Simulation Experiment Description Markup Language (SED-ML) : Level 1 Version 4

July 7, 2021

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The latest release of the Level 1 Version 4 specification is available at
http://identifiers.org/combine.specifications/sed-ml.level-1.version-4

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1. Introduction

The Simulation Experiment Description Markup Language (SED-ML) is an XML-based format for the description of simulation experiments.

The number of computational models of biological systems is growing at an ever increasing pace. At the same time, their size and complexity are also increasing. It is now generally accepted that one must be able to exchange the mathematical structure of such models, for instance to build on existing studies by reusing models or for the reproduction of model results. The efforts to standardize the representation of computational models in various areas of biology, such as the Systems Biology Markup Language (SBML) [16], CellML [9] or NeuroML [13], resulted in an increase of the exchange and re-use of models. However, the description of models is not sufficient for the reproduction of simulation experiments and results. One also needs to describe the procedures the models are subjected to, i.e., the information that must be provided to allow the reproduction of simulation experiments among users and software tools. The increasing use of computational simulation experiments to inform modern biological research creates new challenges to reproduce, annotate, archive, and share such experiments.

SED-ML describes in a computer-readable exchange format the information for the reproduction of simulation experiments. SED-ML is a software-independent format encoded in XML not specific to particular simulation tools and independent of the underlying model language. SED-ML describes the minimum information of a simulation experiment as described by the Minimum Information About a Simulation Experiment (MIASE) [22].

SED-ML is developed as a community project and defined via a detailed technical specification and a corresponding XML Schema.

This document describes Level 1 Version 4 of SED-ML which is the successor of Level 1 Version 3 and Level 1 Version 1 (described in [23]).

1.1 SED-ML overview

SED-ML specifies for a given simulation experiment

- what datasets to use (DataDescription);
- which models to use (Model);
- which modifications to apply to models before simulation (Change);
- which simulation procedures to run on each model (Simulation, and Task);
- what analysis results to plot or report and how to post-process the data (DataGenerator); and
- how these results should be presented (Output).

A SED-ML document contains the following main objects to describe this information: DataDescription, Model, Change, Simulation, Task, DataGenerator, and Output.

DataDescription

The DataDescription class allows to specify datasets for a simulation experiment. Such data can be used for instance for parametrization of model simulations or to plot data together with simulation results.

Model

The Model class allows to reference the models used in a simulation experiment.

The Change class allows to modify models (pre-processing), i.e., changing the value of an observable, computing the change of a value using mathematics, or general changes on any element of the model representation that is addressable by an unambiguous target, such as an XPath expression for an entity in an XML-encoded model, e.g., substituting a piece of XML by an updated one.

Simulation

The Simulation class defines the simulation settings and the steps taken during simulation. These include the particular type of simulation, the algorithm, and the algorithm parameters used for the execution of the simulation.

Task

SED-ML uses the Task class to specify which Simulation is run with which Model.

DataGenerator

The DataGenerator class allows to encode post-processing of simulation results before the generation of outputs, e.g., one can normalize a variable, or apply post-processing like mean value calculation. In the definition of a DataGenerator, any addressable variable or parameter of any model or DataSource may be referenced, and new entities might be specified using MathML.

Output

The Output defines the output of the simulation experiment, which can be either a two dimensional plot (Plot2D), a three dimensional plot (Plot3D), or data table (Report). The Output is based on the post-processed simulation results in the DataGenerator.

This section provided a low level overview over a simulation experiment in SED-ML. For the detailed technical specification see Chapter 2.

1.2 Example simulation experiment

In this section an example simulation experiment in SED-ML for the repressilator model [10] is presented. The corresponding SED-ML is listed in Appendix A.1, the COMBINE Archive for this simulation experiment is available as `L1V3_repressilator.omex` from `http://sed-ml.org/`.

The repressilator is a synthetic oscillating network of transcription regulators in Escherichia coli. The network is composed of the three repressor genes Lactose Operon Repressor (`lacI`), Tetracycline Repressor (`tetR`) and Repressor CI (`cI`), which code for proteins binding to the promoter of the other, blocking their transcription. The three inhibitions together in tandem, form a cyclic negative-feedback loop. To describe the interactions of the molecular species involved in the network, the authors built a simple mathematical model of coupled first-order differential equations. All six molecular species included in the network (three mRNAs, three repressor proteins) participate in creation (transcription/translation) and degradation processes. The model was used to determine the influence of the various parameters on the dynamic behavior of the system. In particular, parameter values were sought which induce stable oscillations in the concentrations of the system components.

1.2.1 Time-course simulation

The first simulation experiment with the model reproduces the oscillation behavior of the model shown in Figure 1c of the reference publication [10]. This simulation experiment can be described as:

1. Import the repressilator model identified by the Unified Resource Identifier (URI) [3] `https://www.ebi.ac.uk/biomodels/model/download/BIOMD0000000012?filename=BIOMD0000000012_url.xml`.
2. Select a deterministic simulation method for the numerical integration.
3. Run a uniform time course simulation for 1000 min with an output interval of 1 min.

4. Plot the amount of `lacI`, `tetR` and `cI` against time in a 2D Plot.

Following those steps and performing the simulation experiment in a simulation tool supporting SED-ML results in the output shown in Figure 1.1 and Figure 1.2.

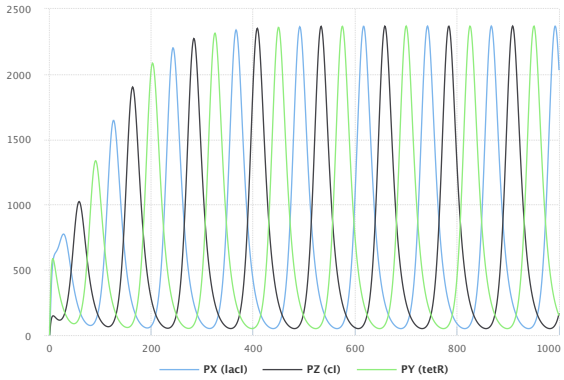


Figure 1.1: *Time-course simulation of the repressilator depicting repressor proteins lacI, tetR and cI. Simulation with SED-ML web tools [2].*

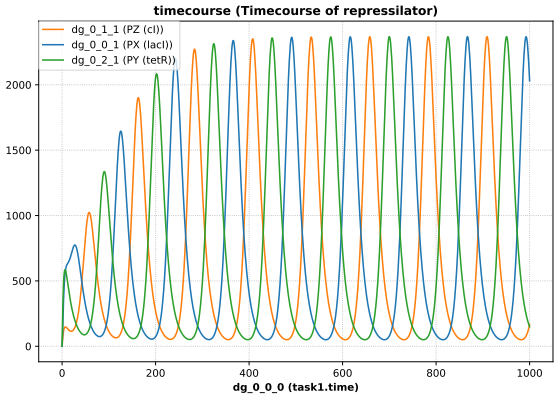


Figure 1.2: *Time-course simulation of the repressilator depicting repressor proteins lacI, tetR and cI. Simulation with tellurium [6].*

1.2.2 Applying pre-processing

A common step in a simulation experiment is the adjustment of model parameters before simulation. When changing the parameter values for the protein copies per promoter `tps_repr` and the leakiness in protein copies per promoter `tps_active` like stated below, the system's behavior switches from sustained oscillations to damped oscillations. The simulation experiment leading to that behavior is described as:

1. Import the model as in Section 1.2.1 above.
2. Change the value of the parameter `tps_repr` from `0.0005` to `1.3e-05`.
3. Change the value of the parameter `tps_active` from `0.5` to `0.013`.
4. Select a deterministic method.
5. Run a uniform time course for the duration of 1000 min with an output interval of 1 min.
6. Plot the amount of `lacI`, `tetR` and `cI` against time in a 2D Plot.

Figure 1.3 on the following page and Figure 1.4 on the next page show the results of the simulation.

1.2.3 Applying post-processing

In a simulation experiment the raw numerical output of the simulation may be subjected to data post-processing before plotting or reporting. In order to describe the production of a normalized plot of the time-course in the first example (section 1.2.1), depicting the influence of one variable on another (in phase-plane), one performs the additional steps:

(Please note that the description steps 1 - 4 remain as given in Section 1.2.1 above.)

5. Collect `lacI(t)`, `tetR(t)` and `cI(t)`.
6. Compute the highest value for each of the repressor proteins, `max(lacI(t))`, `max(tetR(t))`, `max(cI(t))`.
7. Normalize the data for each of the repressor proteins by dividing each time point by the maximum value, i.e., `lacI(t)/max(lacI(t))`, `tetR(t)/max(tetR(t))`, and `cI(t)/max(cI(t))`.

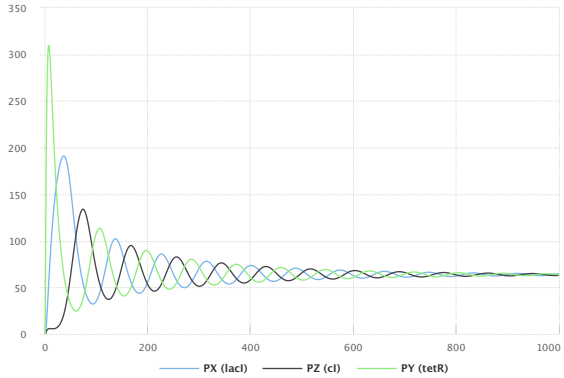


Figure 1.3: *Time-course simulation of the repressilator after changing parameters* `tps_repr` *and* `tps_active`*. Simulation with SED-ML web tools [2].*

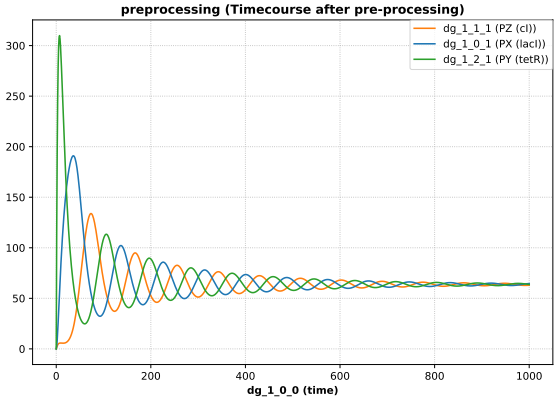


Figure 1.4: *Time-course simulation of the repressilator after changing parameters* `tps_repr` *and* `tps_active`*. Simulation with tellurium [6].*

8. Plot the normalized `lacI` protein as a function of the normalized `cI`, the normalized `cI` as a function of the normalized `tetR` protein, and the normalized `tetR` protein against the normalized `lacI` protein in a 2D plot.

Figure 1.5 and Figure 1.6 show the result of the simulation after post-processing of the output data.

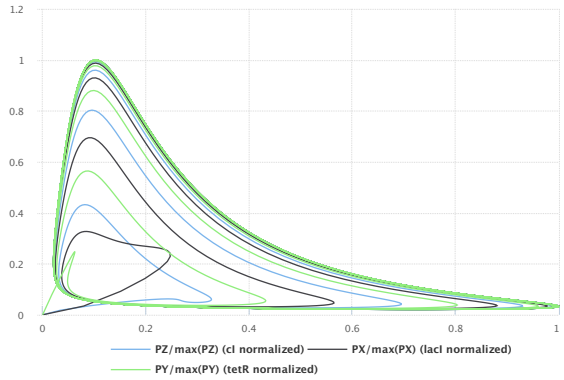


Figure 1.5: *Time-course simulation of the repressilator. Normalized* `lacI`*,* `tetR` *and* `cI` *in phase-plane. Simulation with SED-ML web tools [2].*

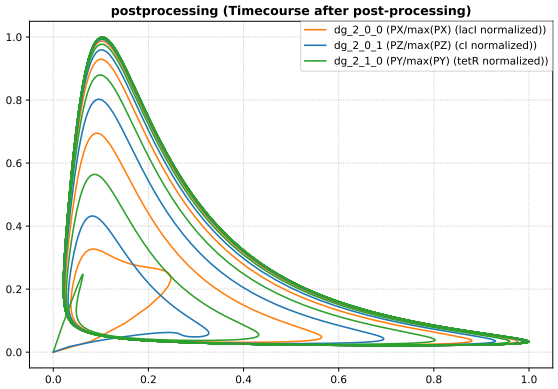


Figure 1.6: *Time-course simulation of the repressilator. Normalized* `lacI`*,* `tetR` *and* `cI` *in phase-plane. Simulation with tellurium [6].*

2. SED-ML technical specification

This document represents the technical specification of SED-ML Level 1 Version 4. The corresponding UML class diagrams are included throughout this document.. Example simulation experiments in SED-ML are provided in Appendix A. However, not all concepts of SED-ML can be captured using UML diagrams alone. In such cases this specification is the normative document.

2.1 General data types, attributes and classes

In this section concepts used repeatedly throughout the SED-ML specification are introduced. This includes primitive data types, classes (*SEDBase*, Notes, Annotation, Parameter, Variable), attributes, and reference relations.

The main SED-ML components based on these general data types, attributes and classes are described in Section 2.2.

2.1.1 Primitive data types

Primitive data types comprise the set of data types used in SED-ML classes. Most primitive types in SED-ML are taken from the data types defined in XML Schema 1.0, including `string`, `boolean`, `int`, `positiveInteger`, `double` and `XML`.

A few additional primitive types are defined by SED-ML itself: `ID`, SId, SIdRef, `TargetType`, `XPath`, `MathML`, `anyURI`, `NuMLSId`, and `NuMLSIdRef`.

2.1.1.1 Type ID

The XML Schema 1.0 type `ID` is identical to the XML 1.0 type `ID`. The literal representation of this type consists of strings of characters restricted as summarized in Figure 2.1. For a detailed description see the SBML specification on type `ID` [15].

```
NameChar   ::=  letter | digit | '.'  | '-' | ' ' | ':'  | CombiningChar | Extender
ID         ::=  ( letter | ' ' | ':'  )  NameChar*
```

Figure 2.1: *The definition of the type ID. The characters (and) are used for grouping, the character * indicates "zero or more times", and the character | indicates "or". Please consult the XML 1.0 specification for the complete definitions of letter, digit, CombiningChar, and Extender.*

2.1.1.2 Type SId

The type `SId` is the type of the id attribute found on the majority of SED-ML components. `SId` is a data type derived from `string`, but with restrictions about the characters permitted and the sequences in which those characters may appear. The definition is shown in Figure 2.2 on the next page. For a detailed description see the SBML specification on type `SId` [15].

```
letter   ::=  'a'..'z','A'..'Z'
digit    ::=  '0'..'9'
idChar   ::=  letter | digit | '_'
SId      ::=  ( letter | '_' ) idChar*
```

Figure 2.2: *The definition of the type SId*

2.1.1.3 Type SIdRef

Type SIdRef is used for all attributes that refer to identifiers of type SId in a model. This type is derived from SId, but with the restriction that the value of an attribute having type SIdRef must equal the value of some SId attribute. In other words, a SIdRef value must be an existing identifier.

As with SId, the equality of SIdRef values is determined by exact character sequence match; i.e., comparisons of these identifiers must be performed in a case-sensitive manner.

2.1.1.4 Type TargetType

Type `TargetType` is used to identify elements of a model. This type is derived from type `string`, and it is up to the target modeling language to define what form makes sense to uniquely identify a particular element of that model. For XML-based languages, using an `XPath` is required when referencing the raw XML of the model in a ChangeXML, AddXML, or RemoveXML, but other schemes may be used when referencing more abstract concepts implied by the model.

2.1.1.5 Type XPath

Type `XPath` is derived from type `TargetType` and is used to identify nodes and attributes within an XML representation. `XPath` in SED-ML is an XPath version 1 expression which can be used to unambiguously identify an element or attribute in an XML file. The concept of XPath is described in Section 3.3. Note that `XPath` may be used by some model languages to imply more abstract concepts implied by the model, such as pointing to an XML element to mean 'the current value of this element in the changed model state'.

2.1.1.6 Type URN

A `URN` is a colon-separated string that reference an external variable, but does not imply accessibility of that variable. The notion of implicit variables is explained in Section 3.2.5.

2.1.1.7 Type MathML

Type `MathML` is used to describe mathematical expression in MathML. The concept of MathML and the allowed subset of MathML on a `MathML` attribute is described in Section 3.1.

2.1.1.8 Type anyURI

Type `anyURI` is used to reference model and data files, specify the language of models, the format of data files, for referencing implicit model variables, and in annotations. For a description of the uses of `anyURI` see Section 3.2.

2.1.1.9 Type NuMLSId

The type `NuMLSId` is the type of the `id` attribute found on NuML components. `NuMLSId` is a data type derived from SId, with the same restrictions about the characters permitted and the sequences in which those characters may appear as SId. The concept of NuML is described in Section 3.4.

2.1.1.10 Type NuMLSIdRef

Type `NuMLSIdRef` is used for all attributes that refer to identifiers of type `NuMLSId` in a model. This type is derived from `NuMLSId`, but with the restriction that the value of an attribute having type `NuMLSIdRef` must equal the value of some `NuMLSId` attribute. In other words, a `NuMLSIdRef` value must be an existing NuML identifier.

As with `NuMLSId`, the equality of `NuMLSIdRef` values is determined by exact character sequence match;

i.e., comparisons of these identifiers must be performed in a case-sensitive manner.

2.1.1.11 Type AxisType

The AxisType primitive data type is used in the definition of the Axis class. AxisType is derived from type string and its values are restricted to being one of the following possibilities: "linear", and "log10". Attributes of type AxisType cannot take on any other values. The meaning of these values is discussed in the context of the Axis class's definition in 2.2.12.4.

2.1.1.12 Type CurveType

The CurveType primitive data type is used in the definition of the Curve class. CurveType is derived from type string and its values are restricted to being one of the following possibilities: "points", "bar", "barStacked", "horizontalBar", and "horizontalBarStacked". Attributes of type CurveType cannot take on any other values. The meaning of these values is discussed in the context of the Curve class's definition in 2.2.12.6.

2.1.1.13 Type SurfaceType

The SurfaceType primitive data type is used in the definition of the Surface class. SurfaceType is derived from type string and its values are restricted to being one of the following possibilities: "parametricCurve", "surfaceMesh", "surfaceContour", "contour", "heatMap", "stackedCurves", and "bar". Attributes of type SurfaceType cannot take on any other values. The meaning of these values is discussed in the context of the Surface class's definition in 2.2.12.8.

2.1.1.14 Type LineType

The LineType primitive data type is used in the definition of the Line class. LineType is derived from type string and its values are restricted to being one of the following possibilities: "none", "solid", "dash", "dot", "dashDot", and "dashDotDot". Attributes of type LineType cannot take on any other values. The meaning of these values is discussed in the context of the Line class's definition in 2.2.18.1.

2.1.1.15 Type SedColor

The SedColor primitive data type is used in the definition of various children of the Style class. SedColor is derived from type string and its values are allowed to be a six-character RGB hex value (where the alpha is assumed to be 100%), or an eight-character RGBA hex value. For example, 808000FF would be red and green 50.2%, blue 0%, and alpha 100%, i.e. a brown. Attributes of type SedColor cannot take on any other values.

2.1.1.16 Type MarkerType

The MarkerType primitive data type is used in the definition of the Marker class. MarkerType is derived from type string and its values are restricted to being one of the following possibilities: "none", "square", "circle", "diamond", "xCross", "plus", "star", "triangleUp", "triangleDown", "triangleLeft", "triangleRight", "hDash", and "vDash". Attributes of type MarkerType cannot take on any other values. The meaning of these values is discussed in the context of the Marker class's definition in 2.2.18.2.

2.1.1.17 Type MappingType

The MappingType primitive data type is used in the definition of the FitMapping class. MappingType is derived from type string and its values are restricted to being one of the following possibilities: "time", "experimentalCondition" and "observable". Attributes of type MappingType cannot take on any other values. The meaning of these values is discussed in the context of the FitMapping class's definition in 2.2.10.7.

2.1.1.18 Type ExperimentType

The ExperimentType primitive data type is used in the definition of the FitExperiment class. ExperimentType is derived from type string and its values are restricted to being one of the following possibilities: "steadyState" and "timeCourse". Attributes of type ExperimentType cannot take on any other values. The meaning of these values is discussed in the context of the FitExperiment class's definition in 2.2.10.6.

2.1.1.19 Type ScaleType

The `ScaleType` primitive data type is used in the definition of the Bounds class. `ScaleType` is derived from type `string` and its values are restricted to being one of the following possibilities: "`lin`", "`log`", and "`log10`". Attributes of type `ScaleType` cannot take on any other values. The meaning of these values is discussed in the context of the Bounds class's definition in 2.2.10.4.

2.1.2 SEDBase

SEDBase is the base class of all SED-ML classes (Figure 2.3). The SEDBase class has the optional attribute `metaid`, and the two optional subelements `notes` and `annotation`.

SEDBase provides means to attach additional information on all other classes. That information can be specified by human readable Notes or custom Annotation.

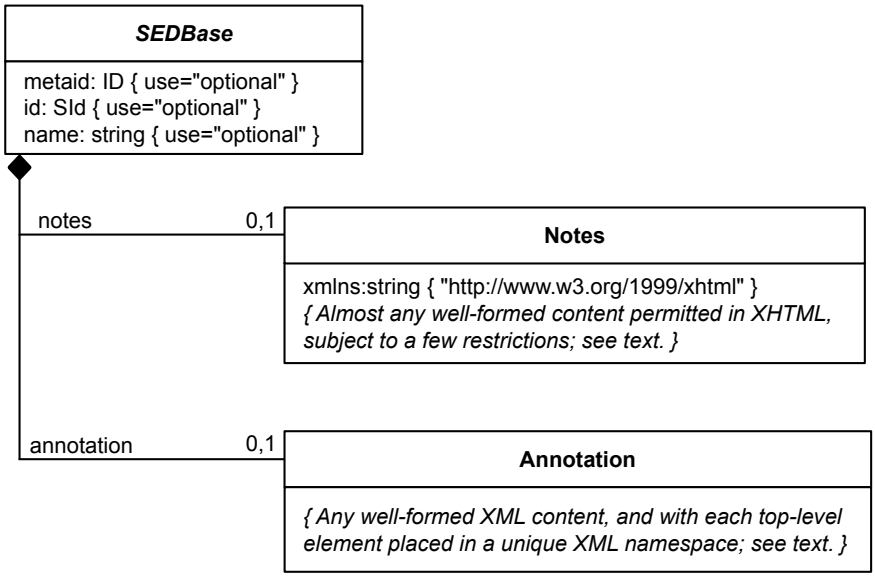


Figure 2.3: *The SEDBase, Notes, and Annotation classes*

id

The `id` attribute is an optional attribute on the *SEDBase* class. The `id` attribute value on an object serves as its *identifier*. The data type of `id` on *SEDBase* is `SId` (Section 2.1.1.2). Every `SId` attribute value in a SED-ML Document must be unique. Whenever a SED-ML element references another SED-ML element, it uses this identifier to do so.

Although `id` is optional on *SEDBase*, object classes derived from *SEDBase* may stipulate that `id` is a required attribute for those classes.

In lower Level/Version combinations of SED-ML, the attributes `id` and `name` are defined on individual object subclasses. The movement of these attributes to *SEDBase* in this version has no practical effect on these classes.

An example for an `id` is given in Listing 2.1. In the example the model has the `id` `m00001`.

```
<model id="m00001" language="urn:sedml:language:sbml"
       source="https://www.ebi.ac.uk/biomodels/model/download/BIOMD0000000012?filename=
           BIOMD0000000012_url.xml">
    [MODEL DEFINITION]
</model>
```

Listing 2.1: *SED-ML `id` definition, e.g., for a model*

name

The attribute **name** is an optional attribute on *SEDBase* of type **string**. In contrast to the **id** attribute, the **name** attribute is not intended to be used for cross-referencing purposes within a model. Its purpose instead is to provide a human-readable label for a component. The data type of **name** is the type **string** defined in XML Schema [4, 21]. SED-ML imposes no restrictions as to the content of **name** attributes beyond those restrictions defined by the **string** type in XML Schema. In addition, there are no restrictions on the uniqueness of **name** values in a SED-ML Document.

Listing 2.2 extends the model definition in Listing 2.1 by a model **name**.

```
<model id="m00001" name="Circadian oscillator" language="urn:sedml:language:sbml"
       source="https://www.ebi.ac.uk/biomodels/model/download/BIOMD0000000012?filename=
           BIOMD0000000012_url.xml">
    [MODEL DEFINITION]
</model>
```

Listing 2.2: *SED-ML* **name** *definition, e.g., for a model*

metaid

The main purpose of the **metaid** attribute of data type **ID** is to attach semantic annotations in form of the Annotation class to SED-ML elements. The **metaid** attribute is globally unique throughout the SED-ML document, i.e., the **metaid** must be unambiguous throughout a whole SED-ML document. As such it identifies the constituent it is related to.

In order to set either Notes or Annotation on a SED-ML class the **metaid** is required.

notes

The optional **notes** element stores Notes on *SEDBase*.

annotation

The optional **annotation** element stores Annotation on *SEDBase*.

2.1.3 Notes

A Notes is considered a human-readable description of the element it is assigned to. Instances of the Notes class may contain any valid XHTML [20]. The namespace URL for **XHTML** content inside the Notes class is **http://www.w3.org/1999/xhtml**, which may be declared either in the SedML element, or directly in the top level XHTML elements contained within the **notes** element. For details on of how to set the namespace and examples see the SBML specification [15].

Table 2.1 shows all attributes and sub-elements for the Notes element.

attribute	**description**
xmlns:string “http://www.w3.org/1999/xhtml”	page 25
sub-elements	
well-formed content permitted in XHTML	

Table 2.1: *Attributes and nested elements for Notes.* ^{o} *denotes optional elements and attributes.*

Notes does not have any further sub-elements defined in SED-ML, nor attributes associated with it.

Listing 2.3 shows the use of the **notes** element.

```
<sedML [..]>
    <notes>
        <p xmlns="http://www.w3.org/1999/xhtml">The enclosed simulation description shows the oscillating
            behaviour of the Repressilator model using deterministic and stochastic simulators.</p>
    </notes>
</sedML>
```

Listing 2.3: *The* **notes** *element*

In this example, the namespace declaration is inside the `notes` element and the note is related to the `sedML` root element of the SED-ML file. A note may, however, occur inside *any* SED-ML XML element, except `note` itself and Annotation.

2.1.4 Annotation

An Annotation is considered a computer-processable piece of information. Annotations may contain any valid XML content. For further guidelines on how to use annotations see the SBML specification [15]. The style of annotations in SED-ML is briefly described in Section 3.2.6.

Listing 2.4 shows the use of the `annotation` element. In the example, a `model` element is annotated with a reference to the original publication. The `model` contains an `annotation` that uses the model-qualifier `isDescribedBy` to link to the external resource `http://identifiers.org/pubmed/10415827`. In natural language the annotation content could be interpreted as "The model is described by the published article available from pubmed under the identifier 10415827".

```
<sedML>
    [..]
    <model id="model1" metaid="_001" language="urn:sedml:language:cellml" source="goldbeter1999a.cellml"
        >
        <annotation>
            <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#" xmlns:bqmodel="http://
                biomodels.net/model-qualifiers/">
                <rdf:Description rdf:about="#_001">
                <bqmodel:isDescribedBy>
                <rdf:Bag>
                    <rdf:li rdf:resource="http://identifiers.org/pubmed/10415827"/>
                </rdf:Bag>
                </bqmodel:isDescribedBy>
                </rdf:Description>
            </rdf:RDF>
        </annotation>
    </model>
    [..]
</sedML>
```

Listing 2.4: *The annotation element*

2.1.5 Parameter

The Parameter class (Figure 2.4) is used to create named parameters with a constant value. The Parameter class introduces the required attribute `value` of type `double`, and inherits other attributes and children from *SEDBase*, with the exception that the attribute `id` is required instead of optional. The `id` takes on the value of the `value` in the context of the Math of the parent Calculation. Its `id` may not be used in a Calculation that is not its parent, but it must nevertheless be globally unique.

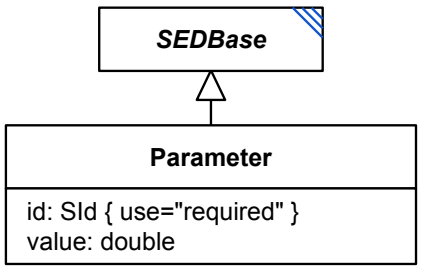


Figure 2.4: *The Parameter class*

A Parameter can be used wherever a mathematical expression to compute a value is defined, e.g., in ComputeChange, FunctionalRange or DataGenerator. The Parameter definitions are local to the particular class defining them. By using Parameters rather than including numbers directly within a mathematical expression is that notes and annotations can be associated with them.

Every Parameter is defined inside a ListOfParameters. The element is optional and may contain zero to many parameters.

Listing 2.5 on the next page shows the use of the `parameter` element. In the example a parameter `p1`

with the value `40` is defined.

```
<listOfParameters>
    <parameter id="p1" name="KM" value="40" />
</listOfParameters>
```

Listing 2.5: *The definition of a parameter in SED-ML*

value

The `value` attribute of data type `double` is required for each Parameter. Each Parameter has exactly one fixed `value`.

2.1.6 Variable

A Variable (Figure 2.5) is a reference to an already existing entity, either explicitly created in the SED-ML Document, or to an implicitly defined symbol. The Variable class inherits the attributes and children of *SEDBase*, changing the attribute `id` to be required, and adds the context dependent attributes `target`, `symbol`, `taskReference`, and `modelReference`. It also may have any number of RemainingDimension children, as members of its ListOfRemainingDimensions optional child.

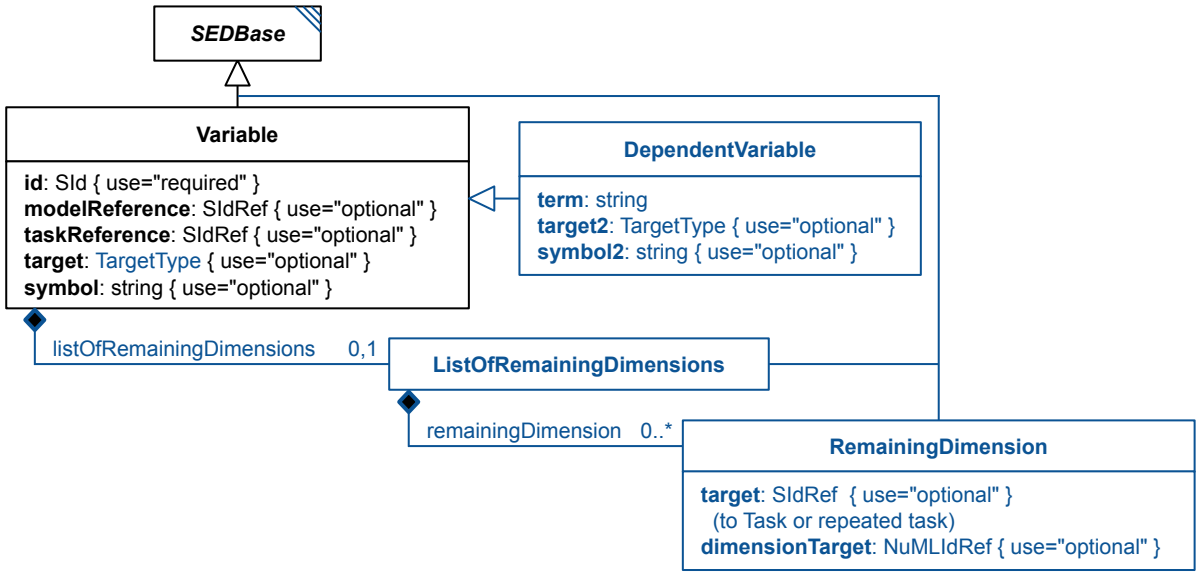


Figure 2.5: *The Variable, DependentVariable, ListOfRemainingDimensions, and RemainingDimension classes*

If the variable is defined through a reference to a model constituent, such as an SBML species, or to an entity within the SED-ML file itself, then the reference is specified using the `target` attribute. If the variable is defined through a reference to a Symbol, rather than one explicitly appearing in the model, then the `symbol` attribute is used.

- A Variable is always placed inside a listOfVariables. If it is the base class, its XML name will be "`variable`"; if it is the derived DependentVariable class, its XML name will be "`dependentVariable`".
- The `symbol` and `target` attributes (plus the `term`, `symbol2`, and `target2` attributes of a DependentVariable) must collectively define exactly one element with mathematical meaning.
- A Variable element must contain a taskReference if it occurs inside a `listOfVariables` inside a dataGenerator element. The only exception is if the Variable references a DataSource, in which case no taskReference is required.
- A Variable element must contain a modelReference if it occurs inside a `listOfVariables` inside a computeChange element. It must also define the `modelReference` if its `taskReference` points to a RepeatedTask that contains references to multiple models.

- A Variable element appearing within a functionalRange or setValue element must contain a modelReference if and only if it references a model variable.

Listing 2.6 shows the use of the `variable` element. In the example a variable `v1` is defined to compute a change on a model constituent (referenced by the `target` attribute on `computeChange`). The value of `v1` corresponds to the value of the targeted model constituent referenced by the `target` attribute. The second variable `v2` is used inside a `dataGenerator`. As the variable is time as used in `task1`, the `symbol` attribute is used to refer to the SED-ML URI for time.

```
<sedML>
    <listOfModels>
        <model [..]>
            <listOfChanges>
                <computeChange target="TARGET ELEMENT OR ATTRIBUTE">
                <listOfVariables>
                   <variable id="v1" name="maximum velocity" target="\changed{Path} TO MODEL ELEMENT/
                        ATTRIBUTE" />
                   [FURTHER VARIABLE DEFINITIONS]
                </listOfVariables>
                [..]
                </computeChange>
            </listOfChanges>
            [..]
        </model>
        [..]
    </listOfModels>
    <listOfDataGenerators>
        <dataGenerator [..]>
            <listOfVariables>
                <variable id="v2" name="time" taskReference="task1" symbol="KISAO:0000832" />
                [FURTHER VARIABLE DEFINITIONS]
            </listOfVariables>
        </dataGenerator>
    </listOfDataGenerators>
    [..]
</sedML>
```

Listing 2.6: *SED-ML `variable` definitions inside the `computeChange` element and inside the `dataGenerator` element*

target

An instance of Variable can refer to a model constituent inside a particular model through the address stored in the `target` attribute, such as an `XPath` expression.

Note that while it is possible to write XPath expressions that select multiple nodes within a referenced model, when used within a `target` attribute, a single element or attribute *must* be selected by the expression.

The `target` attribute may also be used in three situations to reference another SED-ML element with mathematical meaning, by containing a fragment identifier consisting of a hash character (`#`) followed by the SId of the element (i.e. "`#id001`").

The first situation is a Variable inside a RepeatedTask, which may use a `target` to reference a Range. In this situation, the Variable has the mathematical meaning of the scalar value of the Range for that iteration of the RepeatedTask.

The second situation is that any Variable may use a `target` to reference a scalar DataSource. In this situation, the Variable has the mathematical meaning of that scalar value.

The final situation is a Variable inside a DataGenerator, which may use a `target` to reference a multidimensional DataSource. In this situation, the Variable has the mathematical meaning of the referenced external data. If the `id` of the Variable is used inside a Math element, any function applied to it is assumed to apply to each individual scalar value of that data.

There are no other situations in SED-ML where the `id` of a SED-ML element may be used as the `target` of a Variable. Also note that multidimensional DataSource ids may not be used in RepeatedTask elements, nor Range ids in DataGenerator elements. (To access multidimensional data for a Range, a DataRange may be used instead.)

Listing 2.7 shows the use of the `target` attribute in a SED-ML file. In the example the `target` is used to reference a species with `id='PY'` in an SBML model.

```
<listOfVariables>
    <variable id="v1" name="TetR protein" taskReference="task1"
```

```
        target="/sbml:sbml/sbml:listOfSpecies/sbml:species[@id='PY']" />
</listOfVariables>
```

Listing 2.7: *SED-ML* `target` *definition*

It should be noted that the identifiers and names inside the SED-ML document do not have to match the identifiers and names that the model and its constituents have in the model definition. In Listing 2.7, the variable with ID `v1` is defined. It is described as `TetR protein`. The reference points to a species in the referenced SBML model. The particular species can be identified through its ID in the SBML model, namely `PY`. However, SED-ML also permits using identical identifiers and names as in the referenced models. The following Listing 2.8 is another valid example for the specification of a variable, but uses the same naming in the variable definition as in the original model (as opposed to Listing 2.7):

```
<listOfVariables>
    <variable id="PY" name="TetR protein"  taskReference="task1"
        target="/sbml:sbml/sbml:listOfSpecies/sbml:species[@id='PY']" />
</listOfVariables>
```

Listing 2.8: *SED-ML variable definition using the original model identifier and name in SED-ML*

```
<sbml [..]>
    <listOfSpecies>
        <species metaid="PY" id="PY" name="TetR protein" [..]>
        [..]
        </species>
    </listOfSpecies>
    [..]
</sbml>
```

Listing 2.9: *Species definition in the referenced model*

The XPath expression used in the `target` attribute unambiguously leads to the particular place in the SBML model, i.e., the species is to be found in the *sbml* element, and there inside the *listOfSpecies* (Listing 2.9).

symbol

The `symbol` attribute of type `string` is used to refer either to a predefined, implicit variable or to a predefined implicit function to be performed on the `target`. In both cases, the `symbol` should be a `kisaoID` (and follow the format of that attribute) that represents that variable's concept. The notion of implicit variables is explained in Section 3.2.5. For backwards compatibility, the old string "`urn:sedml:symbol:time`" is also allowed, though interpreters should interpret "`KISAO:0000832`" as meaning the same thing.

In the case where the `symbol` refers to a function, the function is applied to the `target` of the Variable. If the function reduces the dimensionality of the Variable, a RemainingDimension child should be used.

Listing 2.10 shows the use of the `symbol` attribute in a SED-ML file. The example encodes a variable "`t1`" defined to be the SED-ML symbol for `time`. How to use this variable to calculate a change is explained in Section 2.2.5.6.

```
<listOfVariables>
    <variable id="t1" name="time" taskReference="task1" symbol="KISAO:0000832" />
</listOfVariables>
```

Listing 2.10: *SED-ML* `symbol` *definition*

taskReference

The `taskReference` element of data type SIdRef is used to reference a Task via a taskReference. The usage depends on the context the Variable is used in.

modelReference

The `modelReference` element of data type SIdRef is used to reference a Model via a modelReference. The usage depends on the context the Variable is used in.

2.1.7 RemainingDimension

A RemainingDimension object is used in two cases when a Variable is multidimensional. In the first case, the `term` of the Variable is a function that reduces the dimensionality of the data. For example, a

variable derived from a Task inside a RepeatedTask will have the dimensionality of both. If the `term` of the parent Variable is the 'mean' function ("`KISAO:0000825`"), the following options are available:

- The Variable contains a single RemainingDimension child that refers to the Task. The resulting data will have the same dimensions as if the Variable referred directly to the Task, but averaged over every repeat of the RepeatedTask. This situation is particularly common when the Task is a stochastic time course simulation, and the RepeatedTask is a simple loop of that Task.
- The Variable contains a single RemainingDimension child that refers to the RepeatedTask. The resulting data will be a vector with the same number of entries as there were repeats of the RepeatedTask. This situation is particularly helpful when the RepeatedTask is a parameter scan, and the Variable is tracking a model variable that oscillates during the Task. The resulting vector will be the average value of that model variable under each of the different starting conditions.
- The Variable contains no RemainingDimension children at all. The resulting data will be a single value, that has been averaged over both the Task and RepeatedTask.

In the second case, the Variable is multidimensional, but some of those dimensions involve a Task that does not reference the Model from which the Variable is drawn. In these cases, if the Variable is given RemainingDimension children for the tasks that change the relevant Model, but not the ones that do not, the resulting data will not include the dimension where the Variable's Model was not involved.

A RemainingDimension inherits the attributes and children of *SEDBase*, and adds the attributes `target` (of type SIdRef), and `dimensionTarget` (of type `NuMLIdRef`), both of which are optional, but one of which must be present.

target

The `target` attribute of a RemainingDimension is used when the remaining dimension is a Task or RepeatedTask, which must be implicitly involved in the construction of the dimensionality of the parent Variable.

Possible values for the `target` attribute include:

- The id of a RepeatedTask
- The id of a Task referenced by a RepeatedTask
- The id of a SubTask child of a RepeatedTask

dimensionTarget

The `dimensionTarget` attribute of a RemainingDimension is used when the Variable references an external data set. The `NuMLIdRef` must reference a dimension of the referenced data.

2.1.8 DependentVariable

The DependentVariable object is a child of the Variable class, extending it to include three new attributes: `term` (of type `string`), `target2` (of type `TargetType`), and `symbol2` (of type string). A dependent variable is necessary when the desired variable is a composite of two other variables, such as 'the rate of change of S1 with respect to time'.

In a DependentVariable, the `term` is used to define an analysis to be performed on the model as a whole, or the relationship of the two variables (i.e. 'rate of change'), the `target` or `symbol` attributes are used to define the first such variable, and the new `target2` and `symbol2` is used to define the second variable.

term

The `term` attribute is of type `string`, and should conform to the syntax of a `kisaoID`, though the string "`urn:sedml:symbol:time`" may be used for backwards compatibility. The `term` may refer to a function (such as 'rate of change', `KISAO:0000834`) that relates two variables to each other, instead of just one, or it may refer to an analysis (such as 'the eigenvalue matrix', `KISAO:0000813`) that is dependent on the model as a whole and not on individual model elements.

target2

A `target2` attribute has exactly the same constraints and behavior as a `target` attribute, but refers to a second mathematical element.

symbol2

A `symbol2` attribute has exactly the same constraints and behavior as a `symbol` attribute, but refers to a second mathematical element.

```
<listOfVariables>
    <dependentVariable id="S1prime" name="S1'"  taskReference="task1"
        term="KISAO:0000834"
        target="/sbml:sbml/sbml:listOfSpecies/sbml:species[@id='S1']"
        symbol2="KISAO:0000832" />
</listOfVariables>
```

Listing 2.11: *SED-ML dependent variable definition of 'the rate of change of S1 with respect to time'*

2.1.9 Calculation

The Calculation class is an abstract base class for the ComputeChange, DataGenerator, and FunctionalRange classes (defined later). A Calculation inherits from *SEDBase*, and adds three children: a required Math child, and optional lists of Variable and Parameter objects. In all three of its uses, it performs a calculation that optionally may depend on locally-defined elements. This abstract class is provided for convenience, since all three other classes contain this same relatively complicated structure. However, as FunctionalRange also inherits from Range, and ComputeChange also inherits from Change, implementations may choose to simply re-instantiate the child elements of Calculation on these or other derived classes, in environments where multiple inheritance is illegal or infeasible.

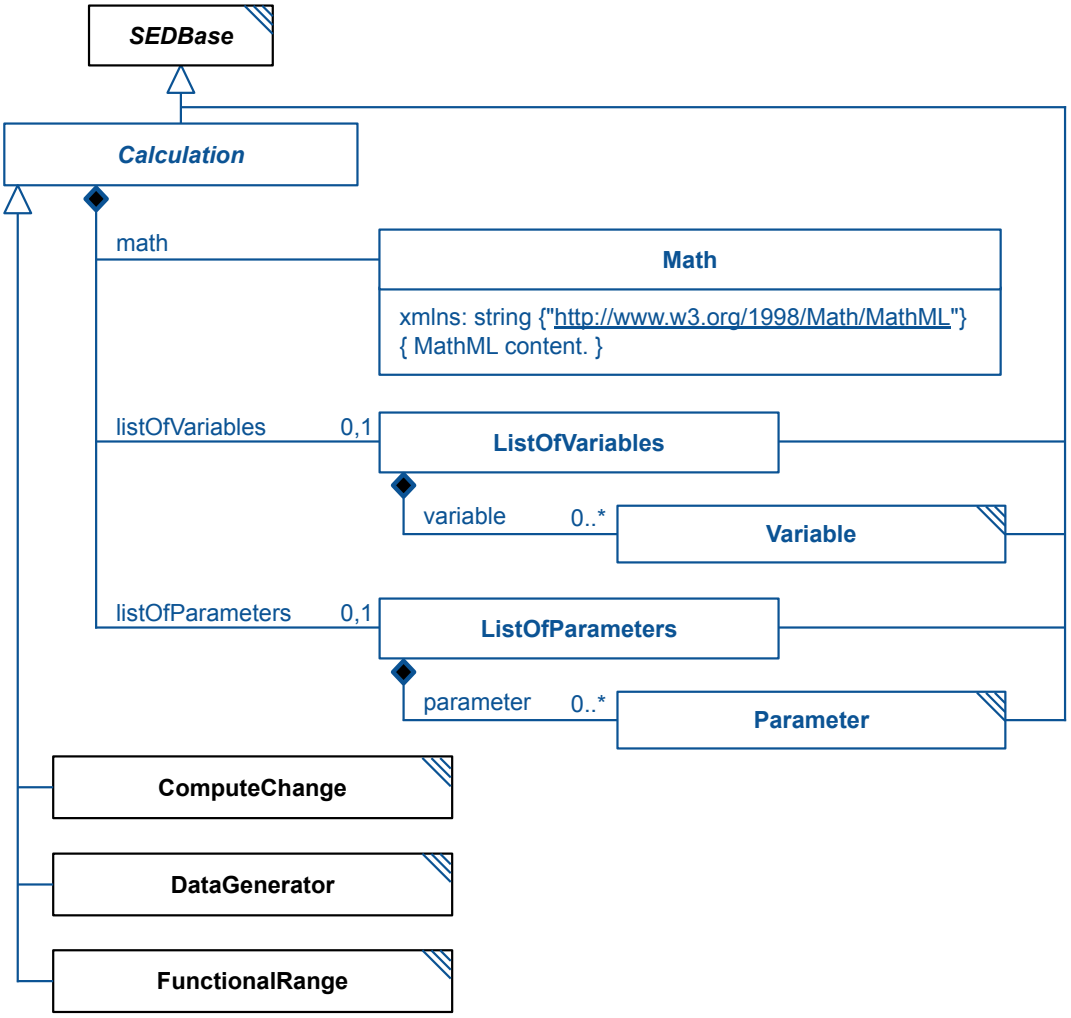


Figure 2.6: *The Calculation, Math, ListOfVariables, ListOfParameters, and Parameter classes.*

In the ListOfVariables, the Variable elements define identifiers referring to model variables or range values, which may then be used within the Math expression. These references always retrieve the current value of the variable in the context of the Calculation. A ListOfVariables may contain any number of Variable and/or DependentVariable entries.

In the ListOfParameters, the Parameter elements define simple values that may be used in the Math of the Calculation.

The Math encompasses the mathematical expression that is used to compute the value for the Calculation.

2.1.9.1 `Math`

A Calculation's mandatory child element `math` contains a MathML expression used to calculate a value in the context of the Calculation. The available subset of mathematical functions and elements which can be used in the Math element are listed in Section MathML.

2.1.10 General attributes and elements

This section describes attributes which occur on multiple SED-ML classes, e.g., `kisaoID`, or `listOf*` constructs.

2.1.10.1 kisaoID

Some classes, e.g., Algorithm and AlgorithmParameter, have a mandatory element `kisaoID` or another attribute which references a term from the KiSAO ontology. The referenced term must be defined in the correct syntax, as defined by the regular expression `KISAO:[0-9]{7}`. The referenced KiSAO term should define the simulation Algorithm or AlgorithmParameter as precisely as possible. Note that the use of a colon predates KiSAO's switch to using an underscore in official KiSAO URLs. We continue to use the colon here for backwards compatibility, and because a `kisaoID` is not a URL.

2.1.10.2 listOf* containers

SED-ML `listOf*` elements serve as containers for a collection of objects of the same type. For example, the `listOfModels` contains all Model objects of a SED-ML document. Lists do not carry any further semantics nor do they add additional attributes. They might, however, be annotated with Notes and Annotation as they are derived from SEDBase. All `listOf*` elements are optional in a SED-ML document (with exception of `listOfRanges` and `listOfSubTasks` in a RepeatedTask, which are mandatory).

2.1.11 Reference relations

The reference concept is used to refer to a particular element inside the SED-ML document. It may occur as an association between:

- two Models (modelReference)
- a Variable and a Model (modelReference)
- a Variable and an *AbstractTask* (taskReference)
- a Task and the simulated Model (modelReference)
- a Task and the Simulation (simulationReference)
- an Output and a DataGenerator (dataReference)

The definition of a Task requires a reference to a particular Model object (modelReference); furthermore, the Task object must be associated with a particular Simulation object (simulationReference).

Depending on the use of the reference relation in connection with a Variable object, it may take different roles:

a. The reference association might occur between a Variable object and a Model object, e.g., if the variable is to define a Change. In that case the `variable` element contains a modelReference to refer to the particular model that contains the variable used to define the change.

b. If the reference is used as an association between a Variable object and an *AbstractTask* object inside the dataGenerator class, then the `variable` element contains a taskReference to unambiguously refer to an observable in a given task.

2.1.11.1 modelReference

The modelReference is a reference used to refer to a particular Model via a SIdRef. The modelReference either represents a relation between two Model objects, a Variable object and a Model object, or a relation between a Task object and a Model object.

The `source` attribute of a Model is allowed to reference either a URI or an SId of a second Model. Circular constructs where a model `A` refers to a model `B` and `B` to `A` (directly or indirectly) are invalid.

If pre-processing needs to be applied to a model before simulation, then the model update can be specified by creating a Change object. In the particular case that a change must be calculated with a mathematical function, variables need to be defined. To refer to an existing entity in a defined Model, the modelReference is used.

The `modelReference` attribute of the `variable` element contains the id of a model that is defined in the document.

Listing 2.12 on the next page shows the use of the `modelReference` element. In the example, a change is applied on model `m0001`. In the `computeChange` element a list of variables is defined. One of those

variable is `v1` which is defined in another model (`cellML`). The XPath expression given in the target attribute identifies the variable in the model which carries the ID `cellML`.

```
<model id="m0001" [..]>
    <listOfChanges>
        <computeChange>
            <listOfVariables>
                <variable id="v1" modelReference="cellML" target="/cellml:model/cellml:component[
                    @cmeta:id='MP']/cellml:variable[@name='vsP']/@initial_value" />
                [..]
            </listOfVariables>
            <listOfParameters [..] />
                <math>
                [CALCULATION OF CHANGE]
                </math>
        </computeChange>
    </listOfChanges>
    [..]
</model>
```

Listing 2.12: *SED-ML `modelReference` attribute inside a variable definition of a `computeChange` element*

The modelReference is also used to indicate that a Model object is used in a particular Task. Listing 2.13 shows how this can be done for a sample SED-ML document.

```
<listOfTasks>
    <task id="t1" name="Baseline" modelReference="model1" simulationReference="simulation1" />
    <task id="t2" name="Modified" modelReference="model2" simulationReference="simulation1" />
</listOfTasks>
```

Listing 2.13: *SED-ML `modelReference` definition inside a `task` element*

The example defines two different tasks; the first one applies the simulation settings of `simulation1` on `model1`, the second one applies the same simulation settings on `model2`.

2.1.11.2 simulationReference

The simulationReference is used to refer to a particular Simulation via a SIdRef, e.g., in a Task.

Listing 2.13 shows the reference to a defined simulation for a sample SED-ML document. In the example, both tasks `t1` and `t2` use the simulation settings defined in `simulation1` to run the experiment.

2.1.11.3 taskReference

The taskReference is a reference used to refer to a particular *AbstractTask* via a SIdRef. The taskReference is used in SubTask to reference the respective subtask, or in Variable within a DataGenerator.

DataGenerator objects are created to apply post-processing to the simulation results before final output. For certain types of post-processing Variable objects need to be created. These link to a task defined within the ListOfTasks from which the model that contains the variable of interest can be inferred. A taskReference association is used to realise that link from a Variable object inside a DataGenerator to an *AbstractTask* object. Listing 2.14 gives an example.

```
<listOfDataGenerators>
    <dataGenerator id="tim3" name="tim mRNA (difference v1-v2+20)">
    <listOfVariables>
        <variable id="v1" taskReference="t1" [..] />
    </listOfVariables>
    <math [..]/>
    </dataGenerator>
</listOfDataGenerators>
```

Listing 2.14: *SED-ML `taskReference` definition inside a `dataGenerator` element*

The example shows the definition of a variable `v1` in a `dataGenerator` element. The variable appears in the model that is used in task `t1`. The task definition of `t1` might look as shown in Listing 2.15.

```
<listOfTasks>
    <task id="t1" name="task definition" modelReference="model1" simulationReference="simulation1" />
</listOfTasks>
```

Listing 2.15: *Use of the reference relations in a task definition*

Task `t1` references the model `model1`. Therefore we can conclude that the variable `v1` defined in Listing 2.14 targets an element of the model with ID `model1`. The targeting process itself will be explained in section 2.1.6 on page 16.

2.2 SED-ML Components

In this section the major components of SED-ML are described. Each section defines the UML for the class described. Example simulation experiments are provided in Appendix A.

2.2.1 `SED-ML` top level element

Each SED-ML Level 1 Version 4 document has a main class called SED-ML which defines the document's structure and content (Figure 2.7 on the following page). It consists of several parts connected to the SED-ML class via `listOf*` constructs:

- DataDescription (for specification of external data),
- Model (for specification of models),
- Simulation (for specification of simulation setups),
- *AbstractTask* (for the linkage of models and simulation setups),
- DataGenerator (for the definition of post-processing),
- Output (for the specification of plots and reports).
- Style (for the specification of plot element styles).
- AlgorithmParameter (for the definition of global algorithm parameters).

A SED-ML document needs to have the SED-ML namespace defined through the mandatory `xmlns` attribute. In addition, the SED-ML `level` and `version` attributes are required.

The root element of each SED-ML XML file is the `sedML` element, encoding `level` and `version` of the file, and setting the necessary namespaces. Nested inside the `sedML` element are the six optional lists serving as containers for the encoded information: `listOfDataDescriptions` for all external data, `listOfModels` for all models, `listOfSimulations` for all simulations, `listOfTasks` for all tasks, `listOfDataGenerators` for all post-processing definitions, `listOfOutputs` for all output definitions, ListOfStyles for all style definitions. and ListOfAlgorithmParameters for parameters that apply to processing this SED-ML file as a whole.

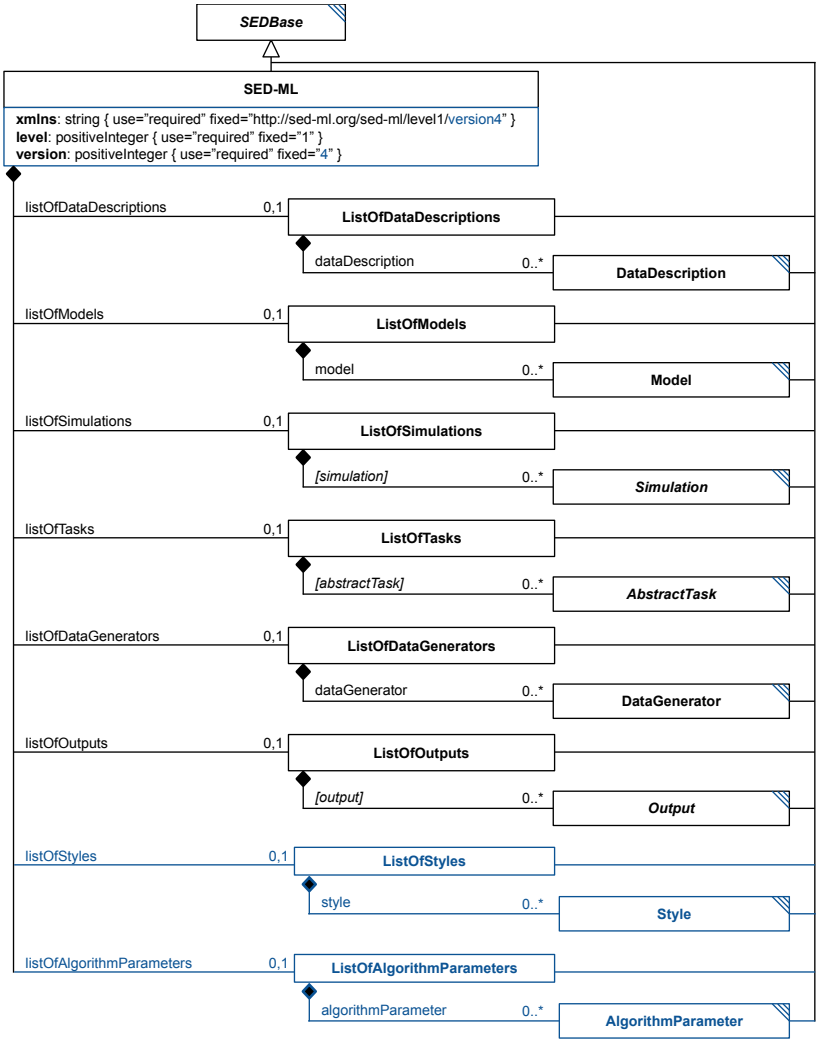


Figure 2.7: *The SED-ML class*

The basic XML structure of a SED-ML file is shown in listing 2.16.

```
<?xml version="1.0" encoding="utf-8"?>
<sedML xmlns:math="http://www.w3.org/1998/Math/MathML"
       xmlns="http://sed-ml.org/sed-ml/level1/version4" level="1" version="4">
    <listOfDataDescriptions>
        [DATA REFERENCES AND TRANSFORMATIONS]
    </listOfDataDescriptions>
    <listOfModels>
        [MODEL REFERENCES AND APPLIED CHANGES]
    </listOfModels>
    <listOfSimulations>
        [SIMULATION SETUPS]
    </listOfSimulations>
    <listOfTasks>
        [MODELS LINKED TO SIMULATIONS]
    </listOfTasks>
    <listOfDataGenerators>
        [DEFINITION OF POST-PROCESSING]
    </listOfDataGenerators>
    <listOfOutputs>
        [DEFINITION OF OUTPUT]
    </listOfOutputs>
    <listOfStyles>
        [DEFINITION OF STYLES]
    </listOfStyles>
    <listOfAlgorithmParameters>
        [PARAMETERS TO APPLY TO THE ENTIRE SIMULATION PROCESS]
    </listOfAlgorithmParameters>
</sedML>
```

Listing 2.16: *The SED-ML root element*

2.2.1.1 xmlns

The xmlns attribute declares the namespace for the SED-ML document. The pre-defined namespace for SED-ML documents is http://sed-ml.org/sed-ml/level1/version4.

In addition, SED-ML makes use of the MathML namespace http://www.w3.org/1998/Math/MathML to enable the encoding of mathematical expressions. SED-ML notes use the XHTML namespace http://www.w3.org/1999/xhtml. Additional external namespaces might be used in annotations.

2.2.1.2 level

The current SED-ML level is 1. Major revisions containing substantial changes will lead to the definition of forthcoming levels. The level attribute is required and its value is a fixed decimal. For SED-ML Level 1 Version 4 the value is set to 1, as shown in the example in Listing 2.16.

2.2.1.3 version

The current SED-ML version is 4. Minor revisions containing corrections and refinements of SED-ML elements, or new constructs which do not affect backwards compatibility, will lead to the definition of forthcoming versions.

The version attribute is required and its value is a fixed decimal. For SED-ML Level 1 Version 4 the value is set to 4, as shown in the example in Listing 2.16.

2.2.1.4 listOfDataDescriptions

In order to reference data in a simulation experiment, the data files along with a description on how to access such files and what information to extract from them have to be defined. The SED-ML document uses the listOfDataDescriptions container to define DataDescriptions for referencing external data (Figure 2.7 on the preceding page). The listOfDataDescriptions is optional and may contain zero or more DataDescriptions.

Listing 2.17 shows the use of the listOfDataDescriptions element.

```
<listOfDataDescriptions>
    <dataDescription id="Data1" name="Oscli Time Course Data" source="./oscli.numl">
        <dimensionDescription>
            <compositeDescription indexType="double" id="time" name="time" xmlns="http://www.numl.org/
                numl/level1/version1">
                <compositeDescription indexType="string" id="SpeciesIds" name="SpeciesIds">
                <atomicDescription valueType="double" name="Concentrations" />
            </compositeDescription>
        </compositeDescription>
    </dimensionDescription>
    <listOfDataSources>
        <dataSource id="dataS1">
            <listOfSlices>
                <slice reference="SpeciesIds" value="S1" />
            </listOfSlices>
        </dataSource>
        <dataSource id="dataTime" indexSet="time" />
    </listOfDataSources>
    </dataDescription>
</listOfDataDescriptions>
```

Listing 2.17: *SED-ML listOfDataDescriptions element*

2.2.1.5 listOfModels

The models used in a simulation experiment are defined in the listOfModels container (Figure 2.7 on the preceding page). The listOfModels is optional and may contain zero or more Models. However, if a SED-ML document contains one or more Tasks, at least one Model must be defined to which the Task elements refer (see Section 2.1.11.1).

Listing 2.18 shows the use of the listOfModels element.

```
<listOfModels>
    <model id="m0001" language="urn:sedml:language:sbml"
        source="https://www.ebi.ac.uk/biomodels/model/download/BIOMD0000000012?filename=
            BIOMD0000000012_url.xml" />
    <model id="m0002" language="urn:sedml:language:cellml"
        source="http://models.cellml.org/workspace/leloup_gonze_goldbeter_1999/@@rawfile/
            d6613d7e1051b3eff2bb1d3d419a445bb8c754ad/leloup_gonze_goldbeter_1999_a.cellml" />
```

```
</listOfModels>
```

Listing 2.18: *SED-ML listOfModels element*

2.2.1.6 listOfSimulations

The `listOfSimulations` element is the container for Simulation descriptions (Figure 2.7 on page 24). The `listOfSimulations` is optional and may contain zero or more Simulations. However, if the SED-ML document contains one or more Tasks, at least one Simulation element must be defined to which the Task elements refer (see Section 2.1.11.2).

Listing 2.19 shows the use of the `listOfSimulation` element.

```
<listOfSimulations>
    <simulation id="s1" [..]>
        [UNIFORM TIMECOURSE DEFINITION]
    </simulation>
    <simulation id="s2" [..]>
        [UNIFORM TIMECOURSE DEFINITION]
    </simulation>
</listOfSimulations>
```

Listing 2.19: *The SED-ML* `listOfSimulations` *element, containing two simulation setups*

2.2.1.7 listOfTasks

The `listOfTasks` element contains the defined tasks for the simulation experiment (Figure 2.7 on page 24). The `listOfTasks` is optional and may contain zero or more tasks, each of which is an instance of a subclass of *AbstractTask*.

Each top-level task is defined such that its execution is independent of the others: if one task is executed after another, the states of the models must be completely reset so there's no cross-contamination of one task to the next. This means that the top-level tasks are particularly well suited to being executed in parallel, should that be desired.

SED-ML interpreters may choose to execute all the tasks in the list, or they may choose to examine the list of outputs, and only execute the tasks that are necessary to produce the requested output. This situation comes up most often when one task is listed as a SubTask of a RepeatedTask: the outputs may well only require the RepeatedTask to be run, meaning an independent execution of the singular Task is not necessary, even though it's on this list.

Listing 2.20 shows the use of the `listOfTasks` element.

```
<listOfTasks>
    <task id="t1" name="simulating v1" modelReference="m1" simulationReference="s1">
    [FURTHER TASK DEFINITIONS]
</listOfTasks>
```

Listing 2.20: *The SED-ML* `listOfTasks` *element, defining one task*

2.2.1.8 listOfDataGenerators

The `listOfDataGenerators` container holds the dataGenerator definitions of a simulation experiment (Figure 2.7 on page 24). The `listOfDataGenerators` is optional and in general may contain zero or more DataGenerators.

In SED-ML, all variable and parameter values used in the Output class need to be defined as a DataGenerator beforehand.

Listing 2.21 shows the use of the `listOfDataGenerators` element.

```
<listOfDataGenerators>
    <dataGenerator id="d1" name="time">
        [DATA GENERATOR DEFINITION FOLLOWING]
    </dataGenerator>
    <dataGenerator id="LaCI" name="LaCI repressor">
        [DATA GENERATOR DEFINITION FOLLOWING]
    </dataGenerator>
</listOfDataGenerators>
```

Listing 2.21: *The* `listOfDataGenerators` *element, defining two data generators* time *and* LaCI repressor

2.2.1.9 listOfOutputs

The `listOfOutputs` container holds the Output definitions of a simulation experiment (Figure 2.7 on page 24). The `listOfOutputs` is optional and may contain zero or more outputs.

Listing 2.22 shows the use of the `listOfOutputs` element.

```
<listOfOutputs>
    <report id="report1">
        [REPORT DEFINITION FOLLOWING]
    </report>
    <plot2D id="plot1">
        [2D PLOT DEFINITION FOLLOWING]
    </plot2D>
</listOfOutputs>
```

Listing 2.22: *The listOfOutput element*

2.2.1.10 listOfStyles

The `listOfStyles` container holds the Style definitions of a simulation experiment (Figure 2.7 on page 24). The `listOfStyles` is optional and may contain zero or more styles.

Listing 2.23 shows the use of the `listOfStyles` element.

```
<listOfStyles>
    <style id="redline">
        [STYLE DEFINITION FOLLOWING]
    </style>
    <plot2D id="redline_bluesquares" baseStyle="redline">
        [STYLE DEFINITION FOLLOWING]
    </plot2D>
</listOfStyles>
```

Listing 2.23: *The listOfStyles element*

2.2.1.11 listOfAlgorithmParameters (global)

The `listOfAlgorithmParameters` container holds the AlgorithmParameter objects that apply globally. This can include parameters like a seed (`KISAO:0000488`) that apply to the simulation experiment as a whole, as well as algorithm parameters that might apply to all tasks of a particular type, such as the absolute tolerance (`KISAO:0000211`). If an AlgorithmParameter is defined for a particular Simulation, it will take precedent over any global AlgorithmParameter with the same KiSAO ID. The `listOfAlgorithmParameters` is optional and may contain zero or more parameters.

```
<listOfAlgorithmParameters>
    <algorithmParameter name="seed" kisaoID="KISAO:0000211" value="23"/>
    <algorithmParameter name="absolute tolerance" kisaoID="KISAO:0000488" value="1001"/>
</listOfAlgorithmParameters>
```

Listing 2.24: *The global listOfAlgorithParameters element*

2.2.2 DataDescription

The DataDescription class (Figure 2.8 on the following page) allows to reference external data, and contains a description on how to access the data, in what format it is, and what subset of data to extract.

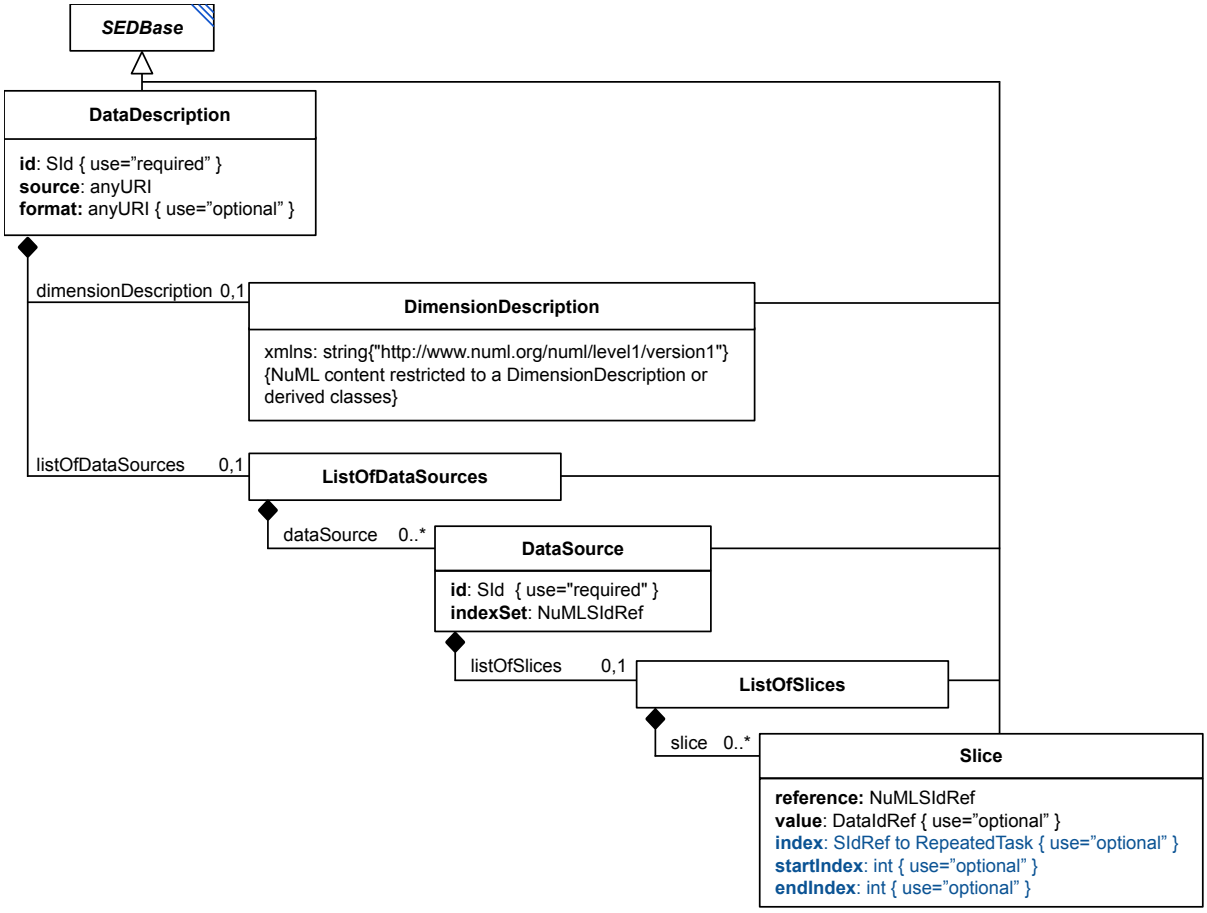


Figure 2.8: *The SED-ML DataDescription class*

The DataDescription class introduces four attributes: the required attributes `id` and `source` and the optional attributes `format` and `name`. In addition two optional elements are defined: `dimensionDescription` and `listOfDataSources`.

Listing 2.25 shows the use of the `dataDescription` element.

```
<dataDescription id="Data1" name="Oscli Time Course Data" format="urn:sedml:format:numl"
    source="http://svn.code.sf.net/p/libsedml/code/trunk/Samples/data/oscli.numl" >
    [...]
</dataDescription>
```

Listing 2.25: *SED-ML `dataDescription` element*

source

The required `source` attribute of data type `anyURI` is used to specify the data file. The `source` attribute provides a location of a data file, analog to how the `source` attribute on the Model is handled. In order to resolve the `source` attribute, the same mechanisms are allowed as for the Model `source` element, i.e., via the local file system, a relative link, or an online resource.

format

The optional `format` attribute of data type `anyURI` is used to specify the format of the DataDescription. The allowed formats are defined in the format references, e.g., NuML (`urn:sedml:format:numl`) or CSV (`urn:sedml:format:csv`). If it is not explicitly defined the default value for `format` is `urn:sedml:format:numl`, referring to NuML representation of the data.

dimensionDescription

The optional `dimensionDescription` contains a DimensionDescription providing the dimension description of the data file. If the format is NuML (`urn:sedml:format:numl`) and a `dimensionDescription` is set, then the `dimensionDescription` must be identical to the `dimensionDescription` of the NuML file. If the format is not NuML, the `dimensionDescription` is required.

listOfDataSources

The optional `listOfDataSources` contains zero or more DataSource elements. A DataSource extracts chunks out of the external data provided by the outer DataDescription element.

2.2.3 DataDescription components

2.2.3.1 *DimensionDescription*

The DimensionDescription class (Figure 2.8 on the preceding page) defines the dimensions and data types of the external data provided by the outer DataDescription element. The DimensionDescription is a NuML container containing the dimension description of the dataset.

In the following example a nested NuML `compositeDescription` with `time` spanning one dimension and `SpeciesIds` spanning a second dimension is given. This two dimensional space is then filled with `double` values representing concentrations.

```
<dimensionDescription>
    <compositeDescription indexType="double" id="time" name="time"
        xmlns="http://www.numl.org/numl/level1/version1">
        <compositeDescription indexType="string" id="SpeciesIds" name="SpeciesIds">
            <atomicDescription valueType="double" id="Concentration" name="Concentration" />
        </compositeDescription>
    </compositeDescription>
</dimensionDescription>
```

Listing 2.26: *SED-ML `dimensionDescription` element*

2.2.3.2 *DataSource*

The DataSource class (Figure 2.8 on the previous page) extracts chunks out of the dataset provided by the outer DataDescription element. The DataSource class introduces three attributes: the required attribute `id` and the optional attributes `name`, `indexSet`, and `listOfSlices` (Figure 2.8 on the preceding page).

DataSource elements can be used anywhere in the SED-ML Description. Specifically their `id` attribute can be referenced as the `target` of any Variable, pre-pended by a `'#'` inside DataGenerator, ComputeChange or SetValue objects if the referenced data is a scalar, and as the `target` of a Variable in any DataGenerator even if the referenced data is multidimensional.

The `id` may also be used as the `sourceRef` of a DataRange, and as the `dataSource` or `pointWeight` of a FitMapping. These referenced data may be multidimensional.

Here an example that references the DataSource `dataS1`:

```
<listOfDataDescriptions>
  <dataDescription id="data1" name="data file" source="./example.numl" format="urn:sedml:format:numl">
    <dimensionDescription>
      <compositeDescription indexType="double" name="Time">
        <compositeDescription indexType="string" name="SpeciesIds">
          <atomicDescription valueType="double" name="Values" />
        </compositeDescription>
      </compositeDescription>
    </dimensionDescription>
    <listOfDataSources>
      <dataSource id="dataS1">
        <listOfSlices>
          <slice reference="SpeciesIds" value="S1" />
        </listOfSlices>
      </dataSource>
      <dataSource id="dataTime" indexSet="Time" />
    </listOfDataSources>
  </dataDescription>
</listOfDataDescriptions>
<listOfDataGenerators>
  <dataGenerator id="dgDataS1" name="S1 (data)">
    <listOfVariables>
      <variable id="varS1" modelReference="model1" target="#dataS1" />
```

```
    </listOfVariables>
    <math xmlns="http://www.w3.org/1998/Math/MathML">
      <ci> varS1 </ci>
    </math>
  </dataGenerator>
  ...
</listOfDataGenerators>
```

This represents a change from Level 1 Version 1 and Level 1 Version 2, in which a `taskReference` was always present for a `variable` in a DataGenerator.

To indicate that the `target` of the Variable is an entity defined within the current SED-ML description (and not an entity in an external document, such as referenced by a XPath expression) the hashtag (#) with the reference to an `id` is used.

In addition, this example uses the `modelReference`, in order to facilitate a mapping of the data with a given model.

Data may contain NA values. All calculations containing a NA value have NA as a result.

Since data elements defined via the DimensionDescription of the DataDescription or within the NuML file are either values or indices, the DataSource element provides two ways of addressing those elements, the `indexSet` and `listOfSlices`.

indexSet

The `indexSet` attribute allows to address all indices provided by NuML elements with `indexType`.

For example for the `indexSet time` below, a dataSource extracts the set of all timepoints stored in the index.

```
<dataSource id="dataTime" indexSet="time" />
```

Similarly

```
<dataSource id="allIds" indexSet="SpeciesIds" />
```

extracts all the species id strings stored in that index set. Valid values for `indexSet` are all NuML Id elements declared in the `dimensionDescription`.

If the `indexSet` attribute is specified the corresponding `dataSource` may not define any `slice` elements.

listOfSlices

The `listOfSlices` contains one or more Slice elements. The `listOfSlices` container holds the Slice definitions of a DataSource (Figure 2.8 on page 28). The `listOfSlices` is optional and may contain zero to many Slices.

2.2.3.3 Slice

If a DataSource does not define the `indexSet` attribute, it will contain Slice elements. Each slice removes one dimension from the data hypercube.

The Slice class introduces a required `reference` attribute of type `NuMLSIdRef`, and four optional attributes: `value` of type `DataIdRef`, `index` of type SIdRef, and `startIndex` and `endIndex`, both of type `int` (Figure 2.8 on page 28).

reference

The `reference` attribute references one of the indices described in the `dimensionDescription`. In the example above, valid values would be: `time` and `SpeciesIds`.

value

The `value` attribute takes the value of a specific index in the referenced set of indices. For example:

```
<dataSource id="dataS1">
    <listOfSlices>
        <slice reference="SpeciesIds" value="S1" />
    </listOfSlices>
</dataSource>
```

isolates the index set of all species ids specified to only the single entry for `S1`, however over the full range of the `time` index set. As stated before, there can be multiple slice elements present, so it is possible to slice the data again to obtain a single time point, for example the initial one:

```
<dataSource id="dataS1">
    <listOfSlices>
        <slice reference="time" value="0" />
        <slice reference="SpeciesIds" value="S1" />
    </listOfSlices>
</dataSource>
```

index

The `index` attribute is an SIdRef to a RepeatedTask. This is for cases where the Slice refers to data generated by potentially-nested RepeatedTask elements.

startIndex and endIndex

The `startIndex` and `endIndex` attributes can be used to further subdivide a subset of dimensional data to only part of the full array of data. If `startIndex` is defined, no data point with an index less than its value should be included, and if `endIndex` is included, no data point with an index greater than its value should be included.

2.2.4 Model

The Model class defines the models used in a simulation experiment (Figure 2.9).

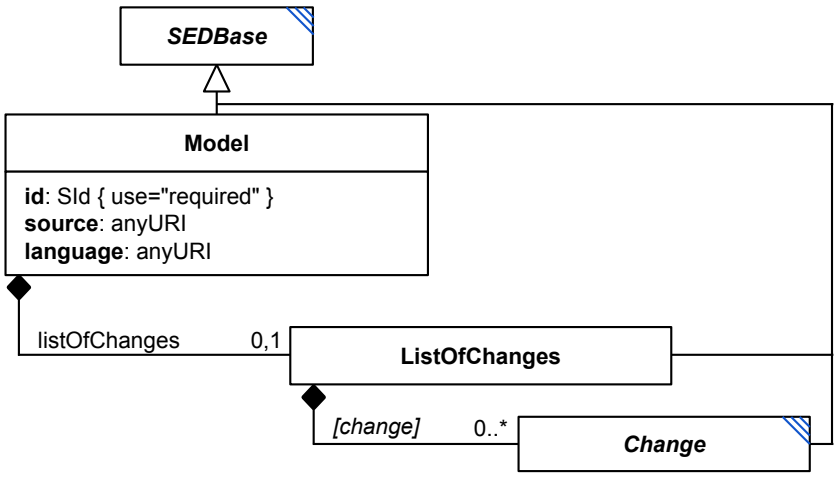


Figure 2.9: *The SED-ML Model class*

Each instance of the Model class has the required attributes `id`, `source`, and `language`, the optional attribute `name`, and the optional child `listOfChanges`.

The `language` attribute defines the format the model is encoded in.

The Model class refers to the particular model of interest through the `source` attribute. The restrictions on the model reference are

- The model must be encoded in a well-defined format.
- To refer to the model encoding language, a reference to a valid definition of that format must be given (`language` attribute).
- To refer to a particular model in an external resource, an unambiguous reference must be given (`source` attribute).

A model might need to undergo pre-processing before simulation. Those pre-processing steps are specified in the `listOfChanges` via the Change class.

Listing 2.27 shows the use of the **model** element. In the example the listOfModels contains three models: The first model **m0001** is the Repressilator model from BioModels Database available from https://www.ebi.ac.uk/biomodels/model/download/BIOMD0000000012?filename=BIOMD0000000012_url.xml. For the SED-ML simulation the model might undergo preprocessing steps described in the listOfChanges. Based on the description of the first model **m0001**, the second model **m00002** is built, which is a modified version of the Repressilator model. **m0002** refers to the model **m001** in its source attribute. **m0002** might then have additional changes applied to it on top of the changes defined in the pre-processing of **m0001**. The third model in the code example is a model in CellML representation. The model **m0003** is available from the given URL in the source attribute. Again, it might have pre-processing steps applied before used in a simulation.

```
<listOfModels>
    <model id="m0001" language="urn:sedml:language:sbml"
        source="https://www.ebi.ac.uk/biomodels/model/download/BIOMD0000000012?filename=
            BIOMD0000000012_url.xml">
        <listOfChanges>
            <change>
                [MODEL PRE-PROCESSING]
            </change>
        </listOfChanges>
    </model>
    <model id="m0002" language="urn:sedml:language:sbml" source="#m0001">
        <listOfChanges>
            [MODEL PRE-PROCESSING]
        </listOfChange>
    </model>
    <model id="m0003" language="urn:sedml:language:cellml" source="http://models.cellml.org/workspace/
        leloup_gonze_goldbeter_1999/@@rawfile/d6613d7e1051b3eff2bb1d3d419a445bb8c754ad/
        leloup_gonze_goldbeter_1999_a.cellml">
        [MODEL PRE-PROCESSING]
    </model>
</listOfModels>
```

Listing 2.27: *SED-ML* **model** *element*

language

The required **language** attribute of data type anyURI is used to specify the format of the model. Example formats are SBML (**urn:sedml:language:sbml**) or CellML (**urn:sedml:language:cellml**). The supported languages are defined in the language references.

The use of the **language** attribute is required for two reasons. Firstly, it helps to decide whether or not one is able to run the simulation, that is to parse the model referenced in the SED-ML file. Secondly, the language attribute is also needed to decide how to handle the Symbols in the Variable class, as the interpretation of Symbols depends on the language of the representation format.

source

To make a model accessible for the execution of a SED-ML file, the **source** must be specified through either an URI or a reference to an **SId** of an existing Model. The URI should follow the proposed URI Scheme for Model references.

There are three typical ways to identify a model with the **source** attribute: by relative path, by identifier, or by URL.

An example for the definition of a model via a relative path URI is given in Listing 2.28. The example defines one model **m1** with the model **source** available from "**oscillator.xml**" in the same directory or location as the SED-ML file. A **source** value of "**./oscillator.xml**" would accomplish the same thing more explicitly, with "**./**" being shorthand for 'the current directory'.

```
<model id="m1" name="repressilator" language="urn:sedml:language:sbml"
    source="oscillator.xml">
    <listOfChanges>
        [MODEL PRE-PROCESSING]
    </listOfChanges>
</model>
```

Listing 2.28: *The SED-ML* **source** *element, using the URI scheme*

An example for the definition of a model using an URL is given in Listing 2.29. In the example one model is defined. The **language** of the model is **CellML**. The *URL* pointing to the model is used in the **source** attribute.

```
<model id="m1" name="repressilator" language="urn:sedml:language:cellml"
```

```
    source="http://models.cellml.org/exposure/bba4e39f2c7ba8af51fd045463e7bdd3/aguda_b_1999.cellml">
    <listOfChanges />
</model>
```

Listing 2.29: *The SED-ML* `source` *element, using a URL*

MIRIAM URNs are no longer recommended due to increased difficulty in resolving them, but the scheme is still valid and interpreters may find SED-ML files that use them. An example for the definition of a model via an URI is given in Listing 2.30. The example defines one model `m1` with the model `source` available from `urn:miriam:biomodels.db:BIOMD0000000012`. The MIRIAM URN can be resolved into the SBML model stored in BioModels Database under the identifier `BIOMD0000000012` by querying the Biomodels webservice and requesting the 'main' SBML file for that biomodel. The resulting URL is `https://www.ebi.ac.uk/biomodels/model/download/BIOMD0000000012?filename=BIOMD0000000012_url.xml`.

```
<model id="m1" name="repressilator" language="urn:sedml:language:sbml"
    source="urn:miriam:biomodels.db:BIOMD0000000012">
    <listOfChanges>
        [MODEL PRE-PROCESSING]
    </listOfChanges>
</model>
```

Listing 2.30: *The SED-ML* `source` *element, using the URI scheme*

listOfChanges

The `listOfChanges` (Figure 2.9 on page 31) contains the Changes to be applied to a particular Model. The `listOfChanges` is optional and may contain zero to many Changes.

Listing 2.31 shows the use of the `listOfChanges` element.

```
<model id="m0001" [..]>
    <listOfChanges>
        [CHANGE DEFINITION]
    </listOfChanges>
</model>
```

Listing 2.31: *The SED-ML* `listOfChanges` *element, defining a change on a model*

2.2.5 Change

The Change class allows to describe changes applied to a model before simulation (Figure 2.10 on the next page). Changes can be of the following types:

- Changes based on mathematical calculations (ComputeChange)
- Changes on attributes of the model (ChangeAttribute)
- For XML-encoded models, changes on any XML snippet of the model's XML representation (AddXML, ChangeXML, RemoveXML)

The Change class is abstract and serves as the base class for different types of changes, the ChangeAttribute, AddXML, ChangeXML, RemoveXML, and ComputeChange.

The Change class has the mandatory attribute target which defines the target of the change. The `target` attribute holds an unambiguous description of the address of the element, elements, attribute, or attributes that are to undergo the defined changes, such as a valid XPath expression pointing to the specified XML. For NewXML, AddXML, ChangeXML, and RemoveXML, target must be an XPath expression. This XPath expression must always select an appropriate target for the particular Change used.

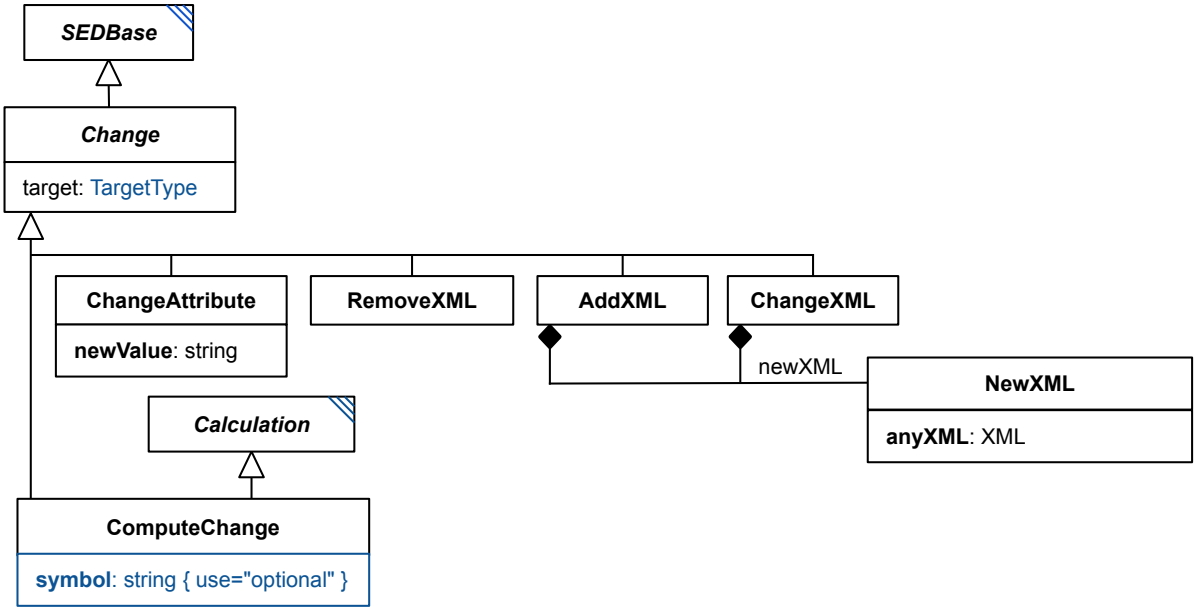


Figure 2.10: *The SED-ML Change class*

target

The `target` attribute holds an unambiguous description of the address of an element or attribute of a model that is to undergo the defined changes. For XML model languages such as SBML, `target` must be a valid XPath expression of data type `xpath` pointing to the XML that is to undergo the defined changes.

2.2.5.1 NewXML

The `newXML` element provides a piece of XML code (Figure 2.10). `NewXML` must hold a valid piece of XML in the appropriate namespace which after insertion into the original model must result in a valid model file (according to the model language specification as given by the `language` attribute of the model).

The `newXML` element is used at two different places inside SED-ML Level 1 Version 4:

1. If it is used as a sub-element of the `addXML` element, then the XML it contains *is inserted as a child* of the XML element addressed by the XPath.
2. If it is used as a sub-element of the `changeXML` element, then the XML it contains *replaces* the XML element or elements addressed by the XPath.

Examples are given in the relevant change class definitions.

2.2.5.2 AddXML

The AddXML class specifies a snippet of XML that is added as a child of the element selected by the XPath expression in the `target` attribute (Figure 2.10). The new piece of XML code is provided by the NewXML class, and may contain one or more XML elements.

An example for a change that adds an additional parameter to a model is given in Listing 2.32. In the example the model is changed so that a parameter with ID `V_mT` is added to its list of parameters. The `newXML` element adds an additional XML element to the original model. The element's name is `parameter` and it is added to the existing parent element `listOfParameters` that is addressed by the XPath expression in the `target` attribute.

```
<model language="urn:sedml:language:sbml" [..]>
    <listOfChanges>
        <addXML target="/sbml:sbml/sbml:model/sbml:listOfParameters" >
            <newXML>
                <sbml:parameter xmlns:sbml="http://www.sbml.org/sbml/level3/version1/core"
                                metaid="metaid_0000010" id="V_mT" value="0.7" />
            </newXML>
```

```
        </addXML>
    </listOfChanges>
</model>
```

Listing 2.32: *The `addXML` element with its `newXML` sub-element*

2.2.5.3 `ChangeXML`

The ChangeXML class allows you to replace any XML element(s) in the model that can be addressed by a valid XPath expression (Figure 2.10 on the preceding page).

The XPath expression is specified in the required `target` attribute, and may target one or more XML elements. The replacement XML content is specified in the NewXML class, and may also contain one or more XML elements.

An example for a change that adds an additional parameter to a model is given in Listing 2.33. In the example the model is changed in the way that its parameter with ID `V_mT` is substituted by two other parameters `V_mT_1` and `V_mT_2`. The `target` attribute defines that the parameter with ID `V_mT` is to be changed. The `newXML` element then specifies the XML that is to be exchanged for that parameter.

```
<model [..]>
    <listOfChanges>
        <changeXML target="/sbml:sbml/sbml:model/sbml:listOfParameters/sbml:parameter[@id='V_mT']" >
            <newXML>
                <sbml:parameter xmlns:sbml="http://www.sbml.org/sbml/level3/version1/core"
                                metaid="metaid_0000010" id="V_mT_1" value="0.7" />
                <sbml:parameter xmlns:sbml="http://www.sbml.org/sbml/level3/version1/core"
                                metaid="metaid_0000050" id="V_mT_2" value="4.6"> />
            </newXML>
        </changeXML>
    </listOfChanges>
</model>
```

Listing 2.33: *The `changeXML` element*

2.2.5.4 `RemoveXML`

The RemoveXML class can be used to delete one or more XML elements or attributes in the model that are addressed by the XPath expression (Figure 2.10 on the previous page). The XPath is specified in the required `target` attribute.

An example for the removal of an XML element from a model is given in Listing 2.34. In the example the model is changed by deleting the reaction with ID `V_mT` from the model's list of reactions.

```
<model [..]>
    <listOfChanges>
        <removeXML target="/sbml:sbml/sbml:model/sbml:listOfReactions/sbml:reaction[@id='J1']" />
    </listOfChanges>
</model>
```

Listing 2.34: *The `removeXML` element*

2.2.5.5 `ChangeAttribute`

The ChangeAttribute class allows to define updates on the attribute values of the corresponding model (Figure 2.10 on the preceding page). ChangeAttribute requires to specify the `target` of the change, i.e., the location of the addressed attribute, and also the `newValue` of that attribute. Note that the `target` must select a single attribute within the corresponding model.

Despite its name, the 'attribute' changed by this class need not be an XML attribute, and hence, its `target` need not be an XPath. Every target model language may define what 'attributes' may be changed by this contruct, and how to indicate those attributes.

The ChangeXML class covers the possibilities provided by the ChangeAttribute class, i.e, everything that can be expressed by a ChangeAttribute construct can also be expressed by ChangeXML. However, for the common case of changing an attribute value ChangeAttribute is easier to use, and so it is recommended to use the ChangeAttribute for any changes of an attribute's value, and to use the more general ChangeXML for other cases.

`newValue`

The mandatory `newValue` attribute of data type `string` assignes a new value to the targeted attribute.

The example in Listing 2.35 shows the update of the value of two parameters inside an SBML model.

```
<model id="model1" name="Circadian Chaos" language="urn:sedml:language:sbml"
    source="https://www.ebi.ac.uk/biomodels/model/download/BIOMD0000000012?filename=BIOMD0000000012_url.
        xml">
    <listOfChanges>
        <changeAttribute target="/sbml:sbml/sbml:model/sbml:listOfParameters/sbml:parameter[@id='V_mT']/
            @value" newValue="0.28"/>
        <changeAttribute target="/sbml:sbml/sbml:model/sbml:listOfParameters/sbml:parameter[@id='V_dT']/
            @value" newValue="4.8"/>
    </listOfChanges>
</model>
```

Listing 2.35: *The* `changeAttribute` *element and its* `newValue` *attribute*

2.2.5.6 `ComputeChange`

The ComputeChange class permits to change, prior to the experiment, the numerical value of any single element or attribute of a Model addressable by a `target`, based on a calculation (Figure 2.10 on page 34). It inherits the `target` attribute from the Change abstract base class, as well as the standard *SEDBase* attributes and children, and adds the optional attribute `symbol` (of type string). Its ability to perform a calculation is described in the Calculation class. (For implementations, if multiple inheritance is not possible, the children of Calculation should just be added directly to the ComputeChange class itself.)

The change is calculated from the Math of the Calculation, and applied to the `target` of the Change. In this context, a `target` that points to an XML element (either the `target` of the ComputeChange or a `target` of a child Variable) is referencing that element's mathematical meaning. For some model languages (such as SBML), this means that the model state must be initialized, so the element value can be read (in the case of a Variable) or changed (in the case of a ComputeChange).

In contrast, a `target` that points to an XML attribute simply is referencing that attribute's value, which may be read or set directly in the XML document without initializing the whole model.

Note also that when a ComputeChange refers to another model, that model is not allowed to be modified by ComputeChanges which directly or indirectly refer to this model, nor to the target of this ComputeChange. In other words, cycles in the definitions of computed changes are prohibited. This does mean that other models may also need to be initialized (and changes applied) in order to apply the changes to this model.

symbol

The optional `symbol` attribute of data type `string` may be used in addition to the `target` when the particular value associated with the `target` may be described in multiple ways. In particular, a species whose value could be expressed either as a concentration or an amount may be set by using the `target` to point to the species, and setting the `symbol` to "`KISAO:0000838`" to set the concentration, or setting the `symbol` to "`KISAO:0000836`" to set the amount.

Listing 2.36 shows the use of the `computeChange` element.

```
<model [..]>
    <listOfChanges>
    <computeChange target="/sbml:sbml/sbml:model/sbml:listOfParameters/sbml:parameter[@id='sensor']">
        <listOfVariables>
            <variable modelReference="model1" id="R" name="regulator"
                target="/sbml:sbml/sbml:model/sbml:listOfSpecies/sbml:species[@id='regulator']" />
            <variable modelReference="model2" id="S" name="sensor"
                target="/sbml:sbml/sbml:model/sbml:listOfParameters/sbml:parameter[@id='sensor']" />
        <listOfVariables/>
        <listOfParameters>
            <parameter id="n" name="cooperativity" value="2">
            <parameter id="K" name="sensitivity" value="1e-6">
        <listOfParameters/>
        <math  xmlns="http://www.w3.org/1998/Math/MathML">
        <apply>
          <times />
          <ci>S</ci>
          <apply>
            <divide />
            <apply>
              <power />
              <ci>R</ci>
              <ci>n</ci>
            </apply>
            <apply>
              <plus />
              <apply>
```

```
                <power />
                <ci>K</ci>
                <ci>n</ci>
              </apply>
              <apply>
                <power />
                <ci>R</ci>
                <ci>n</ci>
              </apply>
            </apply>
        </apply>
        </math>
    </computeChange>
    </listOfChanges>
</model>
```

Listing 2.36: *The computeChange element*

The example in Listing 2.36 computes a change of the variable `sensor` of the model `model2`. To do so, it uses the value of the variable `regulator` coming from model `model1`. In addition, the calculation uses two additional parameters, the cooperativity `n`, and the sensitivity `K`. The mathematical expression in the mathML then computes the new initial value of `sensor` using the equation: $S = S \times \frac{R^n}{K^n + R^n}$

2.2.6 Simulation

A simulation is the execution of some defined algorithm(s). Simulations are described differently depending on the type of simulation experiment to be performed (Figure 2.11).

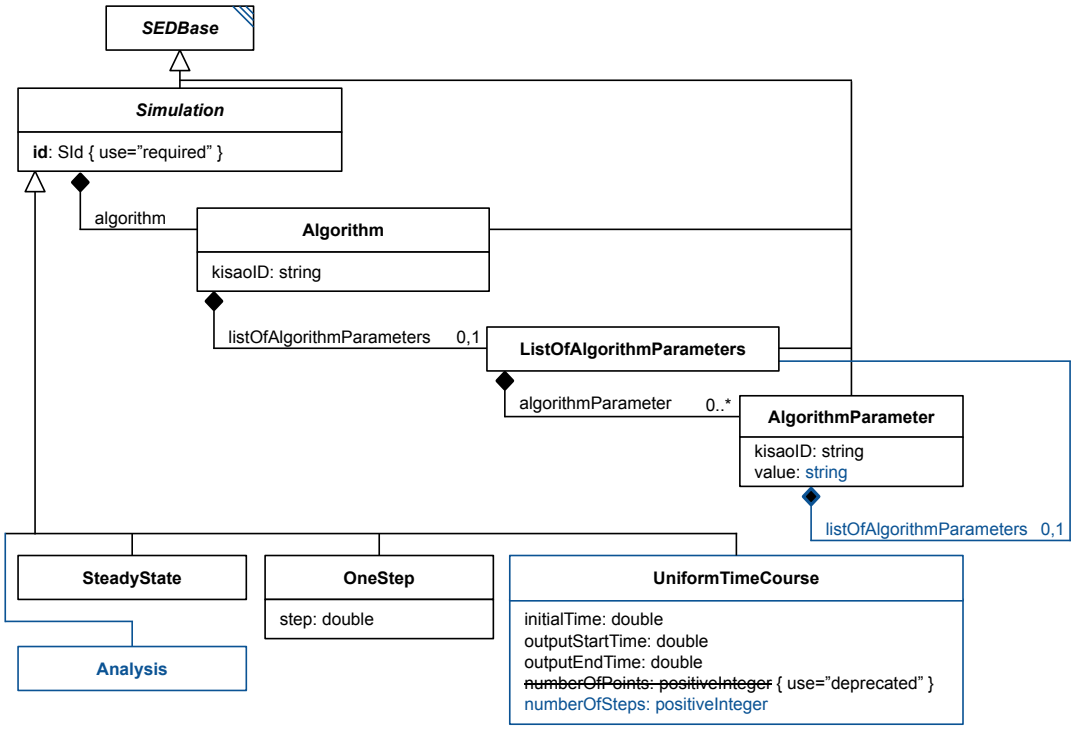


Figure 2.11: *The SED-ML Simulation class*

Simulation is an abstract class and serves as the container for the different types of simulation experiments. SED-ML Level 1 Version 4 provides the predefined simulation classes UniformTimeCourse, OneStep, SteadyState, and Analysis.

Each instance of the Simulation class has an unambiguous and mandatory `id`. An additional, optional `name` may be given to the simulation. Every simulation has a required element `algorithm` describing the simulation Algorithm.

```
<listOfSimulations>
    <uniformTimeCourse [..]>
        [SIMULATION SPECIFICATION]
```

```
    </uniformTimeCourse>
    <uniformTimeCourse [..]>
        [SIMULATION SPECIFICATION]
    </uniformTimeCourse>
</listOfSimulations>
```

Listing 2.37: *The SED-ML* `listOfSimulations` *element, defining two different UniformTimecourse simulations*

algorithm

The mandatory attribute `algorithm` defines the simulation algorithms used for the execution of the simulation. The algorithms are defined via the Algorithm class.

2.2.6.1 *UniformTimeCourse*

Each instance of the UniformTimeCourse class has, in addition to the elements from Simulation, the mandatory elements `initialTime`, `outputStartTime`, `outputEndTime`, and `numberOfSteps` (Figure 2.11 on the preceding page).

Listing 2.38 shows the use of the `uniformTimeCourse` element.

```
<listOfSimulations>
    <uniformTimeCourse id="s1"  name="time course simulation of variable v1 over 100 minutes"
        initialTime="0" outputStartTime="0" outputEndTime="2500" numberOfSteps="1000">
        <algorithm [..] />
    </uniformTimeCourse>
</listOfSimulations>
```

Listing 2.38: *The SED-ML* `uniformTimeCourse` *element, defining a uniform time course simulation over 2500 time units with 1000 simulation points.*

initialTime

The attribute `initialTime` of type `double` represents what the time is at the start of the simulation, for purposes of output variables, and for calculating the `outputStartTime` and `outputEndTime`. In most cases, this will be `0.0`. The model must be set up such that `intialTime` is correct internally with respect to any output variables that may be produced. Listing 2.38 shows an example.

outputStartTime

Sometimes a researcher is not interested in simulation results at the start of the simulation, i.e., the initial time. The `UniformTimeCourse` class uses the attribute `outputStartTime` of type `double`, and describes the time (relative to the `intialTime`) that output is to be collected. To be valid the `outputStartTime` cannot be before `initialTime`. For an example, see Listing 2.38.

outputEndTime

The attribute `outputEndTime` of type `double` marks the end time of the simulation, relative to the `initialTime`. See Listing 2.38 for an example.

numberOfSteps

When executed, the `UniformTimeCourse` simulation produces an output on a regular grid starting with `outputStartTime` and ending with `outputEndTime`. The attribute `numberOfSteps` of type `integer` describes the number of steps expected to produce the result. Software interpreting the `UniformTimeCourse` is expected to produce a first outputPoint at time `outputStartTime` and then `numberOfSteps` output points with the results of the simulation. Thus a total of `numberOfSteps + 1` output points will be produced.

Just because the output points lie on the regular grid described above, does not mean that the simulation algorithm has to work with the same step size. Usually the step size the simulator chooses will be adaptive and much smaller than the required output step size. On the other hand a stochastic simulator might not have any new events occurring between two grid points. Nevertheless the simulator has to produce data on this regular grid. For an example, see Listing 2.38.

This attribute used to be named `numberOfPoints`, but was defined to be 'the number of output points minus one', which was confusing. The old name is thus deprecated, and the new name is more in line with its definition.

2.2.6.2 OneStep

The OneStep class calculates one further output step for the model from its current state. Each instance of the OneStep class has, in addition to the elements from Simulation, the mandatory element `step` (Figure 2.11 on page 37).

Listing 2.39 shows the use of the `oneStep` element.

```
<listOfSimulations>
    <oneStep id="s1" step="0.1">
        <algorithm kisaoID="KISAO:0000019" />
    </oneStep>
</listOfSimulations>
```

Listing 2.39: *The SED-ML `oneStep` element, specifying to apply the simulation algorithm for another output step of size 0.1.*

step

The OneStep class has one required attribute `step` of type `double`. It defines the next output point that should be reached by the algorithm, by specifying the increment from the current output point. Listing 2.39 shows an example.

Note that the `step` does not necessarily equate to one integration step. The simulator is allowed to take as many steps as needed. However, after running oneStep, the desired output time is reached.

2.2.6.3 SteadyState

The SteadyState represents a steady state computation (as for example implemented by NLEQ or Kinsolve). The SteadyState class has no additional elements than the elements from Simulation (Figure 2.11 on page 37).

Listing 2.40 shows the use of the `steadyState` element.

```
<listOfSimulations>
    <steadyState id="steady">
        <algorithm kisaoID="KISAO:0000282" />
    </steadyState >
</listOfSimulations>
```

Listing 2.40: *The SED-ML `steadyState` element, defining a steady state simulation with id `steady`.*

2.2.6.4 Analysis

The Analysis represents any sort of analysis or simulation of a Model, entirely defined by its child Algorithm. If a simulation can be defined by a different Simulation, that should be used instead, so that tools are more likely to recognize the request. But for any simultion or any analysis not covered by SteadyState, OneStep, or UniformTimeCourse, the only thing necessary is a KiSAO term for the Algorithm defining what to do. The following examples illustrate analyses that could not be created with other SED-ML Simulation classes:

Listing 2.41 shows the use of the `analysis` element.

```
<listOfSimulations>
    <analysis id="time_course_to_stop_condition">
        <algorithm kisaoID="KISAO:0000263"name="NFSim">
            <algorithmParameter kisaoID="KISAO:0000525" value="ObsA&gt;9"/>
            <algorithmParameter kisaoID="KISAO:0000xxx" value="0" name="start time"/>
            <algorithmParameter kisaoID="KISAO:0000xxx" value="10000" name="max end time"/>
            <algorithmParameter kisaoID="KISAO:0000xxx" value="0.5" name="observed step size"/>
        </algorithm>
    </analysis >
</listOfSimulations>
```

Listing 2.41: *The SED-ML `analysis` element, defining a time course with a stop condition (ObsA < 9).*

Listing 2.42 shows the use of the `analysis2` element.

```
<listOfSimulations>
    <analysis id="non_uniform_time_course">
        <algorithm kisaoID="KISAO:0000057" name="Brownian diffusion Smoluchowski method">
            <algorithmParameter kisaoID="KISAO:0000525" value="ObsA&gt;9" name="stop condition"/>
            <algorithmParameter kisaoID="KISAO:0000xxx" value="0" name="start time"/>
            <algorithmParameter kisaoID="KISAO:0000xxx" value="100" name="max end time"/>
```

```
        </algorithm>
    </analysis >
</listOfSimulations>
```

Listing 2.42: *The SED-ML* `analysis` *element, defining a non-uniform time course.*

Listing 2.43 shows the use of the `analysis3` element.

```
<listOfSimulations>
    <analysis id="non_uniform_time_course">
        <algorithm kisaoID="KISAO:0000xxx" name="Reachability analysis">
            <algorithmParameter kisaoID="KISAO:0000xxx" value="0" name="something_relevant"/>
        </algorithm>
    </analysis >
</listOfSimulations>
```

Listing 2.43: *The SED-ML* `analysis` *element, defining a reachability analysis.*

2.2.7 Simulation components

2.2.7.1 *Algorithm*

The Algorithm class has a mandatory element `kisaoID` which contains a KiSAO reference to the particular simulation algorithm used in the simulation. In addition, the Algorithm has an optional `listOfAlgorithmParameters`, a collection of algorithmParameter, which are used to parameterize the algorithm.

The example given in Listing 2.37, completed by algorithm definitions results in the code given in Listing 2.44. In the example, for both simulations a algorithm is defined. In the first simulation `s1` a deterministic approach is used (Euler forward method), in the second simulation `s2` a stochastic approach is used (Stochsim nearest neighbor).

```
<listOfSimulations>
    <uniformTimeCourse id="s1" name="time course simulation over 100 minutes" [..]>
        <algorithm kisaoID="KISAO:0000030" />
    </uniformTimeCourse>
    <uniformTimeCourse id="s2" name="time course definition for concentration of p" [..]>
        <algorithm kisaoID="KISAO:0000021" />
    </uniformTimeCourse>
</listOfSimulations>
```

Listing 2.44: *The SED-ML* `algorithm` *element for two different time course simulations, defining two different algorithms. KISAO:0000030 refers to the* Euler forward method *; KISAO:0000021 refers to the* StochSim nearest neighbor algorithm.

listOfAlgorithmParameters

The `listOfAlgorithmParameters` contains the settings for the simulation algorithm used in a simulation (Figure 2.11 on page 37). It may list several instances of the AlgorithmParameter class. The `listOfAlgorithmParameters` is optional and may contain zero to many parameters.

Listing 2.45 shows the use of the `listOfAlgorithmParameters` element.

```
<listOfAlgorithmParameters>
    <algorithmParameter kisaoID="KISAO:0000211" value="23"/>
</listOfAlgorithmParameters>
```

Listing 2.45: *SED-ML listOfAlgorithmParameters element*

2.2.7.2 *AlgorithmParameter*

The AlgorithmParameter class allows to parameterize a particular simulation algorithm. The set of possible parameters for a particular instance is determined by the algorithm that is referenced by the `kisaoID` of the enclosing algorithm element (Figure 2.11 on page 37). Parameters of simulation algorithms are unambiguously referenced by the mandatory `kisaoID` attribute. Their value is set in the mandatory `value` attribute. An AlgorithmParameter may also have child AlgorithmParameter elements through a ListOfAlgorithmParameters.

Any AlgorithmParameter defined in a Simulation overrides any global AlgorithmParameter defined in the SED-ML Document. And in the reverse, any AlgorithmParameter left undefined in a Simulation may be defined by a global AlgorithmParameter element.

NOTE: the global ListOfAlgorithmParameters was added to SED-ML in Level 1 Version 4. As such, the only place to define a random seed (`KISAO:0000211`) for the simulation experiment as a whole in previous versions was in a Simulation, which might be part of a RepeatedTask. Rather than indicating that each repeat was to receive the same seed, resulting in identical traces, users would generally use the 'seed' parameter to indicate that the experiment as a whole was to be replicable from one run to the next. Current users of SED-ML should use a global AlgorithmParameter for this purpose, but older versions or older files may use the previous scheme.

value

The `value` sets the value of the AlgorithmParameter. For XML purposes, it is of type `string`, but should contain a value that makes sense for the `kisaoID` in question: if the KiSAO term is a value, the string should contain a number; if the KiSAO term is a Boolean, the string should contain the string "`true`" or "`false`", etc. The string must be non-empty; to explicitly state that a value is not set, this should be encoded in the string as a value such as "`null`" or "`unset`", as makes sense for the term in question.

```
<algorithm kisaoID="KISAO:0000032">
    <listOfAlgorithmParameters>
        <algorithmParameter kisaoID="KISAO:0000211" value="23"/>
    </listOfAlgorithmParameters>
</algorithm>
```

Listing 2.46: *The SED-ML `algorithmParameter` element setting the parameter value for the simulation algorithm. `KISAO:0000032` refers to the* explicit fourth-order Runge-Kutta method*; `KISAO:00000211` refers to the* absolute tolerance.

listOfAlgorithmParameters

The child `listOfAlgorithmParameters` of an AlgorithmParameter may contain parameters that modify or refine the parent parameter, depending on the KiSAO term used.

```
<algorithm kisaoID="KISAO:0000352">
    <listOfAlgorithmParameters>
        <algorithmParameter kisaoID="KISAO:0000000" value="KISAO:0000019">
            <listOfAlgorithmParameters>
                <algorithmParameter kisaoID="KISAO:0000211" value="1e-07"/>
                <algorithmParameter kisaoID="KISAO:0000475" value="BDF"/>
                <algorithmParameter kisaoID="KISAO:0000481" value="true"/>
                <algorithmParameter kisaoID="KISAO:0000476" value="Newton"/>
                <algorithmParameter kisaoID="KISAO:0000477" value="Dense"/>
                <algorithmParameter kisaoID="KISAO:0000480" value="0"/>
                <algorithmParameter kisaoID="KISAO:0000415" value="500"/>
                <algorithmParameter kisaoID="KISAO:0000467" value="0"/>
                <algorithmParameter kisaoID="KISAO:0000478" value="Banded"/>
                <algorithmParameter kisaoID="KISAO:0000209" value="1e-07"/>
                <algorithmParameter kisaoID="KISAO:0000479" value="0"/>
            </listOfAlgorithmParameters>
        </algorithmParameter>
        <algorithmParameter kisaoID="KISAO:0000000" value="KISAO:0000282">
            <listOfAlgorithmParameters>
                <algorithmParameter kisaoID="KISAO:0000477" value="Dense"/>
                <algorithmParameter kisaoID="KISAO:0000480" value="0"/>
                <algorithmParameter kisaoID="KISAO:0000486" value="200"/>
                <algorithmParameter kisaoID="KISAO:0000479" value="0"/>
            </listOfAlgorithmParameters>
        </algorithmParameter>
    </listOfAlgorithmParameters>
</algorithm>
```

Listing 2.47: *A SED-ML `algorithmParameter` element defining a mixed simulator, each with their own set of algorithm parameters.*

2.2.8 AbstractTask

In SED-ML the subclasses of AbstractTask define which Simulations should be executed with which Models in the simulation experiment. AbstractTask is the base class of all SED-ML tasks, i.e. Task and RepeatedTask. It inherits the attributes and children of *SEDBase*, but changes the `id` attribute to be required instead of optional.

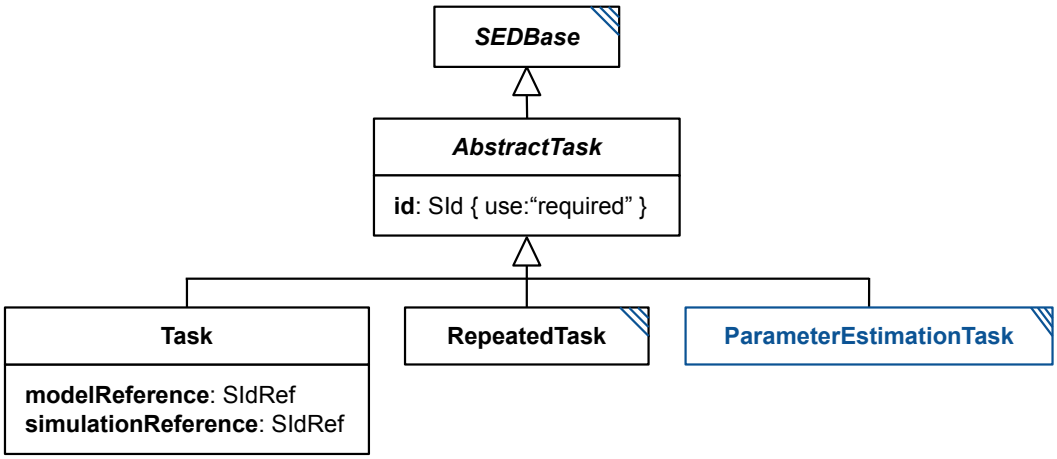


Figure 2.12: *The SED-ML Abstract Task, Task, RepeatedTask, and SimpleRepeatedTask classes*

2.2.8.1 Task

A Task links a Model to a certain Simulation description via their respective identifiers (Figure 2.12), using the `modelReference` and the `simulationReference`. The task class inherits the attributes and children of the *AbstractTask*.

`modelReference`

The `modelReference` attribute of type SIdRef must refer to a Model. Inside a RepeatedTask, the state of the model may have been changed, but in parallel tasks, a Model is to assume to its initial state.

`simulationReference`

the `simulationReference` attribute of type SIdRef must refer to a Simulation.

In SED-ML it is only possible to link one Simulation description to one Model at a time. However, one can define as many tasks as needed within one experiment description. Please note that the tasks may be executed in any order, as determined by the implementation.

In the example, a simulation setting `simulation1` is applied first to `model1` and then to `model2`.

```
<listOfTasks>
    <task id="t1" name="task definition" modelReference="model1"
        simulationReference="simulation1" />
    <task id="t2" name="another task definition" modelReference="model2"
        simulationReference="simulation1" />
</listOfTasks>
```

Listing 2.48: *The `task` element*

2.2.8.2 Repeated Task

The RepeatedTask (Figure 2.13 on the next page) provides a generic looping construct, allowing complex tasks to be composed from individual steps. The RepeatedTask performs a specified task (or sequence of tasks as defined in the `listOfSubTasks`) multiple times (where the exact number is specified through a Range construct as defined in `range`), while allowing specific quantities in the model or models to be altered at each iteration (as defined in the `listOfChanges`).

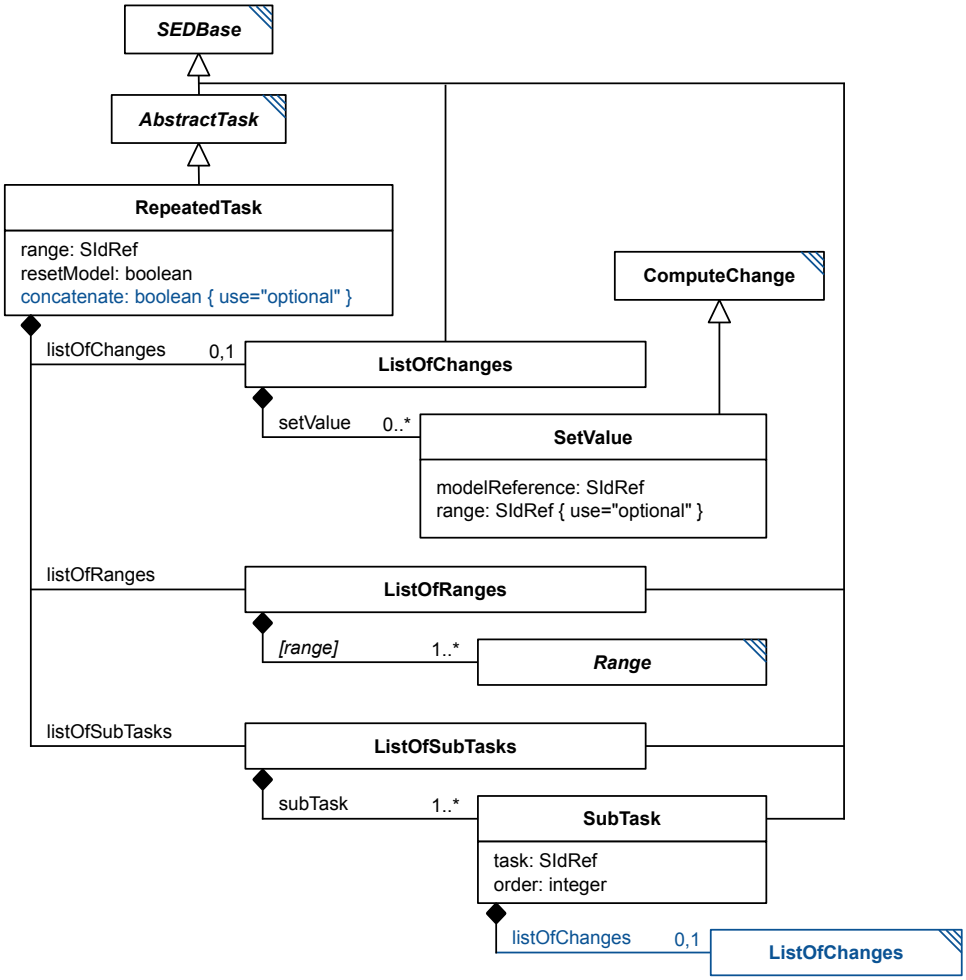


Figure 2.13: *The SED-ML RepeatedTask class*

The RepeatedTask inherits the required attribute `id` and optional attribute `name` from *AbstractTask*. Additionally it has the two required attributes `range` and `resetModel`, an optional attribute `concatenate`, and the child elements `listOfRanges` (required), `listOfChanges` (optional) and `listOfSubTasks` (required).

The order of activities within each iteration of a RepeatedTask is as follows:

- The entire model state for any involved Model is reset if specified by the `resetModel` attribute.
- Any changes to the model or models specified by SetValue objects in the `listOfChanges` are applied to each Model.

Then, for each SubTask child of the RepeatedTask, in the order specified by its `order` attribute:

- Any AlgorithmParameter children of the associated Simulation are applied (with the possible exception of the `seed`; see Section 2.2.7.2).
- Any SetValue children of the SubTask are applied to the relevant Model.
- The referenced Task of the SubTask is executed.

Listing 2.49 shows the use of the `repeatedTask` element. In the example, `task1` is repeated three times, each time with a different value for a model parameter `w`.

```
<task id="task1" modelReference="model1" simulationReference="simulation1" />
<repeatedTask id="task3" resetModel="false" range="current"
    xmlns:s='http://www.sbml.org/sbml/level3/version1/core'>
```

```
  <listOfRanges>
    <vectorRange id="current">
        <value> 1 </value>
        <value> 4 </value>
        <value> 10 </value>
    </vectorRange>
  </listOfRanges>
  <listOfChanges>
     <setValue target="/s:sbml/s:model/s:listOfParameters/s:parameter[@id='w']" modelReference="model1">
       <listOfVariables>
         <variable id="val" name="current range value" target="#current" />
       </listOfVariables>
       <math xmlns="http://www.w3.org/1998/Math/MathML">
         <ci> val </ci>
       </math>
     </setValue>
  </listOfChanges>
  <listOfSubTasks>
    <subTask task="task1" />
  </listOfSubTasks>
</repeatedTask>
```

Listing 2.49: *The `repeatedTask` element*

range

The RepeatedTask has a required attribute **range** of type SIdRef. It specifies which **range** defined in the **listOfRanges** this repeated task iterates over. Listing 2.49 shows an example of a repeatedTask iterating over a single range comprising the values: **1**, **4** and **10**. If there are multiple ranges in the **listOfRanges**, then only the master **range** identified by this attribute determines how many iterations there will be in the repeatedTask. All other ranges must allow for at least as many iterations as the master range, and will be moved through in lock-step; their values can be used in setValue constructs.

resetModel

The repeatedTask has a required attribute **resetModel** of type **boolean**. It specifies whether the model or models should be reset to the initial state before processing an iteration of the defined subTasks. Here initial state refers to the state of the model or models as given in the **listOfModels**.

In the example in Listing 2.49 the repeated task is not to be reset, so a change is made, **task1** is carried out, another change is made, then **task1** continues from there, another change is applied, and **task1** is carried out a last time.

When the **resetModel** attribute is set to "**true**", the individual repeats may be executed in parallel.

concatenate

The RepeatedTask has an optional attribute **concatenate** of type **boolean**. It specifies whether the output of the subtasks should be appended to the results of the previous outputs ("**true**"), or whether it should be added in parallel, as a new dimension of the output ("**false**").

If this attribute is not defined, the interpreter may either concatenate or parallelize the results. As this makes the results less comparable between interpreters, it is strongly suggested that this attribute be defined.

listOfChanges

The optional **listOfChanges** element contains one or many SetValue elements. These elements allow the modification of values in the model or models prior to the next iteration of the RepeatedTask.

listOfSubTasks

The required **listOfSubTasks** contains one or more subTasks that specify which Tasks are performed in every iteration of the RepeatedTask. All subTasks have to be carried out sequentially, each continuing from the current model state or states (i.e. as at the end of the previous subTask). If the **concatentate** attribute is set "**true**", the results are concatenated (thus appearing identical to a single complex simulation), and if set "**false**", the results are added to a matrix with the addtitional dimension of the repeated task. The order in which to run multiple subTasks must be specified using the **order** attribute on the subTask. Subtasks can also be executed in parallel when they do not share any state. Interpreters can determine this from the descriptions of the subtasks.

```
<listOfSubTasks>
    <subTask task="task1" order="2"/>
    <subTask task="task2" order="1"/>
</listOfSubTasks>
```

Listing 2.50: *The* `subTask` *element. In this example the task* `task2` *must be executed before* `task1`*.*

listOfRanges

The `listOfRanges` defines one or more ranges used in the repeatedTask.

2.2.9 Task components

2.2.9.1 SubTask

A SubTask (Figure 2.13 on page 43) defines the subtask which is executed in every iteration of the enclosing RepeatedTask. The SubTask has a required attribute `task` that references the `id` of another *AbstractTask*. The order in which to run multiple subTasks must be specified via the required attribute `order`. It may contain a child ListOfChanges to specify any changes that apply at the beginning of the particular subtask, in contrast to the ListOfChanges child of the RepeatedTask itself, which specifies changes that apply before any of the subtasks.

task

The required element `task` of data type SIdRef specifies the *AbstractTask* executed by this SubTask.

order

The required attribute `order` of data type `integer` specifies the order in which to run multiple subTasks in the `listOfSubTasks`. To specify that one subTask should be executed before another its `order` attribute must have a lower number (e.g. in Listing 2.50).

Leaving the `order` undefined for a SubTask implies that the SubTask may be executed before or after any other SubTask. Giving the same `order` to multiple SubTask elements is an explicit statement that each SubTask in the group may be executed before or after any other SubTask in the group. It is recommended that users always explicitly set the `order` attribute for this reason.

Any `order` value does not imply whether the SubTask may be executed in parallel with other SubTask elements. Interpreters who wish to parallelize subtasks should operate from the assumption that in the default case, each SubTask would be executed in some order, and adjust accordingly.

listOfChanges

The SetValue children of the ListOfChanges of this SubTask define changes to apply to the model state or states before this SubTask is carried out. This allows model changes between individual SubTask elements, perhaps based on the changed state of the model itself. The set of all SetValue children of the first SubTask are applied after the set of SetValue children of the RepeatedTask itself.

2.2.9.2 SetValue

The SetValue class (Figure 2.13 on page 43) allows the modification of a Model. Each SetValue in the ListOfChanges child of the RepeatedTask fires before each repeat, and each SetValue in the ListOfChanges child of a SubTask fires before the execution of that SubTask.

SetValue inherits from the ComputeChange class, which allows it to compute arbitrary expressions involving a number of variables and parameters. SetValue inherits the standard attributes and children from *SEDBase*, a required `target` and optional `symbol` from ComputeChange, and adds a mandatory `modelReference` attribute and the optional attribute `range`.

The value to be changed is identified via the combination of the attributes `modelReference`, `symbol`, and `target`, in order to select an implicit or explicit variable within the referenced model.

The Math contains the expression computing the value by referring to optional parameters, variables or ranges. Again as for functionalRange, variable references retrieve always the current value of the model variable or range at the current iteration of the enclosing repeatedTask.

```
<listOfChanges>
    <setValue target="/s:sbml/s:model/s:listOfParameters/s:parameter[@id='w']"
        range="current" modelReference="model1">
        <math xmlns="http://www.w3.org/1998/Math/MathML">
            <ci> current </ci>
        </math>
    </setValue>
</listOfChanges>
```

Listing 2.51: *A* `setValue` *element setting* `w` *to the values of the range with id* `current`.

modelReference

The required element `modelReference` of data type SIdRef specifies the Model this SetValue is to modify. Each SetValue elements in the same RepeatedTask may potentially reference a different Model.

range

The optional attribute `range` of data type SIdRef, if defined, must reference a Range child of the parent RepeatedTask.

As in functionalRange, the attribute `range` may be used as a shorthand to specify the `id` of another Range. The current value of the referenced range may then be used within the Math defining this FunctionalRange, just as if that range had been referenced using a variable element, except that the `id` of the range is used directly. In other words, whenever the expression contains a `ci` element that contains the value specified in the `range` attribute, the value of the referenced range is to be inserted.

2.2.9.3 Range

The Range class is the abstract base class for the different types of ranges, i.e. UniformRange, VectorRange, FunctionalRange, and DataRange (Figure 2.14).

The Range is the iterative element of the repeated simulation experiment. Each Range defines a collection of values to iterate over. Its `id` may be used as the `target` of a Variable within the RepeatedTask by pre-pending a '#' (i.e. "`#rangeId`"). It is used in that context to mean the value of the range for the current iteration of the RepeatedTask.

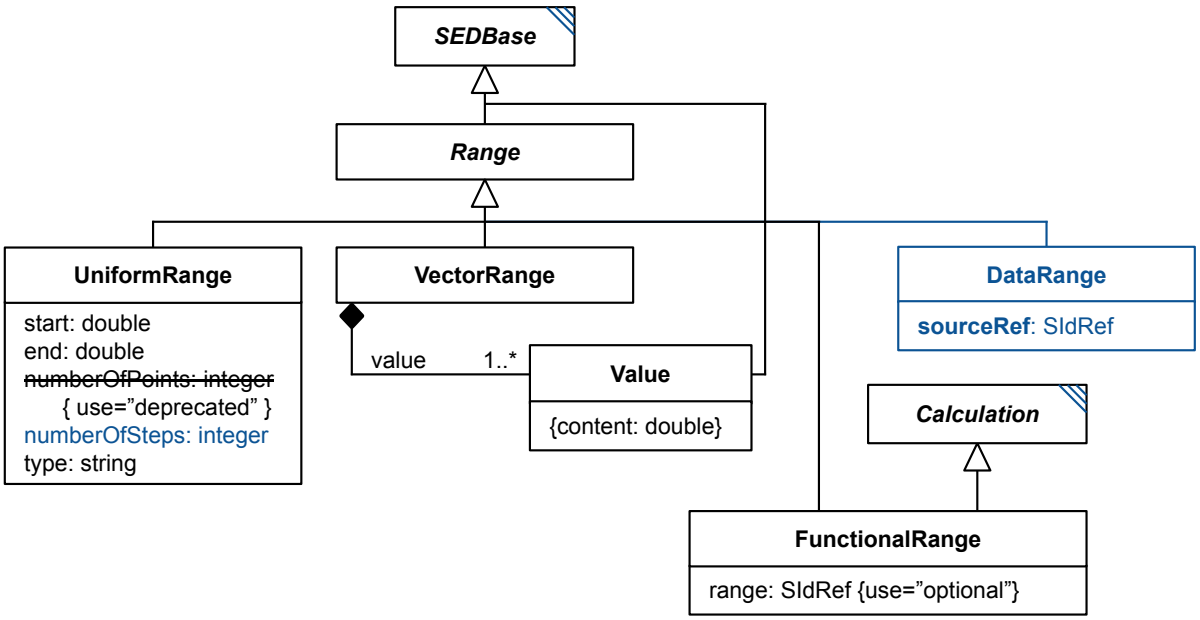


Figure 2.14: *The SED-ML Range class*

2.2.9.3.1 UniformRange

The UniformRange (Figure 2.14 on the preceding page) allows the definition of a Range with uniformly spaced values. In this it is quite similar to what is used in the UniformTimeCourse. The UniformRange is defined via three mandatory attributes: `start`, the start value; `end`, the end value and `numberOfSteps` which defines defines the number of points in addition to the start value (the actual number of points in the range will be `numberOfSteps+1`). A fourth attribute `type` that can take the values `linear` or `log` determines whether to draw the values logarithmically (with a base of 10) or linearly.

The `numberOfSteps` attribute used to be called `numberOfPoints`, but was changed to better reflect the meaning of the attribute. The old attribute name is allowed, but is deprecated. The SED-ML meaning of both attributes is the same, and has not changed.

For example, the following UniformRange will produce `101` values uniformly spaced on the interval $[0, 10]$ in ascending order.

```
<uniformRange id="current" start="0.0" end="10.0" numberOfSteps="100" type="linear" />
```

Listing 2.52: *The `UniformRange` element*

The following logarithmic example generates the three values `1`, `10` and `100`.

```
<uniformRange id="current" start="1.0" end="100.0" numberOfSteps="2" type="log" />
```

Listing 2.53: *The `UniformRange` element with a logarithmic range.*

2.2.9.3.2 VectorRange

The VectorRange (Figure 2.14 on the previous page) describes an ordered collection of real values, listing them explicitly within child `value` elements.

For example, the range below iterates over the values 1, 4 and 10 in that order.

```
<vectorRange id="current">
    <value> 1 </value>
    <value> 4 </value>
    <value> 10 </value>
</vectorRange>
```

Listing 2.54: *The `VectorRange` element*

2.2.9.3.3 Value

The Value (Figure 2.14 on the preceding page) describes a single value, e.g., the Values in a VectorRange.

2.2.9.3.4 FunctionalRange

The FunctionalRange (Figure 2.14 on the previous page) constructs a range through calculations that determine the next value based on the value(s) of other range(s) or model variables. In this it is similar to the ComputeChange element, and shares some of the same child elements (but is not a subclass of ComputeChange). It consists of an optional attribute `range`, two optional elements ListOfVariables and ListOfParameters, and a required element Math.

The optional attribute `range` of type SIdRef may be used as a shorthand to specify the `id` of another Range. The current value of the referenced range may then be used within the function defining this FunctionalRange, just as if that range had been referenced using a variable element, except that the `id` of the range is used directly. In other words, whenever the expression contains a `ci` element that contains the value specified in the `range` attribute, the value of the referenced range is to be inserted.

The value of any Variable child of a FunctionalRange should be calculated before the first simulation begins, and will not be affected by any SubTask in the RepeatedTask.

For example:

```
<functionalRange id="current" range="index"
    xmlns:s='http://www.sbml.org/sbml/level3/version1/core'>
    <listOfVariables>
        <variable id="w" name="current parameter value" modelReference="model2"
            target="/s:sbml/s:model/s:listOfParameters/s:parameter[@id='w']" />
    </listOfVariables>
    <math xmlns="http://www.w3.org/1998/Math/MathML">
      <apply>
        <times/>
```

```
            <ci> w </ci>
            <ci> index </ci>
        </apply>
    </math>
</functionalRange>
```

Listing 2.55: *An example of a* `functionalRange` *where a parameter* `w` *of model* `model2` *is multiplied by* `index` *each time it is called.*

Here is another example, this time using the values in a piecewise expression:

```
<uniformRange id="index" start="0" end="10" numberOfSteps="100" />
<functionalRange id="current" range="index">
    <math xmlns="http://www.w3.org/1998/Math/MathML">
        <piecewise>
            <piece>
                <cn> 8 </cn>
                <apply>
                    <lt />
                    <ci> index </ci>
                    <cn> 1 </cn>
                </apply>
            </piece>
            <piece>
                <cn> 0.1 </cn>
                <apply>
                    <and />
                    <apply>
                        <geq />
                        <ci> index </ci>
                        <cn> 4 </cn>
                    </apply>
                    <apply>
                        <lt />
                        <ci> index </ci>
                        <cn> 6 </cn>
                    </apply>
                </apply>
            </piece>
            <otherwise>
                <cn> 8 </cn>
            </otherwise>
        </piecewise>
    </math>
</functionalRange>
```

Listing 2.56: *A* `functionalRange` *element that returns* `8` *if* `index` *is smaller than* `1`*,* `0.1` *if* `index` *is between* `4` *and* `6`*, and* `8` *otherwise.*

2.2.9.3.5 DataRange

The DataRange (Figure 2.14 on page 46) constructs a range by reference to external data. It inherits from Range, and adds the required atribute `sourceRef` of type SIdRef. The `sourceRef` must point to a DataDescription with a single dimension, whose values are used as the values of the range.

For example:

```
    <dataRange id="current" sourceRef="dosage_times" />
```

Listing 2.57: *An example of a* `dataRange` *which tracks a variable from an external file.*

2.2.10 ParameterEstimationTask

The ParameterEstimationTask inherits from *AbstractTask*, and defines a parameter estimation experiment: given a set of constraints, what are the optimal parameter values for a particular model? A ParameterEstimationTask calculates optimal AdjustableParameter values for every FitExperiment child of the task. It provides access to the optimal values for the estimated parameters, and will also change the model state such that the estimated parameters will have those values. If used in a ParameterEstimationResultsPlot, WaterfallPlot, or ParameterEstimationReport, various other pieces of information will be output, as defined in those classes.

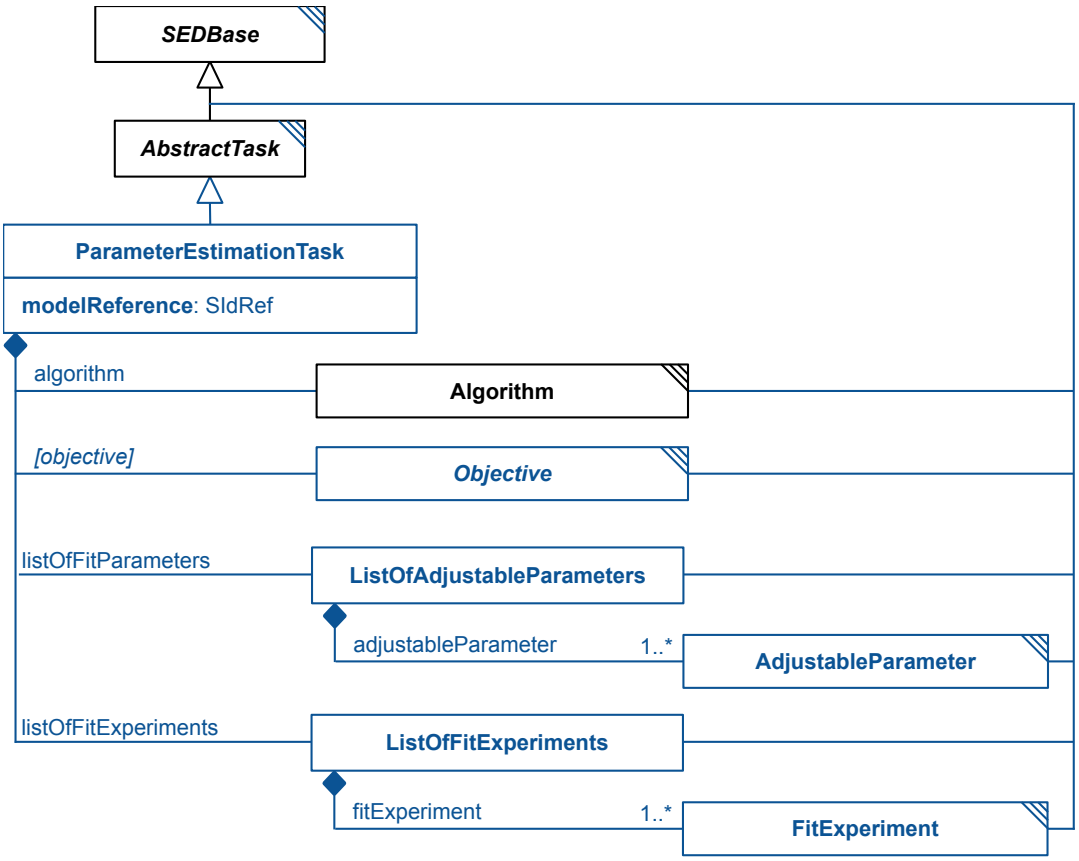


Figure 2.15: *The SED-ML ParameterEstimationTask class*

A ParameterEstimationTask has four required children: an Algorithm, an Objective, at least one AdjustableParameter in a ListOfAdjustableParameters, and at least one FitExperiment in a ListOfFitExperiments. It also has a required `modelReference` attribute of type SIdRef.

`modelReference`

The `modelReference` attribute of data type SIdRef is used to reference a Model in the same SED-ML Document. This model is the one to be used for parameter fitting.

`algorithm`

The `algorithm` child of a ParameterEstimationTask defines the Algorithm to be used for parameter fitting. Any algorithm parameters must be included as child AlgorithmParameter elements. The Algorithm class is defined in section 2.2.7.1. One particular algorithm parameter is KiSAO:0000498 ("`number of runs`"), which can be used to set up a repeated ParameterEstimationTask.

`objective`

The `objective` child of the ParameterEstimationTask defines the objective function to be minimized during the parameter estimation. In Level 1 Version 4, there is only a single Objective option: the LeastSquareObjectiveFunction (called "`leastSquareObjectiveFunction`" instead of "`objective`"). In future versions of SED-ML, other objectives may be introduced that cover additional use cases.

`adjustableParameters`

The required ListOfAdjustableParameters child of a ParameterEstimationTask must contain at least one AdjustableParameter. Each AdjustableParameter defines a single parameter to be estimated.

fitExperiments

The required ListOfFitExperiments child of a ParameterEstimationTask must contain at least one FitExperiment. Each FitExperiment defines a mapping between experimental data and observables from the model as well as any initial conditions that need to be applied to the model.

2.2.10.1 Objective

The Objective inherits from *SEDBase*, and does not introduce any new attributes or children. It is an abstract base class intended to (eventually) organize the different objective function possibilities for parameter estimation tasks.

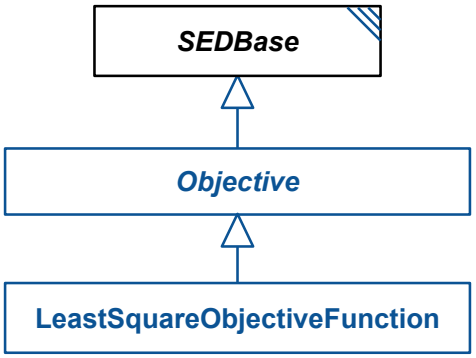


Figure 2.16: *The SED-ML Objective and LeastSquareObjectiveFunction classes*

2.2.10.2 LeastSquareObjectiveFunction

The LeastSquareObjectiveFunction inherits from Objective, and does not introduce any new attributes or children. Its use indicates that the ParameterEstimationTask is to minimize the least squares of the residuals of the fit experiments to estimate the parameters.

The particular method used to determine the least squares can be defined through the use of AlgorithmParameters on the Algorithm of the ParameterEstimationTask.

2.2.10.3 AdjustableParameter

The AdjustableParameter inherits from *SEDBase*, and adds a required attribute `target` of type Target, a required child Bounds, and an optional child ListOfExperimentRefs with zero or more ExperimentRef elements, and an optional attribute `initalValue` of type `double`.

The `target` of an AdjustableParameter must point to an adjustable element of the Model referenced by the parent ParameterEstimationTask. This element is one of the elements whose value can be changed by the task in order to optimize the fit experiments.

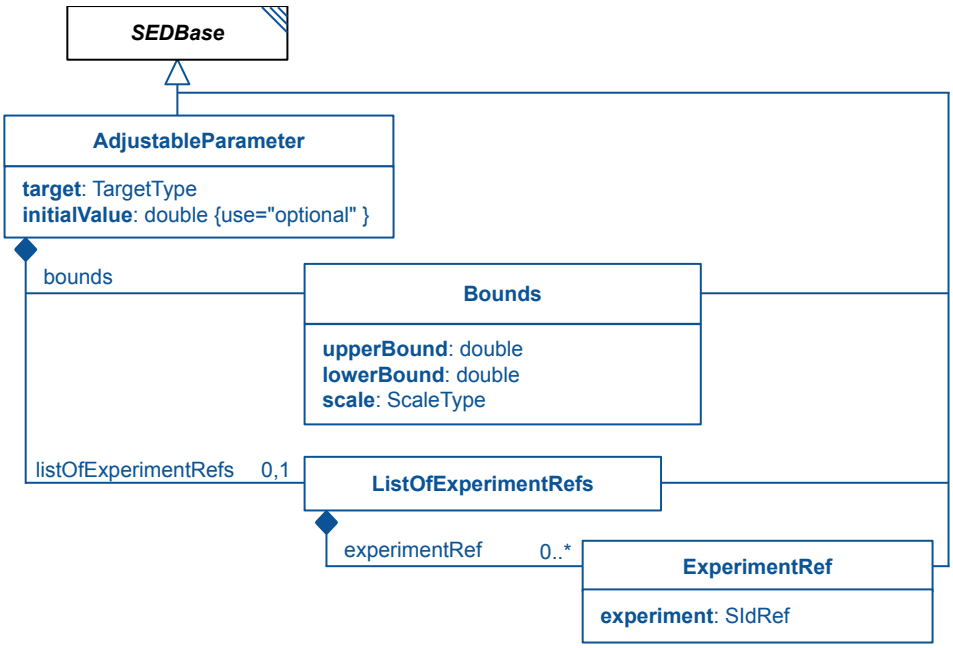


Figure 2.17: *The SED-ML AdjustableParameter, Bounds, ListOfExperimentRefs, and ExperimentRef classes*

The `initialValue`, if defined, is the value that the AdjustableParameter is to be set at the beginning of the ParameterEstimationTask. Otherwise, the value of the AdjustableParameter at the model's current state is used, unless that value is outside the `upperBound` and `lowerBound`, in which case any value between or including those values is allowed.

The required Bounds child of the AdjustableParameter defines the allowed range of values for the targeted element.

If an AdjustableParameter has no ExperimentRef children, it is adjusted for every FitExperiment. If an AdjustableParameter has one or more ExperimentRef children, it is only adjusted in those experiments; in all other experiments it retains its initial value (the value of the optional `initialValue` of the AdjustableParameter, if defined, or the value it obtained from the model, if not).

2.2.10.4 Bounds

A Bounds object defines the allowable range of values for an AdjustableParameter. A Bounds inherits from *SEDBase*, and adds three required attributes (`upperBound` and `lowerBound`, both of type `double`, and `scale`, of type ScaleType), and one optional attribute (`initialValue`, of type `double`).

The `lowerBound` defines the lowest value the parent AdjustableParameter may take during the ParameterEstimationTask, and `upperBound` the highest, with both values being legal outputs of the system. The `lowerBound` must be less than or equal to the `upperBound`, though if it is equal, there is nothing to optimize, since only that single value is allowed.

The `scale`, of type ScaleType, defines the structure of the search space between the upper and lower bounds. The allowed values are:

- lin: The bounds enclose a linear search space
- log: The bounds enclose a search space scaled by its natural log.
- log10: The bounds enclose a search space scaled by its log base-10 values.

2.2.10.5 ExperimentRef

An ExperimentRef inherits from *SEDBase* and adds the single required attribute `experiment`, of type SIdRef, which must point to a FitExperiment in the same ParameterEstimationTask.

2.2.10.6 FitExperiment

The FitExperiment inherits from *SEDBase*, and adds the required attribute `type` of type ExperimentType, a required Algorithm child, and a required ListOfFitMappings child which must in turn contain one or more FitMapping children.

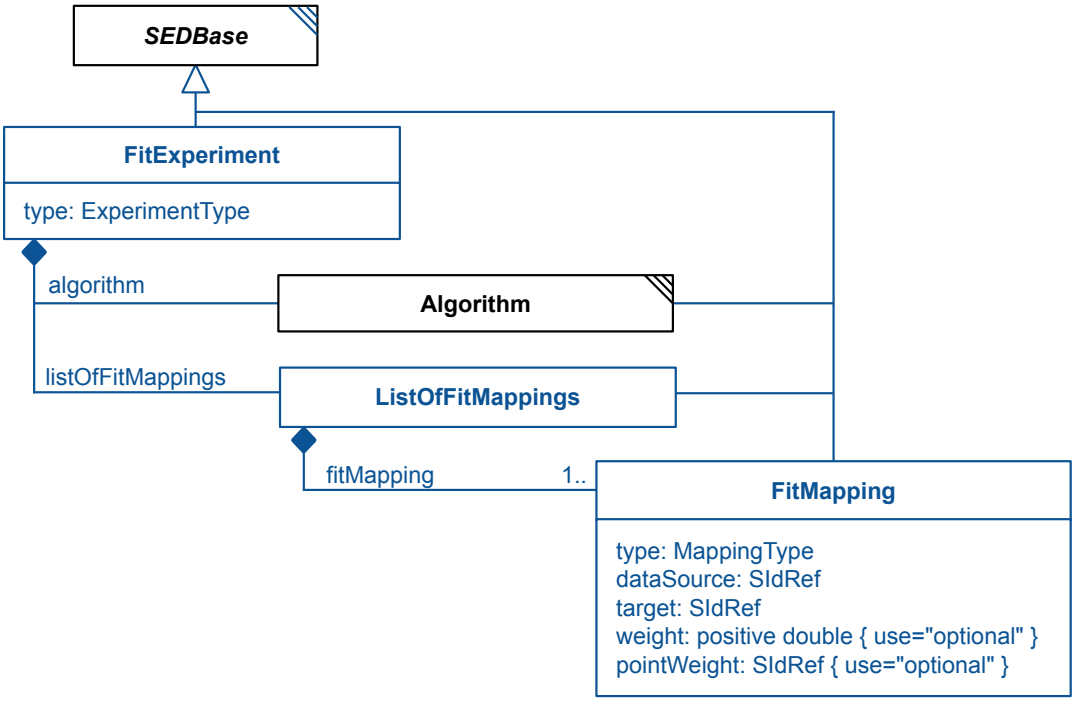


Figure 2.18: *The SED-ML FitExperiment, ListOfFitMappings, and FitMappings classes*

A FitExperiment describes an experiment for which there are known experimental conditions, and expected experimental output. The differences between the expected experimental output and the simulated output is used by the Objective to determine the optimal values to use for the AdjustableParameters.

The `type` attribute indicates whether the experiment is a time-course experiment ("`timeCourse`"), or a steady-state experiment ("`steadyState`").

The Algorithm of a FitExperiment describes the algorithm (time course or steady state), and can also be used to define any algorithm parameters of the experiment.

The FitMapping children are used to map externallly-set experimental conditions, observables, and time (in time course experiments) to the model.

2.2.10.7 FitMapping

A FitMapping inherits from *SEDBase*, and adds three required attributes `dataSouce` and `target`, both of type SIdRef, `type` of type MappingType, and two optional attributes `weight` of type `positive double`, and `pointWeight` of type SIdRef. A FitMapping is used to correlate elements of a model simulation with data for that simulation, whether time, inputs (experimental conditions) or outputs (observables).

The `type` is of type MappingType, and may take one of the following three values:

- time: Used only in time course simulations, a "`time`" FitMapping maps the time points of the observables to the time points of the simulated output. This also serves to declare what time points must be output by the simulation: unlike a UniformTimeCourse, a FitExperiment time course must at least output the time points mapped here, so that the observables may be directly compared to each other. (Note that here as in elsewhere in SED-ML, 'time' is used as a common label of what is more formally an 'independent variable' for some simulators.)

- experimentalCondition: Any FitMapping of type "`experimentalCondition`" maps a single value to a model element. The model element must be set to the value as part of the model's initial condition.
- observable: An "`observable`" FitMapping maps the output of the simulation to a set of data. These data are used by the Objective to calculate the goodness of fit.

The `dataSource` is an SIdRef to a DataSource in the SED-ML Document. This is a pointer to the expected values of the "`observable`" FitMappings, to the time values of "`time`" FitMappings, or the target initial conditions of "`experimentalConditions`" FitMappings.

The `target` is an SIdRef to a DataGenerator in the SED-ML Document. Any Variable in the referenced DataGenerator must contain a `modelRef` to a Model referenced in an AdjustableParameter that applies to this FitExperiment.

The `weight` or `pointWeight` attributes are used for "`observable`" FitMappings to weight the contribution of that particular observable to the Objective function. For every FitMapping of type "`observable`", either `weight` or `pointWeight` must be defined. For FitMappings with `type` of "`experimentalCondition`" or "`time`", neither attribute may be defined.

If `weight` is defined, that value is used as the weight for all values in the series. If `pointWeight` is defined instead, it must be an SIdRef to a DataGenerator or DataSource with the same dimensionality as the `dataSource`. Each value in the referenced `pointWeight` is then used as the weight of the comparison of the corresponding `dataSource` and `target`.

No weight may be negative or infinite. A `NaN` may be used in a `pointWeight` vector for missing data. Commonly, all weights will have a value between zero and one.

2.2.11 `DataGenerator`

The DataGenerator class prepares the raw simulation results for later output (Figure 2.19). It encodes the post-processing to be applied to the simulation data. The post-processing steps could be anything, from simple normalisations of data to mathematical calculations. It inherits from Calculation, changing the `id` attribute to be required instead of optional.

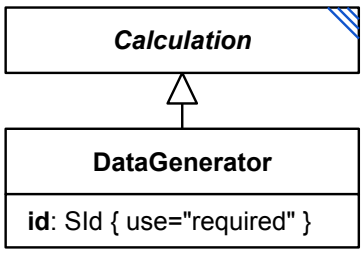


Figure 2.19: *The SED-ML DataGenerator class.*

Variable objects in DataGenerator elements may be scalar or multidimensional. If the Math of a DataGenerator attempts to apply functions to multi-dimensional elements, those functions always apply to the individual scalar values of that data. If multiple multidimensional Variable ids are used in the same Math, those ids must each have the same dimensions as each other. No vector or matrix algebra functions such as dot products or cross products are allowed.

A Variable in a DataGenerator may use the id of a DataSource as its `target`, pre-pended by a '`#`', i.e. "`#dataSourceId`". This Variable may be multidimensional, and if so, must follow the above strictures.

When multidimensional data is output to a Report, information about the dimensions should be stored in the output format chosen for the report, such as CSV or HDF5.

It is left up to interpreters how to store or output 'ragged' matrices, where the data in some dimensions might not have the same lengths as each other. One practice is to leave the data in this uneven state; another option is to fill out the 'missing' data with NaNs. The only requirement is that mathematical operations should not be affected by this choice. For example, the 'mean' of a vector should be the same

whether or not it was extended with NaNs.

Output from multiple models

It is possible to create a RepeatedTask that affects multiple models through different SubTask children. In this situation, individual Variable children of a DataGenerator must define both a `taskReference` to the RepeatedTask and `modelReference` so it's clear which specific element is being tracked. However, the question then becomes: what value does that Variable take while the RepeatedTask is performing a Simulation in a SubTask that does not involve that Model? In this situation, the Variable is assumed to retain its last known value for the duration of the Simulation (which will be its initialized value if no Simulation has been performed yet that affects that Variable).

If those unchanging dimensions are not relevant to the desired output, it is possible to reduce the dimensionality by adding RemainingDimension children, and only adding the ids of the Task elements that involve the Model the Variable points to.

Listing 2.58 shows the use of the `dataGenerator` element. In the example the `listOfDataGenerator` contains two `dataGenerator` elements. The first one, `d1`, refers to the task definition `task1` (which itself refers to a particular model), and from the corresponding model it reuses the symbol `time`. The second one, `d2`, references a particular species defined in the same model (and referred to via the `taskReference="task1"`). The model species with `id PX` is reused for the data generator `d2` without further post-processing.

```
<listOfDataGenerators>
    <dataGenerator id="d1" name="time">
        <listOfVariables>
            <variable id="time" taskReference="task1" symbol="KISAO:0000832" />
        </listOfVariables >
        <listOfParameters />
        <math xmlns="http://www.w3.org/1998/Math/MathML">
            <ci> time </ci>
        </math>
    </dataGenerator>
    <dataGenerator id="d2" name="LaCI repressor">
        <listOfVariables>
            <variable id="v1" taskReference="task1"
                target="/sbml:sbml/sbml:model/sbml:listOfSpecies/sbml:species[@id='PX']" />
        </listOfVariables>
        <math xmlns="http://www.w3.org/1998/Math/MathML">
            <math:ci>v1</math:ci>
        </math>
    </dataGenerator>
</listOfDataGenerators>
```

Listing 2.58: *Definition of two* `dataGenerator` *elements,* time *and* LaCI repressor

2.2.12 Output

The abstract *Output* class describes how the results of a simulation are presented (Figure 2.20). The available output classes are *Plot*, Report, ParameterEstimationReport, and Figure. The data used in an *Output* is provided via the DataGenerator class.

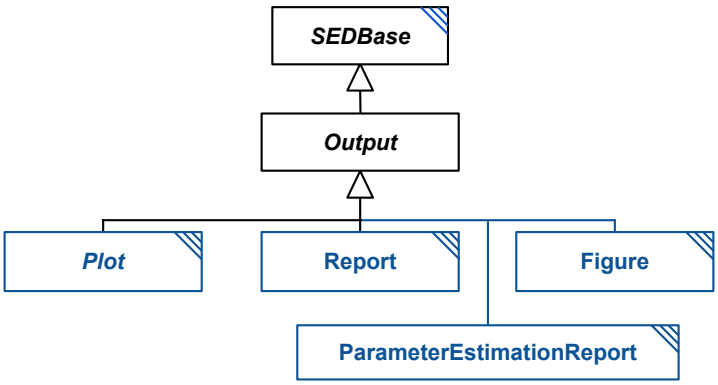


Figure 2.20: *The definition of the SED-ML* Output *class. The subclasses are defined below.*

The *Output* class inherits the `id` and `name` attributes from *SEDBase*, as well as the optional `annotation` and `notes` chidren. When producing a printed table or figure, users may want to use the `name` as the title, and the `notes` as the legend.

The output of a SED-ML file may be used to compare simulation executions from the same tool or from different tools. As such, interpreters may choose to focus on the output of a SED-ML file, and execute only the tasks necessary to produce this output. Repeated executions of the same SED-ML should always produce comparable output. When a stochastic run is given a seed, interpreters should be aware that users may expect to get identical results from repeated runs on the same architecture, including when tasks are run in parallel.

2.2.12.1 Plot

The *Plot* is an abstract base class for two- and three-dimensional plot outputs. It defines the size and axes of a plot, as well as whether or not a legend should be displayed.

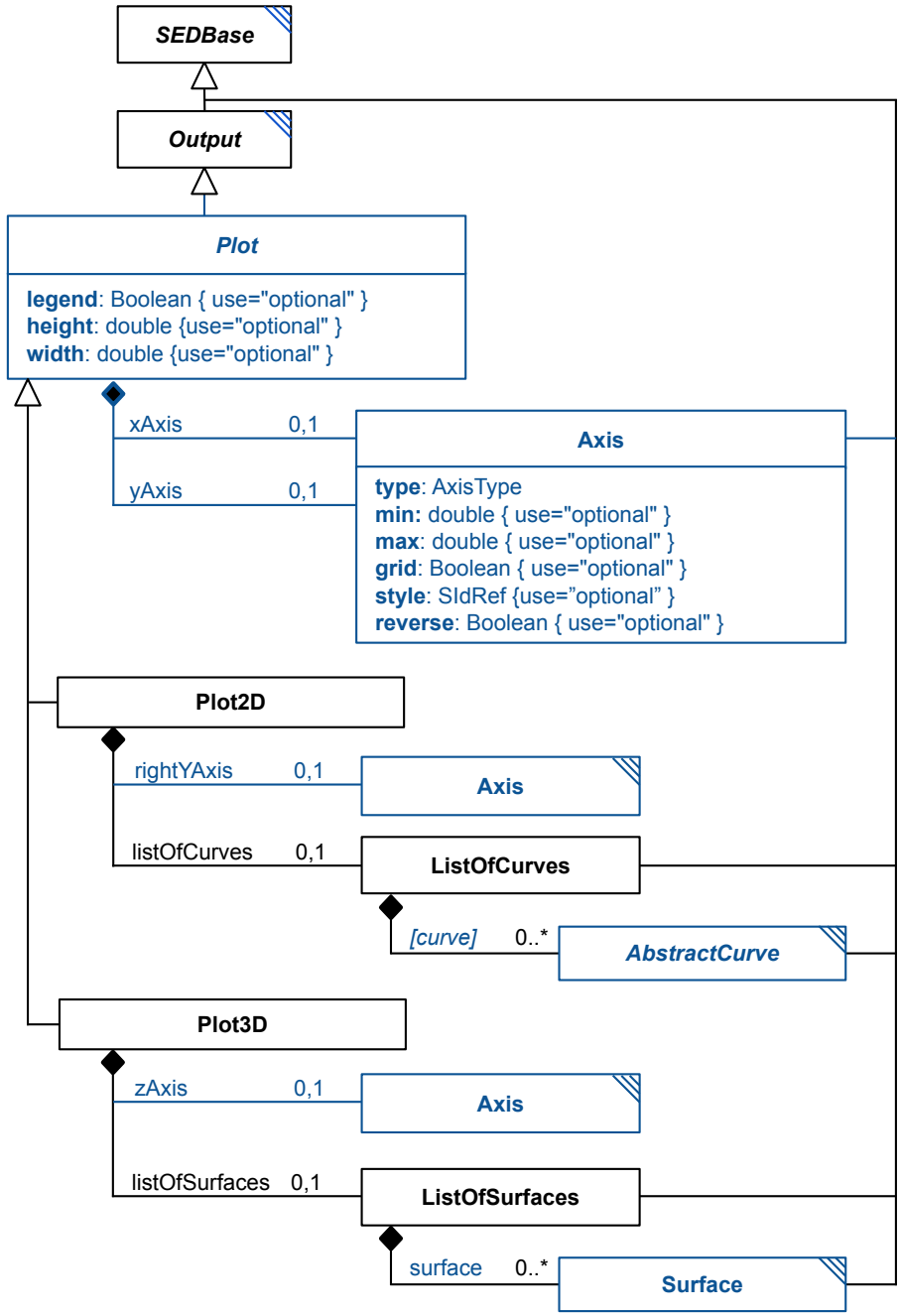


Figure 2.21: *The definition of the SED-ML* Plot, *Plot2D*, *Plot3D*, *Axis*, *ListOfCurves*, *and ListOfSurfaces classes. The* AbstractCurve *and Surface classes are defined below.*

The *Plot* class inherits the attributes and children from *SEDBase*, and adds three optional attributes: `legend`, of type Boolean, `height` of type `double`, and `width` of type `double`. It also defines two optional Axis children, an `xAxis` and a `yAxis`.

`legend`

The `legend` attribute defines whether a legend should be displayed ("`true`") or not ("`false`"). The position and styling of the legend is unspecified. If the attribute is not defined, it is up to the tool whether to display the legend or not, and does not mean that the attribute has a default value of "`false`".

height and width

The **height** and **width** elements, both of type **double**, may be used to define the size of the plot, in pixels (or the equivalent in the application's display environment). If either is not defined, the application may choose what size to display the plot.

xAxis and yAxis

The optional **xAxis** and **yAxis** children, each of type Axis, define the x and y axes (respectively) by which the Curve or Surface children are to be interpreted. If either child is omitted, that axis is undefined, and it is up to the tool whether and how to display any necessary axes, and to decide whether that axis should be linear or logarithmic.

2.2.12.2 Plot2D

The Plot2D class is used for two dimensional plot outputs. In addition to the features it inherits from *Plot*, it may contain any number of Curve definitions in the **listOfCurves**, as well as an optional child **rightYAxis**.

rightYAxis

If a Plot2D contains a child **rightYAxis**, this defines a new Y axis, displayed on the right, which any of the Curve children may be scaled to. Each Curve contains the information about which axis it is to be scaled to. The **rightYAxis** is to be displayed on the right of the plot, and may differ significantly in scale and range from the **yAxis**. A Plot2D with no **yAxis** may not have a **rightYAxis**.

listOfCurves

Each child *AbstractCurve* of a Plot2D represents a line to be displayed on the plot. The *AbstractCurve* itself will define what data it contains, and how it should be displayed.

2.2.12.3 Plot3D

The Plot3D class is used for three dimensional plot outputs (Figure 2.20 on page 54). In addition to the elements it inherits from *Plot*, the Plot3D may contain a number of child Surface definitions in a **listOfSurfaces**, and may additionally define a **zAxis** child, of type Axis.

listOfSurfaces

Each child Surface of a Plot3D represents a surface to be displayed on the plot. The Surface itself will define what data it contains, and how it should be displayed.

zAxis

When a Plot3D contains a child **zAxis**, that Axis defines the characteristics of the z axis. If no **zAxis** is provided, those characteristics are undefined, and the tool may choose how and whether to display that axis, as well as what type it is (linear or logarithmic).

2.2.12.4 Axis

The Axis class is used to define whether an axis for a given *Plot* is linear or logarithmic, and how to display it. It inherits the attributes and children from *SEDBase*, and adds the required attribute **type** of type AxisType (either 'linear' or 'log10'), as well as the optional attributes **min** and **max**, both of type **double**, **grid** of type **boolean**, and **style** of type SIdRef.

name and id

The Axis class inherits the **name** and **id** attributes from *SEDBase*. The **name**, if present, should be used as the label for the axis. If it is not present, the **id** may be used.

type

The **type** value of "**linear**" means the axis should be scaled linearly, while a value of "**log10**" indicates it should have a log10 scale. Other scalings are not possible in this version of SED-ML. This attribute

replaces the "log" attributes that used to be present on Curve objects in previous versions of SED-ML.

min and max

The **min** and **max** values indicate the minimum and maximum values for the axis. Data points outside of this range should not be shown on the parent *Plot*. Either value may be set or not, and if not set, a value must be chosen for display that is less than (for **min**) or greater than (for **max**) the most extreme value along that axis for any Curve or Surface in that *Plot*. Do note that in some cases, a given Curve may not have any data points associated with one Y Axis, as its data may be associated with the alternative Y Axis.

Note that **min** and **max** will have the same units as the data plotted along it, regardless of the value of the **type**. An axis with a **min** value of "1" and a **max** value of "100" will either be plotted with '50' halfway between those two extremes if the **type** is "linear", or with '10' halfway between those two extremes if the **type** is "log10".

grid

The **grid** attribute indicates whether grid lines should ("true") or should not ("false") be displayed in the *Plot* for tick marks along that axis. If the **grid** attribute is not defined, this means it is up to the tool whether or not to display the grid lines; it does not have a default value of "false".

style

The **style** attribute, if present, must be an SIdRef to a Style in the same SED-ML Document. If defined, it indicates how to display the axis itself, for features such as color and/or line thickness for the axis and its labels. If not present, any style may be used. Note that it is possible to suppress an axis from being displayed entirely if the corresponding Style of an Axis has a **line** with a **style** of "none".

reverse

The **reverse** attribute indicates whether the axis should be plotted from the minimum value to the maximum value ("false") or from the maximum value to the minimum value ("true") (i.e. left to right or bottom to top, depending on the axis). If not defined, either is technically possible, but should be assumed to go from minimum to maximum.

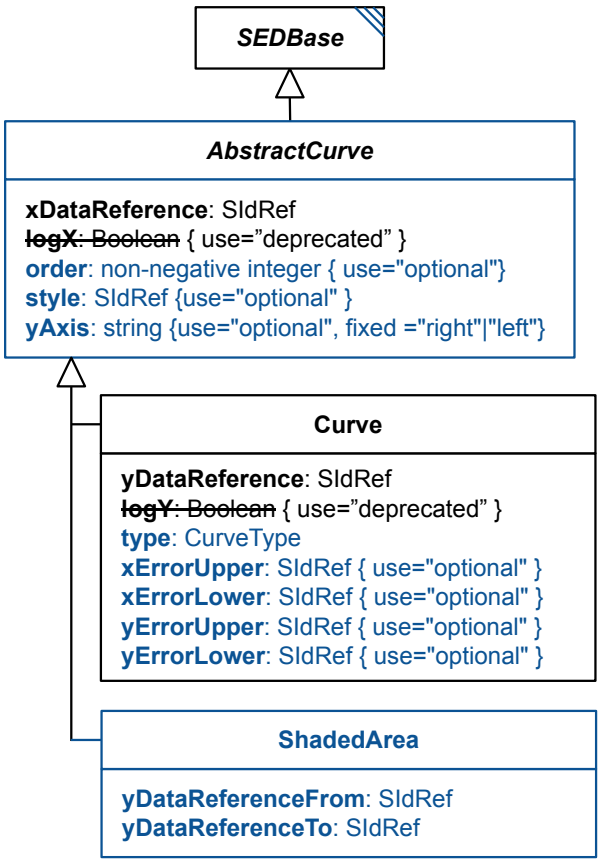


Figure 2.22: *The definition of the SED-ML* AbstractCurve, *Curve, and ShadedArea classes.*

2.2.12.5 `AbstractCurve`

An *AbstractCurve* is a two-dimensional *Output* component representing a (processed) simulation result (Figure 2.22). Zero or more *AbstractCurve* instances define a Plot2D (Figure 2.20 on page 54). The *AbstractCurve* class defines the attributes common to the Curve and ShadedArea child classes. In addition to the optional `id` and `name` attributes it inherits from *SEDBase*, it also defines the required attribute `xDataReference`, and the optional attributes `order`, `style`, and `yAxis`. It is also legal but discouraged to include an attribute `logX`.

The `name` of the *AbstractCurve* should be used to label the curve in the given Plot2D, or, if `name` is not defined, the `id` may be used. If neither are present, the `name` or `id` of the referenced `yDataReference` may be used in the case of a Curve or the `yDataReferenceFrom` and/or `yDataReferenceTo` in the case of a ShadedArea. Because of the complications this can engender, it is highly recommended to define the `name` of all *AbstractCurve* elements.

xDataReference

The `xDataReference` attribute must be an SIdRef to a DataGenerator in the same SED-ML Document. The referenced DataGenerator will contain the information for the x coordinates for the data to be plotted. If the y-coordinate data is ordinal or categorical, this attribute should point to a simple ordinal DataGenerator.

The dimensionality of the `xDataReference` must match the y data, but need not be one-dimensional. When a curve is being displayed, each one-dimensional vector within the x and y data should be displayed on the same plot. This will effectively flatten the data to the two dimensions of the plot. When being displayed as lines, each vector should be plotted separately, so that the plot is not overlaid with spurious lines from the end of one vector to the beginning of the next.

order

The order attribute is of type non-negative integer and, if present, defines the order in which this Curve must be displayed relative to other Curve elements in the same *Plot*. A Curve with a lower order will be added earlier to the displayed curves. This means that for lines, the curve with the highest order will be fully visible, while a Curve with a lower order may be hidden by a Curve with a higher order. A Curve with no order may be displayed in front or behind any other Curve. For adjacent bars, the bar with the lower order is presented to the left of any bar with a higher order. For stacked bars, the bar with the lower order is presented underneath any bar with a higher order. As with lines, any bar with no order defined may be placed in any position relative to the other bars in the Curve.

style

The style attribute is of type SIdRef and, if present, must reference a Style in the same SED-ML Document. It can be used to indicate styling information for the line, marker, and/or fill for this Curve or ShadedArea. If not present, any style may be used.

yAxis

The yAxis attribute is of type string and must be defined if the parent *Plot* defines both a yAxis and a rightYAxis. If it has the value of "left", it means that the data is to be displayed corresponding to the yAxis of the parent *Plot*, and if it has the value of "right", it means that the data is to be displayed corresponding to the rightYAxis of the parent *Plot*. If the parent *Plot* has no defined rightYAxis, this attribute must not be defined.

logX (deprecated)

The logX attribute, of type Boolean, was used in previous versions of SED-ML to indicate whether the x axis of the *Plot* should be linear or log10. This allowed mutliple Curve objects in the same *Plot* to contradict each other, and has therefore been moved to Axis. The logX attribute on Curve has therefore been deprecated, and will always be ignored.

2.2.12.6 Curve

A Curve is a two-dimensional *Output* component representing a (processed) simulation result (Figure 2.20 on page 54). Zero or more Curve instances define a Plot2D (Figure 2.20 on page 54). In addition to the attributes it inherits from *AbstractCurve* (and *SEDBase*), it also defines the required attribute yDataReference of type SIdRef. It also defines the optional attribute type of type CurveType, and the optional attributes xErrorUpper, xErrorLower, yErrorUpper, and yErrorLower, all of type SIdRef.

yDataReference

Like the xDataReference, the yDataReference must be the SId of a DataGenerator in the same SED-ML Document. The referenced DataGenerator will contain the information for the y coordinates for the data to be plotted. The dimensions of the y data should match the x data. If the y data is multi-dimensional (such as time course data over several stochastic replicates), one dimension should match the x data (time, in our example), and the other dimension should simply be replicated as separate curves on the same plot (with the same style and label).

type

The optional type attribute is of type CurveType, and determines the kind of curve being displayed. The possible values are:

- **points**: The curve is plotted as points, with the y values defined via the yDataGenerator. The x values of the points are plotted at the xDataGenerator position. Depending on the style, markers and/or a line are plotted. To display only a set of markers the Line from its Style is set to have a type of "none". Similarly, to display a line only with no markers the Marker from its Style is set to have a type of "none". (If both are set to "none", the curve will not be displayed at all!) The Fill of a Style has no meaning and, if present, will be ignored.
- **bar**: The curve is plotted as bars with the height of the bars defined via the yDataGenerator values. The middle of the bars are plotted at the xDataGenerator position. The style of the bars

is defined via the `style`, with the fill color defined in the Fill and the bar edge style in the Line. The Marker of a Style has no meaning and, if present, will be ignored.

- **barStacked**: The curve is plotted as with `bar`, but stacked instead of adjacent.
- **horizontalBar**: The curve is plotted as a bar plot, but the y axis is vertical and the x axis is horizontal.
- **horizontalBarStacked**: The curve is plotted as a stacked bar plot, but the y axis is vertical and the x axis is horizontal.

`xErrorUpper`, `xErrorLower`, `yErrorUpper`, and `yErrorLower`

The optional attributes `xErrorUpper`, `xErrorLower`, `yErrorUpper`, and `yErrorLower` may be declared to define the error in the data present in the Curve. Each attribute must, if defined, point to a DataGenerator in the same SED-ML Document. The `xErrorUpper` and `xErrorLower` must have the same dimensionality as the `xDataReference`, and the `yErrorUpper` and `yErrorLower` must have the same dimensionality as the `yDataReference`. Each set of data represents the error in that dimension, in distance from the given data point. The `xErrorUpper` refers to the error in the positive direction, and `xErrorLower` refers to the error in the negative direction. To set symmetrical errors `xErrorUpper` and `xErrorLower` should point to the same DataGenerator. The same is true for `yErrorUpper` and `yErrorLower`.

2.2.12.7 `ShadedArea`

A ShadedArea is an *AbstractCurve* that defines an area instead of a series of points. In addition to what is inherited from *AbstractCurve*, a ShadedArea defines the required attributes `yDataReferenceFrom` and `yDataReferenceTo`, both of which must be an SIdRef for a DataGenerator in the same SED-ML Document. The area between these two sets of points is then filled for display. If the `style` is defined, the Fill of that Style is used to color the fill. If both `color` and `secondColor` are defined, the first is associated with the `yDataReferenceFrom`, and the second is associated with the `yDataReferenceTo`. The Marker and Line of a Style has no meaning for a ShadedArea and, if present, will be ignored.

`yDataReferenceFrom` and `yDataReferenceTo`

The attributes `yDataReferenceFrom` and `yDataReferenceTo` are both of type SIdRef, and must reference data of the same dimensionality. The values of the two attributes may be swapped, with the only effect being the direction of the shading between them, if two fill colors are used.

2.2.12.8 `Surface`

A Surface is a parallel class to *AbstractCurve* that defines a three-dimensional surface instead of a two-dimensional curve (Figure 2.23 on the next page). In addition to the optional `id` and `name` attributes it inherits from *SEDBase*, it also defines the required attributes `xDataReference`, `yDataReference`, and `zDataReference`, all of type SIdRef. It also defines the optional attributes `style` of type SIdRef, and `type`, of type SurfaceType.

The `name` of the Surface should be used to label the surface in the given Plot3D, or, if `name` is not defined, the `id` may be used. If neither are present, the `name` or `id` of the referenced `zDataReference` may be used. In general, it is highly recommended to define the `name` of all Surface elements.

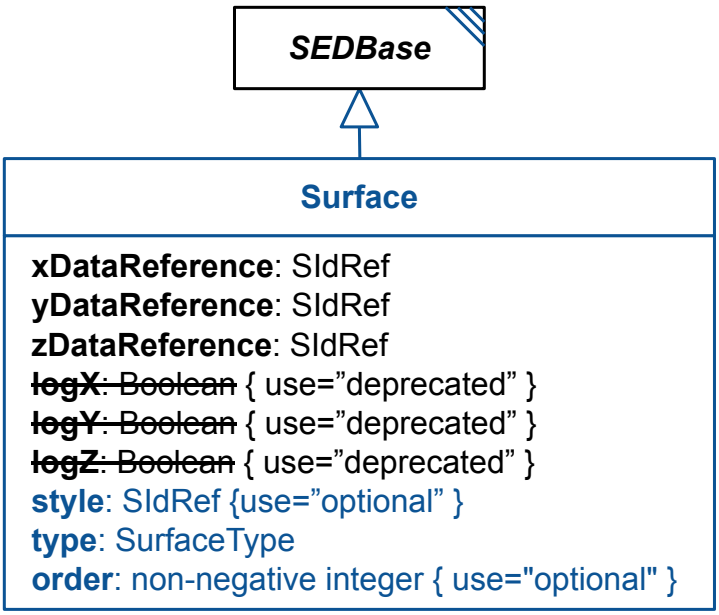


Figure 2.23: *The definition of the SED-ML Surface class.*

xDataReference, yDataReference, and zDataReference

The three data reference attributes must point to DataGenerator elements in the same SED-ML Document, which define the surface to be plotted. All three attributes are required. If the `zDataReference` is intended to be plotted by index, the `xDataReference` and `yDataReference` attributes should point to DataGenerator elements that generate those indices.

As with an *AbstractCurve*, the dimensionality of the `xDataReference`, `yDataReference` and `zDataReference` must match each other, but need not be one-dimensional. When a surface is being displayed, each one-dimensional vector within the x, y, and z data should be displayed on the same plot. This will effectively flatten the data to the three dimensions of the plot. When the data is being plotted as lines, Each vector should be plotted with its own line, so that the plot is not overlaid with spurious lines from the end of one vector to the beginning of the next.

style

The `style` attribute, if defined, must contain the `SId` of a Style object in the same SED-ML Document. This Style determines how any lines, markers, or fills on that surface should be displayed, if present for that type of Surface.

type

The `type` attribute, if present, determines the type of surface and how it should be displayed. The options are:

- **parametricCurve**: Each successive data point is plotted in order, potentially joined by a line. If the z data is 2-dimensional instead of a vector, the last point of the first vector should not be connected to the first point of the next. The line and marker styles can be set from the `style` (including removing them if the `type` of either is set to "`none`").
- **surfaceMesh**: The data are plotted as a wireframe, with adjacent-in-space data points connected with lines. The line style can be set from the `style`.
- **surfaceContour**: The data is plotted as a continuous surface. The fill color can be set from the `style`, as can the lines and/or markers, if displaying those elements are desired.
- **contour**: The 3D data are plotted as a 2D surface, with contour lines (similar to elevation plots). The line style can be set from the `style`.
- **heatMap**: The 3D data are plotted as a 2D surface, with color representing the values. The colors

can be set from the `fill` of the `style`.

- **bar**: The data is plotted as a 3D bar plot.

`logX`, `logY`, `logZ` (deprecated)

The `logX`, `logY` and `logZ` attributes, of type `Boolean`, were used in previous versions of SED-ML to indicate whether the respective axis of the *Plot* should be linear or log10. This allowed multiple objects in the same *Plot* to contradict each other, and has therefore been moved to Axis. The `logX`, `logY` and `logZ` attributes on Surface have therefore been deprecated, and will always be ignored.

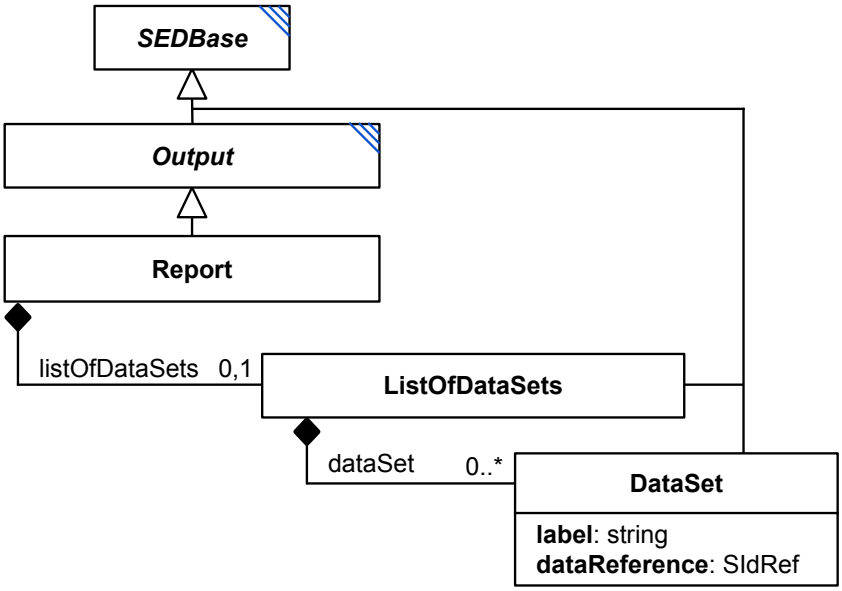


Figure 2.24: *The definition of the SED-ML Report, ListOfDataSets, and DataSet classes.*

2.2.13 `Report`

The Report class defines a data map consisting of several single instances of the DataSet in the child `listOfDataSets` (Figure 2.24). Its output returns the simulation result processed via DataGenerators in actual numbers. The elements of the report are defined by creating an instance of the DataSet for each element of the report and are identified by the `label` of the DataSet.

The simulation result itself, i.e. concrete result numbers, are not stored in SED-ML, but the directive how to calculate them from the output of the simulator is provided through the dataGenerator. The encoding of simulation results is not part of SED-ML Level 1 Version 4, but it is recommended that 2D output be exported as CSV files, using the `label` as column headers, and that output with more dimensions be exported as HDF5, again using the `label` to uniquely identify the data sets.

2.2.13.1 `DataSet`

The DataSet class holds definitions of data to be used in the Report class (Figure 2.24). DataSets are labeled references to instances of the DataGenerator class. It defines the required attributes `label` of type `string` and `dataReference` of type SIdRef.

Each data set in a Report must have an unambiguous `label`. A `label` is a human readable descriptor of a data set for use in a Report. In general the Report is a map between labels and data from DataGenerator instances, but can be interpreted as a data table for certain tasks. For example, in the special case of time series results, the report could be a tabular data set with the `label` being the column heading and the time series results being the columns.

label

The `label` attribute is of type `string` defines a unique label for every DataSet in a given Report.

dataReference

The `dataReference` attribute is of type SIdRef, and must be the ID of a DataGenerator element in the same SED-ML Document. The data produced by that particular DataGenerator fills the according dataSet in the report.

Listing 2.59 shows the use of the `dataSet` element. The example shows the definition of a dataSet. The referenced dataGenerator `dg1` must be defined in the `listOfDataGenerators`.

```
<listOfDataSets>
    <dataSet id="d1" name="v1 over time" dataReference="dg1" label="_1">
</listOfDataSets>
```

Listing 2.59: *The SED-ML `dataSet` element, defining a data set containing the result of the referenced task*

2.2.14 ParameterEstimationReport

A ParameterEstimationReport class is used to create a default report from a ParameterEstimationTask. It has a single required attribute `taskRef` of type SIdRef that points to that task.

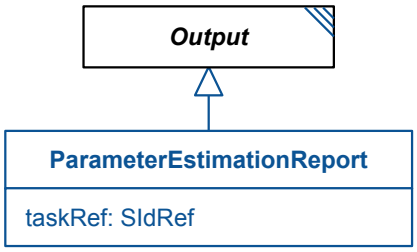


Figure 2.25: *The definition of the SED-ML ParameterEstimationReport class.*

The report should include the relevant information collected during the parameter estimation, but the specifics may vary from tool to tool depending on the particular method used. At the very least, the optimal AdjustableParameter values should be reported, along with any information that would let the user determine the confidence in those estimates.

It is possible to reproduce and/or have more control over the contents of a Report that covers the contents of a ParameterEstimationTask by creating DataGenerator elements that use DependentVariable objects whose `term` references particular elements of a ParameterEstimationTask such as the residuals of the Objective, or the overall χ^2 value of the task. But most of these values should be produced by default in a ParameterEstimationReport.

2.2.15 Figure

The Figure class provides a mechanism to arrange and display several *Plot* elements together. It inherits the attributes and children of *Output*, and additionally defines two required attributes `numRows` and `numCols`, both of type `positive integer`, and can additionally contain any number of SubPlot children through a ListOfSubPlots.

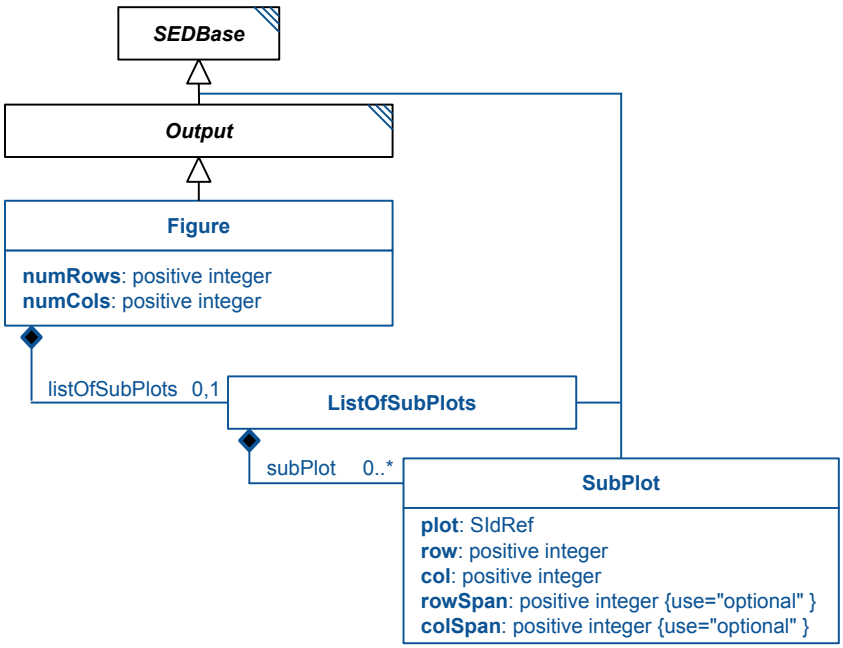


Figure 2.26: *The definition of the SED-ML Figure, ListOfSubPlots, and SubPlot classes.*

numRows and numCols

The `numRows` and `numCols` attributes define the number of rows and columns, respectively, to be contained in the figure. The relative size of each row and columns is not defined, but should be large enough to contain the *Plot* elements to be displayed in them.

listOfSubPlots

The `listOfSubPlots` child of a Figure contains all the *Plot* elements to display. Each SubPlot declares itself where it is to be displayed in the Figure.

2.2.15.1 SubPlot

The SubPlot class inherits from *SEDBase* and additionally defines three required attributes (`plot`, of type SIdRef, and `row` and `col`, both of type `positive integer`), and two optional attributes (`rowSpan` and `colSpan`, both of type `positive integer`). Each SubPlot defines where in the Figure the referenced *Plot* should be displayed.

plot

The `plot` attribute must be an SIdRef to a *Plot*. The referenced *Plot* will be displayed in the Figure. It is not necessary for each `plot` to be unique, if the same *Plot* should be displayed multiple times.

row and col

The `row` and `col` attributes define the row and column, respectively, within the Figure where the *Plot* is to be displayed. This must not conflict with any other SubPlot in the same Figure, and may not be greater than the Figure's `numRows` or `numCols` attributes, respectively. Rows and columns are both numbered starting with "1", rows are ordered top to bottom, and columns are ordered left to right, so `row=''1'' col=''1''` places a *Plot* in the upper left corner of the Figure.

rowSpan and colSpan

The optional `rowSpan` and `colSpan` attributes are used when a *Plot* is to be displayed in multiple rows and/or columns in a Figure. Each attribute indicates the number of rows and/or columns the figure is to span. The value must be a positive integer, and it must not be greater than the number of available rows and/or columns in the Figure.

In the following example, a 3x3 Figure is defined with four subplots. The first is in the upper left corner, the second in the top row occupying columns 2 and 3, the next a 2x2 subplot in the lower left, and the final subplot in the right-most column, occupying rows 2 and 3.

```
<figure id="fig1" name="Figure 1" numRows="3" numCols="3">
    <listOfSubPlots>
        <subPlot id="ax1" plot="plot_y1" row="1" col="1" />
        <subPlot id="ax2" plot="plot_y2" row="1" col="2" colSpan="2"/>
        <subPlot id="ax3" plot="plot_y3" row="2" col="1" colSpan="2" rowSpan="2"/>
        <subPlot id="ax4" plot="plot_y4" row="2" col="3" rowSpan="2"/>
    </listOfSubPlots>
    <notes><p xmlns="xhtml">Figure 1 - Example for figure with text legend and sub-plots.</p></notes>
</figure>
```

Listing 2.60: *The SED-ML* `figure` *element, defining a figure with four subplots of different sizes*

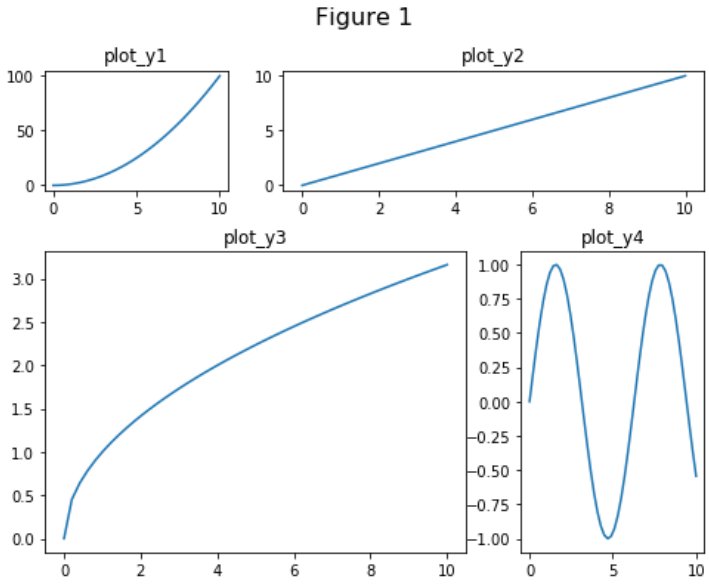


Figure 2.27: *The output of Listing 2.60*

2.2.16 ParameterEstimationResultsPlot

A ParameterEstimationResultsPlot class is used to create a default plot from a ParameterEstimationTask. It inherits from *Plot*, and adds a single required attribute `taskRef` of type SIdRef that points to that task.

Figure 2.28: *The definition of the SED-ML ParameterEstimationResultsPlot and WaterfallPlot classes.*

The plot should display the relevant information collected during the parameter estimation, but the specifics may vary from tool to tool depending on the particular method used. At the very least, the optimal AdjustableParameter values should be reported, along with any information that would let the user determine the confidence in those estimates, such as the residuals.

It is possible to reproduce and/or have more control over the contents of a *Plot* that covers the contents of a ParameterEstimationTask by creating DataGenerator elements that use DependentVariable objects whose `term` references particular elements of a ParameterEstimationTask such as the residuals of the Objective, or the overall χ^2 value of the task. This is the only way to get direct control over the Style of anything displayed in a ParameterEstimationResultsPlot. But the data itself should be displayed in some form by default in a ParameterEstimationReport.

2.2.17 WaterfallPlot

The WaterfallPlot class is used to create a default plot of a particular style from a ParameterEstimationTask. It inherits from *Plot*, and adds a single required attribute `taskRef` of type SIdRef that points to that task.

Like a ParameterEstimationResultsPlot, a WaterfallPlot displays a range of results and data from a ParameterEstimationTask that might not otherwise be easily accessible. Different tools and different experiments may result in different types and styles of waterfall plots. For an overview of the sort of data present in one, see Gillespie, 2012 [12].

2.2.18 Style

The Style class (Figure 2.29) defines a graphical style for use in Figure or *Plot* elements.

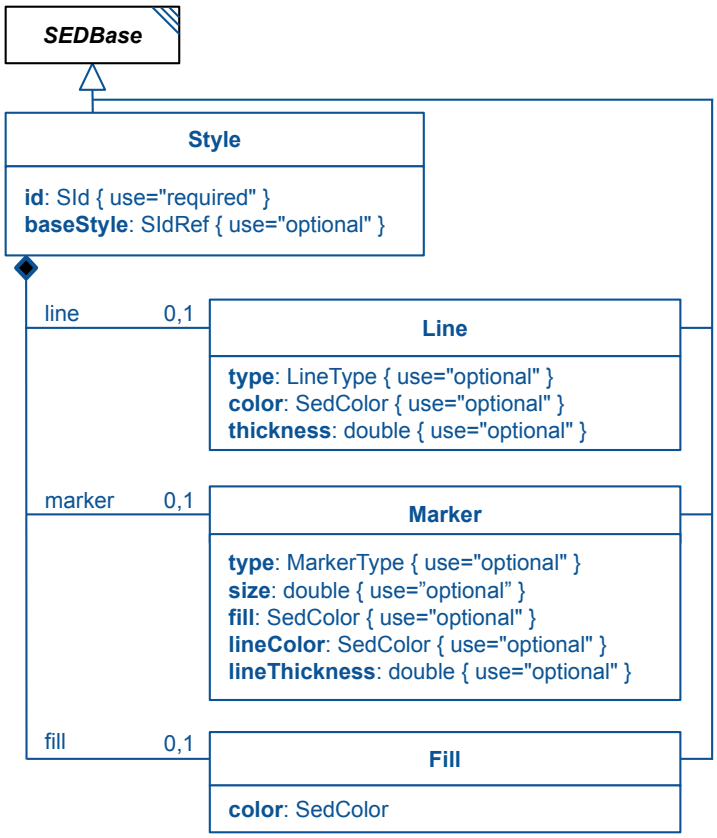


Figure 2.29: *The SED-ML Style class*

The Style class inherits the attributes and children from *SEDBase*, extending the `id` attribute to be required, adding an optional `baseStyle` of type SIdRef, and allowing up to three optional chidren of type Line, Marker, and Fill. Collectively, these elements describe a visual style that can be applied to an *AbstractCurve* or Surface.

baseStyle

The optional `baseStyle` attribute of data type SIdRef is used to reference a different Style in the same SED-ML Document. If present, any defined aspect of the referenced Style is assumed to apply to the current Style, unless superseded by an element of the current Style. For example, if one Style "`style1`" defines a black line with a blue marker, and a second Style "`style2`" has a `baseStyle` of "`style1`" and defines a red line, applying a "`style2`" would result in a red line with a blue marker.

2.2.18.1 Line

The Line class inherits the attributes and children of *SEDBase*, and adds three optional attributes: `type` of type LineType, `color` of type SedColor, and `thickness` of type `double`. If any of these attributes are defined, lines presented in the parent Style should have that type, color, and/or thickness. If any of the attributes is not defined, it can be defined by the Style referenced in the `baseStyle`, or is undefined and can be anything.

type

The `type` attribute defines how lines are to be drawn. The options are:

- **`none`**: The line is not to be displayed at all.
- **`solid`**: The line is to be displayed as a continuous line.
- **`dash`**: The line is to be displayed as a series of short lines.
- **`dot`**: The line is to be displayed as a series of dots.
- **`dashDot`**: The line is to be displayed as a series of single lines and single dot combinations.
- **`dashDotDot`**: The line is to be displayed as a series of single lines and two dot combinations.

color

The `color` attribute defines what color the line should be. See the SedColor for a description of how colors are defined in SED-ML.

thickness

The `thickness` attribute defines the thickness of the line, in pixels (or the equivalent in the application's display environment).

2.2.18.2 Marker

The Marker class inherits the attributes and children of *SEDBase*, and adds five optional attributes: `type` of type MarkerType, `size` of type `double`, `fill` of type SedColor, `lineColor` of type SedColor, and `lineThickness` of type `double`. If any of these attributes are defined, markers presented in the parent Style should have that attribute. If any of the attributes is not defined, it can be defined by the Style referenced in the `baseStyle`, or is undefined and can be anything.

type

The `type` attribute defines how markers are to be drawn. The options are:

- **`none`**: The marker is not to be displayed at all.
- **`square`**: The marker is to be displayed as a square.
- **`circle`**: The marker is to be displayed as a circle.
- **`diamond`**: The marker is to be displayed as a diamond.
- **`xCross`**: The marker is to be displayed as an 'x'.
- **`plus`**: The marker is to be displayed as a plus.
- **`star`**: The marker is to be displayed as a star.

- **triangleUp**: The marker is to be displayed as an upwards-pointing triangle.
- **triangleDown**: The marker is to be displayed as a downwards-pointing triangle.
- **triangleLeft**: The marker is to be displayed as a left-pointing triangle.
- **triangleRight**: The marker is to be displayed as a right-pointing triangle.
- **hDash**: The marker is to be displayed as a horizontal dash.
- **vDash**: The marker is to be displayed as a vertical dash.

size

The `size` attribute defines what size, in pixels, the marker should be (or the equivalent in the application's display environment.

fill

The `fill` attribute defines what color the interior of the marker should be. See the SedColor for a description of how colors are defined in SED-ML.

lineColor

The `lineColor` attribute defines what color the border of the marker should be. See the SedColor for a description of how colors are defined in SED-ML.

lineThickness

The `thickness` attribute defines the thickness of the marker's border, in pixels (or the equivalent in the application's display environment).

2.2.18.3 Fill

The Fill class inherits the attributes and children of *SEDBase*, and adds two optional attributes: `color` of type SedColor, and `secondColor` of type SedColor. If any of these attributes are defined, fills presented in the parent Style should have that color or colors. If any of the attributes is not defined, it can be defined by the Style referenced in the `baseStyle`, or is undefined and can be anything.

color

The `color` attribute defines what color the fill should be. See the SedColor for a description of how colors are defined in SED-ML.

secondColor

The `secondColor` attribute defines what the second color of the fill should be. See the SedColor for a description of how colors are defined in SED-ML. By providing a `secondColor`, gradients can be specified which run linearly from `color` to `secondColor`. If not defined, the fill should be a single color.

3. Concepts used in SED-ML

3.1 MathML

SED-ML encodes mathematical expressions using a subset of MathML 2.0 [5]. MathML is an international standard for encoding mathematical expressions using XML. It is also used as a representation of mathematical expressions in other formats, such as SBML and CellML, two of the model languages supported by SED-ML.

SED-ML files can use mathematical expressions to encode for example pre-processing steps applied to the computational model (ComputeChange), or post processing steps applied to the raw simulation data before output (DataGenerator).

SED-ML classes reference MathML expressions via the element Math of data type `MathML`.

3.1.1 MathML elements

The allowed MathML in SED-ML is restricted to the following subset:

- *token*: `cn`, `ci`, `csymbol`, `sep`
- *general*: `apply`, `piecewise`, `piece`, `otherwise`
- *relational operators*: `eq`, `neq`, `gt`, `lt`, `geq`, `leq`
- *arithmetic operators*: `plus`, `minus`, `times`, `divide`, `power`, `root`, `abs`, `exp`, `ln`, `log`, `floor`, `ceiling`, `factorial`
- *logical operators*: `and`, `or`, `xor`, `not`
- *qualifiers*: `degree`, `logbase`
- *trigonometric operators*: `sin`, `cos`, `tan`, `sec`, `csc`, `cot`, `sinh`, `cosh`, `tanh`, `sech`, `csch`, `coth`, `arcsin`, `arccos`, `arctan`, `arcsec`, `arccsc`, `arccot`, `arcsinh`, `arccosh`, `arctanh`, `arcsech`, `arccsch`, `arccoth`
- *constants*: `true`, `false`, `notanumber`, `pi`, `infinity`, `exponentiale`
- *MathML annotations*: `semantics`, `annotation`, `annotation-xml`

3.1.2 MathML symbols

All the operations listed above describe functions of scalar-valued SED variables, or element-wise computations of matrix-valued SED variables. Matrix-valued SED variables can arise in multiple ways. For example, a variable for a basic task of a non-spatial UniformTimeCourse would be a vector with length equal to the number of steps of the time course plus one. A Variable for a RepeatedTask of a non-spatial time course could be represented a matrix with dimensions for the iterations of the repeated tasks, its subtasks, and the steps of the nested basic task. MathML functions for matrices should be evaluated on an element-wise basis. For example, if M and N were two 2D matrix-valued SED variables, $M + 3$ would add three to every element of M, $R = M + N$ would only be valid if M and N have the same dimensions, and $R_{i,j}$ would be equal to $M_{i,j} + N_{i,j}$. If the lengths of the dimensions are not equal (i.e. if $M_{i,j}$ exists but $N_{i,j}$ does not), the missing value should be assumed to be NaN (not a number). At this point, SED-ML does not define an algebra for matrix computations.

3.1.2.1 MathML csymbols for dimensional input

While the new DependentVariable class provides functionality to reduce the dimensionality of matrices, previous version of SED-ML defined the MathML functions min, max, sum, and product, each of which

would reduce any n-dimensional vector to a single scalar value. It is recommended that users switch to using DependentVariable elements for their increased functionality, but the old functions are still defined here for backwards compatibility. The only allowed symbols to be used in aggregate functions are the identifiers of Variables defined in the `listOfVariables` of a DataGenerator. These Variables represent the data collected from the simulation experiment in the associated Task. They always return scalar values, regardless of the dimensionality of the Variable, and ignore any NaN values the vector or matrix might have.

min

The `min` of a variable represents the smallest value the simulation experiment for that variable (Listing 3.1).

```
<apply>
    <csymbol encoding="text" definitionURL="http://sed-ml.org/#min">
        min
    </csymbol>
    <ci> variableId </ci>
</apply>
```

Listing 3.1: *Example for the use of the MathML* `min` *function.*

max

The `max` of a variable represents the largest value the simulation experiment for that variable (Listing 3.2).

```
<apply>
    <csymbol encoding="text" definitionURL="http://sed-ml.org/#max">
        max
    </csymbol>
    <ci> variableId </ci>
</apply>
```

Listing 3.2: *Example for the use of the MathML* `max` *function.*

sum

The `sum` of a variable represents the sum of all values of the variable returned by the simulation experiment (Listing 3.3).

```
<apply>
    <csymbol encoding="text" definitionURL="http://sed-ml.org/#sum">
        sum
    </csymbol>
    <ci> variableId </ci>
</apply>
```

Listing 3.3: *Example for the use of the MathML* `sum` *function.*

product

The `product` of a variable represents the multiplication of all values of the variable returned by the simulation experiment (Listing 3.4).

```
<apply>
    <csymbol encoding="text" definitionURL="http://sed-ml.org/#product">
        product
    </csymbol>
    <ci> variableId </ci>
</apply>
```

Listing 3.4: *Example for the use of the MathML* `product` *function.*

3.1.2.2 MathML Distribution Functions

The following functions are added to MathML as csymbols to represent draws from distributions: uniform, normal, lognormal, poisson, and gamma:

uniform

The uniform of a variable represents a draw from a uniform distribution. It has two arguments: the first is 'min' and the second is 'max', with 'max' requried to be greater than 'min'. The draw from the distribution must be between 'min' and 'max', and may include 'min', but may not include 'max'.

```
<apply>
    <csymbol encoding="text" definitionURL="http://sed-ml.org/functions/#uniform">
        uniform
    </csymbol>
    <ci> minId </ci>
    <ci> maxId </ci>
</apply>
```

Listing 3.5: *Example for the use of the MathML* `uniform` *function.*

normal

The normal of a variable represents a draw from a normal distribution. It has two arguments: the first is 'mean', and the second is 'stdev', that define the mean and the standard deviation, respectively, of the distribution.

```
<apply>
    <csymbol encoding="text" definitionURL="http://sed-ml.org/functions/#normal">
        normal
    </csymbol>
    <ci> meanId </ci>
    <ci> stdevId </ci>
</apply>
```

Listing 3.6: *Example for the use of the MathML* `normal` *function.*

lognormal

The lognormal of a variable represents a draw from a log-normal distribution. It has two arguments: the first is 'mean', and the second is 'stdev', that define the mean and the standard deviation, respectively, of the distribution.

```
<apply>
    <csymbol encoding="text" definitionURL="http://sed-ml.org/functions/#lognormal">
        lognormal
    </csymbol>
    <ci> meanId </ci>
    <ci> stdevId </ci>
</apply>
```

Listing 3.7: *Example for the use of the MathML* `lognormal` *function.*

gamma

The gamma of a variable represents a draw from a gamma distribution. It has two arguments: the first is 'shape', and the second is 'scale', that define the shape and scale, respectively, of the distribution.

```
<apply>
    <csymbol encoding="text" definitionURL="http://sed-ml.org/functions/#gamma">
        gamma
    </csymbol>
    <ci> shapeId </ci>
    <ci> scaleId </ci>
</apply>
```

Listing 3.8: *Example for the use of the MathML* `gamma` *function.*

poisson

The poisson of a variable represents a discrete value drawn from a poisson distribution. It has a single argument: 'rate', the expected rate of occurrences for the distribution.

```
<apply>
    <csymbol encoding="text" definitionURL="http://sed-ml.org/functions/#poisson">
        poisson
    </csymbol>
    <ci> rateId </ci>
</apply>
```

Listing 3.9: *Example for the use of the MathML* `poisson` *function.*

3.1.3 NA values

NA (not available) values can occur within a simulation experiment. Examples are missing values in a DataSource or simulation results with NA values. All math operations encoded in MathML in SED-ML are well defined on NA values.

NA values in a Curve or Surface should be ignored during plotting.

3.2 URI scheme

URIs are used in SED-ML as a mechanism

- to reference models (3.2.1 Model references)
- to reference data files (3.2.2 Data references)
- to specify the language of the referenced model (3.2.3 Language references)
- to specify the format of the referenced dataset (3.2.4 Data format references)
- to enable addressing implicit model variables (3.2.5 Symbols)

In addition, annotation of SED-ML elements should use a standardised URI Annotations Scheme to ensure long-time availability of information that can unambiguously be identified.

3.2.1 Model references

The two principle recommended methods for referencing data is by URL or by relative pathname. Any URL should preferably point to a public, consistent location that provides the model description file. References to curated, open model bases are recommended, such as the BioModels Database. Relative pathnames are useful both when working with a collection or folder of related files, or when the files are collected into a COMBINE archive.

For additional information see the `source` attribute on Model.

An alternative means to obtain a model may be to provide a single resource containing necessary models and a SED-ML file. Although a specification of such a resource is beyond the scope of this document, the recommended means is the COMBINE archive.

3.2.2 Data references

The two principle recommended methods for referencing data is by URL or by relative pathname. Both of these methods will work if the file or files are transferred to a new location, or to a COMBINE archive. Absolute pathnames will work when used in their original locations, but not when moved to a new location or bundled into an archive, and are therefore not recommended.

For additional information see the `source` attribute on DataDescription.

3.2.3 Language references

The evaluation of a SED-ML document is required in order for software to decide whether or not it can be used in a particular simulation environment. One crucial criterion is the particular model representation language used to encode the model. A simulation software usually only supports a small subset of the representation formats available to model biological systems computationally.

To help software decide whether or not it supports a SED-ML description file, the information on the model encoding for each referenced model can be provided through the `language` attribute, as the description of a language name and version through an unrestricted `String` is error-prone. A prerequisite for a language to be fully supported by SED-ML is that a formalised language definition, e.g., an XML Schema, is provided online. SED-ML also defines a set of standard URIs to refer to particular language definitions.

To specify the language a model is encoded in, a set of pre-defined SED-ML URNs can be used (Table 3.1 on the following page). The structure of SED-ML language URNs is `urn:sedml:language:`*`name.version`*. One can be as specific as defining a model being in a particular version of a language, e.g., SBML Level 3 Version 1 as `urn:sedml:language:sbml.level-3.version-1`.

For additional information see the `language` attribute on Model.

3.2.4 Data format references

To help software decide whether or not it supports a SED-ML file, the information on the dataDescription encoding for each referenced dataDescription can be provided through the `format` attribute.

Language	URN
BNGL (generic)	urn:sedml:language:bngl
CellML (generic)	urn:sedml:language:cellml
CellML 1.0	urn:sedml:language:cellml.1_0
CellML 1.1	urn:sedml:language:cellml.1_1
NeuroML (generic)	urn:sedml:language:neuroml
NeuroML Version 1.8.1 Level 1	urn:sedml:language:neuroml.version-1_8_1.level-1
NeuroML Version 1.8.1 Level 2	urn:sedml:language:neuroml.version-1_8_1.level-2
SBML (generic)	urn:sedml:language:sbml
SBML Level 1 Version 1	urn:sedml:language:sbml.level-1.version-1
SBML Level 1 Version 2	urn:sedml:language:sbml.level-1.version-2
SBML Level 2 Version 1	urn:sedml:language:sbml.level-2.version-1
SBML Level 2 Version 2	urn:sedml:language:sbml.level-2.version-2
SBML Level 2 Version 3	urn:sedml:language:sbml.level-2.version-3
SBML Level 2 Version 4	urn:sedml:language:sbml.level-2.version-4
SBML Level 3 Version 1	urn:sedml:language:sbml.level-3.version-1
SBML Level 3 Version 2	urn:sedml:language:sbml.level-3.version-2
VCML (generic)	urn:sedml:language:vcml

Table 3.1: *Predefined model language URNs. The latest list of language URNs is available from* http://sed-ml.org/.

To specify the format of a dataDescription, a set of pre-defined SED-ML URNs can be used (Table 3.2). The structure of SED-ML format URNs is `urn:sedml:format:`*`name.version`*.

If it is not explicitly defined the default value for `format` is `urn:sedml:format:numl`, referring to NuML representation of the data. However, the use of the `format` attribute is strongly encouraged.

For additional information see the `format` attribute on DataDescription and the description of individual formats and their use in SED-ML below.

Data Format	URN
NuML (generic)	urn:sedml:format:numl
NuML Level 1 Version 1	urn:sedml:format:numl.level-1.version-1
CSV	urn:sedml:format:csv
TSV	urn:sedml:format:tsv
HDF5	urn:sedml:format:hdf5

Table 3.2: *Predefined dataDescription format URNs. The latest list of format URNs is available from* http://sed-ml.org/.

3.2.4.1 NuML (Numerical Markup Language)

NuML is an exchange format for numerical data. Data in the NuML format (`urn:sedml:format:numl`) is defined via `resultComponents` with a single dataset corresponding to a single `resultComponent`. In the case that a NuML file consists of multiple `resultComponents` the first `resultComponent` contains the data used in the DataDescription. There is currently no mechanism in SED-ML to reference the additional `resultComponents`.

If a `dimensionDescription` is set on the DataDescription, than this `dimensionDescription` must be identical to the `dimensionDescription` of the NuML file.

3.2.4.2 CSV (Comma Separated Values)

Data in the CSV format (`urn:sedml:format:csv`) must follow the following rules when used in combination with SED-ML:

- Each record is one line - Line separator may be LF (0x0A) or CRLF (0x0D0A), a line separator may also be embedded in the data (making a record more than one line but still acceptable).

- Fields are separated with commas.
- Embedded commas - Field must be delimited with double-quotes.
- Leading and trailing whitespace is ignored - Unless the field is delimited with double-quotes in that case the whitespace is preserved.
- Embedded double-quotes - Embedded double-quote characters must be doubled, and the field must be delimited with double-quotes.
- Embedded line-breaks - Fields must be surounded by double-quotes.
- Always Delimiting - Fields may always be delimited with double quotes, the delimiters will be parsed and discarded by the reading applications.
- The first record is the header record defining the unique column ids
- Lines starting with "#" are treated as comment lines and ignored
- Empty lines are allowed and ignored
- For numerical data the "." decimal separator is used
- The following strings are interpreted as NaN: "", "#N/A", "#N/A N/A", "#NA", "-1.#IND", "-1.#QNAN", "-NaN", "-nan", "1.#IND", "1.#QNAN", "N/A", "NA", "NULL", "NaN", "nan".

A dataset in CSV is always encoding two dimensional data.

When using data in the CSV format SED-ML, the `dimensionDescription` is required on the DataDescription.

The `dimensionDescription` must consist of an outer `compositeDescription` with `indexType="integer"` which allows to reference the rows of the CSV by index and a inner `compositeDescription` which allows to reference the columns of the CSV by their column header id. Within the inner `compositeDescription` exactly one `atomicDescription` must exist. All data in the CSV must have the same type which is defined via the `valueType` on the `atomicDescription`.

Below an example of the required `dimensionDescription` for a CSV is provided. In the example the `time` and `S1` columns are read from the CSV file

```
# ./example.csv
time, S1, S2
0.0, 10.0, 0.0
0.1, 9.9, 0.1
0.2, 9.8, 0.2
```

Listing 3.10: *Example CSV*

```

<dataDescription id="datacsv" name="Example CSV dataset" source="./example.csv" format="
     urn:sedml:format:csv">
  <dimensionDescription>
    <compositeDescription indexType="integer" name="Index">
      <compositeDescription indexType="string" name="ColumnIds">
        <atomicDescription valueType="double" name="Values" />
      </compositeDescription>
    </compositeDescription>
  </dimensionDescription>
  <listOfDataSources>
    <dataSource id="dataTime">
      <listOfSlices>
        <slice reference="ColumnIds" value="time" />
      </listOfSlices>
    </dataSource>
    <dataSource id="dataS1">
      <listOfSlices>
        <slice reference="ColumnIds" value="S1" />
      </listOfSlices>
    </dataSource>
  </listOfDataSources>
  ...
</dataDescription>
```

Listing 3.11: *SED-ML* `dimensionDescription` *element for the example.csv*

3.2.4.3 TSV (Tab Separated Values)

The format TSV (`urn:sedml:format:tsv`) is defined identical to `CSV` with the exceptions listed below

- Fields are separated with tabs instead of commas.
- Embedded tab - Field must be delimited with double-quotes (embedded comma field must not be delimited with double quotes)

3.2.4.4 HDF5 (Hierarchical Data Format version 5)

The format HDF5 is defined at `https://portal.hdfgroup.org/display/HDF5/HDF5`. It supports the storage of multidimensional data, and is therefore ideal for storing the SED-ML output of repeated tasks; particularly nested repeated tasks.

Each dimension of SED-ML RepeatedTask output should be labeled according to the relevant `id` of the SED-ML object that describes that dimension, namely:

- The `id` of the top-level RepeatedTask
- The `id` of the SubTask
- The `id` of any nested SubTask (for arbitrarily-deeply nested subtasks).
- The dimension of the data itself (i.e. `time` for a UniformTimeCourse).
- The `id` of the requested variable, or the infix representation of the Math from the DataGenerator.

When a DependentVariable is used to reduce the dimensionality of a set of data, the `id`s of whatever dimensions remain should be used (defined by its RemainingDimension children). The dimensions may by annotated to describe the dimension reduction as well. When a DataGenerator contains a DependentVariable that outputs a matrix, that matrix can also be labeled appropriately (such as with species or reaction ids).

When output from multiple tasks are combined mathematically, their dimensions must match exactly, so the ids from either (or a combination of both) may be used. Again, annotations are recommended to describe how the data was combined.

Each dimension may also be annotated in this format, with some ontology such as the 'Semanticscience Integrated Ontology' (SIO, `https://bioportal.bioontology.org/ontologies/SIO`).

3.2.5 Symbols

Some variables used in a simulation experiment are not explicitly defined in the model, but may be implicitly contained in it. For example, to plot a variable's behaviour over time, that variable is defined in an SBML model, whereas time is not explicitly defined.

SED-ML can refer to such implicit variables via the Symbol concept. Such implicit variables are defined using KiSAO through the `kisaoID` format to reference the implied variable.

For example, to refer in a SED-ML file to the definition of time, the string `KISAO:0000832` is used. For backwards compatibility, the string "`urn:sedml:symbol:time`" may be used.

With very few exceptions, symbols refer to mathematics of a model that can be read out of the model, but cannot be set directly. You cannot use a `symbol` attribute to set the time of a model, for example, nor may you set the Stoichiometry matrix nor the elasticities. The only partial exception to this is that the amount, concentation, or particle number of a species may be set by an element using both a `target` attribute to indicate the species and a `symbol` to indicate which form to use.

Table 3.3 on the following page lists the predefined symbols in SED-ML.

3.2.6 Annotation Scheme

When annotating SED-ML elements with semantic annotations, the MIRIAM URI Scheme should be used. In addition to providing the data type (e.g., PubMed) and the particular data entry inside that

Language	URN	KiSAO ID	Definition
SBML	`urn:sedml:symbol:time`	KISAO:0000832	Time in SBML is an intrinsic model variable that is addressable in model equations via a csymbol `time`.

Table 3.3: *The single predefined symbol in SED-ML. For Level 1 Version 4, KiSAO IDs are used instead, though 'time' is still allowed for backwards compatibility. The latest list of KiSAO terms is available from https://github.com/SED-ML/KiSAO.*

data type (e.g., `10415827`), the relation of the annotation to the annotated element should be described using the standardized biomodels.net qualifier. The list of qualifiers, as well as further information about their usage, is available from `http://www.biomodels.net/qualifiers/`.

3.3 XPath

XPath is a language for finding and referencing information in an XML document [7]. Within SED-ML Level 1 Version 4, XPath version 1 expressions can be used to identify nodes and attributes within an XML representation of an XML-encoded model in the following ways:

- Within a Variable definition, where XPath identifies the model variable required for manipulation in SED-ML. In this context, the XPath must always reference a single XML element, and not an attribute nor multiple XML elements.
- Within a Change definition, where XPath is used to identify the target XML to which a change should be applied. In this context, the XPath may point to anything in the XML as appropriate for the Change (i.e. an attribute in a ChangeAttribute; one or more elements or attributes to remove in a RemoveXML, etc.).

For proper application, XPath expressions should contain prefixes that allow their resolution to the correct XML namespace within an XML document. For example, the XPath expression referring to a species X in an SBML model:

`/sbml:sbml/sbml:model/sbml:listOfSpecies/sbml:species[@id='X']` ✔ *-CORRECT*

is preferable to

`/sbml/model/listOfSpecies/species[@id='X']` ✘ *-INCORRECT*

which will only be interpretable by standard XML software tools if the SBML file declares no namespaces (and hence is invalid SBML).

Following the convention of other XPath host languages such as XPointer and XSLT, the prefixes used within XPath expressions must be declared using namespace declarations within the SED-ML document, and be in-scope for the relevant expression. Thus for the correct example above, there must also be an ancestor element of the node containing the ssion that has an attribute like:

`xmlns:sbml='http://www.sbml.org/sbml/level3/version1/core'`

(a different namespace URI may be used; the key point is that the prefix 'sbml' must match that used in the XPath expression).

3.4 NuML

The Numerical Markup Language (NuML) aims to standardize the exchange and archiving of numerical results. Additional information including the NuML specification is available from `https://github.com/NuML/NuML`.

NuML constructs are used in SED-ML for referencing external data sets in the DataDescription class. NuML is used to define the DimensionDescription of external datasets in the DataDescription. In addition, `NuMLSIds` are used for retrieving subsets of data via either the `indexSet` element in the DataSource or within the Slice class.

3.5 KiSAO

The Kinetic Simulation Algorithm Ontology (KiSAO [8]) is used in SED-ML to specify simulation algorithms and algorithmParameters. KiSAO is a community-driven approach of classifying and structuring simulation approaches by model characteristics and numerical characteristics. The ontology is available in OWL format from BioPortal at http://purl.bioontology.org/ontology/KiSAO.

Defining simulation algorithms through KISAO terms not only identifies the simulation algorithm used for the SED-ML simulation, it also enables software to find related algorithms, if the specific implementation is not available. For example, software could decide to use the CVODE integration library for an analysis instead of a specific Runge Kutta 4,5 implementation.

Should a particular simulation algorithm or algorithm parameter not exist in KiSAO, please request one via http://www.biomodels.net/kisao/.

3.6 COMBINE archive

A COMBINE archive [1] is a single file that supports the exchange of all the information necessary for a modeling and simulation experiment in biology. A COMBINE archive file is a ZIP container that includes a manifest file, listing the content of the archive, an optional metadata file adding information about the archive and its content, and the files describing the model. The content of a COMBINE archive consists of files encoded in COMBINE standards whenever possible, but may include additional files defined by an Internet Media Type. Several tools that support the COMBINE archive are available, either as independent libraries or embedded in modeling software.

The COMBINE archive is described at http://co.mbine.org/documents/archive and in [1].

COMBINE archives are the recommended means for distributing simulation experiment descriptions in SED-ML, the respective data and model files, and the Outputs of the simulation experiment (figures and reports). All SED-ML specification examples in Appendix A are available as COMBINE archive from http://sed-ml.org.

3.7 SED-ML resources

Information on SED-ML can be found on http://sed-ml.org. The SED-ML XML Schema, the UML schema, SED-ML examples, and additional information is available from https://github.com/sed-ml.

4. Acknowledgements

The SED-ML specification is developed with the input of many people. The following individuals served as past SED-ML Editors and contributed to SED-ML specifications. Their efforts helped shape what SED-ML is today.

- Richard Adams (editor, 2011-2012)
- Frank Bergmann (editor, 2011-2014, 2020-2022)
- Jonathan Cooper (editor, 2012-2015)
- Alan Garny (editor, 2018-2020)
- Tomas Helikar (editor, 2021-2023)
- Jonathan Karr (editor, 2021-2023)
- Matthias König (editor, 2017-2019, 2020-2022)
- David Nickerson (editor, 2011-2013, 2015-2017, 2019-2021)
- Nicolas Le Novère (editorial advisor, 2011-2012, 2013)
- Brett Olivier (editor, 2015-2017)
- Andrew Miller (editor, 2011-2012)
- Ion Moraru (editor, 2014-2016)
- Sven Sahle (editor, 2014-2016)
- Herbert Sauro (editor, 2018-2020)
- Lucian Smith (editor, 2016-2018)
- Dagmar Waltemath (editor, 2011-2014, 2017-2019)

Moreover, we would like to thank all the participants of the meetings where SED-ML has been discussed as well as the members of the SED-ML community.

A. Examples

This appendix presents selected SED-ML examples. These examples are only illustrative and do not intend to demonstrate the full capabilities of SED-ML. For a more comprehensive view of the SED-ML features refer to the specification (Chapter 2).

The presented examples use models encoded in SBML and CellML, though SED-ML is not restricted to those formats. See Section 3.2.3 for more information.

All specification examples listed below are available as Combine Archives from `http://sed-ml.org/` under the `*.omex` file name for the respective example.

Additional SED-ML examples are available at `http://sed-ml.org/`.

A.1 Example simulation experiment (`L1V3_repressilator.omex`)

This example lists the SED-ML for the example in the introduction (Section 1.2). It illustrates the use of a DependentVariable to calculate the maximum value of a vector with the KiSAO term for 'maximum' ("`KISAO:0000828`") as the `term`.

```
<?xml version="1.0" encoding="UTF-8"?>
<!-- Created by phraSED-ML version v1.0.7 with libSBML version 5.15.0. -->
<sedML xmlns="http://sed-ml.org/sed-ml/level1/version4" level="1" version="4">
  <listOfSimulations>
    <uniformTimeCourse id="sim1" initialTime="0" outputStartTime="0" outputEndTime="1000" numberOfPoints=
        "1000">
      <algorithm kisaoID="KISAO:0000019"/>
    </uniformTimeCourse>
  </listOfSimulations>
  <listOfModels>
    <model id="model1" language="urn:sedml:language:sbml.level-3.version-1" source="https://www.ebi.ac.uk
        /biomodels/model/download/BIOMD0000000012?filename=BIOMD0000000012_url.xml"/>
    <model id="model2" language="urn:sedml:language:sbml.level-3.version-1" source="#model1">
      <listOfChanges>
        <changeAttribute target="/sbml:sbml/sbml:model/sbml:listOfParameters/sbml:parameter[@id='ps_0']/
            @value" newValue="1.3e-05"/>
        <changeAttribute target="/sbml:sbml/sbml:model/sbml:listOfParameters/sbml:parameter[@id='ps_a']/
            @value" newValue="0.013"/>
      </listOfChanges>
    </model>
  </listOfModels>
  <listOfTasks>
    <task id="task1" modelReference="model1" simulationReference="sim1"/>
    <task id="task2" modelReference="model2" simulationReference="sim1"/>
  </listOfTasks>
  <listOfDataGenerators>
    <!-- timecourse -->
    <dataGenerator id="dg_0_0_0" name="task1.time">
      <listOfVariables>
        <variable id="task1_____time" symbol="urn:sedml:symbol:time" taskReference="task1"/>
      </listOfVariables>
      <math xmlns="http://www.w3.org/1998/Math/MathML">
        <ci> task1_____time </ci>
      </math>
    </dataGenerator>
    <dataGenerator id="dg_0_0_1" name="PX (lacI)">
      <listOfVariables>
        <variable id="task1_____PX" target="/sbml:sbml/sbml:model/sbml:listOfSpecies/sbml:species[@id='PX
            ']" taskReference="task1" modelReference="model1"/>
      </listOfVariables>
      <math xmlns="http://www.w3.org/1998/Math/MathML">
        <ci> task1_____PX </ci>
      </math>
    </dataGenerator>
    <dataGenerator id="dg_0_1_1" name="PZ (cI)">
      <listOfVariables>
```

```
42          <variable id="task1_____PZ" target="/sbml:sbml/sbml:model/sbml:listOfSpecies/sbml:species[@id='PZ
                ']" taskReference="task1" modelReference="model1"/>
43        </listOfVariables>
44        <math xmlns="http://www.w3.org/1998/Math/MathML">
45          <ci> task1_____PZ </ci>
46        </math>
47      </dataGenerator>
48      <dataGenerator id="dg_0_2_1" name="PY (tetR)">
49        <listOfVariables>
50          <variable id="task1_____PY" target="/sbml:sbml/sbml:model/sbml:listOfSpecies/sbml:species[@id='PY
                ']" taskReference="task1" modelReference="model1"/>
51        </listOfVariables>
52        <math xmlns="http://www.w3.org/1998/Math/MathML">
53          <ci> task1_____PY </ci>
54        </math>
55      </dataGenerator>
56      <!-- pre-processing -->
57      <dataGenerator id="dg_1_0_0" name="time">
58        <listOfVariables>
59          <variable id="task2_____time" symbol="urn:sedml:symbol:time" taskReference="task2"/>
60        </listOfVariables>
61        <math xmlns="http://www.w3.org/1998/Math/MathML">
62          <ci> task2_____time </ci>
63        </math>
64      </dataGenerator>
65      <dataGenerator id="dg_1_0_1" name="PX (lacI)">
66        <listOfVariables>
67          <variable id="task2_____PX" target="/sbml:sbml/sbml:model/sbml:listOfSpecies/sbml:species[@id='PX
                ']" taskReference="task2" modelReference="model2"/>
68        </listOfVariables>
69        <math xmlns="http://www.w3.org/1998/Math/MathML">
70          <ci> task2_____PX </ci>
71        </math>
72      </dataGenerator>
73      <dataGenerator id="dg_1_1_1" name="PZ (cI)">
74        <listOfVariables>
75          <variable id="task2_____PZ" target="/sbml:sbml/sbml:model/sbml:listOfSpecies/sbml:species[@id='PZ
                ']" taskReference="task2" modelReference="model2"/>
76        </listOfVariables>
77        <math xmlns="http://www.w3.org/1998/Math/MathML">
78          <ci> task2_____PZ </ci>
79        </math>
80      </dataGenerator>
81      <dataGenerator id="dg_1_2_1" name="PY (tetR)">
82        <listOfVariables>
83          <variable id="task2_____PY" target="/sbml:sbml/sbml:model/sbml:listOfSpecies/sbml:species[@id='PY
                ']" taskReference="task2" modelReference="model2"/>
84        </listOfVariables>
85        <math xmlns="http://www.w3.org/1998/Math/MathML">
86          <ci> task2_____PY </ci>
87        </math>
88      </dataGenerator>
89      <!-- post-processing -->
90      <dataGenerator id="dg_2_0_0" name="PX/max(PX) (lacI normalized)">
91        <listOfVariables>
92          <variable id="task1_____PX" target="/sbml:sbml/sbml:model/sbml:listOfSpecies/sbml:species[@id='PX
                ']" taskReference="task1" modelReference="model1"/>
93          <dependentVariable id="task1_____PX_max" target="/sbml:sbml/sbml:model/sbml:listOfSpecies/
                sbml:species[@id='PX']" taskReference="task1" modelReference="model1" term="KISAO:0000828"/>
94        </listOfVariables>
95        <math xmlns="http://www.w3.org/1998/Math/MathML">
96          <apply>
97            <divide/>
98            <ci> task1_____PX </ci>
99            <ci> task1_____PX_max </ci>
100         </apply>
101       </math>
102     </dataGenerator>
103     <dataGenerator id="dg_2_0_1" name="PZ/max(PZ) (cI normalized)">
104       <listOfVariables>
105         <variable id="task1_____PZ" target="/sbml:sbml/sbml:model/sbml:listOfSpecies/sbml:species[@id='PZ
                ']" taskReference="task1" modelReference="model1"/>
106         <dependentVariable id="task1_____PZ_max" target="/sbml:sbml/sbml:model/sbml:listOfSpecies/
                sbml:species[@id='PZ']" taskReference="task1" modelReference="model1" term="KISAO:0000828"/>
107       </listOfVariables>
108       <math xmlns="http://www.w3.org/1998/Math/MathML">
109         <apply>
110           <divide/>
111           <ci> task1_____PZ </ci>
112           <ci> task1_____PZ_max </ci>
113         </apply>
114       </math>
115     </dataGenerator>
116     <dataGenerator id="dg_2_1_0" name="PY/max(PY) (tetR normalized)">
117       <listOfVariables>
118         <variable id="task1_____PY" target="/sbml:sbml/sbml:model/sbml:listOfSpecies/sbml:species[@id='PY
                ']" taskReference="task1" modelReference="model1"/>
119         <dependentVariable id="task1_____PY_max" target="/sbml:sbml/sbml:model/sbml:listOfSpecies/
                sbml:species[@id='PY']" taskReference="task1" modelReference="model1" term="KISAO:0000828"/>
```

```
      </listOfVariables>
      <math xmlns="http://www.w3.org/1998/Math/MathML">
        <apply>
          <divide/>
          <ci> task1_____PY </ci>
          <ci> task1_____PY_max </ci>
        </apply>
      </math>
    </dataGenerator>
  </listOfDataGenerators>
  <listOfOutputs>
    <plot2D id="timecourse" name="Timecourse of repressilator">
      <listOfCurves>
        <curve id="plot_0__plot_0_0_0__plot_0_0_1" logX="false" logY="false" xDataReference="dg_0_0_0"
            yDataReference="dg_0_0_1"/>
        <curve id="plot_0__plot_0_0_0__plot_0_1_1" logX="false" logY="false" xDataReference="dg_0_0_0"
            yDataReference="dg_0_1_1"/>
        <curve id="plot_0__plot_0_0_0__plot_0_2_1" logX="false" logY="false" xDataReference="dg_0_0_0"
            yDataReference="dg_0_2_1"/>
      </listOfCurves>
    </plot2D>
    <plot2D id="preprocessing" name="Timecourse after pre-processing">
      <listOfCurves>
        <curve id="plot_1__plot_1_0_0__plot_1_0_1" logX="false" logY="false" xDataReference="dg_1_0_0"
            yDataReference="dg_1_0_1"/>
        <curve id="plot_1__plot_1_0_0__plot_1_1_1" logX="false" logY="false" xDataReference="dg_1_0_0"
            yDataReference="dg_1_1_1"/>
        <curve id="plot_1__plot_1_0_0__plot_1_2_1" logX="false" logY="false" xDataReference="dg_1_0_0"
            yDataReference="dg_1_2_1"/>
      </listOfCurves>
    </plot2D>
    <plot2D id="postprocessing" name="Timecourse after post-processing">
      <listOfCurves>
        <curve id="plot_2__plot_2_0_0__plot_2_0_1" logX="false" logY="false" xDataReference="dg_2_0_0"
            yDataReference="dg_2_0_1"/>
        <curve id="plot_2__plot_2_1_0__plot_2_0_0" logX="false" logY="false" xDataReference="dg_2_1_0"
            yDataReference="dg_2_0_0"/>
        <curve id="plot_2__plot_2_0_1__plot_2_1_0" logX="false" logY="false" xDataReference="dg_2_0_1"
            yDataReference="dg_2_1_0"/>
      </listOfCurves>
    </plot2D>
  </listOfOutputs>
</sedML>
```

Listing A.1: *SED-ML document for example simulation experiment.*

A.2 Simulation experiments with dataDescriptions

The DataDescription provides means to use external datasets in simulation experiments. In this section simulation experiments using the dataDescription are presented.

A.2.1 Plotting data with simulations (`L1V3_plotting-data-numl.omex`)

This example demonstrates the use of the DataDescription and DataSource to load external data in SED-ML. In the example a model is simulated (using a uniformTimeCourse simulation) and the simulation results are plotted. In addition data is plotted using the dataDescription and DataSource), extracting the `S1` and `time` column from it and renders it. The listed example uses data encoded in NuML as format (`urn:sedml:format:numl`).

The corresponding example using CSV (`urn:sedml:format:csv`) as format to encode the data is available as `L1V3_plotting-data-csv.omex`.

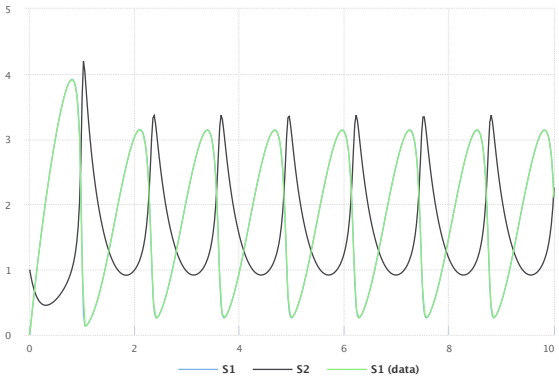


Figure A.1: *The simulation result from the simulation description given in Listing A.2. Simulation with SED-ML web tools [2].*

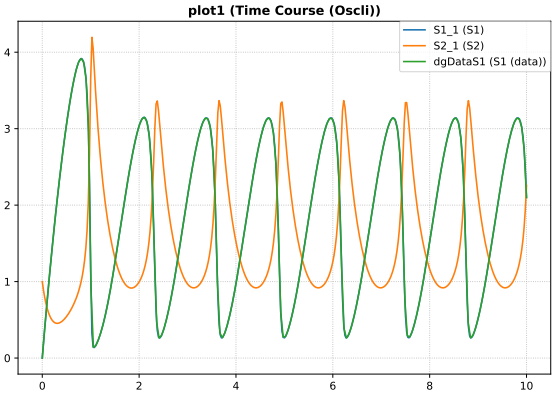


Figure A.2: *Simulation with tellurium [6].*

```
<?xml version="1.0" encoding="utf-8"?>
<sedML level="1" version="3" xmlns="http://sed-ml.org/sed-ml/level1/version3">
    <listOfDataDescriptions>
        <dataDescription id="Data1" name="oscillator data" source="./oscli.numl" format="
             urn:sedml:format:numl">
            <dimensionDescription>
                <compositeDescription indexType="double" id="time" name="time" xmlns="http://www.numl.org
                     /numl/
level1/version1">
                    <compositeDescription indexType="string" id="SpeciesIds" name="SpeciesIds">
                        <atomicDescription valueType="double" name="Concentrations"/>
                    </compositeDescription>
                </compositeDescription>
            </dimensionDescription>
            <listOfDataSources>
                <dataSource id="dataS1">
                    <listOfSlices>
                        <slice reference="SpeciesIds" value="S1"/>
                    </listOfSlices>
                </dataSource>
                <dataSource id="dataTime" indexSet="time"/>
            </listOfDataSources>
        </dataDescription>
    </listOfDataDescriptions>
    <listOfSimulations>
        <uniformTimeCourse id="sim1" initialTime="0" outputStartTime="0" outputEndTime="10"
             numberOfPoints="400">
            <algorithm kisaoID="KISAO:0000019">
                <listOfAlgorithmParameters>
                    <algorithmParameter kisaoID="KISAO:0000209" value="1E-06"/>
                    <algorithmParameter kisaoID="KISAO:0000211" value="1E-12"/>
                    <algorithmParameter kisaoID="KISAO:0000415" value="10000"/>
                </listOfAlgorithmParameters>
            </algorithm>
        </uniformTimeCourse>
    </listOfSimulations>
```

```
    <listOfModels>
        <model id="model1" language="urn:sedml:language:sbml" source="./oscli.xml"/>
    </listOfModels>
    <listOfTasks>
        <task id="task1" modelReference="model1" simulationReference="sim1"/>
    </listOfTasks>
    <listOfDataGenerators>
        <dataGenerator id="time_1" name="time">
            <listOfVariables>
                <variable id="time" name="time" taskReference="task1" symbol="urn:sedml:symbol:time"/>
            </listOfVariables>
            <math xmlns="http://www.w3.org/1998/Math/MathML">
                <ci>time</ci>
            </math>
        </dataGenerator>
        <dataGenerator id="S1_1" name="S1">
            <listOfVariables>
                <variable id="S1" name="S1" taskReference="task1"
                          target="/sbml:sbml/sbml:model/sbml:listOfSpecies/sbml:species[@id='S1']"/>
            </listOfVariables>
            <math xmlns="http://www.w3.org/1998/Math/MathML">
                <ci>S1</ci>
            </math>
        </dataGenerator>
        <dataGenerator id="S2_1" name="S2">
            <listOfVariables>
                <variable id="S2" name="S2" taskReference="task1"
                          target="/sbml:sbml/sbml:model/sbml:listOfSpecies/sbml:species[@id='S2']"/>
            </listOfVariables>
            <math xmlns="http://www.w3.org/1998/Math/MathML">
                <ci>S2</ci>
            </math>
        </dataGenerator>
        <dataGenerator id="dgDataS1" name="S1 (data)">
            <listOfVariables>
                <variable id="varS1" modelReference="model1" target="#dataS1"/>
            </listOfVariables>
            <math xmlns="http://www.w3.org/1998/Math/MathML">
                <ci>varS1</ci>
            </math>
        </dataGenerator>
        <dataGenerator id="dgDataTime" name="Time">
            <listOfVariables>
                <variable id="varTime" modelReference="model1" target="#dataTime"/>
            </listOfVariables>
            <math xmlns="http://www.w3.org/1998/Math/MathML">
                <ci>varTime</ci>
            </math>
        </dataGenerator>
    </listOfDataGenerators>
    <listOfOutputs>
        <plot2D id="plot1" name="Time Course (Oscli)">
            <listOfCurves>
                <curve id="curve1" logX="false" logY="false" xDataReference="time_1" yDataReference="S1_1
                    "/>
                <curve id="curve2" logX="false" logY="false" xDataReference="time_1" yDataReference="S2_1
                    "/>
                <curve id="curve3" logX="false" logY="false" xDataReference="dgDataTime" yDataReference="
                    dgDataS1"/>
            </listOfCurves>
        </plot2D>
    </listOfOutputs>
</sedML>
```

Listing A.2: *SED-ML document using DataSource and DataDescription*

A.3 Simulation experiments with repeatedTasks

The RepeatedTask makes it possible to encode a large number of different simulation experiments. In this section several such simulation experiments are presented.

A.3.1 Time course parameter scan (`L1V3_repeated-scan-oscli.omex`)

In this example a repeatedTask is used to run repeated uniformTimeCourse simulations with a deterministic simulation algorithm. Within the repeatedTask after each run the parameter value is changed, resulting in a time course parameter scan.

NOTE: This example produces three dimensional results (time, species concentration, multiple repeats). SED-ML Level 1 Version 4 provides ways to post-process these values with the DependentVariable class, but here they are not used, meaning that every individual element in the `xDataReference` is plotted vs. every individual element in the `yDataReference`, effectively flattening the values by overlaying them onto the desired plot. The breaks between dimensions should be used as breaks between any connected lines, so that spurious lines from the end of one plot to the beginning of the next are not present.

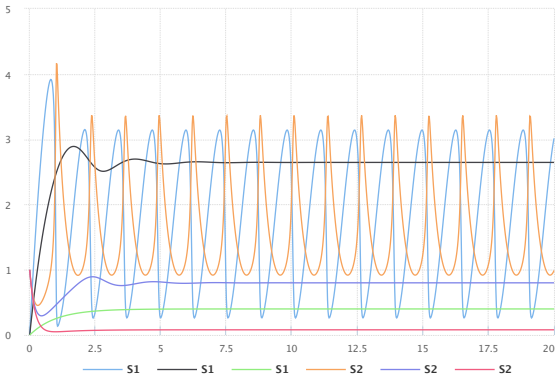


Figure A.3: *The simulation result gained from the simulation description given in Listing A.3. Simulation with SED-ML web tools [2].*

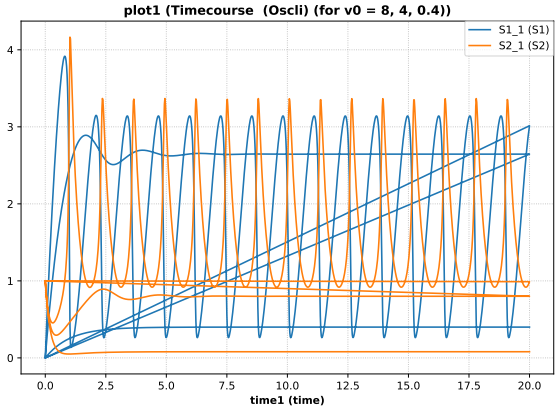


Figure A.4: *Simulation with tellurium [6].*

```
<?xml version="1.0" encoding="utf-8"?>
<sedML xmlns="http://sed-ml.org/sed-ml/level1/version3" level="1" version="3">
  <listOfSimulations>
    <uniformTimeCourse id="timecourse1" initialTime="0" outputStartTime="0" outputEndTime="20"
        numberOfPoints="1000">
      <algorithm kisaoID="KISAO:0000019" />
    </uniformTimeCourse>
  </listOfSimulations>
  <listOfModels>
    <model id="model1" language="urn:sedml:language:sbml" source="./oscli.xml" />
  </listOfModels>
  <listOfTasks>
    <task id="task0" modelReference="model1" simulationReference="timecourse1" />
    <repeatedTask id="task1" resetModel="true" range="current">
      <listOfRanges>
        <vectorRange id="current">
          <value>8</value>
          <value>4</value>
          <value>0.4</value>
        </vectorRange>
      </listOfRanges>
      <listOfChanges>
        <setValue target="/sbml:sbml/sbml:model/sbml:listOfParameters/sbml:parameter[@id='J0_v0']"
          range="current" modelReference="model1">
          <math xmlns="http://www.w3.org/1998/Math/MathML">
            <ci> current </ci>
          </math>
        </setValue>
      </listOfChanges>
      <listOfSubTasks>
        <subTask order="1" task="task0" />
      </listOfSubTasks>
    </repeatedTask>
```

```
  </listOfTasks>
  <listOfDataGenerators>
    <dataGenerator id="time1" name="time">
      <listOfVariables>
        <variable id="time" symbol="urn:sedml:symbol:time" taskReference="task1" />
      </listOfVariables>
      <math xmlns="http://www.w3.org/1998/Math/MathML">
        <ci> time </ci>
      </math>
    </dataGenerator>
    <dataGenerator id="J0_v0_1" name="J0_v0">
      <listOfVariables>
        <variable id="J0_v0" name="J0_v0" taskReference="task1" target="/sbml:sbml/sbml:model/
            sbml:listOfParameters/sbml:parameter[@id='J0_v0']" />
      </listOfVariables>
      <math xmlns="http://www.w3.org/1998/Math/MathML">
        <ci> J0_v0 </ci>
      </math>
    </dataGenerator>
    <dataGenerator id="S1_1" name="S1">
      <listOfVariables>
        <variable id="S1" name="S1" taskReference="task1" target="/sbml:sbml/sbml:model/
            sbml:listOfSpecies/sbml:species[@id='S1']" />
      </listOfVariables>
      <math xmlns="http://www.w3.org/1998/Math/MathML">
        <ci> S1 </ci>
      </math>
    </dataGenerator>
    <dataGenerator id="S2_1" name="S2">
      <listOfVariables>
        <variable id="S2" name="S2" taskReference="task1" target="/sbml:sbml/sbml:model/
            sbml:listOfSpecies/sbml:species[@id='S2']" />
      </listOfVariables>
      <math xmlns="http://www.w3.org/1998/Math/MathML">
        <ci> S2 </ci>
      </math>
    </dataGenerator>
  </listOfDataGenerators>
  <listOfOutputs>
    <plot2D id="plot1" name="Timecourse  (Oscli) (for v0 = 8, 4, 0.4)">
      <listOfCurves>
        <curve id="curve1" logX="false" logY="false" xDataReference="time1" yDataReference="S1_1" />
        <curve id="curve2" logX="false" logY="false" xDataReference="time1" yDataReference="S2_1" />
      </listOfCurves>
    </plot2D>
  </listOfOutputs>
</sedML>
```

Listing A.3: *SED-ML document implementing the one dimensional time course parameter scan*

A.3.2 Steady state parameter scan (`L1V3_repeated-steady-scan-oscli.omex`)

In this example a repeatedTask is used in combination with a steadyState simulation task (performing a steady state computation). On each repeat a parameter is varied resulting in a steady state parameter scan.

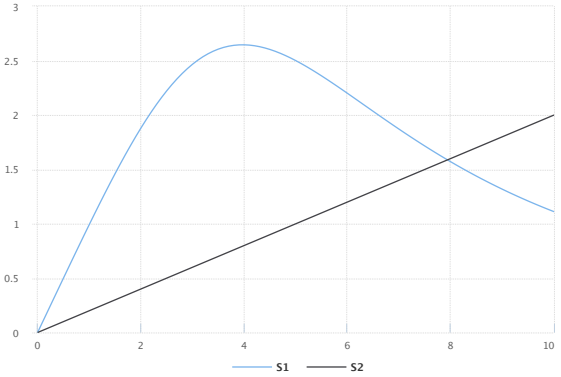


Figure A.5: *The simulation result from the simulation description given in Listing A.4. Simulation with SED-ML web tools [2].*

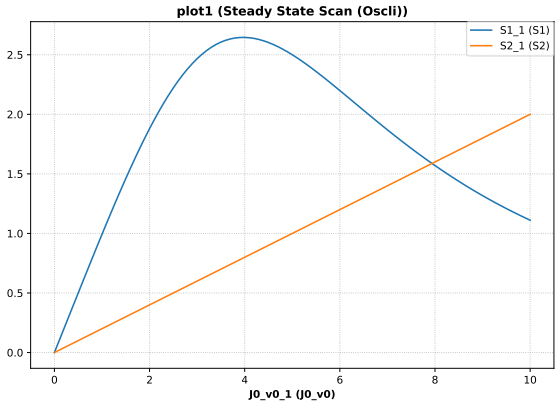


Figure A.6: *Simulation with tellurium [6].*

```xml
<?xml version="1.0" encoding="utf-8"?>
<!-- Written by libSedML v1.1.4992.38982 see http://libsedml.sf.net -->
<sedML xmlns="http://sed-ml.org/sed-ml/level1/version3" level="1" version="3">
  <listOfSimulations>
    <steadyState id="steady1">
      <algorithm kisaoID="KISAO:0000282" />
    </steadyState>
  </listOfSimulations>
  <listOfModels>
    <model id="model1" language="urn:sedml:language:sbml" source="./oscli.xml" />
  </listOfModels>
  <listOfTasks>
    <task id="task0" modelReference="model1" simulationReference="steady1" />
    <repeatedTask id="task1" resetModel="true" range="current">
      <listOfRanges>
        <uniformRange id="current" start="0" end="10" numberOfPoints="100" type="linear" />
      </listOfRanges>
      <listOfChanges>
        <setValue target="/sbml:sbml/sbml:model/sbml:listOfParameters/sbml:parameter[@id='J0_v0']"
          range="current" modelReference="model1">
          <math xmlns="http://www.w3.org/1998/Math/MathML">
            <ci> current </ci>
          </math>
        </setValue>
      </listOfChanges>
      <listOfSubTasks>
        <subTask order="1" task="task0" />
      </listOfSubTasks>
    </repeatedTask>
  </listOfTasks>
  <listOfDataGenerators>
    <dataGenerator id="J0_v0_1" name="J0_v0">
      <listOfVariables>
        <variable id="J0_v0" name="J0_v0" taskReference="task1" target="/sbml:sbml/sbml:model/
            sbml:listOfParameters/sbml:parameter[@id='J0_v0']" />
      </listOfVariables>
      <math xmlns="http://www.w3.org/1998/Math/MathML">
        <ci> J0_v0 </ci>
      </math>
    </dataGenerator>
    <dataGenerator id="S1_1" name="S1">
      <listOfVariables>
        <variable id="S1" name="S1" taskReference="task1" target="/sbml:sbml/sbml:model/
            sbml:listOfSpecies/sbml:species[@id='S1']" />
      </listOfVariables>
      <math xmlns="http://www.w3.org/1998/Math/MathML">
        <ci> S1 </ci>
      </math>
    </dataGenerator>
    <dataGenerator id="S2_1" name="S2">
      <listOfVariables>
        <variable id="S2" name="S2" taskReference="task1" target="/sbml:sbml/sbml:model/
            sbml:listOfSpecies/sbml:species[@id='S2']" />
      </listOfVariables>
      <math xmlns="http://www.w3.org/1998/Math/MathML">
        <ci> S2 </ci>
      </math>
    </dataGenerator>
  </listOfDataGenerators>
  <listOfOutputs>
    <plot2D id="plot1" name="Steady State Scan (Oscli)">
      <listOfCurves>
        <curve id="curve1" logX="false" logY="false" xDataReference="J0_v0_1" yDataReference="S1_1" />
        <curve id="curve2" logX="false" logY="false" xDataReference="J0_v0_1" yDataReference="S2_1" />
      </listOfCurves>
    </plot2D>
    <report id="report1" name="Steady State Values">
      <listOfDataSets>
        <dataSet id="col1" dataReference="J0_v0_1" label="J0_v0" />
        <dataSet id="col2" dataReference="S1_1" label="S1" />
        <dataSet id="col3" dataReference="S2_1" label="S2" />
      </listOfDataSets>
    </report>
  </listOfOutputs>
</sedML>
```

Listing A.4: *SED-ML document implementing the one dimensional steady state parameter scan*

A.3.3 Stochastic simulation (L1V3_repeated-stochastic-runs.omex)

In this example a repeatedTask is used to run a stochastic simulation multiple times. Running just one stochastic trace does not provide a complete picture of the behavior of a system. A large number of such traces is needed. This example demonstrates the basic use case of running ten traces of a simulation by using a repeatedTask which runs ten uniform time course simulations (each performing a stochastic

simulation run).

NOTE: This example produces three dimensional results (time, species concentration, multiple repeats). SED-ML Level 1 Version 4 provides ways to post-process these values with the DependentVariable class, but here they are not used, meaning that every individual element in the `xDataReference` is plotted vs. every individual element in the `yDataReference`, effectively flattening the values by overlaying them onto the desired plot. The breaks between dimensions should be used as breaks between any connected lines, so that spurious lines from the end of one plot to the beginning of the next are not present.

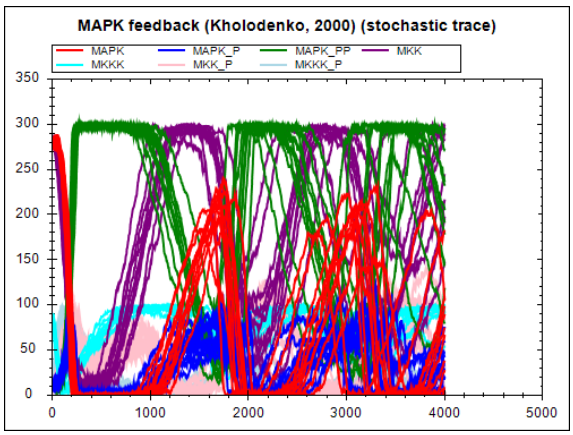


Figure A.7: *The simulation result from the simulation description given in Listing A.5. Simulation with SED-ML web tools [2].*

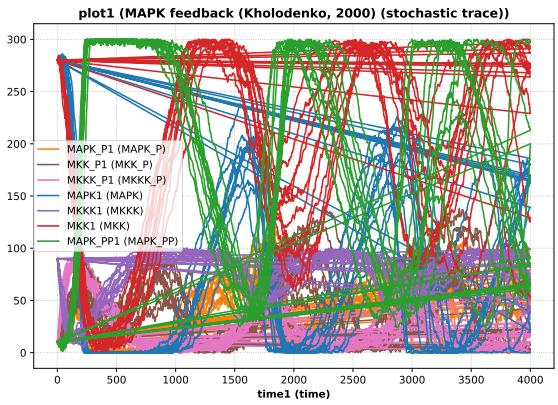


Figure A.8: *Simulation with tellurium [6].*

```
<?xml version="1.0" encoding="utf-8"?>
<sedML xmlns="http://sed-ml.org/sed-ml/level1/version3" level="1" version="3">
  <listOfSimulations>
    <uniformTimeCourse id="timecourse1" initialTime="0" outputStartTime="0" outputEndTime="4000"
        numberOfPoints="1000">
      <algorithm kisaoID="KISAO:0000241" />
    </uniformTimeCourse>
  </listOfSimulations>
  <listOfModels>
    <model id="model1" language="urn:sedml:language:sbml" source="./BorisEJB.xml" />
  </listOfModels>
  <listOfTasks>
    <task id="task0" modelReference="model1" simulationReference="timecourse1" />
    <repeatedTask id="task1" resetModel="true" range="current">
      <listOfRanges>
        <uniformRange id="current" start="0" end="10" numberOfPoints="10" type="linear" />
      </listOfRanges>
      <listOfSubTasks>
        <subTask order="1" task="task0" />
      </listOfSubTasks>
    </repeatedTask>
  </listOfTasks>
  <listOfDataGenerators>
    <dataGenerator id="time1" name="time">
      <listOfVariables>
        <variable id="time" taskReference="task1" symbol="urn:sedml:symbol:time" />
      </listOfVariables>
      <math xmlns="http://www.w3.org/1998/Math/MathML">
        <ci> time </ci>
      </math>
    </dataGenerator>
    <dataGenerator id="MAPK1" name="MAPK">
      <listOfVariables>
        <variable id="MAPK" name="MAPK" taskReference="task1" target="/sbml:sbml/sbml:model/
            sbml:listOfSpecies/sbml:species[@id='MAPK']" />
      </listOfVariables>
      <math xmlns="http://www.w3.org/1998/Math/MathML">
        <ci> MAPK </ci>
      </math>
    </dataGenerator>
    <dataGenerator id="MAPK_P1" name="MAPK_P">
      <listOfVariables>
        <variable id="MAPK_P" name="MAPK_P" taskReference="task1" target="/sbml:sbml/sbml:model/
            sbml:listOfSpecies/sbml:species[@id='MAPK_P']" />
      </listOfVariables>
      <math xmlns="http://www.w3.org/1998/Math/MathML">
```

```
        <ci> MAPK_P </ci>
      </math>
    </dataGenerator>
    <dataGenerator id="MAPK_PP1" name="MAPK_PP">
      <listOfVariables>
        <variable id="MAPK_PP" name="MAPK_PP" taskReference="task1" target="/sbml:sbml/sbml:model/
            sbml:listOfSpecies/sbml:species[@id='MAPK_PP']" />
      </listOfVariables>
      <math xmlns="http://www.w3.org/1998/Math/MathML">
        <ci> MAPK_PP </ci>
      </math>
    </dataGenerator>
    <dataGenerator id="MKK1" name="MKK">
      <listOfVariables>
        <variable id="MKK" name="MKK" taskReference="task1" target="/sbml:sbml/sbml:model/
            sbml:listOfSpecies/sbml:species[@id='MKK']" />
      </listOfVariables>
      <math xmlns="http://www.w3.org/1998/Math/MathML">
        <ci> MKK </ci>
      </math>
    </dataGenerator>
    <dataGenerator id="MKK_P1" name="MKK_P">
      <listOfVariables>
        <variable id="MKK_P" name="MKK_P" taskReference="task1" target="/sbml:sbml/sbml:model/
            sbml:listOfSpecies/sbml:species[@id='MKK_P']" />
      </listOfVariables>
      <math xmlns="http://www.w3.org/1998/Math/MathML">
        <ci> MKK_P </ci>
      </math>
    </dataGenerator>
    <dataGenerator id="MKKK1" name="MKKK">
      <listOfVariables>
        <variable id="MKKK" name="MKKK" taskReference="task1" target="/sbml:sbml/sbml:model/
            sbml:listOfSpecies/sbml:species[@id='MKKK']" />
      </listOfVariables>
      <math xmlns="http://www.w3.org/1998/Math/MathML">
        <ci> MKKK </ci>
      </math>
    </dataGenerator>
    <dataGenerator id="MKKK_P1" name="MKKK_P">
      <listOfVariables>
        <variable id="MKKK_P" name="MKKK_P" taskReference="task1" target="/sbml:sbml/sbml:model/
            sbml:listOfSpecies/sbml:species[@id='MKKK_P']" />
      </listOfVariables>
      <math xmlns="http://www.w3.org/1998/Math/MathML">
        <ci> MKKK_P </ci>
      </math>
    </dataGenerator>
  </listOfDataGenerators>
  <listOfOutputs>
    <plot2D id="plot1" name="MAPK feedback (Kholodenko, 2000) (stochastic trace)">
      <listOfCurves>
        <curve id="curve1" logX="false" logY="false" xDataReference="time1" yDataReference="MAPK1" />
        <curve id="curve2" logX="false" logY="false" xDataReference="time1" yDataReference="MAPK_P1" />
        <curve id="curve3" logX="false" logY="false" xDataReference="time1" yDataReference="MAPK_PP1" />
        <curve id="curve4" logX="false" logY="false" xDataReference="time1" yDataReference="MKK1" />
        <curve id="curve5" logX="false" logY="false" xDataReference="time1" yDataReference="MKKK1" />
        <curve id="curve6" logX="false" logY="false" xDataReference="time1" yDataReference="MKK_P1" />
        <curve id="curve7" logX="false" logY="false" xDataReference="time1" yDataReference="MKKK_P1" />
      </listOfCurves>
    </plot2D>
  </listOfOutputs>
</sedML>
```

Listing A.5: *SED-ML document implementing repeated stochastic runs*

A.3.4 Simulation perturbation (`L1V3_oscli-nested-pulse.omex`)

Often it is interesting to see how the dynamic behavior of a model changes when some perturbations are applied to the model. In this example a repeatedTask is used iterating a oneStep task (that advances an ODE integration to the next output step). During the steps a single parameter is modified effectively causing the oscillations of a model to stop. Once the value is reset the oscillations recover.

Note: In the example a functionalRange is used, although the same result could also be achieved using the setValue element directly.

```
<?xml version="1.0" encoding="utf-8"?>
<sedML xmlns="http://sed-ml.org/sed-ml/level1/version3" level="1" version="3">
  <listOfSimulations>
    <oneStep id="stepper" step="0.1">
      <algorithm kisaoID="KISAO:0000019" />
    </oneStep>
  </listOfSimulations>
  <listOfModels>
```

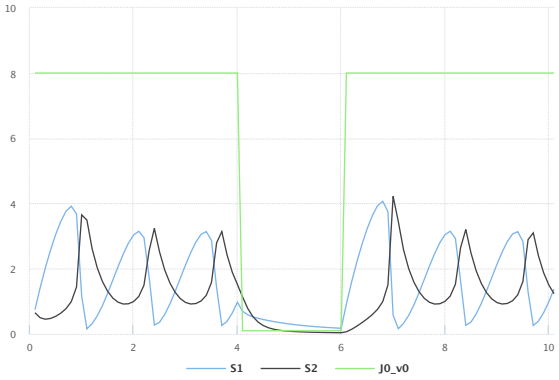


Figure A.9: *The simulation result from the simulation description given in Listing A.6. Simulation with SED-ML web tools [2].*

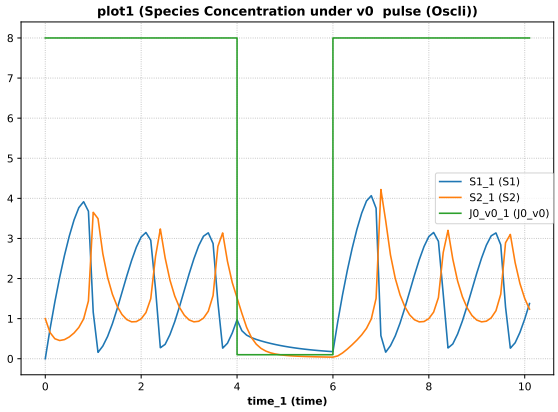


Figure A.10: *Simulation with tellurium [6].*

```
    <model id="model1" language="urn:sedml:language:sbml" source="./oscli.xml" />
  </listOfModels>
  <listOfTasks>
    <task id="task0" modelReference="model1" simulationReference="stepper" />
    <repeatedTask id="task1" resetModel="false" range="index">
      <listOfRanges>
        <uniformRange id="index" start="0" end="10" numberOfPoints="100" type="linear" />
        <functionalRange id="current" range="index">
          <math xmlns="http://www.w3.org/1998/Math/MathML">
            <piecewise>
              <piece>
                <cn> 8 </cn>
                <apply>
                  <lt />
                  <ci> index </ci>
                  <cn> 1 </cn>
                </apply>
              </piece>
              <piece>
                <cn> 0.1 </cn>
                <apply>
                  <and />
                  <apply>
                    <geq />
                    <ci> index </ci>
                    <cn> 4 </cn>
                  </apply>
                  <apply>
                    <lt />
                    <ci> index </ci>
                    <cn> 6 </cn>
                  </apply>
                </apply>
              </piece>
              <otherwise>
                <cn> 8 </cn>
              </otherwise>
            </piecewise>
          </math>
        </functionalRange>
      </listOfRanges>
      <listOfChanges>
        <setValue target="/sbml:sbml/sbml:model/sbml:listOfParameters/sbml:parameter[@id='J0_v0']"
          range="current" modelReference="model1">
          <math xmlns="http://www.w3.org/1998/Math/MathML">
            <ci> current </ci>
          </math>
        </setValue>
      </listOfChanges>
      <listOfSubTasks>
        <subTask order="1" task="task0" />
      </listOfSubTasks>
    </repeatedTask>
  </listOfTasks>
  <listOfDataGenerators>
    <dataGenerator id="time_1" name="time">
      <listOfVariables>
        <variable id="time" symbol="urn:sedml:symbol:time" taskReference="task1" />
      </listOfVariables>
```

```
      <math xmlns="http://www.w3.org/1998/Math/MathML">
        <ci> time </ci>
      </math>
    </dataGenerator>
    <dataGenerator id="J0_v0_1" name="J0_v0">
      <listOfVariables>
        <variable id="J0_v0" name="J0_v0" taskReference="task1" target="/sbml:sbml/sbml:model/
            sbml:listOfParameters/sbml:parameter[@id='J0_v0']" />
      </listOfVariables>
      <math xmlns="http://www.w3.org/1998/Math/MathML">
        <ci> J0_v0 </ci>
      </math>
    </dataGenerator>
    <dataGenerator id="S1_1" name="S1">
      <listOfVariables>
        <variable id="S1" name="S1" taskReference="task1" target="/sbml:sbml/sbml:model/
            sbml:listOfSpecies/sbml:species[@id='S1']" />
      </listOfVariables>
      <math xmlns="http://www.w3.org/1998/Math/MathML">
        <ci> S1 </ci>
      </math>
    </dataGenerator>
    <dataGenerator id="S2_1" name="S2">
      <listOfVariables>
        <variable id="S2" name="S2" taskReference="task1" target="/sbml:sbml/sbml:model/
            sbml:listOfSpecies/sbml:species[@id='S2']" />
      </listOfVariables>
      <math xmlns="http://www.w3.org/1998/Math/MathML">
        <ci> S2 </ci>
      </math>
    </dataGenerator>
  </listOfDataGenerators>
  <listOfOutputs>
    <plot2D id="plot1" name="Species Concentration under v0  pulse (Oscli)">
      <listOfCurves>
        <curve id="curve1" logX="false" logY="false" xDataReference="time_1" yDataReference="S1_1" />
        <curve id="curve2" logX="false" logY="false" xDataReference="time_1" yDataReference="S2_1" />
        <curve id="curve3" logX="false" logY="false" xDataReference="time_1" yDataReference="J0_v0_1" />
      </listOfCurves>
    </plot2D>
    <report id="report1" name="Species Concentration under v0  pulse (Oscli)">
      <listOfDataSets>
        <dataSet id="col0" dataReference="time_1" label="time" />
        <dataSet id="col1" dataReference="J0_v0_1" label="J0_v0" />
        <dataSet id="col2" dataReference="S1_1" label="S1" />
        <dataSet id="col3" dataReference="S2_1" label="S2" />
      </listOfDataSets>
    </report>
  </listOfOutputs>
</sedML>
```

Listing A.6: *SED-ML document implementing the perturbation experiment*

A.3.5 2D steady state parameter scan (`L1V3_parameter-scan-2d.omex`)

This example uses a repeatedTask which runs over another repeatedTask which performs a steady state computation. Each repeated simulation task modifies a different parameter.

NOTE: This example produces three dimensional results (time, species concentration, multiple repeats). SED-ML Level 1 Version 4 provides ways to post-process these values with the DependentVariable class, but here they are not used, meaning that every individual element in the `xDataReference` is plotted vs. every individual element in the `yDataReference`, effectively flattening the values by overlaying them onto the desired plot. The breaks between dimensions should be used as breaks between any connected lines, so that spurious lines from the end of one plot to the beginning of the next are not present.

```
<?xml version="1.0" encoding="utf-8"?>
<sedML xmlns="http://sed-ml.org/sed-ml/level1/version3" level="1" version="3">
  <listOfSimulations>
    <steadyState id="steady1">
      <algorithm kisaoID="KISAO:0000282" />
    </steadyState>
  </listOfSimulations>
  <listOfModels>
    <model id="model1" language="urn:sedml:language:sbml" source="BorisEJB.xml" />
  </listOfModels>
  <listOfTasks>
    <task id="task0" modelReference="model1" simulationReference="steady1" />
    <repeatedTask id="task1" resetModel="false" range="current">
      <listOfRanges>
        <vectorRange id="current">
          <value>1</value>
          <value>5</value>
          <value>10</value>
```

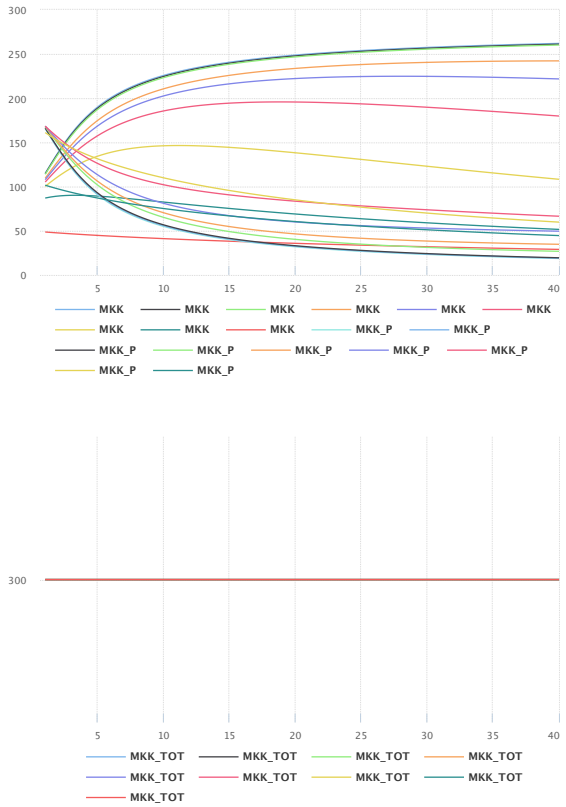


Figure A.11: *The simulation result gained from the simulation description given in Listing A.7. Simulation with SED-ML web tools [2].*

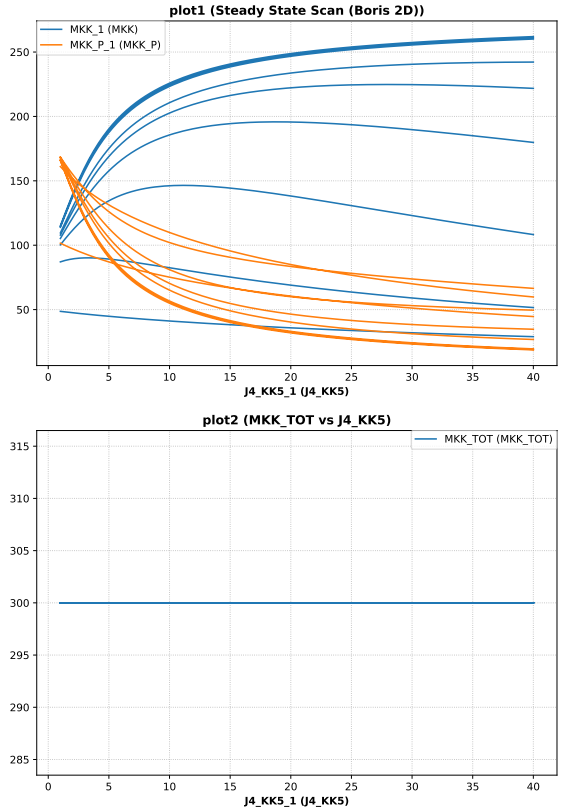


Figure A.12: *Simulation with tellurium [6].*

```
          <value>50</value>
          <value>60</value>
          <value>70</value>
          <value>80</value>
          <value>90</value>
          <value>100</value>
        </vectorRange>
      </listOfRanges>
      <listOfChanges>
        <setValue target="/sbml:sbml/sbml:model/sbml:listOfParameters/sbml:parameter[@id='J1_KK2']"
          range="current" modelReference="model1">
          <math xmlns="http://www.w3.org/1998/Math/MathML">
            <ci> current </ci>
          </math>
        </setValue>
      </listOfChanges>
      <listOfSubTasks>
        <subTask order="1" task="task2" />
      </listOfSubTasks>
    </repeatedTask>
    <repeatedTask id="task2" resetModel="false" range="current1">
      <listOfRanges>
        <uniformRange id="current1" start="1" end="40" numberOfPoints="100" type="linear" />
      </listOfRanges>
      <listOfChanges>
        <setValue target="/sbml:sbml/sbml:model/sbml:listOfParameters/sbml:parameter[@id='J4_KK5']"
          range="current1" modelReference="model1">
          <math xmlns="http://www.w3.org/1998/Math/MathML">
            <ci> current1 </ci>
          </math>
        </setValue>
      </listOfChanges>
      <listOfSubTasks>
        <subTask order="1" task="task0" />
      </listOfSubTasks>
    </repeatedTask>
  </listOfTasks>
  <listOfDataGenerators>
    <dataGenerator id="J4_KK5_1" name="J4_KK5">
```

```
      <listOfVariables>
        <variable id="J4_KK5" name="J4_KK5" taskReference="task1" target="/sbml:sbml/sbml:model/
            sbml:listOfParameters/sbml:parameter[@id='J4_KK5']" />
      </listOfVariables>
      <math xmlns="http://www.w3.org/1998/Math/MathML">
        <ci> J4_KK5 </ci>
      </math>
    </dataGenerator>
    <dataGenerator id="J1_KK2_1" name="J1_KK2">
      <listOfVariables>
        <variable id="J1_KK2" name="J1_KK2" taskReference="task1" target="/sbml:sbml/sbml:model/
            sbml:listOfParameters/sbml:parameter[@id='J1_KK2']" />
      </listOfVariables>
      <math xmlns="http://www.w3.org/1998/Math/MathML">
        <ci> J1_KK2 </ci>
      </math>
    </dataGenerator>
    <dataGenerator id="MKK_1" name="MKK">
      <listOfVariables>
        <variable id="MKK" name="MKK" taskReference="task1" target="/sbml:sbml/sbml:model/
            sbml:listOfSpecies/sbml:species[@id='MKK']" />
      </listOfVariables>
      <math xmlns="http://www.w3.org/1998/Math/MathML">
        <ci> MKK </ci>
      </math>
    </dataGenerator>
    <dataGenerator id="MKK_P_1" name="MKK_P">
      <listOfVariables>
        <variable id="MKK_P" name="MKK_P" taskReference="task1" target="/sbml:sbml/sbml:model/
            sbml:listOfSpecies/sbml:species[@id='MKK_P']" />
      </listOfVariables>
      <math xmlns="http://www.w3.org/1998/Math/MathML">
        <ci> MKK_P </ci>
      </math>
    </dataGenerator>
    <dataGenerator id="MKK_PP_1" name="MKK_PP_1">
      <listOfVariables>
        <variable id="MKK_PP_1" name="MKK_PP" taskReference="task1" target="/sbml:sbml/sbml:model/
            sbml:listOfSpecies/sbml:species[@id='MKK_PP']" />
      </listOfVariables>
      <math xmlns="http://www.w3.org/1998/Math/MathML">
        <ci> MKK_PP_1 </ci>
      </math>
    </dataGenerator>
    <dataGenerator id="MKK_TOT" name="MKK_TOT">
      <listOfVariables>
        <variable id="MKK" name="MKK" taskReference="task1" target="/sbml:sbml/sbml:model/
            sbml:listOfSpecies/sbml:species[@id='MKK']" />
        <variable id="MKK_P" name="MKK_P" taskReference="task1" target="/sbml:sbml/sbml:model/
            sbml:listOfSpecies/sbml:species[@id='MKK_P']" />
        <variable id="MKK_PP" name="MKK_PP" taskReference="task1" target="/sbml:sbml/sbml:model/
            sbml:listOfSpecies/sbml:species[@id='MKK_PP']" />
      </listOfVariables>
      <math xmlns="http://www.w3.org/1998/Math/MathML">
        <apply>
          <plus/>
          <ci> MKK </ci>
          <ci> MKK_P </ci>
          <ci> MKK_PP </ci>
        </apply>
      </math>
    </dataGenerator>
  </listOfDataGenerators>
  <listOfOutputs>
    <plot2D id="plot1" name="Steady State Scan (Boris 2D)">
      <listOfCurves>
        <curve id="curve1" logX="false" logY="false" xDataReference="J4_KK5_1" yDataReference="MKK_1" />
        <curve id="curve2" logX="false" logY="false" xDataReference="J4_KK5_1" yDataReference="MKK_P_1" /
            >
      </listOfCurves>
    </plot2D>
    <plot2D id="plot2" name="MKK_TOT vs J4_KK5">
      <listOfCurves>
        <curve id="curve3" logX="false" logY="false" xDataReference="J4_KK5_1" yDataReference="MKK_TOT" /
            >
      </listOfCurves>
    </plot2D>
    <report id="report1" name="Steady State Values (Boris2D)">
      <listOfDataSets>
        <dataSet id="col0" dataReference="J4_KK5_1" label="J4_KK5" />
        <dataSet id="col1" dataReference="J1_KK2_1" label="J1_KK2" />
        <dataSet id="col2" dataReference="MKK_1" label="MKK" />
        <dataSet id="col3" dataReference="MKK_P_1" label="MKK_P" />
        <dataSet id="col_4" dataReference="MKK_PP_1" label="MKK_PP_1" />
        <dataSet id="col4" dataReference="MKK_TOT" label="MKK_TOT" />
      </listOfDataSets>
    </report>
  </listOfOutputs>
```

```
136 </sedML>
```

Listing A.7: *SED-ML document implementing the two dimensional steady state parameter scan*

A.4 Simulation experiments with different model languages

SED-ML allows to specify models in various languages, e.g., SBML [16] and CellML [9] (see Section 3.2.3 for more information). This section demonstrates the same simulation experiment with the model either in SBML (Appendix A.4.1) or in CellML (Appendix A.4.2).

A.4.1 Van der Pol oscillator in SBML (`L1V3_vanderpol-sbml.omex`)

The following example provides a SED-ML description for the simulation of the Van der Pol oscillator in SBML [16]. The time-course and the behavior in the phase plane are plotted. The mathematical model and the performed simulation experiment are identical to Appendix A.4.2.

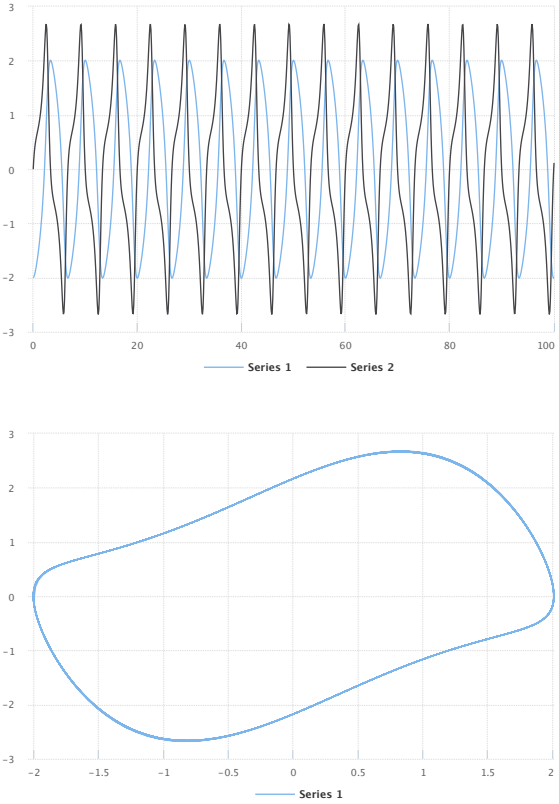


Figure A.13: *The simulation result gained from the simulation description given in Listing A.8. Simulation with SED-ML web tools [2].*

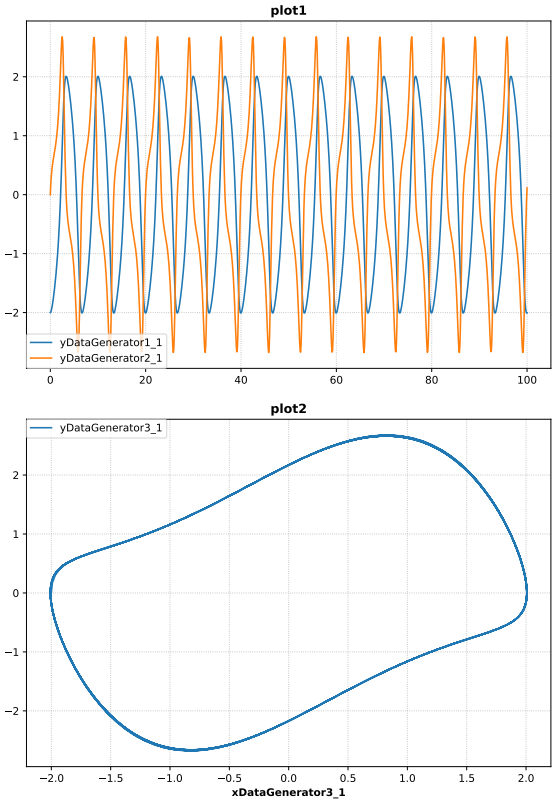


Figure A.14: *Simulation with tellurium [6].*

```
<?xml version='1.0' encoding='UTF-8'?>
<sedML level="1" version="3" xmlns="http://sed-ml.org/sed-ml/level1/version3">
    <listOfSimulations>
        <uniformTimeCourse id="simulation1" initialTime="0" numberOfPoints="1000" outputEndTime="100"
             outputStartTime="0">
            <algorithm kisaoID="KISAO:0000019">
                <listOfAlgorithmParameters>
                    <algorithmParameter kisaoID="KISAO:0000211" value="1e-07"/>
                    <algorithmParameter kisaoID="KISAO:0000475" value="BDF"/>
                    <algorithmParameter kisaoID="KISAO:0000481" value="true"/>
                    <algorithmParameter kisaoID="KISAO:0000476" value="Newton"/>
                    <algorithmParameter kisaoID="KISAO:0000477" value="Dense"/>
                    <algorithmParameter kisaoID="KISAO:0000480" value="0"/>
                    <algorithmParameter kisaoID="KISAO:0000415" value="500"/>
                    <algorithmParameter kisaoID="KISAO:0000467" value="0"/>
                    <algorithmParameter kisaoID="KISAO:0000478" value="Banded"/>
                    <algorithmParameter kisaoID="KISAO:0000209" value="1e-07"/>
                    <algorithmParameter kisaoID="KISAO:0000479" value="0"/>
                </listOfAlgorithmParameters>
            </algorithm>
```

```
        </uniformTimeCourse>
    </listOfSimulations>
    <listOfModels>
        <model id="model" language="urn:sedml:language:sbml" source="vanderpol-sbml.xml"/>
    </listOfModels>
    <listOfTasks>
        <repeatedTask id="repeatedTask" range="once" resetModel="true">
            <listOfRanges>
                <vectorRange id="once">
                    <value> 1 </value>
                </vectorRange>
            </listOfRanges>
            <listOfSubTasks>
                <subTask order="1" task="task1"/>
            </listOfSubTasks>
        </repeatedTask>
        <task id="task1" modelReference="model" simulationReference="simulation1"/>
    </listOfTasks>
    <listOfDataGenerators>
        <dataGenerator id="xDataGenerator1_1">
            <listOfVariables>
                <variable id="xVariable1_1" taskReference="task1" symbol="urn:sedml:symbol:time" />
            </listOfVariables>
            <math xmlns="http://www.w3.org/1998/Math/MathML">
                <ci> xVariable1_1 </ci>
            </math>
        </dataGenerator>
        <dataGenerator id="yDataGenerator1_1">
            <listOfVariables>
                <variable id="yVariable1_1" target="/sbml:sbml/sbml:model/sbml:listOfSpecies/sbml:species
                    [@id='x']" taskReference="repeatedTask" modelReference="model"/>
            </listOfVariables>
            <math xmlns="http://www.w3.org/1998/Math/MathML">
                <ci> yVariable1_1 </ci>
            </math>
        </dataGenerator>
        <dataGenerator id="xDataGenerator2_1">
            <listOfVariables>
                <variable id="xVariable2_1" taskReference="task1" symbol="urn:sedml:symbol:time" />
            </listOfVariables>
            <math xmlns="http://www.w3.org/1998/Math/MathML">
                <ci> xVariable2_1 </ci>
            </math>
        </dataGenerator>
        <dataGenerator id="yDataGenerator2_1">
            <listOfVariables>
                <variable id="yVariable2_1" target="/sbml:sbml/sbml:model/sbml:listOfSpecies/sbml:species
                    [@id='y']" taskReference="repeatedTask" modelReference="model"/>
            </listOfVariables>
            <math xmlns="http://www.w3.org/1998/Math/MathML">
                <ci> yVariable2_1 </ci>
            </math>
        </dataGenerator>
        <dataGenerator id="xDataGenerator3_1">
            <listOfVariables>
                <variable id="xVariable3_1" target="/sbml:sbml/sbml:model/sbml:listOfSpecies/sbml:species
                    [@id='x']" taskReference="repeatedTask" modelReference="model"/>
            </listOfVariables>
            <math xmlns="http://www.w3.org/1998/Math/MathML">
                <ci> xVariable3_1 </ci>
            </math>
        </dataGenerator>
        <dataGenerator id="yDataGenerator3_1">
            <listOfVariables>
                <variable id="yVariable3_1" target="/sbml:sbml/sbml:model/sbml:listOfSpecies/sbml:species
                    [@id='y']" taskReference="repeatedTask" modelReference="model"/>
            </listOfVariables>
            <math xmlns="http://www.w3.org/1998/Math/MathML">
                <ci> yVariable3_1 </ci>
            </math>
        </dataGenerator>
    </listOfDataGenerators>
    <listOfOutputs>
        <plot2D id="plot1">
            <listOfCurves>
                <curve id="curve1_1" logX="false" logY="false" xDataReference="xDataGenerator1_1"
                    yDataReference="yDataGenerator1_1"/>
                <curve id="curve2_1" logX="false" logY="false" xDataReference="xDataGenerator2_1"
                    yDataReference="yDataGenerator2_1"/>
            </listOfCurves>
        </plot2D>
        <plot2D id="plot2">
            <listOfCurves>
                <curve id="curve3_1" logX="false" logY="false" xDataReference="xDataGenerator3_1"
                    yDataReference="yDataGenerator3_1"/>
            </listOfCurves>
        </plot2D>
    </listOfOutputs>
```

```
</sedML>
```

Listing A.8: *Van der Pol Model (SBML) Simulation Description in SED-ML*

A.4.2 Van der Pol oscillator in CellML (`L1V3_vanderpol-cellml.omex`)

The following example provides a SED-ML description for the simulation of the Van der Pol model in CellML [9]. The time-course and the behavior in the phase plane are plotted. The mathematical model and the performed simulation experiment are identical to Appendix A.4.1.

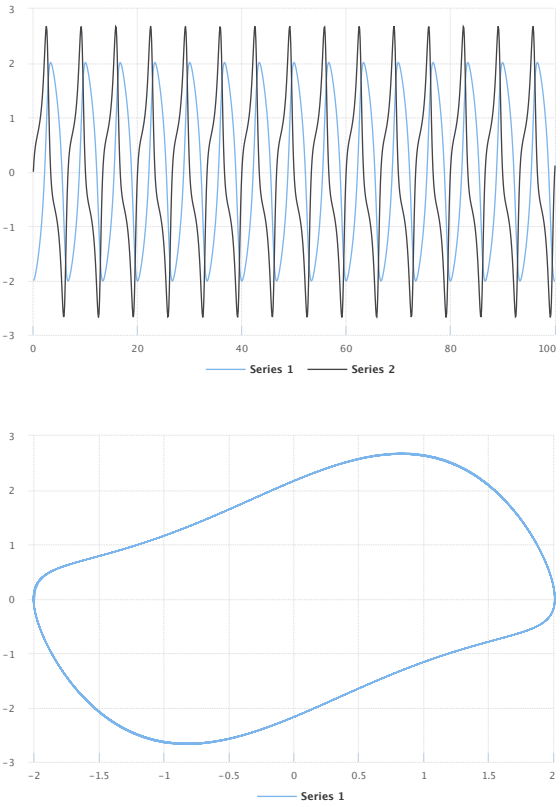


Figure A.15: *The simulation result gained from the simulation description given in Listing A.9. Simulation with SED-ML web tools [2].*

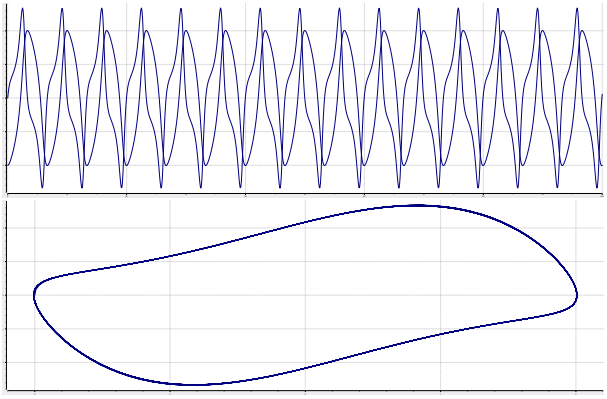


Figure A.16: *Simulation with OpenCOR [11].*

```
<?xml version='1.0' encoding='UTF-8'?>
<sedML level="1" version="3" xmlns="http://sed-ml.org/sed-ml/level1/version3" xmlns:cellml="http://www.
     cellml.org/cellml/1.0#">
    <listOfSimulations>
        <uniformTimeCourse id="simulation1" initialTime="0" numberOfPoints="1000" outputEndTime="100"
             outputStartTime="0">
            <algorithm kisaoID="KISAO:0000019">
                <listOfAlgorithmParameters>
                    <algorithmParameter kisaoID="KISAO:0000211" value="1e-07"/>
                    <algorithmParameter kisaoID="KISAO:0000475" value="BDF"/>
                    <algorithmParameter kisaoID="KISAO:0000481" value="true"/>
                    <algorithmParameter kisaoID="KISAO:0000476" value="Newton"/>
                    <algorithmParameter kisaoID="KISAO:0000477" value="Dense"/>
                    <algorithmParameter kisaoID="KISAO:0000480" value="0"/>
                    <algorithmParameter kisaoID="KISAO:0000415" value="500"/>
                    <algorithmParameter kisaoID="KISAO:0000467" value="0"/>
                    <algorithmParameter kisaoID="KISAO:0000478" value="Banded"/>
                    <algorithmParameter kisaoID="KISAO:0000209" value="1e-07"/>
                    <algorithmParameter kisaoID="KISAO:0000479" value="0"/>
                </listOfAlgorithmParameters>
            </algorithm>
        </uniformTimeCourse>
    </listOfSimulations>
    <listOfModels>
```

```
        <model id="model" language="urn:sedml:language:cellml.1_0" source="vanderpol-model.cellml"/>
    </listOfModels>
    <listOfTasks>
        <repeatedTask id="repeatedTask" range="once" resetModel="true">
            <listOfRanges>
                <vectorRange id="once">
                    <value> 1 </value>
                </vectorRange>
            </listOfRanges>
            <listOfSubTasks>
                <subTask order="1" task="task1"/>
            </listOfSubTasks>
        </repeatedTask>
        <task id="task1" modelReference="model" simulationReference="simulation1"/>
    </listOfTasks>
    <listOfDataGenerators>
        <dataGenerator id="xDataGenerator1_1">
            <listOfVariables>
                <variable id="xVariable1_1" target="/cellml:model/cellml:component[@name='main']/
                    cellml:variable[@name='t']" taskReference="repeatedTask"/>
            </listOfVariables>
            <math xmlns="http://www.w3.org/1998/Math/MathML">
                <ci> xVariable1_1 </ci>
            </math>
        </dataGenerator>
        <dataGenerator id="yDataGenerator1_1">
            <listOfVariables>
                <variable id="yVariable1_1" target="/cellml:model/cellml:component[@name='main']/
                    cellml:variable[@name='x']" taskReference="repeatedTask"/>
            </listOfVariables>
            <math xmlns="http://www.w3.org/1998/Math/MathML">
                <ci> yVariable1_1 </ci>
            </math>
        </dataGenerator>
        <dataGenerator id="xDataGenerator2_1">
            <listOfVariables>
                <variable id="xVariable2_1" target="/cellml:model/cellml:component[@name='main']/
                    cellml:variable[@name='t']" taskReference="repeatedTask"/>
            </listOfVariables>
            <math xmlns="http://www.w3.org/1998/Math/MathML">
                <ci> xVariable2_1 </ci>
            </math>
        </dataGenerator>
        <dataGenerator id="yDataGenerator2_1">
            <listOfVariables>
                <variable id="yVariable2_1" target="/cellml:model/cellml:component[@name='main']/
                    cellml:variable[@name='y']" taskReference="repeatedTask"/>
            </listOfVariables>
            <math xmlns="http://www.w3.org/1998/Math/MathML">
                <ci> yVariable2_1 </ci>
            </math>
        </dataGenerator>
        <dataGenerator id="xDataGenerator3_1">
            <listOfVariables>
                <variable id="xVariable3_1" target="/cellml:model/cellml:component[@name='main']/
                    cellml:variable[@name='x']" taskReference="repeatedTask"/>
            </listOfVariables>
            <math xmlns="http://www.w3.org/1998/Math/MathML">
                <ci> xVariable3_1 </ci>
            </math>
        </dataGenerator>
        <dataGenerator id="yDataGenerator3_1">
            <listOfVariables>
                <variable id="yVariable3_1" target="/cellml:model/cellml:component[@name='main']/
                    cellml:variable[@name='y']" taskReference="repeatedTask"/>
            </listOfVariables>
            <math xmlns="http://www.w3.org/1998/Math/MathML">
                <ci> yVariable3_1 </ci>
            </math>
        </dataGenerator>
    </listOfDataGenerators>
    <listOfOutputs>
        <plot2D id="plot1">
            <listOfCurves>
                <curve id="curve1_1" logX="false" logY="false" xDataReference="xDataGenerator1_1"
                    yDataReference="yDataGenerator1_1"/>
                <curve id="curve2_1" logX="false" logY="false" xDataReference="xDataGenerator2_1"
                    yDataReference="yDataGenerator2_1"/>
            </listOfCurves>
        </plot2D>
        <plot2D id="plot2">
            <listOfCurves>
                <curve id="curve3_1" logX="false" logY="false" xDataReference="xDataGenerator3_1"
                    yDataReference="yDataGenerator3_1"/>
            </listOfCurves>
        </plot2D>
    </listOfOutputs>
```

```
101 </sedML>
```

Listing A.9: *Van der Pol Model (CellML) Simulation Description in SED-ML*

A.5 Reproducing publication results

SED-ML allows to describe simulation experiments from publications in a reproducible manner. This section provides such examples.

A.5.1 Le Loup model (`L1V3_leloup-sbml.omex`)

The following example provides a SED-ML description for the simulation of the model based on the publication [18].

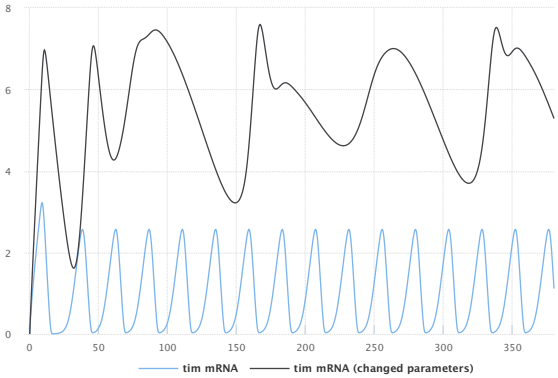
The model is referenced by its SED-ML `id` `model1` and refers to the model with the URL `https://www.ebi.ac.uk/biomodels/model/download/BIOMD0000000012.2?filename=BIOMD0000000012_url.xml`. A second model is defined in the example, using `model1` as a source and applying additional changes to it, in this case updating two model parameters.

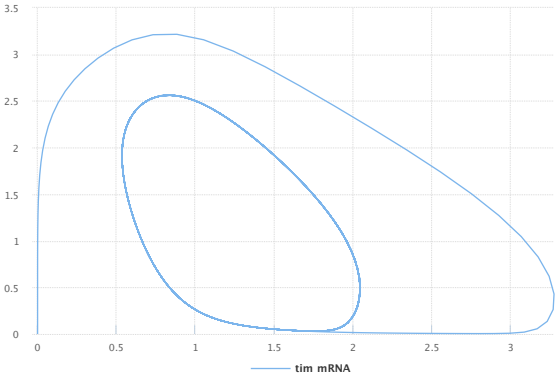
One simulation setup is defined in the `listOfSimulations`. It is a `uniformTimeCourse` over 380 time units, providing 1000 output points. The algorithm used is the CVODE solver, as denoted by the KiSAO ID `KiSAO:0000019`.

A number of dataGenerators are defined, which are the prerequisite for defining the simulation output. The first dataGenerator with `id` `time` collects the simulation time. `tim1` maps on the `Mt` entity in the model that is used in `task1` which in the model `model1`. The dataGenerator named `per_tim1` maps on the `Cn` entity in `model1`. Finally the fourth and fifth dataGenerators map on the `Mt` and `per_tim` entity respectively in the updated model with ID `model2`.

The output defined in the experiment consists of three 2D plots. The first plot has two curves and provides the time course of the simulation using the tim mRNA concentrations from both tasks. The second plot shows the `per_tim` concentration against the `tim` concentration for the oscillating model. The third plot shows the same plot for the chaotic model. The resulting three plots are depicted in Figure A.17 and A.18 .

```
<?xml version="1.0" encoding="utf-8"?>
<sedML  xmlns="http://sed-ml.org/sed-ml/level1/version3" level="1" version="3">
  <listOfSimulations>
    <uniformTimeCourse id="simulation1" initialTime="0" outputStartTime="0" outputEndTime="380"
        numberOfPoints="1000">
      <algorithm kisaoID="KISAO:0000019" />
    </uniformTimeCourse>
  </listOfSimulations>
  <listOfModels>
    <model id="model1" name="Circadian Oscillations" language="urn:sedml:language:sbml" source="https://
        www.ebi.ac.uk/biomodels/model/download/BIOMD0000000012?filename=BIOMD0000000012_url.xml" />
    <model id="model2" name="Circadian Chaos" language="urn:sedml:language:sbml" source="#model1">
      <listOfChanges>
        <changeAttribute target="/sbml:sbml/sbml:model/sbml:listOfParameters/sbml:parameter[@id=&quot;
            V_mT&quot;]/@value" newValue="0.28" />
        <changeAttribute target="/sbml:sbml/sbml:model/sbml:listOfParameters/sbml:parameter[@id=&quot;
            V_dT&quot;]/@value" newValue="4.8" />
      </listOfChanges>
    </model>
  </listOfModels>
  <listOfTasks>
    <task id="task1" modelReference="model1" simulationReference="simulation1" />
    <task id="task2" modelReference="model2" simulationReference="simulation1" />
  </listOfTasks>
  <listOfDataGenerators>
    <dataGenerator id="time" name="time">
      <listOfVariables>
        <variable id="t" taskReference="task1" symbol="urn:sedml:symbol:time" />
      </listOfVariables>
      <math xmlns="http://www.w3.org/1998/Math/MathML">
        <ci> t </ci>
      </math>
    </dataGenerator>
    <dataGenerator id="tim1" name="tim mRNA">
      <listOfVariables>
        <variable id="v1" taskReference="task1" target="/sbml:sbml/sbml:model/sbml:listOfSpecies/
            sbml:species[@id='Mt']" />
      </listOfVariables>
      <math xmlns="http://www.w3.org/1998/Math/MathML">
        <ci> v1 </ci>
      </math>
    </dataGenerator>
    <dataGenerator id="per_tim1" name="nuclear PER-TIM complex">
      <listOfVariables>
        <variable id="v1a" taskReference="task1" target="/sbml:sbml/sbml:model/sbml:listOfSpecies/
            sbml:species[@id='Cn']" />
      </listOfVariables>
```





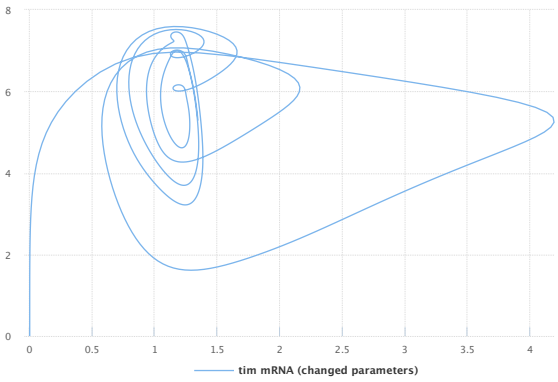
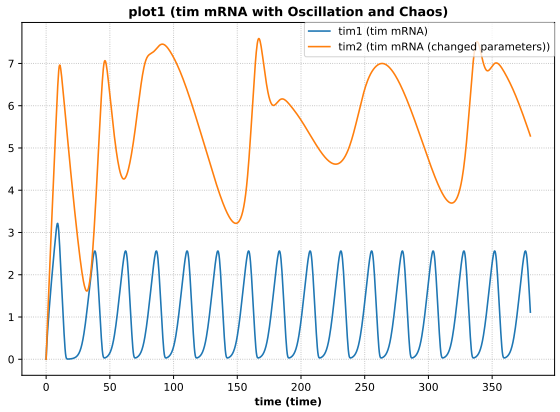
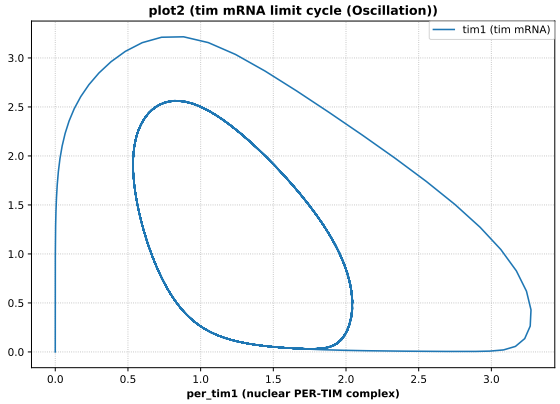


Figure A.17: *The simulation result gained from the simulation description given in Listing A.10. Simulation with SED-ML web tools [2].*





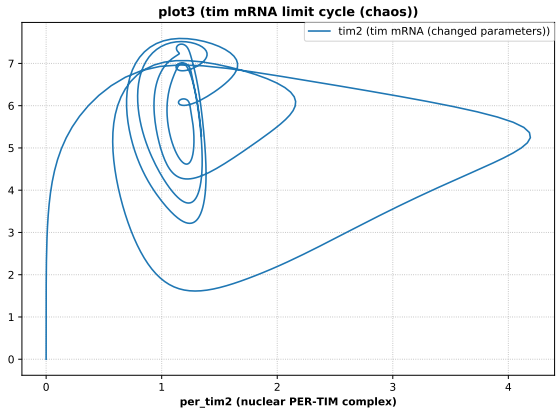


Figure A.18: *Simulation with tellurium [6].*

```
42        <math xmlns="http://www.w3.org/1998/Math/MathML">
43          <ci> v1a </ci>
44        </math>
45      </dataGenerator>
46      <dataGenerator id="tim2" name="tim mRNA (changed parameters)">
47        <listOfVariables>
48          <variable id="v2" taskReference="task2" target="/sbml:sbml/sbml:model/sbml:listOfSpecies/
                sbml:species[@id='Mt']" />
49        </listOfVariables>
50        <math xmlns="http://www.w3.org/1998/Math/MathML">
51          <ci> v2 </ci>
52        </math>
53      </dataGenerator>
54      <dataGenerator id="per_tim2" name="nuclear PER-TIM complex">
55        <listOfVariables>
56          <variable id="v2a" taskReference="task2" target="/sbml:sbml/sbml:model/sbml:listOfSpecies/
                sbml:species[@id='Cn']" />
57        </listOfVariables>
```

```
      <math xmlns="http://www.w3.org/1998/Math/MathML">
        <ci> v2a </ci>
      </math>
    </dataGenerator>
  </listOfDataGenerators>
  <listOfOutputs>
    <plot2D id="plot1" name="tim mRNA with Oscillation and Chaos">
      <listOfCurves>
        <curve id="c1" logX="false" logY="false" xDataReference="time" yDataReference="tim1" />
        <curve id="c2" logX="false" logY="false" xDataReference="time" yDataReference="tim2" />
      </listOfCurves>
    </plot2D>
   <plot2D id="plot2" name="tim mRNA limit cycle (Oscillation)">
      <listOfCurves>
        <curve id="c3" logX="false" logY="false" xDataReference="per_tim1" yDataReference="tim1" />
      </listOfCurves>
    </plot2D>
   <plot2D id="plot3" name="tim mRNA limit cycle (chaos)">
      <listOfCurves>
        <curve id="c4" logX="false" logY="false" xDataReference="per_tim2" yDataReference="tim2" />
      </listOfCurves>
    </plot2D>
  </listOfOutputs>
</sedML>
```

Listing A.10: *LeLoup Model Simulation Description in SED-ML*

A.5.2 IkappaB signaling (`L1V3_ikkapab.omex`)

The following example provides a SED-ML description for the simulation of the IkappaB-NF-kappaB signaling module described in [14].

This model is referenced by its SED-ML ID `model1` and refers to the model with the URL `https://www.ebi.ac.uk/biomodels/model/download/BIOMD0000000140.2?filename=BIOMD0000000140_url.xml`.

The simulation description specifies one simulation `simulation1`, which is a uniform timecourse simulation that simulates the model for 41 hours. `task1` then applies this simulation to the model.

As output this simulation description collects four parameters: `Total_NFkBn`, `Total_IkBbeta`, `Total_IkBeps` and `Total_IkBalpha`. These variables are plotted against the simulation time as shown in Figure A.19 and A.20.

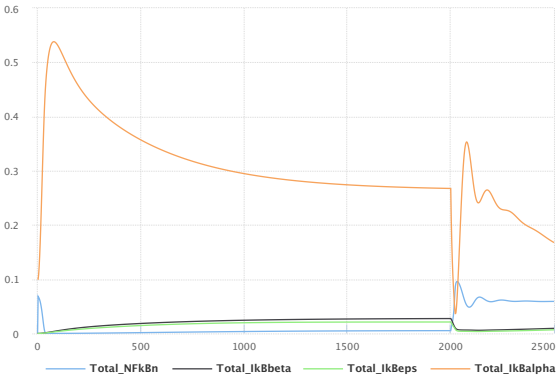


Figure A.19: *The simulation result gained from the simulation description given in Listing A.11. Simulation with SED-ML web tools [2].*

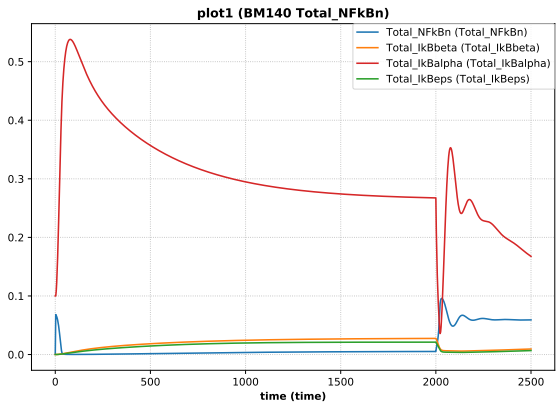


Figure A.20: *Simulation with tellurium [6].*

```
<?xml version="1.0" encoding="utf-8"?>
<sedML xmlns="http://sed-ml.org/sed-ml/level1/version3" level="1" version="3">
  <listOfSimulations>
    <uniformTimeCourse id="simulation1"
    initialTime="0" outputStartTime="0" outputEndTime="2500"
    numberOfPoints="1000" >
      <algorithm kisaoID="KISAO:0000019"/>
    </uniformTimeCourse>
  </listOfSimulations>
  <listOfModels>
```

```
    <model id="model1" language="urn:sedml:language:sbml" source="https://www.ebi.ac.uk/biomodels/model/
        download/BIOMD0000000140?filename=BIOMD0000000140_url.xml"/>
  </listOfModels>
  <listOfTasks>
    <task id="task1" modelReference="model1"
    simulationReference="simulation1"/>
  </listOfTasks>
  <listOfDataGenerators>
    <dataGenerator id="time" name="time">
      <listOfVariables>
        <variable id="time1" taskReference="task1" symbol="urn:sedml:symbol:time"/>
      </listOfVariables>
      <math xmlns="http://www.w3.org/1998/Math/MathML">
        <ci>time1</ci>
      </math>
    </dataGenerator>
    <dataGenerator id="Total_NFkBn" name="Total_NFkBn">
      <listOfVariables>
        <variable id="Total_NFkBn1" taskReference="task1"
        target="/sbml:sbml/sbml:model/sbml:listOfParameters/sbml:parameter[@id='Total_NFkBn']"/>
      </listOfVariables>
      <math xmlns="http://www.w3.org/1998/Math/MathML">
        <ci>Total_NFkBn1</ci>
      </math>
    </dataGenerator>
    <dataGenerator id="Total_IkBbeta" name="Total_IkBbeta">
      <listOfVariables>
        <variable id="Total_IkBbeta1" taskReference="task1"
        target="/sbml:sbml/sbml:model/sbml:listOfParameters/sbml:parameter[@id='Total_IkBbeta']" />
      </listOfVariables>
      <math xmlns="http://www.w3.org/1998/Math/MathML">
        <ci>Total_IkBbeta1</ci>
      </math>
    </dataGenerator>
    <dataGenerator id="Total_IkBeps" name="Total_IkBeps">
      <listOfVariables>
        <variable id="Total_IkBeps1" taskReference="task1"
        target="/sbml:sbml/sbml:model/sbml:listOfParameters/sbml:parameter[@id='Total_IkBeps']" />
      </listOfVariables>
      <math xmlns="http://www.w3.org/1998/Math/MathML">
        <ci>Total_IkBeps1</ci>
      </math>
    </dataGenerator>
    <dataGenerator id="Total_IkBalpha" name="Total_IkBalpha">
      <listOfVariables>
        <variable id="Total_IkBalpha1" taskReference="task1"
        target="/sbml:sbml/sbml:model/sbml:listOfParameters/sbml:parameter[@id='Total_IkBalpha']" />
      </listOfVariables>
      <math xmlns="http://www.w3.org/1998/Math/MathML">
        <ci>Total_IkBalpha1</ci>
      </math>
    </dataGenerator>
  </listOfDataGenerators>
  <listOfOutputs>
    <plot2D id="plot1" name="BM140 Total_NFkBn">
      <listOfCurves>
        <curve  id="c1" logX="false" logY="false" xDataReference="time"
        yDataReference="Total_NFkBn" />
            <curve  id="c2" logX="false" logY="false" xDataReference="time"
        yDataReference="Total_IkBbeta" />
        <curve  id="c3" logX="false" logY="false" xDataReference="time"
        yDataReference="Total_IkBeps" />
        <curve id="c4" logX="false" logY="false" xDataReference="time"
        yDataReference="Total_IkBalpha" />
      </listOfCurves>
    </plot2D>
  </listOfOutputs>
</sedML>
```

Listing A.11: *IkappaB-NF-kappaB signaling Model Simulation Description in SED-ML*

Bibliography

[1] F. T. Bergmann, R. Adams, S. Moodie, J. Cooper, M. Glont, M. Golebiewski, M. Hucka, C. Laibe, A. K. Miller, D. P. Nickerson, B. G. Olivier, N. Rodriguez, H. M. Sauro, M. Scharm, S. Soiland-Reyes, D. Waltemath, F. Yvon, and N. Le Novère. COMBINE archive and OMEX format: one file to share all information to reproduce a modeling project. *BMC bioinformatics*, 15:369, Dec. 2014.

[2] F. T. Bergmann, D. Nickerson, D. Waltemath, and M. Scharm. SED-ML web tools: generate, modify and export standard-compliant simulation studies. *Bioinformatics*, 33(8):1253–1254, 2017.

[3] T. Berners-Lee, R. Fielding, and L. Masinter. Uniform Resource Identifier (URI): Generic Syntax, 2005.

[4] P. V. Biron and A. Malhotra. XML Schema part 2: Datatypes (W3C candidate recommendation 24 October 2000). Available via the World Wide Web at http://www.w3.org/TR/xmlschema-2/., 2000.

[5] D. Carlisle, P. Ion, R. Miner, and N. Poppelier. Mathematical Markup Language (MathML) version 2.0. *W3C Recommendation*, 21, 2001.

[6] K. Choi, J. K. Medley, C. Cannistra, M. König, L. Smith, K. Stocking, and H. M. Sauro. Tellurium: A python based modeling and reproducibility platform for systems biology. *bioRxiv*, 2016.

[7] J. Clarke and S. DeRose. XML Path Language (XPath) version 1.0, 1999.

[8] M. Courtot, N. Juty, C. Knüpfer, D. Waltemath, A. Dräger, A. andFinney, M. Golebiewski, S. Hoops, S. Keating, D. Kell, S. Kerrien, J. Lawson, A. Lister, J. Lu, R. Machne, P. Mendes, M. Pocock, N. Rodriguez, A. Villeger, S. Wimalaratne, C. Laibe, M. Hucka, and N. Le Novère. Controlled vocabularies and semantics in Systems Biology. *Mol Sys Biol*, 7, Oct. 2011.

[9] A. A. Cuellar, C. M. Lloyd, P. F. Nielson, M. D. B. Halstead, D. P. Bullivant, D. P. Nickerson, and P. J. Hunter. An overview of CellML 1.1, a biological model description language. *Simulation*, 79(12):740–747, 2003.

[10] M. Elowitz and S. Leibler. A synthetic oscillatory network of transcriptional regulators. *Nature*, 403(6767):335–338, Jan. 2000.

[11] A. Garny and P. J. Hunter. OpenCOR: a modular and interoperable approach to computational biology. *Frontiers in physiology*, 6, 2015.

[12] T. W. Gillespie. Understanding waterfall plots. *Journal of the advanced practitioner in oncology*, 3(2):106, 2012.

[13] N. Goddard, M. Hucka, F. Howell, H. Cornelis, K. Skankar, and D. Beeman. Towards NeuroML: Model Description Methods for Collaborative Modeling in Neuroscience. *Phil. Trans. Royal Society series B*, 356:1209–1228, 2001.

[14] A. Hoffmann, A. Levchenko, M. L. Scott, and D. Baltimore. The IκB-NF-κB signaling module: temporal control and selective gene activation. *Science*, 298(5596):1241–1245, 2002.

[15] M. Hucka, F. Bergmann, S. Hoops, S. Keating, S. Sahle, and D. Wilkinson. The Systems Biology Markup Language (SBML): Language Specification for Level 3 Version 1 Core (Release 1 Candidate). *Nature Precedings*, January 2010.

[16] M. Hucka, A. Finney, H. M. Sauro, H. Bolouri, J. C. Doyle, H. Kitano, A. P. Arkin, B. J. Bornstein, D. Bray, A. Cornish-Bowden, A. A. Cuellar, S. Dronov, E. D. Gilles, M. Ginkel, V. Gor, I. I. Goryanin, W. J. Hedley, T. C. Hodgman, J. H. Hofmeyr, P. J. Hunter, N. S. Juty, J. L. Kasberger, A. Kremling, U. Kummer, N. Le Novere, L. M. Loew, D. Lucio, P. Mendes, E. Minch, E. D. Mjolsness, Y. Nakayama, M. R. Nelson, P. F. Nielsen, T. Sakurada, J. C. Schaff, B. E. Shapiro, T. S. Shimizu, H. D. Spence, J. Stelling, K. Takahashi, M. Tomita, J. Wagner, and J. Wang. The systems biology markup language (SBML): a medium for representation and exchange of biochemical network models. *Bioinformatics*, 19(4):524–531, March 2003.

[17] N. Le Novère, B. Bornstein, A. Broicher, M. Courtot, M. Donizelli, H. Dharuri, L. Li, H. Sauro, M. Schilstra, B. Shapiro, J. L. Snoep, and M. Hucka. BioModels Database: a free, centralized database of curated, published, quantitative kinetic models of biochemical and cellular systems. *Nucleic Acids Res*, 34(Database issue), January 2006.

[18] J.-C. Leloup, D. Gonze, and A. Goldbeter. Limit cycle models for circadian rhythms based on transcriptional regulation in drosophila and neurospora. *Journal of Biological Rhythms*, 14(6):433–448, 1999.

[19] C. Li, M. Donizelli, N. Rodriguez, H. Dharuri, L. Endler, V. Chelliah, L. Li, E. He, A. Henry, M. Stefan, J. Snoep, M. Hucka, N. Le Novère, and C. Laibe. BioModels Database: An enhanced, curated and annotated resource for published quantitative kinetic models. *BMC Systems Biology*, 4(1):92+, June 2010.

[20] S. Pemberton et al. XHTML 1.0: The Extensible HyperText Markup Language—W3C Recommendation 26 January 2000. *World Wide Web Consortium (W3C)(August 2002)*, 2002.

[21] H. S. Thompson, D. Beech, M. Maloney, and N. Mendelsohn. XML Schema part 1: Structures (W3C candidate recommendation 24 October 2000). Available online via the World Wide Web at the address http://www.w3.org/TR/xmlschema-1/, 2000.

[22] D. Waltemath, R. Adams, D. Beard, F. Bergmann, U. Bhalla, R. Britten, V. Chelliah, M. Cooling, J. Cooper, E. Crampin, A. Garny, S. Hoops, M. Hucka, P. Hunter, E. Klipp, C. Laibe, A. Miller, I. Moraru, D. Nickerson, P. Nielsen, M. Nikolski, S. Sahle, H. Sauro, H. Schmidt, J. Snoep, D. Tolle, O. Wolkenhauer, and N. Le Novère. Minimum Information About a Simulation Experiment (MIASE). *PLoS Comput Biol*, 7:e1001122, 2011.

[23] D. Waltemath, R. Adams, F. T. Bergmann, M. Hucka, F. Kolpakov, A. K. Miller, I. I. Moraru, D. Nickerson, S. Sahle, J. L. Snoep, and N. Le Novère. Reproducible computational biology experiments with SED-ML: the simulation experiment description markup language. *BMC systems biology*, 5(1):198, 2011.