

Simulation Experiment Description

Markup Language (SED-ML) :

Level 1 Version 4

June 8, 2021

Editors

Matthias König
Frank T Bergmann
Lucian Smith
Alan Garny
David Nickerson
Dagmar Waltemath
Thomas Helikar
Jonathan Karr
Herbert Sauro

Humboldt-University Berlin, Germany
Caltech, USA
University of Washington, USA
Auckland Bioengineering Institute, New Zealand
Auckland Bioengineering Institute, New Zealand
University of Rostock, Germany
University of Nebraska, USA
Icahn Institute for Data Science and Genomic Technology, USA
University of Washington, USA

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

To discuss SED-ML and the SED-ML specification write to the mailing list
sed-ml-discuss@googlegroups.com.

To contact the SED-ML editors write to sed-ml-editors@googlegroups.com.



1	Introduction	5
1.1	SED-ML overview	5
1.2	Example simulation experiment	6
1.2.1	Time-course simulation	6
1.2.2	Applying pre-processing	7
1.2.3	Applying post-processing	7
2	SED-ML technical specification	9
2.1	General data types, attributes and classes	9
2.1.1	Primitive data types	9
2.1.1.1	ID	9
2.1.1.2	SId	9
2.1.1.3	SIdRef	10
2.1.1.4	TargetType	10
2.1.1.5	XPath	10
2.1.1.6	URN	10
2.1.1.7	MathML	10
2.1.1.8	anyURI	10
2.1.1.9	NuMLSId	10
2.1.1.10	NuMLSIdRef	10
2.1.1.11	AxisType	10
2.1.1.12	CurveType	11
2.1.1.13	SurfaceType	11
2.1.1.14	LineType	11
2.1.1.15	SedColor	11
2.1.1.16	MarkerType	11
2.1.1.17	MappingType	11
2.1.1.18	ExperimentType	11
2.1.1.19	ScaleType	11
2.1.2	SEDBase	12
2.1.3	Notes	13
2.1.4	Annotation	13
2.1.5	Parameter	14
2.1.6	Variable	15
2.1.7	RemainingDimension	17
2.1.8	DependentVariable	18
2.1.9	Calculation	18
2.1.9.1	Math	19
2.1.10	General attributes and elements	19
2.1.10.1	kisaoID	20
2.1.10.2	listOf* containers	20
2.1.11	Reference relations	20
2.1.11.1	modelReference	20
2.1.11.2	simulationReference	21
2.1.11.3	taskReference	21
2.2	SED-ML Components	22
2.2.1	SED-ML top level element	22
2.2.1.1	xmlns	24
2.2.1.2	level	24
2.2.1.3	version	24
2.2.1.4	listOfDataDescriptions	24
2.2.1.5	listOfModels	24
2.2.1.6	listOfSimulations	25
2.2.1.7	listOfTasks	25
2.2.1.8	listOfDataGenerators	25
2.2.1.9	listOfOutputs	25
2.2.1.10	listOfStyles	26
2.2.1.11	listOfAlgorithmParameters (global)	26
2.2.2	DataDescription	26
2.2.3	DataDescription components	28
2.2.3.1	DimensionDescription	28
2.2.3.2	DataSource	28
2.2.3.3	Slice	29
2.2.4	Model	30
2.2.5	Change	32
2.2.5.1	NewXML	33
2.2.5.2	AddXML	33
2.2.5.3	ChangeXML	34
2.2.5.4	RemoveXML	34

2.2.5.5	ChangeAttribute	34
2.2.5.6	ComputeChange	35
2.2.6	Simulation	36
2.2.6.1	UniformTimeCourse	37
2.2.6.2	OneStep	37
2.2.6.3	SteadyState	38
2.2.7	Simulation components	38
2.2.7.1	Algorithm	38
2.2.7.2	AlgorithmParameter	38
2.2.8	AbstractTask	39
2.2.8.1	Task	40
2.2.8.2	SimpleRepeated Task	40
2.2.8.3	Repeated Task	41
2.2.9	Task components	43
2.2.9.1	SubTask	43
2.2.9.2	SetValue	44
2.2.9.3	Range	44
2.2.10	ParameterEstimationTask	46
2.2.10.1	Objective	48
2.2.10.2	LeastSquareObjectiveFunction	48
2.2.10.3	AdjustableParameter	48
2.2.10.4	Bounds	49
2.2.10.5	ExperimentRef	49
2.2.10.6	FitExperiment	50
2.2.10.7	FitMapping	50
2.2.11	DataGenerator	51
2.2.12	Output	52
2.2.12.1	Plot	52
2.2.12.2	Plot2D	54
2.2.12.3	Plot3D	54
2.2.12.4	Axis	54
2.2.12.5	AbstractCurve	56
2.2.12.6	Curve	57
2.2.12.7	ShadedArea	58
2.2.12.8	Surface	58
2.2.13	Report	60
2.2.13.1	DataSet	60
2.2.14	ParameterEstimationReport	61
2.2.15	Figure	61
2.2.15.1	SubPlot	62
2.2.16	ParameterEstimationResultsPlot	63
2.2.17	WaterfallPlot	64
2.2.18	Style	64
2.2.18.1	Line	65
2.2.18.2	Marker	65
2.2.18.3	Fill	66
3	Concepts used in SED-ML	67
3.1	MathML	67
3.1.1	MathML elements	67
3.1.2	MathML symbols	67
3.1.3	MathML functions	67
3.1.4	NA values	70
3.2	URI scheme	70
3.2.1	Model references	70
3.2.2	Data references	71
3.2.3	Language references	71
3.2.4	Data format references	71
3.2.4.1	NuML (Numerical Markup Language)	71
3.2.4.2	CSV (Comma Separated Values)	72
3.2.4.3	TSV (Tab Separated Values)	73
3.2.5	Symbols	73
3.2.6	Annotation Scheme	74
3.3	XPath	74
3.4	NuML	75
3.5	KiSAO	75
3.6	COMBINE archive	75
3.7	SED-ML resources	75

4	Acknowledgements	76
A	Examples	77
A.1	Example simulation experiment (L1V3_repressilator.omex)	77
A.2	Simulation experiments with dataDescriptions	80
A.2.1	Plotting data with simulations (L1V3_plotting-data-numl.omex)	80
A.3	Simulation experiments with repeatedTasks	82
A.3.1	Time course parameter scan (L1V3_repeated-scan-oscli.omex)	82
A.3.2	Steady state parameter scan (L1V3_repeated-steady-scan-oscli.omex)	83
A.3.3	Stochastic simulation (L1V3_repeated-stochastic-runs.omex)	84
A.3.4	Simulation perturbation (L1V3_oscli-nested-pulse.omex)	86
A.3.5	2D steady state parameter scan (L1V3_parameter-scan-2d.omex)	88
A.4	Simulation experiments with different model languages	91
A.4.1	Van der Pol oscillator in SBML (L1V3_vanderpol-sbml.omex)	91
A.4.2	Van der Pol oscillator in CellML (L1V3_vanderpol-cellml.omex)	93
A.5	Reproducing publication results	96
A.5.1	Le Loup model (L1V3_leloup-sbml.omex)	96
A.5.2	IkappaB signaling (L1V3_ikkapab.omex)	98

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] [urn:miriam:biomodels.db:BIOMD0000000012](http://miriam.org/uri/urn:miriam:biomodels.db:BIOMD0000000012).
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.

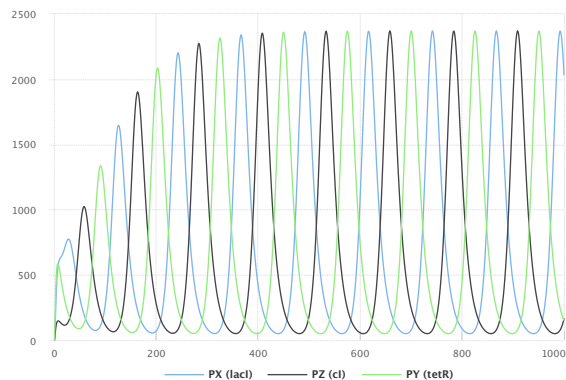


Figure 1.1: Time-course simulation of the repressilator depicting repressor proteins *lacI*, *tetR* and *cI*. Simulation with SED-ML web tools [2].

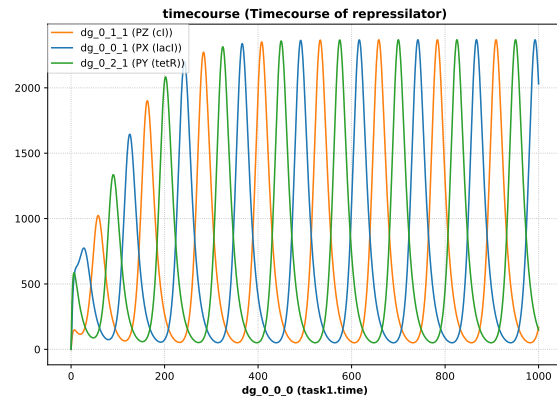


Figure 1.2: Time-course simulation of the repressilator depicting repressor proteins *lacI*, *tetR* and *cI*. Simulation with tellurium [6].

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

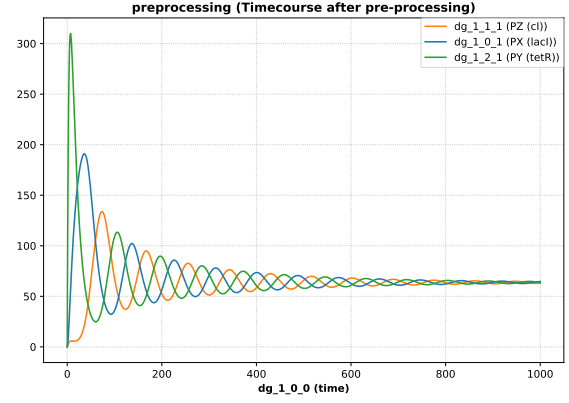


Figure 1.4: Time-course simulation of the repressilator after changing parameters `tps_repr` and `tps_active`. Simulation with tellurium [6].

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

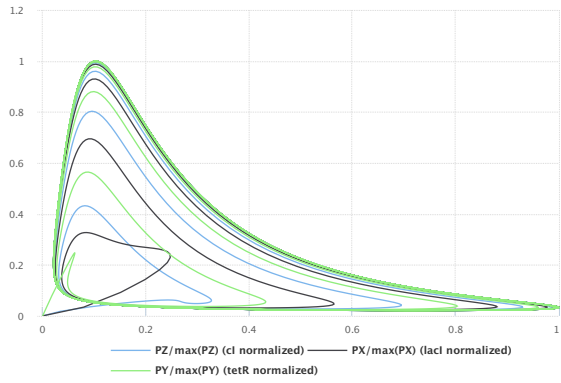


Figure 1.5: Time-course simulation of the repressilator. Normalized `lacI`, `tetR` and `cI` in phase-plane. Simulation with SED-ML web tools [2].



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.

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.

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** [m000001](#).

```

1 <model id="m000001" language="urn:sedml:language:sbml" source="urn:miriam:biomodels.db:BIOMD00000000012">
2   [MODEL DEFINITION]
3 </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**.

```

1 <model id="m00001" name="Circadian oscillator" language="urn:sedml:language:sbml" source="
  urn:miriam:biomodels.db:BIOMD0000000012">
2   [MODEL DEFINITION]
3 </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 24
sub-elements	
	<i>well-formed content permitted in XHTML</i>

Table 2.1: Attributes and nested elements for **Notes**. ° 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.

```

1 <sedML [...]>
2   <notes>
3     <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>
4   </notes>
5 </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”.

```

1 <sedML>
2   [...]
3   <model id="model1" metaid="_001" language="urn:sedml:language:cellml" source="goldbeter1999a.cellml"
4     >
5     <annotation>
6       <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#" xmlns:bqmodel="http://
7         biomodels.net/model-qualifiers/"
8         <rdf:Description rdf:about="#_001">
9           <bqmodel:isDescribedBy>
10            <rdf:Bag>
11              <rdf:li rdf:resource="http://identifiers.org/pubmed/10415827"/>
12            </rdf:Bag>
13          </bqmodel:isDescribedBy>
14        </rdf:Description>
15      </rdf:RDF>
16    </annotation>
17  </model>
18  [...]
19 </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 shows the use of the **parameter** element. In the example a **parameter** **p1** with the value **40** is defined.

```

1 <listOfParameters>
2   <parameter id="p1" name="KM" value="40" />
3 </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.

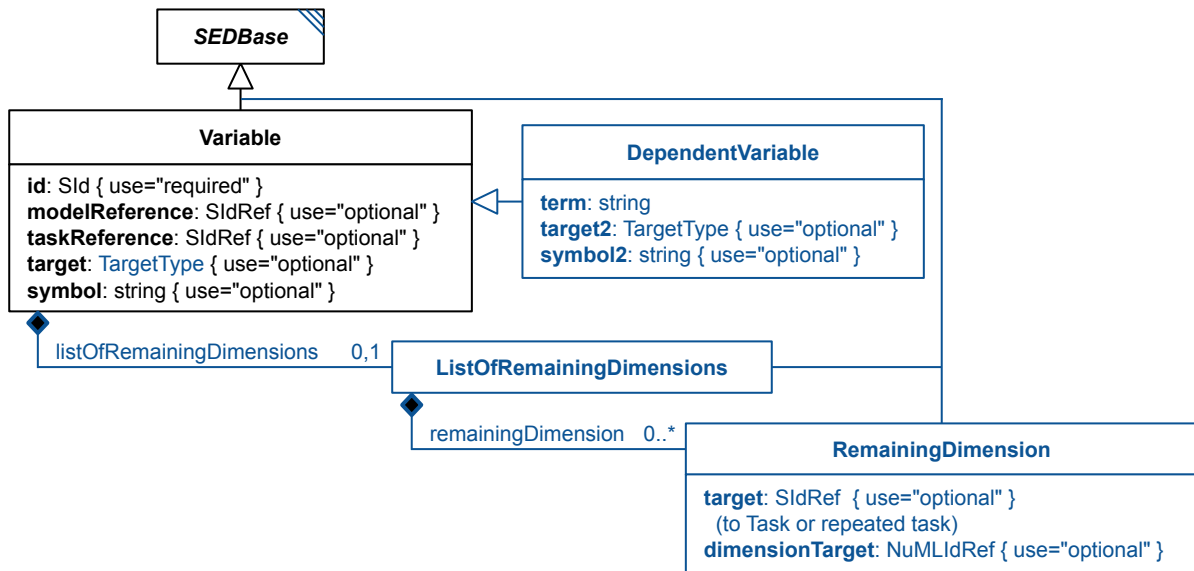


Figure 2.5: The *Variable*, *DependentVariable*, *ListOfRemainingDimensions*, and *RemainingDimension* classes

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**”.
- Exactly one of the **symbol** and **target** attributes must be used, unless the **symbol** references an implicit function instead of an implicit variable. In that case, both must be present.
- A **Variable** element must contain a **taskReference** if it occurs inside a **listOfVariables** inside a **dataGenerator** element. Only exception is if the **Variable** references a **DataSource**, in this case no **taskReference** is required.
- A **Variable** element must contain a **modelReference** if it occurs inside a **listOfVariables** inside a **computeChange** element.
- 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.

```

1 <sedML>
2   <listOfModels>
3     <model [...]>
4       <listOfChanges>
5         <computeChange target="TARGET ELEMENT OR ATTRIBUTE">

```

```

6         <listOfVariables>
7             <variable id="v1" name="maximum velocity" target="\changed{Path} TO MODEL ELEMENT/
              ATTRIBUTE" />
8             [FURTHER VARIABLE DEFINITIONS]
9         </listOfVariables>
10        [...]
11    </computeChange>
12    </listOfChanges>
13    [...]
14    </model>
15    [...]
16    </listOfModels>
17    <listOfDataGenerators>
18        <dataGenerator [...]>
19            <listOfVariables>
20                <variable id="v2" name="time" taskReference="task1" symbol="KISA0:0000832" />
21                [FURTHER VARIABLE DEFINITIONS]
22            </listOfVariables>
23        </dataGenerator>
24    </listOfDataGenerators>
25    [...]
26    </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.

The [target](#) attribute may also be used to reference an entity within the SED-ML file itself, by containing a fragment identifier consisting of a hash character (#) followed by the [SId](#) of the targeted element. As of SED-ML Level 1 Version 4 this is used to refer to a [DataSource](#) in a [Variable](#) or to refer to [ranges](#) within a [repeatedTask](#) (see Listing 2.46).

Note that while it is possible to write [addresses](#) 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.

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.

```

1 <listOfVariables>
2   <variable id="v1" name="TetR protein" taskReference="task1"
3     target="/sbml:sbml:listOfSpecies/sbml:species[@id='PY']" />
4 </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):

```

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

```

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

```

1 <sbml [...]>
2   <listOfSpecies>
3     <species metaid="PY" id="PY" name="TetR protein" [...]>
4       [...]
5     </species>
6   </listOfSpecies>
7   [...]
8 </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 “**KISA0:0000832**” 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.

```
1 <listOfVariables>
2   <variable id="t1" name="time" taskReference="task1" symbol="KISA0:0000832" />
3 </listOfVariables>
```

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

taskReference

The **taskReference** element of data type **SIIdRef** 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 **SIIdRef** 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 when a **Variable** is multidimensional, but the **symbol** 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 **symbol** of the parent **Variable** is the ‘mean’ function (“**KISA0:0000825**”), 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**.

A **RemainingDimension** inherits the attributes and children of **SEDBase**, and adds the attributes **target** (of type **SIIdRef**), 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**.

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.

```
1 <listOfVariables>
2   <dependentVariable id="S1prime" name="S1'" taskReference="task1"
3     term="KISAO:0000834"
4     target="/sbml:sbml/sbml:listOfSpecies/sbml:species[@id='S1']"
5     symbol2="KISAO:0000832" />
6 </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 `KISA0:[0-9]{7}`. The referenced [KiSAO](#) term should define the simulation [Algorithm](#) or [AlgorithmParameter](#) as precisely as possible.

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**.

```

1 <model id="m0001" [...]>
2   <listOfChanges>
3     <computeChange>
4       <listOfVariables>
5         <variable id="v1" modelReference="cellML" target="/cellml:model/cellml:component[
6           @meta:id='MP']/cellml:variable[@name='vsP']/@initial_value" />
7         [...]
8       </listOfVariables>
9       <listOfParameters [...] />
10      <math>
11        [CALCULATION OF CHANGE]
12      </math>
13    </computeChange>
14  </listOfChanges>
15  [...]
16</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.

```

1 <listOfTasks>
2   <task id="t1" name="Baseline" modelReference="model1" simulationReference="simulation1" />
3   <task id="t2" name="Modified" modelReference="model2" simulationReference="simulation1" />
4 </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.

```

1 <listOfDataGenerators>
2   <dataGenerator id="tim3" name="tim mRNA (difference v1-v2+20)">
3     <listOfVariables>
4       <variable id="v1" taskReference="t1" [...] />
5     </listOfVariables>
6     <math [...] />
7   </dataGenerator>
8 </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.

```

1 <listOfTasks>
2   <task id="t1" name="task definition" modelReference="model1" simulationReference="simulation1" />
3 </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.

```

1 <?xml version="1.0" encoding="utf-8"?>
2 <sedML xmlns:math="http://www.w3.org/1998/Math/MathML"
3   xmlns="http://sed-ml.org/sed-ml/level1/version4" level="1" version="4">
4   <listOfDataDescriptions>
5     [DATA REFERENCES AND TRANSFORMATIONS]
6   </listOfDataDescriptions>
7   <listOfModels>
8     [MODEL REFERENCES AND APPLIED CHANGES]
9   </listOfModels>
10  <listOfSimulations>
11    [SIMULATION SETUPS]
12  </listOfSimulations>
13  <listOfTasks>
14    [MODELS LINKED TO SIMULATIONS]
15  </listOfTasks>
16  <listOfDataGenerators>
17    [DEFINITION OF POST-PROCESSING]
18  </listOfDataGenerators>
19  <listOfOutputs>
20    [DEFINITION OF OUTPUT]
21  </listOfOutputs>
22  <listOfStyles>
23    [DEFINITION OF STYLES]
24  </listOfStyles>
25  <listOfAlgorithmParameters>
26    [PARAMETERS TO APPLY TO THE ENTIRE SIMULATION PROCESS]
27  </listOfAlgorithmParameters>
28 </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.

```
1 <listOfDataDescriptions>
2   <dataDescription id="Data1" name="Oscili Time Course Data" source="./oscli.numl">
3     <dimensionDescription>
4       <compositeDescription indexType="double" id="time" name="time" xmlns="http://www.numl.org/
5         numl/level1/version1">
6         <compositeDescription indexType="string" id="SpeciesIds" name="SpeciesIds">
7           <atomicDescription valueType="double" name="Concentrations" />
8         </compositeDescription>
9       </compositeDescription>
10    </dimensionDescription>
11    <listOfDataSources>
12      <dataSource id="dataS1">
13        <listOfSlices>
14          <slice reference="SpeciesIds" value="S1" />
15        </listOfSlices>
16      </dataSource>
17      <dataSource id="dataTime" indexSet="time" />
18    </listOfDataSources>
19  </dataDescription>
20 </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.

```
1 <listOfModels>
2   <model id="m0001" language="urn:sedml:language:sbml"
3     source="urn:miriam:biomodels.db:BIOMD0000000012" />
4   <model id="m0002" language="urn:sedml:language:cellml"
5     source="http://models.cellml.org/workspace/leloup_gonze_goldbeter_1999/@rawfile/
6       d6613d7e1051b3eff2bb1d3d419a445bb8c754ad/leloup_gonze_goldbeter_1999_a.cellml" />
7 </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 23). 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.

```
1 <listOfSimulations>
2   <simulation id="s1" [...]>
3     [UNIFORM TIMECOURSE DEFINITION]
4   </simulation>
5   <simulation id="s2" [...]>
6     [UNIFORM TIMECOURSE DEFINITION]
7   </simulation>
8 </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 23). The `listOfTasks` is optional and may contain zero or more tasks, each of which is an instance of a subclass of `AbstractTask`.

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

```
1 <listOfTasks>
2   <task id="t1" name="simulating v1" modelReference="m1" simulationReference="s1">
3     [FURTHER TASK DEFINITIONS]
4 </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 23). 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.

```
1 <listOfDataGenerators>
2   <dataGenerator id="d1" name="time">
3     [DATA GENERATOR DEFINITION FOLLOWING]
4   </dataGenerator>
5   <dataGenerator id="LaCI" name="LaCI repressor">
6     [DATA GENERATOR DEFINITION FOLLOWING]
7   </dataGenerator>
8 </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 23). The `listOfOutputs` is optional and may contain zero or more outputs.

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

```
1 <listOfOutputs>
2   <report id="report1">
3     [REPORT DEFINITION FOLLOWING]
4   </report>
5   <plot2D id="plot1">
6     [2D PLOT DEFINITION FOLLOWING]
7   </plot2D>
8 </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 23). The `listOfStyles` is optional and may contain zero or more styles.

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

```
1 <listOfStyles>
2   <style id="redline">
3     [STYLE DEFINITION FOLLOWING]
4   </style>
5   <plot2D id="redline_bluesquares" baseStyle="redline">
6     [STYLE DEFINITION FOLLOWING]
7   </plot2D>
8 </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.

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

Listing 2.24: The global *listOfAlgorithmParameters* 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.

```

1 <dataDescription id="Data1" name="Oscili Time Course Data" format="urn:sedml:format:numl"
2   source="http://svn.code.sf.net/p/libsedml/code/trunk/Samples/data/oscli.numl" >
3   [...]
4 </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.

```
1 <dimensionDescription>
2   <compositeDescription indexType="double" id="time" name="time"
3     xmlns="http://www.numl.org/numl/level1/version1">
4     <compositeDescription indexType="string" id="SpeciesIds" name="SpeciesIds">
5       <atomicDescription valueType="double" id="Concentration" name="Concentration" />
6     </compositeDescription>
7   </compositeDescription>
8 </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 within the `listOfVariables` of `DataGenerator`, `ComputeChange` or `SetValue` objects. Here an example that references the `DataSource` `dataS1`:

```
1 <listOfDataDescriptions>
2   <dataDescription id="data1" name="data file" source="./example.numl" format="urn:sedml:format:numl">
3     <dimensionDescription>
4       <compositeDescription indexType="double" name="Time">
5         <compositeDescription indexType="string" name="SpeciesIds">
6           <atomicDescription valueType="double" name="Values" />
7         </compositeDescription>
8       </compositeDescription>
9     </dimensionDescription>
10    <listOfDataSources>
11      <dataSource id="dataS1">
12        <listOfSlices>
13          <slice reference="SpeciesIds" value="S1" />
14        </listOfSlices>
15      </dataSource>
16      <dataSource id="dataTime" indexSet="Time" />
17    </listOfDataSources>
18  </dataDescription>
19 </listOfDataDescriptions>
20 <listOfDataGenerators>
21   <dataGenerator id="dgDataS1" name="S1 (data)">
22     <listOfVariables>
23       <variable id="varS1" modelReference="model1" target="#dataS1" />
24     </listOfVariables>
25     <math xmlns="http://www.w3.org/1998/Math/MathML">
26       <ci> varS1 </ci>
27     </math>
28   </dataGenerator>
29   ...
30 </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.

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

Similarly

```
1 <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 27). 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 **NuMLIdRef**, and four optional attributes: **value** of type **DataIdRef**, **index** of type **IdRef**, and **startIndex** and **endIndex**, both of type **int** (Figure 2.8 on page 27).

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:

```
1 <dataSource id="dataS1">
2   <listOfSlices>
3     <slice reference="SpeciesIds" value="S1" />
4   </listOfSlices>
5 </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:

```
1 <dataSource id="dataS1">
2   <listOfSlices>
3     <slice reference="time" value="0" />
```

```

4     <slice reference="SpeciesIds" value="S1" />
5   </listOfSlices>
6 </dataSource>

```

index

The **index** attribute is an **SIIdRef** 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).

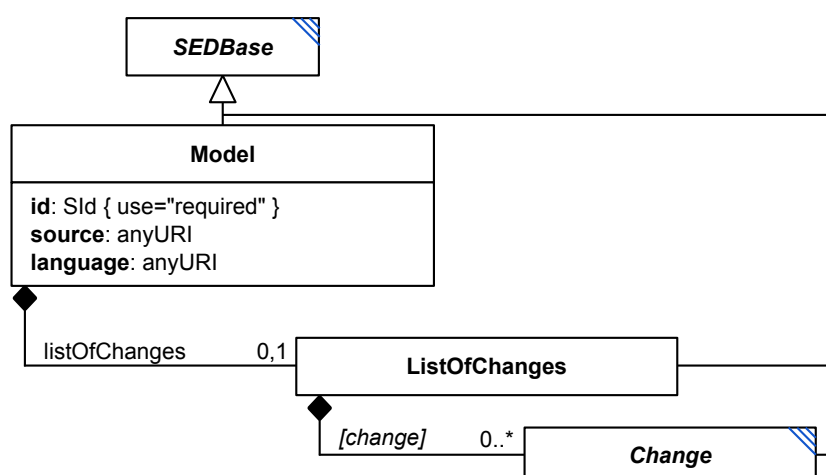


Figure 2.9: The SED-ML Model class

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 on the following page 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 **urn:miriam:biomodels.db:BIOMD0000000012**. 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 **m00012** 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.

```

1 <listOfModels>
2   <model id="m0001" language="urn:sedml:language:sbml"
3     source="urn:miriam:biomodels.db:BIOMD0000000012">
4     <listOfChanges>
5       <change>
6         [MODEL PRE-PROCESSING]
7       </change>
8     </listOfChanges>
9   </model>
10  <model id="m0002" language="urn:sedml:language:sbml" source="m0001">
11    <listOfChanges>
12      [MODEL PRE-PROCESSING]
13    </listOfChange>
14  </model>
15  <model id="m0003" language="urn:sedml:language:cellml" source="http://models.cellml.org/workspace/
16    leloup_gonze_goldbeter_1999/@rawfile/d6613d7e1051b3eff2bb1d3d419a445bb8c754ad/
17    leloup_gonze_goldbeter_1999_a.cellml">
18    [MODEL PRE-PROCESSING]
19  </model>
20 </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’.

```

1 <model id="m1" name="repressilator" language="urn:sedml:language:sbml"
2   source="oscillator.xml">
3   <listOfChanges>
4     [MODEL PRE-PROCESSING]
5   </listOfChanges>
6 </model>

```

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

An example for the definition of a model via an URI is given in Listing 2.29. 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** using the MIRIAM web service. The resulting URL is <https://www.ebi.ac.uk/biomodels-main/BIOMD0000000012>.

```

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

```

Listing 2.29: *The SED-ML source element, using the URI scheme*

An example for the definition of a model using an URL is given in Listing 2.30. In the example one model is defined. The **language** of the model is **CellML**. As the CellML model repository currently does not provide a MIRIAM URI for model reference, the *URL* pointing to the model is used in the **source** attribute.

```

1 <model id="m1" name="repressilator" language="urn:sedml:language:cellml"
2   source="http://models.cellml.org/exposure/bba4e39f2c7ba8af51fd045463e7bdd3/aguda_b_1999.cellml">
3   <listOfChanges />
4 </model>

```

Listing 2.30: The SED-ML *source* element, using a URL

listOfChanges

The **listOfChanges** (Figure 2.9 on page 30) 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.

```

1 <model id="m0001" [...>
2   <listOfChanges>
3     [CHANGE DEFINITION]
4   </listOfChanges>
5 </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**)
- For XML-encoded models, 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 or attribute that is to undergo the defined changes, such as a valid **XPath** expression pointing to the XML element or XML attribute. For **NewXML**, **AddXML**, **ChangeXML**, and **RemoveXML**, **target** must be an **XPath** expression. Except for the cases of **ChangeXML** and **RemoveXML**, this **XPath** expression must always select a single element or attribute within the relevant model.



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 element or XML attribute 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 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 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.

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.

```

1 <model language="urn:sedml:language:sbml" [..]>
2   <listOfChanges>
3     <addXML target="/sbml:sbml/sbml:model/sbml:listOfParameters" >
4       <newXML>
5         <parameter metaid="metaid_0000010" id="V_mT" value="0.7" />
6       </newXML>
7     </addXML>

```

```

8     </listOfChanges>
9 </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. The replacement XML content is specified in the `NewXML` class.

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.

```

1 <model [...]>
2   <listOfChanges>
3     <changeXML target="/sbml:sbml/sbml:model/sbml:listOfParameters/sbml:parameter[@id='V_mT']" >
4       <newXML>
5         <parameter metaid="metaid_0000010" id="V_mT_1" value="0.7" />
6         <parameter metaid="metaid_0000050" id="V_mT_2" value="4.6" />
7       </newXML>
8     </changeXML>
9   </listOfChanges>
10 </model>

```

Listing 2.33: The `changeXML` element

2.2.5.4 RemoveXML

The `RemoveXML` class can be used to delete 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.

```

1 <model [...]>
2   <listOfChanges>
3     <removeXML target="/sbml:sbml/sbml:model/sbml:listOfReactions/sbml:reaction[@id='J1']" />
4   </listOfChanges>
5 </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 attribute` must select a single attribute within the corresponding model.

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` assigns 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.

```

1 <model id="model1" name="Circadian Chaos" language="urn:sedml:language:sbml"
2   source="urn:miriam:biomodels.db:BIOMD0000000021">
3   <listOfChanges>
4     <changeAttribute target="/sbml:sbml/sbml:model/sbml:listOfParameters/sbml:parameter[@id='V_mT']/"
5       @value" newValue="0.28"/>
6     <changeAttribute target="/sbml:sbml/sbml:model/sbml:listOfParameters/sbml:parameter[@id='V_dT']/"
7       @value" newValue="4.8"/>

```

```

6     </listOfChanges>
7 </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 element or attribute of a `Model` addressable by a `target`, based on a calculation (Figure 2.10 on page 33). 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`. This `Math` may in turn depend on values calculated from the `Model` itself, meaning that the interpreters may need to initialize the model state before applying a `ComputeChange` to that state.

Note 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. 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 “KISA0:0000838” to set the concentration, or setting the `symbol` to “KISA0:0000836” to set the amount.

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

```

1 <model [...]>
2   <listOfChanges>
3     <computeChange target="/sbml:sbml/sbml:model/sbml:listOfParameters/sbml:parameter[@id='sensor']">
4       <listOfVariables>
5         <variable modelReference="model1" id="R" name="regulator"
6           target="/sbml:sbml/sbml:model/sbml:listOfSpecies/sbml:species[@id='regulator']" />
7         <variable modelReference="model2" id="S" name="sensor"
8           target="/sbml:sbml/sbml:model/sbml:listOfParameters/sbml:parameter[@id='sensor']" />
9       </listOfVariables>
10      <listOfParameters>
11        <parameter id="n" name="cooperativity" value="2">
12          <parameter id="K" name="sensitivity" value="1e-6">
13        </listOfParameters>
14      <math xmlns="http://www.w3.org/1998/Math/MathML">
15        <apply>
16          <times />
17          <ci>S</ci>
18          <apply>
19            <divide />
20            <apply>
21              <power />
22              <ci>R</ci>
23              <ci>n</ci>
24            </apply>
25            <plus />
26            <apply>
27              <power />
28              <ci>K</ci>
29              <ci>n</ci>
30            </apply>
31          </apply>
32          <apply>
33            <power />
34            <ci>R</ci>
35            <ci>n</ci>
36          </apply>
37        </apply>
38      </math>
39    </computeChange>
40  </listOfChanges>
41 </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).

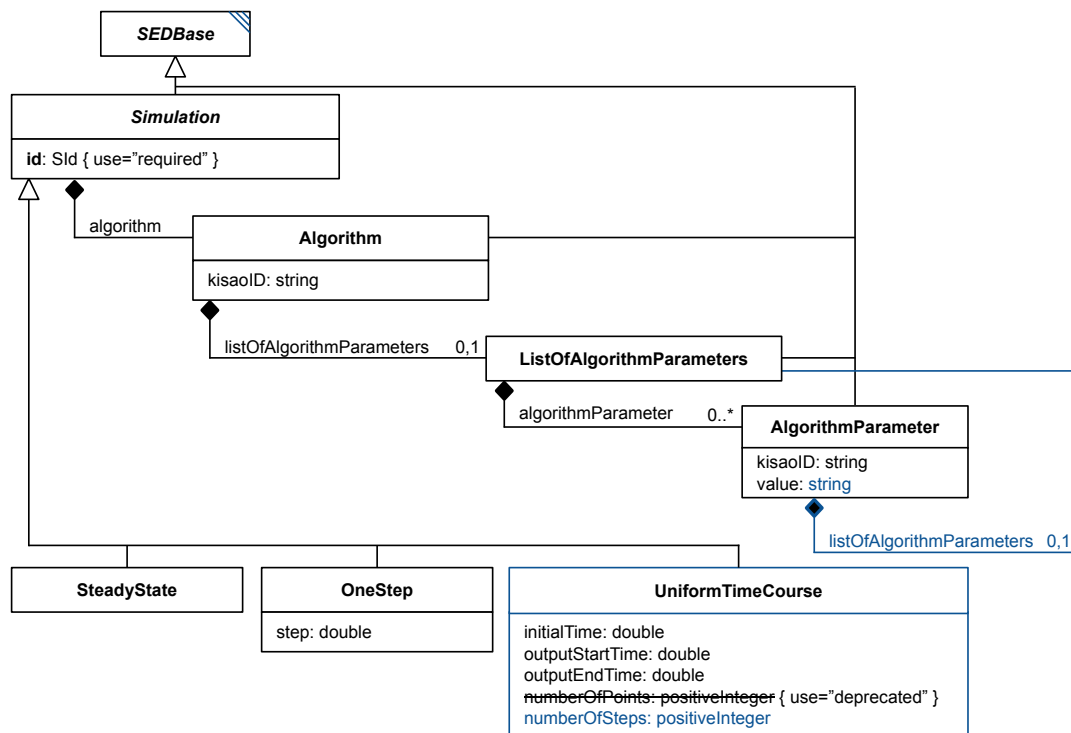


Figure 2.11: The SED-ML Simulation class

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** and **SteadyState**.

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**.

```

1 <listOfSimulations>
2   <uniformTimeCourse [...]>
3     [SIMULATION SPECIFICATION]
4   </uniformTimeCourse>
5   <uniformTimeCourse [...]>
6     [SIMULATION SPECIFICATION]
7   </uniformTimeCourse>
8 </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.

```
1 <listOfSimulations>
2   <uniformTimeCourse id="s1" name="time course simulation of variable v1 over 100 minutes"
3     initialTime="0" outputStartTime="0" outputEndTime="2500" numberOfSteps="1000">
4     <algorithm [...] />
5   </uniformTimeCourse>
6 </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 `initialTime` 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 `initialTime`) 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 the preceding page).

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

```
1 <listOfSimulations>
2   <oneStep id="s1" step="0.1">
3     <algorithm kisaoID="KISAO:0000019" />
4   </oneStep>
5 </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 Kin-solve). The `SteadyState` class has no additional elements than the elements from `Simulation` (Figure 2.11 on page 36).

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

```
1 <listOfSimulations>
2   <steadyState id="steady">
3     <algorithm kisaoID="KISAO:0000282" />
4   </steadyState>
5 </listOfSimulations>
```

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

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 2.41. 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).

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

Listing 2.41: 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 36). It may list several instances of the `AlgorithmParameter` class. The `listOfAlgorithmParameters` is optional and may contain zero to many parameters.

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

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

Listing 2.42: 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 36). 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.

```
1 <algorithm kisaoID="KISAO:0000032">
2   <listOfAlgorithmParameters>
3     <algorithmParameter kisaoID="KISAO:0000211" value="23"/>
4   </listOfAlgorithmParameters>
5 </algorithm>
```

Listing 2.43: 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.

```
1 <algorithm kisaoID="KISAO:0000352">
2   <listOfAlgorithmParameters>
3     <algorithmParameter kisaoID="KISAO:0000000" value="KISAO:0000019">
4       <listOfAlgorithmParameters>
5         <algorithmParameter kisaoID="KISAO:0000211" value="1e-07"/>
6         <algorithmParameter kisaoID="KISAO:0000475" value="BDF"/>
7         <algorithmParameter kisaoID="KISAO:0000481" value="true"/>
8         <algorithmParameter kisaoID="KISAO:0000476" value="Newton"/>
9         <algorithmParameter kisaoID="KISAO:0000477" value="Dense"/>
10        <algorithmParameter kisaoID="KISAO:0000480" value="0"/>
11        <algorithmParameter kisaoID="KISAO:0000415" value="500"/>
12        <algorithmParameter kisaoID="KISAO:0000467" value="0"/>
13        <algorithmParameter kisaoID="KISAO:0000478" value="Banded"/>
14        <algorithmParameter kisaoID="KISAO:0000209" value="1e-07"/>
15        <algorithmParameter kisaoID="KISAO:0000479" value="0"/>
16      </listOfAlgorithmParameters>
17    </algorithmParameter>
18    <algorithmParameter kisaoID="KISAO:0000000" value="KISAO:0000282">
19      <listOfAlgorithmParameters>
20        <algorithmParameter kisaoID="KISAO:0000477" value="Dense"/>
21        <algorithmParameter kisaoID="KISAO:0000480" value="0"/>
22        <algorithmParameter kisaoID="KISAO:0000486" value="200"/>
23        <algorithmParameter kisaoID="KISAO:0000479" value="0"/>
24      </listOfAlgorithmParameters>
25    </algorithmParameter>
26  </listOfAlgorithmParameters>
27 </algorithm>
```

Listing 2.44: 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.

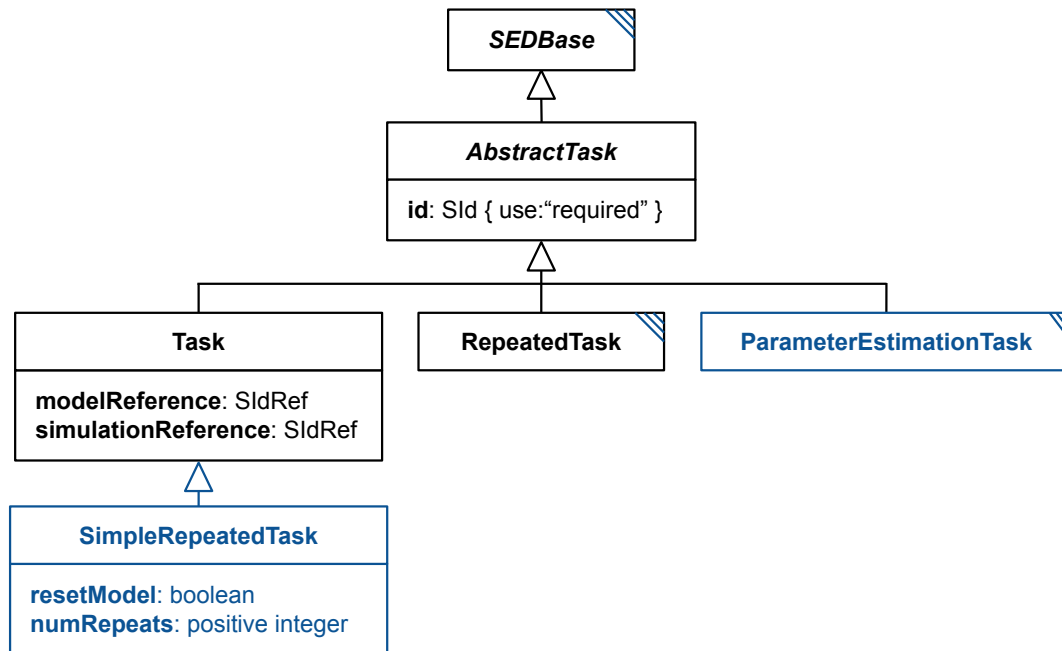


Figure 2.12: The SED-ML Abstract Task, Task, RepeatedTask, and SimpleRepeatedTask classes

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**.

```

1 <listOfTasks>
2   <task id="t1" name="task definition" modelReference="model1"
3     simulationReference="simulation1" />
4   <task id="t2" name="another task definition" modelReference="model2"
5     simulationReference="simulation1" />
6 </listOfTasks>
  
```

Listing 2.45: The task element

2.2.8.2 SimpleRepeated Task

The **SimpleRepeatedTask** inherits from **Task**, and provides a simplified looping construct that performs the **Task** multiple times, resetting the model or not, according to its **resetModel** attribute. The task itself is defined by the **modelReference** and **simulationReference** attributes it inherits from **Task**.

resetModel

The **resetModel** attribute, **boolean** defines whether, for each execution of the simulation, the model is to be reset (“true”) or not (“false”).

numRepeats

The **numRepeats**, of type **positive integer**, defines the number of times the simulation is to be performed.

2.2.8.3 Repeated Task

The **RepeatedTask** (Figure 2.13) 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 to be altered at each iteration (as defined in the **listOfChanges**).

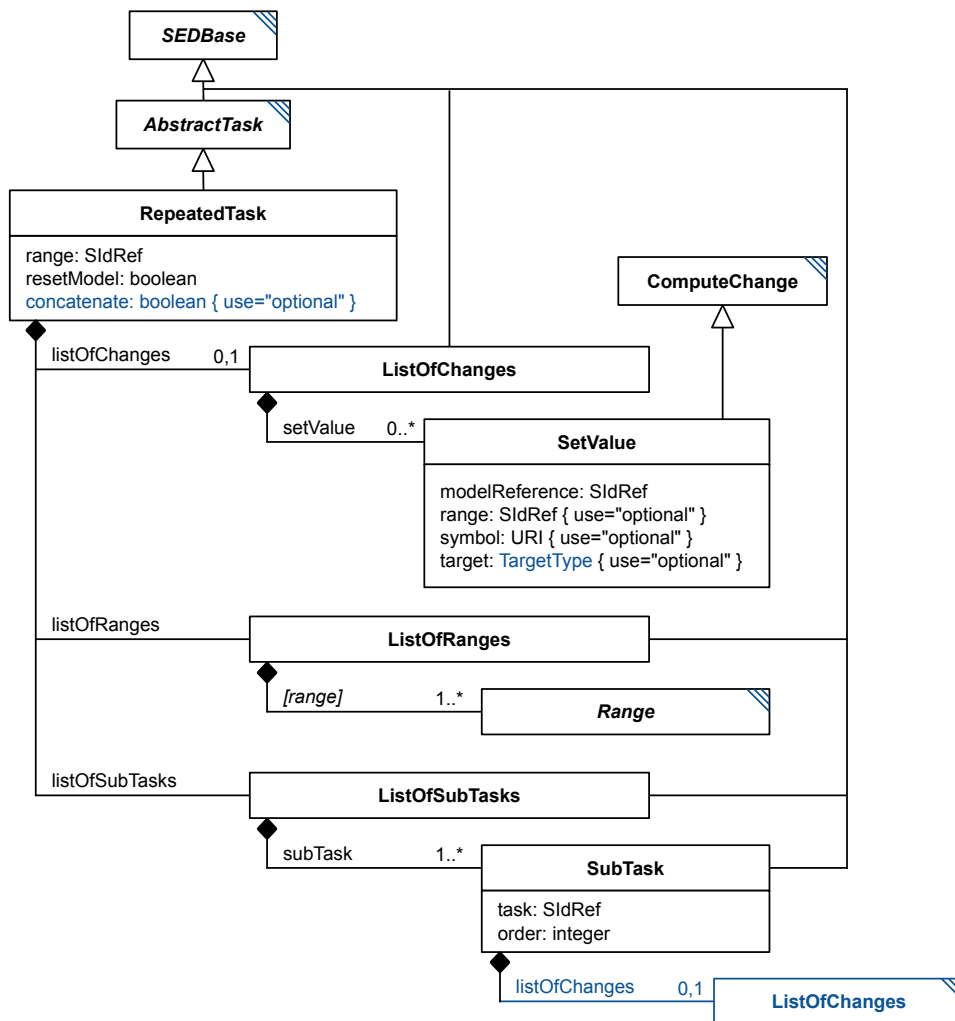


Figure 2.13: The SED-ML *RepeatedTask* class

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 is reset if specified by the `resetModel` attribute.
- Any changes to the model specified by `SetValue` objects in the `listOfChanges` are applied to the `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 2.46 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`.

```

1 <task id="task1" modelReference="model1" simulationReference="simulation1" />
2 <repeatedTask id="task3" resetModel="false" range="current"
3   xmlns:s='http://www.sbml.org/sbml/level3/version1/core'>
4   <listOfRanges>
5     <vectorRange id="current">
6       <value> 1 </value>
7       <value> 4 </value>
8       <value> 10 </value>
9     </vectorRange>
10  </listOfRanges>
11  <listOfChanges>
12    <setValue target="/s:sbml/s:model/s:listOfParameters/s:parameter[@id='w']" modelReference="model1">
13      <listOfVariables>
14        <variable id="val" name="current range value" target="#current" />
15      </listOfVariables>
16      <math xmlns="http://www.w3.org/1998/Math/MathML">
17        <ci> val </ci>
18      </math>
19    </setValue>
20  </listOfChanges>
21  <listOfSubTasks>
22    <subTask task="task1" />
23  </listOfSubTasks>
24 </repeatedTask>

```

Listing 2.46: *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 2.46 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 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 as given in the `listOfModels`.

In the example in Listing 2.46 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.

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 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 (i.e. as at the end of the previous `subTask`, assuming it simulates the same model). If the `concatenate` 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 additional dimension of the repeated task. The order in which to run multiple `subTasks` must be specified using the `order` attribute on the `subTask`.

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

Listing 2.47: 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`.

A `Range` is the iterative element of the repeated simulation experiment. Each `Range` defines a collection of values to iterate over. The `id` attribute of the ranges can be used to refer to the current value of a range. When the `id` attribute is used in a `listOfVariables` within the `RepeatedTask` its value is to be replaced with the current value of the `Range`.

2.2.9 Task components

2.2.9.1 SubTask

A `SubTask` (Figure 2.13 on page 41) 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 2.47).

listOfChanges

The `SetValue` children of the `ListOfChanges` of this `SubTask` define changes to apply to the model state 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 41) allows the modification of the **model** prior to the next execution of the **subTasks**. The changes to the model are defined in the **listOfChanges** of the **RepeatedTask**.

SetValue inherits from the **ComputeChange** class, which allows it to compute arbitrary expressions involving a number of **variables** and **parameters**. **SetValue** has a mandatory **modelReference** attribute, and the optional attributes **range** and **symbol**.

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

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 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 **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**.

```

1 <listOfChanges>
2   <setValue target="/s:sbml/s:model/s:listOfParameters/s:parameter[@id='w']"
3     range="current" modelReference="model1">
4     <math xmlns="http://www.w3.org/1998/Math/MathML">
5       <ci> current </ci>
6     </math>
7   </setValue>
8 </listOfChanges>

```

Listing 2.48: A **setValue** element setting *w* to the values of the range with *id* *current*.

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).

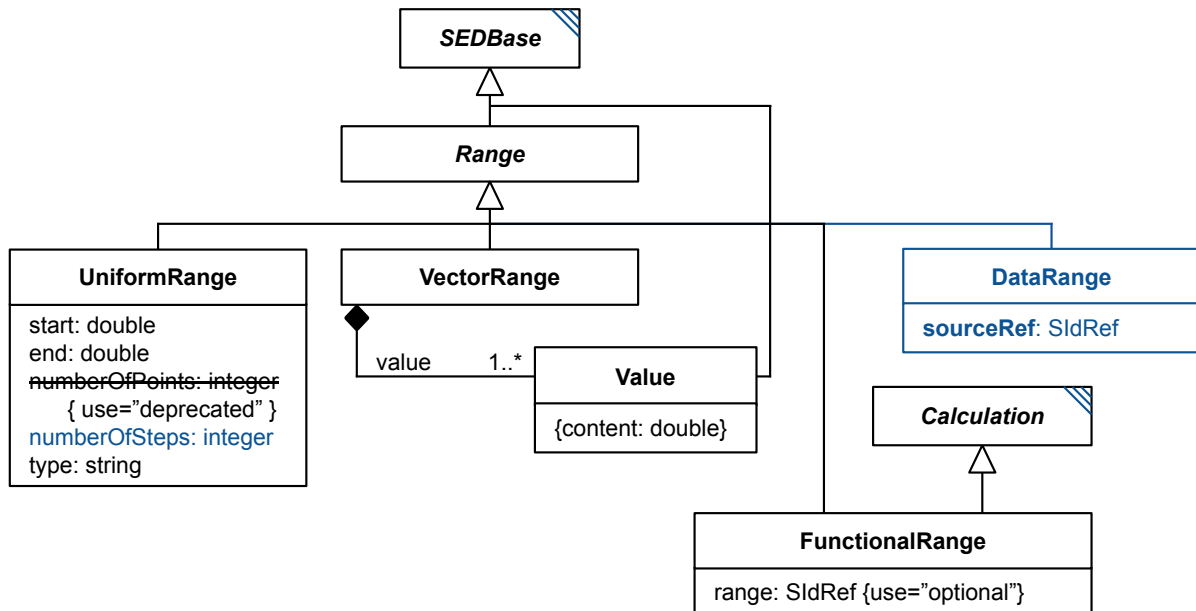


Figure 2.14: The SED-ML Range class

2.2.9.3.1 UniformRange

The **UniformRange** (Figure 2.14 on the previous 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 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.

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

Listing 2.49: The *UniformRange* element

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

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

Listing 2.50: The *UniformRange* element with a logarithmic range.

2.2.9.3.2 VectorRange

The **VectorRange** (Figure 2.14 on the preceding 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.

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

Listing 2.51: The *VectorRange* element

2.2.9.3.3 Value

The **Value** (Figure 2.14 on the previous 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 preceding 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 **SIIdRef** 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.

For example:

```
1 <functionalRange id="current" range="index"
2   xmlns:s='http://www.sbml.org/sbml/level3/version1/core'>
3   <listOfVariables>
4     <variable id="w" name="current parameter value" modelReference="model2"
5       target="/s:sbml/s:model/s:listOfParameters/s:parameter[@id='w']" />
6   </listOfVariables>
7   <math xmlns="http://www.w3.org/1998/Math/MathML">
8     <apply>
9       <times/>
10      <ci> w </ci>
11      <ci> index </ci>
12    </apply>
```

```

13     </math>
14 </functionalRange>

```

Listing 2.52: 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:

```

1 <uniformRange id="index" start="0" end="10" numberOfSteps="100" />
2 <functionalRange id="current" range="index">
3   <math xmlns="http://www.w3.org/1998/Math/MathML">
4     <piecewise>
5       <piece>
6         <cn> 8 </cn>
7         <apply>
8           <lt />
9           <ci> index </ci>
10          <cn> 1 </cn>
11        </apply>
12      </piece>
13      <piece>
14        <cn> 0.1 </cn>
15        <apply>
16          <and />
17          <apply>
18            <geq />
19            <ci> index </ci>
20            <cn> 4 </cn>
21          </apply>
22          <apply>
23            <lt />
24            <ci> index </ci>
25            <cn> 6 </cn>
26          </apply>
27        </apply>
28      </piece>
29      <otherwise>
30        <cn> 8 </cn>
31      </otherwise>
32    </piecewise>
33  </math>
34 </functionalRange>

```

Listing 2.53: 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 44) constructs a range by reference to external data. It inherits from `Range`, and adds the required attribute `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:

```

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

```

Listing 2.54: 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.

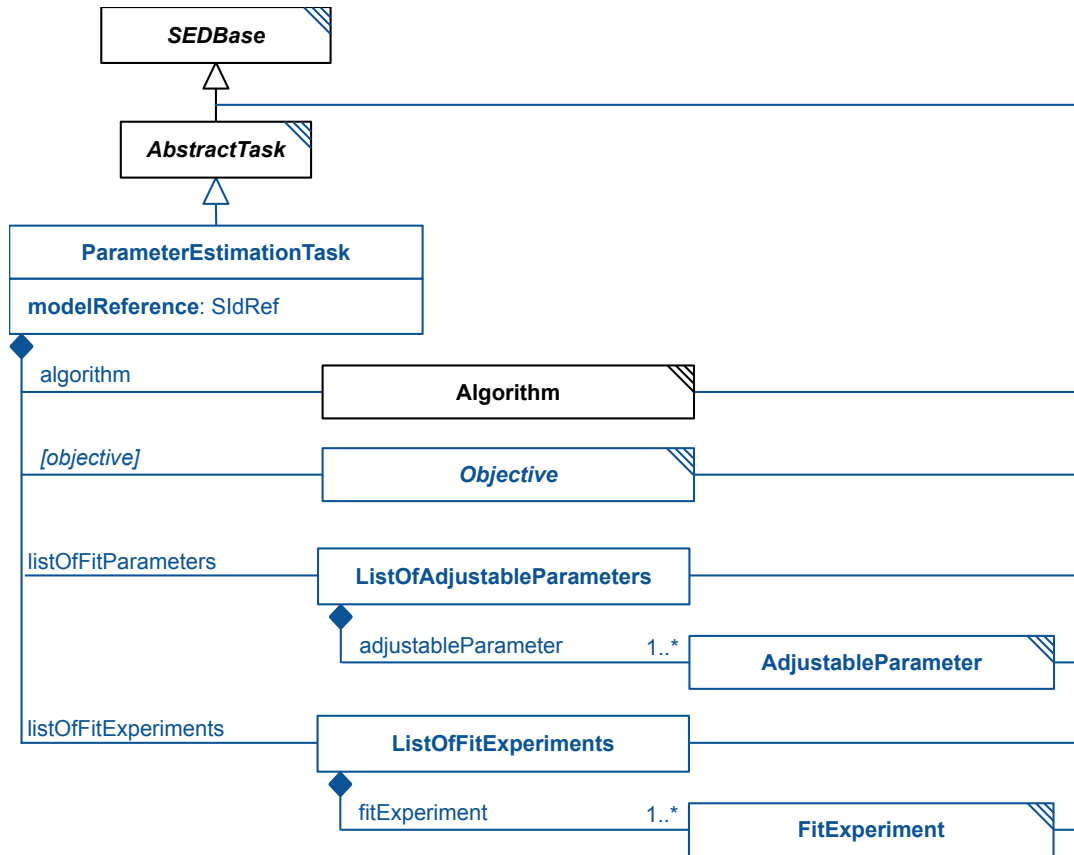


Figure 2.15: The SED-ML *ParameterEstimationTask* class

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.

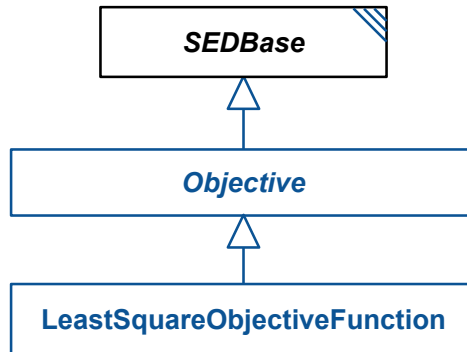


Figure 2.16: The SED-ML `Objective` and `LeastSquareObjectiveFunction` classes

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 `initialValue` 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.

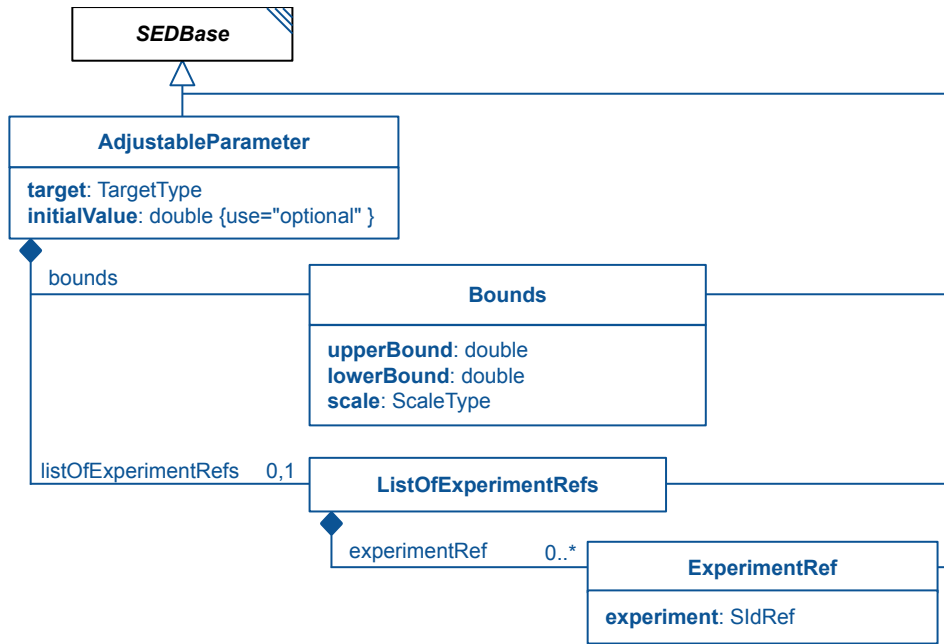


Figure 2.17: The SED-ML *AdjustableParameter*, *Bounds*, *ListOfExperimentRefs*, and *ExperimentRef* classes

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.

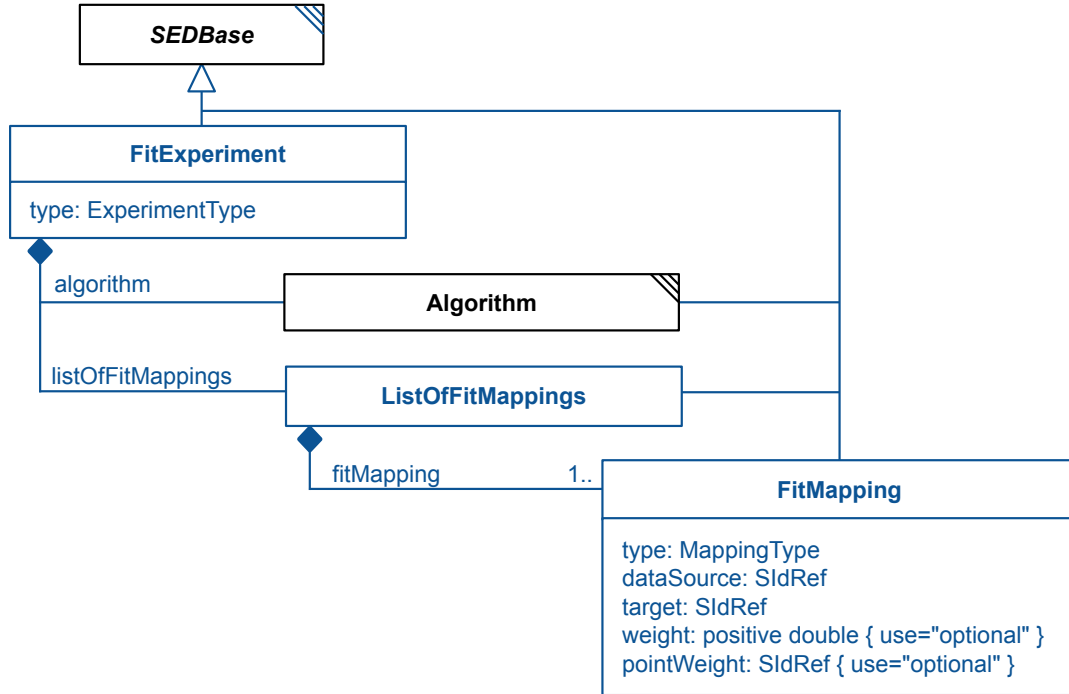


Figure 2.18: The SED-ML `FitExperiment`, `ListOfFitMappings`, and `FitMappings` classes

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 externally-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 `dataSource` 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.

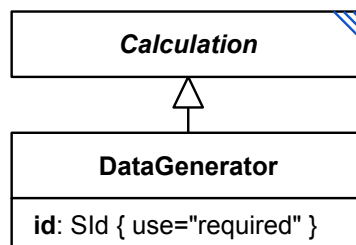


Figure 2.19: The *SED-ML DataGenerator* class.

Listing 2.55 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.

```

1 <listOfDataGenerators>
2   <dataGenerator id="d1" name="time">
3     <listOfVariables>
4       <variable id="time" taskReference="task1" symbol="KISA0:0000832" />
5     </listOfVariables>
6     <listOfParameters />
7     <math xmlns="http://www.w3.org/1998/Math/MathML">
8       <ci> time </ci>
9     </math>
10  </dataGenerator>
11  <dataGenerator id="d2" name="LaCI repressor">
12    <listOfVariables>

```

```

13         <variable id="v1" taskReference="task1"
14             target="/sbml:sbml/sbml:model/sbml:listOfSpecies/sbml:species[@id='PX']" />
15     </listOfVariables>
16     <math xmlns="http://www.w3.org/1998/Math/MathML">
17         <math:ci>v1</math:ci>
18     </math>
19 </dataGenerator>
20 </listOfDataGenerators>

```

Listing 2.55: 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.

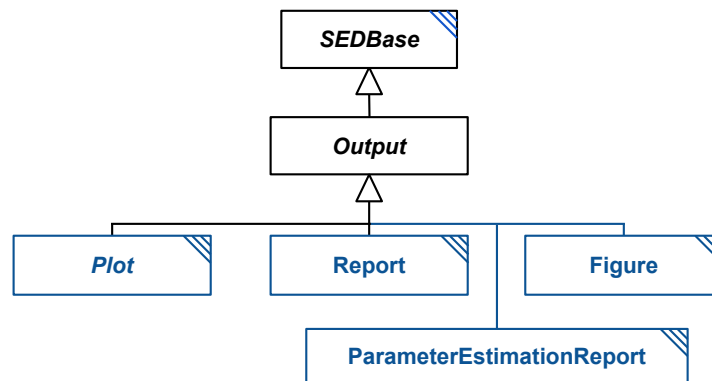


Figure 2.20: The definition of the SED-ML `Output` class. The subclasses are defined below.

The `Output` class inherits the `id` and `name` attributes from `SEDBase`, as well as the optional `annotation` and `notes` children. 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 52). 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 **SideRef**.

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.

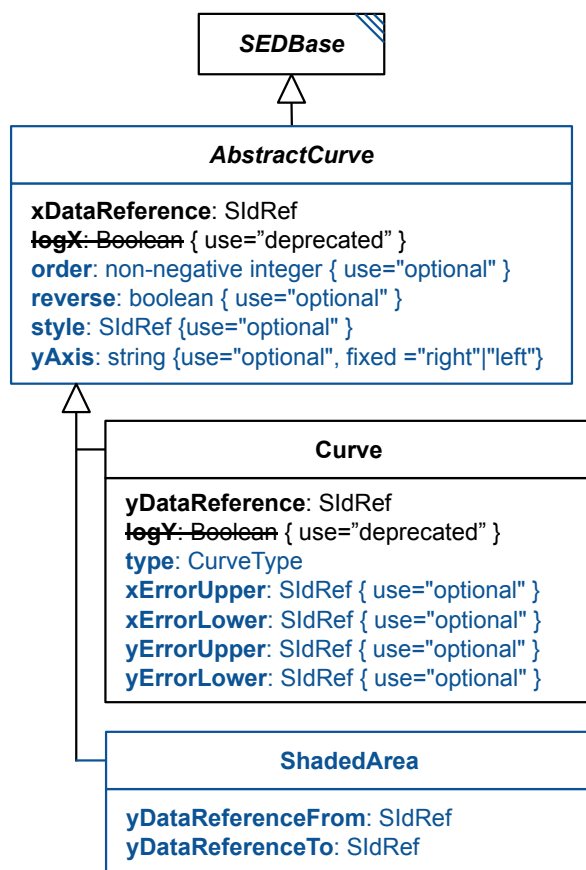


Figure 2.22: The definition of the SED-ML *AbstractCurve*, *Curve*, and *ShadedArea* classes.

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 52). 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 *SldRef* 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*.

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 multiple [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 52). Zero or more [Curve](#) instances define a [Plot2D](#) (Figure 2.20 on page 52). 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 following 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.

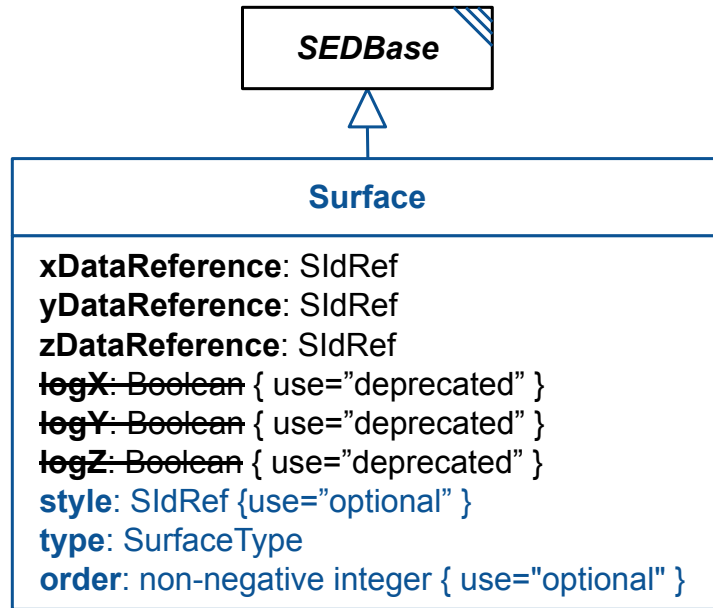


Figure 2.23: The definition of the SED-ML *Surface* class.

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.

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.

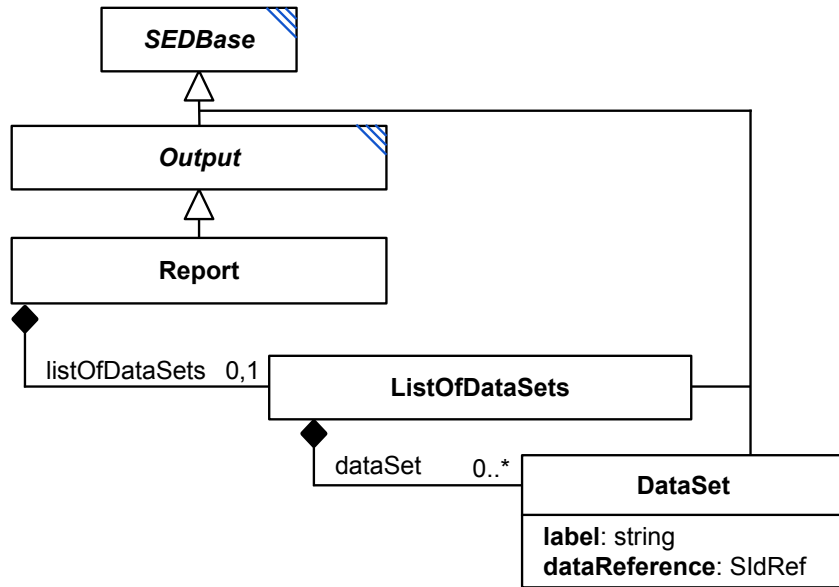


Figure 2.24: The definition of the SED-ML *Report*, *ListOfDataSets*, and *DataSet* classes.

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 2.56 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`.

```

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

```

```
3 </listOfDataSets>
```

Listing 2.56: 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.

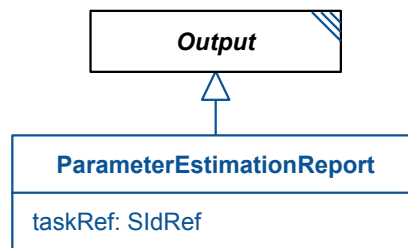


Figure 2.25: The definition of the SED-ML `ParameterEstimationReport` class.

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.

```

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

```

Listing 2.57: The SED-ML *figure* element, defining a figure with four subplots of different sizes

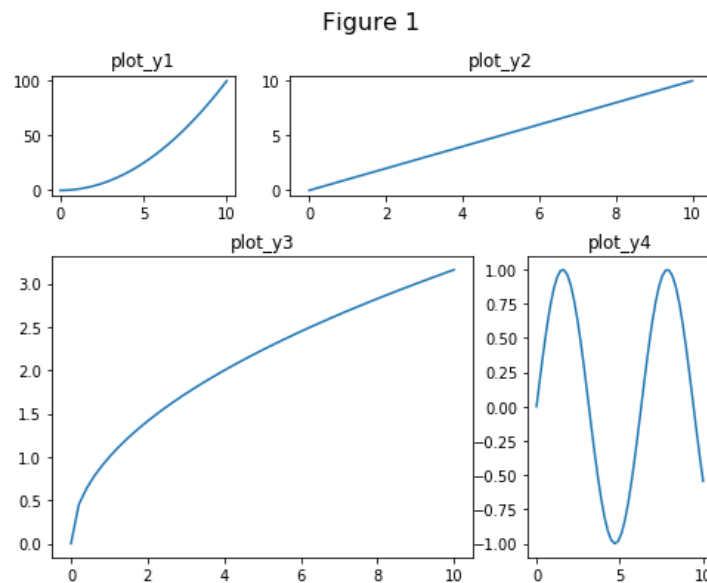


Figure 2.27: The output of Listing 2.57

2.2.16 ParameterEstimationResultsPlot

A [ParameterEstimationResultsPlot](#) class is used to create a default plot from a [ParameterEstimation-Task](#). 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 *SIIdRef* 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.

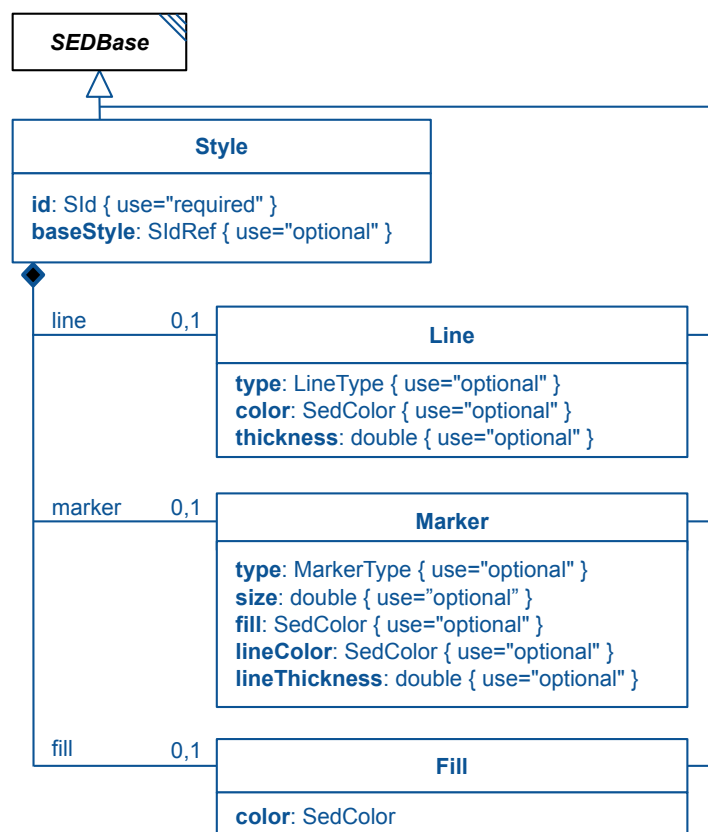


Figure 2.29: The SED-ML *Style* class

The *Style* class inherits the attributes and children from *SEDBase*, extending the **id** attribute to be required, adding an optional **baseStyle** of type *SIIdRef*, and allowing up to three optional children 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`, `lambda`
- *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`, `bvar`, `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 only operate on *scalar* values. However, as one of SED-ML's aims is to provide post processing on the results of simulation experiments, this basic set needs to be extended by some aggregate functions. Therefore a defined set of [MathML symbols](#) that represent vector values are supported by SED-ML. 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](#).

3.1.3 MathML functions

The only aggregate [MathML functions](#) available in SED-ML are `min`, `max`, `sum`, `product`, `count`, `mean`, `stdev`, `variance`, `uniform`, `normal`, `lognormal`, `poisson`, and `gamma`. These represent the only exceptions. At this point SED-ML does not define a complete algebra of vector values.

min

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

```
1 <apply>
2   <csymbol encoding="text" definitionURL="http://sed-ml.org/#min">
3     min
4   </csymbol>
5   <ci> variableId </ci>
6 </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).

```
1 <apply>
2   <csymbol encoding="text" definitionURL="http://sed-ml.org/#max">
3     max
4   </csymbol>
5   <ci> variableId </ci>
6 </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).

```
1 <apply>
2   <csymbol encoding="text" definitionURL="http://sed-ml.org/#sum">
3     sum
4   </csymbol>
5   <ci> variableId </ci>
6 </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).

```
1 <apply>
2   <csymbol encoding="text" definitionURL="http://sed-ml.org/#product">
3     product
4   </csymbol>
5   <ci> variableId </ci>
6 </apply>
```

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

count

The **count** of a variable represents the number of elements in its single argument.

```
1 <apply>
2   <csymbol encoding="text" definitionURL="http://sed-ml.org/#count">
3     count
4   </csymbol>
5   <ci> variableId </ci>
6 </apply>
```

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

mean

The **mean** of a variable represents the mean of the elements in its single argument.

```
1 <apply>
2   <csymbol encoding="text" definitionURL="http://sed-ml.org/#mean">
3     mean
4   </csymbol>
5   <ci> variableId </ci>
6 </apply>
```

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

stdev

The **stdev** of a variable represents the standard deviation of the elements in its single argument.

```
1 <apply>
2   <csymbol encoding="text" definitionURL="http://sed-ml.org/#stdev">
3     stdev
4   </csymbol>
5   <ci> variableId </ci>
6 </apply>
```

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

variance

The **variance** of a variable represents the variance of the elements in its single argument.

```
1 <apply>
2   <csymbol encoding="text" definitionURL="http://sed-ml.org/#variance">
3     variance
4   </csymbol>
5   <ci> variableId </ci>
6 </apply>
```

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

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’ required 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’.

```
1 <apply>
2   <csymbol encoding="text" definitionURL="http://sed-ml.org/#uniform">
3     uniform
4   </csymbol>
5   <ci> maxId </ci>
6   <ci> minId </ci>
7 </apply>
```

Listing 3.9: 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.

```
1 <apply>
2   <csymbol encoding="text" definitionURL="http://sed-ml.org/#normal">
3     normal
4   </csymbol>
5   <ci> meanId </ci>
6   <ci> stdevId </ci>
7 </apply>
```

Listing 3.10: 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.

```
1 <apply>
2   <csymbol encoding="text" definitionURL="http://sed-ml.org/#lognormal">
3     lognormal
4   </csymbol>
5   <ci> meanId </ci>
6   <ci> stdevId </ci>
7 </apply>
```

Listing 3.11: 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.

```

1 <apply>
2   <csymbol encoding="text" definitionURL="http://sed-ml.org/#gamma">
3     gamma
4   </csymbol>
5   <ci> shapeId </ci>
6   <ci> scaleId </ci>
7 </apply>

```

Listing 3.12: 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.

```

1 <apply>
2   <csymbol encoding="text" definitionURL="http://sed-ml.org/#poisson">
3     poisson
4   </csymbol>
5   <ci> rateId </ci>
6 </apply>

```

Listing 3.13: Example for the use of the MathML poisson function.

3.1.4 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 URI of a [model](#) 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. However, any resource registered with MIRIAM resources¹ can easily be referenced.

One way for referencing a model from a SED-ML file is adopted from the [MIRIAM URI Scheme](#). MIRIAM enables identification of a data resource (in this case a model resource) by a predefined URN. A data entry inside that resource is identified by an ID. That way each single model in a particular model repository can be unambiguously referenced. One model repository that is part of MIRIAM resources is the [BioModels Database](#) [19]. Its data resource name in MIRIAM is `urn:miriam:biomodels.db`. To refer to a particular model, a standardised identifier scheme is defined in [MIRIAM Resources](#)². The ID entry maps to a particular model in the model repository. That model is never deleted. A sample BioModels Database ID is `BIOMD0000000048`. Together with the data resource name it becomes unambiguously identifiable by the URN `urn:miriam:biomodels.db:BIOMD0000000048`.

¹<http://www.ebi.ac.uk/miriam/main/>

²<http://www.ebi.ac.uk/miriam/>

SED-ML does not specify how to resolve the URNs. However, MIRIAM Resources offers web services to do so³. For the above example of the `urn:miriam:biomodels.db:BIOMD0000000048` model, the resolved URL may look like <http://www.ebi.ac.uk/biomodels-main/BIOMD0000000048>.

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

One way for referencing a data file from a SED-ML file is adopted from the [MIRIAM URI Scheme](#). MIRIAM enables identification of a data resource by a predefined URN.

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

An alternative means to obtain a data file may be to provide a single resource containing necessary data files and the SED-ML file is the [COMBINE archive](#).

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 next 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.

To specify the format of a `dataDescription`, a set of pre-defined SED-ML URNs can be used (Table 3.2 on the following page). 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.

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`, then this `dimensionDescription` must be

³<http://www.ebi.ac.uk/miriam/>

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/>.*

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

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

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 surrounded 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

```
1 # ./example.csv
2 time, S1, S2
3 0.0, 10.0, 0.0
4 0.1, 9.9, 0.1
5 0.2, 9.8, 0.2
```

Listing 3.14: *Example CSV*

```
1
2 <dataDescription id="datacsv" name="Example CSV dataset" source="./example.csv" format="
   urn:sedml:format:csv">
3   <dimensionDescription>
4     <compositeDescription indexType="integer" name="Index">
5       <compositeDescription indexType="string" name="ColumnIds">
6         <atomicDescription valueType="double" name="Values" />
7       </compositeDescription>
8     </compositeDescription>
9   </dimensionDescription>
10  <listOfDataSources>
11    <dataSource id="dataTime">
12      <listOfSlices>
13        <slice reference="ColumnIds" value="time" />
14      </listOfSlices>
15    </dataSource>
16    <dataSource id="dataS1">
17      <listOfSlices>
18        <slice reference="ColumnIds" value="S1" />
19      </listOfSlices>
20    </dataSource>
21  </listOfDataSources>
22  ...
23 </dataDescription>
```

Listing 3.15: *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)

3.2.5 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 KISA0 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 **KISA0:0000832** 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, concentration, 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 lists the predefined symbols in SED-ML.

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>.*

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 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.
- Within a **Change** definition, where **XPath** is used to identify the target XML to which a change should be applied.

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, [NuML\\$Ids](#) 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](http://sed-ml.org/) 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).

```
1 <?xml version="1.0" encoding="UTF-8"?>
2 <!-- Created by phraSED-ML version v1.0.7 with libSBML version 5.15.0. -->
3 <sedML xmlns="http://sed-ml.org/sed-ml/level1/version3" level="1" version="3">
4   <listOfSimulations>
5     <uniformTimeCourse id="sim1" initialTime="0" outputStartTime="0" outputEndTime="1000" numberOfPoints=
6       "1000">
7       <algorithm kisaoID="KISA0:0000019"/>
8     </uniformTimeCourse>
9   </listOfSimulations>
10  <listOfModels>
11    <model id="model1" language="urn:sedml:language:sbml:level-3.version-1" source="urn:miriam:biomodels.
12      db:BIOMD0000000012"/>
13    <model id="model2" language="urn:sedml:language:sbml:level-3.version-1" source="model1">
14      <listOfChanges>
15        <changeAttribute target="/sbml:sbml/sbml:model/sbml:listOfParameters/sbml:parameter[@id='ps_0']/"
16          @value="1.3e-05"/>
17        <changeAttribute target="/sbml:sbml/sbml:model/sbml:listOfParameters/sbml:parameter[@id='ps_a']/"
18          @value="0.013"/>
19      </listOfChanges>
20    </model>
21  </listOfModels>
22  <listOfTasks>
23    <task id="task1" modelReference="model1" simulationReference="sim1"/>
24    <task id="task2" modelReference="model2" simulationReference="sim1"/>
25  </listOfTasks>
26  <listOfDataGenerators>
27    <!-- timecourse -->
28    <dataGenerator id="dg_0_0_0" name="task1.time">
29      <listOfVariables>
30        <variable id="task1_____time" symbol="urn:sedml:symbol:time" taskReference="task1"/>
31      </listOfVariables>
32      <math xmlns="http://www.w3.org/1998/Math/MathML">
33        <ci> task1_____time </ci>
34      </math>
35    </dataGenerator>
36    <dataGenerator id="dg_0_0_1" name="PX (lacI)">
37      <listOfVariables>
38        <variable id="task1_____PX" target="/sbml:sbml/sbml:model/sbml:listOfSpecies/sbml:species[@id='PX
39          ']" taskReference="task1" modelReference="model1"/>
40      </listOfVariables>
41      <math xmlns="http://www.w3.org/1998/Math/MathML">
42        <ci> task1_____PX </ci>
43      </math>
44    </dataGenerator>
45    <dataGenerator id="dg_0_1_1" name="PZ (cI)">
46      <listOfVariables>
47        <variable id="task1_____PZ" target="/sbml:sbml/sbml:model/sbml:listOfSpecies/sbml:species[@id='PZ
48          ']" taskReference="task1" modelReference="model1"/>
49      </listOfVariables>
50      <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   </listOfVariables>
94   <math xmlns="http://www.w3.org/1998/Math/MathML">
95     <apply>
96       <divide/>
97       <ci> task1_____PX </ci>
98     </apply>
99     <csymbol definitionURL="http://sed-ml.org/#max" encoding="text">max</csymbol>
100     <ci> task1_____PX </ci>
101   </apply>
102 </math>
103 </dataGenerator>
104 <dataGenerator id="dg_2_0_1" name="PZ/max(PZ) (cI normalized)">
105   <listOfVariables>
106     <variable id="task1_____PZ" target="/sbml:sbml/sbml:model/sbml:listOfSpecies/sbml:species[@id='PZ
      ']' taskReference="task1" modelReference="model1"/>
107   </listOfVariables>
108   <math xmlns="http://www.w3.org/1998/Math/MathML">
109     <apply>
110       <divide/>
111       <ci> task1_____PZ </ci>
112     </apply>
113     <csymbol definitionURL="http://sed-ml.org/#max" encoding="text">max</csymbol>
114     <ci> task1_____PZ </ci>
115   </apply>
116 </math>
117 </dataGenerator>
118 <dataGenerator id="dg_2_1_0" name="PY/max(PY) (tetR normalized)">
119   <listOfVariables>
120     <variable id="task1_____PY" target="/sbml:sbml/sbml:model/sbml:listOfSpecies/sbml:species[@id='PY
      ']' taskReference="task1" modelReference="model1"/>
121   </listOfVariables>
122   <math xmlns="http://www.w3.org/1998/Math/MathML">
123     <apply>
124       <divide/>

```

```

127     <ci> task1_____PY </ci>
128     <apply>
129       <csymbol definitionURL="http://sed-ml.org/#max" encoding="text">max</csymbol>
130       <ci> task1_____PY </ci>
131     </apply>
132   </math>
133 </dataGenerator>
134 </listOfDataGenerators>
135 <listOfOutputs>
136   <plot2D id="timecourse" name="Timecourse of repressilator">
137     <listOfCurves>
138       <curve id="plot_0__plot_0_0_0__plot_0_0_1" logX="false" logY="false" xDataReference="dg_0_0_0"
139         yDataReference="dg_0_0_1"/>
140       <curve id="plot_0__plot_0_0_0__plot_0_1_1" logX="false" logY="false" xDataReference="dg_0_0_0"
141         yDataReference="dg_0_1_1"/>
142       <curve id="plot_0__plot_0_0_0__plot_0_2_1" logX="false" logY="false" xDataReference="dg_0_0_0"
143         yDataReference="dg_0_2_1"/>
144     </listOfCurves>
145   </plot2D>
146   <plot2D id="preprocessing" name="Timecourse after pre-processing">
147     <listOfCurves>
148       <curve id="plot_1__plot_1_0_0__plot_1_0_1" logX="false" logY="false" xDataReference="dg_1_0_0"
149         yDataReference="dg_1_0_1"/>
150       <curve id="plot_1__plot_1_0_0__plot_1_1_1" logX="false" logY="false" xDataReference="dg_1_0_0"
151         yDataReference="dg_1_1_1"/>
152       <curve id="plot_1__plot_1_0_0__plot_1_2_1" logX="false" logY="false" xDataReference="dg_1_0_0"
153         yDataReference="dg_1_2_1"/>
154     </listOfCurves>
155   </plot2D>
156   <plot2D id="postprocessing" name="Timecourse after post-processing">
157     <listOfCurves>
158       <curve id="plot_2__plot_2_0_0__plot_2_0_1" logX="false" logY="false" xDataReference="dg_2_0_0"
159         yDataReference="dg_2_0_1"/>
160       <curve id="plot_2__plot_2_1_0__plot_2_0_0" logX="false" logY="false" xDataReference="dg_2_1_0"
161         yDataReference="dg_2_0_0"/>
162       <curve id="plot_2__plot_2_0_1__plot_2_1_0" logX="false" logY="false" xDataReference="dg_2_0_1"
163         yDataReference="dg_2_1_0"/>
164     </listOfCurves>
165   </plot2D>
166 </listOfOutputs>
167 </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`.

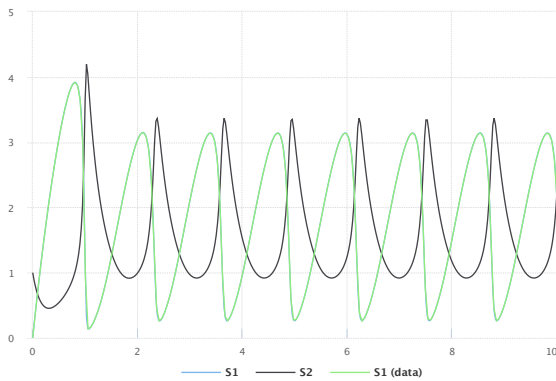


Figure A.1: The simulation result from the simulation description given in Listing A.2. Simulation with SED-ML web tools [2].

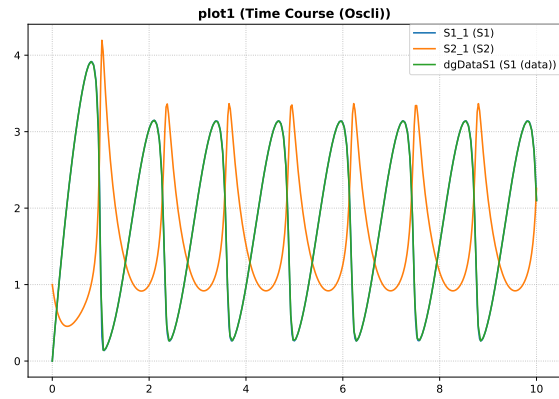


Figure A.2: Simulation with tellurium [6].

```
1 <?xml version="1.0" encoding="utf-8"?>
2 <sedML level="1" version="3" xmlns="http://sed-ml.org/sed-ml/level1/version3">
3   <listOfDataDescriptions>
4     <dataDescription id="Data1" name="oscillator data" source="./oscli.numl" format="
5       urn:sedml:format:numl">
6       <dimensionDescription>
7         <compositeDescription indexType="double" id="time" name="time" xmlns="http://www.numl.org
8           /numl/
9         level1/version1">
10           <compositeDescription indexType="string" id="SpeciesIds" name="SpeciesIds">
11             <atomicDescription valueType="double" name="Concentrations"/>
12           </compositeDescription>
13         </dimensionDescription>
14         <listOfDataSources>
15           <dataSource id="dataS1">
16             <listOfSlices>
17               <slice reference="SpeciesIds" value="S1"/>
18             </listOfSlices>
19           </dataSource>
20           <dataSource id="dataTime" indexSet="time"/>
21         </listOfDataSources>
22       </dataDescription>
23     </listOfDataDescriptions>
24     <listOfSimulations>
25       <uniformTimeCourse id="sim1" initialTime="0" outputStartTime="0" outputEndTime="10"
26         numberOfPoints="400">
27         <algorithm kisaoID="KISAO:0000019">
28           <listOfAlgorithmParameters>
29             <algorithmParameter kisaoID="KISAO:0000209" value="1E-06"/>
30             <algorithmParameter kisaoID="KISAO:0000211" value="1E-12"/>
31             <algorithmParameter kisaoID="KISAO:0000415" value="10000"/>
32           </listOfAlgorithmParameters>
33         </algorithm>
34       </uniformTimeCourse>
35     </listOfSimulations>
```



```

34 <listOfModels>
35   <model id="model1" language="urn:sedml:language:sbml" source="./oscli.xml"/>
36 </listOfModels>
37 <listOfTasks>
38   <task id="task1" modelReference="model1" simulationReference="sim1"/>
39 </listOfTasks>
40 <listOfDataGenerators>
41   <dataGenerator id="time_1" name="time">
42     <listOfVariables>
43       <variable id="time" name="time" taskReference="task1" symbol="urn:sedml:symbol:time"/>
44     </listOfVariables>
45     <math xmlns="http://www.w3.org/1998/Math/MathML">
46       <ci>time</ci>
47     </math>
48   </dataGenerator>
49   <dataGenerator id="S1_1" name="S1">
50     <listOfVariables>
51       <variable id="S1" name="S1" taskReference="task1"
52         target="/sbml:sbml/sbml:model/sbml:listOfSpecies/sbml:species[@id='S1']"/>
53     </listOfVariables>
54     <math xmlns="http://www.w3.org/1998/Math/MathML">
55       <ci>S1</ci>
56     </math>
57   </dataGenerator>
58   <dataGenerator id="S2_1" name="S2">
59     <listOfVariables>
60       <variable id="S2" name="S2" taskReference="task1"
61         target="/sbml:sbml/sbml:model/sbml:listOfSpecies/sbml:species[@id='S2']"/>
62     </listOfVariables>
63     <math xmlns="http://www.w3.org/1998/Math/MathML">
64       <ci>S2</ci>
65     </math>
66   </dataGenerator>
67   <dataGenerator id="dgDataS1" name="S1 (data)">
68     <listOfVariables>
69       <variable id="varS1" modelReference="model1" target="#dataS1"/>
70     </listOfVariables>
71     <math xmlns="http://www.w3.org/1998/Math/MathML">
72       <ci>varS1</ci>
73     </math>
74   </dataGenerator>
75   <dataGenerator id="dgDataTime" name="Time">
76     <listOfVariables>
77       <variable id="varTime" modelReference="model1" target="#dataTime"/>
78     </listOfVariables>
79     <math xmlns="http://www.w3.org/1998/Math/MathML">
80       <ci>varTime</ci>
81     </math>
82   </dataGenerator>
83 </listOfDataGenerators>
84 <listOfOutputs>
85   <plot2D id="plot1" name="Time Course (Oscili)">
86     <listOfCurves>
87       <curve id="curve1" logX="false" logY="false" xDataReference="time_1" yDataReference="S1_1"
88         />
89       <curve id="curve2" logX="false" logY="false" xDataReference="time_1" yDataReference="S2_1"
90         />
91       <curve id="curve3" logX="false" logY="false" xDataReference="dgDataTime" yDataReference="
92         dgDataS1"/>
93     </listOfCurves>
94   </plot2D>
95 </listOfOutputs>
96 </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 does not include a way to post-process these values, so it is left to the implementation on how to display them. One example would be to flatten the values by overlaying them onto the desired plot.

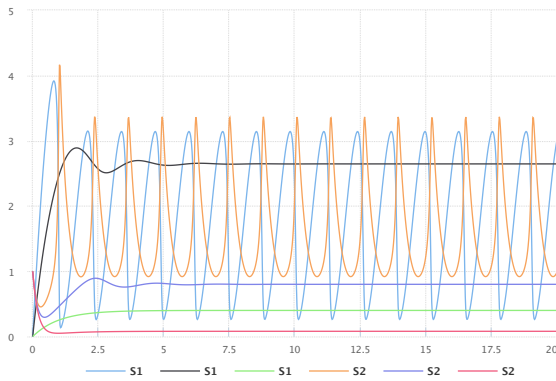


Figure A.3: The simulation result gained from the simulation description given in Listing A.3. Simulation with SED-ML web tools [2].

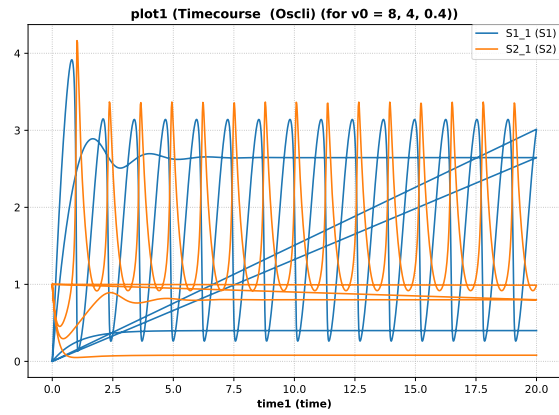


Figure A.4: Simulation with tellurium [6].

```

1 <?xml version="1.0" encoding="utf-8"?>
2 <sedML xmlns="http://sed-ml.org/sed-ml/level1/version3" level="1" version="3">
3   <listOfSimulations>
4     <uniformTimeCourse id="timecourse1" initialTime="0" outputStartTime="0" outputEndTime="20"
5       numberOfPoints="1000">
6       <algorithm kisaoID="KISA0:0000019" />
7     </uniformTimeCourse>
8   </listOfSimulations>
9   <listOfModels>
10    <model id="model1" language="urn:sedml:language:sbml" source="./oscli.xml" />
11  </listOfModels>
12  <listOfTasks>
13    <task id="task0" modelReference="model1" simulationReference="timecourse1" />
14    <repeatedTask id="task1" resetModel="true" range="current">
15      <listOfRanges>
16        <vectorRange id="current">
17          <value>8</value>
18          <value>4</value>
19          <value>0.4</value>
20        </vectorRange>
21      </listOfRanges>
22      <listOfChanges>
23        <setValue target="/sbml:sbml/sbml:model/sbml:listOfParameters/sbml:parameter[@id='J0_v0']"
24          range="current" modelReference="model1">
25          <math xmlns="http://www.w3.org/1998/Math/MathML">
26            <ci> current </ci>
27          </math>
28        </set>
29      </listOfChanges>
30    </repeatedTask>
31  </listOfTasks>
32  <listOfDataGenerators>
33    <dataGenerator id="time1" name="time">

```

```

36     <listOfVariables>
37       <variable id="time" symbol="urn:sedml:symbol:time" taskReference="task1" />
38     </listOfVariables>
39     <math xmlns="http://www.w3.org/1998/Math/MathML">
40       <ci> time </ci>
41     </math>
42   </dataGenerator>
43   <dataGenerator id="J0_v0_1" name="J0_v0">
44     <listOfVariables>
45       <variable id="J0_v0" name="J0_v0" taskReference="task1" target="/sbml:sbml/sbml:model/
46         sbml:listOfParameters/sbml:parameter[@id='J0_v0']" />
47     </listOfVariables>
48     <math xmlns="http://www.w3.org/1998/Math/MathML">
49       <ci> J0_v0 </ci>
50     </math>
51   </dataGenerator>
52   <dataGenerator id="S1_1" name="S1">
53     <listOfVariables>
54       <variable id="S1" name="S1" taskReference="task1" target="/sbml:sbml/sbml:model/
55         sbml:listOfSpecies/sbml:species[@id='S1']" />
56     </listOfVariables>
57     <math xmlns="http://www.w3.org/1998/Math/MathML">
58       <ci> S1 </ci>
59     </math>
60   </dataGenerator>
61   <dataGenerator id="S2_1" name="S2">
62     <listOfVariables>
63       <variable id="S2" name="S2" taskReference="task1" target="/sbml:sbml/sbml:model/
64         sbml:listOfSpecies/sbml:species[@id='S2']" />
65     </listOfVariables>
66     <math xmlns="http://www.w3.org/1998/Math/MathML">
67       <ci> S2 </ci>
68     </math>
69   </dataGenerator>
70 </listOfDataGenerators>
71 <listOfOutputs>
72   <plot2D id="plot1" name="Timecourse (Oscili) (for v0 = 8, 4, 0.4)">
73     <listOfCurves>
74       <curve id="curve1" logX="false" logY="false" xDataReference="time1" yDataReference="S1_1" />
75       <curve id="curve2" logX="false" logY="false" xDataReference="time1" yDataReference="S2_1" />
76     </listOfCurves>
77   </plot2D>
78 </listOfOutputs>
79 </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.

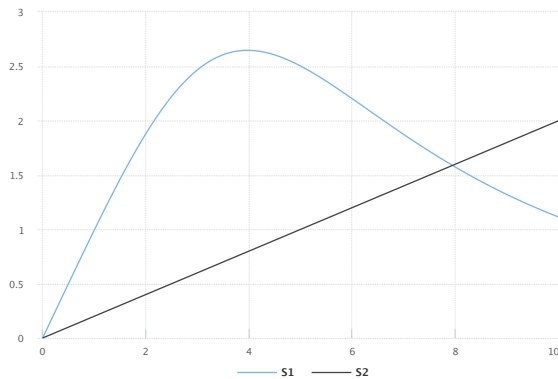


Figure A.5: The simulation result from the simulation description given in Listing A.4. Simulation with SED-ML web tools [2].

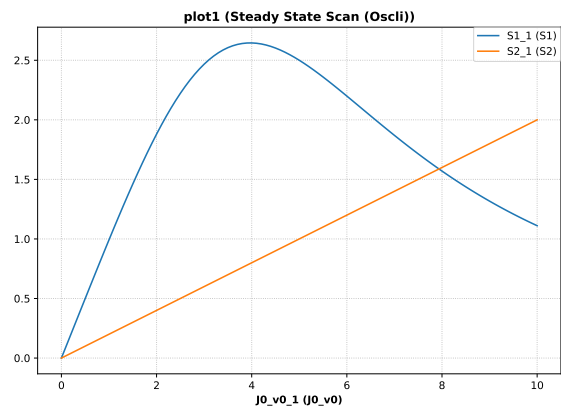


Figure A.6: Simulation with tellurium [6].

```

1 <?xml version="1.0" encoding="utf-8"?>

```

```

2 <!-- Written by libSedML v1.1.4992.38982 see http://libsedml.sf.net -->
3 <sedML xmlns="http://sed-ml.org/sed-ml/level1/version3" level="1" version="3">
4   <listOfSimulations>
5     <steadyState id="steady1">
6       <algorithm kisaoID="KISA0:0000282" />
7     </steadyState>
8   </listOfSimulations>
9   <listOfModels>
10    <model id="model1" language="urn:sedml:language:sbml" source="./oscli.xml" />
11  </listOfModels>
12  <listOfTasks>
13    <task id="task0" modelReference="model1" simulationReference="steady1" />
14    <repeatedTask id="task1" resetModel="true" range="current">
15      <listOfRanges>
16        <uniformRange id="current" start="0" end="10" numberOfPoints="100" type="linear" />
17      </listOfRanges>
18      <listOfChanges>
19        <setValue target="/sbml:sbml/sbml:model/sbml:listOfParameters/sbml:parameter[@id='J0_v0']"
20          range="current" modelReference="model1">
21          <math xmlns="http://www.w3.org/1998/Math/MathML">
22            <ci> current </ci>
23          </math>
24        </setValue>
25      </listOfChanges>
26      <listOfSubTasks>
27        <subTask order="1" task="task0" />
28      </listOfSubTasks>
29    </repeatedTask>
30  </listOfTasks>
31  <listOfDataGenerators>
32    <dataGenerator id="J0_v0_1" name="J0_v0">
33      <listOfVariables>
34        <variable id="J0_v0" name="J0_v0" taskReference="task1" target="/sbml:sbml/sbml:model/
35          sbml:listOfParameters/sbml:parameter[@id='J0_v0']" />
36      </listOfVariables>
37      <math xmlns="http://www.w3.org/1998/Math/MathML">
38        <ci> J0_v0 </ci>
39      </math>
40    </dataGenerator>
41    <dataGenerator id="S1_1" name="S1">
42      <listOfVariables>
43        <variable id="S1" name="S1" taskReference="task1" target="/sbml:sbml/sbml:model/
44          sbml:listOfSpecies/sbml:species[@id='S1']" />
45      </listOfVariables>
46      <math xmlns="http://www.w3.org/1998/Math/MathML">
47        <ci> S1 </ci>
48      </math>
49    </dataGenerator>
50    <dataGenerator id="S2_1" name="S2">
51      <listOfVariables>
52        <variable id="S2" name="S2" taskReference="task1" target="/sbml:sbml/sbml:model/
53          sbml:listOfSpecies/sbml:species[@id='S2']" />
54      </listOfVariables>
55      <math xmlns="http://www.w3.org/1998/Math/MathML">
56        <ci> S2 </ci>
57      </math>
58    </dataGenerator>
59  </listOfDataGenerators>
60  <listOfOutputs>
61    <plot2D id="plot1" name="Steady State Scan (Oscli)">
62      <listOfCurves>
63        <curve id="curve1" logX="false" logY="false" xDataReference="J0_v0_1" yDataReference="S1_1" />
64        <curve id="curve2" logX="false" logY="false" xDataReference="J0_v0_1" yDataReference="S2_1" />
65      </listOfCurves>
66    </plot2D>
67    <report id="report1" name="Steady State Values">
68      <listOfDataSets>
69        <dataSet id="col1" dataReference="J0_v0_1" label="J0_v0" />
70        <dataSet id="col2" dataReference="S1_1" label="S1" />
71        <dataSet id="col3" dataReference="S2_1" label="S2" />
72      </listOfDataSets>
73    </report>
74  </listOfOutputs>
75 </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). While SED-ML Level 1 Version 4 does not include a way to post-processing these values. So it is left to the implementation on how to display them. One example would be to flatten the values by overlaying them onto the desired plot.

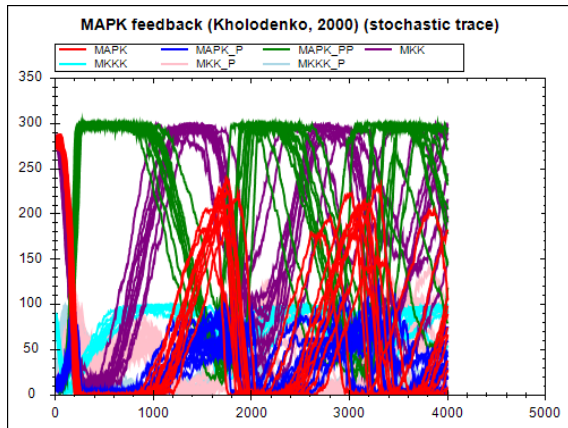


Figure A.7: The simulation result from the simulation description given in Listing A.5. Simulation with SED-ML web tools [2].

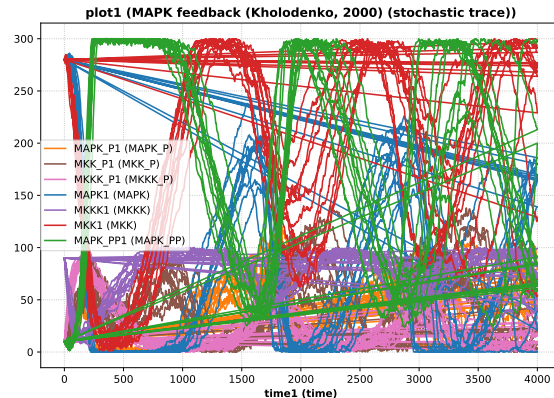


Figure A.8: Simulation with tellurium [6].

```

1 <?xml version="1.0" encoding="utf-8"?>
2 <sedML xmlns="http://sed-ml.org/sed-ml/level1/version3" level="1" version="3">
3   <listOfSimulations>
4     <uniformTimeCourse id="timecourse1" initialTime="0" outputStartTime="0" outputEndTime="4000"
5       numberOfPoints="1000">
6       <algorithm kisaoID="KISA0:0000241" />
7     </uniformTimeCourse>
8   </listOfSimulations>
9   <listOfModels>
10    <model id="model1" language="urn:sedml:language:sbml" source="./BorisEJB.xml" />
11  </listOfModels>
12  <listOfTasks>
13    <task id="task0" modelReference="model1" simulationReference="timecourse1" />
14    <repeatedTask id="task1" resetModel="true" range="current">
15      <listOfRanges>
16        <uniformRange id="current" start="0" end="10" numberOfPoints="10" type="linear" />
17      </listOfRanges>
18      <listOfSubTasks>
19        <subTask order="1" task="task0" />
20      </listOfSubTasks>
21    </repeatedTask>
22  </listOfTasks>
23  <listOfDataGenerators>
24    <dataGenerator id="time1" name="time">
25      <listOfVariables>
26        <variable id="time" taskReference="task1" symbol="urn:sedml:symbol:time" />
27      </listOfVariables>
28      <math xmlns="http://www.w3.org/1998/Math/MathML">
29        <ci> time </ci>
30      </math>
31    </dataGenerator>
32    <dataGenerator id="MAPK1" name="MAPK">
33      <listOfVariables>
34        <variable id="MAPK" name="MAPK" taskReference="task1" target="/sbml:sbml/sbml:model/
35          sbml:listOfSpecies/sbml:species[@id='MAPK']" />
36      </listOfVariables>
37      <math xmlns="http://www.w3.org/1998/Math/MathML">
38        <ci> MAPK </ci>
39      </math>
40    </dataGenerator>
41    <dataGenerator id="MAPK_P1" name="MAPK_P">
42      <listOfVariables>
43        <variable id="MAPK_P" name="MAPK_P" taskReference="task1" target="/sbml:sbml/sbml:model/
44          sbml:listOfSpecies/sbml:species[@id='MAPK_P']" />
45      </listOfVariables>
46      <math xmlns="http://www.w3.org/1998/Math/MathML">
47        <ci> MAPK_P </ci>
48      </math>
49    </dataGenerator>
50    <dataGenerator id="MAPK_PP1" name="MAPK_PP">
51      <listOfVariables>

```

```

49     <variable id="MAPK_PP" name="MAPK_PP" taskReference="task1" target="/sbml:sbml/sbml:model/
      sbml:listOfSpecies/sbml:species[@id='MAPK_PP']" />
50   </listOfVariables>
51   <math xmlns="http://www.w3.org/1998/Math/MathML">
52     <ci> MAPK_PP </ci>
53   </math>
54 </dataGenerator>
55 <dataGenerator id="MKK1" name="MKK">
56   <listOfVariables>
57     <variable id="MKK" name="MKK" taskReference="task1" target="/sbml:sbml/sbml:model/
      sbml:listOfSpecies/sbml:species[@id='MKK']" />
58   </listOfVariables>
59   <math xmlns="http://www.w3.org/1998/Math/MathML">
60     <ci> MKK </ci>
61   </math>
62 </dataGenerator>
63 <dataGenerator id="MKK_P1" name="MKK_P">
64   <listOfVariables>
65     <variable id="MKK_P" name="MKK_P" taskReference="task1" target="/sbml:sbml/sbml:model/
      sbml:listOfSpecies/sbml:species[@id='MKK_P']" />
66   </listOfVariables>
67   <math xmlns="http://www.w3.org/1998/Math/MathML">
68     <ci> MKK_P </ci>
69   </math>
70 </dataGenerator>
71 <dataGenerator id="MKKK1" name="MKKK">
72   <listOfVariables>
73     <variable id="MKKK" name="MKKK" taskReference="task1" target="/sbml:sbml/sbml:model/
      sbml:listOfSpecies/sbml:species[@id='MKKK']" />
74   </listOfVariables>
75   <math xmlns="http://www.w3.org/1998/Math/MathML">
76     <ci> MKKK </ci>
77   </math>
78 </dataGenerator>
79 <dataGenerator id="MKKK_P1" name="MKKK_P">
80   <listOfVariables>
81     <variable id="MKKK_P" name="MKKK_P" taskReference="task1" target="/sbml:sbml/sbml:model/
      sbml:listOfSpecies/sbml:species[@id='MKKK_P']" />
82   </listOfVariables>
83   <math xmlns="http://www.w3.org/1998/Math/MathML">
84     <ci> MKKK_P </ci>
85   </math>
86 </dataGenerator>
87 </listOfDataGenerators>
88 <listOfOutputs>
89   <plot2D id="plot1" name="MAPK feedback (Kholodenko, 2000) (stochastic trace)">
90     <listOfCurves>
91       <curve id="curve1" logX="false" logY="false" xDataReference="time1" yDataReference="MAPK1" />
92       <curve id="curve2" logX="false" logY="false" xDataReference="time1" yDataReference="MAPK_P1" />
93       <curve id="curve3" logX="false" logY="false" xDataReference="time1" yDataReference="MAPK_PP1" />
94       <curve id="curve4" logX="false" logY="false" xDataReference="time1" yDataReference="MKK1" />
95       <curve id="curve5" logX="false" logY="false" xDataReference="time1" yDataReference="MKKK1" />
96       <curve id="curve6" logX="false" logY="false" xDataReference="time1" yDataReference="MKK_P1" />
97       <curve id="curve7" logX="false" logY="false" xDataReference="time1" yDataReference="MKKK_P1" />
98     </listOfCurves>
99   </plot2D>
100 </listOfOutputs>
101 </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.

```

1 <?xml version="1.0" encoding="utf-8"?>
2 <sedML xmlns="http://sed-ml.org/sed-ml/level1/version3" level="1" version="3">
3   <listOfSimulations>
4     <oneStep id="stepper" step="0.1">
5       <algorithm kisaoID="KISA0:0000019" />
6     </oneStep>
7   </listOfSimulations>
8   <listOfModels>
9     <model id="model1" language="urn:sedml:language:sbml" source="./oscli.xml" />
10  </listOfModels>
11  <listOfTasks>
12    <task id="task0" modelReference="model1" simulationReference="stepper" />
13    <repeatedTask id="task1" resetModel="false" range="index">

```

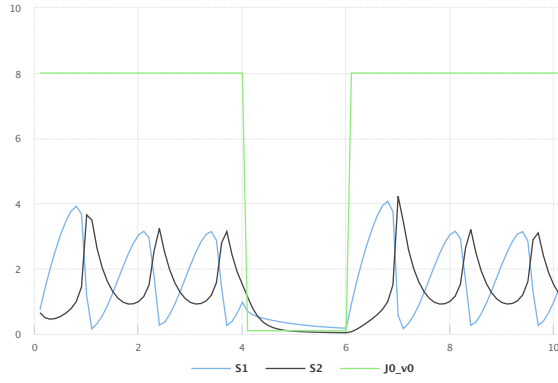


Figure A.9: The simulation result from the simulation description given in Listing A.6. Simulation with SED-ML web tools [2].

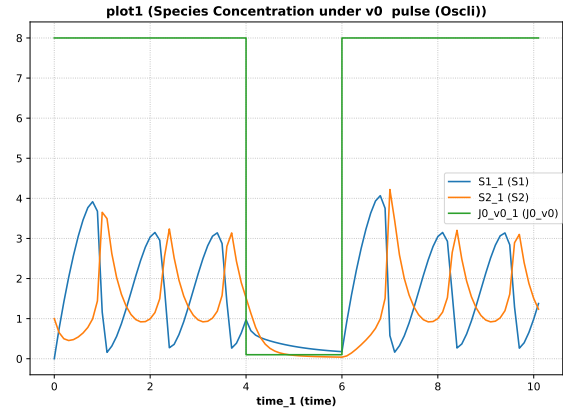


Figure A.10: Simulation with tellurium [6].

```

14     <listOfRanges>
15       <uniformRange id="index" start="0" end="10" numberOfPoints="100" type="linear" />
16       <functionalRange id="current" range="index">
17         <math xmlns="http://www.w3.org/1998/Math/MathML">
18           <piecewise>
19             <piece>
20               <cn> 8 </cn>
21               <apply>
22                 <lt />
23                 <ci> index </ci>
24                 <cn> 1 </cn>
25               </apply>
26             </piece>
27             <piece>
28               <cn> 0.1 </cn>
29               <apply>
30                 <and />
31                 <apply>
32                   <geq />
33                   <ci> index </ci>
34                   <cn> 4 </cn>
35                 </apply>
36                 <apply>
37                   <lt />
38                   <ci> index </ci>
39                   <cn> 6 </cn>
40                 </apply>
41               </apply>
42             </piece>
43             <otherwise>
44               <cn> 8 </cn>
45             </otherwise>
46           </piecewise>
47         </math>
48       </functionalRange>
49     </listOfRanges>
50     <listOfChanges>
51       <setValue target="/sbml:sbml/sbml:model/sbml:listOfParameters/sbml:parameter[@id='J0_v0']"
52         range="current" modelReference="model1">
53         <math xmlns="http://www.w3.org/1998/Math/MathML">
54           <ci> current </ci>
55         </math>
56       </setValue>
57     </listOfChanges>
58     <listOfSubTasks>
59       <subTask order="1" task="task0" />
60     </listOfSubTasks>
61   </repeatedTask>
62 </listOfTasks>
63 <listOfDataGenerators>
64   <dataGenerator id="time_1" name="time">
65     <listOfVariables>
66       <variable id="time" symbol="urn:sedml:symbol:time" taskReference="task1" />
67     </listOfVariables>
68     <math xmlns="http://www.w3.org/1998/Math/MathML">
69       <ci> time </ci>
70     </math>
71   </dataGenerator>
72   <dataGenerator id="J0_v0_1" name="J0_v0">

```



```

73     <listOfVariables>
74       <variable id="J0_v0" name="J0_v0" taskReference="task1" target="/sbml:sbml/sbml:model/
       sbml:listOfParameters/sbml:parameter[@id='J0_v0']" />
75     </listOfVariables>
76     <math xmlns="http://www.w3.org/1998/Math/MathML">
77       <ci> J0_v0 </ci>
78     </math>
79   </dataGenerator>
80   <dataGenerator id="S1_1" name="S1">
81     <listOfVariables>
82       <variable id="S1" name="S1" taskReference="task1" target="/sbml:sbml/sbml:model/
       sbml:listOfSpecies/sbml:species[@id='S1']" />
83     </listOfVariables>
84     <math xmlns="http://www.w3.org/1998/Math/MathML">
85       <ci> S1 </ci>
86     </math>
87   </dataGenerator>
88   <dataGenerator id="S2_1" name="S2">
89     <listOfVariables>
90       <variable id="S2" name="S2" taskReference="task1" target="/sbml:sbml/sbml:model/
       sbml:listOfSpecies/sbml:species[@id='S2']" />
91     </listOfVariables>
92     <math xmlns="http://www.w3.org/1998/Math/MathML">
93       <ci> S2 </ci>
94     </math>
95   </dataGenerator>
96 </listOfDataGenerators>
97 <listOfOutputs>
98   <plot2D id="plot1" name="Species Concentration under v0 pulse (Oscili)">
99     <listOfCurves>
100       <curve id="curve1" logX="false" logY="false" xDataReference="time_1" yDataReference="S1_1" />
101       <curve id="curve2" logX="false" logY="false" xDataReference="time_1" yDataReference="S2_1" />
102       <curve id="curve3" logX="false" logY="false" xDataReference="time_1" yDataReference="J0_v0_1" />
103     </listOfCurves>
104   </plot2D>
105   <report id="report1" name="Species Concentration under v0 pulse (Oscili)">
106     <listOfDataSets>
107       <dataSet id="col0" dataReference="time_1" label="time" />
108       <dataSet id="col1" dataReference="J0_v0_1" label="J0_v0" />
109       <dataSet id="col2" dataReference="S1_1" label="S1" />
110       <dataSet id="col3" dataReference="S2_1" label="S2" />
111     </listOfDataSets>
112   </report>
113 </listOfOutputs>
114 </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). While SED-ML Level 1 Version 4 does not include a way to post-processing these values. So it is left to the implementation on how to display them. One example would be to flatten the values by overlaying them onto the desired plot.

```

1 <?xml version="1.0" encoding="utf-8"?>
2 <sedML xmlns="http://sed-ml.org/sed-ml/level1/version3" level="1" version="3">
3   <listOfSimulations>
4     <steadyState id="steady1">
5       <algorithm kisaoID="KISA0:0000282" />
6     </steadyState>
7   </listOfSimulations>
8   <listOfModels>
9     <model id="model1" language="urn:sedml:language:sbml" source="BorisEJB.xml" />
10  </listOfModels>
11  <listOfTasks>
12    <task id="task0" modelReference="model1" simulationReference="steady1" />
13    <repeatedTask id="task1" resetModel="false" range="current">
14      <listOfRanges>
15        <vectorRange id="current">
16          <value>1</value>
17          <value>5</value>
18          <value>10</value>
19          <value>50</value>
20          <value>60</value>
21          <value>70</value>
22          <value>80</value>
23          <value>90</value>
24          <value>100</value>
25        </vectorRange>
26      </listOfRanges>

```




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].

```

27 <listOfChanges>
28   <setValue target="/sbml:sbml/sbml:model/sbml:listOfParameters/sbml:parameter[@id='J1_KK2']"
29     range="current" modelReference="model1">
30     <math xmlns="http://www.w3.org/1998/Math/MathML">
31       <ci> current </ci>
32     </math>
33   </setValue>
34 </listOfChanges>
35 <listOfSubTasks>
36   <subTask order="1" task="task2" />
37 </listOfSubTasks>
38 </repeatedTask>
39 <repeatedTask id="task2" resetModel="false" range="current1">
40   <listOfRanges>
41     <uniformRange id="current1" start="1" end="40" numberOfPoints="100" type="linear" />
42   </listOfRanges>
43   <listOfChanges>
44     <setValue target="/sbml:sbml/sbml:model/sbml:listOfParameters/sbml:parameter[@id='J4_KK5']"
45       range="current1" modelReference="model1">
46       <math xmlns="http://www.w3.org/1998/Math/MathML">
47         <ci> current1 </ci>
48       </math>
49     </setValue>
50   </listOfChanges>
51   <listOfSubTasks>
52     <subTask order="1" task="task0" />
53   </listOfSubTasks>
54 </repeatedTask>
55 </listOfTasks>
56 <listOfDataGenerators>
57   <dataGenerator id="J4_KK5_1" name="J4_KK5">
58     <listOfVariables>
59       <variable id="J4_KK5" name="J4_KK5" taskReference="task1" target="/sbml:sbml/sbml:model/
60         sbml:listOfParameters/sbml:parameter[@id='J4_KK5']" />
61     </listOfVariables>
62     <math xmlns="http://www.w3.org/1998/Math/MathML">
63       <ci> J4_KK5 </ci>
64     </math>
65   </dataGenerator>

```

```

65 <dataGenerator id="J1_KK2_1" name="J1_KK2">
66   <listOfVariables>
67     <variable id="J1_KK2" name="J1_KK2" taskReference="task1" target="/sbml:sbml/sbml:model/
        sbml:listOfParameters/sbml:parameter[@id='J1_KK2']" />
68   </listOfVariables>
69   <math xmlns="http://www.w3.org/1998/Math/MathML">
70     <ci> J1_KK2 </ci>
71   </math>
72 </dataGenerator>
73 <dataGenerator id="MKK_1" name="MKK">
74   <listOfVariables>
75     <variable id="MKK" name="MKK" taskReference="task1" target="/sbml:sbml/sbml:model/
        sbml:listOfSpecies/sbml:species[@id='MKK']" />
76   </listOfVariables>
77   <math xmlns="http://www.w3.org/1998/Math/MathML">
78     <ci> MKK </ci>
79   </math>
80 </dataGenerator>
81 <dataGenerator id="MKK_P_1" name="MKK_P">
82   <listOfVariables>
83     <variable id="MKK_P" name="MKK_P" taskReference="task1" target="/sbml:sbml/sbml:model/
        sbml:listOfSpecies/sbml:species[@id='MKK_P']" />
84   </listOfVariables>
85   <math xmlns="http://www.w3.org/1998/Math/MathML">
86     <ci> MKK_P </ci>
87   </math>
88 </dataGenerator>
89 <dataGenerator id="MKK_PP_1" name="MKK_PP_1">
90   <listOfVariables>
91     <variable id="MKK_PP_1" name="MKK_PP" taskReference="task1" target="/sbml:sbml/sbml:model/
        sbml:listOfSpecies/sbml:species[@id='MKK_PP']" />
92   </listOfVariables>
93   <math xmlns="http://www.w3.org/1998/Math/MathML">
94     <ci> MKK_PP_1 </ci>
95   </math>
96 </dataGenerator>
97 <dataGenerator id="MKK_TOT" name="MKK_TOT">
98   <listOfVariables>
99     <variable id="MKK" name="MKK" taskReference="task1" target="/sbml:sbml/sbml:model/
        sbml:listOfSpecies/sbml:species[@id='MKK']" />
100    <variable id="MKK_P" name="MKK_P" taskReference="task1" target="/sbml:sbml/sbml:model/
        sbml:listOfSpecies/sbml:species[@id='MKK_P']" />
101    <variable id="MKK_PP" name="MKK_PP" taskReference="task1" target="/sbml:sbml/sbml:model/
        sbml:listOfSpecies/sbml:species[@id='MKK_PP']" />
102   </listOfVariables>
103   <math xmlns="http://www.w3.org/1998/Math/MathML">
104     <apply>
105       <plus/>
106       <ci> MKK </ci>
107       <ci> MKK_P </ci>
108       <ci> MKK_PP </ci>
109     </apply>
110   </math>
111 </dataGenerator>
112 </listOfDataGenerators>
113 <listOfOutputs>
114   <plot2D id="plot1" name="Steady State Scan (Boris 2D)">
115     <listOfCurves>
116       <curve id="curve1" logX="false" logY="false" xDataReference="J4_KK5_1" yDataReference="MKK_1" />
117       <curve id="curve2" logX="false" logY="false" xDataReference="J4_KK5_1" yDataReference="MKK_P_1" />
118     </listOfCurves>
119   </plot2D>
120   <plot2D id="plot2" name="MKK_TOT vs J4_KK5">
121     <listOfCurves>
122       <curve id="curve3" logX="false" logY="false" xDataReference="J4_KK5_1" yDataReference="MKK_TOT" />
123     </listOfCurves>
124   </plot2D>
125   <report id="report1" name="Steady State Values (Boris2D)">
126     <listOfDataSets>
127       <dataSet id="col0" dataReference="J4_KK5_1" label="J4_KK5" />
128       <dataSet id="col1" dataReference="J1_KK2_1" label="J1_KK2" />
129       <dataSet id="col2" dataReference="MKK_1" label="MKK" />
130       <dataSet id="col3" dataReference="MKK_P_1" label="MKK_P" />
131       <dataSet id="col4" dataReference="MKK_PP_1" label="MKK_PP_1" />
132       <dataSet id="col4" dataReference="MKK_TOT" label="MKK_TOT" />
133     </listOfDataSets>
134   </report>
135 </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.

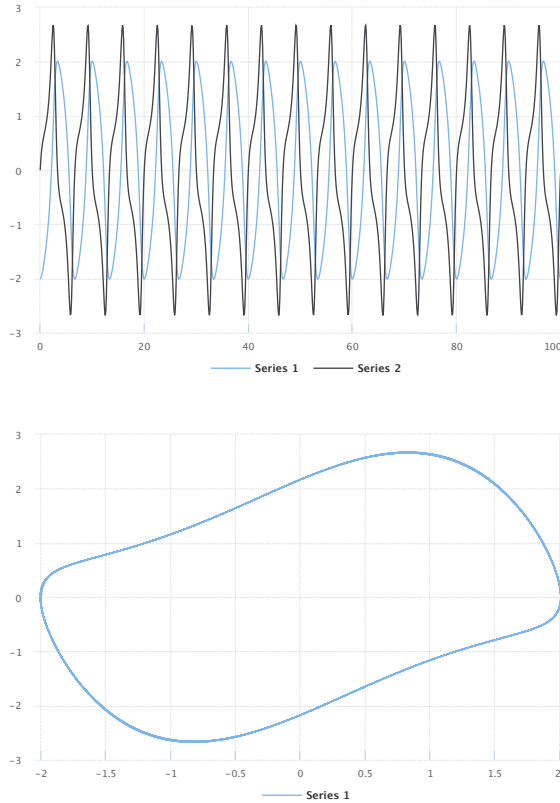


Figure A.13: The simulation result gained from the simulation description given in Listing A.8. Simulation with SED-ML web tools [2].

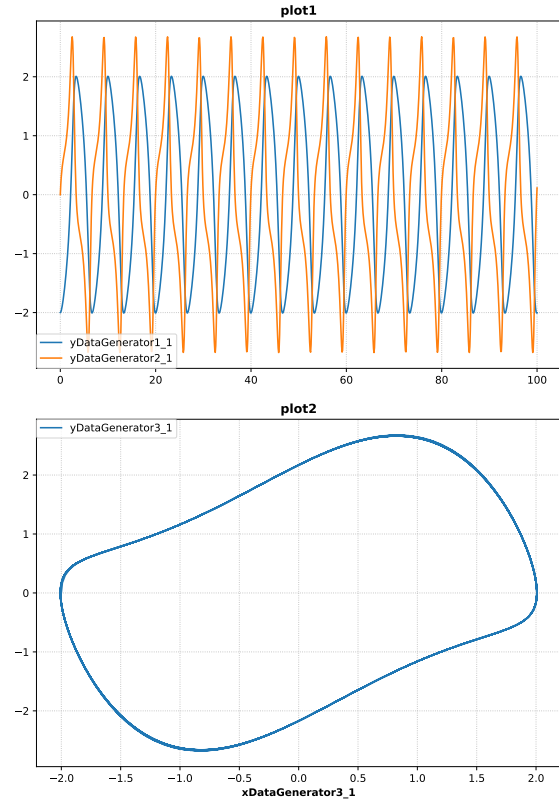


Figure A.14: Simulation with tellurium [6].

```
1 <?xml version='1.0' encoding='UTF-8'?>
2 <sedML level="1" version="3" xmlns="http://sed-ml.org/sed-ml/level1/version3">
3   <listOfSimulations>
4     <uniformTimeCourse id="simulation1" initialTime="0" numberOfPoints="1000" outputEndTime="100"
5       outputStartTime="0">
6       <algorithm kisaoID="KISAO:0000019">
7         <listOfAlgorithmParameters>
8           <algorithmParameter kisaoID="KISAO:0000211" value="1e-07"/>
9           <algorithmParameter kisaoID="KISAO:0000475" value="BDF"/>
10          <algorithmParameter kisaoID="KISAO:0000481" value="true"/>
11          <algorithmParameter kisaoID="KISAO:0000476" value="Newton"/>
12          <algorithmParameter kisaoID="KISAO:0000477" value="Dense"/>
13          <algorithmParameter kisaoID="KISAO:0000480" value="0"/>
14          <algorithmParameter kisaoID="KISAO:0000415" value="500"/>
15          <algorithmParameter kisaoID="KISAO:0000467" value="0"/>
16          <algorithmParameter kisaoID="KISAO:0000478" value="Banded"/>
17          <algorithmParameter kisaoID="KISAO:0000209" value="1e-07"/>
18          <algorithmParameter kisaoID="KISAO:0000479" value="0"/>
19        </listOfAlgorithmParameters>
20      </algorithm>
21    </uniformTimeCourse>
22  </listOfSimulations>
23 </sedML>
```

```

20     </uniformTimeCourse>
21 </listOfSimulations>
22 <listOfModels>
23   <model id="model" language="urn:sedml:language:sbml" source="vanderpol-sbml.xml"/>
24 </listOfModels>
25 <listOfTasks>
26   <repeatedTask id="repeatedTask" range="once" resetModel="true">
27     <listOfRanges>
28       <vectorRange id="once">
29         <value> 1 </value>
30       </vectorRange>
31     </listOfRanges>
32     <listOfSubTasks>
33       <subTask order="1" task="task1"/>
34     </listOfSubTasks>
35   </repeatedTask>
36   <task id="task1" modelReference="model" simulationReference="simulation1"/>
37 </listOfTasks>
38 <listOfDataGenerators>
39   <dataGenerator id="xDataGenerator1_1">
40     <listOfVariables>
41       <variable id="xVariable1_1" taskReference="task1" symbol="urn:sedml:symbol:time" />
42     </listOfVariables>
43     <math xmlns="http://www.w3.org/1998/Math/MathML">
44       <ci> xVariable1_1 </ci>
45     </math>
46   </dataGenerator>
47   <dataGenerator id="yDataGenerator1_1">
48     <listOfVariables>
49       <variable id="yVariable1_1" target="/sbml:sbml/sbml:model/sbml:listOfSpecies/sbml:species
50         [id='x']" taskReference="repeatedTask" modelReference="model"/>
51     </listOfVariables>
52     <math xmlns="http://www.w3.org/1998/Math/MathML">
53       <ci> yVariable1_1 </ci>
54     </math>
55   </dataGenerator>
56   <dataGenerator id="xDataGenerator2_1">
57     <listOfVariables>
58       <variable id="xVariable2_1" taskReference="task1" symbol="urn:sedml:symbol:time" />
59     </listOfVariables>
60     <math xmlns="http://www.w3.org/1998/Math/MathML">
61       <ci> xVariable2_1 </ci>
62     </math>
63   </dataGenerator>
64   <dataGenerator id="yDataGenerator2_1">
65     <listOfVariables>
66       <variable id="yVariable2_1" target="/sbml:sbml/sbml:model/sbml:listOfSpecies/sbml:species
67         [id='y']" taskReference="repeatedTask" modelReference="model"/>
68     </listOfVariables>
69     <math xmlns="http://www.w3.org/1998/Math/MathML">
70       <ci> yVariable2_1 </ci>
71     </math>
72   </dataGenerator>
73   <dataGenerator id="xDataGenerator3_1">
74     <listOfVariables>
75       <variable id="xVariable3_1" target="/sbml:sbml/sbml:model/sbml:listOfSpecies/sbml:species
76         [id='x']" taskReference="repeatedTask" modelReference="model"/>
77     </listOfVariables>
78     <math xmlns="http://www.w3.org/1998/Math/MathML">
79       <ci> xVariable3_1 </ci>
80     </math>
81   </dataGenerator>
82   <dataGenerator id="yDataGenerator3_1">
83     <listOfVariables>
84       <variable id="yVariable3_1" target="/sbml:sbml/sbml:model/sbml:listOfSpecies/sbml:species
85         [id='y']" taskReference="repeatedTask" modelReference="model"/>
86     </listOfVariables>
87     <math xmlns="http://www.w3.org/1998/Math/MathML">
88       <ci> yVariable3_1 </ci>
89     </math>
90   </dataGenerator>
91 </listOfDataGenerators>
92 <listOfOutputs>
93   <plot2D id="plot1">
94     <listOfCurves>
95       <curve id="curve1_1" logX="false" logY="false" xDataReference="xDataGenerator1_1"
96         yDataReference="yDataGenerator1_1"/>
97       <curve id="curve2_1" logX="false" logY="false" xDataReference="xDataGenerator2_1"
98         yDataReference="yDataGenerator2_1"/>
99     </listOfCurves>
100   </plot2D>
101   <plot2D id="plot2">
102     <listOfCurves>
103       <curve id="curve3_1" logX="false" logY="false" xDataReference="xDataGenerator3_1"
104         yDataReference="yDataGenerator3_1"/>
105     </listOfCurves>
106   </plot2D>
107 </listOfOutputs>

```

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.

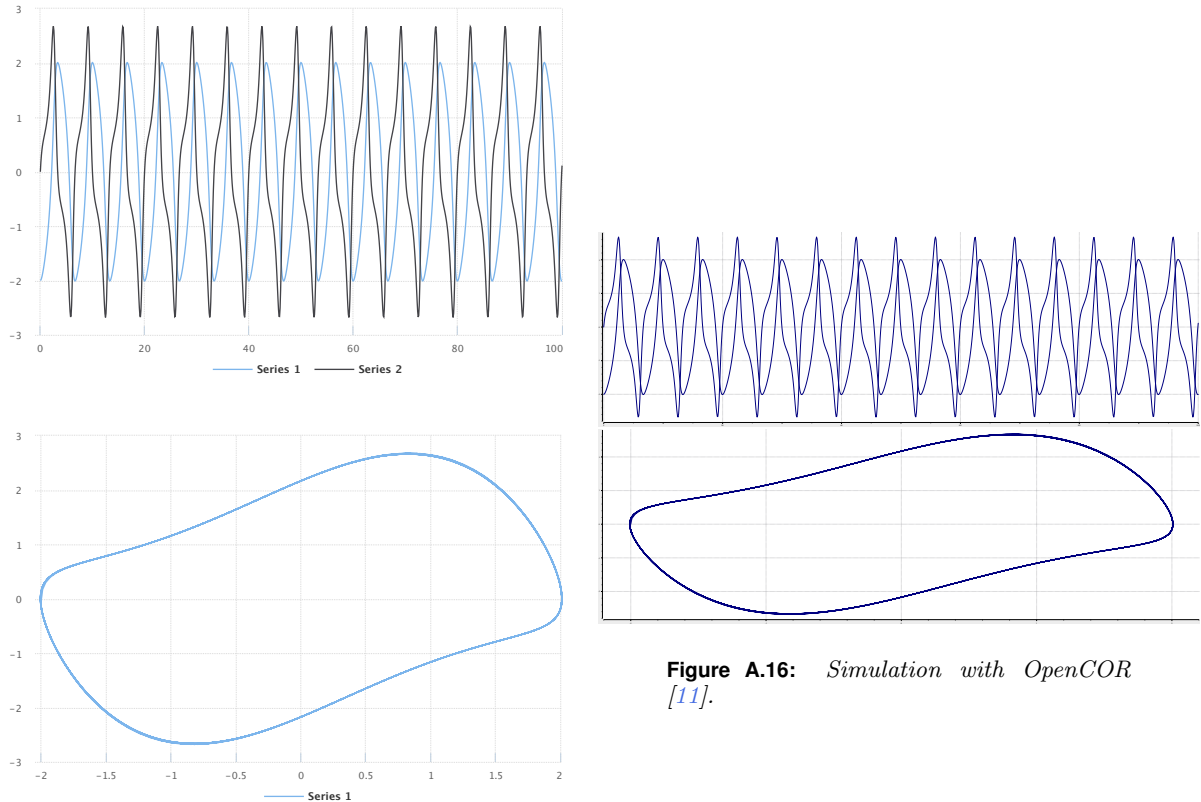


Figure A.16: *Simulation with OpenCOR [11].*

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

```

1 <?xml version='1.0' encoding='UTF-8'?>
2 <sedML level="1" version="3" xmlns="http://sed-ml.org/sed-ml/level1/version3" xmlns:cellml="http://www.
  cellml.org/cellml/1.0#">
3   <listOfSimulations>
4     <uniformTimeCourse id="simulation1" initialTime="0" numberOfPoints="1000" outputEndTime="100"
      outputStartTime="0">
5       <algorithm kisaoID="KISAO:0000019">
6         <listOfAlgorithmParameters>
7           <algorithmParameter kisaoID="KISAO:0000211" value="1e-07"/>
8           <algorithmParameter kisaoID="KISAO:0000475" value="BDF"/>
9           <algorithmParameter kisaoID="KISAO:0000481" value="true"/>
10          <algorithmParameter kisaoID="KISAO:0000476" value="Newton"/>
11          <algorithmParameter kisaoID="KISAO:0000477" value="Dense"/>
12          <algorithmParameter kisaoID="KISAO:0000480" value="0"/>
13          <algorithmParameter kisaoID="KISAO:0000415" value="500"/>
14          <algorithmParameter kisaoID="KISAO:0000467" value="0"/>
15          <algorithmParameter kisaoID="KISAO:0000478" value="Banded"/>
16          <algorithmParameter kisaoID="KISAO:0000209" value="1e-07"/>
17          <algorithmParameter kisaoID="KISAO:0000479" value="0"/>
18        </listOfAlgorithmParameters>
19      </algorithm>
20    </uniformTimeCourse>
21  </listOfSimulations>
22  <listOfModels>

```

```

23     <model id="model" language="urn:sedml:language:cellml:1.0" source="vanderpol-model.cellml"/>
24 </listOfModels>
25 <listOfTasks>
26   <repeatedTask id="repeatedTask" range="once" resetModel="true">
27     <listOfRanges>
28       <vectorRange id="once">
29         <value> 1 </value>
30       </vectorRange>
31     </listOfRanges>
32     <listOfSubTasks>
33       <subTask order="1" task="task1"/>
34     </listOfSubTasks>
35   </repeatedTask>
36   <task id="task1" modelReference="model" simulationReference="simulation1"/>
37 </listOfTasks>
38 <listOfDataGenerators>
39   <dataGenerator id="xDataGenerator1_1">
40     <listOfVariables>
41       <variable id="xVariable1_1" target="/cellml:model/cellml:component[@name='main']/
42         cellml:variable[@name='t']" taskReference="repeatedTask"/>
43     </listOfVariables>
44     <math xmlns="http://www.w3.org/1998/Math/MathML">
45       <ci> xVariable1_1 </ci>
46     </math>
47   </dataGenerator>
48   <dataGenerator id="yDataGenerator1_1">
49     <listOfVariables>
50       <variable id="yVariable1_1" target="/cellml:model/cellml:component[@name='main']/
51         cellml:variable[@name='x']" taskReference="repeatedTask"/>
52     </listOfVariables>
53     <math xmlns="http://www.w3.org/1998/Math/MathML">
54       <ci> yVariable1_1 </ci>
55     </math>
56   </dataGenerator>
57   <dataGenerator id="xDataGenerator2_1">
58     <listOfVariables>
59       <variable id="xVariable2_1" target="/cellml:model/cellml:component[@name='main']/
60         cellml:variable[@name='t']" taskReference="repeatedTask"/>
61     </listOfVariables>
62     <math xmlns="http://www.w3.org/1998/Math/MathML">
63       <ci> xVariable2_1 </ci>
64     </math>
65   </dataGenerator>
66   <dataGenerator id="yDataGenerator2_1">
67     <listOfVariables>
68       <variable id="yVariable2_1" target="/cellml:model/cellml:component[@name='main']/
69         cellml:variable[@name='y']" taskReference="repeatedTask"/>
70     </listOfVariables>
71     <math xmlns="http://www.w3.org/1998/Math/MathML">
72       <ci> yVariable2_1 </ci>
73     </math>
74   </dataGenerator>
75   <dataGenerator id="xDataGenerator3_1">
76     <listOfVariables>
77       <variable id="xVariable3_1" target="/cellml:model/cellml:component[@name='main']/
78         cellml:variable[@name='x']" taskReference="repeatedTask"/>
79     </listOfVariables>
80     <math xmlns="http://www.w3.org/1998/Math/MathML">
81       <ci> xVariable3_1 </ci>
82     </math>
83   </dataGenerator>
84   <dataGenerator id="yDataGenerator3_1">
85     <listOfVariables>
86       <variable id="yVariable3_1" target="/cellml:model/cellml:component[@name='main']/
87         cellml:variable[@name='y']" taskReference="repeatedTask"/>
88     </listOfVariables>
89     <math xmlns="http://www.w3.org/1998/Math/MathML">
90       <ci> yVariable3_1 </ci>
91     </math>
92   </dataGenerator>
93 </listOfDataGenerators>
94 <listOfOutputs>
95   <plot2D id="plot1">
96     <listOfCurves>
97       <curve id="curve1_1" logX="false" logY="false" xDataReference="xDataGenerator1_1"
98         yDataReference="yDataGenerator1_1"/>
99       <curve id="curve2_1" logX="false" logY="false" xDataReference="xDataGenerator2_1"
100         yDataReference="yDataGenerator2_1"/>
101     </listOfCurves>
102   </plot2D>
103   <plot2D id="plot2">
104     <listOfCurves>
105       <curve id="curve3_1" logX="false" logY="false" xDataReference="xDataGenerator3_1"
106         yDataReference="yDataGenerator3_1"/>
107     </listOfCurves>
108   </plot2D>
109 </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 MIRIAM URN `urn:miriam:biomodels.db:BIOMD0000000021`. 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 .

```
1 <?xml version="1.0" encoding="utf-8"?>
2 <sedML xmlns="http://sed-ml.org/sed-ml/level1/version3" level="1" version="3">
3   <listOfSimulations>
4     <uniformTimeCourse id="simulation1" initialTime="0" outputStartTime="0" outputEndTime="380"
5       numberOfPoints="1000">
6       <algorithm kisaoID="KISA0:0000019" />
7     </uniformTimeCourse>
8   </listOfSimulations>
9   <listOfModels>
10    <model id="model1" name="Circadian Oscillations" language="urn:sedml:language:sbml" source="
11      urn:miriam:biomodels.db:BIOMD0000000021" />
12    <model id="model2" name="Circadian Chaos" language="urn:sedml:language:sbml" source="model1">
13      <listOfChanges>
14        <changeAttribute target="/sbml:sbml/sbml:model/sbml:listOfParameters/sbml:parameter[@id='&quot;
15          V_mt&quot;']/@value" newValue="0.28" />
16        <changeAttribute target="/sbml:sbml/sbml:model/sbml:listOfParameters/sbml:parameter[@id='&quot;
17          V_dt&quot;']/@value" newValue="4.8" />
18      </listOfChanges>
19    </model>
20  </listOfModels>
21  <listOfTasks>
22    <task id="task1" modelReference="model1" simulationReference="simulation1" />
23    <task id="task2" modelReference="model2" simulationReference="simulation1" />
24  </listOfTasks>
25  <listOfDataGenerators>
26    <dataGenerator id="time" name="time">
27      <listOfVariables>
28        <variable id="t" taskReference="task1" symbol="urn:sedml:symbol:time" />
29      </listOfVariables>
30      <math xmlns="http://www.w3.org/1998/Math/MathML">
31        <ci> t </ci>
32      </math>
33    </dataGenerator>
34    <dataGenerator id="tim1" name="tim mRNA">
35      <listOfVariables>
36        <variable id="v1" taskReference="task1" target="/sbml:sbml/sbml:model/sbml:listOfSpecies/
37          sbml:species[@id='Mt']" />
38      </listOfVariables>
39      <math xmlns="http://www.w3.org/1998/Math/MathML">
40        <ci> v1 </ci>
41      </math>
42    </dataGenerator>
43    <dataGenerator id="per_tim1" name="nuclear PER-TIM complex">
44      <listOfVariables>
45        <variable id="v1a" taskReference="task1" target="/sbml:sbml/sbml:model/sbml:listOfSpecies/
46          sbml:species[@id='Cn']" />
47      </listOfVariables>
48      <math xmlns="http://www.w3.org/1998/Math/MathML">
```

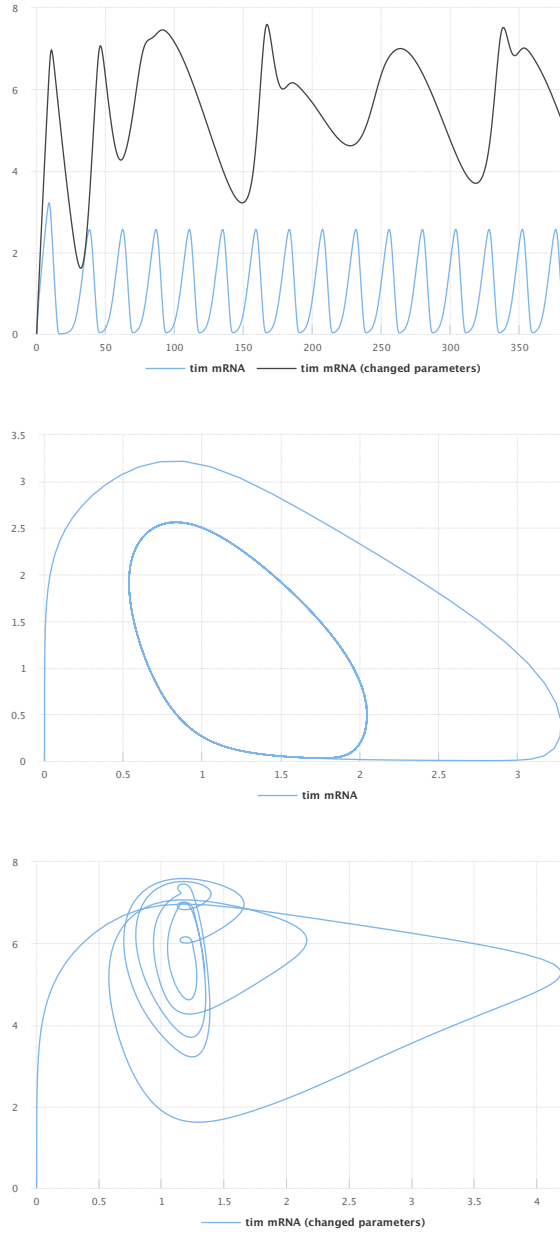



Figure A.17: The simulation result gained from the simulation description given in Listing A.10. Simulation with SED-ML web tools [2].

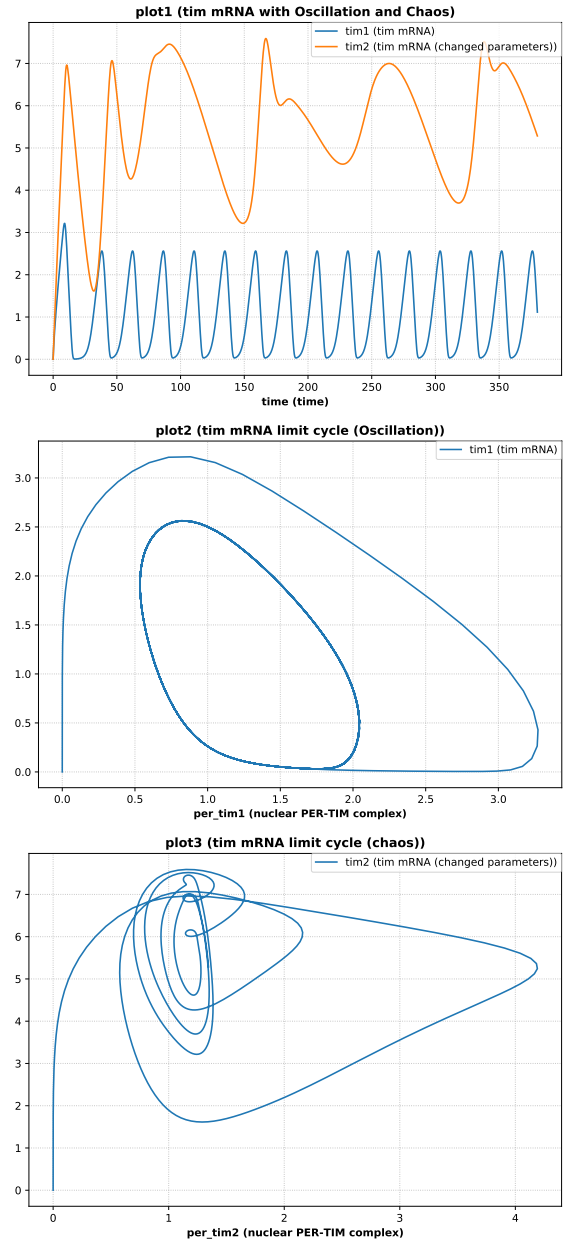


Figure A.18: Simulation with tellurium [6].

```

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/
49       sbml:species[@id='Mt']" />
50   </listOfVariables>
51   <math xmlns="http://www.w3.org/1998/Math/MathML">
52     <ci> v2 </ci>
53   </math>
54 </dataGenerator>
55 <dataGenerator id="per_tim2" name="nuclear PER-TIM complex">
56   <listOfVariables>
57     <variable id="v2a" taskReference="task2" target="/sbml:sbml/sbml:model/sbml:listOfSpecies/
58       sbml:species[@id='Cn']" />
59   </listOfVariables>
60   <math xmlns="http://www.w3.org/1998/Math/MathML">

```

```

59     <ci> v2a </ci>
60 </math>
61 </dataGenerator>
62 </listOfDataGenerators>
63 <listOfOutputs>
64   <plot2D id="plot1" name="tim mRNA with Oscillation and Chaos">
65     <listOfCurves>
66       <curve id="c1" logX="false" logY="false" xDataReference="time" yDataReference="tim1" />
67       <curve id="c2" logX="false" logY="false" xDataReference="time" yDataReference="tim2" />
68     </listOfCurves>
69   </plot2D>
70   <plot2D id="plot2" name="tim mRNA limit cycle (Oscillation)">
71     <listOfCurves>
72       <curve id="c3" logX="false" logY="false" xDataReference="per_tim1" yDataReference="tim1" />
73     </listOfCurves>
74   </plot2D>
75   <plot2D id="plot3" name="tim mRNA limit cycle (chaos)">
76     <listOfCurves>
77       <curve id="c4" logX="false" logY="false" xDataReference="per_tim2" yDataReference="tim2" />
78     </listOfCurves>
79   </plot2D>
80 </listOfOutputs>
81 </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 MIRIAM URN `urn:miriam:biomodels.db:BIOMD0000000140`. Software applications interpreting this example know how to dereference this URN and access the model in BioModels Database [17].

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.

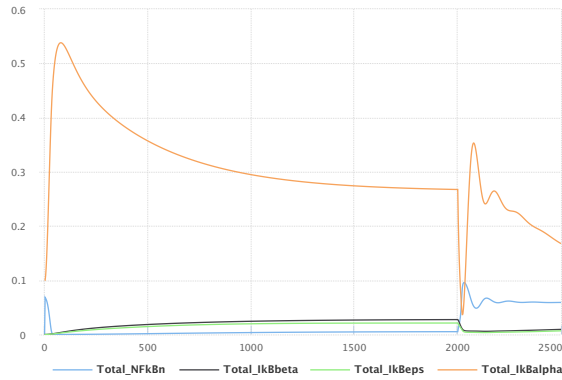


Figure A.19: *The simulation result gained from the simulation description given in Listing A.11. Simulation with SED-ML web tools [2].*

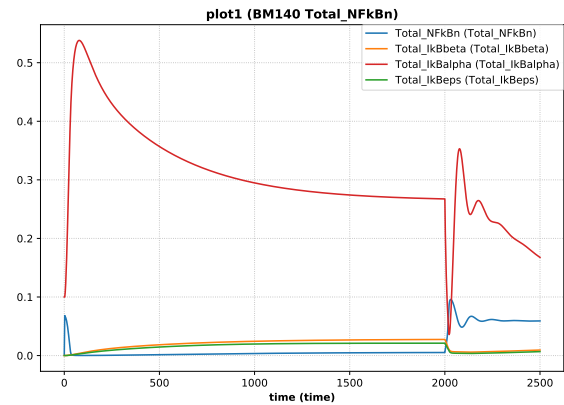


Figure A.20: *Simulation with tellurium [6].*

```

1 <?xml version="1.0" encoding="utf-8"?>
2 <sedML xmlns="http://sed-ml.org/sed-ml/level1/version3" level="1" version="3">
3   <listOfSimulations>
4     <uniformTimeCourse id="simulation1"
5       initialTime="0" outputStartTime="0" outputEndTime="2500"
6       numberOfPoints="1000" >
7       <algorithm kisaoID="KISA0:0000019"/>
8     </uniformTimeCourse>
9   </listOfSimulations>
10  </listOfModels>

```

```

11     <model id="model1" language="urn:sedml:language:sbml" source="urn:miriam:biomodels.db:BIOMD0000000140
12         "/>
13 </listOfModels>
14 <listOfTasks>
15     <task id="task1" modelReference="model1"
16         simulationReference="simulation1"/>
17 </listOfTasks>
18 <listOfDataGenerators>
19     <dataGenerator id="time" name="time">
20         <listOfVariables>
21             <variable id="time1" taskReference="task1" symbol="urn:sedml:symbol:time"/>
22         </listOfVariables>
23         <math xmlns="http://www.w3.org/1998/Math/MathML">
24             <ci>time1</ci>
25         </math>
26     </dataGenerator>
27     <dataGenerator id="Total_NFkBn" name="Total_NFkBn">
28         <listOfVariables>
29             <variable id="Total_NFkBn1" taskReference="task1"
30                 target="/sbml:sbml/sbml:model/sbml:listOfParameters/sbml:parameter[@id='Total_NFkBn']"/>
31         </listOfVariables>
32         <math xmlns="http://www.w3.org/1998/Math/MathML">
33             <ci>Total_NFkBn1</ci>
34         </math>
35     </dataGenerator>
36     <dataGenerator id="Total_IkBbeta" name="Total_IkBbeta">
37         <listOfVariables>
38             <variable id="Total_IkBbeta1" taskReference="task1"
39                 target="/sbml:sbml/sbml:model/sbml:listOfParameters/sbml:parameter[@id='Total_IkBbeta']"/>
40         </listOfVariables>
41         <math xmlns="http://www.w3.org/1998/Math/MathML">
42             <ci>Total_IkBbeta1</ci>
43         </math>
44     </dataGenerator>
45     <dataGenerator id="Total_IkBeps" name="Total_IkBeps">
46         <listOfVariables>
47             <variable id="Total_IkBeps1" taskReference="task1"
48                 target="/sbml:sbml/sbml:model/sbml:listOfParameters/sbml:parameter[@id='Total_IkBeps']"/>
49         </listOfVariables>
50         <math xmlns="http://www.w3.org/1998/Math/MathML">
51             <ci>Total_IkBeps1</ci>
52         </math>
53     </dataGenerator>
54     <dataGenerator id="Total_IkBalpha" name="Total_IkBalpha">
55         <listOfVariables>
56             <variable id="Total_IkBalpha1" taskReference="task1"
57                 target="/sbml:sbml/sbml:model/sbml:listOfParameters/sbml:parameter[@id='Total_IkBalpha']"/>
58         </listOfVariables>
59         <math xmlns="http://www.w3.org/1998/Math/MathML">
60             <ci>Total_IkBalpha1</ci>
61         </math>
62     </dataGenerator>
63 </listOfDataGenerators>
64 <listOfOutputs>
65     <plot2D id="plot1" name="BM140 Total_NFkBn">
66         <listOfCurves>
67             <curve id="c1" logX="false" logY="false" xDataReference="time"
68                 yDataReference="Total_NFkBn"/>
69             <curve id="c2" logX="false" logY="false" xDataReference="time"
70                 yDataReference="Total_IkBbeta"/>
71             <curve id="c3" logX="false" logY="false" xDataReference="time"
72                 yDataReference="Total_IkBeps"/>
73             <curve id="c4" logX="false" logY="false" xDataReference="time"
74                 yDataReference="Total_IkBalpha"/>
75         </listOfCurves>
76     </plot2D>
77 </listOfOutputs>
78 </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 I κ B-NF- κ B 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 Novère, 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.