## Package Dependencies

This package has no dependencies on any other package. It is also designed to work seamlessly with other packages, so one could seamlessly create a set of hierarchical models using Groups or Layout or Spatial (for example). If any incompatibilities are found, please contact the authors of this package.

## Use cases

The following is a simple aggregate model, with one defined model being instantiated twice:

<?xml version="1.0" encoding="UTF-8"?>

<sbml xmlns="http://www.sbml.org/sbml/level3/version1/core" level="3" version="1"

xmlns:comp="http://www.sbml.org/sbml/level3/version1/comp/version1"

comp:required="true">

<listOfModelDefinitions xmlns="http://www.sbml.org/sbml/level3/version1/comp/version1">

<modelDefinition id="enzyme" name="enzyme">

<listOfCompartments>

<compartment id="comp" size="1" constant="true" spatialDimensions="3"/>

</listOfCompartments>

<listOfSpecies>

<species id="S" compartment="comp" hasOnlySubstanceUnits="false" boundaryCondition="false" constant="false"/>

<species id="E" compartment="comp" hasOnlySubstanceUnits="false" boundaryCondition="false" constant="false"/>

<species id="D" compartment="comp" hasOnlySubstanceUnits="false" boundaryCondition="false" constant="false"/>

<species id="ES" compartment="comp" hasOnlySubstanceUnits="false" boundaryCondition="false" constant="false"/>

</listOfSpecies>

<listOfReactions>

<reaction id="J0" reversible="true" fast="false">

<listOfReactants>

<speciesReference species="S" stoichiometry="1" constant="false"/>

<speciesReference species="E" stoichiometry="1" constant="false"/>

</listOfReactants>

<listOfProducts>

<speciesReference species="ES" stoichiometry="1" constant="false"/>

</listOfProducts>

</reaction>

<reaction id="J1" reversible="true" fast="false">

<listOfReactants>

<speciesReference species="ES" stoichiometry="1" constant="false"/>

</listOfReactants>

<listOfProducts>

<speciesReference species="D" stoichiometry="1" constant="false"/>

<speciesReference species="E" stoichiometry="1" constant="false"/>

</listOfProducts>

</reaction>

</listOfReactions>

</modelDefinition>

</listOfModelDefinitions>

<model id="aggregate">

<listOfSubmodels xmlns="http://www.sbml.org/sbml/level3/version1/comp/version1">

<submodel>

<modelRef model="enzyme" />

</submodel>

<submodel>

<modelRef model="enzyme" />

</submodel>

</listOfSubmodels>

</model>

</sbml>

Here we have two-step enzymatic process, with S and E forming a complex, then dissociating to E and D. The aggregate model instantiates it twice, so the resulting model “aggregate” has two parallel processes in two parallel compartments performing the same reaction.

Now we will claim that we have saved the above SBML file to the file “enzyme\_model.xml”, and import the “enzyme” model from it into a new model:

<?xml version="1.0" encoding="UTF-8"?>

<sbml xmlns="http://www.sbml.org/sbml/level3/version1/core" level="3" version="1"

xmlns:comp="http://www.sbml.org/sbml/level3/version1/comp/version1"

comp:required="true">

<model id="onespecies" xmlns:xlink="http://www.w3.org/1999/xlink" xmlns="http://www.sbml.org/sbml/level3/version1/comp/version1">

<listOfSubmodels>

<submodel id="A">

<modelRef xlink:href="enzyme\_model.xml" model="enzyme" />

</submodel>

<submodel id="B">

<modelRef xlink:href="enzyme\_model.xml" model="enzyme" />

</submodel>

</listOfSubmodels>

<listOfCompartments>

<compartment id="comp" size="1" constant="true" spatialDimensions="3">

<replaces>

<subelement submodel="A" symbol="comp" identical="true" />

<subelement submodel="B" symbol="comp" identical="true" />

</replaces>

</compartment>

</listOfCompartments>

<listOfSpecies>

<species id="S" compartment="comp" hasOnlySubstanceUnits="false" boundaryCondition="false" constant="false">

<replaces>

<subelement submodel="A" symbol="S" identical="true" />

<subelement submodel="B" symbol="S" identical="true" />

</replaces>

</species>

</listOfSpecies>

</model>

</sbml>

Here, we again import “enzyme” twice, create a compartment and species local to the parent model, and replace the compartment and species “S” from the two instantiations with the new elements. Now we have a model with a single compartment in which a species S can either bind with enzyme A.E to form A.D, or bind with enzyme B.E to form B.D.

Next, we define one model (“simple”) with a single reaction “S -> D” that has ports, and again import “enzyme”:

<?xml version="1.0" encoding="UTF-8"?>

<sbml xmlns="http://www.sbml.org/sbml/level3/version1/core" level="3" version="1"

xmlns:comp="http://www.sbml.org/sbml/level3/version1/comp/version1"

comp:required="true">

<listOfModelDefinitions xmlns="http://www.sbml.org/sbml/level3/version1/comp/version1">

<modelDefinition id="simple" name="simple">

<listOfCompartments>

<compartment id="comp" size="1" spatialDimensions="3" constant="true" portID="comp\_port"/>

</listOfCompartments>

<listOfSpecies>

<species id="S" initialConcentration="5" compartment="comp" hasOnlySubstanceUnits="false" boundaryCondition="false" constant="false" portID="S\_port"/>

<species id="D" initialConcentration="10" compartment="comp" hasOnlySubstanceUnits="false" boundaryCondition="false" constant="false" portID="D\_port"/>

</listOfSpecies>

<listOfReactions>

<reaction id="J0" reversible="true" fast="false" portID="J0\_port">

<listOfReactants>

<speciesReference species="S" stoichiometry="1" constant="false"/>

</listOfReactants>

<listOfProducts>

<speciesReference species="D" stoichiometry="1" constant="false"/>

</listOfProducts>

</reaction>

</listOfReactions>

</modelDefinition>

</listOfModelDefinitions>

<model id="complexified" xmlns="http://www.sbml.org/sbml/level3/version1/comp/version1">

<listOfSubmodels>

<submodel id="simple">

<modelRef model="simple" />

<listOfDeletions>

<deletion id="oldrxn" port="J0\_port" />

</listOfDeletions>

</submodel>

<submodel id="enzyme">

<modelRef model="enzyme" />

</submodel>

</listOfSubmodels>

<listOfCompartments>

<compartment id="comp" size="1" constant="true" spatialDimensions="3">

<listOfReplacements xmlns="http://www.sbml.org/sbml/level3/version1/comp/version1">

<replace submodel="simple" port="comp\_port" identical="true" />

<replace submodel="enzyme" symbol="comp" identical="true" />

</listOfReplacements>

</compartment>

</listOfCompartments>

<listOfSpecies>

<species id="S" compartment="comp" initialConcentration="5" hasOnlySubstanceUnits="false" boundaryCondition="false" constant="false">

<listOfReplacements xmlns="http://www.sbml.org/sbml/level3/version1/comp/version1">

<replace submodel="simple" port="S\_port" identical="true" />

<replace submodel="enzyme" symbol="S" identical="false" />

</listOfReplacements>

</species>

<species id="D" compartment="comp" initialConcentration="10" hasOnlySubstanceUnits="false" boundaryCondition="false" constant="false">

<listOfReplacements xmlns="http://www.sbml.org/sbml/level3/version1/comp/version1">

<replace submodel="simple" port="D\_port" identical="true" />

<replace submodel="enzyme" symbol="D" identical="false" />

</listOfReplacements>

</species>

</listOfSpecies>

</model>

</sbml>

In “simple”, we give ports to the compartment, the two species, and the reaction. Then, in “complexified”, we import both this and the model “enzyme” from “enzyme\_model.xml”, and replace the simple reaction with the more complex two-step reaction by deleting the J0 reaction from “simple” and replacing “S” and “D” from both models with local replacements. Note that it is “simple” that defined the initial concentrations of S and D, so our modeler set the ‘identical’ flag to ‘true’ for those elements , faithfully reproducing the 5 and 10 in the local copy, and set the ‘identical’ flag to ‘false’ for the replacement of those elements from “enzyme”. Even had our modeler not done so, no warnings would have been produced, since nothing was defined for “S” or “D” in “enzyme” that was not defined for their replacement elements in “complexified”. Also note that since “simple” defined ports, the ‘port’ attribute was used for the subelements that referenced “simple” model elements, but “symbol” still had to be used for subelements referencing “enzyme”.

In the resulting model, S is converted to D by a two-step enzymatic reaction defined wholly in “enzyme”, with S and D’s initial conditions set, in effect, in “simple” (through the ‘identical’ flag). If “simple” had other reactions that created S and destroyed D, S would be created, would bind with E to form D, and D would then be destroyed, even though those reaction steps were defined in separate models.

But what if we had wanted to annotate that the deleted reaction had been ‘replaced’ by the two-step enzymatic process? To do this, we must move those reactions to the parent model, and, since those reactions involve E and ES, we must also move those as well:

<?xml version="1.0" encoding="UTF-8"?>

<sbml xmlns="http://www.sbml.org/sbml/level3/version1/core" level="3" version="1"

xmlns:comp="http://www.sbml.org/sbml/level3/version1/comp/version1"

comp:required="true">

<listOfModelDefinitions xmlns="http://www.sbml.org/sbml/level3/version1/comp/version1">

<modelDefinition id="simple" name="simple">

<listOfCompartments>

<compartment id="comp" size="1" constant="true" spatialDimensions="3" portid="comp"/>

</listOfCompartments>

<listOfSpecies>

<species id="S" compartment="comp" initialConcentration="5" hasOnlySubstanceUnits="false" boundaryCondition="false" constant="false" portid="S\_port"/>

<species id="D" compartment="comp" initialConcentration="10" hasOnlySubstanceUnits="false" boundaryCondition="false" constant="false" portid="D\_port"/>

</listOfSpecies>

<listOfReactions>

<reaction id="J0" reversible="true" fast="false" portid="J0\_port">

<listOfReactants>

<speciesReference species="S" stoichiometry="1" constant="false"/>

</listOfReactants>

<listOfProducts>

<speciesReference species="D" stoichiometry="1" constant="false"/>

</listOfProducts>

</reaction>

</listOfReactions>

</modelDefinition>

<modelDefinition id="enzyme" name="enzyme">

<listOfCompartments>

<compartment id="comp" size="1" constant="true" spatialDimensions="3" portid="comp\_port"/>

</listOfCompartments>

<listOfSpecies>

<species id="S" compartment="comp" hasOnlySubstanceUnits="false" boundaryCondition="false" constant="false" portid="S\_port"/>

<species id="E" compartment="comp" hasOnlySubstanceUnits="false" boundaryCondition="false" constant="false" portid="E\_port"/>

<species id="D" compartment="comp" hasOnlySubstanceUnits="false" boundaryCondition="false" constant="false" portid="D\_port"/>

<species id="ES" compartment="comp" hasOnlySubstanceUnits="false" boundaryCondition="false" constant="false" portid="ES\_port"/>

</listOfSpecies>

<listOfReactions>

<reaction id="J0" reversible="true" fast="false" portid="J0\_port">

<listOfReactants>

<speciesReference species="S" stoichiometry="1" constant="false"/>

<speciesReference species="E" stoichiometry="1" constant="false"/>

</listOfReactants>

<listOfProducts>

<speciesReference species="ES" stoichiometry="1" constant="false"/>

</listOfProducts>

</reaction>

<reaction id="J1" reversible="true" fast="false" portid="J1\_port">

<listOfReactants>

<speciesReference species="ES" stoichiometry="1" constant="false"/>

</listOfReactants>

<listOfProducts>

<speciesReference species="D" stoichiometry="1" constant="false"/>

<speciesReference species="E" stoichiometry="1" constant="false"/>

</listOfProducts>

</reaction>

</listOfReactions>

</modelDefinition>

</listOfModelDefinitions>

<model id="complexified">

<listOfSubmodels>

<submodel id="simple">

<modelRef model="simple" />

<listOfDeletions>

<deletion id="oldrxn" port="J0\_port" />

</listOfDeletions>

</submodel>

<submodel id="enzyme">

<modelRef model="enzyme" />

</submodel>

</listOfSubmodels>

<listOfReactions>

<reaction id="J0" reversible="true" fast="false">

<replaces>

<subelement submodel="simple" deletion="oldrxn" />

<subelement submodel="enzyme" port="J0\_port" identical="true" />

</replaces>

<listOfReactants>

<speciesReference species="S" stoichiometry="1" constant="false"/>

<speciesReference species="E" stoichiometry="1" constant="false"/>

</listOfReactants>

<listOfProducts>

<speciesReference species="ES" stoichiometry="1" constant="false"/>

</listOfProducts>

</reaction>

<reaction id="J1" reversible="true" fast="false">

<replaces>

<subelement submodel="simple" deletion="oldrxn" />

<subelement submodel="enzyme" port="J1\_port" identical="true" />

</replaces>

<listOfReactants>

<speciesReference species="ES" stoichiometry="1" constant="false"/>

</listOfReactants>

<listOfProducts>

<speciesReference species="D" stoichiometry="1" constant="false"/>

</listOfProducts>

</reaction>

</listOfReactions>

<listOfCompartments>

<compartment id="comp" size="1" constant="true" spatialDimensions="3">

<replaces>

<subelement submodel="simple" port="comp\_port" identical="true" />

<subelement submodel="enzyme" port="comp\_port" identical="true" />

</replaces>

</compartment>

</listOfCompartments>

<listOfSpecies>

<species id="S" compartment="comp" initialConcentration="5" hasOnlySubstanceUnits="false" boundaryCondition="false" constant="false">

<replaces>

<subelement submodel="simple" port="S\_port" identical="true" />

<subelement submodel="enzyme" port="S\_port" identical="false" />

</replaces>

</species>

<species id="D" compartment="comp" initialConcentration="10" hasOnlySubstanceUnits="false" boundaryCondition="false" constant="false">

<replaces>

<subelement submodel="simple" port="D\_port" identical="true" />

<subelement submodel="enzyme" port="D\_port" identical="false" />

</replaces>

</species>

<species id="E" compartment="comp" hasOnlySubstanceUnits="false" boundaryCondition="false" constant="false">

<replaces>

<subelement submodel="simple" deletion="oldrxn" />

<subelement submodel="enzyme" port="E\_port" identical="true" />

</replaces>

</species>

<species id="ES" compartment="comp" hasOnlySubstanceUnits="false" boundaryCondition="false" constant="false">

<replaces>

<subelement submodel="simple" deletion="oldrxn" />

<subelement submodel="enzyme" port="ES\_port" identical="true" />

</replaces>

</species>

</listOfSpecies>

</model>

</sbml>

Here, we have recreated “enzyme” so as to give it ports, then recreated basically the entire model in the parent “complexified” so we can reference the deleted “oldrxn” in the replacements lists. Note that we list that reaction deletion both for the two new reactions and for the two new species “E” and “ES”, since those species were themselves elided in the simple form of the S to D reaction in “simple”. The “identical” flag is used throughout, so that any visualization or manipulation software knows that the only reason those elements exist in the parent model is to create a reference, not to actually change the element itself.