

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

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| | | |
|----------|--|-----------|
| 1 | Introduction | 3 |
| 1.1 | Motivation: A sample experiment | 3 |
| 1.2 | Conventions used in this document | 5 |
| 1.3 | The MathML Subset used in SED-ML | 9 |
| 1.4 | The URI Scheme used in SED-ML | 10 |
| 1.5 | KiSAO | 10 |
| 1.6 | Further Resources | 11 |
| 2 | Preliminary definitions and general classes | 12 |
| 2.1 | The <code>xmlns</code> attribute | 12 |
| 2.2 | The <code>id</code> attribute | 12 |
| 2.3 | The <code>name</code> attribute | 12 |
| 2.4 | The SEDBase Class | 12 |
| 2.5 | The SED-ML Class | 14 |
| 2.6 | The reference Relation | 17 |
| 2.7 | The Variable Class | 17 |
| 2.8 | The Parameter Class | 19 |
| 2.9 | The ListOf containers | 20 |
| 3 | SED-ML Components | 25 |
| 3.1 | Model | 25 |
| 3.2 | Change | 27 |
| 3.3 | Simulation | 31 |
| 3.4 | Task | 32 |
| 3.5 | DataGenerator | 34 |
| 3.6 | Output | 35 |
| 3.7 | Curve | 38 |
| 3.8 | Surface | 39 |
| 3.9 | DataSet | 41 |
| A | SED-ML UML Overview | 44 |
| B | Overview of SED-ML | 45 |
| B.1 | Conventions | 45 |
| C | XML Schema | 51 |
| D | Examples | 55 |
| D.1 | Le Loup Model (CellML) | 55 |

1 Introduction

As Systems Biology transforms into one of the main fields in life sciences, the number of available computational models is growing at an ever increasing pace. At the same time, their size and complexity are also increasing. The need to build on existing studies by reusing models therefore becomes more imperative. It is now generally accepted that one needs to be able to exchange the biochemical and mathematical structure of models. The efforts to standardise the representation of computational models in various areas of biology, such as the *Systems Biology Markup Language* (SBML, [Hucka et al. \[2003\]](#)), *CellML* [Lloyd et al. \[2004\]](#) or *NeuroML* [Goddard et al. \[2001\]](#), result in an increase of the exchange and re-use of models. However, the description of the structure of models is not sufficient to enable the reproduction of simulation results. One also needs to describe the procedures the models are subjected to, as described by the *Minimum Information About a Simulation Experiment (MIASE)* [[Waltemath et al., 2010 hopefully](#)].

This document presents the Level 1 Version 1 of the *Simulation Experiment Description Markup Language* (SED-ML), a format that allows for the encoding of simulation experiments. SED-ML files are encoded in the *eXtensible Markup Language* (XML) [[Bray et al., 2006](#)]. The SED-ML language is defined as an XML Schema [[Fallside et al., 2001](#)].

1.1 Motivation: A sample experiment

To demonstrate how a simulation experiment can be described simply and effectively, we make use of a rather simple, though famous, model that may yet display rich and variable behaviors. The simulation example is taken from [[Waltemath et al., 2010 hopefully](#)].

The *repressilator* is a synthetic oscillating network of transcription regulators in *Escherichia coli* [[Elowitz and Leibler, 2000](#)]. 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) participated 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. Oscillations in the levels of the three repressor proteins are obtained by numerical integration.

1.1.1 A simple time-course simulation

The first experiment we intend to run on the model is the simulation that will lead to the oscillation shown in Figure 1c of the reference publication [[Elowitz and Leibler, 2000](#)]. The according simulation experiment can be described through the following steps:

1. Import the model identified by the Unified Resource Identifier [[Berners-Lee et al., 2005](#)] [urn:miriam:biomodels.db:BIOMD0000000012](#).
2. Select a deterministic method.
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 in the simulation tool COPASI [[Hoops et al., 2006](#)] led to the result shown in Figure 1 on the following page.



Figure 1: Time-course of the repressilator model, imported from BioModels Database and simulated in COPASI. The number of repressor proteins *lacI*, *tetR* and *cI* is shown. (taken from [Waltemath et al., 2010 hopefully])

1.1.2 Applying pre-processing

The fine-tuning of the model can be shown by changing parameters before simulation. When changing the initial values of the parameters *protein copies per promoter* and *leakiness in protein copies per promoter* the system's behavior switches from sustained oscillation to asymptotic steady-state. The adjustment towards a new experiment may be described as follows:

1. Import the model as 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 2 on the next page shows the result of the simulation.

1.1.3 Applying post-processing

However, the raw numerical output of the simulation steps 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 1.1.1), depicting the influence of one variable on another (in phase-planes), one could define the following further steps (Please note that the description steps 1 - 4 remain as above):

5. Collect $PX(t)$ (*lacI*), $PY(t)$ (*tetR*) and $PZ(t)$ (*cI*).
6. Compute the highest value for each of the repressor proteins, $\max(PX(t))$, $\max(PY(t))$, $\max(PZ(t))$.
7. Normalize the data for each of the repressor proteins by dividing each time point by the maximum value, i.e., $PX(t)/\max(PX(t))$, $PY(t)/\max(PY(t))$, and $PZ(t)/\max(PZ(t))$.
8. Plot the normalized *lacI* protein in function of the normalized *cI*, the normalized *cI* in function of the normalized *tetR* protein, and the normalized *tetR* protein against the normalized *lacI* protein in a 2D plot.

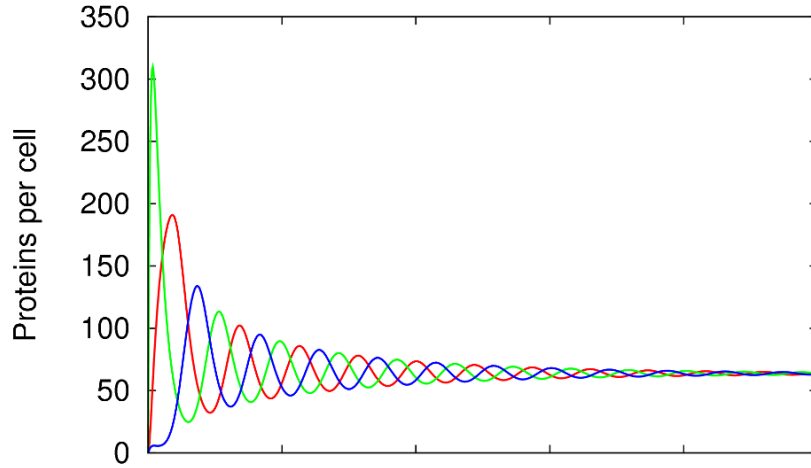


Figure 2: Time-course of the repressilator model, imported from BioModels Databas and simulated in COPASI after modification of the initial values of the protein copies per promoter and the leakiness in protein copies per promoter. The number of repressor proteins *lacI*, *tetR* and *cI* is shown. (taken from [Waltemath et al., 2010 hopefully])

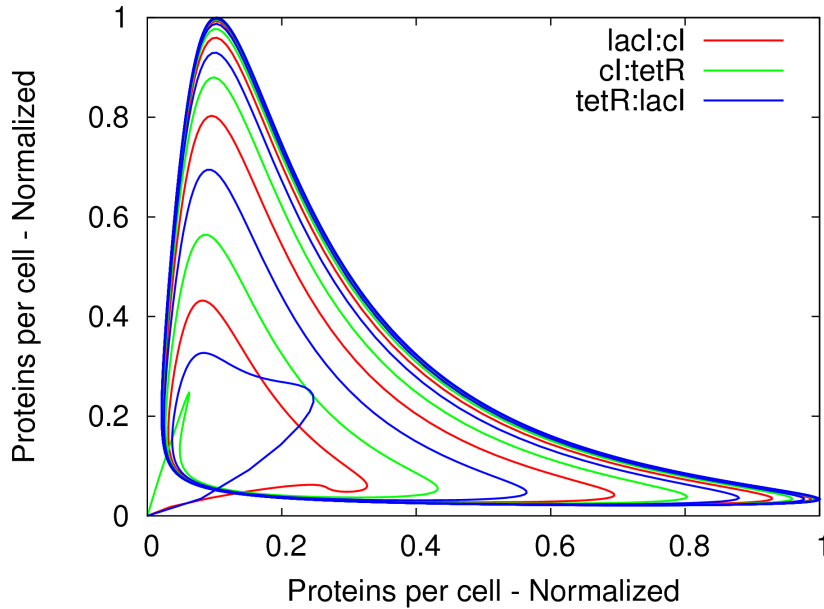


Figure 3: Time-course of the repressilator model, imported from BioModels Database and simulated in COPASI, showing the normalized temporal evolution of repressor proteins *lacI*, *tetR* and *cI* in phase-plane. (taken from [Waltemath et al., 2010 hopefully])

Figure 3 illustrates the result of the simulation after post-processing of the output data.

1.2 Conventions used in this document

SED-ML is specified as an XML Schema [W3C, 2004]. We also provide a UML Class diagram representation of that XML Schema (refer to appendix A). UML class diagrams are a subset of the *Unified Markup Language* notation (UML, [OMG, 2009]). Sample experiment descriptions are given as XML snippets that comply with the XML Schema.

1.2.1 UML Conventions

1.2.1.1 UML Classes

A SED-ML UML class (Figure 4) consists of a class name (**ClassName**) and a number of attributes (**attribute**) each of a specific data type (**type**). The SED-ML UML specification does not make use of UML operations.

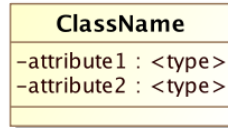


Figure 4: SED-ML UML Class with class names and attributes

Class names always begin with upper case letters, if they are composed of different words, the camel case style is used, as in e. g. **DataGenerator**.

1.2.2 Relationships

1.2.2.1 UML Relation Types

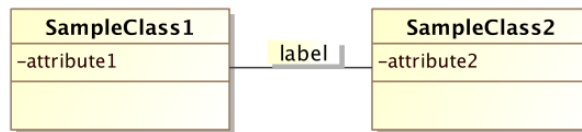


Figure 5: UML Class connectors

Links between classes specify the connection of linked objects with each other (Figure 5). The different relation types used in the SED-ML specification include aggregation, composite aggregation, and generalisation. The label on the line is called symbol (**label**) and describes the relation of the objects of both classes.

The [association](#) (Figure 6 on the next page) indicates the existence of a connection between the objects of the participating classes. Often associations are directed to show how the label should be read (in which direction). Associations can be uni-directional (one arrowhead), or bidirectional (zero or two arrowheads).

The [aggregation](#) (Figure 7 on the following page, top) indicates the objects of the participating classes are connected in a way that one class (**Whole**) consists of several parts (**Part**). In an aggregation, the parts may be independent of the whole. For example, a car (**Whole**) has several parts called wheel (**Part**); however, the wheels can exist independently of the car while the car requires the wheels in order to function.

The [composite aggregation](#) (Figure 7 on the next page, bottom) indicates that the objects of the participating classes are connected in a way that one class (**Whole**) consists of several parts (**Part**). In contrast to the aggregation, the subelements (**Part**) are dependent on the parent class (**Whole**). An example is that a university (**Whole**) consists of a number of departments (**Part**) which have a so-called “lifetime responsibility” with the university, e. g. if the university vanishes, so will with it the departments [Bell \[2003\]](#).

The [generalisation](#) (Figure 8 on the following page) allows to extend classes (**BaseClass**) by



Figure 6: *UML Association*

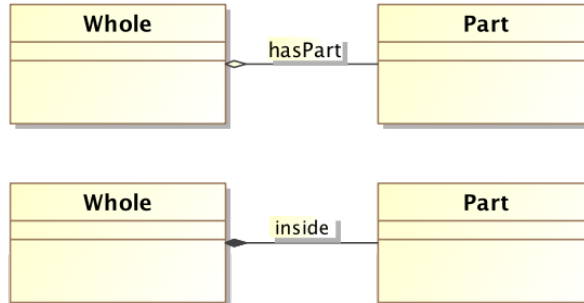


Figure 7: *UML Aggregation*

additional properties. The derived class (**DerivedClass**) inherits all properties of the base class and defines additional ones.

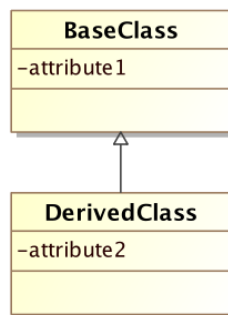


Figure 8: *UML Generalisation*

1.2.2.2 UML multiplicity

UML multiplicity defines the number of objects in one class that can be related to one object in the other class (also known as **cardinality**). Possible types of multiplicity include values (1), ranges (1..4), intervals (1,3,9), or combinations of ranges and intervals. The standard notation for “many” is the asterix (*).

Multiplicity can be defined for both sides of a relationship between classes. The default relationship is “many to many”. The example in Figure 9 on the next page expresses that a class is given by a professor, and a professor might give one to many classes.

1.2.3 XML Schema Constructs

The main building blocks of an XML Schema specification are

- simple and complex types
- element specifications

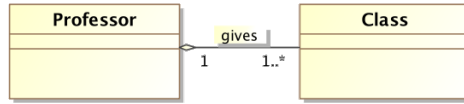


Figure 9: UML Multiplicity in an Aggregation

- attribute specifications

XML Schema [definitions](#) create new types, [declarations](#) define new elements and attributes. Definition of new (simple and complex) types can be based on a number of already existing, predefined types (string, boolean, float). Simple types are restrictions or extensions of predefined types. Complex types describe how attributes can be assigned to elements and how elements can contain further elements. The SED-ML XML Schema only does make use of complex types. An example for a complex type definition is given in listing 1:

```

1 <xs:element name="changeMath">
2   <xs:complexType>
3     <xs:sequence>
4       <xs:element ref="listOfVariables" />
5       <xs:element ref="listOfParameters" />
6       <xs:element ref="math:math" />
7     </xs:sequence>
8     <xs:attribute name="target" type="xs:token" />
9   </xs:complexType>
10 </xs:element>

```

Listing 1: Complex Type definition of the SED-ML *changeMath* element

It shows the declaration of an element called **changeMath** that is used in SED-ML to change mathematical expressions. The element is defined using an *unnamed* complex type which is build of further elements called **listOfVariables**, **listOfParameters**, and **math**. Additionally, the element **changeMath** has an attribute **target** declared. Please note that the definition of the elements inside the complex type are only referred to and will be found elsewhere in the schema. The nesting of elements in the schema can be expressed using the **xs:sequence** (a sequence of elements), **xs:choice** (an alternative of elements to choose from), or **xs:all** (a set of elements that can occur in any order) concepts. The SED-ML XML Schema make use only of the **sequence** of elements.

1.2.4 Multiplicities

The standard multiplicity for each defined **element** is 1. Explicit multiplicity is to be defined using the **minOccurs** and **maxOccurs** attributes inside the complex type definition, as shown in listing 2.

```

1 <xs:element name="dataGenerator">
2   <xs:complexType>
3     <xs:sequence>
4       <xs:element ref="listOfVariables" minOccurs="0" />
5       <xs:element ref="listOfParameters" minOccurs="0" />
6       <xs:element ref="math:math" />
7     </xs:sequence>
8     [..]
9   </xs:complexType>
10 </xs:element>

```

Listing 2: Multiplicity for complex types in XML Schema

The **dataGenerator** type is build of a sequence of three elements: The **listOfVariables** element is not necessary for the definition of a valid **dataGenerator** XML structure (it may occur 0 times or once). The same is true for the **listOfParameters** element (it may as well occur 0 times or once). The **math** element, however, uses the implicit standard multiplicity – it must occur exactly 1 time in the **dataGenerator** specification.

1.2.5 Type extensions

XML Schema offers mechanics to restrict and extend previously defined complex types. Extensions add element or attribute declarations to existing types, while restrictions restrict the types by adding further characteristics and requirements (facets) to a type. An example for a type extension is given in listing 3.

```
1 <xs:element name="sedML">
2   <xs:complexType>
3     <xs:complexContent>
4       <xs:extension base="SEDBase">
5         <xs:sequence>
6           <xs:element ref="listOfSimulations" />
7           <xs:element ref="listOfModels" />
8           <xs:element ref="listOfTasks" />
9           <xs:element ref="listOfDataGenerators" />
10          <xs:element ref="listOfOutputs" />
11        </xs:sequence>
12        <xs:attribute name="version" type="xs:decimal" use="required" fixed="0.1" />
13      </xs:extension>
14    </xs:complexContent>
15  </xs:complexType>
16 </xs:element>
```

Listing 3: Definition of the *sedML* type through extension of *SEDBase* in *SED-ML*

The *sedML* element is an extension of the previously defined *SEDBase* type. It extends *SEDBase* by a sequence of five additional elements (*listOfSimulations*, *listOfModels*, *listOfTasks*, *listOfDataGenerators*, and *listOfOutputs*) and a new attribute *versions*.

1.3 The MathML Subset used in SED-ML

The SED-ML specification allows for the pre-processing of computational models, as well as post processing of the simulation results. The corresponding mathematical expressions are encoded using MathML 2.0. MathML is an international standard for encoding mathematical expressions using XML and is used as representation of mathematical expressions in SBML and CellML, two of the languages supported by SED-ML. A problem arises, because the individual supported model exchange languages allow different subsets of MathML. Thus, when for example a ChangeXML element replaces a mathematical expression of an SBML reaction, only the MathML subset allowed by SBML should be used here.

In order to make the SED-ML format easier to adopt, at the beginning we restrict the MathML subset to the following operations:

- *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`

It should be noted, that all the operations listed above, only operate on singular values. However, as one of SED-ML's aim is to provide post processing on the results of simulation experiments, we need to enhance this basic set of operations by some aggregate functions.

1.3.1 Enabling post processing of simulation experiments

The first step for enabling for post processing, is to define the symbols that represent vector values. To simplify things for SED-ML L1V1 the only symbols to be used are the identifiers of variables defined in the listOfVariables of DataGenerators. These variables represent the data collected from the simulation experiment with the associated task.

To enable post processing the following aggregate functions are available for use with DataGenerator variables:

- *min*: Where the minimum of a variable represents the smallest value the simulation experiment yielded. Example:
`<min> <ci> variableId </ci></min>`
- *max*: Where the maximum of a variables represents the largest value the simulation experiment yielded. Example:
`<max> <ci> variableId </ci></max>`
- *sum*: All values of the variable returned by the simulation experiment are added up. Example:
`<sum> <ci> variableId </ci></sum>`
- *product*: All values of the variable returned by the simulation experiment are multiplied. Example:
`<product> <ci> variableId </ci></product>`

These represent the only exceptions. At this point SED-ML does not define a complete algebra of vector values. For more information see the description of DataGenerators.

1.4 The URI Scheme used in SED-ML

For reference to external models to be run within the simulation experiment, we propose the use of a standardised URI Scheme, as suggested by the [MIRIAM standard](#).

A model may be referenced through it's [ID](#) in a model repository. To be part of the MIRIAM resources, a model repository must ensure permanent and consistent model references, that is stable IDs.

Each such model repository that is part of MIRIAM resources gets it's own identifying "data type" on MIRIAM resources. For example, the MIRIAM data type for BioModels Database is `urn:miriam:biomodels.db`.

should we list the current data types available via MIRIAM resources for reference to model repositories? are there more than biomodels :-)?

1.5 KiSAO

An important aspect of a simulation experiment is the simulation algorithm used to solve the system.

The sole reference of a simulation algorithm through its name in form of a string is error prone and unambiguous. Firstly, typing mistakes or language differences may make the identification of the intended algorithm difficult. Secondly, many algorithms exist with more than one name, having synonyms or various abbreviations that are commonly used.

These problems can be solved by using controlled vocabulary to refer to a particular simulation algorithm. One attempt to provide such a vocabulary is the *Kinetic Simulation Algorithm Ontology* (KiSAO, <http://www.ebi.ac.uk/compneur-srv/kisao/>). KiSAO is a community-driven approach of classifying and structuring simulation approaches by model characteristics and numerical characteristics. Model characteristics include, for instance, the type of variables used for the simulation (such as discrete or continuous variables) and the spatial resolution (spatial or non-spatial descriptions). Numerical characteristics specify whether the system's behavior can be described as deterministic or stochastic, and whether the algorithms use fixed or adaptive time steps. Related algorithms are grouped together, producing classes of algorithms [Courtot et al., submitted 2010, hopefully].

Although work is still at an early stage, the use of KiSAO is recommended when referring to a simulation algorithm from a SED-ML description.

1.6 Further Resources

SED-ML is part of the biomodels.net initiative <http://www.biomodels.net>. Information on SED-ML can be found on www.biomodels.net/sed-ml.

The SED-ML XML Schema, the UML schema and related implementations, such as jlibsdbml can be found on the SED-ML sourceforge project page <http://sed-ml.svn.sourceforge.net/>.

2 Preliminary definitions and general classes

In this section we introduce attributes and concepts used repeatedly throughout the SED-ML specification.

2.1 The `xmlns` attribute

The `xmlns` attribute is used in several places of the SED-ML document. First of all, it declares the namespace for the SED-ML document. The pre-defined standard namespace is <http://www.biomodels.net/sed-ml>.

In addition, SED-ML makes use of the `MathML` namespace <http://www.w3.org/1998/Math/MathML> to enable encoding mathematical expressions in MathML [Carlisle et al., 2001]. SED-ML uses a subset of MathML as described in section 1.2.5 on page 9.

For the `Notes` class, the standard value of `xmlns` is <http://www.w3.org/1999/xhtml>.

2.2 The `id` attribute

Most objects in SED-ML carry the `id` and `name` attributes. The `id` attribute, if existent for an object, is always required. It is used to identify SED-ML constituents unambiguously. Therefore, the `id` attribute can be used to refer to a constituent from other constituents. The `id` data type is `String`. All `ids` have a global scope, meaning that throughout a whole SED-ML document, the `id` should be unambiguous and as such identifying the constituent it is related to. An example for a defined `id` is given in listing 4.

```
1 <model id="m00001" type="SBML" source="urn:miriam:biomodels.db:BIOMD0000000012">
2   [MODEL DEFINITION]
3 </model>
```

Listing 4: SED-ML identifier definition, e. g. for a model

2.3 The `name` attribute

Besides an `id`, a SED-ML constituent may carry an optional `name` attribute. However, names do not have identifying character and so several SED-ML constituents may carry the same name. The purposes of the `name` attribute is to keep a human-readable name of the constituent, e. g. for display to the user. Names are of the data type `String` in the XML Schema representation.

2.4 The `SEDBase` Class

`SEDBase` represents the base class for all elements of the SED-ML Level 1 Version 1 language. That is, all elements are derived from it. It provides means for additional information to be attached on all other classes (Figure 10 on the following page). That information can be specified in form of human readable `Notes` or custom `Annotation` classes.

Table 2.4 shows all attributes and derived classes for the `SEDBase` element as defined in the SED-ML XML Schema.

| attribute | description |
|--------------|-------------------------|
| metaID | page 13 |
| sub-elements | description |
| notes | page 13 |
| annotation | page 14 |

Table 1: Attributes and nested elements for `SEDBase`

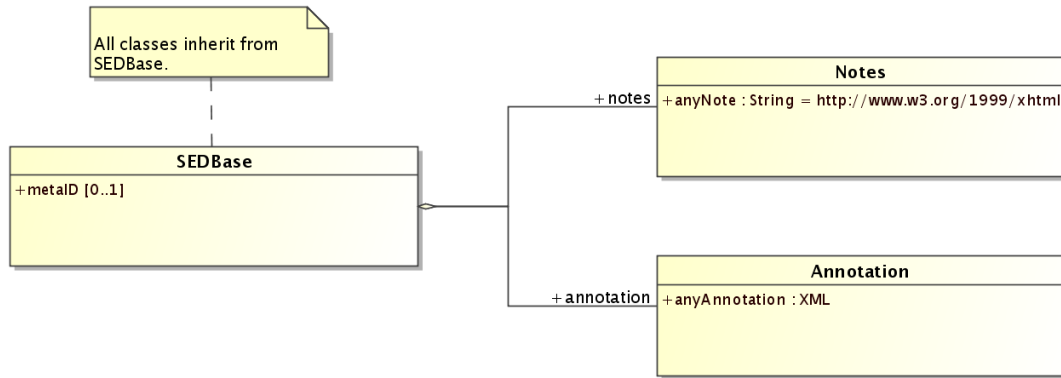


Figure 10: *The SEDBase class*

2.4.1 metaid Attribute

The main purpose of the **metaid** attribute is to attach [Annotations](#) to SED-ML elements. Thus, the **metaID** attribute has to be globally unique throughout the whole SED-ML document.

metaID is of type XML ID.

2.4.2 The Notes Class

A [note](#) is considered a human-readable description of the element it is assigned to. It serves to display information to the user. [Notes](#) contains any valid XHTML [[Pemberton et al., 2002](#)], ranging from short comments to whole HTML pages for display in a Web browser.

[Notes](#) has a mandatory attribute [xmlns](#) to declare the **XHTML** namespace. It does not have any further subclasses nor attributes associated to it (see [Table 2.4.2](#)).

[Table 2.4.2](#) shows all attributes and derived classes for the [Notes](#) element as defined in the SED-ML XML Schema.

| attribute | description |
|--------------|-------------------------|
| xmlns | page 12 |
| sub-elements | description |
| <i>none</i> | |

Table 2: *Attributes and nested elements for Notes*

The namespace URL for **XHTML** content inside the [class](#) is <http://www.w3.org/1999/xhtml>. It may either be declared in the [sedML XML element](#), or directly for use in each **notes** element of the XML file. For further options of how to set the namespace and detailed examples, please refer to ([[Hucka et al., 2010](#)], p. 14).

[Listing 5](#) shows the use of the **notes** attribute in a SED-ML file.

```

1 <sedML version="0.1">
2   <notes http://www.w3.org/1999/xhtml>
3     The enclosed simulation description shows the oscillating behaviour of the Repressilator
4       model using deterministic and stochastic simulators.
5   </notes>
6 </sedML>

```

Listing 5: *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**.

2.4.3 The Annotation Class

An **annotation** is considered a computer-processible piece of information. Annotations may contain any valid XML content. No additional namespace declaration is needed for use of the annotation element. However, for the type of XML inside annotation, the according namespaces should be declared, if necessary. For further guidelines on how to use annotations, we would like to encourage the reading of the according section in the SBML specification ([Hucka et al., 2010], pp. 14-16).

Table 2.4.3 shows all attributes and derived classes for the **Annotation** element as defined in the SED-ML XML Schema.

| attribute | description |
|--------------|-------------|
| <i>none</i> | |
| sub-elements | description |
| <i>none</i> | |

Table 3: Attributes and nested elements for **Annotation**

Listing 6 shows the use of the **annotation** element in a SED-ML file.

```

1 <sedML>
2   [...]
3   <model id="model1" metaID="001" name="Circadian Oscillations" type="CellML"
4     source="http://models.cellml.org/workspace/leloup_gonze_goldebeter_1999/@rawfile/
5       d6613d7e1051b3eff2bb1d3d419a445bb8c754ad/leloup_gonze_goldebeter_1999_a.cellml" >
6     <annotation>
7       <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#"
8         xmlns:bqmodel="http://biomodels.net/model-qualifiers/">
9         <rdf:Description rdf:about="#001">
10          <bqmodel:isDescribedBy>
11            <rdf:Bag>
12              <rdf:li rdf:resource="urn:miriam:pubmed:10415827"/>
13            </rdf:Bag>
14          </bqmodel:isDescribedBy>
15        </rdf:Description>
16      </rdf:RDF>
17    </annotation>
18  </model>
19 </sedML>

```

Listing 6: The annotation element

In the given example a SED-ML **model** element is annotated by referencing the original publication the model is build upon. The **model** contains an **annotation** that uses the model-qualifier **isDescribedBy** to link to the external resource **urn:miriam:pubmed:10415827**. In natural language the annotation content could be interpreted as “The model *is described by* the published article available from *pubmed* under ID *10643740*”. The example annotation follows the proposed **URI Scheme** suggested by MIRIAM. The MIRIAM URN can be resolved to the PubMed (<http://pubmed.gov>) publication with ID 10415827, namely the article “Alternating oscillations and chaos in a model of two coupled biochemical oscillators driving successive phases of the cell cycle.” published by Romond et al. in 1999.

2.5 The SED-ML Class

Each SED-ML Level 1 Version 1 document has a main class called SED-ML (Figure 11 on the next page) which defines the document’s structure and content. A SED-ML document needs to

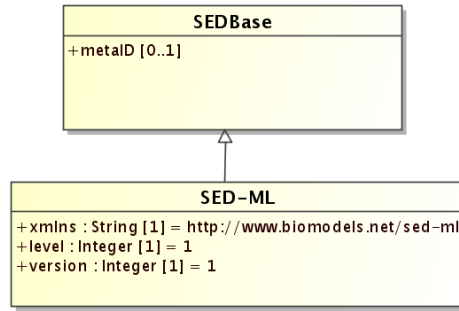


Figure 11: *The SED-ML class*

have the SED-ML namespace defined through the mandatory `xmlns` attribute. In addition, the SED-ML `level` and `version` attributes are mandatory. All of them are explained in more detail in the following subsections.

The SED-ML document is build of several parts which are all connected to the SED-ML class through aggregation: the `Model` class (for model specification, see section 3.1), the `Simulation` class (for simulation setup specification, see section 3.3), the `Task` class (for the linkage of models and simulation setups, see section 3.4), the `DataGenerator` class (for the definition of post-processing, see section 3.5), and the `Output` class (for the output specification, see section 3.6). All of them are shown in Figure 12 and will be explained in more detail in the according sections of this document.

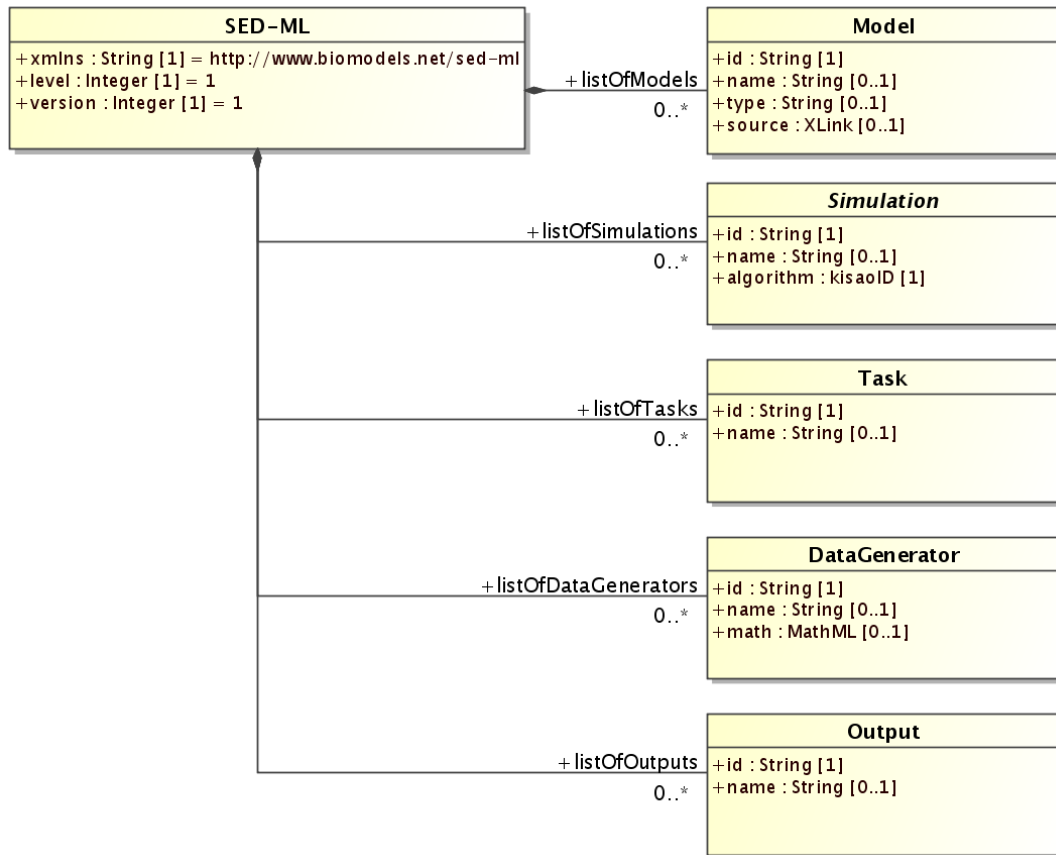


Figure 12: *The sub-classes of SED-ML*

Table 2.5 shows all attributes and derived classes for the [SED-ML](#) element as defined in the SED-ML XML Schema.

| attribute | description |
|---------------|-------------------------|
| metaID | page 13 |
| xmlns | page 12 |
| level | page 16 |
| version | page 16 |
| sub-elements | description |
| notes | page 13 |
| annotation | page 14 |
| model | page 25 |
| simulation | page 31 |
| task | page 32 |
| dataGenerator | page 34 |
| output | page 35 |

Table 4: Attributes and nested elements for [SED-ML](#)

2.5.1 The level attribute

The current SED-ML [level](#) is Level 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 1 the value is set to 1.

2.5.2 The version attribute

The current SED-ML [version](#) is 1. Minor revisions containing corrections and refinements of SED-ML elements 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 1 the value is set to 1.

The basic XML structure of a SED-ML file is shown in listing 7.

```

1 <?xml version="1.0" encoding="utf-8"?>
2 <sedML xmlns:math="http://www.w3.org/1998/Math/MathML"
3     xmlns="http://www.biomodels.net/sed-ml"
4     level="1"
5     version="1">
6   <listOfModels />
7   [MODEL REFERENCES AND APPLIED CHANGES]
8   <listOfSimulations />
9   [SIMULATION SETUPS]
10  <listOfTasks />
11  [MODELS LINKED TO SIMULATIONS]
12  <listOfDataGenerators />
13  [DEFINITION OF POST-PROCESSING]
14  <listOfOutputs />
15  [DEFINITION OF OUTPUT]
16 </sedML>

```

Listing 7: The SED-ML root element

The root element of each SED-ML XML file is the **sedML** element, encoding version and level of the file, and setting the necessary namespaces. Nested inside the **sedML** element are the five aforementioned **lists** serving as containers for the encoded data (**listOfModels** for all models, **listOfSimulations** for all simulations, **listOfTasks** for all tasks, **listOfDataGenerators** for all post-processing definition, and **listOfOutputs** for all output definitions).

2.6 The reference Relation

The **reference** association is used to refer to a particular source. It may occur in four different ways in the SED-ML document:

1. as an association between a **Variable** and a **Model** (modelReference)
2. as an association between a **Variable** and a **Task** (taskReference)
3. as an association between the **Task** and the associated **Model** (modelReference)
4. or as an association between the **Task** and the **Simulation** (simulationReference)

Depending on the use of the **reference** relation in connection with a **Variable** object, it may take different roles: The **reference** association might occur between a Variable and a Model, when the Variable is to define a **Change**. In that case the **variable** element contains a **modelReference**, i. e. a reference to the **model** that must be used to execute the XPath expression given in the **target** attribute of the Variable. An example is shown in listing 8

```

1 <model id="m0001" [..]>
2   <listOfChanges>
3     <changeAttribute modelreference="cellML1" target="/cellml:model/cellml:component[
        @cmeta:id='MP']/cellml:variable[@name='vsP']/@initial_value" newValue="1"/>
4   </listOfChanges>
5   [..]
6 </model>
```

Listing 8: SED-ML reference definition inside a **changeAttribute** element

If the **reference** is used as an association between a **Variable** object and a inside the **dataGenerator** class, then the **variable** contains a **taskReference** to unambiguously refer to an observable in a given task. As SED-ML allows only one model to be taking part in a **Task** definition (see also 3.4), the according **model** can be determined from the referenced task. An example is shown in listing 9

```

1 <model id="m0001" [..]>
2   <listOfDataGenerators>
3     <listOfVariables>
4       <variable id="i1" name="variable 1" taskreference="t1" />
5     </listOfVariables>
6   </listOfChanges>
7   [..]
8 </model>
```

Listing 9: SED-ML reference definition inside a **dataGenerator** element

2.7 The Variable Class

Variables in SED-ML are references to already existing constituents in one of the defined **models**. A variable always is placed inside a **listOfVariables**. Each instance of the **Variable** class (see Figure 13 on the following page) has a required **id** and an optional **name**. Variables are used to refer to a model constituent, i. e. a model observable, such as an SBML species. The referenced constituent is specified through the mandatory **target** attribute.

Table 2.7 on the next page shows all attributes and derived classes for the **Variable** element as defined in the SED-ML XML Schema.

| Variable |
|--|
| +id : String [1] +name : String [0..1] +target : XPath [1] |

Figure 13: *The Variable class*

| attribute | description |
|---------------|-------------------------|
| metaid | page 13 |
| id | page 12 |
| name | page 12 |
| target | page 18 |
| taskReference | page 17 |
| sub-elements | description |
| notes | page 13 |
| annotation | page 14 |

Table 5: *Attributes and nested elements for Variable*

The [reference](#) to an object of the [Variable](#) class may occur in two different places of the SED-ML document:

First, it may occur in the [Change](#) class where it is used for describing the mathematical computation of a change of a model’s observable, using other observables existing in a defined [model](#).

The second use of the [Variable](#) class and its [target](#) attribute is for defining a [DataGenerator](#). Here, a variable in an existing model might be used to define the post-processing of the simulation.

2.7.1 The target attribute

Each instance of [Variable](#) refers to a model constituent inside a particular [model](#) through an [XPath](#) expression stored in the required [target](#) attribute.

tbw

Example

An example for a variable definition is given in listing 10.

```

1 <model id="m0001" type="SBML" source="urn:miriam:biomodels.db:BIOMD0000000012">
2   <listOfVariables>
3     <variable id="v1" name="Tet Repressor protein" taskreference="t1" target="/sbml/
      listOfSpecies/species[@id="PY"]" />
4   </listOfVariables>
5   [...]
6 </model>
```

Listing 10: *SED-ML variable definition*

Please note that the identifier and names inside the SED-ML document do not have to comply with the identifiers and names that the model and its constituents carry in the model definition. In the above example 10, the variable with ID **v1** is defined. It is described as the **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**. The XPath expression used in the [target](#) attribute unambiguously leads to the particular place in the XML SBML model – the species is to be found in the *sbml* element, and there inside the *listOfSpecies*:

```

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

```

Listing 11: Species definition in the referenced model (extracted from [urn:miriam:biomodels.db:BIOMD0000000012](https://miriam.org/urn:miriam:biomodels.db:BIOMD0000000012))

SED-ML does not forbid to use identical identifiers and names as in the referenced models though. The following is the same valid SED-ML example for the specification of a variable as the above in listing 10, but with different naming:

```

1 <model id="m0001" type="SBML" source="urn:miriam:biomodels.db:BIOMD0000000012">
2 <listOfVariables>
3   <variable id="PY" name="TetR protein" target="/sbml/listOfSpecies/species[@id="PY"]" />
4 </listOfVariables>
5 [...]
6 </model>

```

Listing 12: SED-ML variable definition using the original model identifier and name in SED-ML

2.8 The Parameter Class

An instance of the [Parameter](#) class in SED-ML defines a symbol associated with a constant value (see Figure 14). A parameter can unambiguously be identified through its given [id](#). It

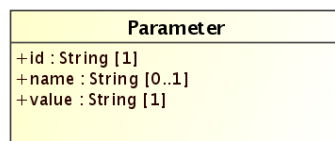


Figure 14: The *Parameter* class

may additionally carry an optional [name](#). Each parameter has one associated [value](#). Table 2.8 on the next page shows all attributes and derived classes for [Parameter](#).

Table 2.8 on the following page shows all attributes and derived classes for the [Parameter](#) element as defined in the SED-ML XML Schema.

| attribute | description |
|--------------|-------------------------|
| metaID | page 13 |
| id | page 12 |
| name | page 12 |
| value | page 19 |
| sub-elements | description |
| notes | page 13 |
| annotation | page 14 |

Table 6: Attributes and nested elements for [Parameter](#)

SED-ML uses parameters in two ways: First, they may occur in the [Change](#) class for describing the mathematical computation of a change of a model's observable through predefined param-

eters. The second use of the [Parameter](#) class is to refer from a [DataGenerator](#) definition to a constant value.

In both cases the parameter definitions are local to the according particular class defining them.

2.8.1 The value attribute

Each instance of [Parameter](#) defines a particular thing with a fixed [value](#). The value in the XML representation is of the data type [String](#). The **value** attribute is required for each **parameter** element. A parameter gets exactly one constant value assigned, meaning that the value is fixed and cannot be changed.

An example for a parameter definition is given in listing 13.

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

Listing 13: The definition of a parameter in SED-ML

2.9 The ListOf containers

[listOf*](#) elements in SED-ML 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 to the language. They might, however, be annotated with [Notes](#) and [Annotations](#) as they are derived from [SBase](#). All [listOf*](#) elements are optional in a SED-ML document.

SED-ML uses the following [listOf*](#) elements:

2.9.1 listOfVariables: The variable definition container

In order to refer to existing entities inside a model, these variables have to be referable from the simulation experiment description. SED-ML uses the XML [listOfVariable](#) element as a container for all necessary variables that need to be defined in order to either describe a change in the mathematics of a model ([ChangeMath](#)) or to define a data generator using existing variables from a given task ([dataGeneratorClass](#)). Figure 15 shows the use of the [listOfVariables](#) container. The [listOfVariables](#) is optional and may contain zero to many models.

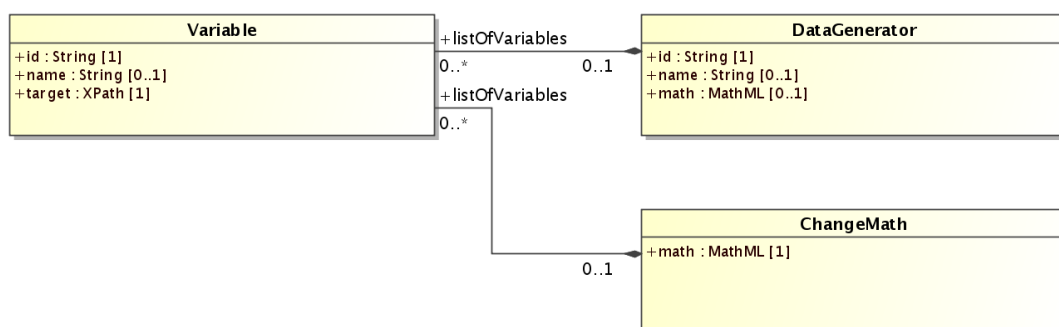


Figure 15: The SED-ML [listOfVariables](#) container

An XML code snippet for the definition of a [listOfVariables](#) element is shown in listing 14.

```
1 <listOfVariables>
2   <variable id="v1" name="maximum velocity" target="/cellml:model/cellml:component[@cmeta:id
3     = 'MP']/cellml:variable[@name='vsP']/@initial_value" />
4   <variable id="v2" target="SBML" />
5 </listOfVariables>
```

```
4 </listOfVariables>
```

Listing 14: *SED-ML listOfVariables element*

2.9.2 listOfParameters: The parameter definition container

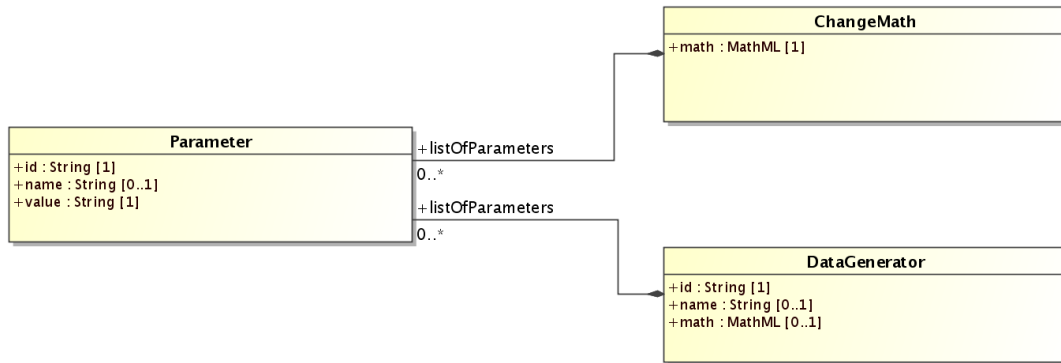


Figure 16: *The SED-ML listOfParameters container*

2.9.3 listOfModels: The model description container

In order to specify a simulation experiment, the participating models have to be defined. SED-ML uses the XML `listOfModels` element as a container for all necessary models (see Figure 17). The `listOfModels` is optional and may contain zero to many models.

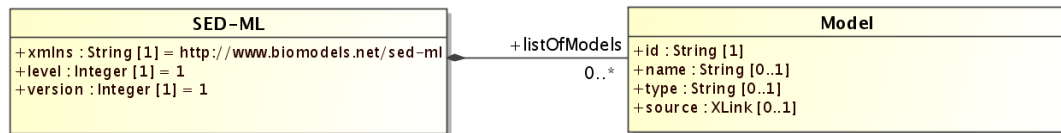


Figure 17: *The SED-ML listOfModels container*

An XML code snippet for the `listOfModels` element is shown in listing 15.

```

1 <listOfModels>
2 <model id="m0001" type="SBML" source="urn:miriam:biomodels.db:BIOMD0000000012">
3 [MODEL PRE-PROCESSING]
4 </model>
5 <model id="m0002" type="SBML" source="m0001">
6 [MODEL PRE-PROCESSING]
7 </model>
8 <model id="m0003" type="CellML" source="http://www.cellml.org/models/
9 leloup_gonze_goldbeter_1999_version02">
10 [MODEL PRE-PROCESSING]
11 </model>
12 </listOfModels>

```

Listing 15: *SED-ML listOfModels element*

The above `listOfModels` references three models: The first model (`m0001`) is the Repressilator model taken from BioModels Database. The model itself is available from [urn:miriam:biomodels.db:BIOMD0000000012](http://www.ebi.ac.uk/ols/ontologies/SED-ML/term/BIOMD0000000012). For the SED-ML simulation, the model might undergo pre-processings, described in the `Change` class. Based on the description of the first model `m0001`, the second model is build. It refers to the model that was originally the [urn:miriam:biomodels.db:BIOMD0000000012](http://www.ebi.ac.uk/ols/ontologies/SED-ML/term/BIOMD0000000012) model, but had changes applied to it. `m0002` might then have even further

changes applied to it on top of the changes defined in the pre-processing of **m0001**. The third model in the code example above is a different model in CellML representation. **m0003** is the model available from [urn:miriam:biomodels.db:BIOMD0000000012](https://miriam.org/ontologies/biomodels.db/BIOMD0000000012), and might have additional pre-processing applied to it before used in the simulation. Such pre-processings might include a (new) parametrisation of model constituents, or a model update in terms of revised reaction equations, as well as the substitution of whole model constituents. Further details will be given in the description of the **Change** class.

A SED-ML description can be a sole storage container for a *general* simulation setting, comparable to an experiment procedure description. In that case, no particular model needs to be related to that description to store the settings for later use in SED-ML format:

```
1 <sedML>
2 <listOfModels />
3 [SIMULATION SETTINGS FOLLOWING]
4 </sedML>
```

2.9.4 *listOfChanges: The change definition container*

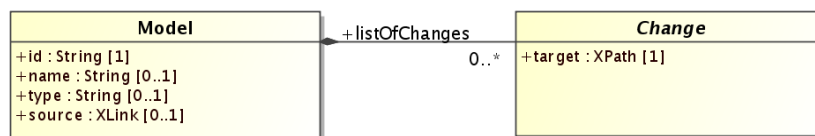


Figure 18: *The SED-ML listOfChanges container*

The **listOfChanges** container contains the defined changes to be applied to a particular **model** (see Figure 18). **listOfChanges** always occurs within a **model** element. It is an optional subelement of the **model** element.

Example 16 shows the definition of a **listOfChanges** container inside a **model** element.

```
1 <model id="m0001" [...]>
2 <listOfChanges>
3 [CHANGE DEFINITION]
4 </listOfChanges>
5 </model>
```

Listing 16: *The SED-ML listOfChanges element, defining a change on a model*

In the example a change is defined on the model **m0001**. To encode the change, a **listOfChanges** is created that contains all changes in single **change** elements, as explained in the definition of the **Change** class.

2.9.5 *listOfSimulations: The simulation description container*

The **listOfSimulation** is the container for **simulation** descriptions. The **listOfSimulations** is optional (see Figure 19 on the following page).

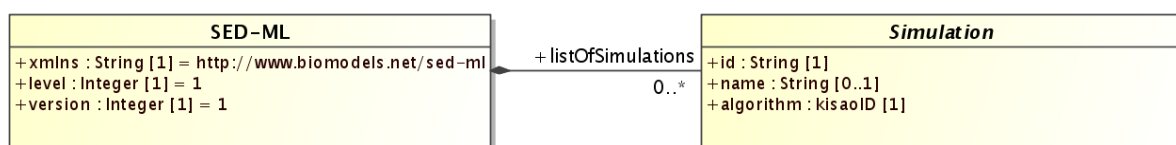


Figure 19: *The listOfSimulations container*

SED-ML version 1 offers the predefined simulation class [UniformTimeCourse](#). Further simulation classes are planned for future versions of SED-ML, including simulation classes for bifurcation analysis and parameter scans.

Example 17 shows the definition of a `listOfSimulations` container inside a `sedML` element.

```

1 <sedML>
2   <listOfSimulations>
3     [UNIFORM TIMECOURSE DEFINITION]
4   </listOfSimulations>
5   [..]
6 </sedML>

```

Listing 17: The SED-ML `listOfSimulations` element, defining a change on a model

In the example a `listOfSimulations` element is created that contains all simulations, encoded in single [simulation](#) elements. For all SED-ML Level 1 Version 1 documents, the encoded simulation definitions are instances of the [Uniform Timecourse](#) class.

2.9.6 `listOfTasks`: The task specification container



Figure 20: The SED-ML `listOfTasks` container

The `listOfTasks` container contains the defined tasks for the simulation experiment (see Figure 20).

An example for the definition of a task inside the `listOfTasks` is given in the XML snippet in listing 18.

```

1 <listOfTasks>
2   <task id="t1" name="simulating v1" modelReference="m1" simulationReference="s1">
3 </listOfTasks>

```

Listing 18: The SED-ML `listOfTasks` element, defining one task

In the given example, a `task` is created that makes use of one of the previously defined [models](#) and runs it with the simulation settings of one of the previously defined [simulations](#).

2.9.7 `listOfDataGenerators`: The post-processing container

In SED-ML, all variables/parameters/values that shall be used in the [Output](#) class need to be defined as a [dataGenerator](#) beforehand, in the `listofDataGenerators` (see Figure Figure 21 on the following page).



Figure 21: The SED-ML `listOfDataGenerators` container

Each [dataGenerator](#) is identifiable within the experiment by its unambiguous `id`. It can be

further characterised by an optional [name](#). The [math](#) element contains a mathML expression for the calculation of the data generator. Within the mathematical expression, variables defined in the [listOfVariables](#) and parameters defined in the [listOfParameters](#) can be used.

2.9.8 *listOfOutputs: The output specification container*

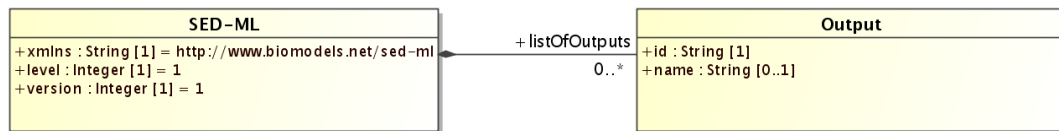


Figure 22: *The SED-ML listOfOutputs container*

The [listOfOutputs](#) container holds the output specifications for a simulation experiment. In SED-ML the output can be defined as either a [report](#), a [plot2D](#) or as a [3D plot](#). The listing 19 shows the definition of two different outputs, one being a data table (report), the other one a 2D plot.

```

1 <listOfOutputs>
2   <report id="report1" name="sample report">
3     <listOfDataSets>
4       [..]
5     </listOfDataSets>
6   </report>
7   <plot2D id="plot1" name="sample 2D plot">
8     <listOfCurves>
9       [..]
10    </listOfCurves>
11  </plot2D>
12 </listOfOutputs>
  
```

Listing 19: *The listOfOutput element*

3 SED-ML Components

In this section we describe the major components of SED-ML. In the following we use the UML notation described in section 1.2.1. For an overview we provide a BNMP diagram in Appendix B and an XML Schema in C.

3.1 Model

The [Model](#) class is the container for a model reference (see Figure 23).

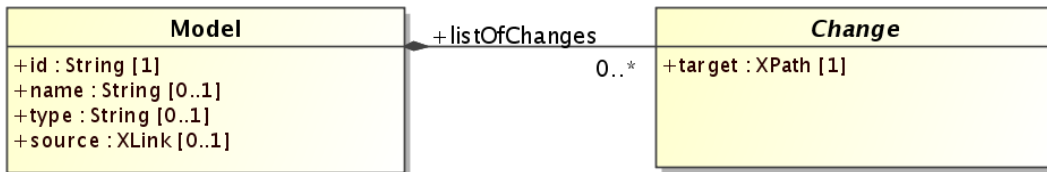


Figure 23: The SED-ML Model class

A model is defined through an unambiguous and mandatory [id](#). An additional, optional [name](#) may be given to the model. For each model, the [type](#) can be specified, defining the format the model is encoded in. The [Model](#) class refers to a particular model available from an external resource; it is addressed through the [target](#) attribute.

Table 3.1 shows all attributes and derived classes for the [Model](#) element as defined in the SED-ML XML Schema.

| attribute | description |
|--------------|-------------------------|
| metaid | page 13 |
| id | page 12 |
| name | page 12 |
| type | page 25 |
| source | page 26 |
| sub-elements | description |
| notes | page 13 |
| annotation | page 14 |
| change | page 27 |

Table 7: Attributes and nested elements for [Model](#)

A model might need to undergo pre-processings before simulation. Those pre-processings are specified in the SED-ML [Change](#) class.

3.1.1 The type attribute

The evaluation of a SED-ML file will decide whether or not it can be used for a particular simulation environment. One crucial criterium is the type of encoding used for the model. A simulation software usually only supports a small subset of the representation formats available to model biological systems computationally. Therefore SED-ML provides information on the model encoding for each referenced model through the [type](#) attribute. Examples for such types are [SBML](#) denoting the standard format SBML [[Hucka et al., 2003](#)], or [CellML](#) denoting the stan-

dard format CellML [Lloyd et al., 2004]. As there is no controlled vocabulary of representation formats for biological models available as of now, the data type for **type** is **String**.

Although the **type** attribute is optional for the XML representation of a SED-ML file, it is recommended to be used whenever possible to enhance the quality of the simulation experiment description.

A list of supported standard formats for model encoding and how they should be declared in the **type** attribute can be found on the SED-ML web site on www.biomodels.net/sed-ml. **to do**

3.1.2 The source attribute

To make the model available during execution of a SED-ML file, the model **source** should be specified through an XLink. The XLink should preferably point to a public, consistent URI that contains the model description file and follows the proposed **URI Scheme**. Consistent URIs ensure the long-term availability of models used in a SED-ML simulation description file. Therefore, reference to curated, open model bases are recommended. Examples for such resources are BioModels Database Le Novère et al. [2006], or the CellML model repository Beard et al. [2009]. A full list of model bases and how to reference a particular model inside the model base can be found on the SED-ML web site on www.biomodels.net/sed-ml. **to do**

Example

An example for the definition of a model inside the **listOfModels** and using the MIRIAM **URI scheme** is given in the XML snippet in listing 20.

```
1 <listOfModels>
2   <model id="m1" name="repressilator" type="SBML"
3     source="urn:miriam:biomodels.db:BIOMD0000000012">
4     <listOfChanges>
5       [DEFINE MODEL PRE-PROCESSING HERE]
6     </listOfChanges>
7   </model>
8 </listOfModels>
```

Listing 20: The SED-ML model element, using the URI scheme

In the example one model is defined. An **id** and a **name** are given. The **type** of the model is **SBML** and the model source code is available from **urn:miriam:biomodels.db:BIOMD0000000012**. The MIRIAM URN can be resolved into the SBML model stored in BioModels Database under ID **BIOMD0000000012**.

An example for the definition of a model inside the **listOfModels** and using a URL is given in the XML snippet in listing 21.

```
1 <listOfModels>
2   <model id="m1" name="repressilator" type="CellML"
3     source="http://models.cellml.org/exposure/bba4e39f2c7ba8af51fd045463e7bdd3/aguda_b_1999.
4       cellml">
5     <listOfChanges>
6       [DEFINE MODEL PRE-PROCESSING HERE]
7     </listOfChanges>
8   </model>
9 </listOfModels>
```

Listing 21: The SED-ML model element, using a URL

In the example one model is defined. An **id** and a **name** are given. The **type** of the model is **CellML**. As CellML currently does not provide a MIRIAM URI scheme for model reference, the URL pointing to the model code is used to refer to the model. The URL is given in the **source** element.

3.2 Change

SED-ML not only allows to use the sole model for simulation, but on the contrary enables the description of changes to be made on the model before simulation using the [listOfChanges](#) element. Changes can be of three different types (see Figure 24):

1. Changes on attributes of the model's XML representation ([ChangeAttribute](#))
2. Changes on any XML snippet of the model's XML representation ([ChangeXML](#))
3. Applying changes based on mathematical calculations ([ChangeMath](#))

The [Change](#) class is abstract and serves as the container for all different types of changes.

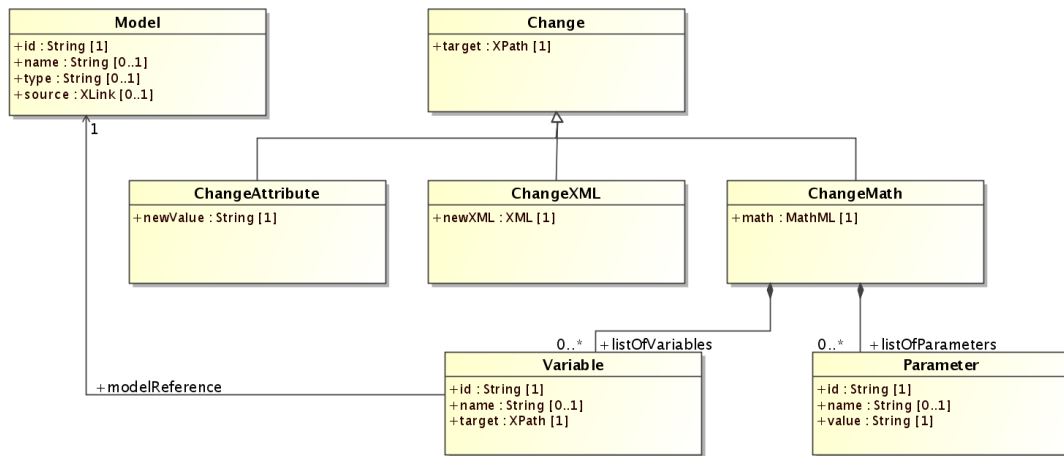


Figure 24: The SED-ML Change class

Table 3.2 shows all attributes and derived classes for the [Change](#) element as defined in the SED-ML XML Schema.

| attribute | description |
|-----------------|-------------------------|
| metaid | page 13 |
| id | page 12 |
| name | page 12 |
| target | page 18 |
| sub-elements | description |
| notes | page 13 |
| annotation | page 14 |
| changeXML | page 28 |
| changeAttribute | page 28 |
| changeMath | page 29 |

Table 8: Attributes and nested elements for [Change](#)

Each Change has a [target](#) attribute that holds a valid XPath expression pointing to the XML element or XML attribute that is to undergo the defined changes.

The [Change](#) class itself is abstract, a SED-ML document therefor will always contain one of the classes derived from [Change](#); those currently are the aforementioned classes [ChangeAttribute](#), [ChangeXML](#), or [ChangeMath](#).

3.2.1 ChangeXML

The [ChangeXML](#) element is used to change any XML element in the model that can be addressed by a valid XPath expression.

Table 3.2.1 shows all attributes and derived classes for the [changeXml](#) element as defined in the SED-ML XML Schema.

| attribute | description |
|------------------------|-------------------------|
| metaid | page 13 |
| id | page 12 |
| name | page 12 |
| target | page 18 |
| newXML | page 28 |
| sub-elements | description |
| notes | page 13 |
| annotation | page 14 |

Table 9: *Attributes and nested elements for [ChangeXML](#)*

The XPath is specified in the required [target](#) (see definition on [page 18](#)).

3.2.2 The newXML attribute

The new piece of XML code that is to substitute the XML element addressed by the XPath is provided in the required [newXML](#) attribute.

An example that adds an additional parameter to a model is given in [listing 22](#).

```

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

Listing 22: *The [changeXML](#) element*

3.2.3 ChangeAttribute

The [ChangeAttribute](#) allows to update the value of an XML attribute in the model. One required attribute for [ChangeAttribute](#) is the [target](#) of change, i. e. the location of the addressed XML attribute.

Table 3.2.3 on the following page lists all attributes of the [ChangeAttribute](#) class.

The [ChangeXML](#) class covers the possibilities provided by the [ChangeAttribute](#) class. That is, everything that can be expressed by a [ChangeAttribute](#) construct can also be expressed by a [ChangeXML](#). However, both concepts exist to allow for being very specific in defining changes. It is recommended to use the [ChangeAttribute](#) for any changes of an XML attribute, and to use the more general [ChangeXML](#) for all other cases.

| attribute | description |
|---------------|-------------------------|
| metaid | page 13 |
| id | page 12 |
| name | page 12 |
| target | page 18 |
| newValue | page 29 |
| derived class | description link |
| Notes | page 13 |
| Annotation | page 14 |

Table 10: Attributes and nested elements for *ChangeAttribute*

3.2.4 The newValue attribute

The second required attribute is the **newValue**, which assigns a new value to the targeted XML attribute. **tbw**

For SBML, an example is the update of the initial concentration of a certain parameter, as shown in listing 23.

```

1 <model id="model1" name="Circadian Chaos" type="SBML" source="urn:miriam:biomodels.
  db:BIOMD00000000021">
2 <listOfChanges>
3 <changeAttribute target="/sbml:sbml/sbml:model/sbml:listOfParameters/sbml:parameter[@id='
  V_mT']/@value" newValue="0.28"/>
4 <changeAttribute target="/sbml:sbml/sbml:model/sbml:listOfParameters/sbml:parameter[@id='
  V_dT']/@value" newValue="4.8"/>
5 </listOfChanges>
6 </model>

```

Listing 23: The *changeAttribute* element

3.2.5 ChangeMath

The *ChangeMath* is used to make changes on any element of the XML file addressable by an XPath expression, where the changes are described by mathematical expressions through MathML.

Table 3.2.5 shows all attributes and derived classes for the *ChangeMath* element as defined in the SED-ML XML Schema.

| attribute | description |
|-----------------|-------------------------|
| metaid | page 13 |
| id | page 12 |
| name | page 12 |
| target | page 18 |
| math | page 30 |
| listOfVariables | page 20 |
| listOfParameter | page 21 |
| sub-elements | description |
| notes | page 13 |
| annotation | page 14 |
| variable | page 17 |
| parameter | page 19 |

Table 11: Attributes and nested elements for *ChangeMath*

The **target** attribute contains the XPath addressing the piece of XML that is to be changed. It is possible to introduce additional parameters for the mathematics. Therefore, the parameters first need to be defined in the [listOfParameters](#). They are then referenced through their ID. To use model variables for the definition of a mathematical expression, those variables need to be defined in the [listOfVariables](#) first, and can then be incorporated through their ID.

3.2.6 The math attribute

The **math** element contains the updated mathematics.

An example for the definition of an updated mathematical function in SBML is given in listing 24.

```

1 <model [..]>
2   <changeMath target="/sbml/model/listOfParameters/parameter[@id='w']">
3
4     <listOfVariables>
5       <variable id="camkii" name="active calcium/calmoduline kinase II"
6         target="/sbml/model[@id='calcium']/listOfSpecies/species[@id='KII']" />
7       <variable id="w" name="synaptic weight"
8         target="/sbml/model[@id='synapse']/listOfParameters/parameter[@id='w']" /
9     </listOfVariables>
10    <listOfParameters>
11      <parameter id="w0" name="synaptic weight change" value="1">
12      <parameter id="n" name="utrasensitivity to calcium" value="2">
13      <parameter id="K" name="sensitivity to calcium" value="1e-6">
14    </listOfParameters>
15
16    <math>
17      <apply>
18        <plus />
19        <ci>w</ci>
20        <apply>
21          <times />
22          <ci>w0</ci>
23          <apply>
24            <divide />
25            <apply>
26              <power />
27              <ci>camkii</ci>
28              <ci>n</ci>
29            </apply>
30            <apply>
31              <plus />
32              <apply>
33                <power />
34                <ci>K</ci>
35                <ci>n</ci>
36              </apply>
37              <apply>
38                <power />
39                <ci> camkii </ci>
40                <ci>n</ci>
41              </apply>
42            </apply>
43          </apply>
44        </apply>
45      </math>
46    </changeMath>
47  </listOfChanges>
48 </model>

```

Listing 24: The *changeMath* element to be validated, currently *math* is defined as attribute in the UML, but handled in the XMLS as an element

3.3 Simulation

A simulation is the execution of some defined algorithm(s). Therefore, a simulation is defined through its **id**, an optional **name**, and the [simulation algorithm](#) used to run the simulation. SED-ML makes use of the [KiSA ontology](#) to refer to a term in the controlled vocabulary identifying the particular simulation algorithm to be used in the simulation.

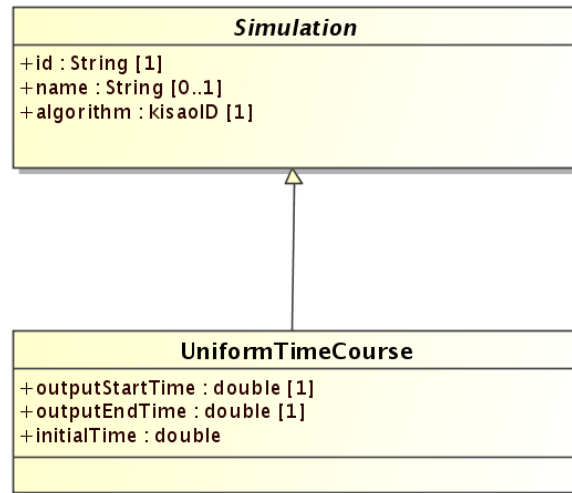


Figure 25: *The SED-ML Simulation class*

In SED-ML 1 every simulation must contain a reference to a simulation algorithm that shall be used to perform the defined simulation.

Table 3.3 shows all attributes and derived classes for the [Simulation](#) element as defined in the SED-ML XML Schema.

| attribute | description |
|--------------|-------------------------|
| metaid | page 13 |
| id | page 12 |
| name | page 12 |
| algorithm | page 10 |
| sub-elements | description |
| notes | page 13 |
| annotation | page 14 |

Table 12: *Attributes and nested elements for [Simulation](#)*

An example for the definition of a set of simulations is given in the XML snippet in [listing 25](#).

```

1 <listOfSimulations>
2   <timeCourse id="s1" name="time course simulation of variable v1 over 100 minutes"
3     algorithm = "KiSA0:ID ">
4   <timeCourse id="s2" name="time course definition for concentration of p" algorithm = "
5     KiSA0:ID ">
6   <timeCourse id="s3" name="time course definition for concentration of p" algorithm = "
7     KiSA0:ID ">
8 </listOfSimulations>
  
```

Listing 25: *The SED-ML `listOfSimulations` element, defining three different simulations*

3.3.1 *UniformTimeCourse*

SED-ML 1 supports time courses, steady state analyses through parameter scans in the one-dimensional space, and bifurcation analyses. [tbc](#)

Table [3.3.1](#) shows all attributes and derived classes for the [UniformTimeCourse](#) element as defined in the SED-ML XML Schema.

| attribute | description |
|-----------------|-------------------------|
| metaid | page 13 |
| id | page 12 |
| name | page 12 |
| algorithm | page 10 |
| initialTime | page 32 |
| outputStartTime | page 32 |
| outputEndTime | page 32 |
| sub-elements | description |
| notes | page 13 |
| annotation | page 14 |
| simulation | page 31 |

Table 13: *Attributes and nested elements for [UniformTimeCourse](#)*

An example for the definition of a time course simulation is given in the XML snippet in listing [26](#).

```
1 <listOfSimulations>
2   <timeCourse id="s1" name="time course simulation of variable v1 over 100 minutes"
3     algorithm = "KiSAO:ID ">
4   <timeCourse id="s2" name="time course simulation of variable v1 over 100 minutes"
5     algorithm = "KiSAO:ID ">
6 </listOfSimulations>
```

Listing 26: *The SED-ML [uniformTimeCourse](#) element, defining a uniform time course simulation over 100 minutes with a stepsize of ?? on variable x, using a stochastic ODE solver in the first case, and a deterministic one in the second.*

3.3.2 *The initialTime attribute*

tbw

3.3.3 *The outputStartTime attribute*

tbw

3.3.4 *The outputEndTime attribute*

tbw

3.4 Task

A task in SED-ML links a [model](#) as defined in the [listOfModels](#) to a certain [simulation](#) description as defined in the [listOfSimulations](#) via the two according IDs (model ID and simulation ID).

Table [3.4](#) on the following page shows all attributes and derived classes for the [Task](#) element as defined in the SED-ML XML Schema.

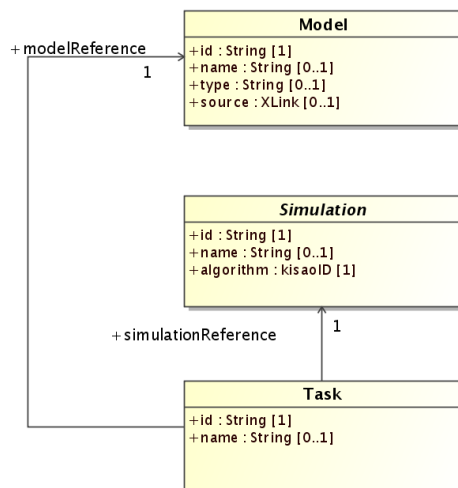


Figure 26: *The SED-ML Task class*

| attribute | description |
|---------------------|-------------------------|
| metaid | page 13 |
| id | page 12 |
| name | page 12 |
| modelReference | page 33 |
| simulationReference | page 33 |
| sub-elements | description |
| notes | page 13 |
| annotation | page 14 |

Table 14: *Attributes and nested elements for [Task](#)*

Each task does have its own task [id](#) for later reference and an optional [name](#).

3.4.1 The *modelReference* attribute

tbw

3.4.2 The *simulationReference* attribute

tbw

An example linking a simulation experiment to two different models using two task definitions within the list of tasks is given in [listing 27](#).

```

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

Listing 27: *The `listOfTasks` element*

In the example, a simulation setting *simulation1* is applied first to *model1* and then is applied to *model2*. Please note, that the tasks may be executed in any order, as XML does not have an ordering concept.

In SED-ML 1 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, i.e. one

SED-ML file.

3.5 DataGenerator

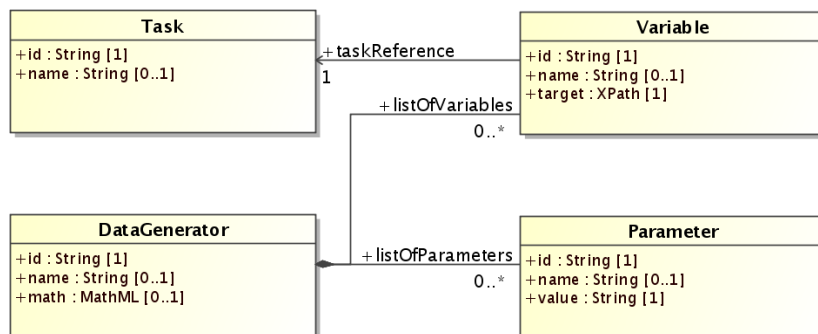


Figure 27: The SED-ML DataGenerator class

Table 3.5 shows all attributes and derived classes for the DataGenerator element as defined in the SED-ML XML Schema.

| attribute | description |
|------------------|-------------------------|
| metaid | page 13 |
| id | page 12 |
| name | page 12 |
| math | page 30 |
| listOfVariables | page 20 |
| listOfParameters | page 21 |
| sub-elements | description |
| notes | page 13 |
| annotation | page 14 |
| variable | page 17 |
| parameter | page 19 |

Table 15: Attributes and nested elements for DataGenerator

The DataGenerator prepares the simulation data for usage in the output. Often, data needs to be post-processed before being returned to the user. Those post-processing steps can be simple normalisation of data, but also mathematical calculations. The data generator describes the rules to build the Output from simulation results and existing entities. The data Generator class is shown in Figure 27.

An example for a data generator is given in listing 28.

```

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

```

```

12 <listOfVariables>
13   <variable id="v1" taskReference="task1"
14     target="/sbml:sbml/sbml:model/sbml:listOfSpecies/
15       sbml:species[@id='PX']" />
16 </listOfVariables>
17 <math:math>
18   <math:ci>v1</math:ci>
19 </math:math>
20 </dataGenerator>
21 </listOfDataGenerators>

```

Listing 28: The *listOfDataGenerators* element, defining two data generators *time* and *LaCI repressor*

3.6 Output

The output container describes how the results of a simulation should be presented to the user. It does not contain the data itself, but only the type of output and the data generators ([data-Generator](#)) which are to be used in the desired output type. Figure 28 shows the UML class definition of the [Output](#) class.

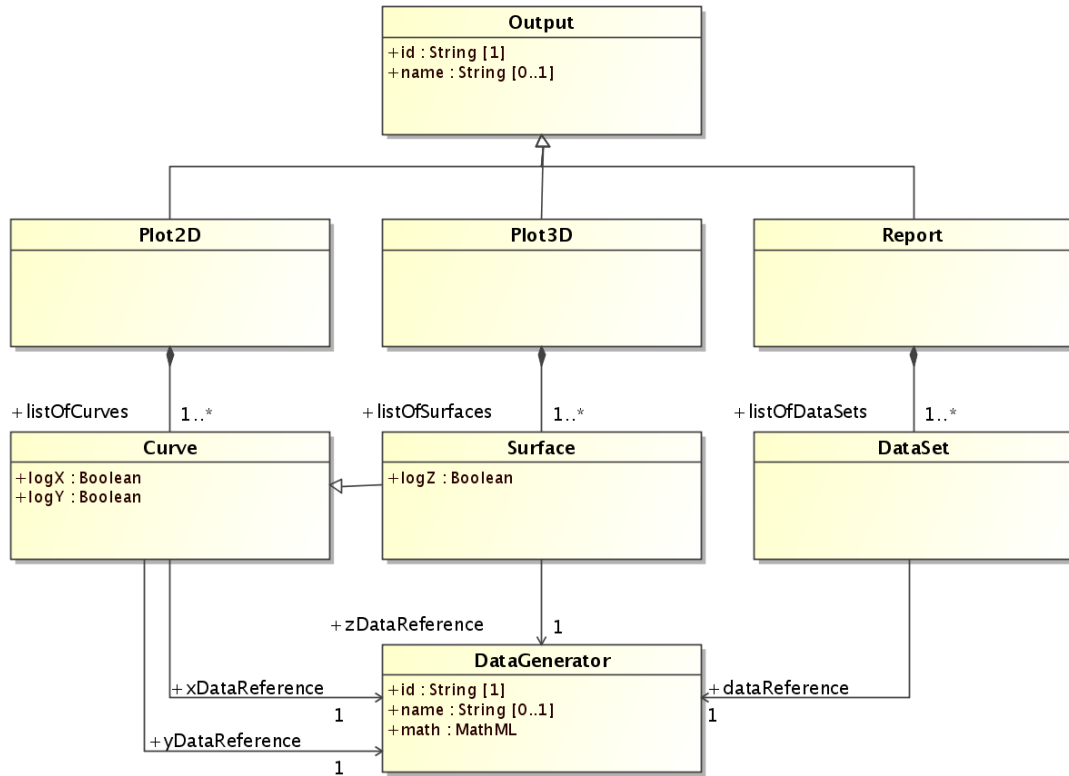


Figure 28: The SED-ML Output class

Table 3.6 on the following page shows all attributes and derived classes for the [Output](#) element as defined in the SED-ML XML Schema.

The types of output pre-defined in SED-ML are plots and [reports](#), also referable as data tables. The output can be defined as a [2D plot](#) or alternatively as a [3D plot](#).

| attribute | description |
|--------------|-------------------------|
| metaid | page 13 |
| id | page 12 |
| name | page 12 |
| sub-elements | description |
| notes | page 13 |
| annotation | page 14 |
| plot2D | page 36 |
| plot3D | page 36 |
| report | page 37 |

Table 16: *Attributes and nested elements for [Output](#)*

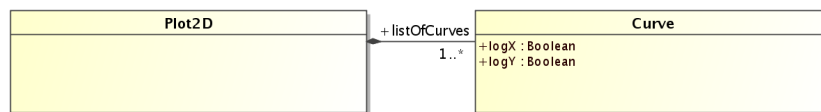


Figure 29: *The SED-ML Plot2D class*

3.6.1 Plot2D

Table 3.6.1 shows all attributes and derived classes for the [Plot2D](#) element as defined in the SED-ML XML Schema.

| attribute | description |
|--------------|-------------------------|
| metaid | page 13 |
| id | page 12 |
| name | page 12 |
| sub-elements | description |
| notes | page 13 |
| annotation | page 14 |

Table 17: *Attributes and nested elements for [Plot2D](#)*

A 2D plot needs a data generator to be assigned to each of its two axes using the [xDataReference](#) to refer to a [dataGenerator](#) for the x-axis and using the [yDataReference](#) to refer to [dataGenerator](#) for the y-axis. Additionally, the curve can be logarithmic on the x-axis ([logX](#) set to true) as well as on the y-axis ([logY](#) set to true).

An example for the definition of a 2D-plot with 2 curves in it is given in listing 29.

```

1 <listOfCurves>
2   <curve logX="true" logY="false" xDataReference="datagenerator1"
3     yDataReference="datagenerator2" />
4   <curve logX="true" logY="false" xDataReference="datagenerator3"
5     yDataReference="datagenerator4"/>
6 </listOfCurves>

```

Listing 29: *The [listOfCurves](#) element*

3.6.2 Plot3D

Table 3.6.2 on the following page shows all attributes and derived classes for the [Plot3D](#) element as defined in the SED-ML XML Schema.



Figure 30: The SED-ML *Plot3D* class

| attribute | description |
|--------------|-------------------------|
| metaid | page 13 |
| id | page 12 |
| name | page 12 |
| sub-elements | description |
| notes | page 13 |
| annotation | page 14 |

Table 18: Attributes and nested elements for *Plot3D*

A 3D plot is defined similarly to a 2D plot, but having 3 axes. To every axis a data generator is assigned using the [xDataReference](#), [yDataReference](#), and the [zDataReference](#). As well, each axis can be defined as logarithmix ([logX/logY/logZ](#) set to true). An example for a 3D plot with one defined surface is given in listing 30.

```

1 <listOfSurfaces>
2   <surface logX="true" logY="false" logZ="false"
3     xDataReference="datagenerator1" yDataReference="datagenerator2"
4     zDataReference="datagenerator3" />
5 </listOfSurfaces>

```

Listing 30: The *listOfSurfaces* element

3.6.3 Report



Figure 31: The SED-ML *Report* class

Table 3.6.3 on the next page shows all attributes and derived classes for the [Report](#) element as defined in the SED-ML XML Schema.

The [Report](#) class defines an output type that returns the simulation result in actual *numbers*. The particular columns of the report table are defined by creating a [DataSet](#) for each column.

Listing 31 provides an example for the definition of such a report.

```

1 <listOfDataSets>
2   <dataReference="datagenerator1" />
3   <dataReference="datagenerator2" />
4 </listOfDataSets>

```

Listing 31: The *listOfReports* element

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](#).

| attribute | description |
|--------------|-------------------------|
| metaid | page 13 |
| id | page 12 |
| name | page 12 |
| sub-elements | description |
| notes | page 13 |
| annotation | page 14 |

Table 19: *Attributes and nested elements for [Report](#)*

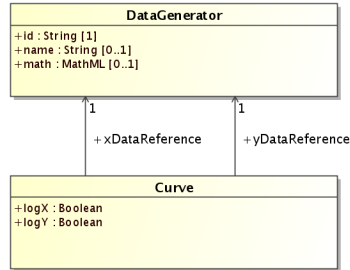


Figure 32: *The SED-ML Curve class*

3.7 Curve

Table 3.7 shows all attributes and derived classes for the [Curve](#) element as defined in the SED-ML XML Schema.

| attribute | description |
|----------------|-------------------------|
| metaid | page 13 |
| id | page 12 |
| name | page 12 |
| logX | page 38 |
| xDataReference | page 39 |
| logY | page 39 |
| yDataReference | page 39 |
| sub-elements | description |
| notes | page 13 |
| annotation | page 14 |

Table 20: *Attributes and nested elements for [Curve](#)*

3.7.1 The logX attribute

[logX](#) is an optional attribute of the [Curve](#) class and defines whether or not the data output on the x-axis is logarithmic or not. The data type of [logX](#) is boolean, the standard value is “false”. To make the output on the x-axis of a plot logarithmic, [logX](#) must be set to “true”, as shown in the sample listing 32:

```

1 <listOfCurves logX="true">
2   <curve id="c1" [..]>
3 </listOfCurves>

```

Listing 32: *The SED-ML logX attribute, defining a logarithmic output on the x-axis of the according output*

[logX](#) is also used in the definition of a [Surface](#) output.

3.7.2 The [logY](#) attribute

[logY](#) is an optional attribute of the [Curve](#) class and defines whether or not the data output on the x-axis is logarithmic or not. The data type of [logY](#) is boolean, the standard value is “false”. To make the output on the y-axis of a plot logarithmic, [logY](#) must be set to “true”, as shown in the sample listing 33:

```
1 <listOfCurves logY="true">
2   <curve id="c1" [...]>
3 </listOfCurves>
```

Listing 33: The SED-ML [logY](#) attribute, defining a logarithmic output on the y-axis of the according output

[logY](#) is also used in the definition of a [Surface](#) output.

3.7.3 The [xDataReference](#) attribute

The [xDataReference](#) is a mandatory attribute of the [Curve](#) object. It’s content refers to a dataGenerator ID which denotes the [DataGenerator](#) object that is used to generate the output on the x-axis of a [Curve](#) in a [2D Plot](#). [xDataReference](#) is also used in the definition of the x-axis of a [Surface](#) in a [3D Plot](#). The [xDataReference](#) data type is string. However, the number of valid values for the [xDataReference](#) is restricted to the IDs of already defined [DataGenerator](#) objects.

An example for the definition of a curve is given in listing 34.

3.7.4 The [yDataReference](#) attribute

The [yDataReference](#) is a mandatory attribute of the [Curve](#) object. It’s content refers to a dataGenerator ID which denotes the [DataGenerator](#) object that is used to generate the output on the y-axis of a [Curve](#) in a [2D Plot](#). [yDataReference](#) is also used in the definition of the y-axis of a [Surface](#) in a [3D Plot](#). The [yDataReference](#) data type is string. However, the number of valid values for the [yDataReference](#) is restricted to the IDs of already defined [DataGenerator](#) objects.

An example for the definition of a curve is given in the XML snippet in listing 34.

```
1 <listOfCurves>
2   <curve id="c1" name="v1 over time" algorithm="KiSAO:ID" xDataReference="dg1"
3     yDataReference="dg2">
4 </listOfCurves>
```

Listing 34: The SED-ML curve element, defining the output curve showing the result of the referenced task

Here, only one curve is created, results shown on the x-axis are generated by the data generator [dg1](#), results shown on the y-axis are generated by the data generator [dg2](#). Both [dg1](#) and [dg2](#) need to be already defined in the [listOfDataGenerators](#).

3.8 Surface

A surface is a three-dimensional Figure representing a simulation result. Figure 33 on the next page shows the definition of the [Surface](#) class used to encode the information needed for the creation of such Figures in SED-ML.

Table 3.8 on the following page shows all attributes and derived classes for the [Surface](#) element as defined in the SED-ML XML Schema. To define a surface, the three different axes have to be defined, that is which data to plot on which axis and in which way. The aforementioned

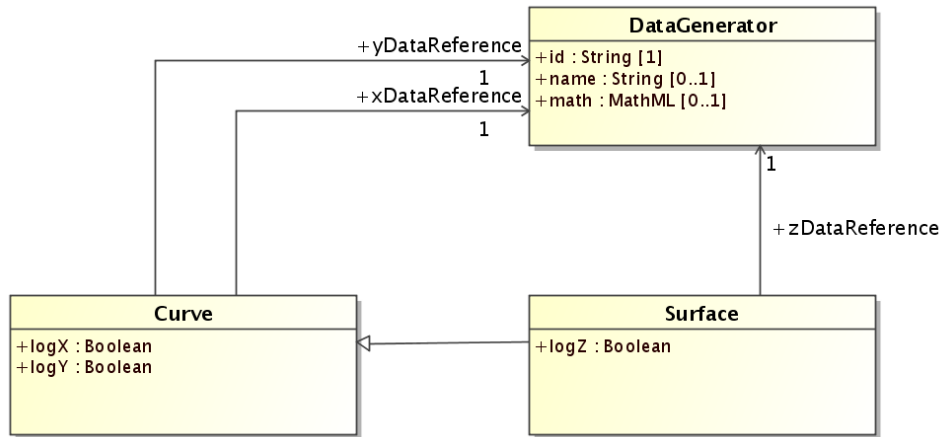


Figure 33: The SED-ML Surface class

| attribute | description |
|----------------|-------------------------|
| metaid | page 13 |
| id | page 12 |
| name | page 12 |
| logX | page 38 |
| xDataReference | page 39 |
| logY | page 39 |
| yDataReference | page 39 |
| logZ | page 40 |
| zDataReference | page 40 |
| sub-elements | description |
| notes | page 13 |
| annotation | page 14 |

Table 21: Attributes and nested elements for *Surface*

[xDataReference](#) and [yDataReference](#) attributes define the according dataGenerators for both the x- and y-axis of a surface. In addition, the [zDataReference](#) attribute defines the output for the z-axis. All axes might be logarithmic or not. This can be specified through the [logX](#), [logY](#), and the [logZ](#) attributes in the according dataReference elements.

3.8.1 The logZ attribute

[logZ](#) is an optional attribute of the [Surface](#) class and defines whether or not the data output on the z-axis is logarithmic or not. The data type of [logZ](#) is boolean, the standard value is “false”. To make the output on the z-axis of a surface plot logarithmic, [logZ](#) must be set to “true”, as shown in the sample listing 35:

```

1 <listOfSurfaces logZ="true">
2   <surface id="s1" [...>
3 </listOfSurfaces>

```

Listing 35: The SED-ML logZ attribute, defining a logarithmic output on the z-axis of the according output

3.8.2 The zDataReference attribute

The [zDataReference](#) is a mandatory attribute of the [Surface](#) object. It’s content refers to a dataGenerator ID which denotes the [DataGenerator](#) object that is used to generate the output on the z-axis of a 3D Plot. The [zDataReference](#) data type is string. However, the number of

valid values for the `zDataReference` is restricted to the IDs of already defined `DataGenerator` objects.

An example for the definition of a surface is given in the XML snippet in listing 36.

```
1 <listOfSurfaces>
2   <surface id="s1" name="surface" algorithm="KiSA0:ID" xDataReference="dg1"
3     yDataReference="dg2" zDataReference="dg3">
4 </listOfSurfaces>
```

Listing 36: The SED-ML curve element, defining the output curve showing the result of the referenced task

Here, only one curve is created, results shown on the x-axis are generated by the data generator `dg1`, results shown on the y-axis are generated by the data generator `dg2`, results shown on the z-axis are generated by the data generator `dg3`. All `dg1`, `dg2` and `dg3` need to be already defined in the `listOfDataGenerators`.

3.9 DataSet

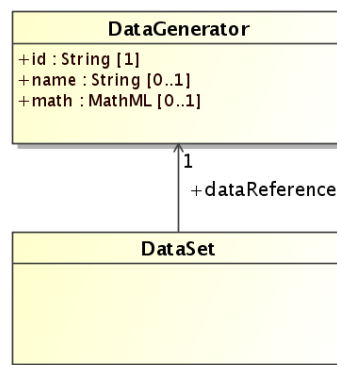


Figure 34: The SED-ML `DataSet` class

Table 3.9 shows all attributes and derived classes for the `DataSet` element as defined in the SED-ML XML Schema.

| attribute | description |
|---------------|-------------------------|
| metaid | page 13 |
| id | page 12 |
| name | page 12 |
| dataReference | page 41 |
| sub-elements | description |
| notes | page 13 |
| annotation | page 14 |

Table 22: Attributes and nested elements for `DataSet`

3.9.1 The `dataReference` attribute

tbw

An example for the definition of a data set in form of a table is given in the XML snippet in listing 37.

```
1 <listOfDataSets>
2   <dataSet id="d1" name="v1 over time" dataReference="dg1">
3 </listOfDataSets>
```

Listing 37: *The SED-ML dataSet element, defining the output showing the result of the referenced task*

Acknowledgements

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A SED-ML UML Overview

Figure 35 shows the complete UML diagram of the SED-ML. It gives the full picture of all implemented classes (see the XML Schema definition in 51).

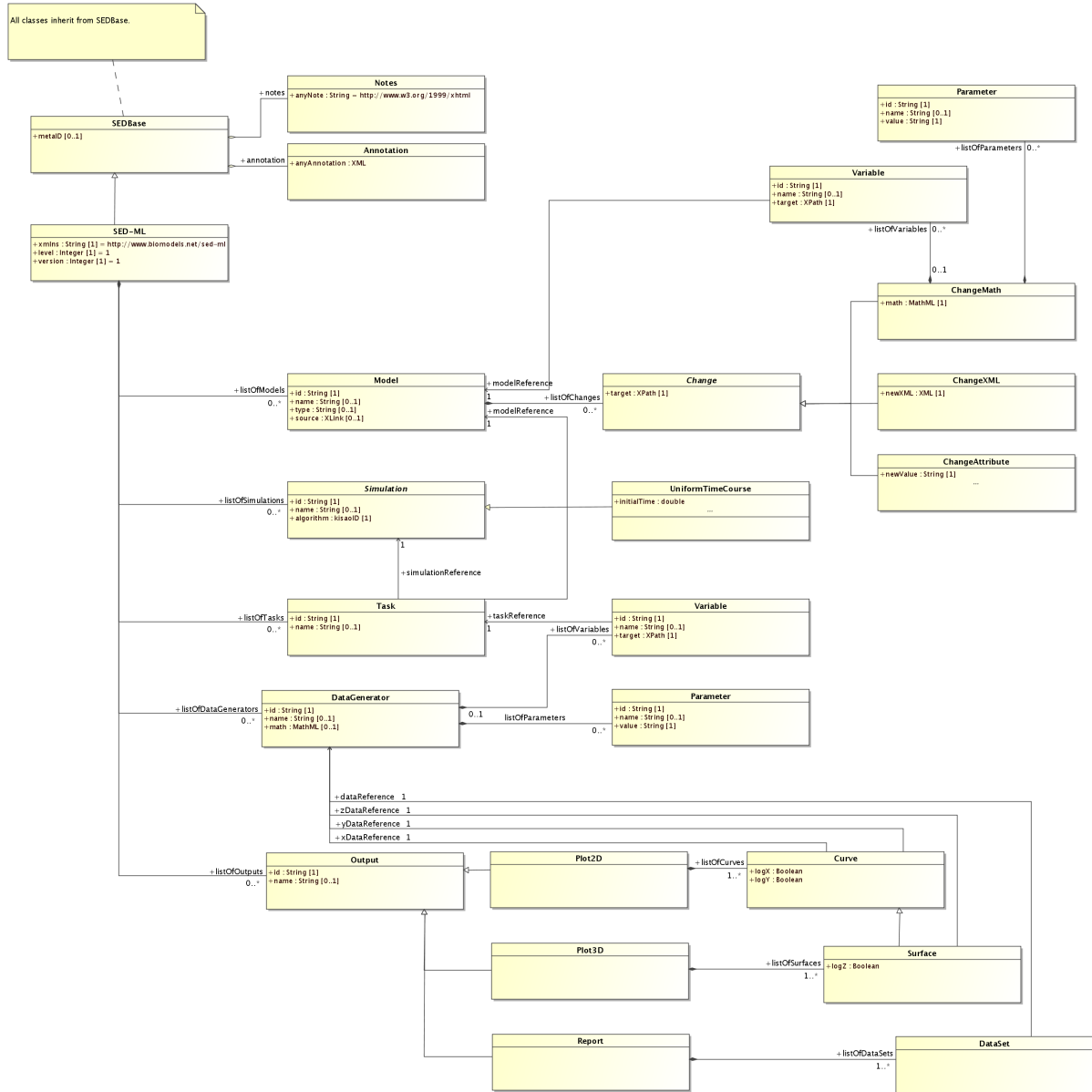


Figure 35: The SED-ML UML class diagram

B Overview of SED-ML

The *Simulation Experiment Description Markup Language* (SED-ML) is an XML-based format for the description of simulation experiments. It serves to store information about the simulation experiment performed on one or more models with a given set of outputs. Support for SED-ML compliant simulation descriptions will enable the exchange of simulation experiments across tools.

B.1 Conventions

The Business Process Modeling Notation Version 1.2 (BPMN) was initially intended to describe internal business procedures (processes) in a graphical way. However, we will use BPMN to graphically describe the steps and processes of setting up a simulation experiment description. The major parts of BPMN that are used to specify SED-ML are activities, gateways, events, data, and documentation.

An *activity* is “work that is performed on a [...] process”, for example “Specify the simulation settings”. Activities may be atomic or non-atomic. SED-ML in particular makes use of the *task* activities, i.e., specific work units that need to be performed. Non-atomic tasks might be collapsed or expanded in the graphical representation (see Figure 36). Each collapsed subprocess has a corresponding expanded subprocess definition.

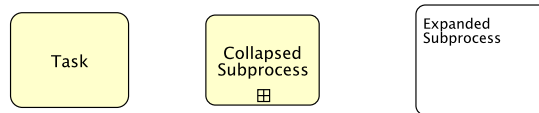


Figure 36: BPMN activities: task, collapsed process, expanded subprocess

Gateways serve as means to control the flow of sequence in the diagram. As the term already implies, a gateway needs some “mechanism that either allows or disallows passage through” [White et al., 2004]. The result of a gateway pass-through can be that processes are merged or splitted. Graphically, a gateway is represented as a diamond.

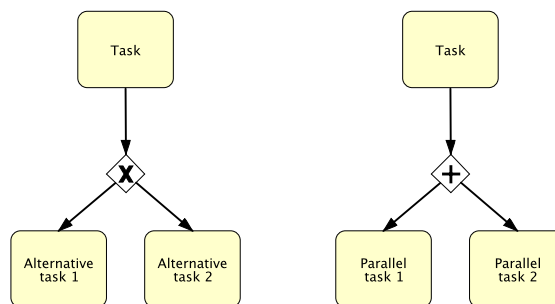


Figure 37: BPML gateway types: Exclusive (left), parallel (right)

While there exist a number of different gateway types (see [White et al., 2004], pp. 93), the SED-ML specification only uses the parallel and the exclusive gates (see Figure 37).

Exclusive gateways – also denoted as decisions – allow the sequence flow to take two or more

alternative paths (Figure 37 on the previous page, left hand side). However, *only one* of the paths may be chosen (not more). Sometimes two alternative branches need to be merged together again, in which case the exclusive gate must be used as well: The sequence flow continues as soon as *one* of the incoming processes send a signal. An exclusive gateways is marked by an **X** in the graphical notation.

Parallel gateways, “provide a mechanism to synchronize parallel flow and to create parallel flow” [White et al., 2004] (Figure 37 on the preceding page, right hand side). They are used to show parallel paths in the workflow; even if sometimes not required they might help in understanding the process. Synchronisation allows to start two processes in parallel at the same time in the sequence flow: The sequence flow will continue with *all* processes leaving the parallel gateway. Joining two processes with a parallel gateway is also possible: the process flow will only continue after a signal has arrived from *all* processes coming in the parallel gateway. A parallel gateway is marked by a + in the graphical notation.

Events mark everything happening during the execution of the sequence flow, usually they interrupt the business process, having some cause or impact on the execution. From the broad range of events that BPMN offers, SED-ML only uses a small subset, namely the start event and the end event (Figure 38).

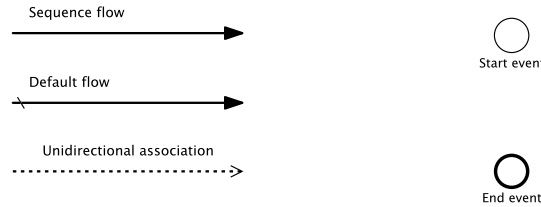


Figure 38: BPML connectors (left) and events (right).

All events are graphically drawn as small circles. A *start event* is drawn with a single thin line and mark the start of a process, it can not have any incoming sequence flow. Start event may be triggered by different mechanisms, for the case of SED-ML the untyped start event (no marker inside the circle) is used. The trigger to start the process is “Create new simulation experiment”. The *end event* is marked with a thick line. It indicates the end of a process. SED-ML specification makes use of the untyped end event (no marker inside the circle). The end event is used to show the end of sub-processes as well as processes. If the end of a sub-process is reached, the sequence flow returns to the according parent process.

Connectors are used to combine different BPMN objects with each other ([White et al., 2004] page 30 shows the full list of valid connections). SED-ML uses only a subset of available connectors, namely sequence flow, default flow, and unidirectional associations (Figure 38). *Sequence flow* defines the execution order of activities. *Default flow* marks the default branch to be chosen if other conditions leave various possibilities for further execution of the sequence flow. A *unidirectional association* is used to indicate that a data object is modified, i.e. read and written during the execution of an activity [Business Process Technology group, 2009].

The rough SED-ML workflow is shown in Figure 39. The process of defining a SED-ML simulation experiment starts by initialising the experiment and creating a new sed-ml file. Afterwards, the **models** needed for the simulation are specified and stored into the existing sed-ml file (see section B.1.1). In a third step, the simulation experiment **setups** are defined and stored into the same file (see section B.1.2). To assign a setup to a number of models used in the experiment, these connections have to be defined and recorded (see section B.1.3), called **task** in SED-ML.

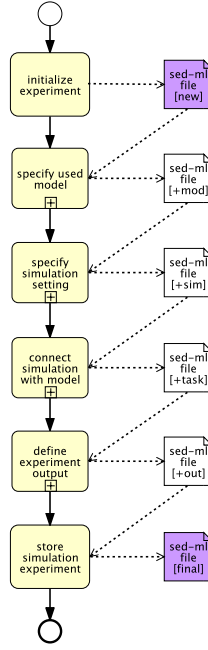


Figure 39: *The process of defining a simulation experiment in SED-ML (overview)*

After simulation, the **output** should be defined, based on the specified tasks and performed simulation experiment. The information is added to the existing SED-ML file (see section B.1.4). In the end, the whole experiment is stored in the final SED-ML file. All collapsed processes are described in the following. Examples in XML are provided in the more technical description

B.1.1 Models

To define a simulation experiment, first a new SED-ML file is created. The models to be used in the experiment (zero or many) are referenced, using a link to a model description in some open, curated model base (such as Biomedicals Database [Le Novère et al. \[2006\]](#), CellML Repository [Beard et al. \[2009\]](#), or alike). Changes that are necessary to simulate the model correctly are defined, e.g. assigning new parameter values or updating the mathematics of the model (Figure 40). The procedure is repeated until all models participating in the experiment

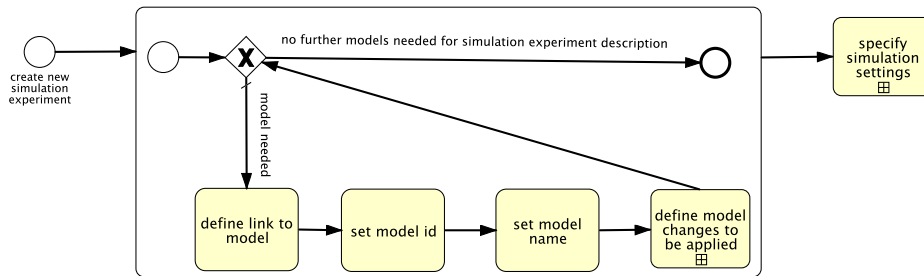


Figure 40: *The process of defining model(s) in SED-ML*

have been described. Each model used gets an internal SED-ML ID and an optional name.

B.1.2 Simulation setup

Secondly, the simulation setups (zero or many) used throughout the simulation experiment are described (Figure 41). Those may stem from various different types of simulation, e.g. steady

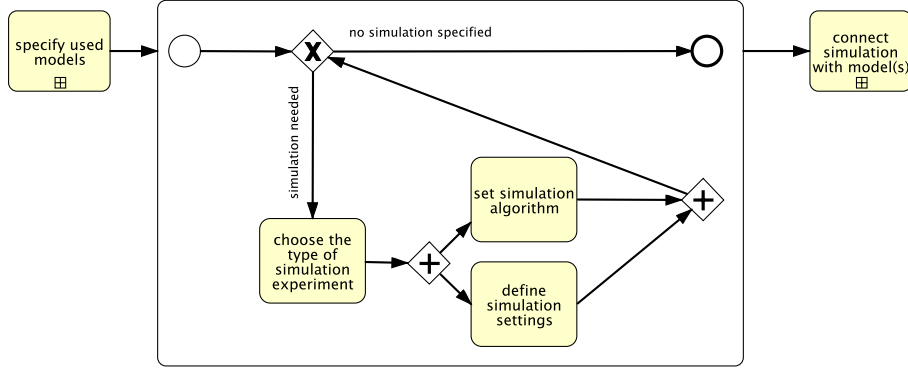


Figure 41: The process of defining simulation(s) in SED-ML

state analysis or bifurcation. Depending on the specific type of experiment, the information encoded for the simulation setup might differ. Thus, the definition of simulation settings is specific to the simulation experiment.

In a simple case the experiment consists of one simulation, but it can get far more complex. For example, one might define a nested sequence of simulations, in which case every simulation has to be defined separately. Each simulation setup gets its own internal ID and an optional name. For each of the setups, the simulation algorithm to be used for that simulation is defined through a reference to a well-defined algorithm name, e.g. an ontology or controlled vocabulary. One approach to define such a controlled vocabulary of simulation algorithms is the *Kinetic Simulation Algorithm Ontology* (KiSAO, Köhn and Le Novère [2008]). The setup definition is repeated until all different simulations have been described.

B.1.3 Task

SED-ML allows to apply one defined simulation setting to one defined model at a time. However, any number of tasks may be defined inside a simulation experiment description (Figure 42). To do so, each task refers to one of the formerly specified models and to one of the formerly specified simulation setups. Each task has its own ID and an optional name. The process of task definition is repeated until all tasks have been defined.

The current SED-ML does not allow to nest or order tasks. However, these features are evaluated for future versions of SED-ML.

B.1.4 Output

The SED-ML finally consists of output definitions that describe what kind of output the experiment uses to present the simulation result to the user, i.e. a plot or a data table (Figure 43), and also which data is part of the output. Therefore, SED-ML first defines a set of data generators (Figure 44), which are then used to specify a particular result, i.e. output (see section B.1.5).

The SED-ML specification comes with three pre-defined types of outputs: 2D- and 3D plots, and reports. All use the aforementioned data generators to specify the information to be plotted

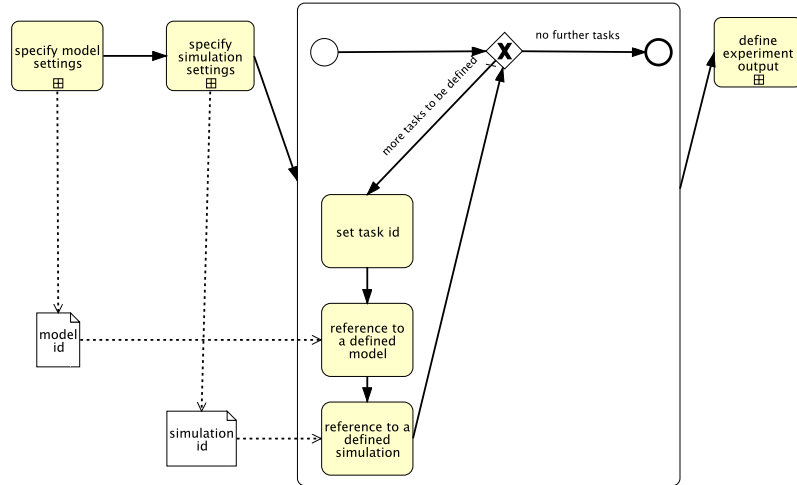


Figure 42: *The process of defining simulation task(s) in SED-ML*

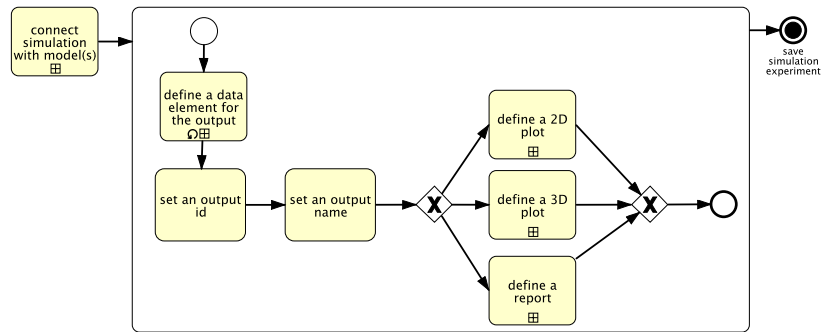


Figure 43: *The process of defining output(s) in SED-ML*

on the different axes, or in the table comlumns respectively.

B.1.5 Data Generator

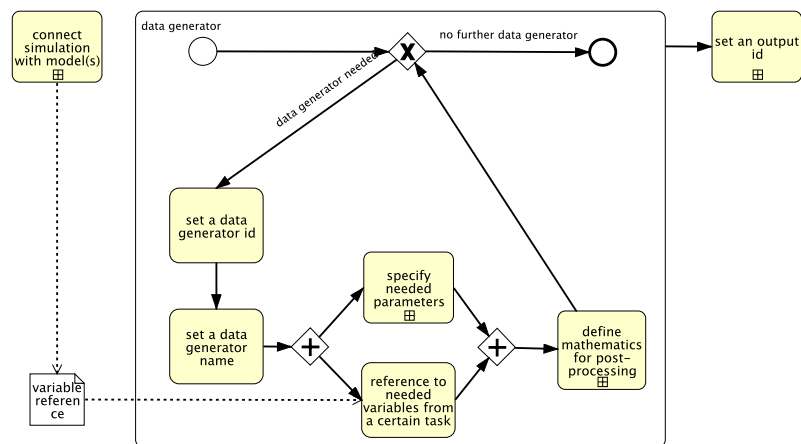


Figure 44: *The process of defining data generator(s) in SED-ML*

A data generator may use data elements, e. g. variables, or parameters, that either (1) have been taken directly from the model, or (2) have been generated in a post-processing step. If post-processing needs to be applied, variables and parameters from the various, previously defined models may be used, but also existing global parameters, such as *time*. If the variables are taken from existing models, a reference to the model and the particular variable needs to be given. If post-processing is necessary, a reference to an existing variable or parameter, including other data generators, has to be provided. Additional mathematical rules to be applied on the referred variable or parameter needs then to be specified. In a SED-ML file, any number of data generators can be created for later re-use in the output definition.

C XML Schema

Listing 38 shows the full SED-ML XML Schema. The code is commented inline.

```
1 <xs:schema targetNamespace="http://www.biomodels.net/sed-ml" xmlns="http://www.biomodels.net/sed-ml" xmlns:xs="http://www.w3.org/2001/XMLSchema" xmlns:math="http://www.w3.org/1998/Math/MathML">
2 <!-- mathML import -->
3 <xs:import namespace="http://www.w3.org/1998/Math/MathML" schemaLocation="sbml-mathml.xsd" />
4
5 <!-- global element declarations -->
6 <!-- variable definition -->
7 <xs:element name="variable">
8   <xs:complexType>
9     <xs:attribute name="taskReference" type="xs:string" use="optional" />
10    <xs:attribute name="modelReference" type="xs:string" use="optional" />
11    <xs:attribute name="name" type="xs:string" use="optional" />
12    <xs:attribute name="target" type="xs:token" />
13    <xs:attribute name="id" type="xs:string" />
14  </xs:complexType>
15 </xs:element>
16 <!-- parameter definition -->
17 <xs:element name="parameter">
18   <xs:complexType>
19     <xs:attribute name="id" type="xs:string" />
20     <xs:attribute name="name" type="xs:string" use="optional" />
21     <xs:attribute name="value" type="xs:string" use="required" />
22   </xs:complexType>
23 </xs:element>
24 <!-- general simulation class definition -->
25 <xs:element name="anySimulation">
26   <xs:complexType>
27     <xs:sequence>
28       <xs:element name="simulationProperty">
29         <xs:complexType>
30           <xs:attribute name="propertyName" type="xs:string" use="required" />
31           <xs:attribute name="propertyValue" type="xs:string" use="required" />
32         </xs:complexType>
33       </xs:element>
34     </xs:sequence>
35   </xs:complexType>
36 </xs:element>
37 <!-- uniform time course simulation definition -->
38 <xs:element name="uniformTimeCourse">
39   <xs:complexType>
40     <xs:attribute name="id" type="xs:string" />
41     <xs:attribute name="outputStartTime" type="xs:double" use="required" />
42     <xs:attribute name="outputEndTime" type="xs:double" use="required" />
43     <xs:attribute name="numberOfPoints" type="xs:integer" use="required" />
44     <xs:attribute name="initialTime" type="xs:double" use="required" />
45     <xs:attribute name="algorithm" type="xs:string" />
46   </xs:complexType>
47 </xs:element>
48 <!-- task definition -->
49 <xs:element name="task">
50   <xs:complexType>
51     <xs:attribute name="simulationReference" type="xs:string" use="required" />
52     <xs:attribute name="name" type="xs:string" use="required" />
53     <xs:attribute name="modelReference" type="xs:string" use="required" />
54     <xs:attribute name="id" type="xs:string" />
55   </xs:complexType>
56 </xs:element>
57 <!-- notes element definition -->
58 <xs:element name="notes" type="xs:string" />
59 <!-- annotation element definition -->
60 <xs:element name="annotation" type="xs:string" />
61
62 <!-- complex type SEDBase definition -->
63 <xs:complexType name="SEDBase">
64   <xs:annotation>
65     <xs:documentation xml:lang="en">
66       The SEDBase type is the base type of all main types in SED-ML. It serves as a container
67       for the annotation of any part of the experiment description.
68     </xs:documentation>
69   </xs:annotation>
70 </xs:complexType>
```

```

68 </xs:annotation>
69 <xs:sequence>
70 <xs:element ref="notes" minOccurs="0" />
71 <xs:element ref="annotation" minOccurs="0" />
72 </xs:sequence>
73 </xs:complexType>
74
75 <!-- root element sedML definition -->
76 <xs:element name="sedML">
77 <xs:complexType>
78 <xs:complexContent>
79 <xs:extension base="SEDBase">
80 <xs:sequence>
81 <xs:element ref="listOfSimulations" />
82 <xs:element ref="listOfModels" />
83 <xs:element ref="listOfTasks" />
84 <xs:element ref="listOfDataGenerators" />
85 <xs:element ref="listOfOutputs" />
86 </xs:sequence>
87 <xs:attribute name="version" type="xs:decimal" use="required" fixed="0.1" />
88 </xs:extension>
89 </xs:complexContent>
90 </xs:complexType>
91 </xs:element>
92 <!-- 2D plot definition -->
93 <xs:element name="plot2D">
94 <xs:complexType>
95 <xs:sequence>
96 <xs:element ref="listOfCurves" />
97 </xs:sequence>
98 <xs:attribute name="name" type="xs:string" use="required" />
99 <xs:attribute name="id" type="xs:string" />
100 </xs:complexType>
101 </xs:element>
102 <!-- 3D plot definition -->
103 <xs:element name="plot3D">
104 <xs:complexType>
105 <xs:sequence>
106 <xs:element ref="listOfSurfaces" />
107 </xs:sequence>
108 <xs:attribute name="name" type="xs:string" use="required" />
109 <xs:attribute name="id" type="xs:string" />
110 </xs:complexType>
111 </xs:element>
112 <!-- report definition -->
113 <xs:element name="report">
114 <xs:complexType>
115 <xs:sequence>
116 <xs:element ref="listOfDataSets" />
117 </xs:sequence>
118 <xs:attribute name="name" type="xs:string" use="required" />
119 <xs:attribute name="id" type="xs:string" />
120 </xs:complexType>
121 </xs:element>
122 <!-- model element definition -->
123 <xs:element name="model">
124 <xs:complexType>
125 <xs:sequence>
126 <xs:element ref="listOfChanges" minOccurs="0" />
127 </xs:sequence>
128 <xs:attribute name="type" type="xs:string" use="required" />
129 <xs:attribute name="source" use="required" type="xs:string" />
130 <xs:attribute name="name" type="xs:string" use="required" />
131 <xs:attribute name="id" type="xs:string" />
132 </xs:complexType>
133 </xs:element>
134
135 <!-- <xs:element name="math" type="math:Math" /> -->
136 <!-- list definitions -->
137 <xs:element name="listOfVariables">
138 <xs:complexType>
139 <xs:sequence>
140 <xs:element ref="variable" />
141 </xs:sequence>
142 </xs:complexType>

```

```

143 </xs:element>
144 <xs:element name="listOfParameters">
145   <xs:complexType>
146     <xs:sequence>
147       <xs:element ref="parameter" />
148     </xs:sequence>
149   </xs:complexType>
150 </xs:element>
151 <xs:element name="listOfTasks">
152   <xs:complexType>
153     <xs:sequence>
154       <xs:element ref="task" maxOccurs="unbounded" />
155     </xs:sequence>
156   </xs:complexType>
157 </xs:element>
158 <xs:element name="listOfSimulations">
159   <xs:complexType>
160     <xs:sequence>
161       <xs:element ref="uniformTimeCourse" minOccurs="0" maxOccurs="unbounded"/>
162       <xs:element ref="anySimulation" minOccurs="0" maxOccurs="unbounded"/>
163     </xs:sequence>
164   </xs:complexType>
165 </xs:element>
166 <xs:element name="listOfOutputs">
167   <xs:complexType>
168     <xs:sequence minOccurs="0">
169       <xs:element ref="plot2D" minOccurs="0" />
170       <xs:element ref="plot3D" minOccurs="0" />
171       <xs:element ref="report" minOccurs="0" />
172     </xs:sequence>
173   </xs:complexType>
174 </xs:element>
175 <xs:element name="listOfModels">
176   <xs:complexType>
177     <xs:sequence>
178       <xs:element ref="model" maxOccurs="unbounded" />
179     </xs:sequence>
180   </xs:complexType>
181 </xs:element>
182 <xs:element name="listOfDataGenerators">
183   <xs:complexType>
184     <xs:sequence>
185       <xs:element ref="dataGenerator" maxOccurs="unbounded" />
186     </xs:sequence>
187   </xs:complexType>
188 </xs:element>
189 <xs:element name="listOfCurves">
190   <xs:complexType>
191     <xs:sequence>
192       <xs:element ref="curve" maxOccurs="unbounded" />
193     </xs:sequence>
194   </xs:complexType>
195 </xs:element>
196 <xs:element name="listOfSurfaces">
197   <xs:complexType>
198     <xs:sequence>
199       <xs:element ref="surface" maxOccurs="unbounded" />
200     </xs:sequence>
201   </xs:complexType>
202 </xs:element>
203 <xs:element name="listOfDataSets">
204   <xs:complexType>
205     <xs:sequence>
206       <xs:element ref="dataSet" maxOccurs="unbounded" />
207     </xs:sequence>
208   </xs:complexType>
209 </xs:element>
210 <xs:element name="listOfChanges">
211   <xs:complexType>
212     <xs:sequence>
213       <xs:element ref="changeAttribute" minOccurs="0" maxOccurs="unbounded" />
214       <xs:element ref="changeXML" minOccurs="0" maxOccurs="unbounded" />
215       <xs:element ref="changeMath" minOccurs="0" maxOccurs="unbounded" />
216     </xs:sequence>
217   </xs:complexType>

```

```

218 </xs:element>
219 <!-- data generator definition -->
220 <xs:element name="dataGenerator">
221   <xs:complexType>
222     <xs:sequence>
223       <xs:element ref="listOfVariables" minOccurs="0" />
224       <xs:element ref="listOfParameters" minOccurs="0" />
225       <xs:element ref="math:math" />
226     </xs:sequence>
227     <xs:attribute name="name" type="xs:string" use="required" />
228     <xs:attribute name="id" type="xs:string" />
229   </xs:complexType>
230 </xs:element>
231 <!-- curve definition (2D plot) -->
232 <xs:element name="curve">
233   <xs:complexType>
234     <xs:attribute name="yDataReference" type="xs:string" use="required" />
235     <xs:attribute name="xDataReference" type="xs:string" use="required" />
236     <xs:attribute name="logY" use="required" type="xs:boolean" />
237     <xs:attribute name="logX" use="required" type="xs:boolean" />
238   </xs:complexType>
239 </xs:element>
240 <!-- surface definition (3D plot) -->
241 <xs:element name="surface">
242   <xs:complexType>
243     <xs:attribute name="yDataReference" type="xs:string" use="required" />
244     <xs:attribute name="xDataReference" type="xs:string" use="required" />
245     <xs:attribute name="zDataReference" type="xs:string" use="required" />
246     <xs:attribute name="logY" use="required" type="xs:boolean" />
247     <xs:attribute name="logX" use="required" type="xs:boolean" />
248     <xs:attribute name="logZ" use="required" type="xs:boolean" />
249   </xs:complexType>
250 </xs:element>
251 <!-- data set definition (report) -->
252 <xs:element name="dataSet">
253   <xs:complexType>
254     <xs:attribute name="dataReference" type="xs:string" use="required" />
255   </xs:complexType>
256 </xs:element>
257 <!-- definition of attribute changes inside a model -->
258 <xs:element name="changeAttribute">
259   <xs:complexType>
260     <xs:attribute name="target" type="xs:token" />
261     <xs:attribute name="newValue" type="xs:string" use="required" />
262   </xs:complexType>
263 </xs:element>
264 <!-- definition of changes in the XML structure of the model -->
265 <xs:element name="changeXML">
266   <xs:complexType>
267     <xs:attribute name="target" type="xs:token" />
268     <xs:attribute name="newValue" type="xs:string" use="required" />
269   </xs:complexType>
270 </xs:element>
271 <!-- definition of changes in the mathematics of the model -->
272 <xs:element name="changeMath">
273   <xs:complexType>
274     <xs:sequence>
275       <xs:element ref="listOfVariables" />
276       <xs:element ref="listOfParameters" />
277       <xs:element ref="math:math" />
278     </xs:sequence>
279     <xs:attribute name="target" type="xs:token" />
280   </xs:complexType>
281 </xs:element>
282 </xs:schema>

```

Listing 38: SED-ML XML Schema definition

D Examples

D.1 Le Loup Model (CellML)

to do: description of the conducted experiment

```
1 <?xml version="1.0" encoding="utf-8"?>
2 <sedML version="0.1" xmlns="http://www.biomodels.net/sed-ml" xmlns:math="http://www.w3.org
  /1998/Math/MathML">
3 <!-- textual information about the experiment (optional) -->
4 <notes>Comparing Limit Cycles and strange attractors for oscillation in Drosophila
5 </notes>
6 <!-- definition of simulation setup -->
7 <listOfSimulations>
8 <!-- definition of a uniform time course over 180 time units using a ??? algorithm (
  KISA0:0000019) -->
9 <uniformTimeCourse id="simulation1" algorithm="KISA0:0000019" initialTime="0"
  outputStartTime="0" outputEndTime="180" numberOfPoints="1000" />
10 </listOfSimulations>
11 <!-- definition of models used during the experiment -->
12 <listOfModels>
13 <!-- reference to a cellML model -->
14 <model id="model1" name="Circadian Oscillations" type="CellML"
15   source="http://www.cellml.org/models/leloup_gonze_goldbeter_1999_version02" >
16 <!-- definition of changes to be applied to the original model (changing initial
  conditions) -->
17 <listOfChanges>
18 <changeAttribute target="/cellml:model/cellml:component[@cmeta:id='MP']/cellml:variable
  [@name='vsP']/@initial_value" newValue="1"/>
19 <changeAttribute target="/cellml:model/cellml:component[@cmeta:id='MP']/cellml:variable
  [@name='vmP']/@initial_value" newValue="0.7"/>
20 <changeAttribute target="/cellml:model/cellml:component[@cmeta:id='P2']/cellml:variable
  [@name='vdP']/@initial_value" newValue="2"/>
21 <changeAttribute target="/cellml:model/cellml:component[@cmeta:id='T2']/cellml:variable
  [@name='vdT']/@initial_value" newValue="2"/>
22 <changeAttribute target="/cellml:model/cellml:component[@name='parameters']/
  cellml:variable[@name='k1']/@initial_value" newValue="0.6"/>
23 <changeAttribute target="/cellml:model/cellml:component[@name='parameters']/
  cellml:variable[@name='K4P']/@initial_value" newValue="1"/>
24 <changeAttribute target="/cellml:model/cellml:component[@name='parameters']/
  cellml:variable[@name='K4T']/@initial_value" newValue="1"/>
25 </listOfChanges>
26 </model>
27 <!-- reference to the above model (model1) with additional changes of initial values of
  MY and T2 -->
28 <model id="model2" name="Circadian Chaos" type="CellML" source="model1">
29 <listOfChanges>
30 <changeAttribute target="/cellml:model/cellml:component[@cmeta:id='MT']/cellml:variable
  [@name='vmT']/@initial_value" newValue="0.28"/>
31 <changeAttribute target="/cellml:model/cellml:component[@cmeta:id='T2']/cellml:variable
  [@name='vdT']/@initial_value" newValue="4.8"/>
32 </listOfChanges>
33 </model>
34 </listOfModels>
35 <!-- definition of tasks (combining simulation setup and model) -->
36 <listOfTasks>
37 <!-- limit cycle on model1 -->
38 <task id="task1" name="Limit Cycle" modelReference="model1" simulationReference="
  simulation1"/>
39 <!-- strange attractors on the further perturbed model model2 -->
40 <task id="task2" name="Strange attractors" modelReference="model2" simulationReference="
  simulation1"/>
41 </listOfTasks>
42 <!-- definition of the data generators needed to produce the output -->
43 <listOfDataGenerators>
44 <!-- definition of data generator for tim mRNA -->
45 <dataGenerator id="tim1" name="tim mRNA">
46 <listOfVariables>
47 <variable id="v1" taskReference="task1" target="/cellml:model/cellml:component[
  @cmeta:id='MT']" />
48 </listOfVariables>
49 <math:math>
50 <math:apply>
51 <math:plus />
52 <math:ci>v1</math:ci>
```

```

53     </math:apply>
54   </math:math>
55 </dataGenerator>
56 <!-- definition of data generator for the nuclear PER-TIM complex -->
57 <dataGenerator id="per-tim" name="nuclear PER-TIM complex">
58   <listOfVariables>
59     <variable id="v1" taskReference="task1" target="/cellml:model/cellml:component[
        @cmeta:id='CN']" />
60   </listOfVariables>
61   <math:math>
62     <math:apply>
63       <math:plus />
64       <math:ci>v1</math:ci>
65     </math:apply>
66   </math:math>
67 </dataGenerator>
68 <!-- definition of data generator for pertubated tim mRNA -->
69 <dataGenerator id="tim2" name="tim mRNA (changed parameters)">
70   <listOfVariables>
71     <variable id="v2" taskReference="task2" target="/cellml:model/cellml:component[
        @cmeta:id='MT']" />
72   </listOfVariables>
73   <math:math>
74     <math:apply>
75       <math:plus />
76       <math:ci>v2</math:ci>
77     </math:apply>
78   </math:math>
79 </dataGenerator>
80 <!-- definition of data generator for perturbed nuclear PER-TIM complex -->
81 <dataGenerator id="per-tim2" name="nuclear PER-TIM complex">
82   <listOfVariables>
83     <variable id="v1" taskReference="task2" target="/cellml:model/cellml:component[
        @cmeta:id='CN']" />
84   </listOfVariables>
85   <math:math>
86     <math:apply>
87       <math:plus />
88       <math:ci>v1</math:ci>
89     </math:apply>
90   </math:math>
91 </dataGenerator>
92 </listOfDataGenerators>
93 <!-- output definition -->
94 <listOfOutputs>
95   <!-- definition of a 2D plot to show the tim mRNA concentration with different initial
        conditions -->
96   <plot2D id="plot1" name="tim mRNA with Oscillation and Chaos">
97     <!-- definition of two output curves, both plotting per-tim (original and perturbed)
        against the tim concentration (original and perturbed) -->
98     <listOfCurves>
99       <curve logX="false" logY="false" xDataReference="per-tim" yDataReference="tim1" />
100      <curve logX="false" logY="false" xDataReference="per-tim2" yDataReference="tim2" />
101    </listOfCurves>
102  </plot2D>
103 </listOfOutputs>
104 </sedML>

```

Listing 39: Example: LeLoup Model Simulation Description in SED-ML

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