

Qualitative translation of relations from BioPAX to SBML qual

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ABSTRACT

Motivation: The Biological Pathway Exchange Language (BioPAX) and the Systems Biology Markup Language (SBML) belong to the most popular modeling and data exchange languages in systems biology. The focus of SBML is quantitative modeling and dynamic simulation of models, whereas the BioPAX specification concentrates mainly on visualization and qualitative analysis of pathway maps. BioPAX describes reactions and relations. In contrast, reactions are the only type of interaction in core SBML. With the SBML Qualitative Models extension (*qual*), it has recently also become possible to describe relations in SBML. Before the *qual* creation, relations could not be translated into SBML at all or were erroneously converted to reactions. Until now, there exists no BioPAX to SBML converter that is fully capable of translating both reactions and relations.

Results: The entire Nature Pathway Interaction Database (PID), which includes pathways from BioCarta, Reactome, and from the National Cancer Institute has been converted from BioPAX into SBML. All available PID BioPAX pathway files (Level 2 and Level 3) have been translated into the SBML format (Level 3 Version 1) including both reactions and relations by using the new *qual* extension package. Additionally, we present the new webtool BioPAX2SBML, which can be used for further BioPAX to SBML conversions. Finally, this converter is compared to existing conversion tools.

Availability: BioPAX2SBML is freely available at <http://webservices.cs.uni-tuebingen.de/> and the complete collection of the PID models at <http://www.cogsys.cs.uni-tuebingen.de/downloads/Qualitative-Models/>.

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1 INTRODUCTION

The goal of systems biology is the model-driven understanding of biological and biochemical processes across all layers and various levels of detail. The Biological Pathway Exchange Language (BioPAX) and the Systems Biology Markup Language (SBML) are common modeling languages that facilitate the exchange and storage of *in-silico* models. BioPAX can be used to describe the biological semantic of metabolic, signaling, molecular, gene-regulatory

and genetic interaction networks (Demir *et al.*, 2010). SBML describes the structure of models, and offers the possibility to include mathematical expressions (Hucka *et al.*, 2003). The SBML core specification defines reactions in detail but no other relationships between molecules. Those relationships are denoted as *relations* that specify enzyme-enzyme relations, protein-protein interactions, interactions of transcription factors and genes, protein-compound interaction, links to other pathways, etc. Before the creation of the Qualitative Models extension for SBML (*qual*, see Berenguier *et al.*, 2011), it was not possible to define relations or to include reactions together with relations in one model. Furthermore, the combination or exchange of information between different databases is hardly feasible if one database uses the BioPAX format and the other one the SBML format. So far, there exist several visualization tools, such as Cytoscape (Zinovyev *et al.*, 2008; Smoot *et al.*, 2011) or CellDesigner (Funahashi *et al.*, 2007; Mi *et al.*, 2011), which can handle BioPAX and SBML by using plugins. But the combination of both formats or conversion of one format into the other is difficult even with these plugins. Hence, converters are needed.

Today, there exist mainly converters from SBML to BioPAX like *The System Biology Format Converter* (see European Bioinformatics Institute – Computational Systems Neurobiology Group, 2011), but no converter for BioPAX to SBML that is capable of properly including relations. Other research groups previously faced the same problem with incompatibilities between BioPAX and SBML. To overcome the limitations of those file formats and to avoid the creation of pseudo-reactions or similar constructions, Rübenacker *et al.* (2009) introduce an intermediate bridging format. The need to combine both formats to use the knowledge from a multitude of databases in various applications becomes more and more urgent.

In this paper we present a webtool for the translation from BioPAX into SBML format. We demonstrate its functionality by converting the whole Nature Pathway Interaction Database (PID, Schaefer *et al.* (2009) from BioPAX Level 2 and Level 3 formats to the SBML format, including the *qual* extension.

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2 MATERIAL AND METHODS

2.1 SBML and the Qualitative Models extension

The SBML Level 3 Version 1 core specification defines a special XML dialect to describe quantitative models. The most important classes are `species`, describing reactive species, and `reactions`, which interconnect species elements. A `species` element can be further specified with the aid of MIRIAM annotations (Novère *et al.*, 2005). The SBML core specification provides no possibility to define other relationships than concrete quantitative reactions.

The SBML Qualitative Models extension (`qual`) introduces qualitative elements, such as `qualitativeSpecies` and `transition`, providing the necessary means to describe relationships that can not be described by reactions, for instance, enzyme-enzyme relations or interactions of transcription factors and genes (Berenguier *et al.*, 2011). Instead of the quantities associated to `species`, which are affected by reactions, `qualitativeSpecies` exhibit discrete states, representing their activities that are changed using transitions. These transitions are linked to input and output elements. The `sign` attribute of the input elements describes whether the relationship between the input and output elements is *positive*, *negative*, *dual*, or *unknown*. *Dual* means that the transition can operate both activating (*positive*) and inhibiting (*negative*). In contrast, *unknown* is assigned to the input if the transition effect is not further specified. If, in a qualitative model, the activity of protein A inhibits the activity of protein B, this would be represented as a transition with an input A, whose `sign` attribute is *negative*, and an output B.

2.2 The BioPAX specification

The Biology Pathway Exchange Language (BioPAX) is an OWL (Web Ontology Language) dialect based on RDF. There is one superclass called `Entity` that is extended by all other BioPAX classes. Two main classes are distinguished: `PhysicalEntity` and `Interaction`. `PhysicalEntity` describes molecules, such as proteins, complexes, small molecules, DNA, or RNA, whereas `Interaction` defines reactions and relations between `PhysicalEntity` classes. `Interaction` is split into `Control` and `Conversion`, which can be separated into the subclasses `Catalysis`, `Modulation`, `TemplateReactionRegulation`, `TemplateReaction`, `GeneticInteraction`, `MolecularInteraction`, `Transport`, `BiochemicalReaction`, `TransportWithBiochemicalReaction`, `Degradation`, and `ComplexAssembly`.

BioPAX is released level-wise with the current level being Level 3. Level 1 is exclusively able to describe metabolic interactions, whereas Level 2 supports signaling pathways and molecular interactions. In addition to Level 2, gene-regulatory networks and genetic interactions can be described with Level 3. For this purpose the `Control` subclass `TemplateReactionRegulation`, the `Conversion` subclass `Degradation`, `TemplateReaction`, `GeneticInteraction`, and `MolecularInteraction` have been added. Furthermore, `PhysicalEntity` is now able to define `DNAregion` and `RNAregion`. Level 3 is not downwards compatible with Level 2, but Level 2 is downwards compatible with Level 1 (Demir *et al.*, 2010). The BioPAX specification of Level 2 denotes all classes in lower case typewriter font and the specification of Level 3 denotes them in upper case typewriter font. For better readability of this paper, all BioPAX element names begin with capital letters and refer to Level 2 and 3. In contrast, SBML classes are written in lower case.

2.3 Conversion of BioPAX to SBML `qual`

The complete Nature Pathway Interaction Database (PID) has been converted from BioPAX to SBML Level 3 Version 1 including the Qualitative Models extension (`qual`). PID provides curated pathways from the National Cancer Institute (L2/L3 2012-03-16), pathways from BioCarta (L2 2009-09-09, L3 2010-08-10), and human Reactome pathways (L2/L3 2010-08-10 Schaefer *et al.* 2009). The translation of the BioPAX Level 2 and Level 3

Table 1. BioPAX `Entity`'s and assigned SBO terms

BioPAX Entity	Assigned SBO term	SBO name
Gene	SBO:0000354	informational molecule segment
Complex	SBO:0000253	non-covalent complex
Protein	SBO:0000252	polypeptide chain
Dna	SBO:0000251	deoxyribonucleic acid
DnaRegion	SBO:0000251	deoxyribonucleic acid
Rna	SBO:0000250	ribonucleic acid
RnaRegion	SBO:0000250	ribonucleic acid
SmallMolecule	SBO:0000247	simple chemical

Each BioPAX `Entity` is converted to an SBML `species` and `qualitativeSpecies`. In BioPAX, one can specify the nature of the real entity by classes that are derived from `Entity` (e.g., DNA, Protein, etc). SBML does not contain specific entities that can be derived from an SBML `species`. The common way to separate different genomic entities in SBML is using SBO terms from the material entity branch. This table specifies the SBO terms that we used to distinguish between various cellular entities in SBML.

pathway files is performed in four steps: (1) initializing the models, (2) translation of `PhysicalEntity` elements, (3) translation of `Interaction` elements, and (4) annotation of all `species`. An overview of the mapping from BioPAX elements to SBML and to SBML `qual` elements is shown in Figure 1.

2.3.1 Step 1: Initializing the models. Firstly, the pathway organism is determined by searching for the `BioSource` reference in the BioPAX file. Furthermore, the SBML model and `qualitativeModel` are built. Both models correspond to the complete pathway represented in the BioPAX file.

2.3.2 Step 2: Translation of `PhysicalEntity` elements. In this step, an SBML `species` and `qualitativeSpecies` are created for each `PhysicalEntity`. Depending on the kind of the `PhysicalEntity`, i.e., if it is a protein, complex, DNA, RNA, or small molecule, the `species` is annotated with the corresponding SBO term (Courtot *et al.*, 2011, see Table 1 for a list of used terms). Furthermore, the `species` compartment is assigned due to the `cellularLocation` of the `PhysicalEntity`. The default compartment is set if the `cellularLocation` is not known.

Then, the BioPAX document is mined for an RDF link from the `PhysicalEntity` to a corresponding Entrez Gene ID. These identifiers are unique and facilitate the automated annotation of this `species` (described in the fourth step). If there exists no Gene ID but a gene symbol, the gene symbol is mapped to a Gene ID.

2.3.3 Step 3: Translation of `Interaction` elements. BioPAX `Interaction` elements are translated into SBML reactions and transitions. An SBML transition describes relationships between molecules that can not be translated into reactions. Examples for such relationships are enzyme-enzyme relations, protein-protein interactions, interactions of transcription factors and genes, protein-compound interaction, links to other pathways, etc. BioPAX `Interaction` elements can be split into `Conversion` and `Control` elements.

The translation of the `Conversion` elements is straightforward, because all elements can unambiguously be mapped to SBML reactions. The translation of those elements is performed by creating the same reaction with all substrates, products and enzymes in SBML. Furthermore, the stoichiometry of the reactants and products of `BiochemicalReaction` and `TransportWithBiochemicalReaction` are also translated into SBML.

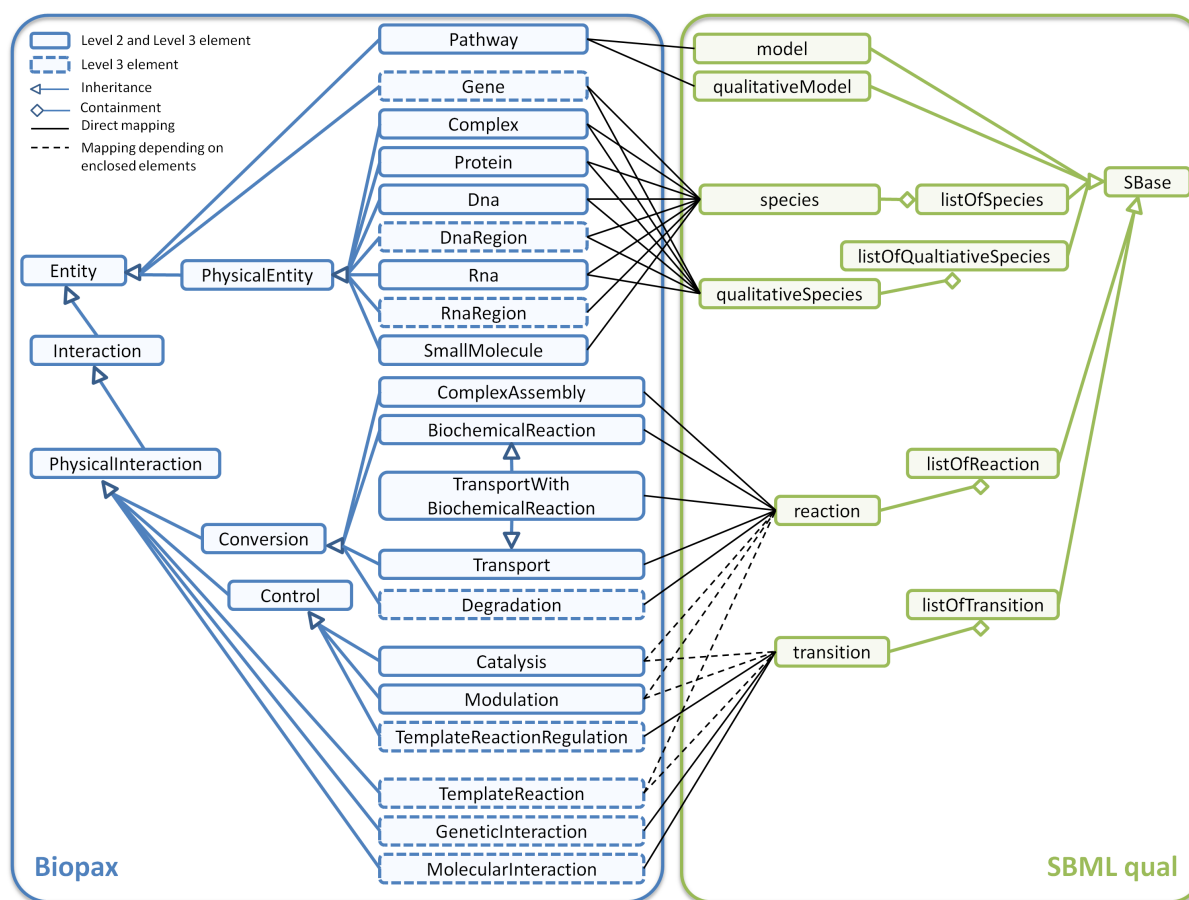


Fig. 1. Conversion from BioPAX Level 2 and Level 3 to SBML Level 3 Version 1 with the Qualitative Models extension (qual). The green rounded rectangles on the righthand site describe the SBML and qual classes, and the blue ones left the BioPAX elements. The distinction between BioPAX Level 2 and Level 3 elements is visualized with dashed rectangles. The dashed rectangles denote elements, which are only available in Level 3. All other elements occur in both levels. The ancestry of both BioPAX and SBML elements is indicated with arrows. Lines, ending with a diamond, indicate elements that are contained in other elements. The conversion from BioPAX to SBML qual is drawn with black lines. For some BioPAX elements, it depends on the enclosed entities if the BioPAX element is translated into a reaction or to a relation. This translation dependency is visualized with black dashed lines. A detailed translation description of those elements is shown in Table 2.

The translation of Control elements is more sophisticated, because they are translated into a transition or a reaction depending on enclosed Control elements. Control elements always consist of zero or more Controller and zero or one Controlled elements. Controller elements are inherited from PhysicalEntity or Pathway, whereas Controlled elements are also Interaction elements. Thus, it depends on the kind of Controller and Controlled element whether the Interaction is translated into an SBML reaction or transition. If the Controller or the Controlled element is a Pathway element, the Interaction is always converted to a transition, because it is biologically not possible to create a reaction with a whole pathway as a reactant or product. A Conversion is translated into a transition if the Controlled element is translated into a transition, too. For instance, the conversion of a Modulation, consisting of a PhysicalEntity as Controller and a BiochemicalReaction as Controlled, is translated into a reaction. An example is shown in Figure 2, which shows the ceramide signaling pathway, where the biochemical reaction from sphingomyelin to ceramide (the Controlled element) is positively modulated from SMPD1+ (the Controller). This modulation will be converted into a reaction where SMPD1+ is modeled as an enzyme of the reaction. But

if the Controlled element is a GeneticInteraction, the Modulation is converted into a transition. A detailed overview of the conversion of the Control elements is shown in Table 2. The sign attribute of the input element describes the relationship between input and output and is determined depending on the ControlType attribute. This attribute is assigned to nearly all Control elements. If the ControlType is activating, sign is set to *active*; if it is inhibiting sign is set to *negative*; if it is both, sign is set to *dual*; otherwise sign is set to *unknown*.

2.3.4 Step 4: Annotation of the translated model. Finally, the SBML instances are further annotated. The BioPAX specification allows users to encode arbitrary identifiers for elements. These can be identifiers for various databases, e.g., UniProt, Entrez Gene, Ensembl, etc. Unfortunately, the syntax used in BioPAX is sometimes inconsistent, which leads to XML database annotations like “UniProt” or “UniProtKB” within BioPAX documents that hamper the automatic reading and interpretation of those models by third party applications.

In SBML, such identifiers can be expressed as standardized MIRIAM URNs that can be added as annotation to any SBML element. We support and add MIRIAM identifiers for the following databases: Entrez Gene,

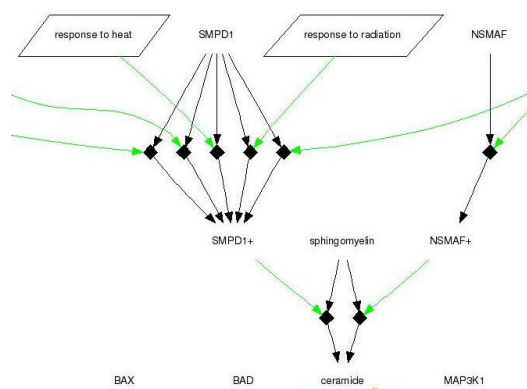


Fig. 2. Part of the ceramide signaling pathway imported from BioCarta into the Pathway Interaction Database (PID). Modifications are drawn with black diamonds. The entities with a black arrow to the diamond describe the modulation inputs and the entities with an black arrow out of the diamond the modulation output. The green arrows symbolize positive regulators and the round rectangles complexes. Pathways are visualized with a trapezium. The ceramide signaling pathway is one pathway example for providing information which could not be translated to SBML before the creation of the Qualitative Models extension (*qual*). With *qual*, it is possible to translate reactions and relations, and to include them in one model. Even pathway-reaction modulations, like the ‘response to heat’ pathway that positively stimulates the reaction from SMPD1 to SMPD1+, can be described. (Figure by courtesy of the National Cancer Institute – <http://www.cancer.gov>).

Omim, Ensembl, UniProt, ChEBI, DrugBank, Gene Ontology, HGNC, PubChem, 3DMET, NCBI Taxonomy, PDBeChem, GlycomeDB, Lipid-Bank, EC-Numbers (enzyme nomenclature) and various KEGG databases (gene, glycan, reaction, compound, drug, pathway, orthology). To obtain identifiers for those databases, we map the Entrez Gene identifier, which we annotated on every element in Step 2, to a KEGG identifier. Using the KEGG API, we then query all of those identifiers to retrieve more descriptive names, descriptions of the elements, and the mentioned database identifiers. The goal of those annotations is to provide models whose components can uniquely be identified by any application and be linked to external data sources.

2.4 Implementation

The conversion was implemented in Java™, using JSBML (?) with the Qualitative Models extension, PaxTools (Demir *et al.*, 2010), and the KEGG API (Kanehisa *et al.*, 2006). PaxTools was used to read the BioPAX files and to manipulate the information content. With the aid of the KEGG API, this information was extended with MIRIAM identifiers (Novère *et al.*, 2005) from the various databases, for instance Entrez Gene, Ensembl, UniProt, etc.

3 RESULTS AND DISCUSSION

The Pathway Interaction Database (PID) is a curated and peer-reviewed pathway database containing human pathways with molecular signaling and regulatory events provided by the Nature Cancer Institute, BioCarta, and Reactome. All pathways are provided in XML, BioPAX Level 2, and Level 3 format.

The BioPAX format is perfectly suitable to encode pathway relations and reactions that can be further used for visualization or

Table 2. Description of the translation of BioPAX Control elements

BioPAX Controller	BioPAX Controlled	Converted SBML <i>qual</i> element
BioPAX Level 3		
PhysicalEntity	BiochemicalReaction	reaction
PhysicalEntity	ComplexAssembly	reaction
PhysicalEntity	Conversion	transition
PhysicalEntity	Degradation	reaction
PhysicalEntity	Transport	reaction
PhysicalEntity	TransportWithBiochemicalReaction	reaction
PhysicalEntity	Pathway	transition
PhysicalEntity	TemplateReaction	transition
Pathway	BiochemicalReaction	transition
Pathway	ComplexAssembly	transition
Pathway	Conversion	transition
Pathway	Degradation	transition
Pathway	Pathway	transition
Pathway	TemplateReaction	transition
Pathway	Transport	transition
Pathway	TransportWithBiochemicalReaction	transition
BioPAX Level 2		
physicalEntity	biochemicalReaction	reaction
physicalEntity	complexAssembly	reaction
physicalEntity	interaction	transition
physicalEntity	pathway	transition
physicalEntity	transport	reaction
physicalEntity	transportWithBiochemicalReaction	reaction
pathway	biochemicalReaction	transition
pathway	complexAssembly	transition
pathway	interaction	transition
pathway	pathway	transition
pathway	transportWithBiochemicalReaction	transition
pathway	transport	transition

BioPAX Control elements consist of a Controller and one or more Controlled elements. Depending on the kind of Controller or Controlled element, the Control entity is translated into an SBML reaction or transition. The table gives an overview of this conversion regarding BioPAX Level 2 and BioPAX Level 3.

pathway analysis. However, this format also has its limitations. Many applications, especially for simulation and modeling of biological networks, use the SBML format (Zinovyev *et al.*, 2008; Funahashi *et al.*, 2007; Hoops *et al.*, 2006). Therefore, a few importers and converters for BioPAX into SBML have been developed. BioPAX Entity elements, which can be genes, proteins, small molecules, etc., can be translated into SBML species and the type of the BioPAX Entity can be encoded as SBO term or MIRIAM annotation of the species itself. Relations between Entity elements, corresponding to edges in a pathway graph, are also provided

with detailed information in BioPAX. These relations can be transports, biochemical reactions, complex assemblies, etc. At this point, most translations to SBML usually produce errors or have a massive loss of information because the SBML core specification only provides reactions, which represents real biochemical reactions with substrates, products and enzymes. Processes, such as modulation of an entity by another one, can not directly be encoded as a reaction, at least not without knowing the exact chemical equation. Hence, former conversion approaches from BioPAX to SBML did either incorrectly convert those relations to reactions or simply removed them during the translation. To fill this gap, the SBML community has recently developed the `qual` specification, which allows users to model arbitrary transitions between species.

Furthermore, the models themselves just provide the base for further analysis or visualization methods. Other applications, such as CellDesigner or COPASI, focus on visualization, simulation, analysis, etc. of those models. Therefore, most of those applications have certain requirements on the models. For example, to uniquely map mass spectrometry data on a model, it may be required for the model to have UniProt IDs. To match mRNA expression data or perform gene set enrichment analyses, Entrez Gene identifiers might be required. Consequently, we provide all annotations that we could gather from the input BioPAX files also in the SBML files and further annotate all `species` with a plethora of additional identifiers.

The `qual` extension has been created recently and, thus, might not be supported by all applications, yet. Therefore, we decided to build joint SBML core and `qual` models. All our SBML files contain a `model` that corresponds to the SBML core specification, and an additional `qualitativeModel` that contains all relations. These models are compatible with older applications, that do not yet support `qual` but still can read all `species` and `reactions`. Newer applications that are ready to handle relations can read the additional `qual` model and process all information that was also available in the BioPAX file.

We converted both, the Level 2 and the Level 3 BioPAX files to SBML core, including the `qual` extension. The reason for converting both levels was the additional description possibility of gene-regulatory networks and genetic interactions in BioPAX Level 3, which is not supported by Level 2 pathway models. Since older simulation applications still work with BioPAX Level 2, we also translated these files into SBML in order to prevent loss of information and to be able to use these models, too. All models are available at <http://www.cogsys.cs.uni-tuebingen.de/downloads/Qualitative-Models/>. Furthermore, we provide our webtool BioPAX2SBML for further BioPAX translations at <http://webservices.cs.uni-tuebingen.de/>.

3.1 Comparison to other BioPAX to SBML converters

Just a few approaches exist to convert BioPAX to SBML and the existing ones use a simple one-to-one conversion. This might be due to the fact that “the inter-conversion between BioPAX and SBML is not trivial as both formats were developed for different purposes” (Bauer-Mehren *et al.*, 2009). Sybill (Rübenacker *et al.*, 2009) and BiNoM (Zinovyev *et al.*, 2008) are two approaches that can be used for the translation of BioPAX into SBML but none of them is able to appropriately translating signaling networks. Sybill is a stand-alone tool that is also integrated in the quantitative modeling environment

VCell (Slepchenko *et al.*, 2003). In contrast, BiNoM is a Cytoscape plugin which offers the possibility to open BioPAX Level 3 files. Following, its main focus lies on the visualization of BioPAX files and not on the conversion. We developed some comparison criteria and show the results in Table 3.

Sybill converts BioPAX Level 2 and Level 3 files and has a very comfortable graphical user interface allowing the user to manipulate the conversion result. Unfortunately, the converted SBML file is not complete and the validator from SBML.org reports errors, because species are used in several reactions that are missing in the species list. Additionally, some groups and pathway links are missing, too. BiNoM generates a complete conversion result, but the validator also reports errors due to empty `listOf` elements and due to the wrong order of these elements. In contrast to Sybill, BiNoM converts BioPAX files without a pathway element, but it is just able to handle a small number of BioPAX files from the Pathway Interaction Database. This is why both tools just partially fulfill the robustness criterion. Another feature of BiNoM is that it can separately visualize reaction networks, pathway structure and protein-protein interaction networks out of one BioPAX file.

Finally, all approaches avoid the translation of duplicate species, but exclusively BioPAX2SBML converter uses the `qual` extension and SBO terms for detailed species description, translates the BioPAX cross-references (`xrefs`) into SBML CV-terms, and augments the SBML file content with further database cross-references.

4 CONCLUSION

Conversion between different formats is important in all parts of computer science. In many cases, conversion leads to errors or a loss of information. The BioPAX to SBML conversion is such an example. Due to limitations of the SBML core specification, it was not possible to include all relationships between reactive species from BioPAX files in SBML files, while producing correct SBML code. But with SBML Level 3 Version 1 and the addition of extensions to the specifications, in particular the Qualitative Models extension (`qual`), it is now possible to create accurate and specification-conform SBML code. Using this extension, we produced error-free SBML models while minimizing or even eliminating the loss of information during the translation.

The SBML models, provided along with this publication, consist of SBML `species` and, wherever possible, exact reaction equations. All relations from the BioPAX documents that could not be converted to exact reactions have been included as qualitative transitions between qualitative species. Additional information, such as various identifiers or the type of an entity, are encoded as SBO terms or MIRIAM URNs of the corresponding elements. By utilizing the KEGG API it was even possible to complement the translated BioPAX documents with a wealth of information from further databases, such as Entrez Gene, KEGG, etc.

This results in comprehensive and correct SBML models, created for all pathways in the Nature Pathway Interaction Database. These models can easily be used, e.g., for further simulation and modeling steps, without having to deal with incorrect input file formats or error-prone conversions.

Table 3. Comparison of different available converters for BioPAX pathways.

	BioPAX2SBML Büchel <i>et al.</i> 1.0 2012-04-02	Sybill Ruebenacker <i>et al.</i> 1.0 (Build 119) 2010-02-11	BiNoM Zinovyev <i>et al.</i> 2.0 2012-04-12
BioPAX Input Level	Levels 2 and 3	Levels 2 and 3	Level 3
SBML Output Level	Level 3 Version 1 including qual	Level 2 Version 4	Level 2 Version 4, Beta Version for Level 3
Qualitative model support (qual)	✓	-	-
Valid SBML	✓	-	-
Complete	✓	-	✓
No duplicate entities	✓	✓	✓
Robustness	✓	○	○
Compartments	✓	✓	✓
Stoichiometry	✓	-	-
Uses SBO terms	✓	-	-
Xrefs converted into CV terms	✓	-	-
Augment model	✓	-	-
Provenance	✓	-	-

The table compares three applications which are able to translate BioPAX into SBML. The checkmark (✓) indicates that the criteria is completely fulfilled, the circles (○) shows that the criterion is partially fulfilled, and the minus (-) is used if it is not fulfilled. A conversion is *valid* if the validator from SBML.org reports no errors in the converted SBML file and the converted model is *complete* if no BioPAX entity is missing. It is important for modeling purposes that there are no duplicate entities in the files, this is represented with the *No duplicate entities* criterion. A converter is *robust* if it can handle all tested files and is able to convert a BioPAX file, which contains no *Pathway* element. The *Compartments*, *Stoichiometry*, and *Uses SBO terms* criteria denote if this information is translated into SBML and if the SBML species are denoted with the corresponding SBO term. Additionally, it is checked if the BioPAX cross-references (Xrefs) are translated into SBML controlled vocabulary terms (CV terms) and if the SBML model is *augmented* with further information. Finally, the *provenance* criterion denotes if the file history and conversion tool information is saved in the converted SBML file.

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