SBML Level 3 Package Specification

Qualitative Models

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DRAFT

This is a working draft of the specification for the SBML Level 3 package "`qual`". It is not a normative document. Please send comments and other feedback to the Package Working Group mailing list, sbml-qual@lists.sourceforge.net.

The latest release, past releases, and other materials related to this specification are available at http://sbml.org/Documents/Specifications/SBML_Level_3/Packages/Qualitative_Models_(qual)

This release of the specification is available at

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1 Introduction

1.1 Motivation

Quantitative methods for modelling biological networks require an in-depth knowledge of the biochemical reactions and their stoichiometric and kinetic parameters. In many practical cases, this knowledge is missing. This has led to the development of several qualitative modelling methods using information such as gene expression data coming from functional genomic experiments.

The qualitative models contemplated in this package are essentially based on the definition of *regulatory* or *influence graphs*. The components of these models differ from species and reactions used in current SBML models. For example, qualitative models typically associate discrete levels of activities with entity pools; the processes involving them cannot be described as reactions per se but rather as transitions between states. These systems can be viewed as reactive systems, which dynamics are represented by means of state transition graphs (or other Kripke structures representing, in the form of a graph, which nodes are the reachable states and the edges are the state transitions). In this context, logical regulatory networks (Boolean or multi-valued) Kauffman (1969); Thomas (1991) and standard Petri nets Chaouiya (2007) are the two formalisms mostly used in biology that give rise to such behaviours. Published models using these approaches cover, far from exhaustiveness, gene regulatory networks and signalling pathways (e.g. Albert and Othmer (2003); Calzone et al. (2010); Fauré et al. (2006); Helikar et al. (2008); Mendoza and Xenarios (2006); Naldi et al. (2010); Sánchez and Thieffry (2003); Thieffry and Thomas (1995)), metabolic pathways (see review in Chaouiya (2007)).

Finally, because their dynamics can be abstracted by Kripke structures, models expressed as systems of piece-wise linear differential equations Batt et al. (2005), may be covered by this package, provided some extension. Specific classes of high-level Petri nets may also be contemplated in the future (see Section B).

Despite differences from traditional SBML models, it is desirable to bring these classes of models under a common format scheme. The purpose of this Qualitative Models package for SBML Level 3 is to support encoding qualitative models in SBML.

1.2 Package dependencies

The QualitativeModels package has no dependencies on other SBML Level 3 packages. (If you find incompatibilities with other packages, please contact the Package Working Group. Contact information is shown on the front page of this document.)

1.3 Document conventions

Following the precedent set by the SBML Level 3 Core specification document (Hucka et al., 2010), we use UML 1.0 (Unified Modeling Language; Eriksson and Penker 1998; Oestereich 1999) class diagram notation to define the constructs provided by this package. We also use color in the diagrams to carry additional information for the benefit of those viewing the document on media that can display color. The following are the colors we use and what they represent:

- *Black*: Items colored black in the UML diagrams are components taken unchanged from their definition in the SBML Level 3 Core specification document.
- *Green*: Items colored green are components that exist in SBML Level 3 Core, but are extended by this package. Class boxes are also drawn with dashed lines to further distinguish them.
- *Blue*: Items colored blue are new components introduced in this package specification. They have no equivalent in the SBML Level 3 Core specification.

We also use the following typographical conventions to distinguish the names of objects and data types from other entities; these conventions are identical to the conventions used in the SBML Level 3 Core specification document:

AbstractClass: Abstract classes are never instantiated directly, but rather serve as parents of other classes. Their names begin with a capital letter and they are printed in a slanted, bold, sans-serif typeface. In electronic document formats, the class names defined within this document are also hyperlinked to their definitions; clicking on these items will, given appropriate software, switch the view to the section in this document containing the definition of that class. (However, for classes that are unchanged from their definitions in SBML Level 3 Core, the class names are not hyperlinked because they are not defined within this document.)

Class: Names of ordinary (concrete) classes begin with a capital letter and are printed in an upright, bold, sans-serif typeface. In electronic document formats, the class names are also hyperlinked to their definitions in this specification document. (However, as in the previous case, class names are not hyperlinked if they are for classes that are unchanged from their definitions in the SBML Level 3 Core specification.)

`SomeThing`, `otherThing`: Attributes of classes, data type names, literal XML, and generally all tokens *other* than SBML UML class names, are printed in an upright typewriter typeface. Primitive types defined by SBML begin with a capital letter; SBML also makes use of primitive types defined by XML Schema 1.0 (Biron and Malhotra, 2000; Fallside, 2000; Thompson et al., 2000), but unfortunately, XML Schema does not follow any capitalization convention and primitive types drawn from the XML Schema language may or may not start with a capital letter.

For other matters involving the use of UML and XML, we follow the conventions used in the SBML Level 3 Core specification document.

2 Background and context

It is possible to represent some qualitative models using SBML Level 2 or indeed SBML Level 3 Core. However, after several attempts, experience showed that the possible confusion caused by the presence of irrelevant attributes and the need to reinterpret the semantics of some SBML elements could lead to ambiguity. At this point the decision was made to develop an SBML Level 3 package that captured the nature of qualitative models.

A first proposal was written in August 2008 by Duncan Berenguier and Nicolas Le Novère and discussed during a dedicated meeting on the 12th and 13th of August 2008. This meeting brought together a number of people who specialised in qualitative modelling. A summary of the meeting is available at http://www.ebi.ac.uk/compneur/xwiki/bin/view/SBML/L3F which also provides a link to the revised proposal document that was produced as a result of this meeting.

A secondary, but very valuable, outcome of this meeting was the formation of the Common Logical Modelling Toolbox (CoLoMoTo) community. A community that focuses on logical modelling but who are committed to making their models exchangeable and reusable as widely as possible. This small focussed community then took control of developing the SBML L3 Qualitative Models package.

The first CoLoMoTo meeting was held at Oeiras, Portugal in November 2010 (see http://compbio.igc.gulbenkian.pt/nmd/node/30, for the program and participants). A revised version of the proposal was discussed and a formal SBML L3 proposal document was written and circulated as a result of these and other discussions. This document is available at http://sbml.org/images/6/61/SBML-L3-qual-proposal_2.1.pdf.

The proposal was voted on and accepted by the SBML community (June 2011) and a dedicated discussion list set up (https://lists.sourceforge.net/lists/listinfo/sbml-qual). The package was presented at COMBINE 2011.

A second CoLoMoTo meeting took place in March 2012 (see http://co.mbine.org/colomoto/meetings/2012). During this meeting it was decided that there were parts of the proposal that had been introduced in anticipation of the future development of models. Whilst these are valuable aspects of the proposal there is no software supporting these features as yet. It was therefore decided to remove these features from a version 1 specification and reconsider them in the future for subsequent versions of the Qualitative Models package. A summary of these features is given in Appendix Section B of this document.

Hence, the current specification covers the needs to handle logical models. It is worth noting that no serious attempt to use this specification for standard PN models has been made so far.

3 Package syntax and semantics

In this section, we define the syntax and semantics of the Qualitative Models package for SBML Level 3 Version 1. We expound on the various data types and constructs defined in this package, then in Section 4 on page 15, we provide complete examples of using the constructs in example SBML models.

3.1 Namespace URI and other declarations necessary for using this package

Every SBML Level 3 package is identified uniquely by an XML namespace URI. For an SBML document to be able to use a given SBML Level 3 package, it must declare the use of that package by referencing its URI. The following is the namespace URI for this version of the Qualitative Models package for SBML Level 3 Version 1:

"`http://www.sbml.org/sbml/level3/version1/qual/version1`"

In addition, SBML documents using a given package must indicate whether understanding the package is required for complete mathematical interpretation of a model, or whether the package is optional. This is done using the attribute `required` on the `<sbml>` element in the SBML document. For the Qualitative Models package, the value of this attribute must be set to "`true`".

The following fragment illustrates the beginning of a typical SBML model using SBML Level 3 Version 1 and this version of the Qualitative Models package:

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns="http://www.sbml.org/sbml/level3/version1/core" level="3" version="1"
      xmlns:qual="http://www.sbml.org/sbml/level3/version1/qual/version1" qual:required="true">
```

3.2 Primitive data types

Section 3.1 of the SBML Level 3 specification defines a number of primitive data types and also uses a number of XML Schema 1.0 data types (Biron and Malhotra, 2000). We assume and use some of them in the rest of this specification, specifically `boolean`, `ID`, `SId`, `SIdRef`, and `string`. The Qualitative Model package defines other primitive types; they are described below.

3.2.1 *Type* `sign`

The `sign` is an enumeration of values used to indicate direction of an **Input** within the system. The possible values are `positive`, `negative`, `dual` and `unknown`.

3.2.2 *Type* `transitionInputEffect`

The `transitionInputEffect` is an enumeration of values used to indicate the effect of an **Input Transition** within the system. The possible values are `none` and `consumption`.

3.2.3 *Type* `transitionOutputEffect`

The `transitionOutputEffect` is an enumeration of values used to indicate the effect of an **Output Transition** within the system. The possible values are `production` and `assignmentLevel`.

3.3 Qualitative modelling

Before describing the classes and their attributes that have been used by this Qualitative Models Specification it is worth clarifying the intended meaning of some of the terms used.

3.3.1 Levels

The entities being modelled have a *level* associated with them that indicates the current state of the entity.

A *level* may be a boolean but may also represent more than two states and thus is considered to be an integer. In the case of the entity being a boolean its allowed levels would be "`0`" or "`1`"; but in other cases it may have any number of levels i.e. integer values up to and including a maximum.

In future versions of the Qualitative Modelling specification, it is intended to introduce a means of specifying symbols to represent any value that might be appropriate in the model (see Appendix Section B).

3.3.2 Transitions

Qualitative Models consider *transitions* that alter the levels of entities involved in the model, depending on the level of some other entities. This may involve the level of an entity being increased or decreased by a fixed amount; the level remaining unchanged; or the level being reassigned to an alternate value. Transitions occur when a set of conditions is met. These conditions may involve the levels falling above or below a given *threshold*.

A simple example of this is the case where there are two entities A and B and the model states that when the level of A exceeds "`1`" (the threshold), the level of B is increased by "`1`".

3.3.3 FunctionTerms

The resulting value of an entity affected by a transition may have several possibilities that are governed by a number of conditions. Each transition can have a list of conditional functions *functionTerms*, each associated with a result that allow the user to specify sets of piecewise conditions. For example a model may wish to encode the following

$$B = \begin{cases} B+1 & \text{if } A < 1 \\ B & \text{if } 1 <= A < 3 \\ B+2 & \text{otherwise} \end{cases}$$

In this case the **Transition** would have a **FunctionTerm** for each of the first two conditions and a **DefaultTerm** for the otherwise component.

3.4 The extended Model class

The extension of SBML Level 3 Core's **Model** class is relatively straightforward: the Qualitative Models Package adds two lists, one for holding qualitativeSpecies (`listOfQualitativeSpecies`, of class **ListOfQualitativeSpecies**), and the other for holding transitions (`listOfTransitions`, of class **ListOfTransitions**). Figure 1 on the next page provides the UML diagram.

The **Model** element may contain at most one **ListOfQualitativeSpecies**, which must contain at least one **QualitativeSpecies**. It may also contain at most one **ListOfTransitions** which must contain at least one **Transition**.The **QualitativeSpecies** class and the **Transition** class are defined in Section 3.5 on the following page and Section 3.6 on page 9 respectively.

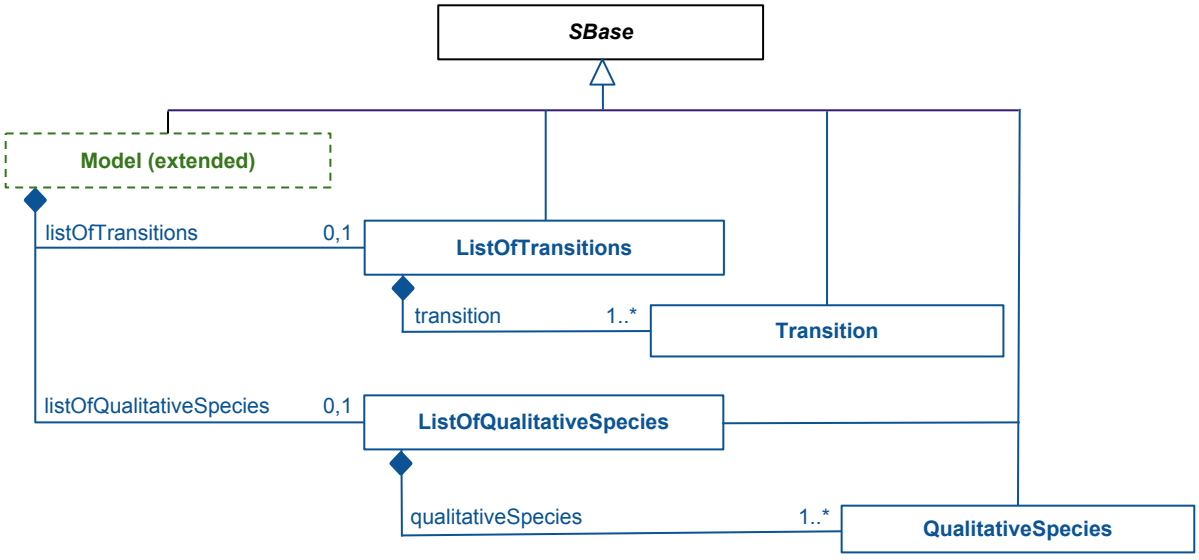

Figure 1: *The definitions of the extended **Model** class. In other respects, **Model** remains defined as in the SBML Level 3 Core specification.*

3.5 The QualitativeSpecies class

Similarly to the **Species** in SBML, the components of qualitative models refer to pools of entities that are considered indistinguishable and are each located in a specific **Compartment**. However, here components are characterised by their qualitative influences rather than by taking part in reactions. Therefore, we define the **QualitativeSpecies** element to represent such pools of entities.

In a Petri net, *qualitative species* refer to the places of the model, while in a logical model, they refer to the variables of this model (i.e. nodes of the influence graph).

A **QualitativeSpecies** describes a pool of indistinguishable entities in a **Compartment**. It is associated with a `level` (an integer representing e.g. an activity state, or a functional level of concentration, etc) These objects classes are defined in Figure 2.

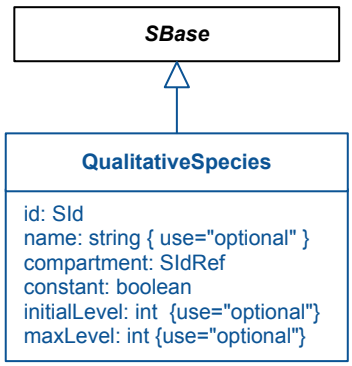

Figure 2: *The definitions of the **QualitativeSpecies** class.*

The `id` *attribute*

The `id` attribute takes a required value of type `SId`. The `id` is used as an identifier for the particular **QualitativeSpecies**. It can be used as a <ci> element within MathML, in which case it it interpreted as the *level* of this **QualitativeSpecies**.

The `name` *attribute*

A **QualitativeSpecies** also has an optional `name` attribute of type `string`. The `name` attribute should be used in the same manner as on SBML Level 3 Core objects; see Section 3.3.2 of the SBML Level 3 Version 1 Core specification for more information.

The `compartment` *attribute*

The required attribute `compartment`, of type `SIdRef`, is used to identify the compartment in which the qualitativeSpecies is located. The attribute's value must be the identifier of an existing **Compartment** object in the model. This attribute is comparable with the `compartment` attribute on the **Species** element.

The `constant` *attribute*

The required attribute `constant`, of type `boolean`, is used to indicate that the `level` of the qualitativeSpecies is fixed or can be varied. This attribute is comparable with the `constant` attribute on the **Species** element.

Typically, in a regulatory or influence graph a **QualitativeSpecies** may receive no interaction and if so, would appear only as an **Input** in the model and have the value of the `constant` attribute set to "`true`". In other influence graphs or in Petri Net models a **QualitativeSpecies** may occur as an **Input** whose level is changed by the **Transition** and would have `constant` set to "`false`". The nature of changes to a **QualitativeSpecies** resulting from a **Transition** is also recorded using the `transitionEffect` attribute on the **Input** (see section Section 3.6.1) and may be set to "`none`" to indicate there is no change. This duplication of information provides a means of validating the modeller's intent and also allows entities on the borders of a system to be easily identified.

The `initialLevel` *attribute*

The `initialLevel` is an `integer` that defines the initial *level* of the **QualitativeSpecies** in its **Compartment**. This attribute is optional but if set it cannot exceed the value of the `maxlevel` attribute, if this has been set.

The `maxLevel` *attribute*

The `maxLevel` is an `integer` that sets the maximal *level* of the **QualitativeSpecies**. This attribute is optional but when set, the *level* of the **QualitativeSpecies** must not exceed this value at any point in a simulation.

In Petri nets, this attribute is meant to define place capacities. Hence, a transition is not enabled if the value resulting from its firing would exceed the `maxLevel` of one of its output places.

In logical models, the `maxLevel` should be coherent with the `resultLevel` values in the function terms defined for the corresponding transition, i.e. the model should not contain a **FunctionTerm** that attempts to set a *level* that exceeds this value.

This attribute is can also be used to indicate the range of possible levels for a **QualitativeSpecies** whose `constant` attribute is true. This may seem a little contradictory, since if the `constant` attribute is true then the level associated with the **QualitativeSpecies** cannot vary. However, it provides additional information regarding the possible levels particularly in the case where no `initialLevel` has been set.

3.6 The Transition class

A **Transition** element contains at most one **ListOfInputs** and one **ListOfOutputs** and exactly one **ListOfFunctionTerms**. These objects classes are defined in Figure 3 on the next page.

The semantics of **Transition** is that commonly used in Petri models, while in logical models, **Transition** is used to

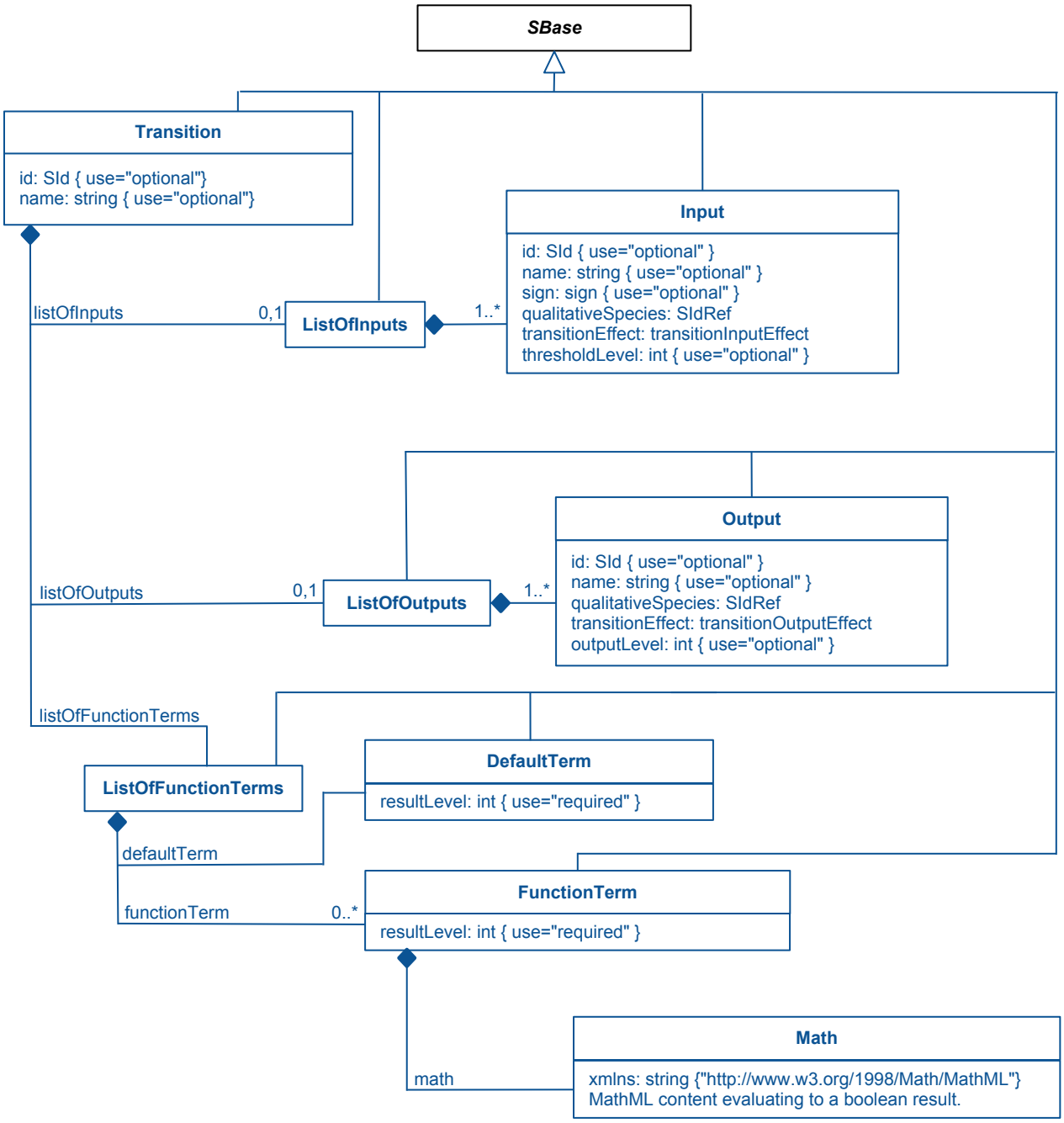

Figure 3: *The definitions of* ***Transition****,* ***Input****,* ***Output****,* ***DefaultTerm*** *and* ***FunctionTerm*** *classes. Note that the* ***DefaultTerm*** *class is not derived from SBase.*

specify the logical rule associated to a **QualitativeSpecies** (that appears as an **Input** of this **Transition**). Hence, in principle, there is at most one **Transition** defined for each component of the model. Note however, that input components, whose `constant` attribute is set to true, have no associated **Transition**.

The `id` *attribute*

A **Transition** element has an optional `id` attribute of type `SId`. In constrast to most SBML classes the `id` attribute on a **Transition** has no mathematical interpretation.

The `name` *attribute*

There is an optional `name` attribute of type `string` that should be used in the same manner as on SBML Level 3 Core objects; see Section 3.3.2 of the SBML Level 3 Version 1 Core specification for more information.

3.6.1 The Input class

The **ListOfInputs** contains at least one element of type **Input**. Each **Input** refers to a **QualitativeSpecies** that participates in the corresponding **Transition**. In Petri nets, these are the input places of the transition. In logical models, they are the regulators of the species whose behaviour is defined by the transition.

The `id` *attribute*

An **Input** element has an optional `id` attribute of type `SId`. The identifier of an **Input** can be used as a <ci> element within MathML, in which case it it interpreted as the `thresholdLevel`.

The `name` *attribute*

There is an optional `name` attribute of type `string` that should be used in the same manner as on SBML Level 3 Core objects; see Section 3.3.2 of the SBML Level 3 Version 1 Core specification for more information.

The `qualitativeSpecies` *attribute*

The required attribute `qualitativeSpecies`, of type `SIdRef`, is used to identify the **QualitativeSpecies** that is the *input* of this **Transition**. The attribute's value must be the identifier of an existing **QualitativeSpecies** object in the model. This attribute is comparable with the `species` attribute on the **SpeciesReference** element.

The `thresholdLevel` *attribute*

The `thresholdLevel` is a `integer` that can be used to set the threshold level of the particular input. This attribute relates to the contribution of this input required for the transition to take place. In logical regulatory models, it refers to the threshold level above which the regulation takes place, while in a Petri net, it refers to the number of tokens required to enable to transition (weight of the arc connecting the input place to the transition). When defined, this attribute should be coherent with the content of the **FunctionTerm**.

The `thresholdLevel` is used by the FunctionTerms associated with the containing **Transition** to determine the applicable `resultLevel` that should be applied. The `id` of the **Input** represents this value and can be used in the `math` element of a **FunctionTerm**. When defined, this attribute should be coherent with the content of the **FunctionTerm**, *i.e.* if a *number* is used in the **FunctionTerm** to compare the current *level* of a species, this number must correspond to the `thresholdLevel` of the corresponding **Input**.

The `transitionEffect` *attribute*

Each **Input** has a required attribute `transitionEffect` of type `transitionInputEffect` which describes how the **QualitativeSpecies** referenced by the **Input** is affected by the **Transition**. Table 1 shows the possible values with the interpretation of each value.

TransitionInputEffect	Interpretation
`none`	The level associated with the `qualitativeSpecies` is not modified.
`consumption`	The level of the `qualitativeSpecies` is decreased by the `resultLevel` of the selected term possibly modified by the `thresholdLevel` of the **Input**.

Table 1: *Interpretation of the* `transitionEffect` *attribute on an* ***Input****.*

The following example illustrates the interpretation of the transitionEffect attribute.

```
<listOfInputs>
    <input qualitativeSpecies="A"   transitionEffect="none"        thresholdLevel="2" />
    <input qualitativeSpecies="B"   transitionEffect="consumption"/>
    <input qualitativeSpecies="C"   transitionEffect="consumption" thresholdLevel="2" />
</listOfInputs>
```

In the case of qualitativeSpecies "A" the `level` is unaltered by the **Transition** and hence the `transitionEffect` attribute is set to "`none`".

The `level` of qualitativeSpecies "B" is reduced; hence the `transitionEffect` is "`consumption`". The `level` is reduced by the value of the `resultLevel` from the whichever **FunctionTerm** is applicable (see Section 3.6.5).

Similarly, the `level` of "C" is also reduced, but on this occasion by 2 (the `threholdLevel`) times the appropriate `resultLevel` .

It should be noted that in logical models the `transitionEffect` is always set to "`none`", while in Petri nets, it can be set to "`none`" (indicating a read arc) or to "`consumption`". The Petri net example in Section 4 provides further example of the use of the `transitionEffect` and `thresholdLevel` attributes.

The `sign` *attribute*

The `sign` of type `sign` can be used as an indication as to whether the contribution of this input is positive, negative, both (dual) or unknown. The sign is usually used for visualization purposes only. This attribute is optional.

3.6.2 The Output class

The **ListOfOutputs** contains at least one element of type **Output**.

Each **Output** refers to a **QualitativeSpecies** that participates in (is affected by) the corresponding **Transition**. When a **Transition** has several outputs, it is because the referenced species share the same regulators and the same logical rules.

In a logical model, a **QualitativeSpecies** should be referenced in at most one **ListOfOutputs**, (that of the **Transition** defining the evolution of this species). This restriction is discussed in more detail in Section 5

The `id` *attribute*

An **Output** element has an optional `id` attribute of type `SId`. The identifier of an **Output** can be used as a <ci> element within MathML, in which case it it interpreted as the `outputLevel`.

The `name` *attribute*

There is an optional `name` attribute of type `string` that should be used in the same manner as on SBML Level 3 Core objects; see Section 3.3.2 of the SBML Level 3 Version 1 Core specification for more information.

The `qualitativeSpecies` *attribute*

The required attribute `qualitativeSpecies`, of type `SIdRef`, is used to identify the **QualitativeSpecies** that is the *output* of this **Transition**. The attribute's value must be the identifier of an existing **QualitativeSpecies** object in the model. This attribute is comparable with the `species` attribute on the **SpeciesReference** element.

The `outputLevel` *attribute*

The `outputLevel` is an `integer` used along with the `transitionEffect` to specify the effect of the **Transition** on the corresponding **QualitativeSpecies**. This attribute is optional. It has no use in logical models. In Petri nets, it relates to the weight of the arc connecting the transition to the output place.

The `transitionEffect` *attribute*

Each **Output** has a required attribute `transitionEffect` of type `transitionOutputEffect` which describes how the **QualitativeSpecies** referenced by the **Output** is affected by the **Transition**. Table 2 shows the possible values with the interpretation of each value.

TransitionOutputEffect	Interpretation
`production`	The level of the `qualitativeSpecies` is increased by the `resultLevel` of the selected term possibly modified by the `outputLevel` of the **Output**.
`assignmentLevel`	The level of the `qualitativeSpecies` is set to the `resultLevel` of the selected term.

Table 2: *Interpretation of the* `transitionEffect` *attribute on an* ***Output****.*

The following example illustrates the interpretation of the transitionEffect attribute. In the case of qualitativeSpecies "`A`" the `level` is assigned the `resultLevel` from the whichever **FunctionTerm** is applicable, whereas the `level` of qualitativeSpecies "`B`" is increased by `resultLevel`. Similarly, the `level` of "`C`" is increased by 2 (`outputlevel`) times `resultLevel` (see also Petri net example in Section 4).

```
<listOfOutputs>
    <output qualitativeSpecies="A"   transitionEffect="assignmentLevel"/>
    <output qualitativeSpecies="B"   transitionEffect="production"/>
    <output qualitativeSpecies="C"   transitionEffect="production"  outputLevel="2" />
</listOfInputs>
```

In logical models the `transitionEffect` is set to "`assignmentLevel`" whilst in standard PetriNets it is set to "`production`". It is envisioned that to encode High level PetriNets it will be necessary to allow the use of "`assignmentLevel`" as an **Output** `transitionEffect`; however that is beyond the scope of the current specification.

3.6.3 The ListOfFunctionTerms class

The **ListOfFunctionTerms** may contain any number of **FunctionTerm** elements, and exactly one **DefaultTerm**. Each **FunctionTerm** encodes the conditions under which this term is selected. The **DefaultTerm** describes the result of the **Transition** applied by default (*i.e.* when no term evaluates to "`true`").

3.6.4 The DefaultTerm class

The **DefaultTerm** defines the default result of a **Transition**. This term is used if there are no other **FunctionTerm** elements or if none of the **Math** elements of the **FunctionTerm** elements evaluates to "`true`".

The `resultLevel` *attribute*

The default result is described by a `resultLevel`. This attribute is required.

The `resultLevel` is an `integer` describing a level. The `resultLevel` is used; possibly together with the `thresholdLevel` or `outputLevel` to determine the level of a **QualitativeSpecies** resulting from the **Transition**.

3.6.5 The FunctionTerm class

Each **FunctionTerm** is also associated with a result and in addition to a Boolean function inside a **Math** element that can be used to set the conditions under which this term is selected.

The `resultLevel` *attribute*

The result of the term is described by a the required attribute `resultLevel`.

The `resultLevel` is an `integer` describing a level. The `resultLevel` is used; possibly together with the `thresholdLevel`

or `outputLevel` to determine the level of a **QualitativeSpecies** resulting from the **Transition**.

The Math element:

Each **FunctionTerm** holds a `boolean` function encoded in a **Math** element, using the subset of MathML 2.0 as defined in SBML L3v1 Section 3.4.6. This element encodes the conditions under which the **FunctionTerm** is selected. When the **Math** element contains the identifier of a **QualitativeSpecies**, **Input** or **Output**, this identifier represents the level, `thresholdLevel` or `outputLevel` of the corresponding element. It should be noted that for the purposes of this specification these all have integer values. This specification does not preclude the use of these identifiers to represent `true` or `false`; however it is highly recommended that any the `math` element unambiguously returns a `boolean` function. Tools should take care to specify how integer values will be interpreted in relation to boolean constructs.

3.6.6 Mathematical interpretation of Transitions and FunctionTerms

In the Qualitative Models package, *transitions* are the central mechanism for describing processes that change the levels of the qualitative species of the model. Here, we clarify their interpretation in the framework of logical modelling.

The *function terms* of a **Transition** define the transition function one **QualitativeSpecies**, *i.e.* its state transitions that depend on the levels of the species that appear as input of that transition (its "regulators"). The *function terms* together with the *default term* thus define a state transition table indicating what level the qualitative species will move to (target level), based on the current level of its regulators. In the case of multi-valued (as opposed to Boolean), this evolution proceeds step-wise towards the target level, *i.e.* each component of two successor states of the system differ at most by 1. The **QualitativeSpecies** affected by the **Transition** is referenced by the **Output** element. In the situation where there is more than one **Output** listed, the referenced species share the same regulators and the same logical rules.

The model must be fully defined. Whatever the state of the system, one single value must apply (that of the **DefaultTerm** or the `resultLevel` of a **FunctionTerm**). More than one **FunctionTerm** can share the same `resultLevel`, which is the equivalent to a single term holding the **disjunction** (OR) of all these terms. There should be no conflicting terms: whenever multiple function terms apply (are true), their `resultLevel` should be the same.

It should be noted that the *level* associated with a **QualitativeSpecies** has values from 0 up to the `maxLevel` (where declared). The mathematics of the model (i.e. the **FunctionTerm** and **DefaultTerm** element together with the `transitionEffect`) should not allow the emph level to either become negative or exceed the maximum.

Importantly, given a model, one has then to choose an updating policy that defines how enabled transitions are processed (synchronously, asynchronously, etc.). However, this information is not part of the model *per se*.

3.7 Namespace scoping rules for identifiers

The values of any `id` attribute of type `SId` within the qual namespace are considered to have the same scope as the `id` attribute in the core SBML namespace. Thus the values of the attributes `id` and `qual:id` must be unique across the set of all `id` and `qual:id` attribute values of all objects in a model. In addition to those classes of objects specifed in the SBML Level 3 Version 1 Core specification; **Model**, **FunctionDefinition**, **Compartment**, **Species**, **Reaction**, **SpeciesReference**, **ModifierSpeciesReference**, **Event**, and **Parameter** objects, this includes the following objects from this Qualitative Modelling package: **QualitativeSpecies**, **Transition**, **Input** and **Output**.

4 Examples

This proposal mainly covers logical models but it can also handle standard Petri nets. We provide one toy example of each and the logical model of the decision between lysis and lysogenization in temperate bacteriophage as defined in Thieffry and Thomas (1995).

4.1 Simple Logical Regulatory Graph

The following example shows a simple LRG with 3 regulators A, B and C, where A can take three values ($A = \{0, 1, 2\}$), and B,C are Boolean. Moreover, A positively regulates B, which positively regulates C, which positively regulates A. In turn A activates itself at level 1 but inhibits itself at a higher level (2) as illustrated by Figure 4.

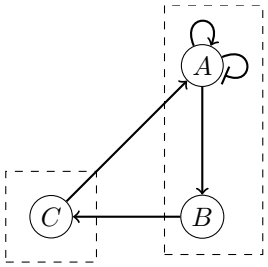

Figure 4: *A simple Logical Regulatory Network.*

The logical functions are the following:

$$A_{t+1} := \begin{cases} 2 & \text{if } (1 <= A_t < 2) \text{ or } ((C_t >= 1) \text{ and } (A_t >= 1)) \\ 1 & \text{if } (A_t < 1) \text{ and } (C_t >= 1) \\ 0 & \text{otherwise} \end{cases} \quad B_{t+1} := \begin{cases} 1 & \text{if } A_t >= 1 \\ 0 & \text{otherwise} \end{cases} \quad C_{t+1} := \begin{cases} 1 & \text{if } B_t >= 1 \\ 0 & \text{otherwise} \end{cases}$$

The state transition tables are thus:

A_t	C_t	A_{t+1}
0	0	0
0	1	1
1	0	2
1	1	2
2	0	0
2	1	2

A_t	B_{t+1}
0	0
1	1
2	1

B_t	C_{t+1}
0	0
1	1

```
<?xml version="1.0" encoding="UTF8"?>
<sbml xmlns="http://www.sbml.org/sbml/level3/version1/core" level="3" version="1"
      xmlns:qual="http://www.sbml.org/sbml/level3/version1/qual/version1" qual:required="true">

    <model id="example">

        <listOfCompartments>
            <compartment id="cytosol" name="cytosol" constant="true"/>
            <compartment id="nucleus" name="nucleus" constant="true"/>
        </listOfCompartments>
```

```
<qual:listOfQualitativeSpecies>
    <qual:qualitativeSpecies qual:compartment="cytosol" qual:constant="false"
                             qual:id="A" qual:maxLevel="2"/>
    <qual:qualitativeSpecies qual:compartment="cytosol" qual:constant="false"
                             qual:id="B" qual:maxLevel="1"/>
    <qual:qualitativeSpecies qual:compartment="nucleus" qual:constant="false"
                             qual:id="C" qual:maxLevel="1"/>
</qual:listOfQualitativeSpecies>

<qual:listOfTransitions>

    <qual:transition qual:id="tr_B">
        <qual:listOfInputs>
            <qual:input qual:id="theta_B_A"     qual:qualitativeSpecies="A"
                        qual:thresholdLevel="1"  qual:transitionEffect="none"
                        qual:sign="positive"/>
        </qual:listOfInputs>

        <qual:listOfOutputs>
            <qual:output qual:transitionEffect="assignmentLevel"
                         qual:qualitativeSpecies="B"/>
        </qual:listOfOutputs>

        <qual:listOfFunctionTerms>
            <qual:functionTerm qual:resultLevel="1">
                <math xmlns="http://www.w3.org/1998/Math/MathML">
                    <!-- A >= 1-->
                    <apply>
                        <geq/>
                        <ci>A</ci>
                        <ci>theta_B_A</ci>
                    </apply>
                </math>
            </qual:functionTerm>
            <qual:defaultTerm qual:resultLevel="0"/>
        </qual:listOfFunctionTerms>
    </qual:transition>

    <qual:transition qual:id="tr_A">
        <qual:listOfInputs>
            <qual:input qual:id="theta_A_A1"     qual:qualitativeSpecies="A"
                        qual:thresholdLevel="1"  qual:transitionEffect="none"
                        qual:sign="positive"/>
            <qual:input qual:id="theta_A_A2"     qual:qualitativeSpecies="A"
                        qual:thresholdLevel="2"  qual:transitionEffect="none"
                        qual:sign="negative"/>
            <qual:input qual:id="theta_A_C"     qual:qualitativeSpecies="C"
                        qual:thresholdLevel="1"  qual:transitionEffect="none"
                        qual:sign="positive"/>
        </qual:listOfInputs>
        <qual:listOfOutputs>
            <qual:output qual:qualitativeSpecies="A"
                         qual:transitionEffect="assignmentLevel"/>
```

```
                </qual:listOfOutputs>

                <qual:listOfFunctionTerms>
                    <qual:functionTerm qual:resultLevel="2">
                        <math xmlns="http://www.w3.org/1998/Math/MathML">
                            <!-- (A >= 1 and A < 2) or (C >= 1 and A >= 1)-->
                            <apply>
                                <or/>
                                <apply>
                                    <and/>
                                    <apply>
                                        <geq/>
                                        <ci>A</ci>
                                        <ci>theta_A_A1</ci>
                                    </apply>
                                    <apply>
                                        <lt/>
                                        <ci>A</ci>
                                        <ci>theta_A_A2</ci>
                                    </apply>
                                </apply>
                                <apply>
                                    <and/>
                                    <apply>
                                        <geq/>
                                        <ci>C</ci>
                                        <ci>theta_A_C</ci>
                                    </apply>
                                    <apply>
                                        <geq/>
                                        <ci>A</ci>
                                        <ci>theta_A_A1</ci>
                                    </apply>
                                </apply>
                            </apply>
                        </math>
                    </qual:functionTerm>
                    <qual:functionTerm qual:resultLevel="1">
                        <math xmlns="http://www.w3.org/1998/Math/MathML">
                            <!-- (A < 1) and C >= 1 -->
                            <apply>
                                <and/>
                                <apply>
                                    <lt/>
                                    <ci>A</ci>
                                    <ci>theta_A_A1</ci>
                                </apply>
                                <apply>
                                    <geq/>
                                    <ci>C</ci>
                                    <ci>theta_A_C</ci>
                                </apply>
                            </apply>
                        </math>
                    </qual:functionTerm>
                    <qual:defaultTerm qual:resultLevel="0"/>
```

```
                </qual:listOfFunctionTerms>
            </qual:transition>
            <qual:transition qual:id="tr_C">
                <qual:listOfInputs>
                    <qual:input qual:id="theta_C_B"      qual:qualitativeSpecies="B"
                                qual:thresholdLevel="1"  qual:transitionEffect="none"
                                qual:sign="positive"/>
                </qual:listOfInputs>
                <qual:listOfOutputs>
                    <qual:output qual:qualitativeSpecies="C"
                                 qual:transitionEffect="assignmentLevel"/>
                </qual:listOfOutputs>
                <qual:listOfFunctionTerms>
                    <qual:functionTerm qual:resultLevel="1">
                        <math xmlns="http://www.w3.org/1998/Math/MathML">
                            <!-- B >= 1-->
                            <apply>
                                <geq/>
                                <ci>B</ci>
                                <ci>theta_C_B</ci>
                            </apply>
                        </math>
                    </qual:functionTerm>
                    <qual:defaultTerm qual:resultLevel="0"/>
                </qual:listOfFunctionTerms>
            </qual:transition>
        </qual:listOfTransitions>
    </model>
</sbml>
```

Listing 1: *Logical Regulatory Graph example*

4.2 Simple Petri net

The following example shows a simple, standard Petri net, with 4 places A, B, C and D and one transition $t1$ as depicted in Figure 5.

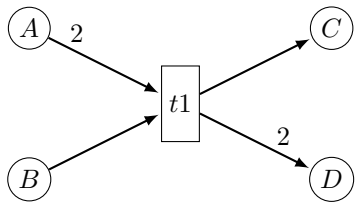

Figure 5: *A Petri net model.*

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns="http://www.sbml.org/sbml/level3/version1/core" level="3" version="1"
      xmlns:qual="http://www.sbml.org/sbml/level3/version1/qual/version1" qual:required="true">
    <model id="PN_exemple">
        <listOfCompartments>
```

```
            <compartment id="default" constant="true"/>
        </listOfCompartments>
        <qual:listOfQualitativeSpecies>
            <qual:qualitativeSpecies qual:id="A"            qual:compartment="default"
                                     qual:initialLevel="2"  qual:constant="false"/>
            <qual:qualitativeSpecies qual:id="B"            qual:compartment="default"
                                     qual:initialLevel="4"  qual:constant="false"/>
            <qual:qualitativeSpecies qual:id="C"            qual:compartment="default"
                                     qual:initialLevel="2"  qual:constant="false"/>
            <qual:qualitativeSpecies qual:id="D"            qual:compartment="default"
                                     qual:initialLevel="3"  qual:constant="false"/>
        </qual:listOfQualitativeSpecies>
        <qual:listOfTransitions>
            <qual:transition qual:id="t1">
                <qual:listOfInputs>
                    <qual:input qual:id="t1_A"          qual:qualitativeSpecies="A"
                                qual:thresholdLevel="2" qual:transitionEffect="consumption" />
                    <qual:input qual:id="t1_B"          qual:qualitativeSpecies="B"
                                qual:thresholdLevel="1" qual:transitionEffect="consumption" />
                </qual:listOfInputs>
                <qual:listOfOutputs>
                    <qual:output qual:qualitativeSpecies="C" qual:outputLevel="1"
                                 qual:transitionEffect="production" />
                    <qual:output qual:qualitativeSpecies="D" qual:outputLevel="2"
                                 qual:transitionEffect="production" />
                </qual:listOfOutputs>
                <qual:listOfFunctionTerms>
                    <qual:functionTerm qual:resultLevel="1">
                        <math xmlns="http://www.w3.org/1998/Math/MathML">
                            <!-- A >= 2 and B >= 1 -->
                            <apply>
                                <and />
                                <apply>
                                    <geq />
                                    <ci>A</ci>
                                    <ci>t1_A</ci>
                                </apply>
                                <apply>
                                    <geq />
                                    <ci>B</ci>
                                    <ci>t1_B</ci>
                                </apply>
                            </apply>
                       </math>
                    </qual:functionTerm>
                    <qual:defaultTerm qual:resultLevel="0" />
                </qual:listOfFunctionTerms>
            </qual:transition>
        </qual:listOfTransitions>
    </model>
</sbml>
```

Listing 2: *Petri net example*

4.3 Logical model of the immunity control in bacteriophage lambda

This last example is the multi-valued, logical model as defined in Thieffry and Thomas (1995) for the core network controlling the decision between lysis and lysogeny in temperate bacteriophage.

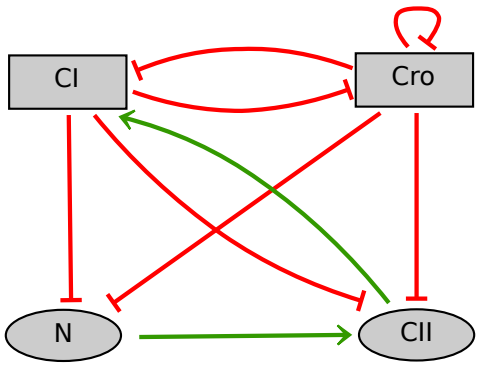

Figure 6: *Interaction graph of the four-variable multi-valued model of phage lambda switch Thieffry and Thomas (1995).*

```
<?xml version="1.0" encoding="UTF8"?>
<sbml xmlns="http://www.sbml.org/sbml/level3/version1/core" level="3" version="1"
      xmlns:qual="http://www.sbml.org/sbml/level3/version1/qual/version1" qual:required="true">
    <model id="phage_lambda">
        <listOfCompartments>
            <compartment id="comp1" constant="true"/>
        </listOfCompartments>

        <qual:listOfQualitativeSpecies>

            <qual:qualitativeSpecies qual:id="s_Cl"     qual:compartment="comp1"
                                     qual:maxLevel="2"  qual:constant="false"/>
            <qual:qualitativeSpecies qual:id="s_Cro"    qual:compartment="comp1"
                                     qual:maxLevel="3"  qual:constant="false"/>
            <qual:qualitativeSpecies qual:id="s_Cll"    qual:compartment="comp1"
                                     qual:maxLevel="1"  qual:constant="false"/>
            <qual:qualitativeSpecies qual:id="s_N"      qual:compartment="comp1"
                                     qual:maxLevel="1"  qual:constant="false"/>

        </qual:listOfQualitativeSpecies>

        <qual:listOfTransitions>

            <qual:transition qual:id="tr_CI">
                <qual:listOfInputs>
                    <qual:input qual:qualitativeSpecies="s_Cro"  qual:sign="negative"
                                qual:transitionEffect="none" />
                    <qual:input qual:qualitativeSpecies="s_Cll"  qual:sign="positive"
                                qual:transitionEffect="none" />
                </qual:listOfInputs>
                <qual:listOfOutputs>
                    <qual:output qual:qualitativeSpecies="s_CI"
                                 qual:transitionEffect="assignmentLevel"/>
                </qual:listOfOutputs>
                <qual:listOfFunctionTerms>
```

```
                <qual:defaultTerm qual:resultLevel="0"/>
                <qual:functionTerm qual:resultLevel="2">
                    <math xmlns="http://www.w3.org/1998/Math/MathML">
                        <apply>
                            <or/>
                            <apply>
                                <eq/>
                                <ci> s_Cro </ci>
                                <cn type="integer"> 0 </cn>
                            </apply>
                            <apply>
                                <and/>
                                <apply>
                                    <geq/>
                                    <ci> s_Cro </ci>
                                    <cn type="integer"> 1 </cn>
                                </apply>
                                <apply>
                                    <eq/>
                                    <ci> s_CII </ci>
                                    <cn type="integer"> 1 </cn>
                                </apply>
                            </apply>
                        </apply>
                    </math>
                </qual:functionTerm>
            </qual:listOfFunctionTerms>
        </qual:transition>


        <qual:transition qual:id="tr_Cro">

            <qual:listOfInputs>
                <qual:input qual:qualitativeSpecies="s_Cl"  qual:sign="negative"
                            qual:transitionEffect="none" />
                <qual:input qual:qualitativeSpecies="s_Cro"  qual:sign="negative"
                            qual:transitionEffect="none" />
            </qual:listOfInputs>

            <qual:listOfOutputs>
                <qual:output qual:qualitativeSpecies="s_Cro"
                             qual:transitionEffect="assignmentLevel"/>
            </qual:listOfOutputs>

            <qual:listOfFunctionTerms>
                <qual:defaultTerm qual:resultLevel="0"/>

                <qual:functionTerm qual:resultLevel="2">
                    <math xmlns="http://www.w3.org/1998/Math/MathML">
                        <apply>
                            <and/>
                            <apply>
                                <leq/>
                                <ci> s_CI </ci>
                                <cn type="integer"> 1 </cn>
                            </apply>
```

```
                            <apply>
                                <eq/>
                                <ci> s_Cro </ci>
                                <cn type="integer"> 3 </cn>
                            </apply>
                        </apply>
                    </math>
                </qual:functionTerm>

                <qual:functionTerm qual:resultLevel="3">
                    <math xmlns="http://www.w3.org/1998/Math/MathML">
                        <apply>
                            <and/>
                            <apply>
                                <leq/>
                                <ci> s_CI </ci>
                                <cn type="integer"> 1 </cn>
                            </apply>
                            <apply>
                                <eq/>
                                <ci> s_Cro </ci>
                                <cn type="integer"> 2 </cn>
                            </apply>
                        </apply>
                    </math>
                </qual:functionTerm>
            </qual:listOfFunctionTerms>
        </qual:transition>


        <qual:transition qual:id="tr_Cll">

            <qual:listOfInputs>
                <qual:input qual:qualitativeSpecies="s_Cl"  qual:sign="negative"
                            qual:transitionEffect="none" />
                <qual:input qual:qualitativeSpecies="s_Cro"  qual:sign="negative"
                            qual:transitionEffect="none" />
                <qual:input qual:qualitativeSpecies="s_N"  qual:sign="negative"
                            qual:transitionEffect="none" />
            </qual:listOfInputs>

            <qual:listOfOutputs>
                <qual:output qual:qualitativeSpecies="s_Cll"
                             qual:transitionEffect="assignmentLevel"/>
            </qual:listOfOutputs>

            <qual:listOfFunctionTerms>
                <qual:defaultTerm qual:resultLevel="0"/>
                <qual:functionTerm qual:resultLevel="1">
                    <math xmlns="http://www.w3.org/1998/Math/MathML">
                        <apply>
                            <and/>
                            <apply>
                                <leq/>
                                <ci> s_CI </ci>
                                <cn type="integer"> 1 </cn>
```

```
                                </apply>
                                <apply>
                                    <leq/>
                                    <ci> s_Cro </ci>
                                    <cn type="integer"> 2 </cn>
                                </apply>
                                <apply>
                                    <eq/>
                                    <ci> s_N </ci>
                                    <cn type="integer"> 1 </cn>
                                </apply>
                            </apply>
                        </math>
                    </qual:functionTerm>
                </qual:listOfFunctionTerms>
            </qual:transition>

            <qual:transition qual:id="tr_N">
                <qual:listOfInputs>
                    <qual:input qual:qualitativeSpecies="s_Cl"  qual:sign="negative"
                                qual:transitionEffect="none" />
                    <qual:input qual:qualitativeSpecies="s_Cro"  qual:sign="negative"
                                qual:transitionEffect="none" />
                </qual:listOfInputs>

                <qual:listOfOutputs>
                    <qual:output qual:qualitativeSpecies="s_N"
                                 qual:transitionEffect="assignmentLevel"/>
                </qual:listOfOutputs>

                <qual:listOfFunctionTerms>
                    <qual:defaultTerm qual:resultLevel="0"/>
                    <qual:functionTerm qual:resultLevel="1">
                        <math xmlns="http://www.w3.org/1998/Math/MathML">
                            <apply>
                                <and/>
                                <apply>
                                    <eq/>
                                    <ci> s_CI </ci>
                                    <cn type="integer"> 0 </cn>
                                </apply>
                                <apply>
                                    <leq/>
                                    <ci> s_Cro </ci>
                                    <cn type="integer"> 1 </cn>
                                </apply>
                            </apply>
                        </math>
                    </qual:functionTerm>
                </qual:listOfFunctionTerms>
            </qual:transition>
        </qual:listOfTransitions>
    </model>
</sbml>
```

Listing 3: *Phage lambda switch example*

5 Best practices

The aim of this specification is provide a common basis for modelling several different types of *qualitative* models. To facilitate this goal the elements defined have attributes that are optional in some types of models but not in others; or indeed have meaning in some contexts but not in others. Here we outline the two cases that can be modelled using the syntax of this specification.

5.1 Logical Regulatory Networks

In these models a **QualitativeSpecies** is listed as an **Input** to a **Transition** if it acts as an activator/inhibitor or regulator in that **Transition** and as an **Output** if the evolution of that **QualitativeSpecies** is governed by the **Transition** i.e. it is a *regulated* species. A **QualitativeSpecies** that is an **Output** must have a `constant` attribute set to "`false`".

The `maxLevel` attribute on the **QualitativeSpecies** can be set to indicate the possible values that the species can take. For example a boolean would have a `maxLevel` of "`1`" indicating that it could have only values of 0 and 1. The *level* of a **QualitativeSpecies** can never exceed this value and a model containing a **FunctionTerm** that assign a level exceeding the `maxLevel` is considered invalid.

In these classes of models the `transitionEffect` of the **Input** species should be set to "`none`" as the **Input** species are not altered by the transition.

The **thresholdLevel**, when specified, indicates the level at which the species participates in the transition. Any reference to the **Input** **id** attribute in a <ci> element within a functionTerm of the transition refers to the value of this **thresholdLevel**. This provides a means of encoding the statement: A transition occurs when the level of A exceeds the threshold level of B; as $A > thresholdB$ rather than $A > 1$; which may provide a modeller with additional information about the number.

The **sign** attribute indicates the type of effect on the **Output** of the **Transition** (the regulated species): "positive" (activation), "negative" (inhibition), "dual" (positive or negative depending e.g. on co-factors) or "unknown". It is optional and mainly used for graphical purposes.

At the time of writing it has been decided a **QualitativeSpecies** should only be referenced by an **Output** with a `transitionEffect` of "`assignmentLevel`" in at most one **Transition**. For logical regulatory networks, this applies to any **Output**. However, it is anticiapted that in the future the specification may be expanded and used in High level Petri Net modeling where this restriction would be prohibitive. Thus this is a recommendation rather than a requirement.

Discussions are still ongoing about the possible incoherency of the **FunctionTerm** elements and the need to avoid cumbersome descriptions. As of the writing of this specification, the following guidelines are recommended to ensure coherent definitions:

- The **FunctionTerm** elements of all the transitions targeting the same output should be "coherent": the conditions of two **FunctionTerm** elements, leading to different effects on the level of the output, should not be fulfilled at the same time(i.e. they should be exclusive).
- If several **FunctionTerm** elements lead to the same effect on the level of the same output, then the importing tool should consider the disjunction (OR) on the conditions of the terms.

5.2 Petri Nets

In Petri Net models the **QualitativeSpecies** represent places within the model. Since the initial conditions are part of the model the `initialLevel` attribute for each **QualitativeSpecies** must be set.

In order to represent an unbound place the `maxLevel` attribute of the **QualitativeSpecies** is left unset.

The **transitionEffect** of an **Input** is set to "consumption", unless this input is connected to the transition by a test arc

(meaning the transition has no effect on its marking).

The **thresholdLevel** of an **Input** indicates the weight of the arc from this place to the transition and is required. It is used to specify the enabling conditions of the transition (and to indicate the number of tokens consumed by the firing of this transition).

In this class of models the **sign** attribute on an **Input** should not be defined.

The **transitionEffect** of an **Output** is set to "production".

The **outputLevel** of an **Output** indicates the weight of the arc from the transition to this place, it should be defined and is interpreted as the number of tokens produced by the firing of this transition.

A Validation of SBML documents

A.1 Validation and consistency rules

This section summarizes all the conditions that must (or in some cases, at least *should*) be true of an SBML Level 3 Version 1 model that uses the Qualitative Models package. We use the same conventions as are used in the SBML Level 3 Version 1 Core specification document. In particular, there are different degrees of rule strictness. Formally, the differences are expressed in the statement of a rule: either a rule states that a condition *must* be true, or a rule states that it *should* be true. Rules of the former kind are strict SBML validation rules—a model encoded in SBML must conform to all of them in order to be considered valid. Rules of the latter kind are consistency rules. To help highlight these differences, we use the following three symbols next to the rule numbers:

☑ A checked box indicates a *requirement* for SBML conformance. If a model does not follow this rule, it does not conform to the Qualitative Models specification. (Mnemonic intention behind the choice of symbol: "This must be checked.")

▲ A triangle indicates a *recommendation* for model consistency. If a model does not follow this rule, it is not considered strictly invalid as far as the Qualitative Models specification is concerned; however, it indicates that the model contains a physical or conceptual inconsistency. (Mnemonic intention behind the choice of symbol: "This is a cause for warning.")

★ A star indicates a strong recommendation for good modeling practice. This rule is not strictly a matter of SBML encoding, but the recommendation comes from logical reasoning. As in the previous case, if a model does not follow this rule, it is not strictly considered an invalid SBML encoding. (Mnemonic intention behind the choice of symbol: "You're a star if you heed this.")

The validation rules listed in the following subsections are all stated or implied in the rest of this specification document. They are enumerated here for convenience. Unless explicitly stated, all validation rules concern objects and attributes specifically defined in the Qualitative Models package.

☞ For convenience and brievity, we use the shorthand "`qual:x`" to stand for an attribute or element name `x` in the namespace for the Qualitative Models package, using the namespace prefix `qual`. In reality, the prefix string may be different from the literal "`qual`" used here (and indeed, it can be any valid XML namespace prefix that the modeler or software chooses). We use "`qual:x`" because it is shorter than to write a full explanation everywhere we refer to an attribute or element in the Qualitative Models package namespace.

General rules about this package

qual-10101 ☑ To conform to the Qualitative Models package specification for SBML Level 3 Version 1, an SBML document must declare the use of the following XML Namespace: "`http://www.sbml.org/sbml/level3/version1/qual/version1`". (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.1 on page 6.)

qual-10102 ☑ Wherever they appear in an SBML document, elements and attributes from the Qualitative Models package must be declared either implicitly or explicitly to be in the XML namespace "`http://www.sbml.org/sbml/level3/version1/comp/version1`". (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.1 on page 6.)

General rules for MathML content

qual-10201 ▲ The MathML `math` element in a **FunctionTerm** object should evalutae to a value of type `boolean`. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.6.5 on page 13.)

General rules about identifiers

qual-10301 ☑ (Extends validation rule #10301 in the SBML Level 3 Version 1 Core specification.) Within a **Model** the values of the attributes `id` and `qual:id` on every instance of the following classes of objects must be unique across the set of all `id` and `qual:id` attribute values of all such objects in a model: the **Model** itself, plus all contained **FunctionDefinition**, **Compartment**, **Species**, **Reaction**, **SpeciesReference**, **ModifierSpeciesReference**, **Event**, and **Parameter** objects, plus the **QualitativeSpecies**, **Transition**, **Input** and **Output** objects defined by the Qualitative Models package. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.7 on page 14.)

Rules for the extended SBML class

qual-20101 ☑ In all SBML documents using the Qualitative Models package, the **SBML** object must include a value for the attribute `qual:required` attribute. (References: SBML Level 3 Version 1 Core, Section 4.1.2.)

qual-20102 ☑ The value of attribute `qual:required` on the **SBML** object must be of the data type `boolean`. (References: SBML Level 3 Version 1 Core, Section 4.1.2.)

qual-20103 ☑ The value of attribute `qual:required` on the **SBML** object must be set to "`true`". (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.1 on page 6.)

Rules for extended Model object

qual-20201 ☑ There may be at most one instance of each of the following kinds of objects within a **Model** object using Qualitative Models: **ListOfTransitions** and **ListOfQualitativeSpecies**. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.4 on page 7.)

qual-20202 ☑ The various **ListOf**__ subobjects with an **Model** object are optional, but if present, these container object must not be empty. Specifically, if any of the following classes of objects are present on the **Model**, it must not be empty: **ListOfQualitativeSpecies** and **ListOfTransitions**. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.4 on page 7.)

qual-20203 ☑ Apart from the general notes and annotation subobjects permitted on all SBML objects, a **ListOfTransitions** container object may only contain **Transition** objects. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.4 on page 7.)

qual-20204 ☑ Apart from the general notes and annotation subobjects permitted on all SBML objects, a **ListOfQualitativeSpecies** container object may only contain **QualitativeSpecies** objects. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.4 on page 7.)

qual-20205 ☑ A **ListOfQualitativeSpecies** object may have the optional `metaid` and `sboTerm` defined by SBML Level 3 Core. No other attributes from the SBML Level 3 Core namespace or the Qualitative Models namespace are permitted on a **ListOfQualitativeSpecies** object. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.4 on page 7.)

qual-20206 ☑ A **ListOfTransitions** object may have the optional attributes `metaid` and `sboTerm` defined by SBML Level 3 Core. No other attributes from the SBML Level 3 Core namespace or the Qualitative Models namespace are permitted on a **ListOfTransitions** object. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.4 on page 7.)

Rules for QualitativeSpecies object

qual-20301 ☑ A **QualitativeSpecies** object may have the optional SBML Level 3 Core attributes `metaid` and `sboTerm`. No other attributes from the SBML Level 3 Core namespaces are permitted on a

QualitativeSpecies. (References: SBML Level 3 Version 1 Core, Section 3.2.)

qual-20302 ☑ A **QualitativeSpecies** object may have the optional SBML Level 3 Core subobjects for notes and annotations. No other elements from the SBML Level 3 Core namespaces are permitted on a **QualitativeSpecies**. (References: SBML Level 3 Version 1 Core, Section 3.2.)

qual-20303 ☑ A **QualitativeSpecies** object must have the required attributes `qual:id`, `qual:compartment` and `qual:constant`, and may have the optional attributes `qual:name`, `qual:initialLevel` and `qual:maxLevel`. No other attributes from the SBML Level 3 Qualitative Models namespace are permitted on a **QualitativeSpecies** object. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.5 on page 8.)

qual-20304 ☑ The attribute `qual:constant` in **QualitativeSpecies** must be of the data type `boolean`. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.5 on page 8.)

qual-20305 ☑ The attribute `qual:name` in **QualitativeSpecies** must be of the data type `string`. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.5 on page 8.)

qual-20306 ☑ The attribute `qual:initialLevel` in **QualitativeSpecies** must be of the data type `integer`. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.5 on page 8.)

qual-20307 ☑ The attribute `qual:maxLevel` in **QualitativeSpecies** must be of the data type `integer`. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.5 on page 8.)

qual-20308 ☑ The value of the attribute `qual:compartment` in a **QualitativeSpecies** object must be the identifier of an existing **Compartment** object defined in the enclosing **Model** object. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.5 on page 8.)

qual-20309 ☑ The value of the attribute `qual:initialLevel` in a **QualitativeSpecies** object cannot be greater than the value of the `qual:maxLevel` attribute for the given **QualitativeSpecies** object. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.5 on page 8.)

qual-20310 ☑ A **QualitativeSpecies** with attribute `qual:constant` set to `true` can only be referred to by an **Input**. It cannot be the subject of an **Output** in a **Transition**. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.5 on page 8.)

qual-20311 ▲ A **QualitativeSpecies** that is referenced by an **Output** with the `qual:transitionEffect` attribute set to "`assignmentLevel`" cannot be referenced by any other **Output** with this `transitionEffect` throughout the set of transitions for the containing model. (References: SBML Level 3 Package Specification for QualitativeModels, Version 1 Section 3.6.2 on page 12)

Rules for Transition object

qual-20401 ☑ A **Transition** object may have the optional SBML Level 3 Core attributes `metaid` and `sboTerm`. No other attributes from the SBML Level 3 Core namespaces are permitted on a **Transition**. (References: SBML Level 3 Version 1 Core, Section 3.2.)

qual-20402 ☑ A **Transition** object may have the optional SBML Level 3 Core subobjects for notes and annotations. No other elements from the SBML Level 3 Core namespaces are permitted on a **Transition**. (References: SBML Level 3 Version 1 Core, Section 3.2.)

qual-20403 ☑ A **Transition** object may have the optional attributes `qual:id` and `qual:name`. No other attributes from the SBML Level 3 Qualitative Models namespace are permitted on a **Transition** object. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.6 on page 9.)

qual-20404 ☑ The attribute `qual:name` in **Transition** must be of the data type `string`. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.6 on page 9.)

qual-20405 ☑ A **Transition** must have one and only one instance of the **ListOfFunctionTerms** objects and may have at most one instance of the **ListOfInputs** and **ListOfOutputs** objects from the Qualitative Models namespace. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.6 on page 9.)

qual-20406 ☑ The **ListOfInputs** and **ListOfOutputs** subobjects on a **Transition** object are optional, but if present, these container object must not be empty. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.6 on page 9.)

qual-20407 ☑ Apart from the general notes and annotation subobjects permitted on all SBML objects, a **ListOfInputs** container object may only contain **Input** objects. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.6 on page 9.)

qual-20408 ☑ Apart from the general notes and annotation subobjects permitted on all SBML objects, a **ListOfOutputs** container object may only contain **Output** objects. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.6 on page 9.)

qual-20409 ☑ Apart from the general notes and annotation subobjects permitted on all SBML objects, a **ListOfFunctionTerms** container object must contain one and only one **DefaultTerm** object and then may only contain **FunctionTerm** objects. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.6 on page 9.)

qual-20410 ☑ A **ListOfInputs** object may have the optional `metaid` and `sboTerm` defined by SBML Level 3 Core. No other attributes from the SBML Level 3 Core namespace or the Qualitative Models namespace are permitted on a **ListOfInputs** object. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.6 on page 9.)

qual-20411 ☑ A **ListOfOutputs** object may have the optional attributes `metaid` and `sboTerm` defined by SBML Level 3 Core. No other attributes from the SBML Level 3 Core namespace or the Qualitative Models namespace are permitted on a **ListOfOutputs** object. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.6 on page 9.)

qual-20412 ☑ A **ListOfFunctionTerms** object may have the optional attributes `metaid` and `sboTerm` defined by SBML Level 3 Core. No other attributes from the SBML Level 3 Core namespace or the Qualitative Models namespace are permitted on a **ListOfFunctionTerms** object. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.6 on page 9.)

qual-20413 ☑ No element of the **ListOfFunctionTerms** object can cause the *level* of a **QualitativeSpecies** to exceed the value `qual:-maxLevel` attribute. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.6.5 on page 14.)

qual-20414 ☑ No element of the **ListOfFunctionTerms** object can cause the *level* of a **QualitativeSpecies** to become negative. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.6.5 on page 14.)

Rules for Input object

qual-20501 ☑ A **Input** object may have the optional SBML Level 3 Core attributes `metaid` and `sboTerm`. No other attributes from the SBML Level 3 Core namespaces are permitted on a **Input**. (References: SBML Level 3 Version 1 Core, Section 3.2.)

qual-20502 ☑ A **Input** object may have the optional SBML Level 3 Core subobjects for notes and annotations. No other elements from the SBML Level 3 Core namespaces are permitted on a **Input**. (References: SBML Level 3 Version 1 Core, Section 3.2.)

qual-20503 ☑ A **Input** object must have the required attributes `qual:qualitativeSpecies` and `qual:transitionEffect`, and may have the optional attributes `qual:id`, `qual:name`, `qual:sign` and `qual:thresholdLevel`. No other attributes from the SBML Level 3 Qualitative Models namespace are permitted on a **Input** object. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.6.1 on page 11.)

qual-20504 ☑ The attribute `qual:name` in **Input** must be of the data type `string`. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.6.1 on page 11.)

qual-20505 ☑ The value of the attribute `qual:sign` of a **Input** object must conform to the syntax of the SBML data type `sign` and may only take on the allowed values of `sign` defined in SBML; that is, the value must be one of the following: "`positive`", "`negative`", "`dual`" or "`unknown`". (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.6.1 on page 11.)

qual-20506 ☑ The value of the attribute `qual:transitionEffect` of a **Input** object must conform to the syntax of the SBML data type `transitionInputEffect` and may only take on the allowed values of `transitionInputEffect` defined in SBML; that is, the value must be one of the following: "`none`" or "`consumption`". (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.6.1 on page 11.)

qual-20507 ☑ The attribute `qual:thresholdLevel` in **Input** must be of the data type `integer`. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.6.1 on page 11.)

qual-20508 ☑ The value of the attribute `qual:qualitativeSpecies` in an **Input** object must be the identifier of an existing **QualitativeSpecies** object defined in the enclosing **Model** object. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.6.1 on page 11.)

qual-20509 ☑ An **Input** that refers to a **QualitativeSpecies** that has a `qual:constant` attribute set to "`true`" cannot have the attribute `qual:transitionEffect` set to "`consumption`". (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.6.1 on page 11.)

Rules for Output object

qual-20601 ☑ A **Output** object may have the optional SBML Level 3 Core attributes `metaid` and `sboTerm`. No other attributes from the SBML Level 3 Core namespaces are permitted on a **Output**. (References: SBML Level 3 Version 1 Core, Section 3.2.)

qual-20602 ☑ A **Output** object may have the optional SBML Level 3 Core subobjects for notes and annotations. No other elements from the SBML Level 3 Core namespaces are permitted on a **Output**. (References: SBML Level 3 Version 1 Core, Section 3.2.)

qual-20603 ☑ A **Output** object must have the required attributes `qual:qualitativeSpecies` and `qual:transitionEffect`, and may have the optional attributes `qual:id`, `qual:name` and `qual:outputLevel`. No other attributes from the SBML Level 3 Qualitative Models namespace are permitted on a **Output** object. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.6.2 on page 12.)

qual-20604 ☑ The attribute `qual:name` in **Output** must be of the data type `string`. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.6.2 on page 12.)

qual-20605 ☑ The value of the attribute `qual:transitionEffect` of a **Output** object must conform to the syntax of the SBML data type `transitionOutputEffect` and may only take on the allowed values of `transitionOutputEffect` defined in SBML; that is, the value must be one of the following: "`production`" or "`assignmentLevel`". (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.6.2 on page 12.)

qual-20606 ☑ The attribute `qual:outputLevel` in **Output** must be of the data type `integer`. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.6.2 on page 12.)

qual-20607 ☑ The value of the attribute `qual:qualitativeSpecies` in an **Output** object must be the identifier of an existing **QualitativeSpecies** object defined in the enclosing **Model** object. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.6.2 on page 12.)

qual-20608 ☑ The **QualitativeSpecies** referred to by the attribute `qual:qualitativeSpecies` in an **Output** object must have the value of its `qual:constant` attribute set to `false`. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.6.2 on page 12.)

Rules for DefaultTerm object

qual-20701 ☑ A **DefaultTerm** object may have the optional SBML Level 3 Core attributes `metaid` and `sboTerm`. No other attributes from the SBML Level 3 Core namespaces are permitted on a **DefaultTerm**. (References: SBML Level 3 Version 1 Core, Section 3.2.)

qual-20702 ☑ A **DefaultTerm** object may have the optional SBML Level 3 Core subobjects for notes and annotations. No other elements from the SBML Level 3 Core namespaces are permitted on a **DefaultTerm**. (References: SBML Level 3 Version 1 Core, Section 3.2.)

qual-20703 ☑ A **DefaultTerm** object must have the required attributes `qual:resultLevel`. No other attributes from the SBML Level 3 Qualitative Models namespace are permitted on a **DefaultTerm** object. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.6.4 on page 13.)

qual-20704 ☑ The attribute `qual:resultLevel` in **DefaultTerm** must be of the data type `integer`. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.6.4 on page 13.)

Rules for FunctionTerm object

qual-20801 ☑ A **FunctionTerm** object may have the optional SBML Level 3 Core attributes `metaid` and `sboTerm`. No other attributes from the SBML Level 3 Core namespaces are permitted on a **FunctionTerm**. (References: SBML Level 3 Version 1 Core, Section 3.2.)

qual-20802 ☑ A **FunctionTerm** object may have the optional SBML Level 3 Core subobjects for notes and annotations. No other elements from the SBML Level 3 Core namespaces are permitted on a **FunctionTerm**. (References: SBML Level 3 Version 1 Core, Section 3.2.)

qual-20803 ☑ A **FunctionTerm** object must have the required attributes `qual:resultLevel`. No other attributes from the SBML Level 3 Qualitative Models namespace are permitted on a **FunctionTerm** object. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.6.5 on page 13.)

qual-20804 ☑ A **FunctionTerm** object may contain exactly one MathML `qual:math` element. No other elements from the SBML Level 3 Qualitative Models namespace are permitted on a **FunctionTerm**

object. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.6.5 on page 13.)

qual-20805 ☑ The attribute `qual:resultLevel` in **FunctionTerm** must be of the data type `integer`. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.6.5 on page 13.)

B Future directions

To account for qualitative models where parameters are not (all) instantiated, as well as models for which timing constraints are specified, an extension of the current specification was contemplated. Here, we briefly recapitulate the elements and attributes that have been discarded in the current specification, with the intent to fuel discussions on future extensions. We also point out other extensions that may be considered in the near future, since they were evoked while discussing the current specification.

Finally, we briefly comment on the possible use of this qual package to represent Petri net models.

B.1 Symbols

Definition of SymbolicValue

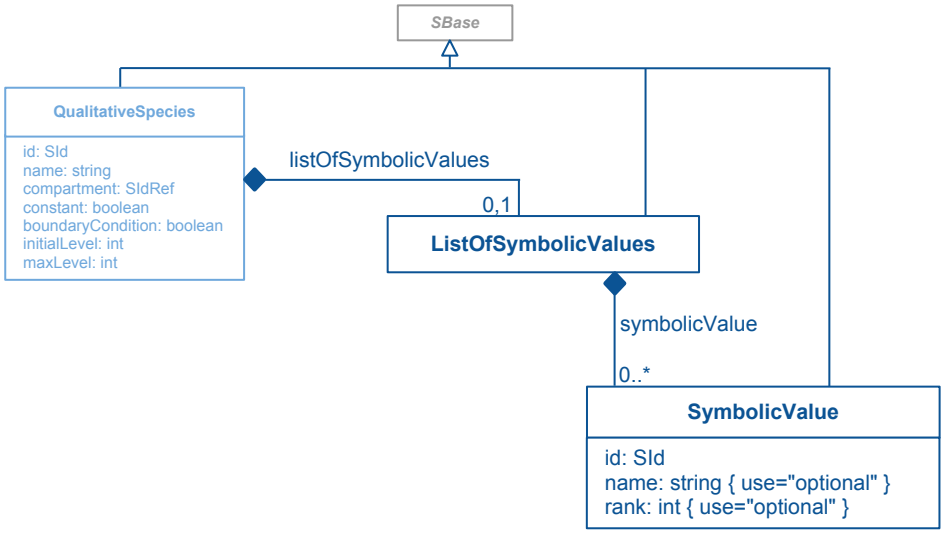

Figure 7: *Possible future extensions of the* ***QualitativeSpecies*** *class.*

The **QualitativeSpecies** element may contain at most one **ListOfSymbolicValues** that contains zero or more **SymbolicValue**s. An empty list is allowed, and useful for e.g. adding annotations. The **SymbolicValue** element defines a non instantiated parameter. Such symbols may represent the different solutions of piecewise linear differential equations, along with different thresholds.

The id and name attributes

These attributes are used according to the SBML L3.1 Section 3.3. The attribute id is mandatory and name is optional.

The rank attribute

The rank is an `integer` that defines the position of the symbol in the **ListOfSymbolicValues**. This attribute is optional.

The thresholdLevel and thresholdSymbol attributes:

The thresholdLevel is an `integer` and thresholdSymbol is a `SIdRef`. They are optional and exclusive.

The resultLevel and resultSymbol attributes:

The result of the term is described by a resultLevel or a resultSymbol. Both are optional, but one of them must be defined.

`assignmentSymbol`: The symbol associated to the qualitativeSpecies is set to the resultSymbol of the selected term.

B.2 Temporisation

The temporisationType attribute:

The temporisationType is an `enumeration` the "temporisation" of the **Transition**, that is the updating policy associated with the **Transition**. It can be set to `timer`, `priority`, `sustain`, `proportion` or `rate`. This attribute is optional.

The temporisationValue attribute and the TemporisationMath element:

The attribute temporisationValue and the element **TemporisationMath** allow the specification of the "temporisation" of the **Transition** under the corresponding **FunctionTerm**. Both are optional. Depending on the value of the temporisationType, either one or both could be used.

The temporisationValue is a `double`. The element **TemporisationMath** holds a MathML function returning a `double`.

B.3 Classes of models and random models

Several comments indicate that a future extension could support the representation of classes of models (*i.e.* models that are not fully parametrised, meaning that e.g. the logical rule of a component is incomplete), or random models, e.g. where several logical rules are associated to a component, the choice of a rule in the course of the dynamical evolution being arbitrary. This might be done by revising the requirement of certain elements as well as the current semantics of *function terms*.

B.4 Interaction with SBML Core concepts

At the time at which this Qualitative Modelling specification was developed, the policy and process for interacting with SBML Level 3 Core constructs was undefined. Thus, this particular specification does not facilitate the use of Core constructs. It is anticipated that in the future the specification will be extended to allow the use of these constructs; in particular Parameters and Events.

B.5 Petri net models

The current specification covers the needs of standard Petri Nets but provides a base for expansion to encompass more sophisticated modelling in this area. Both High Level Petri Nets (also referred to as Coloured PetriNets) and Timed PN should be achievable in future versions.

We note that most PN models currently refer to metabolic or other reaction networks, and PN tools dedicated to this modelling framework often provides support for the SBML core format (see e.g. Rohr et al. (2010)).

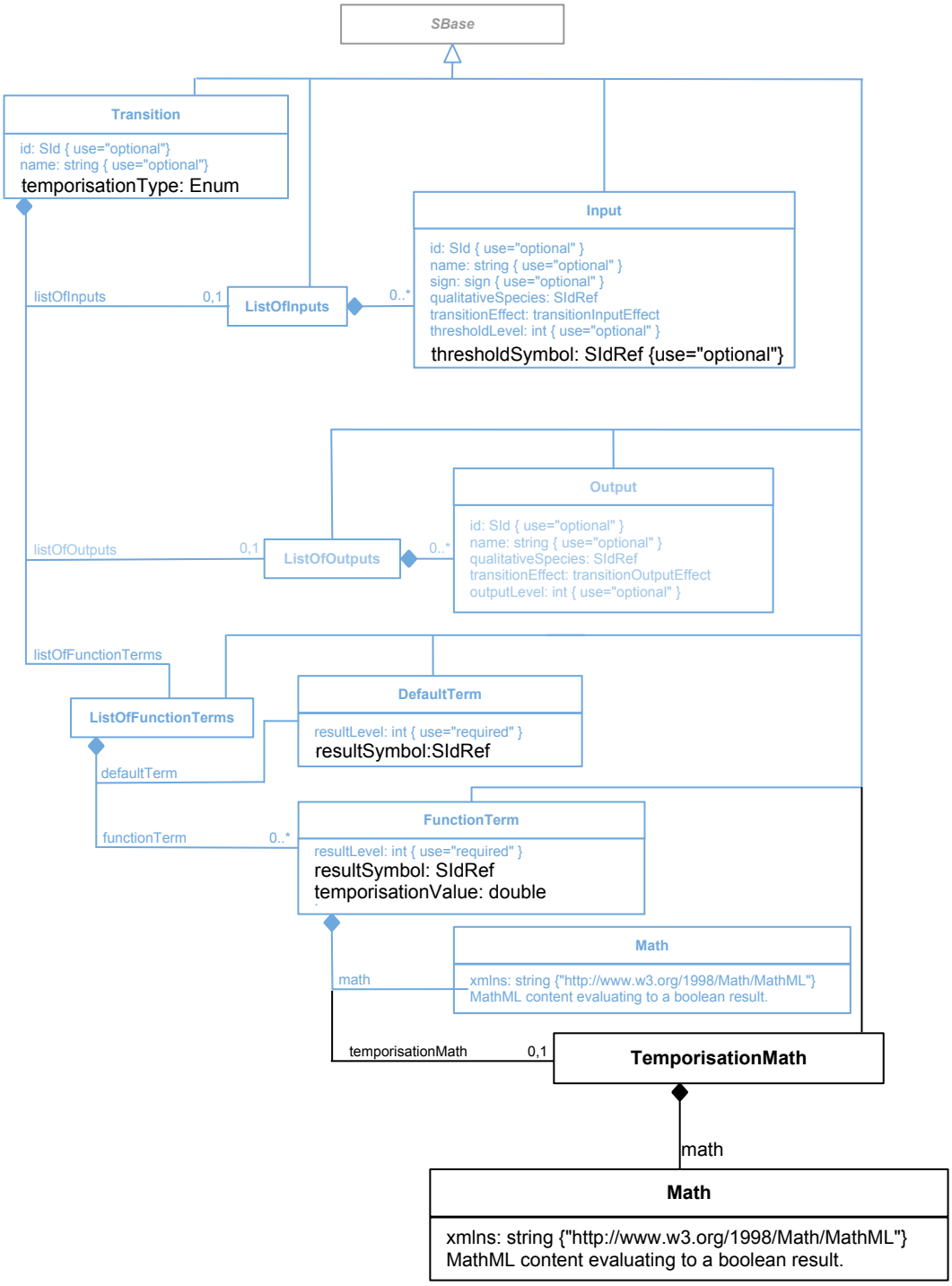

Figure 8: *Possible future extensions of the* ***Transition*** *class.*

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