

# Modeling Biomedical Assertions in the Semantic Web

Deendayal Dinakarbandian

Department of CSEE  
University of Missouri – Kansas City  
Kansas City, MO 64110

dinakard@umkc.edu

Tuanjie Tong

Department of CSEE  
University of Missouri – Kansas City  
Kansas City, MO 64110

tt967@umkc.edu

Yugyung Lee

Department of CSEE  
University of Missouri – Kansas City  
Kansas City, MO 64110

leeyu@umkc.edu

## ABSTRACT

We present an enhanced version of an ontological framework called MachineProse that is meant to represent the evolving knowledge resulting from biomedical research. This framework bridges the semantic gap between the use of keywords or controlled vocabularies to index articles and the expressive free-text content of research papers. The benefits of the framework are the ability to carry out precise searches to retrieve relevant literature, and novel abilities to provide answers to questions. We illustrate MachineProse with a case study of its application to Evidence Based Medicine.

## Categories and Subject Descriptors

I.2.4 [Knowledge Representation Formalisms and Methods]

## General Terms

Management, Design

## Keywords

Semantic Web, Ontology, Scientific Assertion, Representation, Query, Inferenceing.

## 1. INTRODUCTION

The growing number of published papers poses a serious challenge in keeping up with the latest developments in biomedical research. For instance, the number of papers added to MEDLINE [1] in the year 2005 (759672) was almost twice that added in 1995 (395036). In contrast, the population of the world grew by about 79 million in 1995 and by about 74 million in 2005. This is an over-simplified depiction, but the implication is that the ratio of the number of papers published to the number of readers is large, and growing. In principle, there are two aspects that are time-

consuming in the assimilation of new knowledge. First, relevant papers have to be found. Second, the papers have to be read. The advent of the Internet and indexing technologies mitigate the first problem to some extent, and the use of structured abstracts and summaries make it easier to digest new knowledge in a timely manner. At the moment, abstracts serve the role of summarizing papers. Some journals require abstracts to be organized into sections, but this is still not machine-readable as unrestricted prose is used. Valuable time is expended in weeding through material irrelevant to the question of interest.

Analogous to a literature search, when a Web user is performing a complex task, he/she typically needs to identify a set of documents, using key word searches. The user then needs to extract relevant information from each document. All these steps have to be performed manually, in the right order, and with the correct items of information channeled to the correct input areas. The vision of the Semantic Web is to reduce these manual activities and to allow intelligent agents to automatically identify tasks, integrate them and execute them for achieving the intended goals of the user. This will only be possible if documents draw the terms they are using from ontologies. Unfortunately, there is no framework to facilitate the mapping document terms to multiple ontologies. Thus, if documents use terms from different ontologies in the same domain, we face the problem of integrating those ontologies.

Over the past several years, the field that has been most active in building and using terminologies, ontologies and vocabularies has been Biomedical Informatics. There exist a large number of ontologies developed for different purposes (literature indexing and retrieval, electronic patient records, statistical reports on mortality, billing), in different subdomains (diseases, micro-organisms, diagnoses, medical devices, procedures, drugs). Each ontology has its own representation of the world, suitable for the purpose it has been developed for. Yet, universal attempts to represent the medical domain are usually limited in scope (GALEN) or lack a strong organizational structure (UMLS). The UMLS consists of about 100 individual ontologies, but utilizing such ontologies for specific applications is a difficult task that requires a large amount of expensive human expert labor. Existing methods of mapping to use ontologies are based on structural and semantic methods, however, their results are far from satisfactory.

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We have developed an ontological framework called MachineProse [2] that may be used to index and query biomedical knowledge mapped to multiple ontologies in an intuitive fashion, and with unprecedented expressivity. This paper presents recent enhancements to the model, and demonstrates its application to evidence-based medicine.

## 2. ONTOLOGY FRAMEWORK

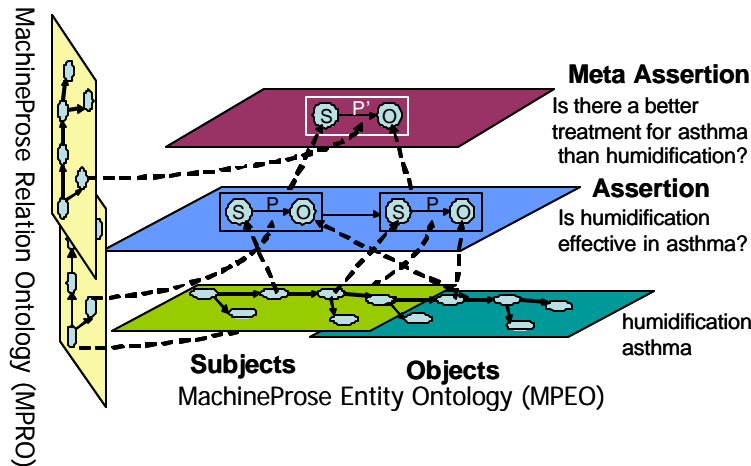


Figure 1. MachineProse Framework

MachineProse (MP) hinges on the observation that the majority of biomedical research is based on a Hypothesis, Conclusion or Verdict regarding the hypothesis, and Evidence in support of the conclusion regarding the hypothesis [2]. Given several publications regarding a hypothesis, multiple (and potentially conflicting) conclusions may be reached regarding it. Thus, evolution of knowledge regarding a hypothesis may be summarized by grouping all corresponding verdicts and supporting evidence.

A scientific assertion ( $A$ ) is defined by a unique hypothesis ( $H$ ), associated with verdict-evidence ( $V, E$ ) pairs. The hypothesis is defined as a tuple  $H = \langle S_a, R_a, O_a \rangle$ , where  $S_a$  is the subject,  $R_a$  a relation and  $O_a$  the object of a scientific assertion (Fig. 1). The subject is a concept in a domain ontology,  $S_a \in \text{MPEO}$ , and the object is a concept in a domain ontology,  $O_a \in \text{MPEO}$  (MachineProse Entity Ontology (MPEO) refers to a single or multiple ontologies of domains – examples of terms are ‘asthma,’ ‘adrenaline’). The relation is defined in the relations ontology,  $R_a \in \text{MPRO}$  (a relation ontology, examples of terms are ‘effective,’ ‘prevents’). Verdict ( $V$ ) denotes whether the particular assertion was upheld ( $P$  = Positive conclusion), opposed ( $N$  = Negative conclusion) or considered uncertain ( $I$  = Inconclusive). Evidence ( $E$ ) describes any proof for the verdict on the hypothesis. The Evidence is typically a reference to a specific journal article, conference publication or other peer-reviewed report. Consider an example of an MP assertion  $\langle \text{Azathioprine, effective, Asthma} \rangle$

$\langle I \rangle$ . This means that the assertion “Azathioprine is *effective in the treatment of asthma*” is inconclusive.

We have refined the representation of the MP scientific assertion [2] to enable more comprehensive encoding of knowledge, but without compromising machine-readability. We do this by adding additional layers of abstraction, at the same time minimizing the increase in complexity by staying with the basic unit of a triplet for knowledge encoding. The Assertion layer in the MachineProse

framework is mapped to multiple Domain ontologies (e.g., UMLS, MeSH, GO, etc). This is augmented by an additional layer comprised of Meta Assertions and their contexts. A Meta Assertion represents an assertion at a higher level of abstraction relating multiple assertions via Meta Relations. Soldatova and King [3] have noted that different levels of ontological representations can significantly increase interoperability between multiple domains. The architecture of the MachineProse framework is depicted in Figure 1.

Meta Assertions are widely applicable, especially to comparative studies. We use the following examples from Evidence Based Medicine (EBM) [4] to illustrate the benefits of using scientific meta-assertions. As EBM studies often focus on a comparative evaluation of several different drugs or protocols, they are particularly suited

to being cast as Meta Assertions.

A Scientific Meta Assertion is defined as a tuple  $MA = \langle H_m, V_m, E_m \rangle$  where  $H_m$  is a Meta Hypothesis together with a Meta Verdict  $V_m$  and Meta Evidence  $E_m$ . In an EBM study, a scientific Meta Assertion represents a comparative study of the effectiveness of various treatments for a given condition or disease. In the MachineProse framework, several Meta Assertion types pertinent to EBM are defined (Table 1). Each type of Meta Assertion is associated with specific semantics that can be exploited during querying and inferencing. The Comparison type implies that several distinct protocols are compared, e.g., *Is drug/treatment A better than drug/treatment B for D?* The Augmentation type refers to the effectiveness of add-on drugs, e.g., *Does the addition of drug/treatment A to drug/treatment B improve control of D?* The Drug-sparing type refers to treatment aimed at mitigating the side effects of a drugs without lowering its effectiveness, e.g., *Does the addition of drug/treatment A to drug/treatment B reduce the side effects of B while maintaining control of D?*

Based on the Comparison type of Meta-Assertion, a comparative hypothesis of several assertions ( $H_m$ ) can be defined and the relationships between these assertions described using Meta Relations such as “better than,” “similar to,” “worse than” and “later than”.  $H_m = \langle S_m, R_m, O_m \rangle$ , where subject  $S_m$  or object  $O_m$  is an assertion and  $R_m$  is a Meta Relation  $R_m \in \text{MPRO}$ .  $V_m$  denotes a comparative conclusion describing whether the evaluation of the particular assertion was changed (from positive to negative, positive to inconclusive, negative to positive, negative to inconclusive, inconclusive to positive, inconclusive to negative)

or stable (unchanged). This is useful to track when a scientific opinion contradicts a previous opinion.

As opposed to global searches like ‘asthma in children,’ it would be useful to carry out specific searches for treating a particular kind of asthma (e.g., exercise-induced asthma) in a particular group of patients (e.g., teenagers). Context terms can be used to qualify domain terms or relations in an assertion. We define three types of context depending upon the scope: Subject context, Relation context and Object context. Some of these terms can be directly borrowed from the MeSH terminology [5], while others will need to be created. In either case, it is important to have the meaning of these terms clearly defined. The details have been described in [2].

### 3. Processing with Assertions

#### 3.1 Assertion Query

Clinical guidelines may evolve based on different results from more recent evaluation of a long-standing hypothesis. Consider the assertion <Influenza\_vaccine, Increases, Exacerbations Asthma>. The verdict of this assertion was inconclusive according to the publication evidence in 2000 (PMID 11034684) but the same hypothesis has been changed to negative according to the publication in 2004 (PMID 15106150). This type of change in an assertion can be represented as a Meta Verdict, Inconclusive-to-Negative. A meta-assertion can track a change in verdict of the hypothesis being re-evaluated.

The “better\_than” meta-relationship has the potential to rank different treatments – even if they were evaluated in different research trials. If a research study concludes that high starting dose inhaled Corticosteroid is better than moderate starting dose inhaled Corticosteroid for Asthma, and another concludes that moderate starting dose inhaled Corticosteroid is better than low starting dose inhaled Corticosteroid for Asthma, it is reasonable to consider the implication that high starting dose inhaled Corticosteroid is better than low starting dose inhaled Corticosteroid for Asthma. Table 1 demonstrates some examples of the queries and inference that the MachineProse framework supports. In the table, ?ARB denotes a variable for representing an assertion consisting with Subject A, Relation R, Object B, and T and V denote time and verdict, respectively.

**Table 1. EBM Query Types and Examples**

<p><b>Assertion Analysis</b></p> <p>Which are the commonest assertions made in the past year?  All ?ARB where <math>\text{Count} (?ARB) &gt; \mu</math> &amp; <math>\text{Year} (?ARB) = \text{CY} - 1</math>, and <math>\mu</math> is a threshold for commonest</p> <p>Which are the most controversial assertions, i.e., have a large number of papers both affirming and countering an assertion?  All ?ARB where <math>\text{Count}(\text{Verdict} (?ARB) = 'p') - \text{Count}(\text{Verdict} (?ARB) = 'n') &gt; \mu</math>, and <math>\mu</math> is a threshold for determining controversial.</p> <p>Which assertions are recent but rare? All ?ARB where <math>\text{Year} (?ARB) - \text{cyear} &lt; ?</math> &amp; <math>\text{Count} (?ARB) &lt; \mu</math>, and ? is a threshold for recentness and <math>\mu</math> is a threshold for rareness.</p>
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#### Discrete Test of Effectiveness

Which are the recent interventions found to improve patient health? All ?ARB where  $\langle ?A, \text{effective}, ?B \rangle$

What are all the treatments for disease D?

All ?A where  $\langle ?A, \text{effective}, D \rangle$

What conditions is treatment A effective in?

All ?D where  $\langle A, \text{effective}, ?D \rangle$

Is a Drug/treatment A effective in a given Disease/condition D? (e.g. Is humidification effective in asthma?)

Any ?ARD where  $A \in \text{Drug/treatment} \ \& \ R = \text{“effective”} \ \& \ D \in \text{Disease/condition}$

#### Independent Comparison or Transitive Closure

Is drug/treatment A better than drug/treatment B for D?

$\langle \text{AR}_1\text{D}_1, \text{better\_than}, \text{BR}_2\text{D}_2 \rangle$  where  $A \neq B \ \& \ R_1 = R_2 \ \& \ D_1 = D_2$

Are there any treatments that have been found to be better than drug/treatment B for disease D?

Any ?AR<sub>1</sub>D<sub>1</sub> where  $\langle ?AR_1D_1, \text{better\_than}, \text{BR}_2D_2 \rangle$  and  $A \neq B \ \& \ R_1 = R_2 \ \& \ D_1 = D_2$

#### Augmentation Comparison

Is the supplementation of a treatment protocol with an additional drug more effective than the original protocol?

Any ?A<sub>1</sub>R<sub>1</sub>D<sub>1</sub> where  $\langle ?A_1R_1D_1, \text{better\_than}, A_2R_2D_2 \rangle$  and  $A_1 \supset A_2 \ \& \ R_1 = R_2 \ \& \ D_1 = D_2$

#### Drug Sparing Comparison

Is there a way to reduce the side-effects of treatment A for disease D without compromising effectiveness?

Any ?A<sub>1</sub>R<sub>1</sub>D<sub>1</sub> where  $\langle ?A_1R_1D_1, \text{better\_than}, A_2R_2D_2 \rangle$  and  $\text{SideEffect}(A_1) \supset \text{SideEffect}(A_2) \ \& \ R_1 = R_2 \ \& \ D_1 = D_2$

**Temporal Re-evaluation:** Has there been any recent change in the guidelines in my specialty?

$\langle (A_1R_1D_1 @ T_1 - V_1 \neq A_2R_2D_2 @ T_2 - V_2) \rangle$ , where  $A_1 = A_2 \ \& \ R_1 = R_2 \ \& \ \text{Object } D_1 = D_2 \ \& \ V_1 \neq V_2 \ \& \ T_1 \neq T_2$

### 3.2 Inferencing with Assertions

One of the advantages offered by an Ontology is the ability to carry out reasoning over instances. Ontologies like the Gene Ontology (GO) and MeSH topics have a hierarchy to describe terms in the Ontology, but both support limited types of relationships. GO supports IS\_A or PART\_OF relationships while MeSH topics only support IS\_A. For example, a query with the MeSH term “Hypersensitivity” also implies searching for articles with its synonyms “Allergy” and “Allergic reaction.” In addition, since “Immune Complex Disease” IS\_A form of “Hypersensitivity” based on the MeSH hierarchy, the automatic inference made is that documents containing “Immune Complex Disease” should also be searched for. MachineProse takes this a step further by offering a unique kind of reasoning that exploits hierarchies of relationships *per se*. For instance, since “Regulates” is a superclass of both “Stimulates” and “Inhibits,” a search for an assertion involving regulation, i.e., “A regulates B”, will also search for documents that have the assertions “A stimulates B” and “A inhibits B.” This is equivalent to a more specific form of the general assertion “Disease is Associated with Protein.” Just

like Chronic auto-immune urticaria and anti-thyroid antibody are specific subclasses of Disease and Protein, so is the relationship Caused a more specific form of Associated.

#### 4. RESULTS

We have implemented the enhanced MP Ontological framework (EBM assertions and meta-assertions) in the Web Ontology Language (OWL) [7] using the Protégé editor [8]. Whenever possible, we derived concepts or relations from existing ontologies including UMLS, MeSH and OBO. The Protégé Ontology Editor [8] supports the construction of ontologies and allows one to integrate multiple knowledge sources through the Protégé knowledge base. The assertions were represented in OWL because Semantic Web technologies [9] offer possibilities for interoperability over the World Wide Web.

For the evaluation of the proposed framework, we analyzed studies from the Cochrane Collaboration [10] repository that were indexed with the Medical Subject Heading (MeSH) [11] term “Asthma,” 87 abstracts were retrieved. Each abstract was read and the relevant clinical question rephrased as an EBM assertion according to the framework proposed in this paper. In contrast to earlier analysis of this corpus [2] as separate assertions, we analyzed these in terms of meta-assertions. A total of 116 assertions, 29 Meta Assertions and 19 Temporal evaluation were derived. 54 new domain terms were introduced and 20 MeSH terms were used. In the MachineProse Relation Ontology (composed of 46 general relations and 54 from UMLS semantic network), 9 new EBM specific relations and 3 Meta relations were implemented. The assertions were mapped to 18 different MeSH categories.

#### 5. DISCUSSION

During the past several years, there have been a number of Semantic Web approaches aimed at improving information retrieval. InfoSleuth [12] focused on linguistic techniques over a limited context of ontology for identification and annotation of concepts in documents. OntoSeek [13] proposed content-based access to Web data and achieved significant increases for both precision and recall using WordNet. SeCo [14] discussed how Semantic Web technologies can be employed in organizing and annotating yellow page services. The main idea is an Ontology-based service indexing based on the users’ viewpoint and the ontology is then used to navigate and browse through the advertisement. Semantic relations between the service classes can be defined in ontologies and recommended links are generated using ontologies.

OntoTag [15] takes into account both ontological and linguistic annotation criterion in multilevel annotation platform. OntoTag can be considered as the base for the intercommunication and metadata storage for querying and retrieving information from annotated web documents in the entertainment domain. The limitation of this technique is that it is too complex to automate the process of obtaining annotated compact, readable, and verifiable pages. Another work focused on the interoperability

between the OntoSem NLP system and Semantic Web. They proposed approaches to convert between OntoSem KR language and Semantic Web language (RDF and OWL) [16] and process annotations encoded in Semantic Web languages and query relevant facts through semantic search engines. Semantic annotation of unstructured and ungrammatical text has been described in [17]. It reveals that the lack of grammar and structure can be overcome by adding a collection of known entities and their common attributes to the information extraction system. Another interesting work [18] focuses on mapping and integration of multiple ontologies using a bridge ontology of complex relationships between them.

The main advantage of an assertion-based approach to indexing knowledge is that it is both human and machine-readable. It mirrors the process of scientific thinking and the biomedical research paradigm. The machine-readability confers scalability to automate searching and analysis of relevant information.

The three level structure of the enhanced version of MachineProse is reminiscent of the two-level structure of UMLS. UMLS consists of three Knowledge Sources of which we are interested in two, the Metathesaurus [19] and the Semantic Network [20]. The Metathesaurus is a compilation of terms, concepts, relationships, and associated information including over 1 million concepts and 5 million concept names in over 100 biomedical source vocabularies (UMLS). The *Semantic Network* of UMLS contains 135 semantic types (e.g., Disease or Syndrome, Virus). One may think of semantic types as high-level concepts, i.e., broad categories, such that a given lower-level concept gains a semantic context (in the Metathesaurus) by being assigned to a semantic type in the Semantic Network.

Machine Prose’s three-level structure offers benefits similar to the UMLS two-level structure. In addition, MachineProse is explicit in the crossing of abstraction boundaries between domain concepts, assertions and meta-assertions as the structure and semantics of the constructs *per se* are different at each level. The knowledge unit at each level is clearly defined and the relations between layers, from domain ontologies to scientific assertions and from scientific assertions to scientific meta-assertions, are defined as “PART-OF” relations. The contexts of each entity at each level can be clearly defined. Navigation, browsing, reasoning and managing of knowledge bases can be conducted in MachineProse with full awareness of the abstraction levels and context boundaries.

The MPRO (MachineProse Relation Ontology) is meant to represent a highly refined view of relationships focused on capturing scientific assertions and has been created from an expansion of the 54 semantic types in UMLS. UMLS does provide implicit support for assertions in the form of relationships like “X IS-PART-OF Y” or “X IS-A Y” but the universe of assertions is limited by the structure of the concept hierarchies and the current number of relational operators. In this respect, MachineProse is similar to the Galen Ontology based on GRAIL [21] which offers a rich variety of relationships like “actsOn” and “hasLocation.” However, Galen has primarily

focused on the representation of medical anatomy and procedures, while MachineProse is customized for scientific assertions reported by research groups.

There are several critical differences between the MachineProse assertion-based representation and other knowledge representations such as controlled terminologies, frame-based and logic-based approaches. A key difference between the role of MachineProse and existing Ontologies is that the latter are typically based on established domain knowledge. In contrast, MP meant to capture findings as they are published in research literature. Ideally, the potential of MP will be realized with minimal cost and unprecedented benefits if providers of information like journals, Pubmed, and Cochrane adopt this inline with the publication or indexing of each research paper.

## 6. CONCLUSION

We have shown how emerging knowledge from biomedical research can be represented by a semantic framework, and how this mitigates the problem of coping with the inexorable growth in research findings. This paper illustrates how sets of inter-related assertions can be used to provide machine-readable snapshots of research papers. As a proof of concept, we have analyzed a small number of diverse Evidence Based Medicine articles in the Asthma domain and modeled several ontologies required to represent the knowledge. We have also implemented a Web-based query/inferencing interface to process the data defined in the ontologies.

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