Systems Biology Markup Language (SBML) Level 1: Structures and Facilities for Basic Model Definitions

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1 Introduction

We present the **S**ystems **B**iology **M**arkup **L**anguage (SBML) Level 1, Version 2, a description language for simulations in systems biology. SBML is oriented towards representing biochemical networks common in research on a number of topics, including cell signaling pathways, metabolic pathways, biochemical reactions, gene regulation, and many others. A recent conference (Kitano, 2001) highlights the range of topics that fall under the umbrella of *systems biology* and are in the domain of the description language defined here. Many contemporary research initiatives demonstrate the growing popularity of this kind of multidisciplinary work (e.g., Abbott, 1999; Gilman, 2000; Popel and Winslow, 1998; Smaglik, 2000a,b).

SBML Level 1 is the result of merging modeling-language features from the following simulation systems: *BioSpice* (Arkin, 2001), *DBSolve* (Goryanin, 2001; Goryanin et al., 1999), *E-Cell* (Tomita et al., 1999, 2001), *Gepasi* (Mendes, 1997, 2001), *Jarnac* (Sauro, 2000; Sauro and Fell, 1991), *StochSim* (Bray et al., 2001; Morton-Firth and Bray, 1998), and *Virtual Cell* (Schaff et al., 2000, 2001). SBML was developed with the help of the authors of these packages. As a result of being based on actual working simulation software, it is a practical and functional description language. Our goal in creating it has been to provide an open standard that will enable simulation software to exchange models, something that is currently impossible because there is no standard model exchange language. We expect SBML models to be encoded using XML, the eXtensible Markup Language (Bosak and Bray, 1999; Bray et al., 1998), and we include here an XML Schema that defines SBML Level 1.

1.1 Summary of Changes in Version 2 of SBML Level 1

This document describes Version 2 of SBML Level 1. Changes with respect to Version 1 of the SBML specification are indicated in red. Most changes in this document are simply textual changes made in an attempt to clarify the language of the specification and to correct typographical and other small errors. The following list is an overview of the more notable changes:

- SBML Level 1 Version 2 deprecates the spelling *specie* in favor of *species*.
- There are additional names in the list of reserved XML Namespaces in Table 1. (Section 3.2.)
- The specified syntax of `SName` now corresponds to the intended syntax (Section 3.3), and the syntax is expressed using the variant of EBNF used by the XML 1.0 specification.
- Table 2 on page 7 no longer lists "`umar`" twice.
- The default scale of units is now correctly defined as zero. (Section 4.2.)
- Compartments are now optional (Section 4.3); however, each species in a model is still required to be located in a compartment, which means that for all meaningful models, compartments are mandatory.
- Species are now optional. (Section 4.4.)
- The `value` of a parameter is now optional. (Section 4.5.)
- The section on rules has greater detail on the intended use and limitations of rules. (Section 4.6.)
- Reactions are optional, and lists of reactants and products in a reaction may be empty. (Section 4.7.)
- The values of attributes on `speciesReference` are required to be positive numbers; also, Section 4.7.1 is now more explicit about the intended use of `speciesReference`.
- The example given in Section 5.3 is a different, corrected example.
- The rate laws in Appendix C are more correct and consistent. In addition, the law `massr` is no longer defined because its definition posed parsing problems and it was redundant. The law `massi` is now called `mass`. SBML Level 1 Version 1's `massr` is equivalent to "$\text{mass}[S_i, k_1] - \text{mass}[P_j, k_2]$".
- The `version` attribute of the `sbml` element now has a value of "`2`" instead of "`1`".

In addition, we have established the web site `http://www.sbml.org` as the home site for SBML, and all documents, schemas and software are available from there.

1.2 Scope and Limitations

SBML Level 1 is meant to support non-spatial biochemical models and the kinds of operations that are possible in existing analysis/simulation tools. A number of potentially desirable features have been intentionally omitted from the language definition. Future software tools will undoubtedly require the evolution of SBML; we expect that subsequent releases of SBML (termed *levels*) will add additional structures and facilities currently missing from Level 1, once the simulation community gains experience with the current language definition. In Section 6.1, we discuss extensions that will likely be included in SBML Level 2 or 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.

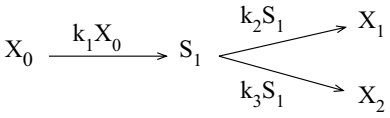
1.3 Notational Conventions

SBML is intended to be a common XML-based format for encoding systems biology models in a simple form that software tools can use as an exchange format. However, for easier communication to human readers, 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. 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 visual notation is implementation-neutral: the defined structures can be encoded in any concrete implementation language—not just XML, but C or Java as well. Third, UML is a de facto industry standard that is documented in many sources. Readers are therefore more likely to be familiar with it than other notations.

Our notation and our approach for mapping UML to XML Schemas is explained in a separate document (Hucka, 2000). A summary of the essential points is presented in Appendix A, and examples throughout this document illustrate the approach. We also follow certain naming and typographical conventions throughout this document. Specifically, the names of data structure attributes or fields begin with a lowercase letter, and the names of data structures and types begin with an uppercase letter. Keywords (names of types, XML elements, etc.) are written in a typewriter-style font; for example, `Compartment` is a type name and `compartment` is a field name. Likewise, literal XML examples are also written in a typewriter-style font.

2 Overview of SBML

The example on the right is a simple, hypothetical network of biochemical reactions that can be represented in SBML. Broken down into its constituents, this model contains a number of components: reactant species, product species, reactions, rate laws, and parameters in the rate laws.



To analyze or simulate this network, additional components must be made explicit, including compartments for the species, and units on the various quantities. The top level of an SBML model definition simply consists of lists of these components:

beginning of model definition
list of unit definitions
list of compartments
list of species
list of parameters
list of rules
list of reactions
end of model definition

The meaning of each component is as follows:

Unit definition: A name for a unit used in the expression of quantities in a model. Units may be supplied in a number of contexts in an SBML model, and it is convenient to have a facility for both setting default units and for allowing combinations of units to be given abbreviated names.

Compartment: A container of finite volume for substances. In SBML Level 1, a compartment is primarily a topological structure with a volume but no geometric qualities.

Species: A substance or entity that takes part in a reaction. Some example species are ions such as Ca^{2+} and molecules such as glucose or ATP. The primary qualities associated with a species in SBML Level 1 are its initial amount and the compartment in which it is located.

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 rate laws describing how quickly they take place.

Parameter: A quantity that has a symbolic name. SBML Level 1 provides the ability to define parameters that are global to a model as well as parameters that are local to a single reaction.

Rule: In SBML, a mathematical expression that is added to the differential equations constructed from the set of reactions and can be used to set parameter values, establish constraints between quantities, etc.

A software package can read in a model expressed in SBML and translate it into its own internal format for model analysis. For instance, a package might provide the ability to simulate a model by constructing a set of differential equations representing the network and then performing numerical integration on the equations to explore the model's dynamic behavior.

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 data structures determine how the resulting model is encoded in XML.

In the sections that follow, the various constructs in SBML and their uses are described in detail. Section 3 first introduces a few basic structures that are used throughout SBML, then Section 4 provides details on each of the main components of SBML. Section 5 provides several complete examples of models encoded in XML using SBML.

3 Preliminary Definitions

This section covers certain constructs that are used repeatedly in the rest of SBML and are useful to discuss before diving into the details of the components provided in SBML.

3.1 Type `SBase`

Each of the main components composing an SBML model definition has a specific data type that is derived directly or indirectly from a single abstract type called `SBase`. This inheritance hierarchy is depicted in Figure 1 on the next page.

The type `SBase` is designed to allow a modeler or a software package to attach information to each component in an SBML model. The definition of `SBase` is presented in Figure 2 on the following page. `SBase` contains two fields, both of which are optional: `notes` and `annotation`. The field `notes` is a container for XHTML content. It is intended for recording optional user-visible annotations. Every data object derived directly or indirectly from type `SBase` can have a separate value for `notes`, allowing users considerable freedom for annotating their models. The second field, `annotation`, is provided for software-generated annotations. It is a container for arbitrary data (XML type `any`) and is intended to store information not intended for human viewing. As with the user-visible `notes` field, every data object can have its own `annotation` value.

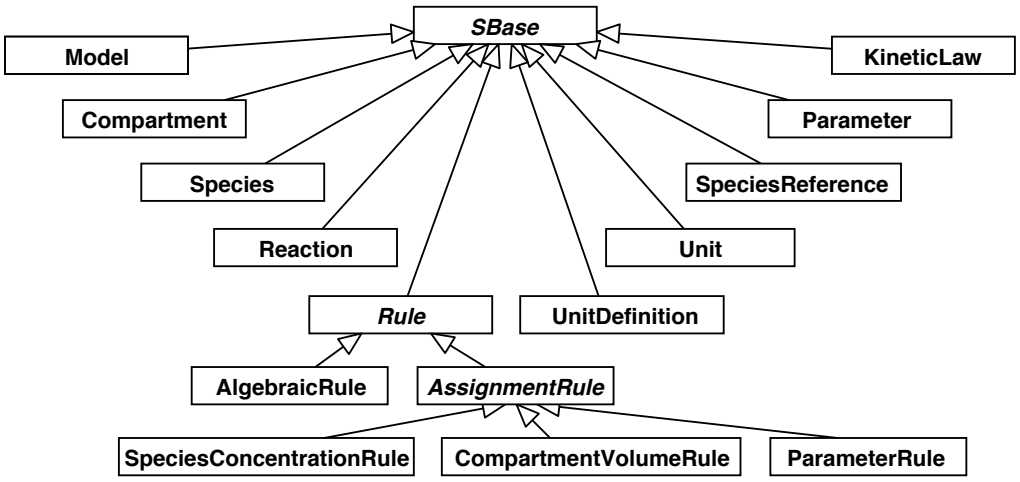


Figure 1: *A UML diagram of the inheritance hierarchy of major data types in SBML. Open arrows indicate inheritance, pointing from inheritors to their parents (Eriksson and Penker, 1998; Oestereich, 1999).*

SBase
notes : (XHTML) {minOccurs="0"}
annotation : (any) {minOccurs="0"}

Figure 2: *The definition of* `SBase`*. Text enclosed in braces next to attribute types (i.e.,* {`minOccurs="1"`}*) indicates constraints on the possible attribute values; we use XML Schema language to express constraints since we are primarily interested in the XML encoding of SBML.*

The Version 1 specification of SBML Level 1 was inconsistent about the spelling of the annotation field. It named the field `annotation` in Figure 2, but used `annotations` (i.e., plural) in the discussions throughout the document. SBML Level 1 Version 2 clarifies that `annotation` (singular) is the intended name.

In other type definitions presented below, we follow the UML convention of eliding the attributes derived from a parent type such as `SBase`. It should be kept in mind that these attributes are always available.

3.2 Guidelines for the Use of the `annotation` Field in `SBase`

The `annotation` field in the definition of `SBase` is formally unconstrained in order that software developers may attach any information they need to different components in an SBML model. However, it is important that this facility not be misused accidentally. In particular, it is critical that information essential to a model definition is *not* stored in `annotation`. Parameter values, functional dependencies between model components, etc., should not be recorded as annotations.

Here are examples of the kinds of data that may be appropriately stored in `annotation`: (a) Information about graphical layout of model components; (b) application-specific processing instructions that do not change the essence of a model; (c) bibliographic information pertaining to a given model; and (d) identification information for cross-referencing components in a model with items in a database. (We expect to introduce an explicit scheme for recording bibliographic information and making database references in a higher level of SBML, at which time using annotations for these purposes will become unnecessary.)

Different applications may use XML Namespaces (Bray et al., 1999) to specify the intended vocabulary of a particular annotation. Here is an example of this kind of usage. Suppose that a particular application wants to annotate data structures in an SBML model definition with screen layout information and a time stamp. The application developers should choose a URI (*Universal Resource Identifier*; Harold and Means 2001; W3C 2000a) reference that uniquely identifies the vocabulary that the application will use for such annotations, and a prefix string to be used in the annotations. For illustration purposes, let us say the URI

reference is "http://www.mysim.org/ns" and the prefix is mysim. An example of an annotation might then be as follows:

```
...
<annotation xmlns:mysim="http://www.mysim.org/ns">
    <mysim:nodecolors mysim:bgcolor="green" mysim:fgcolor="white"/>
    <mysim:timestamp>2000-12-18 18:31 PST</mysim:timestamp>
</annotation>
...
```

The namespace prefix mysim is used to qualify the XML elements mysim:nodecolors and mysim:timestamp; presumably these symbols have meaning to the application. This example places the XML Namespace information on annotation itself rather than on a higher-level enclosing construct or the enclosing document level, but other placements would be valid as well (Bray et al., 1999).

The use of XML Namespaces permits multiple applications to place annotations on XML elements of a model without risking interference or element name collisions. Annotations stored by different simulation packages can therefore coexist in the same model definition. Although XML Namespace names ("http://www.mysim.org/" in the example above) must be URIs references, an XML Namespace name is *not required* to be directly usable in the sense of identifying an actual, retrieval document or resource on the Internet (Bray et al., 1999). The name is simply intended to enable unique identification of constructs, and using URIs is a common and simple way of creating a unique name string. For the convenience of developers of simulation and analysis tools, we reserve certain namespace names for use with annotations in SBML. These reserved names are listed in Table 1.

http://www.sbml.org/2001/ns/basis	http://www.sbml.org/2001/ns/jdesigner
http://www.sbml.org/2001/ns/biocharon	http://www.sbml.org/2001/ns/jigcell
http://www.sbml.org/2001/ns/bioreactor	http://www.sbml.org/2001/ns/jsim
http://www.sbml.org/2001/ns/biosketchpad	http://www.sbml.org/2001/ns/libsbml
http://www.sbml.org/2001/ns/biospice	http://www.sbml.org/2001/ns/mathsbml
http://www.sbml.org/2001/ns/cellerator	http://www.sbml.org/2001/ns/mcell
http://www.sbml.org/2001/ns/copasi	http://www.sbml.org/2001/ns/netbuilder
http://www.sbml.org/2001/ns/cytoscape	http://www.sbml.org/2001/ns/pathdb
http://www.sbml.org/2001/ns/dbsolve	http://www.sbml.org/2001/ns/promot
http://www.sbml.org/2001/ns/ecell	http://www.sbml.org/2001/ns/sbedit
http://www.sbml.org/2001/ns/gepasi	http://www.sbml.org/2001/ns/sigpath
http://www.sbml.org/2001/ns/isys	http://www.sbml.org/2001/ns/stochsim
http://www.sbml.org/2001/ns/jarnac	http://www.sbml.org/2001/ns/vcell

Table 1: *Reserved XML Namespace names in SBML Level 1 Version 2.*

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 in the context of SName and symbols in SBML.

3.3 Type SName

The type SName is used in many places in SBML for expressing names of components in a model. SName is is a data type derived from the basic XML type string, but with restrictions about the types of characters permitted and the sequence in which they may appear. Its definition is shown in Figure 3 on the following page.

The need to define a constrained data type for names stems from the fact that many existing simulation packages allow only a limited set of characters in symbol names. SBML codifies this limitation in the form of a lowest-common-denominator data type (SName), to prevent the creation of models with symbol names that might confuse some simulation software packages. This is important for facilitating model exchange between tools.

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

Figure 3: *The definition of the type SName, expressed in the variant of Extended Backus-Naur Form (EBNF) used by the XML 1.0 specification (Bray et al., 2000). The characters (and) are used for grouping, and the character * signifies "zero or more times" the immediately-preceding term.*

3.4 Component Names and Namespaces in SBML

A biochemical network model can contain a large number of named components representing different parts of a model. This leads to a problem in deciding the scope of a symbol: in what contexts does a given symbol X represent the same thing? The approaches used in existing simulation packages tend to fall into two categories that we may call global and local. The *global* approach places all symbols into a single global namespace, so that a symbol 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 rate laws. The latter approach means that a user may use the same symbol X in different rate laws and have each instance represent a different quantity. The fact that different simulation programs may use different rules for name 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 must therefore include a specific set of rules for treating symbols and namespaces.

The namespace rules in SBML Level 1 are relatively straightforward and are intended to avoid this problem with a minimum of requirements on the implementation of software tools:

- All model-level component names (compartments, species, reactions, parameters, parameter rules, and units) reside in the same global namespace. This means, for example, that a reaction and a species definition cannot both have the same name.
- Each reaction definition (see Section 4.7) establishes a private local namespace for parameter names. Within the definition of a given reaction, parameter names introduced in that reaction override (shadow) identical names in the global namespace.
- Certain names in SBML Level 1 are reserved or otherwise have special meaning. Table 2 lists these reserved names. They are comprised of predefined mathematical functions, certain operators (present and expected in the future), and rate law functions. In order to prevent name collisions, these reserved names cannot be used as names for any component of a model.

abs	cos	hillr	massr	pow	tan	ucii	umai	usii	uur
acos	exp	isouur	not	ppbr	time	ucir	umar	usir	volume
and	floor	log	or	sin	uai	ucti	umi	uuci	xor
asin	hilli	log10	ordbbr	sqr	uaii	uctr	umr	uucr	
atan	hillmmr	mass	ordbur	sqrt	ualii	uhmi	unii	uuhr	
ceil	hillmr	massi	ordubr	substance	uar	uhmr	unir	uui	

Table 2: *The reserved names in SBML Level 1.*

The set of rules above can enable software packages using either local or global namespaces to exchange SBML model definitions. In particular, software environments using local namespaces internally should be able to accept SBML model definitions without needing to change component names. Environments using a global namespace internally can perform a simple manipulation of the names of elements within reaction definitions to avoid name collisions. (An example approach for the latter would be the following: when receiving an SBML-encoded model, prefix each name inside each reaction with a string constructed from the reaction's name; when writing an SBML-encoded model, strip off the prefix.)

The namespace rules described here provide a clean transition path to future levels of SBML, when submodels are introduced (Section 6.1). 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 1'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 1 namespace rule described here, with each submodel having its own (to itself, global) namespace.

3.5 Formulas

Formulas in SBML Level 1 are expressed in text string form. They are used in the definitions of kinetic laws (Section 4.7.2) and in rules (Section 4.6). The formula strings are interpreted as expressions that evaluate to a floating-point value of type `double`. The formula strings may contain operators, function calls, symbols, and white space characters. The allowable white space characters are tab and space. Table 3 presents the precedence rules for the different entities that may appear in formula strings. All operators in formulas return `double` values.

Tokens	Operation	Class	Precedence	Associates
name	symbol reference	operand	6	n/a
(*expression*)	expression grouping	operand	6	n/a
f(...)	function call	prefix	6	left
-	negation	unary	5	right
^	power	binary	4	left
*	multiplication	binary	3	left
/	division	binary	3	left
+	addition	binary	2	left
-	subtraction	binary	2	left
,	argument delimiter	binary	1	left

Table 3: *A table of the expression operators available in SBML. In the* ***Class*** *column, "operand" implies the construct is an operand, "prefix" implies the operation is applied to the following arguments, "unary" implies there is one argument, and "binary" implies there are two arguments. The values in the* ***Precedence*** *column show how the order of different types of operation are determined. For example, the expression* $a * b + c$ *is evaluated as* $(a * b) + c$ *because the* $*$ *operator has higher precedence. The* ***Associates*** *column shows how the order of similar precedence operations is determined; for example,* $a - b + c$ *is evaluated as* $(a - b) + c$ *because the* $+$ *and* $-$ *operators are left-associative. The precedence and associativity rules are taken from the C programming language (Harbison and Steele, 1995; Kernighan and Ritchie, 1988), except for the symbol ^, which is used in C for a different purpose.*

The function call syntax consists of a function name, followed by optional white space, followed by an opening parenthesis token ('('), followed by a sequence of zero or more arguments separated by commas (with each comma optionally preceded and/or followed by zero or more white space characters), followed by a closing parenthesis (')') token. The function name must be chosen from one of the functions available in SBML. Table 6 in Appendix C lists the basic mathematical functions that are defined in SBML at this time, while Table 7 lists a large number of common rate law functions defined in SBML. The names of these predefined functions are reserved and make up the bulk of the list of names in Table 2 on the page before.

A program parsing a formula in an SBML model should assume that name tokens other than function names are names of parameters, compartments or species. When a species name occurs in a formula, it represents the concentration (i.e., *substance*/*volume*) of the species. When a compartment name occurs in a formula, it represents the volume of the compartment. The units of substance and volume are determined from the built-in `substance` and `volume` of Table 5 on page 11.

Readers may wonder why mathematical formulas in SBML are not expressed using MathML (W3C, 2000b), an XML-based mathematical formula language. Although using MathML would be more in the spirit of using XML and would in some ways be a more forward-looking choice, it would require simulation software to use fairly complex parsers to read and write the resulting SBML. Most contemporary systems biology

simulation software simply represent mathematical formulas using text strings. To keep SBML Level 1 simple and compatible with known simulation software, we chose to represent formulas as strings. This does not preclude a later level of SBML from introducing the ability to use MathML as an extension.

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 XML encodings of SBML model components, but we leave full XML examples to Section 5.

4.1 Models

The `Model` structure is the highest-level construct in an SBML data stream or document. The UML definition of `Model` is shown in Figure 4. Only one component of type `Model` is allowed per instance of an SBML document or data stream, although it does not necessarily need to represent a single biological entity.

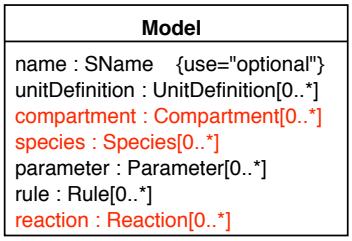


Figure 4: *The definition of `Model`. Additional fields are inherited from `SBase`.*

`Model` serves as a container for `UnitDefinition`, `Compartment`, `Species`, `Parameter`, `Rule`, and `Reaction` components. 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. See in particular Section 4.4 on `Species`.) An instance of a `Model` may also have an optional `name` field that can be used to give the model a name. The name must be a text string conforming to the syntax permitted by the `SName` data type described in Section 3.3.

In the XML encoding of an SBML model, the lists of species, compartments, unit definitions, parameters, reactions, function definitions and rules are translated into lists of XML elements that each have headings of the form `listOf_____s`, where the blank is replaced by the name of the component type (e.g., "`Reaction`"). The resulting XML data object has the form illustrated by the following skeletal model:

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns="http://www.sbml.org/sbml/level1" level="1" version="2">
  <model name="the_name_of_my_model">
    <listOfUnitDefinitions>
        ...
    </listOfUnitDefinitions>
    <listOfCompartments>
        ...
    </listOfCompartments>
    <listOfSpecies>
        ...
    </listOfSpecies>
    <listOfParameters>
        ...
    </listOfParameters>
    <listOfRules>
        ...
    </listOfRules>
    <listOfReactions>
        ...
    </listOfReactions>
  </model>
</sbml>
```

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.

4.2 Unit Definitions

Units may be supplied in a number of contexts in an SBML model. A facility for defining units is convenient to have so that combinations of units can be given abbreviated names. This is the motivation behind the `UnitDefinition` data structure, whose definition is shown in Figure 5.

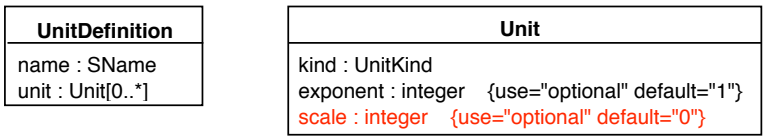


Figure 5: *The definition of `UnitDefinition`.*

A unit definition consists of a `name` field of type `SName` and an optional list of structures of type `Unit`. The approach to defining units in SBML is compositional; for example, *meter* $second^{-2}$ is constructed by combining a `Unit`-type element representing *meter* with a `Unit`-type element representing $second^{-2}$. The `Unit` structure has one required attribute, `kind`, whose value must be a name taken from the list of units in Table 4. The optional `exponent` field on `Unit` represents an exponent on the unit. Its default value is "`1`" (one). In the example just mentioned, $second^{-2}$ is obtained by using `kind="second"` and `exponent="-2"`. Finally, a `Unit` structure also has an optional `scale` field; its value must be an integer exponent on a power of ten multiplier used to set the scale of the unit. For example, a unit that has a `kind` value of "`gram`" and a `scale` value of "`-3`" signifies $10^{-3} * gram$, or milligrams. The default value of `scale` is zero, because $10^0 = 1$.

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

Table 4: *The possible values of `kind` in a `UnitKind` structure. All are names of base or derived SI units, except for "`dimensionless`" and "`item`", which are SBML additions important for handling certain common cases. "`Dimensionless`" is intended for cases where a quantity does not have units, and "`item`" is needed in certain contexts to express such things as "N items" (e.g., "100 molecules"). Although "`Celsius`" should be capitalized, for simplicity SBML requires that all unit names be treated in a case-insensitive manner. Also, note that the gram and liter/litre are not strictly part of SI (Bureau International des Poids et Mesures, 2000); however, they are so commonly used in SBML's areas of application that they are included as predefined unit names. (The standard SI unit of mass is in fact the kilogram, and volume is defined in terms of cubic meters.)*

Unit combinations are constructed by listing several `Unit` structures inside a `UnitDefinition`-type structure. The following example illustrates the definition of an abbreviation named "`mmls`" for the units *mmol* l^{-1} s^{-1}:

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

Name	Allowable Units	Default Units
`substance`	moles *or* number of molecules	moles
`volume`	liters	liters
`time`	seconds	seconds

Table 5: *SBML's built-in quantities. Each of these units has a default* `scale` *value of* `0`.

There are three special unit names in SBML, listed in Table 5, corresponding to the three types of quantities that play roles in biochemical reactions: amount of substance, volume and time. SBML defines default units for these quantities, all with a default `scale` value of `0`. The various components of a model, such as parameters, can use only the predefined units from Table 4, new units defined in unit definitions, or the three predefined names "`substance`", "`time`", and "`volume`" from Table 5. The latter usage signifies that the units to be used should be the designated defaults.

A model may change the default scales by reassigning the special unit names "`substance`", "`time`", and "`volume`" in a unit definition. This takes advantage of the `UnitDefinition` structure's facility for defining scales on units. The following example changes the default units of volume to be milliliters:

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

If the definition above appeared in a model, the volume scale on all components that did not explicitly use different units would be changed to milliliters.

4.3 Compartments

A *compartment* in SBML represents a bounded volume in which species are located. Compartments do not necessarily have to correspond to actual structures inside or outside of a cell, although models are often designed that way. The definition of `Compartment` is shown in Figure 6.

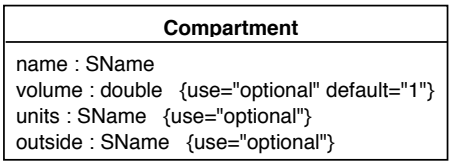


Figure 6: *The definition of* `Compartment`*. Fields inherited from* `SBase` *are omitted here but are assumed.*

`Compartment` has one required field, `name`, to give it a unique name by which other parts of an SBML model definition can refer to it. A compartment can also have an optional floating-point field called `volume` representing the total volume of the compartment. This enables concentrations of species to be calculated in the absence of spatial geometry information. The `volume` attribute defaults to a value of "`1`" (one). The units of volume may be explicitly set using the optional field `units`. The value of this attribute must be one of the following: a predefined unit name from Table 4, the term "`volume`" (which, if used, signifies that the default units of volume should be used—see Section 4.2), or the name of a unit defined by a unit definition in the `Model`. If absent, as in the example above, the units default to the value set by the built-in "`volume`".

The optional field `outside` of type `SName` can be used to express containment relationships between compartments. If present, the value of `outside` for a given compartment must be the name of another compartment

enclosing it, or in other words, the compartment that 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). 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 1 do not have any implied spatial relationships between each other.

In an XML data stream containing an SBML model, compartments are listed inside an XML element called `listOfCompartments` within a `Model`-type data structure. (See the discussion of `Model` in Section 4.1.) The following example illustrates two compartments in an abbreviated SBML example of a model definition:

```
<model>
    ...
    <listOfCompartments>
        <compartment name="cytosol" volume="2.5"/>
        <compartment name="mitochondria" volume="0.3"/>
    </listOfCompartments>
    ...
</model>
```

The following is an example of using `outside` to model a cell membrane. To express that a compartment named 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 name="A"/>
        <compartment name="M" outside="A"/>
        <compartment name="B" outside="M"/>
    </listOfCompartments>
    ...
</model>
```

4.4 Species

The term *species* refers to entities that take part in reactions. These include simple ions (e.g., protons, calcium), simple molecules (e.g., glucose, ATP), and large molecules (e.g., RNA, polysaccharides, and proteins). The `Species` data structure is intended to represent these entities. Its definition is shown in Figure 7.

Species
name : SName
compartment : SName
initialAmount : double
units : SName {use="optional"}
boundaryCondition : boolean {use="optional" default="false"}
charge : integer {use="optional"}

Figure 7: *The definition of `Species`. As usual, fields inherited from `SBase` are omitted here but are assumed.*

`Species` has a required `name` field of type `SName`. The required field `compartment`, also of type `SName`, is used to identify the compartment in which the species is located. The field `initialAmount`, of type `double`, is used to set the initial amount of the species in the named compartment. The units of this quantity may be set explicitly using the optional field `units`. The value of `units` must be chosen from one of the following possibilities: a predefined unit name from Table 4, the term "`substance`" (which, if present, signifies that the default units of quantity should be used—see Section 4.2), or a new unit name defined by a unit definition in the enclosing `Model`. If absent, the units default to the value set by the built-in "`substance`".

The optional boolean field `boundaryCondition` determines whether the amount of the species is fixed or variable over the course of a simulation. The value of `boundaryCondition` defaults to "`false`", indicating that by default, the amount is not fixed. If the amount of a species is defined as being fixed, it implies that some external mechanism maintains a constant quantity in the compartment throughout the course of a reaction. (The term *boundary condition* alludes to the role of this constraint in a simulation.)

The optional field `charge` is an integer indicating the charge on the species (in terms of electrons, not the SI unit Coulombs). This may be useful when the species involved is a charged ion such as calcium (Ca^{2+}).

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

In SBML Level 1 Version 2, the term *specie* (used in SBML Level 1 Version 1) has been replaced with the more commonly-accepted spelling *species* throughout the specification. Models written in SBML Level 1 Version 2 format should use the new spelling. However, for backwards compatibility, software packages intended to be conformant with SBML Level 1 Version 2 should accept *both* spellings on input for all elements and attributes where the term occurs. Beginning with SBML Level 2, the *specie* spelling will be removed entirely and only *species* will be used.

Finally, note that the definition of `Species` in SBML requires a species in a model to be located within a compartment. This means that at least one compartment must be defined in an SBML model that defines any species. The only exception to this is the case of degenerate models that have no species or reactions.

4.5 Parameters

A `Parameter` structure is used to associate a name with a floating-point value so that the symbol can be used in formulas in place of the value. The definition of `Parameter` is shown in Figure 8.

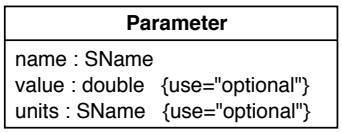


Figure 8: *The definition of* `Parameter`.

The `Parameter` structure has one required field, `name`, representing the parameter's name in the model. The optional field `value` determines the value (of type `double`) assigned to the symbol. The units of the parameter `value` are specified by the field `units`. The value assigned to `units` must be chosen from one of the following possibilities: one of the base unit names from Table 4 on page 10; one of the three names "`substance`", "`time`", or "`volume`" (see Table 5); or the name of a new unit defined in the list of unit definitions in the enclosing `Model` structure.

Parameters can be defined in two places in SBML: in lists of parameters defined at the top level in a `Model`-type structure (in the `listOfParameters` described in Section 4.1), and within individual reaction definitions (as described in Section 4.7). 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 names. (See Section 3.4 for further details.)

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

```
<model>
    ...
    <listOfSpecies>
        ...
    </listOfSpecies>
    <listOfParameters>
        <parameter name="Km1" value="2.3" units="second"/>
        <parameter name="Km2" value="10.7" units="second"/>
    </listOfParameters>
    <listOfReactions>
        ...
    </listOfReactions>
    ...
</model>
```

An example of a full model that uses parameters is presented in Section 5.3.

4.6 Rules

In SBML, *rules* provide a way to create constraints on variables for cases in which the constraints cannot be expressed using reactions (Section 4.7) nor the assignment of an initial value to a component in a model. There are two orthogonal dimensions by which rules can be described. First, there are three different possible functional forms, corresponding to the following three general cases (where x is a variable, f is some arbitrary function, and W is a vector of parameters and variables that may include x):

(Algebraic rule)	left-hand side is zero:	$0 = f(W)$
(Scalar rule)	left-hand side is a scalar:	$x = f(W)$
(Rate rule)	left-hand side is a rate-of-change:	$dx/dt = f(W)$

The second dimension concerns the role of variable x in the equations above: x can be the name of a compartment (to set its volume), the name of a species (to set its concentration), or a parameter name (to set its value).

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

- Scalar rules can simply be evaluated to calculate intermediate values for use in numerical methods.
- Some simulators do not contain numerical solvers capable of solving unconstrained algebraic equations.
- Those simulators that *can* solve algebraic equations normally make a distinction between the different categories listed above; therefore, it is important to distinguish them also in a model definition.
- Some specialized numeric analyses of models may only be applicable to models that do not contain algebraic rules; therefore, it is important to indicate the presence of such rules in a model.

The approach taken to covering these cases in SBML is to define an abstract `Rule` structure that contains just one field, `formula`, to hold the right-hand side expression, then to derive subtypes of `Rule` that add fields to cover the various cases above. Figure 9 on the next page gives the definitions of `Rule` and the subtypes derived from it. The figure shows that `AlgebraicRule` is defined directly from `Rule`, whereas `CompartmentVolumeRule`, `SpeciesConcentrationRule`, and `ParameterRule` are all derived from an intermediate abstract structure called `AssignmentRule`.

The `type` field introduced in `AssignmentRule` is an enumeration of type `RuleType` that determines whether a rule falls into the scalar or rate categories in the list of cases above. In SBML Level 1, the enumeration has two possible values: "`scalar`" and "`rate`". The former means that the expression has a scalar value on the left-hand side [i.e., $x = f(W)$, as in case 2 in the list above]; the latter means that the expression has a rate of change differential on the left-hand side [i.e., $dx/dt = f(X)$, as in case 3 in the list above]. Future releases of SBML may add to the possible values of `RuleType`.

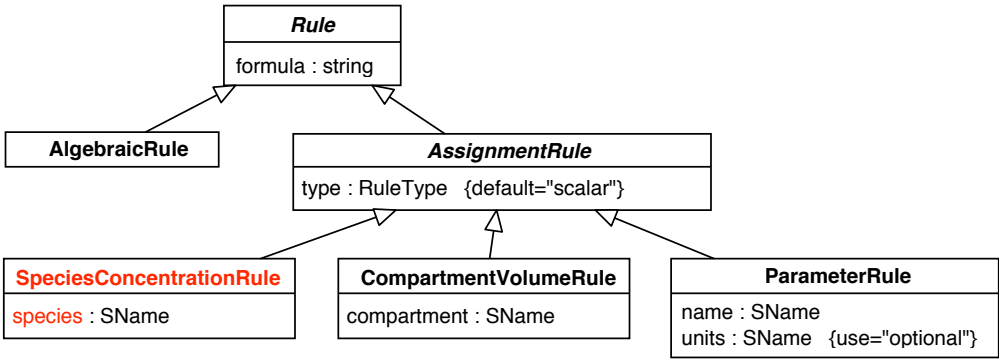


Figure 9: *The definition of* `Rule` *and derived types.*

4.6.1 `AlgebraicRule`

The rule type `AlgebraicRule` is used to express equations whose left-hand sides are zero. `AlgebraicRule` does not add any fields to the basic `Rule`; its role is simply to distinguish this case from the other cases.

4.6.2 `SpeciesConcentrationRule`

The `SpeciesConcentrationRule` structure adds one field, `species`, to the basic `AssignmentRule` type. The field `species` has type `SName` and is used to identify the species affected by the rule. The effect of the rule depends on the value of `type`: if the value is "`scalar`", the rule sets the referenced species' concentration to the value determined by the formula; if the value is "`rate`", the rule sets the rate of change of the species' concentration to the value determined by the formula. The units are in terms of *substance*/*volume*, where the *substance* units are those that are declared on the referenced `Species` element, and the *volume* units are those declared on the `compartment` element that contains the `Species`.

Unless the `boundaryCondition` field of a given species is set to "`true`", that species cannot be named by both a `SpeciesConcentrationRule` structure and a `SpeciesReference` structure (see Section 4.7). This restriction simply codifies the notion that it would be a logical inconsistency to define a rule for a species whose concentration is already being altered by one or more reactions.

4.6.3 `CompartmentVolumeRule`

The `CompartmentRule` structure adds one field, `compartment`, to the basic `AssignmentRule` type. The field `compartment` has type `SName` and is used to identify the compartment affected by the assignment. The effect of the rule depends on the value of `type`: if the type is "`scalar`", the rule sets the referenced compartment's volume to the volume determined by the formula; if the type is "`rate`", the rule sets the rate of change of the compartment's volume to the volume determined by the formula. No more than one `CompartmentVolumeRule` can refer to a given compartment in an SBML model definition.

4.6.4 `ParameterRule`

The `ParameterRule` structure adds two fields, `name` and `units`, to the basic `AssignmentRule` type. The `name` attribute has type `SName` and identifies the parameter. The parameter must already exist and be defined by a `Parameter` structure in the enclosing model; in other words, `ParameterRule` does not create new symbols. The `units` field acts in the same way as in the case of the `Parameter` structure (Section 4.5). The value assigned to `units` must be chosen from one of the following possibilities: one of base unit names from table 4; one of the three names "`substance`", "`time`", or "`volume`" (see Table 5); or the name of a new unit defined in the list of unit definitions in the enclosing `model` structure.

The effect of this rule depends on the value of the `type` field in `AssignmentRule`: if the type is "`scalar`", the rule sets the referenced parameter's value to that determined by the formula in `math`; if the type is "`rate`", the rule sets the rate of change of the parameter's value to that determined by the formula.

4.6.5 Constraints on Rule Use

SBML specifically does not stipulate the form of the algorithms that can be applied to rules and reactions. For example, SBML does not specify when or how often rules should be evaluated. The constraints described by rules and kinetic rate laws are meant to apply collectively to the set of variable values for a specific time.

To prevent ambiguities and inconsistencies in an SBML model, no more than one assignment rule can be defined for a given identifier. A `scalar` rule for a given identifier overrides the initial value of that identifier; i.e., the initial value should be ignored. This does not mean that any structure declaring an identifier can be omitted if there is a `scalar` rule for that identifier. For example, there must be a `Parameter` structure for a given parameter if there is a `ParameterRule` for that parameter.

The ordering of `scalar` rules is significant: they are always evaluated in the order given in SBML. The `formula` field of a `scalar` rule structure can contain any identifier except for the following: (a) identifiers for which there exists a subsequent `scalar` rule, and (b) the identifier for which the rule is defined. These constraints are designed to eliminate algebraic loops among the scalar rules. Eliminating algebraic loops ensures that scalar rules can be evaluated any number of times in a simulation without the result of those evaluations changing.

As an example of all this, consider the following equations, in the order shown:

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

If this set of equations were interpreted as a set of scalar rules, it would be invalid because the rule for x refers to x and the rule for y refers to z before z is defined.

4.6.6 Example of Rule Use

The following is an example use of rules:

```
<model>
    ...
    <listOfRules>
        <parameterRule name="k" formula="k3/k2"/>
        <speciesConcentrationRule species="s2" formula="k * z/(1 + k)"/>
        <compartmentVolumeRule compartment="A" formula="0.10 * k4"/>
    </listOfRules>
    ...
</model>
```

4.7 Reactions

A *reaction* represents some transformation, transport or binding process, typically a chemical reaction, that can change the amount of one or more species. The `Reaction` type is defined in Figure 10.

In SBML, reactions are defined using lists of reactant species, products, and their stoichiometries, and by parameter values for separately-defined kinetic laws. These various quantities are recorded in the fields `reactant`, `product`, and `kineticLaw`. Both `reactant` and `product` are references to species implemented using lists of `SpeciesReference` structures (defined in Section 4.7.1 below). The `SpeciesReference` structure contains fields for recording the names of species and their stoichiometries. `kineticLaw` is an optional field of type `KineticLaw` (defined in Section 4.7.2 below), used to provide a mathematical formula describing the rate of the reaction.

In addition to these fields, the `Reaction` structure also has a boolean field, `reversible`, that indicates whether the reaction is reversible. The field is optional, and if left unspecified in a model, it defaults to a value of "`true`". Information about reversibility is useful in certain kinds of structural analyses such as elementary mode analysis.

The field `fast` is another boolean attribute in the `Reaction` data structure; a value of "`true`" signifies that the given reaction is a "fast" one. This may be relevant when computing equilibrium concentrations of rapidly equilibrating reactions. Simulation/analysis packages may choose to use this information to reduce

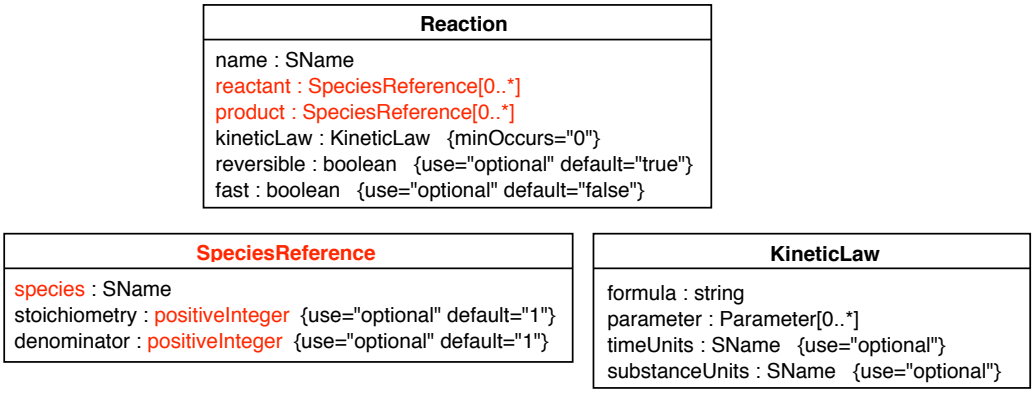


Figure 10: *The definitions of* `Reaction`*,* `KineticLaw` *and* `SpeciesReference`*.*

the number of ODEs required and thereby optimize such computations. The default value of `fast` is "`false`". (A simulator/analysis package that has no facilities for dealing with fast reactions can ignore this attribute. In theory, if the choice of which reactions are fast is correctly made, then a simulation performed with them should give the same results as a simulation performed without fast reactions. However, currently there appears to be no single unambiguous method for designating which reactions should be considered fast, and some users may designate a reaction as fast when in fact it is not. Caveat developer.)

4.7.1 `SpeciesReference`

Each unique species involved in a reaction is listed once in a model, in a list contained in the `species` field of the `Model` data structure discussed in Section 4.1. Lists of products and reactants in `Reaction` type structures refer to those species. The connection between the products and reactants in a reaction definition and the species names listed in the enclosing `Model` definition is achieved using the `SpeciesReference` type data structure defined in Figure 10.

The field `species` of type `SName` in `SpeciesReference` must refer to the name of a species defined in the enclosing `Model`-type structure. The two fields `stoichiometry` and `denominator` together set the stoichiometry value for a species in a reaction. Both take positive integers as values, and both have default values of "`1`" (one). The absolute value of the stoichiometric number is the value of `stoichiometry` divided by `denominator`, and the sign is implicit from the role of the species (i.e., positive for reactants and negative for products). The use of these separate terms allows a simulator to employ rational arithmetic on the stoichiometry matrix if it is capable of it, potentially reducing round-off errors and other problems during computations. Such computations are particularly important when working with large matrices and calculating such things as elementary modes.

The following is a simple example of a species reference in a list of reactants within a reaction named "J1":

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

4.7.2 KineticLaw

A kineticLaw structure describes the rate of the enclosing reaction. The use of a KineticLaw structure in a Reaction component is optional. (In general, there is no useful default value that can be substituted in place of a missing kinetic law, but the element is optional because certain kinds of network analysis are still possible in the absence of information on reaction kinetics.)

The field formula, of type string, expresses the rate in *substance/time* units. (Section 3.5 discusses formulas.) The optional fields substanceUnits and timeUnits determine the units of substance and time. If not set, the units are taken from the defaults defined by the built-in "substance" and "time" of Table 5 on page 11.

A KineticLaw type structure can contain zero or more Parameter structures (Section 4.5) that define symbols that can be used in the formula string. As discussed in Section 3.4, reactions introduce local namespaces for parameter names. Within a KineticLaw structure inside a reaction definition, a parameter whose name is identical to a global parameter defined in the enclosing Model-type structure takes precedence over that global parameter.

The following is an example of a Reaction structure that defines the reaction $J_1 : X_0 \longrightarrow S_1;\ k_1 X_0$. It demonstrates the use of species references and the KineticLaw structure:

```
<model>
    ...
    <listOfReactions>
        <reaction name="J1">
            <listOfReactants>
                <speciesReference species="X0" stoichiometry="1"/>
            </listOfReactants>
            <listOfProducts>
                <speciesReference species="S1" stoichiometry="1"/>
            </listOfProducts>
            <kineticLaw formula="k1*X0">
                <listOfParameters>
                    <parameter name="k1" value="0"/>
                </listOfParameters>
            </kineticLaw>
        </reaction>
    </listOfReactions>
    ...
</model>
```

5 Examples of Full Models Encoded in XML Using SBML

In this section, we present several examples of complete models encoded in XML using SBML Level 1. Our approach to translating the UML-based structure definitions presented in the previous sections is described elsewhere (Hucka, 2000). Appendix B gives the full listing of an XML Schema corresponding to SBML Level 1.

5.1 A Simple Example Application of SBML

Consider the following hypothetical branched system:

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

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

$$S_1 \xrightarrow{k_3 S_1} X_2$$

The following is the main portion of an XML document that encodes the model shown above:

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns="http://www.sbml.org/sbml/level1" level="1" version="2">
    <model name="Branch">
        <notes>
            <body xmlns="http://www.w3.org/1999/xhtml">
                <p>Simple branch system.</p>
                <p>The reaction looks like this:</p>
                <p>reaction-1:   X0 -> S1; k1*X0;</p>
                <p>reaction-2:   S1 -> X1; k2*S1;</p>
                <p>reaction-3:   S1 -> X2; k3*S1;</p>
            </body>
        </notes>
        <listOfCompartments>
            <compartment name="compartmentOne" volume="1"/>
        </listOfCompartments>
        <listOfSpecies>
            <species name="S1" initialAmount="0" compartment="compartmentOne"
                     boundaryCondition="false"/>
            <species name="X0" initialAmount="0" compartment="compartmentOne"
                     boundaryCondition="true"/>
            <species name="X1" initialAmount="0" compartment="compartmentOne"
                     boundaryCondition="true"/>
            <species name="X2" initialAmount="0" compartment="compartmentOne"
                     boundaryCondition="true"/>
        </listOfSpecies>
        <listOfReactions>
            <reaction name="reaction_1" reversible="false">
                <listOfReactants>
                    <speciesReference species="X0" stoichiometry="1"/>
                </listOfReactants>
                <listOfProducts>
                    <speciesReference species="S1" stoichiometry="1"/>
                </listOfProducts>
                <kineticLaw formula="k1 * X0">
                    <listOfParameters>
                        <parameter name="k1" value="0"/>
                    </listOfParameters>
                </kineticLaw>
            </reaction>
            <reaction name="reaction_2" reversible="false">
                <listOfReactants>
                    <speciesReference species="S1" stoichiometry="1"/>
                </listOfReactants>
                <listOfProducts>
                    <speciesReference species="X1" stoichiometry="1"/>
                </listOfProducts>
                <kineticLaw formula="k2 * S1">
                    <listOfParameters>
                        <parameter name="k2" value="0"/>
                    </listOfParameters>
                </kineticLaw>
            </reaction>
            <reaction name="reaction_3" reversible="false">
                <listOfReactants>
                    <speciesReference species="S1" stoichiometry="1"/>
                </listOfReactants>
                <listOfProducts>
                    <speciesReference species="X2" stoichiometry="1"/>
                </listOfProducts>
                <kineticLaw formula="k3 * S1">
                    <listOfParameters>
                        <parameter name="k3" value="0"/>
                    </listOfParameters>
                </kineticLaw>
            </reaction>
        </listOfReactions>
    </model>
</sbml>
```

The XML encoding shown above is quite straightforward. The outermost container is a tag, <smbl>, that identifies the contents as being Systems Biology Markup Language. The first attribute, xmlns, is required for tools that read XML to be able to verify the syntax of a given definition against the XML Schema for SBML. The attributes level and version indicate that the content is formatted according to Version 2 of the Level 1 definition of SBML.

The next-inner container is a single <model> element that serves as the highest-level object in the model. The model has a name, "Branch". The model contains one compartment, four species, and three reactions. 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 includes a <notes> annotation that summarizes the model in text form, with formatting based on XHTML. This may be useful for a software package that is able to read such annotations and, for example, render them in HTML in a graphical user interface.

5.2 Simple Use of Units Feature in a Model

The following model uses the units features of SBML Level 1. In this model, the default value of substance is changed in the list of unit definitions to be mole units with a scale factor of −3, or millimoles. This sets the default substance units in the model, although components can override this scale locally. The volume and time built-ins are left to their defaults, ensuring that volume is in liters and time is in seconds. The result is that, in this model, kinetic law formulas define rates in millimoles per second and the species symbols in them represent concentration values in millimoles per liter. 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 liter per second, and milliMolar, respectively.

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns="http://www.sbml.org/sbml/level1" level="1" version="2">
    <model>
        <listOfUnitDefinitions>
            <unitDefinition name="substance">
                <listOfUnits>
                    <unit kind="mole" scale="-3"/>
                </listOfUnits>
            </unitDefinition>
            <unitDefinition name="mls">
                <listOfUnits>
                    <unit kind="mole"   scale="-3"/>
                    <unit kind="liter"  exponent="-1"/>
                    <unit kind="second" exponent="-1"/>
                </listOfUnits>
            </unitDefinition>
        </listOfUnitDefinitions>
        <listOfCompartments>
            <compartment name="cell"/>
        </listOfCompartments>
        <listOfSpecies>
            <species name="x0" compartment="cell" initialAmount="1"/>
            <species name="x1" compartment="cell" initialAmount="1"/>
            <species name="s1" compartment="cell" initialAmount="1"/>
            <species name="s2" compartment="cell" initialAmount="1"/>
        </listOfSpecies>
        <listOfParameters>
            <parameter name="vm" value="2" units="mls"/>
            <parameter name="km" value="2"/>
        </listOfParameters>
        <listOfReactions>
            <reaction name="v1">
                <listOfReactants>
                    <speciesReference species="x0"/>
                </listOfReactants>
                <listOfProducts>
                    <speciesReference species="s1"/>
```

```
            </listOfProducts>
            <kineticLaw formula="(vm * s1)/(km + s1)"/>
        </reaction>
        <reaction name="v2">
            <listOfReactants>
                <speciesReference species="s1"/>
            </listOfReactants>
            <listOfProducts>
                <speciesReference species="s2"/>
            </listOfProducts>
            <kineticLaw formula="(vm * s2)/(km + s2)"/>
        </reaction>
        <reaction name="v3">
            <listOfReactants>
                <speciesReference species="s2"/>
            </listOfReactants>
            <listOfProducts>
                <speciesReference species="x1"/>
            </listOfProducts>
            <kineticLaw formula="(vm * s1)/(km + s1)"/>
        </reaction>
    </listOfReactions>
  </model>
</sbml>
```

5.3 An Example of Using Rules

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

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

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

$$S_2 \quad \xrightarrow{k_2 S_1} \quad X_1$$

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

This can be approximated with the following system:

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

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

$$S_1 = \frac{T}{1 + K_{eq}}, \quad S_2 = K_{eq} S_1$$

The following SBML example encodes the approximate form.

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns="http://www.sbml.org/sbml/level1" level="1" version="2">
    <model>
        <listOfCompartments>
            <compartment name="cell" volume="1"/>
        </listOfCompartments>
        <listOfSpecies>
            <species id="X0" compartment="cell" initialAmount="1"/>
            <species id="X1" compartment="cell" initialAmount="0"/>
```

```
            <species id="T"  compartment="cell" initialAmount="0"/>
            <species id="S1" compartment="cell" initialAmount="0"/>
            <species id="S2" compartment="cell" initialAmount="0"/>
        </listOfSpecies>
        <listOfParameters>
            <parameter id="Keq" value="2.5"/>
        </listOfParameters>
        <listOfRules>
            <speciesConcentrationRule species="S1" formula="T/(1 + Keq)" />
            <speciesConcentrationRule species="S2" formula="Keq * S1" />
        </listOfRules>
        <listOfReactions>
            <reaction id="in">
                <listOfReactants>
                    <speciesReference species="X0"/>
                </listOfReactants>
                <listOfProducts>
                    <speciesReference species="T"/>
                </listOfProducts>
                <kineticLaw formula="k1 * X0">
                    <listOfParameters>
                        <parameter id="k1" value="0.1"/>
                    </listOfParameters>
                </kineticLaw>
            </reaction>
            <reaction id="out">
                <listOfReactants>
                    <speciesReference species="T"/>
                </listOfReactants>
                <listOfProducts>
                    <speciesReference species="X1"/>
                </listOfProducts>
                <kineticLaw formula="k2 * S2">
                    <listOfParameters>
                        <parameter id="k2" value="0.15"/>
                    </listOfParameters>
                </kineticLaw>
            </reaction>
        </listOfReactions>
    </model>
</sbml>
```

6 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, 2000a). 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, 2000a). 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 biochemical network models. SBML Level 1 provides basic facilities that are necessary for expressing these kinds of models in terms of compartments, species, reactions, parameters, rules and units.

Our vision for SBML is to create an open standard that will enable simulation software to exchange 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.

6.1 Future Enhancements to SBML: Level 2 and Beyond

As mentioned above, SBML Level 1 is intended to provide the most basic foundations for modeling biochemical networks. A number of significant capabilities are lacking from Level 1; these will be introduced in higher-level definitions of SBML. The following summarizes additional features that will likely be included in SBML Level 2 or 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. For example, it should be possible to create a 2-D array of compartments and then a 3-D array of reactions which transport species between the compartments, where the third dimension is the connections between the compartments. Two possible ways of describing a connection scheme are: (1) sparse/explicit, simply listing the relative co-coordinates of connected objects for patterns of points; (2) algebraic, where a conditional equation describes whether two objects are connected.
- *Database Interoperability.* In order to store models in a database, it will be necessary to add additional header information that provides information about authors, version numbers, revision dates, etc.
- *Geometry.* We will develop a scheme for representing the 3-D structure of compartments.
- *Submodels.* 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.
- *Component Identification.* This will enable components to be described using some stable universal identification scheme.
- *References.* This will enable literature/authors to be cited for any component.
- *Diagrams.* This feature will allow components to be annotated with data to enable the display of the model in a diagram.

6.2 Relationships to Other Efforts

There are a number of ongoing efforts with similar goals as those of SBML. Many of them are oriented more specifically toward describing protein sequences, genes and related entities for database storage and search. These are generally not intended to be computational models, in the sense that they do not describe entities and behavioral rules in such a way that a simulation package could "run" the models.

The effort perhaps closest in spirit to SBML is CellML™ (Hedley et al., 2001b,a; Physiome Sciences, 2001). CellML is an XML-based markup language designed for storing and exchanging computer-based biological models. It includes facilities for representing model structure, mathematics and additional information for database storage and search. Models are described in terms of networks of connections between discrete components, where a component is a functional unit that may correspond to a physical compartment or simply a convenient modeling abstraction. Components contain variables and connections contain mappings between the variables of connected components. CellML provides facilities for grouping components and specifying the kinds of relationships that may exist between components. It also uses MathML (W3C, 2000b) for expressing mathematical relationships between components and provides the ability to use ECMAScript (formerly known as JavaScript) to define functions.

The constructs in CellML tend to be at a more abstract and general level than those in SBML Level 1, and describes the structure and underlying mathematics of cellular models in a very general way. By contrast,

SBML is closer to the internal object model used in a number of common model simulation packages. Because SBML Level 1 is being developed in the context of interacting with a number of existing software packages, it is a more concrete language than CellML and may be better suited to its purpose of enabling interoperability with existing simulation tools. However, CellML offers viable alternative ideas and the developers of SBML and CellML are actively engaged in ensuring that the two representations can be translated between each other.

6.3 Availability

The SBML Level 1 definition, the XML Schema corresponding to SBML Level 1, and other related documents are openly available from the Caltech ERATO web site, `http://www.sbml.org/`.

Acknowledgments

SBML was first conceived at the JST/ERATO-sponsored *First Workshop on Software Platforms for Molecular 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 Molecular 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 the final version of SBML Level 1 Version 1 in March 2001 Hucka et al. (2001).

SBML Level 1 Version 2 was developed with the help of many people, especially the authors of BioSpice, CellML, DBSolve, E-Cell, Gepasi, ProMoT/DIVA, StochSim, and Virtual Cell, and members of the `sysbio` and `sbml-discuss` mailing lists. We are particularly grateful to the following people for discussions and knowledge: Adam Arkin, Ben Bornstein, Dennis Bray, Athel Cornish-Bowden, Manuel Corpas, John Doyle, Drew Endy, David Fell, Carl Firth, Akira Funahashi, Ralph Gauges, Martin Ginkel, Victoria Gor, Igor Goryanin, Warren Hedley, Charles Hodgman, Stephan Hoops, Nick Juty, Jay Kaserger, Sarah Keating, Hiroaki Kitano, Ben Kovitz, Andreas Kremling, Nicolas Le Novère, Fred Livingston, Les Loew, Daniel Lucio, Joanne Matthews, Pedro Mendes, Eric Minch, Eric Mjolsness, David Morley, Mineo Morohashi, Poul Nielsen, Gregory Peterson, Mark Poolman, Wayne Rindone, James Schaff, Maria Schilstra, Daniel Segre, Cliff Shaffer, Bruce Shapiro, Tom Shimizu, Hugh Spence, Jörg Stelling, Kouichi Takahashi, Masaru Tomita, John Wagner, Jonathan Webb, Jörg Weimar, Darren Wilkinson, Marc Vass, and Tau-Mu Yi.

We are indebted to Daniel Lucio of the Virtual Cell group for generating the XML Schema of SBML Level 1 Version 1, which forms the basis of the Level 1 Version 2 schema presented in Appendix B.

Appendix

A Summary of Notation

The definitive explanation for the notation used in this document can be found in the companion notation document (Hucka, 2000). Here we briefly summarize some of the main components of the notations used in describing SBML.

Within the definitions of the various object classes introduced in this document, the following types of expressions are used many times:

```
field1 : float
field2 : integer[0..*]
field3 : (XHTML)
field4 : float {use = "default" value = "0.0"}
```

The symbols `field1`, `field2`, etc., represents fields in a data structure. The colon immediately after the name separates the name of the attribute from the type of data that it stores.

More complex specifications use square brackets (`[]`) just after a type name. This is used to indicate that the field contains a list of elements. 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. The approach used here to translate from a list form into XML is, first, create a subelement named `listOf_____s`, where the blank indicates the capitalized name of the field, and then put a list of elements named after the field as the content of the `listOf_____s` element.

A field whose type is shown in parentheses is implemented as an XML subelement rather than an XML attribute. The parentheses indicate that the type refers to the type of the subelement value.

Expressions in curly braces ({}) shown after an attribute type indicate additional constraints placed on the field. We express constraints using XML Schema language. In the examples above, the expression {`use="default" value="0.0"`} indicates that the field `field4` is optional and that it has a default value of 0.0.

B XML Schema for SBML

SBML models expressed in XML must provide an XML Namespace reference on the top-level `sbml` element that encapsulates the model. This XML Namespace reference takes the form of the attribute named `xmlns`. The value of this attribute must be the string "`http://www.sbml.org/sbml/level1`" as shown in the examples of SBML provided in this specification.

The following is an XML Schema definition (using XML Schema 1.0) for the Systems Biology Markup Language Level 1 Version 2. Example applications of this XML Schema are presented in Section 5.

```
<?xml version="1.0" encoding="UTF-8"?>
<xsd:schema xmlns:xsd="http://www.w3.org/2001/XMLSchema"
            xmlns="http://www.sbml.org/sbml/level1"
            targetNamespace="http://www.sbml.org/sbml/level1"
            elementFormDefault="qualified">
  <xsd:annotation>
    <xsd:documentation>
      File name : sbml.xsd
      Author : M. Hucka, D. Lucio, J. Schaff, A. Finney, H. Sauro
      Description : XML Schema for the Systems Biology Markup Language Level 1
      Version : 2
    </xsd:documentation>
  </xsd:annotation>
  <!--The definition of SName follows.-->
  <xsd:simpleType name="SName">
    <xsd:annotation>
      <xsd:documentation>The type SName is used throughout SBML for expressing
                         names of components in a model.</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>
<!--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 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"
                 processContents="skip" maxOccurs="unbounded"/>
      </xsd:sequence>
     </xsd:complexType>
    </xsd:element>
    <xsd:element name="annotation" minOccurs="0">
     <xsd:complexType>
      <xsd:sequence>
        <xsd:any processContents="skip" maxOccurs="unbounded"/>
      </xsd:sequence>
     </xsd:complexType>
    </xsd:element>
  </xsd:sequence>
</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="celsius"/>
    <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="liter"/>
    <xsd:enumeration value="litre"/>
    <xsd:enumeration value="lumen"/>
    <xsd:enumeration value="lux"/>
    <xsd:enumeration value="meter"/>
    <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:integer" default="1"/>
     <xsd:attribute name="scale" type="xsd:integer" default="0"/>
    </xsd:extension>
  </xsd:complexContent>
</xsd:complexType>
<!--The definition of UnitDefinition follows.-->
<xsd:complexType name="UnitDefinition">
  <xsd:complexContent>
    <xsd:extension base="SBase">
     <xsd:sequence>
      <xsd:element name="listOfUnits" minOccurs="0">
        <xsd:complexType>
          <xsd:sequence>
            <xsd:element name="unit" type="Unit" maxOccurs="unbounded"/>
          </xsd:sequence>
        </xsd:complexType>
      </xsd:element>
     </xsd:sequence>
     <xsd:attribute name="name" type="SName" use="required"/>
    </xsd:extension>
  </xsd:complexContent>
</xsd:complexType>
<!--The definition of Compartment follows.-->
<xsd:complexType name="Compartment">
  <xsd:complexContent>
    <xsd:extension base="SBase">
     <xsd:attribute name="name" type="SName" use="required"/>
     <xsd:attribute name="volume" type="xsd:double" default="1"/>
     <xsd:attribute name="units" type="SName" use="optional"/>
     <xsd:attribute name="outside" type="SName" use="optional"/>
    </xsd:extension>
  </xsd:complexContent>
</xsd:complexType>
<!--The definition of Species follows.-->
<xsd:complexType name="Species">
  <xsd:complexContent>
    <xsd:extension base="SBase">
     <xsd:attribute name="name" type="SName" use="required"/>
     <xsd:attribute name="compartment" type="SName" use="required"/>
     <xsd:attribute name="initialAmount" type="xsd:double" use="required"/>
     <xsd:attribute name="units" type="SName" use="optional"/>
     <xsd:attribute name="boundaryCondition" type="xsd:boolean"
                    use="optional" default="false"/>
     <xsd:attribute name="charge" type="xsd:integer" use="optional"/>
    </xsd:extension>
  </xsd:complexContent>
</xsd:complexType>
<!--The definition of Parameter follows.-->
<xsd:complexType name="Parameter">
  <xsd:complexContent>
    <xsd:extension base="SBase">
     <xsd:attribute name="name" use="required"/>
     <xsd:attribute name="value" type="xsd:double" use="optional"/>
     <xsd:attribute name="units" type="SName" use="optional"/>
    </xsd:extension>
  </xsd:complexContent>
</xsd:complexType>
<!--The definition of Rule follows. -->
<xsd:simpleType name="RuleType">
  <xsd:restriction base="xsd:string">
    <xsd:enumeration value="scalar"/>
    <xsd:enumeration value="rate"/>
```

```
  </xsd:restriction>
</xsd:simpleType>
<xsd:complexType name="Rule" abstract="true">
  <xsd:complexContent>
    <xsd:extension base="SBase">
     <xsd:attribute name="formula" type="xsd:string" use="required"/>
    </xsd:extension>
  </xsd:complexContent>
</xsd:complexType>
<xsd:complexType name="AlgebraicRule">
  <xsd:complexContent>
    <xsd:extension base="Rule"/>
  </xsd:complexContent>
</xsd:complexType>
<xsd:complexType name="AssignmentRule" abstract="true">
  <xsd:complexContent>
    <xsd:extension base="Rule">
     <xsd:attribute name="type" type="RuleType" default="scalar"/>
    </xsd:extension>
  </xsd:complexContent>
</xsd:complexType>
<xsd:complexType name="CompartmentVolumeRule">
  <xsd:complexContent>
    <xsd:extension base="AssignmentRule">
     <xsd:attribute name="compartment" type="SName" use="required"/>
    </xsd:extension>
  </xsd:complexContent>
</xsd:complexType>
<xsd:complexType name="SpeciesConcentrationRule">
  <xsd:complexContent>
    <xsd:extension base="AssignmentRule">
     <xsd:attribute name="species" type="SName" use="required"/>
    </xsd:extension>
  </xsd:complexContent>
</xsd:complexType>
<xsd:complexType name="ParameterRule">
  <xsd:complexContent>
    <xsd:extension base="AssignmentRule">
     <xsd:attribute name="name" type="SName" use="required"/>
    </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 name="listOfParameters" minOccurs="0">
        <xsd:complexType>
          <xsd:sequence>
            <xsd:element name="parameter" type="Parameter" maxOccurs="unbounded"/>
          </xsd:sequence>
        </xsd:complexType>
      </xsd:element>
     </xsd:sequence>
     <xsd:attribute name="formula" type="xsd:string" use="required"/>
     <xsd:attribute name="timeUnits" type="SName" use="optional"/>
     <xsd:attribute name="substanceUnits" type="SName" use="optional"/>
    </xsd:extension>
  </xsd:complexContent>
</xsd:complexType>
<xsd:complexType name="SpeciesReference">
  <xsd:complexContent>
    <xsd:extension base="SBase">
     <xsd:attribute name="species" type="xsd:string" use="required"/>
     <xsd:attribute name="stoichiometry" type="xsd:positiveInteger" use="optional" default="1"/>
     <xsd:attribute name="denominator" type="xsd:positiveInteger" use="optional" default="1"/>
    </xsd:extension>
  </xsd:complexContent>
```

```
</xsd:complexType>
<xsd:complexType name="Reaction">
  <xsd:complexContent>
    <xsd:extension base="SBase">
     <xsd:sequence>
      <xsd:element name="listOfReactants" minOccurs="0">
        <xsd:complexType>
          <xsd:sequence>
            <xsd:element name="speciesReference" type="SpeciesReference" maxOccurs="unbounded"/>
          </xsd:sequence>
        </xsd:complexType>
      </xsd:element>
      <xsd:element name="listOfProducts" minOccurs="0">
        <xsd:complexType>
          <xsd:sequence>
            <xsd:element name="speciesReference" type="SpeciesReference" maxOccurs="unbounded"/>
          </xsd:sequence>
        </xsd:complexType>
      </xsd:element>
      <xsd:element name="kineticLaw" type="KineticLaw" minOccurs="0"/>
     </xsd:sequence>
     <xsd:attribute name="name" type="SName" use="required"/>
     <xsd:attribute name="reversible" type="xsd:boolean" use="optional" default="true"/>
     <xsd:attribute name="fast" type="xsd:boolean" use="optional" default="false"/>
    </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="listOfUnitDefinitions" minOccurs="0">
        <xsd:complexType>
          <xsd:sequence>
            <xsd:element name="unitDefinition" type="UnitDefinition" maxOccurs="unbounded"/>
          </xsd:sequence>
        </xsd:complexType>
      </xsd:element>
      <xsd:element name="listOfCompartments" minOccurs="1">
        <xsd:complexType>
          <xsd:sequence>
            <xsd:element name="compartment" type="Compartment"
                         maxOccurs="unbounded" minOccurs="1"/>
          </xsd:sequence>
        </xsd:complexType>
      </xsd:element>
      <xsd:element name="listOfSpecies" minOccurs="0">
        <xsd:complexType>
          <xsd:sequence>
            <xsd:element name="species" type="Species" maxOccurs="unbounded"/>
          </xsd:sequence>
        </xsd:complexType>
      </xsd:element>
      <xsd:element name="listOfParameters" minOccurs="0">
        <xsd:complexType>
          <xsd:sequence>
            <xsd:element name="parameter" type="Parameter" maxOccurs="unbounded"/>
          </xsd:sequence>
        </xsd:complexType>
      </xsd:element>
      <xsd:element name="listOfRules" minOccurs="0">
        <xsd:complexType>
          <xsd:choice maxOccurs="unbounded">
            <xsd:element name="algebraicRule" type="AlgebraicRule" minOccurs="0"/>
            <xsd:element name="compartmentVolumeRule" type="CompartmentVolumeRule"
                         minOccurs="0"/>
            <xsd:element name="speciesConcentrationRule" type="SpeciesConcentrationRule"
                         minOccurs="0"/>
```

```
            <xsd:element name="parameterRule" type="ParameterRule" minOccurs="0"/>
          </xsd:choice>
        </xsd:complexType>
      </xsd:element>
      <xsd:element name="listOfReactions" minOccurs="0">
        <xsd:complexType>
          <xsd:sequence>
            <xsd:element name="reaction" type="Reaction" maxOccurs="unbounded"/>
          </xsd:sequence>
        </xsd:complexType>
      </xsd:element>
    </xsd:sequence>
    <xsd:attribute name="name" type="SName" 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="sbmlDocument">
  <xsd:sequence>
     <xsd:element name="model" type="Model"/>
  </xsd:sequence>
  <xsd:attribute name="level" type="xsd:positiveInteger" use="required" fixed="1"/>
  <xsd:attribute name="version" type="xsd:positiveInteger" use="required"/>
</xsd:complexType>
<!--The following is the (only) top-level element allowed in an SBML document.-->
<xsd:element name="sbml" type="sbmlDocument"/>
<!-- The end. -->
</xsd:schema>
```

C Predefined Functions in SBML

Table 6 lists the basic mathematical functions that are defined in SBML Level 1 at this time.

Name	Args.	Formula or Meaning	Argument Constraints	Result Constraints
abs	x	absolute value of x		
acos	x	arc cosine of x in radians	$-1.0 \leq x \leq 1.0$	$0 \leq acos(x) \leq \pi$
asin	x	arc sine of x in radians	$-1.0 \leq x \leq 1.0$	$-\pi/2 \leq asin(x) \leq \pi/2$
atan	x	arc tangent of x in radians		$-\pi/2 \leq atan(x) \leq \pi/2$
ceil	x	smallest number not less than x whose value is an exact integer		
cos	x	cosine of x		
exp	x	e^x, where e is the base of the natural logarithm		
floor	x	the largest number not greater than x whose value is an exact integer		
log	x	natural logarithm of x	$x > 0$	
log10	x	base 10 logarithm of x	$x > 0$	
pow	x, y	x^y		
sqr	x	x^2		
sqrt	x	$\sqrt{x}$	$x \geq 0$	$sqrt(x) \geq 0$
sin	x	sine of x		
tan	x	tangent of x	$x \neq n\frac{\pi}{2}$, for odd integer n	

Table 6: *Basic mathematical functions defined in SBML.*

Table 7 defines the rate law functions available in formula expressions in SBML. These were extracted from the Gepasi help file (3.21). Segel (1993) provides more information; Hofmeyr and Cornish-Bowden (1997) provide specific details on the reversible Hill equations.

Name	Arguments	Meaning	Formula
mass	S_i, k	Mass Action Kinetics	$v = k \prod_i S_i$
uui	S, V_m, K_m	Irreversible Simple Michaelis-Menten	$v = \frac{V_m S}{K_m + S}$
uur	S, P, V_f, V_r, K_{mS}, K_{mP}	Uni-Uni Reversible Simple Michaelis-Menten	$v = \frac{V_f S/K_{mS} - V_r P/K_{mP}}{1 + S/K_{mS} + P/K_{mP}}$
uuhr	S, P, V_f, K_{m1}, K_{m2}, K_{eq}	Uni-Uni Reversible Simple Michaelis-Menten with Haldane adjustment	$v = \frac{(V_f/K_{m1})(S - P/K_{eq})}{1 + S/K_{m1} + P/K_{m2}}$
isouur	S, P, V_f, K_{mS}, K_{mP}, K_{ii}, K_{eq}	Iso Uni-Uni	$v = \frac{V_f (S - P/K_{eq})}{S(1 + P/K_{ii}) + K_{mS}(1 + P/K_{mP})}$
hilli	S, V, $S_{0.5}$, h	Hill Kinetics	$v = \frac{V S^h}{S_{0.5}^h + S^h}$
hillr	S, P, V_f, $S_{0.5}$, $P_{0.5}$, h, K_{eq}	Reversible Hill Kinetics	$v = \frac{(V_f S/S_{0.5})\left[1 - P/(SK_{eq})\right](S/S_{0.5} + P/P_{0.5})^{h-1}}{1 + (S/S_{0.5} + P/P_{0.5})^h}$
hillmr	S, P, M, $S_{0.5}$, $P_{0.5}$, $M_{0.5}$, V_f, K_{eq}, h, α	Reversible Hill Kinetics with One Modifier	$v = \frac{(V_f S/S_{0.5})\left[1 - P/(SK_{eq})\right](S/S_{0.5} + P/P_{0.5})^{h-1}}{K_1 + K_2}$ where $K_1 = (S/S_{0.5} + P/P_{0.5})^h$, $K_2 = \frac{1 + (M/M_{0.5})^h}{1 + \alpha (M/M_{0.5})^h}$
hillmmr	S, P, M, $S_{0.5}$, $P_{0.5}$, $M_{0.5}$, M_a, $M_{a_{0.5}}$, M_b, $M_{b_{0.5}}$, V_f, K_{eq}, h, a, b, α_1, α_2, α_{12}	Reversible Hill Kinetics with Two Modifiers	$v = \frac{(V_f S/S_{0.5})\left[1 - P/(SK_{eq})\right](S/S_{0.5} + P/P_{0.5})^{h-1}}{K_1 + K_2}$ where $K_1 = (S/S_{0.5} + P/P_{0.5})^h$, $K_2 = \frac{1 + (M_a/M_{a_{0.5}})^h + (M_b/M_{b_{0.5}})^h}{\left[1 + \alpha_1 (M_a/M_{a_{0.5}})^h + \alpha_2 (M_b/M_{b_{0.5}})^h + \alpha_1\alpha_2\alpha_{12} (M_a/M_{a_{0.5}})^h (M_b/M_{b_{0.5}})^h\right]}$

Table 7: *Table of rate law functions in SBML. In all cases, $K_m > 0$, $V_x \geq 0$, $S \geq 0$ and $P \geq 0$.*

Name	Arguments	Meaning	Formula
usii	S, V, K_m, K_i	Substrate Inhibition Kinetics (Irreversible)	$v = V\dfrac{S/K_m}{1 + S/K_m + S^2/K_i}$
usir	S, P, V_f, V_r, K_{mS}, K_{mP}, K_i	Substrate Inhibition Kinetics (Reversible)	$v = \dfrac{V_f S/K_{mS} + V_r P/K_{mP}}{1 + S/K_{mS} + P/K_{mP} + S^2/K_i}$
uai	S, V, K_{sa}, K_{sc}	Substrate Activation	$v = \dfrac{V\,(S/K_{sa})^2}{1 + S/K_{sc} + (S/K_{sa})^2 + S/K_{sa}}$
ucii	S, I, V, K_m, K_i	Competitive Inhibition (Irreversible)	$v = \dfrac{VS/K_m}{1 + S/K_m + I/K_i}$
ucir	S, P, I, V_f, V_r, K_{mS}, K_{mP}, K_i	Competitive Inhibition (Reversible)	$v = \dfrac{V_f S/K_{mS} - V_r P/K_{mP}}{1 + S/K_{mS} + P/K_{mP} + I/K_i}$
unii	S, I, V, K_m, K_i	Noncompetitive Inhibition (Irreversible)	$v = \dfrac{VS/K_m}{1 + I/K_i + (S/K_m)\,(1 + I/K_i)}$
unir	S, P, I, V_f, V_r, K_{mS}, K_{mP}, K_i	Noncompetitive Inhibition (Reversible)	$v = \dfrac{V_f S/K_{mS} - V_r P/K_{mP}}{1 + I/K_i + (S/K_{mS} + P/K_{mP})\,(1 + I/K_i)}$
uuci	S, I, V, K_m, K_i	Uncompetitive Inhibition (Irreversible)	$v = \dfrac{VS/K_m}{1 + (S/K_m)\,(1 + I/K_i)}$
uucr	S, P, I, V_f, V_r, K_{mS}, K_{mP}, K_i	Uncompetitive Inhibition (Reversible)	$v = \dfrac{V_f S/K_{mS} - V_r P/K_{mP}}{1 + (S/K_{mS} + P/K_{mP})\,(1 + I/K_i)}$
umi	S, I, V, K_m, K_{is}, K_{ic}	Mixed Inhibition Kinetics (Irreversible)	$v = \dfrac{VS/K_m}{1 + I/K_{is} + (S/K_m)\,(1 + I/K_{ic})}$
umr	S, P, I, V_f, V_r, K_{mS}, K_{mP}, K_{is}, K_{ic}	Mixed Inhibition Kinetics (Reversible)	$v = \dfrac{V_f S/K_{mS} - V_r P/K_{mP}}{1 + I/K_{is} + (S/K_{mS} + P/K_{mP})\,(1 + I/K_{ic})}$
uaii	S, A_c, V, K_m, K_a	Specific Activation Kinetics - irreversible	$v = \dfrac{VS/K_m}{1 + S/K_m + K_a/A_c}$
uar	S, P, A_c, V_f, V_r, K_{mS}, K_{mP}, K_a	Specific Activation Kinetics (Reversible)	$v = \dfrac{V_f S/K_{mS} - V_r P/K_{mP}}{1 + S/K_{mS} + P/K_{mP} + K_a/A_c}$
ucti	S, A_c, V, K_m, K_a	Catalytic Activation (Irreversible)	$v = \dfrac{VS/K_m}{1 + K_a/A_c + (S/K_m)\,(1 + K_a/A_c)}$

Table 7: *Table of rate law functions in SBML (continued). In all cases, $K_m > 0$, $V_x \geq 0$, $S \geq 0$ and $P \geq 0$.*

Name	Arguments	Meaning	Formula
uctr	S, P, A_c, V_f, V_r, K_{mS}, K_{mP}, K_a	Catalytic Activation (Reversible)	$v = \dfrac{V_f S/K_{mS} - V_r P/K_{mP}}{1 + K_a/A_c + (S/K_{mS} + P/K_{mP})(1 + K_a/A_c)}$
umai	S, A_c, V, K_m, K_{as}, K_{ac}	Mixed Activation Kinetics (Irreversible)	$v = \dfrac{VS/K_m}{1 + K_{as}/A_c + (S/K_m)(1 + K_{ac}/A_c)}$
umar	S, P, A_c, V_f, V_r, K_{mS}, K_{mP}, K_{as}, K_{ac}	Mixed Activation Kinetics (Reversible)	$v = \dfrac{V_f S/K_{mS} - V_r P/K_{mP}}{1 + K_{as}/A_c + (S/K_{mS} + P/K_{mP})(1 + K_{ac}/A_c)}$
uhmi	S, M, V, K_m, K_d, a, b	General Hyperbolic Modifier Kinetics (Irreversible)	$v = \dfrac{(VS/K_m)[1 + bM/(aK_d)]}{1 + M/K_d + (S/K_m)[1 + M/(aK_d)]}$
uhmr	S, P, M, V_f, V_r, K_{mS}, K_{mP}, K_d, a, b	General Hyperbolic Modifier Kinetics (Reversible)	$v = \dfrac{(V_f S/K_{mS} - V_r P/K_{mP})[1 + bM/(aK_d)]}{1 + M/K_d + (S/K_{mS} + P/K_{mP})[1 + M/(aK_d)]}$
ualii	S, I, V, K_s, K_{ii}, n, L	Allosteric inhibition (Irreversible)	$v = \dfrac{V(S/K_s)(1 + S/K_s)^{n-1}}{L(1 + I/K_{ii})^n + (1 + S/K_s)^n}$
ordubr	A, P, Q, V_f, V_r, K_{mA}, K_{mQ}, K_{mP}, K_{iP}, K_{eq}	Ordered Uni Bi Kinetics	$v = \dfrac{V_f(A - PQ/K_{eq})}{\left[K_{mA} + A(1 + P/K_{iP}) + [V_f/(V_r K_{eq})](K_{mQ}P + K_{mP}Q + PQ)\right]}$
ordbur	A, B, P, V_f, V_r, K_{mA}, K_{mB}, K_{mP}, K_{iA}, K_{eq}	Ordered Bi Uni Kinetics	$v = \dfrac{V_f(AB - P/K_{eq})}{\left[AB + K_{mA}B + K_{mB}A + [V_f/(V_r K_{eq})][K_{mP} + P(1 + A/K_{iA})]\right]}$
ordbbr	A, B, P, Q, V_f, V_r, K_{mA}, K_{mB}, K_{mP}, K_{mQ}, K_{iA}, K_{iB}, K_{iP}, K_{eq}	Ordered Bi Bi Kinetics	$v = \dfrac{V_f(AB - PQ/K_{eq})}{AB(1 + P/K_{iP}) + K_{mB}(A + K_{iA}) + K_{mA}B + K_1}$ where $K_1 = [V_f/(V_r K_{eq})][K_{mQ}P(1 + A/K_{iA}) + QK_2]$, $K_2 = K_{mP}[1 + K_{mA}B/(K_{iA}K_{mB}) + P(1 + B/K_{iB})]$
ppbr	A, B, P, Q, V_f, V_r, K_{mA}, K_{mB}, K_{mP}, K_{mQ}, K_{iA}, K_{iQ}, K_{eq}	Ping Pong Bi Bi Kinetics	$v = \dfrac{V_f(AB - PQ/K_{eq})}{AB + K_{mB}A + K_{mA}B(1 + Q/K_{iQ}) + K_1}$ where $K_1 = [V_f/(V_r K_{eq})][K_{mQ}P(1 + A/K_{iA}) + Q(K_{mP} + P)]$

Table 7: *Table of rate law functions in SBML (continued). In all cases, $K_m > 0$, $V_x \geq 0$, $S \geq 0$ and $P \geq 0$.*

Symbol	Meaning
α	Effect of S and P on binding of M (if $M < 1$, M is inhibitor; if $M > 1$, M is activator)
A	First substrate in two-substrate reaction
A_c	Activator
B	Second substrate in two-substrate reaction
I	Inhibitor
K_1	Forward rate constant
K_2	Reverse rate constant
K_a	Activation constant
K_{ac}	Catalytic activation constant
K_{as}	Specific activation constant
K_d	Dissociation constant of the elementary step $E + M = EM$
K_{eq}	Equilibrium constant
K_{ii}	Dissociation constant of the inhibitor from the inactive form of the enzyme
K_i	Inhibition constant for the substrate.
K_{iA}	Product inhibition constant of A acting on the reverse reaction
K_{iB}	Product inhibition constant of B acting on the reverse reaction
K_{ic}	Catalytic (noncompetitive) inhibition constant
K_{iP}	Product inhibition constant of P acting on the forward reaction
K_{iQ}	Product inhibition constant of Q acting on the forward reaction
K_{is}	Specific (competitive) inhibition constant
K_m	Forward Michaelis-Menten constant
K_{mA}	Concentration of A such that $v = V_f/2$ (Michaelis constant) at zero P and zero Q
K_{mB}	Concentration of B such that $v = V_f/2$ (Michaelis constant) at saturating A and zero P
K_{mP}	Concentration of P such that $v = -V_r/2$ (Michaelis constant) at zero A and B
K_{mQ}	Concentration of Q such that $v = -V_r/2$ (Michaelis constant) at zero A and saturating P
K_{mS}	Substrate Michaelis-Menten constant
K_s	Dissociation constant of the substrate from the active form of the enzyme
K_{sa}	Dissociation constant of substrate-activation site
K_{sc}	Dissociation constant of substrate-active site
L	Equilibrium constant between the active and inactive forms of the enzyme
M	Modifier
$M_{0.5}$	Concentration of M that half-saturates its binding site when $S = 0$, $P = 0$
M_a	Modifier
$M_{a_{0.5}}$	Hill kinetics: concent. of M_a that half-saturates its binding site when $S = 0$, $P = 0$, $M_b = 0$
M_b	Modifier
$M_{b_{0.5}}$	Hill kinetics: concent. of M_b that half-saturates its binding site when $S = 0$, $P = 0$, $M_a = 0$
P	First product in two-product reaction
$P_{0.5}$	Product concent. s.t. $v = -V_r/2$ when $P = M = 0$ (V_r is limiting rate of reverse reaction)
Q	Second product in two-product reaction
$S_{0.5}$	Irreversible rate laws: substrate concentration such that $v = V_f/2$ when $P = 0, M = 0$
V	Forward maximum velocity
V_f	Forward maximum velocity
V_m	Forward maximum velocity
V_r	Reverse maximum velocity
a	Ratio of dissociation constant of elementary step $ES+M = ESM$ over that of $E+M = EM$
b	Ratio of rate constant of elementary step $ESM \rightarrow EM + P$ over that of $ES \rightarrow E + P$.
h	Hill Coefficient
n	No. binding sites for substrate & inhibitor (typically the number of monomers in the enzyme)

Table 8: *Table of symbols used in Table 7.*

References

Abbott, A. (1999). Alliance of US labs plans to build map of cell signalling pathways. *Nature*, 402:219–200.

Arkin, A. P. (2001). *Simulac* and *Deduce*. Available via the World Wide Web at `http://gobi.lbl.gov/~aparkin/Stuff/Software.html`.

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, D., Firth, C., Le Novère, N., and Shimizu, T. (2001). *StochSim*. Available via the World Wide Web at `http://www.zoo.cam.ac.uk/comp-cell/StochSim.html`.

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., and Sperberg-McQueen, C. M. (1998). Extensible markup language (XML) 1.0, W3C recommendation 10-February-1998. Available via the World Wide Web at `http://www.w3.org/TR/1998/REC-xml-19980210`.

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`.

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/`.

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`.

Goryanin, I. (2001). *DBsolve*: Software for metabolic, enzymatic and receptor-ligand binding simulation. Available via the World Wide Web at `http://homepage.ntlworld.com/igor.goryanin/`.

Goryanin, I., Hodgman, T. C., and Selkov, E. (1999). Mathematical simulation and analysis of cellular metabolism and regulation. *Bioinformatics*, 15(9):749–758.

Harbison, S. P. and Steele, G. L. (1995). *C: A Reference Manual*. Prentice-Hall.

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. (2001a). CellML specification. Available via the World Wide Web at `http://www.cellml.org/public/specification/20010810/cellml_specification.html`.

Hedley, W. J., Nelson, M. R., Bullivant, D. P., and Nielson, P. F. (2001b). A short introduction to CellML. *Philosophical Transactions of the Royal Society of London A*, 359:1073–1089.

Hofmeyr, J. H. and Cornish-Bowden, A. (1997). The reversible Hill equation: How to incorporate cooperative enzymes into metabolic models. *Computer Applications in the Biosciences*, 13:377–385.

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`.

Kernighan, B. W. and Ritchie, D. M. (1988). *The C Programming Language*. Prentice-Hall, New Jersey: Englewood Cliffs, second edition.

Kitano, H. (2001). *Foundations of Systems Biology*. MIT Press.

Mendes, P. (1997). Biochemistry by numbers: Simulation of biochemical pathways with Gepasi 3. *Trends in Biochemical Sciences*, 22:361–363.

Mendes, P. (2001). Gepasi 3.21. Available via the World Wide Web at `http://www.gepasi.org`.

Morton-Firth, C. J. and Bray, D. (1998). Predicting temporal fluctuations in an intracellular signalling pathway. *Journal of Theoretical Biology*, 192:117–128.

Oestereich, B. (1999). *Developing Software with UML: Object-Oriented Analysis and Design in Practice*. Addison-Wesley Publishing Company.

Physiome Sciences, I. (2001). CellML™ home page. Available via the World Wide Web at `http://cellml.org/`.

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`.

Sauro, H. M. (2000). Jarnac: A system for interactive metabolic analysis. In Hofmeyr, J.-H. S., Rohwer, J. M., and Snoep, J. L., editors, *Animating the Cellular Map: Proceedings of the 9th International Meeting on BioThermoKinetics*. Stellenbosch University Press.

Sauro, H. M. and Fell, D. A. (1991). SCAMP: A metabolic simulator and control analysis program. *Mathl. Comput. Modelling*, 15:15–28.

Schaff, J., Slepchenko, B., and Loew, L. M. (2000). Physiological modeling with the Virtual Cell framework. In Johnson, M. and Brand, L., editors, *Methods in Enzymology*, volume 321, pages 1–23. Academic Press, San Diego.

Schaff, J., Slepchenko, B., Morgan, F., Wagner, J., Resasco, D., Shin, D., Choi, Y. S., Loew, L., Carson, J., Cowan, A., Moraru, I., Watras, J., Teraski, M., and Fink, C. (2001). Virtual Cell. Available via the World Wide Web at `http://www.nrcam.uchc.edu`.

Segel, I. H. (1993). *Enzyme Kinetics*. Wiley Classics Library.

Smaglik, P. (2000a). For my next trick... *Nature*, 407:828–829.

Smaglik, P. (2000b). US grant glues 'virtual cell' together. *Nature*, 407(6806):819.

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/`.

Tomita, M., Hashimoto, K., Takahashi, K., Shimizu, T., Matsuzaki, Y., Miyoshi, F., Saito, K., Tanida, S., Yugi, K., Venter, J. C., and Hutchison, C. (1999). E-Cell: Software environment for whole cell simulation. *Bioinformatics*, 15(1):72–84.

Tomita, M., Nakayama, Y., Naito, Y., Shimizu, T., Hashimoto, K., Takahashi, K., Matsuzaki, Y., Yugi, K., Miyoshi, F., Saito, Y., Kuroki, A., Ishida, T., Iwata, T., Yoneda, M., Kita, M., Yamada, Y., Wang, E., Seno, S., Okayama, M., Kinoshita, A., Fujita, Y., Matsuo, R., Yanagihara, T., Watari, D., Ishinabe, S., and Miyamoto, S. (2001). E-Cell. Available via the World Wide Web at `http://www.e-cell.org/`.

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/`.