Data Integration and Semantic Enrichment of Systems Biology Models and Simulations

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Abstract. The rise of Systems Biology approaches, in conjunction with the availability of numerous powerful and user-friendly modeling environments, brought computational models out of the dusty closets of theoreticians to the forefront of research in biology. Those models are becoming larger, more complex and more realistic. As any other type of data in life sciences, models have to be stored, exchanged and re-used. This was made possible by the development of a series of standards, that, when used in conjunction, can cover the whole life-cycle of a model, including the specification of its structure and syntax, the simulations to be run, and the description of its behaviour and resulting numerical output. We will review those standards, well-accepted or still under development, including the Minimal requirements (MIRIAM, MIASE), the description formats (SBML, SED-ML, SBRML) and the associated ontologies (SBO, KiSAO, TEDDY). We will show how their use by the community, through a rich toolkit of complementary software, can permit to leverage on everyone's efforts, to integrate models and simulations with other types of biological knowledge, and eventually lead to the fulfillment of one of Systems Biology's tenets of collaboration between biology, mathematics and computing science.

Keywords: database annotation, semantic annotation, data integration, quantitative models, computational systems biology, minimal requirement.

1 Introduction

Biological systems such as cellular, gene regulatory and protein interaction networks cannot be understood from studying the functions of their individual components. Systematic studies, considering all components at the same time, help precise understanding of the complex biological processes. Systems Biology focuses on the dynamics of biological processes at a "systems level", (i.e.) by considering interactions of all the components of the system. Computational Systems Biology deals with the construction of mathematical models that

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N.W. Paton, P. Missier, and C. Hedeler (Eds.): DILS 2009, LNBI 5647, pp. 5–15, 2009.

are central for handling the complex biological networks. Mathematical models describe systems in a quantitative manner on their own or in response to their environment and simulate their behaviour. Further, the progress in computational systems biology will lead to practical innovations in medicine and drug discovery.

Deriving a mathematical model, to simulate a biological process is a complex task. The modellers need to have information such as the kinetic law defining the rate of a reaction together with its parameters and experimental conditions, apart from the mathematical and biochemical knowledge. The quality and accuracy of quantitative models, that represent biological processes, depends mainly on the interaction between the experimentalists and the modellers. In recent years, application of modern computational and theoretical tools in modeling lead to an exponential increase both in number and complexity of quantitative models in biology. Modellers increasingly reuse and combine existing models. It often becomes impractical to re-implement models from literature. For easy and efficient use of the already published models, the models should be collected, curated and stored in a well structured databases, such as the BioModels Database [1], the Database of Quantitative Cellular Signalling (DOQCS) [2], JWS online [3] and the CellML Model repository [4] allowing users to search and retrieve models of interest. Recently, journals like Molecular Systems Biology, the BioMedCentral and PLoS journals encourage systems biologists to submit their coded models together with their papers. To enable researchers in quantitative systems biology to the existing models efficiently, a series of standards that includes the model format, the simulation to be run, the description of its behaviour and the resulting numerical outputs should be embedded in the model. In this review, we will discuss about the resources developed by the BioModels.net team in regard to minimum requirements, standard formats for encoding, and associated ontologies for 1) describing quantitative models, 2) describing simulation protocols and 3) describing simulation results (Figure 1).

The Minimal Information Requested In the Annotation of Models (MIRIAM; `http://www.ebi.ac.uk/miriam`) [5] defines the procedure for encoding and annotating models represented in machine-readable format. Minimum Information About a Simulation Experiment (MIASE; `http://www.ebi.ac.uk/compneursrv/miase/`), describes the information needed to run and repeat a numerical simulation experiment derived from a given quantitative model. MIRIAM and MIASE are now, part of the Minimum Information for Biological and Biomedical Investigations project (MIBBI; `http://www.mibbi.org/`) [6]. MIBBI is a web-based, freely accessible resource for checklist projects, providing straight forward access to existing checklists (and to complementary data formats, controlled vocabularies, tools and databases), thereby enhancing both transparency and accessibility.

Biological ontologies play an important role in data integration. Three ontologies are developed by the BioModels.net project, in order to enrich the information provided with the models, to enhance integration of models, and integration of models with other types of knowledge. (1) The Systems Biology

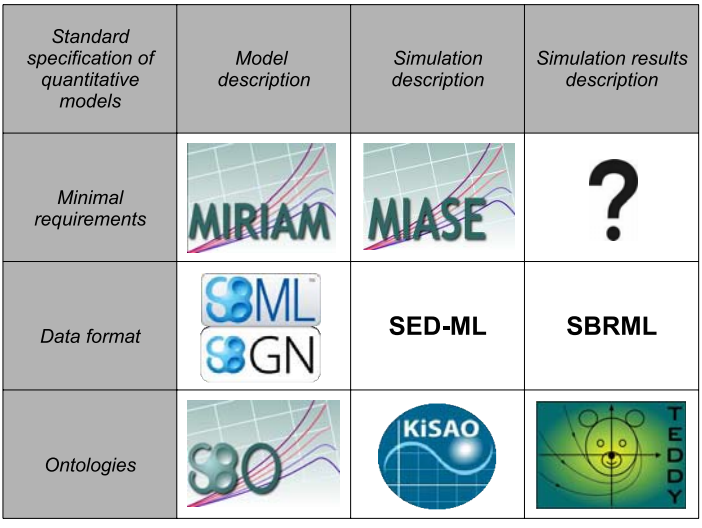

Fig. 1. Standard specifications to encode quantitative systems biology models in three layers i.e 1) Model, 2) Simulation and 3) Simulation results description

Ontology (SBO; `http://www.ebi.ac.uk/sbo`) is a set of controlled vocabularies that add a semantic layer to the biochemical and mathematical description of a model, and act as a glue between different levels and types of representation. (2) The Kinetic Simulation Algorithm Ontology (KiSAO) classifies the approaches by model characteristics and numerical characteristics. Model characteristics include, for instance, the type of variables used for the simulation (such as discrete or continuous) and the spatial resolution. Numerical characteristics specify whether the systems' behaviour can be described as deterministic or stochastic, and whether the algorithms use fixed or adaptive time steps. (3) The TErminology for the Description of DYnamics (TEDDY), is a nascent effort to classify the behaviours of variables (eg. "oscillation", "bistable behaviour"), the characteristics of those behaviours (eg. "period", "bifurcation") and the functionalities of modules (eg. "negative feedback", "integrator"). The Open Biomedical Ontology (OBO) [7] consortium, works on expanding family of ontologies designed to be interoperable and logically well formed and to incorporate accurate representations of biological reality. SBO is available in OBO, OWL [8] and SBO-XML. KiSAO and TEDDY are available in OBO and OWL format respectively.

The most common format to encode quantitative models is SBML (Systems Biology Markup Language; `http://sbml.org/`) [9]. CellML [4] and NeuroML [10] are also used in the communities of physiology and computational neurobiology respectively. The Simulation Experiment Description Markup Language (SED-ML) [11] and the Systems Biology Results Markup Language (SBRML; `http://www.comp-sys-bio.org/static/SBRML-draft-21-08-2008.pdf`) are the formats developed for encoding the required simulation information and representing the simulation results, respectively.

2 Describing Quantitative Models

Quantitative models will be useful only if they can be accessed and reused easily by the scientific community. Most of the published quantitative models in biology are lost because they were not made available, not well formated and characterised. To overcome this problem, the community had defined a set of guidelines for specifying quantitative models.

2.1 MIRIAM

To become part of a database (repository), quantitative models should be able to fulfil certain requirements and rules (MIRIAM: Minimal information requested in the annotation of models) [5]. These rules define procedures for encoding and annotating models represented in machine-readable form. The aim of MIRIAM is to define processes and schemes that will increase the confidence in model collections and enable the assembly of model collections of high quality. Firstly, the models must be 1) referred to a unique publication (that describes precisely the structure of the models, lists all quantitative parameters used, and describe the expected output), 2) encoded in a standard machine- readable format such as SBML or CellML, and 3) reproduce the results described in the reference publication. Secondly, the models must be annotated. The scheme of annotation includes assigning a name to the model, the details of the creators who encoded the model, date and time of creation and last modification of the model and links to external database resources. Model annotation and links to the external database resources are crucial features since they enhance model quality and are essential for search strategies. The data resources that are linked to could be, for instance, controlled vocabularies (Taxonomy, Gene Ontology, ChEBI etc.) or other databases (UniProt, KEGG, Reactome etc).

This annotation relates a piece of knowledge to a model constituent. The referenced information should be described using a triplet "data-type", "identifier", "qualifier". The "data-type" is a unique, controlled, description of the type of data, written as a Uniform Resource Identifier [12]. The "identifier", within the context of the "datatype", points to a specific piece of knowledge. The "qualifier" is a string that serves to refine the relation between the referenced piece of knowledge and the described constituent. Example of qualifiers are "has a", "is version of", "is homologous to", etc. Such a triplet can easily be exported later using RDF [13], to ease further automatic treatment.

2.2 SBO

Though there are many controlled vocabularies available that are used for quantitative models, several additional small controlled vocabularies are required to enable the systematic capture of information of the models. Thus Biomodels.net partners started developing their own ontology, Systems Biology Ontology (SBO).

The SBO provides additional semantics that can be used either to link formal representations of models to biological knowledge, or to interface different representations. SBO is currently composed of six different branches of vocabularies: quantitative parameter, participant type, modelling framework, mathematical expression, interaction and entity.

- quantitative parameter: This vocabulary includes terms such as "forward unimolecular rate constant", "Hill coefficient", "Michaelis constant", that can be used to enhance SBML element parameter. In addition to the sub-classing links, a parameter can be defined in function of others through a mathematical construct.
- participant role: Includes participant functional type, like "catalyst", "substrate", "competitive inhibitor", used for instance to enhance SBML element speciesReference, but also participant physical type, whether material, such as "macromolecule", "simple chemical", or conceptual, such as "gene" or "enzyme", used to enhance SBML element species.
- modelling framework: Defines how to interpret a mathematical expression, such as "deterministic", "stochastic", "boolean"' etc. This branch of SBO is only meant to state the context in which to interpret a mathematical expression, and is not meant to be redundant with KiSAO (for information about KiSAO, see below).
- mathematical expression: Classifies the construction used in biological modelling. In particular, it contains a taxonomy of kinetic rate equations. Examples of terms are "mass action kinetic", "Henri-Michaelis-Menten kinetics", "Hill equation" etc. The terms contain a mathematical construct that refers to the previous three vocabularies.
- interaction: Mutual or reciprocal action or influence that happens at a given place and time between participating entities and/or other interactions.
- entity: A real being, whether functional or material, that may participate in an interaction, a process or relationship of biological significance.

The branches are linked to the root by standard OBO has part relationships. Within a vocabulary, the terms are related by "is a" inheritances, which represent sub-classing, i.e. any instance of the child term is also an instance of the parent term. As a consequence, not only children are versions of the parents, but the mathematical expression associated with a child is a version of the mathematical expressions of the parents. In addition to its identifier and name, an SBO term contains a definition, a list of relationships, and optionally a mathematical construct, comments and synonyms.

Though SBO provide terms that are covered by certain existing ontologies, none of these ontologies provide features such as mathematical formulas corresponding to common biochemical rate laws expressed in ready-to-reuse MathML [14]. Recent versions of the SBML specification (since Level 2 Version 2, [15]) allow model components to be annotated with SBO terms, therefore enhancing semantics of the model beyond the sole topology of interaction and mathematical expression. SBO is an open ontology, accessible in different format (OBO, OWL, SBO-XML) facilitating exchange and support by various tools, and accessible

programmatically via web services. SBO is a part of the OBO (Open BioMedical Ontologies). SBO, documentation and association resources are freely available at `http://www.ebi.ac.uk/sbo/`.

2.3 SBML

Systems Biology Markup Language (SBML), is a XML-based format for representing biochemical reaction networks. Though various formal languages were developed by different communities to encode models at different scales, the most successful format is SBML. The other common format to represent quantitative models is CellML, which is very similar to SBML. SBML is based on hierarchical lists of specified elements while CellML describes a model as a collection of linked generic components, offering the possibility of modular and multiscale models.

SBML can encode models consisting of biochemical entities linked by reactions to form biochemical networks. A model definition in SBML consists of lists of one or more of the following components:

- Compartment: A container of finite volume where the reacting entities may be located.
- Species: A chemical substance or entity that take part in the reaction.
- Reaction: A statement describing some transformation, transport or binding process that can change one or more species. Reactions have associated rate laws describing the manner in which they take place.
- Parameter: A quantity that has a symbolic name. SBML provides the ability to define parameters that are global to a model, as well as parameters that are local to a single reaction.
- Unit definition: A name for a unit used in the expression of quantities in a model. This is a facility for both setting default units and for allowing combinations of units to be given abbreviated names.
- Rule: A mathematical expression that is added to the model equations constructed from the set of reactions. Rules can be used to set parameter values, establish constraints between quantities, etc.

Most people like to look at the graphical representation of the reaction processes, since it gives the precise knowledge of the reaction processes. Graphical notations used by researchers and softwares are informal and are highly variable. So, the SBML community initiated a Systems Biology Graphical Notation (SBGN; `http://sbgn.org/`) project to help standardising a graphical notation for computational models in systems biology.

SBGN defines a comprehensive set of symbols with precise semantics, together with detailed syntactic rules defining their use and how diagrams are to be interpreted. The real payoff will come when researchers are as familiar with the notation as electronics engineers are with the notation of circuit schematics. SBML, SBO and MIRIAM together are useful for the generation of SBGN.

3 Describing Simulation Protocols

The models must be checked whether they can reproduce the results published in the reference scientific article. The simulation software packages read in a model expressed in SBML and translate it into their own internal format for model analysis. For instance, a package might provide the ability to simulate a model by constructing a set of differential equations representing the network and then performing numerical integration on the equations to explore the model's dynamic behaviour. The simulation software for simulating a model should be selected according to the features of the model, based on whether the model is, for example, a deterministic, continuous or stochastic discrete event model. Figure 2 illustrates the life cycle of quantitative models.

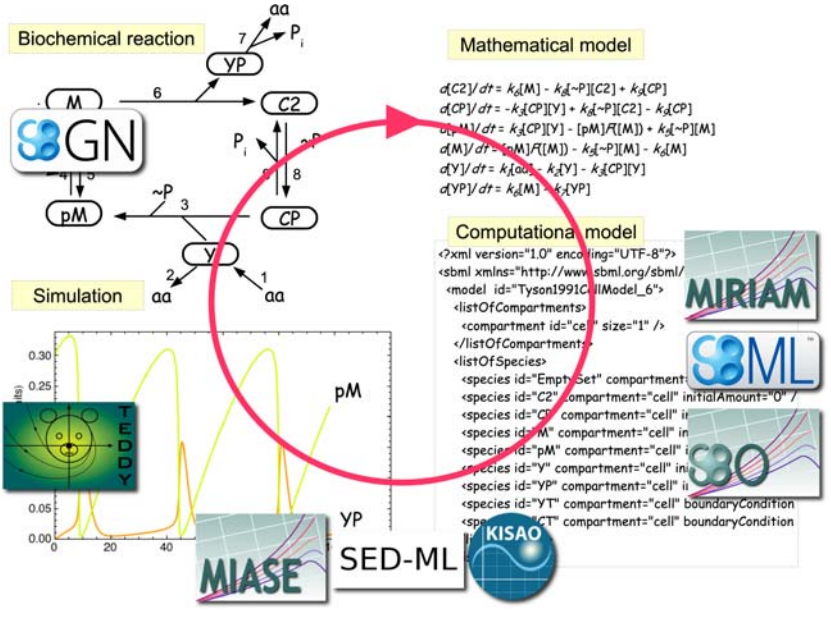

Fig. 2. Life cycle of systems biology models. The location of different logos represents their domain of relevance.

3.1 MIASE

The computational modeling procedure is not limited to the definition of the model structure. According to the MIRIAM specification, "the models must be able to reproduce the results published in the reference publication". The guidelines to run the simulations would highly improve the efficient use of the models deposited in the repositories. This led to the development of the Minimum Information About a Simulation Experiment (MIASE; `http://www.ebi.ac.uk/`

compneur-srv/miase) project. It covers information about the simulated model, the simulation methods, the tasks performed and the output produced.

3.2 KiSAO

A crucial aspect of describing a simulation experiment is to precisely identify the simulation algorithm and simulation approach used for each step. So, it is important to have an ontology which can cover these details. The Kinetic Simulation Algorithm Ontology (KiSAO), characterise and categorise the existing simulation algorithm and approaches available to simulate the quantitative systems biology models. KiSAO is an open ontology, accessible in the OBO format, and is available from http://www.ebi.ac.uk/comp-srv/miase/kiaso.html.

3.3 SED-ML

The Simulation Experiment Description Markup Language (SED-ML) [11] is a formal XML based representation of models, aimed at encoding the simulation information required to implement MIASE guidelines. Each simulation tool that is capable of storing simulation settings uses its own internal storage format. For example, COPASI uses an XML based format for encoding the selected simulation algorithm and the task definitions. However, those formats are restricted to the specific simulation tool, and therefore simulation experiment descriptions cannot be exchanged with others. Similarly, the CellML community, in their CellML Metadata Specification [16] has planned to store simulation specification details inside the model definition and thus this approach is restricted to the CellML models only. SED-ML is independent of the software tools used to run the simulations. SED-ML can encode simulation experiments being run with several models, which can be in different formats (e.g. comparing simulation results of a CellML model and an SBML model). SED-ML can specify different simulation settings applicable to the same model (e.g. running a model with a stochastic and a deterministic simulation algorithm). Combination of both are also possible. It is easy to set up a simulation experiment that results in an output comparing a parameter of a CellML model to a parameter of an SBML model, depending on different simulation algorithms.

However, a number of important issues in simulation experiments is not currently covered. The description of more complex simulation tasks, for example, parameter scans, are not yet supported. Furthermore, currently SED-ML allows to combine variables from different tasks in one output - although the combinations depend on integrity restrictions. Another complex task, that is not yet supported is the linear execution of simulation experiments, meaning that the result of one simulation is used as the input for another simulation task. For example, the result of a steady state analysis will lead to a model with changed parameters. If that model then should be simulated using a time course simulation, the results of the steady state analysis have to be applied to the original model before. The definition of such sequences is not yet supported. Testing the implementation of SED-ML in different simulation tools will help enhancing the coverage and robustness of the format.

4 Describing Simulation Results

Given the computational model semantically-annotated with SBO, and a recipe for reproducing a simulation result with MIASE, there remains the problem of describing the observed behaviour in a systematic and machine-readable way.

4.1 TEDDY

At present, the observed simulation result is explained in a form of text accompanying the model (eg. "the time-course simulation demonstrates oscillations of variable x"). This kind of explanations, however are not clear and opaque to software tools. It would be useful, if one could compare the dynamic behaviour of systems. We must be able to answer questions such as: "How do I find a model containing protein X that displays periodic oscillations?", "What behavioural features do all the models have in common?", "Which model displays a behaviour matching my experimental data?" etc. To answer these questions an ontology that describes the dynamic behaviour of quantitative models is necessary. The Terminoloy for the Description of Dynamics (TEDDY) is an ontology which is designed to fulfil this. TEDDY classifies the behaviour of variables (eg. "oscillation", "bistable behaviour", the characteristics of those behaviour (eg. "period", "bifurcation") and the functionalities of modules (eg. "negative feedback", "integrator"). TEDDY is encoded in OWL format (McGuiness and van Harmelen 2004) and available at `http://www.ebi.ac.uk/compneur-srv/teddy/`.

4.2 SBRML

Mostly quantitative systems biology models are encoded using SBML or CellML, which are community-wide accepted format and there are several hundreds of softwares that support SBML. However, there are no standard formats to represent simulation results. Dada et al., 2008 (`http://www.comp-sys-bio.org/static/SBRML-draft-21-08-2008.pdf`) have proposed a new markup language, Systems Biology Results Markup Language (SBRML), which is complementary to SBML. SBRML is XML based markup language, which is intended to specify results from operations carried out on models. The initial state of a biochemical reaction network is defined in the SBML model. To simulate and analyse the reaction network, a software package takes the SBML model as input and transforms the initial state through an operation that the software implements. The outcome of an operation is a new state of the system. The new states, which may be single or multiple states, are captured and described in SBRML. The result of an operation consists of one or more result components. Software tools implement an operation using a specific algorithm. The type of algorithm used in an operation and the type of operation (e.g. steady state , time course, parameter scan, parameter estimation, etc.) are captured in an ontology term definition. SBRML is intended to allow any type of systems biology results to be represented. It is currently structured as follows: On the top level, SBRML consists of ontology terms, mode, and operations. The second level describes each operation application, which consists of software, algorithm

and result. The next level is the content of the result, which consists of one or more result components. Each result component consists of the description of the data being represented and data itself.

5 Conclusions

A well-curated and annotated model will support reuse, reliability and validation for a range of users, both human and machine. Appropriate curation with semantic enrichment improves the quality of the models, facilitating data integration that is crucial for the efficient usage and analysis of the models. Integrated data enables the user to effectively access a consistent range of data from a single location. As the the methodology for studying system biology matures, the rules for creating models will have to become stricter in order to ensure the quality of the models as well as the value of the repository of quantitative models. Also, more and more software tools hopefully will support common open formats and make use of standardized annotations and allow their manipulation.

Acknowledgements

BioModels.net activities are supported by the European Molecular Biology Laboratory and the National Institute of General Medical Sciences. MIRIAM resources benefited from support by the Biotechnology and Biological Sciences Research Council, SBO by the EU ELIXIR preparatory phase and SBGN by the New Energy and Industrial Technology Development Organization.

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