



HAL
open science

Logical and Semantic Modeling of Complex Biomolecular Networks

Ali Ayadi, Cecilia Zanni-Merk, Francois de Bertrand de Beuvron, Saoussen
Krichen

► **To cite this version:**

Ali Ayadi, Cecilia Zanni-Merk, Francois de Bertrand de Beuvron, Saoussen Krichen. Logical and Semantic Modeling of Complex Biomolecular Networks. 20th International Conference on Knowledge-Based and Intelligent Information and Engineering Systems - KES 2016, Sep 2016, York, United Kingdom. pp.475-484, 10.1016/j.procs.2016.08.108 . hal-02383702

HAL Id: hal-02383702

<https://hal.science/hal-02383702>

Submitted on 27 Nov 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

20th International Conference on Knowledge Based and Intelligent Information and Engineering Systems

Logical and semantic modeling of complex biomolecular networks

Ali Ayadi^{a,b,*}, Cecilia Zanni-Merk^a, François de Bertrand de Beuvron^a, Saoussen Krichen^b

^aICUBE/SDC Team (UMR CNRS 7357)-Pole API BP 10413, Illkirch 67412, France

^bLARODEC Laboratory, Institut Supérieur de Gestion de Tunis, University of Tunis, Rue de la liberté, 2000 Bardo, Tunisia

Abstract

Systems biology models aim to describe and understand the behaviour of a cell. This living organism is represented by a complex biomolecular network. In the literature, most researches focus only on modeling isolated parts of this network, such as the metabolic network or the gene regulatory network. However, to fully understand the behaviour of a cell we should model and analyze the biomolecular network as a whole.

Towards this goal, we firstly present a formalization for describing the logical structure, function and behaviour of complex biomolecular networks. In addition, we propose a semantic approach based on four ontologies to provide a rich description for modeling a biomolecular network and its state changes. This approach contributes to propose to the biologist a platform where to simulate the state changes of biomolecular networks with the hope of steering their behaviours.

© 2016 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Peer-review under responsibility of KES International

Keywords: Complex biomolecular networks; Sensitivity; Logical modeling; Semantic approach.

1. Introduction

Cells do not live in stable conditions, but in environments that vary over the time¹. In fact, they are always subjected to intra and extra-cellular stimuli, such as changes in their physical and chemical properties or in their environment. In order to survive, the cell reacts more or less rapidly by adapting its behaviour in accordance to the new features of their environment.

The suffix "omics" is used to indicate several technologies that describe the cell networks and processes through the study of cellular entities. These technologies operate at various levels such as in genomics (the qualitative study of genes), in proteomics (the quantitative study of proteins) and in metabolomics (the quantitative study of metabolites)^{2,3}. The advances of these mechanisms open the way to a new discipline, the systems biology that aims to describe, model and understand the dynamic behaviour of the cell, and how its functions arise from the interplay of their components^{4,5}. To achieve these goals, it is crucial to define the biological interactions of a cell in the form of a large and complex network called complex biomolecular network. It consists of nodes, denoting cellular entities, and edges, representing interactions among cellular components. This complex network facilitates the understanding of

* Corresponding author. Tel.: +33 6 56 76 34 46.

E-mail address: ali.ayadi@unistra.fr

biological mechanisms of a cell and its transittability. In general, the transittability expresses the idea of steering the complex biomolecular network from an unexpected state to a desired state⁶.

Figure 1 shows an example from⁶ about the p53-mediated DNA damage response network. It consists of 17 cellular entities and 40 interactions and presents a series of p53-transitions to protect the organism from the effects of stress. In fact, the tumor suppressor gene p53 encodes a protein whose major function is to protect organisms from proliferation of potentially tumorigenic cells. In normal conditions (unstressed cells), the p53 protein is inert and maintained at low level through its association with the Mdm2 oncogene (first network in the Figure 1). In response to damaged DNA or to a variety of stresses, p53 accumulates in the nucleus and is activated as a transcriptional transactivator (second and third networks in the Figure 1).

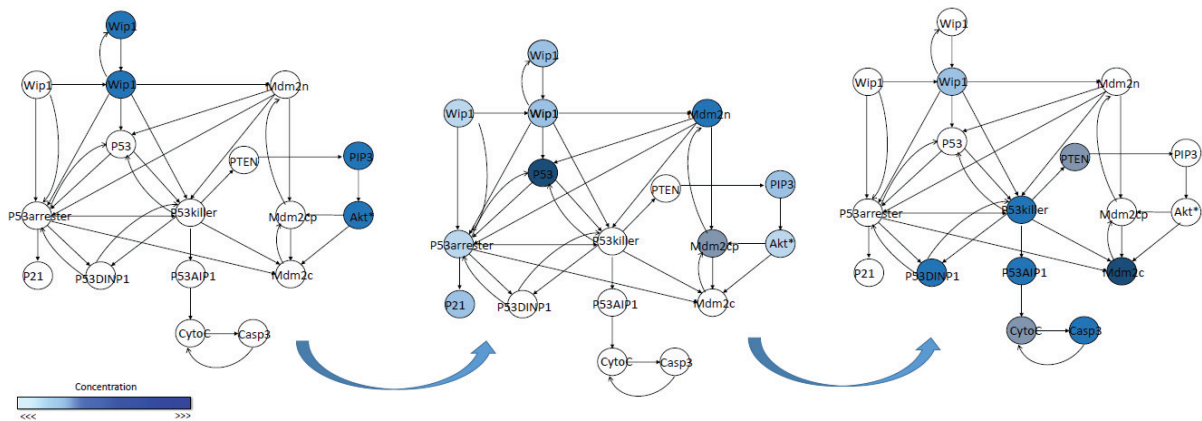


Fig. 1. The transittability of the P53-mediated cell damage response network: colour changes in the nodes indicate changes in the concentration of the associated molecules.

To study the transittability of a complex biomolecular networks, modeling and simulation tools are required. Several studies have been conducted to model, analyse and understand the molecular interactions. Thus, diverse computational methods have been developed: ordinary differential equations, boolean networks, Petri nets, multi-agent systems, etc. Raza and Parveen⁷, Maayan⁸ and Bellouquid and Delitala⁹, have examined these modeling techniques and have compared their characteristics. However, most of these approaches do not examine the interactions among all the intervening molecules types. As a result, these modeling approaches are impractical to understand the transittability of complex biomolecular networks. To do so, it is necessary to take into account the analysis of the structure and dynamics of the whole cell rather than just focusing on isolated parts^{4,10,11,12}.

With the idea of making the biomolecular network evolve, our research works aim to design and develop a platform that provides an optimal set of external stimuli to be applied during a predetermined time interval to steer the biomolecular network from its current state to a desired state¹³. Our original approach is based on the cooperation of semantic technologies¹⁴, combinatorial optimization and simulation.

In this paper, we are only focused on one of the modules of the platform to be developed: the *ontological* module. Our approach consists of two ideas, the first is to propose a detailed logical formalization that describes the complex biomolecular network: its structure, its function and its behaviour. This formalization aims at describing and analysing all the properties and mechanisms of this type of networks. Secondly, we present a semantic approach for analysing the transittability of complex biomolecular networks. This method based on four ontologies is essential to achieve a full understanding of the transition states of complex biomolecular networks.

The paper is organized as follows. Section 2 introduces the complex biomolecular networks and their various types: the Gene Regulatory networks, the Protein-Protein Interaction networks and the Metabolic networks. In Section 3, we propose a logical formalization of biomolecular networks and outline their structures, functions and behaviours. Section 4 presents the semantic approach for analysing the transittability of complex biomolecular networks and describes the characteristics of each ontology. Conclusion and future works are discussed in Section 5.

2. Complex Biomolecular Networks

The cell is a complex system consisting of thousands of diverse molecular entities (genes, proteins and metabolites) which interact with each other physically, functionally and logically creating a biomolecular network^{5,6}.

The complexity of the biomolecular network appears by its decomposition into three levels: the genome level models the genetic material of an organism, it is composed of two types of nucleic acid, the complete set of deoxyribonucleic acid (DNA) molecules which includes the instructions an organism needs to reproduce itself¹ and the entire set of Ribonucleic Acid (RNA) molecules which translates genetic information from DNA into proteins; the proteome level describes the entire set of proteins expressed by the genome; and the metabolism level contains the complete set of small-molecule chemicals¹⁵. Figure 2 depicts these levels.

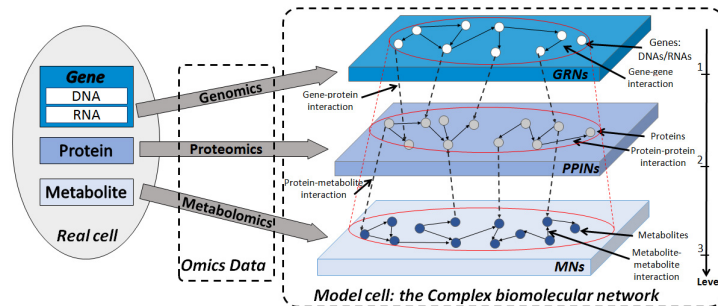


Fig. 2. Multi-level modeling of a biomolecular network from a real cell.

Depending on the type of its cellular elements and their interactions, we can distinguish the three basic types of networks, the Gene Regulatory networks (GRNs); the Protein-Protein Interaction networks (PPINs); and the Metabolic networks (MNs).

- The Gene Regulatory networks (GRNs) describe the interactions among approximately 21,000 genes (DNAs and RNAs). They are represented as directed graphs where the nodes represent genes and arcs model the type of regulation (activation or inhibition), if one gene regulates the transcription of the other gene¹⁶.
- The Protein-Protein-Interaction networks (PPINs) model the interactions between about 80,000 proteins. These networks are represented as undirected graphs where the nodes are the proteins and the undirected edges models the connection between them. These types of interactions depend on the physical or biochemical interaction that exists between the pair of proteins¹⁷. This network mainly contains details on how proteins perform together to ensure the biological processes.
- The metabolic process consists of a series of chemical reactions that begins with a particular metabolite called "substrate" and converts it into some other metabolites named "products"¹⁸. Thus, the Metabolic networks (MNs) describe the biochemical reactions among approximately 42,000 metabolites. They are represented as directed graphs whose nodes are the metabolites and the arcs represent the type of the biochemical reaction which transforms the substrates into products by the help of enzymes, they are labelled by the stoichiometric coefficient of the metabolites in the reaction.

3. Logical modeling of a biomolecular network

In this paper, we focus on the logical and semantic modeling of complex biomolecular networks to obtain a high level of formalisation needed for our future developments.

¹ <http://www.livescience.com/37247-dna.html>

One of the rules for complexity management during the modeling task consists in separating knowledge of different nature. According to a systemic approach, three types of knowledge to describe a system are distinguished: knowledge about the components of the system, knowledge relative to its functions, and knowledge relative to its behaviour¹⁹. These three types of knowledge are necessary in any understandable description of a system, even when a particular type has to play a privileged role in a specific task. The systemic approach thus provides a means of mastering the modeling of a system.

With this aim in mind, the biomolecular network BN is described by its *structure* SR , its *function* FR and its *behaviour* CR that evolves over the time t . Thus, the biomolecular network BN can be described in mathematical terms as follows:

$$BN = (SR, FR, CR_t)$$

3.1. The structure

The *structure* of the biomolecular network SR is a graph defined by:

$$SR = (M, I) \quad \text{where:}$$

- M denotes all the molecules composing the network and represents the nodes of the graph defined by a finite set of vertices $M = \{m_1, m_2, \dots, m_n\}$. We distinguish a tripartite partition of M :
 - M_G the set of genes,
 - M_P the set of proteins,
 - M_M the set of metabolites.

$$M = M_G \cup M_P \cup M_M$$

$$M_x \cap M_y = \emptyset \quad \text{where: } x, y \in \{G, P, M\} \text{ and } x \neq y.$$

- I denotes the set of interactions between the network's molecules. It describes the edges of the graph SR : defined by a finite set of edges $I = \{i_1, i_2, \dots, i_m\}$. An arc $i = (m_i, m_j)$, (where $m_i, m_j \in M$) which start from m_i (origin or tail) and comes to m_j (destination or head) is also noted $m_i \rightarrow m_j$. The partition of the graph nodes induces a partition into a range of different types of interactions:
 - . three interactions between molecular components of the same type (intraomic interactions): the interactions between genes denoted by I_{GG} which models the type of regulation between genes (activation or inhibition), I_{PP} which represents the stable or transitional associations between proteins and I_{MM} modeling the interactions between metabolites (type of chemical reaction between reactants and products).
 - . four interactions (among the 6 possibilities) between the nodes belonging to different networks (interomic interactions): I_{GP} which represents the genes and proteins regulation and the interaction between them, I_{PG} which models the proteins impacts on genes through the transcription factor, I_{PM} represents the enzymes occurring in the chemical reactions of metabolites (catalysis or hydrolysis), I_{MP} models the metabolites impacts on proteins.
 - . two interactions I_{GM} et I_{MG} are not taken into account because there is no direct interaction between the genes and metabolites and vice versa.

$$I = I_{GG} \cup I_{PP} \cup I_{MM} \cup I_{GP} \cup I_{PM} \cup I_{MP} \cup I_{PG}$$

$$I_x \cap I_y = \emptyset \quad \text{where: } x, y \in \{GG, PP, MM, GP, PM, MP, PG\} \text{ and } x \neq y.$$

3.2. The function

The *function* of the biomolecular network, denoted by FR , associates a type to each one of the graph's edges. It is described as:

$$FR : I \longrightarrow \text{TypeInteraction} \quad \text{where:}$$

- *TypeInteraction* belongs to the set of concepts of the Interaction Ontology proposed by Van Landeghem et al.²⁰ (Figure 3). As shown in Table 1, the possible types depend on the type of the edge.

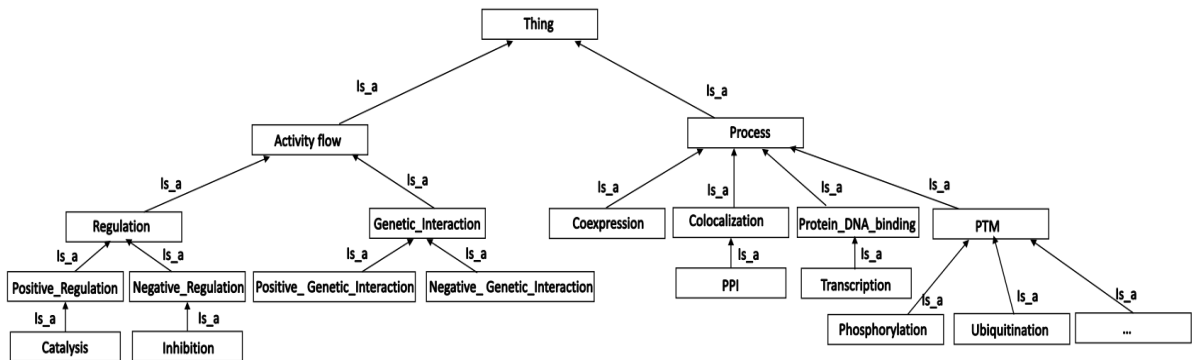


Fig. 3. A subset of the taxonomy of the Interaction Ontology²⁰.

3.3. The behaviour

The *behaviour* of the biomolecular network CR_t is given by the set of its different states in time. The state of the network at a given time is defined by a function $en(n, t)$ which associates to each node its state at the moment t . This state can be formalized as:

- For all $n \in M_P \cup M_M$: $en(n, t) = [c_n(t), S_{min}, S_{max}] \in \mathbb{R}^3$ where: $c_n(t)$: the value of the concentration of the node n at a given time t , and S_{min} and S_{max} : the minimum and maximum thresholds of concentration that allow the triggering of the interaction related to the outgoing arcs. Indeed, this interaction is due to the intra and extra cellular events that disturb the current concentration of the node and may consequently change its value. We can distinguish two types of events, the internal events come from inside the node for example a mutation in a copy of the gene, a lack or an overload of a substance (vitamins, metabolites, etc.) and the external events that originate outside the node such as taking a medication or the exposure to ultraviolet rays, etc.
- For all $n \in M_G$: $en(n, t) = activation$ where: $activation \in \{True, False\}$.
 Associating a gene with a concentration is not meaningful. Instead, a gene may have two specific states, activated or not activated. Genes control the ability of DNA to express itself and protein synthesis. They also control the central metabolism of the organism. They get activated (or not) thanks to the regulatory proteins.

Table 1. Excerpt of interactions appearing in the Interaction Ontology²⁰.

<i>TypeInteraction</i>	<i>Intraomic_Interactions</i>			<i>Interomic_Interactions</i>			
	I_{GG}	I_{PP}	I_{MM}	I_{GP}	I_{PG}	I_{PM}	I_{MP}
Positive Regulation (Catalysis/Hydrolysis)	-	✓	✓	-	✓	✓	✓
Negative Regulation (Inhibition)	-	✓	✓	-	✓	✓	✓
Positive genetic interaction	✓	-	-	-	-	-	-
Negative genetic interaction	✓	-	-	-	-	-	-
Colocalization	-	✓	✓	-	-	✓	✓
Coexpression	-	✓	✓	✓	✓	✓	✓
Transcription	-	-	-	-	✓	-	-
Phosphorylation	-	✓	-	-	-	-	✓
Dephosphorylation	-	✓	-	-	-	-	✓

4. A semantic approach for analysing the transittability of complex biomolecular networks

The transittability of a complex biomolecular network concerns the ability to steer this network from one specific state to another specific state⁶ and is associated with its behaviour.

Modeling the behaviour of complex molecular networks requires, first and foremost, to formalize the domain knowledge. The use of a formalized language such as ontologies provides a rich description but also allows to perform reasoning. Thus, in this section, we propose a semantic architecture composed of four ontologies: there are three of them already exist in the literature and we are develop the last one. These ontologies are linked together in order to have the necessary concepts for modeling the dynamic behaviour and the transition states of a complex biomolecular network.

We will briefly present the general architecture of the ontological process and describe the set of ontologies which compose our approach.

4.1. The global architecture

To study the behaviour of complex biomolecular networks, it is not sufficient to simply describe it. Certainly, the behaviour of complex biomolecular networks is investigated through appropriate semantic structures for the description of their components that must not be overlooked.

To do this, we propose a semantic approach that aims to enrich the structural description of biomolecular networks by contextual knowledge concerning their state transitions, the events that can steer these transitions but also their entire temporal context linked to this information. Thus, we present an approach for understanding the transittability⁶ of biomolecular networks which is basically composed of four ontologies: the Gene Ontology (GO)^{21,22}, the Simple Event Model Ontology (SEMO)²³, the Time Ontology (TO)²⁵ and our development, the Biomolecular Network Ontology (BNO).

Figure 4 describes the global architecture of our semantic approach for analysing the transittability of complex biomolecular networks. These ontologies are described in more detail in the sections below.

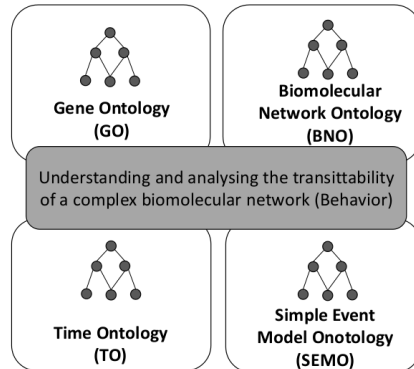


Fig. 4. Global architecture of our ontological module.

4.2. The Gene Ontology

In this study, the Gene Ontology² is considered as a core ontology. In fact, as its name suggests, it is related to the biology field and consists of concepts recognized by a wide community. The Gene Ontology ensures the description and the classification of cellular components. It provides a structured terminology for the description of gene functions and processes, and the relationships between these components²⁶.

² <http://www.geneontology.org>

The Gene Ontology consists of three sub-ontologies^{21,22}, (1) the molecular functions ontology that covers molecular activities of gene products; (2) the cellular components ontology that describes parts of cells; and (3) the biological processes ontology that depicts pathways and larger processes made up of the activities of multiple gene products. Within these three sub-ontologies, we are more interested in the molecular functions ontology and the cellular components ontology.

We chose to use the Gene Ontology for the following reasons, (1) it is an initiative of several genomic databases such as the *Saccharomyces* Genome database (SGD), the *Drosophila* genome database (FlyBase), etc. to build a generic ontology for describing the role of genes and proteins, (2) it is the most developed and most used in biology (since 2000), and (3) it provides annotation files about a large number of cellular entities.

4.3. The Simple Event Model Ontology

The Simple Event Model ontology³ proposed by Van Hage et al.²³ provides the necessary knowledge for the description of events. The ontological architecture of the Simple Event Model ontology consists of four basic classes, *Event* that specifies what is happening. This is related to the following three classes by the properties *hasActor* to indicate the participants involved, *hasPlace* to locate the place and *hasTime* to specify the time; *Actor* that indicates the participants of an event; *Place* that describes the location where the event happened; and *Time* that describes the moment.

These classes are linked by diverse properties, we can cite *eventProperties* that is used to connect the class *Event* with the other main classes, *type* that provides the necessary concepts to specify the type of each class (*Event*, *Actor*, *Place* and *Time*), and other sub-properties such as *accordingTo*, etc.

Indeed, this ontology has been frequently used by many research works to describe the events. This is due to the fact that this ontology can integrate domain-specific vocabularies²⁷.

4.4. The Time Ontology

The time dimension plays a major role in the study of the transittability of complex biomolecular networks. In fact, the temporal links are crucial to provide the succession and the sequence of transitions states that had occurred in each network component. That is why we integrate the Time ontology⁴ developed by Hobbs and Pan^{24, 25}. In fact, the classes defined in this temporal ontology enable a more intuitive use of the time dimension while making the most of semantic knowledge. It gives a rich vocabulary to describe the topological relationships that may exist between time points and intervals, and also provides information about time.

The main classes of this temporal ontology can be summarized as *TemporalEntity* which consists of two sub-classes *Instant* and *ProperInterval*, *DurationDescription*, *DateTimeDescription*, *TemporalUnit*, etc. Also, it contains several properties such as *hasDurationDescription*, *intervalStarts*, *hasDateTimeDescription*, etc.

We chose to use the Time Ontology because of its basic structure that is not specific to a particular application and because it is simple to adapt it in our context.

4.5. The Biomolecular Network Ontology

To study the dynamic behaviour and the transition states of a biomolecular network, it is required to model its domain knowledge. Therefore, we developed the Biomolecular Network ontology. This ontology is the major contribution of this paper, it is intended to describe exhaustively the field of complex biomolecular networks by describing the static aspect of its structure. It was defined in collaboration with domain experts.

Figure 5 presents the Biomolecular Network ontology. Inspired by the works of Brockmans et al.²⁸ and Bārzdīņš et al.²⁹, we use a "à la" visual UML notation where boxes are OWL classes; full lines are object properties and dotted lines are data properties. Full lines can be labelled to indicate restrictions meaning that the range of the relationship is specialized. Only a few of the object properties restrictions are displayed for the sake of clarity.

³ <http://semanticweb.cs.vu.nl/2009/11/sem/>

⁴ <https://www.w3.org/TR/owl-time/>

This domain ontology consists of four main classes:

- The class *Biomolecular_Network*: This class includes the different types of complex biomolecular networks. As mentioned earlier in Section 3, the complex biomolecular network can be composed by Gene Regulatory networks (GRNs), Protein-Protein Interaction networks (PPINs) and Metabolic networks (MNs) which correspond to the following concepts: *Genomic_Network*, *Proteomic_Network* and *Metabolomic_Network*. These types of networks can be connected to the other ontology concepts through three properties, *has_node* that depicts its cellular components, *has_interaction* that describes the interactions linked to its components and the property *has_node only* that specifies exactly the nature and type of its components.
- The class *Node*: This class contains the different types of cellular entities M that constitute the biomolecular network. In fact, we can identify three sub-classes: the *Gene* which describes the set M_G , the *Protein* which models the set M_P and the *Metabolite* which describes the M_M . This class is connected with the *Node_State* through the property *has_state*.
- The class *Interaction*: This class covers all the diverse types of interactions that can be operated among the nodes of the biomolecular network. This class consists of two sub-classes, *Intraomic_Interactions* that covers the interactions between molecular components of the same type and the class *Interomic_Interaction* that describes the interactions between molecular components of the different type. This class is connected to the *Node* class via two properties, *has_source* and *has_end*.
- The class *Node_State* contains the possible states of the nodes. This class is composed of two sub-classes, the *Concentration* and the *Activation*.
- The class *Interaction_Type* allows to specify the types and the nature of the interaction among cellular components. This class is linked to the *BNO:Interaction* class through the properties *Has_type*. To successfully integrate the main Interaction ontology concepts (*IO:Activity_flow* and *IO:Process*) with the Biomolecular Network ontology, we create an abstract BNO UML *BNO:Interaction_Type* to generalise those two Interaction ontology concepts (Figure 5).

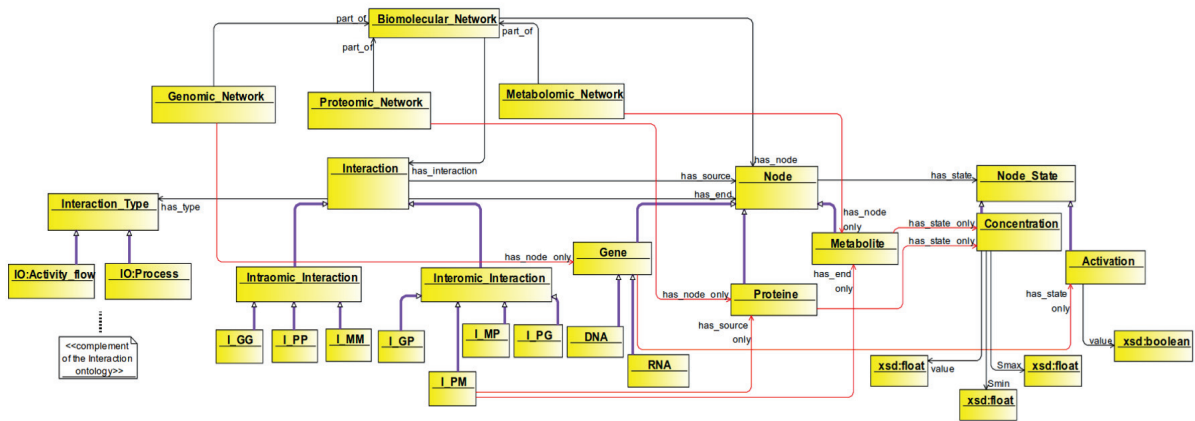


Fig. 5. The Biomolecular Network Ontology (BNO).

4.6. The relations among ontologies

Concepts in the Biomolecular Network ontology are linked to the Gene ontology classes. In fact, the concepts of the Gene Ontology are used to enrich the definitions of the concepts of the Biomolecular Network ontology by an equivalence relation *owl:equivalenceClass*. A subset of the Gene ontology concepts that can be associated with classes of Biomolecular Network Ontology is listed in Table 2. For example, as described in Figure 6b, after infer-

ence the concept *BNO:Protein* will be specialized by the concept *GO:beta-galactosidase* (GO: 0009341) because the *BNO:Node* concept is equivalent to the concept *GO:cellular_component* (GO: 0005575).

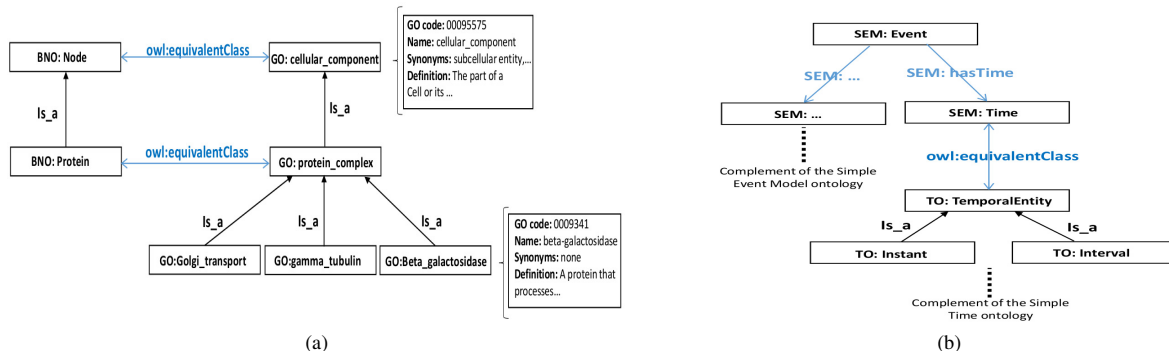


Fig. 6. Example of merging: 6a The Gene ontology concepts to the Biomolecular Network ontology concepts. 6b The Time ontology within the Simple Event Model ontology.

The Biomolecular Network ontology is also linked with the Simple Event Model ontology through the *BNO: Node* concept, in fact an *SEM:event* can stimulate a molecular entity (represented by the concept *BNO: Node*). The Simple Event Model ontology will be used to describe the states of *BNO:Node* and its behaviour.

Moreover, the Time ontology (TO) has been integrated in the Simple Event Model ontology. The concept *sem:Time* was made equivalent to the concept *TO:TemporalEntity* which represents the root of the Time ontology. Hence, the property *sem:hasTime* will connect the Simple Event Model ontology to the Time ontology and, as a consequence, the diverse types of temporal concepts will be defined as specializations of the class *sem:Time*. Figure 6b shows a use of this principle. Thus, we can exploit the wealth of temporal concepts provided by this temporal ontology to describe the *SEM:event* class.

By using these relationships it is possible to merge the four ontologies in order to formalize all the necessary knowledge to study the state changes of the complex biomolecular networks and their behaviour.

5. Conclusions and Future Work

The general aim of our work is to develop a platform to simulate the state changes of the complex biomolecular networks with the hope of understanding and steering their behaviour. This platform consists of three basic modules: (i) the *ontological* module to provide a rich description of cellular entities and their interactions with each other, (ii) the *simulation* module to reproduce the dynamic behaviour of each network component over the time and (iii) the *optimization* module to provide a set of transition sequences with the best steering of the biomolecular network from a given state to another.

In this paper, two concepts constituting the first module of our platform are presented. These concepts form the basic elements for understanding and modeling the complex biomolecular networks.

First, we propose a detailed logical model that describes the structure of a complex biomolecular network, its function and its behaviour.

Second and based on this logical formalization, we propose a semantic approach that consists of four ontologies joined together. This approach provides the necessary concepts for modeling the dynamic behaviour and the transition

Table 2. Linking of Gene Ontology concepts to the Biomolecular Network ontology.

Type of relationship	Biomolecular Network Ontology concept name	Gene Ontology concept name
Equivalence: <i>BNO</i> "owl: equivalenceClass" <i>GO</i>	<i>BNO: Node</i>	<i>GO: cellular_component</i>
	<i>BNO: Interaction</i>	<i>GO: biological_process</i>
	<i>BNO: Protein</i>	<i>GO: protein_complex</i>

states of complex biomolecular networks. Also, we define ontologies composing this approach and we detail how to link them together.

In the short term, we focus on develop mechanisms for reasoning to gain new inferential knowledge.

Acknowledgements

These works are done in collaboration with the Complex Systems and Translational Bioinformatics team (CSTB) team of the ICube Laboratory. The authors would like to thank very specially Mrs Julie Thompson for the fruitful discussions we have had with her and her rich comments and remarks.

References

1. Bowsher, C. G., Voliotis, M. and Swain, P. S.: The fidelity of dynamic signaling by noisy biomolecular networks. *PLoS Comput Biol.* 2013; **9(3)**:e1002965.
2. Pavlopoulos, G. A., Wegener, A. L. and Schneider, R.: A survey of visualization tools for biological network analysis. *Biodata mining.* 2008; **1(1)**:1.
3. Villaamil, V. M., Gallego, G. A., Cainzos, I. S., Valladares-Ayerbes, M. and Aparicio, L. M. A.: State of the art in silico tools for the study of signaling pathways in cancer. *International journal of molecular sciences.* 2012; **13(6)**:6561-6581.
4. Najafi A., Bidkhorji G., Bozorgmehr JH., Koch I. and Masoudi-Nejad A.: Genome Scale Modeling in Systems Biology: Algorithms and Resources. *Current Genomics.* 2014; **15(2)**:130-159.
5. Karp, Gerald.: Biologie cellulaire et molculaire: Concepts and experiments. *De Boeck Suprieur.* 2010.
6. Wu, F. X., Wu, L., Wang, J., Liu, J. and Chen, L.: Transittability of complex networks and its applications to regulatory biomolecular networks. *Scientific reports.* 2014; **4**.
7. Raza, K. and Parveen, R.: Evolutionary algorithms in genetic regulatory networks model. *arXiv preprint arXiv:1205.1986*, 2012.
8. Maayan A.: Introduction to Network Analysis in Systems Biology. *Science signaling.* 2011; **4(190)**:tr5.
9. Bellouquid, A. and Delitala, M.: Mathematical Modeling of Complex Biological Systems. *BirkhÅser Boston.* 2006.
10. Fischer, H. P.: Mathematical modeling of complex biological systems: from parts lists to understanding systems behavior. *Alcohol Research & Health.* 2008; **31(1)**:49.
11. De Jong, H.: Modeling and simulation of genetic regulatory systems: a literature review. *Journal of computational biology.* 2002; **9(1)**:67-103.
12. Karr, J. R., Sanghvi, J. C., Macklin, D. N., Gutschow, M. V., Jacobs, J. M., Bolival, B.J., Assad-Garcia N., Glass, J. I. and Covert, M. W.: A whole-cell computational model predicts phenotype from genotype. *Cell.* 2012; **150(2)**:389-401.
13. Ayadi A., de Bertrand de Beuvron F., Zanni-Merk C. and Thompson J.: Formalisation des rseaux biomolculaires complexes. *EGC 2016 - 16mes Journes Francophones "Extraction et Gestion des Connaissances". Revue des Nouvelles Technologies de l'Information.* Reims; 2016.
14. Zanni-Merk, C.: KREM: A Generic Knowledge-based Framework for Problem Solving in Engineering. *KEOD 2015 - Proceedings of the International Conference on Knowledge Engineering and Ontology Development, part of the 7th International Joint Conference on Knowledge Discovery, Knowledge Engineering and Knowledge Management (IC3K 2015).* 2015; **2**:381-388.
15. Wu, F., Chen, L., Wang, J. and Alhajj, R.: Biomolecular Networks and Human Diseases. *BioMed research international.* 2014; **2014**:363717.
16. MacNeil, L. T. and Walhout, A. J.: Gene regulatory networks and the role of robustness and stochasticity in the control of gene expression. *Genome research.* 2011; **21(5)**:645-657.
17. Bensimon, A., Heck, A. J. and Aebersold, R.: Mass spectrometry-based proteomics and network biology. *Annual review of biochemistry.* 2012; **81**:379-405.
18. Kitano, H.: Systems biology: a brief overview. *Science.* 2002; **295(5560)**:1662-1664.
19. Le Moigne, J. L.: La thorie du systme gnral: thorie de la modlisation. *Presse Universitaire de France.* 1984.
20. Van Landeghem, S., Van Parys, T., Dubois, M., Inz, D. and Van de Peer, Y.: Diffany: an ontology-driven framework to infer, visualise and analyse differential molecular networks. *BMC bioinformatics.* 2016; **17(1)**:1.
21. Smith, B., Williams, J. and Schulze-Kremer, S.: The ontology of the gene ontology. *In AMIA.* 2003; **3**:609-613.
22. Gene Ontology Consortium: The gene ontology project in 2008. *Nucleic acids research.* 2008; **36(suppl 1)**:D440-D444.
23. Van Hage, W. R., Malais, V., Segers, R., Hollink, L. and Schreiber, G.: Design and use of the Simple Event Model (SEM). *Web Semantics: Science, Services and Agents on the World Wide Web.* 2011; **9(2)**:128-136.
24. Hobbs, J. R. and Pan, F.: An ontology of time for the semantic web. *ACM Transactions on Asian Language Information Processing (TALIP).* 2004; **3(1)**:66-85.
25. Hobbs, J. R. and Pan, F.: Time ontology in OWL. *W3C working draft.* 2006; **27**:133.
26. Ashburner, M., Ball, C. A., Blake, J. A., Botstein, D., Butler, H., Cherry, J. M., ... and Harris, M. A.: Gene Ontology: tool for the unification of biology. *Nature genetics.* 2000; **25(1)**:25-29.
27. Duncan, J., Eilbeck, K., Narus, S. P., Clyde, S., Thornton, S. and Staes, C.: Building an Ontology for Identity Resolution in Healthcare and Public Health. *Online journal of public health informatics.* 2015; **7(2)**.
28. Brockmans, S., Volz, R., Eberhart, A., and Löffler, P.: Visual modeling of OWL DL ontologies using UML. *In The Semantic WebISWC 2004.* Springer Berlin Heidelberg. 2004; 198-213.
29. Bärzdiņš, J., Bärzdiņš, G., Čerāns, K., Liepiņš, R., and Sprōģis, A.: UML style graphical notation and editor for OWL 2. *In Perspectives in Business Informatics Research.* Springer Berlin Heidelberg. 2010;102-114.