### SBML Level 3 Package Specification

# Qualitative Models

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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

This release of the specification is available at



# Contents

1	Introduction	3								
	1.1 Motivation	. 3								
	1.2 Package dependencies	. 3								
	1.3 Document conventions	. 3								
2	Background and context	5								
3	Package syntax and semantics	6								
	3.1 Namespace URI and other declarations necessary for using this package	. 6								
	3.2 Primitive data types	. 6								
	3.2.1 Type sign	. 6								
	3.2.2 Type transitionInputEffect	. 6								
	3.2.3 Type transitionOutputEffect	. 6								
	3.3 Qualitative modelling	. 6								
	3.3.1 Levels	. 7								
	3.3.2 Transitions	. 7								
	3.3.3 FunctionTerms	. 7								
	3.4 The extended Model class	. 7								
	3.5 The QualitativeSpecies class	. 7								
	3.6 The <b>Transition</b> class	. 9								
	3.6.1 The Input class	. 9								
	3.6.2 The Output class	. 11								
	3.6.3 The ListOfFunctionTerms class	. 12								
	3.6.4 The <b>DefaultTerm</b> class	. 12								
	3.6.5 The FunctionTerm class	. 12								
4	Examples	13								
	4.1 Simple Logical Regulatory Graph	. 13								
	4.2 Simple Petri net	. 16								
5	Best practices	18								
Α	Validation of SBML documents	19								
	A.1 Validation and consistency rules	. 19								
В	Future directions	25								
	B.1 Symbols	. 25								
	B.2 Temporisation	. 25								
Ac	knowledgments	26								
Re	References 27									

# 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.

Qualitative models are typically based on the definition of regulatory or influence graph.

#### TODO: I think more detail is needed here

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. Boolean networks, logical models and some Petri nets are the most used qualitative formalisms in biology. 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.

13

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# 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

Section 1 Introduction Page 3 of 27

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.

Section 1 Introduction Page 4 of 27

# 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 <a href="http://www.ebi.ac.uk/compneur/xwiki/bin/view/SBML/L3F">http://www.ebi.ac.uk/compneur/xwiki/bin/view/SBML/L3F</a> 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 Qualitaive 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 during this meeting 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 <a href="http://co.mbine.org/colomoto/meetings/2012">http://co.mbine.org/colomoto/meetings/2012</a>). 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.

12

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# 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 13, 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.

18

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.

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 and Section 3.6 on page 9 respectively.

### 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.

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 on the following page.

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**.

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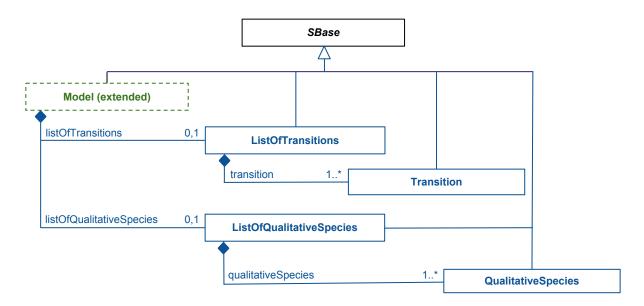


Figure 1: The definitions of the extended Model class. In other respects, Model remains defined as in the SBML Level 3 Core specification.

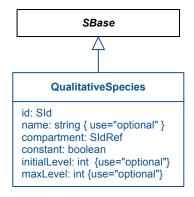


Figure 2: The definitions of the QualitativeSpecies class.

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, a qualitativeSpecies that only appears as Input in the model (thus is never modified by a transition, meaning that it receives no interaction) will have this attribute set to true.

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.

#### 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 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 zero or more elements of type **Input**. A transition with zero inputs can be useful for defining an initial assignment, where the state of an output depends on a function but not on any input values. An empty list is allowed, and useful for e.g. adding annotations. Each **Input** refers to a **QualitativeSpecies** that participates in the corresponding **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. TODO: explain thresholdlevel a b

23

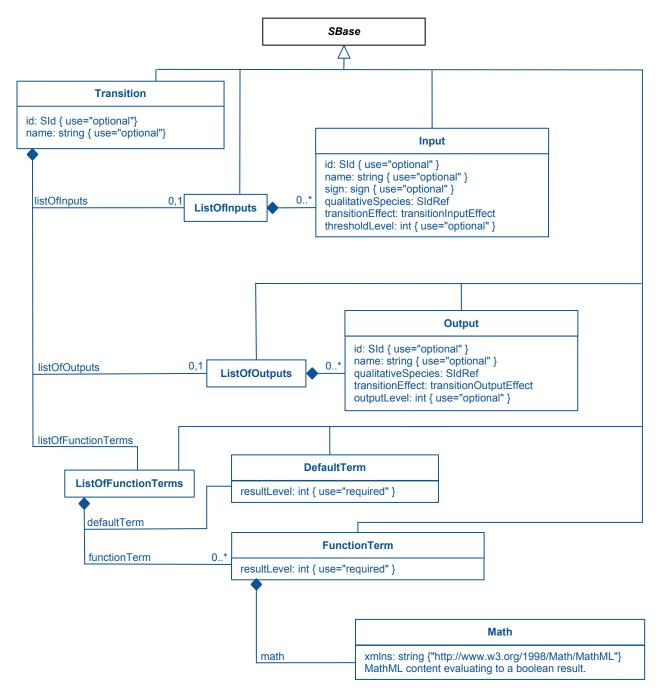


Figure 3: The definitions of Transition, Input, Output, DefaultTerm and FunctionTerm classes. Note that the DefaultTerm class is not derived from SBase.

#### 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 on the following page shows the possible values with the interpretation of each value.

The following example illustrates the interpretation of the transition Effect attribute.

19

TransitionInputEffect	Interpretation
none consumption	The level associated with the qualitativeSpecies is not modified.  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.

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**. 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 zero or more elements of type **Output**. A transition with zero outputs can be useful for **TODO:** what for ... Each **Output** refers to a **QualitativeSpecies** that participates in the corresponding **Transition**.

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.

#### 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 on the next page shows the possible values with the interpretation of each value.

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The following example illustrates the interpretation of the transition Effect attribute. In the case of qualitative Species "A" the level is assigned the resultLevel from the whichever Function Term is applicable, whereas the level of qualitative Species "B" is increased by resultLevel. Similarly, the level of "C" is increased by 2 (output level) times resultLevel (see also Petri net example in Section 4).

```
<list0fOutputs>
     <output qualitativeSpecies="A" transitionEffect="assignmentLevel"/>
     <output qualitativeSpecies="B" transitionEffect="production"/>
           <output qualitativeSpecies="C" transitionEffect="production" outputLevel="2" />
</list0fInputs>
```

TransitionOutputEffe	retation		
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.

#### 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 results of the **Transition** applied by default. The disjunction of the terms defines the *qualitative function* associated with a **Transition**.

#### 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 the 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 25 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.

# 4 Examples

This proposal mainly covers logical models but it can also handle standard Petri nets. We provide one example of each.

# 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.

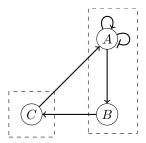


Figure 4: A simple Logical Regulatory Network.

The logical functions are the following:

```
B := 1 \quad \text{if } A => 1
C := 1 \quad \text{if } B => 1
A := \begin{cases} 2 \quad \text{if } (1 <= A < 2) \text{ or } (C >= 1) \\ 1 \quad \text{if } A < 1 \text{ and } C >= 1 \\ 0 \quad \text{otherwise} \end{cases}
```

```
<?xml version="1.0" encoding="UTF8"?>
<sbml xmlns="http://www.sbml.org/sbml/level3/version1/core" level="3" version="1"</pre>
      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"</pre>
                                      qual:id="B" qual:maxLevel="1"/>
            <qual:qualitativeSpecies qual:compartment="nucleus" qual:constant="false"</pre>
                                      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"</pre>
                                                          qual:qualitativeSpecies="A"
                                 qual:thresholdLevel="1" qual:transitionEffect="none"
                                 qual:sign="positive"/>
```

Section 4 Examples Page 13 of 27

```
</qual:listOfInputs>
    <qual:listOfOutputs>
        <qual:output qual:transitionEffect="assignmentLevel"</pre>
                      qual:qualitativeSpecies="B"/>
    </qual:list0f0utputs>
    <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>
            </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"
                                                                                                   23
                     qual:sign="positive"/>
                                               qual:qualitativeSpecies="A"
        <qual:input qual:id="theta_A_A2"</pre>
                     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>
                                                                                                   32
        <qual:output qual:qualitativeSpecies="A"
                                                                                                   33
                     qual:transitionEffect="assignmentLevel"/>
    </qual:listOfOutputs>
    <qual:listOfFunctionTerms>
        <qual:functionTerm qual:resultLevel="2">
            <math xmlns="http://www.w3.org/1998/Math/MathML">
                <!-- (A >= 1 \text{ and } A < 2) \text{ or } C < 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>
                     < lt/>
```

Section 4 Examples Page 14 of 27

```
<ci><ci><</ci>
                                <ci>theta_A_C</ci>
                             </apply>
                         </apply>
                     </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>
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                  </qual:functionTerm>
                  <qual:defaultTerm qual:resultLevel="0"/>
              </qual:listOfFunctionTerms>
          </qual:transition>
           <qual:transition qual:id="tr_C">
              <qual:listOfInputs>
                                                       qual:qualitativeSpecies="B"
                  <qual:input qual:id="theta_C_B"
                              qual:thresholdLevel="1"
                                                       qual:transitionEffect="none"
                              qual:sign="positive"/>
                                                                                                             32
              </qual:listOfInputs>
                                                                                                             33
              <qual:list0f0utputs>
                  <qual:output qual:qualitativeSpecies="C"
                               qual:transitionEffect="assignmentLevel"/>
              </qual:list0f0utputs>
              <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>
                     </qual:functionTerm>
                  <qual:defaultTerm qual:resultLevel="0"/>
              </qual:listOfFunctionTerms>
           </qual:transition>
       </qual:listOfTransitions>
                                                                                                             52
   </model>
                                                                                                             53
</sbml>
                                                                                                             54
55
```

Listing 1: Logical Regulatory Graph example

Section 4 Examples Page 15 of 27

# 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.

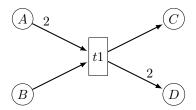


Figure 5: A Petri net model.

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns="http://www.sbml.org/sbml/level3/version1/core" level="3" version="1"</pre>
      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"</pre>
                                  qual:transitionEffect="production" />
                </qual:list0f0utputs>
                <qual:listOfFunctionTerms>
                    <qual:functionTerm qual:resultLevel="1">
                        <math xmlns="http://www.w3.org/1998/Math/MathML">
                            <!-- A >= 2 \text{ and } B >= 1 -->
                            <apply>
                                <and />
                                 <apply>
```

Section 4 Examples Page 16 of 27

<geq />

```
<ci>A</ci>
                                   <ci>t1_A</ci>
                               </apply>
                               <apply>
                                   <geq />
                                   <ci>B</ci>
                                   <ci>t1_B</ci>
                               </apply>
                           </apply>
                      </qual:functionTerm>
                   <qual:defaultTerm qual:resultLevel="0" />
               </qual:listOfFunctionTerms>
           </qual:transition>
       </qual:listOfTransitions>
   </model>
</sbml>
                                                                                                         17
18
```

Listing 2: Petri net example

Section 4 Examples Page 17 of 27

# 5 Best practices

All To be valid, the SBML root element must express the requirement of this package: <sbml ... qual:required="true"... >.

PN In Petri nets the initial conditions are part of the model, the initialLevel must be defined. To represent unbounded places, the maxLevel should be not specified.

LRG Discussions are still ongoing about the possible (but some times convenient to avoid cumbersome descriptions) incoherency of the FunctionTerm elements. For the moment, here are the guidelines 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/symbol 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/symbol of the same output, then the importing tool should consider the disjunction (OR) on the conditions of the terms.

LRG To declare external nodes (ones that have no Boolean expression/truth table associated with them), one should set the attribute boundaryCondition of the QualitativeSpecies to TRUE:

<qualitativeSpecies id="EGF" maxLevel="1" boundaryCoundition="true"

LRG To declare a "delay" node, which is specified to delay its state update for k iterations, one should set, for all the **Transition** elements having this node as their (unique) output, the attribute temporisationType to the value timer and the temporisationValue to k.

compartment="extracellular"/>

22

**LRG** To declare a "sustain" node, which is specified to sustain (i.e., to remain in) its latest state for the next k iterations, one should set, for all the **Transition** elements having this node as their (unique) output, the attribute temporisationType to the value **sustain** and the temporisationValue to k.

Section 5 Best practices Page 18 of 27

# 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.)
- 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 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

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Rules for the exte	ended SBML class			
qual-20101	In all SBML documents using the Qualitative Models package, the <b>SBML</b> object must include a value for the attribute <b>qual:required</b> 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". (R SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.1 or				
Rules for extende	ed Model object			
qual-20201	There may be at most one instance of each of the following kinds of objects within a <b>Model</b> object using Qualitative Models: <b>ListOfTransitions</b> and <b>ListOfQualitativeSpecies</b> . (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.4 on page 7.)			
qual-20202	The various <b>ListOf</b> — subobjects with an <b>Model</b> 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 <b>Model</b> , it must not be empty: <b>ListOfQualitativeSpecies</b> and <b>ListOfTransitions</b> . (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 <b>ListOfTransitions</b> container object may only contain <b>Transition</b> 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 <b>ListOfQualitativeSpecies</b> container object may only contain <b>QualitativeSpecies</b> objects. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.4 on page 7.)			
qual-20205	A <b>ListOfQualitativeSpecies</b> 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 <b>ListOfQualitativeSpecies</b> object. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.4 on page 7.)			
qual-20206	A <b>ListOfTransitions</b> 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 <b>ListOfTransitions</b> 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 <b>QualitativeSpecies</b> 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 <b>QualitativeSpecies</b> . (References: SBML Level 3 Version 1 Core, Section 3.2.)			

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.)

the **QualitativeSpecies**, **Transition**, **Input** and **Output** objects defined by the Qualitative Models package. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1,

**??** on page ??.)

qual-20302 🗹

qual-20303 V 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 7.) qual-20304 V 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 7.) qual-20305 V 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 7.) The attribute qual:initialLevel in QualitativeSpecies must be of the data type integer. qual-20306 V (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.5 on page 7.) qual-20307 V 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 7.) qual-20308 V 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: 18 SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.5 on page 7.) 19 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 7.) 23 qual-20310 V A QualitativeSpecies with attribute qual:constant set to true cannot only be refferred to by an Input. It cannot be the subject of an Output in a Transition. (References: SBML Level 3 25 Package Specification for Qualitative Models, Version 1, Section 3.5 on page 7.) 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. 29 (References: SBML Level 3 Version 1 Core, Section 3.2.) qual-20402 V A Transition object may have the optional SBML Level 3 Core subobjects for notes and an-31 notations. No other elements from the SBML Level 3 Core namespaces are permitted on a 32 **Transition**. (References: SBML Level 3 Version 1 Core, Section 3.2.) qual-20403 V 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 35 object. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, 36 Section 3.6 on page 9.) qual-20404 V 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.) 39 qual-20405 **V** 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.) 43

qual-20406 V The various **ListOfFunctionTerms** subobject with a **Transition** object must not be empty. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.6 on page 9.) qual-20407 V 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 V 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 10 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.) 13 A ListOfInputs object may have the optional metaid and sboTerm defined by SBML Level 3 qual-20410 V Core. No other attributes from the SBML Level 3 Core namespace or the Qualitative Mod-15 els 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 **V** 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 20 Package Specification for Qualitative Models, Version 1, Section 3.6 on page 9.) A ListOfFunctionTerms object may have the optional attributes metaid and sboTerm defined qual-20412 **V** 22 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: 24 SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.6 on page 9.) 25 Rules for Input object qual-20501 V 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: 28 SBML Level 3 Version 1 Core, Section 3.2.) qual-20502 V 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. 31 (References: SBML Level 3 Version 1 Core, Section 3.2.) 32 qual-20503 V A Input object must have the required attributes qual:qualitativeSpecies and qual:transitionEffect, and may have the optional attributes qual4d, qual:name, qual:sign 34 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 9.) qual-20504 V The attribute qual: name in Input must be of the data type string. (References: SBML Level 3 38 Package Specification for Qualitative Models, Version 1, Section 3.6.1 on page 9.) 39 qual-20505 **V** 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 9.)

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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 9.)
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 9.)
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 9.)

#### 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.)
- A Output object must have the required attributes qual:qualitativeSpecies and qual:transitionEffect, and may have the optional attributes qual⁴d, 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 11.)
- 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 11.)
- 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 11.)
- 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 11.)
- 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 11.)
- 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 11.)

#### 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 <b>DefaultTerm</b> object must have the required attributes <b>qual:resultLevel</b> . No other attributes from the SBML Level 3 Qualitative Models namespace are permitted on a <b>DefaultTerm</b> object. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.6.4 on page 12.)	1 2 3 4
qual-20704	The attribute qual:resultLevel in <b>DefaultTerm</b> must be of the data type integer. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.6.4 on page 12.)	5 6 7
Rules for Functi	onTerm object	8
qual-20801	A <b>FunctionTerm</b> object may have the optional SBML Level 3 Core attributes <b>metaid</b> and <b>sboTerm</b> . No other attributes from the SBML Level 3 Core namespaces are permitted on a <b>FunctionTerm</b> . (References: SBML Level 3 Version 1 Core, Section 3.2.)	9 10 11
qual-20802	A <b>FunctionTerm</b> 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 <b>FunctionTerm</b> . (References: SBML Level 3 Version 1 Core, Section 3.2.)	12 13 14
qual-20803	A <b>FunctionTerm</b> object must have the required attributes <b>qual:resultLevel</b> . No other attributes from the SBML Level 3 Qualitative Models namespace are permitted on a <b>Function-Term</b> object. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.6.5 on page 12.)	15 16 17
qual-20804	A <b>FunctionTerm</b> object may contain exactly one MathML <b>qual:math</b> element. No other elements from the SBML Level 3 Qualitative Models namespace are permitted on a <b>FunctionTerm</b> object. (References: SBML Level 3 Package Specification for Qualitative Models, Version 1, Section 3.6.5 on page 12.)	19 20 21 22
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 12.)	23 24 25

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B.1 Symbols

B.2 Temporisation

Section B Future directions Page 25 of 27

# Acknowledgments

Section Acknowledgments Page 26 of 27

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13

Section Acknowledgments Page 27 of 27