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## BNO: An ontology for describing the behaviour of complex biomolecular networks

Ali Ayadi<sup>a,c,\*</sup>, Cecilia Zanni-Merk<sup>b</sup>, François de Bertrand de Beuvron<sup>a</sup>, Saoussen Krichen<sup>c</sup>

<sup>a</sup>ICUBE/SDC Team (UMR CNRS 7357)-Pole API BP 10413, Illkirch 67412, France

<sup>b</sup>LITIS Laboratory, Fédération CNRS Norm@STIC FR 3638, INSA de Rouen Normandie, Avenue de l'Université, 76801 Saint-Etienne-du-Rouvray, France

<sup>c</sup>LARODEC Laboratory, Institut Supérieur de Gestion de Tunis, University of Tunis, Rue de la liberté, 2000 Bardo, Tunisia

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### Abstract

The use of semantic technologies, such as ontologies, to describe and analyse biological systems is at the heart of systems biology. Indeed, understanding the behaviour of cells requires a large amount of context information. In this paper, we propose an ontology entitled "Biomolecular Network ontology" using the OWL language. The BNO ontology standardises the terminology used by biologists experts to address issues including semantic behaviour representation, reasoning and knowledge sharing. The main benefit of this proposed ontology is the ability to reason about dynamical behaviour of complex biomolecular networks over time. We demonstrate our proposed ontology with a detailed example, the bacteriophage T4 gene 32 use case.

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*Keywords:* Complex biomolecular network, ontology, behaviour, SWRL rules, reasoning.

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### 1. Introduction

To understand how our body works it is extremely 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 change 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 Wu et al. 's research<sup>1</sup>, where they introduce and define the transittability of biomolecular networks as their steering from an undesired state to a desired state<sup>1</sup>.

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\* Corresponding author. Tel.: +33 6 56 76 34 46.  
E-mail address: [ali.ayadi@unistra.fr](mailto:ali.ayadi@unistra.fr)

Our research team has already proposed a platform to simulate the state changes in complex biomolecular networks<sup>2</sup>. Our approach is based on semantic technologies. Moreover, intense research in molecular biology has led to major discoveries in cellular components, producing accumulation of a large volume of knowledge about these components. It would therefore be helpful to exploit this knowledge to increase the understanding the behaviour of complex biomolecular networks. In fact, ontologies with their clearly-defined and well-structured descriptions are vital tools for the effective application of ‘omic’ information through computational approaches.

Our previous works<sup>3</sup> propose a semantic architecture for modelling the behaviour of complex biomolecular networks over time. This semantic architecture is based on four ontologies: the Gene Ontology (GO)<sup>1</sup>, the Simple Event Model Ontology (SEMO)<sup>2</sup>, the Time Ontology (TO)<sup>3</sup> and our development, the Biomolecular Network Ontology (BNO). This semantic approach aims at enriching the structural description of biomolecular networks by contextual knowledge concerning their state transitions, the events that can steer these transitions and the complete temporal context linked to this information.

In this article, we detail and describe the Biomolecular Network Ontology, that 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 its heterogeneous components and the relations among them; (2) Define the specific functions of all molecules and the different nature of interactions they provide; (3) Understand how a cell works through the semantic interpretation of knowledge involved in the network’s behaviour; (4) Perturb the network with stimuli by changing the concentration of an element and observe its behaviour; (5) Reasoning and inferring new knowledge; (6) Simulate and identify the different states of the biomolecular network over time.

The presentation of this work is structured as follows. Section 2 reviews the necessary preliminaries from complex biomolecular networks and ontologies, and presents a brief state of the art on the existing ontologies in systems biology. Section 3 describes our proposed biomolecular network ontology in more detail. Section 4 provides a case study to demonstrate how the proposed ontology can be used for reasoning on the bacteriophage T4 gene 32 whereas concluding remarks are in Section 5.

## 2. Background and related work

In this section, we describe approaches close to our works. Especially, we discuss those that use ontologies and semantic information to enable and improve understanding of cells.

### 2.1. 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<sup>1,4</sup>. 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 level contains the complete set of small-molecule chemicals<sup>5</sup>. Depending on the type of their cellular components 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), that were logically and semantically formalized in our previous works<sup>2,3</sup>.

### 2.2. Ontologies in systems biology

The use of ontological reasoning for interoperable data management is an increasingly accepted method in the field of systems biology research<sup>6</sup>. Indeed, over the past decades has emerged an incredible amount of ontologies in the

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<sup>1</sup> <http://www.geneontology.org>

<sup>2</sup> <http://semanticweb.cs.vu.nl/2009/11/sem/>

<sup>3</sup> <https://www.w3.org/TR/owl-time/>

Open Biological and Biomedical Ontologies (OBO) Foundry<sup>4</sup> which provides a large variety of bio-ontologies and the BioPortal<sup>5</sup> web application of the National Center for Biomedical Ontology (NCBO) which provides access to more than 600 biomedical ontologies<sup>7</sup>. By the exploration of these bio-ontologies via browsers such the Ontology Lookup Service<sup>6</sup>, it may be concluded that these ontologies treat different parts of systems biology such as cell types<sup>8,9</sup>, the molecular functions<sup>10</sup>, the diseases<sup>11</sup>, bioinformatics software, experimental data analysis<sup>12</sup>, etc. All 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 modeling the behaviour of complex biomolecular networks. In fact, very few researches use ontologies for defining the possible biological functions, like signal transducer activity in the case of the GO<sup>10</sup>, or the cell behaviour ontology<sup>13</sup> which describes and focuses on cell and tissue biology.

As was discussed, current ontologies for the 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 in a formal way this concrete domain is more than evident. Therefore, in this paper, a new ontology for the representation of this domain is proposed.

### 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. As described in Figure 1, we code and simulate the BNO ontology using OWL-language<sup>14</sup> using protégé editor<sup>7</sup>, version 5.2.0.

#### 3.1. 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 2.1). 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 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.<sup>15</sup>. Figure 1 and Table 1 show the most important BNO classes.

#### 3.2. The major 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. Table 2 summarises of the major properties, including their domain, range and inverse.

<sup>4</sup> <http://www.obofoundry.org/>

<sup>5</sup> <http://biportal.bioontology.org/>

<sup>6</sup> <http://www.ebi.ac.uk/ols/index>

<sup>7</sup> <http://protege.stanford.edu/>

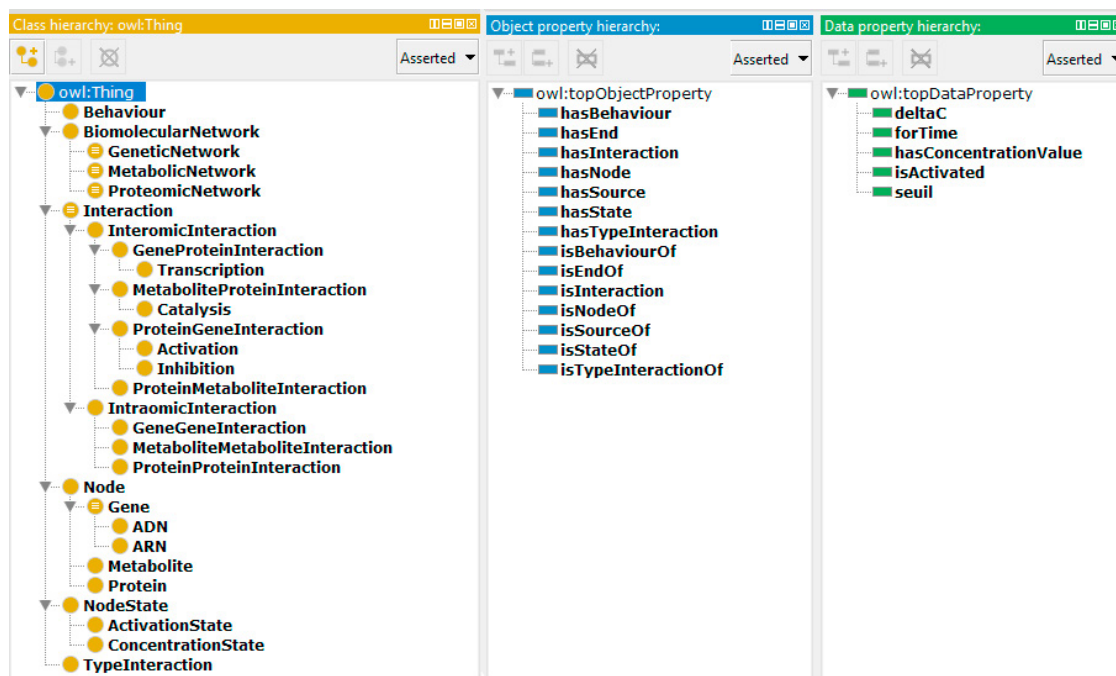


Fig. 1. The Biomolecular Network Ontology: hierarchy of classes, hierarchy of properties and hierarchy of data properties.

#### 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<sup>14</sup>.

##### 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<sup>16</sup>. As described in Figure 2, this biomolecular network consists of three nodes a **gene G32** coding for a **protein p32** and a **metabolite m32** which can catalyse the protein *p32*. In this network, the concentration of *p32* is regulated by itself and normally should remain between  $0.2 \cdot 10^{-6} \text{ Mol}$  and  $0.7 \cdot 10^{-6} \text{ Mol}$ . When the concentration of *p32* exceeds the threshold  $S_{p32} = 0.7 \cdot 10^{-6} \text{ Mol}$ , we talk about an **Inhibition** in which the protein *p32* inhibits the translation of its gene *G32* making it deactivated. However, when the concentration of *p32* decreases and becomes lower than the threshold  $S_{p32} = 0.2 \cdot 10^{-6} \text{ Mol}$ , we talk about an **Activation** in which the protein *p32* activates the translation of its gene *G32* making it activated. When the gene *G32* is activated by the protein *p32*, we talk about a **Translation** in which we have a production of *p32* by increasing the value of its concentration. When the concentration of *m32* exceeds the threshold  $S_{m32} = 0.8 \cdot 10^{-6} \text{ Mol}$ , the metabolite *m32* catalyses the *p32* by decreasing the value of its concentration, here we treat a **Catalysis**.

##### 4.2. Instantiation of the BNO ontology for the given example

Figure 3 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. We use the Protégé editor to instantiate the BNO ontology for the bacteriophage T4 gene 32. Figure 4 illustrates the nodes instantiations respectively, the gene *G32*, protein *p32* and metabolite *m32*. The instantiations of the four reactions are detailed in Figure 5.

Table 1. A summary of classes in the Biomolecular Network ontology. The left column presents the five major classes and their immediate sub-classes. The right column presents the description of these classes.

BNO ontology classes	Description
<b>BNO:BiomolecularNetwork</b>	It defines the different kinds of complex biomolecular networks.
BNO:GenomicNetwork	It defines the interactions among genes forming Gene Regulatory networks.
BNO:ProteomicNetwork	It defines the interactions among proteins forming Protein-Protein Interaction networks.
BNO:MetabolomicNetwork	It defines the interactions among proteins forming Metabolic networks.
<b>BNO:Node</b>	It defines the different types of cellular entities.
BNO:Gene	It describes the set of genes $M_G$ .
BNO:DNA	It describes the set DNA.
BNO:RNA	It describes the set of RNA.
BNO:Protein	It describes the set proteins $M_P$ .
BNO:Metabolite	It describes the set metabolites $M_M$ .
<b>BNO:Interaction</b>	It defines all the types of interactions operated among the nodes.
BNO:IntraomicInteraction	It defines the interactions between molecular components of the same type.
BNO:I.GG	It defines the interactions between genes.
BNO:I.PP	It defines the interactions between proteins.
BNO:I.MM	It defines the interactions between metabolites.
BNO:InteromicInteraction	It defines the interactions between molecular components of the different type.
BNO:I.GP	It defines the interactions between genes and proteins.
BNO:I.PG	It defines the interactions between proteins and genes.
BNO:I.PM	It defines the interactions between proteins and metabolites.
BNO:I.MP	It defines the interactions between metabolites and proteins.
<b>BNO:NodeState</b>	It defines the possible states of the nodes.
BNO:ActivationState	It defines the states of the genes.
BNO:ConcentrationState	It defines the concentration of the proteins and metabolites.
<b>BNO:InteractionType</b>	It defines the nature of the interaction among cellular components.

Table 2. 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

### 4.3. Reasoning with SWRL rules

The Semantic Web Rule Language (SWRL) is an ontological language based on OWL-DL and OWL-Lite that to express the rule description language based on OWL<sup>17</sup>. SWRL can be used to write rules to reason about OWL individuals and to infer new knowledge about those individuals. The rules in SWRL are implication rules, and follow 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. Thus we adopt these SWRL rules to build the reasoning rules in order to represent the dynamic aspect of the biomolecular network. During this reasoning, inferences are

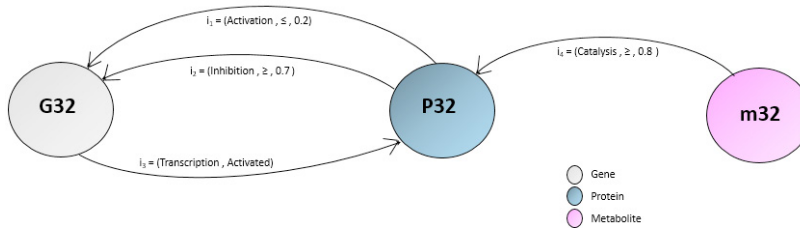


Fig. 2. Instantiation of the BNO ontology for the given example.

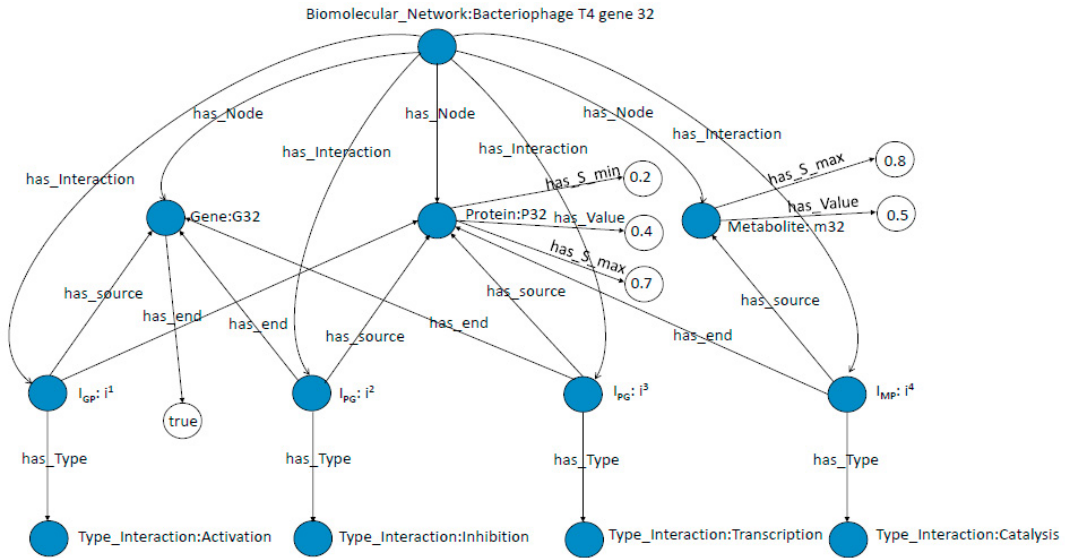


Fig. 3. Instantiation of the BNO ontology for the given example.

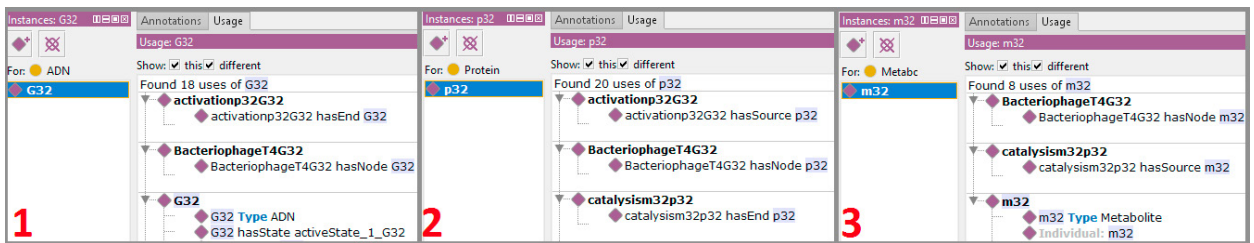


Fig. 4. A snapshot look at the BNO node instances associated with the given example displaying respectively: (1) the gene *G32*, (2) the protein *p32* and (3) the metabolite *m32*.

made, classifying the instances of the BNO ontology and associating new properties to instances while maintaining logical consistency.

4.3.1. Inhibition SWRL rule

The following rule models the inhibition reaction. When the concentration of the protein *p32* exceeds the threshold  $0.7 \cdot 10^{-6}$ , it inhibits the translation of its gene *G32*.

$$ADN(?g) \wedge hasState(?g, ?gs1) \wedge forTime(?gs1, ?t) \wedge hasState(?g, ?gs2) \wedge forTime(?gs2, ?t2) \wedge swrlb:add(?t2, ?t, 1) \wedge Protein(?p) \wedge Activation(?activ) \wedge hasSource(?activ, ?p) \wedge hasEnd(?activ,$$

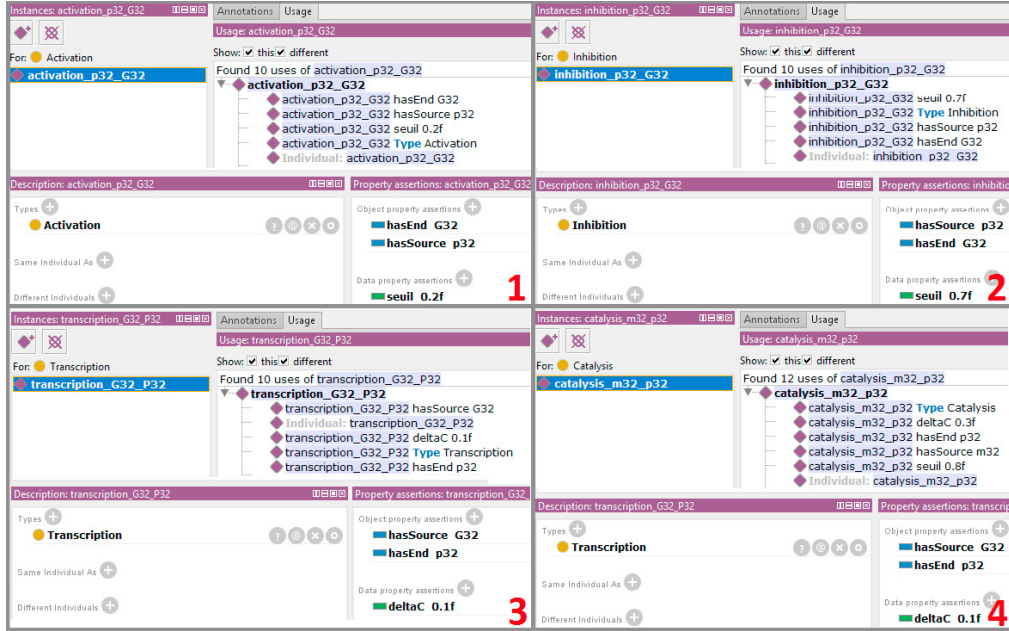


Fig. 5. A snapshot look at the BNO interaction instances associated with the given example displaying respectively: (1) Activation, (2) Inhibition, (3) Transcription and (4) Catalysis.

$$?g \wedge hasState(?p, ?ps) \wedge forTime(?ps, ?t) \wedge hasConcentrationValue(?ps, ?c) \wedge swrlb:greaterThanOrEqual(?c, 0.7) \rightarrow isActivated(?gs2, false)$$

As depicted in Figure 6, the results of this rule means 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  $ps1$  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  $p32$  becomes less than the threshold  $0.2 \cdot 10^{-6}$ , it activates the translation of the Gene  $G32$ .

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

As described in Figure 7, the results of this rule means 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  $ps1$  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. Transcription SWRL rule

The following rule represents the gene transcription. In fact, if the gene  $G32$  is activated, this one generates the protein synthesis and produces an increase in the concentration of this protein  $p32$ .

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

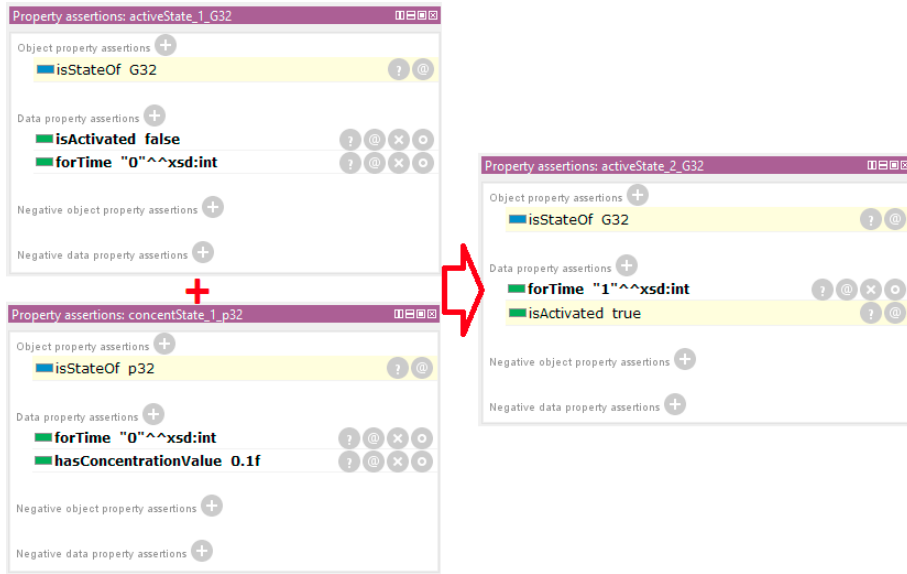


Fig. 6. Results of the reasoning process for the Inhibition SWRL rule.

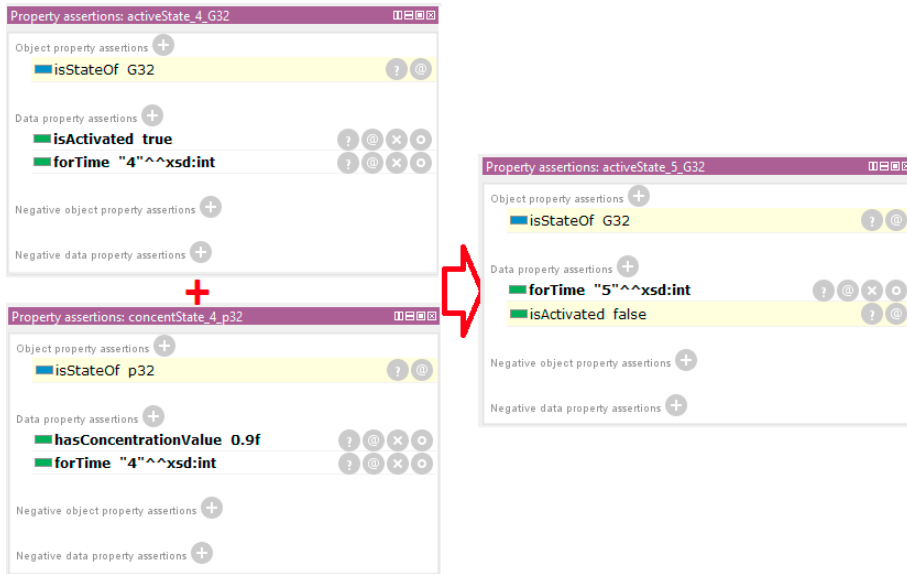


Fig. 7. Results of the reasoning process for the Activation SWRL rule.

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  $ps1$  and a concentration  $c$  at this time  $t$ , and these two molecules  $g$  and  $p$  are related by a Transcription interaction, then the concentration of the protein  $p$  increases at time  $t + 1$ .*

In the opposite case, we have this rule:

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

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  $ps1$  and a concentration  $c$  at this time  $t$ , and these two molecules  $g$  and  $p$  are related by a Transcription 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:

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

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  $ps1$  and a concentration  $c1$  at this time  $t$ , and these two molecules  $m$  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  $m32$  is less than 0.8 we applied the following rule:

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

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  $ps1$  and a concentration  $c1$  at this time  $t$ , and these two molecules  $m$  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  $t + 1$ .*

#### 4.4. Evaluation

The verification of the logical axioms is an essential task in ontology evaluation. Indeed, this evaluation ensures that the logical axioms are satisfiable and consistent. This satisfaction consists in: (i) checking the encoding of the specification; (ii) detecting errors such as: class hierarchies, redundant axioms, etc.; (iii) confirming that the BNO ontology has been built according to certain specified ontology quality criteria. This consistency was ensured by the SWRL rules reasoning discussed in the previous section which must be evaluated by biologists experts. That is why we obtained the assistance and expertise of our colleagues from the CSTB (Complex Systems and Translational Bioinformatics) team who have evaluated the BNO ontology and conclude that it is in accordance with their expert knowledge about the domain. Moreover, this consistency was approved by the results of our experiments as shown in Figures 6 and 7.

In addition to the evaluation conducted by biologists, we adopted a qualitative evaluation method following the validation protocol proposed by d'Aquin et al.<sup>18</sup>. This validation protocol is essentially based on a number of criteria that will enable us to determine whether our ontology is relevant or not. These evaluation criteria focus on: (1) the *accuracy*, which is one of the most important criteria to be met by the ontology classes. (2) The *size* that represents the number of classes, properties, and individuals that an ontology contains. This is one of the most relevant indicators to assess the effectiveness of an ontology. This size determines whether the ontology sufficiently covers the domain that interests us. (3) The *cohesion* which makes it possible to determine the degree of connectivity between the different instances present in the same class. This metric makes it possible to evaluate the number of root classes in the ontology's hierarchy, the number of properties per class, and the longest depth of inheritance of concepts of the ontology. (4) The *coverage* of the domain which is a criterion for assessing the degree of representativeness of a domain of application by a specific class. This criterion makes it possible to determine the ontology's ability to cover and represent exactly the domain of application in question.

## 5. Discussion and concluding remarks

This paper has presented an ontology of complex biomolecular networks behaviour aimed at assisting biologists by providing them sufficient contextual detail for understanding the dynamical behaviour of complex biomolecular networks over time. We developed the BNO ontology from experiences of domain experts biologists to describe the domain of complex biomolecular networks. 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 the sub-network, the type of the node, the conditions of the interactions, the nature of the interaction, etc. This allows to precisely explain and interpret the semantic context in order to achieve intelligent modelling of biomolecular networks and their state changes. All these state changes can be carried out by a rule-based system.

We have experimented these rules on a small biomolecular network but this example is significant and contains all the constraints that are used. This case study with OWL-SWRL rules represents a "proof of concept" since it demonstrates the logical consistency of the proposed BNO ontology and check its relevance. To check the inconsistencies and violations of these SWRL rules, we used the latest version of Hermit reasoning plugin in the Protégé 5 environment <sup>8</sup> version 1.3.8.3. Results prove that our ontology can be successfully integrated into the rest of our project presented in Section 1. However we must emphasise that, even if this ontology provides useful knowledge and rich semantics allowing biologists to understand dynamical behaviour of complex biomolecular networks, it can not simulate large-scale networks. That is why more efficient simulation tools should be used for scaling up and reason on large biomolecular networks.

For further research, we aim to: (1) complete the current version of the BNO ontology and mapping it with other ontologies such as the Gene Ontology, and to (2) consider the complexity of complex biomolecular networks and to simulate large networks by using discrete time simulation tools.

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<sup>8</sup> <http://www.hermit-reasoner.com/>