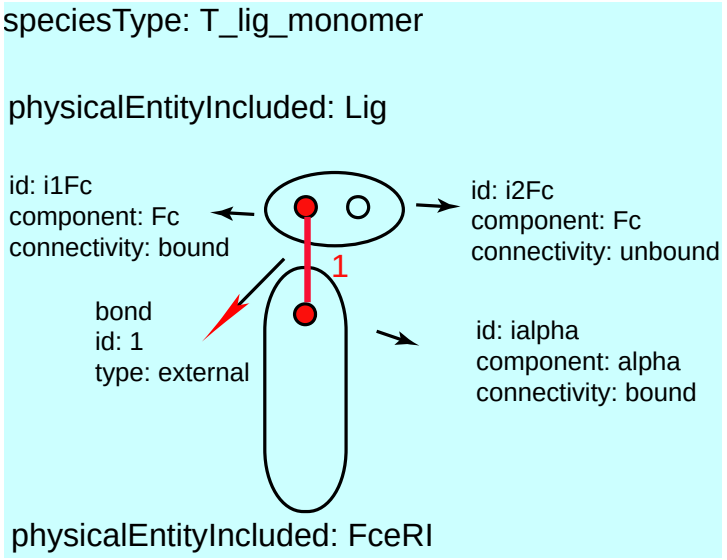
R(a,b~u~p,g~u~p)

speciesType
state: u



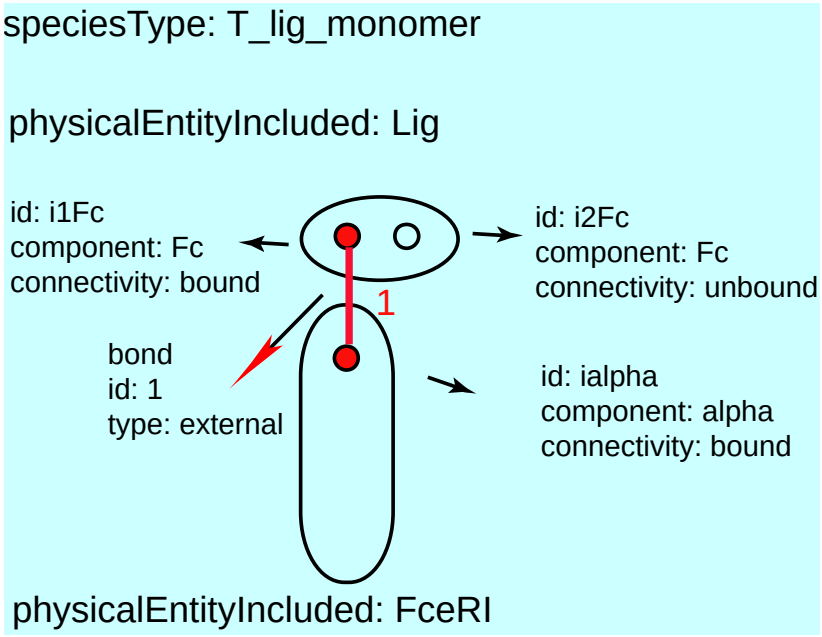
R(a,g~p!?)

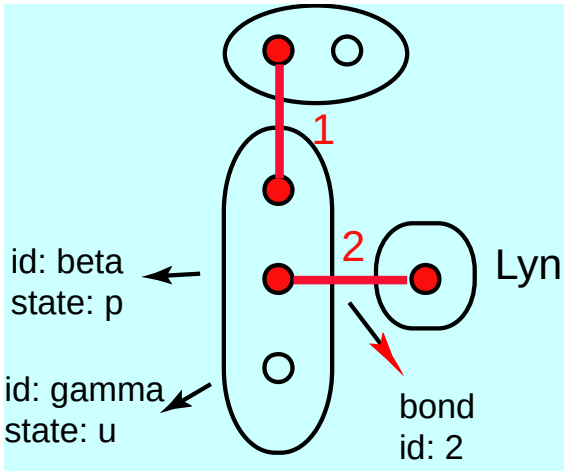
```
<speciesType id="T_L_monomer ">
    <listOfPhysicalEntityIncluded>
        < physicalEntityIncluded physicalEntity="L" id="iL">
            <listOfComponentInstances>
                <componentInstance id="i1Fc" component="Fc" connectivity="bound"/>
                    <listOfBondReferences>
                        <bondReference bond="1"/>
                    </listOfBondReferences>
                </componentInstance>
                <componentInstance id="i2Fc" component="Fc" connectivity="unbound"/>
            </listOfComponentInstances>
        </physicalEntityIncluded>
        <physicalEntityIncluded physicalEntity="R" id="iR">
            <listOfComponentInstances>
                <componentInstance id="ia" component="a" connectivity="bound"/>
                    <listOfBondReferences>
                        <bondReference bond="1"/>
                    </listOfBondReferences>
                </componentInstance>
            </listOfComponentInstances>
        </physicalEntityIncluded>
    </listOfPhysicalEntityIncluded>
    <listOfBonds>
        <bond id="1" type="external"/>
    </listOfBonds>
</speciesType>
```



Species

```
<species id="S_L_monomer_Lyn“
    speciesType=“T_L_monomer_Lyn”>
    <listOfPhysicalEntityInstances>
          .....
          <listOfComponentInstances>
          .....
    <listOfBonds>
        ....
</speciesType>
```

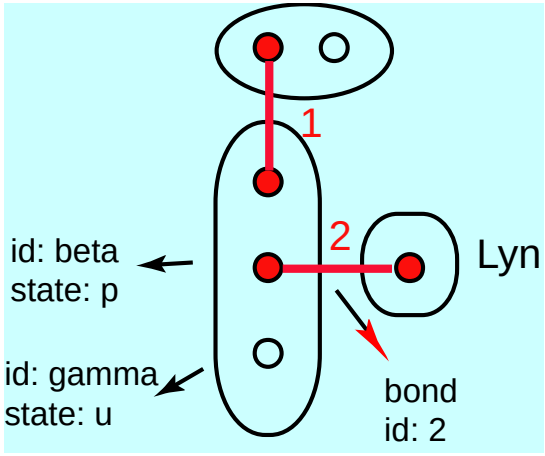




R(a!1).L(Fc!1,Fc)

R(a!1,b~p!2,g~u).L(Fc!1,Fc).Lyn(SH2!2)

```
<species id="S_lig_monomer_Lyn ">
    <listOfPhysicalEntityInstances>
        <physicalEntityInstance physicalEntity="L" id="iL">
            <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="R" id="IR">
            <listOfComponentInstances>
              …….
        </physicalEntityInstance>
        <physicalEntityInstance physicalEntity="Lyn" id="iLyn">
              …….
        </physicalEntityInstance>
    </listOfPhysicalEntityInstances>
    <listOfBonds>
          <bond id="1" type="external"/>
          <bond id="2" type="external"/>
    </listOfBonds>
</speciesType>
```



speciesGroup

```
<speciesGroup id="Receptor-phosph">
    <listOfSpecies>
        <speciesReference species="S1 "/>
        <speciesReference species="S2"/>
    </listOfSpecie>
    <listOfSpeciesTypes>
      <speciesTypeReference speciesType="R-b-phosph"/>
      <speciesTypeReference speciesType="R-g-phosph"/>
    </listOfSpeciesTypes>
  </observable>
```

R(a!1).L(Fc!1,Fc)

R(a!1,b~p!2,g~u).L(Fc!1,Fc).Lyn(SH2!2)

SBML perspective

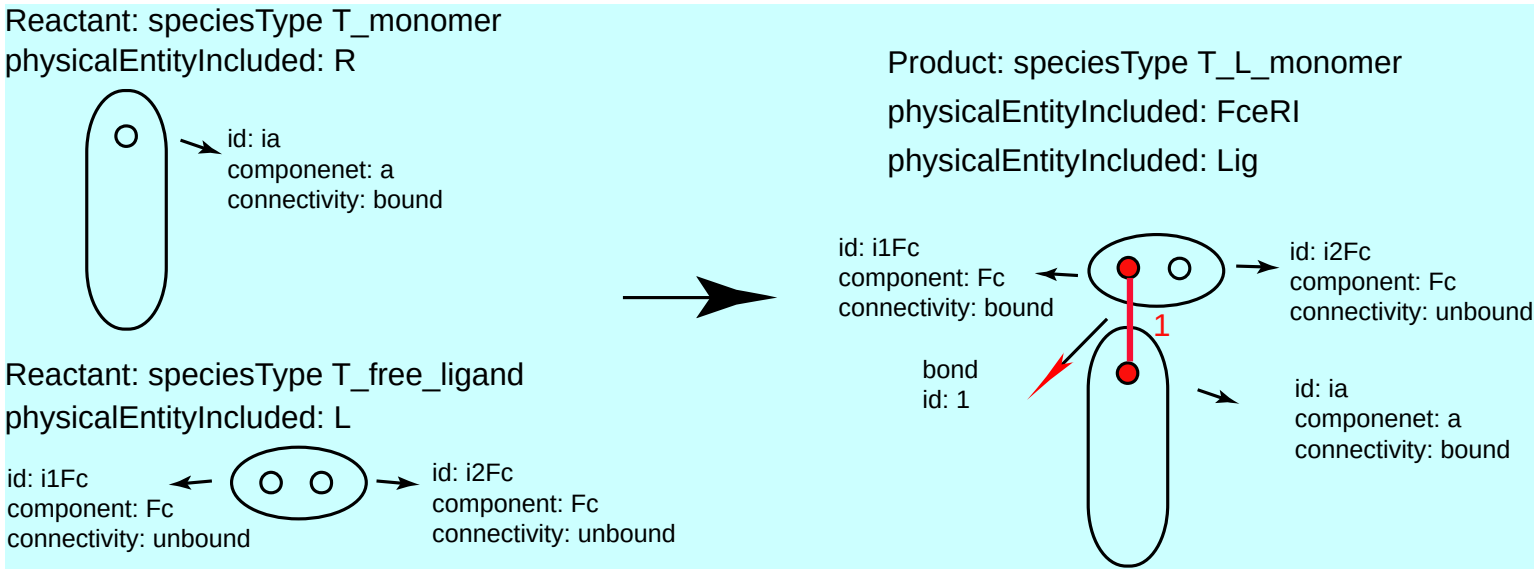
- Create a consistent and self-contained set of abstractions that have a related mathematical formalism (graph theory, rewriting logic?)
- Include comprehensive support for “rule-aware” simulators and analysis tools.
- Avoid changes to the SBML core described in L2V3.
- Enable compatibility with “rule-unaware” tools (L2 or L3).

General SBML L3 structure

Model
id: SId { use=”optional” }
name: string { use=”optional” }
sboTerm: SBOTerm { use=”optional” }
functionDefinition: FunctionDefinition[0..*]
unitDefinition: UnitDefinition[0..*]
compartmentType: CompartmentType[0..*]
physicalEntity: physicalEntity[0..*]
speciesType: SpeciesType[0..*]
compartment: Compartment[0..*]
species: Species[0..*]
parameter: Parameter[0..*]
initialAssignment: InitialAssignment[0..*]
rule: Rule[0..*]
observable: observable[0..*]
constraint: Constraint[0..*]
reaction: Reaction[0..*]
event: Event[0..*]

reactions

```
<reaction id="Ligand_bind" reversible="true">
  <listOfReactants>
     <speciesTemplate id="T_monomer"/>
     <speciesReference species="T_free_L"/>
  </listOfReactants>
  <listOfProducts>
     <speciesTemplate speciesType="T_L_monomer"/>
  </listOfProducts>
</reactionRule>
```



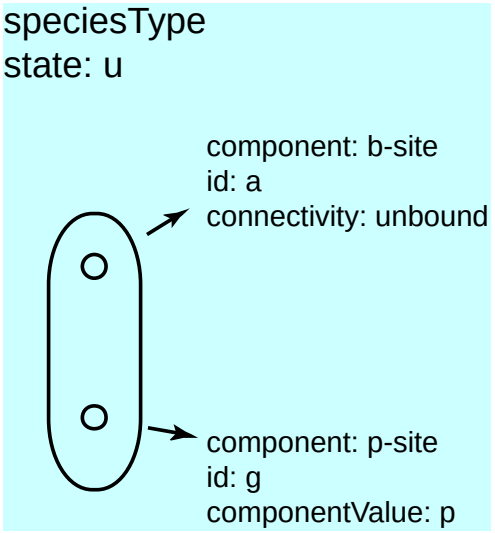
R(a) + L(Fc,Fc) -> R(a!1).L(Fc!1,Fc)

speciesTemplate

id : Sid {use="optional"}
name : string {use="optional"}
physicalEntityIncluded: physicalEntity[0..*]
compartment: Sid {use="optional"}

physicalEntityIncluded
physicalEntityValue: string {use="optional"}
componentInstance: string {use="optional"}
multiplicity: int {use="optional" default="1"}

componentInstance
componentValue: string {use="optional"}
connectivity: {“bound" “unbound" “either“ (default)}



R(a,g~p!?)

Identical to speciesType. Optional Sid.

```
<reaction id="Ligand_bind" reversible="true">
    <listOfReactants>
        <speciesTemplate id="T_monomer">
            <listOfPhysicalEntityIncluded>
                <physicalEntityIncluded physicalEntity="R" id="iR">
                  <listOfComponentInstances>
                     <componentInstance id="ia" component="a" connectivity="unbound"/>
                  </listOfComponentInstances>
                </physicalEntityInstance>
            </listOfPhysicalEntityInstances>
        </speciesTemplate>
        <speciesTemplate id="T_free_ligand">
            <listOfPhysicalEntityInstances>
                <physicalEntityInstance physicalEntity="L" id="iL">
                  <listOfComponentInstances>
                     <componentInstance id="i1Fc" component="Fc" connectivity="unbound"/>
                     <componentInstance id="i2Fc" component="Fc" connectivity="unbound"/>
                  </listOfComponentInstances>
                </physicalEntityInstance>
            </listOfPhysicalEntityInstances>
        </speciesTemplate>
    </listOfReactants>
    <listOfProducts>
        ....
    </listOfProducts>
</reactionRule>
```

```
<reaction id="Ligand_bind" reversible="true">
    <listOfReactants>
        …..
    </listOfReactants>
    <listOfProducts>
        <speciesTemplate speciesType="T_lig_monomer">
            <listOfPhysicalEntityInstances>
                <physicalEntityInstance physicalEntity="L" id="iL">
                    <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="R" id="iR">
                    <listOfComponentInstances>
                        <componentInstance id="ialpha" component="alpha" connectivity="bound">
                            <listOfBondReferences>
                                <bondReference id="1">
                            </listOfBondReferences>
                        </componentInstance>
                    </listOfComponentInstances>
                </physicalEntityInstance>
            </listOfPhysicalEntityInstances>
            <listOfBonds>
                <bond id="1" type="external">
            </listOfBonds>
        </speciesTemplate>
    </listOfProducts>
</reactionRule>
```

Logic and Range (BioPAX)

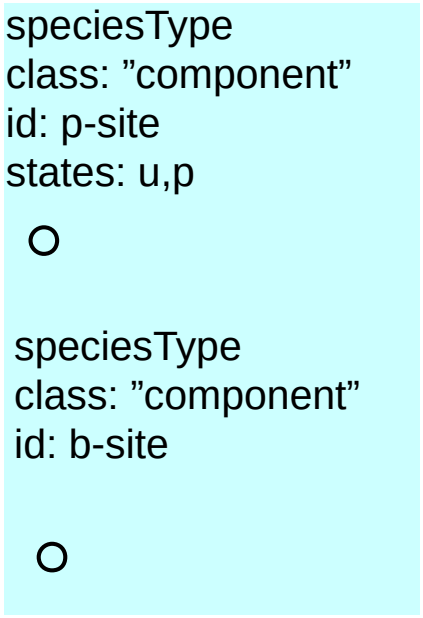
```
<physicalEntity id="R" >
    <listOfComponents>
        <component id="a">
            <listOfStates>
                <state id="sta1"/>
                ……
                <state id="sta6"/>
            </listOfStates>
        </component>
    </listOfComponents>
</physicalEntity>

<speciesType id="T_R">
    <listOfPhysicalEntityInstances>
        <physicalEntityInstance physicalEntity="R" id="iR">
            <listOfComponentInstances>
                <componentInstance value="ia" component="a" state=NOT "sta1"/>
                <componentInstance value="ia" component="a" state="sta1" OR "sta2"/>
                <componentInstance value="ia" component="a" state="[sta3… sta5]"/>
            </listOfComponentInstances>
        </physicalEntityInstance>
    </listOfPhysicalEntityInstances>
</speciesType>
```

Arbitrary level of hierarchy

- Why not specify components and physicalEntities as speciesTypes?
- Advantage: generality
- Cost: complexity of connectivities

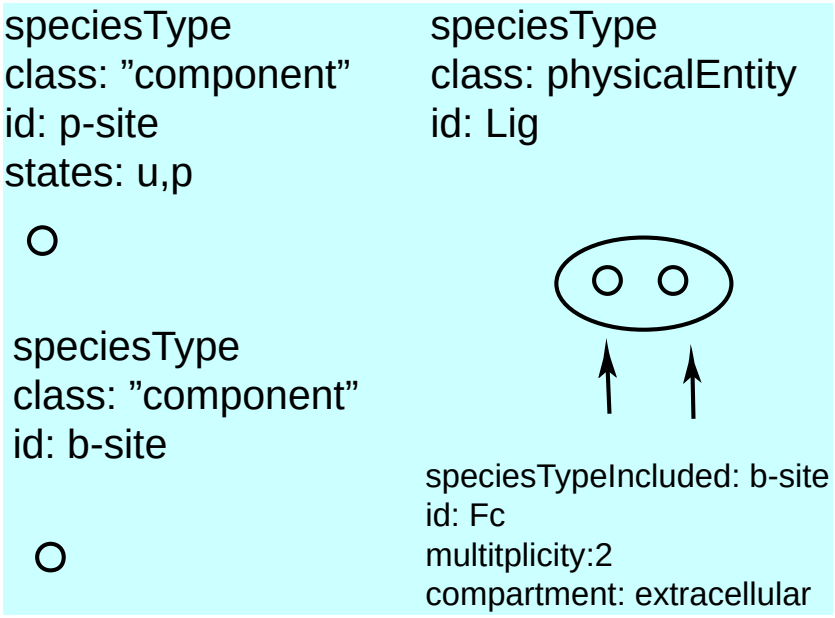
speciesType

id : SId
name : string {use="optional"}
class: string {"component", "physicalEntity", …} {use="optional"}
speciesTypeState: string [0..*] {use="optional"}
speciesTypeIncluded: speciesTypeIncluded[0..*]
compartment: Sid {use="optional"}




```
<speciesType id="p-site" class="components" name="site_of_phosphorylation“
defaultStateValue=“u”>
    <listOfSpeciesTypeStates>
          <speciesTypeState value="u" name="unphosphorylated"/>
          <speciesTypeState value="p" name="phosphorylated"/
     </listOfSpeciesTypeStates>
</speciesType>
```

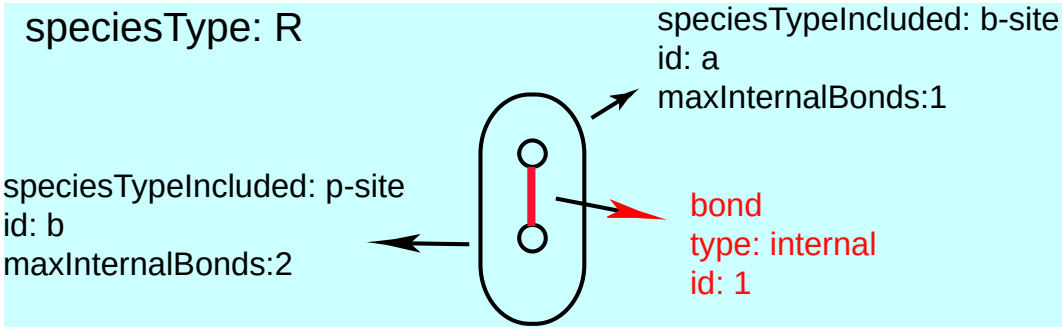
speciesTypeIncluded



Id: SId
name : string {use="optional"}
multiplicity: int { minInclusive="0" use="optional" default="1"}
maxExternalBonds: int { minInclusive="0" use="optional" default="1"}
maxInternalBonds: int { minInclusive="0" use="optional" default="0"}
compartment: Sid {use="optional"}

```
<speciesType class="physicalEntity" id="Lig">
   <listOfSpeciesTypesIncluded>
     <speciesTypeIncluded id="Fc" speciesType="b-site" multiplicity="2“>
   </listOfSpeciesTypesIncluded>
</speciesType>
```

Bonds

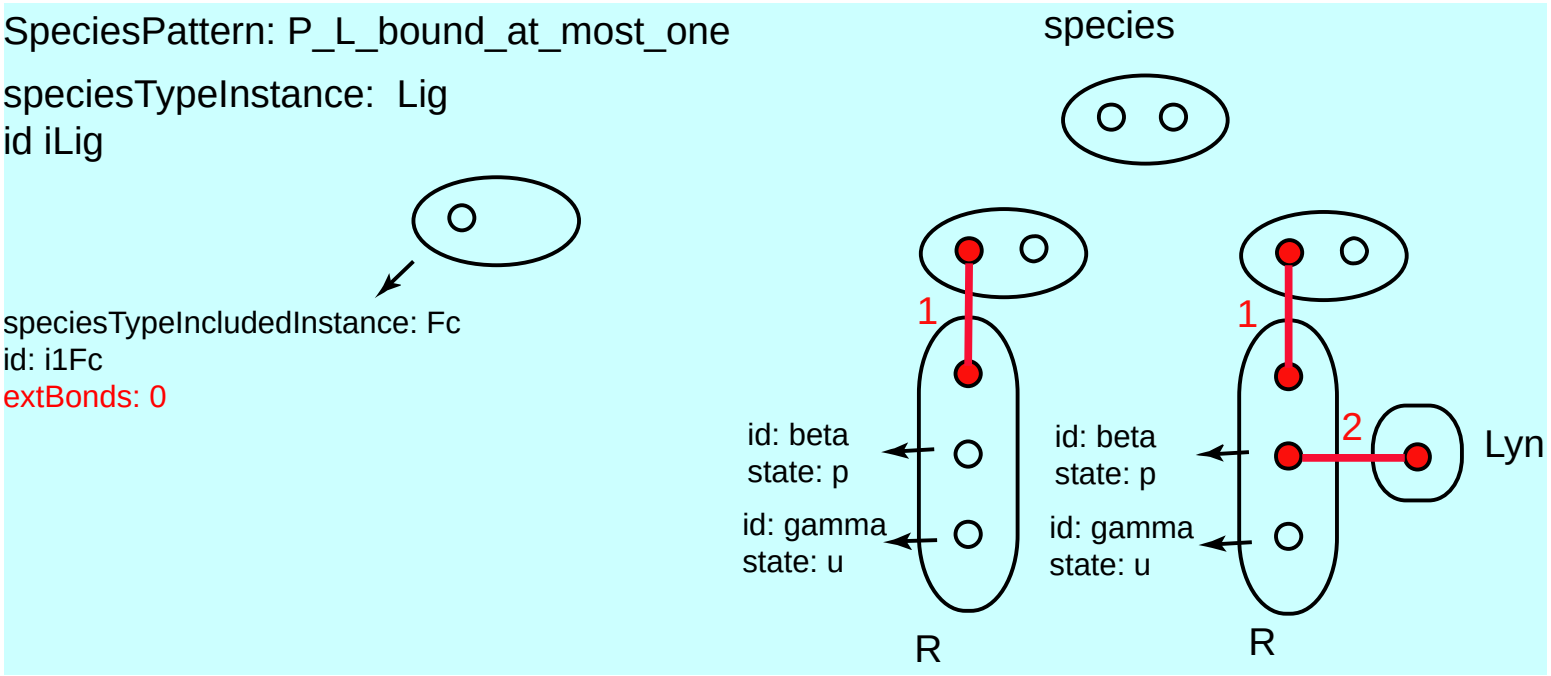



```
<speciesType class="physicalEntity" id="R">
  <listOfSpeciesTypesIncluded>
      <speciesTypeIncluded id="a" speciesType="b-site" maxInternalBonds ="1">
            <listOfBondReferences>
                  <bondReference bond="1"/>
            </listOfBondReferences>
      <speciesTypeIncluded/>
      <speciesTypeIncluded id="b" speciesType="p-site"  maxInternalBonds =“1">
            <listOfBondReferences>
                  <bondReference bond="1"/>
                  <bond Reference bond="2"/>
            </listOfBondReferences>
      <speciesTypeIncluded/>
    </listOfSpeciesTypesIncluded>
    <listOfBonds>
          <bond id="1" bondType="internal"/>
</listOfBonds>
</speciesType>
```

speciesTemplate

id : SId {use="optional"}
name : string {use="optional"}
speciesTypeInstance: speciesType[0..*]
compartment: Sid {use="optional"}

speciesTypeInstance
id : SId
speciesTypeValue: speciesTypeValue {use="optional"}
name : string {use="optional"}
multiplicity: int { minInclusive="0" use="optional" default="1"}
extBonds: int { minInclusive="0" maxInclusive="maxExtBonds" use="optional"}
intBonds: int { minInclusive="0" maxInclusive="maxIntBonds" use="optional"}



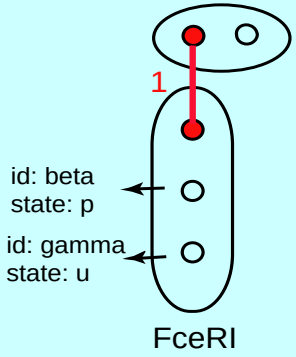

```
<speciesTemplate id="P_ligand_free_on_one_site">
    <listOfSpeciesTypeInstances>
        <speciesTypeInstance speciesType="Lig" id="iLig">
            <listOfSpeciesTypeIncludedInstances>
                <speciesTypeIncludedInstance id="i1Fc"
                            speciesTypeIncluded="Fc" extBonds="0"/>
                </listOfSpeciesTypeIncludedInstances>
        </speciesTypeInstance >
    </listOfSpeciesTypeInstances>
</speciesTemplate>
```

1a SpeciesPattern: P_lig_bound_once
speciesTypeInstance: Lig
id: iLig

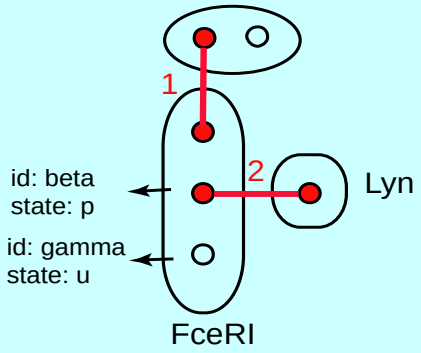
speciesTypeIncludedInstance: Fc
id: i1Fc
extBonds: 1
bondReference: 1

speciesTypeIncludedInstance: Fc
id: i2Fc
extBonds: 0

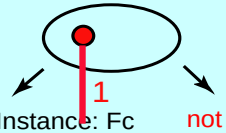
1b Species: S_lig_bound_once



1c Species



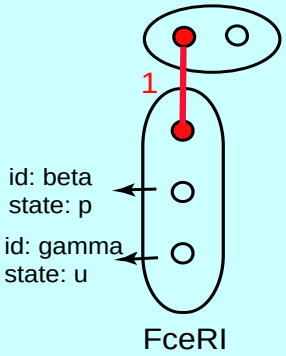
2a SpeciesPattern: P_lig_bound_one_or_more
speciesTypeInstance: Lig
id: iLig



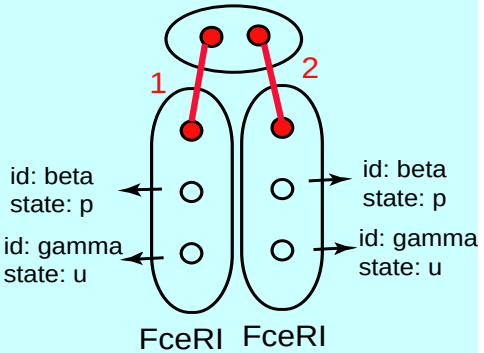
speciesTypeIncludedInstance: Fc
id: i1Fc
extBonds: 1
bondReference: 1

not specified - can have as many bonds as allowed by maxExternalBonds

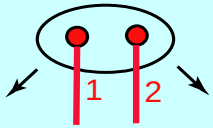
2b Species



2c Species



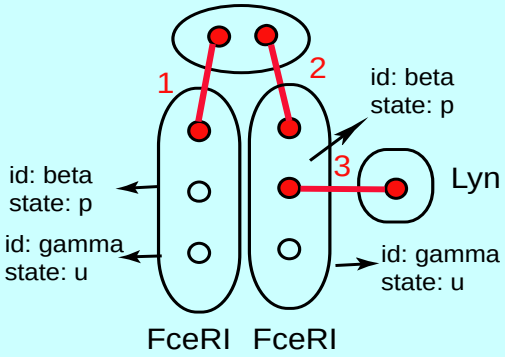
3a SpeciesPattern: P_ligand_bound_two_times
speciesTypeInstance: Lig
id: iLig



speciesTypeIncludedInstance: Fc
id: i1Fc
extBonds: 1
bondReference: 1

speciesTypeIncludedInstance: Fc
id: i2Fc
extBonds: 1
bondReference: 2

3b Species



reaction

```
<reaction id="Ligand_bind" reversible="true">
    <listOfReactants>
        <speciesTempalate id=“T_monomer"/>
        <speciesTempalte id=“T_free_ligand"/>
    </listOfReactants>
    <listOfProducts>
        <speciesTemplate id="P_lig_monomer"/>
    </listOfProducts>
</reactionRule>
```