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Support for multistate species in SBML Level 3

Test case: StochSim SBML Support

Anika Oellrich (EMBL-EBI)

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- Multistates, spatial capabilitites
- Achievements

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- Solution for multistates
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Biological entities...

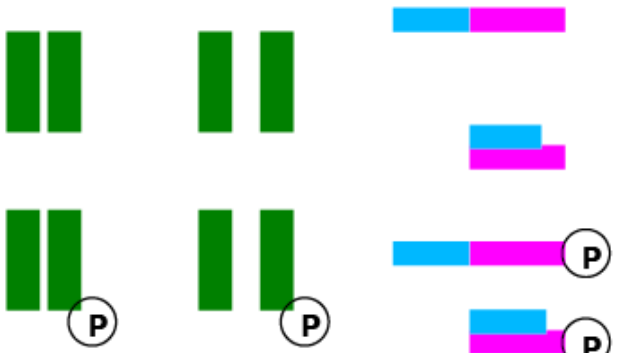
- can have different states
  - covalent modification
  - binding to other molecules
  - alternate conformation
  - multimerization

Two simple examples

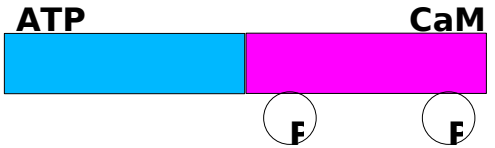
NMDA + CaMKII <=> NMDA-CaMKII

NMDAc + CaMKIIc <=> NMDAc-CaMKIIc
NMDAo + CaMKIIc <=> NMDAc-CaMKIIc
NMDAc + CaMKIIo <=> NMDAc-CaMKIIo
NMDAo + CaMKIIo <=> NMDAc-CaMKIIo

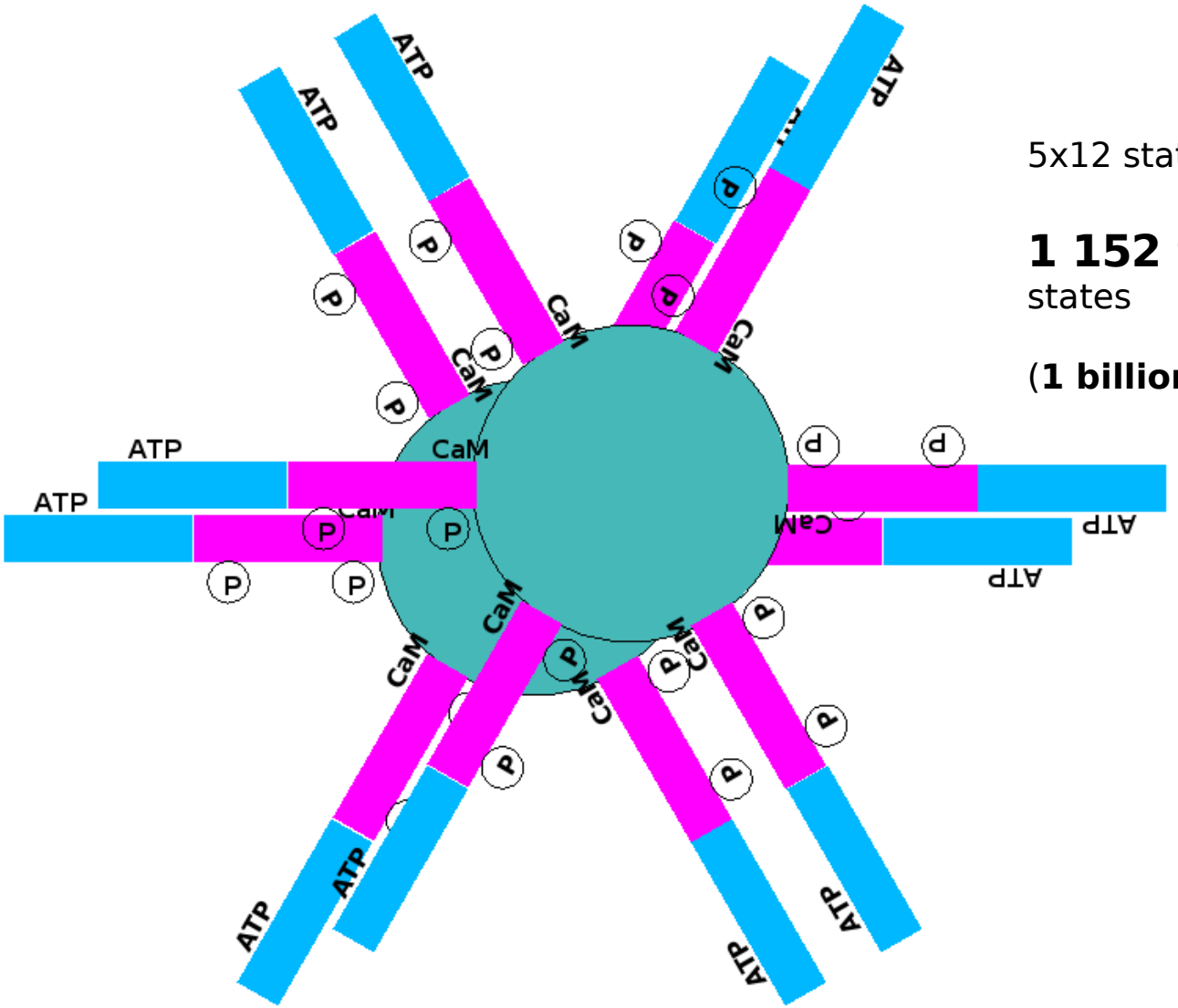
Increasing number of reactions



NMDAc + CaMKIIc <=> NMDAc-CaMKIIc
NMDAo + CaMKIIc <=> NMDAc-CaMKIIc
NMDAc + CaMKIIo <=> NMDAc-CaMKIIo
NMDAo + CaMKIIo <=> NMDAc-CaMKIIo
pNMDAc + CaMKIIc <=> pNMDAc-CaMKIIc
pNMDAo + CaMKIIc <=> pNMDAc-CaMKIIc
pNMDAc + CaMKIIo <=> pNMDAc-CaMKIIo
pNMDAo + CaMKIIo <=> pNMDAc-CaMKIIo
NMDAc + pCaMKIIc <=> NMDAc-pCaMKIIc
NMDAo + pCaMKIIc <=> NMDAc-pCaMKIIc
NMDAc + pCaMKIIo <=> NMDAc-pCaMKIIo
NMDAo + pCaMKIIo <=> NMDAc-pCaMKIIo
pNMDAc + pCaMKIIc <=> pNMDAc-pCaMKIIc
pNMDAo + pCaMKIIc <=> pNMDAc-pCaMKIIc
pNMDAc + pCaMKIIo <=> pNMDAc-pCaMKIIo
pNMDAo + pCaMKIIo <=> pNMDAc-pCaMKIIo



Combinatorial explosion



5x12 state variables=

1 152 900 000 000 000 000
states

(**1 billion of billion**)

Introduction | Stochsim | SBMLINIConverter

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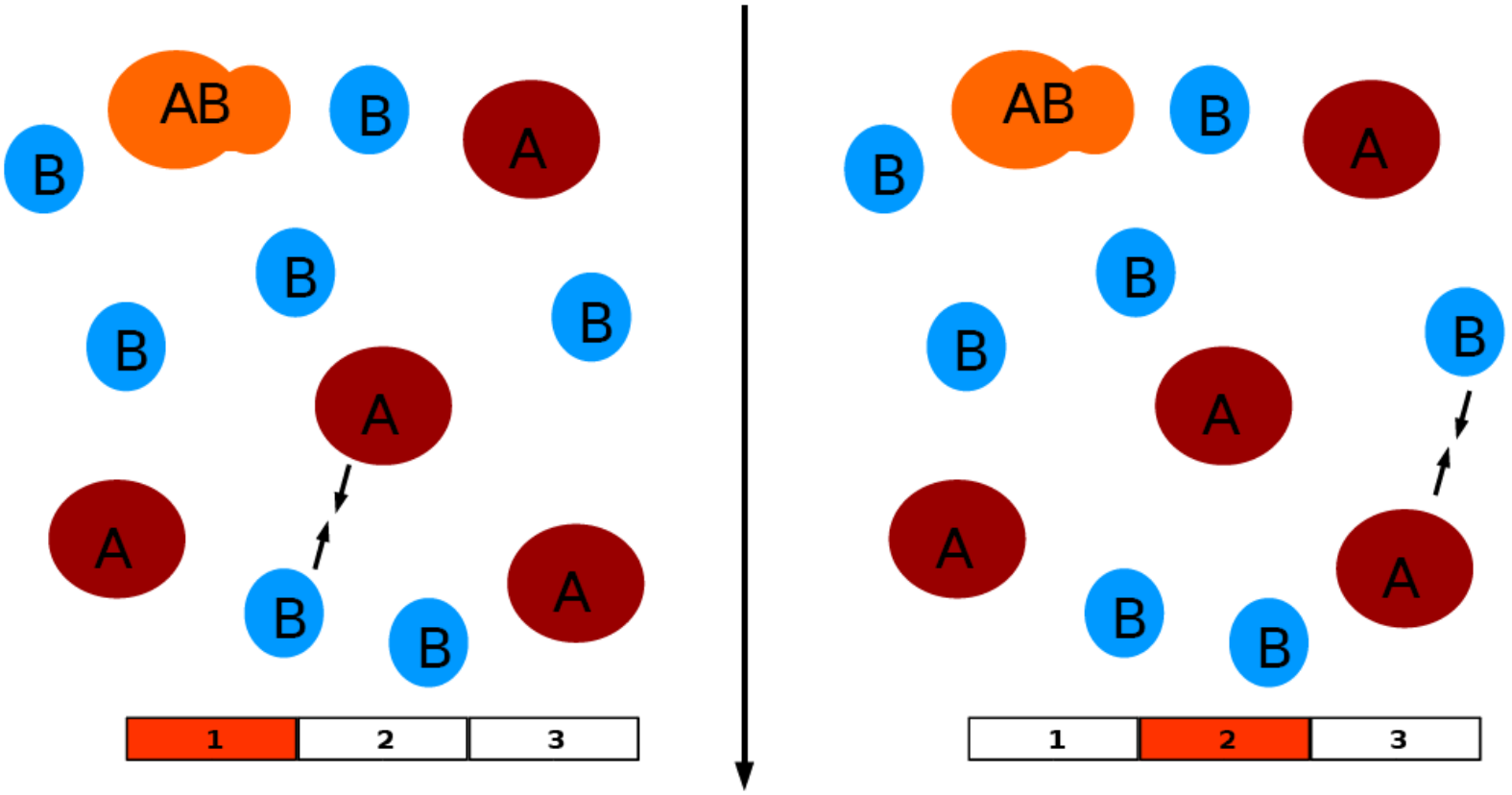
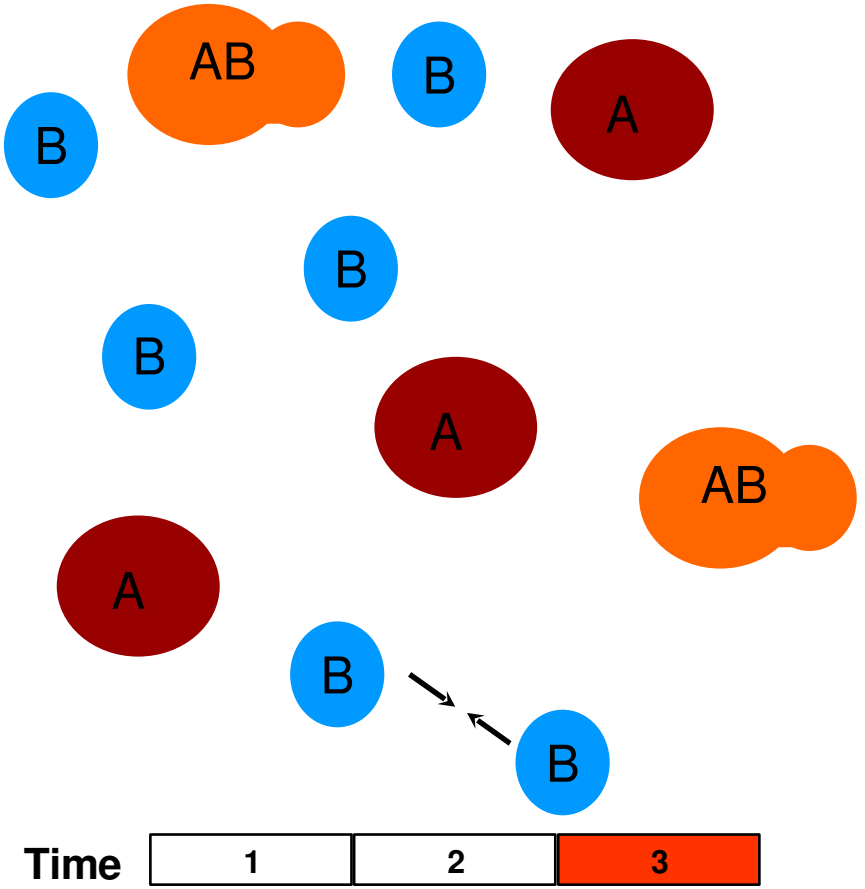
Motivation for StochSim

- Particle-based stochastic simulations
- Possibility of multistate complexes
- 2D lattices of various geometry
- Rapid equilibria
- Settings in StochSim specific INI-files

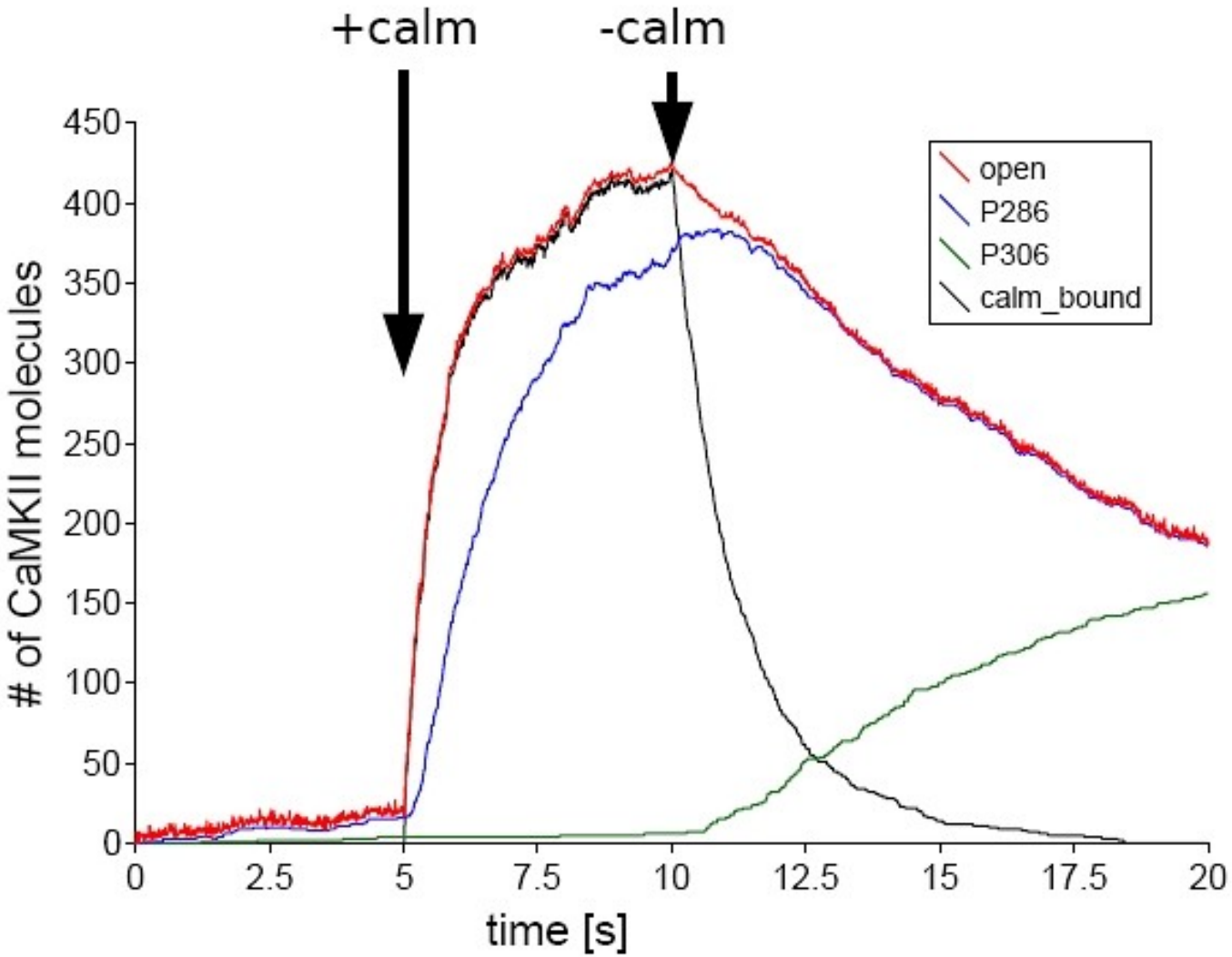
Algorithm



Algorithm



Example: CaMKII



Calculation probability

$$d[A]/dt = -k[A][B] \qquad P = \frac{k\, n(n+n_0)\Delta t}{2VN_A}$$

$$d[A]/dt = -k[A] \qquad P = \frac{k\, n(n+n_0)\Delta t}{n_0}$$

n : # molecules in the system

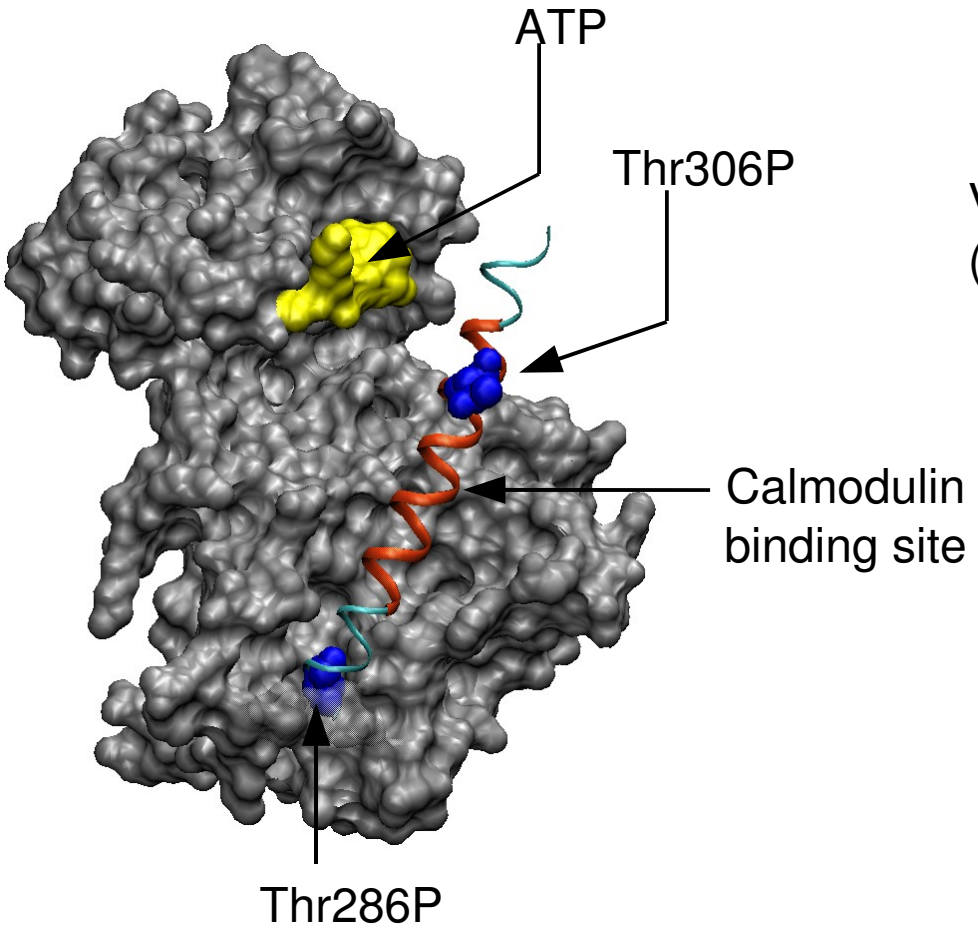
n_0 : # pseudomolecules in the system

V : volume of the system

N_A : Avogadro constant

Multistate molecules

- Internal features = binary flags, states = vector of flags



Vector with 5 state variables:
(a/i,ATP,P1,P2,CaM) -> (1,1,0,0,0)

Multistate reactions

- Reaction probabilities can be modified by the states of the participating multistate complexes

$$p_{MS} = p_{base} \times p_{rel}$$

p_{base} : base probability

p_{rel} : relative probability

Multistates reactions

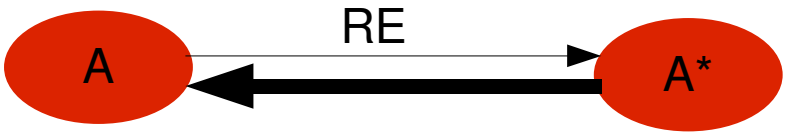
$$(0??0???) \xrightarrow{p_{base} \times p_{rel(0,0)}} (0??1???)$$

$$(1??0???) \xrightarrow{p_{base} \times p_{rel(0,1)}} (1??1???)$$

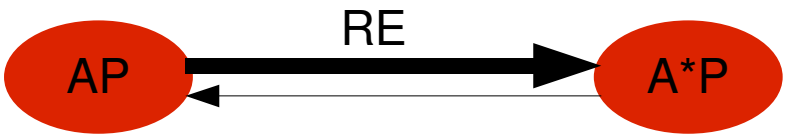
- ? = state variable does not influence reaction
- Only 4 states are needed, not 128

Multistate rapid equilibrium

- predefined probabilities for the states
- probabilities can depend on other flags



(0,0) <--> (1,0)

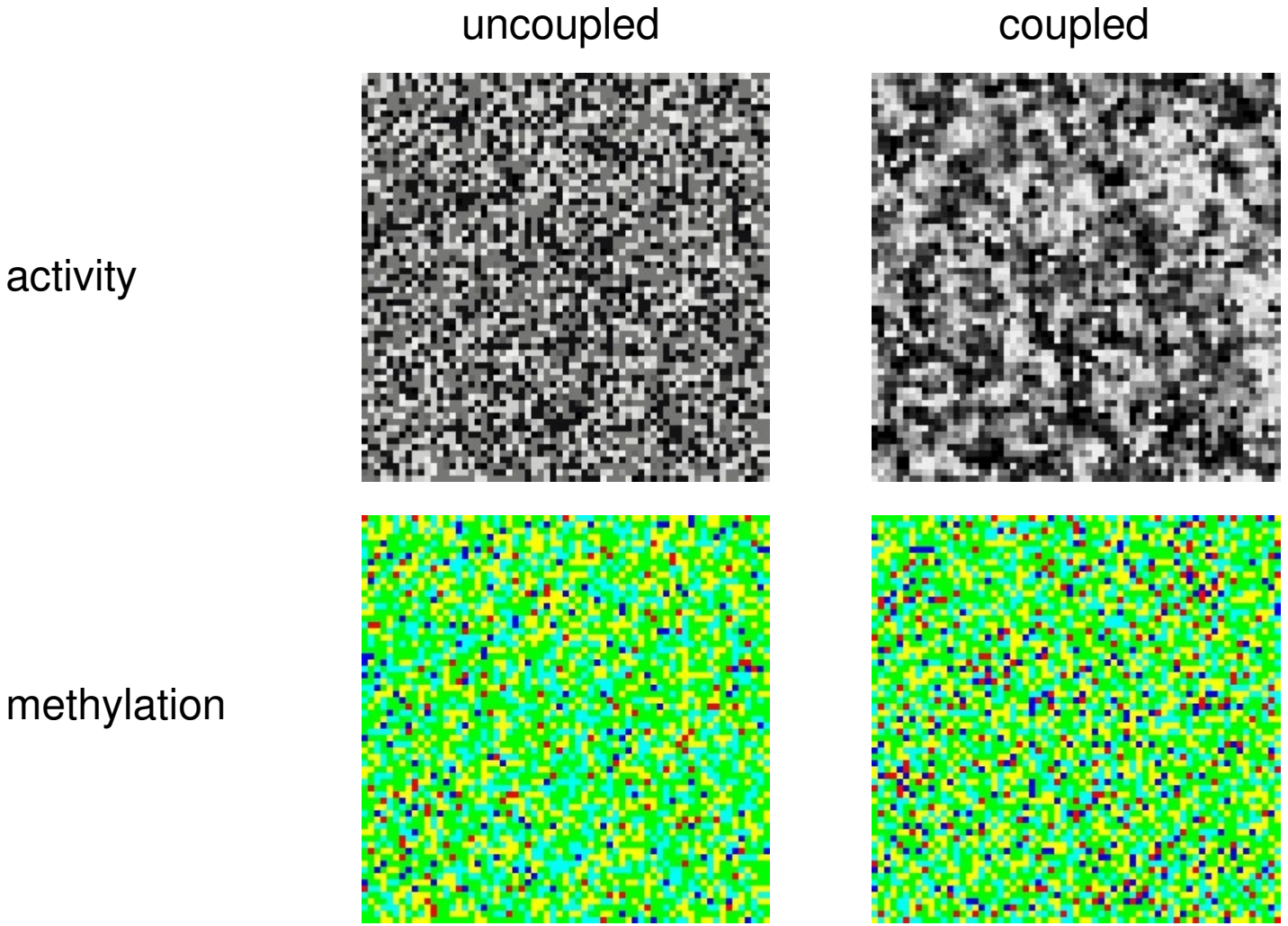


(0,1) <--> (1,1)

Spatial capabilities

- Neighbourhood-sensitive reactions possible in 2D-lattice (triangle, square and hexagon)
- Does not support movement of complexes

Conformational spread

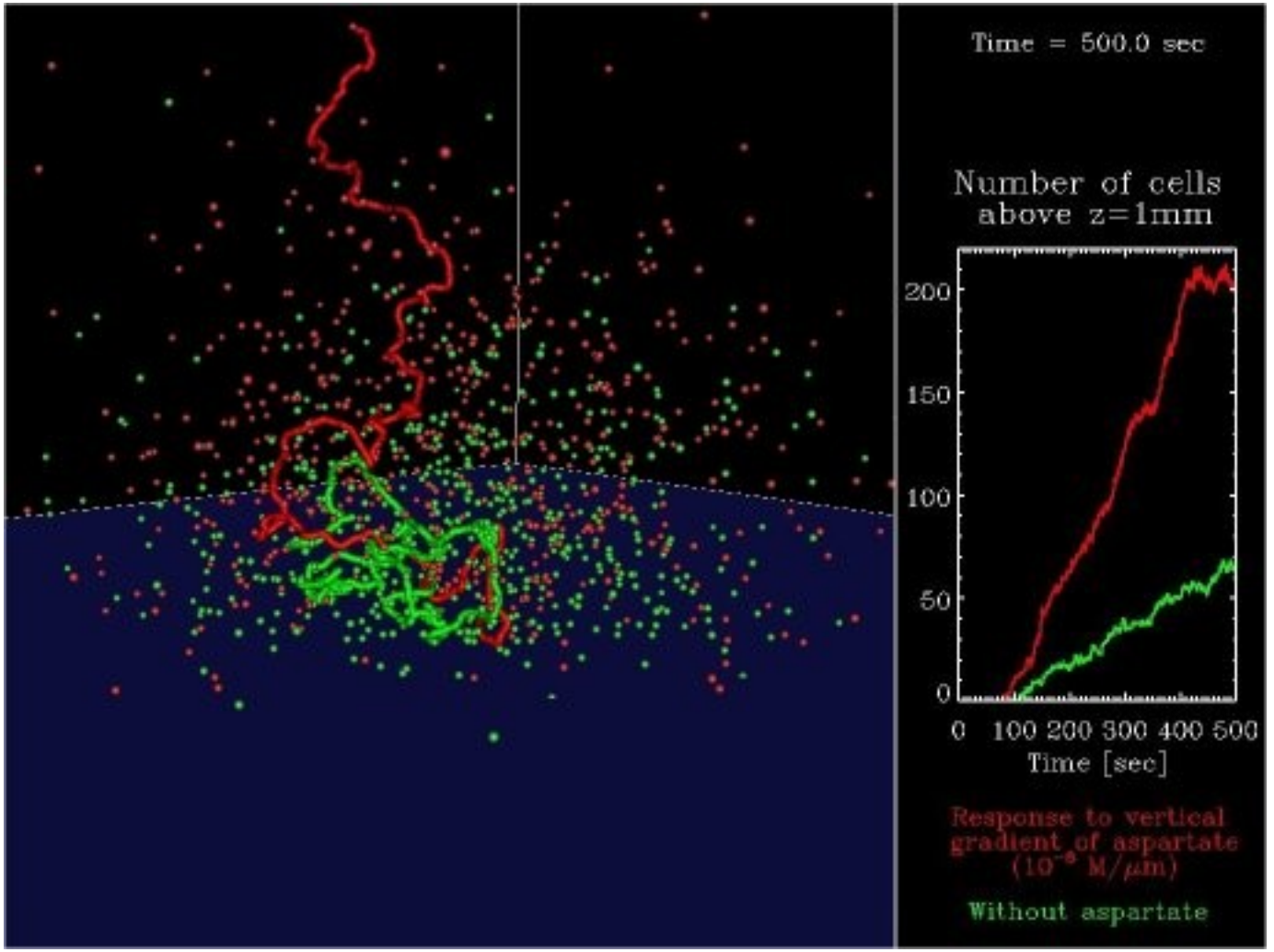


Achievements

- Morton-Firth CJ, Bray D (1998) Predicting temporal fluctuations in an intracellular signalling pathway. *J. Theor. Biol.* 192: 117-28
- Morton-Firth CJ, Shimizu TS, Bray D (1999) A free-energy-based stochastic simulation of the Tar receptor complex. *J. Mol. Biol.* 286: 1059-74
- Shimizu TS, Aksenov SV, Bray D (2003) A spatially extended stochastic model of the bacterial chemotaxis signalling pathway. *J. Mol. Biol.* 329: 291-309

Achievements: AgentCell

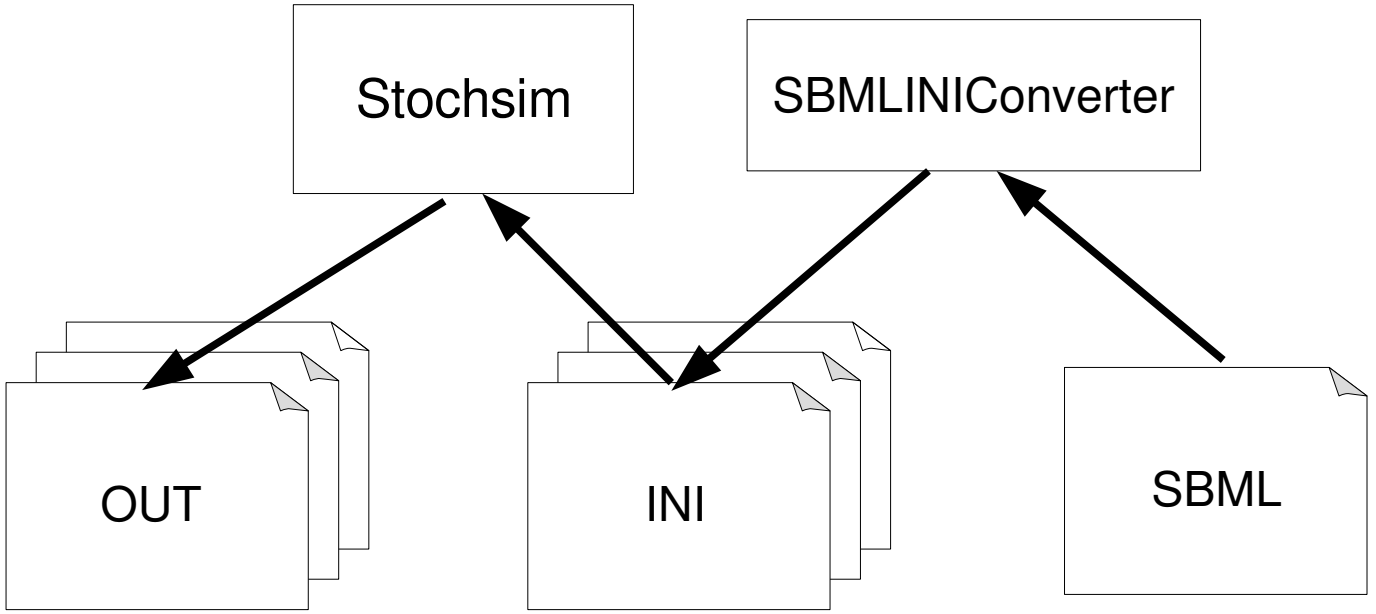
- Emonet T, Macal CM, North MJ, Wickersham CE, Cluzel P (2005) AgentCell: a digital single-cell assay for bacterial chemotaxis. *Bioinformatics* 21: 2714-2721



Future of StochSim

- SBMLImport / SBMLExport (close future)
- Neighbourhood-sensitive reactions in 3D
- GUI

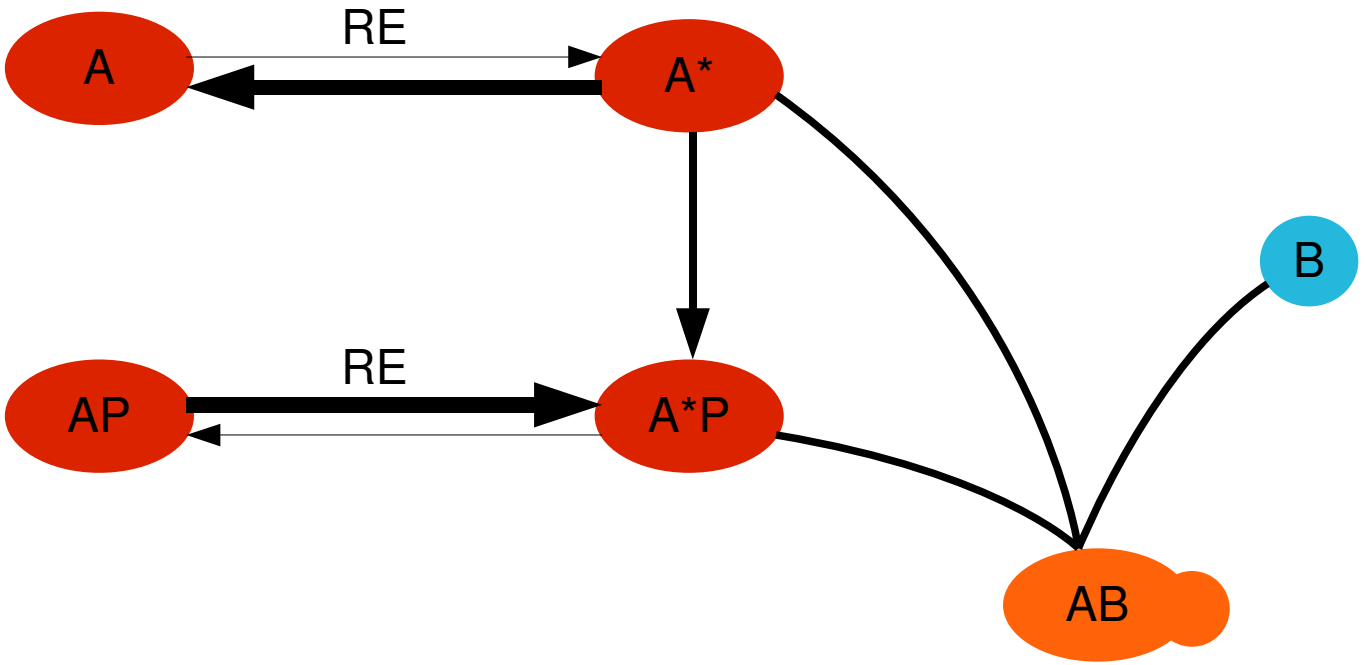
Connection to SBML



Annotation types

- 5 different types of StochSim annotations
  - (1) Model (general settings)
  - (2) Species type (state variables and possible values)
  - (3) Species (initial states)
  - (4) Reaction (rapid equilibria)
  - (5) Species reference (MS reactions, involved states)

Example



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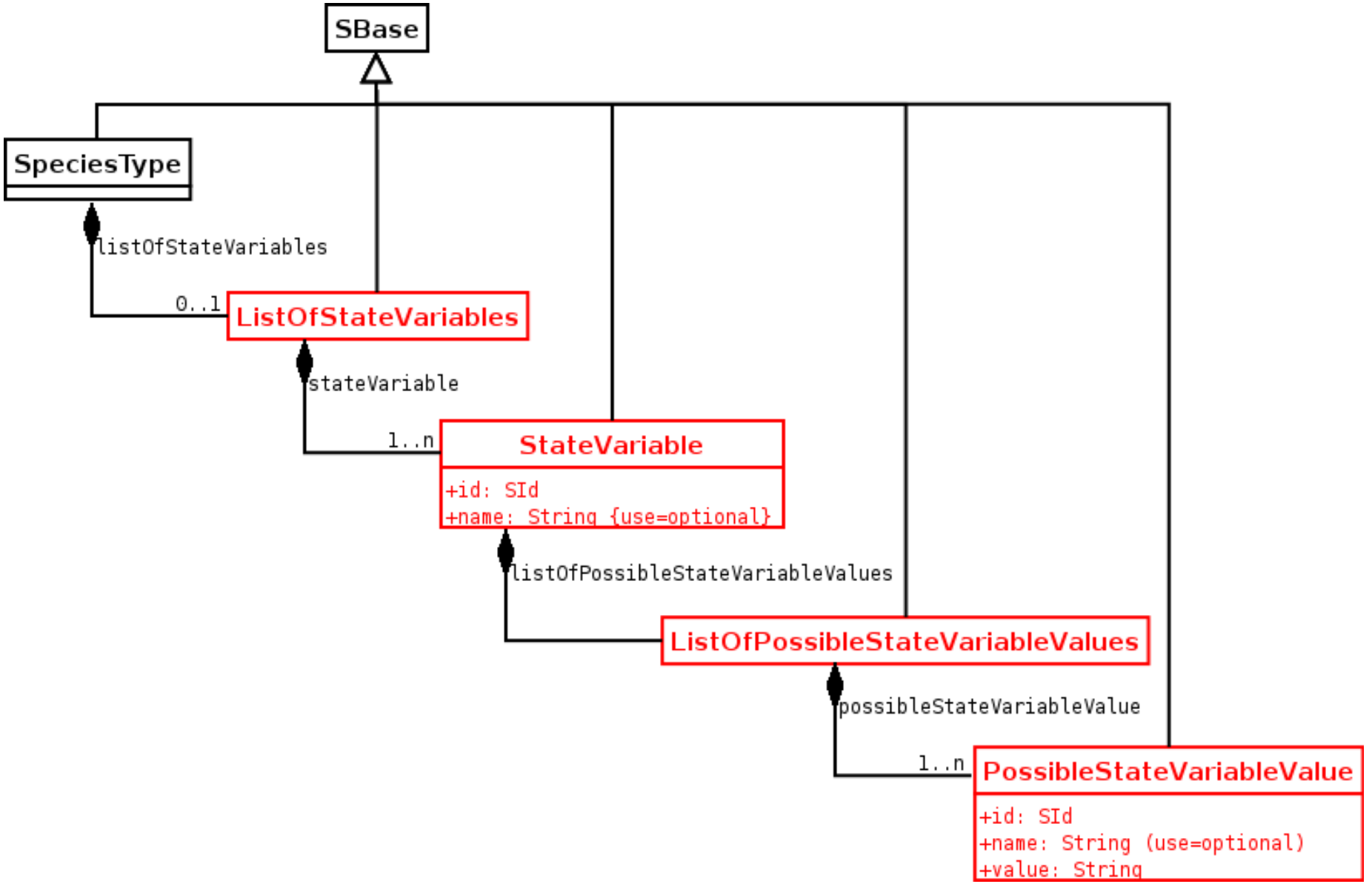
Species Type UML



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Example: Species Type

```
<speciesType id="typeA" name="A">
  <annotation>
    <stsim:stsim xmlns:stsim="http://www.sbml.org/2001/ns/stochsim" >
      <stsim:listOfStateVariables>
        <stsim:stateVariable id="activity">
          <stsim:listOfPossibleStateVariableValues>
            <stsim:possibleStateVariableValue id="inactive">0</stsim:possibleStateVariableValue>
            <stsim:possibleStateVariableValue id="active">1</stsim:possibleStateVariableValue>
          </stsim:listOfPossibleStateVariableValues>
        </stsim:stateVariable>
        <stsim:stateVariable id="phosphorylation">
          <stsim:listOfPossibleStateVariableValues>
            <stsim:possibleStateVariableValue id="non-phosphorylated">0</stsim:possibleStateVariableValue>
            <stsim:possibleStateVariableValue id="phosphorylated">1</stsim:possibleStateVariableValue>
          </stsim:listOfPossibleStateVariableValues>
        </stsim:stateVariable>
      </stsim:listOfStateVariables>
    </stsim:stsim>
  </annotation>
</speciesType>
```

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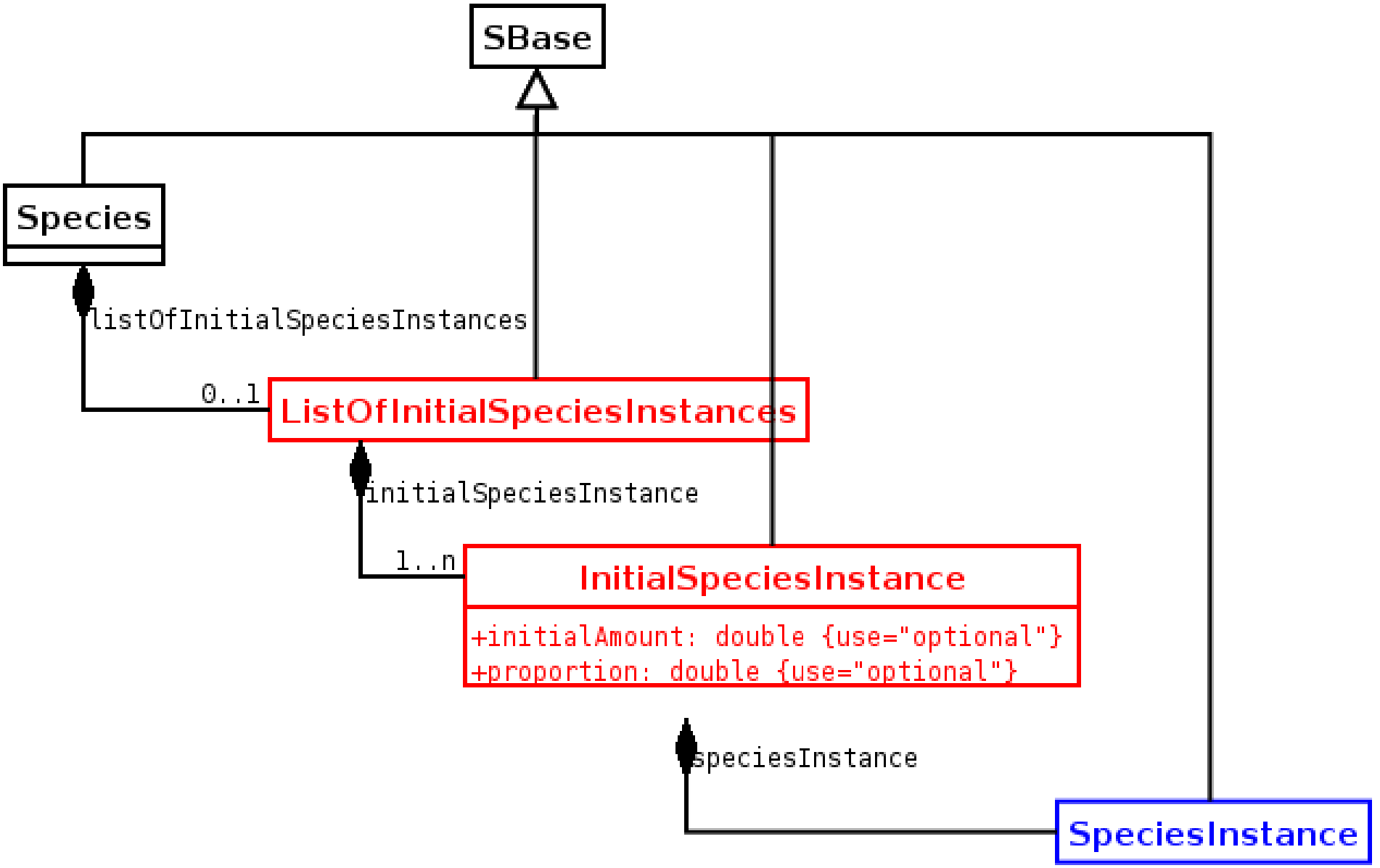
Species UML



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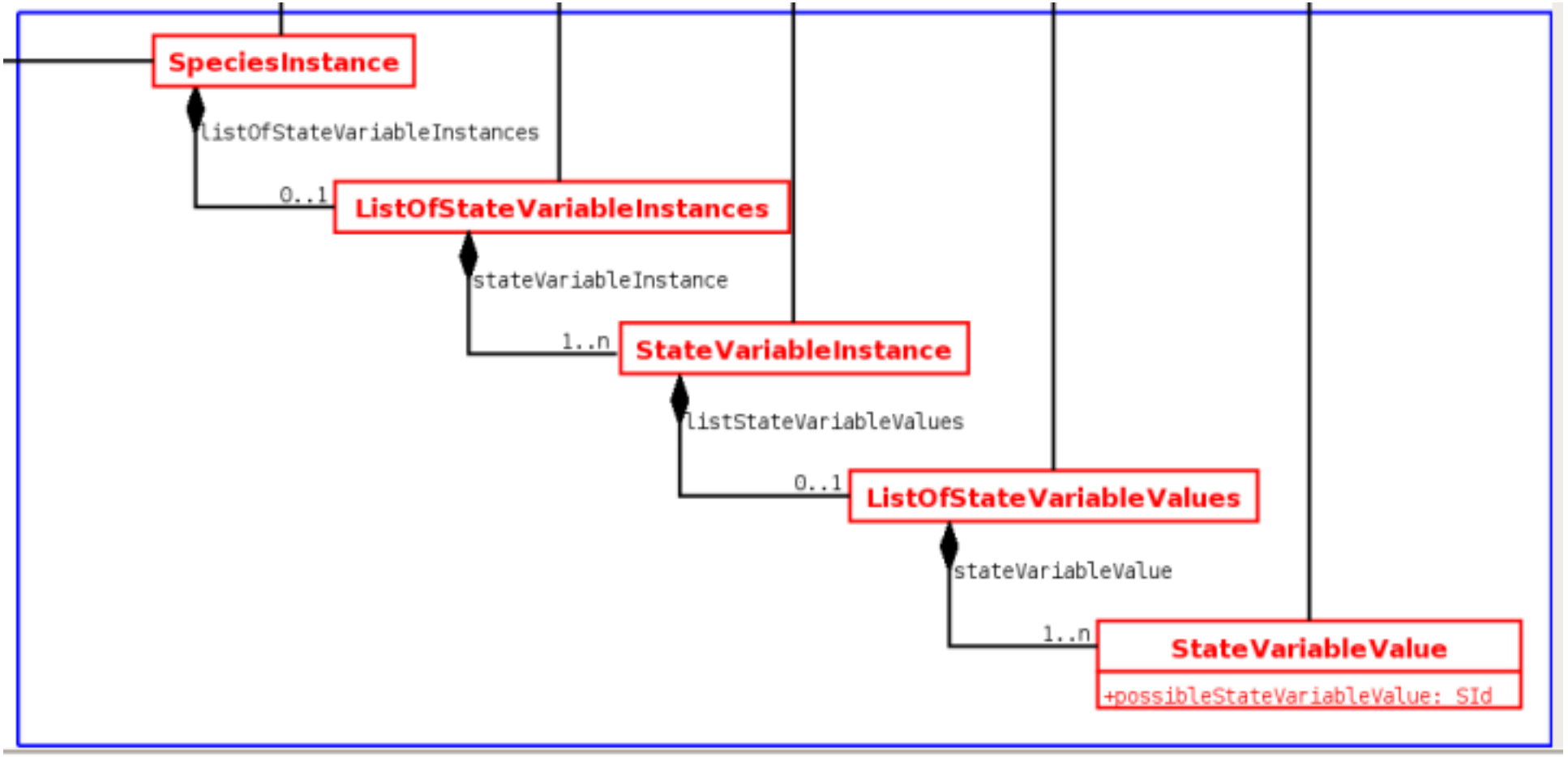
SpeciesInstance UML



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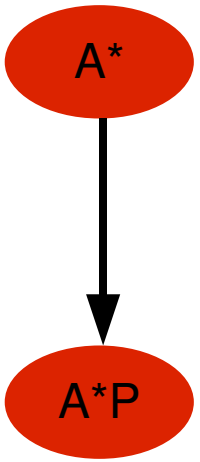
Example: Species

```
<species id="A" name="A" compartment="Compartment1" initialAmount="1000">
  <annotation>
    <stsim:stsim xmlns:stsim="http://www.sbml.org/2001/ns/stochsim">
      <stsim:listOfInitialSpeciesInstances>
        <stsim:initialSpeciesInstance>
          <stsim:speciesInstance>
            <stsim:listOfStateVariableInstances>
              <stsim:stateVariableInstance stateVariable="phosphorylation">
                <stsim:listOfStateVariableValues>
                  <stsim:stateVariableValue
                         possibleStateVariableValue="phosphorylated" />
                </stsim:listOfStateVariableValues>
              </stsim:stateVariableInstance>
            </stsim:listOfStateVariableInstances>
          </stsim:speciesInstance>
          <stsim:initialAmount>500</stsim:initialAmount>
        </stsim:initialSpeciesInstance>
        <stsim:initialSpeciesInstance>
          <stsim:speciesInstance>
            <stsim:listOfStateVariableInstances>
              <stsim:stateVariableInstance stateVariable="phosphorylation">
                <stsim:listOfStateVariableValues>
                  <stsim:stateVariableValue possibleStateVariableValue="non-phosphorylated" />
                </stsim:listOfStateVariableValues>
              </stsim:stateVariableInstance>
            </stsim:listOfStateVariableInstances>
          </stsim:speciesInstance>
          <stsim:initialAmount>500</stsim:initialAmount>
        </stsim:initialSpeciesInstance>
      </stsim:listOfInitialSpeciesInstances>
    </stsim:stsim>
  </annotation>
</species>
```

(?,1)

(?,0)

Example: Phosphorylation



- Modelled as a MS-reaction
- Using annotation of species reference both “listOfReactants” and “listOfProducts”

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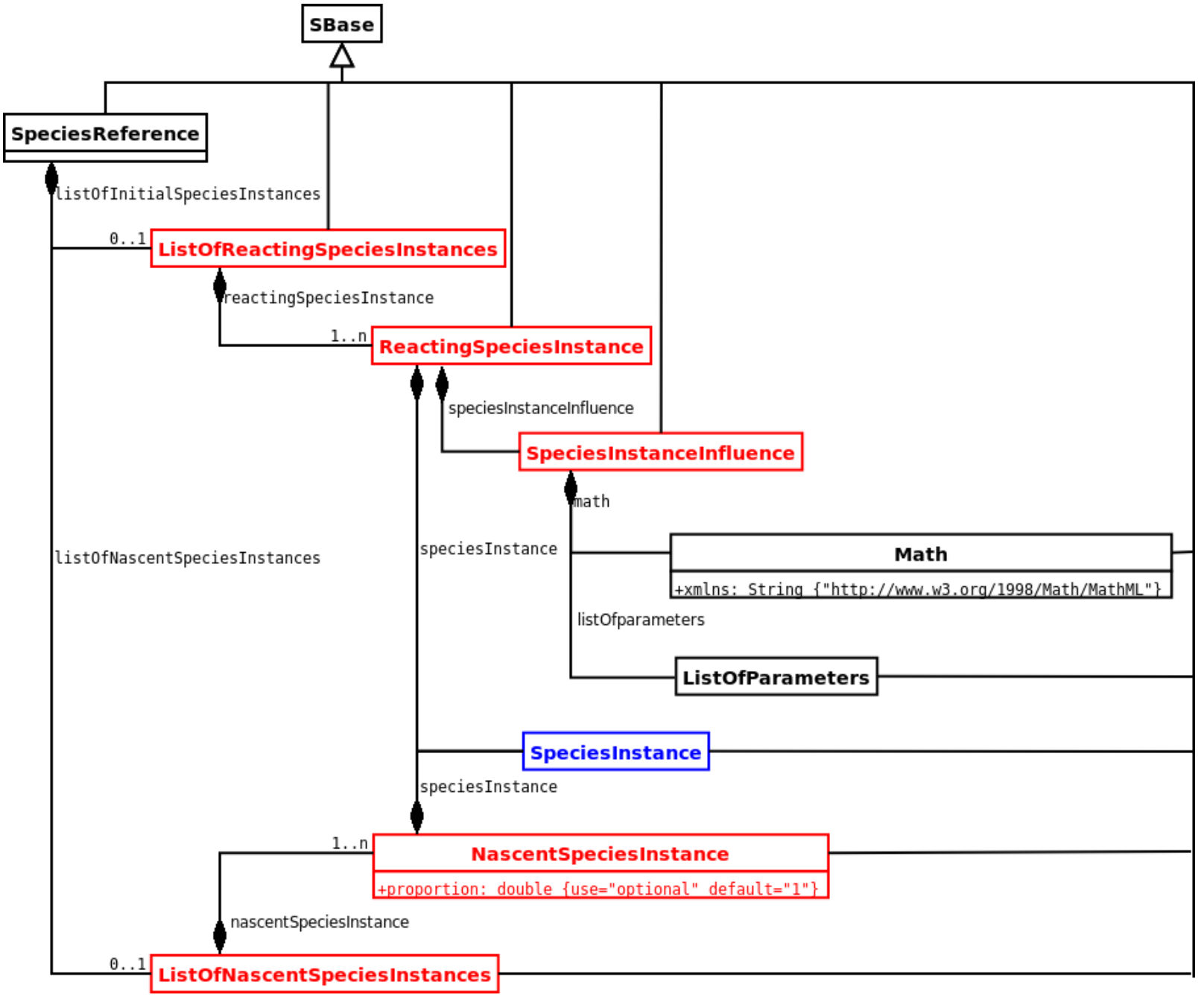
SpeciesReference UML



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Example: Phosphorylation

```
<reaction id="rAP" name="phosphorylation of A" >
  <listOfReactants>
    <speciesReference species="A">
      <annotation>
        <stsim:stsim xmlns:stsim="http://www.sbml.org/2001/ns/stochsim" >
          <stsim:listOfReactingSpeciesInstances>
            <stsim:reactingSpeciesInstance>
              <stsim:speciesInstance>
                <stsim:listOfStateVariableInstances>
                  <stsim:stateVariableInstance stateVariable="phosphorylation">
                    <stsim:listOfStateVariableValues>
                      <stsim:stateVariableValue possibleStateVariableValue="non-phosphorylated" />
                    </stsim:listOfStateVariableValues>
                  </stsim:stateVariableInstance>
                  <stsim:stateVariableInstance stateVariable="activity">
                    <stsim:listOfStateVariableValues>
                      <stsim:stateVariableValue possibleStateVariableValue="active" />
                    </stsim:listOfStateVariableValues>
                  </stsim:stateVariableInstance>
                </stsim:listOfStateVariableInstances>
              </stsim:speciesInstance>
              <stsim:speciesInstanceInfluence>
                <math xmlns="http://www.w3.org/1998/Math/MathML">
                  <apply>
                    <times/>
                    <ci>relProb</ci>
                    <ci>rAP</ci>
                  </apply>
                </math>
                <listOfParameters>
                  <parameter id="relProb" value="1" />
                </listOfParameters>
              </stsim:speciesInstanceInfluence>
            </stsim:reactingSpeciesInstance>
```

(1,0) -> (1,1)

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Example: Phosphorylation

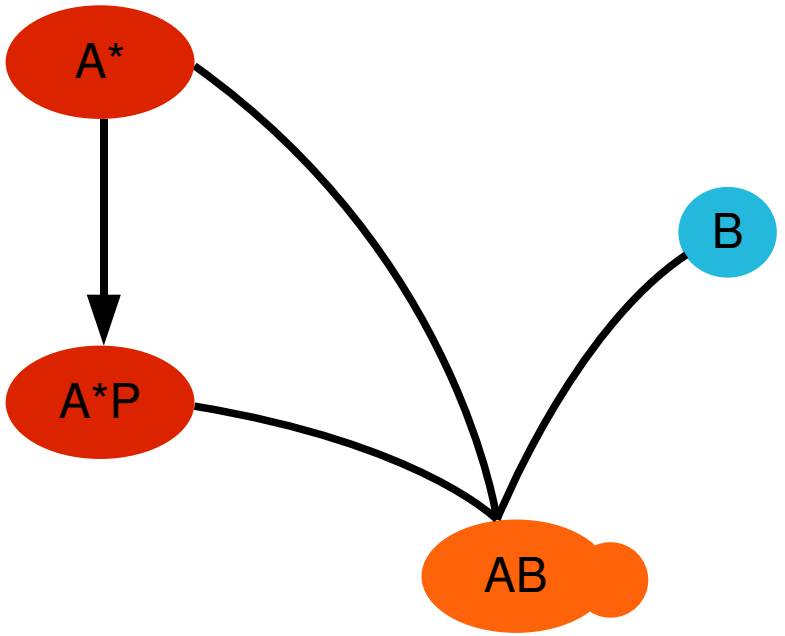
```
          <stsim:reactingSpeciesInstance>
            <stsim:speciesInstance>
              <stsim:listOfStateVariableInstances>
                <stsim:stateVariableInstance stateVariable="phosphorylation">
                  <stsim:listOfStateVariableValues>
                    <stsim:stateVariableValue possibleStateVariableValue="non-phosphorylated" />
                  </stsim:listOfStateVariableValues>
                </stsim:stateVariableInstance>
                <stsim:stateVariableInstance stateVariable="activity">
                  <stsim:listOfStateVariableValues>
                    <stsim:stateVariableValue possibleStateVariableValue="inactive" />
                  </stsim:listOfStateVariableValues>
                </stsim:stateVariableInstance>
              </stsim:listOfStateVariableInstances>
            </stsim:speciesInstance>
            <stsim:speciesInstanceInfluence>
              <math xmlns="http://www.w3.org/1998/Math/MathML">
                <apply>
                  <times/>
                  <ci>relProb</ci>
                  <ci>rAP</ci>
                </apply>
              </math>
              <listOfParameters>
                <parameter id="relProb" value="0" />
              </listOfParameters>
            </stsim:speciesInstanceInfluence>
          </stsim:reactingSpeciesInstance>
        </stsim:listOfReactingSpeciesInstances>
      </stsim:stsim>
    </annotation>
  </speciesReference>
</listOfReactants>
```

(0,0) => (0,1)

Example: Phosphorylation

```
  <listOfProducts>
    <speciesReference species="A">
      <annotation>
        <stsim:stsim xmlns:stsim="http://www.sbml.org/2001/ns/stochsim" >
          <stsim:speciesInstance>
            <stsim:listOfStateVariableInstances>
              <stsim:stateVariableInstance stateVariable="phosphorylation">
                <stsim:listOfStateVariableValues>
                  <stsim:stateVariableValue
                          possibleStateVariableValue="phosphorylated" />
                </stsim:listOfStateVariableValues>
              </stsim:stateVariableInstance>
            </stsim:listOfStateVariableInstances>
          </stsim:speciesInstance>
        </stsim:stsim>
      </annotation>
    </speciesReference>
  </listOfProducts>
</reaction>
```

Example: Reaction A & B



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Example: Reaction A & B

```
<reaction id="rAB" name="AB formation">
  <listOfReactants>
    <speciesReference species="A">
      <annotation>
        <stsim:stsim xmlns:stsim="http://www.sbml.org/2001/ns/stochsim">
      <stsim:listOfReactingSpeciesInstances>
            <stsim:reactingSpeciesInstance>
              <stsim:speciesInstance>
                <stsim:listOfStateVariableInstances>
                  <stsim:stateVariableInstance stateVariable="activity">
                    <stsim:listOfStateVariableValues>
                      <stsim:stateVariableValue possibleStateVariableValue="active" />
                    </stsim:listOfStateVariableValues>
                  </stsim:stateVariableInstance>
                </stsim:listOfStateVariableInstances>
              </stsim:speciesInstance>
              <stsim:speciesInstanceInfluence>
                <math xmlns="http://www.w3.org/1998/Math/MathML">
                  <apply>
                    <times/>
                    <ci>relProb</ci>
                    <ci>rAB</ci>
                  </apply>
                </math>
                <listOfParameters>
                  <parameter id="relProb" value="1" />
                </listOfParameters>
              </stsim:speciesInstanceInfluence>
            </stsim:reactingSpeciesInstance>
```

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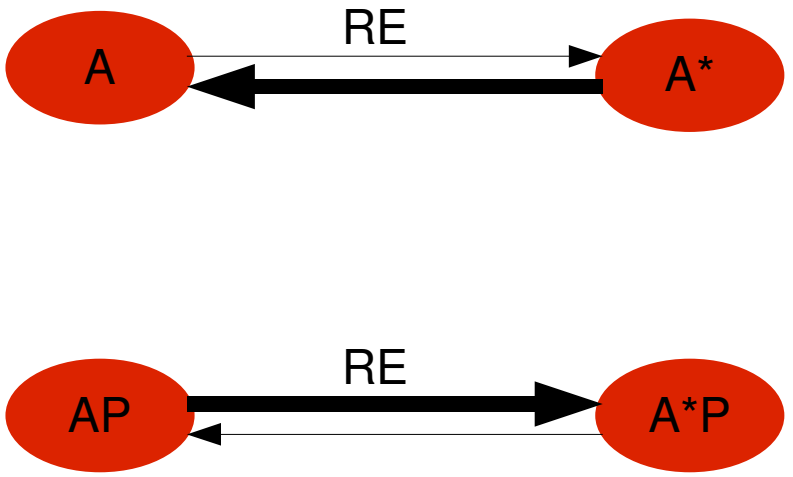
Example: Reaction A* & B

```
            <stsim:reactingSpeciesInstance>
              <stsim:speciesInstance>
                <stsim:listOfStateVariableInstances>
                  <stsim:stateVariableInstance stateVariable="activity">
                    <stsim:listOfStateVariableValues>
                      <stsim:stateVariableValue possibleStateVariableValue="inactive" />
                    </stsim:listOfStateVariableValues>
                  </stsim:stateVariableInstance>
                </stsim:listOfStateVariableInstances>
              </stsim:speciesInstance>
              <stsim:speciesInstanceInfluence>
                <math xmlns="http://www.w3.org/1998/Math/MathML">
                  <apply>
                    <times/>
                    <ci>relProb</ci>
                    <ci>rAB</ci>
                  </apply>
                </math>
                <listOfParameters>
                  <parameter id="relProb" value="0" />
                </listOfParameters>
              </stsim:speciesInstanceInfluence>
            </stsim:reactingSpeciesInstance>
          </stsim:listOfReactingSpeciesInstances>
        </stsim:stsim>
      </annotation>
    </speciesReference>
    <speciesReference species="B" />
  </listOfReactants>
  <listOfProducts>
    <speciesReference species="AB" />
  </listOfProducts>
</reaction>
```

(1,?) + B -> AB

Example: Rapid equilibrium

- (De-)Activation of species A
- Modelled as a reaction with “fast” attribute and kinetic law of 0



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Example: Rapid equilibrium

```
<reaction id="Aact" name="A activation" fast="true" reversible="false">
  <annotation>
    <stsim:stsim xmlns:stsim="http://www.sbml.org/2001/ns/stochsim" >
      <stsim:rapidEquilibrium species="A" stateVariable="activity">
        <stsim:listOfInfluencingSpeciesInstances>
          <stsim:influencingSpeciesInstance>
            <stsim:speciesInstance>
              <stsim:listOfStateVariableInstances>
                <stsim:stateVariableInstance stateVariable="phosphorylation">
                  <stsim:listOfStateVariableValues>
                    <stsim:stateVariableValue possibleStateVariableValue="unphosphorylated" />
                  </stsim:listOfStateVariableValues>
                </stsim:stateVariableInstance>
              </stsim:listOfStateVariableInstances>
            </stsim:speciesInstance>
            <stsim:listOfStateVariableValueProbabilities>
              <stsim:stateVariableValueProbability>
                <stsim:stateVariableValue possibleStateVariableValue="active" />
                <stsim:probability> 0.1 </stsim:probability>
              </stsim:stateVariableValueProbability>
              <stsim:stateVariableValueProbability>
                <stsim:stateVariableValue possibleStateVariableValue="inactive" />
                <stsim:probability> 0.9 </stsim:probability>
              </stsim:stateVariableValueProbability>
            </stsim:listOfStateVariableValueProbabilities>
          </stsim:influencingSpeciesInstance>
```

(0,0) <--> (1,0)

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Example: Rapid equilibrium

```
        <stsim:influencingSpeciesInstance>
          <stsim:speciesInstance>
            <stsim:listOfStateVariableInstances>
              <stsim:stateVariableInstance stateVariable="phosphorylation">
                <stsim:listOfStateVariableValues>
                  <stsim:stateVariableValue possibleStateVariableValue="phosphorylated" />
                </stsim:listOfStateVariableValues>
              </stsim:stateVariableInstance>
            </stsim:listOfStateVariableInstances>
          </stsim:speciesInstance>
          <stsim:listOfStateVariableValueProbabilities>
            <stsim:stateVariableValueProbability>
              <stsim:stateVariableValue possibleStateVariableValue="active" />
              <stsim:probability> 0.9 </stsim:probability>
            </stsim:stateVariableValueProbability>
            <stsim:stateVariableValueProbability>
              <stsim:stateVariableValue possibleStateVariableValue="inactive" />
              <stsim:probability> 0.1 </stsim:probability>
            </stsim:stateVariableValueProbability>
          </stsim:listOfStateVariableValueProbabilities>
        </stsim:influencingSpeciesInstance>
      </stsim:listOfInfluencingSpeciesInstances>
    </stsim:rapidEquilibrium>
  </stsim:stsim>
</annotation>
```

(0,1) <--> (1,1)

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Acknowledgement

Cambridge University

- Carl Morton Firth
- Thomas Simon Shimizu

EMBL-EBI

- Nicolas Le Novère
- Nicolas Rodriguez
- Melanie Stefan

Yale University

- Thierry Emonet

Argonne National Laboratory

- Michael North

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Thanks ...

for your attention!