Web Semantics: Science, Services and Agents on the World Wide Web 57 (2019) 100495

Contents lists available at ScienceDirect

Web Semantics: Science, Services and Agents on the World Wide Web

journal homepage: www.elsevier.com/locate/websem

BNO—An ontology for understanding the transittability of complex biomolecular networks

Ali Ayadi [a,b,*], Cecilia Zanni-Merk [c], François de Bertrand de Beuvron [a], Julie Thompson [a], Saoussen Krichen [b]

[a] ICUBE Laboratory UMR CNRS 7357, Pole API BP 10413, Illkirch 67412, France
[b] LARODEC Laboratory, Institut Supérieur de Gestion de Tunis, University of Tunis, Rue de la liberté, Bardo 2000, Tunisia
[c] LITIS Laboratory, Fédération CNRS Norm@STIC FR 3638, INSA Rouen Normandie, Avenue de l'Université, 76801 Saint-Etienne-du Rouvray, France

ARTICLE INFO

Article history:
Received 29 November 2017
Received in revised form 19 October 2018
Accepted 10 January 2019
Available online 21 January 2019

Keywords:
Systems biology
Complex biomolecular networks
Transittability
Ontology engineering
Qualitative reasoning
SWRL rules

ABSTRACT

Analysis of biological systems is being progressively facilitated by computational tools. Most of these tools are based on qualitative and numerical methods. However, they are not always evident, and there is an increasing need to provide an additional semantic layer. Semantic technologies, especially ontologies, are one of the tools frequently used for this purpose. Indeed, they are indispensable for understanding the semantic knowledge about the operation of cells at a molecular level. We describe here the biomolecular network ontology (BNO) created specially to address the needs of analysing the complex biomolecular network's behaviour. A biomolecular network consists of nodes, denoting cellular entities, and edges, representing interactions among cellular components. The BNO ontology provides a foundation for qualitative simulation of complex biomolecular networks. We test the performance of the proposed BNO ontology by using a real example of a biomolecular network, the bacteriophage T4 gene 32. We illustrate the proposed BNO ontology for reasoning and inferring new knowledge with sets of rules expressed in SWRL. Results demonstrate that the BNO ontology allows to precisely interpret the corresponding semantic context and intelligently model biomolecular networks and their state changes. The Biomolecular Network Ontology (BNO) is freely available at https://github.com/AliAyadi/BNO-ontology-version-1.0.

1. Introduction

1.1. Motivation

To understand how the human body works it is crucial to focus on the behaviour of the cells and how cells correctly respond to their environments. Indeed, cells are exposed to several environmental stimuli. These detectable changes in the cell's environment can be internal, such as the increased concentration of intracellular components, or external effects, such as the ones of taking medication. In general, cell adaptation to these stimuli refers to changes in the state of the cell molecular components. These molecular components interact together creating a complex biomolecular network that consists of a set of nodes, denoting the molecular components and a set of edges, denoting the interactions among these cellular components. These networks are considered as systems that dynamically evolve from a state to another so that the cell can adapt itself to changes in its environment. This issue has already been addressed in the work of Wu et al. [1], where they introduce and define the transittability of biomolecular networks as their steering from an undesired state to a desired state.

Moreover, intense research in molecular biology has led to major discoveries in cellular components, producing an important volume of knowledge about these components. It would, therefore, be helpful to exploit this knowledge to increase the understanding of the behaviour of complex biomolecular networks. In fact, ontologies with their clearly-defined and well-structured descriptions are important tools for the effective application of 'omic' information through computational approaches [2].

1.2. 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 [1,3]. The complexity of the biomolecular network appears by its decomposition into three levels: the genome level models the genetic material of an organism, the proteome level describes the entire set of proteins and the metabolism

* Corresponding author.
E-mail addresses: ali.ayadi@unistra.fr (A. Ayadi), cecilia.zanni-merk@insa-rouen.fr (C. Zanni-Merk), debeuvron@unistra.fr (F.d.B. de Beuvron), thompson@unistra.fr (J. Thompson), saoussen.krichen@isg.rnu.tn (S. Krichen).

https://doi.org/10.1016/j.websem.2019.01.002
1570-8268/

level contains the complete set of small-molecule chemicals [4]. Depending on the type of their cellular components and their interactions, we can distinguish the three basic types of networks (Fig. 1): the Gene Regulatory networks (GRNs), the Protein–Protein-Interaction networks (PPINs) and the Metabolic networks (MNs), that were logically and semantically formalized in our previous works [5].

1.3. Research objectives

This paper details and describes the Biomolecular Network Ontology (BNO) which is freely available at https://github.com/AliAyadi/BNO-ontology-version-1.0 and can be viewed using the standard ontology visualization editor *Protégé*. The BNO aims at giving a formal and semantic representation that models all the necessary biological knowledge to study and reason on complex biomolecular networks.

This semantic representation wishes to meet the following goals: (1) Determine the structure of a biomolecular network by identifying the specific functions of all molecules and the different nature of the interactions they provide; (2) Disturb the network with stimuli by changing the concentration of an element and observe its response; (3) Reason and infer new knowledge;

Moreover, through the application of the BNO ontology, we will understand how a cell works through the semantic interpretation of knowledge involved in the network's behaviour, and identify the different states of the biomolecular network over time and through the simulation of its behaviour.

The remainder of the paper will: (i) briefly summarize the literature review work in two areas, (1) ontology engineering and (2) the application of ontologies in biology, especially, in systems biology; (ii) describe in detail the main components of the BNO ontology on which the transittability of complex biomolecular networks are meant to be contextualized; (iii) present the applicability of the proposed ontology through a concrete case study related to the biological domain; (iv) discuss the validation and quality of the BNO ontology using diverse validation approaches; and (v) finally conclude the paper by deriving the benefits and limitations of the BNO ontology in the context of modelling the behaviour of complex biomolecular networks, and perspectives of future work.

2. Literature review

This section introduces the different types of ontologies and lists the different languages that have been used for representing them. In addition, this section reviews the principal bio-ontologies and their applications in systems biology.

2.1. Ontology engineering

Semantic technologies, especially ontology engineering, provides formal description with a semantically rich knowledge base for the description and interpretation of the terms in a domain and the relationships among them [6]. According to M. Uschold and M. Gruninger [7], an ontology is an explicit, formal specification of a shared conceptualization of a domain of interest. It provides potential terms for describing our knowledge about the domain.

Various classifications of ontologies have been presented in the literature [8–11]. As specified by G. Falquet, et al. [11], ontologies can be subdivided into several levels: (i) Top-level ontology also known as Foundation ontology or upper ontology, which represents very general concepts that are common across all domains; (ii) Core reference ontology which is a basic ontology that is useable and shareable by a community of interest. (iii) Domain ontology which describes fundamental concepts according to a generic domain by specializing the concepts of an upper ontology; (iv) Task ontology, one that describes fundamental concepts according to a generic task, process or activity; and (v) Application ontology which defines specialized knowledge focused on a specific task and domain.

Moreover, the Ontology Web Language (OWL) [9] has become a standard language of the World Wide Web Consortium (W3C)[1] recommendation to describe and build ontologies. OWL ontology contains three basic modelling constituents: concepts, properties, and instances. Concepts are used to identify the most important objects in the model description, they are modelled by classes which provide an abstraction mechanism for grouping concepts (or objects) with similar characteristics. Instances define individuals that are the members of a class. Finally, properties are used to define the relationships among the concepts. OWL defines two properties: object properties which define relationships among couples of individuals, and datatype properties which define the relations between individuals and a data type value [6]. In addition, under OWL language we can query the content of an ontology using the SPARQL query language and reason about these classes and individuals through Semantic Web Rule Language (SWRL).

It is important to be clear about why an ontology is being developed and what its intended uses are. Ontology engineering proposes various methodologies for the process of developing an ontology. We briefly cite some methods: the TOVE (TOronto Virtual Enterprise) methodology proposed by and M. Grüninger and M. S. Fox [12] within the domain of business processes and activities modelling. The TOVE methodology involves building a logical model of the knowledge that is to be specified by means of the ontology. This model consists of two steps: firstly, an informal description is made of the specifications to be met by the ontology and then this description is formalized; The SENSUS methodology [13] assumes that the knowledge between two ontologies can be easily shared if they have a common structure which means if they are based on the common SENSUS ontology that contains more than 70000 concepts; The DILIGENT methodology [14] is a methodology for DIstributed, Loosely-controlled and evolvInG Engineering of oNTologies. This methodology contributes in the development of shared ontologies in distributed settings like the Semantic Web; The Bernaras methodology [15] has been proposed to build an ontology in the domain of electrical networks as part of the Esprit KACTUS project. The construction of ontologies following this methodology is based on the construction of particular applications; The iCAPTURer methodology [16] makes use of text-mining approaches to identify the important concepts and to suggest candidate ontological relationships between them. This methodology has received little influence from knowledge engineering; The GM methodology [17] focuses on knowledge acquisition when developing ontologies within decentralized settings. This methodology has been widely used in biomedical domain received little influence from knowledge engineering; The METHONTOLOGY methodology [18] which is the most mature. However, recommendations for some activities and techniques should be specified in more detail. Additionally, it is recommended by the Foundation for Intelligent PhysicalAgents (FIPA).[2] Also, ontology engineering requires some editing tools for ontology construction, such as the Protégé editor [19], OntoEdit [20], SWOOP [21], Altova Semantic Works [22], and OilEd [23].

2.2. Biology-related ontologies

Over the last decades, new technologies have emerged and revolutionized biological research (such as spectrometer techniques,

[1] https://www.w3.org/.
[2] http://www.fipa.org.

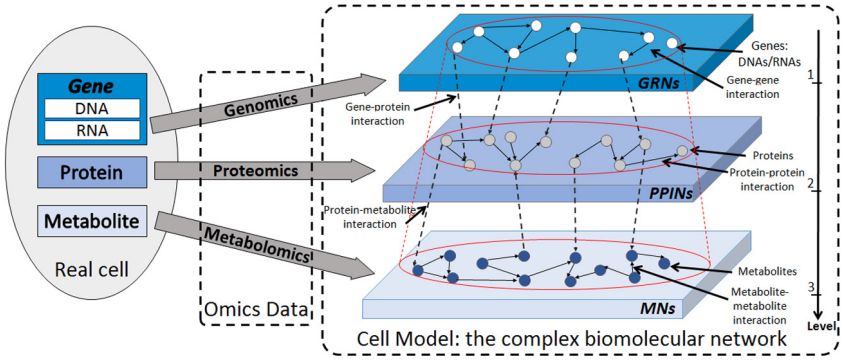

Fig. 1. Multi-level modelling of a biomolecular network from a real cell [5].

etc.) producing an accumulation of data and knowledge about molecular mechanisms in cells. All these data were stored in heterogeneous and various sources of data. In this way, diverse data sources have been developed to allow researchers to share and reuse data in the life sciences [24]. However, the diversity of these data sources induce the propagation of misinformation. These data integration problems open the way to semantic web technologies, especially ontologies which may be used as a unifying framework to solve these problems. In particular, ontologies are used in a wide range of systems biology. Moreover, with the creation of the National Center for Biomedical Ontology (NCBO) in 2006 [25–27], an incredible amount of ontologies emerged in the Open Biological and Biomedical Ontologies (OBO) Foundry[3] providing a large variety of bio-ontologies [28]. By the exploration of these bio-ontologies via browsers such the Ontology Lookup Service[4] and the BioPortal,[5] it is remarked that these ontologies treat different parts of systems biology, such as cell types [29,30], molecular functions [31], experimental data analysis [32], identification and annotation of genes [33,34], etc.

Among these bio-ontologies, we can count the popular Gene Ontology (GO) [31] which aims to formalize knowledge about biological processes, molecular functions, and cell components. The Gene Regulation Ontology (GRO) [35] which is designed to describe the processes that are linked to the regulation of gene expression. The Cell Ontology (CO) [36] which provides a rich vocabulary for cell types. The Protein Ontology (PO) [37] which provides an ontological representation of protein-related entities by explicitly defining them and showing the relationships between them. The Systems Biology Ontology (SBO) [38] which is a set of controlled vocabularies of terms commonly used in Systems Biology, and in particular in computational modelling.

As presented in Table 1 these bio-ontologies differ in the type of knowledge they describe, their intended purpose and their level of abstraction. Although there are several promising bio-ontologies in the systems biology domain, until now and to the best of our knowledge, there is no ontology for modelling the behaviour of complex biomolecular networks. In fact, very few research efforts use ontologies for defining the possible biological functions, like signal transducer activity in the case of the Gene Ontology (GO), or the Gene Regulation Ontology (GRO) which describes and focuses on the regulation of gene expression.

As was discussed, current ontologies for systems biology domain do not focus on the description of the biomolecular network's transittability. In fact, there is a lack of standard representation of entities which take part in the analysis the behaviour of complex biomolecular networks and of the relations among them. As will be shown in the following sections, these entities are complex and have several relations among them. So, developing an ontology to formally define this concrete domain is more than evident. Therefore, in this paper, a new ontology entitled 'the Biomolecular Network Ontology' (BNO) for the representation of this domain is proposed.

Moreover, to increase the interoperability of our proposed BNO ontology and 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, we matched and merged it with some other ontologies, such as the Gene Ontology (GO) [31,39], the Simple Event Model Ontology (SEMO) [40], and the Time Ontology (TO) [41].

3. Description of the biomolecular network ontology

In this section, we describe our ontology for understanding the behaviour of complex biomolecular networks and their transittability. The Biomolecular Network Ontology has been developed following the METHONTOLOGY which better fits our purposes.

3.1. Coding

Fig. 2 presents the diagram of the structure and the architecture of the BNO ontology. As described in Fig. 3, we have developed this ontology using the OWL-language [43] using the Protégé editor, version 5.2.0. Protégé[6] is a free, open-source ontology editor and framework for building intelligent systems [44]. Concepts, relations, and attributes were modelled as *classes*, *object properties* and *data properties*, respectively. Axioms were represented in Protégé using diverse OWL restrictions (existential restrictions, universal restrictions, cardinality restrictions, hasValue restrictions), characteristics of object property, and datatype restrictions.

3.2. The key classes

We define five main classes namely ***BNO:Biomolecular_Network***, ***BNO:Node***, ***BNO:Interaction***, ***NodeState*** and ***BNO:Type_Interaction***. The ***BNO:Biomolecular_Network*** class has been further divided into the three types of networks: the ***BNO:Genomic_Network***, ***BNO:Proteomic_Network*** and ***BNO:Metabolomic_Network*** (as detailed in Section 1.2). The instances of these classes will be defined later, among these instances we will focus on the *BacteriophageT4G32* instance in Section 4. The ***BNO:Node*** class is the super-class of the three types of nodes: the ***BNO:Gene*** which is itself divided into two types the ***BNO:DNA*** and ***BNO:RNA***, the ***BNO:Protein*** and the ***BNO:Metabolite***. The ***Interaction*** class

[3] http://www.obofoundry.org/.
[4] http://www.ebi.ac.uk/ols/index.
[5] http://bioportal.bioontology.org/.
[6] http://protege.stanford.edu/.

Table 1
Description of some main population biological ontologies.

Biological ontology name	Content	Ref.	Link
Gene Ontology (GO)	Biological process	[31]	http://www.geneontology.org/
Gene Regulation Ontology (GRO)	Gene regulation events	[35]	http://purl.bioontology.org/ontology/GRO
Cell Ontology (CO)	Cellular types	[36]	http://obofoundry.org/ontology/cl.html
Protein Ontology (PO)	Protein entities	[37]	http://pir.georgetown.edu/pro/
Systems Biology Ontology (SBO)	Biology systems nomenclature	[38]	http://www.ebi.ac.uk/sbo/main/
Cell Behaviour Ontology (CBO)	Cellular behaviour	[42]	http://cbo.biocomplexity.indiana.edu/cbo/
Simple Event Model Ontology (SEMO)	Modelling events	[40]	http://semanticweb.cs.vu.nl/2009/11/sem/
Time Ontology (TO)	Temporal concepts	[41]	http://www.w3.org/TR/owl-time

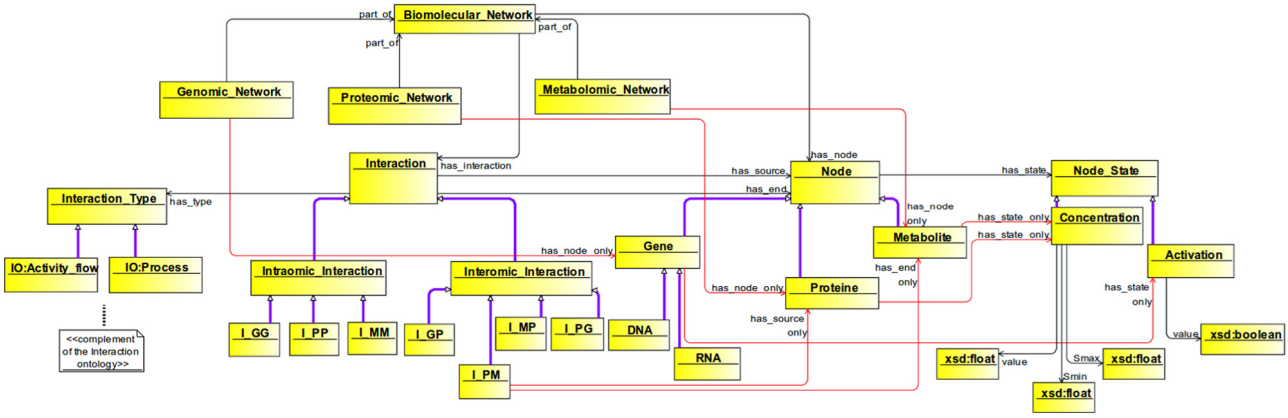

Fig. 2. A diagram of the structure of the proposed Biomolecular Network Ontology (BNO) [5].

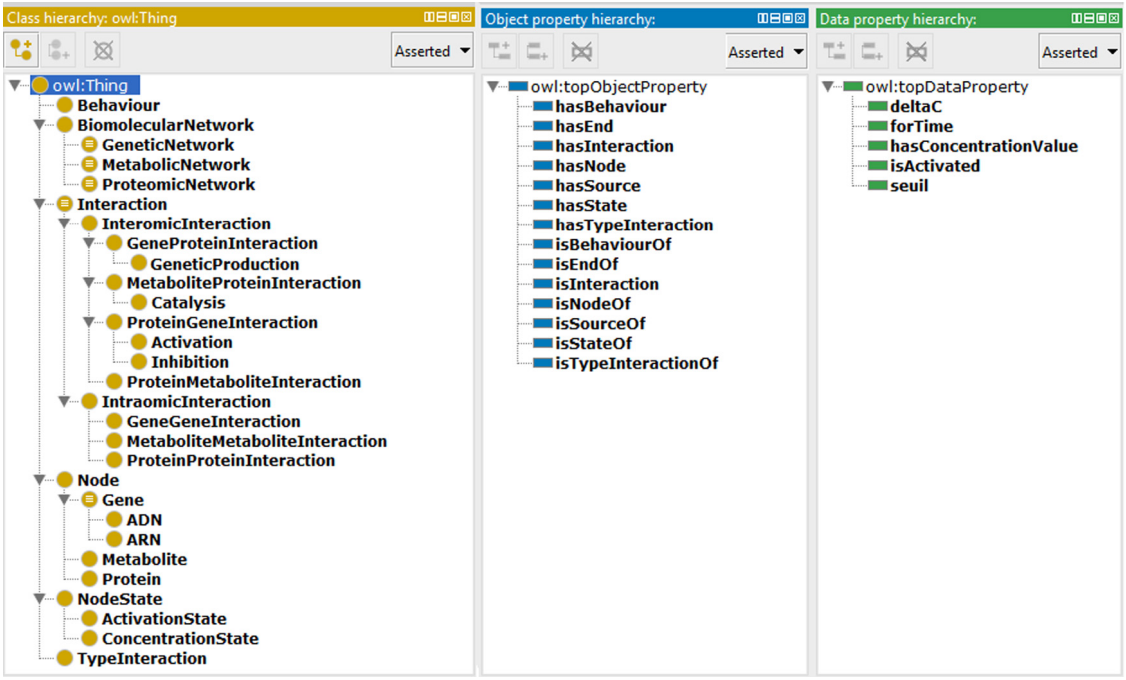

Fig. 3. The Biomolecular Network Ontology: hierarchy of classes, hierarchy of properties and hierarchy of data properties.

contains a list of all the interactions among the different types of nodes as its subclasses. The ***NodeState*** class consists of two subclasses ***ActivationState*** and ***ConcentrationState***. Finally, the ***BNO:Type_Interaction*** class contain a list of all the types of interactions, the instances of this class belong to the set of concepts of the Interaction Ontology proposed by Van Landeghem et al. [45].

Fig. 3 and Table 2 show the most important BNO classes. It is worth noting that these BNO classes have been developed based on a logical-based modelling of complex biomolecular networks with the goal of understanding their transittability [46]. In this logical modelling, the *structure* of the biomolecular network denoted by SR is a graph defined by $SR = (M, I)$ (corresponding to the $BNO : Node$ and $BNO : Interaction$ classes, respectively).

- M denotes all the molecules composing the network and represents the nodes of the graph defined by a finite set of vertices $M = \{m_1, m_2, \ldots, m_n\}$. 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.

$M = M_G \cup M_P \cup M_M$

$M_x \cap M_y = \emptyset$ where: $x, y \in \{G, P, M\}$ 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 $I = \{i_1, i_2, \ldots, i_m\}$. An edge $i = (m_i, m_j)$, (where $m_i, m_j \in M$) which start from m_i (origin) and comes to m_j (destination) 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} modelling 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} and I_{MG} are not taken into account because there is no direct interaction between the genes and metabolites and vice versa.

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

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

Therefore, according to this logical definition of the structure of a biomolecular network, the order of letters matters when specifying protein–gene relationships. For example, as presented in Table 2, the I_{GP} class denotes an interaction which starts from a gene (origin) and comes to a protein (destination). It occurs when a gene is activated, it produces a protein. However, the I_{PG} class denotes an interaction which starts from a protein (origin) and comes to a gene (destination). It occurs when certain proteins impacts on genes through the transcription factor.

Moreover, in our context, the I_{GG} class denotes the interactions between genes that can be an activation or an inhibition interaction between two genes. In relation to cis and trans interactions, this depends on the starting and the target nodes of the interaction:

- If the starting node is a transcription factor (TF) and is able to regulate other genes (the starting node is different than the target node): Here, the I_{GG} interaction is considered as a trans-interaction in general, means "acting from a different molecule". In our works (cited above), we called them by "interomic" interactions. An example of trans-interaction factors include the genes for Proteins that bind to all promoters of specific sequences, but not to RNA polymerase (TFIID factors) [47].
- If the starting node is a transcription factor (TF) and is able to regulate itself (when the starting node and the target node is the same node): Here, the I_{GG} interaction is considered as a cis-interaction in general, means "acting from the same molecule". In our works (cited above), we called them by "intraomic" interactions. For example, where a non-TF gene can regulate itself: Feedbacks in cell signalling which happen via activity modulation by protein phosphorylation [48].

Therefore, the I_{GG} class interaction can cover both cis- and trans-interactions according to the required level of detail and the different modes of gene activity regulation. This type of interaction has been added by expert biologists who estimated that there could be interactions between different level of interaction between genes.

3.3. The main properties and data types

After the definition of the major BNO concepts and in order to describe the semantic relations among them, we need to define the domain, range, property type, and inverse properties as constraint conditions. The different properties and data types of the BNO ontology are explained below.

- *hasBehaviour*(*object*1, *object*2): where object1 is a *BiomolecularNetwork* and object2 is a *Behaviour*.
- *hasInteraction*(*object*1, *object*2):where object1 is a *BiomolecularNetwork* and object2 is an *Interaction*.
- *hasNode*(*object*1, *object*2): where object1 is a *BiomolecularNetwork* and object2 is a *Node*.
- *hasSource*(*object*1, *object*2): where object1 is an *Interaction* and object2 is a *Node*.
- *hasEnd*(*object*1, *object*2): where object1 is an *Interaction* and object2 is a *Node*.
- *hasState*(*object*1, *object*2): where object1 is a *Node* and object2 is a *NodeState*.
- *hasTypeInteraction*(*object*1, *object*2): where object is an *Interaction* and object2 is a *TypeInteraction*.
- *deltaC*(*object*, *datatypes*): where object is an *Interaction* and datatypes is a *float* representing the change in concentration caused by the interaction.
- *forTime*(*object*, *datatypes*): where object is a *NodeState* and datatypes is a *int* representing its time.
- *hasConcentrationValue*(*object*, *datatypes*): where object is a *Protein* or a *Metabolite* and datatypes is a *float* representing the value of its concentration.
- *isActivated*(*object*, *datatypes*): where object is an *Gene* and datatypes is a *boolean* equal to true if the gene is activated.
- *seuil*(*object*, *datatypes*): where object is the threshold of an *Interaction* and datatypes is a *float*.

Table 3 summarizes of the major properties, including their domain, range, and inverse.

3.4. Matching the biomolecular network ontology with existing biomedical ontologies

To study the behaviour of complex biomolecular networks, it is not sufficient to simply describe it using the Biomolecular Network Ontology (BNO). Indeed, It is important to increase the interoperability of our proposed ontology and 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.

In order to achieve its objectives, we matched and merged the BNO ontology with some other ontologies, such as the Gene Ontology (GO) [31,39], the Simple Event Model Ontology (SEMO) [40], and the Time Ontology (TO) [41]. It is also important to mention that the Biomolecular Network Ontology can be matched with the Gene Regulation Ontology (GRO) [35]. Indeed, this ontology can be considered also as a core ontology in which some terms can be reused for describing biomolecular networks, in particular, when we are focusing on the gene expression aspects.

Before explaining how these ontologies are matched together, let us start by introducing each of them.

Table 2
A summary of classes in the Biomolecular Network ontology. The left column displays the five major classes and their immediate sub-classes. The right column presents the description of these classes.

BNO ontology classes	Description
BNO:BiomolecularNetwork	defines the different kinds of complex biomolecular networks.
BNO:GenomicNetwork	defines the interactions among genes forming Gene Regulatory networks.
BNO:ProteomicNetwork	defines the interactions among proteins forming Protein–Protein Interaction networks.
BNO:MetabolomicNetwork	defines the interactions among proteins forming Metabolic networks.
BNO:Node	defines the different types of cellular entities.
BNO:Gene	describes the set of genes M_G.
BNO:DNA	describes the set DNA.
BNO:RNA	describes the set of RNA.
BNO:Protein	describes the set proteins M_P.
BNO:Metabolite	describes the set metabolites M_M.
BNO:Interaction	defines all the types of interactions operated among the nodes.
BNO:IntraomicInteraction	defines the interactions between molecular components of the same type.
BNO:I_GG	defines the interactions between genes.
BNO:I_PP	defines the interactions between proteins.
BNO:I_MM	defines the interactions between metabolites.
BNO:InteromicInteraction	defines the interactions between molecular components of the different type.
BNO:I_GP	defines the interactions between genes and proteins.
BNO:I_PG	defines the interactions between proteins and genes.
BNO:I_PM	defines the interactions between proteins and metabolites.
BNO:I_MP	defines the interactions between metabolites and proteins.
BNO:NodeState	defines the possible states of the nodes.
BNO:ActivationState	defines the states of the genes.
BNO:ConcentrationState	defines the concentration of the proteins and metabolites.
BNO:InteractionType	defines the nature of the interaction among cellular components.

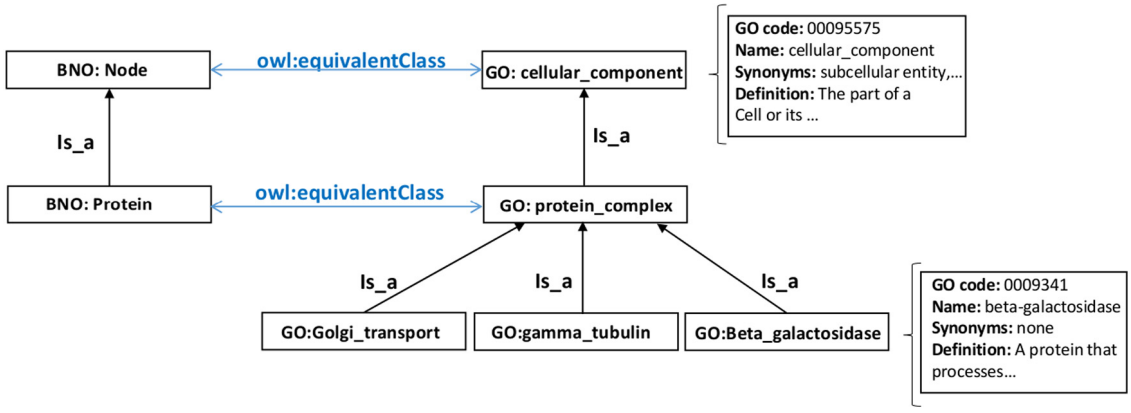

Fig. 4. Example of merging: The Gene ontology concepts to the Biomolecular Network ontology concepts.

Table 3
A summary of the properties, including their domain, range, and inverse.

BNO ontology properties	Domain	Range	Inverse
hasBehaviour	BiomolecularNetwork	Behaviour	isBehaviourOf
hasInteraction	BiomolecularNetwork	Interaction	isInteractionOf
hasNode	BiomolecularNetwork	Node	isNodeOf
hasSource	BiomolecularNetwork	Node	isSourceOf
hasEnd	Interaction	Node	isEndOf
hasState	Interaction	State	isStateOf
hasTypeInteraction	Interaction	TypeInteraction	isTypeInteractionOf

- The Gene Ontology[7] or the Gene Regulation Ontology[8] are considered as core ontologies. In fact, as their name suggests, they are related to the biology field and consist of concepts recognized by a wide community. In our work, we only use the Gene Ontology that 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 components [49].
  The Gene Ontology consists of three sub-ontologies [31,39], (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)

7 http://www.geneontology.org.
8 http://purl.bioontology.org/ontology/GRO.

it provides annotation files about a large number of cellular entities.

- The Simple Event Model ontology[9] proposed by Van Hage et al. [40] 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 vocabularies [50].
- 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 ontology[10] developed by Hobbs and Pan [41]. 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, but 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 proprerties 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.

The relations among these ontologies. Concepts in the Biomolecular Network ontology are linked to the Gene ontology concepts. In fact, the concepts of the Gene ontology are used to enrich the definitions of the concepts of the Biomolecular Network ontology by two relations: an equivalence relation *owl:equivalenceClass* and a specification relation *owl:subClassOf*. Some instances of these relations are shown in Fig. 4. For example, after inference 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). Other examples of these links are illustrated in Table 4.

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 into 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

[9] http://semanticweb.cs.vu.nl/2009/11/sem/.
[10] https://www.w3.org/TR/owl-time/.

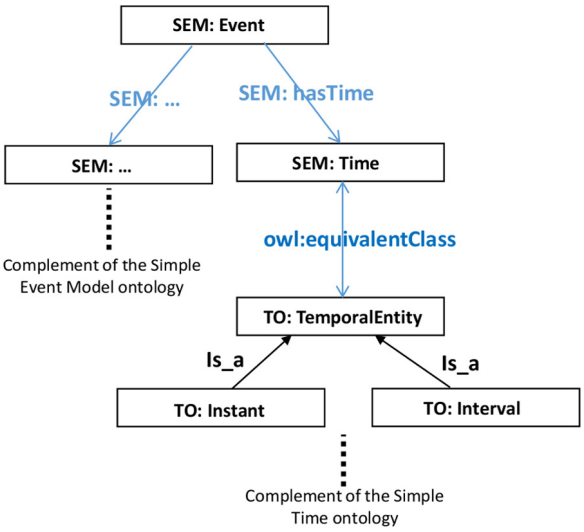

Fig. 5. Example of merging: The Time ontology within the Simple Event Model ontology.

and, as a consequence, the diverse types of temporal concepts will be defined as specializations of the class *SEM:Time*. Fig. 5 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.

Using these relationships these ontologies are linked together in order to provide the necessary concepts for modelling the dynamic behaviour and study the transition states of complex biomolecular networks.

4. Application of BNO

The aim of this section is to illustrate the proposed BNO ontology for reasoning and inferring new knowledge with sets of rules expressed in SWRL [43].

4.1. Example of the bacteriophage T4 gene 32 use case

We test the performance of the proposed BNO ontology by using a real example of a biomolecular network, the bacteriophage T4 gene 32 [51]. As described in Fig. 6, this biomolecular network consists of three nodes a **gene G32** coding for a **protein p32** and a **metabolite m32** which can catalyze the protein p32. In this network, the concentration of p32 is regulated by itself and normally should remain between 0.2 10^{-6} *Mol* and 0.7 10^{-6} *Mol*. When the concentration of p32 exceeds the threshold $S_{p32} = 0.7\ 10^{-6}$ *Mol*, we talk about an **Inhibition** in which the protein p32 inhibits the genetic production of its gene G32 making it deactivated. However, when the concentration of p32 decreases and becomes lower than the threshold $S_{p32} = 0.2\ 10^{-6}$ *Mol*, we talk about an **Activation** in which the protein p32 activates the genetic production of its gene G32 making it activated. When the gene G32 is activated by the protein p32, we talk about a **Genetic production** in which we have a production of p32 by increasing the value of its concentration. When the concentration of m32 exceeds the threshold $S_{m32} = 0.8\ 10^{-6}$ *Mol*, the metabolite m32 catalyses the p32 by decreasing the value of its concentration, here we treat a **Catalysis**.

In our context, the 'Genetic production' refers to the process of gene expression which involves two main stages: (i) the transcription: the production of messenger RNA (mRNA) by the enzyme RNA polymerase, and the processing of the resulting mRNA molecule [DNA → RNA]. (ii) The translation: the use of mRNA to direct protein synthesis, and the subsequent post-translational processing of the protein molecule [RNA → Protein].

Table 4
Linking of Gene Ontology concepts to the Biomolecular Network ontology.

Type of relationship	Biomolecular Network Ontology concept name	Gene Ontology concept name
Equivalence: *BNO* 'owl : *equivalenceClass*' *GO*	*BNO* : *Node* *BNO* : *Protein*	*GO* : *cellular_component* *GO* : *protein_complex*
Subclass: *BNO* 'owl : *subClassOf*' *GO*	*BNO* : *Interaction*	*GO* : *biological_process*

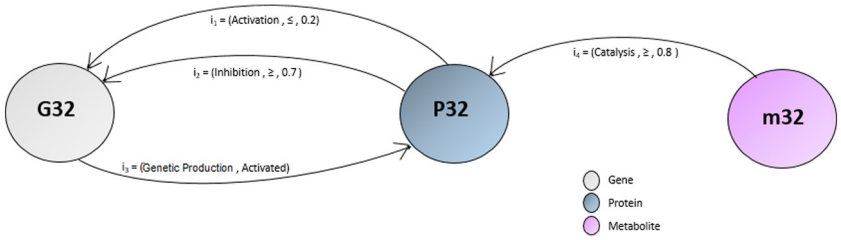

Fig. 6. Motivating example: the bacteriophage T4 gene 32.

4.2. Instantiation of the BNO ontology for the given example

Fig. 7 presents the instantiation of the BNO ontology for the given example of the bacteriophage T4 gene 32. The BNO ontology provides detailed and rigorous semantics to model this biomolecular network. As shown in Fig. 8 we use the Protégé editor to instantiate the BNO ontology for the bacteriophage T4 gene 32. Fig. 9 illustrates the nodes instantiations respectively, the gene *G*32, protein *p*32 and metabolite *m*32. The instantiations of the four reactions are detailed in Fig. 10.

4.3. SWRL rule-based reasoning

The Semantic Web Rule Language (SWRL) is a proposed language for the Semantic Web that can be used to express rules as well as logic, combining OWL DL or OWL Lite with a subset of the Rule Markup Language [9]. SWRL can be used to write rules to reason about OWL individuals and to infer new knowledge about those individuals. SWRL includes a high-level abstract syntax for Horn-like rules, and follows this syntax: *antecedent* $\rightarrow$ *consequent*. This form means that the consequent must be true when the antecedent is satisfied. In the SWRL rules, the symbol $\wedge$ means conjunction, ?*x* is a variable, $\rightarrow$ means implication. A symbol without the leading '?' denotes the name of an instance (an individual) in the ontology. These SWRL rules can provide additional expressiveness to OWL-based ontologies.

As presented in Fig. 11, Protégé provides the SWRLTab as a development environment for working with SWRL rules and creating SQWRL queries. In it, we can edit and execute SWRL rules for querying the BNO ontology in order to infer new knowledge. That way, a query in the BNO ontology with SWRL rules can be used to detect, for example, the transition states of each molecular components over the simulation time, to identify exactly the molecular components involved in a particular interaction, etc.

These results can be used by software applications through APIs, such as Jena Semantic Web Toolkit [52] and Apache Jena [53].

4.3.1. Inhibition SWRL rule

The following rule models the inhibition reaction. When the concentration of the protein *p*32 exceeds the threshold 0.7, it inhibits the genetic production of its gene *G*32.

Inhibition SWRL-rule

ADN(?g) $\wedge$ *hasState(?g, ?gs1)* $\wedge$ *forTime(?gs1, ?t)* $\wedge$ *hasState(?g, ?gs2)* $\wedge$ *forTime(?gs2, ?t2)* $\wedge$ *swrlb:add(?t2, ?t, 1)* $\wedge$ *Protein(?p)* $\wedge$ *Activation(?activ)* $\wedge$ *hasSource(?activ, ?p)* $\wedge$ *hasEnd(?activ, ?g)* $\wedge$ *hasState(?p, ?ps)* $\wedge$ *forTime(?ps, ?t)* $\wedge$ *hasConcentrationValue(?ps, ?c)* $\wedge$ *swrlb:greaterThanOrEqual(?c, 0.7)* $\rightarrow$ *isActivated(?gs2, false)*

As depicted in Fig. 12, the results of this rule mean that, *If there is a gene g having a state gs equal to false at a given time t and there is a protein p having a state ps*1 *and a concentration c at this time t, and these two molecules g and p are related by an Activation interaction, and if the concentration of p is under a threshold equal to 0.2, then the state of g move to true at time t* + 1.

4.3.2. Activation SWRL-rule

In contrast to the first rule, this rule models the activation reaction. When the concentration of the protein *p*32 becomes less than the threshold 0.2, it activates the genetic production of the Gene *G*32.

Activation SWRL-rule

ADN(?g) $\wedge$ *hasState(?g, ?gs1)* $\wedge$ *forTime(?gs1, ?t)* $\wedge$ *hasState(?g, ?gs2)* $\wedge$ *forTime(?gs2, ?t2)* $\wedge$ *swrlb:add(?t2, ?t, 1)* $\wedge$ *Protein(?p)* $\wedge$ *Activation(?activ)* $\wedge$ *hasSource(?activ, ?p)* $\wedge$ *hasEnd(?activ, ?g)* $\wedge$ *hasState(?p, ?ps)* $\wedge$ *forTime(?ps, ?t)* $\wedge$ *hasConcentrationValue(?ps, ?c)* $\wedge$ *swrlb:lessThanOrEqual(?c, 0.2)* $\rightarrow$ *isActivated(?gs2, true)*

As described in Fig. 13, the results of this rule mean that, *If there is a gene g having a state gs equal to true at a given time t and there is a protein p having a state ps*1 *and a concentration c at this time t, and these two molecules g and p are related by an Inhibition interaction, and if the concentration of p exceeds a threshold equal to 0.7, then the state of g move to false at time t* + 1.

4.3.3. Genetic production SWRL rule

The following rule represents the genetic production. In fact, if the gene *G*32 is activated, this one generates the protein synthesis and produces an increase in the concentration of this protein *p*32.

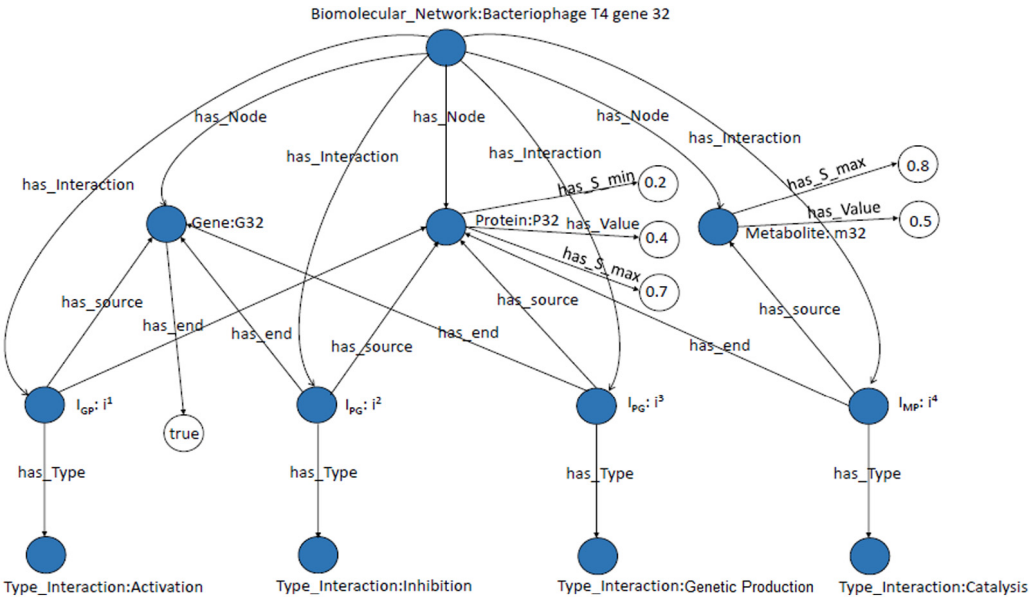

Fig. 7. An example of instantiation of the Biomolecular Network Ontology: the case of the bacteriophage T4 gene 32. The blue-filled nodes represent the individuals, and the edges represent the relationships among each couple of individuals.

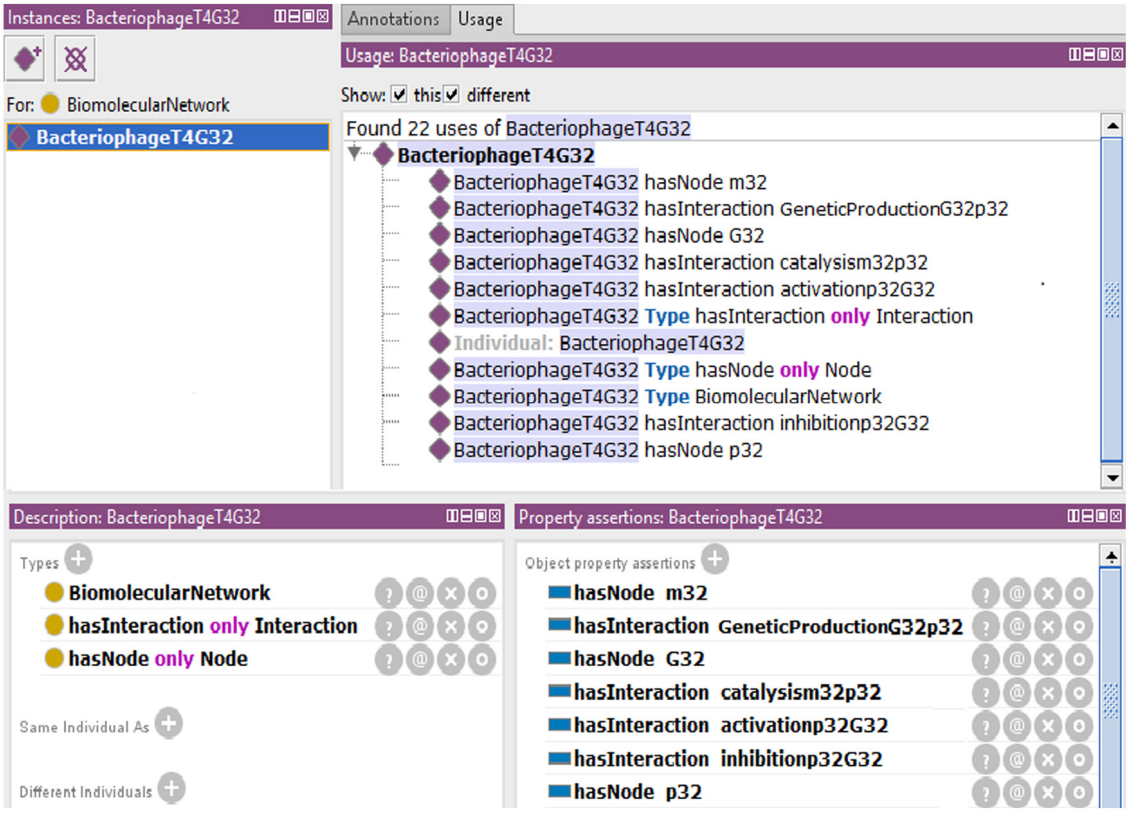

Fig. 8. A screenshot of the BNO ontology, as seen within the protégé program, displaying all the information associated with the given example.

Genetic production SWRL-rule

$$ADN(?g) \wedge hasState(?g, ?gs1) \wedge forTime(?gs1, ?t) \wedge isActivated(?gs1, false) \wedge Protein(?p) \wedge GeneticProduction(?genP) \wedge hasSource(?genP, ?g) \wedge hasEnd(?genP, ?p) \wedge hasState(?p, ?ps1) \wedge forTime(?ps1, ?t) \wedge hasConcentrationValue(?ps1, ?c1) \wedge hasState(?p, ?ps2) \wedge forTime(?ps2, ?t2) \wedge swrlb:add(?t2, ?t, 1) \rightarrow hasConcentrationValue(?ps2, ?c1)$$

The result of this rule is interpreted as, *If there is a gene g having a state gs equal to true at a given time t and there is a protein p having a state ps*1 *and a concentration c at this time t, and these two molecules g and p are related by a Genetic production interaction, then the concentration of the protein p increases at time* $t + 1$.

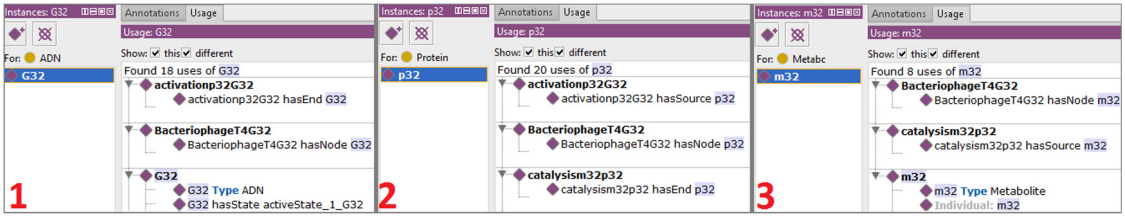

Fig. 9. A snapshot look at the BNO node instances associated with the given example displaying respectively: (1) the gene G32, (2) the protein p32 and (3) the metabolite m32.

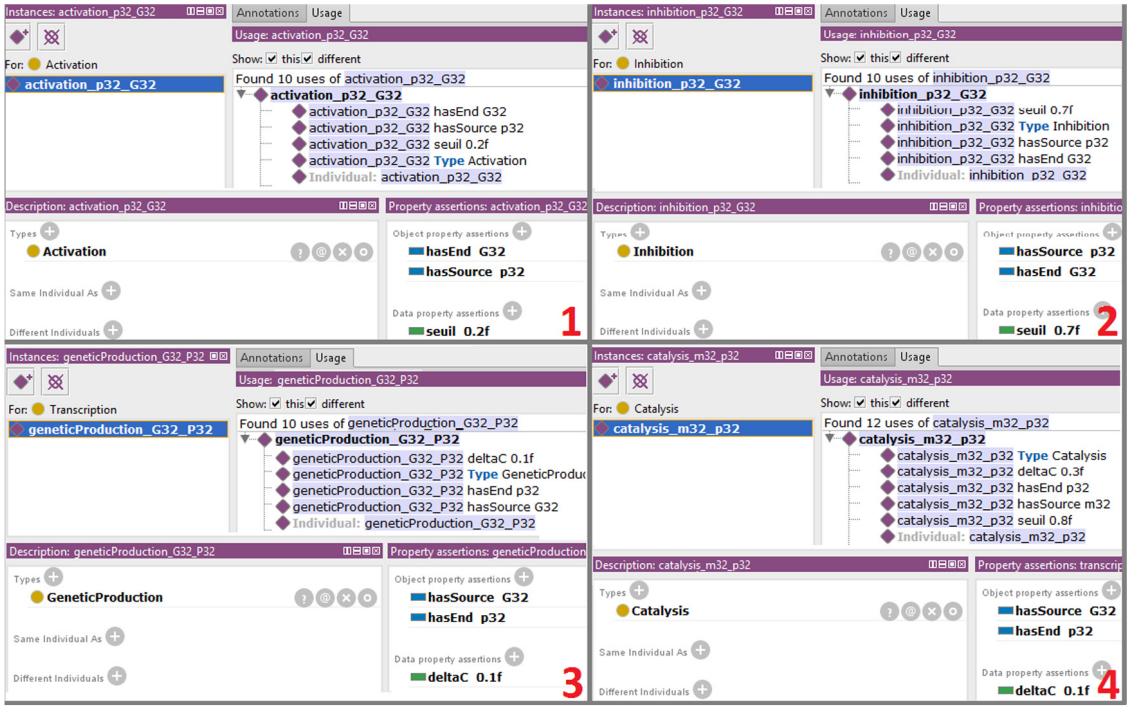

Fig. 10. A snapshot look at the BNO interaction instances associated with the given example displaying respectively: (1) Activation, (2) Inhibition, (3) Genetic production and (4) Catalysis.

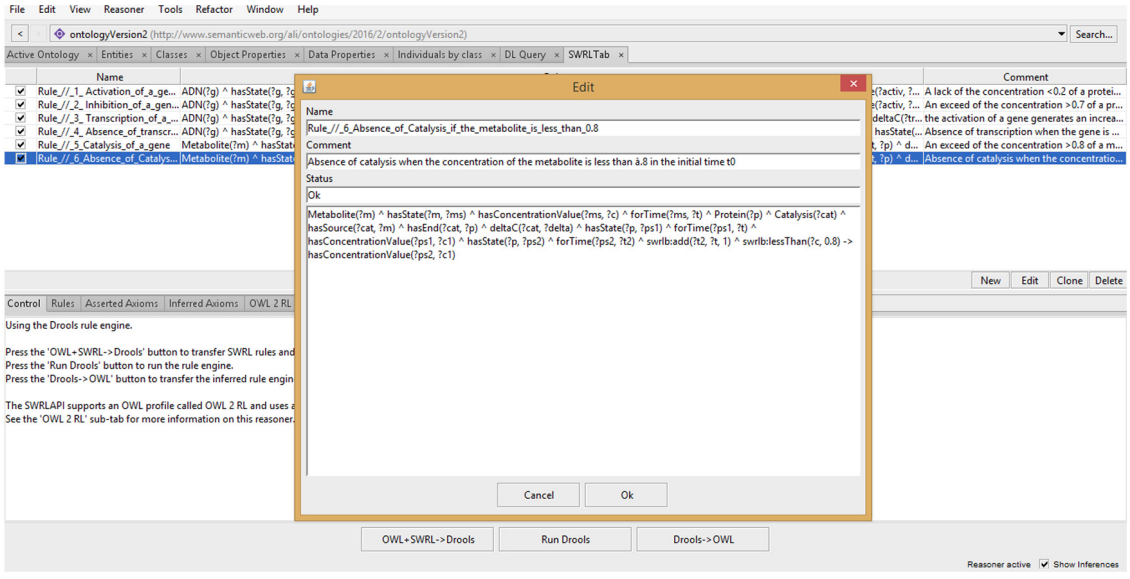

Fig. 11. The SWRL tab in the Protégé OWL Plugin.

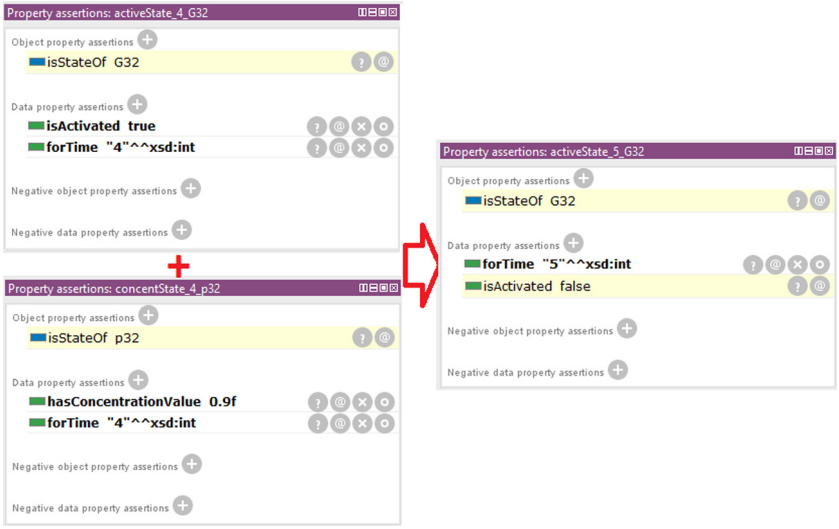

Fig. 12. Results of the reasoning process for the Inhibition SWRL rule.

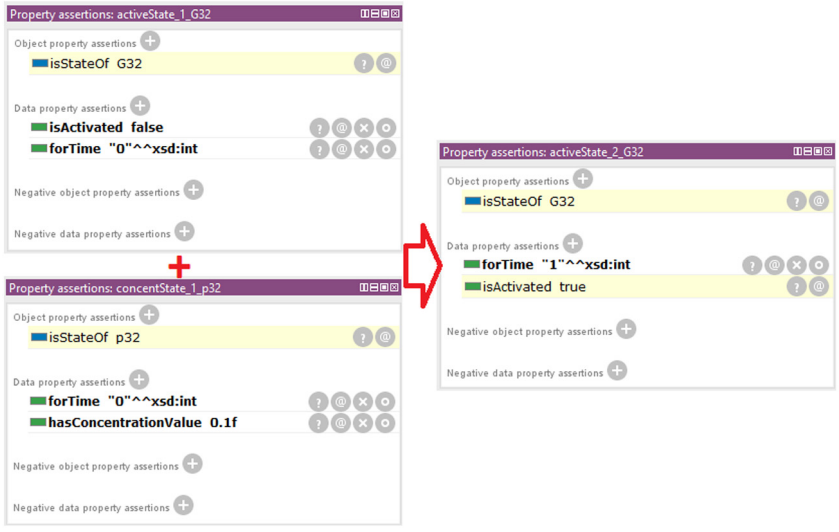

Fig. 13. Results of the reasoning process for the Activation SWRL rule.

In the opposite case, we have this rule:

Inverse of Genetic production SWRL-rule

$$ADN(?g) \wedge hasState(?g, ?gs1) \wedge forTime(?gs1, ?t) \wedge isActivated(?gs1, false) \wedge Protein(?p) \wedge GeneticProduction(?genP) \wedge hasSource(?genP, ?g) \wedge hasEnd(?genP, ?p) \wedge hasState(?p, ?ps1) \wedge forTime(?ps1, ?t) \wedge hasConcentrationValue(?ps1, ?c1) \wedge hasState(?p, ?ps2) \wedge forTime(?ps2, ?t2) \wedge swrlb:add(?t2, ?t, 1) \rightarrow hasConcentrationValue(?ps2, ?c1)$$

The result of this rule means: *If there is a gene g having a state gs equal to false at a given time t and there is a protein p having a state ps*1 *and a concentration c at this time t, and these two molecules g and p are related by a Genetic production interaction, then the concentration of the protein p remains stable at time* $t + 1$.

4.3.4. Catalysis SWRL rule

As well, following the increase of the concentration of the protein $p32$, a catalysis reaction resulted to create hormone balance. This reaction is ensured by the following rule:

Catalysis SWRL-rule

$$Metabolite(?m) \wedge hasState(?m, ?ms) \wedge hasConcentrationValue(?ms, ?c) \wedge forTime(?ms, ?t) \wedge Protein(?p) \wedge Catalysis(?cat) \wedge hasSource(?cat, ?m) \wedge hasEnd(?cat, ?p) \wedge deltaC(?cat, ?delta) \wedge hasState(?p, ?ps1) \wedge forTime(?ps1, ?t) \wedge hasConcentrationValue(?ps1, ?c1) \wedge hasState(?p, ?ps2) \wedge forTime(?ps2, ?t2) \wedge swrlb:add(?t2, ?t, 1) \wedge swrlb:greaterThanOrEqual(?c, 0.8) \wedge swrlb:subtract(?c2, ?c1, ?delta) \rightarrow hasConcentrationValue(?ps2, ?c2)$$

The meaning of this rule is: *If there is a metabolite m having a state ms associated to a concentration value c at a given time t and*

*there is a protein p having a state ps*1 *and a concentration c*1 *at this time t, and these two molecules g and p are related by a Catalysis interaction, and if the concentration of m exceeds a threshold equal to 0.8, then the concentration of the protein p decreases at time t* + 1.

In contrast, when the concentration of the metabolite *m*32 is less than 0.8 we applied the following rule:

Inverse of Catalysis SWRL-rule

Metabolite(?m) ∧ *hasState(?m, ?ms)* ∧ *hasConcentrationValue(?ms, ?c)* ∧ *forTime(?ms, ?t)* ∧ *Protein(?p)* ∧ *Catalysis(?cat)* ∧ *hasSource(?cat, ?m)* ∧ *hasEnd(?cat, ?p)* ∧ *deltaC(?cat, ?delta)* ∧ *hasState(?p, ?ps1)* ∧ *forTime(?ps1, ?t)* ∧ *hasConcentrationValue(?ps1, ?c1)* ∧ *hasState(?p, ?ps2)* ∧ *forTime(?ps2, ?t2)* ∧ *swrlb:add(?t2, ?t, 1)* ∧ *swrlb:lessThan(?c, 0.8)* → *hasConcentrationValue(?ps2, ?c1)*

Which means: *If there is a metabolite m having a state ms associated to a concentration value c at a given time t and there is a protein p having a state ps*1 *and a concentration c*1 *at this time t, and these two molecules g and p are related by a Catalysis interaction, and if the concentration of m is under a threshold equal to 0.8, then the concentration of the protein p remains stable at time t* + 1.

5. Ontology validation

Ontology validation is a very important issue to check the ontology quality. A large group of ontology validation approaches exists, among those, data-driven validation, task-based approach, automated consistency checking, etc. [54]. Table 5 provides an overview of the best-known ontology validation approaches and their limits. However, according to the current literature [55], there is no agreement on a methodology for validation of ontologies. The choice of a suitable approach depends on the purpose of validation, the application in which the ontology is to be used, and on what aspect of the ontology we are trying to validate and evaluate [56]. For all these reasons, we have chosen to evaluate the BNO ontology by following different validation approaches. This choice of hybrid approaches inherits many of the advantages of each of these approaches. The goal is to evaluate our ontology in a different manner. Based on the methods presented in Table 5, we adopted a combination of automated consistency checking, expert knowledge validation, criteria-based validation, and task-based validation for evaluating the BNO ontology.

5.1. Automated consistency checking

The verification of the logical axioms is an essential task in ontology validation. Indeed, this validation ensures that the logical axioms are consistent. This satisfaction consists in (i) checking the encoding of the specification, (ii) detecting errors such as malformed classes, redundant axioms, etc., and (iii) confirming that the BNO ontology has been built according to certain specified ontology quality criteria. By definition, consistency checking ensures that an ontology does not include any contradictory facts. For definitions to be semantically consistent, they must be able to obtain consistent conclusions using the meaning of all definitions and axioms [63,64].

To evaluate the BNO ontology and check the inconsistencies and violations of its SWRL rules, we used the latest version of the Description Logic reasoner HermiT reasoning plugin in the Protégé 5 environment[11] version 1.3.8.3. HermiT cannot only determine whether or not the ontology is consistent but also identify subsumption relationships between classes and resolution of the error. In terms of the time, HermiT is one of the fastest DL reasoners in classifying ontologies [65]. Using its HermiT reasoner plugin, Protégé automatically checked the inferred classes and relations and for hierarchies, domains, ranges, and conflicting disjoint assertions. Contradictory facts and inconsistent classes are marked with red. During the development of the BNO ontology, the automated consistency checking process was iterative. Indeed, the BNO ontology was developed incrementally by adding new definitions and modifying old ones. Moreover, the HermiT reasoner was used to check the correctness of the SWRL rules edited in the SWRLTab (as shown in Fig. 11). Their consistency was verified by the results of our experiments as shown in Figs. 12 and 13.

5.2. Expert knowledge validation

Even if we have used best-known validation methods to test the consistency of an ontology, the intervention of domain experts is always necessary, especially if a quality level of the ontology is expected. The validation here focuses on the semantics of the BNO ontology content and not on its formalization. As a consequence, we proposed a method based on questions expressed in natural language and generated from the BNO ontology in order to test and, if necessary, to correct the content of the ontology using the answers that will be provided by the expert biologists. This questions and answers method facilitates the task of experts. We obtained the assistance and expertise of our collaborators from the Complex Systems and Translational Bioinformatics (CSTB) team[12] who have evaluated the BNO ontology and concluded that it is in accordance with their knowledge in the domain (expert knowledge).

The validation process takes place during discussions with the biology experts, where the experts submit a series of questions (in natural language) with their answers, that the ontology should answer correctly. Table 6 contains examples of questions that we have defined in terms of ontology elements and their translation into OWL queries. Afterwards, these queries are checked by the OWL reasoner and results are compared with expected answers as defined by the experts.

This question answering technique provides a simple means to verify experts requirements' satisfiability either by the identification of the ontology core elements through class assertion knowledge or entailment through their axioms.

For that reason, the questions focusing on the description of the assertional and terminological axioms (i.e. class expression subsumption, instance checking, property hierarchy, etc.) are completed with questions corresponding with more general constraints. Among these constraints, we distinguish two kinds of questions:

- Affirmative constraints: e.g. "*If in a biomolecular network all interactions are of the metabolite interaction type, is this network a Metabolic Network?*". The answer provided by the biologist experts is '*YES*', and the reasoner should confirm the correctness of the following axiom: "**BiomolecularNetwork and (hasInteraction only MetaboliteMetaboliteInteraction) and (hasNode only Metabolite) subclassOf hasInteraction only MetaboliteMetaboliteInteraction**".
- Negative constraints: e.g. "*The metabolite m*32 *can belong to a genetic network*". The answer here is NO. The reasoner should not confirm the correctness of the axiom "**BiomolecularNetwork and (hasNode(oneOf m32)) SubClassOf GenomicNetwork**", but it should rather validate the correctness of it negation: "**GenomicNetwork SubClassOf not(BiomolecularNetwork and(hasNode(oneOf m32)))**".

11 http://www.hermit-reasoner.com/.

12 http://icube-cstb.unistra.fr/en/index.php/Home.

Table 5
A summary of ontology validation approaches.

Validation methods	Description	Limitations
Task-based approach	This approach evaluates an ontology by using it in tasks and assessing the performance. It is an effective approach to assess the capability of an ontology to achieve its purposes and objectives. It is a good method to evaluate the capacity an ontology to achieve its objectives [57].	This method do not evaluate the structure of an ontology and ignore deficits in its conceptualization.
Automated consistency checking	This approach evaluates the consistency of an ontology by using Description Logic reasoner [58]. Most popular DL reasoners are: Hermit, Pellet, Fact++, fuzzyDL, etc.	This method checks the internal consistency of an ontology (the content does not contain contradictory information) and ignore its background knowledge.
Gold standard checking	This approach compares an ontology to a gold standard ontology (a benchmark ontology) and measures their conceptual and lexical similarities [59].	There may be errors in the methods of comparisons and a lack of ontology in the domain of study.
Criteria-based validation	This approach evaluates an ontology by using a set of predefined criteria, such as clarity, consistency, accuracy, computational efficiency, conciseness, completeness, correctness, etc. [60].	Some criteria lack quantitative measures and are frequently rely on expert judgement.
Data driven validation	This approach compares an ontology with a source of data about the domain that is to be covered by the ontology [61].	This approach cannot evaluate the correctness and the clarity of an ontology.
Expert knowledge validation	This approach evaluates an ontology by using expert knowledge who try to assess how well the ontology meets a set of predefined criteria, standards, requirements, etc. [62].	This approach lack quantitative measures.

Moreover, we study the correlation between the number of questions generated (in terms of the number of ontological elements to be evaluated) and the size of the BNO ontology. Table 7 presents the number of questions generated according to the size of the ontologies in terms of concepts, relations, and individuals. The number of questions highlights the role and the intervention of the expert biologists and their knowledge to reduce the potential errors linked to the semantics of the content of the ontology.

The notion of validity in this method depends on the domain expert answering the generated Boolean questions. By broadening the range of questions where the ontology answers are in agreement with the experts' expectations, our confidence in the adequacy between the ontology and the domain semantics increases. Nevertheless, there can be no assurance of perfect correspondence: as for all scientific modelling, it is assumed to be valid if it corresponds to the expert observations and until proven otherwise.

5.3. Criteria-based validation

In this section, we evaluate the BNO ontology against diverse quality criteria described by Vrandecic in [60], which are presented as part of a common framework for ontology validation.

Accuracy: The definitions and descriptions in the ontology agree with the expert's knowledge about the field. The information regarding the concepts of the BNO ontology was developed from the well-known Gene ontology (GO). Moreover, we obtained the assistance and expertise of our collaborators from the LBGI (Bioinformatics and Integrating Genomics) team who have evaluated the BNO ontology and conclude that it is satisfactory. We have also used the OntOlogy Pitfall Scanner[13] tool to check for logical correctness of the *BNO* ontology and diagnostics of ontology-design errors. Analysis results have provided great evidence of the correctness of BNO.

Adaptability: We have opted for developing the BNO ontology as part of a global semantic architecture composed of four ontologies that are related to each other: the Gene Ontology (GO), the Simple Event Model Ontology (SEMO), the Time Ontology (TO) and our development, the BNO ontology. This architecture aims at aligning and merging the BNO ontology with the rest of ontologies through equivalence *owl:equivalenceClass* or subclass *owl:subclassOf* relations. These relations among ontologies are detailed in our previous work [5]. This choice enhances extensibility and reusability. It also makes the BNO ontology easily adaptable to dynamical contexts.

Clarity: In developing the BNO ontology, we have been careful to assign clear unambiguous descriptions to define and categorize concepts and the relationships among concepts within our particular knowledge domain. This clarity is ensured by the use of the *rdfs:comment* that provides the obviously needed capability to annotate an ontology. In this manner, the BNO ontology communicates effectively the intended meaning of its terms.

Completeness: This criterion measures whether the ontology can answer all the questions that it should be able to answer. It provides an estimation of how the BNO ontology represents the domain of the complex biomolecular networks and their transittability. These questions were specified by the expert biologists of the LBGI team and it has been verified that all of them can be answered.

Computational efficiency: An ontology can be analysed by an inference system. In our case, the BNO ontology was treated by the two reasoning mechanisms detailed in the previous section. We concluded that the reasoning on the BNO ontology is consistent and allows inferences in a reasonable time [66]. Moreover, the complexity of this operation is adequate.

Conciseness: The terms of the BNO ontology were checked with the help of expert biologists, we assume that the ontology does not contain any redundant terms.

Consistency: This criterion ensures that the logical axioms are satisfiable and consistent. The satisfaction of the logical axioms is recognized when it is possible to find a situation under which all the axioms are true, and their consistency when it is impossible to find a contradiction within the axioms. As detailed in the previous section, reasoning in the BNO ontology was performed using two reasoning mechanisms. Firstly, via an SWRL rule-based system using the latest version of HermiT reasoning plugin in the Protégé environment version 1.3.8.3. And secondly, through a reasoning which is written in MATLAB/SIMULINK development environment. No inconsistencies or violations were found.

5.4. Validation results

As discussed in Section 5, there is no single best approach to evaluate an ontology. For this reason, we check the BNO ontology with different approaches. Firstly, we focus in particular on automated ontology validation, which is a necessary precondition for the healthy development of an ontology. Automated consistency checking was made through the Hermit reasoner. Based on

[13] http://oops.linkeddata.es/advanced.jsp.

Table 6
An excerpt of ontological Boolean questions and their translation into OWL queries.

Questions made by domain experts	Experts answer	Examples of its corresponding OWL queries	Ontology statements
Is the 'P04040 (CATA_HUMAN)' a type of 'Protein'?	Yes		Sub-sumption
Is the 'G32' a type of 'Gene'?	Yes	Is CLASS a type of CLASS ?	
Is the 'the bacteriophage T4 G32' an example of 'Biomolecular_Network'?	Yes	Is INSTANCE an example of CLASS ?	Type checking
Is the 'G32' a type of 'Gene'?	Yes		
Is the 'Catalysis' a type of 'Interaction'?	Yes	Is SUB-PROPERTY a type of PROPERTY ?	Properties hierarchy
If in a 'Biomolecular_Network' all interactions are of the 'I_{MM}' type and all nodes are of 'Metabolite' type, is this network an 'Metabolic_network'?	Yes	Is BiomolecularNetwork and (hasInteraction only MetaboliteMetaboliteInteraction) and (hasNode only Metabolite) SubClassOf hasInteraction only MetaboliteMetaboliteInteraction"?	General constraints
The 'm32 'molecule can belong to the 'Genomic_Network'?	No	Is GenomicNetwork and (hasNode (oneOf m32))?	Specific constraints

Table 7
Number of questions generated according to the size of the BNO ontology.

Classes	Properties	Individuals	Total	Questions generated
29	20	29	78	75

the feedback of the reasoner, inconsistencies have been corrected along the development process of the BNO ontology in an iterative way. The final results made by the reasoner were statistically significant and revealed that there are no inconsistencies in the BNO ontology. The BNO ontology has been also evaluated with different criteria in terms of accuracy, adaptability, clarity, completeness, etc. For each criterion, the BNO ontology is evaluated. The combination of these criteria allows us to check the BNO ontology from different levels. The final results of the criteria-based validation indicated that the BNO ontology was clear, extendable, and complete. Moreover, we evaluate the usefulness of the BNO ontology through the expert knowledge validation. The BNO ontology was used to model a set of case studies, among them the Bacteriophage T4 G32 case presented in this study. Results proved that the BNO ontology is capable to deduce the main concepts of the case studies and their properties and is capable to infer new knowledge such as to compute the next state of molecular components. These results proved that the BNO ontology is able to describe and model the transittability of a biomolecular network. However, it is important to note that the BNO ontology cannot model the transittability of large-scale networks, and more efficient simulation tools should be used to study larger networks.

6. Discussion

This section states the main strengths and weaknesses of our approach and how to overcome them.

The "case study" presented in this paper represents a "proof of concept" since it demonstrates the logical consistency of the approach and validates the relevance of the BNO ontology. Moreover, we developed a Matlab tool, a qualitative simulator, available on https://github.com/AliAyadi/QualitativeReasoningInMATLAB to check and compare the results in the paper with the results obtained using a qualitative tool. Results demonstrate how the proposed semantic approach provides a powerful formalism for modelling and representing complex biomolecular networks.

Indeed, we have seen that our approach is able to:

- enrich and infer new knowledge,
- detect more properties and relationships among the molecular components,
- provide useful inferring knowledge and rich semantics allowing biologists to model the dynamical behaviour of complex biomolecular networks.

However, while the BNO ontology provides a rich modelling of complex biomolecular networks and their transittability, its usability comes with certain limitations. In particular when the size and the complexity of the biomolecular networks increase.

The BNO ontology is extremely powerful as a way of modelling the static properties of complex biomolecular networks and infer new knowledge for describing them, but relatively powerless for simulating their dynamic behaviours and understanding molecular interaction cascades that drive specific responses to external stimuli or environmental changes.

In our works, we have tested the BNO ontology with different case studies by gradually increasing the complexity and the size of the biomolecular networks. We first tested the proposed ontology on a small real network example, the autoregulation of the bacteriophage T4 gene 32 (presented in this paper), which although small, contains all the elements needed to understand the evolution of biomolecular networks. Afterward, we applied the BNO ontology to two different case studies: the phage lambda and the p53 signalling networks. Experiments demonstrated that current OWL reasoners are able to deal with fairly simple biomolecular networks (e.g. the bacteriophage T4 gene 32) but are unable to simulate more complex biomolecular networks (e.g. the phage lambda and the p53 signalling networks that contains about 17 nodes and 40 interactions) at all. We noticed that existing OWL reasoners cannot simulate the behaviour of these networks due to their complexity and large size. Indeed, these reasoners are only able to classify large, expressive ontologies with a small number of SWRL rules, but they often provide limited support in dealing with a large number of rules and a large number of individuals. To the best of our knowledge, there are no mature reasoners available, that particularly address the tradeoff between expressiveness on the one hand and scalability on the other hand.

Therefore, we believe that such reasoners have not the capacity to reason on large-scale networks and more efficient simulation tools should be used to simulate larger biomolecular networks. To handle this limit, we develop an efficient simulation tool, entitled "the CBNSimulator" for scaling up and reason on large biomolecular networks [67]. The proposed simulator has been integrated into a platform with the BNO ontology and has been tested on both the phage lambda and the p53 signalling networks. Experiments demonstrate that the CBNSimulator combines qualitative and quantitative techniques to simulate and reason on large-scale biomolecular networks.

To conclude, two points must be considered: (i) The concepts defined by the BNO ontology allow to describe biomolecular networks of any size (small or large). (ii) The current inference engines

are not sufficiently fast to reason about all the set of SWRL rules associated with a large scale network. The scalability is only possible by defining specific simulators.

7. Conclusion

The Biomolecular Network Ontology developed in this paper aims to describe the domain knowledge of complex biomolecular networks in their static state. This ontology provides information on the biomolecular network and its components (nodes, interactions, states, transition states, etc.) and an indication of the network's context such as the type of sub-network, the type of node, the conditions and nature of interactions, etc. This allows to precisely analyse and interpret the semantic context in order to achieve intelligent modelling of biomolecular networks and their state changes. These state changes can be computed with a rule-based system.

Moreover, the BNO ontology was evaluated based on automated consistency checking, expert knowledge validation, and criteria-based validation. Results are encouraging and indicated that the BNO is consistent, credible and effective in describing relevant knowledge required in understanding the behaviour of complex biomolecular networks and their state changes. Nevertheless, more efficient simulation tools should be used for simulation of larger biomolecular networks.

Future efforts can be made to integrate the proposed ontology with a discrete event simulator tool able to reproduce the behaviour of large-scale complex biomolecular networks and their components over time. The basic idea is to develop a platform that provides an optimal set of stimuli to be applied during a predetermined time interval to simulate the state changes of complex biomolecular networks using essentially semantic knowledge.

Disclaimer

This research has not received any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

[1] F.-X. Wu, L. Wu, J. Wang, J. Liu, L. Chen, Transittability of complex networks and its applications to regulatory biomolecular networks, Sci. Rep. 4 (2014) http://dx.doi.org/10.1038/srep04819.

[2] W.A. Kibbe, C. Arze, V. Felix, E. Mitraka, E. Bolton, G. Fu, C.J. Mungall, J.X. Binder, J. Malone, D. Vasant, et al., Disease ontology 2015 update: an expanded and updated database of human diseases for linking biomedical knowledge through disease data, Nucleic Acids Res. 43 (D1) (2014) D1071–D1078, http://dx.doi.org/10.1093/nar/gku1011.

[3] G. Karp, Biologie Cellulaire et Moléculaire: Concepts and Experiments, De Boeck Supérieur, 2010.

[4] F. Wu, L. Chen, J. Wang, R. Alhajj, Biomolecular networks and human diseases, BioMed Res. Intl. 2014 (2014) http://dx.doi.org/10.1155/2014/363717.

[5] A. Ayadi, C. Zanni-Merk, F.d.B. de Beuvron, S. Krichen, Logical and semantic modeling of complex biomolecular networks, Proc. Comput. Sci. 96 (2016) 475–484, http://dx.doi.org/10.1016/j.procs.2016.08.108.

[6] J. Heflin, et al., An Introduction to the OWL Web Ontology Language, Lehigh University. National Science Foundation (NSF), 2007, doi: 10.1.1.120.5135.

[7] M. Uschold, M. Gruninger, Ontologies: Principles, methods and applications, Knowl. Eng. Rev. 11 (2) (1996) 93–136, doi: 10.1.1.111.5903.

[8] F.T. Fonseca, M.J. Egenhofer, C. Davis, K.A. Borges, Ontologies and knowledge sharing in urban GIS, Comput. Environ. Urban Syst. 24 (3) (2000) 251–272, http://dx.doi.org/10.1016/S0198-9715(00)00004-1.

[9] D.L. McGuinness, F. Van Harmelen, et al., OWL web ontology language overview, W3C Recommend. 10 (10) (2004) 2004, doi: citeulike:100176.

[10] A. Gomez-Perez, M. Fernández-López, O. Corcho, Ontological Engineering: With Examples from the Areas of Knowledge Management, e-Commerce and the Semantic Web, Springer Science & Business Media, 2006, http://dx.doi.org/10.1007/b97353.

[11] G. Falquet, C. Métral, J. Teller, C. Tweed, Ontologies in Urban Development Projects, Springer Science & Business Media, 2011, http://dx.doi.org/10.1007/978-0-85729-724-2.

[12] M. Grüninger, M.S. Fox, The role of competency questions in enterprise engineering, in: Benchmarking–Theory and Practice, Springer, 1995, pp. 22–31, http://dx.doi.org/10.1007/978-0-387-34847-6_3.

[13] B. Swartout, R. Patil, K. Knight, T. Russ, Toward distributed use of large-scale ontologies, in: Proc. of the Tenth Workshop on Knowledge Acquisition for Knowledge-Based Systems, 1996, pp. 138–148.

[14] H. Pinto, S. Staab, C. Tempich, Diligent: towards a fine-grained methodology for distributed, loosely-controlled and evolving engineering of ontologies, in: Proceedings of the 16th European Conference on Artificial Intelligence, IOS Press, 2004, pp. 393–397, doi: 10.1.1.5.8078.

[15] A. Bernaras, I. Laresgoiti, J. Corera, Building and reusing ontologies for electrical network applications', in: ECAI, PITMAN, 1996, pp. 298–302.

[16] B.M. Good, E.M. Tranfield, P.C. Tan, M. Shehata, G.K. Singhera, J. Gosselink, E.B. Okon, M.D. Wilkinson, Fast, cheap and out of control: a zero curation model for ontology development, in: Pacific Symposium on Biocomputing, Hawaii, USA, vol. 11, 2006, pp. 128–139, http://dx.doi.org/17094234.

[17] A.G. Castro, P. Rocca-Serra, R. Stevens, C. Taylor, K. Nashar, M.A. Ragan, S.-A. Sansone, The use of concept maps during knowledge elicitation in ontology development processes–the nutrigenomics use case, BMC Bioinform. 7 (1) (2006) 267, http://dx.doi.org/10.1186/1471-2105-7-267.

[18] M. Fernández-López, A. Gómez-Pérez, N. Juristo, Methontology: From Ontological Art Towards Ontological Engineering, American Association for Artificial Intelligence, 1997.

[19] N.F. Noy, M. Crubézy, R.W. Fergerson, H. Knublauch, S.W. Tu, J. Vendetti, M.A. Musen, et al., Protege-2000: an open-source ontology-development and knowledge-acquisition environment, in: AMIA Annu Symp Proc., vol. 953, 2003, pp. 953, http://dx.doi.org/PMC1480139.

[20] Y. Sure, M. Erdmann, J. Angele, S. Staab, R. Studer, D. Wenke, OntoEdit: Collaborative ontology development for the semantic web, in: The Semantic Web–ISWC 2002, Springer, 2002, pp. 221–235, http://dx.doi.org/10.1007/3-540-48005-6_18.

[21] A. Kalyanpur, B. Parsia, E. Sirin, B.C. Grau, J. Hendler, Swoop: a web ontology editing browser, Web Semantics 4 (2) (2006) 144–153, http://dx.doi.org/10.1016/j.websem.2005.10.001.

[22] J. Cardoso, Semantic Web Services: Theory, Tools and Applications: Theory, Tools and Applications, IGI Global, 2007, http://dx.doi.org/10.4018/978-1-59904-045-5.

[23] S. Bechhofer, I. Horrocks, C. Goble, R. Stevens, OilEd: a reason-able ontology editor for the semantic web, KI 2001: Adv. Artif. Intell. (2001) 396–408, http://dx.doi.org/10.1007/3-540-45422-5_28.

[24] C. Messaoudi, R. Fissoune, H. Badir, A survey of semantic integration approaches in bioinformatics, World Acad. Sci. Eng. Technol. Intl. J. Comput. Electr. Autom. Control Inform. Eng. 10 (12) (2016) 2001–2006, http://dx.doi.org/10.1999/1307-6892/60697.

[25] D.L. Rubin, S.E. Lewis, C.J. Mungall, S. Misra, M. Westerfield, M. Ashburner, I. Sim, C.G. Chute, M.-A. Storey, B. Smith, et al., National center for biomedical ontology: advancing biomedicine through structured organization of scientific knowledge, Omics 10 (2) (2006) 185–198, doi: 10(2):185-98.

[26] R.W. Fergerson, P.R. Alexander, M. Dorf, R.S. Gonçalves, M. Salvadores, A. Skrenchuk, J. Vendetti, M.A. Musen, NCBO BioPortal Version 4, 2015.

[27] J. Hancock, Editorial: Biological ontologies and semantic biology, in: Frontiers in Genetics, vol. 5, 2014, p. 18, doi: 10.3389%2Ffgene.2014.00018.

[28] M. d'Aquin, N.F. Noy, Where to publish and find ontologies? A survey of ontology libraries, Web Semantics 11 (Supplement C) (2012) 96–111, http://dx.doi.org/10.1016/j.websem.2011.08.005.

[29] J. Bard, S.Y. Rhee, M. Ashburner, An ontology for cell types, Genome Biol. 6 (2) (2005) R21.

[30] S. Seltmann, H. Stachelscheid, A. Damaschun, L. Jansen, F. Lekschas, J.-F. Fontaine, T.N. Nguyen-Dobinsky, U. Leser, A. Kurtz, CELDA — an ontology for the comprehensive representation of cells in complex systems, BMC Bioinf. 14 (1) (2013) 228, http://dx.doi.org/10.1186/1471-2105-14-228.

[31] M.A. Harris, J.I. Deegan, J. Lomax, M. Ashburner, S. Tweedie, S. Carbon, S. Lewis, C. Mungall, J. Day-Richter, K. Eilbeck, et al., The gene ontology project in 2008, Nucleic Acids Res. 36 (2008) D440–D444, http://dx.doi.org/10.1093/nar/gkm883.

[32] P. Khatri, S. Drăghici, Ontological analysis of gene expression data: current tools, limitations, and open problems, Bioinformatics 21 (18) (2005) 3587–3595.

[33] T. Miksa, A. Rauber, Using ontologies for verification and validation of workflow-based experiments, Web Semantics 43 (Supplement C) (2017) 25–45, http://dx.doi.org/10.1016/j.websem.2017.01.002.

[34] K. Belhajjame, J. Zhao, D. Garijo, M. Gamble, K. Hettne, R. Palma, E. Mina, O. Corcho, J.M. Gómez-Pérez, S. Bechhofer, G. Klyne, C. Goble, Using a suite of ontologies for preserving workflow-centric research objects, Web Semantics 32 (Supplement C) (2015) 16–42, http://dx.doi.org/10.1016/j.websem.2015.01.003.

[35] E. Beisswanger, V. Lee, J.-J. Kim, D. Rebholz-Schuhmann, A. Splendiani, O. Dameron, S. Schulz, U. Hahn, et al., Gene Regulation Ontology (GRO): design principles and use cases, in: MIE, 2008, pp. 9–14.

[36] J. Bard, S.Y. Rhee, M. Ashburner, An ontology for cell types, Genome Biol. 6 (2) (2005) R21, doi: 10.1186%2Fgb-2005-6-2-r21.

[37] D.A. Natale, C.N. Arighi, W.C. Barker, J.A. Blake, C.J. Bult, M. Caudy, H.J. Drabkin, P. D'Eustachio, A.V. Evsikov, H. Huang, et al., The Protein Ontology: a structured representation of protein forms and complexes, Nucleic Acids Res. 39 (suppl_1) (2010) D539–D545, http://dx.doi.org/10.1093/nar/gkq907.
[38] N. Juty, N. le Novère, Systems biology ontology, Encyclopedia Syst. Biol. (2013) 2063–2063.
[39] B. Smith, J. Williams, S. Schulze-Kremer, The ontology of the gene ontology, in: AMIA, vol. 3, 2003, pp. 609–613.
[40] W.R. Van Hage, V. Malaisé, R. Segers, L. Hollink, G. Schreiber, Design and use of the Simple Event Model (SEM), Web Semantics 9 (2) (2011) 128–136.
[41] J.R. Hobbs, F. Pan, Time ontology in OWL, W3C Working Draft 27 (2006) 133.
[42] J.P. Sluka, A. Shirinifard, M. Swat, A. Cosmanescu, R.W. Heiland, J.A. Glazier, The cell behavior ontology: describing the intrinsic biological behaviors of real and model cells seen as active agents, Bioinformatics (2014) btu210, http://dx.doi.org/10.1093/bioinformatics/btu210.
[43] V. Fortineau, T. Paviot, L. Louis-Sidney, S. Lamouri, Swrl as a rule language for ontology-based models in power plant design, in: L. Rivest, A. Bouras, B. Louhichi (Eds.), Product Lifecycle Management. Towards Knowledge-Rich Enterprises: IFIP WG 5.1 International Conference, PLM 2012, Montreal, QC, Canada, July 9-11, 2012, Revised Selected Papers, Springer Berlin Heidelberg, Berlin, Heidelberg, 2012, pp. 588–597, http://dx.doi.org/10.1007/978-3-642-35758-9_53.
[44] H. Knublauch, R.W. Fergerson, N.F. Noy, M.A. Musen, The Protégé OWL plugin: An open development environment for semantic web applications, in: International Semantic Web Conference, vol. 3298, Springer, 2004, pp. 229–243, http://dx.doi.org/10.1007/978-3-540-30475-3_17.
[45] S.V. Landeghem, T.V. Parys, M. Dubois, D. Inzé, Y.V. de Peer, Diffany: an ontology-driven framework to infer, visualise and analyse differential molecular networks, BMC Bioinformatics 17 (1) (2016) 1–12, http://dx.doi.org/10.1186/s12859-015-0863-y.
[46] A. Ayadi, C. Zanni-Merk, F. ois de Bertrand de Beuvron, S. Krichen, Logical and semantic modeling of complex biomolecular networks, in: Knowledge-Based and Intelligent Information & Engineering Systems: Proceedings of the 20th International Conference KES-2016, Proc. Comput. Sci. 96 (2016) 475–484, http://dx.doi.org/10.1016/j.procs.2016.08.108.
[47] E. Martinez, C.-M. Chiang, H. Ge, R. Roeder, TATA-binding protein-associated factor (s) in TFIID function through the initiator to direct basal transcription from a TATA-less class II promoter, EMBO J. 13 (13) (1994) 3115–3126.
[48] M.K. Dougherty, J. Müller, D.A. Ritt, M. Zhou, X.Z. Zhou, T.D. Copeland, T.P. Conrads, T.D. Veenstra, K.P. Lu, D.K. Morrison, Regulation of Raf-1 by direct feedback phosphorylation, Molecular Cell 17 (2) (2005) 215–224.
[49] M. Ashburner, C.A. Ball, J.A. Blake, D. Botstein, H. Butler, J.M. Cherry, A.P. Davis, K. Dolinski, S.S. Dwight, J.T. Eppig, et al., Gene ontology: tool for the unification of biology, Nature Genet. 25 (1) (2000) 25–29, http://dx.doi.org/10.1038/75556.
[50] J. Duncan, K. Eilbeck, S.P. Narus, S. Clyde, S. Thornton, C. Staes, Building an ontology for identity resolution in healthcare and public health, Online J. Public Health Inform. 7 (2) (2015) http://dx.doi.org/10.5210/ojphi.v7i2.6010.
[51] B. Lewin, C. Sanlaville, Gènes VI, De Boeck Supérieur, 1998, https://books.google.fr/books?id=otAEqpJxInYC.
[52] S. Harris, A. Seaborne, E. Prud'hommeaux, SPARQL 1.1 query language, W3C Recommend. 21 (10) (2013).
[53] B. McBride, D. Boothby, C. Dollin, An introduction to RDF and the Jena RDF API, Retrieved August 1 (2004) 2007.
[54] J. Brank, et al., Gold standard based ontology evaluation using instance assignment, in: Proc. of the EON 2006 Workshop, 2006, http://dx.doi.org/10.1.1.71.3681.
[55] F. Neuhaus, A. Vizedom, K. Baclawski, M. Bennett, M. Dean, M. Denny, M. Grüninger, A. Hashemi, T. Longstreth, L. Obrst, et al., Towards ontology evaluation across the life cycle, Appl. Ontol. 8 (3) (2013) 179–194.
[56] A.I. Walisadeera, A. Ginige, G.N. Wikramanayake, Ontology evaluation approaches: a case study from agriculture domain, in: International Conference on Computational Science and Its Applications, Springer International Publishing, 2016, pp. 318–333, http://dx.doi.org/10.1007/978-3-319-42089-9_23.
[57] R. Porzel, R. Malaka, A task-based approach for ontology evaluation, in: ECAI Workshop on Ontology Learning and Population, Valencia, Spain, 2004, pp. 1–6, http://dx.doi.org/10.1186/2041-1480-4-S1-S4.
[58] A.-Y. Turhan, Description logic reasoning for semantic web ontologies, in: Proceedings of the International Conference on Web Intelligence, Mining and Semantics, in: WIMS '11, ACM, New York, NY, USA, 2011, pp. 6:1–6:5, http://dx.doi.org/10.1145/1988688.1988696.
[59] A. Maedche, S. Staab, in: A. Gómez-Pérez, V.R. Benjamins (Eds.), Measuring Similarity between Ontologies, Springer Berlin Heidelberg, Berlin, Heidelberg, 2002, pp. 251–263, http://dx.doi.org/10.1007/3-540-45810-7_24.
[60] D. Vrandečić, Ontology evaluation, in: S. Staab, R. Studer (Eds.), Handbook on Ontologies, Springer Berlin Heidelberg, Berlin, Heidelberg, 2009, pp. 293–313, http://dx.doi.org/10.1007/978-3-540-92673-3_13.
[61] C. Brewster, H. Alani, S. Dasmahapatra, Y. Wilks, Data driven ontology evaluation, in: International Conference on Language Resources and Evaluation, 2004, Event Dates: 24–30 May.
[62] A. Lozano-Tello, A. Gómez-Pérez, Ontometric: A method to choose the appropriate ontology, J. Database Manag. 2 (15) (2004) 1–18, http://oa.upm.es/6467/.
[63] A. Gangemi, N. Guarino, A. Oltramari, Conceptual analysis of lexical taxonomies: the case of wordnet top-level, in: Proceedings of the International Conference on Formal Ontology in Information Systems, vol. 2001, in: FOIS '01, ACM, New York, NY, USA, 2001, pp. 285–296, http://dx.doi.org/10.1145/505168.505195.
[64] D.L. Nuñez, M. Borsato, An ontology-based model for prognostics and health management of machines, J. Ind. Inform. Integr. (2017) http://dx.doi.org/10.1016/j.jii.2017.02.006.
[65] R. Shearer, B. Motik, I. Horrocks, HermiT: a highly-efficient owl reasoner, in: OWLED, vol. 432, 2008, p. 91.
[66] K. Dentler, R. Cornet, A. Ten Teije, N. De Keizer, Comparison of reasoners for large ontologies in the OWL 2 EL profile, Semantic Web 2 (2) (2011) 71–87.
[67] A. Ayadi, F.d.B. de Beuvron, C. Zanni-Merk, S. Krichen, CBNSimulator: a simulator tool for understanding the behaviour of complex biomolecular networks using discrete time simulation, Proc. Comput. Sci. 112 (2017) 514–523.