The Distributions Package for SBML Level 3

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Disclaimer: This is a working draft of the SBML Level 3 "distib" package proposal. It is not a normative document. Please send comments and other feedback to the mailing list: sbml-distrib@lists.sourceforge.net.

Contents

Revision History

Version	Date	Author	Comments
0.1 (Draft)	15 Oct 2011	Stuart Moodie	First draft
0.2 (Draft)	16 Oct 2011	Stuart Moodie	Added introductory text and background info. Other minor changes etc.
0.3 (Draft)	16 Oct 2011	Stuart Moodie	Filled empty invocation semantics section.
0.4 (Draft)	4 Jan 2012	Stuart Moodie	Incorporated comments from NlN, MS and SK. Some minor revisions and corrections.
0.5 (Draft)	6 Jan 2012	Stuart Moodie	Incorporated addition comments on aim of package from NlN.
0.6 (Draft)	19 Jul 2012	Stuart Moodie	Incorporated revisions discussed and agreed at HARMONY 2012.
0.7 (Draft)	6 Aug 2012	Stuart Moodie	Incorporated review comments from Maciej Swat and Sarah Keating.

1 Introduction and motivation

1.1 What is it?

The Distributions package (also affectionately known as distrib for short) provides an extension to SBML Level 3 that enables it to encode models that sample values from statistical distributions. Applications of the package include for instance descriptions population based models: an important subset of which are pharmacokinetic/pharmacodynamic (PK/PD) models[1], which are used to model the action of drugs.

Note that originally the package was called Distributions and Ranges, but Ranges are no longer in the scope of this hence the name change.

1.2 Scope

The Distributions package adds support to SBML for sampling from a probability distribution in parts of an SBML model that are **not** continuously evaluated. in particular the following are in scope:

- Sampling from a continuous distribution.
- Sampling from a discrete distribution.
- Sampling from user-defined probability density function.
- Sampling from user-defined discrete probability density.

At one point the following were considered for inclusion in this package but are now **out of scope**:

- Stochastic differential equations.
- Cumulative distribution functions.
- Description of the uncertainty of a model parameter: for example, standard deviation, standard error and similar descriptive statistics.[2]

1.3 This Document

The authors' expectation is that this is close to a final draft of the proposal with only a limited number of issues to be resolved. In its current state this document aims to establish a consensus about what has been agreed and what work remains to be carried out to complete the definition of this package.

This proposal is a working document and once finalised will be the first step towards the formal adoption of the distrib as a package in SBML Level 3. After this two implementations based on this proposal are required and then a vote on its adoption by the SBML community. The proposal will then provide the basis for a future package specification document. More details of the SBML package adoption process can be found at: http://sbml.org/Documents/SBML_Development_Process.

Please also note that in this draft of the proposal a list of the exact probability distributions to be supported has not been included. This is because at present it is envisaged that distrib will refer to an external definition of probability distributions (see sections 3.10 and 7).

1.4 Conventions used in this document

As we are early in the package proposal process there will be some parts of this proposal where there is no clear consensus on the correct solution or only recent agreement or agreement by a group which may not be representative of the SBML community as a whole. These cases are indicated by the question mark in the left margin

?

[1] for more information see: http://www.pharmpk.com/.

[2] It is proposed that this be provided descriptive statistics in a separate package.

(illustrated). The reader should pay particular attention to these points and ideally provide feedback, especially if they disagree with what is proposed. Similarly there will be points — especially as the proposal is consolidated — ☞ which are agreed, but which the reader should take note of and perhaps read again. These points are emphasised by the hand pointer in the left margin (illustrated.

2 Background

2.1 Problems with current SBML approaches

SBML Level 3 Core has no direct support for providing random values within a model. Currently there is no workaround and this makes it impossible to describe models that use probability distributions.

2.2 Past work on this problem or similar topics

2.2.1 The Newcastle Proposal

In 2005 there was a proposal from Colin Gillespie and others [3] to introduce support for probability distributions in the SBML core specification. This was based on their need to use such distributions to represent the models they were creating as part of the BASIS project http://www.basis.ncl.ac.uk).

They proposed that distributions could be referred to in SBML using the **csymbol** element in the MathML subset used by the SBML Core specification. An example is below:

```
<xmlns=''http://www.w3.org/1998/Math/MathML''>
  <apply>
    <csymbol encoding=''text''
        definitionURL=''http://www.sbml.org/sbml/symbols/uniformRandom''>
      uniformRandom
    </csymbol>
    <ci>mu</ci>
    <ci>sigma</ci>
  </apply>
</math>
```

This required that a library of definitions be maintained as part of the SBML standard and in their proposal they defined an initial small set of commonly used distributions. The proposal was never implemented.

2.2.2 Seattle 2010

The "distrib" package was discussed at the Seattle SBML Hackathon[4]. There one of the authors (DW) presented an overview of the problem[5][6], building on the old proposal from the Newcastle group (see above: 2.2.1). There was broad support at the meeting for development of such a package, and for the proposed feature set. Discussion following the presentation led to a consensus on the following points:

- There is an urgent need for such a package.
- It is important to make a distinction between a description of uncertainty regarding a model parameter and the mechanistic process of selecting a random number from a probability distribution, for applications such as parameter scans and experimental design
- It is probably worth including the definition of PMFs, PDFs and CDFs in the package
- It is worth including the definition of random distributions using particle representations within such a package, though some work still needs to be done on the precise representation
- It could be worth exploring the use of xinclude to point at particle representations held in a separate file
- Random numbers must not be used in rate laws or anywhere else that is continuously evaluated, as then simulation behaviour is not defined

[3] http://sbml.org/Community/Wiki/SBML_Level_3_Proposals/Distributions_and_Ranges
[4] http://sbml.org/Events/Hackathons/The_2010_SBML-BioModels.net_Hackathon
[5] Slides: http://sbml.org/images/3/3b/Djw-sbml-hackathon-2010-05-04.pdf
[6] Audio: http://sbml.org/images/6/67/Wilkinson-distributions-2010-05-04.mov

- Although there is a need for a package for describing extrinsic noise via stochastic differential equations in SBML, such mechanisms should not be included in this package due to the considerable implications for simulator developers
- We probably don't want to layer on top of UncertML (www.uncertml.org), as this spec is fairly heavy-weight, and somewhat tangential to our requirements
- A random number seed is not part of a model and should not be included in the package
- The definition of truncated distributions and the specification of hard upper and lower bounds on random quantities should be considered.

It was suggested that new constructs should be introduced into SBML by the package embedded as user-defined functions using the following syntax:

```
<listOfFunctionDefinitions>
  <functionDefinition id="myNormRand">
    <distrib:####>
      #### distrib binding information here ####
    </distrib:####>
    <math>
      <lambda>
        <bvar>
          <ci>mu</ci>
          <ci>sigma</ci>
        </bvar>
        <ci>mu</ci>
      </lambda>
    </math>
  </functionDefinition>
</listOfFunctionDefinitions>
```

which allows the use of a "default value" by simulators which do not understand the package (but simulators which do will ignore the <math> element). The package would nevertheless be "required", as it will not be simulated correctly by software which does not understand the package.

Informal discussions following the break-out covered topics such as how to work with vector random quantities in the absence of the vector element in the MathML subset used by SBML, and the care that must be taken with the semantics of random variables and the need to both a) reference multiple independent random quantities at a given time and b) make multiple references to the same random quantity at a given time.

2.2.3 Hinxton 2011

Detailed discussion was continued at the Statistical Models Workshop in Hinxton in June 2011[7]. There those interested in representing Statistical Models in SBML came together to work out the details of how this package would work in detail. Dan Cornford from the UncertML project[8] attended the meeting and described how that resource could be used to describe uncertainty and in particular probability distributions. Perhaps the most significant decision at this meeting was to adopt the UncertML resource as a controlled vocabulary that is referenced by the Distributions package.

Much of the detail and the examples in this proposal are based on the work of this workshop and so its outcomes are essentially presented below. However, at the end of the meeting there remained a number of unresolved issues that are still unresolved in this proposal. See section 7 on page 24 for more details.

2.2.4 HARMONY 2012: Maastricht

Two sessions were dedicated to discussion of Distributions at HARMONY based around the proposals described in version 0.5 of this document. In addition there was discussion about the Arrays and Sets proposal which was

[7] http://sbml.org/Events/Other_Events/statistical_models_workshop_2011
[8] http://www.uncertml.org/

very helpful in solving the problem of multivariate distributions in Distributions. The following were the agreed outcomes of the meeting:

- The original proposal included UncertML markup directly in the function definition. This proved unwieldy and confusing and has been replaced by a more elegant solution that eliminates the UncertML markup and integrates well with the fallback function (see details below).
- Multivariate distributions can be supported using the Arrays and Sets package to define a covariance matrix.
- User defined continuous distributions would define a PDF in MathML.
- Usage semantics were clarified so that invokation of a function definition implied a value was sampled from the specified distribution.
- It was agreed from which sections of an SBML model a distribution could be invoked.
- Statistical descriptors of variables (for example mean and standard deviation) would be separated from Distributions and either provided in a new package or in a later version of SBML L3 core.

2.2.5 COMBINE 2012: Toronto

3 Proposed syntax and semantics

3.1 Colour Conventions

Throughout this document, in all UML diagrams, classes that exists in SBML Level 3 core or another existing standard are displayed in black. If those elements are extended in this proposal, those extensions are displayed in green. Classes that are new to this proposal are shown in blue.

3.2 Defining Distributions

The Distributions package has a very simple purpose. It defines a statistical distribution, range or statistic from which you can obtain a value that is used in other parts of an SBML model. The distribution is defined using UncertML, which is a resource that defines probabilistic uncertainties Williams et al. (2009), or explicitly using MathML Ausbrooks et al. (2003).

SBML Core is extended at the **FunctionDefinition** class as can be seen in the UML representation in figure 1. The extended **FunctionDefinition** can optionally contain a single instance of a new class **externalDefinition** or **explicitPDF** or **explicitPMF**.

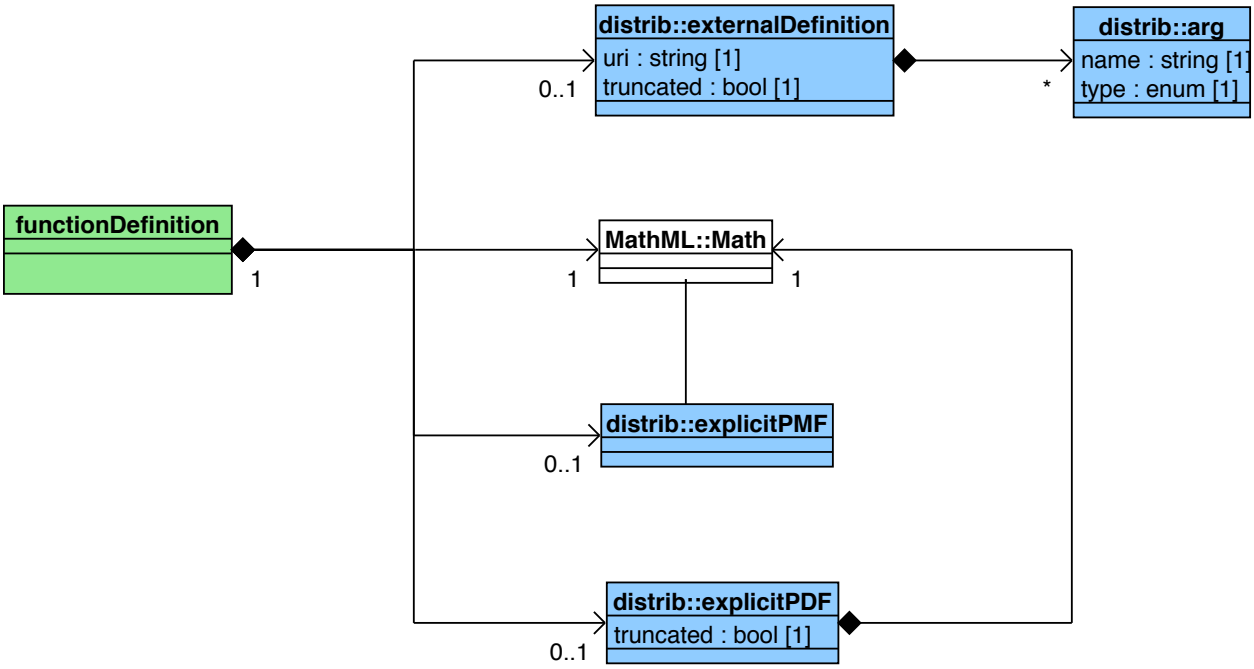

Figure 1: *UML class diagram for the Distributions package. This diagram describes the classes involved and not instances of those classes. Note the UML packages indicate that the classes belong to different namespaces. The namespace of the SBML Core is not shown.*

3.3 Extension Handling

The Distributions package is defined as a required package, which means that an SBML model that uses that extension will not be correctly defined unless the features of the extension are used and interpreted correctly by supporting software.

3.4 FunctionDefinition Extension

As outlined above the **FunctionDefinition** is extended to contain the following classes from distrib.

- **externalDefinition**
- **explicitPDF**
- **explicitPMF**

3.5 externalDefinition

This declares a statistical distribution by referring to an external normative definition. UncertML is the recommended source of such definitions. The attributes of the class are defined below.

`uri`

This provides the external definition of the distribution to be invoked. The value of the attribute should be a URI that uniquely identifies a definition from an external resource. The exact nature of this URI and the external resource to use is discussed below (section 3.10). The attribute is mandatory.

`truncated`

This attribute indicates that a distribution is to be truncated, if true or not if false. How this truncation is to be implemented is tool specific. When set to true an additional two arguments are implied when invoking the distribution. These arguments are appended to those already required by the distribution and are invoked in the order they are described below.

lower limit The lower boundary of the truncation.

upper limit The upper boundary of the truncation.

3.6 explicitPDF

This class defines a probability density function (PDF) explicitly and so provides a continuous probability distribution that can be sampled. The PDF is defined as a mathematical function using MathML. The distribution can be truncated.

truncated

See the truncated attribute in section 3.5.

3.7 explicitPMF

This class defines a discrete probability distribution described by a user-defined probability mass function (PMF). Here the PMF is defined as a category and its associated probability.

3.8 Using the distrib package

The distribution defined by a **FunctionDefinition** instance can be used by instances of the following SBML classes:

- InitialAssignment
- EventAssignments
- Delays
- Priorities

An invocation of a distribution behaves like any other function call in SMBL and the function is executed. For a statistical distribution this means that one or more values are sampled from the distribution each time the function definition is invoked.

3.9 Permitted Types

The Distributions package will support arrays and matrices via the Arrays and Sets package. This means that paramaters passed to a function definition can be arrays, matrices or scalar values and that a functions return type can be either a scalar or the above non-scalar types. Type consistency and conversion behaviour between scalar and non-scalar types is defined by the Arrays and Sets package.

3.10 External Definition of Distributions

The external definition is a URI that should refer to a standardised dictionary of distributions. It should unambiguously define the following:

- A globally unique URI by which to refer to it.
- The parameter arguments used by the function, including for each argument: its name and type (scalar or non-scalar). Note that all arguments are mandatory.
- The value and its type returned by the function.
- A detailed mathematics description of the statistical distribution being sampled from.

The recommended external definition for distributions is UncertML. We have been liaising with the UncertML team to ensure that they meet the above criteria.

3.11 Equivalence with Fallback Function

The MathML definition directly contained by the **functionDefinition** is not used and is provided solely to satisfy the *validity upon reduction* rule for packages. This rules states that the SBML document must be syntactically valid if all package specific elements are removed from it. To ensure that this is the case the fallback function used in relation to distrib must satisfy the following rules:

- the lambda function should have the same number of arguments as its equivalent distribution (defined by distrib).
- Each argument should match the type of the equivalent argument in the external function.
- The lambda function should have the same return type as the *sampled* distribution. For example an explicit PDF when sampled will return a scalar value, in which case the dummy function should also do so.

Clearly these rules can only be enforced by a distrib aware validator.

4 Package dependencies

This package is dependent on the Arrays and Sets package to provide array and matrix structures. It is also dependent on MathML Ausbrooks et al. (2003) to define distributions explicitly. It uses the the subset of MathML set out in the SMBL Level 3 Core Specification Hucka et al. (2010).

5 Use-cases and examples

5.0.1 Sampling from a distribution: PK/PD Model

This is a very straightforward use of an externally defined distribution. The key point to note is that a value is sampled from the distribution and assigned to a variable when it is invoked. In the initialAssignments element in this example. Later use of the variable does not result in re-sampling from the distribution. This is consistent with current SBML semantics.

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns="http://www.sbml.org/sbml/level3/version1/core" level="3" version="1"
    xmlns:distrib="http://www.sbml.org/sbml/level3/version1/distrib/version1"
    distrib:required="true">
    <model id="PKModel" name="PKModel" substanceUnits="item"
          timeUnits="second" volumeUnits="litre" extentUnits="item">
        <listOfFunctionDefinitions>
    <functionDefinition id="logNormal">
      <!-- Note that this is the same as a truncated distribution. In this example the upper
     and lower bounds are infinity so there is no truncation -->
      <distrib:externalDefinition uri="http://www.uncertml.org/distributions/log-normal" truncated="false">
        <distrib:arg name="mean" type="scalar"/>
        <distrib:arg name="variance" type="scalar"/>
      </distrib:externalDefinition>
      <!-- below is a dummy function provided to ensure valid SBML Core
     for software that do not understand distrib. -->
      <math xmlns="http://www.w3.org/1998/Math/MathML">
        <lambda>
    <bvar><ci>mean</ci></bvar>
    <bvar><ci>variance</ci></bvar>
    <apply>
      <cn>0</cn>
    </apply>
        </lambda>
      </math>
    </functionDefinition>
        </listOfFunctionDefinitions>
        <listOfCompartments>
            <compartment id="central" name="central" size="0" constant="true"/>
            <compartment id="gut" name="gut" size="0" constant="true"/>
        </listOfCompartments>
        <listOfSpecies>
            <species id="Qc" compartment="central" initialAmount="1"
               hasOnlySubstanceUnits="true" boundaryCondition="false" constant="false"/>
            <species id="Qg" compartment="gut" initialAmount="1"
               hasOnlySubstanceUnits="true" boundaryCondition="false" constant="false"/>
        </listOfSpecies>
        <listOfParameters>
            <parameter id="ka" value="1" constant="true"/>
            <parameter id="ke" value="1" constant="true"/>
            <parameter id="Cc" value="1" constant="false"/>
            <parameter id="Cc_obs" value="1" constant="false"/>
        </listOfParameters>
        <listOfInitialAssignments>
            <initialAssignment symbol="central">
                <math xmlns="http://www.w3.org/1998/Math/MathML">
                    <apply>
                        <ci>logNormal</ci>
                        <cn>0.5</cn>
                        <cn>0.1</cn>
                    </apply>
                </math>
            </initialAssignment>
            <initialAssignment symbol="ka">
                <math xmlns="http://www.w3.org/1998/Math/MathML">
```

```
                <apply>
                    <ci>logNormal</ci>
                    <cn>0.5</cn>
                    <cn>0.1</cn>
                </apply>
            </math>
        </initialAssignment>
        <initialAssignment symbol="ke">
            <math xmlns="http://www.w3.org/1998/Math/MathML">
                <apply>
                    <ci>logNormal</ci>
                    <cn>0.5</cn>
                    <cn>0.1</cn>
                </apply>
            </math>
        </initialAssignment>
    </listOfInitialAssignments>
    <listOfRules>
        <assignmentRule variable="Cc">
            <math xmlns="http://www.w3.org/1998/Math/MathML">
                <apply>
                    <divide/>
                    <ci> Qc </ci>
                    <ci> central </ci>
                </apply>
            </math>
        </assignmentRule>
        <assignmentRule variable="Cc_obs">
            <math xmlns="http://www.w3.org/1998/Math/MathML">
                <apply>
                    <plus/>
                    <ci> Cc </ci>
                    <cn type="integer"> 1 </cn>
                </apply>
            </math>
        </assignmentRule>
    </listOfRules>
    <listOfReactions>
        <reaction id="absorption" reversible="false" fast="false">
            <listOfReactants>
                <speciesReference species="Qg" stoichiometry="1" constant="false"/>
            </listOfReactants>
            <listOfProducts>
                <speciesReference species="Qc" stoichiometry="1" constant="false"/>
            </listOfProducts>
            <kineticLaw>
                <math xmlns="http://www.w3.org/1998/Math/MathML">
                    <apply>
                        <times/>
                        <ci> ka </ci>
                        <ci> Qg </ci>
                    </apply>
                </math>
            </kineticLaw>
        </reaction>
        <reaction id="excretion" reversible="false" fast="false">
            <listOfReactants>
                <speciesReference species="Qc" stoichiometry="1" constant="false"/>
            </listOfReactants>
            <kineticLaw>
                <math xmlns="http://www.w3.org/1998/Math/MathML">
                    <apply>
                        <divide/>
                        <apply>
                            <times/>
                            <ci> ke </ci>
                            <ci> Qc </ci>
```

```
                            </apply>
                            <ci> central </ci>
                        </apply>
                    </math>
                </kineticLaw>
            </reaction>
        </listOfReactions>
    </model>
</sbml>
```

5.1 Truncated distribution

To encode a truncated distribution we rely on external definitions. Clearly it would be cumbersome if every distribution and multivariate distribution required a truncated equivalent definition, but at present this is what is required. Perhaps this problem could be solved if optional function arguments were permitted, but this cases problems with the fallback function (see section 7).

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns="http://www.sbml.org/sbml/level3/version1/core" level="3" version="1"
      xmlns:distrib="http://www.sbml.org/sbml/level3/version1/distrib/version1"
      distrib:required="true">
  <!-- Note that this is a code snippet and not a valid model -->
  <model>
    <listOfFunctionDefinitions>
      <!-- We treat truncated distributions as any other distribution. The externally
     defined function handles the truncation. -->
      <functionDefinition id="normal">
  <distrib:externalDefinition uri="http://www.uncertml.org/distributions/normal" truncated="true">
    <distrib:arg name="mean" type="scalar" order="1"/>
    <distrib:arg name="variance" type="scalar" order="2"/>
  </distrib:externalDefinition>
  <math xmlns="http://www.w3.org/1998/Math/MathML"
        xmlns:sbml="http://www.sbml.org/sbml/level3/version1/core">
    <lambda>
      <bvar><ci>mu</ci></bvar>
      <bvar><ci>sigma</ci></bvar>
      <bvar><ci>lower</ci></bvar>
      <bvar><ci>upper</ci></bvar>
      <apply>
        <ci>mu</ci>
      </apply>
    </lambda>
  </math>
      </functionDefinition>
    </listOfFunctionDefinitions>
    <listOfParameters>
      <parameter id="V" constant="true"/>
      <parameter id="V_pop" constant="true"/>
      <parameter id="V_omega" constant="true"/>
      <parameter id="V_upper" constant="true"/>
      <parameter id="V_lower" constant="true"/>
    </listOfParameters>
    <initialAssignments>
      <initialAssignment symbol="V_pop">
  <math xmlns="http://www.w3.org/1998/Math/MathML"
        xmlns:sbml="http://www.sbml.org/sbml/level3/version1/core">
    <apply>
      <cn>105</cn>
    </apply>
  </math>
      </initialAssignment>
      <initialAssignment symbol="V_upper">
  <math xmlns="http://www.w3.org/1998/Math/MathML"
        xmlns:sbml="http://www.sbml.org/sbml/level3/version1/core">
```

```
    <apply>
      <cn>150</cn>
    </apply>
  </math>
      </initialAssignment>
      <initialAssignment symbol="V_lower">
  <math xmlns="http://www.w3.org/1998/Math/MathML"
        xmlns:sbml="http://www.sbml.org/sbml/level3/version1/core">
    <apply>
      <cn>15</cn>
    </apply>
  </math>
      </initialAssignment>
      <initialAssignment symbol="V_omega">
  <math xmlns="http://www.w3.org/1998/Math/MathML"
        xmlns:sbml="http://www.sbml.org/sbml/level3/version1/core">
    <apply>
      <cn>0.70</cn>
    </apply>
  </math>
      </initialAssignment>
      <initialAssignment symbol="V">
  <math xmlns="http://www.w3.org/1998/Math/MathML"
        xmlns:sbml="http://www.sbml.org/sbml/level3/version1/core">
    <apply>
      <ci>normal</ci>
      <ci>V_pop</ci>
      <ci>V_omega</ci>
      <ci>V_upper</ci>
      <ci>V_lower</ci>
    </apply>
  </math>
      </initialAssignment>
    </initialAssignments>
  </model>
</sbml>
```

5.2 Multivariate distribution

In this example two correlated parameters are sampled from a multivariate distribution. The correlation is defined using a covariance matrix and the sampled values are returned as a vector of 2 values, which are then assigned to the individual parameters. This example relies heavily on the arrays package, which will be a dependency of the distrib package.

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns="http://www.sbml.org/sbml/level3/version1/core" level="3" version="1"
      xmlns:distrib="http://www.sbml.org/sbml/level3/version1/distrib/version1"
      distrib:required="true"
      xmlns:arrays="http://www.sbml.org/sbml/level3/version1/arrays/version1"
      arrays:required="true">
  <!-- NOTE: This requires the arrays package! -->
  <model id="MultivariateExample" name="Multivariate␣Example" substanceUnits="item"
   timeUnits="second" volumeUnits="litre" extentUnits="item">
    <listOfFunctionDefinitions>
      <functionDefinition id="multivariateNormal">
  <distrib:externalDefinition uri="http://identifiers.org/Distribution/MultivariateNormal"/>
  <math xmlns="http://www.w3.org/1998/Math/MathML"
        xmlns:sbml="http://www.sbml.org/sbml/level3/version1/core">
    <lambda>
      <bvar><ci>meanVector</ci></bvar>
      <bvar><ci>covarianceMatrix</ci></bvar>
      <bvar><ci>lowerVector</ci></bvar>
      <bvar><ci>upperVector</ci></bvar>
      <apply>
```

```
      <ci>meanVector</ci>
    </apply>
  </lambda>
</math>
    </functionDefinition>
  </listOfFunctionDefinitions>
  <listOfParameters>
    <parameter id="V">
      <arrays:ArrayParameter>

      </arrays:ArrayParameter>
    </parameter>
    <parameter id="V" constant="true"/>
    <parameter id="V_pop" constant="true"/>
    <parameter id="V_omega" constant="true"/>
    <parameter id="Cl" constant="true"/>
    <parameter id="Cl_pop" constant="true"/>
    <parameter id="Cl_omega" constant="true"/>
    <parameter id="covariance" constant="true">
<arrays:listOfDimensions>
  <arrays:dimension id="i" lowerLimit="1" upperLimit="2" />
  <arrays:dimension id="j" lowerLimit="1" upperLimit="2" />
</arrays:listOfDimensions>
    </parameter>
    <parameter id="correlated_means" constant="true">
<arrays:listOfDimensions>
  <arrays:dimension id="i" lowerLimit="1" upperLimit="2" />
</arrays:listOfDimensions>
    </parameter>
    <parameter id="limit_vector" constant="true">
<arrays:listOfDimensions>
  <arrays:dimension id="i" lowerLimit="1" upperLimit="2" />
</arrays:listOfDimensions>
    </parameter>
    <parameter id="correlated_params" constant="true">
<arrays:listOfDimensions>
  <arrays:dimension id="i" lowerLimit="1" upperLimit="2" />
</arrays:listOfDimensions>
    </parameter>
  </listOfParameters>
  <listOfInitialAssignments>
    <initialAssignment symbol="V_pop">
<math xmlns="http://www.w3.org/1998/Math/MathML"
      xmlns:sbml="http://www.sbml.org/sbml/level3/version1/core">
  <apply>
    <cn>105</cn>
  </apply>
</math>
    </initialAssignment>
    <initialAssignment symbol="V_omega">
<math xmlns="http://www.w3.org/1998/Math/MathML"
      xmlns:sbml="http://www.sbml.org/sbml/level3/version1/core">
  <apply>
    <cn>0.70</cn>
  </apply>
</math>
    </initialAssignment>
    <initialAssignment symbol="Cl_pop">
<math xmlns="http://www.w3.org/1998/Math/MathML"
      xmlns:sbml="http://www.sbml.org/sbml/level3/version1/core">
  <apply>
    <cn>73</cn>
  </apply>
</math>
    </initialAssignment>
    <initialAssignment symbol="Cl_omega">
<math xmlns="http://www.w3.org/1998/Math/MathML"
```

```
      xmlns:sbml="http://www.sbml.org/sbml/level3/version1/core">
  <apply>
    <cn>0.70</cn>
  </apply>
</math>
    </initialAssignment>
    <initialAssignment symbol="covariance">
<math xmlns="http://www.w3.org/1998/Math/MathML"
      xmlns:sbml="http://www.sbml.org/sbml/level3/version1/arraymaths/version1">
  <!-- This is an unresolved issue. The l3 V1 Core mathml subset does not support
      matrices. One solution - as above is to use a different MathML subset definition.
  -->
  <matrix>
    <matrixrow>
      <apply><times/><ci>V_omega</ci><ci>V_omega</ci></apply>
      <apply><times/><ci>V_omega</ci><ci>C_omega</ci><ci>V_C_rho</ci></apply>
    </matrixrow>
    <matrixrow>
      <ci>0</ci>
      <apply><times/><ci>C_omega</ci><ci>C_omega</ci></apply>
    </matrixrow>
  </matrix>
</math>
    </initialAssignment>
    <initialAssignment symbol="correlated_means">
<math xmlns="http://www.w3.org/1998/Math/MathML"
      xmlns:sbml="http://www.sbml.org/sbml/level3/version1/core">
  <vector>
    <ci>V_pop</ci>
    <ci>C_pop</ci>
  </vector>
</math>
    </initialAssignment>
    <initialAssignment symbol="limit_vector">
<math xmlns="http://www.w3.org/1998/Math/MathML"
      xmlns:sbml="http://www.sbml.org/sbml/level3/version1/core">
  <vector>
    <infinity/>
    <infinity/>
  </vector>
</math>
    </initialAssignment>
    <initialAssignment symbol="correlated_params" >
<math xmlns="http://www.w3.org/1998/Math/MathML"
      xmlns:sbml="http://www.sbml.org/sbml/level3/version1/core">
  <apply>
    <ci>multivariateNormal</ci><ci>correlated_means</ci><ci>covariance</ci><ci>limitVector</ci><ci>limitVector</ci>
  </apply>
</math>
    </initialAssignment>
    <initialAssignment symbol="Cl">
<math xmlns="http://www.w3.org/1998/Math/MathML"
      xmlns:sbml="http://www.sbml.org/sbml/level3/version1/core">
  <apply>
    <selector/>
    <ci>correlated_params</ci>
    <cn type="integer">2</cn>
  </apply>
</math>
    </initialAssignment>
    <initialAssignment symbol="V">
<math xmlns="http://www.w3.org/1998/Math/MathML"
      xmlns:sbml="http://www.sbml.org/sbml/level3/version1/core">
  <apply>
    <selector/>
    <ci>correlated_params</ci>
    <cn type="integer">1</cn>
```

```
    </apply>
  </math>
      </initialAssignment>
    </listOfInitialAssignments>
    <-- This is an incomplete model snippet, sufficient to illustrate the use of
    a multivariate distribution. -->
  </model>
</sbml>
```

5.3 User-defined continuous distribution

In this example an additional construct is used to indicate:

- that the MathML within the function definition defines a PDF and so is not a fallback.
- that when invoked a value should be sampled from this PDF.

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns="http://www.sbml.org/sbml/level3/version1/core" level="3" version="1"
      xmlns:distrib="http://www.sbml.org/sbml/level3/version1/distrib/version1"
      distrib:required="true">
  <!-- Code snippet. Not a valid model. -->
  <model id="UserDefined" name="User␣Defined␣Example" substanceUnits="item"
         timeUnits="second" volumeUnits="litre" extentUnits="item">
    <listOfFunctionDefinitions>
      <functionDefinition>
  <distrib:explicitPDF truncated="false">
        <!-- Function defines a PDF using MathML. The implied behaviour is that
            A value will be sampled from the distribution described by this PDF -->
        <math xmlns="http://www.w3.org/1998/Math/MathML">
          <lambda>
            <bvar><ci>mu</ci></bvar>
            <bvar><ci>omega</ci></bvar>
            <apply>
              <apply>
                <times />
                <apply>
                  <power />
                  <exponentiale />
                  <apply>
                    <times />
                    <apply>
                      <times />
                      <cn type='integer'>-1</cn>
                      <cn type='rational'>1<sep />2</cn>
                    </apply>
                    <apply>
                      <power />
                      <apply>
                        <times />
                        <apply>
                          <plus />
                          <ci>x</ci>
                          <apply>
                            <times />
                            <cn type='integer'>-1</cn>
                            <ci>mu</ci>
                          </apply>
                        </apply>
                        <apply>
                          <power />
                          <ci>sigma</ci>
                          <cn type='integer'>-1</cn>
                        </apply>
```

```
                    </apply>
                    <cn type='integer'>2</cn>
                  </apply>
                </apply>
                <apply>
                  <power />
                  <apply>
                    <times />
                    <ci>omega</ci>
                    <apply>
                      <ci>sqrt</ci>
                      <apply>
                        <times />
                        <cn type='integer'>2</cn>
                        <pi/>
                      </apply>
                    </apply>
                  </apply>
                  <cn type='integer'>-1</cn>
                </apply>
              </apply>
            </apply>
          </lambda>
        </math>
  </distrib:explicitPDF>
  <math xmlns="http://www.w3.org/1998/Math/MathML"
        xmlns:sbml="http://www.sbml.org/sbml/level3/version1/core">
    <lambda>
      <bvar><ci>arg1</ci></bvar>
      <bvar><ci>arg2</ci></bvar>
      <apply>
        <ci>arg1</ci>
      </apply>
    </lambda>
  </math>
      </functionDefinition>
    </listOfFunctionDefinitions>
    <listOfParameters>
      <parameter id="V" constant="true"/>
      <parameter id="V_pop" value="100" constant="true"/>
      <parameter id="V_omega" value="0.25" constant="true"/>
    </listOfParameters>
    <listOfInitialAssignments>
      <initialAssignment symbol="V">
  <math xmlns="http://www.w3.org/1998/Math/MathML">
    <apply>
      <ci>normal</ci>
      <cn>V_pop</cn>
      <cn>V_omega</cn>
    </apply>
  </math>
      </initialAssignment>
    </listOfInitialAssignments>
  </model>
</sbml>
```

5.4 User-defined discrete distribution

In this example we don't use any special distrib features, by invoke an externally defined function that constructs a PMF from a matrix of values and their associated probabilities. The example is not biologically meaningful, but illustrates that the matrix contains the values and probabilities possible when throwing two dice. These values are encoded in a matrix, which is passed as a parameter in a function, however, it may be that this information is defined using NuML or by referring to an external file.

?

? There has been very little discussion about how to treat user-defined PMFs so this example should be regarded as a starting point for discussion rather than a final proposal.

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns="http://www.sbml.org/sbml/level3/version1/core" level="3" version="1"
      xmlns:distrib="http://www.sbml.org/sbml/level3/version1/distrib/version1"
      distrib:required="true"
      xmlns:arrays="http://www.sbml.org/sbml/level3/version1/arrays/version1"
      arrays:required="true">
  <!-- Code snippet. Not a valid model. -->
  <model id="UserDefined" name="User␣Defined␣Example" substanceUnits="item"
         timeUnits="second" volumeUnits="litre" extentUnits="item">
    <listOfFunctionDefinitions>
      <functionDefinition id="myDistribution">
  <distrib:explicitPMF>
    <math xmlns="http://www.w3.org/1998/Math/MathML"
    xmlns:sbml="http://www.sbml.org/sbml/level3/version1/arraymaths/version1">
      <!-- This is an unresolved issue. The l3 V1 Core mathml subset does not support
     matrices. One solution - as above is to use a different MathML subset definition.
     We may choose to use numml here too.
      -->
      <matrix>
        <matrixrow>
    <cn>2</cn>
    <cn>3</cn>
    <cn>4</cn>
    <cn>5</cn>
    <cn>6</cn>
    <cn>7</cn>
    <cn>8</cn>
    <cn>9</cn>
    <cn>10</cn>
    <cn>11</cn>
    <cn>12</cn>
        </matrixrow>
        <matrixrow>
    <apply><divide/><cn>1</cn><cn>36</cn></apply>
    <apply><divide/><cn>2</cn><cn>36</cn></apply>
    <apply><divide/><cn>3</cn><cn>36</cn></apply>
    <apply><divide/><cn>4</cn><cn>36</cn></apply>
    <apply><divide/><cn>5</cn><cn>36</cn></apply>
    <apply><divide/><cn>6</cn><cn>36</cn></apply>
    <apply><divide/><cn>5</cn><cn>36</cn></apply>
    <apply><divide/><cn>4</cn><cn>36</cn></apply>
    <apply><divide/><cn>3</cn><cn>36</cn></apply>
    <apply><divide/><cn>2</cn><cn>36</cn></apply>
    <apply><divide/><cn>1</cn><cn>36</cn></apply>
        </matrixrow>
      </matrix>
    </math>
  </distrib:explicitPMF>
  <!-- below is a dummy function provided to ensure valid SBML Core
       for software that do not understand distrib. -->
  <math xmlns="http://www.w3.org/1998/Math/MathML">
    <lambda>
      <apply>
        <cn>0</cn>
      </apply>
    </lambda>
  </math>
      </functionDefinition>
    </listOfFunctionDefinitions>
    <listOfParameters>
      <parameter id="W" constant="true"/>
    </listOfParameters>
    <listOfInitialAssignments>
```

```
      <initialAssignment symbol="W">
  <math xmlns="http://www.w3.org/1998/Math/MathML"
        xmlns:sbml="http://www.sbml.org/sbml/level3/version1/core">
    <apply>
      <ci>myDistribution</ci>
    </apply>
  </math>
      </initialAssignment>
    </listOfInitialAssignments>
  </model>
</sbml>
```

6 Prototype implementations

None as yet.

7 Unresolved issues

what external distrib definition? A key decision is what form the external definition of the distributions will take. In particular should we use UncertML, a definition based on a snapshot of UncertML, another controlled vocabulary yet to be identified or do we create our own?

Optional function arguments It would be useful to provide optional arguments to functions, which at the moment is not possible. This would provide a convenient method for defining truncated distributions: all distributions could have an optional min and max argument that defaults to $-\inf$ and $+\inf$ respectively, but when set to a value it explicitly defines a truncated function.

8 Acknowledgements

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