

# 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 comprehensive 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
  - 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>
```

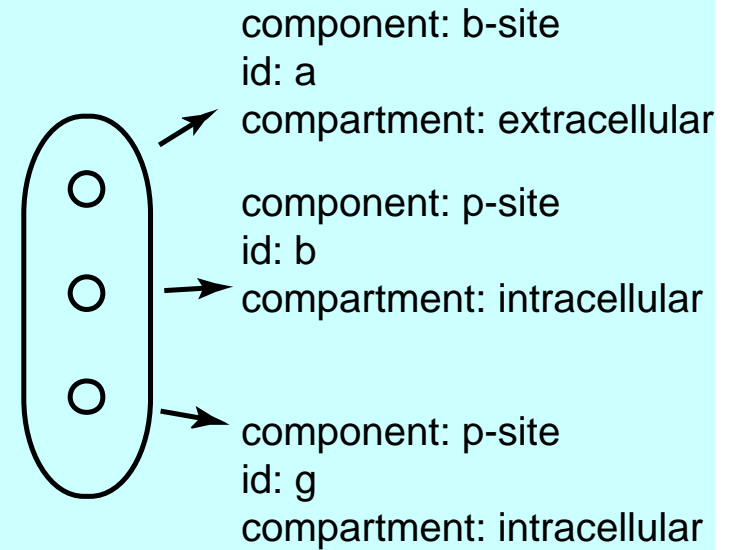
```
<componentType id="b-site" name="binding site">
```

# physical entities

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

```
<physicalEntity id="R" 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>
```

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



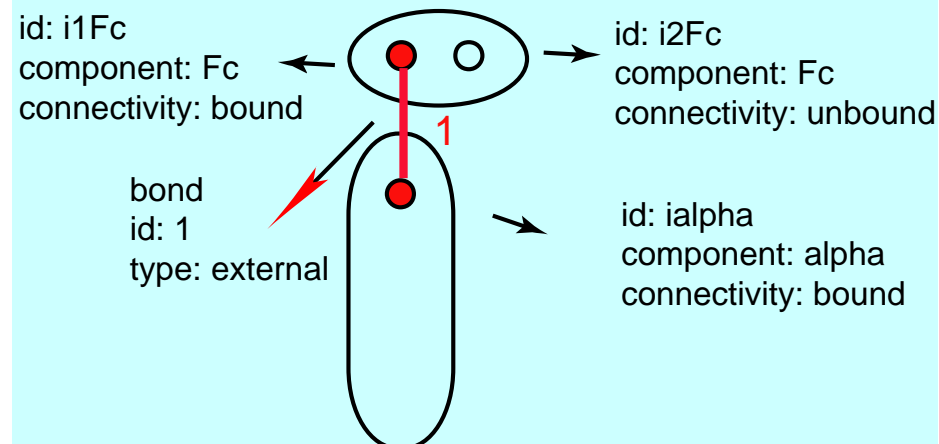
R(a[ec],b~u~p[ic],g~u~p[ic])~u~f[m]

# speciesType

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

speciesType: T\_lig\_monomer

physicalEntityIncluded: Lig



physicalEntityIncluded: FceRI

**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"}

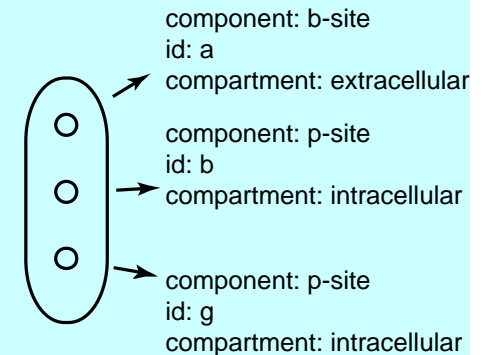
## physicalEntityIncluded

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

## componentInstance

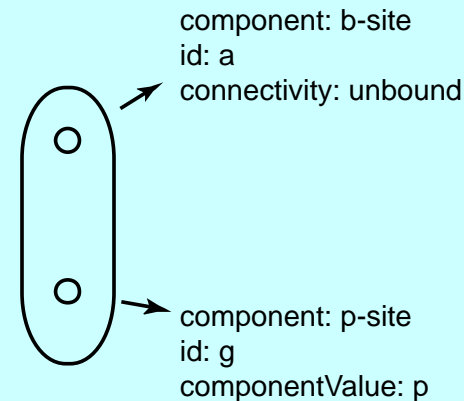
componentValue: string {use="optional"}  
connectivity: {"bound" "unbound" "either" (default)}

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



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

speciesType  
state: u

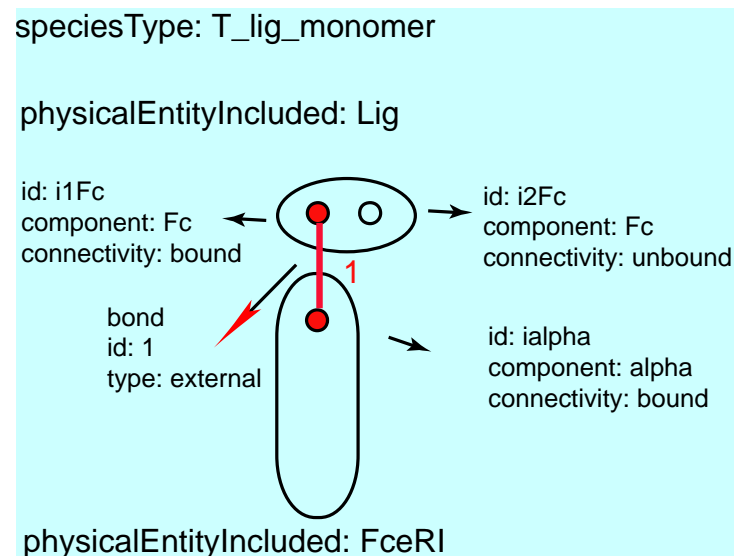


## R(a,g~p!?)

```

<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>

```



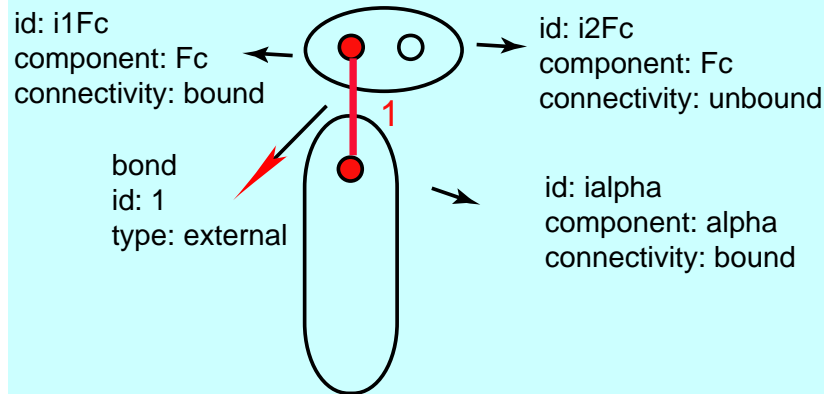
# Species

```

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

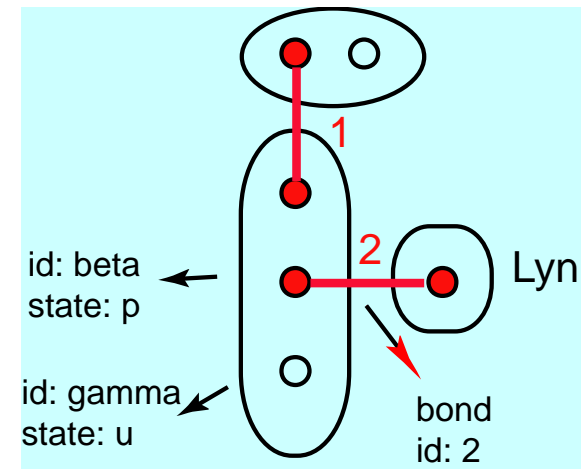
speciesType: T\_lig\_monomer

physicalEntityIncluded: Lig



physicalEntityIncluded: FceRI

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

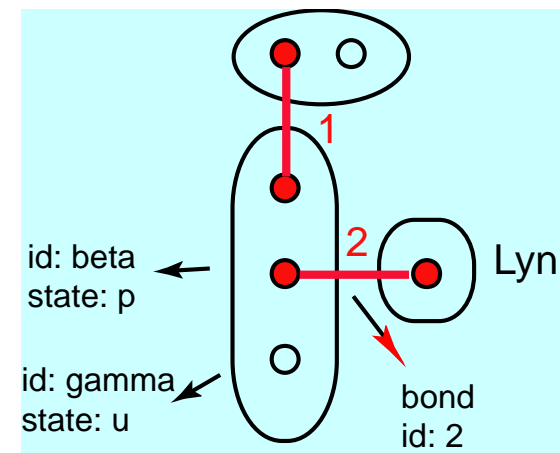


R(a!1,b~p!2,g~u).L(Fc!1,Fc).Lyn(SH2!2)

```

<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>
        .....
      </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"/>  
  </listOfSpecies>  
  <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 “rule-unaware” tools (L2) read sbml 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..\*]

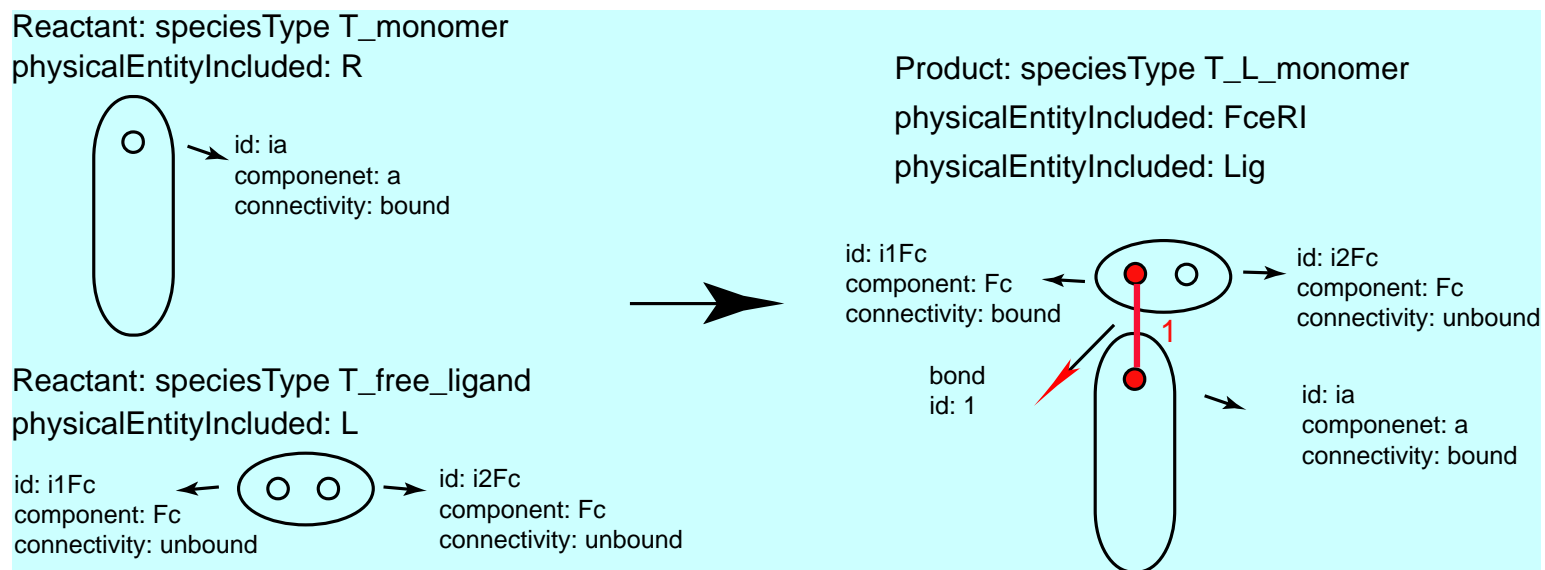
event: Event[0..\*]

# reactions

```

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

```





# speciesTemplate

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

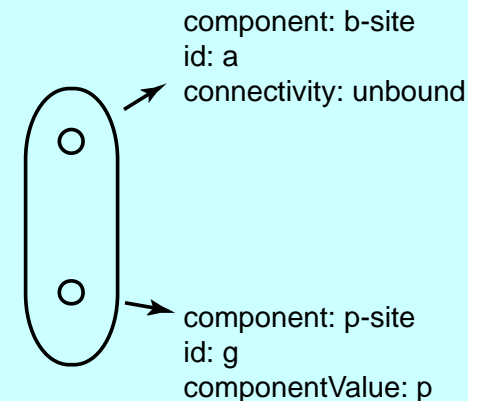
## physicalEntityIncluded

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

## componentInstance

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

speciesType  
state: u



**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>
        </physicalEntityIncluded>
      </listOfPhysicalEntityIncluded>
    </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>
```

speciesType  
class: "component"  
id: p-site  
states: u,p

○

speciesType  
class: "component"  
id: b-site

○

# 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>
```

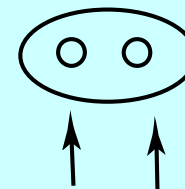
speciesType  
class: "component"  
id: p-site  
states: u,p



speciesType  
class: "component"  
id: b-site

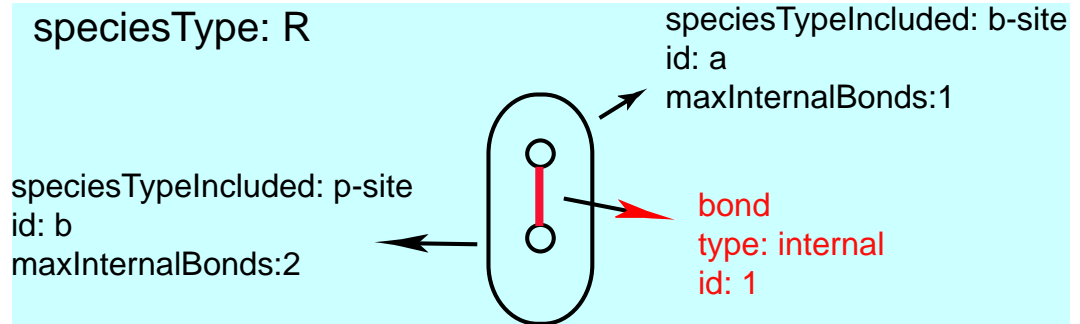


speciesType  
class: physicalEntity  
id: Lig



speciesTypeIncluded: b-site  
id: Fc  
multiplicity:2  
compartment: extracellular

# 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"/>
      </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"}

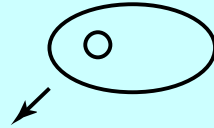
## speciesTypeInstance

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"}

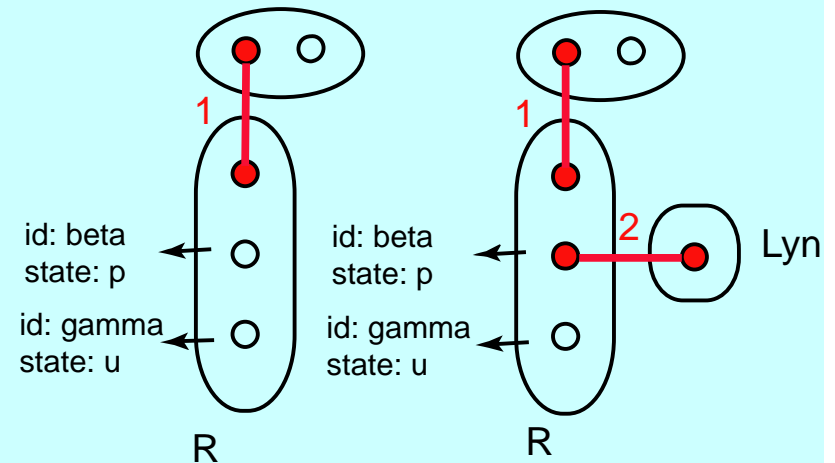
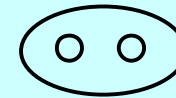
SpeciesPattern: P\_L\_bound\_at\_most\_one

speciesTypeInstance: Lig  
id iLig

speciesTypeIncludedInstance: Fc  
id: i1Fc  
extBonds: 0

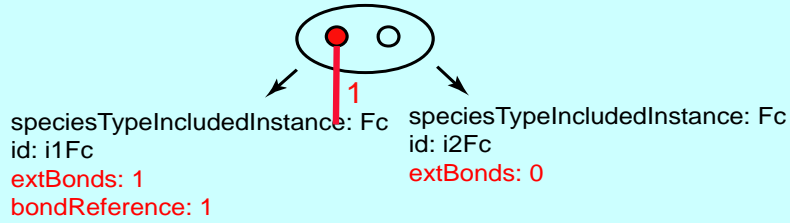


species

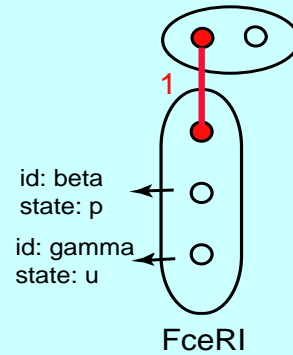


```
<speciesTemplate id="P_ligand_free_on_one_site">  
  <listOfSpeciesTypeInstances>  
    <speciesTypeInstance speciesType="Lig" id="iLig">  
      <listOfSpeciesTypeIncludedInstances>  
        <speciesTypeIncludedInstance id="i1Fc"  
          speciesTypeIncluded="Fc" extBonds="0"/>  
      </listOfSpeciesTypeIncludedInstances>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

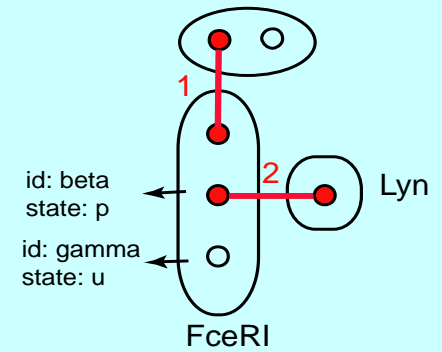
1a SpeciesPattern: P\_lig\_bound\_once  
 speciesTypeInstance: Lig  
 id: iLig



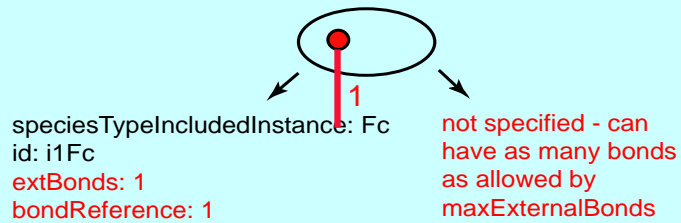
1b Species: S\_lig\_bound\_once



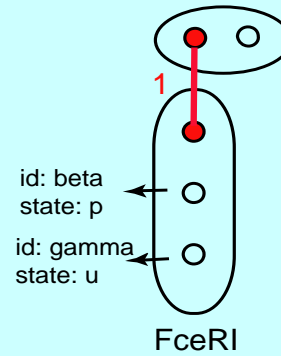
1c Species



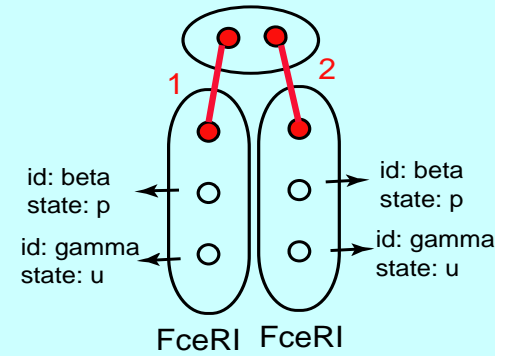
2a SpeciesPattern: P\_lig\_bound\_one\_or\_more  
 speciesTypeInstance: Lig  
 id: iLig



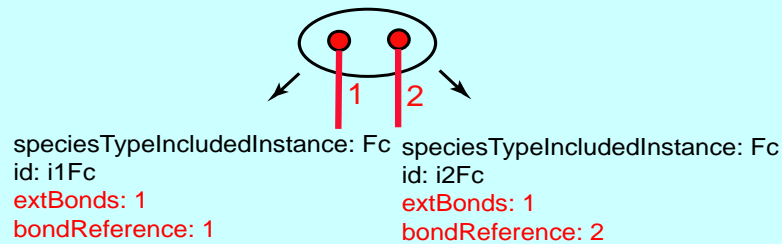
2b Species



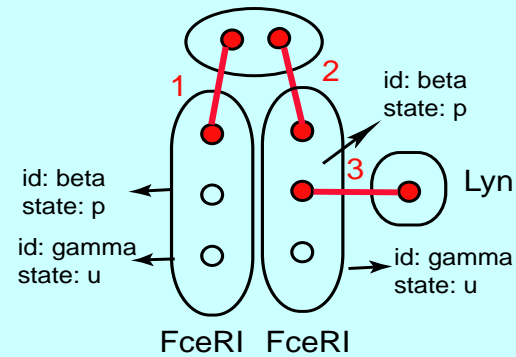
2c Species



3a SpeciesPattern: P\_ligand\_bound\_two\_times  
 speciesTypeInstance: Lig  
 id: iLig



3b Species



# reaction

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