

Biomedical Engineering through Ontologies

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Abstract: Biomedical engineering is the application of scientific and mathematical principles to practical ends in the medicine and biology fields. It comprises many research directions including computational model of HIV infection, integration of clinical and experimental data, etc. Much of the work in biomedical engineering consists in providing solutions to the problem of securing an effective integration of biomedical content. To this end, ontologies, as sharable, reusable and machine-readable artifacts capable of knowledge representation, contribute to the interoperability between systems, the access of heterogeneous information sources, and the reuse of voluminous and complex information. The aim of this paper is to present the literature on biomedical ontologies in order to highlight how current research of the ontology field can be brought to bear on the practical problems associated with biomedical engineering. Thus, we discuss the fundamental role of ontologies in biomedical engineering, we review several methodologies suitable for building specialized biomedical ontologies, and we present some peculiarities related to the creation of biomedical ontologies that continue to constitute research challenges.

1 INTRODUCTION

Biomedical engineering aims at combining research advances from disciplines such as biology, medicine, computer science, mathematics, bioinformatics and areas such as knowledge representation, information retrieval, data mining, reasoning and visualization, by attracting contributions that are currently scattered in different fields. Typically it involves the design, implementation and operation of efficient biomedical structures, processes and systems for diagnostic, monitoring, or therapeutic purposes.

Currently, biomedical engineering focuses on activities that aim at developing novel algorithmic processes which lead to the creation of new knowledge, by harmonizing basic types of biomedical and clinical data, such as biomedical images, biological sequences and biosignals. Their successful application is strongly tied to the effective adoption of semantic technologies, such as terminologies, thesauri, ontologies, in order to represent, acquire, process and manage knowledge and data in the biomedical domain (Bodenreider, 2008).

Although various terminologies, such as MeSH (Medical Subject Headings)

(<http://www.nlm.nih.gov/mesh/>) and UMLS (Unified Medical Language System) (<http://www.nlm.nih.gov/research/umls/>) have been used in order to provide a sort of semantics in biomedicine (Freitas et al., 2009), the need to develop ontologies has accelerated in recent years, due to the availability of huge biomedical data sets that cannot manually be analyzed, interpreted or processed to acquire inferred knowledge efficiently (Saripalle, 2013). Unlike terminologies, which collect the name of entities employed in the domain, ontologies are concerned with the principled description of classes of entities (i.e., substances, qualities, processes) and the relations among them (Bodenreider and Burgun, 2005).

While the number of biomedical ontologies continues to increase, as new areas of biomedical content become formalized, their creation still remains a challenging task, due to the complex and dynamic nature of the biomedical domain.

The objective of this paper is not to examine how applications in biomedicine benefit from using ontologies, but rather to present the critical issues related with the construction of specialized biomedical ontologies. In particular, we review the fundamental role of ontologies in the biomedical

engineering field, by studying the challenging issue of creating a specialized biomedical ontology.

The rest of this paper is organized as follows: Section 2 provides basic definitions and Section 3 a brief overview of ontologies that semantically support biomedical engineering. Section 4 refers to peculiarities related to the creation of biomedical ontologies that continue to constitute research challenges. Finally, Section 5 draws some conclusions.

2 ROLE OF ONTOLOGIES IN BIOMEDICAL ENGINEERING

Although many definitions of ontologies exist in the scientific literature (Neches et al., 1991), (Gruber, 1993), (Guarino and Giaretta, 1995), (Chandrasekaran et al., 1999), (Stevens et al., 2000), (Fonseca, 2007) quite a few notions are common to these definitions. Conclusively, an ontology can be defined as an explicit representation of a shared understanding of the important concepts in some domain of interest. The role of an ontology is to support knowledge sharing and reuse within and among groups of agents (people, software programs, or both). In their computational form, ontologies often comprise definitions of terms organized in a hierarchy lattice, along with a set of relationships that hold between these definitions. These constructs collectively impose a structure on the domain being represented and constrain the possible interpretations of terms. Ideally, an ontology should capture a shared understanding of a domain of interest and provide a formal and machine manipulable model of the domain.

In the case of biomedical engineering, ontologies, as computational knowledge resources that capture the precise meaning of biomedical terms, are used in order to enhance the design and execution of experiments, data analysis, synthesis of biomedical information, creation of research hypotheses and discovery of new knowledge (Bard and Rhee, 2004), (Blake, 2004).

Moreover, since ontologies are developed in order to share common understanding of the structure of the biomedical information among people, or software agents, they are widely used in order to resolve semantic conflicts that inhibit interoperability among heterogeneous biomedical systems (Horrocks, 2013).

According to Goh (Goh, 1997), there are three main causes which are responsible for these

semantic conflicts: (a) Confounding conflicts, which occur when different meaning is attributed to the same term, according to the context in which it is interpreted. For example, the Paget's disease may be interpreted, either as a rare type of breast cancer, or as a chronic disorder affecting bones commonly quoted as osteodystrophia deformans; (b) Scaling conflicts, which refer to different reference systems for measuring some kind of values. For example, the measurement of normal glucose level in blood can be represented either as 60-110 mg/dL, or as 3,5-6 mmol/L; and (c) Naming conflicts, which refer to the use of synonyms in different knowledge representation systems. For example, diabetes and polygenic disorder, despite their lexicographic incongruity, have the same meaning, that is, a metabolic disease whereby a person has high levels of blood sugar due to an inability to produce, or metabolize sufficient quantities of the hormone insulin.

In general, the main reason for developing ontologies in the biomedical field is to capture the exact meaning of biomedical terms, aiming mainly at the integration and management of terminologies in e-health and biomedicine, interoperability and sharing, information retrieval, decision making and automated logical inference (Cinimo, 2000), (Rector, 2003), (Brand, 2003), (Rubin et al., 2007).

Although ontologies can have several applications, such as representation of encyclopedic knowledge, semantic search and query, data exchange, data integration, and reasoning, the creation of biomedical ontologies still remains a critical issue, as discussed later on.

3 SPECIALIZED BIOMEDICAL ONTOLOGY ENGINEERING

The construction of a specialized biomedical ontology is difficult due to the dynamics and complexity of the biomedical domain. It requires methodological guidelines for the specification (i.e., identification of the scope and domain of the ontology under construction), conceptualization (i.e., definition of the basic concepts structured in a hierarchy, relations, instances and axioms), implementation (i.e., selection of the ontology development tool and the language in which the ontology will be implemented) and evaluation (i.e. the final outcome is evaluated against a gold standard, or within an application) of the produced artifacts.

The establishment of international centers, such as the National Center for Biomedical Ontology (NCBO) (<http://www.bioontology.org>), the Open Biomedical Ontologies (OBO) Foundry (<http://obofoundry.org>), the Semantic Web Health Care and Life Sciences Interest Group (HCLS IG) (<http://www.w3.org/blog/hcls/>), the Stanford Center for Biomedical Informatics Research (<http://bmir.stanford.edu/>), etc. promote best practices in the development of biomedical ontologies. The Web Ontology Language (OWL) (<http://www.w3.org/TR/owl-features/>) is widely accepted as the standard language for representing biomedical ontologies and Protégé (<http://protege.stanford.edu/>) as the most suitable and commonly used ontology development environment in the biomedical field.

The OBO Foundry proposes a set of principles for ontology development that guide the modular creation of biomedical ontologies. These principles refer to the design to which biomedical ontologies should adhere, such as openness (i.e., the ontology must be open and available to be used by all without any constraint), the employment of a shared syntax (i.e., the ontology must be expressed in the OBO syntax, or OWL for facilitating shared software implementations), orthogonality (i.e., the ontology must be orthogonal to other ontologies already lodged within OBO in order to allow two different ontologies to be combined through additional relationships), the inclusion of textual definitions (i.e., the ontology should include textual definitions for all terms, so that their precise meaning will be clear to a human reader), and the application of standardized relations (i.e., the ontology must use relations which are unambiguously defined in the OBO Relation Ontology) (Smith et al., 2005).

Hereafter we present a set of techniques for constructing specialized biomedical ontologies and indicative real world applications.

- In (Valarakos et al., 2006) a methodology is proposed for the design and implementation of a formally defined ontology on allergens consisting of the exploitation of existing taxonomies and documents that describe the allergen nomenclature, the semi-automatic maintenance of the allergens ontology by discovering knowledge from domain specific corpora using machine learning techniques, and the evaluation of the maintenance process through the study of the factors that may affect its performance;
- In (Sahay et al., 2007), an ontology for the Nuclear Cardiology domain is built

automatically from text using existing medical resources, as well as parsing and extracting methods. First, a set of abstracts from the Journal of Nuclear Cardiology is collected. Then, from these abstracts, by using statistical natural language processing techniques, concepts and relations are extracted in the form of Subject-Verb-Object and thereby a semantic network is created;

- In (Baneyx et al., 2007) an ontology of pulmonary diseases is created, by applying a methodology which combines two approaches to enrich ontology building: (1) a method which consists in building terminological resources through distributional analysis and (2) a method based on the observation of corpus sequences, in order to reveal semantic relationships;
- In (Satria et al., 2012) the development of a medical ontology in the domain of tropical diseases is discussed. The ontology building process is based on the reuse of existing biomedical ontologies with overlapping content, such as the Infectious Disease Ontology (Cowell and Smith, 2010), the Human Malaria Control Ontology (Daramola and Fatumo, 2009) and the Disease Ontology (Schulz et al., 2006);
- In (Warrender, 2013) the Mitochondrial Disease Ontology is constructed by applying the following steps: (1) term capture in order to acquire knowledge of the domain of interest, (2) definition of competency questions which the ontology should reasonably be able to answer, (3) refinement in order to filter the terms and competency questions for discarding the non-relevant ones, (4) combination of manual and automated construction in order to incorporate data that already exists in autonomous structured formats, and (5) evaluation of the terminology and the taxonomy of the ontology, as well as, the ontology's fitness for purpose;
- In (Xiang and He, 2013) the Human Interaction Network Ontology (HINO) is generated by extending the BFO (Basic Formal Ontology)-aligned Interaction Network Ontology (INO) and by importing terms from ontologies, such as CHEBI and GO. It represents various human molecular interaction pathways and networks as classes.

From analyzing the various techniques used during the construction of the specialized biomedical ontologies, it is evident that there appears to be no

strict interrelationship between the technique used during a specialized biomedical ontology building and the special characteristics of the corresponding biomedical subfield. A general conclusion could be that, when the biomedical subfield in question is too specialized (e.g., allergens, nuclear cardiology, pulmonary diseases), then the construction of the corresponding ontologies is based on automated analysis of text, while in the case of fields, such as tropical diseases, or human molecular interactions and pathways, where there exist many available ontologies with overlapping content, their reuse is the common technique used. There are also some exceptions (e.g. Mitochondrial Disease Ontology), whose generation is based on the combination of two techniques (reuse and construction from scratch); these are cases where the corresponding biomedical subfield is too specialized thus there do not exist ontologies related to it.

4 PECULIARITIES IN CREATING BIOMEDICAL ONTOLOGIES

In this section, we present specific issues related to the creation of biomedical ontologies that continue to constitute research challenges.

- **Modularization:** The biomedical ontologies tend to be complex and large in size, so it is difficult to maintain them or incorporate changes to them (Pathak et al., 2008). A desirable feature of biomedical ontologies is to be organized into discrete units (modules), in order to be easily manipulable and extensible (Rector, 2003), (Schulz and Lopez-Garcia, 2011). The basic problem in building modular biomedical ontologies is the need of a predefined set of relationships among the different modules (Bittner and Smith, 2003);
- **Reusability:** Biomedical ontologies should be reusable in order to adhere to their general purpose, that is, to support interoperability issues. For example, the construction of a coronary artery disease ontology may be facilitated by reusing the Disease Ontology; the ontology of genetic susceptibility factor can be constructed by reusing the Basic Formal Ontology (Lin and He, 2013). This feature requires the use of a standard representation language, so that the structure and semantics of the ontology are fully understood;
- **Size:** As biomedical ontologies become larger, their development and maintenance become more difficult and error prone. To address this challenging issue human judgment is still necessary (Mortensen et al., 2013). Moreover the large size of biomedical ontologies makes the generation of correct alignments a time-consuming process (Ba and Diallo, 2013);
- **Uncertainty in knowledge representation:** In the biomedical domain, the use of certain indicators such as HDL (High Density Lipoprotein) and LDL (Low Density Lipoprotein) is commonplace. The values of these indicators give a threshold between two states (normal and abnormal). The representation of this kind of medical knowledge requires the use of fuzzy logic, which allows representing the imprecision that is inherent to the definition of some biomedical concepts (Kayaalp, 2005), (Hudelot et al., 2008);
- **Alignability:** Biomedical ontologies should be alignable (Musen, 2006), that is, semantic correspondences among different biomedical ontologies should be easily generated. This contributes to the evaluation of biomedical ontologies, since the more alignments an ontology has, the more reliable it is, because this means that it has been reused multiple times by different applications. The alignability of ontologies is mainly achieved by using terms from other commonly accepted ontologies;
- **Perdurants and endurants:** A consistent representation of biomedical knowledge requires the clear distinction between the entities for representing endurants (or continuants) and perdurants (or occurrents) (Yu, 2006). Endurants are those entities that continue to exist through time as a whole (e.g. an organ), while perdurants are entities that unfold themselves in successive temporal phases (e.g. breathing). A clear interdependence of these two types of entities arises, since perdurants depend on the existence of endurants. For example, a molecular protein, which is an endurant, tends to perform a specific function (e.g. binding), which is a perdurant;
- **Semantic ambiguity:** Resolving semantic ambiguity is a very challenging issue which refers to the existence of polysemy and homonymy during the knowledge representation process (Beisswanger et al.,

2008). Polysemy terms may have the same lexicographic form but refer to totally different concepts, even in the same field (e.g., the term “gene” in Biomedicine may encode either the concept of “the recorded segment of DNA that translates protein” or the concept of “biological interest DNA region that carries a genetic phenotype”. In contrast, synonyms usually have different lexicographic form but refer to the same concept (e.g., the terms “cell” and “closet” may be both interpreted as “one of the parts into which an enclosed space is divided”, depending on the context);

- **Multidimensionality:** In the biomedical domain a concept exhibits diverse characteristics, so during its ontological representation it may be structured in different ways (e.g., an organ may be considered either as an anatomical entity, or as a functional entity). The case in which a node in a tree hierarchy appears to have more than two parent-nodes is called multidimensionality (Madsen et al., 2005). For example, the term “pulmonary tuberculosis” can be classified either as a respiratory, or as an infectious disease;
- **Diversity:** Diversity in biomedical ontologies occurs when a concept may be expressed in many variants of the same term. The most common cases involve morphological (e.g., gene vs genes), orthographic (e.g., hemolysis vs Hemolysis), lexical (e.g., cancer vs carcinoma), structural (enzyme activity vs activity of enzyme), and semantic diversity (e.g., genetic disease vs hereditary disease) (Wächter, 2010);
- **Abbreviations and acronyms:** The increasing number of neologisms in Biomedicine for gene names, diseases, etc. has led to the use of abbreviated terms and acronyms, which has created uncertainty in modeling knowledge, since for any given acronym or abbreviation, there are often multiple possible long form expansions. For example, the acronym TTP can refer, either to “thiamine triphosphate”, or to “thymidine triphosphate” (Melton et al., 2010);
- **Ordinary statements:** Statements such as “Lmo-2 interacts with Elf-2” which refer to the behavior of biomedical entities (e.g., about the interaction between two proteins) occur in biomedical literature. However, from an ontological perspective, these statements may have more than one possible interpretations (e.g., this interaction did actually happen, or the molecules Lmo-2 and Elf-2 have the tendency to interact in such a way). Thus, such statements reveal a kind of ambiguity that has to be taken into account in the practice of biomedical ontology engineering (Schulz and Janses, 2009);
- **Multi-word terms and nested terms:** The majority of concepts used in the biomedical domain consist of multiword terms (e.g., bel-2 protein level, or RA mediated tumor cell invasion), or nested terms (e.g., Leukemic [T cell] line Kit255), where the brackets denote nested terms in a multi-word term (Ananiadou et al., 2000). Although, their interpretation is obvious to a domain expert, it remains a challenging issue for a machine;
- **Reverse transformations:** Pathological transformations in Biomedicine, such as the transformations of erythrocytes into echinocytes and back again, or of a healthy organ into an unhealthy organ and back again complicate the ontological engineering process, since it is unknown in advance whether all instances of a class have been transformed into pathological ones and whether all instances of a pathological entity return to the original normal state, for example after a medical intervention (e.g., 5 of 100 patients with lung cancer survive and keep their lungs) (Keet, 2009);
- **Mereotopological and location relations:** Explicitly representing general truths such as “a given clump of tissue is part of the left gyrus frontalis medius, which in turn, is part of the brain, which is part of the nervous system, which is part of the body”, “the stomach and the small intestine are connected but they have no parts in common”, “in males, the urinary system and the reproductive system overlap”, “a myocardial parasite is located in a hole in the heart tissue”, etc. requires the definition of parthood and location relations (Donnelly, 2004). Parthood relations describe the spatial arrangement of parts of the human body at different levels of granularity. The location relations are used to describe the location of body parts within the body and the location of foreign occupants in the body. This knowledge is important for biomedical informatics, because it can be used for example in automated reasoning about parts of the body affected by disease (Schulz and Hahn, 2001);

- **Updating biomedical knowledge:** Although the use of ontologies in biology and medicine for the semantic integration of heterogeneous data receives increased attention, problems occur due to the changing and evolving nature of biomedical knowledge (McGarry et al., 2006). Advances in molecular biology, genetics and genomics through the use of new technologies, such as microarrays, provide vast quantities of experimental data. Thus, existing biomedical ontologies require review and updating of their contained knowledge. For example, an ontology for diabetes should be updated on any new advances regarding the effects of insulin resistance on protein expression and insulin regulated protein trafficking in fat cells (McGarry et al., 2007);
- **Searching and selecting biomedical ontologies:** Nowadays, the number and variety of biomedical ontologies is so large, that selecting one for an annotation task, for the construction of a new ontology, or for designing a specific application, is a challenging issue. It mainly relies on evaluation and comparison of the available ontologies (Tan and Lambrix, 2009). Although the National Center for Biomedical Ontology through its web portal offers integrated access to a library of biomedical ontologies (Rubin et al., 2006), the process of choosing the most suitable one is often a time consuming task. Therefore, during the ontology engineering process, the use of an ontology recommendation system to facilitate the identification of the ontology that is best suited to a specific application is needed (Jonquet et al., 2010);
- **The dynamics of relationships within the construction team:** Care should be taken to the efficient communication among ontology experts, knowledge engineers and domain experts during the biomedical ontology engineering process, in order to assure that the ontology is logically consistent, it adequately represents the domain of biomedicine under consideration and it explicitly aligns to ontological principles. The opposite may lead to wrong design decisions in biomedical ontologies (Boeker et al., 2012).

Development of specialized biomedical ontologies is still quite an empirical process. Due to the complex and dynamic nature of the biomedical domain, a flexible methodology is required which should take into account all the above mentioned

peculiarities related to the explicit representation of the biomedical knowledge.

5 CONCLUSIONS

Biomedical engineering involves activities that mainly require effective integration of biomedical content. This paper highlighted the fundamental role of ontologies in addressing this critical issue, by reviewing related work on biomedical ontology building, which is essential in designing next generation biomedical applications, such as magnetic nanoparticles, comparative analysis of human genome sequences, advanced imaging technologies, etc. Its main focus is on presenting the peculiarities emerged during biomedical ontology engineering.

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