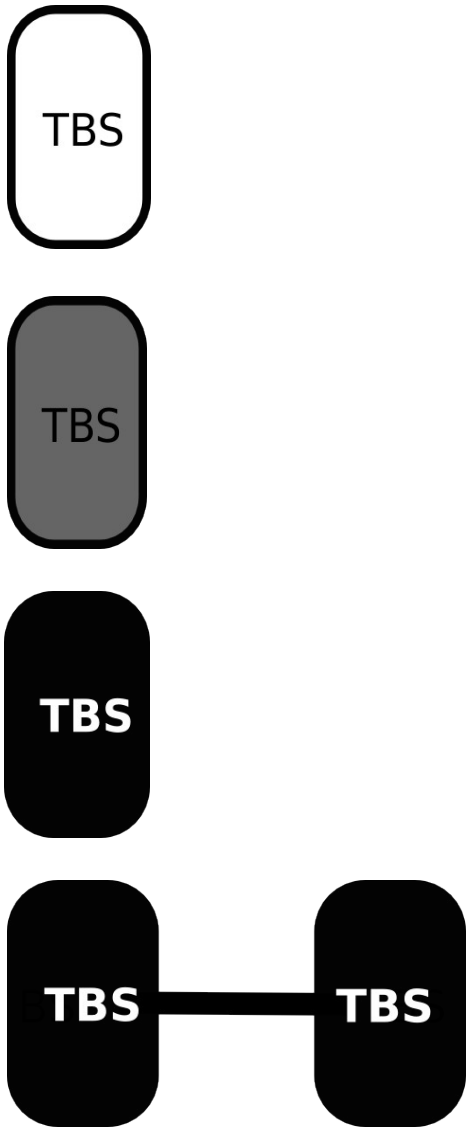
SBML Level 3 package **multi** Version 1

Conventions on binding sites



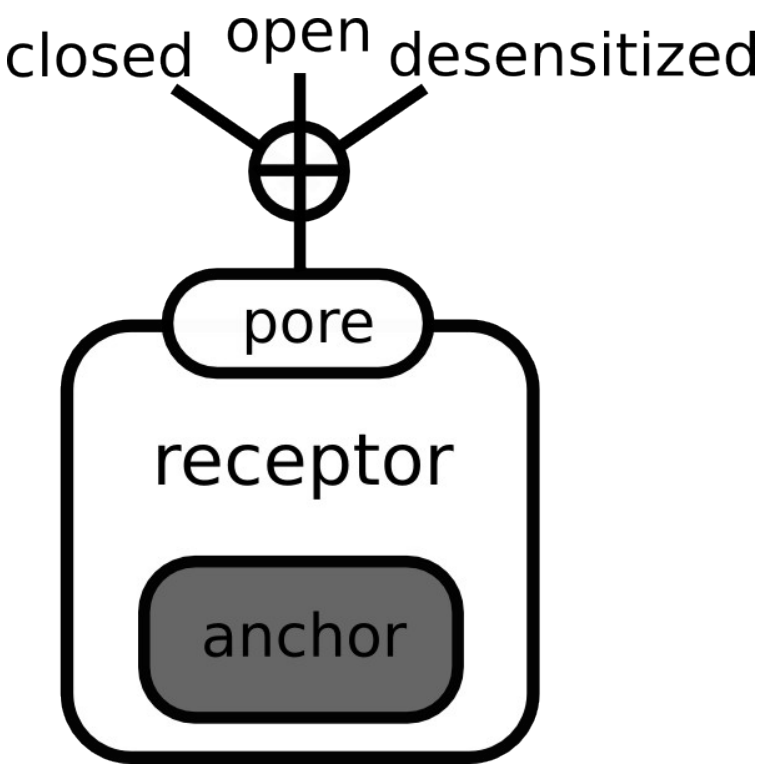
free

free or bond

generic bond

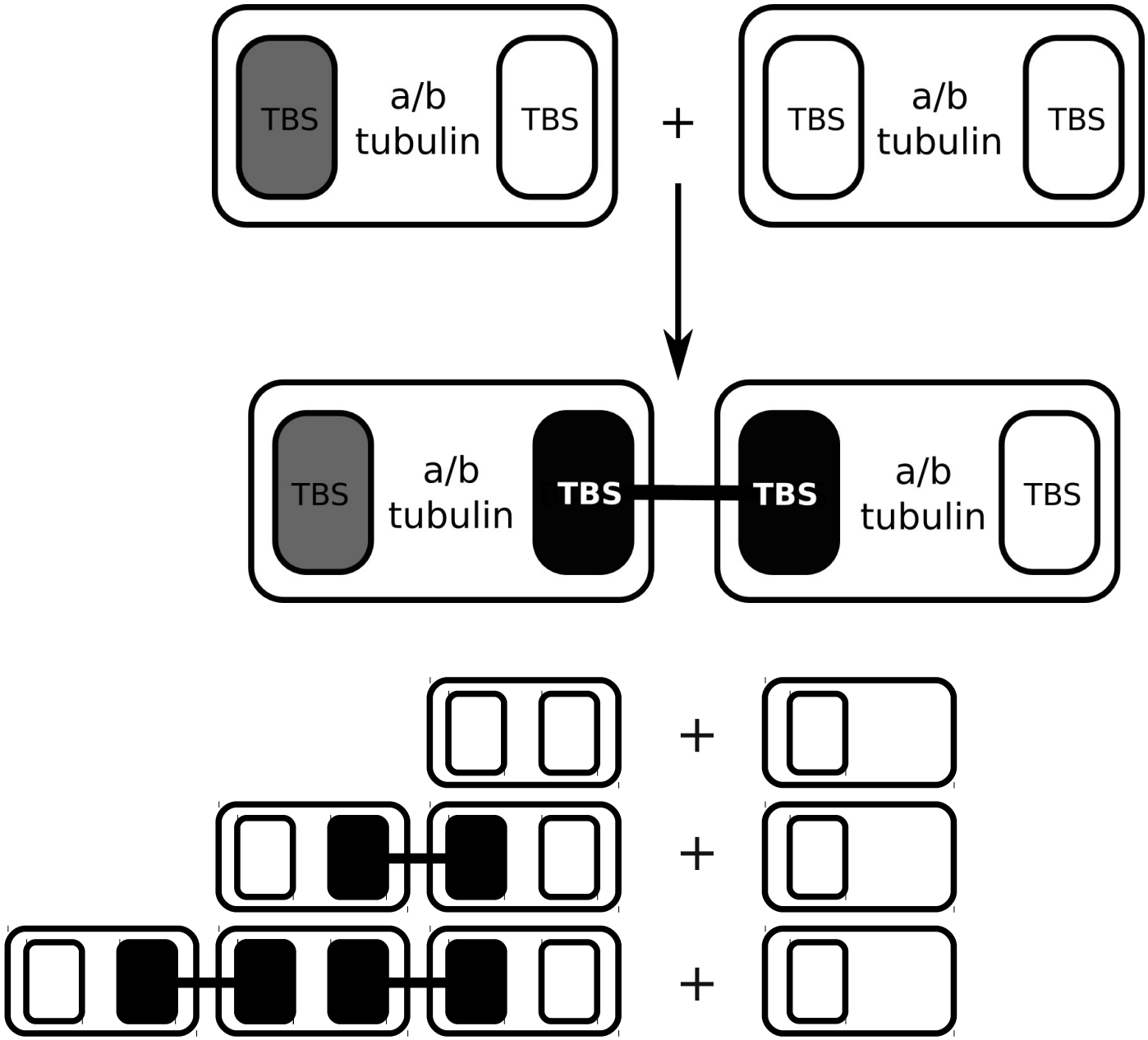
specific bond

Rational 1: tackling combinatorial explosion



{free, closed}
{free, open}
{free, desensitized}
{anchored, closed}
{anchored, open}
{anchored, desensitized}

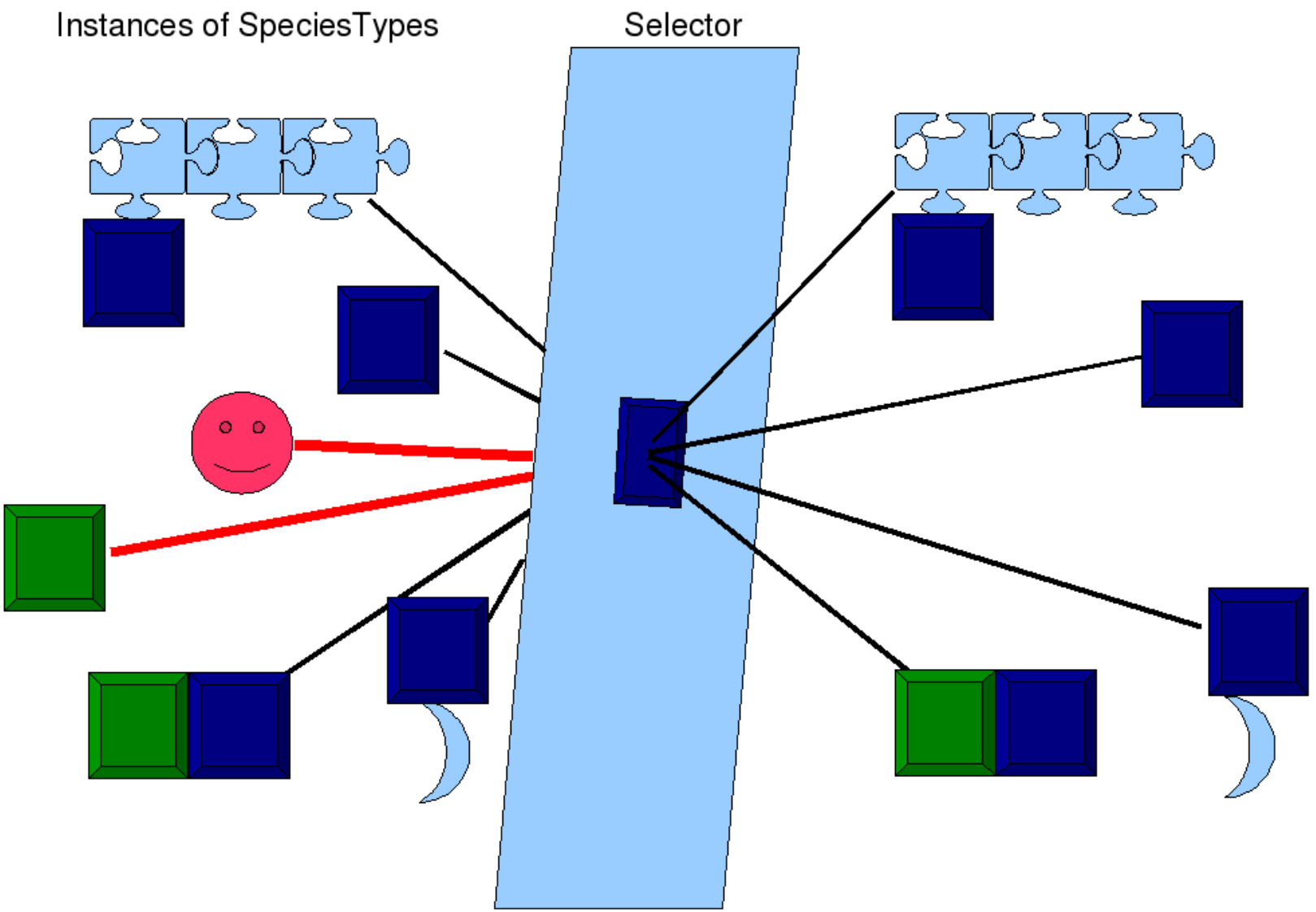
Rational 2: Defining uncertain knowledge



History of multi-components multi-state complexes in SBML

- March 2001: First proposed SBML extension for complex species by Andrew Finney. June 2001: Proposal to cover multistate component by Nicolas Le Novère
- July 2001: First proposed SBML extension for encoding and using states by Nicolas Le Novère and Tom Shimizu; Complete description by Nicolas Le Novère, Tom Shimizu and Andrew Finney
- March 2004: Updated proposal to encode complex species by Andrew Finney. Introduction of SpeciesTypes, later part of Level 2 V2-4
- October 2004: Alternative proposal for encoding multi-component species, also containing some multistate features by Michael Blinov, Jim Fader, Byron Goldstein, Andrew Finney and Bill Hlavacek.
- June 2007: New proposal for Level 3 by Le Novère and Anika Oellrich, to work in conjunction with 2004 Finney's multicomponents proposal.
- October 2007: Updated version of Michael Blinov's proposal, with and without hierarchical speciesTypes.
- December 2007, an SBML Focused Videoconference was held, which launched the effort to develop the current Level 3 package multi. See sbml.org

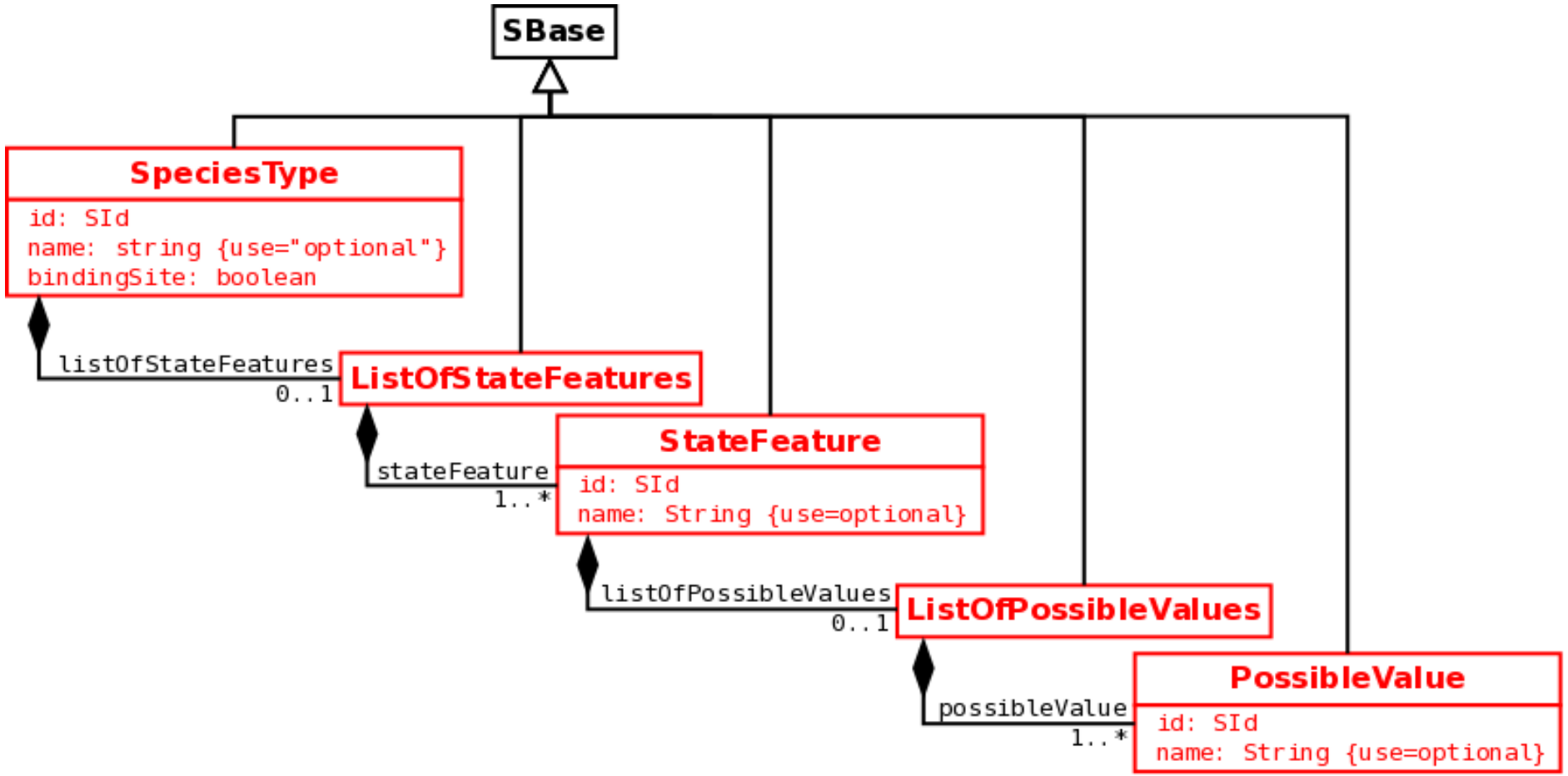
The idea of the selector



Model element with the package multi

```
<model
xmlns:multi="http://www.sbml.org/sbml/level3/version1/multi/version1">
  <!-- some compartments -->
  <multi:listOfSpeciesTypes>
    <!-- some species types -->
  </multi:listOfSpeciesTypes>
  <multi:listOfSelectors>
    <!-- some selectors -->
  </multi:listOfSelectors>
  <!-- some species, initialAssignments, rules,  reactions, events -->
</model>
```

Definition of species types

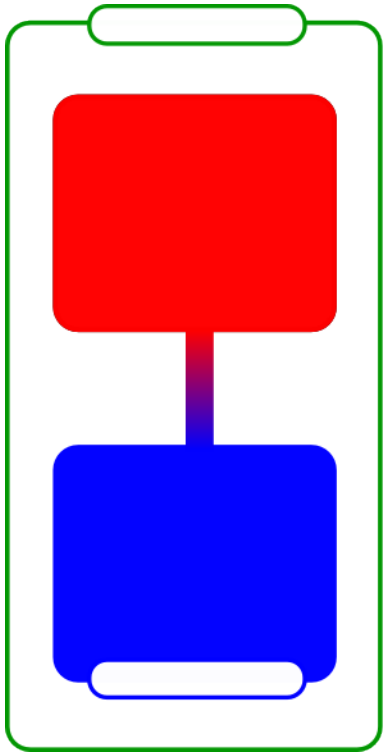


Example of a SpeciesType

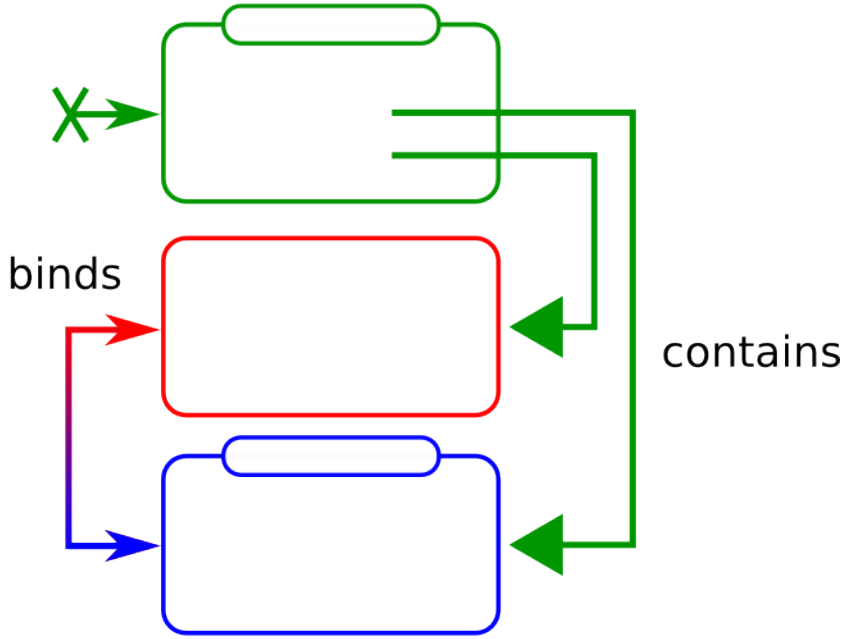
```
<multi:speciesType
          xmlns:core="http://www.sbml.org/sbml/level3/version1"
          xmlns:multi="http://www.sbml.org/sbml/level3/version1/multi/version1"
          xmlns:xhtml="http://www.w3.org/1999/xhtml"
          multi:id="speciesType1"
          multi:bindingSite="false">
  <core:notes>
    <xhtml:body>
      <xhtml:p>
        LGIC is a Ligand-Gated Ion Channel.
        It contains a pore that can be open or closed.
      </xhtml:p>
    </xhtml:body>
  </core:notes>
  <multi:listOfStateFeatures>
    <multi:stateFeature multi:id="stateFeature1"
                        multi:name="pore">
      <multi:listOfPossibleValues>
        <multi:possibleValue id="possibleValue1"
                             multi:name="open"/>
        <multi:possibleValue id="possibleValue2"
                             multi:name="closed"" />
      </multi:listOfPossibleValues>
    </multi:stateFeature>
  </multi:listOfStateFeature>
</multi:speciesType>
```

How to build a selector?

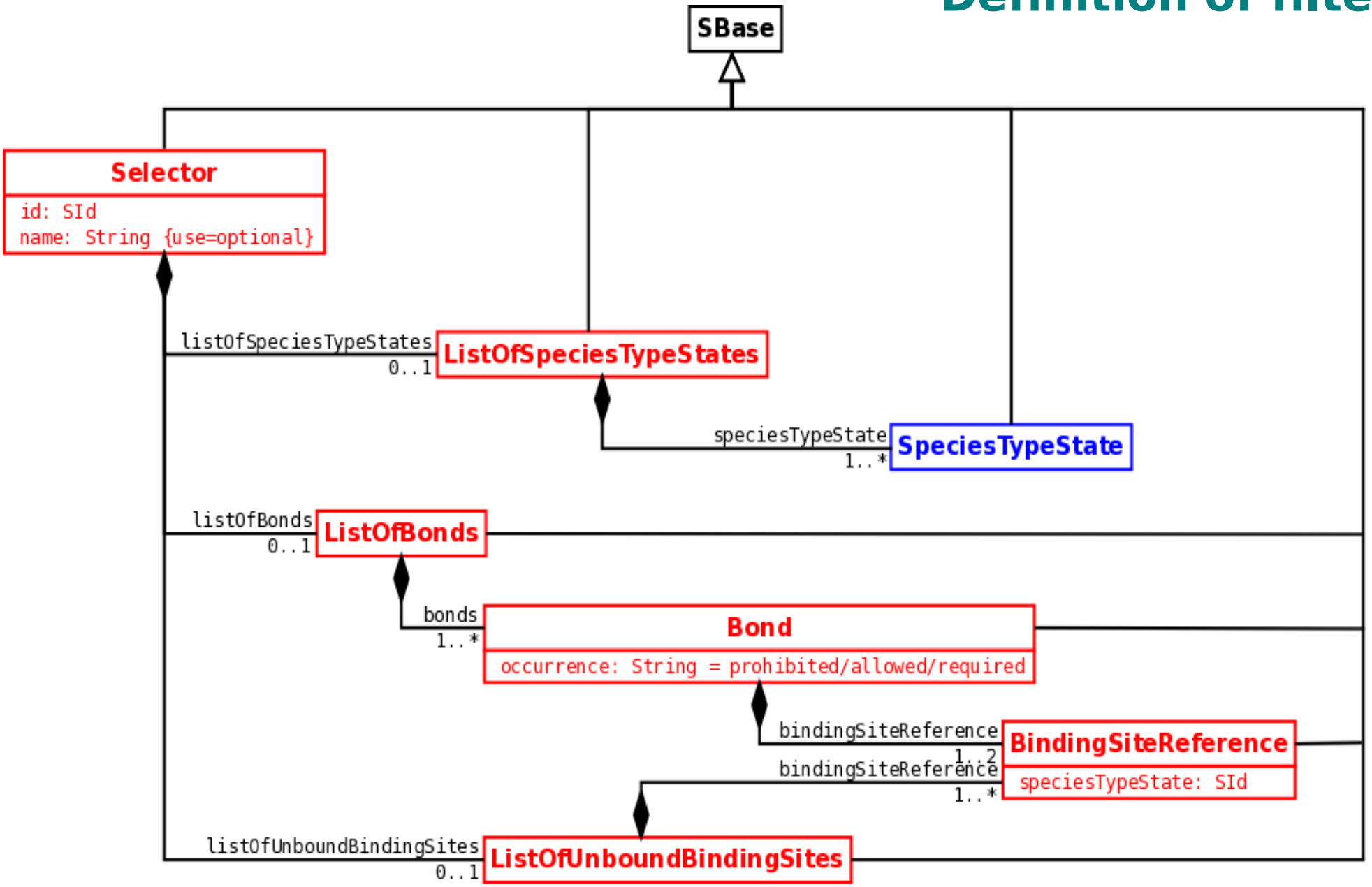
to describe:



we encode:



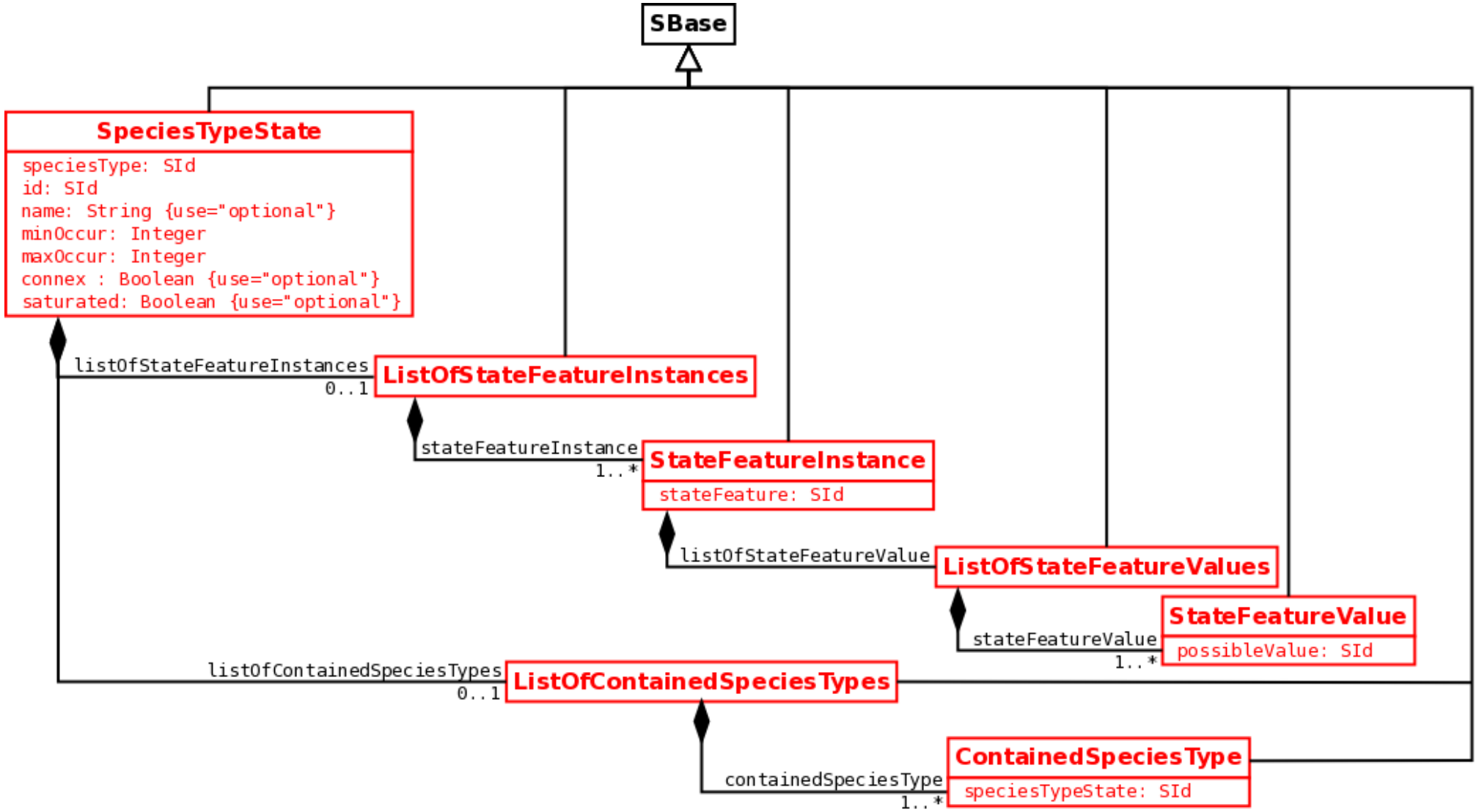
Definition of filters



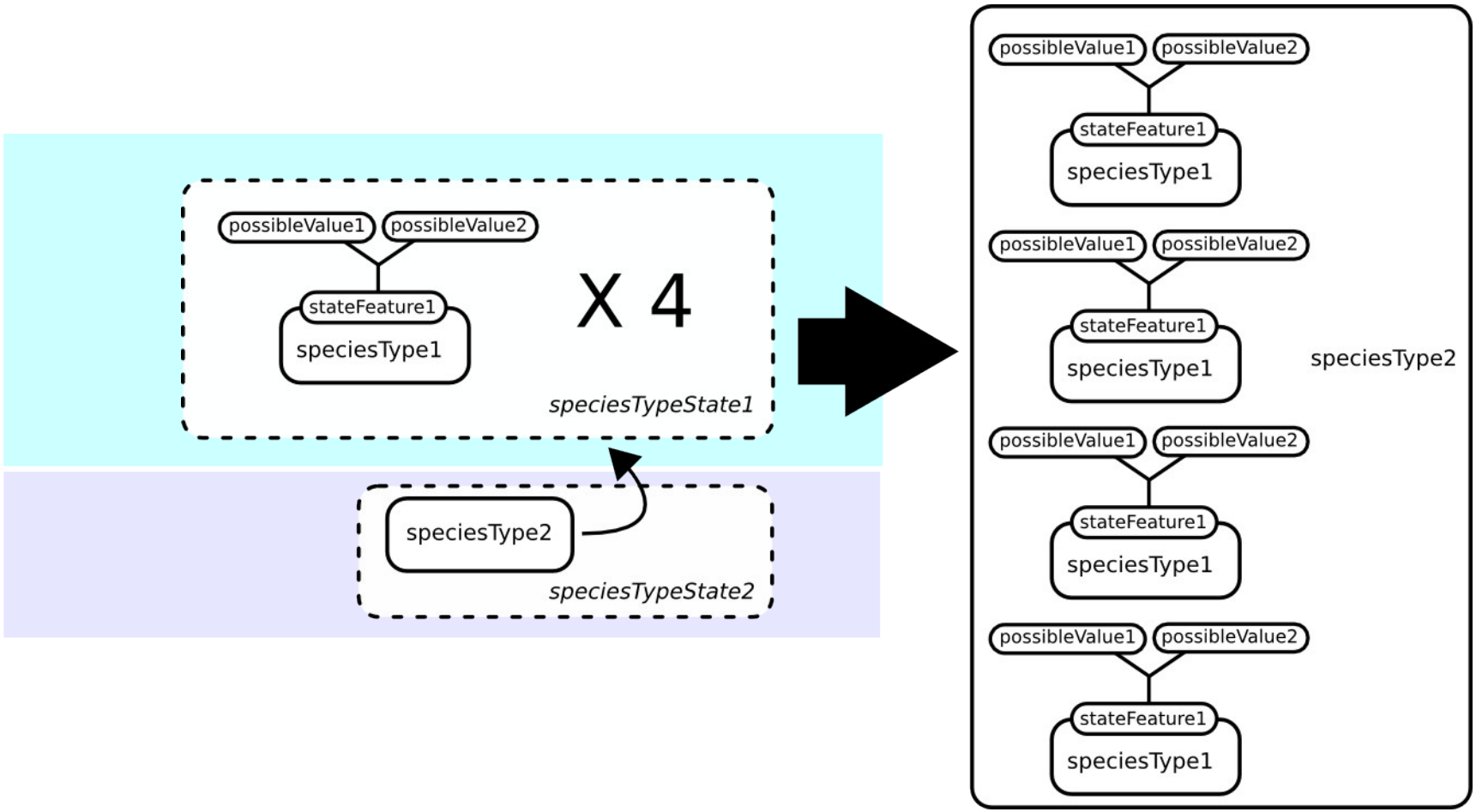
General structure of the selector

```
<multi:selector
  xmlns:multi="http://www.sbml.org/sbml/level3/version1/multi/version1"
                multi:id="selector1"
                multi:name="unbound_receptor">
  <multi:listOfSpeciesTypeStates>
    <!-- some species type state -->
  </multi:listOfSpeciesTypeStates>
  <multi:listOfBonds>
    <!-- some bonds -->
  </multi:listOfBonds>
  <multi:listOfUnboundBindingSites>
    <!-- some unbound binding sites -->
  </multi:listOfUnboundBindingSites>
</multi:selector>
```

Definition of filters



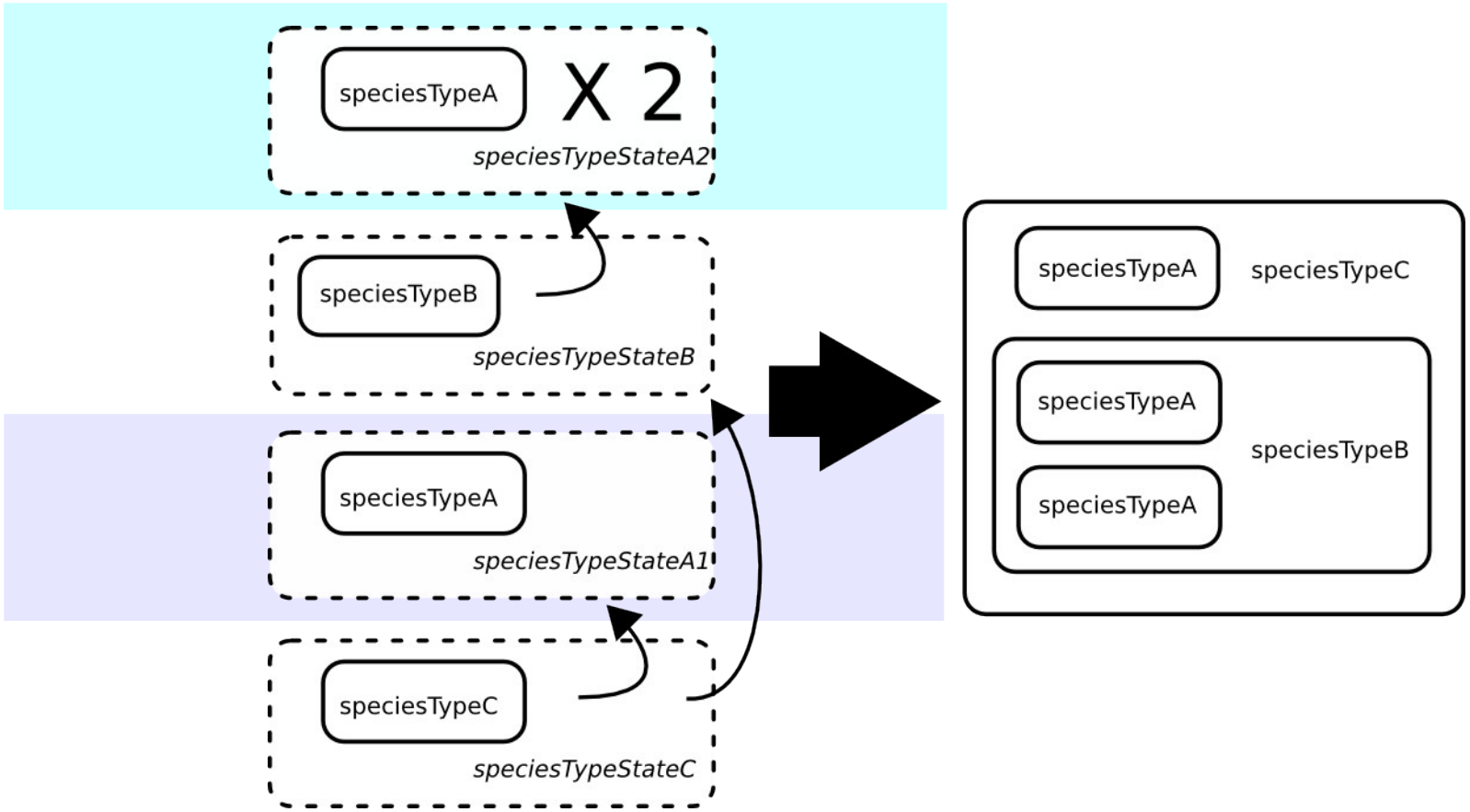
Example of speciesTypeStates



Example of speciesTypeStates

```
<multi:listOfSpeciesTypeStates
          xmlns:multi="http://www.sbml.org/sbml/level3/version1/multi/version1">
  <multi:speciesTypeState multi:id="speciesTypeState1"
                          multi:speciesType="speciesType1"
                          multi:minOccur="4" multi:maxOccur="4"
                          multi:connex="true" multi:saturated="true">
    <multi:listOfStateFeatureInstances>
      <multi:stateFeatureInstance multi:stateFeature="stateFeature1">
        <multi:listOfStateFeatureValues>
          <multi:stateFeatureValue multi:possibleValue="possibleValue1" />
          <multi:stateFeatureValue multi:possibleValue="possibleValue2" />
        </multi:listOfStateFeatureValues>
      </multi:stateFeatureInstance>
    </multi:listOfStateFeatureInstances>
  </multi:speciesTypeState>
  <multi:speciesTypeState multi:id="speciesTypeState2"
                          multi:speciesType="speciesType2"
                          multi:minOccur="1" multi:maxOccur="1">
    <multi:listOfContainedSpeciesTypes>
      <multi:containedSpeciesType multi:speciesTypeState="speciesTypeState1" />
    </multi:listOfContainedSpeciesTypes>
  </multi:speciesTypeState>
</multi:listOfSpeciesTypeStates>
```

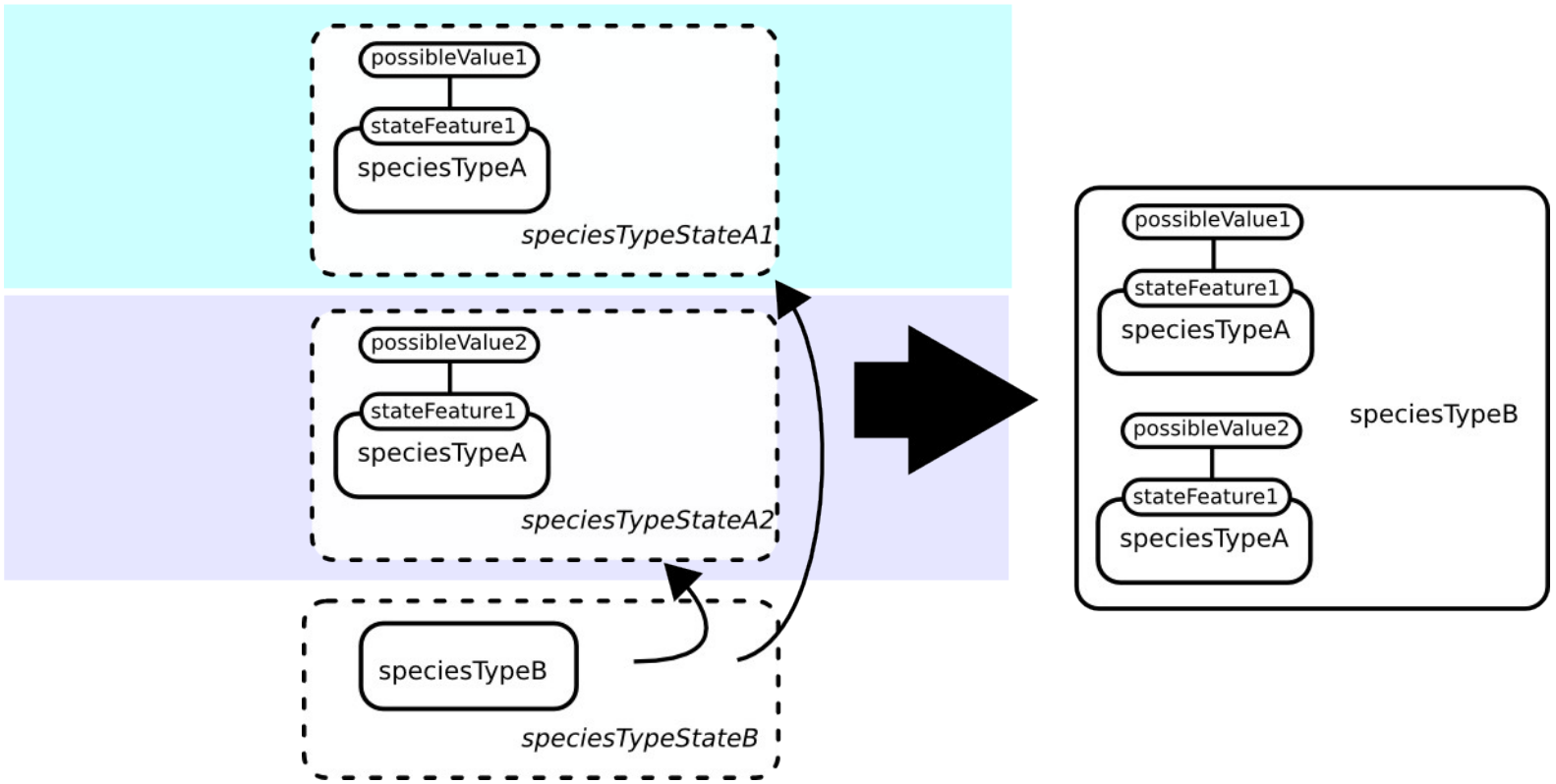
Same SpeciesType in multiple roles



Same SpeciesType in multiple roles

```
<multi:listOfSpeciesTypeStates
          xmlns:multi="http://www.sbml.org/sbml/level3/version1/multi/version1">
  <multi:speciesTypeState multi:id="speciesTypeStateA1"
                          multi:speciesType="speciesTypeA"
                          multi:minOccur="1" multi:maxOccur="1" />
  <multi:speciesTypeState multi:id="speciesTypeStateA2"
                          multi:speciesType="speciesTypeA"
                          multi:minOccur="2" multi:maxOccur="2" />
  <multi:speciesTypeState multi:id="speciesTypeStateB"
                          multi:speciesType="speciesTypeB"
                          multi:minOccur="1" multi:maxOccur="1" />
    <multi:listOfContainedSpeciesTypes>
      <multi:containedSpeciesType multi:speciesTypeState="speciesTypeStateA2" />
    </multi:listOfContainedSpeciesTypes>
  </multi:speciesTypeState>
  <multi:speciesTypeState multi:id="speciesTypeStateC"
                          multi:speciesType="speciesTypeC"
                          multi:minOccur="1" multi:maxOccur="1" >
    <multi:listOfContainedSpeciesTypes>
      <multi:containedSpeciesType multi:speciesTypeState="speciesTypeStateA1" />
      <multi:containedSpeciesType multi:speciesTypeState="speciesTypeStateB" />
    </multi:listOfContainedSpeciesTypes>
  </multi:speciesTypeState>
</multi:listOfSpeciesTypeStates>
```

Same speciesType with different stateFeatures



Same speciesType with different stateFeatures

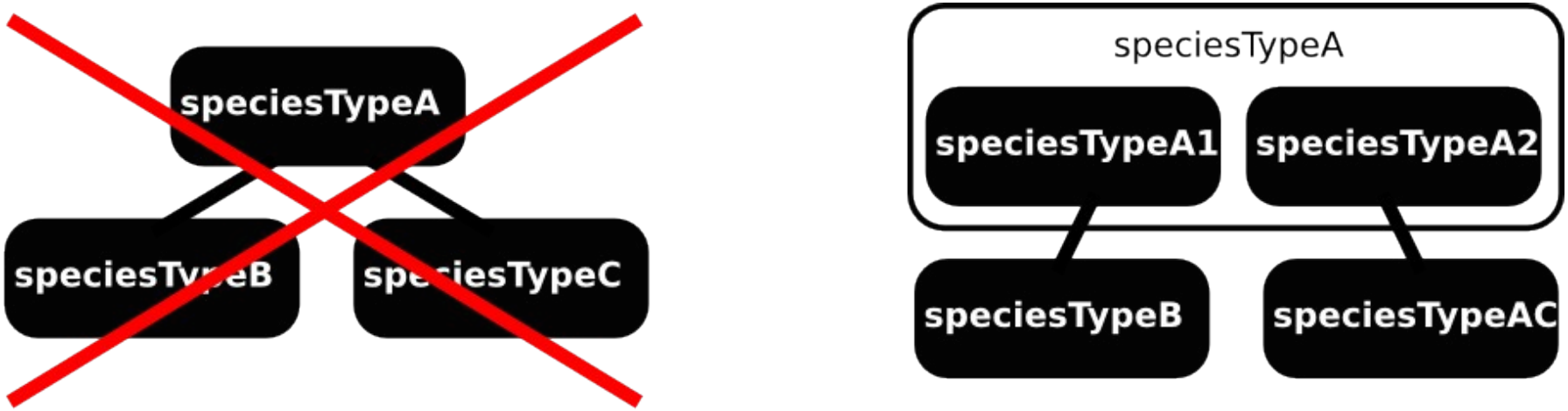
```
<multi:listOfSpeciesTypeStates
              xmlns:multi="http://www.sbml.org/sbml/level3/version1/multi/version1">
  <multi:speciesTypeState multi:id="speciesTypeStateA1" multi:speciesType="speciesTypeA"
                          multi:minOccur="1" multi:maxOccur="1"
    <multi:listOfStateFeatureInstances>
      <multi:stateFeatureInstance multi:stateFeature="stateFeature1">
        <multi:listOfStateFeatureValues>
          <multi:stateFeatureValue multi:possibleValue="possibleValue1" />
        </multi:listOfStateFeatureValues>
      </multi:stateFeatureInstance>
    </multi:listOfStateFeatureInstances>
  </multi:speciesTypeState>
  <multi:speciesTypeState multi:id="speciesTypeStateA2" multi:speciesType="speciesTypeA"
                          multi:minOccur="1" multi:maxOccur="1"
    <multi:listOfStateFeatureInstances>
      <multi:stateFeatureInstance multi:stateFeature="stateFeature1">
        <multi:listOfStateFeatureValues>
          <multi:stateFeatureValue multi:possibleValue="possibleValue2" />
        </multi:listOfStateFeatureValues>
      </multi:stateFeatureInstance>
    </multi:listOfStateFeatureInstances>
  </multi:speciesTypeState>
  <multi:speciesTypeState multi:id="speciesTypeStateB" multi:speciesType="speciesTypeB"
                          multi:minOccur="1" multi:maxOccur="1">
    <multi:listOfContainedSpeciesTypes>
      <multi:containedSpeciesType multi:speciesTypeState="speciesTypeStateA1" />
      <multi:containedSpeciesType multi:speciesTypeState="speciesTypeStateA2" />
    </multi:listOfContainedSpeciesTypes>
  </multi:speciesTypeState>
</multi:listOfSpeciesTypeStates>
```

Impossible selector

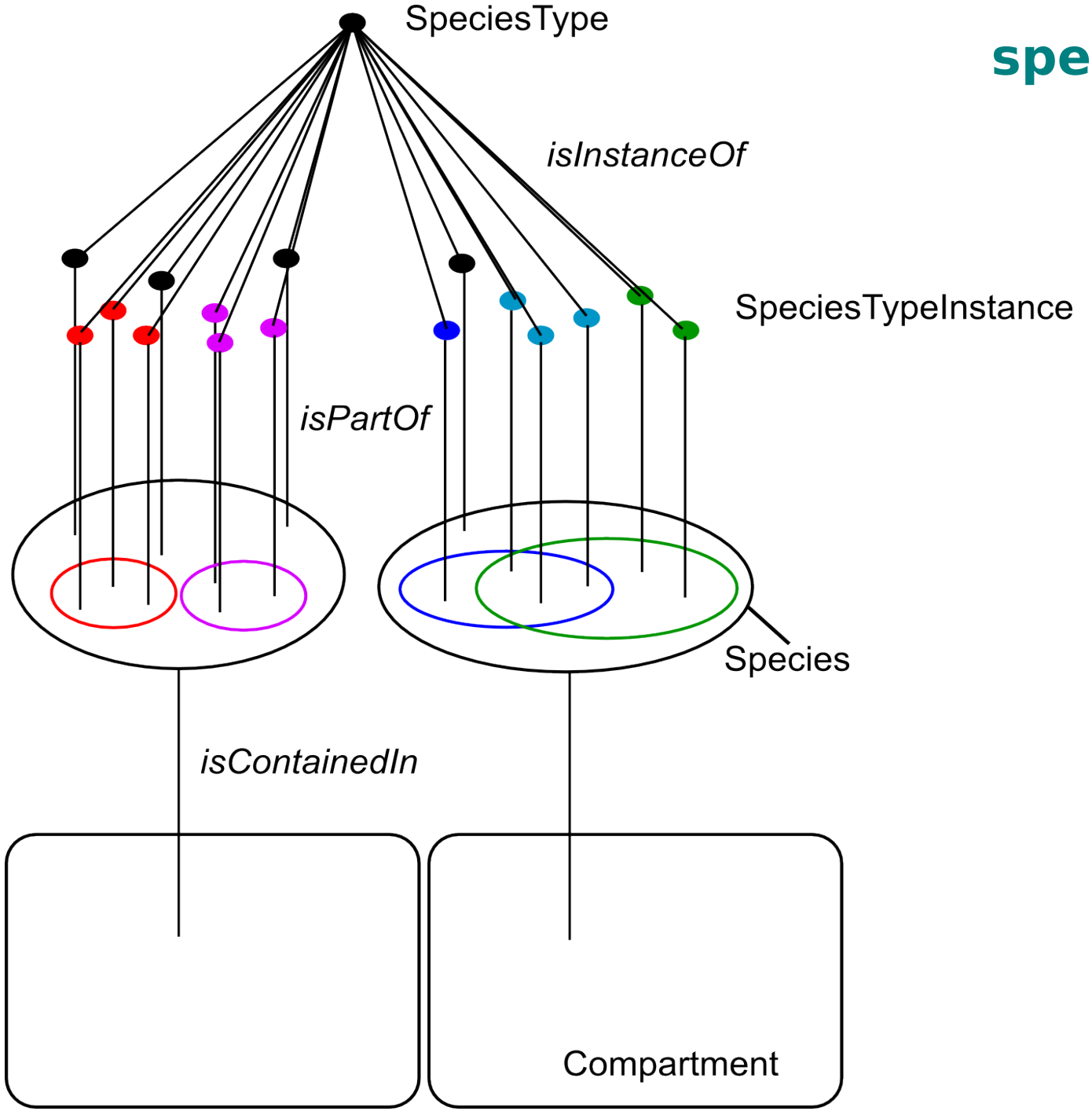
```
<multi:listOfSpeciesTypeStates
         xmlns:multi="http://www.sbml.org/sbml/level3/version1/multi/version1">
  <multi:speciesTypeState multi:id="speciesTypeState1"
                          multi:speciesType="speciesType1"
                          multi:minOccur="1" multi:maxOccur="1" >
    <multi:listOfContainedSpeciesTypes>
      <multi:containedSpeciesType multi:speciesTypeState="speciesTypeState2" />
    </multi:listOfContainedSpeciesTypes>
  </multi:speciesTypeState>
  <multi:speciesTypeState multi:id="speciesTypeState2"
                          multi:speciesType="speciesType2"
                          multi:minOccur="1" multi:maxOccur="1" >
    <multi:listOfContainedSpeciesTypes>
      <multi:containedSpeciesType multi:speciesTypeState="speciesTypeState1" />
    </multi:listOfContainedSpeciesTypes>
  </multi:speciesTypeState>
</multi:listOfSpeciesTypeStates>
```

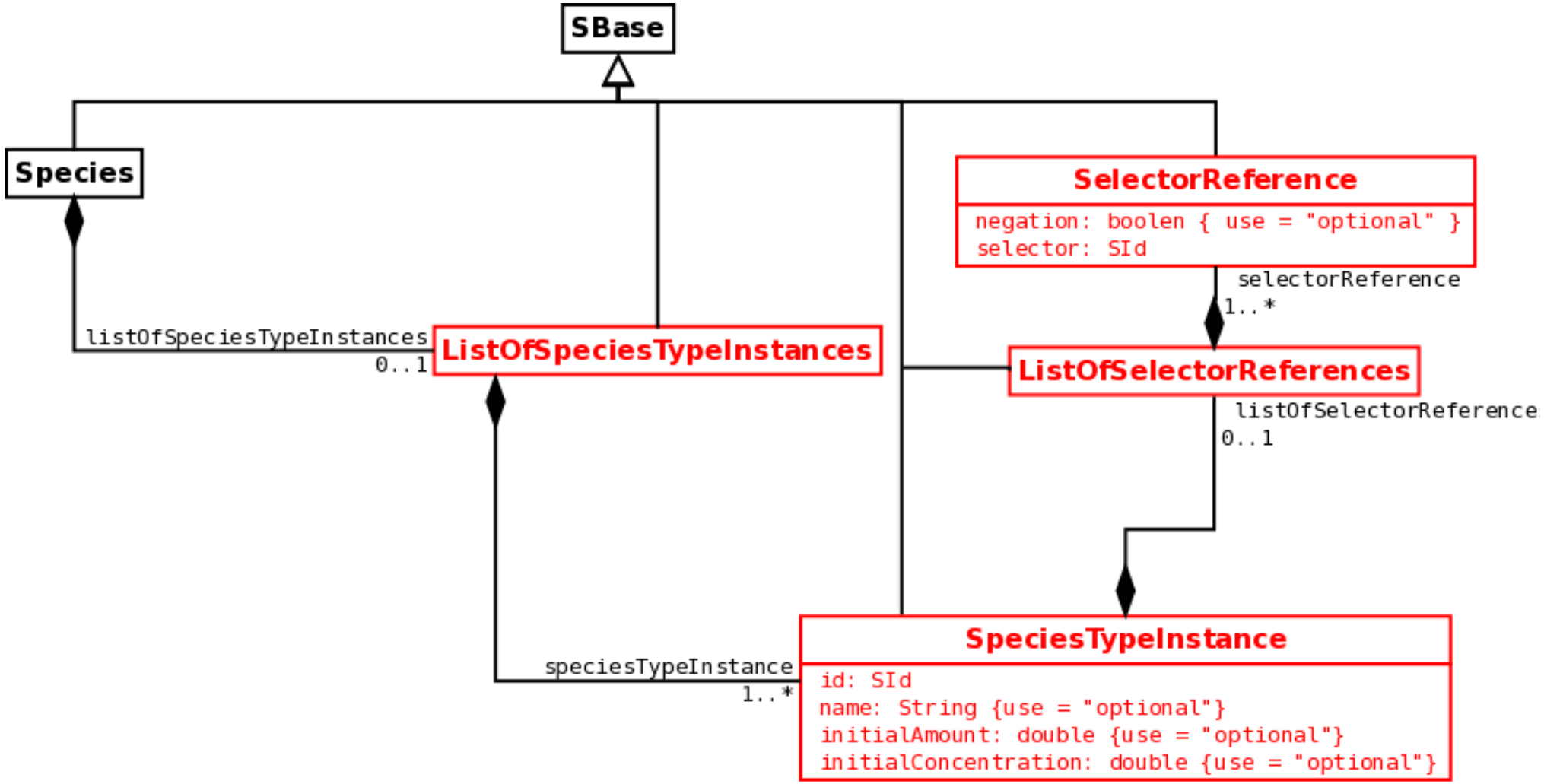
speciesTypeState1 contains speciesTypeState2
speciesTypeState2 contains speciesTypeState1

A binding site can only engage in one bond

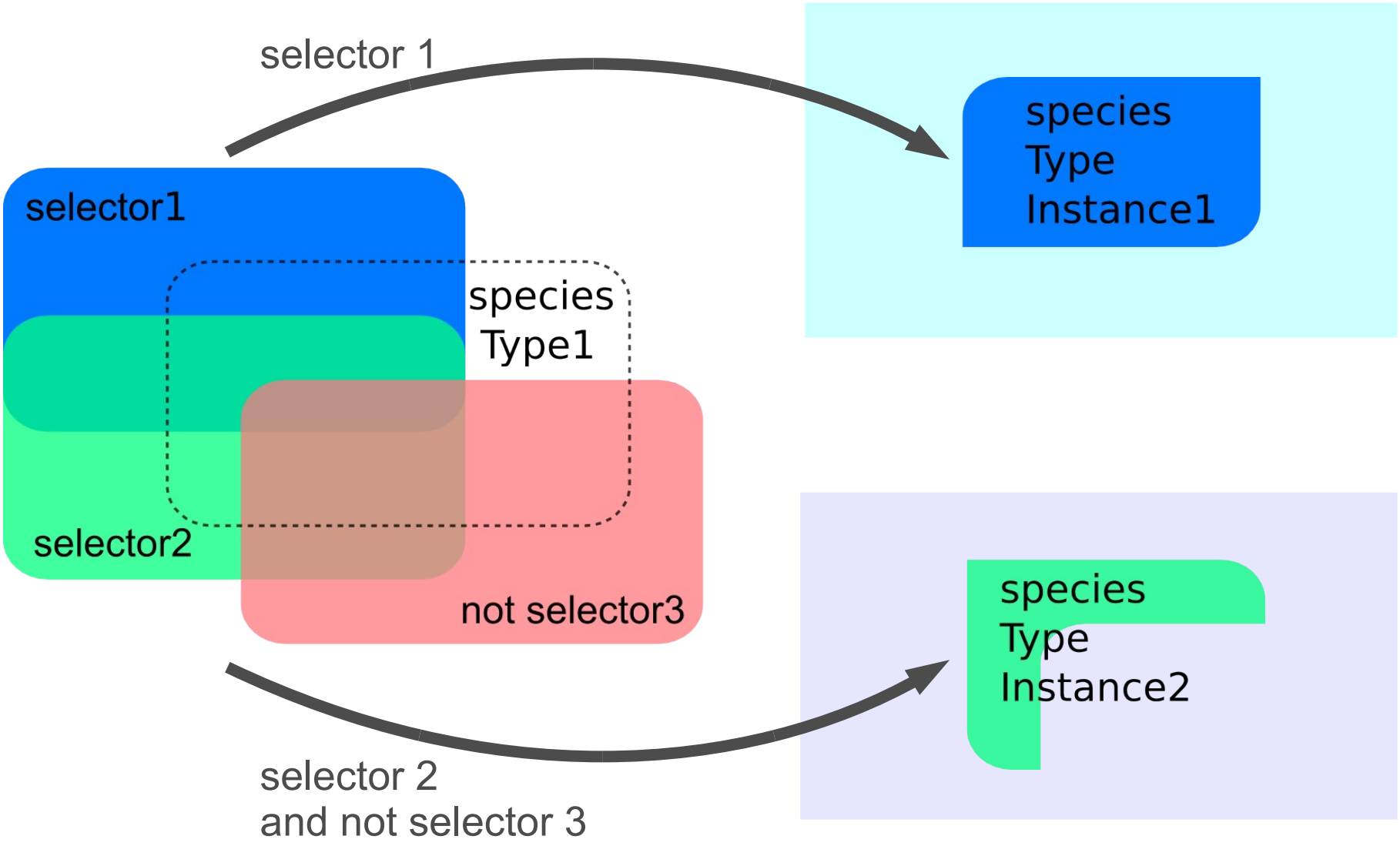


On sub-pools and speciesType instances




SBase
Species
SelectorReference
negation: boolen { use = "optional" }
selector: SId
selectorReference
1..*
listOfSpeciesTypeInstances
0..1
ListOfSpeciesTypeInstances
ListOfSelectorReferences
listOfSelectorReference
0..1
SpeciesTypeInstance
id: SId
name: String {use = "optional"}
initialAmount: double {use = "optional"}
initialConcentration: double {use = "optional"}
speciesTypeInstance
1..*

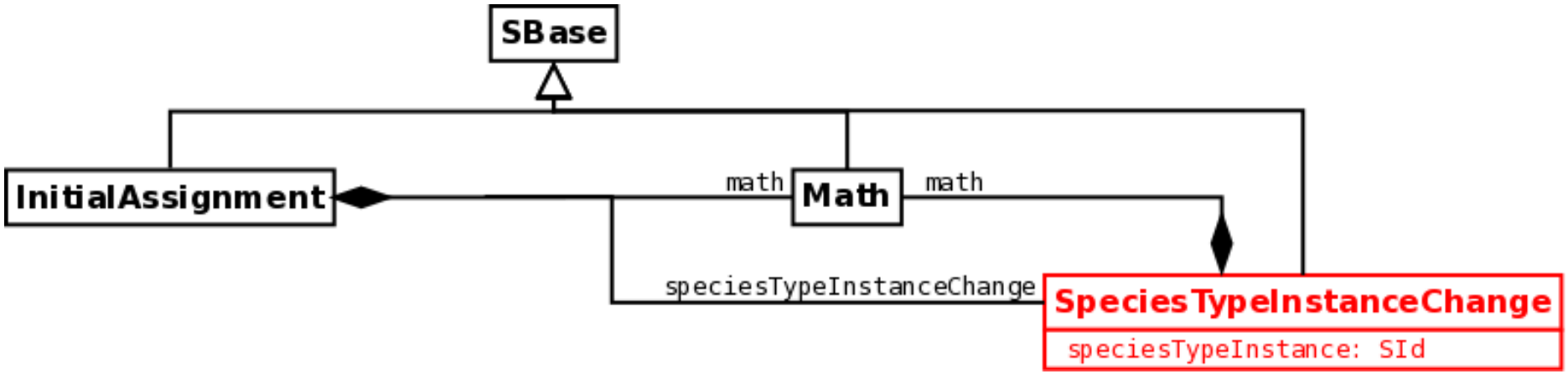
Selection of sub-pools by combination of selectors



Selection of sub-pools by combination of selectors

```
<species id="species1" boundaryCondition=false" hasOnlySubstanceUnit=false"
         constant=false" compartment="compartment1" initialAmount="1000"
         xmlns:multi="http://www.sbml.org/sbml/level3/version1/multi/version1"
         multi:speciesType="speciesType1" >
  <multi:listOfSpeciesTypeInstances>
    <multi:SpeciesTypeInstance multi:id="speciesTypeInstance1"
                               multi:initialAmount="1">
      <multi:listOfSelectorReferences>
        <multi:selectorReference multi:selector="selector1">
      <multi:listOfSelectorReferences>
    </multi:speciesTypeInstance>
    <multi:SpeciesTypeInstance multi:id="speciesTypeInstance2">
      <multi:listOfSelectorReferences>
        <multi:selectorReference multi:selector="selector2">
        <multi:selectorReference multi:selector="selector3"
                                 multi:negation="true">
      <multi:listOfSelectorReferences>
    </multi:speciesTypeInstance>
  </multi:listOfSpeciesTypeInstances>
</species>
```

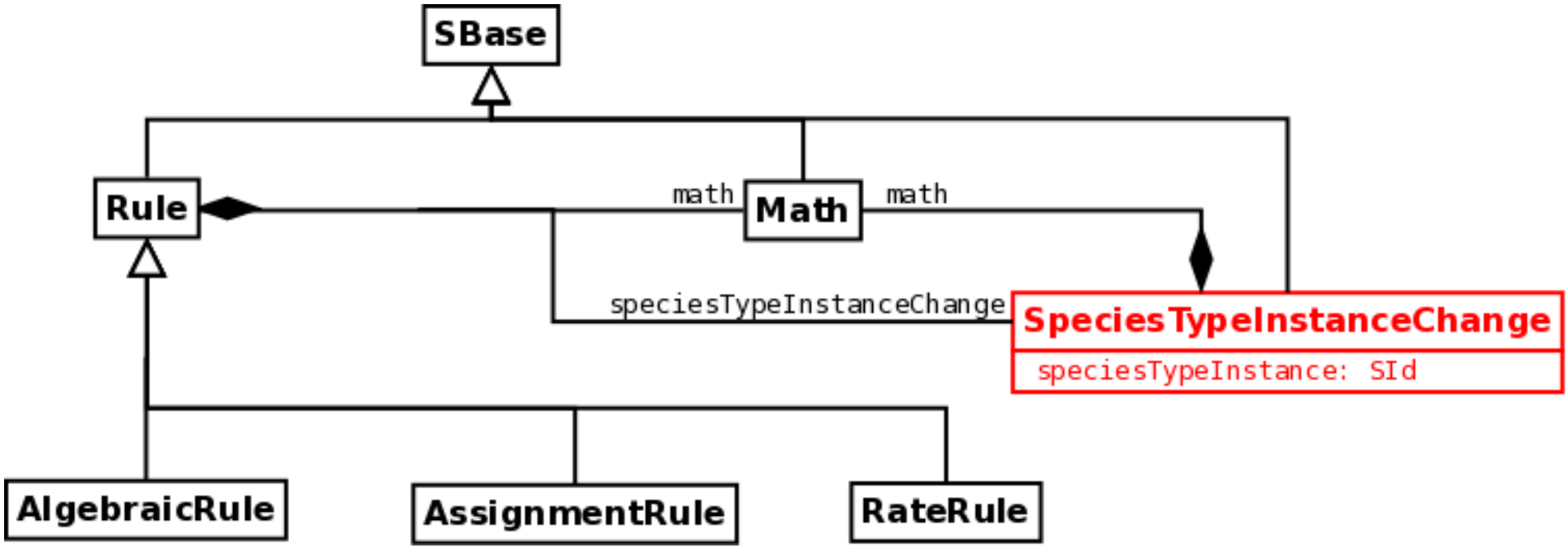
Initial size of sub-pools



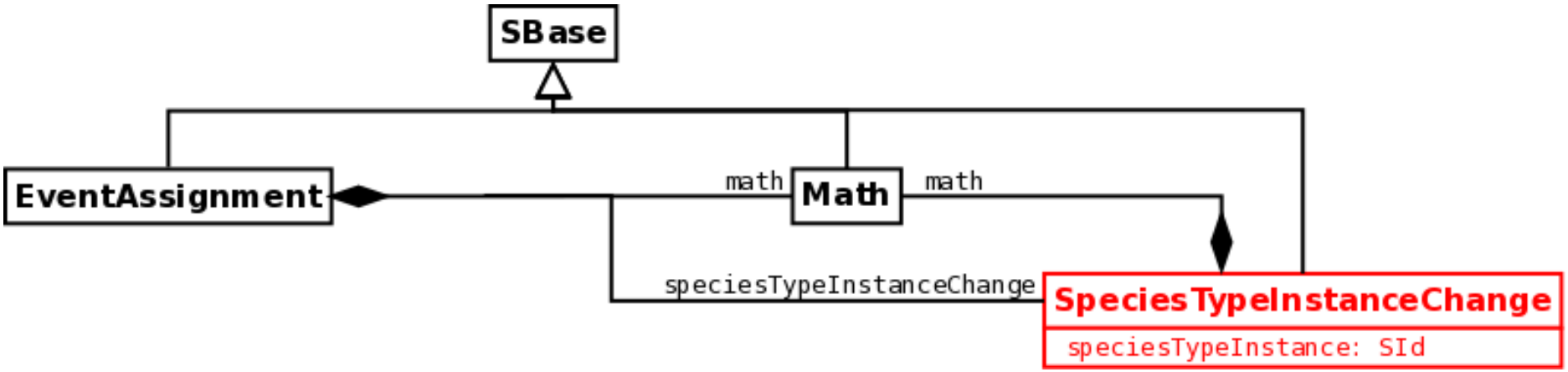
Initial size of sub-pools

```
<species id="species1"
         boundaryCondition="false" hasOnlySubstanceUnit="false" constant="false"
         compartment="compartment1" initialAmount="1000"
         xmlns:multi="http://www.sbml.org/sbml/level3/version1/multi/version1"
         multi:speciesType="speciesType1" >
  <multi:listOfSpeciesTypeInstances>
    <multi:SpeciesTypeInstance multi:id="speciesTypeInstance1"
                               multi:initialAmount="1">
      <multi:listOfSelectorReferences>
        <multi:selectorReference multi:selector="selector1">
      <multi:listOfSelectorReferences>
    </multi:speciesTypeInstance>
  </multi:listOfSpeciesTypeInstances>
</species>
<initialAssignement symbol="species1">
  <multi:speciesTypeInstanceChange
                              multi:speciesTypeInstance="speciesTypeInstance1">
    <math xmlns="http://www.w3.org/1998/Math/MathML">
      <apply>
        <times/>
        <ci> x </ci>
        <ci> y </ci>
      </apply>
    </math>
  </multi:speciesTypeInstanceChange>
  <math xmlns="http://www.w3.org/1998/Math/MathML" />
</initialAssignement>
```

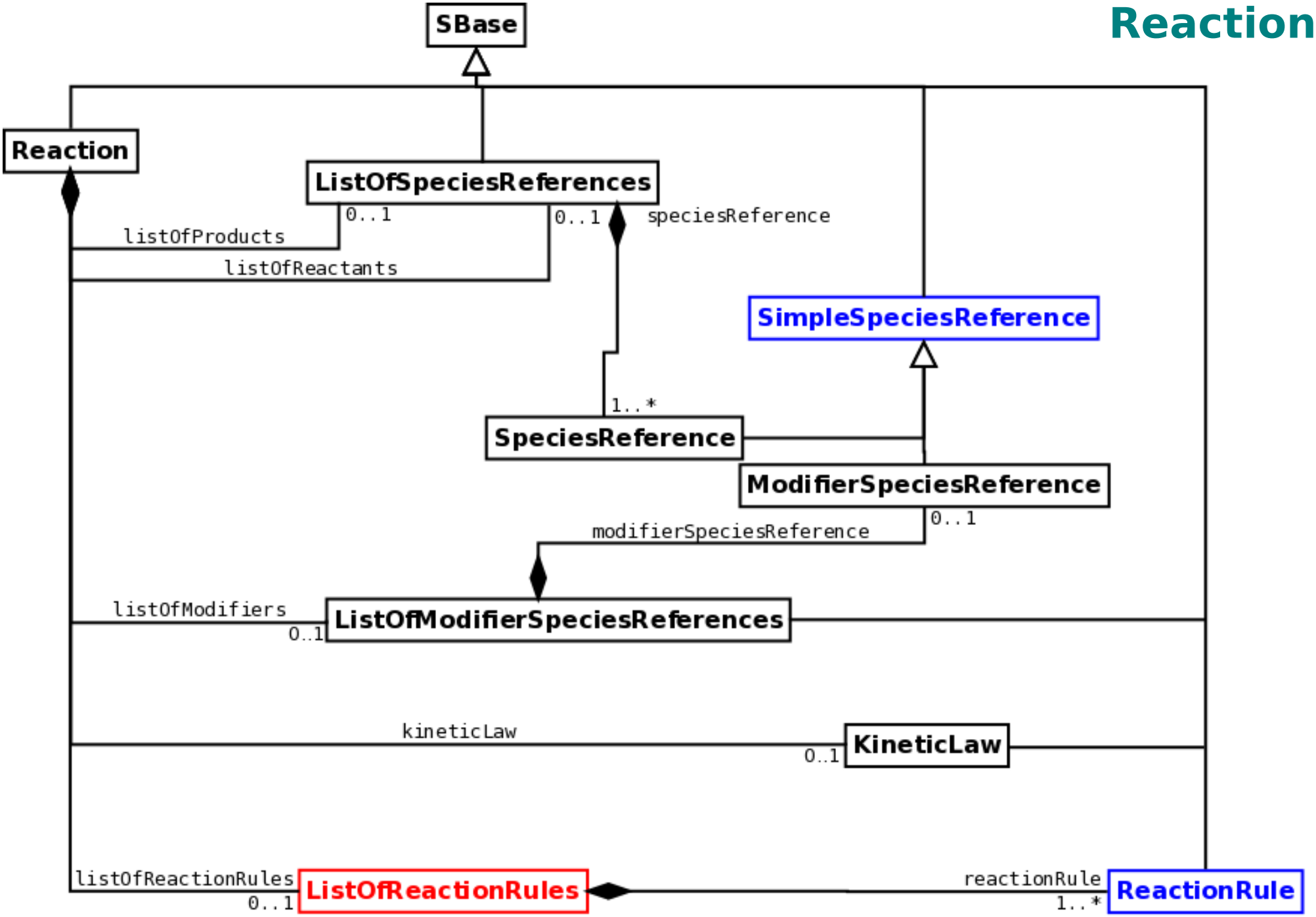
Rules applied to speciesTypeInstances

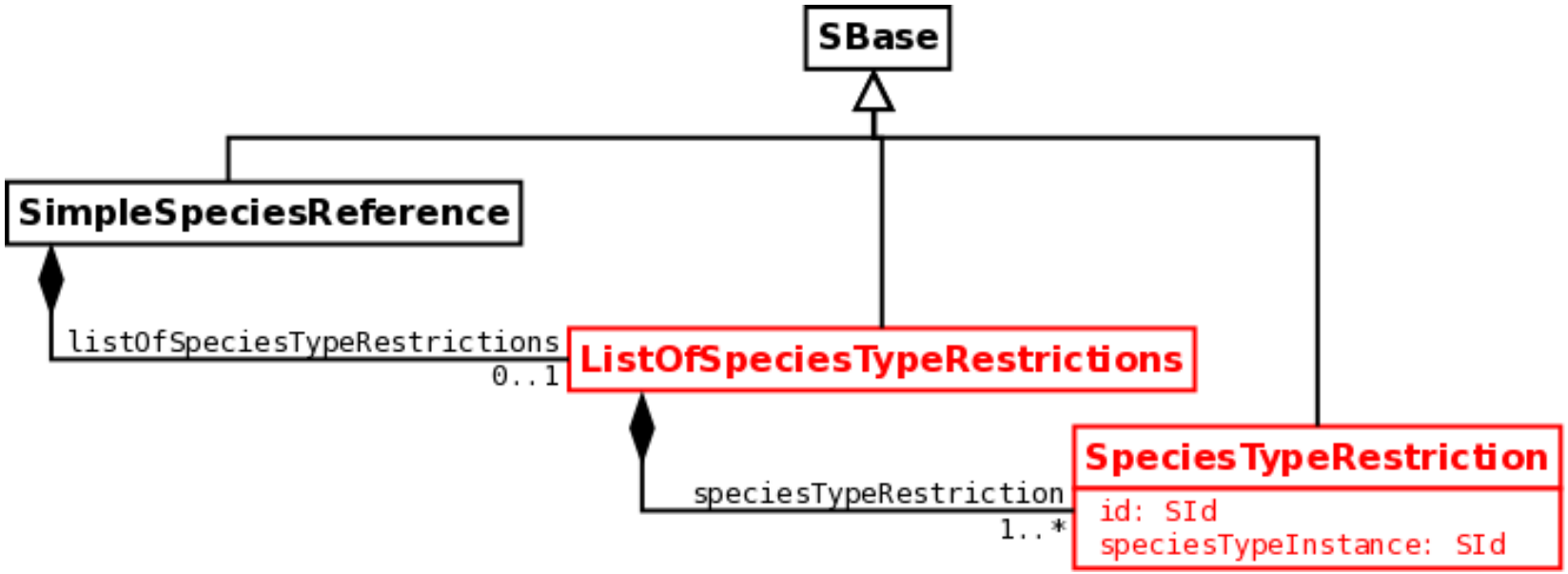


Event assigning values to speciesTypeInstances



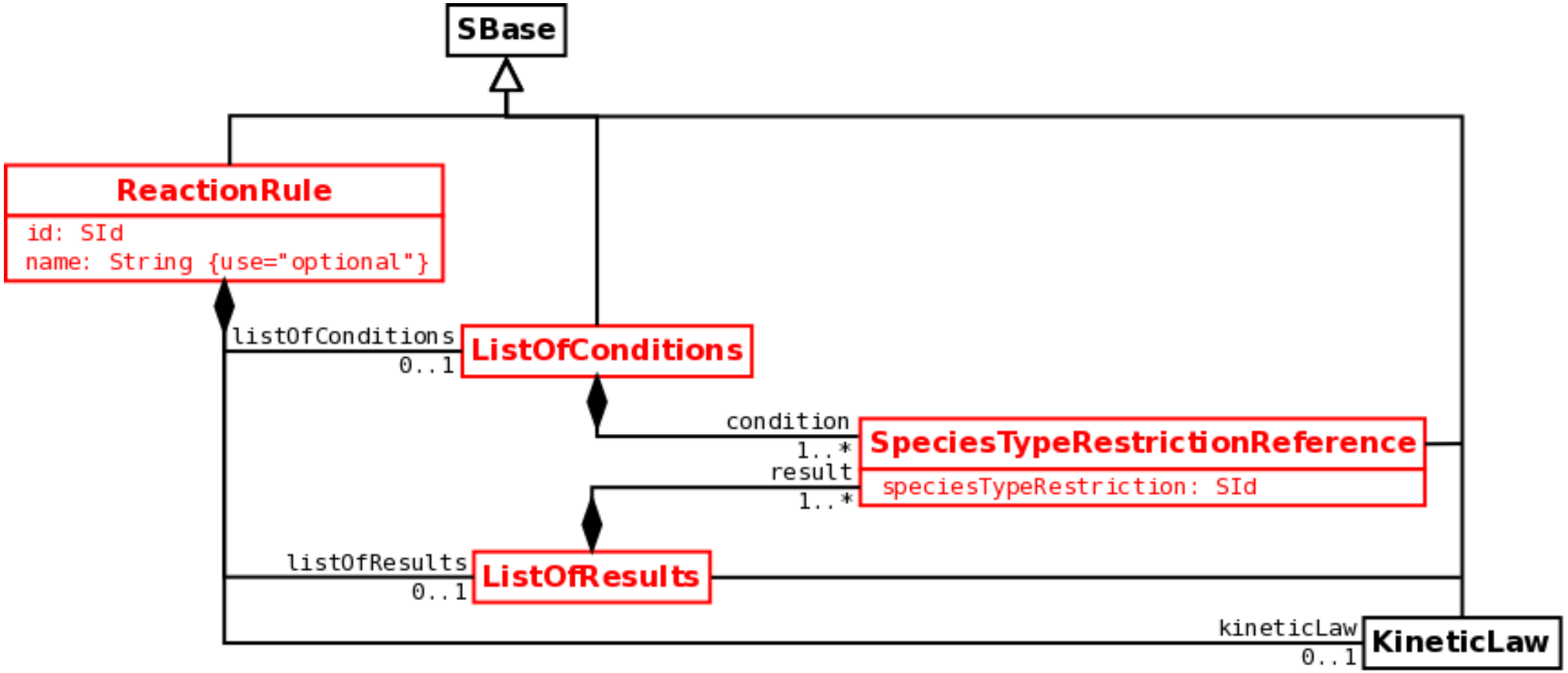
Reactions


SBase
Reaction
ListOfSpeciesReferences
0..1
0..1
speciesReference
listOfProducts
listOfReactants
SimpleSpeciesReference
1..*
SpeciesReference
ModifierSpeciesReference
0..1
modifierSpeciesReference
listOfModifiers
0..1
ListOfModifierSpeciesReferences
kineticLaw
0..1
KineticLaw
listOfReactionRules
0..1
ListOfReactionRules
reactionRule
1..*
ReactionRule


SBase
SimpleSpeciesReference
listOfSpeciesTypeRestrictions
0..1
ListOfSpeciesTypeRestrictions
speciesTypeRestriction
1..*
SpeciesTypeRestriction
id: SId
speciesTypeInstance: SId

Definition of restrictions

```
<listOfReactants>
  <speciesReference species="recept" stoichiometry="1">
    <multi:listOfSpeciesRestriction>
      <multi:speciesRestriction multi:id="freeR"
                                multi:speciesTypeInstance="freereceptor">
     </multi:listOfSpeciesRestriction>
  </speciesReference>
  <speciesReference species="lig" stoichiometry="1">
    <multi:listOfSpeciesRestriction>
      <multi:speciesRestriction multi:id="freeL"
                                multi:speciesTypeInstance="freeligand">
    </multi:listOfSpeciesRestriction>
  </speciesReference>
</listOfReactants>
<listOfProducts>
  <speciesReference species="recept" stoichiometry="1">
    <multi:listOfSpeciesRestriction>
      <multi:speciesRestriction multi:id="boundR"
                                multi:speciesTypeInstance="boundreceptor">
    </multi:listOfSpeciesRestriction>
  </speciesReference>
  <speciesReference species="lig" stoichiometry="1">
    <multi:listOfSpeciesRestriction>
      <multi:speciesRestriction multi:id="boundL"
                                multi:speciesTypeInstance="boundligand">
    </multi:listOfSpeciesRestriction>
  </speciesReference>
</listOfProducts>
```


SBase
ReactionRule
id: SId
name: String {use="optional"}
listOfConditions
0..1
ListOfConditions
condition
1..*
SpeciesTypeRestrictionReference
speciesTypeRestriction: SId
result
1..*
listOfResults
0..1
ListOfResults
kineticLaw
0..1
KineticLaw

Definition of restrictions

```
<multi:reactionRule multi:id="bindingNonPhospho">
  <multi:listOfConditions>
    <multi:speciesTypeRestrictionReference
                                    multi:speciesTypeRestriction="freeR">
    <multi:speciesTypeRestrictionReference
                                    multi:speciesTypeRestriction="freeL">
  </multi:listOfConditions>
  <multi:listOfResults>
    <multi:speciesTypeRestrictionReference
                                    multi:speciesTypeRestriction="boundR">
    <multi:speciesTypeRestrictionReference
                                    multi:speciesTypeRestriction="boundL">
  </multi:listOfResults>
  <kineticLaw>
    <math xmlns="http://www.w3.org/1998/Math/MathML" >
      <apply>
        <times />
        <ci> cell </ci>
        <ci> kon_nonphos </ci>
        <ci> recept </ci>
        <ci> lig </ci>
      </apply>
    </math>
    <listOfParameters>
      <parameter id="kon_nonphos" value="1">
    </listOfParameters>
  </kineticLaw>
</multi:reactionRule>
```