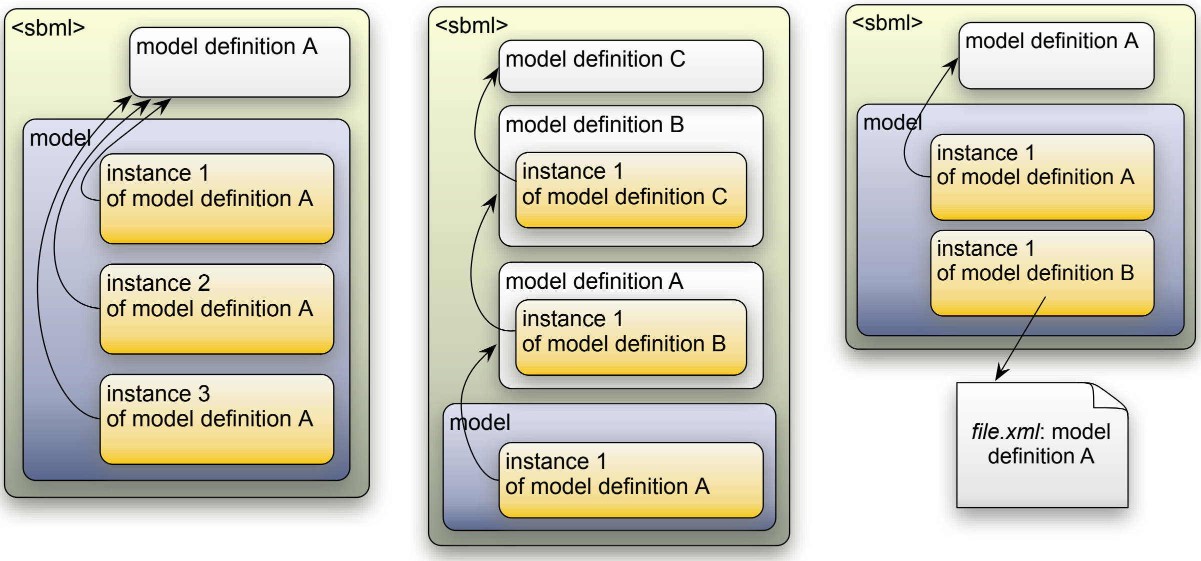
Introduction and motivation

In the context of SBML, *hierarchical model composition* refers to the ability to include models as submodels inside other models. The goal is to support the ability of modelers and software tools to do such things as (1) decompose larger models into smaller ones, as a way to manage model complexity; (2) incorporate multiple instances of the same component model within one or more enclosing models, to avoid literal duplication of repeated elements; and (3) create libraries of vetted models, much as is done in software development and other engineering fields.

This document describes a proposal for an SBML Level 3 package to support hierarchical model composition. The figure below illustrates some of the scenarios targetted by this proposal. From left to right, the figure shows: a model composed of multiple instances of a single, internally-defined submodel definition; a model composed of a submodel that is itself composed of submodels; and a model composed of submodels, one of which is defined in an external file.


<sbml>
model definition A
model
instance 1 of model definition A
instance 2 of model definition A
instance 3 of model definition A
<sbml>
model definition C
model definition B
instance 1 of model definition C
model definition A
instance 1 of model definition B
model
instance 1 of model definition A
<sbml>
model definition A
model
instance 1 of model definition A
instance 1 of model definition B
file.xml: model definition A

The effort to create a hierarchical model composition mechanism in SBML has a long history, which we summarize in the next section. It has also been known by different names. Originally, it was called *modularity* because it allows a model to be divided into structural and conceptual modules. It was renamed *model composition* when it became apparent that the name "modularity" was too-easily confused with other notions modularity, particularly XHTML 1.1 modularity[1] (which concerns decomposition into separate files). To make clear that the purpose is structural *model* decomposition, regardless of whether the components are stored in separate files, the SBML community adopted the name SBML Hierarchical Model Composition.

To support a variety of composition scenarios, this package provides for optional black-box encapsulation by means of defined data communication interfaces (here called *ports*). In addition, it also separates model *definitions* (i.e., blueprints, or templates) from *instances* of those definitions, it supports optional external file storage, and it allows recursive model decomposition with arbitrary submodel nesting.

[1] "XHTML 1.1—Module-based XHTML", http://www.w3.org/TR/xhtml11/, W3C, 31 May 2001.

Background

Problems with current SBML approaches

SBML Level 3 Core has no direct support for allowing a model to include other models as submodels. Software tools either have to implement their own schemes outside of SBML, or (in principle) one could also use annotations to augment a plain SBML Level 2 model with the necessary information to allow a software tool to compose a model out of submodels. However, such solutions would be proprietary and tool-specific, and not conducive to interoperability. There is a clear need for an official SBML language facility for hierarchical model composition.

Past work on this problem or similar topics

The SBML community has discussed the need to add model composition features to SBML since its very beginning, some ten years ago. In an internal discussion document titled "Possible extensions to the Systems Biology Markup Language"[2] principally authored by Andrew Finney (and, notably, written even before SBML Level 1 Version 1 was finalized in March of 2001), the first of the four titular possible extensions is for "submodels". In that document, the main model object can contain a list of submodels, each of which are model definitions only, and a list of submodel instantiations, each of which are references to elements in the submodel list. Finney's proposal also extends the syntax of SBML identifiers (the SId data type) to allow entity references using a dotted notation, in which `X.y` signifies element `y` of submodel instance `X`; the proposal also defines a form of linking model elements through "substitutions". The proposal also introduced the concept of validation through what it called the "expanded" version of the model (now commonly referred to as the "flattened" form, meaning translation to a plain SBML format that does not use composition features): if the flat version of the model is valid, then the model as a whole must also be valid.

In June of 2001, at the Third Workshop on Software Platforms for Systems Biology, Martin Ginkel and Jörg Stelling presented their proposal titled "XML Notation for Modularity"[3], complete with an accompanying proposal document and sample XML file, partially in response to deficiencies or missing elements they believed existed in the proposal by Finney. In their proposal, Ginkel and Stelling present a "classic view" of modularity, where models are packaged as black boxes with interfaces. One of their design goals is to support the substitution of one module for another with the same defind interface, thereby supporting the simplification or elaboration of models as needed. Their proposal emphasizes the reuse of models and with the possibility of developing libraries of models.

Martin Ginkel presented an expanded version of that proposal[4] in the July 2002 Fifth Workshop on Software Platforms for Systems Biology, in the hope that it could be incorporated into the definition of SBML Level 2 that was being developed at the time. This proposal clarified the

[2] http://sbml.svn.sourceforge.net/viewvc/sbml/trunk/specifications/sbml-level-3/old/sbml-team-proposals/original/sbmlext.pdf

[3] Presentation at http://sbml.org/images/7/73/Vortrag.pdf, pre-meeting proposal at http://sbml.org/images/3/3d/Joerg-sbml-proposals.pdf, and sample file at http://sbml.org/images/1/18/Sbml2.txt

[4] http://sbml.org/images/9/90/Sbml-modular.pdf

need to separate model definitions from model instantiations, and, further, the need to designate one model per document as the "main" model.

In March of 2003, an independent proposal[5] by Jonathan Webb was posted to the sbml-discuss mailing list. The proposal itself has not survived intact on the web (the host site disallowed indexing of their site, preventing even Archive.org from saving it), but from the follow-up discussions between him, Andrew Finney, and Martin Ginkel, it seems that this proposal included a unified, generic approach to making links and references to elements in submodels using XPath. Previous proposals used separate mechanisms for species, parameters, compartments, and reactions. Webb also raised the issue of how to successfully resolve conflicting attributes of linked elements, debated whether formal interfaces were necessary or even preferable to directly access model elements, discussed type checking for linkages, and discussed issues with unit incompatibilities. Around this time, Martin Ginkel formed the Model Composition Special Interest Group[6], a group that eventually reached 18 members, including Jonathan Webb.

Model composition did not make it into SBML Level 2 when that specification was released in June of 2003, because the changes between SBML Level 1 and Level 2 were already substantial enough that sofware developers at the time expressed a desire to delay the introduction of composition to a later revision of SBML. Andrew Finney (now the co-chair of the Model Composition SIG) presented yet another proposal[7] in May of 2003, even before SBML Level 2 Version 1 was finalized, that aimed to add model composition to SBML Level 3. With only two years having passed between SBML Level 1 and Level 2, the feeling at the time was that Level 3 was likely to be released in 2005 or 2006, and the model composition proposal would be ready when it was. However, Level 2 ended up occupying the SBML community longer than expected, with four versions of Level 2 produced to adjust features in response to user feedback and developers' experiences.

In the interim, the desire to develop model composition features for SBML continued unabated. Finney revised his 2003 proposal in October 2003[8]; this new version represented an attempt to synthesize the earlier proposals by Ginkel and Webb, supplemented with his own original submodel ideas, and was envisioned to exist in parallel with another proposal by Finney, for arrays and sets of SBML elements (including submodels)[9]. Finney attempted to resolve the differences in the two basic philosophies (essentially, black-box versus white-box encapsulation) by introducing optional "ports" as interfaces between a submodel and its containing model, as well as including an XPath-based method to allow referencing model entities. The intention was that a modeler who wanted to follow the classic modularity (black-box) approach could do so, but other modelers could still use models in ways not envisioned by the original modeler simply by accessing a model's elements directly via XPath-based references. In both schemes, elements in the submodels were replaced by corresponding elements of the containing model.

[5] http://sbml.org/Forums/index.php?t=msg&th=67&rid=0#msg_111

[6] http://www.mpi-magdeburg.mpg.de/zlocal/martins/sbml-comp

[7] http://www.mpi-magdeburg.mpg.de/zlocal/martins/sbml-comp/model-composition.pdf

[8] http://sbml.org/images/7/73/Model-composition.pdf

[9] Posted to sbml-discuss, http://sbml.org/Forums/index.php?t=msg&th=234&rid=0#msg_683

Finney's proposal also provided a direct link facility that allows a containing model to refer directly to submodel elements without providing placeholder elements in the containing model. For example, a containing model could have a reaction that converts a species in one submodel to a species in a different submodel, and in the direct-link approach, it would only need to define the reaction, with the reactant and product being expressed as links directly to the species defined in the submodels.

After Finney's last effort, activities in the SBML community focused on updates to SBML Level 2, and since model composition was slated for Level 3, not much progress was made for several years, apart from Finney including a summary of his 2003 proposal and of some of the unresolved issues in a poster[10] at the 2004 Intelligent Systems for Molecular Biology (ISMB) conference held in Glasgow.

Finally, in June of 2007, unplanned discussions at the Fifth SBML Hackathon[11] prompted the convening of a workshop specifically to revitalize the model composition package, and in September of 2007, the SBML Composition Workshop[12] was held at the University of Connecticut Health Center, hosted by the Virtual Cell group and organized by Ion Moraru and Michael Blinov. This event produced several artifacts, still available online:

1. Martin Ginkel provided a list of goals for model composition[13], including use cases, and summarized many of the issues discussed in the present document to this point, including the notion of definition versus instantiation, linking, referencing elements that lack SBML identifiers, and the creation of optional interfaces. It also mentioned the need of allowing parameterization of instances (i.e., setting new numerical values that override the defaults), and the need to be able to "delete" or elide elements out of submodels. (He also provided a summary of ProMoT's model composition approach and a summary of other approaches[14].)

2. Andrew Finney wrote up a list of issues and comments, recorded on the meeting wiki page[15]; these included some old issues as well as some new ones:

   - There should perhaps be a flag for ports to indicate whether a given port must be overloaded.

   - There should be support for *N-to-M* links, when a set of elements in one model are replaced as a group, conceptually, with one or more elements from a different model.

   - The proposal should be generic enough to accommodate future updates and other SBML Level 3 packages.

[10] http://sbml.org/images/9/9c/Ismb-2004-sbml-level-3-poster.pdf

[11] http://sbml.org/Events/Hackathons/The_5th_SBML_Hackathon

[12] http://sbml.org/Events/Other_Events/SBML_Composition_Workshop_2007

[13] http://sbml.org/Events/Other_Events/SBML_Composition_Workshop_2007/Martin_Goals

[14] http://ntcnp.org/twiki/bin/view/VCell/OoModelingPromot

[15] http://sbml.org/Andrew_2007_Comments_about_Model_Composition

3. Wolfram Liebermeister presented his group's experience with SBMLMerge[16], dealing with the pragmatics of merging multiple models. As far as this proposal goes, he noted that the annotations in a composed model need to be considered, particularly since they can be crucial to successfully merging models in the first place.

4. On behalf of Ranjit Randhawa, Cliff Shaffer summarized Ranjit's work in the JigCell group on model fusion, aggregation, and composition[17]. Highlights of this presentation and work include the following:

   - A description of different methods which all need some form of model composition, along with the realization that model fusion and model composition, though philosophically different, entail exactly the same processes and require the same information.

   - A software application (the JigCell Composition Wizard) that can perform conversion between types. The application can, for example, promote a parameter to a species, a concept which had been assumed to be impossible and undesirable in previous proposals.

   - The discovery that merging of SBML models should be done in the order Compartments → Species → Function Definitions → Rules → Events → Units → Reactions → Parameters. If done in this order, potential conflicts are resolved incrementally along the way.

5. Nicolas le Novère created a proposal for SBML modularity in Core[18]. This is actually unrelated to the efforts described above; it is an attempt to modularize a "normal" SBML model in the sense of divvying up the information into modules or blocks, rather than composing a model from different chunks. It was agreed at the workshop that this is a completely separate idea, and while it has merits, should be handled separately.

6. As a collective, the group produced an "Issues to Address" document[19], with several conclusions:

   - It should be possible to "flatten" a composed model to produce a valid SBML Level 3 Core model, and all questions of validity can then be simply applied to the flattened model. If the Core-only version is valid, the composed model is valid.

   - The model composition proposal should cover both designed-ahead-of-time as well as ad-hoc composition. (The latter refers to composing models out of components that were not originally developed with the use of ports or the expectation of being incorporated into other models.)

[16] http://sbml.org/images/c/c1/SemanticSBML_SBMLcomposition.pdf

[17] Presentation at http://sbml.org/documents/proposals/CCB2007DemoPresentation.pdf and publication at http://en.scientificcommons.org/53559395

[18] http://sbml.org/Events/Other_Events/SBML_Composition_Workshop_2007/Modularity_In_Core

[19] http://sbml.org/Events/Other_Events/SBML_Composition_Workshop_2007/Issues_To_Address

- The approach probably needs a mechanism for deleting SBML model elements. The deletion syntax should be explicit, instead of being implied by (e.g.) using a generic replacement construct and omitting the target of the replacement.
- It should be possible to link any part of a model, not just (e.g.) compartments, species and parameters.
- The approach should support "object overloading"[20] and be generally applicable to all SBML objects. However, contrary to what is provided in the JigCell Composition Wizard, changing SBML component types is not supported in object overloading.
- A proposition made during the workshop is that elements in the outer model always override elements in the submodels, and perhaps that sibling linking be disallowed. This idea was hotly debated.
- Interfaces (ports) are indeed considered helpful, but should be optional. They do not need to be directional as in the electrical engineering "input" and "output" sense—the outer element always overrides the inner element, but apart from that, biology does not tend to work in the directional way that electrical components do.
- The ability to refer to or import external files may need a mechanism to allow an application to check whether what is being imported is the same as it was when the modeler created the model. The mechanism offered in this context was the use of MD5 hashes.
- A model composition approach should probably only allow whole-model imports, not importing of individual SBML elements such as species or reactions. The reason is that model components are invariably defined within a larger context, and attempting to pull a single piece out of a model is unlikely to be safe or desirable.
- The model composition approach must provide a means to handle the conversion of units, so that the units of entities defined in a submodel can be made congruent with the entities that refer to them in the enclosing model.

During the workshop, the attendees collectively worked on a rough draft proposal. Stefan Hoops acted as principal editor. The proposal for the SBML package (which was renamed the *Hierarchical Model Composition*[21]), was issued a mere one day after the end of the workshop. It represented an attempt to summarize the workshop as a whole, and provide a coherent whole, suitable as a Level 3 package. It provided a brief overview of the history and goals of the proposal, as well as several UML diagrams of the proposed additions. Stefan presented[22] the proposal in August of 2008 at the 13th SBML Forum, and subsequently gave the same presentation again at the 7th SBML Hackathon in March of 2009 and at the 14th SBML Forum in September of 2009, in a continuing effort to raise interest.

Roughly concurrently, Herbert Sauro, one of the original developers of SBML, received a grant to develop a modular human-readable model definition language, and hired Lucian Smith in

[20] http://sbml.org/Events/Other_Events/SBML_Composition_Workshop_2007/Overloading_Semantics

[21] http://sbml.org/Community/Wiki/SBML_Level_3_Proposals/Hierarchical_Model_Composition_(Hoops_2007)

[22] http://sbml.org/images/e/e9/HierarchicalModelGothenburg.pdf

November of 2007 to work on the project. Sauro and Frank Bergmann, then a graduate student with Herbert, had previously written a proposal[23] for a human-readable language that provided composition features, and this was the design document Lucian Smith initially used to create a system that was eventually called *Antimony*. Through a few iterations, the design[24] eventually settled on was very similar in concept (largely by coincidence) to that developed by the group at the 2007 Connecticut workshop: namely, with model definitions placed separately from their instantiations in other models, and with the ability to link (or "synchronize", in Antimony terminology) elements of models with each other. Because Antimony was designed to be "quick and dirty", it allowed type conversions much like the JigCell Composition Wizard, whereby a parameter could become a species, compartment, or even reaction. Synchronized elements could end up with aspects of both parent elements in their final definitions: if one element defined a starting condition and the other how it changed in time, the final element would have both. If both elements defined the same aspect (like a starting condition), the one designated the "default" would be used in the final version. Smith developed methods to import other Antimony files and even SBML models, which could then be used as submodels of other models and exported as flattened SBML.

At the 2010 SBML-BioModels.net Hackathon, in response to popular demand from people at the workshop, Smith put together a short presentation[25] about model composition and some of the limitations he found with the 2007 proposal. In particular, he proposed the separation of the replacement concept (where old references to replaced values are still valid) from the deletion concept (where old references to replaced values are no longer valid). Smith wrote a summary of that discussion, added some more of thoughts, and posted it to sbml-discuss[26]. In this posting, he proposed and/or reported eight possible modifications to the Hoops et al. 2007 proposal, including the following:

- Separation of *replacement* from *deletion*.
- Separation of model definitions from instantiations.
- Elimination of ports, and the use of annotations instead.
- Annotation of N-to-N replacements, instead of giving them their own construct.

The message to sbml-discuss was met with very limited discussion. Howver, in turns out that several of the issues raised by Smith were brought up at the 2007 meeting, and had simply been missed in the generation of the initial (and incomplete) proposal placed on the wiki. The separation of definitions from instantiations, for example, had been a part of every proposal up until 2007, and indeed was mentioned in the notes for that meeting, so its omission was likely merely an oversight. Similarly, the group had indeed preferred to differentiate deletions from replacements more strongly than by simply having an empty list of replacements.

[23] http://www.sys-bio.org/sbwWiki/_media/sbw/standards/2006-12-17_humanreadable_mdl.pdf

[24] http://antimony.sourceforge.net/Tutorial.pdf

[25] http://sbml.org/images/b/b6/Smith-Hierarchical_Model_Composition-2010-05-03.pdf

[26] http://www.sbml.org/Forums/index.php?t=tree&goto=6124

Genesis of the current proposal

A candidate Level 3 Version 1 Core specification was not released until the end of 2009, and it is only today (near the end of 2010) that the release of a final Level 3 Version 1 Core specification is imminent. As a consequence of the lack of a concrete, finalized SBML Level 3 Core specification, all of the model composition efforts up to this point have been theoretical: they could not define a precise syntax as long as the underlying SBML Level 3 syntax was not finalized. The few SBML-compatible software tools that *did* implement some form of composition had to do so using proprietary approaches or extensions to SBML. This has now changed, thanks to the finalization of SBML Level 3 Version 1 Core, and the present proposal is an attempt to blend features of previous efforts into a concrete, Level 3-compatible syntax.

The current proposal was written from scratch, but draws strongly on the Hoops 2007 and Finney 2003 proposals, as well as, to some degree, every one of the sources mentioned above. Some practical decisions are new to this proposal, often due to additional design constraints resulting from the final incarnation of SBML Level 3, but all of them draw from a wealth of history and experimentation by many different people over the last decade. Where this proposal differs from the historical consensus, the reasoning is explained, but for the most part, the proposal follows the road most traveled, and focuses on being clear, simple, only as complex as necessary, and applicable to the largest number of situations.

Design goals

The following are the basic design goals followed in this proposal:

- *Allow modelers to build models by aggregation, composition, or modularly*. These methods are so similar to one another, and the process of creating an SBML Level 3 package is so involved, that we believe it is not advantageous to create one SBML package for aggregation and composition, and a separate package for modularity. Users of the hierarchical model composition package should be able to use and create models in the style that is best suited for their individual tasks, using any of these mechanisms, and to exchange and reuse models from other groups simply and straightforwardly.
- *Interoperate cleanly with other packages*. The rules of composition should be such that they could apply to any SBML element, even unanticipated elements not defined in SBML Level 3 Core and introduced by some future Level 3 package.
- *Allow models produced with these constructs to be valid SBML if they the constructs are ignored*. As proposed by Nicolas le Novère[27] and affirmed by the current SBML Editors[28], whenever possible, ignoring elements defined in a Level 3 package namespace should result in syntactically-correct SBML models that can still be interpreted to some degree, even if it cannot produce the intended simulation results of the full (i.e., interpreting the package constructs) model. For example, inspection and visualization of the Core model should still be possible.

[27] http://www.sbml.org/Forums/index.php?t=tree&goto=6104

[28] http://sbml.org/Events/SBML_Editors'_Meetings/Minutes/2010-06-22

- *Ignore verbosity of models*. We assume that software will deal with the "nuts and bolts" of reading and writing SBML. If there are two approaches to designing a mechanism for this hierarchical composition package, where one approach is clear but verbose and the other approach is concise but complex or unobvious, we prefer the clear and verbose approach. We assume that software tools can abstract away the verbosity for the user. (However, tempering this goal is the next point.)

- *Avoid over-complicating the specification*. Apart from the base constructs defined by the proposal, any new element or attribute being introduced should have a clear use case that cannot be achieved in any other way.

- *Incorporate most, if not all, of the desirable features of past proposals*. The names may change, but the aims of past efforts at SBML model composition should still be achievable with the present proposal.