BIOINFORMATICS
Vol. 00 no. 00 2012
Pages 1–6

Qualitative translation of relations from BioPAX to SBML qual

Finja Büchel [1,*], Clemens Wrzodek [1], Florian Mittag [1], Andreas Dräger [1], Johannes Eichner [1], Nicolas Rodriguez [2], Nicolas Le Novère [2], and Andreas Zell [1]

[1]Center for Bioinformatics Tuebingen (ZBIT), University of Tuebingen, Tübingen, Germany
[2]Computational Systems Neurobiology Group, European Bioinformatics Institute, Hinxton, United Kingdom

Received on XXXXX; revised on XXXXX; accepted on XXXXX

Associate Editor: XXXXXXX

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.

Availability: BioPAX2SBML is freely available at

Contact: finja.buechel@uni-tuebingen.de

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.

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

*to whom correspondence should be addressed

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 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.

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.

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).

Then, the BioPAX document is mined for an RDF link from the PhysicalEntity to a corresponding Entrez Gene ID. These identifers 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.

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 the 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

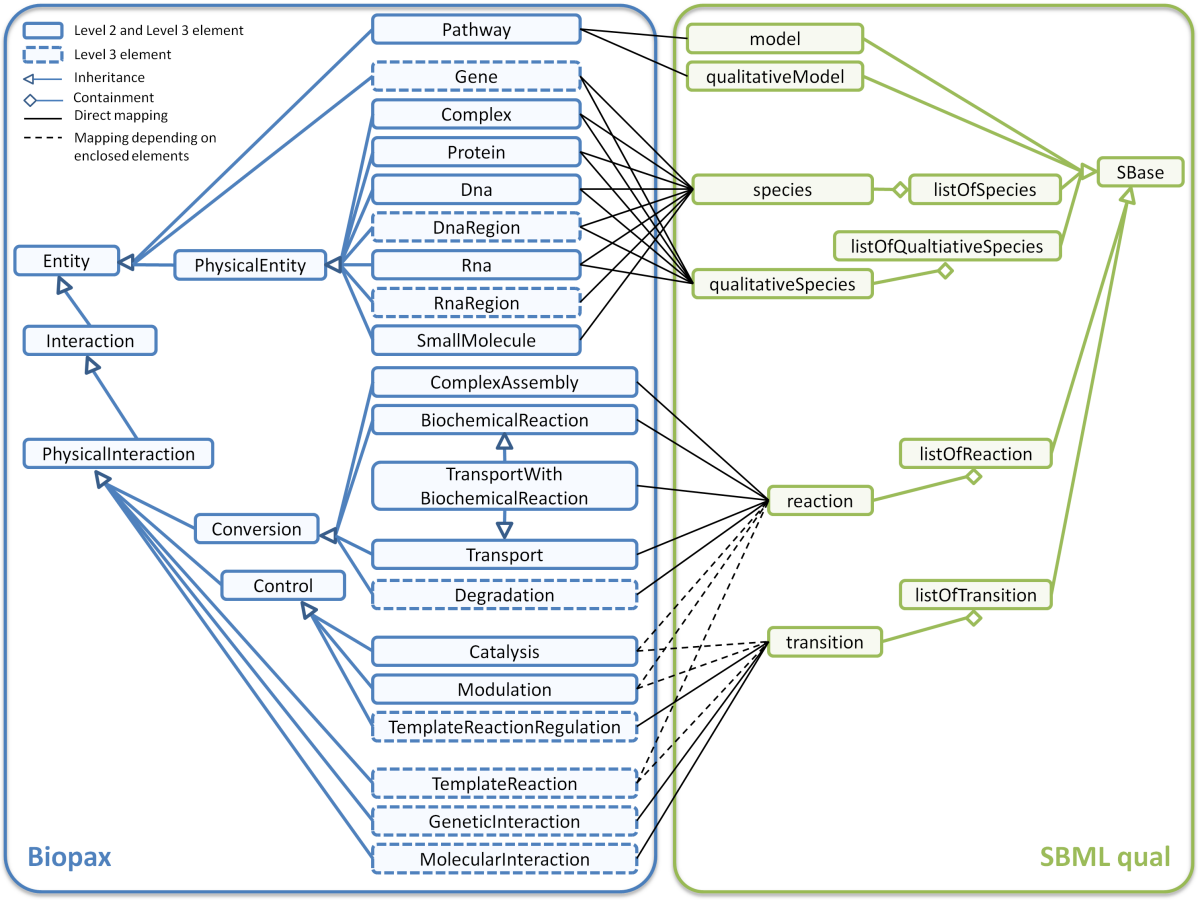

Fig. 1. Conversion from BioPAX Level 2 and Level 3 to SBML Level 3 Version 1 with the Qualitative Models extension (`qual`). The green rounded rectangles on the righthand site describe the SBML and `qual` classes, and the blue ones left the BioPAX elements. The distinction between BioPAX Level 2 and 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.

`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, Omim, Ensembl, UniProt, ChEBI, DrugBank, Gene Ontology, HGNC, PubChem, 3DMET, NCBI Taxonomy, PDBeChem, GlycomeDB, LipidBank, 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.

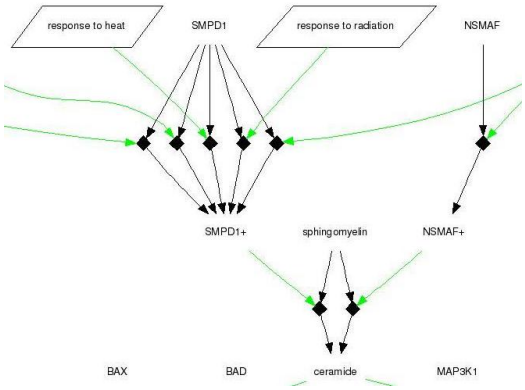

Fig. 2. Part of the ceramide signaling pathway imported from BioCarta into the Pathway Interaction Database (PID). Modifications are drawn with black diamonds. The entities with a black arrow to the diamond describe the modulation inputs and the entities with an black arrow out of the diamond the modulation 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).

2.4 Implementation

The conversion was implemented in Java™, using JSBML (Dräger *et al.*, 2011) 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 pathway analysis. However, this format also has its limitations. Many applications, especially for simulation and modeling of biological networks, use the SBML format (**?**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

Table 2. Description of the translation of BioPAX `Control` elements

BioPAX `Controller`	BioPAX `Controlled`	Converted SBML `qual` 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.

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 Furthermore, we provide our webtool BioPAX2SBML for further BioPAX translations at

3.1 Comparison to other BioPAX to SBML converters

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.

ACKNOWLEDGEMENTS

We wish to acknowledge the Qualitative Models and JSBML teams.

Funding: Federal Ministry of Education and Research (BMBF, Germany) in the National Genome Research Network (NGFN+) under grant number 01GS08134 and Virtual Liver Network under grant number 0315756.

Conflict of interest: None declared.

REFERENCES

Berenguier, D., Chaouiya, C., Naldi, A., Thieffry, D., and van Iersel, M. P. (2011). Qualitative Models (qual). Specification available at http://sbml.org/Community/Wiki/SBML_Level_3_Proposals/Qualitative_Models. Accessed 2012 Mar 22.

Courtot, M., Juty, N., Knüpfer, C., Waltemath, D., Zhukova, A., Dräger, A., Dumontier, M., Finney, A., Golebiewski, M., Hastings, J., Hoops, S., Keating, S., Kell, D. B., Kerrien, S., Lawson, J., Lister, A., Lu, J., Machne, R., Mendes, P., Pocock, M., Rodriguez, N., Villeger, A., Wilkinson, D. J., Wimalaratne, S., Laibe, C., Hucka, M., and Novère, N. L. (2011). Controlled vocabularies and semantics in systems biology. *Mol Syst Biol*, **7**, 543.

Demir, E., Cary, M. P., Paley, S., Fukuda, K., Lemer, C., Vastrik, I., Wu, G., D'Eustachio, P., Schaefer, C., Luciano, J., Schacherer, F., Martinez-Flores, I., Hu, Z., Jimenez-Jacinto, V., Joshi-Tope, G., Kandasamy, K., Lopez-Fuentes, A. C., Mi, H., Pichler, E., Rodchenkov, I., Splendiani, A., Tkachev, S., Zucker, J., Gopinath, G., Rajasimha, H., Ramakrishnan, R., Shah, I., Syed, M., Anwar, N., Babur, O., Blinov, M., Brauner, E., Corwin, D., Donaldson, S., Gibbons, F., Goldberg, R., Hornbeck, P., Luna, A., Murray-Rust, P., Neumann, E., Reubenacker, O., Samwald, M., van Iersel, M., Wimalaratne, S., Allen, K., Braun, B., Whirl-Carrillo, M., Cheung, K.-H., Dahlquist, K., Finney, A., Gillespie, M., Glass, E., Gong, L., Haw, R., Honig, M., Hubaut, O., Kane, D., Krupa, S., Kutmon, M., Leonard, J., Marks, D., Merberg, D., Petri, V., Pico, A., Ravenscroft, D., Ren, L., Shah, N., Sunshine, M., Tang, R., Whaley, R., Letovksy, S., Buetow, K. H., Rzhetsky, A., Schachter, V., Sobral, B. S., Dogrusoz, U., McWeeney, S., Aladjem, M., Birney, E., Collado-Vides, J., Goto, S., Hucka, M., Novère, N. L., Maltsev, N., Pandey, A., Thomas, P., Wingender, E., Karp, P. D., Sander, C., and Bader, G. D. (2010). The BioPAX community standard for pathway data sharing. *Nat Biotechnol*, **28**(9), 935–942.

Dräger, A., Rodriguez, N., Dumousseau, M., Dörr, A., Wrzodek, C., Le Novère, N., Zell, A., and Hucka, M. (2011). JSBML: a flexible Java library for working with SBML. *Bioinformatics*, **27**(15), 2167–2168.

European Bioinformatics Institute – Computational Systems Neurobiology Group (2011). System Biology Format Converter (SBFC). Software available from http://www.ebi.ac.uk/compneur-srv/sbml/converters/SBMLtoBioPax.html. Accessed 2012 Mar 22.

Funahashi, A., Jouraku, A., Matsuoka, Y., and Kitano, H. (2007). Integration of CellDesigner and SABIO-RK. *In Silico Biol*, **7**(2 Suppl), S81–S90.

Hoops, S., Sahle, S., Gauges, R., Lee, C., Pahle, J., Simus, N., Singhal, M., Xu, L., Mendes, P., and Kummer, U. (2006). Copasi–a complex pathway simulator. *Bioinformatics*, **22**(24), 3067–3074.

Hucka, M., Finney, A., Sauro, H. M., Bolouri, H., Doyle, J. C., Kitano, H., Arkin, A. P., Bornstein, B. J., Bray, D., Cornish-Bowden, A., Cuellar, A. A., Dronov, S., Gilles, E. D., Ginkel, M., Gor, V., Goryanin, I. I., Hedley, W. J., Hodgman, T. C., Hofmeyr, J.-H., Hunter, P. J., Juty, N. S., Kasberger, J. L., Kremling, A., Kummer, U., Novère, N. L., Loew, L. M., Lucio, D., Mendes, P., Minch, E., Mjolsness, E. D., Nakayama, Y., Nelson, M. R., Nielsen, P. F., Sakurada, T., Schaff, J. C., Shapiro, B. E., Shimizu, T. S., Spence, H. D., Stelling, J., Takahashi, K., Tomita, M., Wagner, J., Wang, J., and Forum, S. B. M. L. (2003). The systems biology markup language (SBML): a medium for representation and exchange of biochemical network models. *Bioinformatics*, **19**(4), 524–531.

Kanehisa, M., Goto, S., Hattori, M., Aoki-Kinoshita, K. F., Itoh, M., Kawashima, S., Katayama, T., Araki, M., and Hirakawa, M. (2006). From genomics to chemical genomics: new developments in KEGG. *Nucleic Acids Res*, **34**(Database issue), D354–D357.

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

	BioPAX2SBML converter Büchel *et al.*	**BiNom** Zinovyev *et al.*	**Sybill** Ruebenacker *et al.*
Version	1.0	2.0	1.0 (Build 119)
Release date	2012-04-02	2012-04-12	2010-02-11
BioPAX Input Level	Level 2 and 3	Level 3	Level 2 and 3
SBML Output Level	Level 3 Version 1 including qual	Level 2 Version 4, Beta Version for Level 3	Level 2 Version 4
Signaling support (qual)	✓	×	×
Valid	✓	×	×
Complete	✓	✓	×
Robustness	✓	✓	○
Machine readable	✓	✓	✓
Human readable	✓	○	✓
No dublicate entities	✓	✓	✓
Compartements	✓	✓	✓
Stoichiometry	✓	×	×
SBO-terms	✓	×	×
Uses appropriate SBO (material entity)	✓	×	×
Xrefs to MIRIAM annotations	✓	×	×
References to original file	✓	×	×

Sybill (everything is translated to a reaction, there are no reaction modifiers defined), (species are used in reactions, without listing in the species list) (groups are missing, proteins are missing, links to other pathways are missing)
- different entity states are different SBML species, but they are not defined in detail
- Wenn kein Pathwayobjekt definiert wurde, wird der pathway nicht bersetzt
Binom (order of the reaction lists not correct, some reaction lists are empty, that's ot allowed), human readable (abhnging von der Eingabedatei, keine allgemeinen Regeln) - Bietet die Moeglichkeit aus einer Datei, die mehrere Pathways enthaelt, einen Pathway auszuwaehlen und als BioPAX file zu speichern - Auftrennung in Reaction Network, Pathway Structure und Protein-protein interaction moeglich"
- Luft bei owl Dateien grer 50kb nicht mehr stabil

Mi, H., Muruganujan, A., Demir, E., Matsuoka, Y., Funahashi, A., Kitano, H., and Thomas, P. D. (2011). BioPAX support in CellDesigner. *Bioinformatics*, **27**(24), 3437–3438.

Novère, N. L., Finney, A., Hucka, M., Bhalla, U. S., Campagne, F., Collado-Vides, J., Crampin, E. J., Halstead, M., Klipp, E., Mendes, P., Nielsen, P., Sauro, H., Shapiro, B., Snoep, J. L., Spence, H. D., and Wanner, B. L. (2005). Minimum information requested in the annotation of biochemical models (MIRIAM). *Nat Biotechnol*, **23**(12), 1509–1515.

Rübenacker, O., Moraru, I. I., Schaff, J. C., and Blinov, M. L. (2009). Integrating BioPAX pathway knowledge with SBML models. *IET Syst Biol*, **3**(5), 317–328.

Schaefer, C. F., Anthony, K., Krupa, S., Buchoff, J., Day, M., Hannay, T., and Buetow, K. H. (2009). PID: the Pathway Interaction Database. *Nucleic Acids Res*, **37**(Database issue), D674–D679.

Smoot, M. E., Ono, K., Ruscheinski, J., Wang, P.-L., and Ideker, T. (2011). Cytoscape 2.8: new features for data integration and network visualization. *Bioinformatics*, **27**(3), 431–432.

Zinovyev, A., Viara, E., Calzone, L., and Barillot, E. (2008). BiNoM: a Cytoscape plugin for manipulating and analyzing biological networks. *Bioinformatics*, **24**(6), 876–877.