SBML Level 3 Package Specification

SBML Level 3 Package: Flux Balance Constraints ('fbc')

Brett G. Olivier

b.g.olivier@vu.nl

Systems Bioinformatics
VU University Amsterdam
Amstedam, NH, The Netherlands

Frank T. Bergmann

fbergmann@caltech.edu

Computing and Mathematical Sciences
California Institute of Technology
Pasadena, CA, US

July 24, 2012

Version 1 (Draft)

The latest release, past releases, and other materials related to this specification are available at
http://sbml.org/Documents/Specifications/Fbc

This release of the specification is available at
http://sbml.org/Documents/Specifications/Fbc_Level_1_Version_1

Contents

1 Preamble

1.1 Proposal tracking number

Item http://sourceforge.net/tracker/?func=detail&aid=3154219&group_id=71971&atid=8947113154219 in the SBML issue tracking system.

1.2 Version information

1.2.1 Version number and date of public release

Version 1 draft (July 24, 2012).

1.2.2 URL for the previous versions of this proposal

Version 2 (March 2011) of this proposal: http://sbml.org/Community/Wiki/SBML_Level_3_Proposals/Flux_Constraints_Proposal

Version 1 (February 2010) of this proposal: http://precedings.nature.com/documents/4236/version/1

2   Introduction and motivation

Constraint based modelling is a widely used methodology used to analyse and study biological networks on both a small and whole organism (genome) scale. Typically these models are underdetermined and constraint based methods (e.g., linear, quadratic optimization) are used to optimise specific model properties. This is assumed to occur under a defined set of constraints (e.g., stoichiometric, metabolic) and bounds (e.g., thermodynamic, experimental and environmental) on the values that the solution fluxes can obtain.

Perhaps the most well known (and widely used) analysis method is Flux Balance Analysis (FBA; **?**), where for a Genome Scale Reconstruction (GSR) model (**?**) a target flux is maximised (typically a flux to biomass) where other input/output fluxes have been bounded to simulate a selected growth environment.

As constraint based models are generally underdetermined, i.e., few or none of the kinetic rate equations and related parameters are known, it is crucial that a model definition includes the ability to define optimization parameters such as objective functions, flux bounds and constraints ... currently this is not possible in SBML.

The question of how to encode constraint based (or historically FBA) models in SBML is not new. However, with the advances in the methods used to construct GSR scale models and the wider adoption of constraint based modelling in biotechnological/medical applications has led to a rapid increase in both the number of models being constructed and the tools used to analyse them.

Faced with such rapidly growing diversity, the need for a standardised description for the definition, exchange and annotation of constraint based models is vital. As the core model components (e.g., species, reactions, stoichiometry) can already be effectively described in SBML (with its significant community, software and tool support) it seems prudent to use it as a basis for such a description. In addition, the modularised extension mechanism now available in SBML Level 3 provides an ideal platform for an efficient implementation.

3 Background

3.1 Problems with current SBML approaches

While there is currently no official way of encoding constraint based models in SBML L2 there have been *pragmatic* approaches used by a variety of groups and applications. Perhaps the most widely used is that used by the COBRA toolbox where the reaction network is defined as reactions and for e.g. the constraint-based models: the COBRA Toolbox everyone using the same parameter names to describe e.g. the upper or lower bounds. In a similar way the objective function is indicated by a local parameter having a value of one (as such it is not clear how to deal with multiple objective functions or objective functions that may contain more than one flux). While currently the most widely used way of describing GSR/constraint based models, as is, it is not suitable for implementation in SBML Level 3.

3.2 Past work on this problem or similar topics

The problem of describing and annotating constraint based (or FBA) models in SBML has been discussed on various occasions:

* 2006 Karthik Raman: http://sbml.org/images/d/d9/Raman-flux-annotations.pdf Flux annotations in SBML
* 2009 Brett Olivier: http://sbml.org/images/4/4a/Olivier_sbml_forum_2009_09_04.pdf L3 FBA package discussion * 2010 Frank Bergmann and Brett Olivier: http://precedings.nature.com/documents/4236/version/1 SBML Level 3 Package Proposal: Flux * 2010 Brett Olivier and Frank Bergmann: http://sbml.org/images/a/a0/Olivier_combine_flux_2010-10-09.pdf The SBML Flux Balance Analysis Package

A pre 2005 (and presumed to be unmaintained) SBML L2 annotation is also known to exist: * Metabolic flux model annotations http://sbml.org/Community/Wiki/Old_known_SBML_annotations_list details

4 Proposed syntax and semantics

In this section, we define the syntax and semantics of the Flux Balance Constraints package for SBML Level 3 Version 1. We expound on the various data types and constructs defined in this package, then in Section 5, we provide complete examples of using the constructs in example SBML models.

4.1 Namespace URI and other declarations necessary for using this package

Every SBML Level 3 package is identified uniquely by an XML namespace URI. For an SBML document to be able to use a given SBML Level 3 package, it must declare the use of that package by referencing its URI. The following is the namespace URI for this version of the Flux Balance Constraints package for SBML Level 3 Version 1:

"`http://www.sbml.org/sbml/level3/version1/fbc/version1`"

In addition, SBML documents using a given package must indicate whether understanding the package is required for complete mathematical interpretation of a model, or whether the package is optional. This is done using the attribute `required` on the `<sbml>` element in the SBML document. For the Flux Balance Constraints package, the value of this attribute must be set to "`true`".

The following fragment illustrates the beginning of a typical SBML model using SBML Level 3 Version 1 and this version of the Flux Balance Constraints package:

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns="http://www.sbml.org/sbml/level3/version1/core" level="3" version="1"
      xmlns:fbc="http://www.sbml.org/sbml/level3/version1/fbc/version1" fbc:required="true">
```
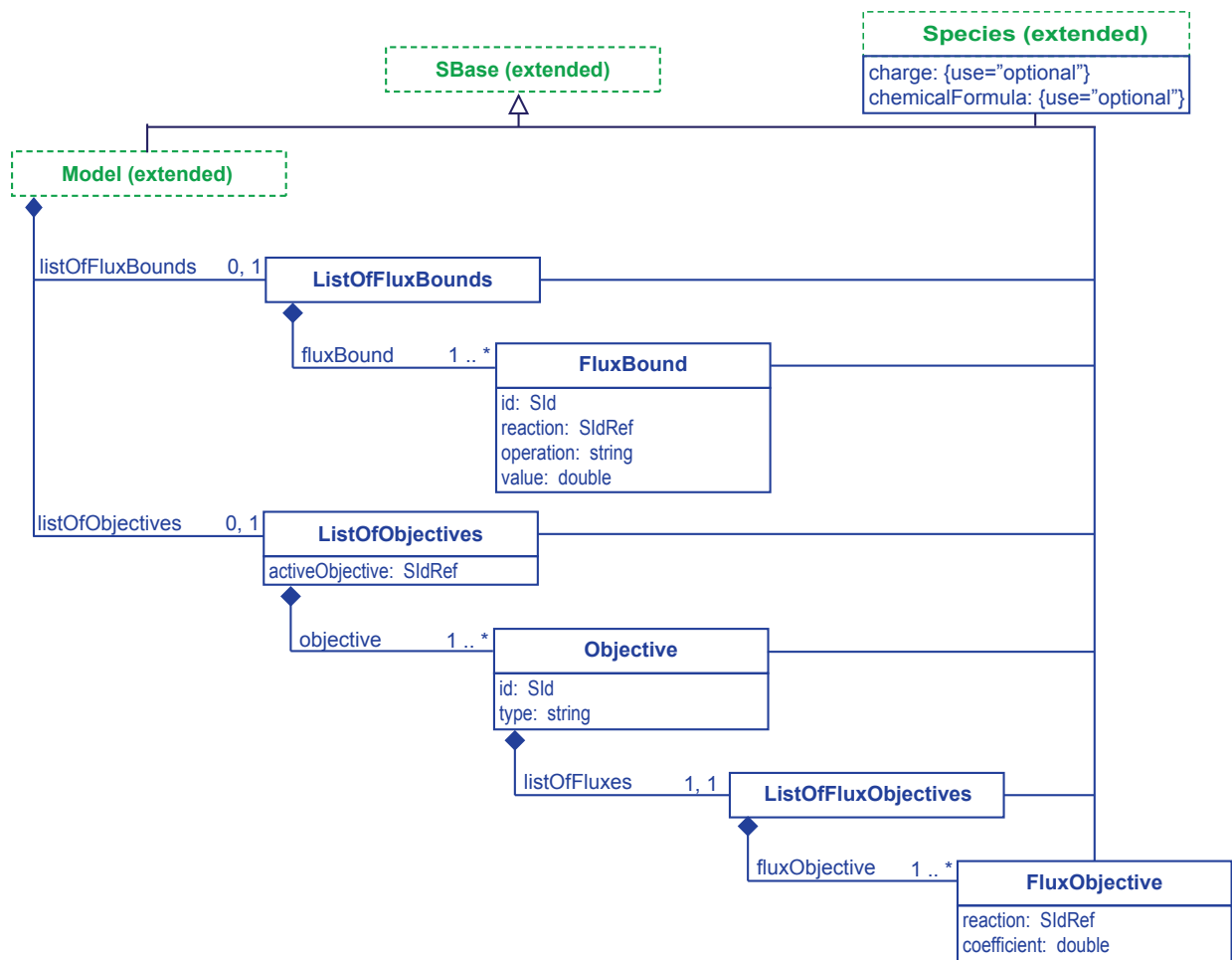
Figure 1: *UML diagram*

5 Examples

This section contains a variety of examples of SBML Level 3 Version 1 documents employing the Flux Balance Constraints package.

6 Best practices

In this section, we recommend a number of practices for using and interpreting various constructs in the Flux Balance Constraints package. These recommendations are non-normative, but we advocate them strongly; ignoring them will not render a model invalid, but may reduce interoperability between software and models.

Acknowledgments