Systems Biology Markup Language (SBML) Level 2: Structures and Facilities for Model Definitions

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The latest revision of the SBML Level 2 Version 2 specification is available at
http://sbml.org/specifications/sbml-level-2/version-2/

This revision of the SBML Level 2 Version 2 specification is available at
http://sbml.org/specifications/sbml-level-2/version-2/revision-1/

The list of errata for all revisions of the SBML Level 2 Version 2 specification is available at
http://sbml.org/specifications/sbml-level-2/version-2/errata/

The XML Schema for SBML Level 2 Version 2 is available at
http://sbml.org/xml-schemas/

Contents

1 Introduction

We present the **S**ystems **B**iology **M**arkup **L**anguage (SBML) Level 2 Version 2, a model representation formalism for systems biology. SBML is oriented towards describing systems of biochemical reactions of the sort common in research on a number of topics, including cell signaling pathways, metabolic pathways, biochemical reactions, gene regulation, and many others. SBML is defined in a neutral fashion with respect to programming languages and software encoding; however, it is primarily oriented towards allowing models to be encoded using XML, the eXtensible Markup Language (Bosak and Bray, 1999; Bray et al., 2000). This document contains many examples of SBML models written in XML, as well as an XML Schema (Biron and Malhotra, 2000; Fallside, 2000; Thompson et al., 2000) that defines SBML Level 2 Version 2. A downloadable copy of the XML Schema and other related documents and software are also available from the SBML project web site, `http://sbml.org/`.

The SBML project is not an attempt to define a universal language for representing quantitative models. The rapidly evolving views of biological function, coupled with the vigorous rates at which new computational techniques and individual tools are being developed today, are incompatible with a one-size-fits-all idea of a universal language. A more realistic alternative is to acknowledge the diversity of approaches and methods being explored by different software tool developers, and seek a common intermediate format—a *lingua franca*—enabling communication of the most essential aspects of the models.

1.1 Developments, discussions, and notifications of updates

SBML has been, and continues to be, developed in collaboration with an international community of researchers and software developers. As in many projects, the primary mode of interaction between members is electronic mail, with discussions taking place on the mailing list `sbml-discuss@caltech.edu`. The mailing list archives and a Web browser-based interface to the list are available at `http://sbml.org/forums/`. It is *vitally important that all users of SBML stay informed about developments and revisions* by monitoring the mailing list or periodically visiting the SBML project web site, `http://sbml.org/`.

In Section 8.1, we attempt to acknowledge as many contributors to SBML's development as we can, but as SBML evolves, it becomes increasingly difficult to detail the individual contributions on a project that has truly become an international community effort.

1.2 SBML Levels, Versions, and Revisions

Major releases of SBML are termed *levels* and represent substantial changes to the composition and structure of the language. The release of SBML defined in this document, SBML Level 2, represents an incremental evolution of the language resulting from the practical experiences of many users and developers working with SBML Level 1 since its introduction in the year 2001 (Hucka et al., 2001, 2003). All of the structures of Level 1 can be mapped in a straightforward fashion to Level 2. In addition, a subset of the structures in Level 2 can be mapped to Level 1. However, the levels remain distinct; a valid SBML Level 1 document is not a valid SBML Level 2 document, and likewise, a valid SBML Level 2 document is not a valid SBML Level 1 document.

Minor releases of SBML are termed *versions* and constitute changes within an SBML Level to correct, adjust and refine language features. The present document defines SBML Level 2 Version 2. Appendix A lists the differences between SBML Level 2 Version 2 and Level 1 Version 2. Differences in the specifications of Version 1 and Version 2 of SBML Level 2 are highlighted in the UML diagrams (see Section 1.6 in the body of this specification and are also listed in Appendix B.

Language specification documents inevitably require minor editorial changes as its communities of users discover errors and ambiguities. As a practical reality, these discoveries occur over time. In the context of SBML, such problems are formally announced publicly as *errata* in a given specification document. Borrowing concepts and processes from the World Wide Web consortium (Jacobs, 2004), we define SBML errata as changes of the following types: (a) formatting changes that do not result in changes to textual content; (b) corrections that do not affect conformance of software implementing support for a given combination of

SBML Level and Version; and (c) corrections that *may* affect such software conformance, but add no new language features. A change that affects conformance is one that either turns conforming data, processors, or other conforming software into non-conforming software, or turns non-conforming software into conforming software, or clears up an ambiguity or insufficiently documented part of the specification in such a way that software whose conformance was once unclear now becomes clearly conforming or non-conforming (Jacobs, 2004). In short, errata do not change the fundamental semantics or syntax of SBML, but rather clarify and disambiguate the specification and correct errors. (New syntax and semantics are only introduced in SBML Versions and Levels.)

Errata result in new *Revisions* of the SBML specification. Each revision is numbered with an integer, with the first revision of the specification being given the number 1. Subsequent revisions of an SBML specification document contain a section listing the accumulated errata issued since the first revision. A complete list of the errata for SBML Level 2 Version 2 since the publication of Revision 1 is made publicly available at `http://sbml.org/specifications/sbml-level-2/version-2/errata/`.

1.3 Language features deprecated or removed

Some language features of previous SBML Levels and Versions have been either deprecated or removed entirely in SBML Level 2 Version 2. A *deprecated language feature* in SBML is one that is still present but its use is discouraged; more precisely,

> If a given feature is marked as deprecated, software implementations may chose to ignore that feature and still be considered compliant with the SBML specification. Beginning with the Level and Version in which a given feature is deprecated, software tools should not generate models containing the deprecated feature.

On the other hand, a *removed language feature* is one that existed in previous Levels and/or Versions of SBML, but no longer exists beginning with the SBML Level and Version in which it is removed.

The features deprecated in SBML Level 2 Version 2 are as follows:

- The `charge` field on Species. (See Section 4.8.7.) This field does not appear to have been supported by any existing software, so the impact of this change is expected to be small.

The features removed in SBML Level 2 Version 2 are as follows:

- The `offset` field on UnitDefinition. (See Section 4.4.2.) The definition of offsets in SBML Level 2 Version 1 was in fact incorrect; moreover, a proper implementation would have required a nearly complete change in the SBML unit scheme. Few models appeared to use offsets on unit definitions, so the impact of this change on models is expected to be small.
- The "`Celsius`" predefined unit. (See Section 4.4.2.) The removal of offsets on unit definitions meant an inconsistency existed if the Celsius unit was left in the system.
- The `substanceUnit` and `timeUnits` fields on KineticLaw. (See Section 4.13.5.) The ability to redefine the substance units on each reaction created the potential for reaction definitions whose units could not be properly converted.

As a matter of SBML design philosophy, the preferred approach to removing features is by deprecating them if possible. Immediate removal of SBML features is not done unless serious problems have been discovered involving those features, and keeping them would create logical inconsistencies or unresolvable problems. The deprecation or outright removal of features in a language, whether SBML or other, can have significant impact on backwards compatibility. It is also inevitable over the course of a language's evolution. SBML must by necessity continue evolving through the experiences of its users and implementors. Eventually, some features will be deemed unhelpful despite the best intentions of the language editors.

1.4 Backwards compatibility between Level 2 Version 2 and Level 2 Version 1

SBML Level 2 Version 2 is designed to be maximally backward compatible with SBML Level 2 Version 1. An XML document defining a valid model in SBML Level 2 Version 1, after changing the XML namespace and `version` attribute values on the `sbml` container element (see Section 4.1), can become a valid SBML Level 2 Version 2 document, subject to the following provisions:

1. UnitDefinition in SBML Level 2 Version 2 does not contain an `offset` field, and the interpretation of unit definitions has been defined and clarified more explicitly in this specification document. As a result of the changes, previous models containing `offset` on UnitDefinition objects are incompatible syntactically with Level 2 Version 2. See Section 4.4 for more explanation of SBML unit definitions and the implications of this change.

2. SBML Level 2 Version 1 did not define a default value for the field `fast` on Reaction. In SBML Level 2 Version 2, a default value *is* defined, and the value is "`false`". Further, software tools *must* respect the value or indicate to the user that they do not have the capacity to do so. See Section 4.13.1.

3. SBML Level 2 Version 2 is somewhat stricter about how the content of `annotation` elements must be organized. Previously valid SBML Level 2 Version 1 documents *may* need changes to their `annotation` elements to comply with the new specification. See Section 3.3.3 for more details.

4. SBML Level 2 Version 2 corrects numerous errata discovered in SBML Level 2 Version 1 since the time of the latter's introduction. These errata are listed in Section B. As a result of changes to SBML Level 2 implied by these errata, some existing SBML Level 2 Version 1 models, even when modified as explained above, may still not be compliant with Version 2. The ultimate impact of the changes depends on the specific features used by a given model and the assumptions under which the model was created.

1.5 Scope and limitations

SBML is designed to encode quantitative and qualitative models of biochemical reaction networks. The model representation scheme is designed to capture the data required by simulation and analysis tools that operate on these models. Although the focus of SBML is on models of biochemical reaction networks, SBML is also capable of encoding more general models composed of first-order ordinary differential equations and algebraic equations. Future software tools will undoubtedly require further evolution of SBML, and we expect that higher SBML levels will add structures and facilities on top of Level 2 after the simulation community has had time to gain experience with the current language definition. In Section 8.1, we discuss extensions that will likely be included in SBML Level 3.

The definition of the model description language presented here does not specify *how* programs should communicate or read/write SBML. We assume that for a simulation program to communicate a model encoded in SBML, the program will have to translate its internal data structures to and from SBML, use a suitable transmission medium and protocol, etc., but these issues are outside of the scope of this document.

1.6 Notational conventions

We define SBML using a graphical notation based upon UML, the Unified Modeling Language (Eriksson and Penker, 1998; Oestereich, 1999). This UML-based definition in turn is used to define an XML Schema (Biron and Malhotra, 2000; Fallside, 2000; Thompson et al., 2000) for SBML. The XML Schema defines the encoding of SBML documents in XML. In this section, we briefly summarize this UML-based approach and notation and its mapping to XML Schema 1.0. More details are available in a separate document (Hucka, 2000).

There are three main advantages to using UML as a basis for defining SBML data structures. First, compared to using other notations or a programming language, the UML visual representations are generally easier to grasp by readers who are not computer scientists. Second, the notation is implementation-neutral: the defined structures can be encoded in any concrete implementation language—not just XML, but C, Java and other languages as well. Third, UML is a de facto industry standard that is documented in many resources.

Readers are therefore more likely to be familiar with it than other notations.

1.6.1 Typographical conventions for names

The following typographical notations are used in this document to distinguish object classes from other kinds of entities:

AbstractClass: Abstract classes are classes that 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 sans-serif typeface. In electronic document formats, the class names are also hyperlinked to their definitions in the specification. For example, in the PDF and HTML versions of this document, clicking on the word *Sbase* will send the reader to the figure showing the definition of this class.

Class: Names of ordinary (concrete) classes begin with a capital letter and are printed in an upright sans-serif typeface. In electronic document formats, the class names are also hyperlinked to their definitions in the specification. For example, in the PDF and HTML versions of this document, clicking on the word Species will send the reader to the figure showing the definition of this class.

`SomeThing`, `otherThing`: Fields within classes, primitive data type names, literal XML strings, and generally all tokens *other* than SBML UML class names, are printed in an upright typewriter typeface. Primitive types defined in SBML begin with a capital letter, but unfortunately, XML Schema 1.0 does not follow any convention and primitive XML types may either start with a capital letter (e.g,. `ID`) or not (e.g., `double`).

1.6.2 Notational conventions for object fields

The basis of this UML-to-XML Schema approach is to translate object classes such as *Sbase* into XML Schema 1.0 complex types. When instances of these classes are expressed in XML, they are implemented as XML *elements* and their fields are implemented either as *attributes* on the elements, or as subelements. The following example class definition illustrates the notation used for different types of fields in this specification document:

ExampleClass
field1: int
field2: Species[0..*]
field3: double { use=”optional” default=”0.0” }
math: Math { namespace=”http://www.w3.org/1998/Math/MathML” }
field4: (math : Math { namespace=”http://www.w3.org/1998/Math/MathML” })

The symbols `field1`, `field2`, etc., represent fields in an object class. The colon immediately after the name separates the name of the field (on the left) from the type of data that it stores (on the right).

The order of fields implemented as subelements in the XML encoding *is* significant and *must* follow the order given in the corresponding UML diagram. Fields are implemented as subelements when they are a complex object comprised of fields, or if they are a list of objects. Fields implemented as subelements are `field2`, `math` and `field4` in the example. This ordering constraint also holds true when a subclass inherits fields from a base class: the base class field elements must occur before those introduced by the subclass. This ordering constraint is introduced by aspects of XML Schema beyond SBML's control. (Software developers should beware that the ordering requirement is a frequent cause of compatibility problems; validating XML parsers will generate errors if the field ordering of an XML element does not correspond to the SBML object class definition.)

Expressions in curly braces ({}) shown after a field type indicate additional constraints placed on the field. We express constraints using the XML Schema language. In the examples above, the text {`use="optional" default="0.0"`} indicates that the field `field3` is optional and that it has a default value of 0.0. A constraint of the form {`namespace="`X`"`} indicates that the field is not in the SBML Level 2 XML namespace but resides

in the given XML namespace X. If a field is in a different namespace, then the type of the field will not be defined by the SBML UML but rather by another source. In the examples above, the `math` field and its content is defined in the MathML namespace.

Simple attribute fields

A field whose value can be a simple scalar type such as `string`, `SId` and `double`, as well as enumeration types is implemented as an XML attribute. In the example above `field1` and `field3` are fields that would be translated into XML attributes.

Lists

Square brackets (`[]`) just after a type name indicate that the field contains a list of elements each having the same type. Specifically, the notation `[0..*]` signifies a list containing zero or more elements, the notation `[1..*]` signifies a list containing at least one element, and so on, with the asterisk character indicating an unbounded upper limit.

The approach used here to translate from a list form into XML is, first, to create a subelement named `listOf_____s`, where the blank indicates the capitalized name of the field. (For example, `listOfField2s`.) Within this subelement are placed elements each of which has the name of the type, beginning with a lowercase letter. Here is an example:

```
<listOfCompartments>
    <compartment id="cytosol" size="2.5"/>
    <compartment id="mitochondria" size="0.3"/>
</listOfCompartments>
```

When list fields can have zero elements (i.e., the type name is followed by `[0..*]`), the `listOf_____s` element is optional. That is, a missing `listOf_____` element in an SBML XML instance document indicates that the list is empty. The `listOf_____` elements, when present, should always have content.

Substructures

As we have seen a field definition of the form `X : B` defines a field X of type B. If B is a complex type consisting of multiple fields then X is implemented as an element. A field definition of the form `X : (A : B)` defines an element X that contains a field A with type B. If A is the string `any` then the element X contains an arbitrary sequence of elements. A field definition of the form `X : ( A : B ) { C }` is similar except that the field X and its content is constrained by constraint C. A field definition of the form `X : ( A : B { C } )` is similar except that the field A and its content is constrained by constraint C. In the examples above the field `field4` is an element which contains a `math` field. The `math` field is in the MathML namespace but `field4` is in the SBML namespace.

Additional notes about the translation to XML Schema

The class definitions are mapped to XML Schema 1.0 `complexType` elements. A class inheriting fields from a base class is constructed in XML Schema using a `extension` element. The fields that are implemented as XML attributes are represented in XML Schema as `attribute` elements. The fields that are implemented as XML elements are represented in XML Schema as `element` elements within a `sequence` element. See Appendix C for a mapping of this SBML specification to XML schema. Not all of the constraints on SBML documents described in this document can be practically expressed in XML Schema 1.0. Appendix E defines additional rules, beyond what is encoded in the XML Schema for SBML, that must followed to produce a valid SBML document. See Walmsley (2002) for more information on XML Schema.

1.7 Guide to the rest of this SBML specification document

In the rest of this document, we describe in detail SBML's various constructs and their uses, provide examples and guidelines, and describe the differences compared to previous releases of SBML. More specifically:

- Section 2 provides a high-level overview of SBML Level 2 Version 2 and its constructs;

- Section 3 introduces concepts, definitions and principles that are used throughout SBML;
- Section 4 describes in detail each of the main components of SBML Level 2 Version 2;
- Section 5 describes the Systems Biology Ontology, a source of controlled vocabulary terms for optionally annotating a model with terms indicating each component's role;
- Section 6 describes a recommended format for certain kinds of annotations on SBML components;
- Section 7 provides a number of complete examples of models encoded in XML;
- Section 8 contains a list of changes that are anticipated for Level 3;
- Appendix A describes the differences between SBML Level 1 Version 2 and SBML Level 2 Version 1;
- Appendix B describes the differences between SBML Level 2 Version 1 and SBML Level 2 Version 2;
- Appendix C provides the complete XML Schema for SBML Level 2 Version 2;
- Appendix D provides the XML schema for the subset of MathML 2.0 used in SBML; and
- Appendix E lists the validation rules that are required to determine the correctness of an SBML document beyond simple XML Schema conformance.

2 Overview of SBML

The following is an example of a simple network of biochemical reactions that can be represented in SBML:

$$S_1 \xrightarrow{k_1[S_1]/([S_1]+k_2)} S_2$$

$$S_2 \xrightarrow{k_3[S_2]} S_3 + S_4$$

In this particular set of chemical equations above, the symbols in square brackets (e.g., "$[S_1]$") represent concentrations of molecular species, the arrows represent reactions, and the formulas above the arrows represent the rates at which the reactions take place. (And while this example uses concentrations, it could equally have used other measures such as molecular counts.) Broken down into its constituents, this model contains a number of components: reactant species, product species, reactions, reaction rates, and parameters in the rate expressions. To analyze or simulate this network, additional components must be made explicit, including compartments for the species, and units on the various quantities.

SBML allows models of arbitrary complexity to be represented. Each type of component in a model is described using a specific type of data structure that organizes the relevant information. The top level of an SBML model definition consists of lists of these components, with every list being optional:

beginning of model definition
- *list of function definitions (optional)*
- *list of unit definitions (optional)*
- *list of compartment types (optional)*
- *list of species types (optional)*
- *list of compartments (optional)*
- *list of species (optional)*
- *list of parameters (optional)*
- *list of initial assignments (optional)*
- *list of rules (optional)*
- *list of constraints (optional)*
- *list of reactions (optional)*
- *list of events (optional)*

end of model definition

The meaning of each component is as follows:

Function definition: A named mathematical function that may be used throughout the rest of a model.

Unit definition: A named definition of a new unit of measure, or a redefinition of an existing SBML default unit. Named units can be used in the expression of quantities in a model.

Compartment Type: A type of location where reacting entities such as chemical substances may be located.

Species type: A type of entity that can participate in reactions. Examples of species types include ions such as Ca^{2+}, molecules such as glucose or ATP, and more.

Compartment: A well-stirred container of a particular type and finite size where species may be located. A model may contain multiple compartments of the same compartment type. Every species in a model must be located in a compartment.

Species: A pool of entities of the same *species type* located in a specific *compartment*.

Parameter: A quantity with a symbolic name. In SBML, the term *parameter* is used in a generic sense to refer to named quantities regardless of whether they are constants or variables in a model. SBML Level 2 provides the ability to define parameters that are global to a model as well as parameters that are local to a single reaction.

Initial Assignment: A mathematical expression used to determine the initial conditions of a model. This type of structure can only be used to define how the value of a variable can be calculated from other values and variables at the start of simulated time.

Rule: A mathematical expression added to the set of equations constructed based on the reactions defined in a model. Rules can be used to define how a variable's value can be calculated from other variables, or used to define the rate of change of a variable. The set of rules in a model can be used with the reaction rate equations to determine the behavior of the model with respect to time. The set of rules constrains the model for the entire duration of simulated time.

Constraint: A mathematical expression that defines a constraint on the values of model variables. The constraint applies at all instants of simulated time. The set of constraints in model should not be used to determine the behavior of the model with respect to time.

Reaction: A statement describing some transformation, transport or binding process that can change the amount of one or more species. For example, a reaction may describe how certain entities (reactants) are transformed into certain other entities (products). Reactions have associated kinetic rate expressions describing how quickly they take place.

Event: A statement describing an instantaneous, discontinuous change in a set of variables of any type (species quantity, compartment size or parameter value) when a triggering condition is satisfied.

Table 1 provides a summary of the sections in this document where each of these components is described in more detail.

A software package can read an SBML model description and translate it into its own internal format for model analysis. For example, a package might provide the ability to simulate the model by constructing differential equations representing the network and then perform numerical time integration on the equations to explore the model's dynamic behavior.

Component	Section	Starting page	New in Version 2?
Function definition	4.3	31	
Unit definition	4.4	32	
Compartment type	4.5	38	Yes
Species type	4.6	39	Yes
Compartment	4.7	40	
Species	4.8	43	
Parameter	4.9	47	
Initial assignment	4.10	49	Yes
Rule	4.11	51	
Constraint	4.12	56	Yes
Reaction	4.13	58	
Event	4.14	69	

Table 1: *A guide to the sections, and their starting page numbers, where each major SBML component is described in this specification document. The "New?" column indicates whether a given component is new as of SBML Level 2 Version 2.*

3 Preliminary definitions and principles

This section covers certain concepts and constructs that are used repeatedly in the rest of SBML Level 2.

3.1 Primitive data types

Most primitive types in SBML are taken from the data types defined in XML Schema 1.0 (Biron and Malhotra, 2000; Fallside, 2000; Thompson et al., 2000). A few other primitive types are defined by SBML itself. What follows is a summary of the XML Schema types and the definitions of the SBML-specific types. Note that while we have tried to provide accurate and complete summaries of the XML Schema types, the following should not be taken to be normative definitions of these types. Readers should consult the XML Schema 1.0 specification for the normative definitions of the XML types used by SBML.

3.1.1 Type `string`

The XML Schema 1.0 type `string` is used to represent finite-length strings of characters. The characters permitted to appear in XML Schema `string` include all Unicode characters (Unicode Consortium, 1996) except for two delimiter characters, 0xFFFE and 0xFFFF (Biron and Malhotra, 2000). In addition, the following quoting rules specified by XML for character data (Bray et al., 2000) must be obeyed:

- The ampersand (`&`) character must be escaped using the entity `&`.
- The apostrophe (`'`) and quotation mark (`"`) characters must be escaped using the entities `&apos;` and `&quot;`, respectively, when those characters are used to delimit a string attribute value.

Other XML built-in character or entity references, e.g., `<` and `&x1A;`, are permitted in strings.

3.1.2 Type `boolean`

The XML Schema 1.0 type `boolean` is used to represent the mathematical concept of binary-valued logic. The permitted literal values of a data field having type `boolean` are the following: "`true`", "`false`", "`1`", and "`0`". The value "`1`" maps to "`true`" and the value "`0`" maps to "`false`".

3.1.3 Type `int`

The XML Schema 1.0 type `int` is used to represent decimal integer numbers in SBML. The literal representation of an `int` is a finite-length sequence of decimal digit characters with an optional leading sign ("+" or "-"). If the sign is omitted, "+" is assumed. The value space of `int` is the same as a standard 32-bit signed integer in programming languages such as C, i.e., 2147483647 to −2147483648.

3.1.4 Type `positiveInteger`

The XML Schema 1.0 type `positiveInteger` is used to represent nonzero, nonnegative, decimal integers: i.e., 1, 2, 3, ... The literal representation of an integer is a finite-length sequence of decimal digit characters, optionally preceded by a positive sign ("+"). There is no restriction on the absolute size of `positiveInteger` values in XML Schema; however, the only situations where this type is used in SBML involve very low-numbered integers. Consequently, applications may safely treat `positiveInteger` as unsigned 32-bit integers.

3.1.5 Type `double`

The XML Schema 1.0 type `double` is the data type of floating point fields in SBML objects. It is restricted to IEEE double-precision 64-bit floating point type IEEE 754-1985. The value space of `double` consists of (a) the numerical values $m \times 2^x$, where m is an integer whose absolute value is less than 2^{53}, and x is an integer between -1075 and 970, inclusive, (b) the special value positive infinity (`INF`), (c) the special value negative infinity (`-INF`), and (d) the special value not-a-number (`NaN`). The order relation on the values is the following: $x < y$ if and only if $y - x$ is positive for values of x and y in the value space of `double`. Positive infinity is greater than all other values other than `NaN`. `NaN` is equal to itself but is neither greater

nor less than any other value in the value space. (Software implementors should consult the XML Schema 1.0 definition of `double` for additional details about equality and relationships to IEEE 754-1985.)

The literal representation of a `double` value consists of a mantissa with an optional leading sign ("+" or "-"), optionally followed by the character `E` or `e` followed by an integer (the exponent). The mantissa must be a decimal number (an integer optionally followed by a period (`.`) optionally followed by another integer). If the leading sign is omitted, "+" is assumed. An omitted `E` or `e` and exponent means that a value of 0 is assumed for the exponent. If the `E` or `e` is present, it must be followed by an integer or an error results. The integer acting as an exponent must consist of a decimal number optionally preceded by a leading sign ("+" or "-"). If the sign is omitted, "+" is assumed. The following are examples of legal literal `double` values:

`-1E4`, `+4`, `234.234e3`, `6.02E-23`, `0.3e+11`, `2`, `0`, `-0`, `INF`, `-INF`, `NaN`

As described in Section 3.5, SBML uses a subset of the MathML 2.0 standard (W3C, 2000b) for expressing mathematical formulas in XML. This is done by stipulating that the MathML language be used whenever a mathematical formula must be written into an SBML model. Doing this, however, requires facing two problems: first, the syntax of numbers in scientific notation ("e-notation") is different in MathML from that just described for `double`, and second, the value space of integers and floating-point numbers in MathML is not defined in the same way as in XML Schema 1.0. We elaborate on these issues in Section 3.5.2; here we summarize the solution taken in SBML. First, within MathML, the mantissa and exponent of numbers in "e-notation" format must be separated by one `<sep/>` element. This leads to numbers of the form `<cn type="e-notation"> 2 <sep/> -5 </cn>`. Second, SBML stipulates that the representation of numbers in MathML expressions obey the same restrictions on values as defined for types `double` and `int` (Section 3.1.3).

3.1.6 Type ID

The XML Schema 1.0 type `ID` is identical to the XML 1.0 type `ID`. The literal representation of this type consists of strings of characters restricted as shown in Figure 1.

```
letter      ::=  'a'..'z','A'..'Z'
digit       ::=  '0'..'9'
NCNameChar  ::=  letter | digit | '.'  | '-' | '_' | CombiningChar | Extender
ID          ::=  ( letter | '_' ) NCNameChar*
```

Figure 1: *The definition of the XML Schema type `ID` expressed in the variant of BNF used by the XML 1.0 specification (Bray et al., 2000). The characters `(` and `)` are used for grouping, the character `*` indicates "zero or more times", and the character `|` indicates "or". The `CombiningChar` production is a list of characters that add such things as accents to the preceding character. (For example, the Unicode character `#x030A` when combined with 'a' produces 'å'.) The `Extender` production is a list of characters that extend the shape of the preceding character. Please consult the XML 1.0 specification (Bray et al., 2000) for the complete definition of these last two productions.*

An important aspect of `ID` is the XML requirement that a given value of `ID` must be unique throughout an XML document. All data values of type `ID` are considered to reside in a single common global namespace spanning the entire XML document, regardless of the data fields (or XML attributes) where type `ID` is used and regardless of the level of nesting of the object structures (or XML elements).

3.1.7 Type SId

The type `SId` is the type of the `id` field found on the majority of SBML components. `SId` is a data type derived from the basic XML type `string`, but with restrictions about the characters permitted and the sequences in which those characters may appear. The definition of the type is shown in Figure 2.

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

Figure 2: *The definition of the type `SId`. (Please see the caption of Figure 1 for an explanation of the notation.)*

The equality of `SId` values is determined by an exact character sequence match; i.e., comparisons of these identifiers must be performed in a case-sensitive manner. This applies to all uses of `SId`.

The `SId` is purposefully not derived from the XML `ID` type (Section 3.1.6). Using XML's `ID` would force all SBML identifiers to exist in a single global namespace, which would affect not only the form of local parameter definitions but also future SBML extensions for supporting model/submodel composition. Further, the use of the `ID` type for SBML identifiers would have limited utility because MathML 2.0 `ci` elements are not of the type `IDREF` (see Section 3.5). Since the `IDREF`/`ID` linkage cannot be exploited in MathML constructs, the utility of the XML `ID` type is greatly reduced.

3.1.8 Type `UnitSId`

The type `UnitSId` is derived from `SId` (Section 3.1.7) and has identical syntax. The `UnitSId` type is used as the data type for the identifiers of units (Section 4.4.1) and for references to unit identifiers in SBML object structures. The purpose of having a separate data type for such identifiers is enable the space of possible unit identifier values to be separated from the space of all other identifier values in SBML. The equality of `UnitSId` values is determined by an exact character sequence match; i.e., comparisons of these identifiers must be performed in a case-sensitive manner.

3.1.9 Type `SBOTerm`

The type `SBOTerm` is used as the data type of a field called `sboTerm` available in many SBML objects. The type consists of strings of characters matching the restricted pattern described in Figure 3.

```
SBOTerm ::= SBO:[0-9][0-9][0-9][0-9][0-9][0-9][0-9]
```

Figure 3: *The definition of `SBOTerm`. The `SBOTerm` type consists of strings beginning with `SBO:` and followed by seven decimal digits. (Please see the caption of Figure 1 for an explanation of the notation.)*

Examples of valid string values of type `SBOTerm` are "`SBO:0000014`" and "`SBO:0003204`". These values are meant to be the identifiers of terms from an ontology whose vocabulary describes entities and processes in computational models. Section 5 provides more information about the ontology and principles for the use of these terms in SBML models.

3.1.10 Type `any`

The XML Schema element type `any` is used to indicate that a given SBML element allows arbitrary well-formed XML content. The content can be a mixture of character data and XML tags. In all situations where `any` is used in SBML, certain additional conditions apply; for example, the content may be restricted to being within a specific XML namespace. Please consult the relevant SBML structure definitions in the rest of this document.

3.2 The SBML object inheritance hierarchy

As explained above, most base data types in SBML are taken directly from XML Schema (Biron and Malhotra, 2000; Fallside, 2000; Thompson et al., 2000) or are derived from XML Schema data types. SBML defines additional object classes beyond this. The overall SBML inheritance hierarchy is depicted in Figure 4 on the next page.

Although not appearing explicitly in the diagram, the various `listOf`_____ lists, as well as substructures such as `trigger` on Event (Section 4.14), are also derived from *Sbase*. However, substructures such as `math`, containing MathML content, are not derived from *Sbase*, nor are the `notes` and `annotation` fields defined in *Sbase* itself (discussed in Section 3.3.2 and 3.3.3).

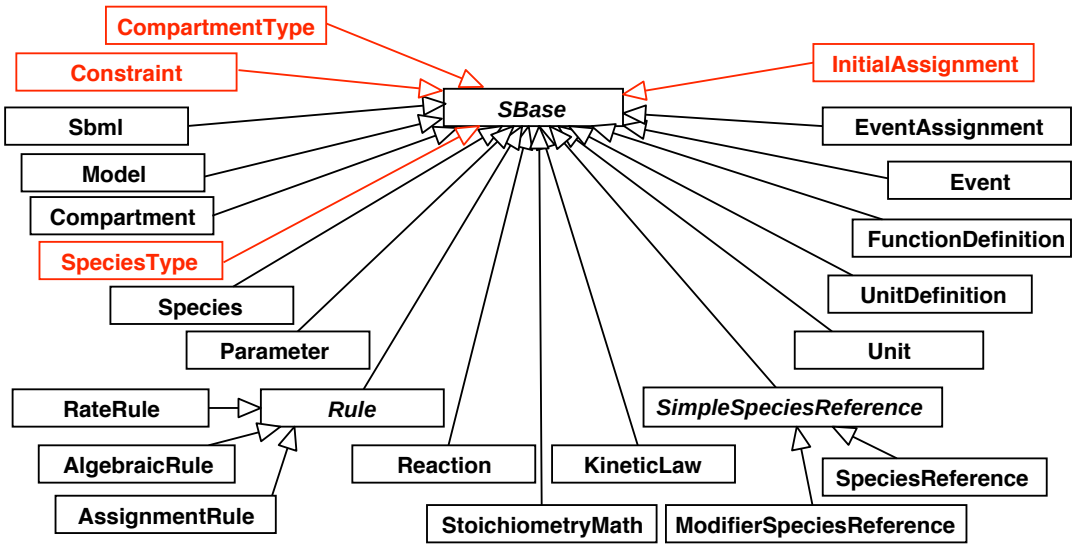

Figure 4: *A UML diagram of the inheritance hierarchy of major data types in SBML. Open arrows indicate inheritance, pointing from inheritors to their parents (Eriksson and Penker, 1998; Oestereich, 1999). In addition to these types, all substructures in SBML (including, for example, all the* `listOf` *lists) are also derived from Sbase. See text for details.*

3.3 Type SBase

Every structure composing an SBML Level 2 model definition has a specific data type that is derived directly or indirectly from a single abstract type called *Sbase*. In addition to serving as the parent class for most other classes of objects in SBML, this base type is designed to allow a modeler or a software package to attach arbitrary information to each major structure or list in an SBML model. The definition of *Sbase* is presented in Figure 5.

SBase
metaid: ID { use="optional" }
notes: (any : { namespace="http://www.w3.org/1999/xhtml" }) { minOccurs="0" maxOccurs="1" }
annotation: (any) { minOccurs="0" maxOccurs="1" }

Figure 5: *The definition of Sbase. Text enclosed in braces next to field types (e.g.,* {`minOccurs="0"`}*) indicates constraints on the possible field values. We use the XML Schema language to express constraints because we are primarily interested in the XML encoding of SBML. The constraint expression* {`use="optional"`} *means that the indicated field is optional and may be omitted in a particular instance in a model. The constraint expression* `minOccurs="0"` *likewise means the indicated field is optional; this alternate form of expression must be used for those fields that are containers (i.e., fields encoded as subelements in XML).*

Sbase contains three fields, all of which are optional: `metaid`, `notes` and `annotation`. These fields are discussed separately in the following subsections.

3.3.1 The `metaid` field

The `metaid` field is present for supporting metadata annotations using RDF (Resource Description Format; Lassila and Swick, 1999). It has a data type of XML `ID` (the XML identifier type), which means each `metaid` value must be globally unique within an SBML file. The `metaid` value serves to identify a model component for purposes such as referencing that component from metadata placed within `annotation` structures (see Section 3.3.3). Such metadata can use RDF `description` elements, in which an RDF attribute called "`describes`" contains the `metaid` identifier of an object defined in the SBML model. This topic is discussed in greater detail in Section 6.

3.3.2 The `notes` field

The field **notes** in *Sbase* is a container for XHTML 1.0 (Pemberton et al., 2002) content. It is intended to serve as a place for storing optional information intended to be seen by humans. An example use of the **notes** field would be to contain formatted user comments about the model component in which the **notes** field is enclosed. Every data object derived directly or indirectly from type *Sbase* can have a separate value for **notes**, allowing users considerable freedom when adding comments to their models.

XHTML 1.0 is simply a formulation of HTML 4 in XML 1.0. This means the full power of HTML formatting is available for use in **notes** content. The intention behind requiring XHTML (rather than, for example, plain HTML or plain text) for **notes** content is to balance several conflicting goals: (1) chosing a format for notes that is compatible with the XML form of SBML (plain HTML would not be); (2) supportting an international formatting standard so that users have more control over the appearance of notes and can predict to some degree how their notes will be displayed in different tools and environments (which argues against using plain-text notes); and (3) achieving these goals using an approach that is hopefully easy enough for software developers to support using off-the-shelf programming libraries. It is worth noting in passing that the requirement for XHTML does not *prevent* users from entering plain-text content with simple space/tab/newline formatting: it merely requires using the standard <pre>...</pre> element of (X)HTML.

Modern libraries for displaying and editing (X)HTML content are commonly available in contemporary software programming environments, and software developers may wish to avail themselves of these facilities rather than implementing their own XHTML support systems.

XML Namespace requirements for `notes`

The XML content of **notes** elements must declare the use of the XHTML XML namespace. This can be done in multiple ways. One way is to place a namespace declaration for the appropriate namespace URI (which is **http://www.w3.org/1999/xhtml**) on the top-level Sbml object (see Section 4.1) and then reference the namespace in the **notes** content using a prefix. The following example illustrates this approach:

```
<sbml xmlns="http://www.sbml.org/sbml/level2/version2" level="2" version="2"
      xmlns:xhtml="http://www.w3.org/1999/xhtml">
  ...
  <notes>
    <xhtml:body>
      <xhtml:center><xhtml:h2>A Simple Mitotic Oscillator</xhtml:h2></xhtml:center>
      <xhtml:p>A minimal cascade model for the mitotic oscillator
      involving cyclin and cdc2 kinase</xhtml:p>
    </xhtml:body>
  </notes>
  ...
```

Another approach is to declare the XHTML namespace within the **notes** content itself, as in the following example:

```
...
<notes>
  <body xmlns="http://www.w3.org/1999/xhtml">
    <center><h2>A Simple Mitotic Oscillator</h2></center>
    <p>A minimal cascade model for the mitotic oscillator
    involving cyclin and cdc2 kinase</p>
  </body>
</notes>
...
```

The **xmlns="http://www.w3.org/1999/xhtml"** declaration on **body** as shown above changes the default XML namespace within it, such that all of its content is by default in the XHTML namespace. This is a particularly convenient approach because it obviates the need to prefix every element with a namespace prefix (e.g., **xhtml:center** as in the previous case). Other approaches are also possible.

The content of `notes`

SBML does not require the content of **notes** to be any particular XHTML element; the content can be almost any well-formed XHTML content. There are only two simple restrictions. The first restriction comes from the requirements of XML: the **notes** element must not contain an XML declaration nor a DOCTYPE declaration. That is, **notes** must *not* contain

```
<?xml version="1.0" encoding="UTF-8"?>
```

nor (where the following is only one specific example of a DOCTYPE declaration)

```
<!DOCTYPE html PUBLIC "-//W3C//DTD XHTML 1.0 Strict//EN"
 "http://www.w3.org/TR/xhtml1/DTD/xhtml1-strict.dtd">
```

The second restriction is intended to balance freedom of content with the complexity of implementing software that can interpret the content. The content of **notes** in SBML can consist only of the following possibilities:

1. A complete XHTML document (minus the XML and DOCTYPE declarations, of course), that is, XHTML content beginning with the **html** tag. The following is an example skeleton:

```
<notes>
    <html xmlns="http://www.w3.org/1999/xhtml">
    ...
    </html>
</notes>
```

2. The **body** element from an XHTML document. The following is an example skeleton:

```
<notes>
    <body xmlns="http://www.w3.org/1999/xhtml">
    ...
    </body>
</notes>
```

3. Any XHTML content that would be permitted within a **body** element. Note that if this consists of multiple elements, each one must declare the XML namespace separately. The following is an example skeleton example:

```
<notes>
    <p xmlns="http://www.w3.org/1999/xhtml">
    ...
    </p>
    <p xmlns="http://www.w3.org/1999/xhtml">
    ...
    </p>
</notes>
```

Another way to summarize the restrictions above is simply to say that the content of an SBML **notes** element can be only be a complete **html** element, a **body** element, or whatever is permitted inside a **body** element. In practice, this does not limit in any meaningful way what can be placed inside a **notes** element; for example, if an application or modeler wants to put a complete XHTML page, including a **head** element, it can be done by putting in everything starting with the **html** container. However, the restrictions above do make it somewhat simpler to write software that can read and write the **notes** content. Appendix H describes one possible approach to doing just that.

3.3.3 The `annotation` *field*

Whereas the **notes** field described above is a container for content to be shown directly to humans, the **annotation** field is a container for optional software-generated content *not* meant to be shown to humans. Every data object derived from *Sbase* can have its own value for **annotation**. The field's data type is XML type **any**, allowing essentially arbitrary data content. SBML places only a few restrictions on the organization of the content; these are intended to help software tools read and write the data as well as help reduce conflicts between annotations added by different tools.

The use of XML Namespaces in `annotation`

At the outset, software developers should keep in mind that multiple software tools may attempt to read and write annotation content. To reduce the potential for collisions between annotations written by different applications, SBML Level 2 Version 2 stipulates that tools must use XML namespaces (Bray et al., 1999) to specify the intended vocabulary of every annotation. The application's developers must choose a URI (*Universal Resource Identifier*; Harold and Means 2001; W3C 2000a) reference that uniquely identifies the vocabulary the application will use, and a prefix string for the annotations. Here is an example. Suppose an application uses the URI `http://www.mysim.org/ns` and the prefix `mysim` when writing annotations related to screen layout. The content of an annotation might look like the following:

```
<annotation>
    <mysim:nodecolors xmlns:mysim="http://www.mysim.org/ns"
         mysim:bgcolor="green"
         mysim:fgcolor="white"/>
</annotation>
```

In this particularly simple case, the content consists of a single XML element (`nodecolors`) with two attributes (`bgcolor`, `fgcolor`), all of which are prefixed by the string `mysim`. (Presumably this particular content would have meaning to the hypothetical application in question.) The content in this particular example is small, but it should be clear that there could easily have been an arbitrarily large amount of data placed inside the `mysim:nodecolors` element.

The key point of the example above is that application-specific annotation data is entirely contained inside a single *top-level element* within the SBML `annotation` container. SBML Level 2 Version 2 places the following restrictions on annotations:

- Within a given SBML `annotation` element, there can only be one top-level element using a given namespace. An annotation element can contain multiple top-level elements but each must be in a different namespace.
- No top-level element in an `annotation` may use an SBML XML namespace, either explicitly by referencing one of the SBML XML namespace URIs or implicitly by failing to specify any namespace on the annotation. (As of SBML Level 2 Version 2, the defined SBML namespaces are the following URIs: `http://www.sbml.org/sbml/level1`, `http://www.sbml.org/sbml/level2`, as well as `http://www.sbml.org/sbml/level2/version2`.)
- The ordering of top-level elements within a given `annotation` element is *not* significant. An application should not expect that its annotation content appears first in the `annotation` element, nor in any other particular location.

The use of XML namespaces in this manner is intended to improve the ability of multiple applications to place annotations on SBML model structures with reduced risks of interference or name collisions. Annotations stored by different simulation packages can therefore coexist in the same model definition. The rules governing the content of `annotation` elements are designed to enable applications to easily add, change, and remove their annotations from SBML elements while simultaneously preserving annotations inserted by other applications when mapping SBML from input to output.

Some more examples hopefully will make this more clear. The next example is invalid because it contains a top-level element in the SBML XML namespace—this happens because no namespace is declared for the `<cytoplasm>` element, which means by default it falls into the SBML namespace:

```
<annotation>
    <cytoplasm/>
</annotation>
```

The following example is invalid because it contains two top-level elements using the same XML namespace. Note that it does not matter that these are two different top-level elements (`<nodecolors>` and `<textcolors>`); what matters is that these separate elements are both in the same namespace rather than having been collected and placed inside one overall container element for that namespace.

```
<annotation>
    <mysim:nodecolors xmlns:mysim="http://www.mysim.org/ns"
        mysim:bgcolor="green"
        mysim:fgcolor="white"/>
    <mysim:textcolors xmlns:mysim="http://www.mysim.org/ns"
        mysim:bgcolor="green"
        mysim:fgcolor="white"/>
</annotation>
```

On the other hand, the following example is valid:

```
<annotation>
    <mysim:geometry xmlns:mysim="http://www.mysim.org/ns"
         mysim:bgcolor="green" mysim:fgcolor="white">
        <graph:node xmlns:graph="http://www.graph.org/ns" graph:x="4" graph:y="5" />
    </mysim:geometry>
    <othersim:icon xmlns:othersim="http://www.othersim.com/">
        WS2002
    </othersim:icon>
</annotation>
```

It is worth keeping in mind that although XML namespace names must be URIs, they are (like all XML namespace names) *not required* to be directly usable in the sense of identifying an actual, retrieval document or resource on the Internet (Bray et al., 1999). URIs such as `http://www.mysim.org/` may appear as though they are (e.g.,) Internet addresses, but there are not the same thing. This style of URI strings, using a domain name and other parts, is only a simple and commonly-used way of creating a unique name string.

Finally, note that the namespaces being referred to here are XML namespaces specifically in the context of the `annotation` field on *Sbase*. The namespace issue here is unrelated to the namespaces discussed in Section 3.4.1 in the context of component identifiers in SBML.

Content of annotations and implications for software tools

The `annotation` field in the definition of *Sbase* exists in order that software developers may attach optional application-specific data to the structures in an SBML model. However, it is important that this facility not be misused. In particular, it is *critical* that data essential to a model definition or that can be encoded in existing SBML structures is *not* stored in `annotation`. Parameter values, functional dependencies between model structures, etc., should not be recorded as annotations. It is crucial to keep in mind the fact that data placed in annotations can be freely ignored by software applications. If such data affects the interpretation of a model, then software interoperability is greatly impeded.

Here are examples of the kinds of data that may be appropriately stored in `annotation`: (a) information about the graphical layout of model components; (b) application-specific processing instructions that do not change the essential meaning of a model; (c) identification information for cross-referencing components in a model with items in a data resource such as a database.

Standardized format for certain classes of annotations

For case (c) above (i.e., information for cross-referencing components in a model to data resources), SBML Level 2 Version 2 recommends a standard format for use within an `annotation` field. This format should be used in preference to proprietary syntaxes to maximize the likelihood that multiple software tools will converge on the same syntax for this kind of information. The SBML Level 2 Version 2 recommended scheme is described in Section 6.

3.4 The `id` and `name` fields on SBML components

As will become apparent below, most structures in SBML include two common fields: `id` and `name`. These fields are not defined on *Sbase* (as explained in Section 3.4.3 below), but where they do appear, the common rules of usage described below apply.

3.4.1 The `id` field and identifier scoping

The `id` field is a mandatory field on most structures in SBML. It is used to identify a component within the model definition. Other SBML structures can refer to the component using this identifier. The data type of `id` is always either `Sid` (Section 3.1.7) or `UnitSId` (Section 3.1.8), depending on the object in question.

A biochemical network model can contain a large number of components representing different parts of a model. This leads to a problem in deciding the scope of an identifier: in what contexts does a given identifier X represent the same thing? The approaches used in existing simulation packages tend to fall into two categories which we may call global and local. The *global* approach places all identifiers into a single global namespace, so that an identifier X represents the same thing wherever it appears in a given model definition. The *local* approach places symbols in different namespaces depending on the context, where the context may be, for example, individual reaction rate expressions. The latter approach means that a user may use the same identifier X in different rate expressions and have each instance represent a different quantity.

The fact that different simulation programs may use different rules for identifier resolution poses a problem for the exchange of models between simulation tools. Without careful consideration, a model written out in SBML format by one program may be misinterpreted by another program. SBML Level 2 must therefore include a specific set of rules for treating identifiers and their scopes.

The scoping rules in SBML Level 2 are relatively straightforward and are intended to avoid this problem with a minimum of requirements on the implementation of software tools:

- The identifiers (i.e., the values of the field `id`) of functions, compartment types, compartments, species types, species, reactions, species references, modifier species references, events, global parameters, and the model object, must be unique across the set of all such identifiers in the model. This means, for example, that a reaction and a species definition cannot both have the same identifier.
- Each Reaction instance (see Section 4.13) establishes a private local namespace for local parameter identifiers. Within the definition of that reaction, local parameter identifiers override (shadow) identical identifiers outside of that reaction. Of course, the corollary of this is that local parameters inside a Reaction object instance are not visible to other objects outside of that reaction.

The set of rules above can enable software packages using either local or global namespaces for parameters to exchange SBML model definitions. Software systems using local namespaces for parameters internally should, in principle, be able to accept SBML model definitions without needing to change component identifiers. Environments using a global namespace for parameters internally can perform manipulations of the identifiers of local parameter elements within reaction definitions to avoid identifier collisions.

The namespace rules described here will hopefully provide a clean transition path to future levels of SBML, when submodels are introduced (Section 8.1). Submodels will provide the ability to compose one model from a collection of other models. This capability will have to be built on top of SBML Level 2's namespace organization. A straightforward approach to handling namespaces is to make each submodel's space be private. The rules governing namespaces within a submodel can simply be the Level 2 namespace rule described here, with each submodel having its own (to itself, global) namespace.

3.4.2 The `name` field

In contrast to the `id` field, the `name` field is optional and is not intended to be used for cross-referencing purposes within a model. Its purpose instead is to provide a human-readable label for the component. The data type of the `name` field is the type `string` defined in XML Schema (Biron and Malhotra, 2000; Thompson et al., 2000) and discussed further in Section 3.1. SBML imposes no restrictions as to the content of `name` fields beyond those restrictions defined by the `string` type in XML Schema.

The recommended practice for handling `name` is as follows. If a software tool has the capability for displaying the content of `name` fields, it should display this content to the user as a component's label instead of the component's `id` field. If the user interface does not have this capability (e.g., because it cannot display or use special characters in symbol names), or if the `name` field is missing on a given component, then the user

interface should display the value of the `id` field instead. (Script language interpreters are especially likely to display `id` fields instead of `name` fields.)

As a consequence of the above, authors of systems that automatically generate the values of `id` fields should be aware some systems may display the `id`'s to the user. Authors therefore may wish to take some care to have their software create `id` values that are: (a) reasonably easy for humans to type and read; and (b) likely to be meaningful, e.g., the id field is an abbreviated form of the name field value.

An additional point worth mentioning is although there are restrictions on the uniqueness of `id` values (see Section 3.4.1 above), there are no restrictions on the uniqueness of `name` values in a model. This allows software packages leeway in assigning component identifiers.

3.4.3 Why `id` and `name` are not defined on SBase

Although many SBML components also feature two other fields named `id` and `name`, these fields are purposefully not defined on *Sbase*. There are several reasons for this.

- The presence of an SBML identifier field (`id`) necessarily requires specifying scoping rules for the corresponding identifiers. However, the *Sbase* abstract type is used as the basis for defining components whose scoping rules are in some cases different from each other. (See Section 3.4.1 for more details). If *Sbase* where to have an `id` field, then the specification of *Sbase* would need a default scoping rule and this would then have to be overloaded on derived classes that needed different scoping. This would make the SBML specification more complex.

- The identifier field is optional on some SBML components and required on most others. If `id` was defined as optional on *Sbase*, most component classes would separately have to redefine `id` as being mandatory. This is hardly an improvement over the current arrangement. Conversely, if `id` was defined as mandatory on *Sbase*, it would prevent the field from being optional on those components where it *is* currently optional.

- The *Sbase* abstract type is used as the base type for certain structures such as Sbml, Unit, AssignmentRule, AlgebraicRule, etc., which do not have identifiers at all because these structures do not need to be referenced by other structures. If *Sbase* had a mandatory `id` field, *all* objects of these other types in a model would then need to be assigned unique identifiers. Similarly, because *Sbase* is the base type of the `listOf_____` lists (see Section 3.2), putting `id` on *Sbase* would require all of these lists in a model to be given identifiers. This would be a needless burden on software developers, tools, and SBML users, requiring them to generate and store additional identifiers for objects that never need them.

- *Sbase* does not have a `name` simply because such a field is always paired with an `id` field. Without `id` on *Sbase*, it does not make sense to have `name`.

3.5 Mathematical formulas in SBML Level 2

Mathematical expressions in SBML Level 2 are represented using MathML 2.0 (W3C, 2000b). MathML is an international standard for encoding mathematical expressions using XML. There are two principal facets of MathML, one for encoding content (i.e., the semantic interpretation of a mathematical expression), and another for encoding presentation or display characteristics. SBML only makes direct use of a subset of the content portion of MathML. By borrowing a separately-developed XML standard, we can avoid having to define a specialized syntax for mathematical expressions in SBML and simultaneously leverage existing intellectual and technological work already done in the MathML community. However, it is not possible to produce a completely smooth and conflict-free interface between MathML and other standards used by SBML (in particular, XML Schema). Two specific issues and their resolutions are discussed in Sections 3.5.2.

The XML namespace URI for all MathML elements is `http://www.w3.org/1998/Math/MathML`. Everywhere MathML content is allowed in SBML, the MathML elements must be properly placed within the MathML 2.0 namespace. In XML, this can be accomplished in a number of ways, and the examples throughout this

specification illustrate the use of this namespace and MathML in SBML. Please refer to the W3C document by Bray et al. (1999) for more technical information about using XML namespaces.

3.5.1 Subset of MathML used in SBML Level 2

The subset of MathML 2.0 elements used in SBML Level 2 is similar to that used by CellML (Hedley et al., 2001), another model definition language with similar goals as SBML. The subset of MathML elements used in SBML is listed below:

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

The inclusion of logical operators, relational operators, `piecewise`, `piece`, and `otherwise` elements facilitates the encoding of discontinuous expressions. Note that MathML elements for representing partial differential calculus are not included. We anticipate that the requirements for partial differential calculus will be addressed in proposals for future SBML geometry representations (see Section 8.1).

As defined by MathML 2.0, the semantic interpretation of the mathematical functions listed above follows the definitions of the functions laid out by Abramowitz and Stegun (1977) and Zwillinger (1996). Readers are directed to these sources and the MathML specification for information about such things as which principle values of the inverse trigonometric functions to use.

Software authors should take particular note of the MathML semantics of the N-ary operators `plus`, `times`, `and`, `or` and `xor`, when they are used with different numbers of arguments. The MathML specification (W3C, 2000b) appendix C.2.3 describes the semantics for these operators with zero, one, and more arguments.

The following are the only attributes permitted on MathML elements in SBML:

- `style`, `class` and `id` on any element;
- `encoding` and `definitionURL` on `csymbol` elements; and
- `type` on `cn` elements.

Missing values for these attributes are to be treated in the same way as defined by MathML. These restrictions on attributes are designed to confine the MathML elements to their default semantics and to avoid conflicts in the interpretation of the type of token elements.

3.5.2 Numbers and `cn` elements

In MathML, literal numbers are written as the content portion of a particular element called `cn`. This element takes an optional attribute, `type`, used to indicate the *type* of the number (such as whether it is meant to be an integer or a floating-point quantity). Here is an example of its use:

```
<math xmlns="http://www.w3.org/1998/Math/MathML">
    <apply>
        <times/>
```

```
            <cn type="integer"> 42 </cn>
            <cn type="real"> 3.3 </cn>
        </apply>
    </math>
```

The content of a `cn` element must be a number. The number can be preceded and succeeded by whitespace (see Section 3.5.4). The following are the only permissible values for the `type` attribute on MathML `cn` elements: "`e-notation`", "`real`", "`integer`", and "`rational`". The value of the `type` attribute defaults to "`real`" if it is not specified on a given `cn` element.

Value space restrictions on cn content

SBML imposes certain restrictions on the value space of numbers allowed in MathML expressions. According to the MathML 2.0 specification, the values of the content of `cn` elements do not necessarily have to conform to any specific floating point or integer representations designed for CPU implementation. For example, in strict MathML, the value of a `cn` element could exceed the maximum value that can be stored in a IEEE 64 bit floating point number (IEEE 754). This is different from the XML Schema type `double` that is used in the definition of floating point fields of structures in SBML, which *is* restricted to IEEE double-precision 64-bit floating point type IEEE 754-1985. To avoid an inconsistency that would result between numbers elsewhere in SBML and numbers in MathML expressions, SBML Level 2 Version 2 imposes the following restriction on MathML content appearing in SBML:

- Integer values (i.e., the content of `cn` elements having `type`="`integer`") must conform to the `int` type used elsewhere in SBML (Section 3.1.3)
- Floating-point values (i.e., the content of `cn` elements having `type`="`real`" or `type`="`e-notation`") must conform to the `double` type used elsewhere in SBML (Section 3.1.5)

Syntactic differences in the representation of numbers in scientific notation

It is important to note that MathML uses a style of scientific notation that differs from what is defined in XML Schema, and consequently what is used in SBML attribute values. The MathML 2.0 type "`e-notation`" requires the mantissa and exponent to be separated by one `<sep/>` element. The mantissa must be a real number and the exponent part must be a signed integer. This leads to expressions such as

```
<cn type="e-notation"> 2 <sep/> -5 </cn>
```

for the number 2×10^{-5}. It is especially important to note that the expression

```
<cn type="e-notation"> 2e-5 </cn>
```

is *not valid* in MathML 2.0 and therefore cannot be used in MathML content in SBML. However, elsewhere in SBML, when an attribute value is declared to have the data type `double` (a type taken from XML Schema), the compact notation "`2e-5`" is in fact allowed. In other words, within MathML expressions contained in SBML (and *only* within such MathML expressions), numbers in scientific notation must take the form `<cn type="e-notation"> 2 <sep/> -5 </cn>`, and everywhere else they must take the form "`2e-5`".

This is a regrettable difference between two standards that SBML replies upon, but it is not feasible to redefine these types within SBML because the result would be incompatible with parser libraries written to conform with the MathML and XML Schema standards. It is also not possible to use XML Schema to define a data type for SBML attribute values permitting the use of the `<sep/>` notation, because XML attribute values cannot contain XML elements—that is, `<sep/>` cannot appear in an XML attribute value.

3.5.3 Use of `ci` elements in MathML expressions in SBML

The content of a `ci` element must be an SBML identifier that is declared elsewhere in the model. The identifier can be preceded and succeeded by whitespace. The set of possible identifiers that can appear in a `ci` element depends on the containing structure in which the `ci` is used:

- If a `ci` element appears in the body of a function definition (Section 4.3), the referenced identifier must be either (i) one of the declared arguments to that function, or (ii) the identifier of a previously defined function.

- In all other situations, the referenced identifier must be the identifier of a species, compartment, parameter, function or reaction declared in the model. The following are the only possible interpretations of using such an identifier in SBML:
  - *Species identifier*: When a species identifier occurs in a `ci` element, it represents the quantity (*amount of substance* or *concentration*) of that species. The units associated with a species identifier are *the units of the species*, defined in Section 4.8.5.
  - *Compartment identifier*: When a compartment identifier occurs in a `ci` element, it represents the size of the compartment. The units associated with the size of the compartment are those given on the Compartment structure that declares the identifier; see Section 4.7.5.
  - *Parameter identifier*: When a parameter identifier occurs in a `ci` element, it represents the numerical value assigned to that parameter. The units associated with the parameter value are the units assigned in its instance of a Parameter structure; see Section 4.9.3.
  - *Function identifier*: When a function identifier occurs in a `ci` element, it represents a call to that function. Function references in MathML occur in the context of using MathML's `apply` and often involve supplying arguments to the function; see Section 4.3.
  - *Reaction identifier*: When a reaction identifier occurs in a `ci` element, it represents the rate of the reaction, which is given by the kinetic law of the reaction if present. The units associated with the reaction value are the units assigned to the KineticLaw structure contained within the Reaction structure; see Section 4.13.5. (The units of the reaction identifier follow the defaults described in Section 4.13.5 when the KineticLaw structure is not present.)

The content of `ci` elements in MathML formulas outside of a KineticLaw or FunctionDefinition must always refer to objects declared in the top level global namespace; i.e., SBML uses "early binding" semantics. Inside of KineticLaw, a `ci` element can additionally refer to local parameters defined within that KineticLaw instance; see Section 4.13.5 for more information.

3.5.4 Handling of whitespace

MathML 2.0 defines "whitespace" in the same way as XML does, i.e., the space character (Unicode hexadecimal code 0020), horizontal tab (code 0009), newline or line feed (code 000A), and carriage return (code 000D). In MathML, the content of elements such as `cn` and `ci` can be surrounded by whitespace characters. Prior to using the content, this whitespace is "trimmed" from both ends: all whitespace at the beginning and end of the content is removed Ausbrooks et al. (2003).

For example, in `<cn> 42 </cn>`, the amount of white space on either side of the "`42`" inside the `<cn>` ... `</cn>` container does not matter. Prior to interpreting the content, the whitespace is removed altogether.

3.5.5 Use of `csymbol` elements in MathML expressions in SBML

SBML Level 2 uses the MathML `csymbol` element to denote certain built-in mathematical entities without introducing reserved names into the component identifier namespace. The `encoding` field of `csymbol` should be set to "`text`". The `definitionURL` should be set to one of the following predefined SBML symbol URIs:

- `http://www.sbml.org/sbml/symbols/time`. This represents the current simulation time. See Section 3.5.6 for more information. The units of the current time entity are determined from the built-in `time` of Table 3 on page 37.

- `http://www.sbml.org/sbml/symbols/delay`. This represents a delay function. The delay function has the form $delay(x, d)$, taking two MathML expressions as arguments. Its value is the value of argument x at d time units before the current time. There are no restrictions on the form of x. The units of the d parameter are determined from the built-in `time`. The value of the d parameter, when evaluated, must

be numerical and be greater than or equal to 0. The *delay* function is useful for representing biological processes having a delayed response, but where the detail of the processes and delay mechanism is not relevant to the operation of a given model. See Section 3.5.6 below for additional considerations surrounding the use of this `csymbol`.

The following examples demonstrate these concepts. The XML fragment below encodes the formula $x + t$, where t stands for time.

```
<math xmlns="http://www.w3.org/1998/Math/MathML">
    <apply>
        <plus/>
        <ci> x </ci>
        <csymbol encoding="text" definitionURL="http://www.sbml.org/sbml/symbols/time">
            t
        </csymbol>
    </apply>
</math>
```

In the fragment above, the use of the token `t` is mostly a convenience for human readers—the string inside the `csymbol` could have been almost anything, because it is essentially ignored by MathML parsers and SBML. Some MathML and SBML processors will take note of the token and use it when presenting the mathematical formula to users, but the token used has no impact on the interpretation of the model and it does *not* enter into the SBML component identifier namespace. In other words, the SBML model cannot refer to `t` in the example above. The content of the `csymbol` element is for rendering purposes only and can be ignored by the parser.

As a further example, the following XML fragment encodes the equation $k + delay(x, 0.1)$ or alternatively $k_t + x_{t-0.1}$:

```
<math xmlns="http://www.w3.org/1998/Math/MathML">
    <apply>
        <plus/>
        <ci> k </ci>
        <apply>
            <csymbol encoding="text" definitionURL="http://www.sbml.org/sbml/symbols/delay">
                delay
            </csymbol>
            <ci> x </ci>
            <cn> 0.1 </cn>
        </apply>
    </apply>
</math>
```

Note that the URI in the value of `definitionURL`, as all URIs, is intended to serve as a unique identifier and is not intended to be dereferenced as an Internet address. There is nothing actually located at the address `http://www.sbml.org/sbml/symbols/delay`.

3.5.6 Simulation time

The principal use of SBML is to represent quantitative dynamical models whose behaviors manifest themselves over time. In defining an SBML model using constructs such as reactions, time is most often implicit and does not need to be referred to in the mathematical expressions themselves. However, sometimes an explicit time dependency needs to be stated, and for this purpose, the *time* `csymbol` (described above in Section 3.5.5) may be used. This *time* symbol refers to "instantaneous current time" in a simulation, frequently given the literal name t in one's equations.

An assumption in SBML is that "start time" or "initial time" in a simulation is zero, that is, if t_0 is the initial time in the system, $t_0 = 0$. This corresponds to the most common scenario. Initial conditions in SBML take effect at time $t = 0$. There is no mechanism in SBML for setting the initial time to a value other than 0. To refer to a different time in a model, one approach is to define a Parameter for a new time variable and use an AssignmentRule in which the assignment expression subtracts a value from the `csymbol` *time*. For example, if the desired offset is 2 time units, the MathML expression would be

```
<math xmlns="http://www.w3.org/1998/Math/MathML">
    <apply>
        <minus/>
        <csymbol encoding="text" definitionURL="http://www.sbml.org/sbml/symbols/time">
            t
        </csymbol>
        <cn> 2 </cn>
    </apply>
</math>
```

SBML's assignment rules (Section 4.11.4) can be used to express mathematical statements that hold true at all moments, so using an assignment rule with the expression above will result in the value being equal to $t - 2$ at every point in time. A parameter assigned this value could then be used elsewhere in the model, its value could be plotted by a simulator, etc.

3.5.7 Initial conditions and special considerations

The identifiers of Species, Compartment, Parameter, and Reaction object instances in a given SBML model refer to the main variables in the model. Depending on certain attributes of these objects (e.g., the `constant` flag on species, compartments and parameters—this and other conditions are explained in the relevant sections elsewhere in this document), some of the variables may have constant value throughout a simulation, and others' values may change. These changes in values over time are determined by the system of equations constructed from the model's reaction, assignment, rule and event definitions.

As described in Section 3.5.6, an SBML model's simulation is assumed to begin at $t = 0$. The availability of the *delay* `csymbol` (Section 3.5.5) introduces the possibility that at $t = 0$, mathematical expressions in a model may draw on values of model components from time *prior* to $t = 0$. A simulator may therefore need to begin calculations at some point in time $t_i \leq 0$ deemed sufficiently far before $t = 0$ to allow the calculation of necessary values for delay expressions in the model. If there are no delays in the model, then $t_i = 0$.

The following is how the definitions of the model should be applied:

1. At time t_i:
   - The values of all Species, Compartment, and Parameter objects whose identifiers are not the subject of an InitialAssignment are assigned by the definition of the object in the model; else, InitialAssignment values are computed and assigned as the relevant Species quantity, Compartment size, or Parameter value. All assignments are performed once and thereafter are in effect for $t \geq t_i$. If an object is defined with `constant`="`false`", its value may be changed by other constructs or reactions in a model; if `constant`="`true`", the rest of the steps described below cannot change the value.
2. For time $t \geq t_i$:
   - AssignmentRule and AlgebraicRule definitions are in effect from this point in time forward. These may influence the values of Species quantity, Compartment size, or Parameter value. (Note that there cannot be an AssignmentRule for an identifier that is also the subject of an InitialAssignment; see Sections 4.10 and 4.11.4.)
3. At time $t = 0$:
   - The system of equations constructed by combining AssignmentRule equations, AlgebraicRule equations, RateRule equations, and the equations constructed from the Reaction definitions in the model, used to obtain the initial conditions for the numerical solver algorithms.
   - Constraint definitions begin to take effect. (The result may be a constraint violation; see Section 4.12.)
4. For time $t > 0$:
   - RateRule definitions begin to take effect.
   - Event definitions begin to take effect.
   - System simulation proceeds.

3.5.8 Math expression types

MathML operators in SBML each return results in one of two possible types: boolean and numeric. The following guidelines summarize the different possible cases.

The relational operators (`eq`, `neq`, `gt`, `lt`, `geq`, `leq`), the logical operators (`and`, `or`, `xor`, `not`), and the boolean constants (`false`, `true`) always return boolean values.

The type of an operator referring to an SBML FunctionDefinition is determined by the type of the top-level operator of the MathML expression in the `math` field of the function definition. This type may be boolean or numeric.

All other operators, values and symbols return numeric results.

The roots of the expression trees used in the following contexts must yield boolean values:

- the arguments of the MathML logical operators (`and`, `or`, `xor`, `not`);
- the second argument of a MathML `piece` operator;
- the `trigger` field of an SBML Event structure; and
- the `math` field of an SBML Constraint structure.

The roots of the expression trees used in the following contexts can optionally yield boolean values:

- the arguments to the `eq` and `neq` operators;
- the first arguments of MathML `piece` and `otherwise` operators; and
- the top level expression of a function definition.

The roots of expression trees in other contexts must yield numeric values.

The type of expressions should be used consistently. The set of expressions that make up the first arguments of the `piece` and `otherwise` operators within the same `piecewise` operator should all return values of the same type. The arguments of the `eq` and `neq` operators should return the same type.

4 SBML components

In this section, we define each of the major data structures in SBML. To provide illustrations of their use, we give partial model definitions in XML. Section 7 provides many full examples of SBML in XML.

In type definitions presented throughout this section, we follow the UML convention of hiding the attributes derived from a parent type such as *Sbase*. It should be kept in mind that these attributes are always available.

4.1 The SBML container

The outermost portion of an SBML Level 2 Version 2 model definition consists of a single Sbml structure enclosing a single Model structure (see next Section). The definition of Sbml is shown in Figure 6. The element has two required attributes: `level` and `version`. For SBML Level 2 Version 2, these attributes must both be set to "2".

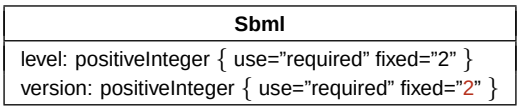

Figure 6: *The definition of Sbml for SBML Level 2 Version 2. Following UML notation, additional fields that are inherited from a base class, in this case Sbase, are not shown.*

In the transformation of UML to XML used in SBML, the structure of Figure 6 is turned into an element named `sbml`. This element constitutes the outermost container of XML content. To be a well-formed XML document, this container should be preceded by a string known as the *XML declaration*, which specifies both the version of XML assumed and the document character encoding. The XML declaration begins with the characters `<?xml`. The version of XML used by the SBML Level 2 Version 2 specification is version 1.0, and the character encoding is required to be UTF-8. The following is an abbreviated example of these essential XML elements for a SBML Level 2 Version 2 document:

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns="http://www.sbml.org/sbml/level2/version2" level="2" version="2">
  ...
</sbml>
```

Note the additional attribute `xmlns` on `sbml`. This declares the default XML namepace used within the `sbml` element. The namespace URI for SBML Level 2 Version 2 is `http://www.sbml.org/sbml/level2/version2`. All SBML Level 2 Version 2 elements must be encoded using this URI by assigning it to either the default XML namespace as shown above, or using a tag prefix on every element.

An SBML XML document must not contain elements or attributes in the SBML namespace that are not defined in this SBML Level 2 Version 2 specification. Documents containing unknown elements or attributes placed in the SBML namespace do not conform to the SBML Level 2 Version 2 specification.

Readers may wonder why the SBML top-level XML element uses both a namespace URI identifying the SBML level and version, as well as separate XML attributes giving the level and version. Why is the information duplicated? There are several reasons. First, XML is only one possible serialization of SBML (albeit an extremely popular one at this time). Though most of this document is written with XML in mind, it is the intention behind the design of SBML that its object structure should be implementable in other languages and software systems. Programmatic access is easier if the level and version information are accessible directly as data rather than have to be extracted from a string. Second, generic high-level XML parsers may not give their calling programs access to the value of the `xmlns` attribute. Providing the information via separate attributes is a good backup measure. And finally, earlier in the history of SBML, it was expected that only the level needed to be encoded as part of the namespace URI (e.g., `http://www.sbml.org/sbml/level1`) because it was hoped that changes within levels would not require XML Schema changes. This has proven to be false, but SBML Level 1 (both versions) and the first version

of SBML Level 2 still subscribe to this principle. This means that for these variants of SBML, software tools must look for a `version` attribute on the top-level element. For backwards compatibility with software that expects this, it makes more sense to keep the version and level attributes.

4.2 Model

The Model structure is the highest-level construct in an SBML data stream or document. Its definition is shown in Figure 7. Only one component of type Model is allowed per instance of an SBML Level 2 Version 2 document or data stream, although it does not necessarily need to represent a single biological entity.

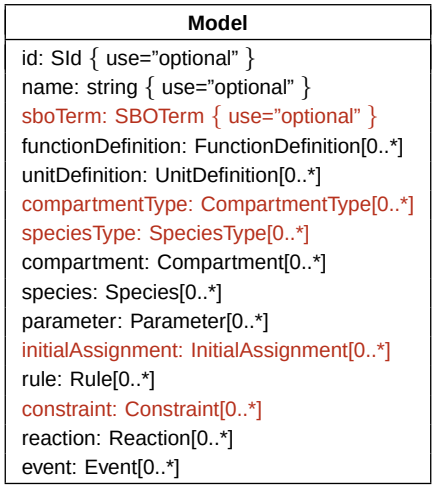

Figure 7: *The definition of Model. Following UML notation, additional fields that are inherited from a base class, in this case Sbase, are not shown.*

Model serves as a container for components of object classes FunctionDefinition, UnitDefinition, CompartmentType, SpeciesType, Compartment, Species, Parameter, InitialAssignment, *Rule*, Constraint, Reaction and Event. All of these components are optional; that is, the lists in each of the respective fields are permitted to have zero length. (However, there are dependencies between components, such that defining some requires defining others. For example, as explained in other sections below, defining a species requires defining a compartment, and defining a reaction requires defining a species.)

The Model structure has an optional field, `id`, used to give the model an identifier. The identifier must be a text string conforming to the syntax permitted by the `SId` data type described in Section 3.1.7. Model also has an optional `name` field, of type `string`. The `name` and `id` fields must be used as described in Section 3.4.

In the XML encoding of an SBML model, the lists of compartment types, compartments, species types, species, unit definitions, parameters, initial assignments, reactions, function definitions, constraints, rules and events are translated into lists of XML elements enclosed within elements of the form `listOf_____s`, where the blank is replaced by the name of the component type. If the word already ends in "s", such as "species", then the extra letter is omitted from the end, leading to `listOfSpecies`. The resulting XML data object has the form illustrated by the following skeletal model:

```
<model id="My_Model">
    <listOfFunctionDefinitions>
        ...
    </listOfFunctionDefinitions>
    <listOfUnitDefinitions>
        ...
    </listOfUnitDefinitions>
    <listOfCompartmentTypes>
        ...
    </listOfCompartmentTypes>
```

```
        <listOfSpeciesTypes>
            ...
        </listOfSpeciesTypes>
        <listOfCompartments>
            ...
        </listOfCompartments>
        <listOfSpecies>
            ...
        </listOfSpecies>
        <listOfParameters>
            ...
        </listOfParameters>
        <listOfInitialAssignments>
            ...
        </listOfInitialAssignments>
        <listOfRules>
            ...
        </listOfRules>
        <listOfConstraints>
            ...
        </listOfConstraints>
        <listOfReactions>
            ...
        </listOfReactions>
        <listOfEvents>
            ...
        </listOfEvents>
    </model>
```

Readers may wonder about the motivations for the `listOf_____s` notation. A simpler approach to creating the lists of components would be to place them all directly at the top level under `<model> ... </model>`. We chose instead to group them within XML elements named after `listOf_____s`, because we believe this helps organize the components and makes visual reading of model definitions easier. These `listOf_____s` elements are derived from *Sbase* which enables each list to contain its own `metaid`, `notes` and `annotation` fields. Further details of how `listOf_____s` elements implement UML lists is described in Section 1.6.

4.2.1 The `sboTerm` field

The Model structure has an optional `sboTerm` field of type `SBOTerm` (see Sections 3.1.9 and 5). When a value is given to this field in a model, the value must be an SBO (`http://www.biomodels.net/SBO/`) identifier referring to a modeling framework defined in SBO (i.e., terms derived from `SBO:0000004`, "modeling framework"). The SBO term chosen should be the most precise (narrow) term that defines the mathematical framework assumed by the *entire* model. An example framework might be "discrete stochastic", which would mean the *entire* model was created under the assumption it will be simulated in a tool that turns substance quantities into discrete numbers and applies a stochastic simulation algorithm (e.g., Gillespie, 1977) to the model. Other frameworks are possible.

The value given to `sboTerm` on a Model interacts with the SBO labels on the model's Reaction elements in the following way. The label on Model should apply to the model as a whole, meaning that *all* reactions in the model assume the same framework. In that case, the `sboTerm` values on individual Reaction elements may be omitted, but only the Reaction SBO labels can be thus omitted; the SBO labels on KineticLaw within Reaction must still be supplied, as must the terms on other components of the model, in order to characterize the model completely.

The absence of a `sboTerm` value means that either the model has not been labeled with SBO terms at all, or there was no available SBO modeling framework term at the time the model was created that was deemed suitable for characterizing the model as a whole. If Model has no value for `sboTerm`, the `sboTerm` fields on each Reaction in a model may still indicate the framework assumed for each reaction separately.

As discussed in Section 5, SBO labels are optional information on a model. Applications are free to ignore `sboTerm` values, and a model must be interpretable without the benefit of SBO labels.

4.3 Function definitions

The FunctionDefinition structure associates an identifier with a function definition. This identifier can then be used as the function called in subsequent MathML `apply` elements. FunctionDefinition is shown in Figure 8.

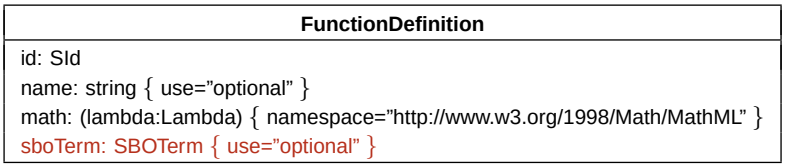

Figure 8: *The definition of FunctionDefinition. Following UML notation, additional fields that are inherited from a base class, in this case Sbase, are not shown.*

Function definitions in SBML (also informally known as "user-defined functions") have relatively limited capabilities. As is made more clear below, a function cannot reference parameters or other model quantities outside of itself; values must be passed as parameters to the function. Moreover, recursive and mutually-recursive functions are not permitted. The purpose of these limitations is to balance power against complexity of implementation. With the restrictions as they are, function definitions could be implemented as textual substitutions—they are simply macros. Software implementations therefore do not need the full function-definition machinery typically associated with programming languages.

The FunctionDefinition structure has three fields: `id`, `name` and `math`. Their purposes are explained in the following subsections.

4.3.1 The `id` and `name` fields

The `id` and `name` fields have types `SId` and `string`, respectively, and operate in the manner described in Section 3.4. MathML `ci` elements in an SBML model can refer to the function defined by a FunctionDefinition using the value of its `id` field.

4.3.2 The `math` field

The `math` field is a container for MathML content that defines the function. The content of this field can only be a MathML `lambda` element. The `lambda` element must begin with zero or more `bvar` elements, followed by any other of the elements in the MathML subset listed in Section 3.5.1 *except* `lambda` (i.e., a `lambda` element cannot contain another `lambda` element). This is the only place in SBML where a `lambda` element can be used. The function defined by a FunctionDefinition is only available for use in other MathML elements that *follow* the FunctionDefinition definition in the model. (These restrictions prevent recursive and mutually-recursive functions from being expressed. They also make it possible for user-defined functions to be implemented as textual substitutions by software systems.)

A further restriction on the content of the `math` field is that it cannot contain references to variables other than the variables declared to the `lambda` itself. That is, the contents of MathML `ci` elements inside the body of the `lambda` can only be the variables declared by its `bvar` elements, or the identifiers of other FunctionDefinitions defined earlier in the model. This implies that functions must be written so that all variables or parameters they may need are passed to them via their function parameters.

4.3.3 The `sboTerm` field

The FunctionDefinition structure has an optional `sboTerm` field of type `SBOTerm` (see Sections 3.1.9 and 5). When a value is given to this field in a function definition, the value must be an SBO identifier referring to a `SBO:0000064`, "mathematical expression" defined in SBO. The relationship is of the form "the function definition *is a* X", where X is the SBO term. The term chosen should be the most precise (narrow) one that captures the role of the function in the model.

As discussed in Section 5, SBO labels are optional information on a model. Applications are free to ignore `sboTerm` values. A model must be interpretable without the benefit of SBO labels.

4.3.4 Examples

The following abbreviated SBML example shows a FunctionDefinition structure defining `pow3` as the identifier of a function computing the mathematical expression x^3, and after that, the invocation of that function in the mathematical formula of a rate law. Note how the invocation of the function uses its identifier

```
<model>
    ...
    <functionDefinition id="pow3">
        <math xmlns="http://www.w3.org/1998/Math/MathML">
            <lambda>
                <bvar><ci> x </ci></bvar>
                <apply>
                    <power/>
                    <ci> x </ci>
                    <cn> 3 </cn>
                </apply>
            </lambda>
        </math>
    </functionDefinition>
    ...
    <listOfReactions>
        <reaction id="reaction_1">
            ...
            <kineticLaw>
                <math xmlns="http://www.w3.org/1998/Math/MathML">
                    <apply>
                        <ci> pow3 </ci>
                        <ci> S1 </ci>
                     </apply>
                </math>
            </kineticLaw>
            ...
        </reaction>
    </listOfReactions>
    ...
</model>
```

4.4 Unit definitions

Units of measurement may be supplied in a number of contexts in an SBML model. The units of the following mathematical entities can be specified explicitly: the size of a compartment, the initial amount of a species, the units of constant and variable parameter values, the units of time and of substance in which a reaction rate is expressed, the units of time in an event's execution delay, and the results of mathematical formulas. Rather than requiring a complete unit definition on every structure, SBML provides a facility for defining units that can be referenced throughout a model. In addition, every kind of SBML mathematical entity has units assigned to it from a set of built-in defaults (see Section 4.4.3 below, and also Sections 4.7.5, 4.8.5 and 4.13.5). By redefining these built-in default units, it is possible to change the units used throughout a model in a simple and consistent manner.

The SBML unit definition facility uses two classes of objects, UnitDefinition and Unit. Their definitions are shown in Figure 9 and explained in more detail in Sections 4.4.1 and 4.4.2 below.

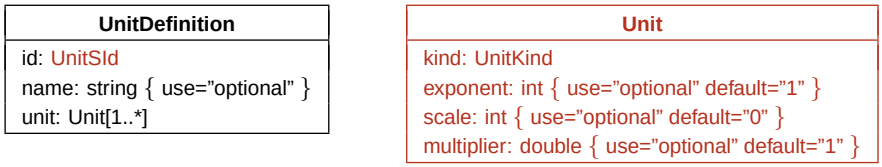

Figure 9: *The definition of UnitDefinition and Unit. Following UML notation, additional fields that are inherited from a base class, in this case Sbase, are not shown.*

The approach to defining units in SBML is compositional; for example, *meter* $second^{-2}$ is constructed by combining a Unit object representing *meter* with another Unit object representing $second^{-2}$. The combination is wrapped inside a UnitDefinition, which provides for assigning an identifier and optional name to the combination. The identifier can then be referenced from elsewhere in a model.

The vast majority of modeling situations requiring new SBML unit definitions involve simple multiplicative combinations of base units and factors. An example of this might be "moles per litre per second". What distinguishes these sorts of simpler unit definitions from more complex ones is that they may be expressed without the use of an additive offset from a zero point. The use of offsets complicates all unit definition system, yet in the domain of SBML the real-life cases requiring offsets are few (and in fact, to the best of our knowledge, only involve temperature). Consequently, the SBML unit system has been consciously designed in a way that attempts to simplify implementation of unit support for the most common cases in systems biology, at the cost of an asymmetry in unit calculations introduced when offsets are used.

4.4.1 The UnitDefinition structure

A unit definition in SBML consists of an instance of a UnitDefinition object, shown in Figure 9.

The `id` and `name` fields

The required field **`id`** and optional field **`name`** have data types **`UnitSId`** and **`string`**, respectively. The **`id`** field is used to give the defined unit a unique identifier by which other parts of an SBML model definition can refer to it. The **`name`** field is intended to be used for giving the unit definition an optional human-readable name; see Section 3.4.2 for more guidelines about the use of names.

There are two important restrictions and guidelines about the use of unit definition **`id`** values:

1. The **`id`** of a UnitDefinition must not contain a value from Table 2 (i.e., the enumeration of predefined **`UnitKind`** values). This constraint simply prevents the redefinition of the SBML base units.
2. There is a set of predefined identifiers for the built-in default units in SBML; these identifiers are "**`substance`**", "**`volume`**", "**`area`**", "**`length`**", and "**`time`**". Using one of these values for **`id`** in a UnitDefinition has the effect of redefining the model-wide default units for the corresponding quantities. We discuss this in more detail in Section 4.4.3.

The list of Units

A UnitDefinition object must contain one or more Unit objects within the **`unit`** container. In the XML form of SBML, this container becomes a **`listOfUnits`** element. Section 4.4.2 explains the meaning and use of Unit.

Example

The following skeleton of a unit definition illustrates an example use of UnitDefinition:

```
<listOfUnitDefinitions>
    <unitDefinition id="unit1">
        <listOfUnits>
            ...
        </listOfUnits>
    </unitDefinition>
    <unitDefinition id="unit2">
        <listOfUnits>
            ...
        </listOfUnits>
    </unitDefinition>
</listOfUnitDefinitions>
```

4.4.2 The Unit structure

A Unit structure represents a (possibly transformed) reference to a base unit chosen from **`UnitKind`** (Table 2). The field **`kind`** indicates the chosen base unit, whereas the three fields **`exponent`**, **`scale`**, and **`multiplier`** define how the base unit is being transformed. These various fields are described in detail below.

Compatibility note: in SBML Level 2 Version 1, Unit had an additional field called **offset**. This field has been removed entirely from SBML Level 2 Version 2. Modelers and software authors are instead directed to use other methods of encoding units requiring offsets. The reasons for this change, and some suggestions for how to achieve equivalent effects of unit offsets, are discussed in more detail below.

The kind field

The Unit data structure has one required field, **kind**, whose value must be taken from **UnitKind**, an enumeration of base units. The possible values of **UnitKind** are given in Table 2.

ampere	gram	katal	metre	second	watt
becquerel	gray	kelvin	mole	siemens	weber
candela	henry	kilogram	newton	sievert	
coulomb	hertz	litre	ohm	steradian	
dimensionless	item	lumen	pascal	tesla	
farad	joule	lux	radian	volt	

Table 2: *The possible values of kind in a UnitKind structure. All are names of base or derived SI units (Bureau International des Poids et Mesures, 2000), except for "dimensionless" and "item", which are SBML additions important for handling certain common situations. "Dimensionless" is intended for cases where a quantity does not have units, and "item" for expressing such things as "N items" (e.g., "100 molecules"). Also, note that the gram and litre are not strictly part of SI; however, they are frequently used in SBML's areas of application and therefore are included as predefined unit identifiers. (The standard SI unit of mass is in fact the kilogram, and volume is defined in terms of cubic metres.) Comparisons of values from UnitKind must performed in a case-sensitive manner.*

Note that the set of acceptable values for the field **kind** does *not* include units defined by UnitDefinition structures. This means that the units definition system in SBML is not hierarchical: user-defined units cannot be built on top of other user-defined units, only on top of base units. SBML differs from CellML Hedley et al. (2001) in this respect; CellML allows the construction of hierarchical unit definitions.

The exponent, scale and multiplier fields

The optional **exponent** field on Unit represents an exponent on the unit. Its default value is "1" (one). A Unit structure also has an optional **scale** field; its value must be an integer exponent for a power-of-ten multiplier used to set the scale of the unit. For example, a unit having a **kind** value of "**gram**" and a **scale** value of "-3" signifies $10^{-3} * gram$, or milligrams. The default value of **scale** is "**0**" (zero), because $10^0 = 1$. Lastly, the optional **multiplier** field can be used to multiply the **kind** unit by a real-numbered factor; this enables the definition of units that are not power-of-ten multiples of SI units. For instance, a **multiplier** of 0.3048 could be used to define "**foot**" as a measure of length in terms of a metre. The **multiplier** field has a default value of "1" (one).

The unit system allows model quantities to be expressed in units other than the base units of Table 2. For analyses and computations, the consumer of the model (be it a software tool or a human) will want to convert all model quantities to base SI units for purposes such as verifying the consistency of units throughout the model. Suppose we begin with a quantity having numerical value y when expressed in units $\{u\}$. The relationship between y and a quantity y_b expressed in base units $\{u_b\}$ is

$$y_b\,\{u_b\} = y\,\{u\}\left(\frac{w\,\{u_b\}}{\{u\}}\right) \tag{1}$$

The term in the parentheses on the right-hand side is a factor w for converting a quantity in units $\{u\}$ to another quantity in units $\{u_b\}$. The ratio of units leads to canceling of $\{u\}$ in the equation above and leaves a quantity in units $\{u_b\}$. It remains to define this factor. In terms of the SBML unit system, it is:

$$\{u\} = (\mathbf{multiplier} \cdot 10^{\mathbf{scale}}\,\{u_b\})^{\mathbf{exponent}} \tag{2}$$

where the dot $(\cdot)$ represents simple scalar multiplication. The variables **multiplier**, **scale**, and **exponent** in the equation above correspond to the fields with the same names in the Unit structure defined in Figure 9.

The exponent in the equation above may make it more difficult to grasp the relationship immediately; so let us suppose for the moment that `exponent`="`1`". Then, it is easy to see that

$$\{u\} = \texttt{multiplier} \cdot 10^{\texttt{scale}}\,\{u_b\}$$

Dividing both sides by $\{u\}$ produces the ratio in the parenthesized portion of Equation 1, which means that $w = \texttt{multiplier} \cdot 10^{\texttt{scale}}$. To take a concrete example, one foot expressed in terms of the metre (a base unit) requires `multiplier`="`0.3048`", `exponent`="`1`", and `scale`="`0`":

$$\text{foot} = 0.3048 \cdot 10^{0} \cdot \text{metre}$$

leading to a conversion between quantities of

$$y_b \text{ metres} = 0.3048 \cdot y \text{ feet}$$

Given a quantity of, say, $y = 2$, the conversion results in $y_b = 0.6096$. To relate this to SBML terms more concretely, the following fragment of SBML illustrates how this is represented using the Unit and UnitDefinition constructs:

```
<listOfUnitDefinitions>
    <unitDefinition id="foot">
        <listOfUnits>
            <unit kind="metre" multiplier="0.3048"/>
        </listOfUnits>
    </unitDefinition>
</listOfUnitDefinitions>
```

The case above is the simplest possible situation, involving the transformation of quantities from a single defined unit $\{u\}$ into a quantity expressed in a single base unit $\{u_b\}$. If, instead, multiple base units $\{u_{b_1}\}, \{u_{b_2}\}, \ldots, \{u_{b_n}\}$ are involved, the following equation holds (where the m_i terms are the `multiplier` values, the s_i terms are the `scale` values, and the x_i terms are the `exponent` values):

$$\begin{aligned}\{u\} &= (m_1 \cdot 10^{s_1}\{u_{b_1}\})^{x_1} \cdot (m_2 \cdot 10^{s_2}\{u_{b_2}\})^{x_2} \cdot \ldots \cdot (m_n \cdot 10^{s_n}\{u_{b_n}\})^{x_n} \\ &= m_1^{x_1} \cdot m_2^{x_2} \cdot \ldots \cdot m_n^{x_n} \cdot 10^{(s_1x_1 + s_2x_2 + \ldots + s_nx_n)}\{u_{b_1}\}^{x_1}\{u_{b_2}\}^{x_2} \ldots \{u_{b_n}\}^{x_n} \end{aligned} \tag{3}$$

Software developers should take care to track the exponents carefully because they can be negative integers. The overall use of Equation 3 is analogous to that of Equation 2, and leads to the following final expression. First, to simplify, let

$$\begin{aligned} m &= m_1^{x_1} \cdot m_2^{x_2} \cdot \ldots \cdot m_n^{x_n} \\ p &= s_1x_1 + s_2x_2 + \ldots + s_nx_n \end{aligned}$$

then,

$$y_b\,\{u_{b_1}\}\{u_{b_2}\}\ldots\{u_{b_n}\} = y\,\{u\}\left(\frac{m \cdot 10^{p}\{u_{b_1}\}^{x_1}\{u_{b_2}\}^{x_2}\ldots\{u_{b_n}\}^{x_n}}{\{u\}}\right) \tag{4}$$

Some additional points are worth discussing about the unit scheme introduced so far. First, and most importantly, the equations above are formulated with the assumption that the base units do not require an additive offset as part of their definition. *When temperature values in units other than kelvin are being considered, then a different interpretation must be made*, as discussed below.

A second point is that care is needed to avoid seemingly-obvious but incorrect translations of units described in textbooks. The scheme above makes it easy to formulate statements such as "1 foot = 0.3048 metres" in the most natural way. However, the most common expression of the relationship between temperature in Fahrenheit and kelvin, "$T_{Fahrenheit} = 1.8 \cdot (T_{kelvin} - 273.15) + 32$" might lead one to believe that defining Fahrenheit degrees in terms of kelvin degrees involves using `multiplier`="`1.8`". *Not so*, when degree changes

are being considered and not temperature values. Converting *temperature values* is different from expressing a relationship between degree measurements. The proper value for the multiplier in the latter case is 5/9, i.e., `multiplier`="`0.555556`" (where we picked an arbitrary decimal precision). If, on the other hand, the actual temperature is relevant to a quantity (e.g., if a model uses a quantity that has particular values at particular temperatures), then offsets are required in the unit calculations and a formula must be used as discussed above.

Handling units requiring the use of offsets in SBML Level 2 Version 2

Unit definitions and conversions requiring offsets cannot be done using the simple approach above. The most general case, involving offsets, multipliers and exponents, requires a completely different approach to defining units than what has been presented up to this point.

In previous versions of SBML, not only was the general case incorrectly presented (i.e., in the same terms described above, when in reality a different approach is required), but few if any developers even attempted to support offset-based units in their software. In the development of SBML Level 2 Version 2, a consensus among SBML developers has emerged that a fully generalized unit scheme is so confusing and complicated that it actually impedes interoperability. Level 2 Version 2 acknowledges this reality by reducing and simplifying the unit system, specifically by removing the `offset` field on Unit and Celsius as a pre-defined unit, and by describing approaches for handling Celsius and other temperature units. This is a backwards-incompatible change relative to SBML Level 2 Version 1 and SBML Level 1 Version 2, but it is believed to have limited real-life impact because so few tools and models appeared to have employed this feature anyway. By simplifying the unit system to the point that it only involves multiplicative factors as described above, we expect that more software tools will be able to support the SBML unit system from this point forward, ultimately improving interoperability.

We first address the question of how to handle units that *do* require offsets:

- *Handling Celsius.* A model in which certain quantities are temperatures measured in degrees Celsius can be converted straightforwardly to a model in which those temperatures are in kelvin. A software tool could do this by performing a straightforward substitution using the following relationship:

$$T_{kelvin} = T_{Celsius} + 273.15 \tag{5}$$

  In every mathematical formula of the model where a quantity (call it x) in degrees Celsius appears, replace x with $x_k + 273.15$ where x_k is now in kelvin. An alternative approach would be to use a FunctionDefinition to define a function encapsulating this relationship above and then using that in the rest of the model as needed. Since Celsius is a commonly-used unit, software tools could help users by providing users with the ability to express temperatures in Celsius in the tools' interfaces, and making substitutions automatically when writing out the SBML.

- *Handling other units requiring offsets.* The only other units requiring offsets in SBML's domain of common applications are other temperature units such as Fahrenheit. Few modern scientists employ Fahrenheit degrees; therefore, this is an unusual situation. The complication inherent in converting between degrees Fahrenheit and kelvin is that both a multiplier and an offset are required:

$$T_{kelvin} = \frac{T_F + 459.67}{1.8} \tag{6}$$

  One approach to handling this is to use a FunctionDefinition to define a function encapsulating the relationship above, then to substitute a call to this function wherever the original temperature in Fahrenheit appears in the model's mathematical formulas. Here is a candidate definition as an example:

```
<functionDefinition id="Fahrenheit_to_kelvin">
    <math xmlns="http://www.w3.org/1998/Math/MathML">
        <lambda>
            <bvar><ci> temp_in_fahrenheit </ci></bvar>
            <apply>
                <divide/>
```

```
                        <apply>
                            <plus/>
                            <ci> temp_in_fahrenheit </ci>
                            <cn> 459.67 </cn>
                        </apply>
                        <cn> 1.8 </cn>
                    </apply>
                </lambda>
            </math>
        </functionDefinition>
```

An alternative approach not requiring the use of function definitions is to use an AssignmentRule for each variable in Fahrenheit units. The AssignmentRule could compute the conversion from Fahrenheit to (say) kelvin, assign its value to a variable (in Kelvin units), and then that variable could be used elsewhere in the model. Still another approach is to rewrite the mathematical formulas of a model to directly incorporate the conversion Equation 6 wherever the quantity appears.

All of these approaches provide general solutions to the problem of supporting any units requiring offsets in the unit system of SBML Level 2 Version 2. It can be used for other temperature units requiring an offset (e.g., degrees Rankine, degrees Réaumur), although the likelihood of a real-life model requiring such other temperature units seems exceedingly small.

In summary, the removal of `offset` in SBML Level 2 Version 2 does not impede the creation of models using alternative units. If conversions are needed, then converting between temperature in degrees Celsius and thermodynamic temperature can be handled rather easily by the simple substitution described above. For the rarer case of Fahrenheit and other units requiring combinations of multipliers and offsets, users are encouraged to employ the power of FunctionDefinition, AssignmentRule, or other constructs in SBML.

Examples

The following example illustrates the definition of an abbreviation "`mmls`" for the units $mmol\ l^{-1}\ s^{-1}$:

```
<listOfUnitDefinitions>
    <unitDefinition id="mmls">
        <listOfUnits>
            <unit kind="mole"   scale="-3"/>
            <unit kind="litre"  exponent="-1"/>
            <unit kind="second" exponent="-1"/>
        </listOfUnits>
    </unitDefinition>
</listOfUnitDefinitions>
```

4.4.3 Built-in units

There are five special unit identifiers in SBML, listed in Table 3, corresponding to the five types of quantities or that play roles in biochemical reactions: substance, volume, area, length and time. All SBML mathematical entities apart from parameters have default units drawn from these predefined values. Table 3 lists the default values; all of the defaults have `multiplier`="`1`" and `scale`="`0`".

Identifier	Possible Scalable Units	Default Units
`substance`	dimensionless, mole, item, gram, kilogram	mole
`volume`	dimensionless, litre, cubic metre	litre
`area`	dimensionless, square metre	square metre
`length`	dimensionless, metre	metre
`time`	dimensionless, second	second

Table 3: *SBML's built-in units.*

Redefinition of built-in units

Table 3 also lists alternative base units that are allowed as the basis of redefined values. For example, a redefinition of the built-in unit of time must be based on units of seconds. Within certain limits, a model may change the built-in units by reassigning the keywords **substance**, **length**, **area**, **time**, and **volume** in a UnitDefinition. The limitations on redefinitions of base units are the following:

1. The UnitDefinition of a redefined built-in unit can only contain a single Unit object within it.
2. The value of the **unitKind** field in the Unit object must be drawn from one of the values in the second column of the appropriate row of Table 3.

Examples

The following example illustrates how to change the built-in units of volume to be millilitres. If this definition appeared in a model, the units of volume on all components that did not explicitly specify different units would be changed to millilitres.

```
<model>
    ...
    <listOfUnitDefinitions>
        <unitDefinition id="volume">
            <listOfUnits>
                <unit kind="litre" scale="-3"/>
            </listOfUnits>
        </unitDefinition>
    </listOfUnitDefinitions>
    ...
</model>
```

4.4.4 References to units

A field that defines the units of a mathematical entity (e.g., the field **units** on Parameter) can refer to a defined unit whose identifier is chosen from among the following:

- A new unit identifier defined by a UnitDefinition as described at the start of Section 4.4;
- The predefined units from Table 2 on page 34; and
- The predefined units defined in Section 4.4.3 and listed in Table 3. (These are "**substance**", "**volume**", "**area**", "**length**", and "**time**".)

Software developers are asked to pay special attention to the units used in an SBML model. Different users and developers sometimes are accustomed to making different assumptions about units, and these assumptions may not correspond to what is actually defined in SBML. The numerical values in a model become meaningless if the corresponding units are not those being assumed. Sections 3.5.3, 4.8.5 and 4.13.5 have particularly important notes about the usage of units in SBML.

4.5 Compartment types

A *compartment type* in SBML is a grouping construct used to establish a relationship between multiple *compartments* (Section 4.7). A compartment type is represented by the CompartmentType data structure, defined in Figure 10 on the next page.

In SBML Level 2 Version 2, a compartment type only has an identity, and this identity can only be used to indicate that particular compartments belong to this type. This may be useful for conveying a modeling intention, such as when a model contains many similar compartments, either by their biological function or the reactions they carry; without a compartment type construct, it would be impossible in the language of SBML to indicate that all of the compartments share an underlying conceptual relationship because each SBML compartment must be given a unique and separate identity.

Figure 10: *The definition of CompartmentType. Following UML notation, additional fields that are inherited from a base class, in this case Sbase, are not shown.*

Compartment types have no mathematical meaning in SBML Level 2 Version 2—they have no effect on a model's mathematical interpretation. Simulators and other numerical analysis software may ignore CompartmentType structures and references to them in a model.

There is no mechanism in SBML for representing hierarchies of compartment types. One CompartmentType structure cannot be the subtype of another CompartmentType structure; SBML provides no means of defining such relationships.

4.5.1 The `id` and `name` fields

As with other major structures in SBML, CompartmentType has a mandatory field, `id`, used to give the compartment type an identifier. The identifier must be a text string conforming to the syntax permitted by the `SId` data type described in Section 3.1.7. CompartmentType also has an optional `name` field, of type `string`. The `name` and `id` fields must be used as described in Section 3.4.

4.5.2 Examples

The following partial SBML example illustrates a compartment type used to relate together many individual compartments in a hypothetical model.

```
<model>
    ...
    <listOfCompartmentTypes>
        <compartmentType id="mitochondria"/>
    </listOfCompartmentTypes>
    <listOfCompartments>
        <compartment id="m1" size="0.013" compartmentType="mitochondria" outside="cell"/>
        <compartment id="m2" size="0.013" compartmentType="mitochondria" outside="cell"/>
        <compartment id="m3" size="0.013" compartmentType="mitochondria" outside="cell"/>
        <compartment id="m4" size="0.013" compartmentType="mitochondria" outside="cell"/>
        <compartment id="cell" size="190.0"/>
    </listOfCompartments>
    ...
</model>
```

4.6 Species types

The term *species type* refers to reacting entities independent of location. These include simple ions (e.g., protons, calcium), simple molecules (e.g., glucose, ATP), large molecules (e.g., RNA, polysaccharides, and proteins), and others. The SpeciesType data structure is intended to represent these entities. Its definition is shown in Figure 11.

Figure 11: *The definition of SpeciesType. Following UML notation, additional fields that are inherited from a base class, in this case Sbase, are not shown.*

SpeciesType structures are included in SBML to enable Species (Section 4.8) of the same type to be related together. It is a conceptual construct; the existence of SpeciesType structures in a model has no effect on the model's numerical interpretation. Except for the requirement for uniqueness of species/species type

combinations located in compartments (described in Section 4.8.2), simulators and other numerical analysis software may ignore SpeciesType structures and references to them in a model.

There is no mechanism in SBML for representing hierarchies of species types. One SpeciesType structure cannot be the subtype of another SpeciesType structure; SBML provides no means of defining such relationships.

4.6.1 The `id` and `name` fields

As with other major structures in SBML, SpeciesType has a mandatory field, `id`, used to give the species type an identifier. The identifier must be a text string conforming to the syntax permitted by the `SId` data type described in Section 3.1.7. SpeciesType also has an optional `name` field, of type `string`. The `name` and `id` fields must be used as described in Section 3.4.

4.6.2 Example

The following XML fragment is an example of two SpeciesType structures embedded in an SBML model.

```
<listOfSpeciesTypes>
    <speciesType id="Glucose"/>
    <speciesType id="Glucose_6_P"/>
</listOfSpeciesTypes>
```

4.7 Compartments

A *compartment* in SBML represents a bounded space in which species are located. Compartments do not necessarily have to correspond to actual structures inside or outside of a biological cell, although models are often designed that way. The definition of Compartment is shown in Figure 12.

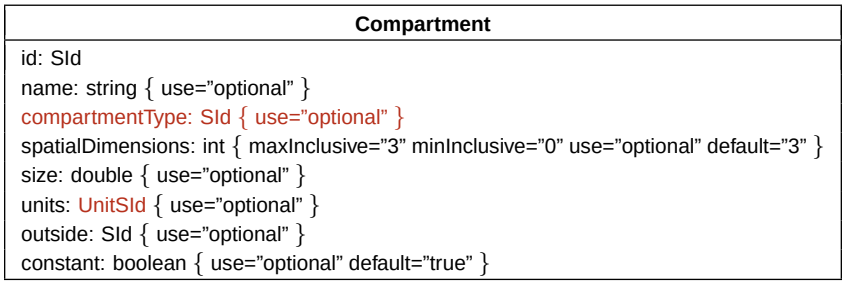

Figure 12: *The definition of Compartment. Following UML notation, additional fields that are inherited from a base class, in this case Sbase, are not shown.*

It is important to note that although compartments are optional in the overall definition of Model (see Section 4.2), every species in an SBML model must be located in a compartment. This in turn means that if a model defines any species, the model must also define at least one compartment. The reason is simply that species represent physical things, and therefore must exist *somewhere*. Compartments represent the *somewhere*.

4.7.1 The `id` and `name` fields

Compartment has one required field, `id`, of type `SId`, to give the compartment a unique identifier by which other parts of an SBML model definition can refer to it. A compartment can also have an optional `name` field of type `string`. Identifiers and names must be used according to the guidelines described in Section 3.4.

4.7.2 The `compartmentType` field

Each compartment in a model may optionally be designated as belonging to a particular compartment type. The optional field `compartmentType` of type `SId` is used identify the compartment type represented by the

Compartment structure. The `compartmentType` field's value must be the identifier of an existing CompartmentType structure in the model. If the `compartmentType` field is not present on a particular compartment definition, a unique virtual compartment type is assumed for that compartment, and no other compartment can belong to that compartment type.

The values of `compartmentType` attributes on compartments have no effect on the numerical interpretation of a model. Simulators and other numerical analysis software may ignore `compartmentType` attributes.

4.7.3 The `spatialDimensions` field

A Compartment structure has an optional field `spatialDimensions`, whose value must be a positive integer indicating the number of spatial dimensions possessed by the compartment. The maximum value is "`3`", meaning a three-dimensional structure (a volume). Other permissible values are "`2`" (for a two-dimensional area), "`1`" (for a one-dimensional curve), and "`0`" (for a point). The default value is "`3`". Note that the number of spatial dimensions possessed by a compartment affects certain aspects of the compartment's size and units-of-size; see the following two subsections.

4.7.4 The `size` field

Each compartment has an optional floating-point field named `size`, representing the initial total size of the compartment. The size may be a volume (if the compartment is a three-dimensional one), or it may be an area (if the compartment is two-dimensional), or a length (if the compartment is one-dimensional).

It is important to note that in SBML Level 2, a missing `size` value *does not imply that the compartment size is 1*. There is no default value of compartment size. (This is unlike the definition of compartment `volume` in SBML Level 1.) When the `spatialDimensions` field does not have a value of "`0`", a missing value for `size` for a given compartment signifies that the value either is unknown, or to be obtained from an external source, or determined by an initial assignment (Section 4.10) or a rule (Section 4.11) elsewhere in the model. The `size` field must not be present if the `spatialDimensions` field has a value of "`0`"; otherwise, a logical inconsistency would exist because a zero-dimensional object cannot have a physical size.

A compartment's size is set by its `size` field exactly once. If the compartment's `constant` field has the value "`true`" (the default), then the size is fixed and cannot be changed except by an InitialAssignment. These two methods of setting the compartment size differ in that the `size` field can only be used to set the compartment size to a literal scalar value, whereas InitialAssignment allows the value to be set using an arbitrary mathematical expression. If the compartment's `constant` field has the value "`false`", the compartment's size value may be overridden by an InitialAssignment or changed by an AssignmentRule or AlgebraicRule, and in addition, for simulation time $t > 0$, it may also be changed by a RateRule or Events. (However, some of these constructs are mutually exclusive; see Sections 4.11 and 4.14.) It is not an error to define `size` on a compartment and also redefine the value using an InitialAssignment, but the `size` value in that case is ignored. Section 3.5.7 provides additional information about the semantics of assignments, rules and values for simulation time $t \leq 0$.

For the reasons given above, the `size` field on a compartment must be defined as optional; however, it is extremely good practice to specify values for compartment sizes when such values are available. There are two major technical reasons for this. First, models ideally should be instantiable in a variety of simulation frameworks. A commonly-used one is the discrete stochastic framework Gillespie (1977); Wilkinson (2006) in which species are represented as item counts (e.g., molecule counts). If species' initial quantities are given in terms of concentrations or densities, it is impossible to convert the values to item counts without knowing compartment sizes. Second, and more importantly, if a model contains multiple compartments whose sizes are not all identical to each other, it is impossible to quantify the reaction rate expressions without knowing the compartment volumes. The reason for the latter is that reaction rates in SBML are defined in terms of *substance/time* (see Section 4.13.5), and when species quantities are given in terms of concentrations or densities, the compartment sizes become factors in the reaction rate expressions.

4.7.5 The `units` field

The units associated with the compartment's `size` value may be set explicitly using the optional field `units`. The default units, and the kinds of units allowed as values of the field `units` interact with the number of spatial dimensions of the compartment. The value of the `units` field of a Compartment object must be one of the base units from Table 2 on page 34, or the built-in units "`volume`", "`area`", "`length`" or "`dimensionless`", or a new unit defined by a unit definition in the enclosing model, subject to the restrictions detailed in Table 4.

Value of field `spatialDimensions`	Field `size` allowed?	Field `units` allowed?	Allowable kinds of units	Default value of field `units`
"`3`"	yes	yes	units of volume, or `dimensionless`	"`volume`"
"`2`"	yes	yes	units of area, or `dimensionless`	"`area`"
"`1`"	yes	yes	units of length, or `dimensionless`	"`length`"
"`0`"	no	no	(no units allowed)	

Table 4: *The types of units permitted for the units of compartment size. If the value of `spatialDimensions` is "`0`", the `units` field must not be present because a compartment with no dimensions has no size and units cannot be meaningfully associated with the (non-existent) size.* Units of volume *means litres, cubic metres, or units derived from them;* units of area *means square metres or units derived from square metres; and* units of length *means metres or units derived from metres. (See also Table 3 on page 37 and Table 2 on page 34.)*

The units of the compartment size, as defined by the `units` field, are used in the following ways:

- The value of the `units` field is used as the units of the `size` field of the compartment structure (see Section 4.7.4).
- The value of the `units` field is used as the units of the compartment identifier when it appears as a numerical quantity in a mathematical formula expressed in MathML (discussed in Section 3.5.3).
- The value of the `units` field is used as the units of the `math` field provided on AssignmentRule and InitialAssignment structures for setting a compartment's size (see Section 4.11.4).
- In a RateRule structure that sets the rate of change of the compartment's size (Section 4.11.5), the units on the rule's `math` field are those in the compartment's `units` field divided by the default *time* units. (In other words, the units for the rate of change of compartment size are *compartment size*/*time* units.)

4.7.6 The `constant` field

A Compartment also has an optional boolean field called `constant` that indicates whether the compartment's size stays constant or can vary during a simulation. A value of "`false`" indicates the compartment's `size` can be changed by other constructs in SBML. The default value for the `constant` field is "`true`" because in the most common modeling scenarios at the time of this writing, compartment sizes remain constant. The `constant` field must default to or be set to "`true`" if the value of the `spatialDimensions` field is "`0`", because a zero-dimensional compartment cannot ever have a size.

4.7.7 The `outside` field

The optional field `outside` of type `SId` can be used to express containment relationships between compartments. If present, the value of `outside` for a given compartment must be the `id` field value of another compartment already defined in the model. Doing so means that the other compartment contains it or is is "outside" of it. This enables the representation of simple topological relationships between compartments, for those simulation systems that can make use of the information (e.g., for drawing simple diagrams of compartments).

There are two restrictions on the containment relationships permitted in an SBML model. First, because a compartment with `spatialDimensions` of "`0`" has no size, such a compartment cannot act as the container of any other compartment *except* compartments that *also* have `spatialDimensions` values of "`0`". Second, the directed graph formed by representing Compartment structures as vertexes and the `outside` attribute values as edges must be acyclic. The latter condition is imposed to prevent a compartment from being contained inside itself.

Although containment relationships are partly taken into account by the compartmental localization of reactants and products, it is not always possible to determine purely from the reaction equations whether one compartment is meant to be located within another. In the absence of a value for `outside`, compartment definitions in SBML Level 2 do not have any implied spatial relationships between each other. For many modeling applications, the transfer of substances described by the reactions in a model sufficiently express the relationships between the compartments. (As discussed in Section 8.1, SBML Level 3 is expected introduce the ability to define geometries and spatial qualities.)

4.7.8 Examples

The following example illustrates two compartments in an abbreviated SBML example of a model definition:

```
<model>
    ...
    <listOfCompartments>
        <compartment id="cytosol" size="2.5"/>
        <compartment id="mitochondria" size="0.3"/>
    </listOfCompartments>
    ...
</model>
```

The following is an example of using `outside` to model a cell membrane. To express that a compartment with identifier "`B`" has a membrane that is modeled as another compartment "`M`", which in turn is located within another compartment "`A`", one would write:

```
<model>
    ...
    <listOfCompartments>
        <compartment id="A"/>
        <compartment id="M" spatialDimensions="2" outside="A"/>
        <compartment id="B" outside="M"/>
    </listOfCompartments>
    ...
</model>
```

4.8 Species

A *species* refers to a pool of reacting entities of a specific *species type* that take part in reactions and are located in a specific *compartment*. The Species data structure is intended to represent these pools. Its definition is shown in Figure 13 on the next page.

Although the exact definition of Species given here has changed from the definition in the specification of SBML Level 2 Version 1 (e.g., through the introduction of species types), the concept represented by Species remains the same.

4.8.1 The `id` and `name` fields

As with other major structures in SBML, Species has a mandatory field, `id`, used to give the species an identifier. The identifier must be a text string conforming to the syntax permitted by the `SId` data type described in Section 3.1.7. Species also has an optional `name` field, of type `string`. The `name` and `id` fields must be used as described in Section 3.4.

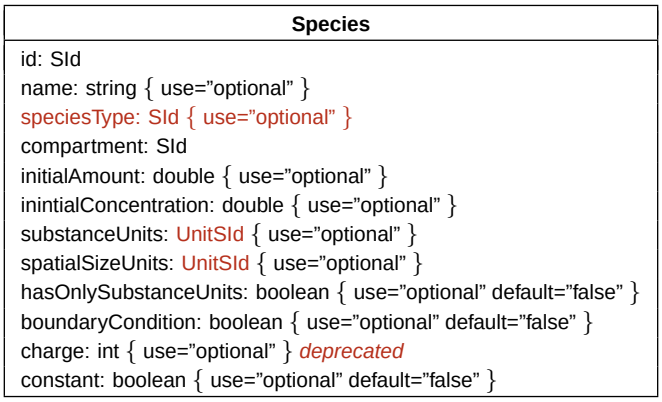

Figure 13: *The definition of Species. Following UML notation, additional fields that are inherited from a base class, in this case Sbase, are not shown.*

4.8.2 The `speciesType` field

Each species in a model may optionally be designated as belonging to a particular species type. The optional field `speciesType` of type `SId` is used to identify the species type of the chemical entities that make up the pool represented by the Species structure. The field's value must be the identifier of an existing SpeciesType structure. If the `speciesType` field is not present on a particular species definition, it means the pool contains chemical entities of a type unique to that pool; in effect, a virtual species type is assumed for that species, and no other species can belong to that species type.

There can be only one species of a given species type in any given compartment of a model. More specifically, for all Species structures having a value for the `speciesType` field, the pair

(`speciesType` field value, `compartment` field value)

must be unique across the set of all Species structures in a model.

The value of `speciesType` attributes on species have no effect on the numerical interpretation of a model. Simulators and other numerical analysis software may ignore `speciesType` attributes.

4.8.3 The `compartment` field

The required field `compartment`, also of type `SId`, is used to identify the compartment in which the species is located. The field's value must be the identifier of an existing Compartment structure. It is important to note that there is no default value for the `compartment` field on Species; every species in an SBML model must be assigned a compartment, and consequently, a model must define at least one compartment if that model contains any species.

4.8.4 The `initialAmount` and `initialConcentration` fields

The optional fields `initialAmount` and `initialConcentration`, both having a data type of `double`, are used to set the initial quantity of the species in the compartment where the species is located. These fields are mutually exclusive; i.e., *only one* can have a value on any given instance of a Species structure.

Missing `initialAmount` and `initialConcentration` values implies that their values either are unknown, or to be obtained from an external source, or determined by an initial assignment (Section 4.10) or rule (Section 4.11) elsewhere in the model. In the case where a species' compartment has a `spatialDimensions` value of "`0`", the species cannot have a value for `initialConcentration` because the concepts of "concentration" and "density" break down when a container has zero dimensions.

A species' initial quantity is set by the `initialAmount` or `initialConcentration` fields exactly once. If the species' `constant` field has the value "`true`" (the default), then the size is fixed and cannot be changed except by an InitialAssignment. These two methods of setting the species quantity differ in that the `initialAmount`

and `initialConcentration` fields can only be used to set the species quantity to a literal scalar value, whereas InitialAssignment allows the value to be set using an arbitrary mathematical expression. If the species' `constant` field has the value "`false`", the species' quantity value may be overridden by an InitialAssignment or changed by AssignmentRule or AlgebraicRule, and in addition, for $t > 0$, it may also be changed by a RateRule or Events. (However, some of these constructs are mutually exclusive; see Sections 4.11 and 4.14.) It is not an error to define `initialAmount` or `initialConcentration` on a species and also redefine the value using an InitialAssignment, but the `initialAmount` or `initialConcentration` setting in that case is ignored. Section 3.5.7 provides additional information about the semantics of assignments, rules and values for simulation time $t \leq 0$.

The units of the value in the `initialAmount` field are set by the `substanceUnits` field of the species structure. The units of the value in the `initialConcentration` field are *substance*/*size* units. The units of *substance* are those defined in the `substanceUnits`, and the *size* units are those given in the `spatialSizeUnits` field as described in Section 4.8.5 below.

4.8.5 The `substanceUnits`, `spatialSizeUnits` and `hasOnlySubstanceUnits` fields

The units associated with a species' quantity, referred to as the *units of the species*, are determined via the optional fields `substanceUnits`, `spatialSizeUnits` and `hasOnlySubstanceUnits`.

The field `hasOnlySubstanceUnits` takes on boolean values and defaults to "`false`". This field's role is to indicate whether the units of the species, when the species identifier appears in mathematical formulas, are intended to be concentration or amount. Although it may seem as though this intention could be determined based on whether `initialConcentration` or `initialAmount` is set, the fact that these two fields are optional means that a separate flag is needed. (Consider the situation where neither is set, and instead the species' quantity is established by an InitialAssignment or AssignmentRule.)

The possible values of *units of the species* are summarized in Table 5. The *units of the species* are of the form *substance*/*size* units (i.e., *concentration* units, using a broad definition of concentration) if the compartment's `spatialDimensions` is non-zero and `hasOnlySubstanceUnits` has the value "`false`". The *units of the species* are of the form *substance* if `spatialDimensions` is zero *or* `hasOnlySubstanceUnits` has the value "`true`". (This dependence on the spatial dimensions of the compartment is due to the fact that a zero-dimensional compartment cannot support concentrations or densities.) The units of *substance* are those defined by the `substanceUnits` field, and the *size* units are those defined by the `spatialSizeUnits` field of a Species instance.

value of `hasOnlySubstanceUnits`	*units of the species* when Spatial Dimensions is greater than 0	*units of the species* when Spatial Dimensions is 0
`false` (default)	*substance*/*size*	*substance*
`true`	*substance*	*substance*

Table 5: *How to interpret the value the `hasOnlySubstanceUnits` field of the Species structure.*

For both `substanceUnits` and `spatialSizeUnits`, the value chosen must be either a base unit from Table 2 on page 34, a built-in unit from Table 3 on page 37, or a new unit defined by a unit definition in the enclosing model. The chosen units for `substanceUnits` must be be `dimensionless`, `mole`, `item`, `kilogram`, `gram`, or units derived from these. The `substanceUnits` field defaults to the the built-in unit "`substance`" shown in Table 3 on page 37.

The type of units assigned to the `spatialSizeUnits` field must agree with the number of spatial dimensions of the species' compartment. Specifically, they must be units of volume or "`dimensionless`" if the value of the compartment's `spatialDimensions` is "`3`"; they must be units of area or "`dimensionless`" if the value of `spatialDimensions` is "`2`"; and they must be units of length or "`dimensionless`" if the value of `spatialDimensions` is "`1`". The `spatialSizeUnits` field must not have a value if `spatialDimensions` on the compartment has a value of "`0`", or if the species' `hasOnlySubstanceUnits` field has a value of "`true`". The default value of the `spatialSizeUnits` is the value of the `units` field of the species' compartment.

The *units of the species* are used in the following ways:

- The species identifier has these units when it appears as a numerical quantity in a mathematical formula expressed in MathML (discussed in Section 3.5.3).
- The `math` field of AssignmentRule and InitialAssignment structures determining the species' quantity (see Section 4.11.4) has these units.
- In RateRule structures that set the rate of change of the species' quantity (Section 4.11.5), the units on the rule's `math` field are the *units of the species* divided by the built-in *time* units.

4.8.6 The `constant` and `boundaryCondition` fields

The Species structure has two optional boolean fields named `constant` and `boundaryCondition`, used to indicate whether and how the quantity of that species can vary during a simulation. Table 6 shows how to interpret the combined values of the `boundaryCondition` and `constant` fields.

`constant` value	`boundaryCondition` value	can have assignment or rate rule	can be reactant or product	species' quantity can be changed by
true	true	no	yes	(never changes)
false	true	yes	yes	rules and events
true	false	no	no	(never changes)
false	false	yes	yes	reactions *or* rules (but not both), and events

Table 6: *How to interpret the values of the `constant` and `boundaryCondition` fields of the Species structure.*

By default, when a species is a product or reactant of one or more reactions, its quantity is determined by those reactions. In SBML, it is possible to indicate that a given species' quantity is *not* determined by the set of reactions even when that species occurs as a product or reactant; i.e., the species is on the *boundary* of the reaction system, and its quantity is not determined by the reactions. The boolean field `boundaryCondition` can be used to indicate this. The value of the field defaults to "`false`", indicating the species *is* part of the reaction system.

The `constant` field indicates whether the species' quantity can be changed at all, regardless of whether by reactions, rules, or constructs other than InitialAssignment. The default value is "`false`", indicating that the species' quantity can be changed. Note that the initial quantity of a species can be set by an InitialAssignment irrespective of the value of the `constant` field.

In practice, a `boundaryCondition` value of "`true`" means a differential equation derived from the reaction definitions should not be generated for the species. However, the species' quantity may still be changed by AssignmentRule, RateRule, AlgebraicRule, Event, and InitialAssignment constructs if its `constant` field is "`false`". Conversely, if the species' `constant` field is "`true`", then its value cannot be changed by anything except InitialAssignment.

A species having `boundaryCondition`="`false`" and `constant`="`false`" can appear as a product and/or reactant of one or more reactions in the model. If the species is a reactant or product of a reaction, it must not also appear as the target of any AssignmentRule or RateRule structure in the model. If instead the species has `constant`="`true`", then it cannot appear as a reactant or product, or as the target of any AssignmentRule or RateRule structure in the model.

The example model in section 7.6 contains all four possible combinations of the `boundaryCondition` and `constant` fields on `species` elements. Section 7.7 gives an example of how one can translate into ODEs a model that uses `boundaryCondition` and `constant` fields.

4.8.7 The charge field

The optional field `charge` takes an integer indicating the charge on the species (in terms of electrons, not the SI unit coulombs). This may be useful when the species is a charged ion such as calcium (Ca^{2+}). The `charge` field is deprecated in SBML Level 2 Version 2: parsers are free to ignore this field and generators do not need to create this field.

4.8.8 Example

The following example shows two species definitions within an abbreviated SBML model definition. The example shows that species are listed under the heading `listOfSpecies` in the model:

```
<model>
    ...
    <listOfSpecies>
        <species id="Glucose" compartment="cell" initialConcentration="4"/>
        <species id="Glucose_6_P" compartment="cell" initialConcentration="0.75"/>
    </listOfSpecies>
    ...
</model>
```

4.9 Parameters

A Parameter structure is used to declare a variable for use in mathematical formulas in an SBML model definition. By default, parameters have constant value for the duration of a simulation and for this reason are called "parameters" instead of variables in SBML. The definition of Parameter is shown in Figure 14.

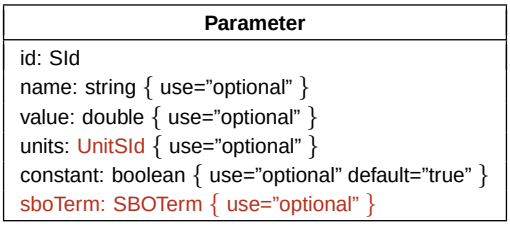

Figure 14: *The definition of Parameter. Following UML notation, additional fields that are inherited from a base class, in this case Sbase, are not shown.*

Parameters can be defined in two places in SBML: in lists of parameters defined at the top level in a Model structure, and within individual reaction definitions (as described in Section 4.13). Parameters defined at the top level are *global* to the whole model; parameters that are defined within a reaction are local to the particular reaction and (within that reaction) *override* any global parameters having the same identifiers (See Section 3.4.1 for further details).

4.9.1 The id and name fields

Parameter has one required field, `id`, of type `SId`, to give the parameter a unique identifier by which other parts of an SBML model definition can refer to it. A parameter can also have an optional `name` field of type `string`. Identifiers and names must be used according to the guidelines described in Section 3.4.

4.9.2 The value field

The optional field `value` determines the value (of type `double`) assigned to the identifier. A missing `value` implies that the `value` either is unknown, or to be obtained from an external source, or determined by an initial assignment (Section 4.10) or a rule (Section 4.11) elsewhere in the model.

A parameter's value is set by its `value` field exactly once. If the parameter's `constant` field has the value "`true`" (the default), then the value is fixed and cannot be changed except by an InitialAssignment. These two methods of setting the parameter's value differ in that the `value` field can only be used to set it to a literal

scalar value, whereas InitialAssignment allows the value to be set using an arbitrary mathematical expression. If the parameter's `constant` field has the value "`false`", the parameter's value may be overridden by an InitialAssignment or changed by AssignmentRule or AlgebraicRule, and in addition, for simulation time $t > 0$, it may also be changed by a RateRule or Events. (However, some of these constructs are mutually exclusive; see Sections 4.11 and 4.14.) It is not an error to define `value` on a parameter and also redefine the value using an InitialAssignment, but the `value` in that case is ignored. Section 3.5.7 provides additional information about the semantics of assignments, rules and values for simulation time $t \leq 0$.

4.9.3 The `units` field

The units associated with the value of the parameter are specified by the field `units`. These units are relevant when the parameter identifier appears in: (a) RateRule, AssignmentRule and InitialAssignment structures setting the value of the parameter; and (b) MathML expressions. A RateRule structure that may determine the value of the parameter has units *parameter units*/*time*, where *parameter units* are the units assigned to the parameter using the `units` field and *time* is the built-in `time` units. The value assigned to the parameter's `units` field must be chosen from one of the following possibilities: one of the base unit identifiers from Table 2 on page 34; one of the built-in unit identifiers appearing in first column of Table 3 on page 37; or the identifier of a new unit defined in the list of unit definitions in the enclosing Model structure. There are no constraints on which units can be chosen from these sets. There are no default units for parameters.

4.9.4 The `constant` field

The Parameter structure has an optional boolean field named `constant` which indicates whether the parameter's value can vary during a simulation. The field's default value is "`true`". A value of "`false`" indicates the parameter's value can be changed by rules (see Section 4.11) and that the `value` is actually intended to be the initial value of the parameter.

Parameters local to a reaction (i.e., those defined within a Reaction's KineticLaw structure, as described in Section 4.13.5) cannot be changed by rules and therefore are implicitly always constant; thus, parameter definitions within Reaction structures should *not* have their `constant` field set to "`false`".

What if a global parameter has its `constant` field set to "`false`", but there are no rules, events or other constructs that ever change its value over time? Although the model may be suspect, this situation is not strictly an error. A value of "`false`" for `constant` only indicates that a parameter *can* change value, not that it *must*.

4.9.5 The `sboTerm` field

The Parameter structure has an optional `sboTerm` field of type `SBOTerm` (see Sections 3.1.9 and 5). When a value is given to this field in a parameter definition, the value must be an SBO identifier referring to a quantitative parameter defined in SBO (i.e., terms derived from `SBO:0000002`, "quantitative parameter"). The relationship is of the form "the SBML parameter *is a* X", where X is the SBO term. The term chosen should be the most precise (narrow) one that captures the role of the parameter in the model.

As discussed in Section 5, SBO labels are optional information on a model. Applications are free to ignore `sboTerm` values. A model must be interpretable without the benefit of SBO labels.

4.9.6 Example

The following is an example of parameters defined at the Model level:

```
<model>
    ...
    <listOfParameters>
        <parameter id="tau1" value="2.3" units="second"/>
        <parameter id="Km1" value="10.7" units="moleperlitre"/>
    </listOfParameters>
    ...
</model>
```

4.10 Initial assignments

SBML Level 2 Version 2 provides two ways of assigning initial values to entities in a model. The simplest and most basic is to set the values of the appropriate `double` fields in the relevant components; for example, the initial value of a model parameter (whether it is a constant or a variable) can be assigned by setting its `value` field directly in the model definition (Section 4.9). However, this approach is not suitable when the value must be calculated, because the initial value fields on different components such as species, compartments, and parameters are single values and not mathematical expressions. This is the reason for the introduction of InitialAssignment: to permit the calculation of the value of a constant or the initial value of a variable from the values of *other* quantities in a model. The definition of InitialAssignment is shown in Figure 15.

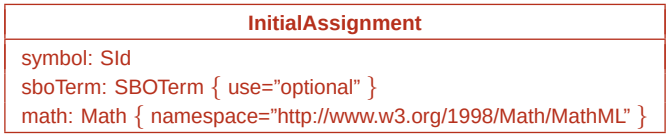

Figure 15: *The definition of InitialAssignment. Following UML notation fields that are inherited from a base class are not shown.*

As explained below, the provision of InitialAssignment does not mean that models necessarily must use this construct when defining initial values of quantities in a model. If a value can be set directly using the relevant field of a component in a model, then that approach may be more efficient and more portable to other software tools. InitialAssignment should be used when the other mechanism is insufficient for the needs of a particular model.

Initial assignments have some similarities to assignment rules (Section 4.11.4). The main differences are (a) an InitialAssignment can set the value of a constant whereas an AssignmentRule cannot, and (b) unlike AssignmentRule, an InitialAssignment definition only applies up to and including the beginning of simulation time, i.e., $t \leq 0$, while an AssignmentRule applies at all times.

4.10.1 The `symbol` field

InitialAssignment contains the field `symbol`, of type `SId`. The value of this field in an InitialAssignment object can be the identifier (i.e., the value of the `id` field) of a Compartment, Species or Parameter elsewhere in the model. The purpose of the InitialAssignment is to define the initial value of the constant or variable referred to by the `symbol` field.

An initial assignment cannot be made to reaction identifiers, that is, the `symbol` field value of an InitialAssignment cannot be an identifier that is the `id` field value of a Reaction object in the model. This is identical to a restriction placed on rules (see Section 4.11.6).

4.10.2 The `math` field

The `math` field contains a MathML expression that is used to calculate the value of the constant or the initial value of the variable. The units of the value computed by the formula in the `math` field are taken to be the units associated with the identifier given in the `symbol` field. (That is, the units are the units of the species, compartment, or parameter, as appropriate for the kind of object identified by the value of `symbol`.)

4.10.3 The `sboTerm` field

InitialAssignment has an optional `sboTerm` field of type `SBOTerm` (see Sections 3.1.9 and 5). When a value is given to this field in an initial assignment definition, the value must be a valid SBO identifier referring to a mathematical expression (i.e., terms derived from `SBO:0000064`, "mathematical expression"). The InitialAssignment object should have a "is a" relationship with the SBO term, and the term should be the most precise (narrow) term that captures the role of the InitialAssignment in the model.

As discussed in Section 5, SBO labels are optional information on a model. Applications are free to ignore

`sboTerm` values. A model must be interpretable without the benefit of SBO labels.

4.10.4 Semantics of initial assignments

The value calculated by an InitialAssignment object overrides the value assigned to the given symbol by the object defining that symbol. For example, if a Compartment's `size` is set in its definition, and the model also contains an InitialAssignment having that compartment's `id` as its `symbol` value, then the interpretation is that the `size` assigned in the Compartment definition should be ignored and the value assigned based on the computation defined in the InitialAssignment.

This does not mean that a definition of a symbol can be omitted if there is an InitialAssignment object for that symbol; the symbols must always be defined even if they are assigned a value separately. For example, there must be a Parameter definition for a given parameter if there is an InitialAssignment for that parameter.

The actions of all InitialAssignment objects are in general terms the same, but differ in the precise details depending on the type of variable being set:

- *In the case of a species*, an InitialAssignment sets the referenced species' initial quantity (*concentration* or *amount of substance*) to the value determined by the formula in `math`. (See Section 4.8.5 for an explanation of how the units of the species' quantity are determined.)
- *In the case of a compartment*, an InitialAssignment sets the referenced compartment's initial size to the size determined by the formula in `math`. The overall units of the formula are the units specified for the size of the compartment. (See Section 4.7.5 for an explanation of how the units of the compartment's size are determined.)
- *In the case of a parameter*, an InitialAssignment sets the referenced parameter's initial value to that determined by the formula in `math`. The overall units of the formula are the units defined for the parameter. (See Section 4.9.3 for an explanation of how the units of the parameter are determined.)

In the context of a simulation, initial assignments establish values that are in effect prior to and including the start of simulation time, i.e., $t \leq 0$. Section 3.5.7 provides information about the interpretation of assignments, rules, and entity values for simulation time up to and include the start time $t = 0$; this is important for establishing the initial conditions of a simulation, especially if the model involves expressions containing the *delay* `csymbol` (Section 3.5.5).

There cannot be two initial assignments for the same symbol in a model; that is, a model must not contain two or more InitialAssignment objects that both have the same identifier as their `symbol` field value. A model must also not define initial assignments *and* assignment rules for the same entity. That is, there cannot be *both* an InitialAssignment and an AssignmentRule for the same symbol in a model, because both kinds of constructs apply prior to and at the start of simulated time (allowing both to exist for a given symbol would result in indeterminism). (See also Section 4.11.6.)

The ordering of InitialAssignment objects is not significant. The combined set of InitialAssignment, AssignmentRule and KineticLaw objects form a set of assignment statements that must be considered as a whole. The combined set of assignment statements should not contain algebraic loops: a chain of dependency between these statements should terminate. (More formally, consider the directed graph of assignment statements where nodes are a model's assignment statements and directed arcs exist for each occurrence of a symbol in an assignment statement `math` field. The directed arcs in this graph start from the statement assigning the symbol and end at the statement that contains the symbol in their math fields. Such a graph must be acyclic.) Examples of valid and invalid set of assignment statements are given in Section 4.11.6.

Finally, it is worth being explicit about the expected behavior in the following situation. Suppose (1) a given symbol has a value x assigned to it in its definition, and (2) there is an initial assignment having the identifier as its `symbol` value and reassigning the value to y, *and* (3) the identifier is also used in the mathematical formula of a second initial assignment. What value should the second initial assignment use? It is y, the value assigned to the symbol by the first initial assignment, not whatever value was given in the symbol's definition. This follows directly from the behavior at the defined at the beginning of this section:

if an InitialAssignment object exists for a given symbol, then the symbol's value is overridden by that initial assignment. (The order of the two initial assignments in the model is irrelevant.)

4.10.5 Example

The following example shows how the species "x" can assigned the initial value $2 \times y$, where "y" is an identifier defined elsewhere in the model:

```
<model>
    ...
    <listOfSpecies>
        <species id="x" initialConcentration="5"/>
    </listOfSpecies>
    ...
    <listOfInitialAssignments>
        <initialAssignment symbol="x">
            <math xmlns="http://www.w3.org/1998/Math/MathML">
                <apply>
                    <times/>
                    <ci> y </ci>
                    <cn> 2 </cn>
                </apply>
            </math>
        </initialAssignment>
    </listOfInitialAssignments>
    ...
</model>
```

The next example illustrates the more complex behavior discussed above, when a symbol has a value assigned in its definition but there also exists an InitialAssignment for it *and* another InitialAssignment uses its value in its mathematical formula.

```
<model>
    ...
    <listOfSpecies>
        <species id="x" initialConcentration="5"/>
    </listOfSpecies>
    ...
    <listOfInitialAssignments>
        <initialAssignment symbol="x">
            <math xmlns="http://www.w3.org/1998/Math/MathML">
                <cn> 2 </cn>
            </math>
        </initialAssignment>
        <initialAssignment symbol="othersymbol">
            <math xmlns="http://www.w3.org/1998/Math/MathML">
                <apply>
                    <times/>
                    <ci> x </ci>
                    <cn> 2 </cn>
                </apply>
            </math>
        </initialAssignment>
    </listOfInitialAssignments>
    ...
</model>
```

The value of "othersymbol" in the SBML excerpt above will be "4". The case illustrates the rule of thumb that if there is an initial assignment for a symbol, the value assigned to the symbol in its definition must be ignored and the value created by the initial assignment used instead.

4.11 Rules

In SBML, *Rules* provide a way to add additional relationships between the variables of a model to determine the dynamical behavior of those variables. *Rules* enable the encoding of relationships that cannot be

expressed using reactions alone (Section 4.13) nor by the assignment of an initial value to a variable in a model.

SBML separates rules into three subclasses for the benefit of model analysis software. The three subclasses are based on the following three different possible functional forms (where x is a variable, f is some arbitrary function returning a numeric result, $\mathbf{V}$ is a vector of variables that does not include x, and $\mathbf{W}$ is a vector of variables that may include x):

Algebraic	left-hand side is zero:	$0 = f(\mathbf{W})$
Assignment	left-hand side is a scalar:	$x = f(\mathbf{V})$
Rate	left-hand side is a rate-of-change:	$dx/dt = f(\mathbf{W})$

In their general form given above, there is little to distinguish between *assignment* and *algebraic* rules. They are treated as separate cases for the following reasons:

- *Assignment* rules can simply be evaluated to calculate intermediate values for use in numerical methods;
- SBML needs to place restrictions on assignment rules, for example the restriction that assignment rules cannot contain algebraic loops (discussed further in Section 4.11.6);
- Some simulators do not contain numerical solvers capable of solving unconstrained algebraic equations, and providing more direct forms such as assignment rules may enable those simulators to process models they could not process if the same assignments were put in the form of general algebraic equations;
- Those simulators that *can* solve these algebraic equations make a distinction between the different categories listed above; and
- Some specialized numerical analyses of models may only be applicable to models that do not contain *algebraic* rules.

The approach taken to covering these cases in SBML is to define an abstract *Rule* structure containing only one field, `math`, to hold the right-hand side expression, then to derive subtypes of *Rule* that add fields to distinguish the cases of algebraic, assignment and rate rules. Figure 16 gives the definitions of *Rule* and the subtypes derived from it. The figure shows there are three subtypes, AlgebraicRule, AssignmentRule and RateRule derived directly from *Rule*. These correspond to the cases *Algebraic*, *Assignment*, and *Rate* described above respectively.

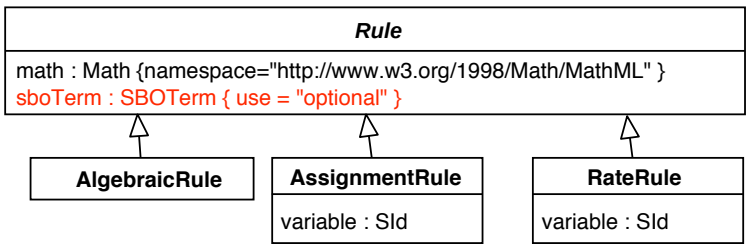

Figure 16: *The definition of Rule and derived types. Following UML notation fields that are inherited from a base class are not shown.*

4.11.1 The `math` field

A *Rule* structure has a required field called `math`, containing a MathML expression defining the mathematical formula of the rule. This MathML formula must return a numerical value. The formula can be an arbitrary expression referencing the variables and other entities in an SBML model. The interpretation of `math` and the units of the formula are described in more detail in Sections 4.11.3, 4.11.4 and 4.11.5 below.

4.11.2 The sboTerm field

The *Rule* structure has an optional `sboTerm` field of type `SBOTerm` (see Sections 3.1.9 and 5). When a value is given to this field, it must be a valid SBO identifier referring to a mathematical expression defined in SBO (i.e., terms derived from `SBO:0000064`, "mathematical expression"). The AlgebraicRule, AssignmentRule, or RateRule object should have a "is a" relationship with the SBO term, and the term should be the most precise (narrow) term that captures the role of that rule in the model.

As discussed in Section 5, SBO labels are optional information on a model. Applications are free to ignore `sboTerm` values. A model must be interpretable without the benefit of SBO labels.

4.11.3 AlgebraicRule

The rule type AlgebraicRule is used to express equations that are neither assignments of model variables nor rates of change. AlgebraicRule does not add any fields to the basic *Rule*; its role is simply to distinguish this case from the other cases. An example of the use of AlgebraicRule structures is given in Section 7.5.

In the context of a simulation, algebraic rules are in effect at all times, $t \geq 0$. For purposes of evaluating expressions that involve the *delay* `csymbol` (Section 3.5.5), algebraic rules are considered to apply also at $t \leq 0$. Section 3.5.7 provides additional information about the semantics of assignments, rules, and entity values for simulation time $t \leq 0$.

The ability to define arbitrary algebraic expressions in an SBML model introduces the possibility that a model is mathematically overdetermined by the overall system of equations constructed from its rules and reactions. An SBML model must not be overdetermined; this is discussed in Section 4.11.6 below.

4.11.4 AssignmentRule

The rule type AssignmentRule is used to express equations that set the values of variables. The left-hand side (the `variable` field) of an assignment rule can refer to the identifier of a species, compartment, or parameter (but not a reaction). The entity identified must not have its `constant` field set to "`true`". The effects of an AssignmentRule are in general terms the same, but differ in the precise details depending on the type of variable being set:

- *In the case of a species*, an AssignmentRule sets the referenced species' quantity (*concentration* or *amount of substance*) to the value determined by the formula in `math`. The units of the formula in `math` must be the same as the *units of the species* (Section 4.8.5) for the species identified by the `variable` field of the AssignmentRule.

  Restrictions: There must not be both an AssignmentRule `variable` field and a SpeciesReference `species` field having the same value, unless that species has its `boundaryCondition` field set to "`true`". In other words, an assignment rule cannot be defined for a species that is created or destroyed in a reaction unless that species is defined as a boundary condition in the model.

- *In the case of a compartment*, an AssignmentRule sets the referenced compartment's size to the value determined by the formula in `math`. The overall units of the formula in `math` must be the same as the units of the size of the compartment (Section 4.7.5).

- *In the case of a parameter*, an AssignmentRule sets the referenced parameter's value to that determined by the formula in `math`. The overall units of the formula in `math` must be the same as the units defined for the parameter (Section 4.9.3).

In the context of a simulation, assignment rules are in effect at all times, $t \geq 0$. For purposes of evaluating expressions that involve the *delay* `csymbol` (Section 3.5.5), assignment rules are considered to apply also at $t \leq 0$. Section 3.5.7 provides additional information about the semantics of assignments, rules, and entity values for simulation time $t \leq 0$.

A model must not contain more than one AssignmentRule or RateRule object having the same value of `variable`; in other words, in the set of all assignment rules and rate rules in an SBML model, each variable

appearing in the left-hand sides can only appear once. This simply follows from the fact that an indeterminate system would result if a model contained more than one assignment rule for the same variable or both an assignment rule and a rate rule for the same variable.

Similarly, a model must also not contain *both* an AssignmentRule and an InitialAssignment for the same variable, because both kinds of constructs apply prior to and at the start of simulation time, i.e., $t \leq 0$. If a model contained both an initial assignment and an assignment rule for the same variable, an indeterminate system would result. (See also Section 4.10.4.)

The value calculated by an AssignmentRule object overrides the value assigned to the given symbol by the object defining that symbol. For example, if a Compartment's `size` is set in its definition, and the model also contains an AssignmentRule having that compartment's `id` as its `variable` value, then the `size` assigned in the Compartment definition is ignored and the value assigned based on the computation defined in the AssignmentRule. Note that this does *not* mean that a definition for a given symbol can be omitted if there is an AssignmentRule object for it. For example, there must be a Parameter definition for a given parameter if there is an AssignmentRule for that parameter.

4.11.5 RateRule

The rule type RateRule is used to express equations that determine the rates of change of variables. The left-hand side (the `variable` field) can refer to the identifier of a species, compartment, or parameter (but not a reaction). The entity identified must have its `constant` field set to "`false`". The effects of a RateRule are in general terms the same, but differ in the precise details depending on which variable is being set:

- *In the case of a species*, a RateRule sets the rate of change of the species' quantity (*concentration* or *amount of substance*) to the value determined by the formula in `math`. The overall units of the formula in `math` must be *species quantity*/*time*, where the *time* units are the built-in units of time described in Section 4.4 and the *species quantity* units are the *units of the species* as defined in Section 4.8.5.

  Restrictions: There must not be both a RateRule `variable` field and a SpeciesReference `species` field having the same value, unless that species has its `boundaryCondition` field is set to "`true`". This means a rate rule cannot be defined for a species that is created or destroyed in a reaction, unless that species is defined as a boundary condition in the model.

- *In the case of a compartment*, a RateRule sets the rate of change of the compartment's size to the value determined by the formula in `math`. The overall units of the formula must be *size*/*time*, where the *time* units are the built-in units of time described in Section 4.4 and the *size* units are the units of size on the compartment (Section 4.7.5).

- *In the case of a parameter*, a RateRule sets the rate of change of the parameter's value to that determined by the formula in `math`. The overall units of the formula must be $x/time$, where x are the units of the parameter (Section 4.9.3).

In the context of a simulation, rate rules are in effect for simulation time $t > 0$. Other types of rules and initial assignments are in effect at different times; Section 3.5.7 describes these conditions.

As mentioned in Section 4.11.4 for AssignmentRule, a model must not contain more than one RateRule or AssignmentRule object having the same value of `variable`; in other words, in the set of all assignment rules and rate rules in an SBML model, each variable appearing in the left-hand sides can only appear once. This simply follows from the fact that an indeterminate system would result if a model contained more than one assignment rule for the same variable or both an assignment rule and a rate rule for the same variable.

4.11.6 Additional restrictions on rules

In addition to the conditions described above regarding the use of AlgebraicRule, AssignmentRule and RateRule, SBML needs to place two additional restrictions on rule use. The first concerns algebraic loops in the system of assignments in a model, and the second concerns overdetermined systems.

The model must not contain algebraic loops

The combined set of InitialAssignment, AssignmentRule and KineticLaw objects constitute a set of assignment statements that should be considered as a whole. (A KineticLaw object is counted as an assignment because it assigns a value to the symbol contained in the `id` field of the Reaction object in which it is defined.) This combined set of assignment statements must not contain algebraic loops—dependency chains between these statements must terminate. To put this more formally, consider a directed graph in which nodes are assignment statements and directed arcs exist for each occurrence of an SBML species, compartment or parameter symbol in an assignment statement's `math` field. Let the directed arcs point from the statement assigning the symbol to the statements that contain the symbol in their `math` field expressions. This graph must be acyclic.

SBML does not specify when or how often rules should be evaluated. Eliminating algebraic loops ensures that assignment statements can be evaluated any number of times without the result of those evaluations changing. As an example, consider the following equations:

$$x = x + 1, \quad y = z + 200, \quad z = y + 100$$

If this set of equations were interpreted as a set of assignment statements, it would be invalid because the rule for x refers to x (exhibiting one type of loop), and the rule for y refers to z while the rule for z refers back to y (exhibiting another type of loop).

Conversely, the following set of equations would constitute a valid set of assignment statements:

$$x = 10, \quad y = z + 200, \quad z = x + 100$$

The model must not be overdetermined

An SBML model must not be overdetermined. A SBML model that does not contain AlgebraicRule structures cannot be overdetermined.

Assessing whether a given continuous, deterministic, mathematical model is overdetermined does not require dynamic analysis; it can be done by analyzing the system of equations created from the model. One approach is to construct a bipartite graph in which one set of vertices represents the variables and the other the set of vertices represents the equations. Place edges between vertices such that variables in the system are linked to the equations that determine them. For algebraic equations, there will be edges between the equation and each variable occurring in the equation. For ordinary differential equations (such as those defined by rate rules or implied by the reaction rate definitions), there will be a single edge between the equation and the variable determined by that differential equation. A mathematical model is overdetermined if the maximal matchings Chartrand (1977) of the bipartite graph contain disconnected vertexes representing equations. (If one maximal matching has this property, then all the maximal matchings will have this property; i.e., it is only necessary to find one maximal matching.) Appendix F describes a method of applying this procedure to specific SBML data objects.

4.11.7 Example of rule use

This section contains an example set of rules. Consider the following set of equations:

$$k = \frac{k_3}{k_2}, \quad s_2 = \frac{k\,x}{1 + k_2}, \quad A = 0.10\,x$$

This can be encoded by the following scalar rule set (where the definitions of `x`, `s`, `k`, `k2`, `k3` and `A` are assumed to be located elsewhere in the model and not shown in this abbreviated example):

```
<listOfRules>
    <assignmentRule variable="k">
        <notes>
            <xhtml:p>
                k = k3/k2
```

```
                    </xhtml:p>
                </notes>
                <math xmlns="http://www.w3.org/1998/Math/MathML">
                    <apply>
                        <divide/>
                        <ci> k3 </ci>
                        <ci> k2 </ci>
                    </apply>
                </math>
            </assignmentRule>
            <assignmentRule variable="s2">
                <notes>
                    <xhtml:p>
                        s2 = (k * x)/(1 + k2)
                    </xhtml:p>
                </notes>
                <math xmlns="http://www.w3.org/1998/Math/MathML">
                    <apply>
                        <divide/>
                        <apply>
                            <times/>
                            <ci> k </ci>
                            <ci> x </ci>
                        </apply>
                        <apply>
                            <plus/>
                            <cn> 1 </cn>
                            <ci> k2 </ci>
                        </apply>
                    </apply>
                </math>
            </assignmentRule>
            <assignmentRule variable="A">
                <notes>
                    <xhtml:p>
                        A = 0.10 * x
                    </xhtml:p>
                </notes>
                <math xmlns="http://www.w3.org/1998/Math/MathML">
                    <apply>
                        <times/>
                        <cn> 0.10 </cn>
                        <ci> x </ci>
                    </apply>
                </math>
            </assignmentRule>
        </listOfRules>
```

4.12 Constraints

The Constraint structure is a mechanism for stating the assumptions under which a model is designed to operate. The *constraints* are statements about permissible values of different quantities in a model. Figure 17 shows the definition of the Constraint data structure.

Constraint
sboTerm: SBOTerm { use="optional" }
math: Math { namespace="http://www.w3.org/1998/Math/MathML" }
message: (any: { namespace="http://www.w3.org/1999/xhtml" }) { minOccurs="0" maxOccurs="1" }

Figure 17: *The definition of Constraint. Following UML notation fields that are inherited from a base class are not shown.*

4.12.1 The `math` field

A Constraint structure has a required field called `math`, containing a MathML formula defining the condition of the constraint. The formula must return a boolean value of "`true`" when the model is a *valid* state. The MathML formula can be an arbitrary expression referencing the variables and other entities in an SBML model. The evaluation of `math` and behavior of constraints are described in more detail in Section 4.12.4 below.

4.12.2 The `message` field

A Constraint structure has an optional field called `message`. This can contain a message in XHTML format that may be displayed to the user when the condition of the constraint in `math` evaluates to a value of "`false`". Software tools are not required to display the message, but it is recommended that they do so as a matter of best practice.

4.12.3 The `sboTerm` field

The Constraint structure has an optional `sboTerm` field of type `SBOTerm` (see Sections 3.1.9 and 5). When a value is given to this field in a constraint definition, the value must be a valid SBO identifier referring to a mathematical expression (i.e., terms derived from `SBO:0000064`, "mathematical expression"). The Constraint should have an "is a" relationship with the SBO term, and the term should be the most precise (narrow) term that captures the role of the Constraint in the model.

As discussed in Section 5, SBO labels are optional information on a model. Applications are free to ignore `sboTerm` values. A model must be interpretable without the benefit of SBO labels.

4.12.4 Semantics of constraints

In the context of a simulation, a Constraint has effect at all times $t >= 0$. Each Constraint's `math` field is first evaluated after any InitialAssignment definitions in a model at $t = 0$ and can conceivably trigger at that point. (In other words, a simulation could fail a constraint immediately.)

Constraint structures *cannot and should not* be used to compute the dynamical behavior of a model as part of, for example, simulation. Constraints may be used as input to non-dynamical analysis, for example by expressing flux constraints for flux balance analysis.

The results of a simulation of a model containing a constraint are invalid from any simulation time at and after a point when the function given by the `math` returns a value of "`false`". (Invalid simulation results do not make a prediction of the behavior of the biochemical reaction network represented by the model.) The precise behavior of simulation tools is left undefined with respect to constraints. If invalid results are detected with respect to a given constraint, the `message` field (Section 4.12.2) may optionally be displayed to the user. The simulation tool may also halt the simulation or clearly delimit in output data the simulation time point at which the simulation results become invalid.

SBML does not impose restrictions on duplicate Constraint definitions or the order of evaluation of Constraint definitions in a model. It is possible for a model to define multiple constraints all with the same `math` field. Since the failure of any constraint indicates that the model simulation has entered an invalid state, a software system is not required to attempt to detect whether other constraints have failed once any one constraint has failed.

4.12.5 Example

As an example, the following SBML fragment demonstrates the constraint that species S_1 should only have values between 1 and 100:

```
<listOfConstraints>
    <constraint>
        <math xmlns="http://www.w3.org/1998/Math/MathML">
            <apply>
                <and/>
```

```
                    <apply>
                        <lt/>
                        <cn> 1 </cn>
                        <ci> S1 </ci>
                    </apply>
                    <apply>
                        <lt/>
                        <ci> S1 </ci>
                        <cn> 100 </cn>
                    </apply>
                </apply>
            </math>
            <message>
                <p xmlns="http://www.w3.org/1999/xhtml">
                    Species S1 is out of range
                </p>
            </message>
        </constraint>
    </listOfConstraints>
```

4.13 Reactions

A *reaction* represents any transformation, transport or binding process, typically a chemical reaction, that can change the amount of one or more species. In SBML, a reaction is defined primarily in terms of the participating reactants and products (and their corresponding stoichiometries), along with optional modifier species, an optional rate at which the reaction takes place, and optional parameters. These various parts of a reaction are recorded in the SBML Reaction structure and other supporting data structures, defined in Figure 18 on the following page.

4.13.1 The Reaction structure

Each reaction in an SBML model is defined using an instance of a Reaction structure. As shown in Figure 18 on the next page, it contains several scalar fields and several lists of objects.

The `id` and `name` fields

As with most other main structures in SBML, the Reaction data structure includes a mandatory field called **`id`**, of type **`SId`**, and an optional field **`name`**, of type **`string`**. The **`id`** field is used to give the reaction a unique identifier in the model. This identifier can be used in mathematical formulas elsewhere in an SBML model to represent the rate of that reaction; this usage is explained in detail in Section 4.13.7 below. The **`name`** field can be used to give the reaction a more free-form, descriptive name. The **`name`** and **`id`** fields must be used as described in Section 3.4.

The lists of reactants, products and modifiers

The species participating as reactants, products, and/or modifiers in a reaction are declared using lists of SpeciesReference and/or ModifierSpeciesReference instances stored in **`listOfReactants`**, **`listOfProducts`** and **`listOfModifiers`**. The SpeciesReference and ModifierSpeciesReference structures are described in more detail in Sections 4.13.3 and 4.13.4 below.

Certain restrictions are placed on the appearance of species in reaction definitions:

- The ability of a species to appear as a reactant or product of any reaction in a model is governed by certain flags in that species' definition; see Section 4.8.6 for more information.
- Any species appearing in the mathematical formula of the **`kineticLaw`** of a Reaction instance must be declared in at least one of that Reaction's lists of reactants, products, and/or modifiers. Put another way, it is an error for a reaction's kinetic law formula to refer to species that have not been declared for that reaction.
- A reaction definition can contain an empty list of reactants *or* an empty list of products, but it must

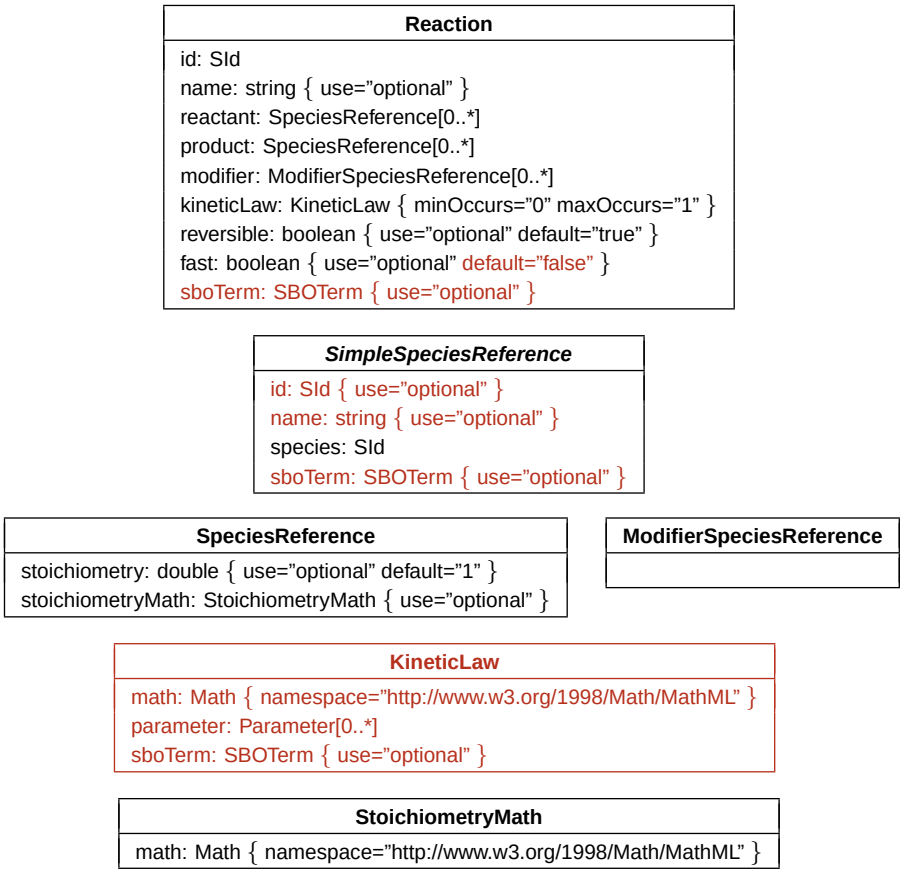

Figure 18: *The definitions of Reaction, KineticLaw, SpeciesReference and ModifierSpeciesReference. Following UML notation fields that are inherited from a base class are not shown.*

have at least one reactant or product; in other words, a reaction without any reactant or product species is not permitted. (This restriction does not apply to modifier species, which remain optional in all cases.)

The `kineticLaw` field

A reaction can contain up to one KineticLaw structure in the **`kineticLaw`** field of the Reaction. This "kinetic law" defines the speed at which the process defined by the reaction takes place. A detailed description of KineticLaw is left to Section 4.13.5 below.

Note that the inclusion of a KineticLaw structure in an instance of a Reaction component is optional; however, in general there is no useful default that can be substituted in place of a missing rate expression in a reaction. Moreover, a reaction's rate cannot be defined in any other way in SBML—InitialAssignment, AssignmentRule, RateRule, AlgebraicRule, Event, and other constructs in SBML cannot be used to set the reaction rate separately. Nevertheless, for some modeling applications, reactions without any defined rate can be perfectly acceptable.

The `reversible` field

The optional boolean field **`reversible`** indicates whether the reaction is reversible. The default is "**`true`**".

To say that a reaction is *reversible* is to say it can proceed in either the forward or the reverse direction. Although the reversibility of a reaction can sometimes be deduced by inspecting its rate expression, this is not always the case, especially for complicated expressions. Having a separate field supports the ability to perform some kinds of model analyses in the absence of performing a time-course simulation of the model. Moreover, the need in SBML to allow rate expressions (i.e., KineticLaw) to be optional leads to the need for

a separate flag indicating reversibility. Information about reversibility in the absence of a KineticLaw in a Reaction is useful in certain kinds of structural analyses such as elementary mode analysis.

Mathematically, the `reversible` field on Reaction has no impact on the construction of the equations giving the overall rates of change of each species quantity in a model. A concrete explanation may help illustrate this. Suppose a model consists of multiple reactions, of which two particular irreversible reactions R_f and R_r are actually the forward and reverse processes of the same underlying reaction. The product species of R_f necessarily will be the reactants of R_r, and the reactants of R_f will be the products of R_r. Let $f_f(\mathbf{X})$ and $f_r(\mathbf{X})$ be the SBML kinetic rate formulas of R_f and R_r, respectively, with $\mathbf{X}$ representing the species, parameters and compartments in the model. For the sake of this example, suppose we are using a continuous differential equation framework to simulate the system of reactions. Then for each species, we need to construct an expression representing the overall rate of change of that species' amount in the model. This overall expression will be a sum of the contributions of all the relevant rate formulas,

$$\frac{dS}{dt} = \ldots - n \cdot f_f(\mathbf{X}) + n \cdot f_r(\mathbf{X}) + \ldots$$

where S is a reactant species of R_f and a product of R_r, n is the effective stoichiometry of S in R_f (which by implication must be the same as its stoichiometry in R_r), and "$\ldots$" indicates other rate formulas in the model involving the particular species S. Now, contrast this to the case of an identical second SBML model, except that instead of having separate Reaction definitions for the forward and reverse reactions, this model has a single Reaction R_c labeled as reversible and whose reactants and products are the same as those of R_f in the first model. The rate of this reaction will be a formula $f_c = f_f(\mathbf{X}) - f_r(\mathbf{X})$. In constructing an expression representing the overall rate of change for the species S involved in that reaction, we will have

$$\begin{aligned} \frac{dS}{dt} &= \ldots - n \cdot f_c(\mathbf{X}) + \ldots \\ &= \ldots - n \cdot f_f(\mathbf{X}) + n \cdot f_r(\mathbf{X}) + \ldots \end{aligned}$$

In other words, the result is the same final expression for the rate of change of a species. Although in this simple example we used an expression for f_c that had clearly separated terms, in the general case the expression may have a more complicated form.

Note that labeling a reaction as irreversible is an assertion that the reaction always proceeds in the given forward direction. (Why else would it be flagged as irreversible?) This implies the rate expression in the KineticLaw always has a non-negative value during simulations. Software tools could provide a means of optionally testing that this condition holds. The presence of reversibility information in two places (i.e., the rate expression and the `reversible` flag) leaves open the possibility that a model could contain contradictory information, but the creation of such a model would be an error on the part of the software generating it.

The `fast` field

The optional boolean field `fast` is another optional boolean field in the Reaction data structure. The field's default value is "`false`".

Previous definitions of SBML indicated that software tools could ignore this field if they did not implement support for the corresponding concept; however, further research has revealed that this is incorrect and `fast` *cannot be ignored* if it is set to "`true`". SBML Level 2 Version 2 therefore stipulates that if a model has any reactions with `fast` set to "`true`", a software tool must be able to respect the field or else indicate to the user that it does not have the capacity to do so. Analysis software cannot ignore the value of the `fast` attribute because doing so may lead to different results as compared to a software system that *does* make use of `fast`.

When a model contains values for `fast` on any of its reactions, it is an indication that the creator of the model is distinguishing different time scales of reactions in the system. The model's reaction definitions are divided into two sets by the values of the `fast` fields. The set of reactions having `fast`="`true`" (known as *fast reactions*) should be assumed to be operating on a time scale significantly faster than the other reactions (the *slow reactions*). Fast reactions are considered to be instantaneous relative to the slow reactions.

Software tools must use a pseudo steady-state approximation for the set of fast reactions when constructing the system of equations for the model. More specifically, the set of reactions that have the `fast` attribute set to "`true`" forms a subsystem that should be described by a pseudo steady-state approximation in relationship to all other reactions in the model. Under this description, relaxation from any initial condition or perturbation from any intermediate state of this subsystem would be infinitely fast. Appendix G provides a technical explanation of an approach to solving systems with fast reactions.

Modelers and software developers should take care to note that the correctness of the approximation requires a significant separation of time scales between the fast reactions and other processes. This is not trivial to estimate a priori, and may even change over the course of a simulation, but can reasonably be assessed a posteriori in most cases.

The `sboTerm` field

The Reaction structure has an optional `sboTerm` field of type `SBOTerm` (see Sections 3.1.9 and 5). When a value is given to this field in a reaction definition, the value must be a valid SBO identifier referring to a modeling framework (i.e., terms derived from `SBO:0000004`, "modeling framework"). The Reaction structure should have an "is a" relationship with the SBO term. The SBO term chosen should be the most precise (narrow) term that defines the mathematical framework used in the reaction.

As discussed in Section 4.2.1, the value given to `sboTerm` on a Reaction object interacts with the value of the `sboTerm` field on the Model element. If the Model's `sboTerm` field has a value, it should be interpreted to mean that all the reactions in a model assume the same modeling framework. In that case, the `sboTerm` labels on individual reactions may be omitted, but only the Reaction `sboTerm` labels can be thus omitted; the `sboTerm` field on KineticLaw within Reaction must still be given a value, as must the terms on other components of the model, in order to characterize the model completely. (See Section 4.2.1 for more discussion about this topic.)

SBO labels are optional information on a model. Applications are free to ignore `sboTerm` values, and a model must be interpretable without the benefit of SBO labels. Section 5 gives more information about this principle and the use of SBO.

4.13.2 The SimpleSpeciesReference abstract type

As mentioned above, every species that enters into a given reaction must appear in that reaction's lists of reactants, products and/or modifiers. In an SBML model, all species that may participate in any reaction are listed in the `listOfSpecies` field of the top-level Model data structure (see Section 4.2). Lists of products, reactants and modifiers in Reaction structures do not introduce new species, but rather, they refer back to those listed in the model's top-level `listOfSpecies`. For reactants and products, the connection is made using the SpeciesReference data structure; for modifiers, it is made using the ModifierSpeciesReference data structure. *SimpleSpeciesReference*, defined in Figure 18 on page 59, is an abstract type that serves as the parent class of both SpeciesReference and ModifierSpeciesReference. It is used simply to hold the fields `species`, `id`, `name`, and `sboTerm` that are common to the latter two structures.

The `id` and `name` fields

The optional identifier stored in the `id` field allows SpeciesReference and ModifierSpeciesReference instances to be referenced from other structures. There are as yet no SBML structures that do this; however, such structures are anticipated in future levels of SBML. The identifier must be a text string conforming to the syntax permitted by the `SId` data type described in Section 3.1.7. The `id` value (whether it is in a SpeciesReference or ModifierSpeciesReference object) exists in the global namespace of the model, as described in Section 3.4. *SimpleSpeciesReference* also has an optional `name` field, of type `string`. The `name` and `id` fields must be used as described in Section 3.4.

The `species` field

The *SimpleSpeciesReference* structure has a mandatory field, **species**, of type **SId**. As with the other fields, this field is inherited by the SpeciesReference and ModifierSpeciesReference subtypes derived from *SimpleSpeciesReference*. The value of **species** must be the identifier of a species defined in the enclosing Model. The species is thereby declared as participating in the reaction being defined. The precise role of that species as a reactant, product, or modifier in the reaction is determined by the subtype of *SimpleSpeciesReference* (i.e., either SpeciesReference or ModifierSpeciesReference) in which the identifier appears.

The `sboTerm` field

The *SimpleSpeciesReference* structure has an optional **sboTerm** field of type **SBOTerm** (see Sections 3.1.9 and 5). This means that the object classes derived from *SimpleSpeciesReference*, namely SpeciesReference and ModifierSpeciesReference, all have **sboTerm** fields. When a value is given to this field, it must be a valid SBO referring to a participant role. The appropriate term depends on whether the object is a reactant, product or modifier. If a reactant, then it should be a term in the **SBO:0000010**, "reactant" hierarchy; if a product, then it should be a term in the **SBO:0000011**, "product" hierarchy; and if a modifier, then it should be a term in the **SBO:0000019**, "modifier" hierarchy. The SpeciesReference and ModifierSpeciesReference structures should have an "is a" relationship to the term identified by the SBO term identifier. The SBO terms chosen should be the most precise (narrow) one that defines the role of the species in the reaction.

A product term must only be used when the SpeciesReference structure is contained in the **product** field of the containing Reaction structure. Similarly, a reactant term must only be used when the SpeciesReference structure is contained in the **reactant** field of the containing Reaction structure.

As discussed in Section 5, SBO labels are optional information on a model. Applications are free to ignore **sboTerm** values. A model must be interpretable without the benefit of SBO labels.

4.13.3 SpeciesReference

The Reaction structure provides a way to express which species act as reactants and which species act as products in a reaction. In a given reaction, references to those species acting as reactants and/or products are made using instances of SpeciesReference structures in Reaction's lists of reactants and products. The SpeciesReference structure inherits the mandatory field **species** and optional fields **id**, **name**, and **sboTerm**, from the parent type *SimpleSpeciesReference*; see Section 4.13.2 for their definitions. It also defines two new fields, **stoichiometry** and **stoichiometryMath**, described below.

The value of the **species** field must be the identifier of an existing species defined in the enclosing Model; this species is thereby designated as a reactant or product in the reaction. Which one it is (reactant or product) is determined by whether the SpeciesReference instance appears in the Reaction's **reactant** or **product** lists.

The `stoichiometry` and `stoichiometryMath` fields

Product and reactant stoichiometries can be specified using *either* **stoichiometry** or **stoichiometryMath** in the SpeciesReference structure. The **stoichiometry** field is of type double and should contain values greater than zero (0). The **stoichiometryMath** field is implemented as an element containing a MathML expression. These two fields are mutually exclusive; only one of **stoichiometry** or **stoichiometryMath** should be defined in a given SpeciesReference instance. When neither field is present, the value of **stoichiometry** in the SpeciesReference instance defaults to "**1**".

For maximum interoperability, the **stoichiometry** field should be used in preference to **stoichiometryMath** when a species's stoichiometry in a reaction is a simple scalar number (integer or decimal). When the stoichiometry is a rational number, or when it is a more complicated formula, **stoichiometryMath** must be used. The MathML expression in **stoichiometryMath** may also refer to identifiers of entities in a model (except reaction identifiers), as discussed in Section 3.5.3. However, the only species identifiers that can be used in **stoichiometryMath** are those listed in the **reactant**, **product** and **modifier** fields of the containing Reaction structure.

The following is a simple example of a species reference for species "X0", with stoichiometry "2", in a list of reactants within a reaction having the identifier "J1":

```
<model>
    ...
    <listOfReactions>
        <reaction id="J1">
            <listOfReactants>
                <speciesReference species="X0" stoichiometry="2">
            </listOfReactants>
            ...
        </reaction>
        ...
    </listOfReactions>
    ...
</model>
```

The following is a more complex example of a species reference for species "X0", with a stoichiometry formula consisting of the parameter x:

```
<model>
    ...
    <listOfReactions>
        <reaction id="J1">
            <listOfReactants>
                <speciesReference species="X0">
                    <stoichiometryMath>
                        <math xmlns="http://www.w3.org/1998/Math/MathML">
                            <ci>x</ci>
                        </math>
                    </stoichiometryMath>
                </speciesReference>
            </listOfReactants>
            ...
        </reaction>
        ...
    </listOfReactions>
    ...
</model>
```

A species can occur more than once in the lists of reactants and products of a given Reaction instance. The effective stoichiometry for a species in a reaction is the sum of the stoichiometry values given on the SpeciesReference structures in the list of products minus the sum of stoichiometry values given on the SpeciesReference structures in the list of reactants. A positive value indicates the species is effectively a product and a negative value indicates the species is effectively a reactant. SBML places no restrictions on the effective stoichiometry of a species in a reaction; for example, it can be zero. In the following SBML fragment, the two reactions have the same effective stoichiometry for all their species:

```
<reaction id="x">
    <listOfReactants>
        <speciesReference species="a"/>
        <speciesReference species="a"/>
        <speciesReference species="b"/>
    </listOfReactants>
    <listOfProducts>
        <speciesReference species="c"/>
        <speciesReference species="b"/>
    </listProducts>
</reaction>
<reaction id="y">
    <listOfReactants>
        <speciesReference species="a" stoichiometry="2"/>
    </listOfReactants>
    <listOfProducts>
        <speciesReference species="c"/>
    </listProducts>
</reaction>
```

4.13.4 The ModifierSpeciesReference structure

Sometimes a species appears in the kinetic rate formula of a reaction but is itself neither created nor destroyed in that reaction (for example, because it acts as a catalyst or inhibitor). In SBML, all such species are simply called *modifiers* without regard to the detailed role of those species in the model. The Reaction structure provides a way to express which species act as modifiers in a given reaction. This is the purpose of the list of modifiers available in Reaction. The list contains instances of ModifierSpeciesReference structures.

As shown in Figure 18 on page 59, the ModifierSpeciesReference structure inherits the mandatory field `species` and optional fields `id`, `name`, and `sboTerm`, from the parent type *SimpleSpeciesReference*; see Section 4.13.2 for their precise definitions.

The value of the `species` field must be the identifier of a species defined in the enclosing Model; this species is designated as a modifier for the current reaction. A reaction may have any number of modifiers. It is permissible for a modifier species to appear simultaneously in the list of reactants and products of the same reaction where it is designated as a modifier, as well as to appear in the list of reactants, products and modifiers of other reactions in the model.

4.13.5 The KineticLaw structure

The KineticLaw structure is used to describe the rate at which the process defined by the Reaction takes place. As shown in Figure 18 on page 59, KineticLaw has fields called `math`, `parameter` and `sboTerm`, described below.

Previous definitions of SBML included two additional fields called `substanceUnits` and `timeUnits`, which allowed the *substance*/*time* units of the reaction rate expression to be defined on a per-reaction basis. SBML Level 2 Version 2 removes these fields for several reasons. First, the introduction in SBML Level 2 Version 2 of mass and dimensionless units as possible units of *substance*, coupled with the previous facility for defining the units of each reaction separately and the ability to use non-integer stoichiometries, lead to the possibility of creating a valid model whose reactions nevertheless could not be integrated into a system of equations without outside knowledge for converting the quantities used. (As a simple example, consider if one reaction is defined to be in grams per second and another in moles per second, and species are given in moles: converting from mass to moles would require knowing the molecular mass of the species.) Second, the ability to change the units of a reaction provided the potential of creating unintuitive and difficult-to-reconcile systems of equations, yet the feature added little functionality to SBML. The *absence* of `substanceUnits` does not prevent the definition of any reactions; it only results in requiring the generator of the model to be explicit about any necessary conversion factors. Third, few software tools have ever correctly implemented support for `substanceUnits`, which made the use of this field in a model an impediment to interoperability. Fourth, examination of real-life models revealed that a frequent reason for using `substanceUnits` was to set the units of all reactions to the same set of substance units, which is better achieved by setting the model-wide values of "`substance`".

The `math` field

As shown in Figure 18 on page 59, the KineticLaw structure has a field called `math` for holding a MathML formula defining the rate of the reaction. The expression in `math` may refer to species identifiers, as discussed in Section 3.5.3. The only species identifiers that can be used in `math` are those declared in the lists of reactants, products and modifiers in the Reaction structure.

Section 4.13.6 provides important discussions about the meaning and interpretation of SBML "kinetic laws".

The list of parameters

An instance of a KineticLaw type structure can contain a list of zero or more Parameter structures (Section 4.9) which define new parameters whose identifiers can be used in the `math` formula. As discussed in Section 3.4.1, reactions introduce local namespaces for parameter identifiers. This means that within a KineticLaw object, a local parameter whose identifier is identical to a global parameter defined in the model takes precedence over that global parameter.

The type of structure used to define a parameter inside KineticLaw is the same Parameter structure used to define global parameters (Section 4.9). This simplifies the SBML language and reduces the number of unique types of data objects. However, there is a difference between local and global parameters: in the case of parameters defined locally to a KineticLaw, there is no means by which the parameter values can be changed. Consequently, such parameters' values are always constant, and the `constant` field in their definitions must always have a value of "`true`" (either explicitly or left to its default value).

The `sboTerm` field

The KineticLaw structure has an optional field called `sboTerm` of type `SBOTerm` (see Section 5). When a value is given to this field, the value must be an SBO identifier referring to a term from the `SBO:0000001`, "rate law" vocabulary defined in SBO. The relationship is of the form "the kinetic law *is a* X", where X is the SBO term. The SBO term chosen should be the most precise (narrow) term that defines the type of kinetic law encoded by the structure.

Example

The following is an example of a Reaction structure that defines a reaction with identifier J_1, in which $X_0 \rightarrow S_1$ at a rate given by $k\,[X_0][S_2]$, where S_2 is a catalyst and k is a parameter, and the square brackets symbolizes that the species quantities have units of concentration. The example demonstrates the use of species references and the KineticLaw structure. The units on the species here are the defaults of *substance*/*volume* (see Section 4.8), and so the rate expression $k\,[X_0][S_2]$ needs to be multiplied by the compartment volume (represented by its identifier, "`c1`") to produce the final units of *substance*/*time* for the rate expression.

```
<model>
    ...
    <listOfUnitDefinitions>
        <unitDefinition id="per_concent_per_time">
            <listOfUnits>
                <unit kind="litre"/>
                <unit kind="mole"   exponent="-1"/>
                <unit kind="second" exponent="-1"/>
            </listOfUnits>
        </unitDefinition>
    </listOfUnitDefinitions>
    ...
    <listOfSpecies>
        <species id="S1" compartment="c1" initialConcentration="2.0"/>
        <species id="S2" compartment="c1" initialConcentration="0.5"/>
        <species id="X0" compartment="c1" initialConcentration="1.0"/>
    </listOfSpecies>
    ...
    <listOfReactions>
        <reaction id="J1">
            <listOfReactants>
                <speciesReference species="X0"/>
            </listOfReactants>
            <listOfProducts>
                <speciesReference species="S1"/>
            </listOfProducts>
            <listOfModifiers>
                <modifierSpeciesReference species="S2"/>
            </listOfModifiers>
            <kineticLaw>
                <math xmlns="http://www.w3.org/1998/Math/MathML">
                    <apply>
                        <times/>
                        <ci> k </ci>
                        <ci> S2 </ci>
                        <ci> X0 </ci>
                        <ci> c1 </ci>
                    </apply>
                </math>
```

```
                    <listOfParameters>
                        <parameter id="k" value="0.1" units="per_concent_per_time"/>
                    </listOfParameters>
                </kineticLaw>
            </reaction>
        </listOfReactions>
        ...
    </model>
```

4.13.6 Traditional rate laws versus SBML "kinetic laws"

It is important to make clear that a "kinetic law" in SBML is *not* identical to a traditional rate law. The reason is that SBML must support multicompartment models, and the units used in traditional rate laws as well as some conventional single-compartment modeling packages are problematic when used for defining reactions between multiple compartments.

When modeling species as continuous amounts (e.g., concentrations), the rate laws used are traditionally expressed in terms of *amount of substance concentration per time* because they embody the tacit assumption that reactants and products are all located in a single, constant volume. Attempting to describe reactions between multiple volumes using *concentration/time* (which is to say, *substance/volume/time*) quickly leads to difficulties. For example, suppose we have two species pools S_1 and S_2, with S_1 located in a compartment having volume V_1, and S_2 located in a compartment having volume V_2. Let the volume $V_2 = 3V_1$. Now consider a transport reaction $S_1 \rightarrow S_2$ in which the species S_1 is moved from the first compartment to the second. Assume the simplest type of chemical kinetics, in which the rate of the transport reaction is controlled by the activity of S_1 and this rate is equal to some constant k times the activity of S_1. For the sake of simplicity, assume S_1 is in a diluted solution and thus that the activity of S_1 can be taken to be equal to its concentration $[S_1]$. The rate expression will therefore be $k \cdot [S_1]$. Then:

$$\frac{d[S_2]}{dt} = -\frac{d[S_1]}{dt} = k \cdot [S_1]$$

So far, this looks normal—until we consider the number of molecules of S_1 that disappear from the compartment of volume V_1 and appear in the compartment of volume V_2. The number of molecules of S_1 (call this n_{S_1}) is given by $[S_1] \cdot V_1$ and the number of molecules of S_2 (call this n_{S_2}) is given by $[S_2] \cdot V_2$. Since our volumes have the relationship $V_2/V_1 = 3$, the relationship above implies that $n_{S_1} = k \cdot [S_1] \cdot V_1$ molecules disappear from the first compartment and $n_{S_2} = 3 \cdot k \cdot [S_1] \cdot V_1$ molecules appear in the second compartment. In other words, we have created matter out of nothing!

The problem lies in the use of concentrations as the measure of what is transfered by the reaction, because concentrations depend on volumes and the scenario involves multiple unequal volumes. The problem is not limited to using concentrations or volumes; the same problem also exists when using density, i.e., *mass/volume*, and dependency on other spatial distributions (i.e., areas or lengths). What must be done instead is to consider the number of "items" being acted upon by a reaction process irrespective of their distribution in space (volume, area or length). An "item" in this context may be a molecule, particle, mass, or other "thing", as long as the substance measurement is independent of the size of the space in which the items are located.

For the current example, the expressions in terms of n_{S_1} and n_{S_2} are straightforward:

$$\frac{dn_{S_2}}{dt} = -\frac{dn_{S_1}}{dt} = k \cdot [S_1] \cdot V_1$$

Given numbers of items, it is then easy to recover concentrations by dividing the item counts of each species by the volume of the compartment in which the species is located: $[S_1] = n_{S_1}/V_1$ and $[S_2] = n_{S_2}/V_2$.

The need to support multicompartment models requires that the reaction rates in SBML to be expressed in terms of *substance/time*, rather than the more typical *substance/size/time*. As a result, modelers and software tools in general cannot insert textbook rate laws unmodified as the rate expression in the `math` field of a KineticLaw. The unusual term "kinetic law" was chosen to alert users to this difference. We explain the general principles of converting rate laws in the following paragraphs.

Basic cases

Let us expand the simple example above by adding a second reaction, to create the system

$$S_1 \rightarrow S_2 \rightarrow S_3$$

with the left-hand reaction's rate (call this r_1) being given as $k_1 \cdot [S_1]$ and the rate of the right-hand reaction (call it r_2) as $k_2 \cdot [S_2]$. Also assume each species is located in a different compartment:

S_1	located in compartment C_1	with volume V_1
S_2	located in compartment C_2	with volume V_2
S_3	located in compartment C_3	with volume V_3

As before, converting the rate of the first reaction ($S_1 \rightarrow S_2$) to units of *substance/time* in this case is a simple matter of multiplying by the volume of the compartment where the reactants are located, leading to the following rate formula:

$$r_1 = -k_1 \cdot [S_1] \cdot V_1$$

The second rate expression becomes

$$r_2 = -k_2 \cdot [S_2] \cdot V_2$$

The expressions r_1 and r_2 are what would be written in KineticLaw `math` definitions for the two reactions in this system. The formulas give the speed of each reaction in terms of the substance change over time. The reader of the SBML model needs to combine the individual contributions of each reaction to construct equations for the *overall* rates of change of each species in the model using these expressions. In terms of differential equations, these are:

$$\begin{aligned}
\frac{dn_{S_1}}{dt} &= -r_1 &&= -k_1 \cdot [S_1] \cdot V_1 \\
\frac{dn_{S_2}}{dt} &= +r_1 - r_2 &&= +k_1 \cdot [S_2] \cdot V_1 - k_2 \cdot [S_2] \cdot V_2 \\
\frac{dn_{S_3}}{dt} &= +r_2 &&= +k_2 \cdot [S_2] \cdot V_2
\end{aligned}$$

To recover the concentration values, we add the following to the system of equations:

$$\begin{aligned}
[S_1] &= n_{S_1}/V_1 \\
[S_2] &= n_{S_2}/V_2 \\
[S_3] &= n_{S_3}/V_3
\end{aligned}$$

Note that this formulation works properly even if the compartment sizes V_1, V_2 and V_3 vary during simulation.

Extrapolating from this example, we can now provide a general approach to translating a system of reactions involving species located in multiple compartments, for the restricted case where all reactants of any given reaction are in the same compartment (but where the compartments involved may be different for each reaction). For a species S_i located in a compartment of size V_i and involved in m reactions $r_1, r_2, \ldots, r_m$, where the reactants of r_j are located in the compartment of size V_j,

$$\begin{aligned}
\frac{dn_{S_i}}{dt} = \quad & \mathrm{sign}_1 \cdot \mathrm{stoich}_1 \cdot r_1 \cdot V_1 \\
& + \mathrm{sign}_2 \cdot \mathrm{stoich}_2 \cdot r_2 \cdot V_2 \\
& + \ldots \\
& + \mathrm{sign}_m \cdot \mathrm{stoich}_m \cdot r_m \cdot V_m
\end{aligned} \tag{7}$$

$$[S_i] = n_{S_i}/V_i$$

In Equation (7), each term sign_j is "−" if S_i is a reactant in r_j and "+" if it is a product, and each term stoich_j is the stoichiometry of S_i in reaction r_j.

This approach preserves the use of concentration terms within the reaction rate expressions so that the core of those rate expressions can be ordinary rate laws. This is important when modeling species as continuous quantities, because most textbook rate expressions are measured in terms of concentrations, and most rate constants have units involving concentration rather than item counts. For example, the second-order rate constant in a mass-action rate law has units of $1/(M \cdot s)$, which is to say, $volume/(substance \cdot time)$; this constant is then multiplied by two concentration terms. Reaction definitions in SBML models can be constructed by taking such expressions and multiplying them by the volume of the compartment in which the reactants are located. By contrast, if we were to simply replace concentrations of species by item counts in such rate laws, it would in most cases be incorrect. At the very least, the constants in the equations would need to be converted in some way to make such expressions valid.

The preceding discussion of problems involving rate laws concerns modeling approaches that use continuous quantities. There is an alternative approach to modeling that instead treats species as discrete populations (Wilkinson, 2006). In those cases, the rate expressions already use substance or item counts rather than concentrations and there is no need to convert them.

A full SBML example of translating a complete multicompartmental model into ODEs is given in Section 7.7. An example of translating a discrete model is given in Section 7.3.

Advanced cases

The explanation above applies to reactions where all of the reactants are in the same compartment. What about cases where two or more reactant species are in separate compartments?

This is a more difficult situation, and the guidelines described above for Equation (7) cannot always be applied because there will be more than one compartment size term by which the core rate expression needs to be multiplied. Unfortunately, there is often no straightforward way to mechanically convert such models without requiring a more significant change to the reaction rate expression. An example will help illustrate the difficulty. Suppose we have a simple reaction system consisting of only

$$S_1 + S_2 \rightarrow S_3$$

where S_1, S_2 and S_3 are each located in separate compartments with volumes V_1, V_2 and V_3, and the rate expression is given as $k \cdot [S_1] \cdot [S_2]$. (In reality, one would not use such a rate law in this case, but for the sake of this example, let us ignore the fact that a mass-action rate law would actually involve an assumption that all reactants are in a well-mixed solution.) A straightforward examination of the possibilities eventually leads to the conclusion that in order to take account of the multiple volumes, the rate expressions in terms of $substance/time$ have to be written as

$$\frac{dn_{S_i}}{dt} = -k'(V_1, V_2) \cdot \big([S_1] \cdot V_1\big) \cdot \big([S_2] \cdot V_2\big)$$

The crux of the problem is that the new factor $k'(V_1, V_2)$ is not the original k; to make the overall units of the expression work out, $k'(V_1, V_2)$ must be a function of the volumes, and its value must change if V_1 or V_2 changes. It is no longer a standard rate constant. In an SBML model, it is easy to define an AssignmentRule to compute the value of k' based on k, V_1, V_2, and possibly other variables in the system as needed, but only the modeler can determine the proper formula for their particular modeling situation. (For example, the modeler may know that in their hypothesized physical system, the reaction actually takes place completely in one or the other compartment and therefore the factor should be designed accordingly, or perhaps the reaction takes place on a membrane between compartments and a scaling factor based on the area should be used.)

Thus, although these models can be represented in SBML, constructing the correct rate expression in terms of $substance/time$ units depends on problem-specific knowledge, and we cannot provide a general recipe.

4.13.7 Use of reaction identifiers in mathematical expressions

The value of the `id` field of a Reaction structure can be used as the content of a `ci` element in MathML formulas elsewhere in the model. Such a `ci` element or symbol represents the rate of the given reaction as given by the KineticLaw structure of the reaction. The symbol has the units of *substance/time*.

A KineticLaw structure in effect forms an assignment statement assigning the evaluated value of the `math` field to the symbol value contained in the Reaction `id` field. No other structure can assign a value to such a reaction symbol; i.e., the `variable` fields of InitialAssignment, RateRule, AssignmentRule and EventAssignment structures cannot contain the value of a Reaction `id` field.

The combined set of InitialAssignment, AssignmentRule and KineticLaw structures form a set of assignment statements that should be considered as a whole. The combined set of assignment rules should not contain algebraic loops: a chain of dependency between these statements should terminate. (More formally, consider the directed graph of assignment statements where nodes are statements and directed arcs exist for each occurrence of a symbol in a assignment statement `math` field. The directed arcs start from the statement defining the symbol to the statements that contain the symbol in their math fields. Such a graph must be acyclic.) Examples of valid and invalid set of assignment statements are given in Section 4.11.6.

4.14 Events

Model has an optional list of Event structures that describe the time and form of explicit instantaneous discontinuous state changes in the model. For example, an event may describe that one species quantity is halved when another species quantity exceeds a given threshold value.

An Event structure defines when the event can occur, the variables that are affected by the event, and how the variables are affected. The effect of the event can optionally be delayed after the occurrence of the condition which invokes it. The operation of an Event structure is divided into two phases (even when the event is not delayed): one when the event is *fired* and the other when the event is *executed*. The Event type is defined in Figure 19. Both Event and EventAssignment are derived from *Sbase* (see Section 3.3). An example of a model which uses events is given below.

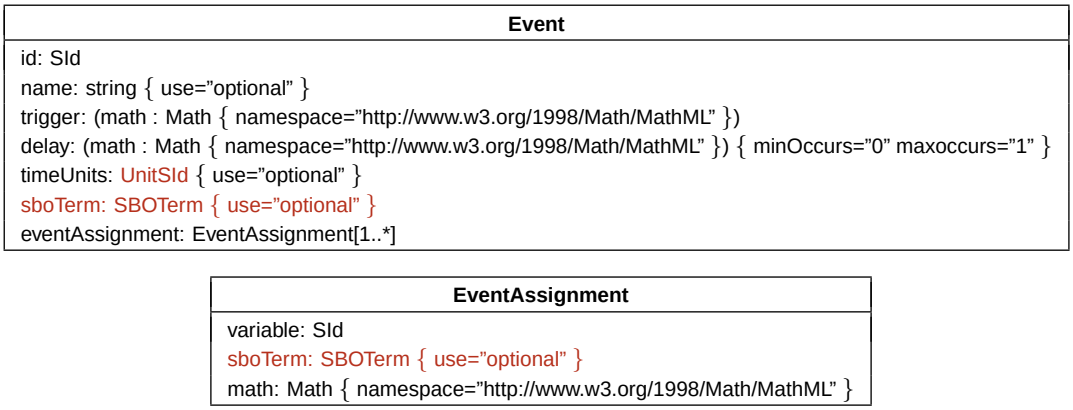

Figure 19: *The definitions of Event and EventAssignment. Following UML notation, additional fields that are inherited from a base class, in this case Sbase, are not shown.*

4.14.1 Event

An Event definition has three required parts: an identifier, a trigger condition and at least one EventAssignment. In addition there is an optional delay expression. These are described below.

The `id` and `name` fields

These optional fields are available to support external references to event structures. These fields operate in the manner described in Section 3.4 except that the `id` field is optional.

The `trigger` field

The `trigger` field defines when the Event structure has an effect on the model. The `trigger` field contains a MathML boolean expression. The exact instant that the expression evaluates to true is the time point when

the Event is *fired*. The event only fires when the `trigger` makes the transition from false to true. The event will fire at any further time points when the `trigger` make this transition.

An important question is whether an event can fire prior to or at initial simulation time, i.e., $t \leq 0$. The answer is no: an event can only be triggered immediately after initial simulation time i.e., $t > 0$.

The `delay` field

The optional `delay` field defines a mathematical expression used to compute the length of time after the event has *fired* that the event is *executed*. This expression must be evaluated at the time the rule is *fired*. The default value for the `delay` field is 0. The `delay` expression must always evaluate to a positive number (otherwise, a nonsensical situation would arise where an event is defined to fire before it is triggered!). The units of the `delay` field are those given on the `timeUnits` field.

The `timeUnits` field

The optional field `timeUnits` determines the units of time that apply to the `delay` field. The value of the `timeUnits` field must be either "`second`" or "`dimensionless`" from Table 2 on page 34, "`time`" from Table 3 on page 37, or a new unit defined by a unit definition in the enclosing model which must be a variant of "`second`" units. The default value of the `timeUnits` field is "`time`".

The `sboTerm` field

The Event structure has an optional `sboTerm` field of type `SBOTerm` (see Sections 3.1.9 and 5). The term is associated with the trigger condition on the event. When a value is given to this field, it must be a valid SBO referring to a mathematical expression (i.e., terms derived from `SBO:0000064`, "mathematical expression"). The Event's trigger should have a "is a" relationship with the SBO term, and the term should be the most precise (narrow) term that captures the form of the trigger formula in the model.

As discussed in Section 5, SBO labels are optional information on a model. Applications are free to ignore `sboTerm` values. A model must be interpretable without the benefit of SBO labels.

The `eventAssignment` field

The `eventAssignment` field consists of a non-empty list of EventAssignment structures. This field is implemented as a `listOfEventAssignments` element containing one or more `eventAssignment` elements. The EventAssignment structures represent variable assignments that have effect when the event is *executed*.

4.14.2 EventAssignment

The EventAssignment structure is shown in Figure 19.

The `variable` field

The `variable` field is of type `SId` and contains the identifier of a variable, i.e., a compartment, species or parameter. The value of the component referenced by this identifier is changed by the EventAssignment to the value computed by the `math` field; see below.

The `variable` field must not contain the identifier of a reaction. The values of the `variable` field must be unique among the set of EventAssignment structures within an Event structure. The structure referenced by the `variable` field must have its `constant` field set to "`false`".

A variable cannot be assigned a value in an EventAssignment structure and be assigned a value by an AssignmentRule structure, i.e., the value of a `variable` attribute on a EventAssignment structure cannot be the same as the value of a `variable` attribute on a AssignmentRule structure. This restriction is imposed because in the invalid case the EventAssignment is redundant because the variable would assume the value of given by the AssignmentRule.

The `sboTerm` field

The EventAssignment structure has an optional **sboTerm** field of type **SBOTerm** (see Sections 3.1.9 and 5). When a value is given to this field, it must be a valid SBO term identifier referring to a mathematical expression (i.e., terms derived from **SBO:0000064**, "mathematical expression"). The EventAssignment should have an "is a" relationship with the SBO term, and the term should be the most precise (narrow) term that captures the form of the assignment formula in the model.

As discussed in Section 5, SBO labels are optional information on a model. Applications are free to ignore **sboTerm** values. A model must be interpretable without the benefit of SBO labels.

The `math` field

The **math** field contains a MathML expression that defines the new value of the variable. This expression is evaluated when the Event is *fired* but the variable only acquires the result or new value when the Event is *executed*. The order of the EventAssignment structures is not significant; the effect of one assignment cannot affect the result of another assignment. The identifiers occurring in the MathML **ci** fields of the EventAssignment structures represent the value of the identifier at the point when the Event is *fired*.

In all cases, as would be expected, the units of the formula in an EventAssignment are identical to the units associated with the **variable** field, when that variable appears in other formulas. However, the precise details, which are identical to those of AssignmentRule structures, depend on the variable that is being set:

- *In the case of a species*, an EventAssignment sets the referenced species' quantity (*concentration* or *amount of substance*) to the value determined by the formula in **math**. The units of the formula are the *units of the species* as defined in Section 4.8.5.
- *In the case of a compartment*, an EventAssignment sets the referenced compartment's size to the size determined by the formula in **math**. The overall units of the formula are the units specified for the size of the compartment identified by the value of the EventAssignment's **variable** field. (See Section 4.7.5 for an explanation of how the units of the compartment's size are determined.)
- *In the case of a parameter*, an EventAssignment sets the referenced parameter's value to that determined by the formula in **math**. The overall units of the formula are the units defined for the parameter identified by the value of the EventAssignment's **variable** field. (See Section 4.9.3 for an explanation of how the units of the parameter are determined.)

4.14.3 Example Event structure

A example of an Event structure follows. This structure makes the assignment $k_2 = 0$ at the point when $P_1 \leq t$:

```
<event>
    <trigger>
        <math xmlns="http://www.w3.org/1998/Math/MathML">
            <apply>
                <leq/>
                <ci> P1 </ci>
                <ci> t </ci>
            </apply>
        </math>
    </trigger>
    <listOfEventAssignments>
        <eventAssignment variable="k2">
            <math xmlns="http://www.w3.org/1998/Math/MathML">
                <cn> 0 </cn>
            </math>
        </eventAssignment>
    <listOfEventAssignments>
</event>
```

A complete example of a model using events is given in Section 7.10.

4.14.4 Detailed semantics of events

The description of events above describes the action of events in isolation from each other. This section describes how events interact. Events whose `trigger` expression is true at the start of a simulation do not *fire* at the start of the simulation. Events *fire* only when the trigger *becomes* true, i.e. the trigger expression transitions from false to true. It is possible for events to *fire* other events, i.e. an event assignment can cause an event to *fire*, therefore it is possible for model to be entirely encoded in Event structures.

Any transition of a `trigger` expression from false to true will cause an `event` to *fire*. Consider an `event` E with delay d where the `trigger` expression makes a transition from false to true at times t_1 and t_2. The EventAssignment structure will have effect at $t_1 + d$ and $t_2 + d$ irrespective of the relative times of t_1 and t_2. For example events can "overlap" so that $t_1 < t_2 < t_1 + d$ still causes an event assignments to occur at $t_1 + d$ and $t_2 + d$.

It is entirely possible for two events to be *executed* simultaneously in simulated time. It is assumed that, although the precise time at which these events are *executed* is not resolved beyond the given point in simulated time, the order in which the events occur is resolved. This order can be significant in determining the overall outcome of a given simulation. SBML Level 2 does not define the algorithm for determining this order (the tie-breaking algorithm). As a result, the results of simulations involving events may vary when simultaneous events occur during simulation. It is anticipated that future versions or levels of SBML will define a specific set of tie-breaking algorithms and a mechanism for models to indicate which algorithm should be applied during simulation.

Despite the absence of a specific tie-breaking algorithm, SBML event simulation is constrained as follows. When an event X *fires* another event Y and event Y has zero delay then event Y is added to the existing set of simultaneous events that are pending *execution*. Events such as Y do not have a special priority or ordering within the tie-breaking algorithm. Events X and Y form a cascade of events at the same point in simulation time. All events in a model are open to being in a cascade. The position of an event in the event list does not affect whether it can be in the cascade: Y can be triggered whether it is before or after X in the list of events. A cascade of events can be infinite (never terminate). When this occurs a simulator should indicate this has occurred, i.e. it is incorrect for the simulator to arbitrarily break the cascade and continue the simulation without at least indicating the infinite cascade occurred. A variable can change more than once when processing simultaneous events at simulation time t. The model behavior (output) for such a variable is the value of the variable at the end of processing all the simultaneous events at time t.

5 The Systems Biology Ontology and the sboTerm field

The values of `id` fields on SBML components allow the components to be cross-referenced within a model. The values of `name` fields on SBML components provide meaningful labels suitable for display to humans (Section 3.4). The specific identifiers and labels used in a model necessarily must be unrestricted by SBML, so that software and users are free to pick whatever they need. However, this freedom makes it more difficult for software tools to determine, without additional human intervention, the semantics of models more precisely than the semantics provided by the SBML structures defined in other sections of this document. For example, there is nothing inherent in a parameter with identifier "`k`" that would indicate to a software tool it is a first-order rate constant (if that's what "`k`" happened to be in some given model). An advanced software tool *might* be able to deduce the semantics of some model components by detailed analysis of the kinetic rate expressions and other parts of the model, but this quickly becomes infeasible for any but the simplest of models.

An approach to solving this problem is to associate model components with terms from a regulated, controlled vocabulary (CV). This is the purpose of the optional `sboTerm` field provided on the SBML classes Model, FunctionDefinition, Reaction, Parameter, InitialAssignment, AlgebraicRule, AssignmentRule, RateRule, Constraint, Reaction, KineticLaw, SpeciesReference, ModifierSpeciesReference, Event, and EventAssignment . The `sboTerm` field always refers to terms in the Systems Biology Ontology (SBO). In this section, we discuss the `sboTerm` field, SBO, the motivations and theory behind their introduction, and guidelines for their use.

SBO is not part of SBML; it is being developed separately, to allow the modeling community to evolve the ontology independently of SBML. However, the terms in the ontology are being designed with SBML components in mind, and are classified into subsets that can be related one-to-one with SBML components such as reaction rate expressions, parameters, and a few others.

5.1 Principles

Labeling model components with terms from a shared controlled vocabulary allows a software tool to identify each component using identifiers that are not tool-specific. An example of where this is useful is the desire by many software developers to provide users with meaningful names for reaction rate equations. Software tools with model editing interfaces frequently provide these names in menus or lists of choices for users. However, without a standardized set of names or identifiers shared between developers, a given software package cannot reliably interpret the names or identifiers of reactions in models written by other tools.

The first solution that might come to mind is to stipulate that certain common reactions always have the same name (e.g., "Michaelis-Menten"), but this is simply impossible to do: not only do humans often disagree on the names themselves, but it would not allow for correction of errors or updates to the list of predefined names except by issuing new revisions of the SBML specification—to say nothing of many other limitations with this approach. Moreover, the parameters and variables that appear in rate expressions also need to be identified in a way that software tools can interpret mechanically, implying that the names of these entities would also need to be regulated.

The Systems Biology Ontology (SBO) provides vocabularies for identifying common reaction rate expressions, common reactant/product/modifier roles in reactions, common parameter types and their roles in rate expressions, and common modeling frameworks (e.g., "continuous", "discrete", etc.). The relationship implied by an `sboTerm` value on an SBML model component is "is a": the thing defined by that SBML component "is a" instance of the thing defined in SBO having the identifier given by the `sboTerm` field value. By adding SBO term references on the components of a model, a software tool can provide additional details using an independent, shared vocabulary that can enable *other* software tools to recognize precisely what the component is meant to be. Those tools can then act on that information. For example, if the SBO identifier `SBO:0000049` is assigned to the concept of "first-order irreversible mass-action kinetics, continuous framework", and a given KineticLaw object in a model has an `sboTerm` field with this value, then regardless of the identifier and name given to the reaction itself, a software tool could use this to inform users that the reaction is a first-order irreversible mass-action reaction. This kind of reverse engineering of the meaning of reactions in a model would be difficult to do otherwise, especially for more complex reaction types.

The presence of the label on a kinetic expression can also allow software tools to make more intelligent decisions about reaction rate expressions. For example, an application could recognize certain identifiers as being ones it knows how to solve with optimized procedures. The application could then use internal, optimized code implementing the rate formula indexed by identifiers such as `SBO:0000049` appearing in SBML models.

Although the use of SBO labels can be beneficial, it is critical to keep in mind that the presence of an `sboTerm` value on an object *must not change the fundamental mathematical meaning* of the model. An SBML model must be defined such that it stands on its own and does not depend on additional information added by SBO terms for a correct mathematical interpretation. SBO term definitions will not imply any alternative mathematical semantics for any SBML structure labeled with that term. Two important reasons motivate this principle. First, it would be too limiting to require that all software tools be able to understand the SBO vocabularies in addition to understanding SBML Level 2 Version 2. Supporting SBO is not only additional work for the software developer; for some kinds of applications, it may not make sense. If the SBO terms on a model are optional, it follows that the SBML model *must* remain unambiguous and fully interpretable without them, because an application reading the model may ignore the terms. Second, we believe allowing the use of `sboTerm` to alter the mathematical meaning of a model would give software authors too much leeway to shoehorn inconsistent concepts into SBML structures, ultimately reducing the interoperability of the models.

5.2 Using SBO and `sboTerm`

The `sboTerm` field data type is always `SBOTerm`, defined in Section 3.1.9. When present in a given model object instance, the field's value must be an identifier taken from the Systems Biology Ontology (SBO; `http://www.biomodels.net/SBO/`). This identifier must refer to a single SBO term that best defines the entity encoded by the SBML object in question. An example of the type of relationship intended is: *the KineticLaw in reaction R1 is a first-order irreversible mass action rate law.*

Note the careful use of the words "defines" and "entity encoded by the SBML object" in the paragraph above. As mentioned, the relationship between the SBML object and the URI is:

> The "thing" encoded by this SBML object *is an* instance of the "thing" represented by the referenced SBO term.

5.2.1 The structure of the Systems Biology Ontology

The goal of SBO labeling for SBML is to clarify to the fullest extent possible the nature of each reaction rate equation in a model. The approach taken in SBO begins with a hierarchically-structured set of controlled vocabularies with four main divisions: (1) modeling framework, (2) participant role, (3) quantitative parameter, and (4) mathematical expression. Figure 20 illustrates the highest level of SBO.

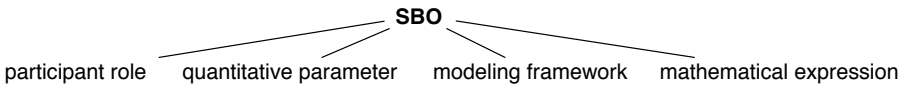

Figure 20: *The four controlled vocabularies (CVs) that make up the main branches of SBO. (Other CVs in SBO may evolve in time, but are not discussed here.)*

Each of the four branches of Figure 20 have a hierarchy of terms underneath them. At this time, we can only begin to list some initial concepts and terms in SBO; what follows is not meant to be complete, comprehensive or even necessarily consistent with future versions of SBO. The web site for SBO (`http://www.biomodels.net/SBO/`) should be consulted for the current version of the ontology. Section 5.4.1 describes how the impact of SBO changes on software applications is minimized.

Figure 21 shows the anticipated structure for the *participant role* CV which reflects the hierarchical conceptual groupings of the concepts. For example, in reaction rate expressions, there are a variety of possible

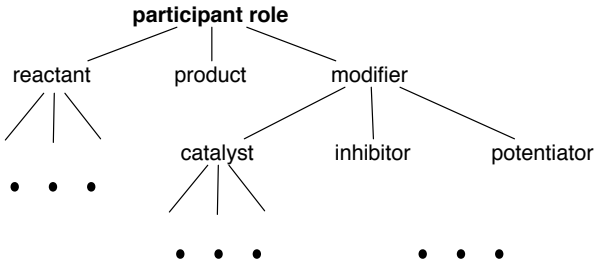

Figure 21: *Partial expansion of some of the terms in the* participant role *CV of SBO.*

modifiers. Some classes of modifiers can be further subdivided and grouped. All of this is easy to capture in the CV. As more agreement is reached in the modeling community about how to define and name modifiers for different cases, the CV can grow to accommodate it.

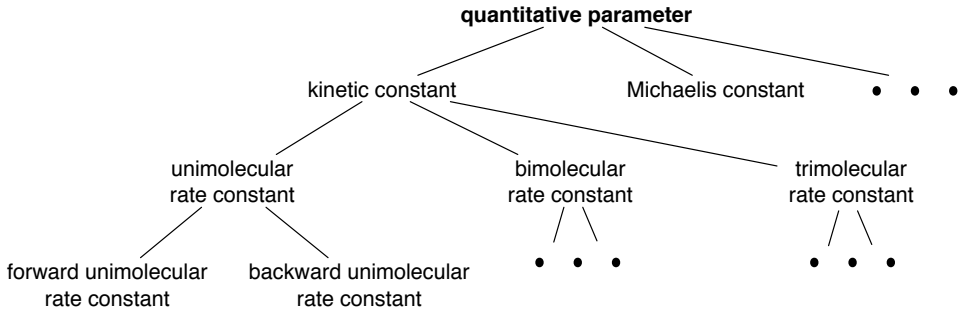

Figure 22: *Partial expansion of some of the terms in the* quantitative parameter *CV.*

Similar to the above, the controlled vocabulary for quantitative parameters also has a hierarchical structure, as illustrated in Figure 22. Note the separation of *kinetic constant* into separate terms for unimolecular, bimolecular, etc. reactions, as well as for for forward and reverse reactions. The need to have separate terms for forward and reverse rate constants arises in reversible mass-action reactions. This distinction is not always necessary for all quantitative parameters; for example, there is no comparable concept for the Michaelis constant. Another distinction for some quantitative parameters is a decomposition into different versions based on the modeling framework being assumed. For example, different terms for continuous and discrete formulations of kinetic constants represent specializations of the constants for particular simulation frameworks. Not all quantitative parameters will need to be distinguished along this dimension.

The *modeling framework* controlled vocabulary is needed to support labeling models and reactions with the framework for which they are designed. Figure 23 illustrates the structure of this CV, which is at this point extremely simple, but we expect that more terms will evolve in the future.

Figure 23: *Partial expansion of some of the terms in the* modeling framework *CV.*

Finally, there is the *mathematical expression* framework. This controlled vocabulary encompasses the various mathematical expressions that constitute a model. Figure 24 illustrates a portion of the hierarchy. Rate law formulas are part of the mathematical expression hierarchy, and subdivided by successively more refined distinctions until the leaf terms represent precise statements of common reaction types. Other types of mathematical expressions are likely to be included in order to be able to characterize other mathematical components of a model, namely initial assignments, assignment rules, rate rules, algebraic rules, constraints, and event triggers and assignments.

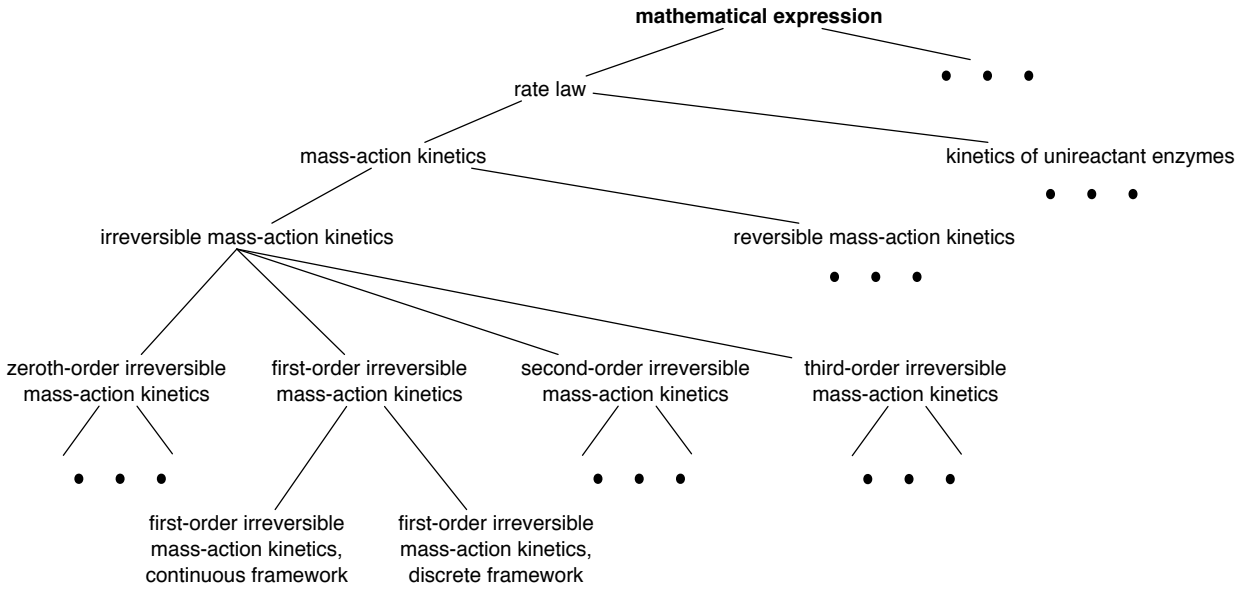

Figure 24: *Partial expansion of some of the terms in the* mathematical expression *CV.*

The leaf terms of the rate law portion of the SBO mathematical expression framework contain the mathematical formulas for the rate laws encoded using MathML 2.0. There are many potential uses for this. One is to allow a software application to obtain the formula and insert it into a model. In effect, the formulas given in the CV act as templates for what to put into an SBML KineticLaw definition. The MathML definition also acts as a precise statement about the rate law in question.

To make this discussion concrete, here is an example definition of an entry in the SBO rate law hierarchy at the time of this writing. This term represents second-order, irreversible, mass-action kinetics with one reactant, formulated for use in a continuous modeling framework:

> *ID*: SBO:0000052
>
> *Name*: second order irreversible mass action kinetics, one reactant, continuous scheme
>
> *Definition*: Reaction scheme where the products are created from the reactants and the change of a product quantity is proportional to the product of reactant activities. The reaction scheme does not include any reverse process that creates the reactants from the products, and the change of a product quantity is proportional to the square of one reactant quantity. It is to be used in a reaction modeled using a continuous framework.
>
> *Parent(s)*: SBO:0000052, first-order irreversible mass-action kinetics (is a)
>
> *MathML*:

```
<math xmlns="http://www.w3.org/1998/Math/MathML">
   <lambda>
     <bvar><ci definitionURL="http://biomodels.net/SBO/#SBO:0000036">k</ci></bvar>
     <bvar><ci definitionURL="http://biomodels.net/SBO/#SBO:0000010">R</ci></bvar>
     <apply>
         <times/>
         <ci>k</ci>
         <ci>R</ci>
         <ci>R</ci>
     </apply>
   </lambda>
</math>
```

In the MathML definition of the term shown above, the bound variables in the `lambda` expression are tagged with references to terms in the SBO quantitative parameter (for `k`) and SBO participant role (for

R) vocabularies. This makes it possible for software applications to interpret the intended meanings of the parameters in the expression.

One of the goals of SBO is to permit a tool to traverse up and down the hierarchy in order to find equivalent terms in different frameworks. The hope is that when a software tool encounters a given rate formula in a model, the formula will be a specific form (say, "mass-action kinetics, second order, one reactant, for discrete simulation"), but by virtue of the consistent organization of the reaction rate CV into framework-specific definitions, the tool should in principle be able to determine the definitions for other frameworks (say, "mass-action kinetics, second order, one reactant for *continuous* simulation"). If the software tool is designed for continuous simulation and it encounters an SBML model with rate laws formulated for discrete simulation, it could in principle look up the rate laws' identifiers in the CV and search for alternative definitions intended for discrete simulation. And of course, the converse is true, for when a tool designed for discrete simulation encounters a model with rate laws formulated for continuous simulation.

5.2.2 Relationships between individual SBML components and SBO terms

The availability of `sboTerm` fields on various SBML components is limited to those for which an SBO label is appropriate given the goals and principles of SBO's use in SBML (Section 5.1). Table 7 summarizes the relationship between SBML components having `sboTerm` fields and the vocabularies within SBO that apply to that component.

SBML Component	SBO Vocabulary	Parent SBO Identifier
Model	modeling framework	SBO:0000004
Reaction	modeling framework	SBO:0000004
Parameter	quantitative parameter	SBO:0000002
SpeciesReference	participant role	SBO:0000003
ModifierSpeciesReference	participant role	SBO:0000003
FunctionDefinition	mathematical expression	SBO:0000064
KineticLaw	mathematical expression	SBO:0000064
InitialAssignment	mathematical expression	SBO:0000064
AlgebraicRule	mathematical expression	SBO:0000064
AssignmentRule	mathematical expression	SBO:0000064
RateRule	mathematical expression	SBO:0000064
Constraint	mathematical expression	SBO:0000064
Event	mathematical expression	SBO:0000064
EventAssignment	mathematical expression	SBO:0000064

Table 7: *SBML components and the main types of SBO terms that may be assigned to them. The parent identifiers are provided for guidance, but actual annotations should use more specific child terms. See text for explanation.*

The parent identifiers shown in Table 7 are provided for reference. They are the highest-level terms in their respective vocabularies; however, these are *not* the terms that would be used to annotate an element in SBML, because there are more specific terms underneath the parents shown here. A software tool should use the most specific SBO term available for a given concept rather than using the top-level identifier acting as the root of that particular vocabulary.

5.3 Relationships to the SBML `annotation` field

Another means of providing this kind of information would be to place it inside the `annotation` field (Sections 3.3 and 6). Although `sboTerm` is just another kind of optional annotation in SBML, the SBO references are separated out and given a separate field on SBML components, both to simplify their use for software tools and because they assert a slightly stronger and more focused connection in a more regimented fashion. SBO term references are intended to allow a modeler to make a statement of the form "this object is identical in meaning and intention to the definition of X in the SBO vocabulary" and do so in a way that a *software tool can interpret unambiguously.*

5.3.1 Tradeoffs in using SBO terms

The SBO-based approach to annotating SBML components with controlled terms has the following strengths:

1. The syntax is minimally intrusive and maximally simple, requiring only one string-valued attribute.
2. It supports a significant fraction of what SBML users have wanted to do with controlled vocabularies.
3. It does not interfere with any other scheme. The more general annotation-based approach described in Section 6 can still be used simultaneously in the same model.

The scheme has the following weaknesses:

1. An object can only have one `sboTerm` field, therefore, it can only be related to a single term in SBO. (This also impacts the design of SBO: it must be structured such that a class of SBML elements can logically only be associated with one class of terms in the ontology.)
2. The only relationship that can be expressed by `sboTerm` is "is a". It is not possible to represent different relationships (known as *verbs* in ontology-speak). This limits what can be expressed.

The weaknesses are not shared by the annotation scheme described in Section 6. If an application's needs cannot be met using SBO terms, software developers should examine the approach described in Section 6.

5.3.2 When to use SBO and when to use other annotations

The general annotation guidelines described in Section 6 could also be used to make references to SBO terms. However, in the interest of making the use of SBO in SBML maximally interoperable between software tools, the best-practice recommendation is to place SBO references in the `sboTerm` field rather than in the `annotation` field of an object.

Some software applications may have their own vocabulary of terms similar in purpose to SBO. For maximal software interoperability, the best-practice recommendation in SBML is nonetheless to use SBO terms in preference to using application-specific annotation schemes. Software applications should therefore attempt to translate their private terms to and from SBO terms when writing and reading SBML, respectively.

5.4 Discussion

Here we discuss some additional points about the SBO-based approach.

5.4.1 Frequency of change in the ontology

The SBO development approach follows conventional ontology development approaches in bioinformatics. One of the principles being followed is that identifiers and meanings of terms in the CVs never change and the terms are never deleted. Where some terms are deemed obsolete, the introduction of new terms refine or supersede existing terms, but the existing identifiers are left in the CV. Thus, references never end up pointing to nonexistent entries. In the case where synonymous terms are merged after agreement that multiple terms are identical, the term identifiers are again left in the CV and they still refer to the same concept as before. Out-of-date terms cached or hard-coded by an application remain usable in all cases. (Also, with machine-readable CV encodings and appropriate software design, it should be possible to develop API libraries that automatically map older terms to newer terms as the CVs evolve.)

Therefore, a model is never in danger of ending up with SBO identifiers that cannot be dereferenced. If an application finds an old model with a term `SBO:0000065`, it can be assured that it will be able to find this term in SBO, even if it has been superseded by other, more preferred terms.

5.4.2 Consistency of information

If you have a means of linking (say) a reaction rate formula to a term in a CV, is it possible to have an inconsistency between the formula in the SBML model and the one defined for the CV term? Yes, but this

is not a new problem; it arises in other situations involving SBML models already. The guideline for these situations is that the model must be self-contained and stand on its own. Therefore, in cases where they differ, the definitions in the SBML model take precedence over the definitions referenced by the CV. In other words, the model (and its MathML) is authoritative.

5.4.3 Implications for network access

Must a software tool have the ability to access the network or read the CV every time it encounters a model or otherwise works with SBML? No. Since the SBO will likely stabilize and change infrequently once a core set of terms is defined, applications can cache the controlled vocabulary and not make network accesses to the master SBO copy unless something forces them to (e.g., detecting a reference in a model to an SBO term that the application does not recognize). In addition, applications could have user preference settings indicating how often the CV definitions should be refreshed (similar to how modern applications provide a setting dictating how often they should check for new versions of themselves). Simple applications may go further and hard code references to terms in SBO that have reached stability and community consensus.

5.4.4 Implications for software tools

What if a software tool does not pay attention to the SBO annotations described here? Then one is faced with exactly the situation that exists today: the SBML model must be interpreted as-is, without benefit of the information added by the SBO terms. The purpose of introducing an ontology scheme and guidelines for its use is to give tools enough information that they *could* perform added processing, if they were designed to take advantage of that information.

5.4.5 Is another ontology really needed?

It may seem that developing a new, separate ontology is overkill for the intended purpose. However, it turns out that no existing ontology contains the necessary details for this role in SBML. In particular, none of the existing ontologies provide mathematical formulas for reaction rates.

6 A standard format for the annotation field

This section describes the standard non-proprietary format for `annotation` elements when (a) referring to controlled vocabulary terms and database identifiers which define and describe biological and biochemical entities; and (b) describing the creator of a model and its modification history. Such a structured format should facilitate the generation of models compliant with the MIRIAM standard of model curation (Le Novère et al., 2005).

This format should *not* be used to refer to SBO terms (Section 5), because SBO defines terms about mathematical modeling constructs and not the biological and biochemical entities that the mathematics represent.

This format describes the form of one of the top level elements that could reside in a given `annotation` structure. As such this format is compliant with the constraints placed on the form of annotation elements described in Section 3.3.3.

6.1 Motivation

The SBML structures described elsewhere in this document do not have any biochemical or biological semantics. The format described in this section provides a scheme for linking SBML structures to external resources so that those structures can have such semantics. The motivation for the introduction of this scheme is similar to that given for the introduction of `sboTerm` however this scheme is significantly more flexible.

6.2 XML Namespaces in the standard annotation

This format uses a restricted form of Dublin Core (Dublin Core Metadata Initiative, 2005) and BioModels qualifier elements (see `http://sbml.org/wiki/Biomodels_Qualifiers`) embedded in RDF (W3C, 2004b). It uses a number of external XML standards and associated XML namespaces. Table 8 lists these namespaces and relevant documentation on those namespaces. The format constrains the order of elements in these namespaces beyond the constraints defined in the standard definitions for those namespaces. For each standard listed, the format only uses a subset of the possible syntax defined by the given standard. Thus it is possible for an `annotation` element to include XML that is compliant with those external standards but is not compliant with the format described here. Parsers wishing to support this format should be aware that a valid `annotation` element may contain an `rdf:RDF` element which is not compliant with the format described here. A parser should check that all aspects of the syntax defined here before assuming that the contained data is encoded in the format.

Namespace Prefix	Namespace URI	Definition Document
`dc`	`http://purl.org/dc/elements/1.1/`	(Powell and Johnston, 2003)
`rdf`	`http://www.w3.org/1999/02/22-rdf-syntax-ns#`	(W3C, 2004a)
`dcterms`	`http://purl.org/dc/terms/`	(Kokkelink and Schwänzl, 2002) (DCMI Usage Board, 2005)
`vcard`	`http://www.w3.org/2001/vcard-rdf/3.0#`	(Iannella, 2001)
`bqbiol`	`http://biomodels.net/biology-qualifiers/`	
`bqmodel`	`http://biomodels.net/model-qualifiers/`	

Table 8: *The XML standards used in the SBML standard format for annotation. The namespace prefix are shown to indicate only the prefix used in the main text.*

6.3 General syntax for the standard annotation

An outline of the format syntax is shown below.

```
<SBML_ELEMENT +++ metaid="SBML_META_ID" +++ >
```

```
    +++
    <annotation>
      +++
      <rdf:RDF
        xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#"
        xmlns:dc="http://purl.org/dc/elements/1.1/"
        xmlns:dcterm="http://purl.org/dc/terms/"
        xmlns:vcard="http://www.w3.org/2001/vcard-rdf/3.0#"
        xmlns:bqbiol="http://biomodels.net/biology-qualifiers/"

        xmlns:bqmodel="http://biomodels.net/model-qualifiers/"

      >
        <rdf:Description rdf:about="#SBML_META_ID">
          [MODEL_HISTORY]
          <RELATION_ELEMENT>
            <rdf:Bag>
              <rdf:li rdf:resource="URI" />
              ...
            </rdf:Bag>
          </RELATION_ELEMENT>
          ...
        </rdf:Description>
        +++
      </rdf:RDF>
      +++
    </annotation>
    +++
  </SBML_ELEMENT>
```

The above outline shows the order of the elements. The capitalized identifiers refer to generic strings of a particular type: `SBML_ELEMENT` refers to any SBML element name that can contain an `annotation` element; `SBML_META_ID` is a XML `ID` string; `RELATION_ELEMENT` refers to element names in either the namespace `http://biomodels.net/biology-qualifiers/` or `http://biomodels.net/model-qualifiers/`; and `URI` is a URI. `[MODEL_HISTORY]` refers to an optional section described in Section 6.6 which can only be present within SBML model elements. '+++' is a placeholder for either no content or valid XML syntax that is not defined by the standard annotation scheme but is consistent with the relevant standards for the enclosing elements. '`...`' is a placeholder for zero or more elements of the same form as the immediately preceding element. The precise form of whitespace and the XML namespace prefix definitions is not constrained however the elements and attributes must be in the namespaces shown. The rest of this section describes the format formally in English.

In this format the annotation of an element is located in a single `rdf:RDF` element contained within an SBML `annotation` element. The annotation element can contain other elements in any order as described in Section *3.3.3*. The format described in this section only defines the form of the `rdf:RDF` element. The containing SBML *Sbase* element must have a `metaid` field value. (As this attribute is of the type `ID` its value must unique to the entire SBML document.)

The first element of the `rdf:RDF` element must be an `rdf:Description` element with an `rdf:about` attribute. (This format doesn't define the form of subsequent elements of the `rdf:RDF` element.) The value of the `rdf:about` attribute must be of the form `#<string>` where the string component is equal to the value of the `metaid` field of the containing SBML element.

The `rdf:Description` element can contain only an optional model history section (see Section 6.6) followed by a sequence of zero or more BioModels relation elements. The optional model history section can only be present within an SBML Model element. The specific type of the relation elements will vary depending on the relationship between the SBML component and referenced information or resource.

Although Section 6.5 describes the detailed semantics of each of the relation element types the content of these elements follows exactly the same form. The Biomodels qualifiers relation elements must only contain a single `rdf:Bag` element which in turn must only contain one or more `rdf:li` elements. The `rdf:li` elements must only have a `rdf:resource` attribute containing a URI referring to an information resource (See Section 6.4).

Annotations in this format can be located at different depths within a model component as is appropriate.

6.4 Use of URIs

The format represents a set of relationships between the SBML element and the resources referred to by the contained `rdf:resource` attribute values. The BioModels relation elements simply define the type of the relationship.

For instance a Species element representing a protein could be annotated with a reference to the database UniProt by the `http://www.uniprot.org/#P12999` resource identifier, identifying exactly the protein described by the Species element. This identifier maps to a unique entry in UniProt which is never deleted from the database. In the case of UniProt, this is the "accession" of the entry. When the entry is merged with another one, both "accession" are conserved. Similarly in a controlled vocabulary resource, each term is associated with a perennial identifier. The UniProt entry also possess an "entry name" (the Swiss-Prot "identifier"), a "protein name", "synonyms" etc. Only the "accession" is perennial and should be used.

The value of a `rdf:resource` attribute is a URI that both uniquely identifies the resource, and the data in the resource. In this case the resource constraining the identifier precedes the '#' symbol and the term or database identifier follows the '#' symbol. In the above example, the resource `http://www.uniprot.org/` includes the entry P12999.

The value of the `rdf:resource` attribute is a URI, not a URL; as such, a URI does not have to reference a physical web object but simply identifies a controlled vocabulary term or database object (a URI is a label that, in this case, just happens to look like a URL). For instance, a true URL for an Internet resource such as `http://www.uniprot.org/entry/P12999` might correspond to the URI `http://www.uniprot.org/#P12999`.

SBML does not specify how a parser is to interpret a URI. In the case of a transformation into a physical URL, there could be several solutions. For instance, the URI `http://www.geneontology.org/#GO:0007268` can be translated into:

`http://www.ebi.ac.uk/ego/DisplayGoTerm?selected=GO:0007268`
`http://www.godatabase.org/cgi-bin/amigo/go.cgi?view=details&query=GO:0007268`
`http://www.informatics.jax.org/searches/GO.cgi?id=GO:0007268`

Similarly the URI `http://www.ec-code.org/#3.5.4.4` can refer to:

`http://www.ebi.ac.uk/intenz/query?cmd=SearchEC&ec=3.5.4.4`
`http://www.expasy.org/cgi-bin/nicezyme.pl?3.5.4.4`
`http://www.chem.qmul.ac.uk/iubmb/enzyme/EC3/5/4/4.html`
`http://www.genome.jp/dbget-bin/www_bget?ec:3.5.4.4`
etc.

To enable interoperability, the community has agreed on an initial set of standardized valid URI syntax rules which may be used within the standard annotation format. This set of rules is not part of the SBML standard but will grow independently from specific SBML Levels and Versions. As the set changes a given URI syntax rule will not be modified although the physical resource associated with the rule may change. These URIs will always be composed as `resource#id`. The web page http://sbml.org/wiki/MIRIAM_URI_Set lists URI syntaxes and possible physical links to controlled vocabulary and databases. Each entry contains a list of SBML and relation elements in which the given URI can be appropriately embedded. To enable consistent and thus useful links to external resources, the URI syntax rule set must have a consistent view of the concepts represented by the different SBML elements for the purposes of this format. For example as the rule set is designed to link SBML biological and biochemical resources the rule set assumes that a Species element represents the concept of a biochemical entity type rather than mathematical symbol. The URI rule list will evolve with the evolution of databases and resources. The annotation format described in this section does not require a simple parser of this format to access this list.

6.5 Relation elements

To enable the format to encode different types of relationships between SBML elements and resources, different BioModel qualifier elements are used to enclose a set of `rdf:li` elements. The relation elements imply a specific relationship between the enclosing SBML element and the resources referenced by the `rdf:li` elements.

The detailed semantics (i.e. from the perspective of automatic parser) of the relation elements is defined by the URI list at http://sbml.org/wiki/MIRIAM_URI_Set, and thus is outside the scope of SBML. The URI list generally assumes that the biological entity represented by the element is the concept linked to the reference resource.

Several relation elements with a given tag, enclosed in the same SBML element, each represent an alternative annotation to the SBML element. For example two bqbiol:hasPart elements within a Species SBML element represent two different sets of references to the parts making up the the chemical entity represented by the species. (The species is not made up of all the entities represented by all the references combined).

The complete list of the qualifier elements in the Biomodels qualifier namespaces is documented at http://sbml.org/wiki/Biomodels_Qualifiers. The list is divided into two namespaces one for model qualifiers `http://biomodels.net/biology-qualifiers/` (prefix used here `bqbiol`) and the other for biological qualifiers `http://biomodels.net/model-qualifiers/`) (prefix used here `bqmodel`. This list will only grow i.e no element will be removed from the list. The following is the list of elements at the time of writing:

- `bqmodel:is` The modeling object encoded by the SBML component is the subject of the referenced resource. For instance, this qualifier might be used to link the model to a model database.
- `bqmodel:isDescribedBy` The modeling object encoded by the SBML component is described by the referenced resource. This relation might be used to link SBML components to the literature that describes this model or this kinetic law.
- `bqbiol:is` The biological entity represented by the SBML component is the subject of the referenced resource. This relation might be used to link a reaction to its exact counterpart in KEGG or Reactome for instance.
- `bqbiol:hasPart` The biological entity represented by the SBML component includes the subject of the referenced resource, either physically or logically. This relation might be used to link a complex to the description of its components.
- `bqbiol:isPartOf` The biological entity represented by the SBML component is a physical or logical part of the subject of the referenced resource. This relation might be used to link a component to the description of the complex is belongs to.
- `bqbiol:isVersionOf` The biological entity represented by the SBML component is a version or an instance of the subject of the referenced resource.
- `bqbiol:hasVersion` The subject of the referenced resource is a version or an instance of the biological entity represented by the SBML component.
- `bqbiol:isHomologTo` The biological entity represented by the SBML component is homolog, to the subject of the referenced resource, i.e. they share a common ancestor.
- `bqbiol:isDescribedBy` The biological entity represented by the SBML component is described by the referenced resource. This relation should be used for instance to link a species or a parameter to the literature that describes the quantity of the species or the value of the parameter.

6.6 Model history

When enclosed in an SBML Model element, the format described in previous sections can include additional elements to describe the history of the model. This history data must occur immediately before the first

BioModels relation elements. These additional elements encode information on the model creator and a sequence of dates recording changes to the model. The syntax for this section is outlined below.

```
<dc:creator rdf:parseType="Resource">
  <rdf:Bag>
    <rdf:li rdf:parseType="Resource">
      [[
      +++
      <vCard:N rdf:parseType="Resource">
        <vCard:Family>FAMILY_NAME</vCard:Family>
        <vCard:Given>GIVEN_NAME</vCard:Given>
      </vCard:N>
      +++
      [<vCard:EMAIL>EMAIL_ADDRESS</vCard:EMAIL>]
      +++
      [<vCard:ORG>
        <vCard:Orgname>ORGANIZATION_NAME</vCard:Orgname>
      </vCard:ORG>]
      +++
      ]]
    </rdf:li>
    ...
  </rdf:Bag>
</dc:creator>
<dcterms:created rdf:parseType="Resource">
  <dcterms:W3CDTF>DATE<dcterms:W3CDTF>
</dcterms:created>
<dcterms:modified rdf:parseType="Resource">
  <dcterms:W3CDTF>DATE<dcterms:W3CDTF>
</dcterms:modified>
```

The order of elements is as shown above except that elements of the format contained between `[[` and `]]` can occur in any order. The capitalized identifiers refer to generic strings of a particular type: `FAMILY_NAME` is the family name of a person who created the model; `GIVEN_NAME` is the first name of the same person who created the model; `EMAIL_ADDRESS` is the email address of the same person who created the model; and `ORGANIZATION_NAME` is the name of the organization with which the same person who created the model is affiliated `DATE` is a date in W3C date format (Wolf and Wicksteed, 1998). `W3CDTF`, `N`, `ORG` and `EMAIL` are literal strings. The elements of the format contained between `[` and `]` are optional. '+++' is a placeholder for either no content or valid XML syntax that is not defined by the standard annotation scheme but is consistent with the relevant standards for the enclosing elements. '`...`' is a placeholder for zero or more elements of the same form as the immediately preceding element. The precise form of whitespace and the XML namespace prefix definitions is not constrained. The remaining text in this section describes the syntax formally in English.

The additional elements of the model history sub-format consist in sequence of a `dc:creator` element, a `dcterms:created` element and zero or more `dcterms:modified` elements. All these elements must have the attribute `rdf:parseType` set to `Resource`.

The `dc:creator` element describes the person who created the SBML encoding of the model and contains a single `rdf:Bag` element. The `rdf:Bag` element can contain any number of elements however the first element must be a `rdf:li` element. The `rdf:li` element can contain any number of elements in any order. The set of elements contained with the `rdf:li` element can include the following informative elements: `vCard:N`, `vCard:EMAIL` and `vCard:ORG`. The `vCard:N` contains the name of the creator and must consist of a sequence of two elements: `vCard:Family` and the `vCard:Given` whose content is the family (surname) and given (first) names of the creator respectively. The `vCard:N` must have the attribute `rdf:parseType` set to `Resource`. The content of the `vCard:EMAIL` element must be the email address of the creator. The content of the `vCard:ORG` element must contain a single `vCard:Orgname` element. The `vCard:Orgname` element must contain the name of an organization to which the creator is affiliated.

The `dcterms:created` and `dcterms:modified` elements must each contain a single `dcterms:W3CDTF` element whose content is a date in W3C date format (Wolf and Wicksteed, 1998) which is a a profile of (restricted form of) ISO 8601.

6.7 Examples

The following shows the annotation of a model with model creation data and links to external resources:

```
<model metaid="_180340" id="GMO" name="Goldbeter1991_MinMitOscil">
    <annotation>
        <rdf:RDF
                xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#"
                xmlns:dc="http://purl.org/dc/elements/1.1/"
                xmlns:dcterms="http://purl.org/dc/terms/"
                xmlns:vCard="http://www.w3.org/2001/vcard-rdf/3.0#"
                xmlns:bqbiol="http://biomodels.net/biology-qualifiers/"
                xmlns:bqmodel="http://biomodels.net/model-qualifiers/"
        >
            <rdf:Description rdf:about="#_180340">
                <dc:creator rdf:parseType="Resource">
                    <rdf:Bag>
                        <rdf:li rdf:parseType="Resource">
                            <vCard:N rdf:parseType="Resource">
                                <vCard:Family>Shapiro</vCard:Family>
                                <vCard:Given>Bruce</vCard:Given>
                            </vCard:N>
                            <vCard:EMAIL>bshapiro@jpl.nasa.gov</vCard:EMAIL>
                            <vCard:ORG>
                                <vCard:Orgname>NASA Jet Propulsion Laboratory</vCard:Orgname>
                            </vCard:ORG>
                        </rdf:li>
                    </rdf:Bag>
                </dc:creator>
                <dcterms:created rdf:parseType="Resource">
                    <dcterms:W3CDTF>2005-02-06T23:39:40</dcterms:W3CDTF>
                </dcterms:created>
                <dcterms:modified rdf:parseType="Resource">
                    <dcterms:W3CDTF>2005-09-13T13:24:56</dcterms:W3CDTF>
                </dcterms:modified>
                <bqmodel:is>
                    <rdf:Bag>
                        <rdf:li rdf:resource="http://www.ebi.ac.uk/biomodels/#BIOMD0000000003"/>
                    </rdf:Bag>
                </bqmodel:is>
                <bqmodel:isDescribedBy>
                     <rdf:Bag>
                         <rdf:li rdf:resource="http://www.pubmed.gov/#1833774"/>
                     </rdf:Bag>
                <bqmodel:isDescribedBy>
                <bqbiol:isVersionOf>
                    <rdf:Bag>
                        <rdf:li rdf:resource="http://www.genome.jp/kegg/pathway/#hsa04110"/>
                        <rdf:li rdf:resource="http://www.reactome.org/#69278"/>
                    </rdf:Bag>
                </bqbiol:isVersionOf>
        </rdf:Description>
    </rdf:RDF>
</annotation>
```

The following example shows a Reaction structure annotated with a reference to its exact Reactome counterpart.

```
<reaction id="cdc2Phospho" metaid="jb007">
  <annotation>
    <rdf:RDF
      xmlns:bqbiol="http://biomodels.net/biology-qualifiers/"
      xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#"
    >
      <rdf:Description rdf:about="#jb007">
        <bqbiol:is>
          <rdf:Bag>
            <rdf:li rdf:resource="http://www.reactome.org/#170156"/>
          </rdf:Bag>
```

```
            </bqbiol:is>
          </rdf:Description>
        </rdf:RDF>
      </annotation>
      <listOfReactants>
        <speciesReference species="cdc2"/>
      </listOfReactants>
      <listOfProducts>
        <speciesReference species="cdc2-Y15P"/>
      </listOfProducts>
      <listOfModifiers>
        <modifierSpeciesReference species="wee1"/>
      </listOfModifiers>
    </reaction>
```

The following example describes a species that represents a complex between the protein calmodulin and calcium ions:

```
    <species id="Ca_calmodulin" metaid="cacam">
      <annotation>
        <rdf:RDF
          xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#"
          xmlns:bqbiol="http://biomodels.net/biology-qualifiers/"
        >
          <rdf:Description rdf:about="#cacam">
            <bqbiol:hasPart>
              <rdf:Bag>
                <rdf:li rdf:resource="http://www.uniprot.org/#P62158"/>
                <rdf:li rdf:resource="http://www.genome.jp/kegg/compound/#C00076"/>
              </rdf:Bag>
            </bqbiol:hasPart>
          </rdf:Description>
        </rdf:RDF>
      </annotation>
    </species>
```

The following example describes a species that represents either “Calcium/calmodulin-dependent protein kinase type II alpha chain” or “Calcium/calmodulin-dependent protein kinase type II beta chain”. This is the case for instance in the somatic cytoplasm of striatal medium-size spiny neurons, where both are present but they cannot be functionally differentiated.

```
    <species id="calcium_calmodulin" metaid="cacam">
      <annotation>
        <rdf:RDF
          xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#"
          xmlns:bqbiol="http://biomodels.net/biology-qualifiers/"
        >
          <rdf:Description rdf:about="#cacam">
            <bqbiol:hasVersion>
              <rdf:Bag>
                <rdf:li rdf:resource="http://www.uniprot.org/#Q9UQM7"/>
                <rdf:li rdf:resource="http://www.uniprot.org/#Q13554"/>
              </rdf:Bag>
            </bqbiol:hasVersion>
          </rdf:Description>
        </rdf:RDF>
      </annotation>
    </species>
```

The above approach should not be used to describe “any Calcium/calmodulin-dependent protein kinase type II chain” because such an annotation requires references to the products of other genes such as gamma or delta. All the known proteins could be enumerated but such an approach would almost surely lead to inaccuracies due to the evolution of biological knowledge. Instead the annotation should refer to a generic information such as Ensembl family ENSF00000000194 “CALCIUM/CALMODULIN DEPENDENT KINASE TYPE II CHAIN” or PIR superfamily PIRSF000594 “Calcium/calmodulin-dependent protein kinase type II”.

The following two examples show how to use the qualifier `is Version Of`. The first example is the relationship between a reaction and an EC code. An EC code describes an enzymatic activity and an enzymatic reaction involving a particular enzyme can be seen as an instance of this activity. For instance the following reaction represents the phosphorylation of a glutamate receptor by a complex calcium/calmodulin kinase II.

```
<reaction id="NMDAR_phosphorylation" metaid="thx1138">
  <annotation>
    <rdf:RDF
      xmlns:bqbiol="http://biomodels.net/biology-qualifiers/"
      xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#"
    >
      <rdf:Description rdf:about="#thx1138">
        <bqbiol:isVersionOf>
          <rdf:Bag>
            <rdf:li rdf:resource="http://www.ec-code.org/#2.7.1.17"/>
          </rdf:Bag>
        </bqbiol:isVersionOf>
      </rdf:Description>
    </rdf:RDF>
  </annotation>
  <listOfReactants>
    <speciesReference species="NMDAR"/>
  </listOfReactants>
  <listOfProducts>
    <speciesReference species="P-NMDAR"/>
  </listOfProducts>
  <listOfModifiers>
    <modifierSpeciesReference species="CaMKII"/>
  </listOfModifiers>
  <kineticLaw>
    <math xmlns="http://www.w3.org/1998/Math/MathML">
      <apply>
        <times/>
        <ci>CaMKII</ci>
        <ci>kcat</ci>
        <apply>
          <divide/>
          <ci>NMDAR</ci>
          <apply>
            </times>
            <ci>NMDAR</ci>
            <ci>Km</ci>
          </apply>
        </apply>
      </apply>
    </math>
    <listOfParameters>
      <parameter id="kcat" value="1"/>
      <parameter id="Km" value="5e-10"/>
    </listOfParameters>
  </kineticLaw>
</reaction>
```

The second example of the use of isVersionOf is the complex between Calcium/calmodulin-dependent protein kinase type II alpha chain and Calcium/calmodulin, that is only one of the "calcium- and calmodulin-dependent protein kinase complexes" described by the Gene Ontology term GO:0005954.

```
<species id="CaCaMKII" metaid="C8H10N4O2">
  <annotation>
    <rdf:RDF
      xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#"
      xmlns:bqbiol="http://biomodels.net/biology-qualifiers/"
    >
      <rdf:Description rdf:about="#C8H10N4O2">
        <bqbiol:isVersionOf>
          <rdf:Bag>
            <rdf:li rdf:resource="http://www.geneontology.org/#GO:0005954"/>
          </rdf:Bag>
```

```
            </bqbiol:isVersionOf>
          </rdf:Description>
        </rdf:RDF>
      </annotation>
    </species>
```

The previous case is different form the following one, although they could seem similar at first sight. The "Calcium/calmodulin-dependent protein kinase type II alpha chain" is a part of the above mentioned "calcium- and calmodulin-dependent protein kinase complex".

```
    <species id="CaMKIIalpha" metaid="C10H14N2">
      <annotation>
        <rdf:RDF
          xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#"
          xmlns:bqbiol="http://biomodels.net/biology-qualifiers/"
        >
          <rdf:Description rdf:about="#C10H14N2">
            <bqbiol:isPartOf>
              <rdf:Bag>
                <rdf:li rdf:resource="http://www.geneontology.org/#GO:0005954"/>
              </rdf:Bag>
            </bqbiol:isPartOf>
          </rdf:Description>
        </rdf:RDF>
      </annotation>
    </species>
```

It is possible describe a component with several alternative sets of qualified annotations. For instance, the following species represents a pool of GMP, GDP and GDP. We annotate it with the three corresponding KEGG compound identifiers but also with the three corresponding ChEBI identifiers. The two alternative annotations are encoded in separate `hasVersion` qualifier elements.

```
    <species id="GXP" metaid="GXP">
      <annotation>
        <rdf:RDF
          xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#"
          xmlns:bqbiol="http://biomodels.net/biology-qualifiers/"
        >
          <rdf:Description rdf:about="#GXP">
            <bqbiol:hasVersion>
              <rdf:Bag>
                <rdf:li rdf:resource="http://www.ebi.ac.uk/chebi/#CHEBI:17345"/>
                <rdf:li rdf:resource="http://www.ebi.ac.uk/chebi/#CHEBI:17552"/>
                <rdf:li rdf:resource="http://www.ebi.ac.uk/chebi/#CHEBI:17627"/>
              </rdf:Bag>
            </bqbiol:hasVersion>
            <bqbiol:hasVersion>
              <rdf:Bag>
                <rdf:li rdf:resource="http://www.genome.jp/kegg/compound/#C00035"/>
                <rdf:li rdf:resource="http://www.genome.jp/kegg/compound/#C00044"/>
                <rdf:li rdf:resource="http://www.genome.jp/kegg/compound/#C00144"/>
              </rdf:Bag>
            </bqbiol:hasVersion>
          </rdf:Description>
        </rdf:RDF>
      </annotation>
    </species>
```

The following example presents a reaction being actually the combination of three different elementary molecular reactions. We annotate it with the three corresponding KEGG reactions, but also with the three corresponding enzymatic activities. Again the two hasPart elements represent two alternative annotations. The process represented by the Reaction structure is composed of three parts, and not six parts.

```
    <reaction id="adenineProd" metaid="adeprod">
      <annotation>
        <rdf:RDF
          xmlns:bqbiol="http://biomodels.net/biology-qualifiers/"
```

```
            xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#"
          >
            <rdf:Description rdf:about="#adeprod">
              <bqbiol:hasPart>
                <rdf:Bag>
                  <rdf:li rdf:resource="http://www.ec-code.org/#2.5.1.22"/>
                  <rdf:li rdf:resource="http://www.ec-code.org/#3.2.2.16"/>
                  <rdf:li rdf:resource="http://www.ec-code.org/#4.1.1.50"/>
                </rdf:Bag>
              </bqbiol:hasPart>
              <bqbiol:hasPart>
                <rdf:Bag>
                  <rdf:li rdf:resource="http://www.genome.jp/kegg/reaction/#R00178"/>
                  <rdf:li rdf:resource="http://www.genome.jp/kegg/reaction/#R01401"/>
                  <rdf:li rdf:resource="http://www.genome.jp/kegg/reaction/#R02869"/>
                </rdf:Bag>
              </bqbiol:hasPart>
            </rdf:Description>
          </rdf:RDF>
        </annotation>
      </reaction>
```

It is possible to mix different URIs in a given set. The following example presents two alternative annotations of the human hemoglobin, the first with ChEBI heme and the second with KEGG heme.

```
      <species id="heme" metaid="heme">
        <annotation>
          <rdf:RDF
            xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#"
            xmlns:bqbiol="http://biomodels.net/biology-qualifiers/"
          >
           <rdf:Description rdf:about="#heme">
            <bqbiol:hasPart>
              <rdf:Bag>
                <rdf:li rdf:resource="http://www.uniprot.org/#P69905"/>
                <rdf:li rdf:resource="http://www.uniprot.org/#P68871"/>
                <rdf:li rdf:resource="http://www.ebi.ac.uk/chebi/#CHEBI:17627">
              </rdf:Bag>
            </bqbiol:hasPart>
            <bqbiol:hasPart>
              <rdf:Bag>
               <rdf:li rdf:resource="http://www.uniprot.org/#P69905"/>
                <rdf:li rdf:resource="http://www.uniprot.org/#P68871"/>
                <rdf:li rdf:resource="http://www.genome.jp/kegg/compound/#C00032"/>
              </rdf:Bag>
            </bqbiol:hasPart>
           </rdf:Description>
         </rdf:RDF>
        </annotation>
      </species>
```

As formally defined above it is possible to use different qualifiers in the same annotation element. The following phosphorylation is annotated by its exact KEGG counterpart and by the generic GO term "phosphorylation".

```
      <reaction id="phosphorylation" metaid="phosphorylation">
        <annotation>
          <rdf:RDF
            xmlns:bqbiol="http://biomodels.net/biology-qualifiers/"
            xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#"
          >
            <rdf:Description rdf:about="#phosphorylation">
              <bqbiol:is>
                <rdf:Bag>
                  <rdf:li rdf:resource="http://www.genome.jp/kegg/reaction/#R03313" />
                </rdf:Bag>
              </bqbiol:is>
              <bqbiol:isVersionOf>
```

```
                  <rdf:Bag>
                    <rdf:li rdf:resource="http://www.geneontology.org/#GO:0016310" />
                  </rdf:Bag>
                </bqbiol:isVersionOf>
              </rdf:Description>
            </rdf:RDF>
          </annotation>
        </reaction>
```

7 Example models expressed in XML using SBML

In this section, we present several examples of complete models encoded in XML using SBML Level 2.

7.1 A simple example application of SBML

Consider the following representation of an enzymatic reaction:

$$E + S \underset{k_{\mathrm{off}}}{\overset{k_{\mathrm{on}}}{\rightleftharpoons}} ES \xrightarrow{k_{\mathrm{cat}}} E + P$$

The following is the minimal SBML document encoding the model shown above:

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml level="2" version="2" xmlns="http://www.sbml.org/sbml/level2/version2">
    <model name="EnzymaticReaction">
        <listOfCompartments>
            <compartment id="cytosol" size="1e-14"/>
        </listOfCompartments>
        <listOfSpecies>
            <species compartment="cytosol" id="ES" initialAmount="0" name="ES" />
            <species compartment="cytosol" id="P" initialAmount="0" name="P" />
            <species compartment="cytosol" id="S" initialAmount="1e-20" name="S" />
            <species compartment="cytosol" id="E" initialAmount="5e-21" name="E" />
        </listOfSpecies>
        <listOfReactions>
            <reaction id="veq">
                <listOfReactants>
                    <speciesReference species="E"/>
                    <speciesReference species="S"/>
                </listOfReactants>
                <listOfProducts>
                    <speciesReference species="ES"/>
                </listOfProducts>
                <kineticLaw>
                    <math xmlns="http://www.w3.org/1998/Math/MathML">
                        <apply>
                            <times/>
                            <ci>cytosol</ci>
                            <apply>
                                <minus/>
                                <apply>
                                    <times/>
                                    <ci>kon</ci>
                                    <ci>E</ci>
                                    <ci>S</ci>
                                </apply>
                                <apply>
                                    <times/>
                                    <ci>koff</ci>
                                    <ci>ES</ci>
                                </apply>
                            </apply>
                        </apply>
                    </math>
                    <listOfParameters>
                        <parameter id="kon" value="1000000"/>
                        <parameter id="koff" value="0.2"/>
                    </listOfParameters>
                </kineticLaw>
            </reaction>
            <reaction id="vcat" reversible="false" >
                <listOfReactants>
                    <speciesReference species="ES"/>
                </listOfReactants>
                <listOfProducts>
                    <speciesReference species="E"/>
                    <speciesReference species="P"/>
```

```
                    </listOfProducts>
                    <kineticLaw>
                        <math xmlns="http://www.w3.org/1998/Math/MathML">
                            <apply>
                                <times/>
                                <ci>cytosol</ci>
                                <ci>kcat</ci>
                                <ci>ES</ci>
                            </apply>
                        </math>
                        <listOfParameters>
                            <parameter id="kcat" value="0.1"/>
                        </listOfParameters>
                    </kineticLaw>
                </reaction>
            </listOfReactions>
        </model>
    </sbml>
```

In this example, the model has the identifier "`EnzymaticReaction`". The model contains one compartment (with identifier "`cytosol`"), four species (with identifiers "`ES`", "`P`", "`S`", and "`E`"), and two reactions ("`veq`" and "`vcat`"). The elements in the `listOfReactants` and `listOfProducts` in each reaction refer to the names of elements listed in the `listOfSpecies`. The correspondences between the various elements is explicitly stated by the `speciesReference` elements.

The model also features local parameter definitions in each reaction. In this case, the three parameters ("`kon`", "`koff`", "`kcat`") all have unique identifiers and they could also have just as easily been declared global parameters in the model. Local parameters frequently become more useful in larger models, where it may become tedious to assign unique identifiers for all the different parameters.

7.2 Example involving units

The following model uses the units features of SBML Level 2. In this model, the default value of `substance` is changed to be mole units with a scale factor of -3, or millimoles. This sets the default substance units in the model. The `size` and `time` built-ins are left to their defaults, meaning size is in litres and time is in seconds. The result is that, in this model, kinetic law formulas define rates in millimoles per second and the species identifiers in them represent concentration values in millimoles per litres. All the `species` elements set the initial amount of every given species to 1 millimole. The parameters "`vm`" and "`km`" are defined to be in millimoles per litres per second, and milliMoles per litres, respectively.

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns="http://www.sbml.org/sbml/level2/version2" level="2" version="2"
      xmlns:xhtml="http://www.w3.org/1999/xhtml">
    <model>
        <listOfUnitDefinitions>
            <unitDefinition id="substance">
                <listOfUnits>
                    <unit kind="mole" scale="-3"/>
                </listOfUnits>
            </unitDefinition>
            <unitDefinition id="mmls">
                <listOfUnits>
                    <unit kind="mole" scale="-3"/>
                    <unit kind="litre" exponent="-1"/>
                    <unit kind="second" exponent="-1"/>
                </listOfUnits>
            </unitDefinition>
            <unitDefinition id="mml">
                <listOfUnits>
                    <unit kind="mole" scale="-3"/>
                    <unit kind="litre" exponent="-1"/>
                </listOfUnits>
            </unitDefinition>
        </listOfUnitDefinitions>
        <listOfCompartments>
```

```
    <compartment id="cell" size="1"/>
</listOfCompartments>
<listOfSpecies>
    <species id="x0" compartment="cell" initialConcentration="1"/>
    <species id="x1" compartment="cell" initialConcentration="1"/>
    <species id="s1" compartment="cell" initialConcentration="1"/>
    <species id="s2" compartment="cell" initialConcentration="1"/>
</listOfSpecies>
<listOfParameters>
    <parameter id="vm" value="2" units="mmls"/>
    <parameter id="km" value="2" units="mml"/>
</listOfParameters>
<listOfReactions>
    <reaction id="v1">
        <listOfReactants>
            <speciesReference species="x0"/>
        </listOfReactants>
        <listOfProducts>
            <speciesReference species="s1"/>
        </listOfProducts>
        <kineticLaw>
            <notes>
                <xhtml:p>((vm * s1)/(km + s1))*cell</xhtml:p>
            </notes>
            <math xmlns="http://www.w3.org/1998/Math/MathML">
                <apply>
                    <times/>
                    <apply>
                        <divide/>
                        <apply>
                            <times/>
                            <ci> vm </ci>
                            <ci> s1 </ci>
                        </apply>
                        <apply>
                            <plus/>
                            <ci> km </ci>
                            <ci> s1 </ci>
                        </apply>
                    </apply>
                    <ci> cell </ci>
                </apply>
            </math>
        </kineticLaw>
    </reaction>
    <reaction id="v2">
        <listOfReactants>
            <speciesReference species="s1"/>
        </listOfReactants>
        <listOfProducts>
            <speciesReference species="s2"/>
        </listOfProducts>
        <kineticLaw>
            <notes>
                <xhtml:p>((vm * s2)/(km + s2))*cell</xhtml:p>
            </notes>
            <math xmlns="http://www.w3.org/1998/Math/MathML">
                <apply>
                    <times/>
                    <apply>
                        <divide/>
                        <apply>
                            <times/>
                            <ci> vm </ci>
                            <ci> s2 </ci>
                        </apply>
                        <apply>
                            <plus/>
                            <ci> km </ci>
```

```
                                    <ci> s2 </ci>
                                </apply>
                            </apply>
                            <ci> cell </ci>
                        </apply>
                    </math>
                </kineticLaw>
            </reaction>
            <reaction id="v3">
                <listOfReactants>
                    <speciesReference species="s2"/>
                </listOfReactants>
                <listOfProducts>
                    <speciesReference species="x1"/>
                </listOfProducts>
                <kineticLaw>
                    <notes>
                        <xhtml:p>((vm * x1)/(km + x1))*cell</xhtml:p>
                    </notes>
                    <math xmlns="http://www.w3.org/1998/Math/MathML">
                        <apply>
                            <times/>
                            <apply>
                                <divide/>
                                <apply>
                                    <times/>
                                    <ci> vm </ci>
                                    <ci> x1 </ci>
                                </apply>
                                <apply>
                                    <plus/>
                                    <ci> km </ci>
                                    <ci> x1 </ci>
                                </apply>
                            </apply>
                            <ci> cell </ci>
                        </apply>
                    </math>
                </kineticLaw>
            </reaction>
        </listOfReactions>
    </model>
</sbml>
```

7.3 Example of discrete version of a simple dimerization reaction

(Model contributed by Darren J. Wilkinson, Newcastle University, Newcastle upon Tyne, UK.)

This example illustrates subtle differences between models formulated for use in a continuous simulation framework (e.g., using differential equations) and those intended for a discrete simulation framework. The model shown here is suitable for use with a discrete stochastic simulation algorithm of the sort developed by Gillespie (1977). In such an approach, species are described in terms of molecular counts and stimulation proceeds by computing the probability of the time and identity of the next reaction, then updating the species amounts appropriately.

The model involves a simple dimerization reaction for a protein named "`P`":

$$2P \leftrightarrow P_2$$

The SBML representation is shown below. There are several important points to note. First, the species "`P`" and "`P2`" declare they are always in discrete amounts by using the flag `hasOnlySubstanceUnits`="`true`". This indicates that when the species identifiers appear in mathematical formulas, the units are *substance*, not the default of *substance/size*. A second point is that, as a result, the corresponding "kinetic law" formulas do not need volume corrections. In Gillespie's approach, the constants in the rate expressions (here, "`c1`" and "`c2`") contain a contribution from the kinetic constants of the reaction and the size of the compartment

in which the reactions take place. Finally, it is worth noting the rate expression for the forward reaction is a second-order mass-action reaction, but it is the *discrete* formulation of such a reaction rate (Gillespie, 1977).

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns="http://www.sbml.org/sbml/level2/version2" level="2" version="2">
   <model id="dimerization">
      <listOfUnitDefinitions>
          <unitDefinition id="substance">
              <listOfUnits>
                 <unit kind="item" multiplier="1" />
              </listOfUnits>
          </unitDefinition>
      </listOfUnitDefinitions>
      <listOfCompartments>
         <compartment id="Cell" size="1e-15" />
      </listOfCompartments>
      <listOfSpecies>
         <species id="P" compartment="Cell" initialAmount="301" hasOnlySubstanceUnits="true" />
         <species id="P2" compartment="Cell" initialAmount="0" hasOnlySubstanceUnits="true" />
      </listOfSpecies>
      <listOfReactions>
         <reaction id="Dimerization" reversible="false">
            <listOfReactants>
               <speciesReference species="P" stoichiometry="2" />
            </listOfReactants>
            <listOfProducts>
               <speciesReference species="P2" />
            </listOfProducts>
            <kineticLaw>
               <math xmlns="http://www.w3.org/1998/Math/MathML">
                  <apply>
                     <divide/>
                     <apply>
                        <times/>
                        <ci> c1 </ci>
                        <ci> P </ci>
                        <apply>
                           <minus/>
                           <ci> P </ci>
                           <cn type="integer"> 1 </cn>
                        </apply>
                     </apply>
                     <cn type="integer"> 2 </cn>
                  </apply>
               </math>
               <listOfParameters>
                  <parameter id="c1" value="0.00166" />
               </listOfParameters>
            </kineticLaw>
         </reaction>
         <reaction id="Dissociation" reversible="false">
            <listOfReactants>
               <speciesReference species="P2" />
            </listOfReactants>
            <listOfProducts>
               <speciesReference species="P" stoichiometry="2" />
            </listOfProducts>
            <kineticLaw>
               <math xmlns="http://www.w3.org/1998/Math/MathML">
                  <apply>
                     <times/>
                     <ci> c2 </ci>
                     <ci> P </ci>
                  </apply>
               </math>
               <listOfParameters>
                  <parameter id="c2" value="0.2" />
               </listOfParameters>
            </kineticLaw>
```

```
            </reaction>
          </listOfReactions>
        </model>
    </sbml>
```

This example also illustrates the need to provide additional information in a model so that software tools using different mathematical frameworks can properly interpret it. In this case, a simulation tool designed for continuous ODE-based simulation would likely misinterpret the model (in particular the reaction rate formulas), unless it deduced that a discrete stochastic simulation was intended. One of the purposes of SBO annotations (Section 5) is to enable such interpretation without the need for deduction.

7.4 Example involving assignment rules

This section contains a model that simulates a system containing a fast reaction. This model uses rules to express the mathematics of the fast reaction explicitly rather than using the `fast` field on a reaction element. The system modeled is

$$X_0 \xrightarrow{k_1 X_0} S_1$$

$$S_1 \xrightarrow{k_f S_1 - k_r S_2} S_2$$

$$S_2 \xrightarrow{k_2 S_2} X_1$$

$$k_1 = 0.1, \quad k_2 = 0.15, \quad k_f = K_{eq}10000, \quad k_r = 10000, \quad K_{eq} = 2.5.$$

where X_0, S_1, and S_2 are species in concentration units, and k_1, k_2, k_f, k_r, and K_{eq} are parameters. This system of reactions can be approximated with the following new system:

$$X_0 \xrightarrow{k_1 X_0} T$$

$$T \xrightarrow{k_2 S_2} X_1$$

$$S_1 = \frac{T}{1 + K_{eq}}$$

$$S_2 = K_{eq} S_1$$

where T is a new species. The following example SBML model encodes the second system.

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns="http://www.sbml.org/sbml/level2/version2" level="2" version="2"
      xmlns:math="http://www.w3.org/1998/Math/MathML">
    <model>
        <listOfCompartments>
            <compartment id="cell" size="1"/>
        </listOfCompartments>
        <listOfSpecies>
            <species id="X0" compartment="cell" initialConcentration="1"/>
            <species id="X1" compartment="cell" initialConcentration="0"/>
            <species id="T" compartment="cell" initialConcentration="0"/>
            <species id="S1" compartment="cell" initialConcentration="0"/>
            <species id="S2" compartment="cell" initialConcentration="0"/>
        </listOfSpecies>
        <listOfParameters>
            <parameter id="Keq" value="2.5"/>
        </listOfParameters>
        <listOfRules>
            <assignmentRule variable="S1">
                <math xmlns="http://www.w3.org/1998/Math/MathML">
                    <apply>
                        <divide/>
                        <ci> T </ci>
```

```
                            <apply>
                                <plus/>
                                <cn> 1 </cn>
                                <ci> Keq </ci>
                            </apply>
                        </apply>
                    </math>
                </assignmentRule>
                <assignmentRule variable="S2">
                    <math xmlns="http://www.w3.org/1998/Math/MathML">
                        <apply>
                            <times/>
                            <ci> Keq </ci>
                            <ci> S1 </ci>
                        </apply>
                    </math>
                </assignmentRule>
            </listOfRules>
            <listOfReactions>
                <reaction id="in">
                    <listOfReactants>
                        <speciesReference species="X0"/>
                    </listOfReactants>
                    <listOfProducts>
                        <speciesReference species="T"/>
                    </listOfProducts>
                    <kineticLaw>
                        <math xmlns="http://www.w3.org/1998/Math/MathML">
                            <apply>
                                <times/>
                                <ci> k1 </ci>
                                <ci> X0 </ci>
                                <ci> cell </ci>
                            </apply>
                        </math>
                        <listOfParameters>
                            <parameter id="k1" value="0.1"/>
                        </listOfParameters>
                    </kineticLaw>
                </reaction>
                <reaction id="out">
                    <listOfReactants>
                        <speciesReference species="T"/>
                    </listOfReactants>
                    <listOfProducts>
                        <speciesReference species="X1"/>
                    </listOfProducts>
                    <listOfModifiers>
                        <modifierSpeciesReference species="S2"/>
                    </listOfModifiers>
                    <kineticLaw>
                        <math xmlns="http://www.w3.org/1998/Math/MathML">
                            <apply>
                                <times/>
                                <ci> k2 </ci>
                                <ci> S2 </ci>
                                <ci> cell </ci>
                            </apply>
                        </math>
                        <listOfParameters>
                            <parameter id="k2" value="0.15"/>
                        </listOfParameters>
                    </kineticLaw>
                </reaction>
            </listOfReactions>
        </model>
    </sbml>
```

7.5 Example involving algebraic rules

This section contains an example model that contains an AlgebraicRule structure. The model contains a different formulation of the fast reaction described in Section 7.4. The system described in Section 7.4 can be approximated with the following system:

$$X_0 \xrightarrow{k_1 X_0} T$$

$$T \xrightarrow{k_2 S_1} X_1$$

with the constraint:

$$S_2 = K_{eq} S_1$$

$$S_1 + S_2 - T = 0$$

The following example SBML model encodes this approximate form.

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns="http://www.sbml.org/sbml/level2/version2" level="2" version="2">
    <model>
        <listOfCompartments>
            <compartment id="cell" size="1"/>
        </listOfCompartments>
        <listOfSpecies>
            <species id="X0" compartment="cell" initialConcentration="1"/>
            <species id="X1" compartment="cell" initialConcentration="0"/>
            <species id="T" compartment="cell" initialConcentration="0"/>
            <species id="S1" compartment="cell" initialConcentration="0"/>
            <species id="S2" compartment="cell" initialConcentration="0"/>
        </listOfSpecies>
        <listOfParameters>
            <parameter id="Keq" value="2.5"/>
        </listOfParameters>
        <listOfRules>
            <assignmentRule variable="S2">
                <math xmlns="http://www.w3.org/1998/Math/MathML">
                    <apply>
                        <times/>
                        <ci> Keq </ci>
                        <ci> S1 </ci>
                    </apply>
                </math>
            </assignmentRule>
            <algebraicRule>
                <math xmlns="http://www.w3.org/1998/Math/MathML">
                    <apply>
                        <minus/>
                        <apply>
                            <plus/>
                            <ci> S2 </ci>
                            <ci> S1 </ci>
                        </apply>
                        <ci> T </ci>
                    </apply>
                </math>
            </algebraicRule>
        </listOfRules>
        <listOfReactions>
            <reaction id="in">
                <listOfReactants>
                    <speciesReference species="X0"/>
                </listOfReactants>
                <listOfProducts>
                    <speciesReference species="T"/>
                </listOfProducts>
                <kineticLaw>
                    <math xmlns="http://www.w3.org/1998/Math/MathML">
                        <apply>
```

```
                                <times/>
                                <ci> k1 </ci>
                                <ci> X0 </ci>
                                <ci> cell </ci>
                            </apply>
                        </math>
                        <listOfParameters>
                            <parameter id="k1" value="0.1"/>
                        </listOfParameters>
                    </kineticLaw>
                </reaction>
                <reaction id="out">
                    <listOfReactants>
                        <speciesReference species="T"/>
                    </listOfReactants>
                    <listOfProducts>
                        <speciesReference species="X1"/>
                    </listOfProducts>
                    <kineticLaw>
                        <math xmlns="http://www.w3.org/1998/Math/MathML">
                            <apply>
                                <times/>
                                <ci> k2 </ci>
                                <ci> S2 </ci>
                                <ci> cell </ci>
                            </apply>
                        </math>
                        <listOfParameters>
                            <parameter id="k2" value="0.15"/>
                        </listOfParameters>
                    </kineticLaw>
                </reaction>
            </listOfReactions>
        </model>
    </sbml>
```

7.6 Example with combinations of `boundaryCondition` and `constant` values on Species with RateRule structures

In this section, we discuss a model that includes four species, each with a different combination of values for their `boundaryCondition` and `constant` fields. The model represents a hypothetical system containing one reaction,

$$S_1 + S_2 \xrightarrow{k_1 S_1 S_2 S_3} S_4$$

where S_3 is a species that catalyzes the conversion of species S_1 and S_2 into S_4. S_1 and S_2 are on the boundary of the system (i.e., S_1 and S_2 are reactants but their values are not determined by a kinetic law). The value of S_1 in the system is determined over time by the rate rule:

$$\frac{dS_1}{dt} = k_2$$

The values of constant parameters in the system are:

$$S_2 = 1, \quad S_3 = 2, \quad k_1 = 0.5, \quad k_2 = 0.1$$

and the initial values of species are:

$$S_1 = 0, \quad S_4 = 0$$

The value of S_1 varies over time so in SBML S_1 has a `constant` field with a default value of "`false`". The values of S_2 and S_3 are fixed so in SBML they have a `constant` field values of "`true`". S_3 only occurs as a modifier so the value of its `boundaryCondition` field can default to "`false`". S_4 is a product whose value is determined by a kinetic law and therefore in the SBML representation has "`false`" (the default) for both its `boundaryCondition` and `constant` fields.

The following is the SBML rendition of the model shown above:

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns="http://www.sbml.org/sbml/level2/version2" level="2" version="2">
    <model id="BoundaryCondExampleModel">
        <listOfCompartments>
            <compartment id="compartmentOne" size="1"/>
        </listOfCompartments>
        <listOfSpecies>
            <species id="S1" initialConcentration="0" compartment="compartmentOne"
                boundaryCondition="true" />
            <species id="S2" initialConcentration="1" compartment="compartmentOne"
                boundaryCondition="true" constant="true" />
            <species id="S3" initialConcentration="3" compartment="compartmentOne"
                constant="true"/>
            <species id="S4" initialConcentration="0" compartment="compartmentOne"/>
        </listOfSpecies>
        <listOfParameters>
            <parameter id="k1" value="0.5"/>
            <parameter id="k2" value="0.1"/>
        </listOfParameters>
        <listOfRules>
            <rateRule variable="S1">
                <math xmlns="http://www.w3.org/1998/Math/MathML">
                    <ci> k2 </ci>
                 </math>
            </rateRule>
        </listOfRules>
        <listOfReactions>
            <reaction id="reaction_1" reversible="false">
                <listOfReactants>
                    <speciesReference species="S1"/>
                    <speciesReference species="S2"/>
                </listOfReactants>
                <listOfProducts>
                    <speciesReference species="S4"/>
                </listOfProducts>
                <listOfModifiers>
                    <modifierSpeciesReference species="S3"/>
                </listOfModifiers>
                <kineticLaw>
                    <math xmlns="http://www.w3.org/1998/Math/MathML">
                        <apply>
                            <times/>
                            <ci> k1 </ci>
                            <ci> S1 </ci>
                            <ci> S2 </ci>
                            <ci> S3 </ci>
                            <ci> compartmentOne </ci>
                         </apply>
                    </math>
                </kineticLaw>
            </reaction>
        </listOfReactions>
    </model>
</sbml>
```

7.7 Example of translation from a multi-compartmental model to ODEs

This section contains a model with 2 compartments and 4 reactions. The model is derived from Lotka-Volterra, with the addition of a reversible transport step. When observed in a time-course simulation, three of this model's species display damped oscillations.

Figure 25 illustrates the arrangement of compartments and reactions in the model `LotkaVolterra_tranport`. The text of the SBML representation of the model is shown below, and it is followed by its complete translation into ordinary differential equations. In this SBML model, the reaction equations are in substance per time units. The reactions have also been simplified to reduce common stoichiometric factors. The species

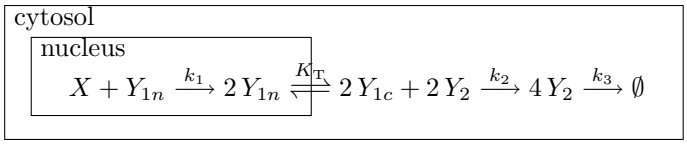

Figure 25: *A example multi-compartmental model.*

variables are in concentration units; their initial quantities are declared using the attribute `initialAmount` on the `species` definitions, but since the attribute `hasOnlySubstanceUnits` is *not* set to true, the identifiers of the species represent their concentrations when those identifiers appear in mathematical expressions elsewhere in the model. Note that the species whose identifier is "`X`" is a boundary condition, as indicated by the attribute `boundaryCondition`="`true`" in its definition. The attribute `speciesType`="`Y`" in the definitions of "`Y1n`" and "`Y1c`" indicates that these species are pools of the same participant, but located in different compartments.

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns="http://www.sbml.org/sbml/level2/version2" level="2" version="2">
    <model name="LotkaVolterra_tranport">
        <listOfSpeciesTypes>
            <speciesType id="Y1" />
        </listOfSpeciesTypes>
        <listOfCompartments>
            <compartment id="cytoplasm" size="5"/>
            <compartment id="nucleus" outside="cytoplasm" size="1" />
        </listOfCompartments>
        <listOfSpecies>
            <species id="X" compartment="nucleus" initialAmount="1"
                           constant="true" boundaryCondition="true" />
            <species id="Y1n" compartment="nucleus" speciesType="Y1" initialAmount="1" />
            <species id="Y1c" compartment="nucleus" speciesType="Y1" initialAmount="0" />
            <species id="Y2" compartment="cytoplasm" initialAmount="1" />
        </listOfSpecies>
        <listOfParameters>
            <parameter id="k1" value="2500" />
            <parameter id="k2" value="2500" />
            <parameter id="kT" value="25000" />
            <parameter id="k3" value="2500" />
        </listOfParameters>
        <listOfReactions>
            <reaction id="production" reversible="false">
                <listOfReactants>
                    <speciesReference species="X"/>
                    <speciesReference species="Y1n"/>
                </listOfReactants>
                <listOfProducts>
                    <speciesReference species="Y1n"/>
                    <speciesReference species="Y1n"/>
                </listOfProducts>
                <kineticLaw>
                    <math xmlns="http://www.w3.org/1998/Math/MathML">
                        <apply>
                            <times/>
                            <ci>nucleus</ci>
                            <ci>k1</ci>
                            <ci>X</ci>
                            <ci>Y1n</ci>
                        </apply>
                    </math>
                </kineticLaw>
            </reaction>
            <reaction id="transport" reversible="true">
                <listOfReactants>
                    <speciesReference species="Y1n"/>
                </listOfReactants>
```

```
                    <listOfProducts>
                        <speciesReference species="Y1c"/>
                    </listOfProducts>
                    <kineticLaw>
                        <math xmlns="http://www.w3.org/1998/Math/MathML">
                            <apply>
                                <times/>
                                <ci>cytoplasm</ci>
                                <ci>kT</ci>
                                <apply>
                                    <minus/>
                                    <ci>Y1n</ci>
                                    <ci>Y1c</ci>
                                </apply>
                            </apply>
                        </math>
                    </kineticLaw>
                </reaction>
                <reaction id="transformation" reversible="false">
                    <listOfReactants>
                        <speciesReference species="Y1c"/>
                        <speciesReference species="Y2"/>
                    </listOfReactants>
                    <listOfProducts>
                        <speciesReference species="Y2"/>
                        <speciesReference species="Y2"/>
                    </listOfProducts>
                    <kineticLaw>
                        <math xmlns="http://www.w3.org/1998/Math/MathML">
                            <apply>
                                <times/>
                                <ci>cytoplasm</ci>
                                <ci>k2</ci>
                                <ci>Y1c</ci>
                                <ci>Y2</ci>
                            </apply>
                        </math>
                    </kineticLaw>
                </reaction>
                <reaction id="degradation" reversible="false">
                    <listOfReactants>
                        <speciesReference species="Y2"/>
                    </listOfReactants>
                    <kineticLaw>
                        <math xmlns="http://www.w3.org/1998/Math/MathML">
                            <apply>
                                <times/>
                                <ci>cytoplasm</ci>
                                <ci>k3</ci>
                                <ci>Y2</ci>
                            </apply>
                        </math>
                    </kineticLaw>
                </reaction>
            </listOfReactions>
        </model>
    </sbml>
```

The ODE translation of this model is as follows. First, we give the values of the constant parameters:

$$k_1 = 2500, \quad k_2 = 2500, \quad K_3 = 25000, \quad K_T = 2500$$

Next, here are the initial conditions of the variables. The species variables X, Y_{1n}, Y_{1c}, and Y_2 in the following equations are all in terms of concentrations, and we use V_n to represent for the size of compartment "`nucleus`" and V_c to represent for the size of compartment "`cytoplasm`":

$$V_n = 1, \quad V_c = 5, \quad X = 1, \quad Y_{1n} = 1, \quad Y_{1c} = 0, \quad Y_2 = 1$$

And finally, here are the differential equations:

$$\frac{dX}{dt} = 0$$

$$V_n \frac{dY_{1n}}{dt} = k_1 \cdot X \cdot Y_{1n} \cdot V_n - K_T \cdot (Y_{1n} - Y_{1c}) \cdot V_c \qquad \text{reactions production and transport}$$

$$V_c \frac{dY_{1c}}{dt} = K_T \cdot (Y_{1n} - Y_{1c}) \cdot V_c - k_2 \cdot Y_{1c} \cdot Y_2 \cdot V_c \qquad \text{reactions transport and transformation}$$

$$V_c \frac{dY_2}{dt} = k_2 \cdot Y_{1c} \cdot Y_2 \cdot V_c - k_3 \cdot Y_2 \cdot V_c \qquad \text{reactions transformation and degradation}$$

As formulated here, this example assumes constant volumes. If the sizes of the compartments "`cytoplasm`" or "`nucleus`" could change during simulation, then it would be preferable to use a different approach to constructing the differential equations. In this alternative approach, the ODEs would compute substance change rather than concentration change, and the concentration values would be computed using separate equations. This approach is used in Section 4.13.6.

7.8 Example involving function definitions

This section contains a model that uses the function definition feature of SBML. Consider the following hypothetical system:

$$S_1 \xrightarrow{f(S_1)} S_2$$

where

$$f(x) = 2 \times x$$

The following is the XML document that encodes the model shown above:

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns="http://www.sbml.org/sbml/level2/version2" level="2" version="2">
    <model id="Example">
        <listOfFunctionDefinitions>
            <functionDefinition id="f">
                <math xmlns="http://www.w3.org/1998/Math/MathML">
                    <lambda>
                        <bvar><ci> x </ci></bvar>
                        <apply>
                            <times/>
                            <ci> x </ci>
                            <cn> 2 </cn>
                        </apply>
                    </lambda>
                </math>
            </functionDefinition>
        </listOfFunctionDefinitions>
        <listOfCompartments>
            <compartment id="compartmentOne" size="1"/>
        </listOfCompartments>
        <listOfSpecies>
            <species id="S1" initialConcentration="1" compartment="compartmentOne"/>
            <species id="S2" initialConcentration="0" compartment="compartmentOne"/>
        </listOfSpecies>
        <listOfReactions>
            <reaction id="reaction_1" reversible="false">
                <listOfReactants>
                    <speciesReference species="S1"/>
                </listOfReactants>
                <listOfProducts>
                    <speciesReference species="S2"/>
                </listOfProducts>
```

```
                    <kineticLaw>
                        <math xmlns="http://www.w3.org/1998/Math/MathML">
                            <apply>
        <times/>
        <apply>
                                    <ci> f </ci>
                                    <ci> S1 </ci>
        </apply>
        <ci> compartmentOne </ci>
                             </apply>
                        </math>
                    </kineticLaw>
                </reaction>
            </listOfReactions>
        </model>
    </sbml>
```

7.9 Example involving *delay* functions

The following is a simple model illustrating the use of *delay* to represent a gene that suppresses its own expression. The model can be expressed in a single rule:

$$\frac{dP}{dt} = \frac{\frac{1}{1 + m(P_{delayed})^q} - P}{\tau}$$

where

$P_{delayed}$	is $delay(P, \Delta_t)$ or P at $t - \Delta_t$
P	is protein concentration
τ	is the response time
m	is a multiplier or equilibrium constant
q	is the Hill coefficient

and the species quantities are in concentration units. The text of an SBML encoding of this model is given below:

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns="http://www.sbml.org/sbml/level2/version2" level="2" version="2">
    <model>
        <listOfCompartments>
            <compartment id="cell" size="1"/>
        </listOfCompartments>
        <listOfSpecies>
            <species id="P" compartment="cell" initialConcentration="0"/>
        </listOfSpecies>
        <listOfParameters>
            <parameter id="tau" value="1"/>
            <parameter id="m" value="0.5"/>
            <parameter id="q" value="1"/>
            <parameter id="delta_t" value="1"/>
        </listOfParameters>
        <listOfRules>
            <rateRule variable="P">
                <math xmlns="http://www.w3.org/1998/Math/MathML">
                 <apply>
                  <divide/>
                  <apply>
                   <minus/>
                   <apply>
                    <divide/>
                    <cn> 1 </cn>
                    <apply>
                     <plus/>
                     <cn> 1 </cn>
                     <apply>
                      <times/>
```

```
                        <ci> m </ci>
                        <apply>
                         <power/>
                         <apply>
                          <csymbol encoding="text"
                                   definitionURL="http://www.sbml.org/sbml/symbols/delay">
                              delay
                          </csymbol>
                          <ci> P </ci>
                          <ci> delta_t </ci>
                         </apply>
                         <ci> q </ci>
                        </apply>
                       </apply>
                      </apply>
                      </apply>
                      <ci> P </ci>
                     </apply>
                     <ci> tau </ci>
                    </apply>
                   </math>
               </rateRule>
           </listOfRules>
       </model>
   </sbml>
```

7.10 Example involving events

This section presents a simple model system that demonstrates the use of events in SBML. Consider a system with two genes, k_1 and k_2. k_1 is initially on and k_2 is initially off. When turned on, the two genes lead to the production of two products, P_1 and P_2, respectively, at a fixed rate. When P_1 reaches a given concentration, k_2 switches off. This system can be represented mathematically as follows:

$$\begin{aligned} \frac{dP_1}{dt} &= k_1 - P_1 \\ \frac{dP_2}{dt} &= k_2 - P_2 \\ k_2 &= \begin{cases} 0 & \text{when } P_1 \leq \tau, \\ 1 & \text{when } P_1 > \tau. \end{cases} \end{aligned}$$

The initial values are:

$$k_1 = 1, \quad k_2 = 0, \quad \tau = 0.25, \quad P_1 = 0, \quad P_2 = 0$$

The SBML Level 2 representation of this as follows:

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns="http://www.sbml.org/sbml/level2/version2" level="2" version="2"
      xmlns:math="http://www.w3.org/1998/Math/MathML">
    <model>
        <listOfCompartments>
            <compartment id="cell" size="1"/>
        </listOfCompartments>
        <listOfSpecies>
            <species id="P1" compartment="cell" initialConcentration="0"/>
            <species id="P2" compartment="cell" initialConcentration="0"/>
        </listOfSpecies>
        <listOfParameters>
            <parameter id="k1" value="1" constant="false"/>
            <parameter id="k2" value="0" constant="false"/>
            <parameter id="tau" value="0.25"/>
        </listOfParameters>
        <listOfRules>
            <rateRule variable="P1">
```

```
                    <math:math>
                        <math:apply>
                            <math:minus/>
                            <math:ci> k1 </math:ci>
                            <math:ci> P1 </math:ci>
                        </math:apply>
                    </math:math>
                </rateRule>
                <rateRule variable="P2">
                    <math:math>
                        <math:apply>
                            <math:minus/>
                            <math:ci> k2 </math:ci>
                            <math:ci> P2 </math:ci>
                        </math:apply>
                    </math:math>
                </rateRule>
            </listOfRules>
            <listOfEvents>
                <event>
                    <trigger>
                        <math:math>
                            <math:apply>
                                <math:gt/>
                                <math:ci> P1 </math:ci>
                                <math:ci> tau </math:ci>
                            </math:apply>
                        </math:math>
                    </trigger>
                    <listOfEventAssignments>
                        <eventAssignment variable="k2">
                            <math:math>
                                <math:cn> 1 </math:cn>
                            </math:math>
                        </eventAssignment>
                    </listOfEventAssignments>
                </event>
                <event>
                    <trigger>
                        <math:math>
                            <math:apply>
                                <math:leq/>
                                <math:ci> P1 </math:ci>
                                <math:ci> tau </math:ci>
                            </math:apply>
                        </math:math>
                    </trigger>
                    <listOfEventAssignments>
                        <eventAssignment variable="k2">
                            <math:math>
                                <math:cn> 0 </math:cn>
                            </math:math>
                        </eventAssignment>
                    </listOfEventAssignments>
                </event>
            </listOfEvents>
        </model>
    </sbml>
```

7.11 Example involving two-dimensional compartments

The following example is a model that uses a two-dimensional compartment. It is a fragment of a larger model of calcium regulation across the plasma membrane of a cell. The model includes a calcium influx channel, "`Ca_channel`", and a calcium-extruding PMCA pump, "`Ca_Pump`". It also includes two cytosolic proteins that buffer calcium via the "`CalciumCalbindin_gt_BoundCytosol`" and "`CalciumBuffer_gt_BoundCytosol`" reactions. Finally, the rate expressions in this model do not include explicit factors of the compartment

volumes; instead, the various rate constants are assume to include any necessary corrections for volume.

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns="http://www.sbml.org/sbml/level2/version2" level="2" version="2">
    <model id="facilitated_ca_diffusion">
        <listOfUnitDefinitions>
            <unitDefinition id="substance">
                <listOfUnits>
                    <unit kind="mole" scale="-6"/>
                </listOfUnits>
            </unitDefinition>
            <unitDefinition id="area">
                <listOfUnits>
                    <unit kind="metre" scale="-6" exponent="2" />
                </listOfUnits>
            </unitDefinition>
        </listOfUnitDefinitions>
        <listOfCompartments>
            <compartment id="Extracellular" spatialDimensions="3" size="1"/>
            <compartment id="PlasmaMembrane" outside="Extracellular"
                         spatialDimensions="2" size="1"/>
            <compartment id="Cytosol" outside="PlasmaMembrane"
                         spatialDimensions="3" size="1"/>
        </listOfCompartments>
        <listOfSpecies>
            <species
              id="CaBPB_C"
              compartment="Cytosol"
              initialConcentration="47.17"/>
            <species
              id="B_C"
              compartment="Cytosol"
              initialConcentration="396.04"/>
            <species
              id="CaB_C"
              compartment="Cytosol"
              initialConcentration="3.96"/>
            <species
              id="Ca_EC"
              compartment="Extracellular"
              initialConcentration="1000"/>
            <species
              id="Ca_C"
              compartment="Cytosol"
              initialConcentration="0.1"/>
            <species
              id="CaCh_PM"
              compartment="PlasmaMembrane"
              initialConcentration="1"/>
            <species
              id="CaPump_PM"
              compartment="PlasmaMembrane"
              initialConcentration="1"/>
            <species
              id="CaBP_C"
              compartment="Cytosol"
              initialConcentration="202.83"/>
        </listOfSpecies>
        <listOfReactions>
            <reaction id="CalciumCalbindin_gt_BoundCytosol" fast="true">
                <listOfReactants>
                    <speciesReference species="CaBP_C"/>
                    <speciesReference species="Ca_C"/>
                </listOfReactants>
                <listOfProducts>
                    <speciesReference species="CaBPB_C"/>
                </listOfProducts>
                <kineticLaw>
                           <notes>
                           <p xmlns="http://www.w3.org/1999/xhtml">
```

```
                        (((Kf_CalciumCalbindin_BoundCytosol * CaBP_C) * Ca_C) -
                           (Kr_CalciumCalbindin_BoundCytosol * CaBPB_C))
                      </p>
                      </notes>
                <math xmlns="http://www.w3.org/1998/Math/MathML">
                    <apply>
                        <minus/>
                        <apply>
                            <times/>
                            <ci> Kf_CalciumCalbindin_BoundCytosol </ci>
                            <ci> CaBP_C </ci>
                            <ci> Ca_C </ci>
                        </apply>
                        <apply>
                            <times/>
                            <ci> Kr_CalciumCalbindin_BoundCytosol </ci>
                            <ci> CaBPB_C </ci>
                        </apply>
                    </apply>
                </math>
                     <listOfParameters>
                        <parameter id="Kf_CalciumCalbindin_BoundCytosol" value="20.0"/>
                        <parameter id="Kr_CalciumCalbindin_BoundCytosol" value="8.6"/>
                     </listOfParameters>
            </kineticLaw>
        </reaction>
        <reaction id="CalciumBuffer_gt_BoundCytosol" fast="true">
            <listOfReactants>
                <speciesReference species="Ca_C"/>
                <speciesReference species="B_C"/>
            </listOfReactants>
            <listOfProducts>
                <speciesReference species="CaB_C"/>
            </listOfProducts>
            <kineticLaw>
                <notes>
                  <p xmlns="http://www.w3.org/1999/xhtml">
                    (((Kf_CalciumBuffer_BoundCytosol * Ca_C) * B_C) -
                        (Kr_CalciumBuffer_BoundCytosol * CaB_C))
                  </p>
                </notes>
                <math xmlns="http://www.w3.org/1998/Math/MathML">
                    <apply>
                        <minus/>
                        <apply>
                            <times/>
                            <ci> Kf_CalciumBuffer_BoundCytosol </ci>
                            <ci> Ca_C </ci>
                            <ci> B_C </ci>
                        </apply>
                        <apply>
                            <times/>
                            <ci> Kr_CalciumBuffer_BoundCytosol </ci>
                            <ci> CaB_C </ci>
                        </apply>
                    </apply>
                </math>
                <listOfParameters>
                    <parameter id="Kf_CalciumBuffer_BoundCytosol" value="0.1"/>
                    <parameter id="Kr_CalciumBuffer_BoundCytosol" value="1.0"/>
                </listOfParameters>
            </kineticLaw>
        </reaction>
        <reaction id="Ca_Pump">
            <listOfReactants>
                <speciesReference species="Ca_C"/>
            </listOfReactants>
            <listOfProducts>
                <speciesReference species="Ca_EC"/>
```

```
                    </listOfProducts>
                    <listOfModifiers>
                        <modifierSpeciesReference species="CaPump_PM"/>
                    </listOfModifiers>
                    <kineticLaw>
                        <notes>
                          <p xmlns="http://www.w3.org/1999/xhtml">
                            ((Vmax * kP * ((Ca_C - Ca_Rest) / (Ca_C + kP)) / (Ca_Rest + kP)) *
                                CaPump_PM)
                          </p>
                        </notes>
                        <math xmlns="http://www.w3.org/1998/Math/MathML">
                            <apply>
                                <divide/>
                                <apply>
                                    <times/>
                                    <ci> Vmax </ci>
                                    <ci> kP </ci>
                                    <ci> CaPump_PM </ci>
                                    <apply>
                                        <minus/>
                                        <ci> Ca_C </ci>
                                        <ci> Ca_Rest </ci>
                                    </apply>
                                </apply>
                                <apply>
                                    <times/>
                                    <apply>
                                        <plus/>
                                        <ci> Ca_C </ci>
                                        <ci> kP </ci>
                                    </apply>
                                    <apply>
                                        <plus/>
                                        <ci> Ca_Rest </ci>
                                        <ci> kP </ci>
                                    </apply>
                                </apply>
                            </apply>
                        </math>
                        <listOfParameters>
                            <parameter id="Vmax" value="-4000"/>
                            <parameter id="kP" value="0.25"/>
                            <parameter id="Ca_Rest" value="0.1"/>
                        </listOfParameters>
                    </kineticLaw>
                </reaction>
                <reaction id="Ca_channel">
                    <listOfReactants>
                        <speciesReference species="Ca_EC"/>
                    </listOfReactants>
                    <listOfProducts>
                        <speciesReference species="Ca_C"/>
                    </listOfProducts>
                    <listOfModifiers>
                        <modifierSpeciesReference species="CaCh_PM"/>
                    </listOfModifiers>
                    <kineticLaw>
                        <notes>
                          <p xmlns="http://www.w3.org/1999/xhtml">
                            (J0 * Kc * (Ca_EC - Ca_C) / (Kc + Ca_C) * CaCh_PM)
                          </p>
                        </notes>
                        <math xmlns="http://www.w3.org/1998/Math/MathML">
                            <apply>
                                <divide/>
                                <apply>
                                    <times/>
                                    <ci> CaCh_PM </ci>
```

```
                                    <ci> J0 </ci>
                                    <ci> Kc </ci>
                                    <apply>
                                        <minus/>
                                        <ci> Ca_EC </ci>
                                        <ci> Ca_C </ci>
                                    </apply>
                                </apply>
                                <apply>
                                    <plus/>
                                    <ci> Kc </ci>
                                    <ci> Ca_C </ci>
                                </apply>
                            </apply>
                        </math>
                        <listOfParameters>
                            <parameter id="J0" value="0.014"/>
                            <parameter id="Kc" value="0.5"/>
                        </listOfParameters>
                    </kineticLaw>
                </reaction>
            </listOfReactions>
        </model>
    </sbml>
```

8 Discussion

The volume of data now emerging from molecular biotechnology leave little doubt that extensive computer-based modeling, simulation and analysis will be critical to understanding and interpreting the data (Abbott, 1999; Gilman, 2000; Popel and Winslow, 1998; Smaglik, 2000). This has lead to an explosion in the development of computer tools by many research groups across the world. The explosive rate of progress is exciting, but the rapid growth of the field is accompanied by problems and pressing needs.

One problem is that simulation models and results often cannot be directly compared, shared or re-used, because the tools developed by different groups often are not compatible with each other. As the field of systems biology matures, researchers increasingly need to communicate their results as computational models rather than box-and-arrow diagrams. They also need to reuse published and curated models as library components in order to succeed with large-scale efforts (e.g., the Alliance for Cellular Signaling; Gilman, 2000; Smaglik, 2000). These needs require that models implemented in one software package be portable to other software packages, to maximize public understanding and to allow building up libraries of curated computational models.

We offer SBML to the systems biology community as a suggested format for exchanging models between simulation/analysis tools. SBML is an open model representation language oriented specifically towards representing systems of biochemical reactions.

Our vision for SBML is to create an open standard that will enable different software tools to exchange computational models. SBML is not static; we continue to develop and experiment with it, and we interact with other groups who seek to develop similar markup languages. We plan on continuing to evolve SBML with the help of the systems biology community to make SBML increasingly more powerful, flexible and useful.

8.1 Future enhancements: SBML Level 3 and beyond

Many people have expressed a desire to see additional capabilities added to SBML. The following summarizes additional features that are under consideration to be included in SBML Level 3:

- *Arrays.* This will enable the creation of arrays of components (species, reactions, compartments and submodels).
- *Connections.* This will be a mechanism for describing the connections between items in an array.
- *Geometry.* This will enable the encoding of the spatial characteristics of models including the geometry of compartments, the diffusion properties of species and the specification of different species concentrations across different regions of a cell.
- *Model Composition.* This will enable a large model to be built up out of instances of other models. It will also allow the reuse of model components and the creation of several instances of the same model.
- *Multi-state and Complex Species.* This will allow the straight-forward construction of models involving species with a large number of states or species composed of subcomponents. The representation scheme would be designed to contain the combinatorial explosion of objects that often results from these types of models.
- *Diagrams.* This feature will allow components to be annotated with data to enable the display of the model in a diagram.
- *Dynamic Structure.* This will enable model structure to vary during simulation. One aspect of this allowing rules and reactions to have their effect conditional on the state of the model system. For example in SBML Level 2 it is possible to create a rule with the effect:

$$\frac{ds}{dt} = \begin{cases} 0 & \text{if } s > 0 \\ y & \text{otherwise} \end{cases}$$

Dynamic restructuring would enable the expression of the following example:

$$\text{if } s > 0 \quad \frac{ds}{dt} = y$$

where s is not determined by the rule when $s \leq 0$.

- *Tie-breaking algorithm.* This will include a controlled vocabulary and associated fields on models to indicate the simultaneous event tie-breaking algorithm required to correctly simulate the model.
- *Distributions.* This will provide a means of specifying random variables and statistical distribution of values.

Acknowledgments

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We gratefully acknowledge sponsorship from many funding agencies. Support for the continued development of SBML and associated software, meetings and activities today comes from the following sources: the National Institute of General Medical Sciences (USA) via grant number GM070923; the National Human Genome Research Institute (USA); the International Joint Research Program of NEDO (Japan); the JST ERATO-SORST Program (Japan); the Japanese Ministry of Agriculture; the Japanese Ministry of Education, Culture, Sports, Science and Technology; the BBSRC e-Science Initiative (UK); the DARPA IPTO Bio-Computation Program (USA); and the Air Force Office of Scientific Research (USA). Additional support has been or continues to be provided by the California Institute of Technology (USA), the University of Hertfordshire (UK), the Molecular Sciences Institute (USA), and the Systems Biology Institute (Japan).

SBML was first conceived at the JST/ERATO-sponsored *First Workshop on Software Platforms for Systems Biology*, held in April, 2000, at the California Institute of Technology in Pasadena, California, USA. The participants collectively decided to begin developing a common XML-based declarative language for representing models. A draft version of the Systems Biology Markup Language was developed by the Caltech ERATO team and delivered to all collaborators in August, 2000. This draft version underwent extensive discussion over mailing lists and then again during the *Second Workshop on Software Platforms for Systems Biology* held in Tokyo, Japan, November 2000. A revised version of SBML was issued by the Caltech ERATO team in December, 2000, and after further discussions over mailing lists and in meetings, we produced a specification for SBML Level 1 (Hucka et al., 2001).

SBML Level 2 was conceived at the *5th Workshop on Software Platforms for Systems Biology*, held in July 2002, at the University of Hertfordshire, UK. The participants collectively decided to revise the form of SBML in Level 2. The first draft of the Level 2 Version 1 document was released in August 2002. The final set of features in SBML Level 2 Version 1 was finalized in May 2003 at the *7th Workshop on Software Platforms for Systems Biology* in Ft. Lauderdale, Florida.

SBML Level 2 Version 2 was developed with contributions from so many people constituting the worldwide *SBML Forum* that we regret it has become infeasible to list individuals by name. We are grateful to everyone on the `sbml-discuss` and `libsbml-discuss` mailing lists, the creators of CellML (Hedley et al., 2001), the members of the DARPA Bio-SPICE project, and the authors of the following software SBML-aware systems: BALSA, BASIS, BIOCHAM, BioCharon, ByoDyn, BioCyc, BioGrid, BioModels, BioNetGen, BioPathway Explorer, Bio Sketch Pad, BioSens, BioSPICE Dashboard, BioSpreadsheet, BioTapestry, BioUML, BSTLab, CADLIVE, CellDesigner, Cellerator, CellML2SBML, Cellware, CL-SBML, CLEML, COPASI, Cyto-Sim, Cytoscape, DBsolve, Dizzy, E-CELL, ecellJ, ESS, FluxAnalyzer, Fluxor, Gepasi, Gillespie2, HSMB, HybridSBML, INSILICO discovery, JACOBIAN, Jarnac, JDesigner, JigCell, JSim, JWS Online, KEGG2SBML, Kineticon, libSBML, MathSBML, MesoRD, MetaboLogica, MetaFluxNet, MMT2, Modesto , Moleculizer, Monod, Narrator, NetBuilder, Oscill8, PANTHER Pathway, PathArt, PathScout, PathwayLab, Pathway Tools, PathwayBuilder, PATIKAweb, PaVESy, PET, PNK, Reactome, ProcessDB, PROTON, pysbml, PySCeS, runSBML, SABIO-RK, SBML ODE Solver, SBML-PET, SBMLeditor, SBMLmerge, SBMLR, SBMLSim, SBMLToolbox, SBliD, SBToolbox, SBW, SCIpath, SigPath, SigTran, SIMBA, SimBiology, Simpathica, SimWiz, SloppyCell, SmartCell, SRS Pathway Editor, StochSim, StochKit, STOCKS, TERANODE Suite, Trelis, Virtual Cell, WebCell, WinSCAMP, and XPPAUT.

A Differences between SBML Level 1 Version 2 and Level 2 Version 1

Compared to SBML Level 1 Version 2, SBML Level 2 Version 1 introduces the following changes:

- SBML Level 2 supports the inclusion of metadata using the same approach as CellML (Cuellar et al., 2002). All structures in SBML can be annotated with optional content in RDF (Resource Description Format; Lassila and Swick, 1999) following the guidelines put forward by Cuellar et al.. (Section 3.3.)

- All data structures, including Sbml and `listOf`_____ elements, are now derived from the type *Sbase*. (Section 3.3.) This means all major structures in SBML can have separate annotations and metadata associated with them.

- A new field, **`id`**, replaces the **`name`** field previously defined for most SBML structures to identify each part of a model. (See Section 3.4.) The **`id`** field has a type of **`SId`**, whose definition is similar to **`SName`** in Level 1. In SBML Level 2, the **`name`** field is optional and is defined to allow any Unicode characters allowed by the **`string`** type of XML Schema (Biron and Malhotra, 2000).

- Formulas in Level 2 are expressed using MathML (W3C, 2000b) 2.0. The field named **`formula`** previously available on the KineticLaw and *Rule* structures has been replaced by a MathML element named **`math`** containing MathML content. In addition, stoichiometry numbers may now be expressed using MathML, allowing for more flexibility in defining reactions. (Sections 3.5, 4.11 and 4.13.)

- The namespace for identifiers in a model does not contain any built-in symbols; gone, for example, are the predefined rate laws of SBML Level 1. The approach taken in SBML Level 2 is that each model must itself define whatever functions it needs using the new FunctionDefinition mechanism. Although SBML Level 2 *does* define two built-in entities (a symbol representing time and another symbol representing delay functions), these are referenced using a feature of MathML and are not in the same namespace as identifiers defined by a model. (Section 3.5.5.)

- SBML Level 2 makes explicit a previously unstated assumption, that the XML encoding of a model uses UTF-8. SBML documents must refer to the UTF-8 encoding in their XML declaration. (Section 4.1.)

- The top-level Model structure can contain an optional list of global user-defined functions expressed in MathML and organized in new structures of type FunctionDefinition. (Sections 4.2 and 4.3.)

- The top-level Model structure can contain an optional list of event definitions organized in structures of type Event. Events define discrete changes in model behavior at specific times during a time simulation of the model. (Section 4.2 and 4.14.)

- Unlike in SBML Level 1, unit identifiers in Level 2 are in a separate namespace from the namespace used for models, functions, species, compartments, reactions and parameters. Also, the unit identifiers "**`meter`**" and "**`liter`**" are not defined in Level 2 because the SBML user community deemed these alternative spellings of "**`metre`**" and "**`litre`**" unnecessary. Finally, Unit structures now have the additional fields **`multiplier`** and **`offset`** to enable the definition of non-SI units. (Section 4.4.)

- The Compartment structure has a new field, **`spatialDimensions`**, whose value is a positive integer specifying the number of dimensions in space the compartment possesses. This enables the definition of such things as two-dimensional membranes. As a side-effect, the units of species concentration (when concentration is being used) in SBML Level 2 depend on the spatial dimensions of the compartment where the species is located. To support these new capabilities, **`Compartment`** now uses a field named **`size`** instead of **`volume`**, and there are two new built-in units for area and length. (Sections 4.4 and 4.7.)

- All fields representing initial conditions or parameter values, including compartment sizes and species quantities, are optional in Level 2. A missing value for one of these fields implies that the value is either unknown, not required for analysis, or should be obtained from an external source. (Sections 4.7, 4.8 and 4.9.)

- The Compartment, Species and Parameter structures each have a new boolean field named `constant`. This field specifies whether the variables represented by these structures can be changed by rules and reactions. (Sections 4.7, 4.8 and 4.9.)

- The Species structure has a new field, `initialConcentration`, for setting the initial value of a species in terms of its concentration. This is in addition to the ability, carried over from Level 1, to set the values in terms of amounts. (Section 4.8.)

- The Species structure has two new fields, `spatialSizeUnits` and `substanceUnits`, which replace the `units` field in Level 1. These fields are composed to form the concentration units of the species symbol. (Section 4.8.)

- The rule structures are simpler compared to SBML Level 1. There is no longer a `type` field on AssignmentRule. A redesigned structure AssignmentRule and new RateRule structure replace SBML Level 1's `ParameterRule`, `SpeciesConcentrationRule` and `CompartmentVolumeRule`. (Section 4.11.)

- The Reaction structure has a new list of *modifiers* in addition to the list of reactants and products. The `listOfModifiers` enumerates species that affect a reaction but are neither created nor destroyed by the reaction. (Section 4.13.)

B Differences between SBML Level 2 Version 1 and Level 2 Version 2

The changes introduced by SBML Level 2 Version 2 over SBML Level 2 Version 1 as described by this specification are divided into 2 parts: (a) new and changed features and, (b) Version 1 errata corrected in Version 2.

B.1 Feature changes relative to Level 2 Version 1

The features introduced or changed in Version 2 are:

- *XML namespace.* Version 2 uses the XML namespace `http://www.sbml.org/sbml/level2/version2`.
- *Removal of predefined annotation namespaces.* In Section 3.3.3, previous Levels and Versions of SBML reserved a set of XML Namespace names corresponding to software tools known to exist at the time. Due to the explosion of SBML-compatible software tools in recent years, it has become infeasible to maintain such a list; moreover, informal discussions with SBML users revealed that no one paid much attention to the list anyway. Beginning with SBML Level 2 Version 2, no such namespaces are defined in the SBML specification.
- *One top level element per XML Namespace per* ***`annotation`*** *element and associated restrictions.* An `annotation` element cannot contain two or more top level elements in the same XML namespace. An `annotation` element cannot contain a top level element in the SBML namespace. The order of top level elements within an `annotation` element is not significant.
- *Introduction of* ***`sboTerm`****.* In Version 2, there is a new field named `sboTerm` on the following objects: Model, FunctionDefinition, Reaction, Parameter, InitialAssignment, AlgebraicRule, AssignmentRule, RateRule, Constraint, Reaction, KineticLaw, SpeciesReference, ModifierSpeciesReference, Event, and EventAssignment . This field is of type `SBOTerm`. Its value is permitted to be only valid Systems Biology Ontology (SBO) identifiers. (Section 5.)
- *New format for linking external resources to SBML.* A new format for using RDF and Dublin Core within `annotation` elements to link SBML models to external resources and record model version history is introduced. Although CellML metadata can be included in SBML the specification does not make any specific mention of CellML metadata.
- *New type* ***`UnitSId`****.* In Level 2 Version 2, there is a new data type `UnitSId` that serves as the data type for identifiers of units and the fields that refer to units. (Section 3.1.8.)
- *Built-in units can be dimensionless.* In Level 2 Version 2, the built-in units (e.g., `substance`, `volume` and others), can be assigned `dimensionless` units. This facilities the correct encoding of models based on dimensionless experimental data.
- *Unit no longer has an* ***`offset`*** *field.* In Version 2, the `offset` field on Unit has been removed because it was impossible to define consistently with the rest of the SBML unit system. Either a complicated set of special exceptions and rules would have had to be introduced to enable proper interpretation of units with offsets, or the offset field could be removed. Since the situations requiring offsets are so infrequent, removing the offsets was judged to be the lesser of evils. As a benefit, the unit system of SBML Level 2 Version 2 is streamlined and straightforward to implement, which may encourage more software developers to support it.
- *Celsius is no longer a predefined unit.* Prior versions of SBML defined Celsius as a unit. With the removal of the `offset` field from Unit, Celsius became an inconsistent unit in the system, because its definition requires an offset. It could not be related to kelvin units without being treated as a special case by software applications. A majority vote by the SBML community in 2006 resulted in a decision to remove Celsius to avoid the inconsistency, and instead, have software tools introduce explicit conversions as needed in a model.

- *Compartment Type.* In Version 2 the Model structure has an addition list of CompartmentType structures. Each of these structures represents a type of compartment and consists of just `name` and `id` fields. The `id` field can optionally be referenced from an Compartment structure using a new `compartmentType` field.

- *Species Type.* In Version 2 the Model structure has an addition list of SpeciesType structures. A SpeciesType structure represents a type of chemical entity independent of location and consists of just `name` and `id` fields. The `id` field can optionally be referenced from an Species structure using a new `speciesType` field.

- *`charge` field deprecated.* In Version 2 the Species structure `charge` field is deprecated.

- *Constraints.* In Version 2, the Model structure has an addition list of Constraint structures. The `math` field of Constraint contains a boolean expression which is is function of the model state which returns whether the state is valid. Unlike the *Rule* structures Constraint should not be used to compute the dynamical behavior of the model.

- *`Id` on SimpleSpeciesReference .* Version 2 adds `id` and `name` fields to the *SimpleSpeciesReference* structure. The `id` field declares an identifier which is in the global namespace of objects.

- *Reaction identifier as a symbol in math expressions.* In Version 2 the value of the `id` of any reaction can appear in an expression within a MathML `ci` element. The symbol represents the rate of the reaction which is given by the KineticLaw structure of the Reaction. It is not possible to explicitly assign a value to the symbol using InitialAssignment, EventAssignment, AssignmentRule or RateRule structures.

- *KineticLaw no longer has fields `substanceUnits` or `timeUnits`.* Previous versions of SBML defined these fields to allow per-reaction definitions of the units of *substance*/*time*. For reasons explained in Section 4.13.5, this feature was discovered to be problematic.

- *Initial Assignment Structures.* In Version 2 the Model structure has an additional list of InitialAssignment structures. This list of structures is evaluated before any reactions or other rules to determine the values of constants and the initial values of variables. Assignment rules override the values calculated by the InitialAssignment structures.

- *The order of AssignmentRule structures is not significant.* In Version 2 the order of AssignmentRule is not significant however the set of assignment rules formed from KineticLaw, InitialAssignment and AssignmentRule structures as a whole must not contain algebraic loops.

- *Strong interpretation of `fast` on Reaction*

  Until Level 2 Version 2, it was assumed that the `fast` field on Reaction could be ignored by software tools that did not have the capacity to support it. Further research has shown that this is not true. SBML Level 2 Version 2 stipulates that if a model has values for `fast`, a software tool must be able to respect the field or else indicate to the user that it does not have the capacity to do so.

B.2 Incorporation of errata from SBML Level 2 Version 1

The errata in the SBML Level 2 Version 1 specification that corrected in this Version 2 specification are as follows. The page and section numbers refer to the final PDF version of the SBML Level 2 Version 1 specification.

- page 1: The specification should contain a link to the latest version of the specification and to this specific *issue* of the document.

- page 2: Each additional errata to the specification should result in an new issue of the specification each with a unique number. The first issue of the specification should be numbered 1. The errata on this specification should recorded in a new section starting in issue 2. Each errata will be numbered with the issue in which the errata is introduced. Errata should not change the fundamental semantics or syntax of SBML but merely clarify and disambiguate the specification.

- page 2: The specification should make explicit the features which are not backwards compatible between Level 2 Version 2 and Level 2 Version 1.
- page 3 Section 1.2: The specification should make explicit the differences in the numeric types of XML Schema and MathML.
- page 4 Section 3.1: This section should include an explanation of why `id` and `name` fields are not present on *Sbase*.
- page 8 Figure 3: Change `nameChar` and `name` to `idChar` and `SId` to indicate clearly the use of the BNF syntax definition.
- page 9 Section 3.6: The specification should reference existing documents to clarify the semantics of the MathML operators in the MathML subset.
- page 9 Section 3.6: The specification should constrain the use of MathML operators which return different types of result (numeric or boolean) appropriately.
- page 9 Section 3.6.1: The `encoding` attribute is permitted on `annotation` and `annotation-xml` elements in MathML, not only on `csymbol` as stated on that page.
- page 9 Section 3.6.1: The MathML 2.0 standard specifies the result of n-ary operators when the number of operands is critically small, for example for `times` and `add` elements, when the number of operands are zero or one. This is an obscure part of MathML and the specification should highlight the relevant sections of the MathML specification.
- page 9 Section 3.6.2: The specification should make explicit the differences in the numeric types of XML Schema and MathML.
- page 9 Section 3.6.2: The specification should describe the MathML whitespace rules for `cn` elements.
- page 10 Section 3.6.3: The specification should describe the MathML whitespace rules for `ci` elements.
- page 10 Section 3.6.3: The specification should state whether SBML has early or late binding semantics.
- page 10, Section 3.6.4: The delay function is not clearly defined. There is no explanation of what range of values is valid for the time. For example, can delay times be less than zero? Also, are there restrictions on the acceptable values of the argument x?
- page 13, Section 4.3.1: The 'can' in the second sentence should be replaced by 'should'.
- page 14, Section 4.4.2: The `id` field of a UnitDefinition structure must not contain a value from Table 2, the table of `UnitKind` values. This restriction is necessary because otherwise a unit definition could redefine one of the base unit kinds.
- page 14, Section 4.4.2: The first formula should be the following:

$$u_{new} = (multiplier \cdot 10^{scale} \cdot u)^{exponent} + offset$$

  This equation is superseded by modifications to the Unit and UnitDefinition structures in this specification SBML Level 2 Version 2.
- page 16, Section 4.4.3: The example code redefining the built-in unit `volume` should replace `liters` with `litre`. `liters` is not a valid value for the `kind` attribute.
- page 18 section 4.5.6: the value of `outside` field for a given Compartment structure must be the value of an `id` field of another Compartment structure.
- page 18 Section 4.5.6: The graph formed where compartments are nodes and the arcs are implied by the values of `outside` attributes must be acyclic otherwise a compartment can be outside itself.

- page 19 Section 4.6.3: On Species elements the `initialConcentration` attribute can have a value even if the `hasOnlySubstanceUnits` attribute is "`true`".
- page 19 Section 4.6.4: This section should contain a table that shows how the units of a species is determined from the spatial dimensions of the species and the value of the `hasOnlySubstanceUnits` attribute.
- page 24 Section 4.8.4: This section should specify that the model should not be overdetermined as defined in Section 4.11.6 of the SBML Level 2 Version 2 specification (i.e. this document).
- page 24 Section 4.8.4: This section should not refer to assignment rules using the term 'scalar rule'.
- page 27 Section 4.9.5: If a species id occurs in any `ci` element MathML element including KineticLaw and StoichiometryMath elements it should appear in a *SimpleSpeciesReference* element in the reaction. The specification only applies this rule to the KineticLaw element. Such a species is at a minimum a modifier of the reaction.
- page 29 Section 4.9.5: The relationship of the abstract class *SimpleSpeciesReference* to the concrete classes SpeciesReference and ModifierSpeciesReference should be made explicit.
- page 29 Section 4.9.6: Despite being redundant it is possible for a species to be referenced from the `modifier` field whilst being referenced from the `product` and/or `reactant` fields of the same reaction.
- page 29 section 4.9.7: 3rd paragraph: The text is overly restrictive and contradictory with respect of the units of species symbols. Species symbols can be either amount or concentration units depending on the species declaration.
- page 29 section 4.9.7: Final paragraph: The kinetic law expression is composed so that the units are of the parameter are not those conventionally used. This is not good practice. The rate expression should be changed to include the compartment volume so that the units of the parameter are those that would be measured by an experimentalist and used in practice by a modeler.
- page 31 Section 4.10.5: A `variable` attribute on a EventAssignment element should be unique among the set of assignments within an Event element if not the effect of event assignment is ambiguous.
- page 31 Section 4.10.5: A `variable` attribute on a EventAssignment element should not have the same value as a `variable` attribute on a AssignmentRule element.
- page 32 Section 4.10.7: *Any* transition of a `trigger` expression from false to true will cause an `event` to *fire*. Consider an `event` E with delay d where the `trigger` expression makes a transition from false to true at times t_1 and t_2. The EventAssignment structure will have effect at $t_1 + d$ and $t_2 + d$ irrespective of the relative times of t_1 and t_2. For example events can "overlap" so that $t_1 < t_2 < t_1 + d$ still causes event assignments to occur at $t_1 + d$ and $t_2 + d$.
- page 32 Section 4.10.7: Events cannot be triggered at $t = 0$.
- page 34 Section 5.2: The units of parameter `Km` should be moles per litre as the parameter is added to the concentration of a species.
- page 38 Example 5.3: The `out` reaction should have a `listOfModifiers` which refers to species `S2` since it is referenced in the reaction's KineticLaw.
- page 40 Example 5.5: The one rule in `listOfRules` should not use `<apply> ... </apply>`; these tags should be omitted.
- page 42 Example 5.6: The MathML in the two RateRule definitions should not use `<apply> ... </apply>`; these tags should be omitted.
- page 46 Example 5.8: The value of the `definitionURL` attribute on a `csymbol` delay should be `http://www.sbml.org/sbml/symbols/delay`, not `http://www.sbml.org/symbols/delay` (the incorrect form omitted "`sbml`").

- page 55 Appendix A: The appendix states that UML inheritance is mapped, in XML Schema, to the `extension` of `complexType` elements. This is by far the most natural interpretation and the one used in the schema available on the SBML web site and used by libSBML. However, this approach introduced a restriction: an ordering of elements is imposed on all extended types because the definition of XML Schema effectively requires the use of `sequence` ordering in order to be able to use type inheritance in this way. (A full explanation of the details can be found in Section 13.5 of Walmsley (2002)) The result is that the ordering of subelements in SBML XML is important. For example, `notes` and `annotation` elements must occur before `listOfReactants` elements within a Reaction element. Appendix A should state this restriction explicitly. Appendix A should be moved into the main text. The dependence on `sequence` is a result of using XML Schema.

- page 55 Appendix A: The SCHUCS document doesn't state what model group element should be used in the XML schema interpretation of UML. (Examples of XML schema are that `xs:element` elements should be enclosed in `xs:choice`, `xs:all` or `xs:sequence` elements; see p.488 table A-1 of Walmsley (2002).) To be consistent with the previous errata item, `xs:sequence` elements should be used. (The SBML schemas use this interpretation).

- page 56, Appendix B: The last bullet, second sentence starts: "there is no longer a `type` field on *Rule*". Technically, this should read: "there is no longer a `type` field on AssignmentRule".

C XML Schema for SBML

The following is an XML Schema definition for SBML Level 2 Version 2, using the W3C Recommendation for XML Schema version 1.0 of 2 May 2001 (Biron and Malhotra, 2000; Fallside, 2000; Thompson et al., 2000). This Schema does not define all aspects of SBML Level 2: an SBML document validated by this schema is not necessarily a valid SBML Level 2 document. Appendix D contains a a schema for the SBML MathML subset. Appendix E contains a list of the remaining checks required to validate a model that is already consistent with these two schemas.

The following schema is self-contained and makes reference to the official XML Schema for MathML hosted at the W3. However, for use in software systems, it is more efficient to store the MathML subset Schema of Appendix D in a file on a user's local disk, and change the `schemaLocation` value on line 27 below to refer to this local copy of the MathML subset Schema. Doing so will avoid requiring a network access every time this SBML Schema is used.

```
<?xml version="1.0" encoding="UTF-8"?>
<xsd:schema
    targetNamespace="http://www.sbml.org/sbml/level2/version2"
    xmlns="http://www.sbml.org/sbml/level2/version2"
    xmlns:mml="http://www.w3.org/1998/Math/MathML"
    xmlns:xlink="http://www.w3.org/1999/xlink"
    xmlns:xsi="http://www.w3.org/2001/XMLSchema-instance"
    xmlns:xsd="http://www.w3.org/2001/XMLSchema"
    elementFormDefault="qualified"
    attributeFormDefault="unqualified"
    version="SBML L2 V2">
    <xsd:import
        namespace="http://www.w3.org/1998/Math/MathML"
        schemaLocation="http://www.w3.org/Math/XMLSchema/mathml2/mathml2.xsd"/>
    <xsd:annotation>
        <xsd:documentation>
 * Filename    : sbml.xsd
 * Description: XML Schema for SBML Level 2 Version 2.
 * Author(s)  : Michael Hucka, Andrew Finney, Daniel Lucio
 * Revision   : $ Id: sbml.xsd,v 1.17 2006/09/23 02:03:39 mhucka Exp $
 * $ Source: /cvsroot/sbml/specifications/sbml-level-2/version-2/schema/sbml.xsd,v $
 *
 * Copyright 2003-2006 California Institute of Technology, the Japan Science
 * and Technology Corporation, and the University of Hertfordshire.
 *
 * This software is licensed according to the terms described in the file
 * named "LICENSE.txt" included with this distribution and available
 * online at http://sbml.org/xml-schemas/LICENSE.txt
        </xsd:documentation>
    </xsd:annotation>
    <!--The definition of SId follows.-->
    <xsd:simpleType name="SId">
        <xsd:annotation>
            <xsd:documentation>The type SId is used throughout
            SBML as the type of the 'id' attributes on model elements.</xsd:documentation>
        </xsd:annotation>
        <xsd:restriction base="xsd:string">
            <xsd:pattern value="(_|[a-z]|[A-Z])(_|[a-z]|[A-Z]|[0-9])*"/>
        </xsd:restriction>
    </xsd:simpleType>
    <xsd:simpleType name="UnitSId">
        <xsd:annotation>
            <xsd:documentation>The type UnitSId is used to refer to units.</xsd:documentation>
        </xsd:annotation>
        <xsd:restriction base="SId" />
    </xsd:simpleType>
    <xsd:simpleType name="SBOTerm">
        <xsd:annotation>
            <xsd:documentation>The data type for sboTerm attribute values.</xsd:documentation>
        </xsd:annotation>
        <xsd:restriction base="xsd:string">
            <xsd:pattern value="(SBO:)([0-9]{7})"/>
        </xsd:restriction>
    </xsd:simpleType>
    <!--The definition of SBase follows.-->
    <xsd:complexType name="SBase" abstract="true">
        <xsd:annotation>
            <xsd:documentation>The SBase type is the base type of all main components in SBML.
            It supports attaching metadata, notes and annotations to components.</xsd:documentation>
```

```
            </xsd:annotation>
            <xsd:sequence>
                <xsd:element name="notes" minOccurs="0">
                    <xsd:complexType>
                        <xsd:sequence>
                            <xsd:any namespace="http://www.w3.org/1999/xhtml"
                                     minOccurs="0" maxOccurs="unbounded"
                                     processContents="skip"/>
                        </xsd:sequence>
                    </xsd:complexType>
                </xsd:element>
                <xsd:element name="annotation" minOccurs="0">
                    <xsd:complexType>
                        <xsd:sequence>
                            <xsd:any processContents="skip" minOccurs="0" maxOccurs="unbounded"/>
                        </xsd:sequence>
                    </xsd:complexType>
                </xsd:element>
            </xsd:sequence>
            <xsd:attribute name="metaid" type="xsd:ID" use="optional"/>
        </xsd:complexType>
        <!--The definition of FunctionDefinition follows.-->
        <xsd:complexType name="FunctionDefinition">
            <xsd:complexContent>
                <xsd:extension base="SBase">
                    <xsd:sequence>
                        <xsd:element ref="mml:math"/>
                    </xsd:sequence>
                    <xsd:attribute name="id" type="SId" use="required"/>
                    <xsd:attribute name="name" type="xsd:string" use="optional"/>
                    <xsd:attribute name="sboTerm" type="SBOTerm" use="optional"/>
                </xsd:extension>
            </xsd:complexContent>
        </xsd:complexType>
        <!--The definition of UnitKind follows.-->
        <xsd:simpleType name="UnitKind">
            <xsd:restriction base="xsd:string">
                <xsd:enumeration value="ampere"/>
                <xsd:enumeration value="becquerel"/>
                <xsd:enumeration value="candela"/>
                <xsd:enumeration value="coulomb"/>
                <xsd:enumeration value="dimensionless"/>
                <xsd:enumeration value="farad"/>
                <xsd:enumeration value="gram"/>
                <xsd:enumeration value="gray"/>
                <xsd:enumeration value="henry"/>
                <xsd:enumeration value="hertz"/>
                <xsd:enumeration value="item"/>
                <xsd:enumeration value="joule"/>
                <xsd:enumeration value="katal"/>
                <xsd:enumeration value="kelvin"/>
                <xsd:enumeration value="kilogram"/>
                <xsd:enumeration value="litre"/>
                <xsd:enumeration value="lumen"/>
                <xsd:enumeration value="lux"/>
                <xsd:enumeration value="metre"/>
                <xsd:enumeration value="mole"/>
                <xsd:enumeration value="newton"/>
                <xsd:enumeration value="ohm"/>
                <xsd:enumeration value="pascal"/>
                <xsd:enumeration value="radian"/>
                <xsd:enumeration value="second"/>
                <xsd:enumeration value="siemens"/>
                <xsd:enumeration value="sievert"/>
                <xsd:enumeration value="steradian"/>
                <xsd:enumeration value="tesla"/>
                <xsd:enumeration value="volt"/>
                <xsd:enumeration value="watt"/>
                <xsd:enumeration value="weber"/>
            </xsd:restriction>
        </xsd:simpleType>
        <!--The definition of Unit follows.-->
        <xsd:complexType name="Unit">
            <xsd:complexContent>
                <xsd:extension base="SBase">
                    <xsd:attribute name="kind" type="UnitKind" use="required"/>
                    <xsd:attribute name="exponent" type="xsd:int" default="1"/>
                    <xsd:attribute name="scale" type="xsd:int" default="0"/>
                    <xsd:attribute name="multiplier" type="xsd:double" default="1"/>
                </xsd:extension>
```

```
            </xsd:complexContent>
        </xsd:complexType>
        <!--The definition of UnitDefinition follows.-->
        <xsd:complexType name="ListOfUnits">
            <xsd:complexContent>
                <xsd:extension base="SBase">
                    <xsd:sequence>
                        <xsd:element name="unit" type="Unit" maxOccurs="unbounded"/>
                    </xsd:sequence>
                </xsd:extension>
            </xsd:complexContent>
        </xsd:complexType>
        <xsd:complexType name="UnitDefinition">
            <xsd:complexContent>
                <xsd:extension base="SBase">
                    <xsd:sequence>
                        <xsd:element name="listOfUnits" type="ListOfUnits"/>
                    </xsd:sequence>
                    <xsd:attribute name="id" type="UnitSId" use="required"/>
                    <xsd:attribute name="name" type="xsd:string" use="optional"/>
                </xsd:extension>
            </xsd:complexContent>
        </xsd:complexType>
        <!--The definition of CompartmentType follows.-->
        <xsd:complexType name="CompartmentType">
            <xsd:complexContent>
                <xsd:extension base="SBase">
                    <xsd:attribute name="id" type="SId" use="required"/>
                    <xsd:attribute name="name" type="xsd:string" use="optional"/>
                </xsd:extension>
            </xsd:complexContent>
        </xsd:complexType>
        <!--The definition of SpeciesType follows.-->
        <xsd:complexType name="SpeciesType">
            <xsd:complexContent>
                <xsd:extension base="SBase">
                    <xsd:attribute name="id" type="SId" use="required"/>
                    <xsd:attribute name="name" type="xsd:string" use="optional"/>
                </xsd:extension>
            </xsd:complexContent>
        </xsd:complexType>
        <!--The definition of Compartment follows.-->
        <xsd:complexType name="Compartment">
            <xsd:complexContent>
                <xsd:extension base="SBase">
                    <xsd:attribute name="id" type="SId" use="required"/>
                    <xsd:attribute name="name" type="xsd:string" use="optional"/>
                    <xsd:attribute name="compartmentType" type="SId" use="optional"/>
                    <xsd:attribute name="spatialDimensions" use="optional" default="3">
                        <xsd:simpleType>
                            <xsd:restriction base="xsd:int">
                                <xsd:minInclusive value="0"/>
                                <xsd:maxInclusive value="3"/>
                            </xsd:restriction>
                        </xsd:simpleType>
                    </xsd:attribute>
                    <xsd:attribute name="size" type="xsd:double" use="optional"/>
                    <xsd:attribute name="units" type="UnitSId" use="optional"/>
                    <xsd:attribute name="outside" type="SId" use="optional"/>
                    <xsd:attribute name="constant" type="xsd:boolean" use="optional" default="true"/>
                </xsd:extension>
            </xsd:complexContent>
        </xsd:complexType>
        <!--The definition of Species follows.-->
        <xsd:complexType name="Species">
            <xsd:complexContent>
                <xsd:extension base="SBase">
                    <xsd:attribute name="id" type="SId" use="required"/>
                    <xsd:attribute name="name" type="xsd:string" use="optional"/>
                    <xsd:attribute name="speciesType" type="SId"  use="optional"/>
                    <xsd:attribute name="compartment" type="SId" use="required"/>
                    <xsd:attribute name="initialAmount" type="xsd:double" use="optional"/>
                    <xsd:attribute name="initialConcentration" type="xsd:double" use="optional"/>
                    <xsd:attribute name="substanceUnits" type="UnitSId" use="optional"/>
                    <xsd:attribute name="spatialSizeUnits" type="UnitSId" use="optional"/>
                    <xsd:attribute name="hasOnlySubstanceUnits" type="xsd:boolean" use="optional" default="false"/>
                    <xsd:attribute name="boundaryCondition" type="xsd:boolean" use="optional" default="false"/>
                    <xsd:attribute name="charge" type="xsd:int" use="optional"/>
                    <xsd:attribute name="constant" type="xsd:boolean" use="optional" default="false"/>
                </xsd:extension>
```

```
            </xsd:complexContent>
        </xsd:complexType>
        <!--The definition of Parameter follows.-->
        <xsd:complexType name="Parameter">
            <xsd:complexContent>
                <xsd:extension base="SBase">
                    <xsd:attribute name="id" type="SId" use="required"/>
                    <xsd:attribute name="name" type="xsd:string" use="optional"/>
                    <xsd:attribute name="value" type="xsd:double" use="optional"/>
                    <xsd:attribute name="units" type="UnitSId" use="optional"/>
                    <xsd:attribute name="constant" type="xsd:boolean" use="optional" default="true"/>
                    <xsd:attribute name="sboTerm" type="SBOTerm" use="optional"/>
                </xsd:extension>
            </xsd:complexContent>
        </xsd:complexType>
        <xsd:complexType name="ListOfParameters">
            <xsd:complexContent>
                <xsd:extension base="SBase">
                    <xsd:sequence>
                        <xsd:element name="parameter" type="Parameter" maxOccurs="unbounded"/>
                    </xsd:sequence>
                </xsd:extension>
            </xsd:complexContent>
        </xsd:complexType>
        <!--The definition of Initial Assignment follows.-->
        <xsd:complexType name="InitialAssignment">
            <xsd:complexContent>
                <xsd:extension base="SBase">
                    <xsd:sequence>
                        <xsd:element ref="mml:math"/>
                    </xsd:sequence>
                    <xsd:attribute name="symbol" type="SId" use="required"/>
                    <xsd:attribute name="sboTerm" type="SBOTerm" use="optional"/>
                </xsd:extension>
            </xsd:complexContent>
        </xsd:complexType>
        <!--The definition of Rule follows. -->
        <xsd:complexType name="Rule" abstract="true">
            <xsd:complexContent>
                <xsd:extension base="SBase">
                    <xsd:sequence>
                        <xsd:element ref="mml:math"/>
                    </xsd:sequence>
                    <xsd:attribute name="sboTerm" type="SBOTerm" use="optional"/>
                </xsd:extension>
            </xsd:complexContent>
        </xsd:complexType>
        <xsd:complexType name="AlgebraicRule">
            <xsd:complexContent>
                <xsd:extension base="Rule"/>
            </xsd:complexContent>
        </xsd:complexType>
        <xsd:complexType name="AssignmentRule">
            <xsd:complexContent>
                <xsd:extension base="Rule">
                    <xsd:attribute name="variable" type="SId" use="required"/>
                </xsd:extension>
            </xsd:complexContent>
        </xsd:complexType>
        <xsd:complexType name="RateRule">
            <xsd:complexContent>
                <xsd:extension base="Rule">
                    <xsd:attribute name="variable" type="SId" use="required"/>
                </xsd:extension>
            </xsd:complexContent>
        </xsd:complexType>
        <!--The definition of Constraint follows.-->
        <xsd:complexType name="Constraint">
            <xsd:complexContent>
                <xsd:extension base="SBase">
                    <xsd:sequence>
                        <xsd:element ref="mml:math"/>
                        <xsd:element name="message" minOccurs="0">
                            <xsd:complexType>
                                <xsd:sequence>
                                    <xsd:any namespace="http://www.w3.org/1999/xhtml"
                                             minOccurs="0" maxOccurs="unbounded"
                                             processContents="skip"/>
                                </xsd:sequence>
                            </xsd:complexType>
```

```
                    </xsd:element>
                </xsd:sequence>
                <xsd:attribute name="sboTerm" type="SBOTerm" use="optional"/>
            </xsd:extension>
        </xsd:complexContent>
    </xsd:complexType>
    <!--The definition of Reaction follows.-->
    <xsd:complexType name="KineticLaw">
        <xsd:complexContent>
            <xsd:extension base="SBase">
                <xsd:sequence>
                    <xsd:element ref="mml:math"/>
                    <xsd:element name="listOfParameters" type="ListOfParameters" minOccurs="0"/>
                </xsd:sequence>
                <xsd:attribute name="sboTerm" type="SBOTerm" use="optional"/>
            </xsd:extension>
        </xsd:complexContent>
    </xsd:complexType>
    <xsd:complexType name="SimpleSpeciesReference" abstract="true">
        <xsd:complexContent>
            <xsd:extension base="SBase">
                <xsd:attribute name="id" type="SId" use="optional"/>
                <xsd:attribute name="name" type="xsd:string" use="optional"/>
                <xsd:attribute name="species" type="SId" use="required"/>
                <xsd:attribute name="sboTerm" type="SBOTerm" use="optional"/>
            </xsd:extension>
        </xsd:complexContent>
    </xsd:complexType>
    <xsd:complexType name="ModifierSpeciesReference">
        <xsd:complexContent>
            <xsd:extension base="SimpleSpeciesReference"/>
        </xsd:complexContent>
    </xsd:complexType>
    <xsd:complexType name="ListOfModifierSpeciesReferences">
        <xsd:complexContent>
            <xsd:extension base="SBase">
                <xsd:sequence>
                    <xsd:element name="modifierSpeciesReference"
                                 type="ModifierSpeciesReference" maxOccurs="unbounded"/>
                </xsd:sequence>
            </xsd:extension>
        </xsd:complexContent>
    </xsd:complexType>
    <xsd:complexType name="StoichiometryMath">
        <xsd:complexContent>
            <xsd:extension base="SBase">
                <xsd:sequence>
                    <xsd:element ref="mml:math"/>
                </xsd:sequence>
            </xsd:extension>
        </xsd:complexContent>
    </xsd:complexType>
    <xsd:complexType name="SpeciesReference">
        <xsd:complexContent>
            <xsd:extension base="SimpleSpeciesReference">
                <xsd:sequence>
                    <xsd:element name="stoichiometryMath" type="StoichiometryMath" minOccurs="0"/>
                </xsd:sequence>
                <xsd:attribute name="stoichiometry" type="xsd:double" use="optional" default="1"/>
            </xsd:extension>
        </xsd:complexContent>
    </xsd:complexType>
    <xsd:complexType name="ListOfSpeciesReferences">
        <xsd:complexContent>
            <xsd:extension base="SBase">
                <xsd:sequence>
                    <xsd:element name="speciesReference" type="SpeciesReference" maxOccurs="unbounded"/>
                </xsd:sequence>
            </xsd:extension>
        </xsd:complexContent>
    </xsd:complexType>
    <xsd:complexType name="Reaction">
        <xsd:complexContent>
            <xsd:extension base="SBase">
                <xsd:sequence>
                    <xsd:element name="listOfReactants" type="ListOfSpeciesReferences" minOccurs="0"/>
                    <xsd:element name="listOfProducts" type="ListOfSpeciesReferences" minOccurs="0"/>
                    <xsd:element name="listOfModifiers" type="ListOfModifierSpeciesReferences" minOccurs="0"/>
                    <xsd:element name="kineticLaw" type="KineticLaw" minOccurs="0"/>
                </xsd:sequence>
```

```
                <xsd:attribute name="id" type="SId" use="required"/>
                <xsd:attribute name="name" type="xsd:string" use="optional"/>
                <xsd:attribute name="reversible" type="xsd:boolean" use="optional" default="true"/>
                <xsd:attribute name="fast" type="xsd:boolean" use="optional" default="false"/>
                <xsd:attribute name="sboTerm" type="SBOTerm" use="optional"/>
            </xsd:extension>
        </xsd:complexContent>
    </xsd:complexType>
    <!--The definition of Event follows.-->
    <xsd:complexType name="EventAssignment">
        <xsd:complexContent>
            <xsd:extension base="SBase">
                <xsd:sequence>
                    <xsd:element ref="mml:math"/>
                </xsd:sequence>
                <xsd:attribute name="variable" type="SId" use="required"/>
                <xsd:attribute name="sboTerm" type="SBOTerm" use="optional"/>
            </xsd:extension>
        </xsd:complexContent>
    </xsd:complexType>
    <xsd:complexType name="ListOfEventAssignments">
        <xsd:complexContent>
            <xsd:extension base="SBase">
                <xsd:sequence>
                    <xsd:element name="eventAssignment" type="EventAssignment" maxOccurs="unbounded"/>
                </xsd:sequence>
            </xsd:extension>
        </xsd:complexContent>
    </xsd:complexType>
    <xsd:complexType name="MathField">
        <xsd:complexContent>
            <xsd:extension base="SBase">
                <xsd:sequence>
                    <xsd:element ref="mml:math"/>
                </xsd:sequence>
            </xsd:extension>
        </xsd:complexContent>
    </xsd:complexType>
    <xsd:complexType name="Event">
        <xsd:complexContent>
            <xsd:extension base="SBase">
                <xsd:sequence>
                    <xsd:element name="trigger" type="MathField"/>
                    <xsd:element name="delay" type="MathField" minOccurs="0"/>
                    <xsd:element name="listOfEventAssignments" type="ListOfEventAssignments"/>
                </xsd:sequence>
                <xsd:attribute name="id" type="SId" use="optional"/>
                <xsd:attribute name="name" type="xsd:string" use="optional"/>
                <xsd:attribute name="timeUnits" type="UnitSId" use="optional"/>
                <xsd:attribute name="sboTerm" type="SBOTerm" use="optional"/>
            </xsd:extension>
        </xsd:complexContent>
    </xsd:complexType>
    <!-- The definition of Model follows.-->
    <xsd:complexType name="Model">
        <xsd:complexContent>
            <xsd:extension base="SBase">
                <xsd:sequence>
                    <xsd:element name="listOfFunctionDefinitions" minOccurs="0">
                        <xsd:complexType>
                            <xsd:complexContent>
                                <xsd:extension base="SBase">
                                    <xsd:sequence>
                                        <xsd:element name="functionDefinition"
                                                     type="FunctionDefinition" maxOccurs="unbounded"/>
                                    </xsd:sequence>
                                </xsd:extension>
                            </xsd:complexContent>
                        </xsd:complexType>
                    </xsd:element>
                    <xsd:element name="listOfUnitDefinitions" minOccurs="0">
                        <xsd:complexType>
                            <xsd:complexContent>
                                <xsd:extension base="SBase">
                                    <xsd:sequence>
                                        <xsd:element name="unitDefinition"
                                                     type="UnitDefinition" maxOccurs="unbounded"/>
                                    </xsd:sequence>
                                </xsd:extension>
                            </xsd:complexContent>
```

```
    </xsd:complexType>
</xsd:element>
<xsd:element name="listOfCompartmentTypes" minOccurs="0">
    <xsd:complexType>
        <xsd:complexContent>
            <xsd:extension base="SBase">
                <xsd:sequence>
                    <xsd:element
                        name="compartmentType"
                        type="CompartmentType"
                        maxOccurs="unbounded"/>
                </xsd:sequence>
            </xsd:extension>
        </xsd:complexContent>
    </xsd:complexType>
</xsd:element>
<xsd:element name="listOfSpeciesTypes" minOccurs="0">
    <xsd:complexType>
        <xsd:complexContent>
            <xsd:extension base="SBase">
                <xsd:sequence>
                    <xsd:element name="speciesType" type="SpeciesType"
                                 maxOccurs="unbounded"/>
                </xsd:sequence>
            </xsd:extension>
        </xsd:complexContent>
    </xsd:complexType>
</xsd:element>
<xsd:element name="listOfCompartments" minOccurs="0">
    <xsd:complexType>
        <xsd:complexContent>
            <xsd:extension base="SBase">
                <xsd:sequence>
                    <xsd:element name="compartment" type="Compartment"
                                 maxOccurs="unbounded"/>
                </xsd:sequence>
            </xsd:extension>
        </xsd:complexContent>
    </xsd:complexType>
</xsd:element>
<xsd:element name="listOfSpecies" minOccurs="0">
    <xsd:complexType>
        <xsd:complexContent>
            <xsd:extension base="SBase">
                <xsd:sequence>
                    <xsd:element name="species" type="Species"
                                 maxOccurs="unbounded"/>
                </xsd:sequence>
            </xsd:extension>
        </xsd:complexContent>
    </xsd:complexType>
</xsd:element>
<xsd:element name="listOfParameters" type="ListOfParameters" minOccurs="0"/>
<xsd:element name="listOfInitialAssignments" minOccurs="0">
    <xsd:complexType>
        <xsd:complexContent>
            <xsd:extension base="SBase">
                <xsd:sequence>
                    <xsd:element name="initialAssignment"
                                 type="InitialAssignment" maxOccurs="unbounded"/>
                </xsd:sequence>
            </xsd:extension>
        </xsd:complexContent>
    </xsd:complexType>
</xsd:element>
<xsd:element name="listOfRules" minOccurs="0">
    <xsd:complexType>
        <xsd:complexContent>
            <xsd:extension base="SBase">
                <xsd:choice maxOccurs="unbounded">
                    <xsd:element name="algebraicRule" type="AlgebraicRule"
                                 minOccurs="0"/>
                    <xsd:element name="assignmentRule" type="AssignmentRule"
                                 minOccurs="0"/>
                    <xsd:element name="rateRule" type="RateRule" minOccurs="0"/>
                </xsd:choice>
            </xsd:extension>
        </xsd:complexContent>
    </xsd:complexType>
</xsd:element>
```

```
                    <xsd:element name="listOfConstraints" minOccurs="0">
                        <xsd:complexType>
                            <xsd:complexContent>
                                <xsd:extension base="SBase">
                                    <xsd:sequence>
                                        <xsd:element name="constraint" type="Constraint"
                                                     maxOccurs="unbounded"/>
                                    </xsd:sequence>
                                </xsd:extension>
                            </xsd:complexContent>
                        </xsd:complexType>
                    </xsd:element>
                    <xsd:element name="listOfReactions" minOccurs="0">
                        <xsd:complexType>
                            <xsd:complexContent>
                                <xsd:extension base="SBase">
                                    <xsd:sequence>
                                        <xsd:element name="reaction" type="Reaction"
                                                     maxOccurs="unbounded"/>
                                    </xsd:sequence>
                                </xsd:extension>
                            </xsd:complexContent>
                        </xsd:complexType>
                    </xsd:element>
                    <xsd:element name="listOfEvents" minOccurs="0">
                        <xsd:complexType>
                            <xsd:complexContent>
                                <xsd:extension base="SBase">
                                    <xsd:sequence>
                                        <xsd:element name="event" type="Event"
                                                     maxOccurs="unbounded"/>
                                    </xsd:sequence>
                                </xsd:extension>
                            </xsd:complexContent>
                        </xsd:complexType>
                    </xsd:element>
                </xsd:sequence>
                <xsd:attribute name="id" type="SId" use="optional"/>
                <xsd:attribute name="name" type="xsd:string" use="optional"/>
                <xsd:attribute name="sboTerm" type="SBOTerm" use="optional"/>
            </xsd:extension>
        </xsd:complexContent>
    </xsd:complexType>
    <!-- The following is the type definition for the top-level element in an SBML document.-->
    <xsd:complexType name="Sbml">
        <xsd:complexContent>
            <xsd:extension base="SBase">
                <xsd:sequence>
                    <xsd:element name="model" type="Model"/>
                </xsd:sequence>
                <xsd:attribute name="level" type="xsd:positiveInteger" use="required" fixed="2"/>
                <xsd:attribute name="version" type="xsd:positiveInteger" use="required" fixed="2"/>
            </xsd:extension>
        </xsd:complexContent>
    </xsd:complexType>
    <!--The following is the (only) top-level element allowed in an SBML document.-->
    <xsd:element name="sbml" type="Sbml"/>
    <!--The end.-->
</xsd:schema>
```

D XML Schema for MathML subset

The following XML schema defines the syntax of the MathML syntax that is used in SBML Level 2 version 1 and 2.

```
<?xml version="1.0" encoding="UTF-8"?>
<!--
 * Filename    : sbml-mathml.xsd
 * Description : Schema for the MathML subset used by SBML L2.
 * Author(s)   : Andrew Finney, Michael Hucka
 * Organization: SBML Team <sbml-team@caltech.edu>
 * Revision    : $ Id: sbml-mathml.xsd,v 1.3 2006/07/20 23:46:31 mhucka Exp $
 * Source      : $ Source: /cvsroot/sbml/specifications/sbml-mathml/sbml-mathml.xsd,v $
 *
 * Copyright 2003-2006 California Institute of Technology, the Japan Science
 * and Technology Corporation, and the University of Hertfordshire.
 *
 * This software is licensed according to the terms described in the file
 * named "LICENSE.txt" included with this distribution and available
 * online at http://sbml.org/xml-schemas/LICENSE.txt
 *
 * Summary:
 *
 * This is a reduced version of the XML Schema for MathML 2.0.  It
 * corresponds to the subset of MathML 2.0 used in SBML Level 2, and
 * should be used by validating XML parsers instead of the actual
 * MathML XML Schema when validating SBML files.  To accomplish that,
 * changed the value of the attribute 'schemaLocation' in the SBML
 * XML Schema file (sbml.xsd) to refer to a copy of this Schema file
 * on your computer's local hard disk.
-->
<xs:schema xmlns="http://www.w3.org/1998/Math/MathML"
           xmlns:xsi="http://www.w3.org/2001/XMLSchema-instance"
           xmlns:xs="http://www.w3.org/2001/XMLSchema"
           targetNamespace="http://www.w3.org/1998/Math/MathML"
           elementFormDefault="qualified"
           attributeFormDefault="unqualified">
    <xs:attributeGroup name="MathAttributes">
        <xs:attribute name="class" type="xs:NMTOKENS" use="optional"/>
        <xs:attribute name="style" type="xs:string" use="optional"/>
        <xs:attribute name="id" type="xs:ID" use="optional"/>
    </xs:attributeGroup>
    <xs:complexType name="MathBase">
        <xs:attributeGroup ref="MathAttributes"/>
    </xs:complexType>
    <xs:attributeGroup name="CnAttributes">
        <xs:attribute name="type">
            <xs:simpleType>
                <xs:restriction base="xs:NMTOKEN">
                    <xs:enumeration value="e-notation"/>
                    <xs:enumeration value="integer"/>
                    <xs:enumeration value="rational"/>
                    <xs:enumeration value="real"/>
                </xs:restriction>
            </xs:simpleType>
        </xs:attribute>
        <xs:attributeGroup ref="MathAttributes"/>
    </xs:attributeGroup>
    <xs:complexType name="SepType"/>
    <xs:complexType name="Cn" mixed="true">
        <xs:choice minOccurs="0">
            <xs:element name="sep" type="SepType"/>
        </xs:choice>
        <xs:attributeGroup ref="CnAttributes"/>
    </xs:complexType>
    <xs:complexType name="Ci">
        <xs:simpleContent>
            <xs:extension base="xs:string">
                <xs:attributeGroup ref="MathAttributes"/>
            </xs:extension>
        </xs:simpleContent>
    </xs:complexType>
    <xs:simpleType name="CsymbolURI">
        <xs:restriction base="xs:string">
            <xs:enumeration value="http://www.sbml.org/sbml/symbols/time"/>
            <xs:enumeration value="http://www.sbml.org/sbml/symbols/delay"/>
        </xs:restriction>
    </xs:simpleType>
```

```
        <xs:complexType name="Csymbol">
            <xs:simpleContent>
                <xs:extension base="xs:string">
                    <xs:attribute name="encoding" use="required" fixed="text"/>
                    <xs:attribute name="definitionURL" type="CsymbolURI" use="required"/>
                    <xs:attributeGroup ref="MathAttributes"/>
                </xs:extension>
            </xs:simpleContent>
        </xs:complexType>
        <xs:complexType name="NodeContainer">
            <xs:complexContent>
                <xs:extension base="MathBase">
                    <xs:group ref="Node"/>
                </xs:extension>
            </xs:complexContent>
        </xs:complexType>
        <xs:complexType name="Apply">
            <xs:complexContent>
                <xs:extension base="MathBase">
                    <xs:sequence>
                        <xs:choice>
                            <xs:element name="ci" type="Ci"/>
                            <xs:element name="csymbol" type="Csymbol"/>
                            <xs:element name="eq" type="MathBase"/>
                            <xs:element name="neq" type="MathBase"/>
                            <xs:element name="gt" type="MathBase"/>
                            <xs:element name="lt" type="MathBase"/>
                            <xs:element name="geq" type="MathBase"/>
                            <xs:element name="leq" type="MathBase"/>
                            <xs:element name="plus" type="MathBase"/>
                            <xs:element name="minus" type="MathBase"/>
                            <xs:element name="times" type="MathBase"/>
                            <xs:element name="divide" type="MathBase"/>
                            <xs:element name="power" type="MathBase"/>
                            <xs:sequence>
                                <xs:element name="root" type="MathBase"/>
                                <xs:element name="degree" type="NodeContainer" minOccurs="0"/>
                            </xs:sequence>
                            <xs:element name="abs" type="MathBase"/>
                            <xs:element name="exp" type="MathBase"/>
                            <xs:element name="ln" type="MathBase"/>
                            <xs:sequence>
                                <xs:element name="log" type="MathBase"/>
                                <xs:element name="logbase" type="NodeContainer" minOccurs="0"/>
                            </xs:sequence>
                            <xs:element name="floor" type="MathBase"/>
                            <xs:element name="ceiling" type="MathBase"/>
                            <xs:element name="factorial" type="MathBase"/>
                            <xs:element name="and" type="MathBase"/>
                            <xs:element name="or" type="MathBase"/>
                            <xs:element name="xor" type="MathBase"/>
                            <xs:element name="not" type="MathBase"/>
                            <xs:element name="sin" type="MathBase"/>
                            <xs:element name="cos" type="MathBase"/>
                            <xs:element name="tan" type="MathBase"/>
                            <xs:element name="sec" type="MathBase"/>
                            <xs:element name="csc" type="MathBase"/>
                            <xs:element name="cot" type="MathBase"/>
                            <xs:element name="sinh" type="MathBase"/>
                            <xs:element name="cosh" type="MathBase"/>
                            <xs:element name="tanh" type="MathBase"/>
                            <xs:element name="sech" type="MathBase"/>
                            <xs:element name="csch" type="MathBase"/>
                            <xs:element name="coth" type="MathBase"/>
                            <xs:element name="arcsin" type="MathBase"/>
                            <xs:element name="arccos" type="MathBase"/>
                            <xs:element name="arctan" type="MathBase"/>
                            <xs:element name="arcsec" type="MathBase"/>
                            <xs:element name="arccsc" type="MathBase"/>
                            <xs:element name="arccot" type="MathBase"/>
                            <xs:element name="arcsinh" type="MathBase"/>
                            <xs:element name="arccosh" type="MathBase"/>
                            <xs:element name="arctanh" type="MathBase"/>
                            <xs:element name="arcsech" type="MathBase"/>
                            <xs:element name="arccsch" type="MathBase"/>
                            <xs:element name="arccoth" type="MathBase"/>
                        </xs:choice>
                        <xs:group ref="Node" maxOccurs="unbounded"/>
                    </xs:sequence>
                </xs:extension>
```

```
            </xs:complexContent>
        </xs:complexType>
        <xs:complexType name="Piece">
            <xs:complexContent>
                <xs:extension base="MathBase">
                    <xs:group ref="Node" minOccurs="2" maxOccurs="2"/>
                </xs:extension>
            </xs:complexContent>
        </xs:complexType>
        <xs:complexType name="Otherwise">
            <xs:complexContent>
                <xs:extension base="MathBase">
                    <xs:group ref="Node"/>
                </xs:extension>
            </xs:complexContent>
        </xs:complexType>
        <xs:complexType name="Piecewise">
            <xs:complexContent>
                <xs:extension base="MathBase">
                    <xs:sequence>
                        <xs:element name="piece" type="Piece" minOccurs="0" maxOccurs="unbounded"/>
                        <xs:element name="otherwise" type="Otherwise" minOccurs="0" maxOccurs="1"/>
                    </xs:sequence>
                </xs:extension>
            </xs:complexContent>
        </xs:complexType>
        <xs:attributeGroup name="AnnotationAttributes">
            <xs:attributeGroup ref="MathAttributes"/>
            <xs:attribute name="encoding" type="xs:string" use="required"/>
        </xs:attributeGroup>
        <xs:complexType name="Annotation">
            <xs:simpleContent>
                <xs:extension base="xs:string">
                    <xs:attributeGroup ref="AnnotationAttributes"/>
                </xs:extension>
            </xs:simpleContent>
        </xs:complexType>
        <xs:complexType name="Annotation-xml">
            <xs:sequence maxOccurs="unbounded">
                <xs:any processContents="skip"/>
            </xs:sequence>
            <xs:attributeGroup ref="AnnotationAttributes"/>
        </xs:complexType>
        <xs:complexType name="Semantics">
            <xs:complexContent>
                <xs:extension base="MathBase">
                    <xs:sequence>
                        <xs:group ref="Node"/>
                        <xs:sequence maxOccurs="unbounded">
                            <xs:choice>
                                <xs:element name="annotation" type="Annotation"/>
                                <xs:element name="annotation-xml" type="Annotation-xml"/>
                            </xs:choice>
                        </xs:sequence>
                    </xs:sequence>
                </xs:extension>
            </xs:complexContent>
        </xs:complexType>
        <xs:group name="Node">
            <xs:choice>
                <xs:element name="apply" type="Apply"/>
                <xs:element name="cn" type="Cn"/>
                <xs:element name="ci" type="Ci"/>
                <xs:element name="csymbol" type="Csymbol"/>
                <xs:element name="true" type="MathBase"/>
                <xs:element name="false" type="MathBase"/>
                <xs:element name="notanumber" type="MathBase"/>
                <xs:element name="pi" type="MathBase"/>
                <xs:element name="infinity" type="MathBase"/>
                <xs:element name="exponentiale" type="MathBase"/>
                <xs:element name="semantics" type="Semantics"/>
                <xs:element name="piecewise" type="Piecewise"/>
            </xs:choice>
        </xs:group>
        <xs:complexType name="Bvar">
            <xs:complexContent>
                <xs:extension base="MathBase">
                    <xs:sequence>
                        <xs:element name="ci" type="Ci"/>
                    </xs:sequence>
```

```
                </xs:extension>
            </xs:complexContent>
        </xs:complexType>
        <xs:complexType name="Lambda">
            <xs:complexContent>
                <xs:extension base="MathBase">
                    <xs:sequence>
                        <xs:element name="bvar" type="Bvar" minOccurs="0" maxOccurs="unbounded"/>
                        <xs:group ref="Node"/>
                    </xs:sequence>
                </xs:extension>
            </xs:complexContent>
        </xs:complexType>
        <xs:complexType name="Math">
            <xs:complexContent>
                <xs:extension base="MathBase">
                    <xs:choice>
                        <xs:group ref="Node"/>
                        <xs:element name="lambda" type="Lambda"/>
                    </xs:choice>
                </xs:extension>
            </xs:complexContent>
        </xs:complexType>
        <xs:element name="math" type="Math">
            <!--This is the top-level element for a 'math' container in SBML.-->
        </xs:element>
    </xs:schema>
```

E Validation rules for SBML

This section contains a summary of all the conditions that should be true of a model, in addition to consistency with the XML Schemas given in Appendixes C and D, for that model to considered valid SBML.

E.1 General XML validation

10101. An SBML XML file must use UTF-8 as the character encoding. More precisely, the `encoding` attribute of the XML declaration at the beginning of the XML data stream cannot have a value other than "`UTF-8`". An example valid declaration is `<?xml version="1.0" encoding="UTF-8"?>`. (References: L2V2 Section 4.1.)

10102. An SBML XML document must not contain undefined elements or attributes in the SBML namespace. Documents containing unknown elements or attributes placed in the SBML namespace do not conform to the SBML Level 2 specification. (References: L2V2 Section 4.1.)

E.2 General MathML validation

10201. All MathML content in SBML must appear within a `math` element, and the `math` element must be either explicitly or implicitly in the XML namespace "`http://www.w3.org/1998/Math/MathML`". (References: L2V2 Section 3.5.)

10202. The only permitted MathML 2.0 elements in SBML Level 2 are the following: `cn`, `ci`, `csymbol`, `sep`, `apply`, `piecewise`, `piece`, `otherwise`, `eq`, `neq`, `gt`, `lt`, `geq`, `leq`, `plus`, `minus`, `times`, `divide`, `power`, `root`, `abs`, `exp`, `ln`, `log`, `floor`, `ceiling`, `factorial`, `and`, `or`, `xor`, `not`, `degree`, `bvar`, `logbase`, `sin`, `cos`, `tan`, `sec`, `csc`, `cot`, `sinh`, `cosh`, `tanh`, `sech`, `csch`, `coth`, `arcsin`, `arccos`, `arctan`, `arcsec`, `arccsc`, `arccot`, `arcsinh`, `arccosh`, `arctanh`, `arcsech`, `arccsch`, `arccoth`, `true`, `false`, `notanumber`, `pi`, `infinity`, `exponentiale`, `semantics`, `annotation`, and `annotation-xml`. (References: L2V2 Section 3.5.1.)

10203. In the SBML subset of MathML 2.0, the MathML attribute `encoding` is only permitted on `csymbol`. No other MathML elements may have the `encoding` attribute. (References: L2V2 Section 3.5.1.)

10204. In the SBML subset of MathML 2.0, the MathML attribute `definitionURL` is only permitted on `csymbol`. No other MathML elements may have a `definitionURL` attribute. (References: L2V2 Section 3.5.1.)

10205. In SBML Level 2, the only values permitted for the `definitionURL` attribute on a `csymbol` element are "`http://www.sbml.org/sbml/symbols/time`" and "`http://www.sbml.org/sbml/symbols/delay`". (References: L2V2 Section 3.5.5.)

10206. In the SBML subset of MathML 2.0, the MathML attribute `type` is only permitted on the `cn` construct. No other MathML elements may have a `type` attribute. (References: L2V2 Section 3.5.1.)

10207. The only permitted values for the `type` attribute on MathML `cn` elements are "`e-notation`", "`real`", "`integer`", and "`rational`". (References: L2V2 Section 3.5.2.)

10208. MathML `lambda` elements are only permitted as the first element inside the `math` element of a FunctionDefinition; they may not be used elsewhere in an SBML model. (References: L2V2 Section 4.3.2.)

10209. The arguments of the MathML logical operators `and`, `or`, `xor`, and `not` must have boolean values. (References: L2V2 Section 3.5.8.)

10210. The arguments to the following MathML constructs must have a numeric type: `plus`, `minus`, `times`, `divide`, `power`, `root`, `abs`, `exp`, `ln`, `log`, `floor`, `ceiling`, `factorial`, `sin`, `cos`, `tan`, `sec`, `csc`, `cot`, `sinh`, `cosh`, `tanh`, `sech`, `csch`, `coth`, `arcsin`, `arccos`, `arctan`, `arcsec`, `arccsc`, `arccot`, `arcsinh`, `arccosh`, `arctanh`, `arcsech`, `arccsch`, `arccoth`. (References: L2V2 Section 3.5.8.)

10211. The values of all arguments to `eq` and `neq` operators should have the same type (either all boolean or all numeric). (References: L2V2 Section 3.5.8.)

10212. The types of values within `piecewise` operators should all be consistent: the set of expressions that make up the first arguments of the `piece` and `otherwise` operators within the same `piecewise` operator should all return values of the same type. (References: L2V2 Section 3.5.8.)

10213. The second argument of a MathML `piece` operator must have a boolean value. (References: L2V2 Section 3.5.8.)

10214. Outside of a FunctionDefinition, if a `ci` element is the first element within a MathML `apply`, then the `ci`'s value can only be chosen from the set of identifiers of FunctionDefinitions defined in the SBML model. (References: L2V2 Section 4.3.2.)

10215. Outside of a FunctionDefinition, if a `ci` element is not the first element within a MathML `apply`, then the `ci`'s value can only be chosen from the set of identifiers of Species, Compartment, Parameter or Reaction objects defined in the SBML model. (References: L2V2 Section 3.5.3.)

10216. The `id` value of a Parameter defined within a KineticLaw can only be used in `ci` elements within the MathML content of that same KineticLaw; the identifier is not visible to other parts of the model. (References: L2V2 Section 3.5.3.)

10217. The MathML formulas in the following elements must yield numeric expressions: `math` in KineticLaw, `stoichiometryMath` in SpeciesReference, `math` in InitialAssignment, `math` in AssignmentRule, `math` in RateRule, `math` in AlgebraicRule, and `delay` in Event, and `math` in EventAssignment.

E.3 General identifier validation

10301. The value of the `id` field on every instance of the following type of object in a model must be unique: Model, FunctionDefinition, CompartmentType, Compartment, SpeciesType, Species, Reaction, SpeciesReference, ModifierSpeciesReference, Event, and model-wide Parameters. Note that UnitDefinition and parameters defined inside a reaction are treated separately. (References: L2V1 Section 3.5; L2V2 Section 3.4)

10302. The value of the `id` field of every UnitDefinition must be unique across the set of all UnitDefinitions in the entire model. (References: L2V2 Section 4.4; L2V1 Section 3.4.1 and 4.4.1.)

10303. The value of the `id` field of each parameter defined locally within a KineticLaw must be unique across the set of all such parameter definitions in that KineticLaw. (References: L2V2 Sections 3.4.1 and 4.13.9; L2V1 Sections 3.4.1 and 4.13.5.)

10304. The value of the `variable` field in all AssignmentRule and RateRule definitions must be unique across the set of all such rule definitions in a model. (References: L2V1 Section 4.8.4; L2V2 Section 4.11.4.)

10305. In each Event, the value of the `variable` field within every EventAssignment definition must be unique across the set of all EventAssignments within that Event. (References: L2V1 erratum 17; L2V2 Section 4.14.)

10306. An identifier used as the value of `variable` in an EventAssignment cannot also appear as the value of `variable` in an AssignmentRule. (References: L2V1 Section 4.10.5; L2V2 Section 4.14.)

10307. Every `metaid` field value must be unique across the set of all `metaid` values in a model. (References: L2V2 Sections 3.3.1 and 3.1.6.)

10308. The value of a `sboTerm` attribute must have the data type `SBOTerm`, which is a string consisting of the characters 'S', 'B', 'O', ':', followed by exactly seven digits. (References: L2V2 Section 3.1.9.)

10309. The syntax of `metaid` field values must conform to the syntax of the XML type `ID`. (References: L2V2 Sections 3.3.1 and 3.1.6.)

10310. The syntax of `id` field values must conform to the syntax of the SBML type `SId`. (References: L2V2 Sections 3.1.7.)

E.4 General Annotation validation

10401. Every top-level element within an `annotation` element must have a namespace declared. (References: L2V2 Section 3.3.3.)

10402. There cannot be more than one top-level element using a given namespace inside a given `annotation` element. (References: L2V2 Section 3.3.3.)

10403. Top-level elements within an `annotation` element cannot use any SBML namespace, whether explicitly (by declaring the namespace to be one of the URIs "`http://www.sbml.org/sbml/level1`", "`http://www.sbml.org/sbml/level2`", or "`http://www.sbml.org/sbml/level2/version2`"), or implicitly (by failing to declare any namespace). (References: L2V2 Section 3.3.3.)

E.5 General Unit validation

10503. The units of the expressions used as arguments to a function call must match the units expected for the arguments of that function. (References: L2V2 Section 3.5.)

10511. When the `variable` in an AssignmentRule refers to a Compartment, the units of the rule's right-hand side must be consistent with the units of that compartment's size. (References: L2V2 Section 4.11.4.)

10512. When the `variable` in an AssignmentRule refers to a Species, the units of the rule's right-hand side must be consistent with the units of the species' quantity. (References: L2V2 Section 4.11.4.)

10513. When the `variable` in an AssignmentRule refers to a Parameter, the units of the rule's right-hand side must be consistent with the units declared for that parameter. (References: L2V2 Section 4.11.4.)

10521. When the `variable` in an InitialAssignment refers to a Compartment, the units of the InitialAssignment's `math` expression must be consistent with the units of that compartment's size. (References: L2V2 Section 4.10.)

10522. When the `variable` in an InitialAssignment refers to a Species, the units of the InitialAssignment's `math` expression must be consistent with the units of that species' quantity. (References: L2V2 Section 4.11.4.)

10523. When the `variable` in an InitialAssignment refers to a Parameter, the units of the InitialAssignment's `math` expression must be consistent with the units declared for that parameter. (References: L2V2 Section 4.11.4.)

10531. When the `variable` in a RateRule definition refers to a Compartment, the units of the rule's right-hand side must be of the form *x per time*, where *x* is either the `units` in that Compartment definition, or (in the absence of explicit units declared for the compartment size) the default units for that compartment, and *time* refers to the units of time for the model. (References: L2V2 Section 4.11.5.)

10532. When the `variable` in a RateRule definition refers to a Species, the units of the rule's right-hand side must be of the form *x per time*, where *x* is the units of that species' quantity, and *time* refers to the units of time for the model. (References: L2V2 Section 4.11.5.)

10533. When the `variable` in a RateRule definition refers to a Parameter, the units of the rule's right-hand side must be of the form *x per time*, where *x* is the `units` in that Parameter definition, and *time* refers to the units of time for the model. (References: L2V2 Section 4.11.5.)

10541. The units of the `math` formula in a KineticLaw definition must be the equivalent of *substance per time*. (References: L2V2 Section 4.13.5.)

10551. When a value for `delay` is given in a Event definition, the units of the delay formula must correspond to either the value of `timeUnits` in the Event or (if no `timeUnits` are given), the model's default units of time. (References: L2V2 Section 4.14.)

E.6 General Model validation

20601. The value of `compartment` in a Species definition must be the identifier of an existing Compartment defined in the model. (References: L2V1 Section 4.6.2; Section 4.8.3.)

E.7 SBML container validation

20101. The `sbml` container element must declare the XML Namespace for SBML, and this declaration must be consistent with the values of the `level` and `version` attributes on the `sbml` element. (References: L2V2 Section 4.1.)

20102. The `sbml` container element must declare the SBML Level using the attribute `level`, and this declaration must be consistent with the XML Namespace declared for the `sbml` element. (References: L2V2 Section 4.1.)

20103. The `sbml` container element must declare the SBML Version using the attribute `version`, and this declaration must be consistent with the XML Namespace declared for the `sbml` element. (References: L2V2 Section 4.1.)

E.8 Model validation

20201. An SBML document must contain a Model definition. (References: L2V1 and L2V2 Section 4.1).

20202. The order of subelements within a Model object instance must be the following (where any one may be optional): `listOfFunctionDefinitions`, `listOfUnitDefinitions`, `listOfCompartmentTypes`, `listOfSpeciesTypes`, `listOfCompartments`, `listOfSpecies`, `listOfParameters`, `listOfInitialAssignments`, `listOfRules`, `listOfConstraints`, `listOfReactions`, `listOfEvents`. (References: L2V2 Section 4.2.)

20203. The `listOf___` containers in a Model are optional, but if present, the lists cannot be empty. Specifically, if any of the following are present in a Model, they must not be empty: `listOfFunctionDefinitions`, `listOfUnitDefinitions`, `listOfCompartmentTypes`, `listOfSpeciesTypes`, `listOfCompartments`, `listOfSpecies`, `listOfParameters`, `listOfInitialAssignments`, `listOfRules`, `listOfConstraints`, `listOfReactions` and `listOfEvents`. (References: This is a requirement stemming from the XML Schema used for SBML.)

20204. If a model defines any Species, then the model must also define at least one Compartment. This is an implication of the fact that the `compartment` field on Species is not optional. (References: L2V1 Section 4.5; Section 4.8.3.)

E.9 FunctionDefinition validation

20301. The top-level element within `math` in a FunctionDefinition must be `lambda`. (References: L2V1 Section 4.3.2; L2V2 Section 4.3.2.)

20302. Inside the `lambda` of a FunctionDefinition, if a `ci` element is the first element within a MathML `apply`, then the `ci`'s value can only be chosen from the set of identifiers of other SBML FunctionDefinitions defined prior to that point in the SBML model. In other words, forward references to user-functions are not permitted. (References: L2V2 Section 4.3.2.)

20303. Inside the `lambda` of a FunctionDefinition, the identifier of that FunctionDefinition cannot appear as the value of a `ci` element. SBML functions are not permitted to be recursive. (References: L2V2 Section 4.3.2.)

20304. Inside the `lambda` of a FunctionDefinition, if a `ci` element is not the first element within a MathML `apply`, then the `ci`'s value can only be the value of a `bvar` element declared in that `lambda`. In other words, all model entities referenced inside a function definition must be passed arguments to that function. (References: L2V2 Section 4.3.2.)

20305. The value type returned by a FunctionDefinition's `lambda` must be either boolean or numeric. (References: L2V2 Section 3.5.8.)

E.10 Unit and UnitDefinition validation

20401. The value of the `id` field in a UnitDefinition must not be identical to any unit predefined in SBML. That is, the identifier must not be the same as a value from the `UnitKind` enumeration (i.e., "`ampere`" "`gram`" "`katal`" "`metre`" "`second`" "`watt`" "`becquerel`" "`gray`" "`kelvin`" "`mole`" "`siemens`" "`weber`" "`candela`" "`henry`" "`kilogram`" "`newton`" "`sievert`" "`coulomb`" "`hertz`" "`litre`" "`ohm`" "`steradian`" "`dimensionless`" "`item`" "`lumen`" "`pascal`" "`tesla`" "`farad`" "`joule`" "`lux`" "`radian`" "`volt`".) (References: L2V1 erratum 14; L2V2 Section 4.4.2.)

20402. Redefinitions of the built-in unit `substance` must be based on the units `mole`, `item`, `gram`, `kilogram`, or `dimensionless`. More formally, a UnitDefinition for `substance` must simplify to a single Unit whose `kind` field has a value of "`mole`", "`item`", "`gram`", "`kilogram`", or `dimensionless`, and whose `exponent` field has a value of "`1`". (References: L2V1 Section 4.4.3; L2V2 Section 4.4.3.)

20403. Redefinitions of the built-in unit `length` must be based on the unit `metre` or `dimensionless`. More formally, a UnitDefinition for `length` must simplify to a single Unit in which either (a) the `kind` field has a value of "`metre`" and the `exponent` field has a value of "`1`", or (b) the `kind` field has a value of "`dimensionless`" with any `exponent` value. (References: L2V1 Section 4.4.3; L2V2 Section 4.4.3.)

20404. Redefinitions of the built-in unit `area` must be based on squared `metre`s or `dimensionless`. More formally, a UnitDefinition for `area` must simplify to a single Unit in which either (a) the `kind` field has a value of "`metre`" and the `exponent` field has a value of "`2`", or (b) the `kind` field has a value of "`dimensionless`" with any `exponent` value. (References: L2V1 Section 4.4.3; L2V2 Section 4.4.3.)

20405. Redefinitions of the built-in unit `time` must be based on `second`. More formally, a UnitDefinition for `time` must simplify to a single Unit in which either (a) the `kind` field has a value of "`second`" and the `exponent` field has a value of "`1`", or (b) the `kind` field has a value of "`dimensionless`" with any `exponent` value. (References: L2V1 Section 4.4.3; L2V2 Section 4.4.3.)

20406. Redefinitions of the built-in unit `volume` must be based on `litre`, `metre` or `dimensionless`. More formally, a UnitDefinition for `volume` must simplify to a single Unit in which the `kind` field value is either "`litre`", "`metre`", or "`dimensionless`". Additional constraints apply if the kind is "`litre`" or "`metre`". (References: L2V1 Section 4.4.3; L2V2 Section 4.4.3.)

20407. If a UnitDefinition for `volume` simplifies to a Unit in which the `kind` field value is "`litre`", then its `exponent` field value must be "`1`". (References: L2V1 Section 4.4.3; L2V2 Section 4.4.3.)

20408. If a UnitDefinition for `volume` simplifies to a Unit in which the `kind` field value is "`metre`", then its `exponent` field value must be "`3`". (References: L2V1 Section 4.4.3; L2V2 Section 4.4.3.)

20409. The `listOfUnits` container in a UnitDefinition cannot be empty. (References: L2V2 Section 4.4.)

20410. The value of the `kind` field of a Unit can only be one of the predefined units enumerated by `UnitKind`; that is, the SBML unit system is not hierarchical and user-defined units cannot be defined using other user-defined units. (References: L2V2 Section 4.4.2.)

20411. The `offset` field on Unit previously available in SBML Level 2 Version 1, has been removed as of SBML Level 2 Version 2. (References: L2V2 Section 4.4.)

20412. The predefined unit "`Celsius`", previously available in SBML Level 1 and Level 2 Version 1, has been removed as of SBML Level 2 Version 2. (References: L2V2 Section 4.4.)

E.11 Compartment validation

20501. The size of a Compartment must not be set if the compartment's `spatialDimensions` field has value `0`. (References: L2V1 Section 4.5.3; L2V2 Section 4.7.5.)

20502. If a Compartment definition has a `spatialDimensions` value of "`0`", then its `units` field must not be set. If the compartment has no dimensions, then no units can be associated with a non-existent size. (References: L2V1 Section 4.5.4; Section 4.7.5.)

20503. If a Compartment definition has a `spatialDimensions` value of "`0`", then its `constant` field value must either default to or be set to "`true`". If the compartment has no dimensions, then its size can never change. (References: L2V1 Section 4.5.5; L2V2 Section 4.7.6.)

20504. The `outside` field value of a Compartment must be the identifier of another Compartment defined in the model. (References: L2V1 Section 4.5.6; Section 4.7.7.)

20505. A Compartment may not enclose itself through a chain of references involving the `outside` field. This means that a compartment cannot have its own identifier as the value of `outside`, nor can it point to another compartment whose `outside` field points directly or indirectly to the compartment. (References: L2V1 erratum 11; L2V2 Section 4.7.7.)

20506. The `outside` field value of a Compartment cannot be a compartment whose `spatialDimensions` value is "`0`", unless both compartments have `spatialDimensions`="`0`". Simply put, a zero-dimensional compartment cannot enclose compartments that have anything other than zero dimensions themselves. (References: L2V2 Section 4.7.7.)

20507. The value of the `units` field on a Compartment having `spatialDimensions` of "`1`" must be either "`length`", "`metre`", "`dimensionless`", or the identifier of a UnitDefinition based on either `metre` (with `exponent` equal to "`1`") or `dimensionless`. (References: L2V1 Section 4.5.4; L2V2 Section 4.7.5.)

20508. The value of the `units` field on a Compartment having `spatialDimensions` of "`2`" must be either "`area`", "`dimensionless`", or the identifier of a UnitDefinition based on either `metre` (with `exponent` equal to "`2`") or `dimensionless`. (References: L2V1 Section 4.5.4; L2V2 Section 4.7.5.)

20509. The value of the `units` field on a Compartment having `spatialDimensions` of "`3`" must be either "`volume`", "`litre`", or the identifier of a UnitDefinition based on either `litre`, `metre` (with `exponent` equal to "`3`"), or `dimensionless`. (References: L2V1 Section 4.5.4; L2V2 Section 4.7.5.)

20510. If the `compartmentType` field is given a value in a Compartment definition, it must contain the identifier of an existing CompartmentType. (References: L2V2 Section 4.7.2.)

E.12 Species validation

20601. The value of `compartment` in a Species definition must be the identifier of an existing Compartment defined in the model. (References: L2V1 Section 4.6.2; Section 4.8.3.)

20602. If a Species definition sets `hasOnlySubstanceUnits` to "`true`", then it must not have a value for `spatialSizeUnits`. (References: L2V1 Section 4.6.4; L2V2 Section 4.8.5.)

20603. A Species definition must not set `spatialSizeUnits` if the Compartment in which it is located has a `spatialDimensions` value of "`0`". (References: L2V1 Section 4.6.4; L2V2 Section 4.8.5.)

20604. If a Species located in a Compartment whose `spatialDimensions` is set to "`0`", then that Species definition cannot set `initialConcentration`. (References: L2V1 Section 4.6.3; L2V2 Section 4.8.4.)

20605. If a Species is located in a Compartment whose `spatialDimensions` has value "`1`", then that Species definition can only set `spatialSizeUnits` to a value of "`length`", "`metre`", "`dimensionless`", or the identifier of a UnitDefinition derived from either `metre` (with an `exponent` value of "`1`") or "`dimensionless`". (References: L2V1 Section 4.6.4; L2V2 Section 4.8.5.)

20606. If a Species is located in a Compartment whose `spatialDimensions` has value "2", then that Species definition can only set `spatialSizeUnits` to a value of "`area`", "`dimensionless`", or the identifier of a UnitDefinition derived from either `metre` (with an `exponent` value of "2") or "`dimensionless`". (References: L2V1 Section 4.6.4; L2V2 Section 4.8.5.)

20607. If a Species is located in a Compartment whose `spatialDimensions` has value "3", then that Species definition can only set `spatialSizeUnits` to a value of "`volume`", "`litre`", "`dimensionless`", or the identifier of a UnitDefinition derived from either `litre`, `metre` (with an `exponent` value of "3") or `dimensionless`. (References: L2V1 Section 4.6.4; L2V2 Section 4.8.5.)

20608. The value of a Species's `substanceUnits` field can only be one of the following: "`substance`", "`mole`", "`item`", "`gram`", "`kilogram`", "`dimensionless`", or the identifier of a UnitDefinition derived from "`mole`" (with an `exponent` of "1"), "`item`" (with an `exponent` of "1"), "`gram`" (with an `exponent` of "1"), "`kilogram`" (with an `exponent` of "1"), or "`dimensionless`". (References: L2V1 Section 4.6.4; L2V2 Section 4.8.5.)

20609. A Species cannot set values for both `initialConcentration` and `initialAmount` because they are mutually exclusive. (References: L2V1 Section 4.6.3; L2V2 Section 4.8.4.)

20610. A Species' quantity cannot be determined simultaneously by both reactions and rules. More formally, if the identifier of a Species definition having `boundaryCondition`="`false`" and `constant`="`false`" is referenced by a SpeciesReference anywhere in a model, then this identifier cannot also appear as the value of a `variable` in an AssignmentRule or a RateRule. (References: L2V1 Section 4.6.5; L2V2 Section 4.8.6.)

20611. A Species having `boundaryCondition`="`false`" cannot appear as a reactant or product in any reaction if that Species also has `constant`="`true`". (References: L2V1 Section 4.6.5; L2V2 Section 4.8.6.)

20612. The value of `speciesType` in a Species definition must be the identifier of an existing SpeciesType. (References: L2V2 Section 4.8.2.)

20613. There cannot be more than one species of a given SpeciesType in the same compartment of a model. More formally, for any given compartment, there cannot be more than one Species definition in which both of the following hold simultaneously: (i) the Species' `compartment` value is set to that compartment's identifier and (ii) the Species' `speciesType` is set the same value as the `speciesType` of another Species that also sets its `compartment` to that compartment identifier. (References: L2V2 Section 4.8.2.)

E.13 Parameter validation

20701. The `units` in a Parameter definition must be a value chosen from among the following: a value from the `UnitKind` enumeration (e.g., "`litre`", "`mole`", "`metre`", etc.), a built-in unit (e.g., "`substance`", "`time`", etc.), or the identifier of a UnitDefinition in the model. (References: L2V1 Section 4.7.3; L2V2 Section 4.9.3.)

E.14 InitialAssignment validation

20801. The value of `symbol` in an InitialAssignment definition must be the identifier of an existing Compartment, Species, or Parameter defined in the model. (References: L2V2 Section 4.10.)

20802. A given identifier cannot appear as the value of more than one `symbol` field across the set of InitialAssignments in a model. (References: L2V2 Section 4.10.)

20803. The value of a `symbol` field in any InitialAssignment definition cannot also appear as the value of a `variable` field in an AssignmentRule. (References: L2V2 Section 4.10.)

E.15 AssignmentRule and RateRule validation

20901. The value of an AssignmentRule's `variable` must be the identifier of an existing Compartment, Species, or globally-defined Parameter. (References: L2V1 Section 4.8.2; L2V2 Section 4.11.4.)

20902. The value of a RateRule's `variable` must be the identifier of an existing Compartment, Species, or globally-defined Parameter. (References: L2V1 Section 4.8.3; L2V2 Section 4.11.5.)

20903. Any Compartment, Species or Parameter whose identifier is the value of a `variable` field in an AssignmentRule, must have a value of "`false`" for `constant`. (References: L2V1 Section 4.8.4; L2V2 Section 4.11.4.)

20904. Any Compartment, Species or Parameter whose identifier is the value of a `variable` field in an RateRule, must have a value of "`false`" for `constant`. (References: L2V1 Section 4.8.4; L2V2 Section 4.11.5.)

20905. A given identifier cannot appear as the value of more than one `variable` field across the combined set of AssignmentRules and RateRules in a model. (References: L2V2 Section 4.11.6.)

20906. There must not be circular dependencies in the combined set of InitialAssignment, AssignmentRule and KineticLaw definitions in a model. Each of these constructs has the effect of assigning a value to an identifier (i.e., the identifier given in the field `symbol` in InitialAssignment, the field `variable` in AssignmentRule, and the field `id` on the KineticLaw's enclosing Reaction). Each of these constructs computes the value using a mathematical formula. The formula for a given identifier cannot make reference to a second identifier whose own definition depends directly or indirectly on the first identifier. (References: L2V2 Section 4.11.6.)

E.16 Constraint validation

21001. A Constraint `math` expression must evaluate to a value of type `boolean`. (References: L2V2 Section 4.12.)

21002. The order of subelements within Constraint must be the following: `math`, `message`. The `message` element is optional, but if present, must follow the `math` element. (References: L2V2 Section 4.12.)

E.17 Reaction validation

21101. A Reaction definition must contain at least one SpeciesReference, either in its `listOfReactants` or its `listOfProducts`. A reaction without any reactant or product species is not permitted, regardless of whether the reaction has any modifier species. (References: L2V2 Section 4.13.3.)

21102. The order of subelements within Reaction must be the following (where every one is optional): `listOfReactants`, `listOfProducts`, `listOfModifiers`, `kineticLaw`. (References: L2V2 Section 4.13.)

21103. The following containers are all optional in a Reaction, but if any present is, it must not be empty: `listOfReactants`, `listOfProducts`, `listOfModifiers`, `kineticLaw`. (References: L2V2 Section 4.13.)

21104. The list of reactants (`listOfReactants`) and list of products (`listOfProducts`) in a Reaction can only contain `speciesReference` elements. (References: L2V1 Section 4.9; L2V2 Section 4.13.)

21105. The list of modifiers (`listOfModifiers`) in a Reaction can only contain `modifierSpeciesReference` elements. (References: L2V1 Section 4.9; L2V2 Section 4.13.)

21106. The `substanceUnits` field on Reaction, previously available in SBML Level 1 and Level 2 Version 1, has been removed as of SBML Level 2 Version 2. In SBML Level 2 Version 2, the substance units of a reaction rate expression are those of the global "`substance`" units of the model. (References: L2V2 Section 4.13.5.)

21107. The `timeUnits` field on Reaction, previously available in SBML Level 1 and Level 2 Version 1, has been removed as of SBML Level 2 Version 2. In SBML Level 2 Version 2, the time units of a reaction rate expression are those of the global "`time`" units of the model. (References: L2V2 Section 4.13.5.)

E.18 SpeciesReference and ModifierSpeciesReference validation

21111. The value of a SpeciesReference `species` field must be the identifier of an existing Species in the model. (References: L2V1 Section 4.9.5; L2V2 Section 4.13.3.)

21112. The value of a SpeciesReference's `species` field must not be the identifier of a Species having both a `constant` field value of "`true`" and a `boundaryCondition` field value of "`false`". (References: L2V1 Section 4.6.5; L2V2 Section 4.8.6.)

21113. A SpeciesReference must not have a value for both `stoichiometry` and `stoichiometryMath`; they are mutually exclusive. (References: L2V1 Section 4.9.5; L2V2 Section 4.13.3.)

E.19 KineticLaw validation

21121. All species referenced in the KineticLaw formula of a given reaction must first be declared using SpeciesReference or ModifierSpeciesReference. More formally, if a Species identifier appears in a `ci` element of a Reaction's KineticLaw formula, that same identifier must also appear in at least one SpeciesReference or ModifierSpeciesReference in the Reaction definition. (References: L2V2 Section 4.13.5.)

21122. The order of subelements within KineticLaw must be the following: `math`, `listOfParameters`. The `listOfParameters` is optional, but if present, must follow `math`. (References: L2V2 Section 4.13.5.)

21123. If present, the `listOfParameters` in a KineticLaw must not be an empty list. (References: L2V2 Section 4.13.)

21124. The `constant` field on a Parameter local to a KineticLaw cannot have a value other than "`true`". The values of parameters local to KineticLaw definitions cannot be changed, and therefore they are always constant. (References: L2V2 Section 4.13.5.)

E.20 StoichiometryMath validation

21131. All species referenced in the StoichiometryMath formula of a given reaction must first be declared using SpeciesReference or ModifierSpeciesReference. More formally, if a Species identifier appears in a `ci` element of a Reaction's StoichiometryMath formula, that same identifier must also appear in at least one SpeciesReference or ModifierSpeciesReference in the Reaction definition. (References: L2V2 Section 4.13.5.)

E.21 Event validation

21201. An Event object must have a `trigger`. (References: L2V1 Section 4.10.2; L2V2 Section 4.14.)

21202. An Event `trigger` expression must evaluate to a value of type `boolean`. (References: L2V1 Section 4.10.2; L2V2 Section 4.14.)

21203. An Event object must have at least one EventAssignment object in its `listOfEventAssignments`. (References: L2V1 Section 4.10.5; L2V2 Section 4.14.)

21204. The value of an Event's `timeUnits` must be "`time`", "`second`", "`dimensionless`", or the identifier of a UnitDefinition derived from either `second` (with an `exponent` value of "`1`") or "`dimensionless`". (References: L2V1 Section 4.10.4; L2V2 Section 4.14.)

21205. The order of subelements within an Event object instance must be the following: `trigger`, `delay`, `listOfEventAssignments`. The `delay` element is optional, but if present, must follow `trigger`. (References: L2V2 Section 4.14.)

E.22 EventAssignment validation

21211. The value of `variable` in an EventAssignment can only be the identifier of a Compartment, Species, or model-wide Parameter definition. (References: L2V1 Section 4.10.5; L2V2 Section 4.14.)

21212. Any Compartment, Species or Parameter definition whose identifier is used as the value of `variable` in an EventAssignment must have a value of "`false`" for its `constant` field. (References: L2V1 Section 4.10.5; L2V2 Section 4.14.)

F Method for assessing whether an SBML model is overdetermined

(Example contributed by Sarah M. Keating, University of Hertfordshire STRI, Hatfield, UK.)

As explained in Section 4.11.6, an SBML model must not be overdetermined. It is possible to use purely static analysis to assess this for the system of equations implied by a model, by constructing a bipartite graph of the model's variables and equations and then searching for a maximal matching Chartrand (1977). A efficient algorithm for finding a maximal matching is described by Hopcroft and Karp (1973). In this appendix, we provide a concrete application to SBML of the general approach described in Section 4.11.6. The approach is defined in terms of the ordinary differential equations (ODEs) implied by an SBML model; it should be understood that this use of ODEs has no implication about the framework actually used to simulate the model.

F.1 Definition of the method

First, we treat both assignment rules and formulas in KineticLaw objects as SBML-style algebraic equations. (Both are essentially assignment statements, and assignment statements can be trivially converted to algebraic equations with zero on the left-hand side.) We also assume that an ODE is constructed for each species determined by one or more Reaction's KineticLaw `math` expressions. Finally, we assume that the model has already been determined to be valid in all other respects (e.g., there are no undefined variables in the equations), and what remains is to evaluate whether it is overdetermined.

We construct the bipartite graph for a given SBML model as follows:

1. For each of the following in the model, create one vertex representing an equation:
   (a) Every Species object having `boundaryCondition`="`false`", `constant`="`false`", and which is referenced as a reactant or product in one or more Reaction objects containing KineticLaw objects
   (b) Every AssignmentRule object
   (c) Every RateRule object
   (d) Every AlgebraicRule object
   (e) Every KineticLaw object
2. For each of the following in the model, create one vertex representing a variable:
   (a) Every Species object having `constant`="`false`"
   (b) Every Compartment object having `constant`="`false`"
   (c) Every global Parameter having `constant`="`false`"
   (d) Every Reaction object
3. For each of the following, create one edge:
   (a) Every vertex created in step 2(a) to that species' equation vertex created in step 1(a)
   (b) Every vertex created in step 1(b) to the particular vertex created in steps 2(a)–2(d) that represents the variable referenced by the `variable` field of the rule
   (c) Every vertex created in step 1(c) to the particular vertex created in steps 2(a)–2(d) that represents the variable referenced by the `variable` field of the rule
   (d) Every vertex created in step 1(e) to the particular vertex created in step 2(d) that is the Reaction object containing that particular KineticLaw object
   (e) Every vertex created in steps 2(a)–2(d) representing an identifier appearing as the content of a MathML `ci` element within an expression of an AssignmentRule, to the vertex for that particular AssignmentRule created in step 1(b)
   (f) Every vertex created in steps 2(a)–2(d) representing an identifier appearing as the content of a MathML `ci` element within an expression of an AlgebraicRule, to the vertex for that particular AlgebraicRule created in step 1(d)

(g) Every vertex created in steps 2(a)–2(c) representing an identifier appearing as the content of a MathML `ci` element within an expression of a KineticLaw, to the vertex for that particular KineticLaw created in step 1(e)

F.2 Example application of the method

What follows is an example of applying the method above to the SBML model shown below:

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns="http://www.sbml.org/sbml/level2" level="2" version="2">
  <model id="example">
    <listOfCompartments>
      <compartment id="C" size="1"/>
    </listOfCompartments>
    <listOfSpecies>
      <species id="S1" compartment="C" initialConcentration="1"/>
      <species id="S2" compartment="C" initialConcentration="0"/>
    </listOfSpecies>
    <listOfRules>
      <algebraicRule>
        <math xmlns="http://www.w3.org/1998/Math/MathML">
          <apply>
            <plus/> <ci> S1 </ci> <ci> S2 </ci>
          </apply>
        </math>
      </algebraicRule>
      </listOfRules>
    <listOfReactions>
      <reaction id="R">
        <listOfReactants>
          <speciesReference species="S1"/>
        </listOfReactants>
        <listOfProducts>
          <speciesReference species="S2"/>
        </listOfProducts>
        <kineticLaw>
          <math xmlns="http://www.w3.org/1998/Math/MathML">
            <apply>
              <times/> <ci> k1 </ci> <ci> S1 </ci>
            </apply>
          </math>
          <listOfParameters>
            <parameter id="k1" value="0.1"/>
          </listOfParameters>
        </kineticLaw>
      </reaction>
    </listOfReactions>
  </model>
</sbml>
```

For the model above, we create *equation* vertices as follows:

1. [Corresponding to step 1(a) in Section F.1.] *Every Species object having* `boundaryCondition`=*"*`false`*", *`constant`=*"*`false`*", *and which is referenced as a reactant or product in one or more Reaction objects containing KineticLaw objects.* This generates two vertices, for "`S1`" and "`S2`".
2. [Corresponding to step 1(b) in Section F.1.] *Every AlgebraicRule object.* This generates one vertex, for the model's lone algebraic rule (call it "`rule`").
3. [Corresponding to step 1(e) in Section F.1.] *Every KineticLaw object.* This generates one vertex, for the lone kinetic law in the model (call it "`law`").

We create *variable* vertices for the following:

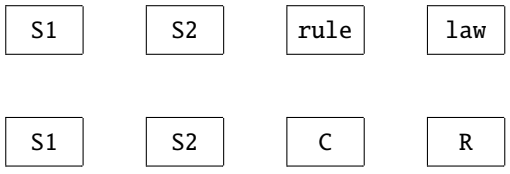
1. [Corresponding to step 2(a) in Section F.1.] *Every Species object having* `constant`=*"*`false`*".* This generates two vertices, for "`S1`" and "`S2`".

2. [Corresponding to step 2(b) in Section F.1.] *Every* Compartment *object having* `constant`="`false`". This generates one vertex, for "`C`".

3. [Corresponding to step 2(d) in Section F.1.] *Every* Reaction *object.* This generates one vertex, for "`R`".

Note that it is not necessary to include parameters declared within KineticLaw objects because they are local to a particular reaction and cannot be affected by rules. With the steps above, we have the following set of graph nodes:

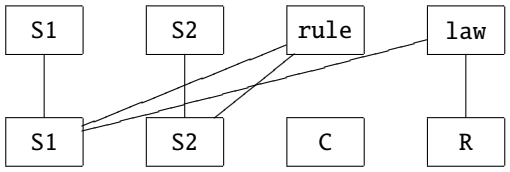
Vertices for equations



Vertices for variables

Next, we create edges following the procedure described above. Doing so results in the following graph:

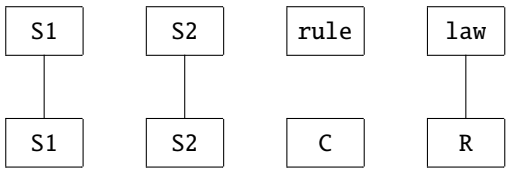
Vertices for equations



Vertices for variables

The algorithm of Hopcroft and Karp (1973) can now be applied to search for a maximal matching of the bipartite graph. A maximal matching is a graph in which each vertex is connected to at most one other vertex and the maximum possible number of connections have been made. Doing so here results in the following:

Vertices for equations



Vertices for variables

If the maximal matching of the bipartite graph leaves any equation vertex unconnected, then the model is considered overdetermined. That is the case for the example shown here, because the equation vertex for "`rule`" is unconnected in the maximal matching.

G Mathematical consequences of the `fast` attribute on Reaction

(Appendix contributed by James C. Schaff, University of Connecticut Health Center, Connecticut, U.S.A.)

Section 4.13.1 described the `fast` flag available on Reaction. In this appendix, we discuss the principles involved in interpreting this attribute in the context of a simple biochemical reaction model. The derivation presented here is not fully rigorous and this section is not considered normative; achieving a higher level of rigor would require considerably more background exposition and a much longer appendix. Nevertheless, we hope this section is sufficient to answer unambiguously the question "How should a system of reactions be treated if some of the reactions have `fast`=`true`?"

G.1 Identification of "fast" reactions

First, it is worth noting that the identification of so-called *fast* reactions is actually a modeling issue, not an SBML representation issue. The notion of fast reactions is the following. A system may be decomposable into two sets of reactions, where one set may have characteristic times that are much faster than the other time scales in the system. An approximation that is sometimes useful is to assume that the fast reactions have kinetics that settle infinitely fast compared to the other reactions in the system. In other words, the fast reactions are assumed to be always in equilibrium. This is called a pseudo-steady state approximation (PSSA), and is also known as a quasi-steady state approximation (QSSA). Given a case where the time-scale separation between fast and other reactions in the system is large, an accurate and efficient approach for computing the time-course of the system behavior is to treat the fast reactions as being always in equilibrium.

The key to successful application of a PSSA is that there should be a significant separation of time scales between these fast reactions and other reactions in the system. The determination of which reactions qualify as fast is up to the creator of the model, because there is currently no known general algorithm for doing so.

G.2 Simple one-compartment biochemical system model

To explain how to solve a system containing fast reactions, we use a simple model of a biochemical reaction network located in a single compartment. Let $\mathbf{x}^*$ represent a vector of all the species in the system, $\mathbf{v}^*$ a vector of the reaction rates, and $\mathbf{A}^*$ the stoichiometry matrix, with the vector dimension being $\mathbf{n}^*$. Then the system can be described using the following matrix equation:

$$\frac{d\mathbf{x}^*}{dt} = \mathbf{A}^*\mathbf{v}^*(\mathbf{x}^*)$$

This system can be optionally reduced by noting that mass conservation usually implies there are linear combinations of species quantities in the system and the value of these combinations do not change over time. Identifying these combinations is the topic of structural analysis and is described in the literature (Reder, 1988; Sauro and Ingalls, 2003). Briefly, let $\mathbf{N}$ be defined as the left null space of $\mathbf{A}^*$:

$$\mathbf{N}\mathbf{A}^* = \mathbf{0}$$

Now, premultiply the previous equation by $\mathbf{N}$ to get

$$\mathbf{N}\frac{d\mathbf{x}^*}{dt} = \mathbf{N}\mathbf{A}^*\mathbf{v}^*(\mathbf{x}^*) = \mathbf{0}$$

Thus, $\mathbf{N}$ captures the space of solutions to the equation

$$\mathbf{m}^T\left(\frac{d\mathbf{x}^*}{dt}\right) = 0$$

where $\mathbf{m}$ is a vector representing the coefficients in a mass conservation relationship, that is, combinations of species that are time-invariant. Now, let

$$r = \mathrm{rank}(\mathbf{A}^*)$$
$$n = \dim(\mathbf{x}^*)$$

Then the system has $n - r$ mass conservation relationships, each of which is a linear equation. We can use these $n - r$ linear equations to solve for $n - r$ dependent variables in terms of r independent variables and the initial masses of all species. Doing that allows us to decompose $\mathbf{x}^*$ into $n - r$ dependent variables $\mathbf{x}_d$ and r independent variables $\mathbf{x}_i$ where $\mathbf{L}$ is an $(n - r) \times r$ matrix that is derived from $\mathbf{N}$ and represents $\mathbf{x}_d$ in terms of $\mathbf{x}_i$, $\mathbf{I}$ is the $r \times r$ identity matrix, and $\mathbf{T}$ is an $n \times r$ matrix:

$$\mathbf{x}^* \equiv \begin{bmatrix} \mathbf{x}_i \\ \mathbf{x}_d \end{bmatrix} = \begin{bmatrix} \mathbf{I} \\ \mathbf{L} \end{bmatrix} \mathbf{x}_i = \mathbf{T}\mathbf{x}_i$$

Using this equation, we can define a new vector of reaction velocities $\mathbf{v}$ in terms of $\mathbf{x}_i$ only:

$$\mathbf{v}(\mathbf{x}_i) \equiv \mathbf{v}^*(\mathbf{T}\mathbf{x}_i)$$

With this $\mathbf{v}$, we can now write a reduced system by substituting terms. First we define $\mathbf{A}$ as the r independent rows of $\mathbf{A}^*$corresponding to $\mathbf{x}_i$. Then:

$$\frac{d\mathbf{x}_i}{dt} = \mathbf{A}\mathbf{v}(\mathbf{x}_i)$$

This is a set of r independent differential equations in r unknowns (i.e., an r-dimensional system). To simplify the notation slightly, let

$$\mathbf{x} \equiv \mathbf{x}_i$$

and, thus,

$$\frac{d\mathbf{x}}{dt} = \mathbf{A}\mathbf{v}(\mathbf{x})$$

G.3 Application of a PSSA to biochemical systems

Assume that we have eliminated redundant variables and equations using the mass conservation analysis above. Further assume that we have some external means of classifying some reactions in a given system as being *fast* as discussed earlier. We now need to apply this to the system under study. We begin by decomposing the vector of reaction velocities $\mathbf{v}$ according to fast and slow reactions:

$$\frac{d\mathbf{x}}{dt} = \mathbf{A}_1\mathbf{v}_f(\mathbf{x}) + \mathbf{A}_2\mathbf{v}_s(\mathbf{x})$$

We find the left null space of $\mathbf{A}_1$ (i.e., the space of solutions to $\mathbf{m}^T[d\mathbf{x}/dt] = 0$ on a fast time scale), and call this matrix $\mathbf{B}$:

$$\mathbf{B}\mathbf{A}_1 = \mathbf{0}$$

The matrix $\mathbf{B}$ represents the linear combination of species that do not change on a fast time scale, i.e., the slow species in the system. Now, we premultiply the equation for $d\mathbf{x}/dt$ by $\mathbf{B}$:

$$\begin{aligned} \mathbf{B}\frac{d\mathbf{x}}{dt} &= \mathbf{B}\mathbf{A}_1\mathbf{v}_f(\mathbf{x}) + \mathbf{B}\mathbf{A}_2\mathbf{v}_s(\mathbf{x}) \\ &= \mathbf{B}\mathbf{A}_2\mathbf{v}_s(\mathbf{x}) \end{aligned}$$

where the second line follows from the fact that $\mathbf{B}\mathbf{A}_1 = \mathbf{0}$. The above is an ordinary differential equation in terms of only the slow dynamics. The remaining fast dynamics are handled by applying the pseudo-steady state approximation, with fast transients assumed to have settled with respect to the slow time scale. This produces a system of nonlinear algebraic equations:

$$\mathbf{A}_1\mathbf{v}_f = \mathbf{0}$$

The last two equations form the system of equations resulting from the application of the PSSA. If $r_1 = \text{rank}(\mathbf{A}_1)$ and $r = \text{rank}(\mathbf{A})$, then there will be r_1 degrees of freedom that will be determined by solving an algebraic system (the equation $\mathbf{A}_1\mathbf{v}_f = \mathbf{0}$ above), and there will be $r - r_1$ degrees of freedom that will be determined by ordinary differential equations (the equation for $\mathbf{B}\,d\mathbf{x}/dt$).

H Processing and validating `notes` content

In Section 3.3.2, we discussed the **notes** field defined on *Sbase* and how it can contain a number of possible XHTML elements. In this appendix, we describe a general procedure for how application software can process such content. We concentrate on the common case of an SBML-reading application that needs to take the contents and pass it to an XHTML display and/or editing function obtained from a third-party API library. The content of the **notes** may not be a complete XHTML document, so the application will have to perform some processing before handing it to the XHTML editor or validator. How should this be done?

Based on the three forms of **notes** content described in Section 3.3.2, there are only three cases possible. Here we give an example approach for handling them, although the actual implementation details will differ depending on various factors such as the requirements of the software libraries being used. This example approach would be performed for each **notes** to be viewed or edited:

Step 1. If the XHTML viewing/editing function requires a fully compliant XML document, the SBML application could create a temporary data object containing an appropriate XML declaration and a DOCTYPE declaration; otherwise, the XML data object can be initially blank.

Step 2. The application should look at the first element inside the **notes** (or rather, the first element that is not an XML comment), and take action based on the following three possibilities:

- If the first element inside **notes** begins with `<html xhtml="http://www.w3.org/1999/xhtml">`, the application could assume that the content is a complete XHTML document and insert this into the temporary data object.
- Else, if the first element is `<body>`, the application should insert the following into the temporary data object,

  ```
  <html xhtml="http://www.w3.org/1999/xhtml">
      <head><title></title></head>
  ```

  then insert the content of the **notes**, and finally insert a closing `</html>`.
- Else, if the **notes** content begins with neither of the above elements, the application should insert the following into the temporary data object,

  ```
  <html xhtml="http://www.w3.org/1999/xhtml">
      <head><title></title></head>
      <body>
  ```

  then insert the content of the **notes**, and finally insert `</body></html>` to close the XHTML document.

The result of the above would be a temporary XML data object that the application could then pass to the XHTML viewing/editing API function.

References

Abbott, A. (1999). Alliance of US labs plans to build map of cell signalling pathways. *Nature*, 402:219–200.

Abramowitz, M. and Stegun, I. A., editors (1977). *Mathematical Fuctions: With Formulas, Graphs, and Mathematical Tables*. Dover Publications Inc.

Ausbrooks, R., Buswell, S., Carlisle, D., Dalmas, S., Devitt, S., Diaz, A., Froumentin, M., Hunter, R., Ion, P., Kohlhase, M., Miner, R., Poppelier, N., Smith, B., Soiffer, N., Sutor, R., and Watt, S. (2003). Mathematical Markup Language (MathML) Version 2.0 (second edition): W3C Recommendation 21 October 2003. Available via the World Wide Web at http://www.w3.org/TR/2003/REC-MathML2-20031021/.

Biron, P. V. and Malhotra, A. (2000). XML Schema part 2: Datatypes (W3C candidate recommendation 24 October 2000). Available via the World Wide Web at http://www.w3.org/TR/xmlschema-2/.

Bosak, J. and Bray, T. (1999). XML and the second-generation Web. *Scientific American*, 280(5):89–93.

Bray, T., D. Hollander, D., and Layman, A. (1999). Namespaces in XML. World Wide Web Consortium 14-January-1999. Available via the World Wide Web at http://www.w3.org/TR/1999/REC-xml-names-19990114/.

Bray, T., Paoli, J., Sperberg-McQueen, C. M., and Maler, E. (2000). Extensible markup language (XML) 1.0 (second edition), W3C recommendation 6-October-2000. Available via the World Wide Web at http://www.w3.org/TR/1998/REC-xml-19980210.

Bureau International des Poids et Mesures (2000). The International System of Units (SI) supplement 2000: addenda and corrigenda to the 7th edition (1998). Available via the World Wide Web at http://www.bipm.fr/pdf/si-supplement2000.pdf.

Chartrand, G. (1977). *Introductory Graph Theory*. Dover Publishing, Inc., New York.

Cuellar, A. A., Nelson, M., and Hedley, W. (2002). The CellML metadata 1.0 specification working draft—16 January 2002. Available via the World Wide Web at http://cellml.org/public/metadata/cellml_metadata_specification.html.

DCMI Usage Board (2005). DCMI Metadata Terms. Available via the World Wide Web at http://www.dublincore.org/documents/dcmi-terms/.

Dublin Core Metadata Initiative (2005). Dublin core metadata initiative. Available via the World Wide Web at http://dublincore.org/.

Eriksson, H.-E. and Penker, M. (1998). *UML Toolkit*. John Wiley & Sons, New York.

Fallside, D. C. (2000). XML Schema part 0: Primer (W3C candidate recommendation 24 October 2000). Available via the World Wide Web at http://www.w3.org/TR/xmlschema-0/.

Gillespie, D. (1977). Exact stochastic simulation of coupled chemical reactions. *J. Phys. Chem.*, 81:2340–2361.

Gilman, A. (2000). A letter to the signaling community. Alliance for Cellular Signaling, The University of Texas Southwestern Medical Center. Available via the World Wide Web at http://afcs.swmed.edu/afcs/Letter_to_community.htm.

Harold, E. R. and Means, E. S. (2001). *XML in a Nutshell*. O'Reilly & Associates.

Hedley, W. J., Nelson, M. R., Bullivant, D., Cuellar, A., Ge, Y., Grehlinger, M., Jim, K., Lett, S., Nickerson, D., Nielsen, P., and Yu, H. (2001). CellML specification. Available via the World Wide Web at http://www.cellml.org/public/specification/20010810/cellml_specification.html.

Hopcroft, J. E. and Karp, R. M. (1973). An $n^{5/2}$ algorithm for maximum matchings in bipartite graphs. *SIAM Journal on Computing*, 2(4):225–231.

Hucka, M. (2000). SCHUCS: A notation for describing model representations intended for XML encoding. Available via the World Wide Web at http://www.sbml.org/.

Hucka, M., Finney, A., Sauro, H. M., and Bolouri, H. (2001). Systems Biology Markup Language (SBML) Level 1: Structures and facilities for basic model definitions. Available via the World Wide Web at http://www.sbml.org.

Hucka, M., Finney, A., Sauro, H. M., Bolouri, H., Doyle, J. C., Kitano, H., Arkin, A. P., Bornstein, B. J., Bray, D., Cornish-Bowden, A., Cuellar, A. A., Dronov, S., Gilles, E. D., Ginkel, M., Gor, V., Goryanin, I. I., Hedley, W. J., Hodgman, T. C., Hofmeyr, J.-H., Hunter, P. J., Juty, N. S., Kasberger, J. L., Kremling, A., Kummer, U., Le Novère, N., Loew, L. M., Lucio, D., Mendes, P., Minch, E., Mjolsness, E. D., Nakayama, Y., Nelson, M. R., Nielsen, P. F., Sakurada, T., Schaff, J. C., Shapiro, B. E., Shimizu, T. S., Spence, H. D., Stelling, J., Takahashi, K., Tomita, M., Wagner, J., and Wang, J. (2003). The Systems Biology Markup Language (SBML): A medium for representation and exchange of biochemical network models. *Bioinformatics*, 19(4):524–531.

Iannella, R. (2001). Representing vCard objects in RDF/XML. Available via the World Wide Web at http://www.w3.org/TR/vcard-rdf.

Jacobs, I. (2004). World wide web consortium process document. Available via the World Wide Web at http://www.w3.org/2004/02/Process-20040205/.

Kokkelink, S. and Schwänzl, R. (2002). Expressing qualified Dublin Core in RDF/XML. Available via the World Wide Web at http://dublincore.org/documents/dcq-rdf-xml/index.shtml.

Lassila, O. and Swick, R. (1999). Resource description framework (RDF) model and syntax specification. Available via the World Wide Web at http://www.w3.org/TR/REC-rdf-syntax/.

Le Novère, N., Finney, A., Hucka, M., Bhalla, U., Campagne, F., Collado-Vides, J., Crampin, E. J., Halstead, M., Klipp, E., Mendes, P., Nielsen, P., Sauro, H., Shapiro, B., Snoep, J. L., Spence, H. D., and Wanner, B. L. (2005). Minimum information requested in the annotation of biochemical models (MIRIAM). *Nature Biotechnology*, 23:1509–1515.

Oestereich, B. (1999). *Developing Software with UML: Object-Oriented Analysis and Design in Practice*. Addison-Wesley Publishing Company.

Pemberton, S., Austin, D., Axelsson, J., Celik, T., Dominiak, D., Elenbaas, H., Epperson, B., Ishikawa, M., Matsui, S., McCarron, S., Navarro, Peruvemba, S., Relyea, R., Schnitzenbaumer, S., and Stark, P. (2002). XHTML™ 1.0 the Extensible HyperText Markup Language (second edition): W3C Recommendation 26 January 2000, revised 1 August 2002. Available via the World Wide Web at http://www.w3.org/TR/xhtml1/.

Popel, A. and Winslow, R. L. (1998). A letter from the directors... Center for Computational Medicine & Biology, Johns Hopkins School of Medicine, Johns Hopkins University. Available via the World Wide Web at http://www.bme.jhu.edu/ccmb/ccmbletter.html.

Powell, A. and Johnston, P. (2003). Guidelines for implementing Dublin Core in XML. Available via the World Wide Web at http://dublincore.org/documents/dc-xml-guidelines/index.shtml.

Reder, C. (1988). Metabolic Control Theory: a structural approach. *Journal of Theoretical Biology*, 135:175–201.

Sauro, H. M. and Ingalls, B. (2003). Conservation analysis in biochemical networks: Computational issues for software writers. Available via the World Wide Web at http://www.math.uwaterloo.ca/~bingalls/Pubs/conservation.pdf.

Smaglik, P. (2000). For my next trick... *Nature*, 407:828–829.

Thompson, H. S., Beech, D., Maloney, M., and Mendelsohn, N. (2000). XML Schema part 1: Structures (W3C candidate recommendation 24 October 2000). Available via the World Wide Web at http://www.w3.org/TR/xmlschema-1/.

Unicode Consortium (1996). *The Unicode Standard, Version 2.0*. Addison-Wesley Developers Press, Reading, Massachusetts.

W3C (2000a). Naming and addressing: URIs, URLs, ... Available via the World Wide Web at http://www.w3.org/Addressing/.

W3C (2000b). W3C's math home page. Available via the World Wide Web at http://www.w3.org/Math/.

W3C (2004a). Rdf/xml syntax specification (revised). Available via the World Wide Web at http://www.w3.org/TR/rdf-syntax-grammar/.

W3C (2004b). Resource description framework (RDF). Available via the World Wide Web at http://www.w3.org/RDF/.

Walmsley, P. (2002). *Definitive XML Schema*. Prentice Hall PTR, Upper Saddle River, NJ 07458, USA.

Wilkinson, D. J. (2006). *Stochastic Modelling for Systems Biology*. Chapman & Hall/CRC.

Wolf, M. and Wicksteed, C. (1998). Date and time formats. Available via the World Wide Web at http://www.w3.org/TR/NOTE-datetime.

Zwillinger, D., editor (1996). *Standard Mathematical Tables and Formulae*. CRC Press LLC, 30th edition.