Ontological reasoning for understanding the behaviour of complex biomolecular networks

Ali Ayadi
ICUBE Laboratory
Pole API, Illkirch 67412, France
and LARODEC laboratory
Institut Supérieur de Gestion, Université de Tunis,
2000 Bardo, Tunisia
Email: ali.ayadi@unistra.fr

Cecilia Zanni-Merk
LITIS Laboratory
Fédération CNRS Norm@STIC FR 3638,
INSA de Rouen Normandie,
76801 Saint-Etienne-du Rouvray, France
Email: cecilia.zanni-merk@insa-rouen.fr

François de Bertrand de Beuvron
ICUBE Laboratory
Pole API, Illkirch 67412, France
Email: debeuvron@unistra.fr

Saoussen Krichen
LARODEC Laboratory
Institut Supérieur de Gestion, Université de Tunis,
2000 Bardo, Tunisia
Email: saoussen.krichen@isg.rnu.tn

***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. In fact, they are indispensable for understanding the semantic knowledge about the functioning of cells on 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. The BNO ontology is freely available at https://github.com/AliAyadi/The-Biomolecular-Network-Ontology and can be viewed using the standard ontology visualization editor *Protégé*. This ontology provides qualitative simulation of large and complex biomolecular networks. Therefore, in order to evaluate the efficacy of the BNO ontology we present two kinds of reasoning mechanisms. The first consists on an SWRL rule based reasoning developed using the SWRL rules editor tab, and another consists on an implementation of a rule-based system under the MATLAB/SIMULINK development environment and can be freely downloaded at https://github.com/AliAyadi/QualitativeReasoningInMATLAB. Both of these reasoning mechanisms have been applied to the analysis of a real network of biological interest, the "bacteriophage T4 gene 32" use case.**

***Keywords*—Complex biomolecular networks, transittability, ontologies, knowledge representation, SWRL reasoning.**

I. Introduction

The domain of complex biomolecular networks is very well-suited to be formalized with ontologies. Focusing on the behaviour of the cells and how cells correctly respond to their environments is crucial to understand how our bodies work. Indeed, cells are exposed to several environmental stimuli. These detectable changes in the cell environment can be internal such as the increased concentration of intracellular, or external effects such as 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 [1], where they introduce and define the transittability of biomolecular networks as their steering from an undesired state to a desired state [1]. In this way, the purpose of the research project, a doctoral thesis entitled Semantic technologies for the optimization of complex molecular networks is to develop a platform to simulate the state changes of complex biomolecular networks with the hope of understanding and steering their behaviour. In our previous works [2], we have proposed a semantic architecture which is composed of four ontologies: the Gene Ontology (GO)[1], the Simple Event Model Ontology (SEMO)[2], the Time Ontology (TO)[3] and our development, the Biomolecular Network Ontology (BNO). Further details of each ontology composed the semantic architecture are given in [2]. 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. It aims at guiding the development of an OWL ontology capable of representing in a connected and comprehensive way all the content relevant for a given decision support request.

This paper however will focus on our development the *Biomolecular Network Ontology* by detailing and describing its terms. The BNO ontology aims at giving a formal and semantic representation that models all the necessary biological knowledge to study and reason on complex biomolecular networks.

[1] http://www.geneontology.org
[2] http://semanticweb.cs.vu.nl/2009/11/sem/
[3] https://www.w3.org/TR/owl-time/

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The remainder of this paper is organized as follows: Section II introduces complex biomolecular networks and defines the owl description of ontologies. Section III presents a brief state of the art on the existing ontologies in systems biology. Section IV presents a motivating example in biology domain. Section V provides a detailed description of the BNO ontology. Section VI demonstrates an application of the BNO ontology by presenting results for reasoning on the bacteriophage T4 gene 32. We evaluate our ontology against diverse criteria in Section VII. Section VIII concludes the paper and provides an outlook to meaningful extensions of this work.

II. Background

A. 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 set of proteins and the metabolism 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: 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 [2], [5].

B. OWL description of ontologies

Semantic technologies, especially ontologies, provide 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]. The Ontology Web Language (OWL) [7] is the standard language of the World Wide Web Consortium (W3C)[4] recommendation to describe and build Ontology. OWL ontology contains three basic modeling 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].

III. Literature review work

The use of ontological reasoning for interoperable data management is an increasingly accepted method in the field of systems biology research [8]. Indeed, over the past decades has emerged an incredible amount of ontologies in the Open Biological and Biomedical Ontologies (OBO) Foundry[5] which provides a large variety of bio-ontologies and the BioPortal[6] web application of the National Center for Biomedical Ontology (NCBO) which provides access to more than 600 biomedical ontologies [9]. By the exploration of these bio-ontologies via browsers such the Ontology Lookup Service[7], it is remarked that these ontologies treat different parts of systems biology such as the cell types [10], [11], the molecular functions [12], the ndiseases [13], bioinformatics software, experimental data analysis [14], 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 [12], or the cell behavior ontology [15] 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.

IV. Biological example

To illustrate the concepts of all our approaches in this paper, we use a motivating example of a biomolecular network, the bacteriophage T4 gene 32 [16]. As described in Figure 1, 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 $0.2\ 10^{-6}\ Mol$ 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 translation of its gene $G32$ making it deactivated. However, when the concentration of $p32$ decreases and becomes lower than the threshold $S_{p32} = 0.2\ 10^{-6}\ Mol$, 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 $S_{m32} = 0.8\ 10^{-6}\ Mol$, the metabolite $m32$ catalyses the $p32$ by decreasing the value of its concentration, here we treat a **Catalysis**.

V. 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 Figures 2 and 3,

[4] https://www.w3.org/

[5] http://www.obofoundry.org/

[6] http://bioportal.bioontology.org/

[7] http://www.ebi.ac.uk/ols/index

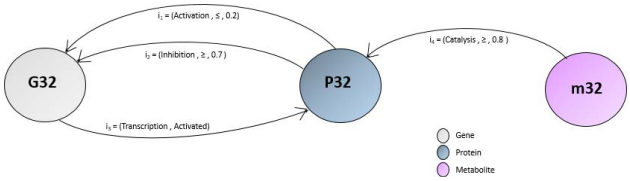

Fig. 1. The bacteriophage T4 gene 32 use case.

we code and simulate the BNO ontology using OWL-language [17] using Protégé editor[8], version 5.2.0. The ontology is freely available at https://github.com/AliAyadi/The-Biomolecular-Network-Ontology and can be viewed using the Protégé editor.

A. The key classes

As shown in Figure 2, 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 II-A). The instances of these classes will be defined later, among these instances we will focus on the $BacteriophageT4G32$ instance in Section VI-A. 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. [18]. Figure 3 shows the most important BNO classes.

B. 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. The different properties and data types of the BNO ontology are explained below.

- $hasBehaviour(object1, object2)$: where object1 is a $BiomolecularNetwork$ and object2 is a $Behaviour$.
- $hasInteraction(object1, object2)$:where object1 is a $BiomolecularNetwork$ and object2 is an $Interaction$.
- $hasNode(object1, object2)$: where object1 is a $BiomolecularNetwork$ and object2 is a $Node$.
- $hasSource(object1, object2)$: where object1 is an $Interaction$ and object2 is a $Node$.

[8]http://protege.stanford.edu/

TABLE I. A SUMMARY OF THE PROPERTIES, INCLUDING THEIR DOMAIN, RANGE AND INVERSE

BNO 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

- $hasEnd(object1, object2)$: where object1 is an $Interaction$ and object2 is a $Node$.
- $hasState(object1, object2)$: where object1 is a $Node$ and object2 is a $NodeState$.
- $hasTypeInteraction(object1, object2)$: 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 I summarises the major properties, including their domain, range and inverse.

VI. REASONING MECHANISMS

A. Instantiation of the BNO ontology for the bacteriophage T4 gene 32 use case

We have instantiated the BNO ontology by designing and implementing the given example of the bacteriophage T4 gene 32 within the Protégé editor (detailed in Section IV). 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 instantiation of the four reactions are detailed in Figure 5.

B. SWRL Rule-based Reasoning

The aim of this section is to illustrate the proposed BNO ontology for reasoning and inferring new knowledge with sets of rules expressed in Semantic Web Rule Language (SWRL) [17]. SWRL is an ontological language based on OWL-DL and OWL-Lite that to express the rule description language based on OWL [17]. SWRL can be used to write rules to reason

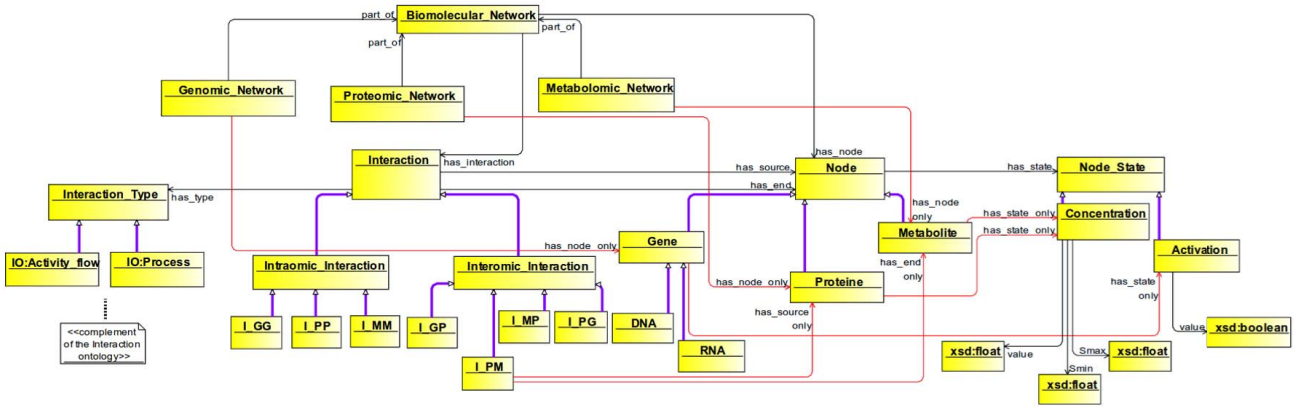

Fig. 2. Excerpt of the proposed Biomolecular Network Ontology (BNO) [2]

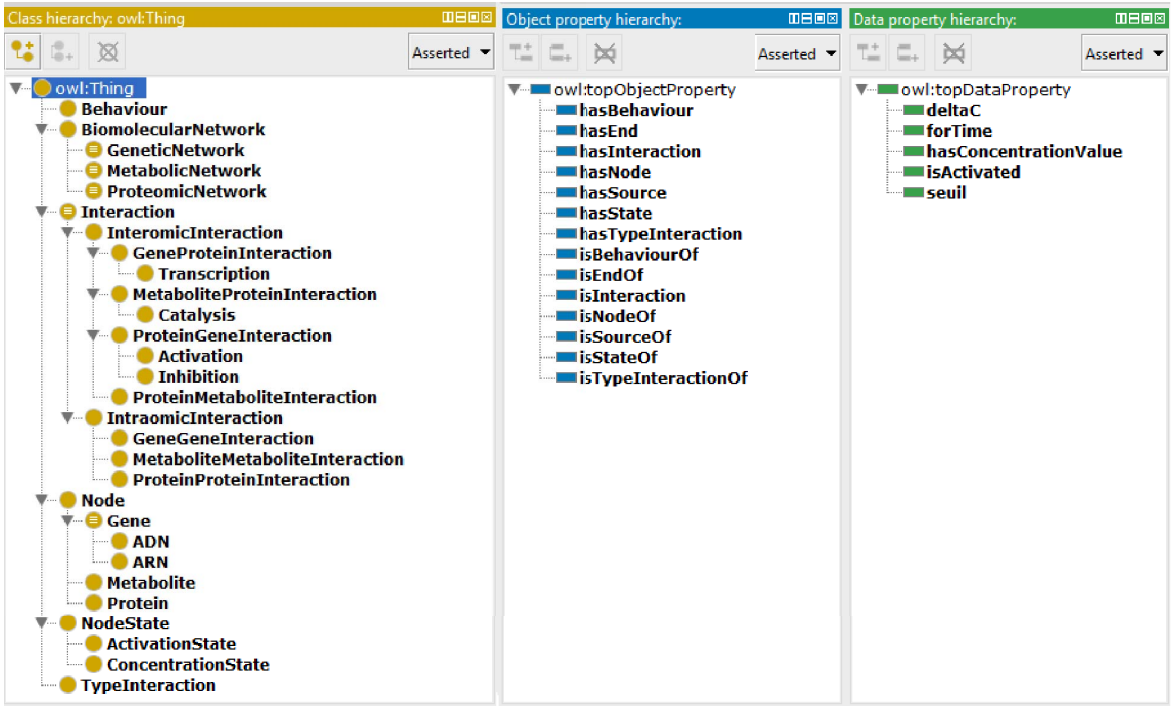

Fig. 3. The Biomolecular Network Ontology: hierarchy of classes, hierarchy of properties and hierarchy of data properties

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

1) Inhibition SWRL rule: The SWRL rule **A** in Figure 6 models the inhibition reaction. When the concentration of the protein $p32$ exceeds the threshold $0.7\ 10^{-6}$, it inhibits the translation of its gene $G32$. Which means:

> *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 $t+1$.*

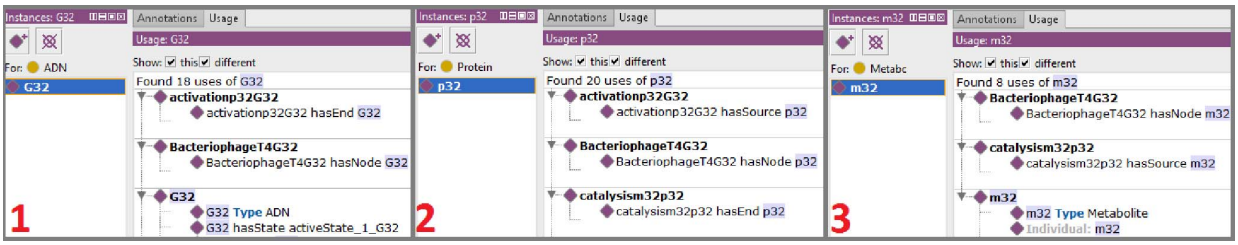

Fig. 4. A snapshot look at the BNO node instances associated with the given example displaying respectively: (1) the gene G32, (2) the protein p32 and (3) the metabolite m32

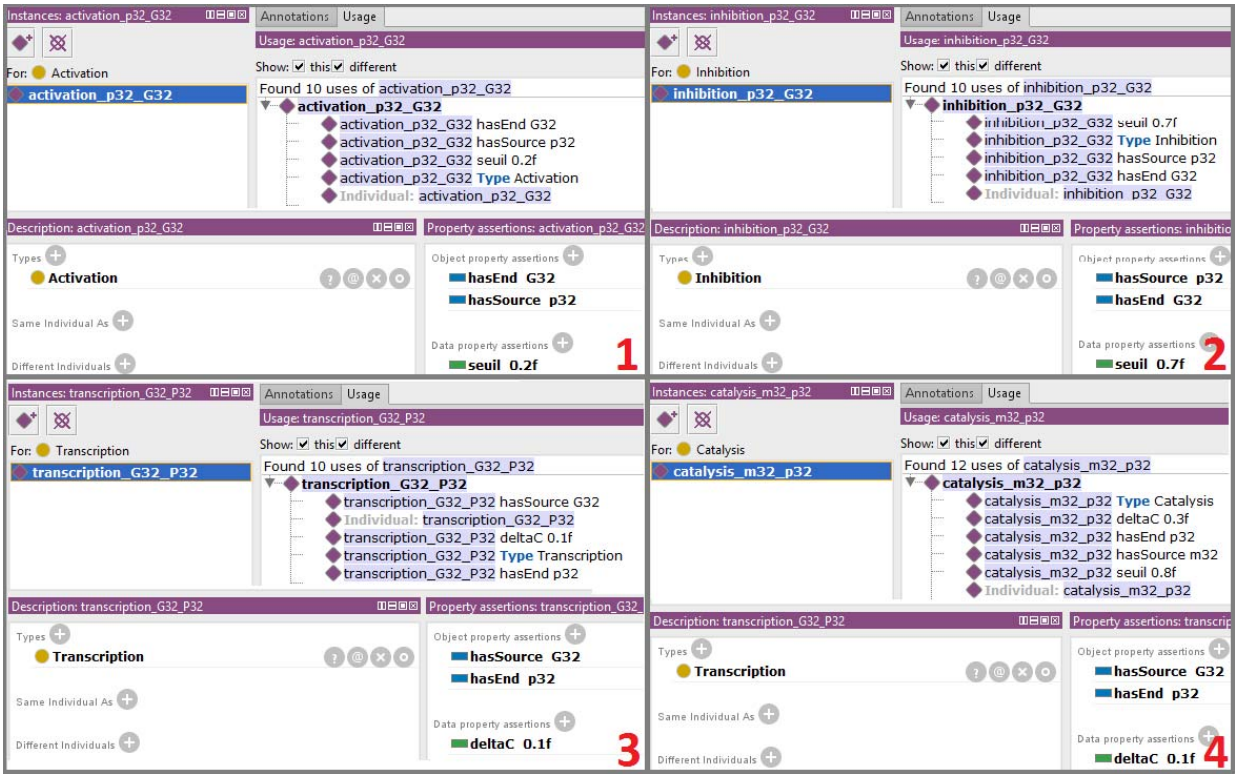

Fig. 5. A snapshot look at the BNO interaction instances associated with the given example displaying respectively: (1) Activation, (2) Inhibition, (3) Transcription and (4) Catalysis

2) Activation SWRL rule: In contrast to the first rule, the rule **B** in Figure 6 models the activation reaction. When the concentration of the protein $p32$ becomes less than the threshold $0.2\ 10^{-6}$, it activates the translation of the Gene $G32$. This rule means:

> *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 0.2, then the state of g move to false at time $t+1$.*

3) Transcription SWRL rule: The rule **C** in Figure 6 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 $p32$. Which means:

> *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 rule **D** in Figure 6:

> *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*

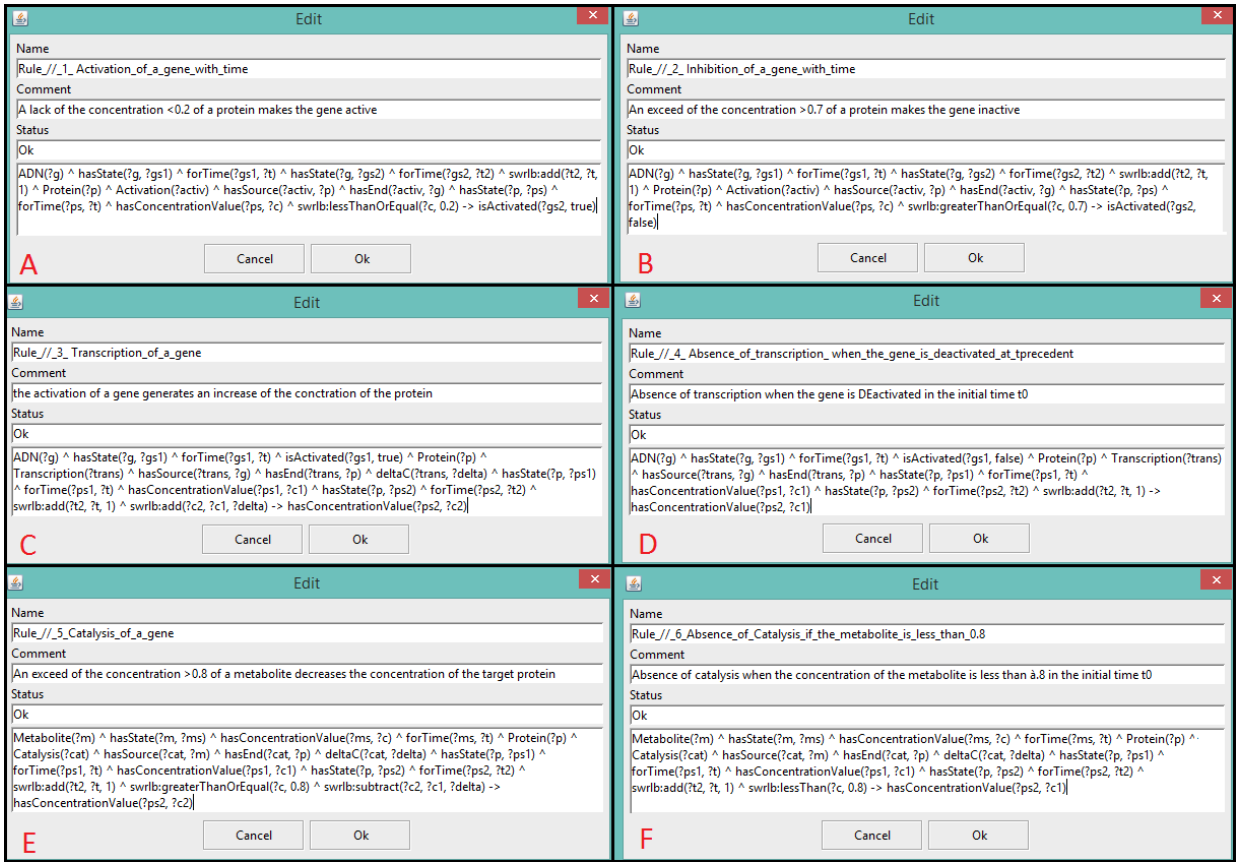

Fig. 6. A fragment of SWRL rules defined in the SWRL rules editor tab

of the protein p remains stable at time $t+1$.

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 rule **E** in Figure 6. This rule 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 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 $m32$ is less than 0.8 we applied the rule **F** depicted in Figure 6. This rule 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 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 $t+1$.*

For lack of space we only give results of the last rule (rule **F** in Figure 6). These results are detailed in Figure 7.

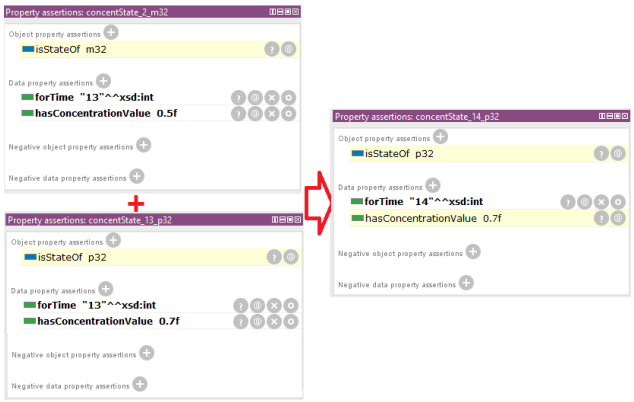

Fig. 7. Results of the reasoning process for the SWRL rule 6 in Figure 6

C. Rule-based qualitative reasoner within MATLAB

Extensive experiments were conducted to validate our proposed ontology including the implementation of rule-based qualitative reasoner. This rule-based reasoner is implemented under the MATLAB/SIMULINK development environment and can be freely downloaded at https://github.com/AliAyadi/QualitativeReasoningInMATLAB. The reasoner is based on a qualitative simulation algorithm 1, with specific reference to the SWRL rules defined in Section VI-B.

Algorithm 1 provides a high level description of the general reasoning algorithm of a complex biomolecular network.

Algorithm 1 Pseudocode of the qualitative simulation algorithm

```
Definition of the set of SWRL rules and their thresholds.
Initialization of time and network's state.
for All time step from begining to end_of_simulation do
    for Each molecular component do
        Evaluate the node state
        if the component's state achieves one a threshold then
            Execution of the reaction defined by the SWRL rule corresponding to this threshold.
        ▷ Measure the state if it is a gene and the concentration if it is a protein or a metabolite
            Update the novel state of the node.
        end if
    end for
end for
```

Figure 8 depicts the individual qualitative behaviour of the biomolecular components. Indeed, for each node a description of its dynamical time-evolution is graphically presented. The evolution is displayed as a graph to easily see when and how the molecular component evolves during the simulation, and to precisely detect changes on the state in time. These results are not difficult to interpret, because they are purely qualitative.

VII. Ontology Evaluation

In this section, we evaluate the BNO ontology against diverse quality criteria described by Vrandecic in [19], which are presented as part of a common framework for ontology evaluation.

Accuracy: The definitions and descriptions in the ontology agree with the experts knowledge about the field. The information regarding the concepts of the BNO ontology were 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 satisfiable.

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 [2]. This choice enhances extensibility and reusability, and makes the BNO ontology easily adaptable to dynamical contexts.

Clarity: In developing the BNO ontology, we have been careful to assign a clear and unambiguous descriptions to define and categorize concepts and the relationships among concepts within our particular knowldge domain. This clarity is ensured by the use of the *rdfs:comment* that provides the obvious 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 analyzed 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 reasonable time. Moreover, the complexity of this operation is adequate.

Conciseness: The terms of the BNO ontology was 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 ontoloy 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.

We have also used the OntOlogy Pitfall Scanner[9] tool to check for logical correctness of the BNO ontology and diagnostics of ontology-design errors. Analysis results has provided great evidence of the correctness of BNO.

VIII. Conclusion and future work

In this paper, a proposed an ontology untitled "the BNO ontology" has been proposed. The BNO has been developed to describe the domain of knowledge of biomolecular networks and the evolution of their states over time. It is developed in collaboration with domain experts. This ontology provides knowledge on the biomolecular network and its components and an indication of the network's context such as: the type of the sub-network, the type of the node, the conditions of

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

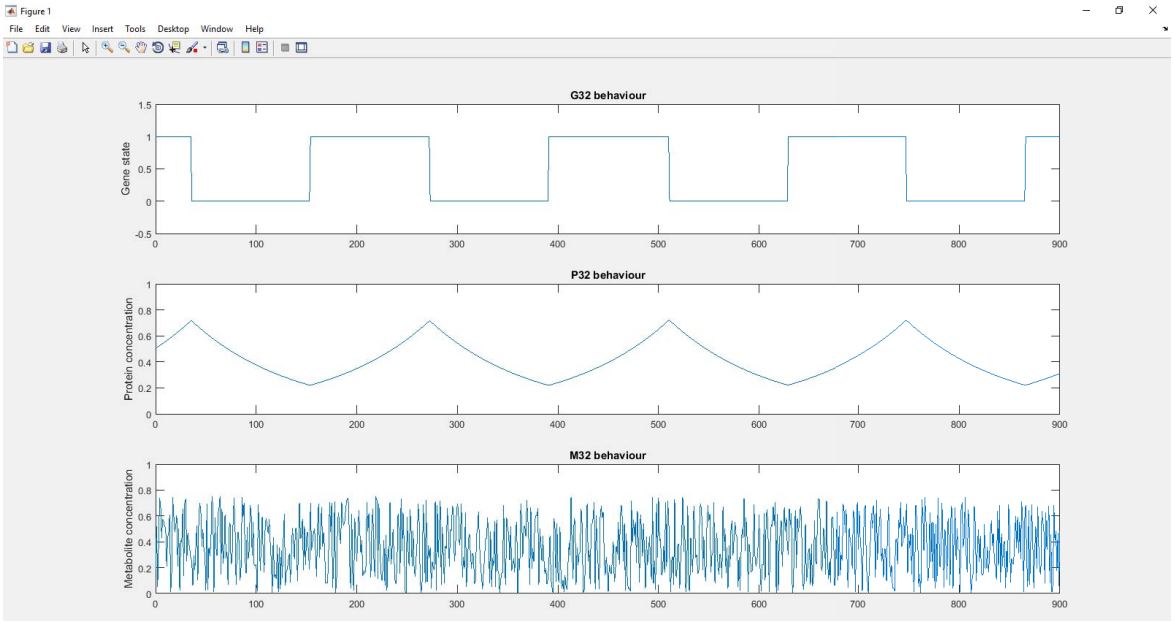

Fig. 8. Simulation results plotted with MATLAB environment: the individual qualitative behaviour of the biomolecular components

the interactions, the nature of the interaction, etc. This allows to precisely explain the semantic context in order to achieve intelligent modeling of biomolecular networks and their state changes. Indeed, we have experimented the BNO ontology on a small network example "the bacteriophage T4 gene 32" but this example is significant and contains all the constraints that are used. The consistency and the conformity of the ontology are checked by reasoning and querying of BNO ontology using two rule-based systems. The first, is an SWRL rule-based reasoner using to demonstrate the logical consistency of the approach and check the relevance of the BNO ontology. However, more efficient simulation tools should be used for representing simulation results in various formats, such as graphs. This explains the reason why we propose qualitative simulation reasoning implemented under MATLAB/SIMULINK environment to simulate the transition changes of the biomolecular network to interpret graphically its behaviour over time. The application of BNO to real biomolecular networks has shown that our ontology can be successfully applied to analyse and simulate qualitatively the behaviour of complex biomolecular networks over time. Nevertheless, improvements in many directions are current and future topics of our research. An interesting question which we are currently investigating is the problem of finding a simulation methodology that combines both the aspect of numerical and qualitative simulation.

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