The Biology Petri Net Markup Language

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Abstract: In this paper a proposal for the Biology Petri Net Markup Language (BioPNML) is presented. The concepts and terminology of the interchange format as well as its syntax that is based on XML (eXtensible Markup Language) are introduced. BioPNML is designed to provide a starting point for the development of a standard interchange format for Bioinformatics and Petri nets. The language will make it possible to present biology Petri net diagrams between all supported hardware platforms and versions. It is also designed to bridge Petri net models to other known metabolic simulators.

1 Introduction

Petri nets were first introduced and formally defined by Prof. Dr. Carl Adam Petri. Petri nets and its concepts have been extended and developed since then and both the theory and the applications of this model have been flourishing. Its intuitively understandable graphical notation and the representation of multiple independent dynamic entities within a system is supported make Petri nets the model of choice highly suitable for many applications, such as manufacturing systems, communication networks, business process management, traffic and logistic systems, client-server networks and control systems. A large amount of literature on Petri net investigations has been compiled [http://www.daimi.au.dk/PetriNets/bibl/].
With the rapid development of bioinformatics, more and more experimental data both on genome and cell levels are systematically collected and stored in specific databases [Bax02]. In the post-genomic era, new methods are proposed to store, retrieve and analyze these data. XML, as an emerging standard for data exchange, is widely adopted as a structured data format in bioinformatics.
In this paper, prospects and problems concerning the use of Petri nets for biological data exchange are discussed; a proposal for Biology Petri Net Markup Language (BioPNML) is introduced. It is dedicated to serve as a starting point for the development of a standard interchange format for Petri nets and bioinformatics.

1.1 XML & Bioinformatics

There are already two good review papers on this topic by V.H.Guerrini [GJ00] and F.Achard [AVB01]. We would like to highlight a few of their points and supplement them with examples for metabolic pathway applications.

XML is derived from the Standard Generalized Markup Language (SGML), the international standard for defining descriptions of the structure and content of different types of electronic documents. XML is a web-dedicated data exchange language, which omits the complex and less used parts of SGML. The World Wide Web Consortium (W3C) has supervised the specifications of XML since its inception in 1996. More documentation can be found at http://www.w3.org/XML/.
In bioinformatics, XML is widely used within the last few years, and several XML based data formats have been developed. BSML (Bioinformatic Sequence Markup Language) [http://www.bsml.org/] uses XML to provide genomic information and a graphical BSML browser was developed. BioML (Biopolymer Markup Language) [http://www.bioml.com/BIOML/] integrates nucleotide and protein sequence data. The XML based RDF format [http://www.w3.org/RDF/] is also adopted by the Gene Ontology Consortium [http://www.geneontology.org] to provide controlled vocabularies for the description of molecular functions, biological processes and cellular locations of gene products. Moreover, major biology databases such as NCBI, WIT and Expasy also provide XML output after users' database queries. Obviously, XML is widely adopted as a standard for the exchange of biological data.
Both CellML (Cell Markup Language) [http://www.cellml.org/] and SBML (Systems Biology Markup Language) [http://www.cds.caltech.edu/erato/] present description languages for cellular simulation. CellML is intended to be used to represent many different types of models, for instance biochemical pathway models. Aside from specifying a model purely in terms of mathematics, CellML can use some additional elements to fully capture the information in biochemical pathway models. SBML is oriented towards representing biochemical networks common in research on a number of topics, including cell signaling pathways, metabolic pathways, biochemical reactions, genomic interactions, and many others. The main difference is that CellML has a very general and flexible syntax, while SBML's syntax is specific to metabolic pathway modeling. Currently, SBML is closely collaborated among several teams that develop metabolic simulators.
Although many biological databases and bioinformatic research groups use XML, XML is so flexible that anyone can create his/her own versions in entirely different ways. XML enables advancements in application integration, but they are hard to achieve without a consistent framework for XML implementations.

1.2 Petri nets & Bioinformatics

Modeling and simulation of metabolic networks becomes a promising field of bioinformatics in the post-genomic era. The development of computer science makes it possible to represent the complex metabolic network of physical and functional interactions that take place in the living cell, in ways which enable to manipulate, analyze and achieve understanding of how cells function. Petri net theory exhibits a mathematical formalism to model, analyze and simulate discrete event systems with inherent concurrency.
Following its first application of modeling metabolic pathways [RML93][Ho94], Petri nets as a new tool for modeling and simulation of biological systems are investigated more and more. Later Reddy [RLM96] exemplarily combined the glycolytic and pentose phosphate pathways of the erythrocyte cell to illustrate the concepts of the methodology. However, the reactions and other biological processes were modeled as discrete events and it was not possible to simulate kinetic effects. Hofestaedt [HT98] investigated a

formalization showing that different classes of conditions can be interpreted as genes, proteins, enzymes or cell communication; he also showed how self-modifying Petri nets [Va78] could be applied to the quantitative modeling of regulatory biochemical networks. Chen [Ch00] introduced a hybrid Petri net (HPNs) approach, for expressing the glycolysis pathway. Using this approach, quantitative modeling of metabolic networks is also possible. Koch I. and M. Heiner et al. extended the model proposed by Reddy by taking into account the reversibility of chemical reactions and time dependencies [KSH99]. Later they analyzed steady states in metabolic pathways using Petri nets [HKV01]. Kueffener [KZL00] exploited the knowledge available in current metabolic databases for functional predictions and the interpretation of expression data on the level of complete genomes. To achieve this, the enzyme databases BRENDA, ENZYME [http://www.expasy.ch/enzyme/] and KEGG were compiled both into individual Petri nets and unified Petri nets. They also discussed executable Petri net models for the analysis of metabolic pathways [GKV01]. Goss [GP99] and Matsuno [Ma00] applied Petri nets to model gene regulatory networks by using stochastic Petri nets (SPNs) and HPNs respectively.
The above-mentioned papers are dedicated to the applications of Petri nets to bioinformatics and show that Petri nets are suitable to model special molecular biological systems. However, they lack unity in their concepts, notations, and terminologies. This makes it very difficult for new scientists to understand the potential applications of Petri nets due to the various interpretations presented by different authors. Furthermore, no Petri net tools exist which fulfill all requirements needed for the task of virtual cell modeling. In principle it should be possible to build Petri nets semi-automatically from data stored in molecular biological databases. However, the available Petri net tools do not support this. Our motivation for the presentation of a standard interchange format is to bridge this gap.

1.3 Petri nets & XML

At present most Petri net tools import and/or export Petri nets in proprietary file formats and poorly support other data formats. In these proprietary file formats it is difficult to add and remove features to the language and to make modularization of diagrams as easy as it might be in an ASCII based text format such as XML.
In order to solve the problems caused by the use of different file formats, many Petri net tools are currently being equipped with XML support. Matthias Jüngel et al. [JKW00] presented the concepts and terminology of PNML (Petri Net Markup Language), and thus provided a starting point for the development of a standard interchange format for Petri nets.
Although the above mentioned Petri net XML standards are available, they are incompatible due to different design destinations. PNML is generic and can be extended according to users' specific needs. A special "Bio-PNTD" for PNML can be defined when a simple biological system is modeled. However, a metabolic network model can contain a large number of named components representing different parts of a model. In this case, SBML model definitions are more suitable. Therefore, with regard to the application of Petri net methodology to bioinformatics, particularly for modeling and simulation of metabolic networks, a new interchange format is wanting.

2 Concepts and terminology

The intended BioPNML is a XML based description language that allows the representation of metabolic networks as Petri nets. Before introducing the syntax of the interchange format, we briefly discuss its basic concepts and terminology, which is independent of the XML representation. Previous approaches proved that by using hybrid Petri net methodology, it is feasible to model and simulate metabolic systems [Ma00][Ma01][Ch00][Ch02]. Therefore the primer version of BioPNML supports the hybrid Petri net type. BioPNML contains Petri net objects as well as data needed for the exchange and graphical representation of metabolic networks; An XML schema defines the labels for a Petri net and its objects and metabolic models.

2.1 Petri net objects and labels

It is possible to translate molecular biological terms into Petri net terms in a natural way (Table 1).

Table 1. Mapping Metabolism to Petri nets

Metabolism terms	Petri net terms
•S, P, E, metabolites, genes, promoters, signals...	•Places
•Bioreaction, interaction, other bioprocesses, ...	•Transitions
•Defines reagent of bioprocess	•Input arcs
•Defines product of bioprocess	•Output arcs
•Initial token or state of system	•Initial marking
•State of reaction system	•Marking
•Rate of reaction system	•Weight function or differential function
•All reagents must be provided for the reaction	•A transition enabled
•A single reaction	•A firing transition
•...	•...

Places can be used for the representation of biological subjects such as genes, metabolites, proteins, enzymes, compounds and other molecules while transitions represent biochemical reactions and interactions. The value of tokens in places can represent the actual concentrations of biological subjects. Transitions can be classified into two types: discrete and continuous. A discrete transition fires if it has concession and a delay time can be assigned to it. Continuous transitions are not comparable to the abrupt firing of discrete transition. The firing speed assigned to a continuous transition is defined by a constant or a function. Arcs between places and transitions fall into three categories: normal arcs, inhibitor arcs and test arcs. In metabolic pathways, arc weights of continuous transitions are assigned according to the stoichiometric coefficients of the biochemical reactions.

2.2 Petri net graphics

Every object is equipped with some graphical information. For a place and transition, the information is its shape, size and position; for an arc, it is a list of positions that defines start and end points of this arc. In biological Petri net models, the main properties are

that the arc weights are described by the stoichiometric coefficient of the biochemical reaction and the transition condition is described by using functions or by assigning a delay time. Fig. 1 shows the Petri net representation of a biochemical reaction. ***S***, ***E***, ***P*** and ***ES*** denote substrate, enzyme and product. ***ES*** denotes the enzyme-substrate complex. The biochemical reaction indicates that a substrate is enzymatically catalyzed into a product with a transformation rate *v*. Three places represent substrate, enzyme and product with ***S***, ***E*** and ***P*** as the label of places. The tokens (real concentrations) of each place in the Petri net can be used as variables, s_1, s_2 and s_3, while the transition rate is assigned with a known function, Michaelis-Menten equation.

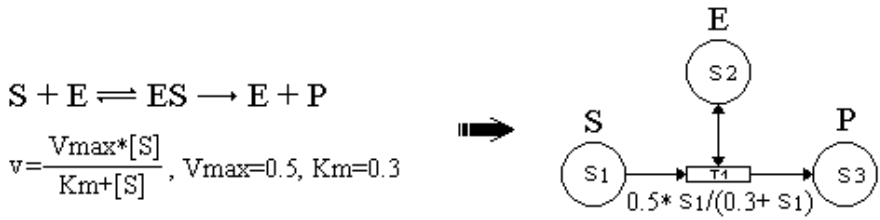

Fig. 1 Petri net presentation in BioPNML

2.3 Molecular biological networks

In a living cell, hundreds and thousands of biochemical reactions occur simultaneously per second. These reactions are catalyzed by enzymes. Most metabolites (substrates and products) involved in a reaction, can also be found in other reactions where the metabolite acts as a substrate or regulates the reaction speed (activators, repressors). Proteins and enzymes are synthesized from genes which can also be switched on or off by molecules. Thus, a densely connected, intricate and precisely regulated network is built. Traditionally, people divide those metabolic networks into three levels, namely metabolic pathways, gene regulatory networks and signal transduction pathways.

2.3.1 Metabolic pathways

A metabolic pathway consists of enzymatically catalyzed metabolic reactions which are interconnected in a way, that products of some reactions are the substrates of other reactions. In BioPNML, the metabolic reaction class is defined as biochemical reactions and related objects such as: enzyme, substrate(s), product(s), their stoichiometries, and parametric values for separately defined kinetic laws. In the fig. 2, the metabolic reaction class structure that was derived by extending SBML's biochemical reaction class [Hu01] is shown.

The metabolic reaction class contains mandatory fields (enzyme, substrate, product, and KineticLaw) as well as optional fields (enhancer and inhibitor). Enzyme is a reference to the gene which encodes the enzyme. Both substrate and product are references to molecules implemented using lists of SpecieReference structures. The SpecieReference structure contains fields for recording the names of molecules, the types of molecules which are references to lists of TypeRef structure, the stoichiometry filed indicates the propor-

tions of substrate and product within a reaction. The KineticLaw structure is an optional field of the type KineticLaw, used to provide a mathematical formula for the reaction rate. The Boolean field, reversibility, indicates whether the reaction is reversible. The field is optional, and should default to "true" when it is not specified. Information about reversibility is useful in certain kinds of structural analyses such as elementary mode analysis [SDF99].
In addition to these fields, the reaction structure also has a Thermodynamics field as a reference to ThermodynamicsRef. The ThermodynamicsRef structure is an optional field that is used to provide the Gibbs energy which indicates the favorability of the reaction.

2.3.2 Gene regulatory networks

A gene regulatory network is most often described and interpreted as the on-off switches and/or rheostats of a cell, operating at the gene level. They dynamically orchestrate the level of expression for each gene in the genome by controlling whether and how vigorously that gene will be transcribed into RNA. Each RNA transcript then functions as the template for synthesis of a specific protein by the translation process. These gene products may act as transcription factors which regulate the expression of other genes. Gene regulatory networks are not restricted to the level of transcription, but may also be carried out at the levels of translation, splicing, posttranslational protein degradation, active membrane transport and other processes [AKK00]. In BioPNML, the gene regulation class is defined as a set of objects such as gene, promoter, transcription factor, inducer, repressor, the gene encoding protein, other metabolites and the effect of interaction and kinetics (Fig. 2).

2.3.3 Signal transduction pathways

Cell communication or signal transduction is the means by which cells respond to signals coming from outside those cells. A "biological signal" could be defined as a molecule which acts as a pre-arranged sign, indicating either the commencement and/or the termination of (one or more) intracellular processes. In other words, the nature of the signaling molecule decides it's effects, just as pre-arranged signals have pre-arranged affects [Cl96]. The Signal transduction class in the BioPNML is defined as a set of signal instances through the message passing between source and target.

2.3.4 Other bioprocesses

Biological cells are highly complex systems. Some biological systems such as membrane transportation do not fit in one of the above-mentioned three basic categories, but should also be taken into account when required. Many models assume that the amount of metabolites in a cell is uniform across the cell, i.e. it is assumed that the cell is a "well-mixed pool". In many situations, however, concentration gradients exist which will affect the local rate of biochemical reactions. In particular for large systems with

different compartments, we must consider explicitly the effect of diffusion or transportation.
In BioPNML, other bioprocesses classes can be defined. This concerns not only all effects of metabolites, but also different compartments and properties of biological processes.

2.4 Pathway class diagram

BioPNML consists of two parts, one based on SMBL and another based on PNML. This first draft of BioPNML was developed in a way, which should enable both SMBL and PNML tools allow to read BioPNML.
Fig. 2 shows the classdiagram of BioPNML. The left side shows the Petri net part of BioPNML which was derived by extending PNML slightly. The right part shows the Biological part which is based on SBML. The Petri net part contains only very few extensions to PNML. More changes to SBML were made in the biological part, although those changes are open for discussion. This is due to the fact that Petri nets have a comparatively long history and well defined generally accepted syntax and semantics, whereas molecular biology is still evolving at a rapid pace. The purpose of the schema is to give a rough idea of how Petri nets and biological systems are related. This diagram can also serve as a conceptual guidance to researchers who are designing databases to store networks and reaction data.

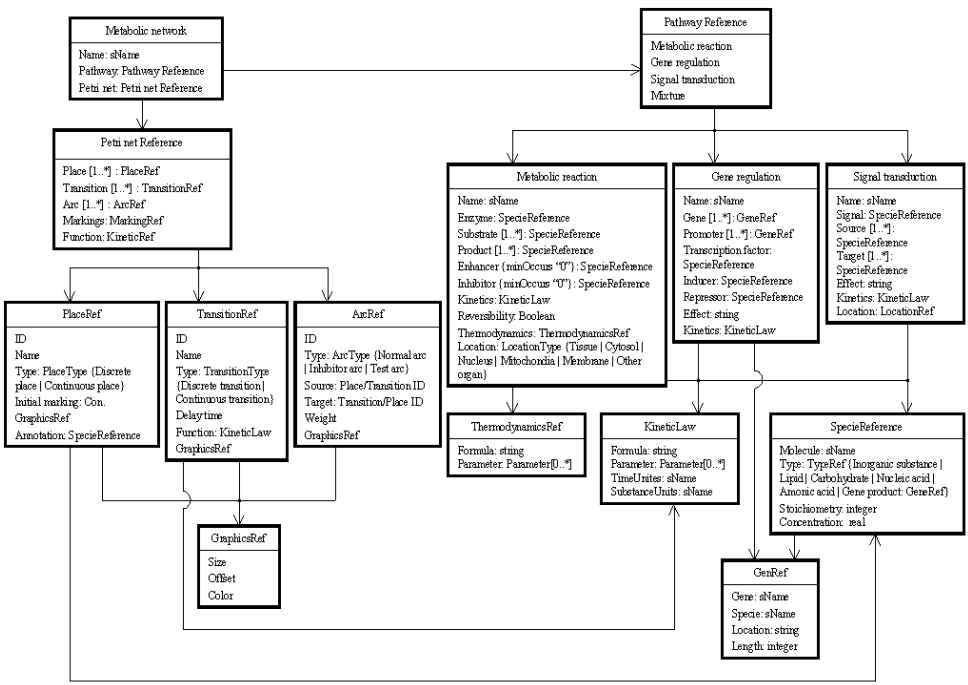

Fig. 2 Diagrammatic class relations of BioPNML

3 An example

In this section, we present some concrete XML syntax in order to exemplify the concepts discussed in Section 2 by using a simple enzymatically catalyzed reaction (Fig. 3). The model defines the single biochemical reaction from L-arginine to L-ornithine catalyzed with the enzyme arginase. We assume the reaction kinetics complies with the Michaelis-Menten equation, and the values of Km and Vmax are 0.5mM and 0.3mM respectively.

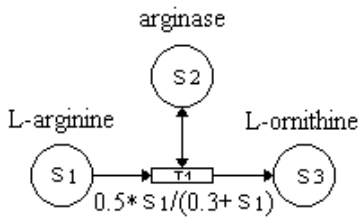

Fig. 3 An example for a biology Petri net model, where S1, S2 and S3 are variables for the concentrations of the substances involved

The first part of the XML example contains the biological information, whereas the second part is mainly PNML. idref tags are used to link the PNML 'place' and 'transition' tag to the respective SBML based 'spiecie' tag. Since it was tried to develop BioPNML in a way that it should be readable both by existing PNML and SBML tools, some redundancies could not be avoided, i.e. the names of the compounds and the initial concentrations appear in both parts of the file. Properties which are not part of the present PNML standard, such as the formula used to calculate the changes in the concentrations of the substrates and the product are only stored in the SBML part of the file. The example shows the basics of idea of BioPNML. In real applications, the PNML part may contain many reactions.

```
<?xml version="1.0" encoding="UTF-8"?>
<!DOCTYPE net SYSTEM "BioPNML.dtd">
<BioPNML>
    <!--***BIO***-->
    <Bionet>
        <model name="Metabolic reaction">
            <listOfCompartments>
                <compartment name="Cytosol" volume="1"/>
            </listOfCompartments>
            <listOfSpecies>
                <specie id="s1" name="L-arginine" initialAmount="0.1" compartment="Cytosol"
                        boundaryCondition="false"/>
                <specie id="s2" name="arginase" initialAmount="0.5" compartment="Cytosol"
                        boundaryCondition="true"/>
                <specie id="s3" name="L-ornithine" initialAmount="0" compartment="Cytosol"
                        boundaryCondition="false"/>
            </listOfSpecies>
            <listOfReactions>
                <reaction id="r1" name="arginase" reversible="false">
                    <listOfReactants>
```

```
                    <specieReference specie="L-arginine" stoichiometry="1"/>
                </listOfReactants>
                <listOfProducts>
                    <specieReference specie="L-ornithine" stoichiometry="1"/>
                </listOfProducts>
                <kineticLaw formula="Vm1*S1/(Km1+S1)">
                    <listOfParameters>
                        <parameter name="Vm1" value="0.5"/>
                        <parameter name="Km1" value="0.3"/>
                    </listOfParameters>
                </kineticLaw>
            </reaction>
        </listOfReactions>
    </model>
</Bionet>
<!--***PNML***-->
<Petrinet id="pn1" type="Hybrid">
    <!--place-->
    <place id="p1" idref="s1" type="continuous">
        <name>
            <text>L-arginine</text>
            <value>0.1</value>
        </name>
        <graphics>
            <size>10</size>
            <position x="-20" y="10"/>
            <color>red</color>
        </graphics>
        <initialMarking>
            <value>1</value>
        </initialMarking>
    </place>
    <!--transition-->
    <transition id="t1" idref="r1" type="continuous">
        <graphics>
            <size>10</size>
            <position x="-30" y="0"/>
            <color>yellow</color>
        </graphics>
    </transition>
    <!--arc-->
    <arc id="a1" source="p1" target="t1" type="normal">
        <graphics>
            <size>1</size>
            <offset x="0" y="0"/>
            <color>blue</color>
        </graphics>
        <weight>
            <value>1</value>
        </weight>
    </arc>
    <!--more places and arcs-->
    …
</Petrinet>
</BioPNML>
```

4 Disscussions

BioPNML is a XML framework for the exchange and unification of molecular biological Petri net models. By formalizing the process of expressing bioprocess interchanges in a consistent and extendible way, BioPNML makes it easier for users and developers of biological software to map data in different formats. Easier mapping enables developers of biological software who are using open standards, such as XML, to adopt changes in biological data formats faster.

BioPNML defines a core set of XML elements, attributes, and tags that enable researchers to develop technologies that are optimized for data exchange. This XML based core data model is important because it eliminates the need to find a common application programming interface or implementation platform. Currently its XML schema is based on the SBML and PNML standard. However, BioPNML is not static; we continue to develop it. BioPNML will be updated in line with future changes of SBML and PNML.

Extensions to Petri nets have been developed which transform Petri nets into a powerful tool for modeling biological systems. These enhancements include timing, token typing, non-homogeneous places, priorities and resources. It is possible to extend our BioPNML classes to these requirements by using additional tag sets.

BioPNML files can be generated computationally from existing data sources. By using the W3C recommended Extensible Stylesheet Language Transformations (XSLT), new structured data formats can be created from existing XML documents. That is, XSLT is a language for transforming XML documents into other XML documents. Users can extract XML data from molecular biological databases via the Internet and transform them into BioPNML files via XSLT (Fig. 4).

There are many approaches that address the challenging problem of interoperability among biological databases. They are based on different data integration techniques, e.g. federated database systems, multi database systems and data warehouses. In order to model and simulate gene controlled metabolic networks, we focus on a flexible and thin, but universally applicable solution with powerful query and retrieval capabilities. The architecture of our system MARGBench is a mediator-based approach for database integration. The aim of MARGBench is to support the seamless integration of multiple heterogeneous molecular biology databases and to allow the development and the execution of global applications that extend beyond the boundaries of individual databases [Fr02].

The general principle of BioPNML data integration is shown in Fig. 4. Integration of heterogeneous and physically distributed databases is implemented by the BioData-Server (BDS) system, which provides a homogeneous database view. IIUDB (Individually Integrated User Database) accesses JDBC (Java Database Connectivity) interfaces followed up by an object network. Provided with the JDBC driver, the IIUDB is developed for users to define their own specific integrated schemes, i.e., the system is adaptive by connecting to heterogeneous databases and integrates the information retrieved into user-defined persistent databases and analyses the networks that can be found in theses databases. The structure of metabolic networks and the molecular information contained is changing and depending on the user view. Then based on the Object Management (OMG) architecture, we can do SQL queries and build up a metabolic network. IIUDB also includes several interfaces to export the resulting networks into common formats, e.g., CORBA, GML and XML as well as BioPNML.

So far, the IIUDB offers integrated access to biological databases, currently mainly to KEGG, BRENDA and RegulonDB, which cover considerable features including details on the enzymatic reactions, substrates and products, binding parameters, catalytic constants and gene regulations. Based on these techniques, bio-Petri net tools could be provided with models of metabolic pathways, gene regulation and signaling pathways.

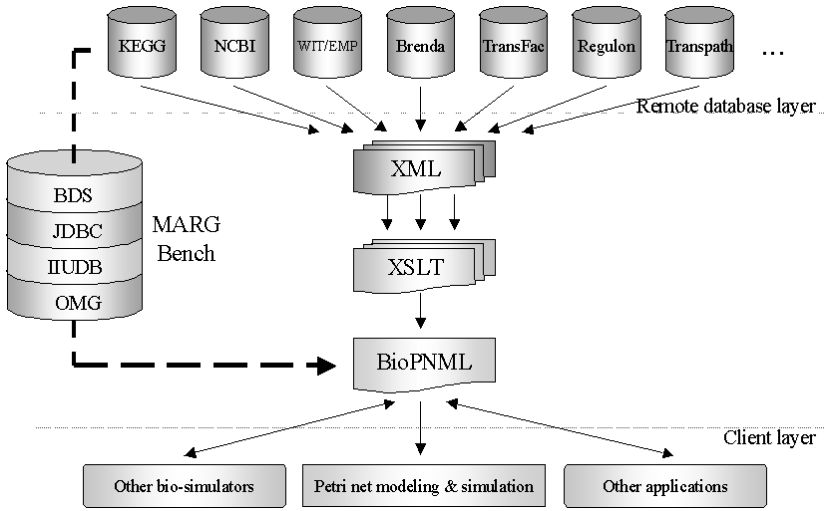

Fig. 4 BioPNML data integration schema

5 Conclusions

This paper presents, in its draft version, the concepts and the terminology of the Biology Petri Net Markup Language. BioPNML can represent both graphical information and metabolic network information. It serves as a starting point for the development of a standard interchange format for Petri nets and other molecular biological modeling and simulation tools.

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References

[AVB01] Achard, F., Vaysseix, G., Barillot, E.: XML, Bioinformatics and Data Integration: Bioinformatics. 2001, 17(2); pp. 115-125

[AKK00] Ananko E.A., Kolpakov F.A., Kolchanov N.A.: GeneNet database: a technology for a formalized description of gene networks: Proc. of the BGRS'2000. Novosibirsk, Russia, 2000; pp. 174-177

[Bax02] Baxevanis, A.D.: The Molecular Biology Database Collection: 2002 update. Nucleic Acids Res, vol 28, issue 1; pp. 1-7

[Ch00] M. Chen: Modelling the glycolysis metabolism using hybrid petri nets: DFG-Workshop, Modellierung und simulation metabolischer netzwerke, Magdeburg, 2000

[Ch02] M. Chen: Modelling and Simulation of Metabolic Networks: Petri Nets Approach and Perspective: in the proceeding of ESM'02, Darmstadt, 2002

[Cl96] Clark, L.: Information Processing Perspectives Of Cellular Communication: available via http://www.csc.liv.ac.uk/~laurence/research/report.html; 1996

[Fr02] A. Freier, R. Hofestädt, Matthias Lange, et al.: BioDataServer: A SQL-based service for the online integration of life science data: In Silico Biology 2002(2): 0005

[GKV01] H. Genrich, R. Kueffner, K. Voss: Executable Petri Net Models for the Analysis of Metabolic Pathways: Intl. J. STTT, 2001, 3; pp. 394-404

[GP99] P.J.E. Goss and J. Peccoud: Analysis of the stabilizing effect of Rom on the genetic network controlling ColE1 plasmid replication: Pacific Symposium on Biocomputing'99, 1999; pp. 65-76

[GJ00] Guerrini VH, Jackson D.: Bioinformatics and extended markup language (XML): Online Journal of Bioinformatics 2000, 1; pp. 1-13

[HKV01] M. Heiner, I. Koch, K. Voss: Analysis and simulation of steady states in metabolic pathways with Petri nets: In: CPN'01, Denmark, 2001; pp. 15-34

[Ho94] Hofestädt, R.: A Petri Net Application of Metabolic Processes: Journal of System Analysis, Modelling and Simulation. 1994, 16; pp. 113-122

[HT98] Hofestaedt, R. and S.Thelen: Quantitative Modeling of Biochemical Networks: In silico Biol. 1998, (1): 980006

[Hu01] M. Hucka, A. Finney, H. Sauro, et al.: Systems Biology Markup Language (SBML) Level 1, Version 1 (Final), 2 March 2001

[JKW00] M. Jüngel, E. Kindler, M. Weber: Towards a Generic Interchange Format for Petri Nets, XML/SGML based Interchange Formats for Petri Nets, Aarhus, Denmark, 2000

[KSH99] I. Koch, S. Schuster and M. Heiner: Simulation and analysis of metabolic networks by time-dependent Petri nets, Computer Science and Biology: Proceedings of the GCB'99, Hannover, Germany, 1999

[KZL00] R. Kueffner, R. Zimmer, and T. Lengauer: Pathway Analysis in Metabolic Databases via Differential Metabolic Display (DMD): Bioinformatics. 2000, 16(9); pp. 825-836

[Ma00] H. Matsuno, A. Doi, M. Nagasaki, et al.: Hybrid Petri net Representation of Gene Regulatory Network: Pacific Symposium on Biocomputing. 2000, 5; pp. 338-349

[Ma01] H. Matsuno, A. Doi, R. Drath et al.: Genomic Object Net: Basic Architecture for Representing and Simulating Biopathways: in: RECOMB 2001

[RML93] Reddy, V. N., Mavrovouniotis, M. L. and Liebman, M. N.: Petri Net Representation in Metabolic Pathways. In: Proceedings of the First International Conference on Intelligent Systems for Molecular Biology, AAAI Press, Menlo Park, 1993; pp. 328-336

[RLM96] Reddy V.N., Liebman M.N., Mavrovouniotis M.L.: Qualitative analysis of biochemical reaction systems: Comput Biol. Med. 1996, 26(1); pp. 9-24

[SDF99] S. Schuster, T. Dandekar and D. A. Fell: Detection of elementary flux modes in biochemical networks: a promising tool for pathway analysis and metabolic engineering: Trends. Biotechnol. 1999, 17; pp. 53-60

[SM01] Stumme, G. and Maedche, A.: FCA-Merge: A Bottom-Up Approach for Merging Ontologies: In International Joint Conference on Artificial Intelligence. Washington, USA. 2001; pp. 225-234

[Va78] Valk, R.: Self-Modifying Nets: A Natural Extension of Petrinets: LNCS. 1978, 62; pp. 464-476