MathSBML.m

The Mathematica SBML Reader

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1. Introduction

The `MathSBML` package provides facilities for reading models expressed in SBML and converting the models to systems of ordinary differential equations for simulation and plotting in *Mathematica*.

The current release of `MathSBML` is version 2.1.3 and can read SBML Level 1 (Version 1 and Version 2) and SBML Level 2. Future releases will be able to read higher levels and versions.

For details on SBML and *Mathematica* the user should consult the references listed at the end of this document.

Installation Instructions

`MathSBML` requires *Mathematica* 4.2 or above. It will not work properly with earlier versions of *Mathematica*. MathSBML is also fully compatible with *Mathematica* version 5.0, and additional functionality, notably the solution of differentnial-algebraic equations (DAEs) becomes available with with version 5.0.

The only file required is `MathSBML.m`. Do not edit or modify this file, as it is machine-generated. The file can be copied anywhere on your hard drive. To use the file you need to include the line

```
<< path/MathSBML.m
```

where path is the full path name, relative to your home directory, of the directory in which you have placed `MathSBML`. An alternative syntax is

```
Get["MathSBML.m", Path → path]
```

Mathematica knows about a set of default directories that it will search when looking for a file. If you put your files in one of these directories, you do not need to specify the path; e.g., you can omit the "path" from the above `Get` (`<<`) command:

```
<< MathSBML.m
```

A message such as the following will be displayed on the next line to indicate that MathSBML has completed loading correcly.

```
MathSBML 2.1.3 (28 Aug 2003) loaded 28-August-2003 10:41:01.254403
```

If you get any other message, then an error has occured during loading.

You can determine the current path by entering `$Path` at the *Mathematica* prompt. Additional information on the *Mathematica* path is given in the *Mathematica* help files.

The file `MathSBML.nb` contains the source code for `MathSBML.m`. This file is not required unless you want to change the functionality of `MathSBML`. If you open this file in *Mathematica* you may get a warning message to the effect that the file has been edited outside of *Mathematica*. This is because of the manner in which version information is added to the file by the software repository and does not affect the coding contents of the file. This version information is stored in text boxes within the file.

Functions Provided by This Package

`MathSBML` contains three functions that can be invoked directly: `SBMLRead`, `SBMLNDSolve`, and `SBMLPlot`.

`SBMLRead` is the primary function provided by this package - it reads a model encoded in SBML into *Mathematica*, converting the model into a system of differential and algebraic equations, if such informaiton is contained in the model. It also contains options to generate a formatted listing of the model, as well as call `SBMLNDSolve` and `SBMLPlot` automatically upon reading the model. It is discussed in greater detail in the following section.

`SBMLNDSolve` solves the system of differential-algebraic equations produced by `SBMLRead` using `NDSolve`. The user can optionally pass the output of `SBMLRead` directly to `NDSolve` without using `SBMLNDSolve`. (The solution of DAE's requires *Mathematica* Version ≥ 5.0; the solution of ODEs can be performed with earlier *Mathematica* versions) Examples of how to perform both of these operations are given below.

`SBMLPlot` can be used to generate plots of the resulting solutions. Plots can also be generated directly with `Plot`.

`SBMLWrite` will read an SBML file and translate it into another format. At the present time, the only output formats supported are "Fortran", "HTML", and "XPP". It is anticipated that addtional formats will be added in future releases.

`SBMLCopy` will read one SBML file and copy it to a second file, processing the file to "pretty-print" the XML with indentations as determined by *Mathematica*'s ExportString function. The purpose of this function is to make a machine-generated XML file more readable.

These functions are illustrated below in detail.

2. Using MathSBML

2.1. Using SBMLRead

The basic function used to read SBML files is SBMLRead. This section describes what SBMLRead returns and what its basic options are. The following sections provide examples on using SBMLRead.

2.1.1.SBMLRead Return Values

SBMLRead reads an SBML file and translates it into a *Mathematica* data structure consisting of *Mathematica* differential equations, intitial conditions, a list of variables, and replacement rules for constant parameters. SBMLRead can also be used to generate an interpretive listing of the SBML file. The return value of SBMLRead is a *Mathematica* rule list of the form

```
{SBMLODES → list of differential equations,
 SBMLParameters → list of parameter rules,
 SBMLIC → list of initial conditions,
 SBMLSpecies → list of variables,
 SBMLAlgebraicRules → list of algebraic rules,
 SBMLUnitDefinitions → list of unit definitions,
 SBMLUnitAssociations → list of unit associations,
 SBMLReactions → list of reactions,
 SBMLFunctions → list of pure function defintions,
 SBMLNameIDAssociations → list id / name associations,
 SBMLEvents → list of events,
 SBMLModelName → name of the model,
 SBMLNumericalSolution → numericalSolution
}
```

By default, all of this information is returned. However, the user is allowed to inhibit return of any portions of this information by using the return option to SBMLRead. The items highlighted in red (SBMLFunctions, SBMLNameIDAssociations, and SBMLEvents) are only provided for SBML Level 2.0 files and above.

Here *list of variables* has the form

```
{var1[t], var2[t], ... }
```

where each of var1, var2, etc., are variables that are governed by rate laws in the SBML models; i.e., any species, parameter, or compartment that is described by a rate law in a rule, and species that are either products or reactants in reactions, and are not boundary conditions. Each species in the SBML model is translated into a time-dependent function in the *Mathematica* model. In level 2, the "id" field is used to identify the variable. In level 1, the "name" field is used.

The global variable (i.e., in the *Mathematica* context Global`) t is reserved for time. It is anticipated that in future releases of MathSBML the name and context of the time variable can be reassigned at the user's direction. In contrast to the SBML specification, SBMLRead does not make use of the csymbol for time; this will also be corrected in future versions.

The *list of differential equations* has the form

```
{var1'[t] == expression1, var2'[t] == expression2, ... }
```

where *expression1*, *expression2*, ... are *Mathematica* expressions formed by applying all of the rules and reactions that affect that corresponding species. In level 2, the "id" field is used to identify all variables and constants in the expression. In level 1, the "name" field is used.

The *list of parameter rules* has the form

{par1 → *expression1*, par2 → *expression2*, ...}

where par2, par2, etc., are constant parameters or variable parameters described by scalar type ParameterRules; compartments with volumes that are either fixed or described by scalar type CompartmentVolumeRules; species that are described by scalar type SpeciesConcentrationRules; or species that are boundary condtions. The expressions are either constants (for fixed values) or algebraic expressions that give the value of the parameter. It is possible for the same parameter to be listed more than once in this list if the same local parameter name is used in multiple reactions. The parameters are listed in the same order in which they are defined in the SBML model. In level 2, the "id" field is used to identify the parameter. In level 1, the "name" field is used.

The *list of initial conditions* has the form

{var1[0] == *value1*, var2[0] == *value2*, ...}

where each of var1, var2, etc., are the same as defined in *list of variable*s above. There lengths of the lists of initial conditions, variables, and differential equations are all the same. As usual, In level 2, the "id" field is used to identify the variable. In level 1, the "name" field is used.

The *list of algebraic rules* has the form

{*expression1*==0, *expression2*==0, ...}

where *expression1*, *expression2*, ... are *Mathematica* expressions formed from the corresponding algebraicRule in the SBML file. In level 2, the "id" field is used to identify all variables. In level 1, the "name" field is used.

The *list of unit defintions* has the form

{*name1*→*def1*, *name2*→*def2*, ...}

where *name1*, *name2*, ... are *Mathematica* variables corrseponding to the name field of the corresponding unitDefinition; and *def1*, *def2*,... are *Mathematica* expressions defining the units in terms of the basic pre-defined units.

The *list of unit associations* has the form

{*name1*→*units1*, *name2*→*units2*, ...}

where *name1*, *name2*, ... are *Mathematica* variables (species, parameters, or compartments) and *units1*, *units2*,... are the units, either predefined or user-defined, corresponding to those variables.

The *list of reactions* has the form

{*reaction1*, *reaction2*, ...}

where each of the reactioni has the form

$$n_1\ r_1 + n_2\ r_2 + ... \longrightarrow m_1\ p_1 + m_2\ p_2 + ...$$

where $r_1, r_2,$ ... and $p_1, p_2,$ ... are the reactants and products in the reaction and n_1 ... and $m_1,$ ..., are the corresponding composite stoichiometry for each reactant or product. In level 1, the composite stoichiometry is given by $\sum (s_k / d_k)$ where s_k and d_k are the values of the `stoichiometry` and `denominator` field of the kth occurance of the corresponding reactanct or product in the reaction. In level 2, the stoichiometry is given by whatever mathematical formula is supplied. If the reaction is specified to be `reversible` in the model, then the double arrow form

$$n_1\ r_1 + n_2\ r_2 + ... \rightleftarrows m_1\ p_1 + m_2\ p_2 + ...$$

is used instead. Note: it is anticipated that the particular arrow used in the reactions (⟶, LongRightArrow) will be replaced in subsequent versions of MathSBML with (→, ShortRightArrow) because it provides more suitable infix-operator precedence. Both arrows are different from the **`Rule`** arrow (→, keystrokes ->).

The *list of pure function definitions* has the form

```
{id1→Function[...], id2→Function[...], ...}
```

where each *id1, id2*, ... are the function "`id`" fields specified in the SBML `Function[...],` is a standard *Mathematica* technique for defining a function. A pure function definition can be applied to an argument in *Mathematica* as *Function*`[...][`*argument*`]`. To illustrate what this means, suppose that the SBML model has the following function definition to implement the function foo(x) = $1 / (1 + x^2)$:

```
<functionDefinition id="foo">
    <math xmlns="http://www.w3.org/1998/Math/MathML">
    <lambda>
        <bvar><ci>x</ci></bvar>
        <apply>
            <times/>
            <cn>1</cn>
            <apply>
                <power/>
                <apply>
                    <plus/>
                    <apply>
                        <power/>
                        <ci>x</ci>
                        <cn>2</cn>
                    </apply>
                    <cn >1</cn>
                </apply>
                <cn>-1</cn>
            </apply>
        </apply>
    </lambda>
    </math>
    </functionDefinition>
```

This function will be expressed by MathSBML as

```
Example`foo→Function[{x},1/(x^2 + 1)]
```

which is a direct *Mathematica* implementation of a lambda-form. To evaluate this function, say to find *foo*(*y*+*z*), one would write

```
Function[{x},1/(x^2+1)][y+z]
```

to which *Mathematica* would return the expression

```
(1+(y+z)^2)^(-1).
```

Alternatively, one could define a function

```
foo[u_]:=Function[{x},1/(x^2 + 1)][u]
```

Typing `foo[y+z]` will evaluate the function at the point `y+z`, returning the same expression as before. More detail on pure functions is given *The Mathematica Book* [5th Edition, S. Wolfram, Cambridge University Press/Wolfram Media, 2003].

The *list of name/id associations* is a list of the form {*id1→name1, id2→name2,....*} describing the "`id`" and "`name`" fields for every object in the model for which a "`name`" is given.

The *list of events* describes the events in the SBML file in the following form,

```
{eventid1 →{"trigger"→trigger expression,
    "delay"→delay expression,
    "events"→{id1→event expression, id2→event expression, ...},
eventid2→{...}, ...}
```

where *eventid1, eventid2,* ... are the "`id`" fields of the named events; the *trigger expression* is the event trigger formatted as a *Mathematica* logical expression whose value will be True if and only if the trigger condition is met; the *delay expression* is a *Mathematica* algebraic expression giving the required time delay; and each *event expression* is a *Mathematica* algebraic expression that evaluates to the desired value as specified in the event.

The *numerical solution* is a list of interpolating functions as would typically be returned by NDSolve. Normally no numerical solution is generated by SBMLRead. To obtain a numerical solution the user would typically first call SBMLRead and then pass the result to SBMLNDSolve. For example,

```
m = SBMLRead["myfile.xml", ... ];
n = SBMLNDSolve[m, 200];
```

would read the file `myfile.xml` into the model m and then solve the model for 200 time units, returning a list of Interpolating Functions,

```
{{foo`var1→InterpolatingFunction[{0, 200}},<>][t],
  foo`var2→InterpolatingFunction[{0, 200}},<>][t],...}
```

In this situation, the model m would contain `{..., SBMLNumericalSolution→{}}`. Alternatively, the user can do this in a single step as

```
m = SBMLRead["myfile.xml",
        return→{...,SBMLNumericalSolution->200,...}, ... ];
```

in which case the value of SBMLNumericalSolution would be the same list of Interpolating Functions previously quoted. Using this option does not preclude the user for sending the model m to SBMLNDSolve again; however, the new solution will not overwrite the old solution in the model. Furthermore, the user can automatically send the output of SBMLNDSolve, if it is generated by SBMLRead, to SBMLPlot, but setting the option PlotOptions to anything besides a null list.

2.1.2.SBMLRead Options

The following table summarizes the options that are available to SBMLRead.

Option	Value	Description
context	Automatic	Context to use for model. Context → Automatic means generate context from the name of the model in the XML file. Context → None means place all variables in the Global` context. Note that if variables are placed in the Global` context then a clash with global or default *Mathematica* variables may occur, for example, the variables *E* and Pi, if they occur in the model, will be treated as the constants 2.718 ... and 3.14 ..., etc.
defaultIC	Indeterminate	Value to be used for initial conditions of variables when that are not assigned initial conditions in the model.
defaultParameterValue	Indeterminate	Value to be used for parameters thatare not assigned values inthe model.
evaluateParameters	True	Immediately evaluate all parameters before returning the model. Otherwise all parameters are returned in their symbolic form.
return	(see below)	Controls what gets returned by SBMLRead
PlotOptions	{}	If PlotOptions → True or PlotOptions → *any non – null list*, then the numerical solution will automatically be plotted. If the numerical solution is not requested (See return, below) then this will generate an error. PlotOptions may simply be True or any list of options to be passed to SBMLPlot and / or Plot.
verbose	False	Produce an interpretive listing; described in greater detail below.

The option return controls what is returned by SBMLRead. It is a list of option/value pairs; the default value is:

```
return→{
    SBMLODES→True,
    SBMLIC→True,
    SBMLParameters→True,
    SBMLSpecies→True,
    SBMLAlgebraicRules→True,
    SBMLUnitDefinitions→True,
```

```
SBMLUnitAssociations→True,
SBMLReactions→True,
SBMLNameIDAssociations→True,
SBMLEvents→True,
SBMLFunctions→True,
SBMLModelName→True,
SBMLNumericalSolution→0}
```

If any of the boolean options are set to `False`, then the corresponding field of the same name is not returned by . If `SBMLNumericalSolution` is any positive number then the model will automatically be passed to `SBMLNDSolve`.

In addition, `SBMLRead` may be used to produce a detailed interpretive listing of an SBML file. The additional options required for this are discussed below.

2.1.3. Variable naming conventions

SBMLRead will attempt to match the variable names (objects of type `SName`) in the *Mathematica* version of the model as closely as possible to the name given in the SBML version of the model.

SBML characters not allowed by *Mathematica:* The character "_" is reserved for pattern matching in *Mathematica*, and will normally be replaced with the character "‗". A different underline character may be used by setting the value of the option `underscore` to `SBMLRead`. The default value is `underscore→"‗"`. Hence an identifier `A_B` in the SBML becomes `A‗B` in the *Mathematica* model. To force all underscores to be replaced by a happy face character (ESC`:)`ESC), for example, use `SBMLRead[..., underscore→"☺"]`. The under-bracket character can be entered at the keyboard with either of the following keystroke sequences: the backslash character ("\") immediately followed by the string "[Under-Bracket]", or the key sequence ESC u [ESC (with no spaces between the characters). Note that when you hit the escape key, ESC, a vertical array of three short lines (⋮) will be displayed by *Mathematica*.

***Mathematica* representation of invalid characters in a model.** If a variable contains a character that is not in the standard `SName` set {'a'..'z', 'A'..'Z','0',..,'9'}, to ensure that the variable name is a legal *Mathematica* variable, the character will be replaced with the string *#n#* where *n* is the decimal unicode representation of the unusual character and # is the *Mathematica* (unicode 63268) character. (Aside note: The NumberSign character is not equivalent to the "#" on the keyboard, which has a unicode representation of 35. It may also be entered as ESC#ESC where # is the keyboard number sign, normally found on the number 3 key of US-standard keyboards, or us the backslash character ("`\`") followed by the string `[NumberSign]`). Thus if there is an (invalid) SBML identifier "`hello[world]`" in the SBML model it will be represented as "`Hello#91#World#93#`" in the *Mathematica* model. While this does not conform to the SBML standard, it provides consistent error recovery in the event of incorrectly formatted variables.

Scope of Variables. SBML model variables are defined in a local context; the name of the context is determined by the name of the model. Thus if the SBML model `foo` contains species `A` and `B`, and global parameters `f` and `k`, they will be represented as `foo`A`, `foo`B`, `foo`f`, and `foo`k`, respectively. Local parameters `k` and `kf` defined in reactions `R1` and `R2` will become `foo`R1`k`, `foo`R1`kf`, `foo`R2`k`, and `foo`R2`kf, respectively.

To override the use of the model name as the context, the `SBMLRead` option `context` may be used.

A short background on contexts is given in the following paragraphs; for additional information the user should refer to *The Mathematica Book* section 2.6.8.

Background on Contexts. *Mathematica* represents the scope of a symbol by its context. Different variables of the same name may exists independently of one another if they are defined in different contexts. They symbols `fred`foo` and

`barney`foo` represent to different variables, the first on context `fred`` and the second one in context `barney``. The "grave" or "backquote" character (unicode decimal representation 96, normally found just to the left of the number "1" key on most US keyboards) is used to separate the context name from the variable name.

Variables defined in the current context (which may be determined by entering `$Context`; the default value of `$Context` is `"Global`"`) do not have to be qualified by their context, although *Mathematica* is perfectly happy if you always use the full name `context`variable`. Normally all variables defined during an interactive *Mathematica* session are added to the Global` context. Thus if the variable `foo` is referenced during an interactive session, it is interpreted as `Global`foo`.

Mathematica also provides a global variable `$ContextPath` (its default value is `{Global`, System`}` that gives a list of contexts to search, after `$Context,` in trying to find the definintion of a symbol. After MathSBML is loaded (with the `<<MathSBML` command) then value of `$ContextPath` will be `{MathSBML`,Global`,System`}`. Thus if you refer to foo, *Mathematica* will first look for `MathSBML`foo`, then if it does not find it, will look for `Global`foo`, and then if it does not find it, will look for `System`foo`. If it still is not found, a new variable `$Context`foo` will be defined.

2.2. Example: Inport a model, run a simulation, and plot the results

Suppose we have a simple enzyme kinetic system

$$E + S \underset{r}{\overset{k_1}{\rightleftarrows}} \text{ES} \xrightarrow{k_2} P$$

where E, S, and P represent enzyme, substrate, and product, respectively, and ES is an intermediate complex that is formed during the reaction, and the rate constants are $k_1 = 3,\ r = 6,\ k_2 = 9$. Suppose also that the amount of S and P are assumed to be constant, while the amount of E and ES are allowed to vary. Initial conditions are taken as E(0)=1, ES(0)=0.01, S(0)=1, P(0)=0.01. These assumptions are taken to illustrate the properties of `MathSBML` and are not necessarily meant to represent a "real" biological system.

The SBML model shown in the box on the following page represents this model as a pair of reactions

$$E + S \underset{r}{\overset{k}{\rightleftarrows}} \text{ES}$$

$$\text{ES} \xrightarrow{k} P$$

where the k's in the two different reactions are assumed to be "local" parameters, i.e., the k in the first reaction is different from the k in the second reaction. Again, this assumption is made to illustrate `MathSBML` and would typically not be used by human-generated models (altough it might occur in machine generated models).

Suppose that this model resides in the file "`desktop/enzyme.xml`". To read the file into a *Mathematica* model stored in the variable r, we would use

```
r = SBMLRead["desktop/enzyme.xml"]
```

```
{SBMLODES → {EnzymeKinetics`E'[t] == -3. EnzymeKinetics`E[t] + 15. EnzymeKinetics`ES[t],
   EnzymeKinetics`ES'[t] == 3. EnzymeKinetics`E[t] - 15. EnzymeKinetics`ES[t]},
 SBMLIC → {EnzymeKinetics`E[0] == 1., EnzymeKinetics`ES[0] == 0.01}, SBMLParameters →
  {EnzymeKinetics`Cell → 1., EnzymeKinetics`S → 1., EnzymeKinetics`P → 0.01},
 SBMLSpecies → {EnzymeKinetics`E[t], EnzymeKinetics`ES[t]}, SBMLAlgebraicRules → {},
 SBMLUnitDefinitions → {substance → mole, volume → liter, time → second},
 SBMLUnitAssociations → {EnzymeKinetics`Cell → volume,
   EnzymeKinetics`S → substance, EnzymeKinetics`E → substance,
   EnzymeKinetics`ES → substance, EnzymeKinetics`P → substance},
 SBMLReactions → {EnzymeKinetics`E + EnzymeKinetics`S ⇄ EnzymeKinetics`ES,
   EnzymeKinetics`ES → EnzymeKinetics`E + EnzymeKinetics`P}}
```

Since there are two variable species (E, ES) and two fixed species (S, P), there are only two ODEs. The first three fields are directly compatible with NDSolve:

```
NDSolve[Join[SBMLODES /. r, SBMLIC /. r], SBMLSpecies /. r, {t, 0, 5}]
```

which returns:

```
{{EnzymeKinetics`E[t] → InterpolatingFunction[{{0., 5.}}, <>][t],
  EnzymeKinetics`ES[t] → InterpolatingFunction[{{0., 5.}}, <>][t]}}
```

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns="http://www.sbml.org/sbml/level1"  level="1" version="2">
    <model name="EnzymeKinetics">
        <listOfCompartments>
            <compartment name="Cell" volume="1"/>
        </listOfCompartments>
        <listOfSpecies>
            <species name="S" compartment="Cell"  initialAmount="1"
                boundaryCondition="true"/>
            <species name="E" compartment="Cell"  initialAmount="1"
                boundaryCondition="false"/>
            <species name="ES" compartment="Cell"  initialAmount=".01"
                boundaryCondition="false"/>
            <species name="P" compartment="Cell"  initialAmount="0.01"
                boundaryCondition="true"/>
        </listOfSpecies>
        <listOfReactions>
            <reaction name="Reaction1"  reversible="true">
                <listOfReactants>
                    <speciesReference  species="S"  stoichiometry="1"/>
                    <speciesReference  species="E"  stoichiometry="1"/>
                </listOfReactants>
                <listOfProducts>
                    <speciesReference  species="ES"  stoichiometry="1"/>
                </listOfProducts>
                <kineticLaw  formula="k*S*E-r*ES">
                    <listOfParameters>
                        <parameter name="k"  value="3"/>
                        <parameter name="r"  value="6"/>
                    </listOfParameters>
                </kineticLaw>
            </reaction>
            <reaction name="Reaction2"  reversible="false">
                <listOfReactants>
                    <speciesReference  species="ES"  stoichiometry="1"/>
                </listOfReactants>
                <listOfProducts>
                    <speciesReference  species="E"  stoichiometry="1"/>
                    <speciesReference  species="P"  stoichiometry="1"/>
                </listOfProducts>
                <kineticLaw  formula="k*ES">
                    <listOfParameters>
                        <parameter name="k"  value="9"/>
                    </listOfParameters>
                </kineticLaw>
            </reaction>
        </listOfReactions>
    </model>
</sbml>
```

The SBML model **enzyme.xml** used in section 2.2

The "a/.b" notation used above instructs *Mathematica* to evaluated all rules in the rule list b to expression a. A rule in *Mathematica* is an expression such as x→7. Thus the expression (x+y)/.{x→5,y→17+z*x} (or the equivalent expression ReplaceAll[x+y,{x→5,y→17+z*x}) would evaluate to 22+z*x. If additional rules are included in the list that are not relevant to the expression "a", they are ignored. Note that rules are only evaluated once; the x in the second rule is not set equal to 5. To do this, one would use the expression (x+y)//.{x→5,y→17+z*x} (or its equivalent expression ReplaceRepeated[x+y,{x→5,y→17+z*x}) which would evaluated to 22+5 (ReplaceRepeated can lead to infinite loops and should be used with care).

Since the above command is somewhat arduous to type in, the function SBMLNDSolve is available. The following syntax produces the same identical results as the preceeding one:

```
n = SBMLNDSolve[r, 5]
```

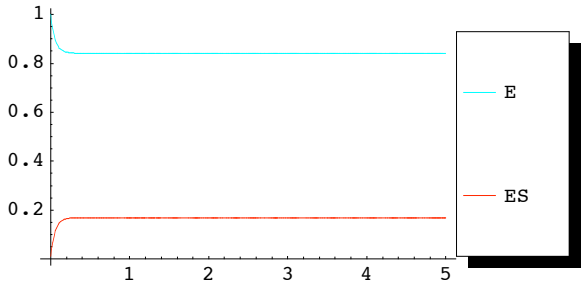
which returns:

```
{{EnzymeKinetics`E[t] → InterpolatingFunction[{{0., 5.}}, <>][t],
  EnzymeKinetics`ES[t] → InterpolatingFunction[{{0., 5.}}, <>][t]}}
```

SBMLNDSolve accepts any options that are valid for NDSolve. Additional details are provided in the Function Reference below.

The results may be plotted using SBMLPlot, which accepts as input the output of SBMLNDSolve.

```
SBMLPlot[n];
```



Observe that the context is not shown in the plot legend; in fact, it is EnzymeKinetics`E and EnzymeKinetics`ES that are plotted. This is done to improve readability of the plot.

2.3. Plotting with SBMLPlot

The output of `SBMLNDSolve` can be sent directly to `Plot`; however, because this can be tedious the function `SBMLPlot` is provided. It has the following formats:

Format	Description
`SBMLPlot[solution, options]`	Plot all variables in the solution for the entire duration of the simulation.
`SBMLPlot[solutions, {tbegin, tend}, options]`	Plot all variables in the solution from `t = tbegin` to `t = tend.`
`SBMLPlot[solution, {var1, var2,...}, {tbegin, tend}, options]`	Plot `var1, var2, ...` from `t = tbegin` to `t = tend.`

Any valid option for Plot may be used. In addition, the option

`type→"Log"`

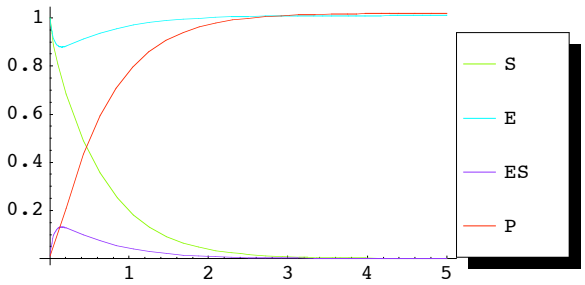
can be used to plot the y-axis on a log scale. For additional control over logarithmic plots the user should directly use `Graphics`Graphics`LogPlot` (to plot $log(y)$ as a function of x) , `Graphics`Graphics`LogLinearPlot` (to plot y as a function of $log(x)$, `Graphics`Graphics`LogLogPlot` (to plot $log(y)$ as a function of $log(x)$) (All of these functions are in the subcontext `` `Graphics `` of package `Graphics`, hence the word Graphics is repeated).

Suppose we modify the file `enzyme.xml` so that all the variables are allowed to change. We can do this by setting `boundaryCondition="false"` for all the variables in the SBML file, Suppose we name the modified file "`desktop/enzyme2.xml`". Now we will have four variables in our model.

```
r = SBMLRead["desktop/enzyme2.xml"];
n = SBMLNDSolve[r, 5]
```

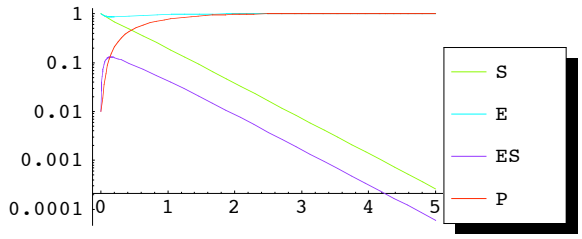
```
{{EnzymeKinetics`S[t] → InterpolatingFunction[{{0., 5.}}, <>][t],
  EnzymeKinetics`E[t] → InterpolatingFunction[{{0., 5.}}, <>][t],
  EnzymeKinetics`ES[t] → InterpolatingFunction[{{0., 5.}}, <>][t],
  EnzymeKinetics`P[t] → InterpolatingFunction[{{0., 5.}}, <>][t]}}
```

```
SBMLPlot[n]
```



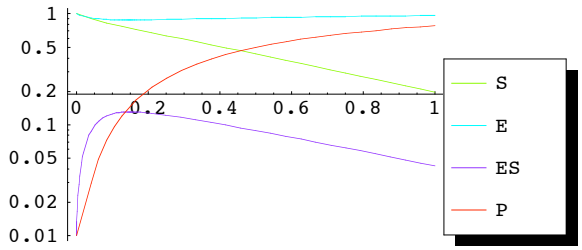
We can also plot the concentrations logarithmically,

```
SBMLPlot[n, type → "Log"]
```



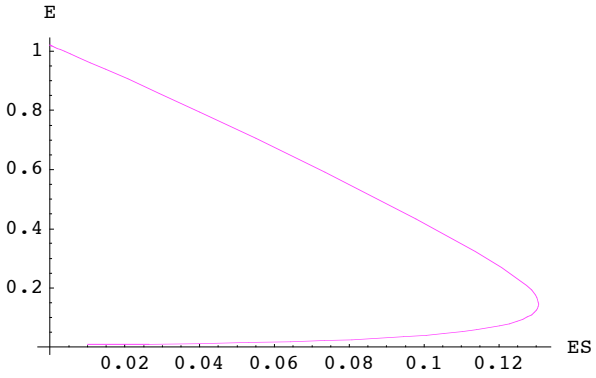
or zoom in on an interesting section of the plot:

```
SBMLPlot[n, {0, 1}, type → "Log"]
```



The output of `SBMLNDSolve` can be sent directly to any standard *Mathematica* plotting function; for example, the reaction in the E-ES phase plane can be produced as follows:

```
ParametricPlot[Evaluate[{EnzymeKinetics`ES[t], EnzymeKinetics`P[t]} /. n],
  {t, 0, 5}, AxesLabel → {"ES", "E"}, PlotStyle → RGBColor[1, 0, 1]];
```



2.4. Using MathSBML as an SBML file interpreter

The verbose option to SBMLRead allows one to produce readable listings of the files.

A number of options control the content of the verbose listing. These are summarized in the following table.

Option	Value	Description
align	Left	Alignment of verbose listing; any valid value for TextAlignment may be used.
concise	False	When True, overrides all verbose options. This option causes the most minimal output to be returned.
shortenODES	True	Display ODE's in short form, similar to the Short[] function.
showKineticLaw	True	Include kineticLaw in verbose reaction list.
showReactionParameters	True	Include list of local parameters for each reaction.
stats	False	Include a statistical summary of the file.
verbose	False	Print an interpretive listing of the SBML file.
verboseContext	False	Include the entire context of all variables in the verbose listing.

For example, to produce an interpretive listing of the file "desktop/enzyme.xml", we would use the following:

```
SBMLRead["desktop/enzyme.xml", verbose → True];
```

The output produced by this command is illustrated on the following page; the fonts are reduced somewhat in size to fit the information on a single page.

File Name:desktop/mathsbml−dbgfiles/enzyme.xml
SBML Level 1 Version 2

Model: EnzymeKinetics

Unit Definitions

----- None -----

Compartments

Name	Volume	Units	Derived Units	Outside
Cell	1.	volume	liter	···

Species

Name	I.C.	Units	Derived Units	Charge	Compartment	Var/B.C.
S	1.	substance	mole	0	Cell	Bound. Cond.
E	1.	substance	mole	0	Cell	Variable
ES	0.01	substance	mole	0	Cell	Variable
P	0.01	substance	mole	0	Cell	Bound. Cond.

Global Parameters

----- None -----

Rules

----- None -----

Reactions

Name	Reaction	Parameters	Kinetic Law
Reaction1	E + S ⇄ ES	k→3. r→6.	3.*E[t] - 6.*ES[t]
Reaction2	ES → E + P	k→9.	9.*ES[t]

Differential Equations from Reactions

Species	Differential Equations
E	E'[t] == -3.*E[t] + 15.*ES[t]
ES	ES'[t] == 3.*E[t] - 15.*ES[t]

3. Function Reference

This section contains usage information for MathSBML functions. This information may be retrieved during a *Mathematica* session any time after MathSBML has been imported by typing ?*functionName*. Pre-defined rate laws for SBML level 1 are defined in section 4. The functions in this section are listed alphabetically.

■ MathSBML`SBMLCopy

```
SBMLCopy[input, output, options] makes a copy of an SBML file to another SBML file,
  filtering the file through Mathematica's XML support to pretty-print the output
  in a more readable form.  The content of the XML is unchanged, but the formatting/
  indentation is standardized. The names of the file must be specified as strings.
If the output file already exists the output will be displayed on the screen. When
  checking for a pre-existing output file, the comparison is case-insensitive.
SBMLCopy[input] will write the output to the screen instead of to a file.

Options:
ExportOptions→option list
ImportOptions→option list

Example:SBMLCopy["myfile.xml", "yourfile.xml", ImportOptions→
  {CharacterEncoding→ "UTF8", ExportOptions→{CharacterEncoding-> "PrintableASCII"}]
```

For example, suppose the file "l1v1-minimal.xml" is formatted as follws:

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns="http://www.sbml.org/sbml/level1" level="1" version="1">
<model>
<listOfCompartments>
<compartment name="x"/>
</listOfCompartments>
<listOfSpecies>
<specie name="y" compartment="x" initialAmount="1"/>
</listOfSpecies>
<listOfReactions>
<reaction name="x">
<listOfReactants>
<specieReference specie="y"/>
</listOfReactants>
<listOfProducts>
<specieReference specie="y"/>
</listOfProducts>
</reaction>
</listOfReactions>
</model>
</sbml>
```

Then the expression

```
SBMLCopy["l1v1-minimal.xml", "l1v1-minimal-pretty-file.xml"]
```

will produce a second file, "l1v1-minimal-pretty-file.xml", as follows. The name of the file produced will be returned as the value of the function.

```
<?xml version='1.0' encoding='UTF-8'?>
<sbml xmlns='http://www.sbml.org/sbml/level1'
    level='1'
    version='1'>
 <model>
  <listOfCompartments>
   <compartment name='x'/>
  </listOfCompartments>
  <listOfSpecies>
   <specie name='y'
       compartment='x'
       initialAmount='1'/>
  </listOfSpecies>
  <listOfReactions>
   <reaction name='x'>
    <listOfReactants>
     <specieReference specie='y'/>
    </listOfReactants>
    <listOfProducts>
     <specieReference specie='y'/>
    </listOfProducts>
   </reaction>
  </listOfReactions>
 </model>
</sbml>
```

MathSBML`SBMLNDSolve

```
SBMLNDSolve[model, tmax,options] evaluates NDSolve on an
  SBML model, where model is the ouptput of SBMLRead, tmax is the duration
  of the NDSolve run, and options are any valid options for NDSolve.

Additional Notes and Limitations:

(1) units are ignored by SBMLNDSolve

(2) events are not currently processed by SBMLNDSolve. It is anticipated
  that this functionality will be added in a later version of SBMLNDSolve

(3) The inclusion of algebraic constraints (rules) along with
  differential equations to produce a system of Differential-Algebraic Equations
  requires Mathematica Version ≥ 5.0; version checking is performed dynamically.
```

Example

```
r = SBMLRead["desktop/enzyme.xml", concise → True];
n = SBMLNDSolve[r, 300, MaxSteps → 5000]
```

```
{{EnzymeKinetics`E[t] → InterpolatingFunction[{{0., 300.}}, <>][t],
  EnzymeKinetics`ES[t] → InterpolatingFunction[{{0., 300.}}, <>][t]}}
```

```
{{X[t] → InterpolatingFunction[{{0., 300.}}, <>][t],
  Y[t] → InterpolatingFunction[{{0., 300.}}, <>][t],
  Z[t] → InterpolatingFunction[{{0., 300.}}, <>][t]}}
```

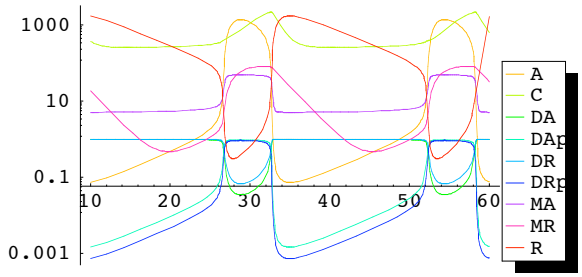
■ MathSBML`SBMLPlot

```
SBMLPlot[solution, {var1, var2,...}, {tbegin, tend}, options] plots the results of a simulation.
solution is either the output of SBMLNDSolve
  or the output of an SBMLRead run with numerical solution enabled.
The variables named var1, var2,.. are plotted from t=tbegin to t=tend on a
  single plot. The context of the variable name must be specified, i.e., if
  the model identifier is foo, to plot variables A and C only but not any other
  variable, one would invoke SBMLPlot[solution, {foo`A,foo`C}, {tbegin,tend}].
SBMLPlot[solutions,{tbegin,tend}, options] plots all variables
  in the solution set for the specified time range.
SBMLPlot[solution,options] plots all variables for the entire duration of the run.

Any valid option for Plot may be used.

Additional options:
variables→ var or {var1, var2, ...} or "All"; gives the names of the variables to
  be plotted. If this option is omitted all variables are plotted. The context of
  the variable name must be specified, i.e., if the model identifier is foo, to plot
  variables A and C only but not any other variable, one would specify variables→
  {foo`A,foo`C}. If any of the variable names is All then all variables will be
  plotted. Note: This option is only available in SBMLPlot[solution,options] form.
type→"Log", if specified, the y-axis is logarithmic.
```

■ Example

The following example reads the file "vilar.xml" that is available on the http://www.sbml.org model repository, runs a simulation for 100 time units, and plots the results on a logarithmic scale from t=10 through t = 60.

```
r = SBMLRead["desktop/vilar.xml", concise → True];
n = SBMLNDSolve[r, 100, MaxSteps → 25000];
SBMLPlot[n, {10, 60}, type → "Log"]
```



■ MathSBML`SBMLRead

```
? SBMLRead

SBMLRead[filename, options] returns an option list of the form:

{
SBMLODES→{v1'[t]==expression, v2'[t]==expression,...},
SBMLParameters→{k1→value,k2→value,...},
SBMLIC→{v1[0]==value,v2[0]==value,...},
SBMLSpecies→{v1[t],v2[2],..},
SBMLAlgebraicRules→{expression1==0, expression2==0, ...},
SBMLUnitDefinitions→{unitName1→unitDefinition1, unitName2→unitDefinition2,...},
SBMLUnitAssociations→{var1→units1,var2→units2,...},
SBMLReactions→{reaction1, reaction2,...},
SBMLModelName→name,
SBMLNameIDAssociations→{id1→name1,id2→name2},
SBMLFunctions→{function1→def, function2→def,...},
SBMLEvents→{event1def1, eventdef2,,..},
SBMLNumericalSolution→numerical solution
}

where v1,v2,... give all of the species in the SBML file; the expression gives the derived
  differential equation for that species; value (following SBMLParameters or SBMLIC) is the SBML
  value of the associated parameter or initial condition; unitName1,... are user-defined units;
  unitDefinition1,... are expressions that give the unit definitions in terms of pre-defined
  units; units1,... are the units that correspond to variable var1,..., which can be either
  species, parameter, or compartment; reaction1,reaction2,... are the reactions in standard
  biochemical form Σi Ri ⟶ Σj Pj, where R and P are the reactants and products in each reaction.
SBMLFunctions, SBMLEvents, and SBMLNameIDAssociations only apply for Level 2.
Event definitions have the form id→{"trigger"→expression,"delay"→
  expression,"events"→{var1→exp1,var2→exp2,...}} where id is the event id (assigned
  to Event__n if not provided); and expression, etc., are Mathematica expressions.
SBMLFunctions have the form {id→Function[...], id→Function[...],..} where Function[...] gives
  a pure Mathematica Function definition and id is the corresponding SBML id for the function.
Any portion of the returned option list may be turned off with the option return.
SBMLNumericalSolution is the output of SBMLNDsolve, if a numerical solution is requested.

The intention is that this format contains all information
  necessary to pass the model to NDSolve in the following manner:

r=SBMLRead[filename,options]
Apply[NDSolve,{Join[SBMLODES/.r, SBMLIC/.r]/.
  (SBMLParameters/.r), SBMLSpecies/.r,{t,0,tmax},NDSolveOptions}]

where NDSolveOptions are any valid options
  for NDSolve and tmax is the duration of the NDSolve Rule.

Options for SBMLRead are:

align→"Left", alignment of verbose output on screen. Any valid
  values of TextAlignment may be used; since the value is passed directly to
  TextAlignment without error checking invalid values will result in the default
  value of TextAlignment ("Left"). This option is ignored unless verbose→True.
concise→False. When  True, overrides whatever values are set to verbose, warnings,
  and stats to set all of them to False. This option minimizes the written output.
context→"Automatic" (default), assign all global model variables to a context
  given by the model name; thus variables x,y,z in them SBML become modelname`x,
  modelname`y, modelname`z in the Mathematica representation.  Local parameters
  in reactions will be assigned a context modelname`reactionname, i.e., if
```

reaction20 in model foo has a parameter k it will be called foo`reaction20`k.
context→str, where str is any string. All variables will be assigned to the context str` (reaction parameters to context str`reactioname`) instead of modelname`. The terminating "`" character is optional.
context→"None", all model variables are placed in the Global` context. Be aware that this could be dangerous, as symbols in the model could collide with other variables previously defined in the Mathematica environment and lead to unexpected results.
defaultIC→Indeterminate, if reassigned, then all unspecified initial conditions will be set to the value of defaultIC. Otherwise they will remain Indeterminate.
defaultParameterValue→Indeterminate, if reassigned, then all unspecified parameter values will be set to the value of defaultIC. Otherwise they will remain Indeterminate.
evaluateParameters→True, immediately evaluate parameters in reactions, otherwise return reactions with symbolic parameters.
NDSolveOptions→{}, options to be passed to NDSolve; ignored unless SBMLNumericalSolution→ n, withing return, as in return→{SBMLNumericalSolution→ 25, ...}, where n>0 is a number.
PlotOptions→{} contains a list of options to be passed to SBMLPlot, including any options to be passed to Plot. If this option is omitted or a null list, no plot is generated. A warning message will be generated if the user does not also request a numerical solution by setting SBMLNumericalSolution to a positive value as part of the return options.
return→{SBMLODES→True, SBMLIC→True, SBMLParameters→True, SBMLSpecies→True, SBMLAlgebraicRules→True, SBMLUnitDefinitions→True, SBMLUnitAssociations→True, SBMLReactions→True, SBMLFunctions→True, SBMLEvents→True, SBMLNameIDAssociations→True, SBMLModelName→True, SBMLNumericalSolution→0}; this option allows the user to control the return value of SBMLRead. All boolean items are returned except for those set to False. A numerical solution is only returned if SBMLNumericalSolution evaluates to a positive number. Setting return→None is equivalent to setting everything to False.
shortenODES→False, ignored unless verbose→True and showKineticlaw→True. If shortenODES→ False (default), then the entire differential equation will be displayed in the verbose listing; if shortenODES→True then the Mathematica Short[..] version will be used.
showKineticLaw→True, ignored unless verbose→True; if showKineticLaw→True(default), the SBML kinetic law is shown in the reaction-listing of the verbose display; otherwise the kinetic laws are not displayed in the reactions table
showReactionParameters→True, ignored unless verbose→True; if showReactionParameters→True(default), the local parameters in each reaction are shown in the reaction-listing of the verbose display; otherwise the local parameters are not displayed in the reactions table
stats→False, print a statistical summary of the file
underscore→"__", character (or string) that is used to replace the underscore ("_") charcter in SBML indentifiers.
verbose→False, if True, print an interpretive table of the SBML
verbosecontext→False, if True, the context (scope) of all variables will be indicated in the verbose display. If False, only the pure model variable will be indicated. This option will be ignored unless verbose→True.
warnings→ True, if False, warning messages will be suppressed.

Additional Notes and Limitations of SBMLRead

(1) SBMLRead does not perform XML or SBML validation. If invalid SBML or XML is supplied, unexpected results can occur. In general, incorrectly formatted XML will cause *Mathematica*'s Import[..] function to print an error message indicating the line number for the first error and then *Mathematica* will terminate.

(2) SBMLRead is currently only compatible with SBML Level 1 (versions 1 and 2) and Level 2 (version 1). Subsequent releases will support higher levels.

(3) In SBML Level 1, all of the mathematical functions (e.g., abs, acos, etc.) are fully supported. Thus cos(x)becomes Cos[x], etc. Predefined rate law functions are recognized as functions but are not implemented. Thus,if the function umr(*argument list*) is specified in the SBML,it will be recognized as a predefined function and will be expanded in the *Mathematica* model as umr[*argument list*]. However, unlike the mathematical functions,no implementation is provided.Thus if the model contains ths functions,the user must supply a *Mathematica*i mplementation for umr,etc.

(4) By default, all parameters are replaced with their numerical values as specified in the model. This can be switched off using the option evaluateParameters, in which case SBMLRead will return a list of *Mathematica* replacement rules of the form *name→ value*.

(5) The topological relationship specified by the outside attribute in a compartment definition is ignored, although SBMLRead will display the relationship in the verbose listing. If no outside component exists, the *Mathematica* variable Indeterminate is displayed.

(6) The reversible parameter of the reaction type is ignored with the following exception: reversible reactions in the list of reactions returned (SBMLReactions) will use the double arrow (⇄) instead of the single forward arrow (⟶).

(7) In SBML Level 1, Unspecified initial conditions and parameter values will be labeled as Indeterminate if they are not specified,and a warning message will be printed. Models with Indeterminate parameters and initial conditions will cause an error in NDSolve. To prevent this from happening,the user can optionally specify the options defaultParameterValue and defaultIC to set all Indeterminate parameter values and initial conditions.For example, defaultParameterValue-> 1 will set all Indeterminate parameters equal to 1. Unspecified units will be labeled as Indeterminate in the verbose listing,but no association will be returned for indeterminate units.

(8) Annotations and notes are ignored.

■ Example

```
r = SBMLRead["desktop/enzyme.xml", concise → True]
```

```
{SBMLODES → {EnzymeKinetics`E′[t] == -3. EnzymeKinetics`E[t] + 15. EnzymeKinetics`ES[t],
   EnzymeKinetics`ES′[t] == 3. EnzymeKinetics`E[t] - 15. EnzymeKinetics`ES[t]},
 SBMLIC → {EnzymeKinetics`E[0] == 1., EnzymeKinetics`ES[0] == 0.01}, SBMLParameters →
  {EnzymeKinetics`Cell → 1., EnzymeKinetics`S → 1., EnzymeKinetics`P → 0.01},
 SBMLSpecies → {EnzymeKinetics`E[t], EnzymeKinetics`ES[t]}, SBMLAlgebraicRules → {},
 SBMLUnitDefinitions → {substance → mole, volume → liter, time → second},
 SBMLUnitAssociations → {EnzymeKinetics`Cell → volume,
   EnzymeKinetics`S → substance, EnzymeKinetics`E → substance,
   EnzymeKinetics`ES → substance, EnzymeKinetics`P → substance},
 SBMLReactions → {EnzymeKinetics`E + EnzymeKinetics`S ⇄ EnzymeKinetics`ES,
   EnzymeKinetics`ES → EnzymeKinetics`E + EnzymeKinetics`P}}
```

MathSBML`SBMLWrite

SBMLWrite[options] will write a model in a specified format as determined by the options.

Options are:

inputfile→*string*, name of SBML file that is to be converted (read).An inputfile is required.
outputfile→*string*, name of file that output is
written to. If not specified, the output is written to the screen
format→*string*, type of output to produce. If no format is specified or an
invalid format is specified the original model will be returned. Valid formats
are: "Fortran", "HTML", "XPP" (the value of format is case-insensitve).
It is anticipated that other formats will be added in future releases.

Notes for XPP format:

(1) XPP implmentation is limited to ODEs, parameters, and intial condtions. It is
anticipated that more complex forms will be allowed in future release of MathSBML.

(2) SBML functions are not implemented in XPP files. Instead, they are instantiated in place.

(3) By default, assignment rules are not instantiated
before evaluation. To force evaluate of assignment rules, use the option
evaluateParameters→True. This will also force evaluation of all parameters.

(4) SBML events are not implemented in XPP files.

(5) Parameters or initial conditions that are not set in the model will be
assigned a value of Indeterminate in the XPP file, which is not a valid XPP value.

Notes for Fortran Format:

(1) Fortran format is developmental

(2) The output file will contain the three subroutines res, addp, and jac required by lsodi

(3) Documentation of lsodi can be found at http://netlib.org/alliant/ode/prog/lsodi.f

(4) The output file will also contain a subroutine init that sets the initial condition.

(5) The output file also contains two modules for each event in the file, a
logical function trigger_<*event*> that returns the boolean value of the event's
trigger given the values of all the system's state variables, and a subroutine
activate_<*event*> that modifies the system's state variables as per the event.

(6) The user is expected implement his/her own driver software
that utilizes the event files and calls lsodi or some other solver as
required. An example (without events) is provided in the lsodi documentation.

(7) Because lsodi does not directly support events, if
the model contains events the user will need to write wrappers for the
subroutines provided that make them compatible with his/her chosen solver.

(8) Parameters in the model such as foo`k and foo`r1`k will become fooxk and fooxr1xk

Example - XPP output to screen

```
SBMLWrite[inputfile → "enzyme.xml", format → "XPP"]
```

```
# Model Name:    EnzymeKinetics
#
# Creation Time: 30-June-2003 16:51:05.965258
# User:          jamestkirk
# Machine:       Slartibartifast
# System:        PowerPC PowerMac MacOSX
# Generated by MathSBML 2.0 beta 16 (1 July 2003)
#
# Differential Equations
#
EnzymeKinetics_E'=-3.*EnzymeKinetics_E+15.*EnzymeKinetics_ES
EnzymeKinetics_ES'=3.*EnzymeKinetics_E-15.*EnzymeKinetics_ES
#
#
# Parameters
#
par EnzymeKinetics_Cell=1.
par EnzymeKinetics_S=1.
par EnzymeKinetics_P=0.01
#
#
# Initial Conditions
#
init EnzymeKinetics_E=1.
init EnzymeKinetics_ES=0.01
#
done
```

Example - XPP output to file

```
SBMLWrite[inputfile → "enzyme.xml", format → "XPP", outputfile → "desktop/test.ode"]
```

```
desktop/test.ode
```

Example - Fortran output for pure differential system without algebraic rules

```
SBMLWrite[inputfile → "enzyme.xml", format → "Fortran"]
```

```
C SBML Model Name:  EnzymeKinetics
C
C Generated by MathSBML 2.0.3 (7 Aug 2003)
C Creation Time: 7-August-2003 18:31:25.176289
C User:          jamestkirk
C Machine:       Slartibartifast
C Processor:     PowerPC
C Machine type:  PowerMac
```

```
C Oper. System:  MacOSX
C ------------------------------------------------------
C
C lsodi compliant SBML model
C Reference: http://netlib.org/alliant/ode/prog/lsodi.f
C
C ------------------------------------------------------
C
C This file contains the following modules:
C
C Module Name       Description
C ----------------- ---------------------------------------
C addp (subroutine) Add A to any matrix - required by lsodi
C init (subroutine) Set initial conditions
C jac (subroutine)  Compute Jacobian - required by lsodi
C res (subroutine)  Calculate Residuals - required by lsodi
C
C ------------------------------------------------------
C
      subroutine res(neq,t,y,s,r,ires)
      double precision r,s,t,y
C
C This is subroutine res for lsodi
C This function computes the residuals r(i)=g(t,y)- A(t,y)(dy/dt)
C for the linear-implicit system system (A)*(dy/dt)=g(t,y)
C where A is a constant, possibly singular, matrix.
C
C Here A is diagonal with (restriction imposed by SBML, not lsodi)
C       A(i,i)=1, i=1,...,m, where m=# of odes in the SBML Model
C       A(i,i)=0, i=m+1,...,m+nrules, where nrules =# of algebraic rules
C       A(i,i)=0, i=nrules+1,...,nvars, where nvars is the total number
C                 of variables in the system and nvars-nrules-m>0 is the
C                 number of variables controlled purely by events
C
C If the system is purely differential
C the right-hand side of the system dydt = g(y,t) will
C be returned if s is zero-filled.
C
C Representation of Model Variables by the array y
C ------------------------------------------------
C y(1) = E
C y(2) = ES
C
      dimension r(2),s(2),y(2)
      r(1)=-s(1) - 3.*y(1) + 15.*y(2)
      r(2)=-s(2) + 3.*y(1) - 15.*y(2)
      return
      end
C
C
C ------------------------------------------------------
C
      subroutine addp(neq, t, y, ml, mu, p, nrowp)
C
C Subroutine addp required by lsodi
C
      double precision p, t, y
      dimension y(2), p(nrowp,2)
```

```
      integer i
      Do i = 1,2
         p(i,i) = p(i,i)+1
      End Do
      return
      end
C
C -----------------------------------------------------------
C
      subroutine jac (neq,t,y,s,ml,mu,p,nrowp)
C
C Subroutine jac required by lsodi, computes jacobian
C
      dimension y(2), s(2),p(nrowp,2)

      p(1,1)=-3.
      p(1,2)=15.
      p(2,1)=3.
      p(2,2)=-15.

      return
      end
C
C -----------------------------------------------------------
C
      Subroutine init(neq,y)
      double precision y
      dimension y(2)
      y(1)=1.
      y(2)=0.01
      return
      end
```

4. Predefined Rate Laws

The rate laws for **hillmr**, **hillmmr**, **ucii**, **icir**, **unii**, **unir**, **uuci**, **umi**, **ucti**, **umail**, **uhmi**, **ordubr**, **ordbur**, **ordbbr** and **ppbr** are tentative pending clarification of ambiguities in the SBML spec. The order and number of arguments in the functions **hillmr**, **hillmmr**, **uci**, **ucir**, **unir**, **ordbur**, and **ordbbr** is subject to change when these ambiguites are resolved.

The function **massr** is not implemented. It is equivalent to **massi[Si,k1]-massi[Pj,k2]**

■ massi

massi[S_1,S_2,...,S_n,k] is a predefined rate law for
  Irreversible Mass Action Kinetics that returns a velocity v=k*S_1*S_2*S_3⋯S_n;
massi[k] returns v=k;
massi[] returns v=1.

■ massr

massr is not implemented in MathSBML becasue massr[S_i,...,P_j,...,
  k_1,k_2] can be unambiguously written as massr[S_i,...,k_1]-massr[,P_j,...,k_2].

■ uui

uui[S,V_m,K_m] is is a predefined rate law for Irreversible
  Simple Michaelis-Mentin Kinetics that returns a velocity $v=\frac{V_m * S}{K_m + S}$.

■ uur

uur[S,P,V_f,V_r,K_{ms},K_{mp}] is a predefined rate law for Uni-Uni Reversible
  Simple Michaelis-Menten Kinetics that returns a velocity $v=\frac{V_f\ (S / K_{ms}) - V_r\ (P / K_{mp})}{1 + (P / K_{mp}) + (S / K_{ms})}$.

■ uuhr

uuhr[S,P,V_f,K_{m1},K_{m2},K_{eq}] is a predefined rate law for Uni-Uni Reversible Simple Michaelis-
  Menten Kinetics with Haldane Adjustment. The rate law returned is $v=\frac{(V_f / m1)\ (S - P / K_{eq})}{1 + S / m1 + P / K_{m2}}$.

■ isouur

isouur[S, P, V_f, K_{ms}, K_{mp}, K_{ii}, K_{eq}]is a predefined rate law for Iso Uni-Uni kinetics. The rate law returned is $\frac{V_f\ (S - P / K_{eq})}{(S\ (1 + P / K_{ii}) + K_{ms}\ (1 + P / K_{mp}))}$.

■ hilli

hilli[S, V, K,h] is a predefined rate law for Hill Kinetics. The rate law returned is v= $\frac{V * S^h}{K^h + S^h}$.

■ hillr

hillr[S, P,V_f, S_{half},P_{half},h, K_{eq}] is a predefined rate law for reversible Hill kinetics. The rate law is $\frac{S\left(1 - \frac{P}{S\,K_{eq}}\right)\left(\frac{P}{P_{half}} + \frac{S}{S_{half}}\right)^{-1+h} V_f}{\left(1 + \left(\frac{P}{P_{half}} + \frac{S}{S_{half}}\right)^h\right) S_{half}}$.

■ hillmr

hillmr[S,P,V_f, $S_{0.5}$,$P_{0.5}$, $M_{0.5}$, V_f, K_{eq},k,h,α] is a predefined rate law for reversible Hill kinetics with one modifier. The rate law is $\frac{S\left(1 - \frac{P}{S\,K_{eq}}\right)\left(\frac{P}{P_{0.5}} + \frac{S}{S_{0.5}}\right)^{-1+h} V_f}{(K_1 + K_2)\,S_{0.5}}$ where $K_1 = \left(\frac{P}{P_{0.5}} + \frac{S}{S_{0.5}}\right)^h$ and $K_2 = \frac{1 + \left(\frac{V_f}{M_{0.5}}\right)^h}{1 + \alpha\left(\frac{V_f}{M_{0.5}}\right)^h}$.

■ hillmmr

hillmmr::usage

■ usii

usii[S,V,K_m,K_i] is a predefined rate law for substrate inhibition kinetics (irreversible). The rate law returned is $\frac{S\,V}{\left(1 + \frac{S^2}{K_i} + \frac{S}{K_m}\right) K_m}$.

■ usir

usir[S,P,V_f,V_r,K_{ms},K_{mp},K_i] is a predefined rate law for substrate inhibition kinetics (reversible). The rate law returned is $\frac{\frac{S V_f}{K_{ms}} + \frac{P V_r}{K_{mp}}}{1 + \frac{S^2}{K_i} + \frac{P}{K_{mp}} + \frac{S}{K_{ms}}}$.

■ uai

uai[S,V,K_{sa},K_{sc}] is a predefined rate law for substrate activation. The rate law returned is $\frac{S^2 V}{K_{sa}^2 \left(1 + \frac{S^2}{K_{sa}^2} + \frac{S}{K_{sa}} + \frac{S}{K_{sc}}\right)}$.

■ ucii

ucii[S,V,K_m,K_i] is a predefined rate law for competitive inhibition (irreversible). The rate law returned is $\frac{S V}{\left(1 + \frac{1}{K_i} + \frac{S}{K_m}\right) K_m}$.

■ ucir

ucir[S, P,Inh, V_f, V_r, K_{ms}, K_{mp}, K_i] is a predefined rate law for competitive inhibition (reversible). The rate law returned is $\frac{\frac{S V_f}{K_{ms}} - \frac{P V_r}{K_{mp}}}{1 + \frac{Inh}{K_i} + \frac{P}{K_{mp}} + \frac{S}{K_{ms}}}$.

■ unii

unii[S, Inh, V, K_m,K_i]is a predefined rate law for noncompetitive inhibition (irreversible). The rate law returned is $\frac{S V}{\left(1 + \frac{Inh}{K_i} + \frac{S\left(1+\frac{Inh}{K_i}\right)}{K_m}\right) K_m}$.

■ unir

unir[S, P, Inh, V_f, V_r,K_{ms}, K_{mp}, K_i] is a predefined rate law for noncompetitive inhibition (reversible). The rate law returned is $\frac{\frac{S V_f}{K_{ms}} - \frac{P V_r}{K_{mp}}}{1 + \frac{Inh}{K_i} + \left(1 + \frac{Inh}{K_i}\right)\left(\frac{P}{K_{mp}} + \frac{S}{K_{ms}}\right)}$.

■ uuci

uuci[S,Inh,V,K_m,K_i] is a predefined rate law for uncompetitive inhibition (irreversible). The rate law returned is $\frac{S\,V}{\left(1+\frac{S\left(1+\frac{Inh}{K_i}\right)}{K_m}\right)K_m}$.

■ uucr

uucr[S,P,Inh,V_f, V_r, K_{ms},K_{mp}, K_i] is a predefined rate law for uncompetitive inhibition (reversible). The rate law returned is $\frac{\frac{S\,V_f}{K_{ms}}-\frac{P\,V_r}{K_{mp}}}{1+\left(1+\frac{Inh}{K_i}\right)\left(\frac{P}{K_{mp}}+\frac{S}{K_{ms}}\right)}$.

■ umi

umi[S,Inh,V,K_m, K_{is}, K_{ic}] is a predefined rate law for mixed inhibition kinetics (irreversible). The rate law returned is $\frac{S\,V}{\left(1+\frac{Inh}{K_{is}}+\frac{S\left(1+\frac{Inh}{K_{ic}}\right)}{K_m}\right)K_m}$.

■ umr

umr[S,P,Inh,V_f,V_r, K_{ms},K_{mp}, K_{is}, K_{ic}] is a predefined rate law for mixed inhibition kinetics (reversible). The rate law returned is $\frac{\frac{S\,V_f}{K_{ms}}-\frac{P\,V_r}{K_{mp}}}{1+\frac{Inh}{K_{is}}+\left(1+\frac{Inh}{K_{ic}}\right)\left(\frac{P}{K_{mp}}+\frac{S}{K_{ms}}\right)}$.

■ uaii

uaii[S, A_c,V,K_m,K_a] is a predefined rate law for specific action kinetics (irreversible). The rate law returned is $\frac{S\,V}{\left(1+\frac{K_a}{A_c}+\frac{S}{K_m}\right)K_m}$.

■ uar

uar[S,P,A_c,V_f, V_r, K_{ms}, K_{mp}, K_a] is a predefined rate law for specific action kinetics (reversible). The rate law returned is $\frac{\frac{S\,V_f}{K_{ms}}-\frac{P\,V_r}{K_{mp}}}{1+\frac{K_a}{A_c}+\frac{P}{K_{mp}}+\frac{S}{K_{ms}}}$.

■ ucti

ucti[S, A_c, V, K_m, K_a] is a predefined rate law for catalytic activation (irreversible). The rate law returned is $\frac{S\,V}{\left(1+\frac{K_a}{A_c}+\frac{S\left(1+\frac{K_a}{A_c}\right)}{K_m}\right)K_m}$.

■ uctr

uctr[S, P, A_c, V_f, V_r, K_{ms}, K_{mp}, K_a] is a predefined rate law for catalytic activation (reversible). The rate law returned is $\frac{\frac{S\,V_f}{K_{ms}}-\frac{P\,V_r}{K_{mp}}}{1+\frac{K_a}{A_c}+\left(1+\frac{K_a}{A_c}\right)\left(\frac{P}{K_{mp}}+\frac{S}{K_{ms}}\right)}$.

■ umai

umai[S, A_c, V, K_m, K_{as}, K_{ac}] is a predefined rate law for mixed activation kinetics (irreversible). The rate law returned is $\frac{S\,V}{\left(1+\frac{K_{as}}{A_c}+\frac{S\left(1+\frac{K_{ac}}{A_c}\right)}{K_m}\right)K_m}$.

■ umar

umar[S, P, A_c, V_f, V_r, K_{ms}, K_{mp}, K_{as}, K_{ac}] is a predefined rate law for mixed activation kinetics (reversible). The rate law returned is $\frac{\frac{S\,V_f}{K_{ms}}-\frac{P\,V_r}{K_{mp}}}{1+\frac{K_{as}}{A_c}+\left(1+\frac{K_{ac}}{A_c}\right)\left(\frac{P}{K_{mp}}+\frac{S}{K_{ms}}\right)}$.

■ uhmi

uhmi[S, M, V, K_m, K_d, a, b] is a predefined rate law for general hyperbolic modifier kinetics (irreversible). The rate law returned is $\frac{S\,V\left(1+\frac{b\,M}{a\,K_d}\right)}{\left(1+\frac{M}{K_d}+\frac{S\left(1+\frac{M}{a\,K_d}\right)}{K_m}\right)K_m}$.

■ uhmr

uhmr[S, P, M,V_f, V_r, K_{ms}, K_{mp}, K_d, a, b] is a predefined rate law for general hyperbolic modifier kinetics (reversible). The rate law returned is $\frac{\left(1+\frac{b\,M}{a\,K_d}\right)\left(\frac{S\,V_f}{K_{ms}}-\frac{P\,V_r}{K_{mp}}\right)}{1+\frac{M}{K_d}+\left(1+\frac{M}{a\,K_d}\right)\left(\frac{P}{K_{mp}}+\frac{S}{K_{ms}}\right)}$.

■ ualii

ualii[S, Inh, V, K_s, K_{ii}, n, L] is a predefined rate law for allosteric inhibition (irreversible). The rate law returned is $\frac{S\,V\left(1+\frac{S}{K_s}\right)^{-1+n}}{\left(L\left(1+\frac{Inh}{K_{ii}}\right)^n+\left(1+\frac{S}{K_s}\right)^n\right)K_s}$.

■ ordubr

ordubr[A, P, Q, V_f, V_r, K_{ma}, K_{mq}, K_{mp}, K_{ip},K_{eq}] is a predefined rate for Ordered Uni-Bi Kinetics. The rate law returned is $\frac{\left(A-\frac{P\,Q}{K_{eq}}\right)V_f}{A\left(1+\frac{P}{K_{ip}}\right)+K_{ma}+\frac{(P\,Q+Q\,K_{mp}+P\,K_{mq})\,V_f}{K_{eq}\,V_r}}$.

■ ordbur

ordbur[A, B, P, V_f, V_r, K_{ma}, K_{mb}, K_{mp}, K_{ia}, K_{eq}] is a predefined rate for Ordered Bi-Uni Kinetics. The rate law returned is $\frac{\left(A\,B-\frac{P}{K_{eq}}\right)V_f}{A\,B+B\,K_{ma}+A\,K_{mb}+\frac{\left(P\left(1+\frac{A}{K_{ia}}\right)+K_{mp}\right)V_f}{K_{eq}\,V_r}}$.

■ ordbbr

ordbbr[argument list tbd] is a predefined rate for Ordered Bi-Bi Kinetics. The rate law returned is not defined because of ambiguities in the SBML specification.

■ ppbr

ppbr[A, B, P, Q, V_f,V_r, K_{ma}, K_{mb}, K_{mp}, K_{mq}, K_{ia},K_{iq}, K_{eq}] is a predefined rate for Ping-Pong Bi-Bi Kinetics. The rate law returned is $\frac{\left(A\,B-\frac{P\,Q}{K_{eq}}\right)V_f}{A\,B+B\left(1+\frac{Q}{K_{iq}}\right)K_{ma}+A\,K_{mb}+\frac{\left(Q\,(P+K_{mp})+P\left(1+\frac{A}{K_{ia}}\right)K_{mq}\right)V_f}{K_{eq}\,V_r}}$.

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