SBML Level 3 Package Specification

The Distributions and Ranges Package for SBML Level 3

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The latest release, past releases, and other materials related to this specification are available at
http://sbml.org/Community/Wiki/SBML_Level_3_Proposals/Distributions_and_Ranges

This release of the specification is available at

Contents

Revision History

Version	Date	Author	Comments	
0.1 (Draft)	15 Oct 2011	Stuart Moodie	First draft	3
0.2 (Draft)	16 Oct 2011	Stuart Moodie	Added introductory text and background info. Other minor changes etc.	4
0.3 (Draft)	16 Oct 2011	Stuart Moodie	Filled empty invocation semantics section.	5

1   Introduction and motivation

1.1   What is it?

The Distributions and Ranges package provides an extension to SBML Level 3 that supports models that require random values obtained from a statistical distribution. The package itself defines probabilistic uncertainties that are parameterised to obtain a value that can be used elsewhere in the model. Its application are primarily in statistical models or models that require the use of random values, such an PK/PD models or **Need so other examples here please.**.

Original motivation for development of distrib package. Even in the context of deterministic simulations, it is sometimes useful to describe the sampling of a random number during simulation. One example is that of a cell dividing once it has grown to a given volume. It would be more realistic to initialise species concentrations in the resultant daughter cell with random numbers to reflect stochastic segragation of proteins, than to have a wholly deterministic segregation.

1.2   This Document

This proposal presents ideas for the Distributions and Ranges package proposal, also "colloquially" referred to by SBML developers as the package. This is an early draft of the proposal and there are still many 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 should be regarded as a first step towards the formal adoption of the as a package in SBML Level 3. Later versions of this document will aim to record the details of the package specification as they evolve, and it will ultimately serve as a basis for a vote on its adoption by the SBML community and be 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.

1.3   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 (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. **Author Note: Need to elaborate on this. What is currently done (if anything) to get round this.**

2.2   Past work on this problem or similar topics

2.2.1   Seattle 2010

The "distrib" package was discussed at the Seattle SBML Hackathon[1]. There one of the authors (DW) presented an overview of the problem[2,3], building on the old proposal from the Newcastle group[4]. 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

- 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>
```

---

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

```
      <bvar>                                       1
        <ci>mu</ci>                                2
        <ci>sigma</ci>                             3
      </bvar>                                      4
      <ci>mu</ci>                                  5
    </lambda>                                      6
  </math>                                          7
  </functionDefinition>                            8
</listOfFunctionDefinitions>                       9
                                                  10
```

which allows the use of a "default value" by simulators which do not understand the package (but simulators which   11
do will ignore the <math> element). The package would nevertheless be "required", as it will not be simulated   12
correctly by software which does not understand the package.   13

Informal discussions following the break-out covered topics such as how to work with vector random quantities   14
in the absence of the vector element in the MathML subset used by SBML, and the care that must be taken with   15
the semantics of random variables and the need to both a) reference multiple independent random quantities at a   16
given time and b) make multiple references to the same random quantity at a given time.   17

2.2.2 Hinxton 2011   18

Detailed discussion was continued at the Statistical Models Workshop in Hinxton in June 2011[5]. There those inter-   19
ested in representing Statistical Models in SBML came together to work out the details of how this package would   20
work in detail. Dan Cornford from the UncertML project[6] attended the meeting and describe how that resource   21
could be used to describe uncertainty and in particular probability distributions. Perhaps the most significant   22
decision at this meeting was to adopt the UncertML resource as a controlled vocabulary that is referenced by the   23
Distributions and Ranges package.   24

Much of the detail and the examples in this proposal are based on the work of this workshop and so its outcomes   25
are essentially presented below. However, at the end of the meeting there remained a number of unresolved issues   26
that are still unresolved in this proposal. See section 7 on page 19 for more details.   27

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[5]http://sbml.org/Events/Other_Events/statistical_models_workshop_2011
[6]http://www.uncertml.org/

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 and Ranges package has a very simple purpose. It defines a statistical distribution or range 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 **Distribution** that is part of the distrib package extension to SBML Level 3 Core. The **Distribution** class can then either refer to a distribution or range defined in UncertML using classes that extend the *IUncertainty* abstract class. Alternatively a **Distribution** can contain a **Lambda** class that defines the distribution explicitly.
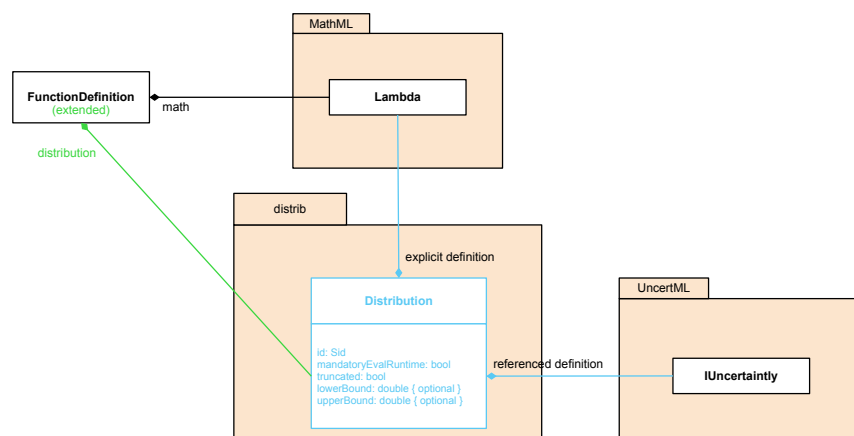
Figure 1: *UML model of Distributions and Ranges package. Note the UML packages indicate that the classes belong to different namespaces. The namespace of the SBML Core is not shown.*

3.3 Extension Handling

The Distributions and Ranges 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 include the **Distribution** class. When **FunctionDefinition** contains an instance of **Distribution** this instance must also be accompanied by an instance of **Lambda**. This enables software that cannot understand the extension to fallback to the **Lambda** definition of the function and so ensure that the SBML representation is self-consistent without the extension features. We refer to it as the *fallback lambda function*. The fallback lambda function must contain the same number of input parmeters as the

equivalent distribution defined within **Distribution**.

3.5   Distribution

The **Distribution** class contains either one instance of *IUncertainty* from UncertML or an instance of **Lambda**. These instances are mutually exclusive so only one instance of one type is permitted. An *IUncertainty* is used to reference a distribution defined by UncertML, while **Lambda** enables the explicit definition of the distribution using MathML.

If it is not a standard distribution (listed in the spec), one can describe it using a density function. The spec will list the restrictions. Necessary flags e.g. normalised or not. We need to be able to describe them using PMF (but it is fiddly to do said Darren). We need to describe truncation. CDF and quantile as well.

The MathML used in **Lambda** is restricted to the same subset as used in SBML Core. The reader should refer to the SBML Level 3 Core specification document for more details Hucka et al. (2010).

3.6   Attributes

Here we define the attributes used by the **Distribution** class. Each attribute will have a primitive type and will be always required (mandatory) or not (optional).

`mandatoryEvalRuntime`

This attribute is a `boolean` and is mandatory. If its value is then this indicates that the uncertainty is intrinsic to the model. There is no selection of given values prior to simulation or analysis. Values are generated during simulation as needed. For example, a noisy measurement from which any particular value would lead to a bias and there is no reason to select a particular value, or white noise where at each realisation, we (may) get a different value.

If the attribute's value is , then the uncertainty may be resolved before simulation. The generation of initial conditions from the distribution is described in SED-ML. One can choose for instance to use the mean, or to do a sampling (e.g. parameter scan, random sampling). For example, a measured parameter for which there are two different values, or a parameter following a distribution from which to draw individuals prior to simulation.

`truncated`

This attribute is of type `boolean` and is mandatory. It indicates that the distribution is being used only between a given range and that the attributes `lowerBound` and `upperBound` must be set when this instance is invoked.

`lowerBound`

This value is of type `double` and is not mandatory. It defines the lower bounds of range within which this distribution will be used.

`upperBound`

This value is of type `double` and is not mandatory. It defines the upper bounds of a range within which this distribution will be used.

3.7   Use of UncertML Definitions

The abstract class *IUncertainty* is the super-class of the distributions,samples and statistics defined by UncertML. The appropriate concrete sub-class from UncertML should be selected and the appropriate parameters supplied for the distribution. A selection of UncertML classes is shown in figure 2 on the following page.

Note that to satisfy UncertML the attributes of a given distribution class must be supplied with a value. These values act as a placeholder and must be of the correct type. Some UncertML distributions may require an array or a matrix of values as an attribute.
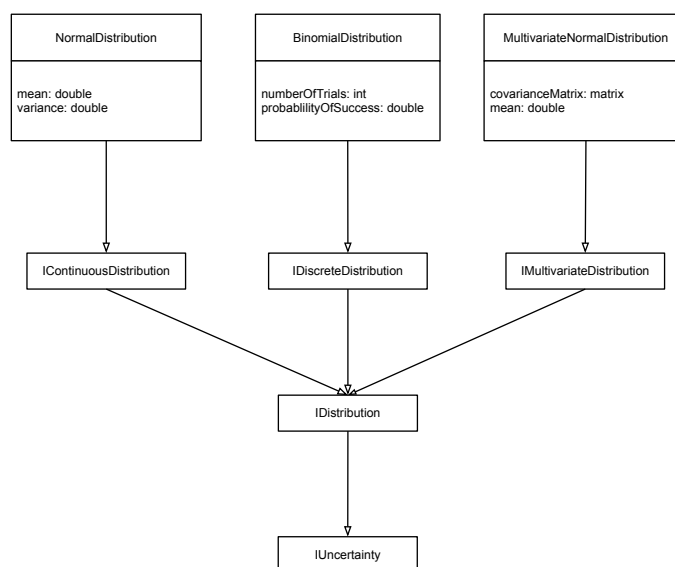
Figure 2: A selection of the distributions in UncertML represented as a UML model.

3.8 Referencing the Distributions and Ranges package

The distribution defined by a **Distribution** instance is defined by the name of its owning **FunctionDefinition** instance. Therefore other **SBML** elements can reference a distribution as a function in the same way that they reference other instances of **FunctionDefinition**. The arguments to the function should match those defined within the **Distribution** instance.

Scalar Assumption

? It is assumed that all the UncertML classes will enable the retrieval of a scalar result of type `double`. Not that some UncertML classes, for example **Range**[7] currently return an array of values. This is an inconsistency that needs to be resolved.

Type Consistency

When invoking a **FunctionDefinition** that contains a **Distribution** instance one must ensure that the value types are consistent. When the distribution is defined by a concrete sub-class of *IUncertainty* the paramaters used in the function call must match those defined in the UncertML class specification. For example the **PoissonDistribution**[8] can be instantiated with either a single rate value (`double`) or an array of rate values.

Truncated Distributions

? When invoking **FunctionDefinition** that contains an instance of **Distribution** with `truncated`=, it is necessary to also define the range over which the distribution applies. In this case the attributes `lowerBound` and `upperBound` of **Distribution** must be assigned a value. These are always the last two values of the function call and come after all the other parameters required by the distribution function definition are satisfied. The convention used is that the parameters are appended in the following order: `lowerBound` then `upperBound`. See section 5.1 on page 14 for an example of this usage.

---

[7]http://www.uncertml.org/statistics/range
[8]http://www.uncertml.org/distributions/poisson

Restrictions on Use

References to definitions cannot be used in all SMBL constructs. In particular the results should not be used in constructs that are being continually evaluated. For example rate laws.

Invocation Semantics

The invocation semantics are currently undefined. This is discussed below (section 7 on page 19).

4 Package dependencies

This package is not dependent on any other SBML Level 3 packages. It is however 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). Distributions, samples and statistics are referenced from the UncertML standard. Note that it is undecided whether a subset of UncertML will be used and what that subset will be.

?

5 Use-cases and examples

5.0.1 PK/PD Model

```
<?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="logNormalVc">
                <distrib:distribution distrib:mandatoryEvalRuntime="false">
                    <un:LogNormalDistribution xmlns:un="http://www.uncertml.org/2.0">
                        <un:logScale>3.14</un:logScale>
                        <un:shape>3.14</un:shape>
                    </un:LogNormalDistribution>
                </distrib:distribution>
                <math xmlns="http://www.w3.org/1998/Math/MathML">
                    <lambda>
                        <bvar><ci>mu</ci></bvar>
                        <bvar><ci>sigma</ci></bvar>
                        <ci>mu</ci>
                    </lambda>
                </math>
            </functionDefinition>
            <functionDefinition id="logNormalka">
                <distrib:distribution distrib:mandatoryEvalRuntime="false">
                    <un:LogNormalDistribution xmlns:un="http://www.uncertml.org/2.0">
                        <un:logScale>3.14</un:logScale>
                        <un:shape>3.14</un:shape>
                    </un:LogNormalDistribution>
                </distrib:distribution>
                <math xmlns="http://www.w3.org/1998/Math/MathML">
                    <lambda>
                        <bvar><ci>mu</ci></bvar>
                        <bvar><ci>sigma</ci></bvar>
                        <ci>mu</ci>
                    </lambda>
                </math>
            </functionDefinition>
            <functionDefinition id="logNormalke">
                <distrib:distribution distrib:mandatoryEvalRuntime="false">
                    <un:LogNormalDistribution xmlns:un="http://www.uncertml.org/2.0">
                        <un:logScale>3.14</un:logScale>
                        <un:shape>3.14</un:shape>
                    </un:LogNormalDistribution>
                </distrib:distribution>
                <math xmlns="http://www.w3.org/1998/Math/MathML">
                    <lambda>
                        <bvar><ci>mu</ci></bvar>
                        <bvar><ci>sigma</ci></bvar>
                        <ci>mu</ci>
                    </lambda>
                </math>
            </functionDefinition>
            <functionDefinition id="NormalCc_obs">
                <distrib:distribution distrib:mandatoryEvalRuntime="false">
                    <un:NormalDistribution xmlns:un="http://www.uncertml.org/2.0">
                        <un:mean>3.14</un:mean>
                        <un:variance>3.14</un:variance>
                    </un:NormalDistribution>
                </distrib:distribution>
                <math xmlns="http://www.w3.org/1998/Math/MathML">
```

```
                <lambda>                                                                        1
                    <bvar><ci>mu</ci></bvar>                                                    2
                    <bvar><ci>sigma</ci></bvar>                                                 3
                    <ci>mu</ci>                                                                 4
                </lambda>                                                                       5
            </math>                                                                             6
        </functionDefinition>                                                                   7
    </listOfFunctionDefinitions>                                                                8
    <listOfCompartments>                                                                        9
        <compartment id="central" name="central" size="0" constant="true"/>                    10
        <compartment id="gut" name="gut" size="0" constant="true"/>                            11
    </listOfCompartments>                                                                       12
    <listOfSpecies>                                                                             13
        <species id="Qc" compartment="central" initialAmount="1"                              14
          hasOnlySubstanceUnits="true" boundaryCondition="false" constant="false"/>           15
        <species id="Qg" compartment="gut" initialAmount="1"                                  16
          hasOnlySubstanceUnits="true" boundaryCondition="false" constant="false"/>           17
    </listOfSpecies>                                                                            18
    <listOfParameters>                                                                          19
        <parameter id="ka" value="1" constant="true"/>                                        20
        <parameter id="ke" value="1" constant="true"/>                                        21
        <parameter id="Cc" value="1" constant="false"/>                                       22
        <parameter id="Cc_obs" value="1" constant="false"/>                                   23
    </listOfParameters>                                                                         24
    <listOfInitialAssignments>                                                                  25
        <initialAssignment symbol="central">                                                   26
            <math xmlns="http://www.w3.org/1998/Math/MathML">                                  27
                <apply>                                                                         28
                    <ci>logNormalVc</ci>                                                        29
                    <cn>0.5</cn>                                                                30
                    <cn>0.1</cn>                                                                31
                </apply>                                                                        32
            </math>                                                                             33
        </initialAssignment>                                                                    34
        <initialAssignment symbol="ka">                                                        35
            <math xmlns="http://www.w3.org/1998/Math/MathML">                                  36
                <apply>                                                                         37
                    <ci>logNormalka</ci>                                                        38
                    <cn>0.5</cn>                                                                39
                    <cn>0.1</cn>                                                                40
                </apply>                                                                        41
            </math>                                                                             42
        </initialAssignment>                                                                    43
        <initialAssignment symbol="ke">                                                        44
            <math xmlns="http://www.w3.org/1998/Math/MathML">                                  45
                <apply>                                                                         46
                    <ci>logNormalke</ci>                                                        47
                    <cn>0.5</cn>                                                                48
                    <cn>0.1</cn>                                                                49
                </apply>                                                                        50
            </math>                                                                             51
        </initialAssignment>                                                                    52
    </listOfInitialAssignments>                                                                 53
    <listOfRules>                                                                               54
        <assignmentRule variable="Cc">                                                         55
            <math xmlns="http://www.w3.org/1998/Math/MathML">                                  56
                <apply>                                                                         57
                    <divide/>                                                                   58
                    <ci> Qc </ci>                                                               59
                    <ci> central </ci>                                                          60
                </apply>                                                                        61
            </math>                                                                             62
        </assignmentRule>                                                                       63
        <assignmentRule variable="Cc_obs">                                                     64
            <math xmlns="http://www.w3.org/1998/Math/MathML">                                  65
                <apply>                                                                         66
                    <plus/>                                                                     67
```

```
                        <ci> Cc </ci>                                                            1
                        <cn type="integer"> 1 </cn>                                              2
                    </apply>                                                                     3
                </math>                                                                          4
            </assignmentRule>                                                                    5
        </listOfRules>                                                                           6
        <listOfReactions>                                                                        7
            <reaction id="absorption" reversible="false" fast="false">                          8
                <listOfReactants>                                                                9
                    <speciesReference species="Qg" stoichiometry="1" constant="false"/>         10
                </listOfReactants>                                                               11
                <listOfProducts>                                                                 12
                    <speciesReference species="Qc" stoichiometry="1" constant="false"/>         13
                </listOfProducts>                                                                14
                <kineticLaw>                                                                     15
                    <math xmlns="http://www.w3.org/1998/Math/MathML">                            16
                        <apply>                                                                  17
                            <times/>                                                             18
                            <ci> ka </ci>                                                        19
                            <ci> Qg </ci>                                                        20
                        </apply>                                                                 21
                    </math>                                                                      22
                </kineticLaw>                                                                    23
            </reaction>                                                                          24
            <reaction id="excretion" reversible="false" fast="false">                           25
                <listOfReactants>                                                                26
                    <speciesReference species="Qc" stoichiometry="1" constant="false"/>         27
                </listOfReactants>                                                               28
                <kineticLaw>                                                                     29
                    <math xmlns="http://www.w3.org/1998/Math/MathML">                            30
                        <apply>                                                                  31
                            <divide/>                                                            32
                            <apply>                                                              33
                                <times/>                                                         34
                                <ci> ke </ci>                                                    35
                                <ci> Qc </ci>                                                    36
                            </apply>                                                             37
                            <ci> central </ci>                                                   38
                        </apply>                                                                 39
                    </math>                                                                      40
                </kineticLaw>                                                                    41
            </reaction>                                                                          42
        </listOfReactions>                                                                       43
    </model>                                                                                     44
</sbml>                                                                                          45
                                                                                                 46
```

5.1 Truncated distribution

```
                                                                                                 48
<?xml version="1.0" encoding="UTF-8"?>                                                           49
<sbml xmlns="http://www.sbml.org/sbml/level3/version1/core" level="3" version="1"                50
    xmlns:distrib="http://www.sbml.org/sbml/level3/version1/distrib/version1"                    51
    distrib:required="true">                                                                     52
    <model>                                                                                      53
        <listOfFunctionDefinitions>                                                              54
            <functionDefinition id="logNormalVc">                                                55
                <distrib:distribution distrib:mandatoryEvalRuntime="false" distrib:truncated="true">  56
                    <un:LogNormalDistribution xmlns:un="http://www.uncertml.org/2.0">            57
                        <un:logScale>3.14</un:logScale>                                          58
                        <un:shape>3.14</un:shape>                                                59
                    </un:LogNormalDistribution>                                                  60
                </distrib:distribution>                                                          61
                <math xmlns="http://www.w3.org/1998/Math/MathML">                                62
                    <lambda>                                                                     63
                        <bvar><ci>mu</ci></bvar>                                                 64
```

```
                        <bvar><ci>sigma</ci></bvar>                                          1
                        <bvar><ci>lower</ci></bvar>                                          2
                        <bvar><ci>upper</ci></bvar>                                          3
                        <ci>mu</ci>                                                          4
                    </lambda>                                                                5
                </math>                                                                      6
            </functionDefinition>                                                            7
        </listOfFunctionDefinitions>                                                         8
    </model>                                                                                 9
</sbml>                                                                                     10
                                                                                            11
```

5.2   Multivariate Distribution

No example has been prepared yet.

5.3   A Range

```
<?xml version="1.0" encoding="UTF-8"?>                                                      16
<sbml xmlns="http://www.sbml.org/sbml/level3/version1/core" level="3" version="1"           17
    xmlns:distrib="http://www.sbml.org/sbml/level3/version1/distrib/version1"               18
    distrib:required="true">                                                                19
    <model>                                                                                 20
        <listOfFunctionDefinitions>                                                         21
            <functionDefinition id="Range">                                                 22
                <distrib:distribution distrib:mandatoryEvalRuntime="false"                  23
                        distrib:truncated="false">                                          24
                    <un:Range xmlns:un="http://www.uncertml.org/2.0"/>                      25
                </distrib:distribution>                                                     26
                <math xmlns="http://www.w3.org/1998/Math/MathML">                           27
                    <lambda>                                                                28
                        <bvar><ci>lower</ci></bvar>                                          29
                        <bvar><ci>upper</ci></bvar>                                          30
                        <apply>                                                             31
                            <divide/>                                                       32
                            <apply>                                                         33
                                <plus/>                                                     34
                                <ci> lower </ci>                                            35
                                <ci> upper </ci>                                            36
                            </apply>                                                        37
                            <cn> 2.0 </cn>                                                  38
                        </apply>                                                            39
                        <ci></ci>                                                           40
                    </lambda>                                                               41
                </math>                                                                     42
            </functionDefinition>                </listOfFunctionDefinitions>               43
    </model>                                                                                44
</sbml>                                                                                     45
                                                                                            46
```

5.4   Random Sample

This example was taken from day 3 of the 3 day Statistical Models Workshop Workshop Participants (2011). The
? `distrib::listOfSymbols` was probably dropped later in the workshop, but this needs to be clarified.

```
<?xml version="1.0" encoding="UTF-8"?>                                                      51
<sbml xmlns="http://www.sbml.org/sbml/level3/version1/core" level="3" version="1"           52
    xmlns:distrib="http://www.sbml.org/sbml/level3/version1/distrib/version1"               53
    distrib:required="true">                                                                54
    <model>                                                                                 55
        <listOfFunctionDefinitions>                                                         56
            <functionDefinition id="mySample">                                              57
             <distrib:distribution distrib:mandatoryEvalRuntime="true">                     58
```

```xml
          <distrib:listOfSymbols>
            <distrib:symbol>k1</distrib:symbol>
            <distrib:symbol>P_1</distrib:symbol>
            <distrib:symbol>P_2</distrib:symbol>
          </distrib:listOfSymbols>
          <distrib:annot realization="ID2" valueIndex="2" whatever="Thispublication" />
       <un:RandomSample xmlns:un="http://www.uncertml.org/2.0">
            <un:samplingMethodDescription>
              Importance sampler with uniform proposal
              distribution
            </un:samplingMethodDescription>
            <un:Realisation id="ID1">
              <un:weight>0.5</un:weight>
              <un:values>3.14 6.28 9.42</un:values>
            </un:Realisation>
            <un:Realisation id="ID2">
              <un:weight>0.25</un:weight>
              <un:values> 3.14 6.28 9.42</un:values>
            </un:Realisation>
            <un:Realisation id="ID3">
              <un:weight>0.25</un:weight>
              <un:values>3.14 6.28 9.42</un:values>
            </un:Realisation>
         </un:RandomSample>
       </distrib:distribution>
          <math xmlns="http://www.w3.org/1998/Math/MathML">
            <lambda>
            <bvar><ci distrib:useValues="false">index</ci></bvar>
            <cn>0.0</cn>
            </lambda>
            </math>
      </functionDefinition>
      <functionDefinition id="normRuntime">
         <distrib:distribution distrib:runtime="true">
            <un:NormalDistribution xmlns:un="http://www.uncertml.org/2.0">
              <un:mean>mu</un:mean>
              <un:variance>sigma</un:variance>
            </un:NormalDistribution>
         </distrib:distribution>
          <math xmlns="http://www.w3.org/1998/Math/MathML">
            <lambda>
              <bvar><ci>mu</ci></bvar>
              <bvar><ci>sigma</ci></bvar>
              <ci>mu</ci>
            </lambda>
          </math>
      </functionDefinition>
 </listOfFunctionDefinitions>
 <listOfInitialAssignments>
      <initialAssignment symbol="x">
          <math xmlns="http://www.w3.org/1998/Math/MathML">
              <apply>
                  <ci>normStatic</ci>
                  <cn>0.5</cn>
                  <cn>0.1</cn>
              </apply>
          </math>
      </initialAssignment>
      <initialAssignment symbol="P_1">
          <math xmlns="http://www.w3.org/1998/Math/MathML">
              <apply>
                  <ci>mySample</ci>
                  <ci>P_1</ci>
              </apply>
          </math>
      </initialAssignment>
 </listOfInitialAssignments>
```

```
        <listOfParameters>                                              1
            <parameter id="x" constant="true"/>                         2
            <parameter id="P_1" constant="true"/>                       3
            <parameter id="P_2" constant="true"/>                       4
        </listOfParameters>                                             5
    </model>                                                            6
</sbml>                                                                 7
                                                                        8
```

6 Prototype implementations

None as yet.

7 Unresolved issues

At the Statistical Models Workshop Workshop Participants (2011) a number of issues were identified as remaining unresolved and requiring more work or more discussion[9]. The are listed below:

Circular dependency It is possible to create circular dependency in which .... [**Complete!e**].

Multivariate distributions No examples were worked on for Multivariate Distributions. The main issue to be resolved is to identify how it can be parameterised as it requires a covariance matrix and a list on mean values. These constructs are not currently available in SBML Level 3 Core.

User defined distributions No examples were produced that illustrated how a distribution might be defined explicitly in MathML, i.e. without referencing UncertML.

Defining a random quantity No example was created illustrating how to define a random quantity with a mean and a standard deviation for a known distribution.

UncertML coverage It is still to be agreed whether the complete UncertML conceptual model will be used complete or just a subset. In addition it is unclear whether a snapshot of the UncertML definitions will be taken and used as the reference specification for this package. This snapshot could be maintained separately from the UncertML core effort.

Usage semantics We need to clarify the use of random numbers in continually evaluating contexts.

SDE It was agreed that SDEs are out of scope.

Invokation semantics When a distribution is referenced we need to clarify whether this implies a new invocation of the distribution. In other words if I reference the same **Distribution** more than once within an SMBL model should the distribution be recalculated each time it is reference or only the first time. The latter case allows one to always return the same random value in different parts of the model, but requires you to define separate instances of **Distribution** if you wish to generate separate random values using an identically configured distribution.

Grouped moments There is no documentation surrounding this issue and there was some discussion during the workshop on this topic, particularly on the last day. At the end of the last session it was agreed that to group a mean and a standard deviation a class called **Moments** would be created within this package that would reference the **Mean** and **StandardDeviation** from UncertML. Examples and more discussion is probably required about this construct. In particular whether this would be better provided by UncertML.

During the writing of this specification the authors has come across some issues that need resolving:

Distribution function parameters The mechanisms of defining the parameters of a function are rather cumbersome and seem likely to make implementation more difficult. In the XML examples this means providing the UncertML XML element with dummy values. Should we have a convention for what these placeholder values should be. Can we get rid of them?

UncertML is a Controlled Vocabulary UncertML is essentially being used as a controlled vocabulary to define distributions etc. However, it is being referenced by incorporating is XML elements into the distrib package, which is proving cumbersome and will increase the complexity of software implementation. Could another mechanism be used to refer to it. Perhaps using it in a similar way to SBO in SMBL Core?

The issue of defining arrays and matrixes has not really been address so far. This will prevent the completion of this specification unless it is resolved. Perhaps by the parallel specification of another SBML Level 3 package — arrays?

---

[9]The original document containing this list has been lost and so the list has been reconstructed from a audio recording of the final session. It may be incomplete or contain inaccuracies

The authors are not clear how random distributions are supposed to work. The example from the Hinxton workshop is included, but a more detailed explanation is not.

UncertML to snapshot or not This is the key decision to make in this specification. If a snapshot of UncertML is taken the in the authors' view this will effectively be the first step in creating and maintaining a separate resource. In my view it would be better to work with UncertML to help them address any issues/concerns that we have.

8 Acknowledgements

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