

SBML Level 3 Package: Flux Balance Constraints (‘fbc’)

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Version 1 (Draft)

Under construction, beware fast mutating text!

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



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1 Preamble

1.1 Tracking number

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

1.2 History of the ‘fbc’ package proposal

This specification is based on a set of proposals proposed and refined by the authors and **SBML** community. Reference to these previous versions are presented here while details of previous proposals are provided in [Section 3](#).

Version 3 (March 2012)

[http://sbml.org/Community/Wiki/SBML_Level_3_Proposals/Flux_Balance_Constraints_Proposal_\(2012\)](http://sbml.org/Community/Wiki/SBML_Level_3_Proposals/Flux_Balance_Constraints_Proposal_(2012))

Version 2 (March 2011)

http://sbml.org/Community/Wiki/SBML_Level_3_Proposals/Flux_Constraints_Proposal

Version 1 (February 2010)

<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; [Orth et al., 2010](#)) which is performed on Genome Scale Reconstructions (GSR's; [Oberhardt et al., 2009](#)). Using FBA a target flux is optimized (e.g. maximising a flux to biomass or minimising ATP production) while other fluxes can be bounded to simulate a selected growth environment or specific metabolic state.

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 optimisation parameters such as objective functions, flux bounds and constraints ... currently this is not possible in the Systems Biology Markup Language (**SBML**) Level 2 or Level 3 core specification ([Hucka et al., 2011, 2003](#)).

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

Faced with such growth, both in number and diversity, the need for a standardised data format for the definition, exchange and annotation of constraint based models has become critical. As the core model components (e.g. species, reactions, stoichiometry) can already be efficiently described in **SBML** (with its significant community, software and tool support) the 'FBC' package aims to extend **SBML** core by adding the elements necessary to describe current and future constraint based models.

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. Arguably the best and most widely used format is that used by the COBRA toolbox (Becker et al., 2007) where the metabolic network is well defined using **SBML Reaction** and **Species** objects. However, flux bounds and reactions that take part in the objective function are defined as **LocalParameter** objects and (implicitly) rely on all tools using the same naming convention. Similarly, reaction annotations are generally stored as key-value pairs in HTML **Notes** elements which has led to different groups routinely using different keys describing describing the same thing. While a step in the right direction this format 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 'FBA' models in **SBML** has been raised at various times in the past few years. In this regard there are two known putative proposals that of Karthik Raman and the Church Laboratory. As far as we are aware these proposals never developed beyond their initial presentation.

Karthik Raman (2006) Flux annotations in SBML

<http://sbml.org/images/d/d9/Raman-flux-annotations.pdf>

Church laboratory (2005) Metabolic flux model annotations

http://sbml.org/Community/Wiki/Old_known_SBML_annotations_list

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 on page 8](#), 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">
```

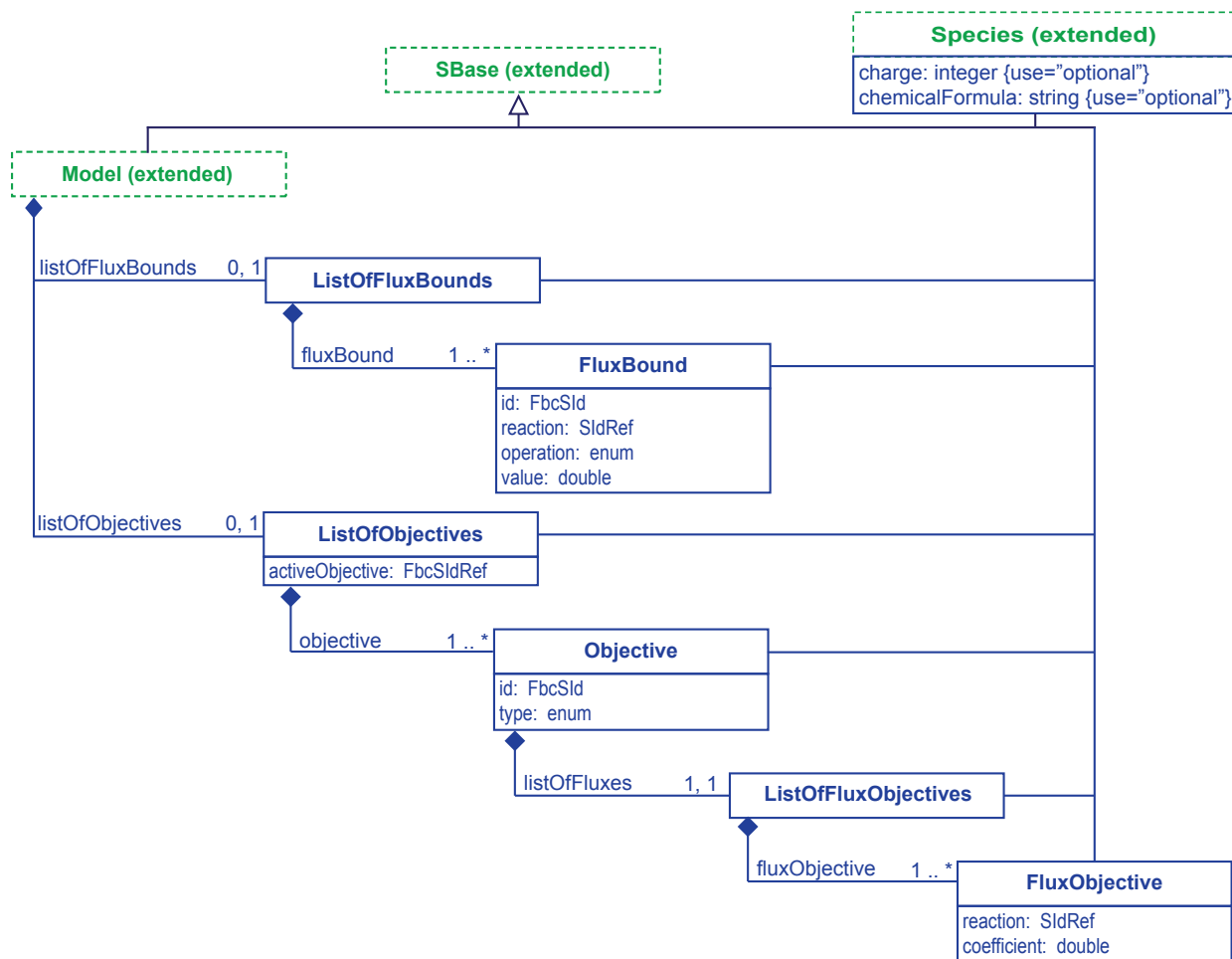


Figure 1: UML diagram

5 Examples

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

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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.

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