

# DISCOVERING RELATIONSHIP ASSOCIATIONS IN LIFE SCIENCES USING ONTOLOGY AND INFERENCE

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**Abstract:** Over one million papers are published annually in life sciences. Bioinformatics and knowledge discovery fields aim to help researchers conduct scientific discovery using the existing published knowledge. Existing literature-based discovery methods and tools mainly use text-mining techniques to extract non-specified relationships between two concepts. We present an approach that uses semantic web techniques to measure the relevance between two relationships with specified types that involve a particular entity. We consider two highly relevant relationships as a relationship association. Relationship associations could help researchers generate scientific hypotheses or create computer-interpretable semantic descriptors for their papers. The relationship association extraction process is described and the results of experiments for extracting relationship associations from 392 semantic graphs representing MEDLINE papers are presented.

## 1 INTRODUCTION

The field of life sciences is one of the fastest growing academic disciplines (Marrs and Novak, 2004). More than one million papers are published each year in a wide range of biology and medicine journals (King and Roberts, 1986). Recent progress in genomics and proteomics has generated large volumes of data on expression, function, and interactions of gene products. As a result, there is an overwhelming amount of experimental data and published scientific information, much of which is available online. Researchers in the bioinformatics and knowledge discovery fields have been studying how to use the existing literature to discover novel knowledge or generate novel hypotheses.

Scientific discovery is a type of human intellectual activity. Based on observations and theory, researchers define hypotheses that they test experimentally. However, due to the explosive growth of the literature, individual scientists cannot study all of the experimental data and scientific information that is available.

Computational methods have been used to help scientists generate hypotheses (Langley, 2000; Racunas *et al.*, 2004). For example, several attempts have been reported to develop informatics tools that replicate Swanson's discovery in 1986 that fish oil

may benefit patients with Raynaud's disease solely from studying the literature (Swanson and Smalheiser, 1997; Weeber *et al.*, 2005; Hristovski *et al.*, 2005; Srinivasan, 2004). The possibility of linking different scientific disciplines through intermediate, or shared, interests has commonly been described as Swanson's ABC model. Most of these literature-based discovery methods employ text-mining techniques to find relationships of unspecified type between two domain-related concepts that are implied by the literature.

In this paper, we present a technique for literature-based discovery of hypotheses based on measuring the association between two relationships of specified type that involve a particular entity or concept. We call this a relationship association. A relationship association is a special kind of association rule that states "if concept A has relationship R1 with concept B, then it is likely that concept A has relationship R2 with concept C."

Most scientific papers describe relationships between concepts from the study domain, which have been identified through research. A relationship is essentially a semantic statement that predicates the way in which one concept modifies the other semantically. Our goal is to discover interesting association rules between these relationships.



based on the other part of the association.

Our approach is based on two assumptions. First, because relationship associations describe associations of relationships between classes of entities, we assume that similar entities have similar relationships. Second, because we use semantic graphs from a small part of the scientific literature to extract the relationship associations, we assume that if one relationship association appears in the sample data with a high probability, then it will also appear in the whole literature with a similar probability.

This paper is organized as follows. In Section 2, we describe our work that forms the background for this paper. In Section 3, we present our approach to extract the relationship associations. In Section 4, we describe experiments using 392 semantic graphs for papers from MEDLINE to obtain relationship associations. The presentation and experimental application of the algorithm for extracting relationship associations are the main contributions of this paper. In Section 5, we discuss related work.

## 2 PRELIMINARY WORK

Many applications of semantic web technologies in the life sciences have appeared recently, including several large ontologies for annotating scientific abstracts, such as the Open Biomedical Ontologies (OBO) and the Unified Medical Language System (UMLS) Semantic Network. In order to describe a paper from MEDLINE as a semantic graph, we developed the UoT ontology based on a subset of the Medical Subject Headings (MeSH) vocabulary.

EKOSS (Expert Knowledge Ontology-based Semantic Search) (Kraines *et al.*, 2006) is a web-based knowledge-sharing system that enables users to create semantic graphs describing their knowledge resources, such as scientific papers, using ontologies. Figure 1 shows a semantic graph created to describe a paper from MEDLINE (Aoyama and Kamiya, 2005). The semantic graph contains 19 instances of classes from the UoT ontology together with 23 relationships between the instances.

In preliminary work, we have used EKOSS to create these kinds of semantic graphs for 392 papers selected from MEDLINE (unpublished material).

## 3 RELATIONSHIP ASSOCIATION EXTRACTION

There are three main aspects to extracting relationship associations: the data structure, the

method for determining if a relationship association appears in a particular semantic graph, and the algorithm for extracting the relationship associations from a set of semantic graphs.

### 3.1 Semantic Graphs

The data structure determines the extracting algorithm. Our approach uses an ontology to represent papers semantically and unambiguously. We use one semantic graph to represent one MEDLINE paper. The nodes of a semantic graph are instances of ontology classes, and the edges are relationships between the instances that are specified by properties also defined in the ontology. Each instance can have a descriptive text label. Semantic graphs, such as the one shown in figure 1, act to structure the knowledge contained in the MEDLINE papers for extracting relationship associations.

### 3.2 Semantic Matching

Matching semantic graphs is different from text matching, such as calculating the similarity of two strings (Cohen *et al.*, 2003). Semantic matching techniques compare two data structures at a semantic level, often by using some logic inference methods.

We use a description logics reasoner software, RacerPro ([www.racer-systems.com](http://www.racer-systems.com)), to evaluate the match between a search semantic graph and a target semantic graph through a combination of logic and rule-based inference. First, we add the target graph to the reasoner's knowledge base together with the ontology used to create the graph. Then, we convert the search graph into a set of semantic queries by creating sub graphs of the search graph that contain a specified number of properties and instances. In most cases, this is one property and two instances, i.e. a semantic triple. Queries are created by replacing the instances in the sub graphs with class variables. Rules for replacing instance classes with super classes and properties with super properties can be applied to increase matching recall. Finally, we ask the reasoner how many of the queries match the target graph, where a query matches if instances in the target graph binding to each of the class variables in the query subject to the specified relationship(s) can be found. The fraction of matching queries gives the semantic similarity between the two graphs. A simple example is shown in Figure 2. Details are given in (Guo and Kraines, 2008).

### 3.3 Extraction Process

The process of extracting relationship associations

takes the set of semantic graphs as the input. The output is a set of linked pairs of semantic relationships, where each relationship is defined as a triple consisting of a subject or “domain” class, an object or “range” class, and a directed property specifying the relationship between the two classes. A linked pair of semantic relationships is a pair of semantic relationships that share one class in common. We refer to these linked pairs of semantic relationships as relationship associations.

### 3.3.1 Generating Triple Queries

A semantic triple – consisting of a domain instance, a range instance, and a property between them – is the minimum unit of a semantic graph. One semantic graph contains several semantic triples. The definitions are formalized as follows:

$$\text{Graph} = \{\text{Triple}^*\}$$

$$\text{Triple} = \{\text{domain}, \text{property}, \text{range}\}$$

First, for each triple in a semantic graph, we create one triple query, defined as follows:

$$\text{TripleQuery} = \{ \text{domain class variable}, \text{property}, \text{range class variable} \}$$

In a triple query the instances of the triple are converted to variables with the same classes. Thus, a triple query converts the asserted relationship between two specific entities made by the triple into a generalized relationship between ontology classes.

There may be some duplicate triple queries generated from the set of semantic graphs. However, because we only want to link two triple queries whose triples both appear in the same semantic graph and share a common entity, we keep all of the generated triple queries at this point.

### 3.3.2 Matching Triple Queries

We use RacerPro to infer matches between queries and graphs via both logical and rule-based reasoning. The logic is built into the ontology using formalisms provided by the description logic that is supported by the ontology specification we used (OWL-DL). The rules are pre-defined for a particular ontology by domain experts. Details are given in (Kraines *et al.*, 2006; Guo and Kraines, 2008).

If the reasoner can find a pair of instances in a particular semantic graph meeting the class and relationship constraints of a triple query *Query1*, then we say that the triple *Triple1* represented by *Query1* appears in the semantic graph. By using both logical and rule-based reasoning, we can get matching results that are implied at a semantic level because the reasoner can infer relationships between instances that are not explicitly stated in the semantic graph. For example, consider the segment of the

semantic graph in figure 1 between the instance of Flagellum called *chlamydomonas flagellum* and the instance of Cell Movement called *tip-directed movement*. The triple query “find some instance of a Flagellum that is the location of some instance of Cell Movement” does not actually occur in the graph because there is no property between *chlamydomonas flagellum* and *tip-directed movement*. However, figure 2 shows that the query matches with the semantic graph because the relationship is implied by the relationships specified with the instance of Cytoskeleton called *frayed axonemes*. This match is a result of the rule “If A has structure part B and B is location of C, then A is location of C” together with the transitivity of the “location of” relationship.

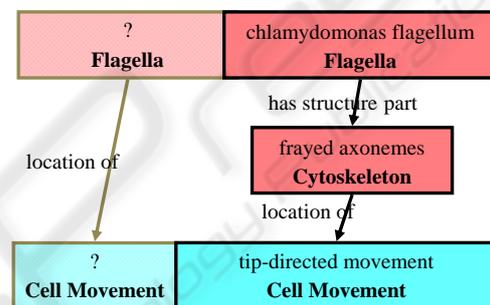


Figure 2: An example of semantic matching. Instances are indicated with boxes where the first line of text gives the instance name and the second line of text gives the instance class. Properties are shown by directed arrows labelled with the property name. The part in outlined in black is from the semantic graph. The part in outlined in gray is the query.

Using the reasoner, we match all triple queries with all semantic graphs. We then calculate the frequency that each triple query occurs in the semantic graphs. If a triple query only occurs in the semantic graphs a few times, then it is not likely to be involved in a relationship association. Therefore, we use a user-specified threshold value to filter the triple queries. Queries with frequencies less than the threshold value are removed, and the rest are used to create association queries in the next step.

### 3.3.3 Generating Association Queries

Now, we have a set of triple queries together with the frequencies in which they occur in a set of semantic graphs. In this step, we create association queries from this set of triple queries.

For each graph, we find all pairs of triples that share one instance and therefore comprise two connected arcs of the semantic graph; that is, they form a connected segment with three instances and

two properties. If both of the corresponding triple queries are in the set of triple queries generated in 3.3.2, then the pair of triples is a candidate for creating an association query.

We create an association query from each triple pair meeting the conditions above. However, to decrease the computational load of matching them with the set of graphs, we remove duplicate association queries in the next step.

### 3.3.4 Removing Duplicate Queries

Because we use semantic matching to match an association query with a semantic graph, two queries with same semantic meaning will get the same matching results. By removing association queries with the same semantic meaning, we can reduce the number of reasoning tasks that must be performed.

The graphs are directed, so even if two queries have the same classes and properties, if the directions of the properties are different, then the queries are different. Therefore, we must consider the three types of association queries shown in Figure 3.

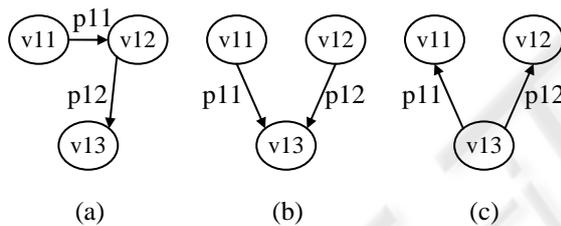


Figure 3: Three types of association queries.

We use three rules to remove duplicate association queries. The rules are presented using a query with type (a) as the original query  $Q1$  (queries with types (b) and (c) are similar):

$$Q1 = \{v11 \rightarrow p11 \rightarrow v12; v12 \rightarrow p12 \rightarrow v13\}$$

Each rule compares  $Q1$  to a second query  $Q2$  to determine whether or not to remove  $Q2$ .

**Rule 1**, if  $Q1$  and  $Q2$  meet the following conditions at the same time, then  $Q2$  is removed.

- $Q2 = \{v21 \rightarrow p21 \rightarrow v22; v22 \rightarrow p22 \rightarrow v23\}$
- The class of  $v2i$  is the same as or subsumes the class of  $v1i$  ( $i = 1, 2, \text{ or } 3$ ).
- The property of  $p2i$  is the same as or subsumes the property of  $p1i$  ( $i = 1 \text{ or } 2$ ).

**Rule 2**, if  $Q1$  and  $Q2$  meet the following conditions at the same time, then  $Q2$  is removed.

- $Q2 = \{v21 \rightarrow p21 \rightarrow v22; v23 \rightarrow p22 \rightarrow v22\}$
- The class of  $v2i$  is the same as or subsumes the class of  $v1i$  ( $i = 1, 2, \text{ or } 3$ ).
- The property of  $p21$  is the same as or subsumes the property of  $p11$ .

- The inverse property of  $p22$  is the same as or subsumes the property of  $p12$ .

**Rule 3**, if  $Q1$  and  $Q2$  meet the following conditions at the same time, then  $Q2$  is removed.

- $Q2 = \{v22 \rightarrow p21 \rightarrow v21; v22 \rightarrow p22 \rightarrow v23\}$
- The class of  $v2i$  is the same as or subsumes the class of  $v1i$  ( $i = 1, 2, \text{ or } 3$ ).
- The property of  $p22$  is the same as or subsumes the property of  $p12$ .
- The inverse property of  $p21$  is the same as or subsumes the property of  $p11$ .

As a result of this step we get a set of association queries with unique semantics.

### 3.3.5 Matching Association Queries

The matching method described in Step 3.3.2 is used to match the association queries with each of the graphs and calculate the frequencies in which they occur. Association queries whose frequency is less than a given threshold are removed. The rest of the queries are candidates for relationship associations.

### 3.3.6 Calculating Probabilities

From the previous steps, we get a set of association queries meeting a specified frequency. In order to help users find useful relationship associations, we calculate two conditional probabilities for each association query from the frequencies of occurrence for the two triples that make up the association query:

The probability that the second triple appears if the first triple appears,  $prob_{1,2} = P(t2 | t1)$ .

The probability that the first triple appears if the second triple appears,  $prob_{2,1} = P(t1 | t2)$ .

Generally, a high value of  $prob_{1,2}$  ( $prob_{2,1}$ ) means that if the first (second) triple appears in a semantic graph, then it is likely that the second (first) triple will also appear. If both probabilities are high, then it is likely that the two triples will only appear at the same time.

## 3.4 Relationship Associations

As a result of the extraction process described above, we get a set of association queries together with their probabilities of occurrence. However, this information can be difficult for users to understand. So we use templates and simple natural language generation algorithms to create natural language expressions of the relationship associations from the association queries. The users can examine these relationship associations to identify those that are most reasonable and interesting. These final relationship associations can be used to generate

scientific hypotheses or to help users to create new semantic graphs.

## 4 EXPERIMENTS

Using the process described above, we have conducted experiments to obtain relationship associations from a set of 392 MEDLINE papers. In this section, we report the results of this experiment

As described in section 2, semantic graphs were created for 392 papers selected from MEDLINE using the UoT ontology that we have developed in other work. The UoT ontology has 1,762 classes and 151 properties. We used those classes and properties to create 392 semantic graphs. On average, each semantic graph has 26 instances and 34 properties. The entire set of graphs contains 10,186 instances and 13,283 properties.

We created 13,283 triple queries from the 392 semantic graphs and then used the reasoner to determine how many semantic graphs contain each triple. We removed all triple queries that only matched with one semantic graph, since that was the graph from which the triple was obtained. As a result, there were 8,200 triple queries available for creating association queries.

We created 18,704 association queries based on the 8,200 triple queries and 392 graphs. We removed duplicates using the method from 3.3.4. We also removed highly general queries. For example, the property “associated with” in UoT ontology is the top-level of the property hierarchy. Therefore, a query containing that property does not give us any information about the relationship type. Other highly general “stop list” queries can be added as required. The result is 3,483 association queries from the 392 semantic graphs.

We matched these association queries with all of the semantic graphs using the reasoner and removed all queries that only appeared once. This resulted in a total of 1,215 association queries appearing in at least two of the semantic graphs.

Next, we calculated the two probabilities  $prob_{1,2}$  and  $prob_{2,1}$  for each of the 1,215 association queries. There are 629 association queries whose  $prob_{1,2}$  is greater than 0.5. There are 639 association queries whose  $prob_{2,1}$  is greater than 0.5. There are 891 association queries, for which at least one probability ( $prob_{1,2}$  or  $prob_{2,1}$ ) is greater than 0.5.

Finally, we converted the association queries into natural language expressions, and we asked an expert in life sciences to identify the most interesting relationship associations.

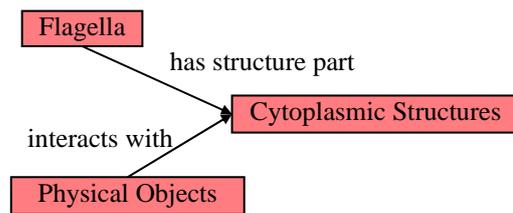


Figure 4: An example of a relationship association.

One example of a relationship association that was extracted in this experiment is shown in figure 4. The natural language representation is: “If a **Cytoplasmic Structure** is part of a **Flagellum**, then the probability that there is a **Physical Object** that interacts with the **Cytoplasmic Structure** is very high.”

This relationship association appears in five papers in our experiment:

“*Eukaryotic flagellum* is a **Flagellum** that has as a part some **Cellular Structure** called *flagellar axoneme*. The *flagellar axoneme* has as a part some **Microtubule** called *doublet microtubule* that interacts with a **Dynein ATPase** called *dynein arms*.” (Morita and Shingyoji, 2004)

“There is a **Flagellum** that has as a part some **Cellular Structure** called *axoneme*. *Sliding disintegration* is a **molecular process** that consumes the *axonome* and that is regulated by some **Ion** called *Ca(2+)*.” (Nakano *et al.*, 2003)

“*Chlamydomonas flagellum* is a **Flagellum** that has as a part a **Cytoskeleton** called *axoneme*. The *axoneme* has as a part some **Microtubule** called a *pair of doublet microtubules* that participates in some **binding process** called *dyein-microtubule interaction*. The *dyein-microtubule interaction* has as a participant a **Dynein ATPase** called *dynein*.” (Aoyama and Kamiya 2005) The semantic graph for this paper is shown in figure 1.

“*Flagellar* is a **Flagellum** that has as a part some **Cytoplasmic Structure** called *axoneme*. There is a **Microtubule** that is part of the *axoneme*. There is a **molecular process** that has as an actor the *Microtubule* and that is regulated by some **molecule part** called *dynein arm*.” (Yanagisawa and Kamiya, 2004)

“There is a **Flagellum** that has as a part some **Cytoplasmic Structure** called *axoneme*. *Glass substrate* is a **physical object** that binds to the *axoneme*.” (Sakakibara *et al.*, 2004)

## 5 RELATED WORK

The goal of the work presented in this paper is to discover new knowledge or hypotheses from the

literature. There are several previous attempts to attain this goal as we mentioned in Section 1.

Swanson presented one of the first literature-based hypotheses that fish oil may have beneficial effects in patients with Raynaud's disease (Swanson, 1986). His original discoveries were based on an exhaustive reading of the literature. Swanson described the process of his literature-based hypotheses discovery with his ABC model: if A and B are related, and B and C are related, he suggested that A and C might be indirectly related.

The text analysis scripts developed from Swanson's initial work evolved into the Arrowsmith system (Swanson and Smalheiser, 1997). The Arrowsmith system considers the titles of papers from MEDLINE. If two concepts co-occur in a title, then they are considered to be related. Therefore, the Arrowsmith system uses the relationships of co-occurrence of concepts in titles to infer the implicit relationships between two concepts.

Gordon and Lindsay developed a methodology for replicating Swanson's discovery based on lexical statistics. They used different word frequency-based statistics, including words and multiword phrases from entire MEDLINE records in addition to title words (Gordon and Lindsay, 1996; Lindsay and Gordon, 1999).

Weeber and colleagues used the Unified Medical Language System (UMLS) Metathesaurus to identify biomedically interesting concepts in MEDLINE titles and abstracts. They also exploited the semantic categorisation that is included in the UMLS framework (Weeber *et al.*, 2003, 2005).

Hristovski and colleagues used the manually assigned MeSH terms rather than the natural language text from MEDLINE citations. Their tool BITOLA computes association rules between MeSH terms. They used association rules to measure the relationship between MeSH term concepts in the form  $X \rightarrow Y$  (*confidence, support*). They used concept co-occurrence as an indication of a relationship between concepts, but they did not try to identify the kind of relationship. Therefore, although their association rule method determines whether or not there is implicit relationship between two concepts, it cannot identify the specific type of relationships that are associated. Their association rules are between two concepts, not two relationships (Hristovski *et al.*, 2001, 2005).

All these existing approaches focus on extracting non-specified relationships between two concepts in the target domain. In contrast, our approach tries to discover an implicit association between a pair of relationships, each of which predicates the specific way that one concept modifies another. We call a pair of relationships that are found to be relevant a

relationship association. Our approach uses semantic web techniques to enable this kind of discovery of implied associations between relationships. Although Hristovski *et al.* suggested that MeSH terms represent more precisely what a particular document is about than plain text, MeSH terms cannot represent the relationships between the entities that are described. Our approach uses concepts and properties specified in an ontology that logically structures a set of MeSH terms in order to represent the relationships between entities described in a MEDLINE paper, which we believe provides a more precise representation of that paper.

## 6 CONCLUSIONS

How to help researchers make scientific discoveries using the existing published knowledge is an important problem in bioinformatics and knowledge discovery fields. Recently, many literature-based discovery methods and tools have been proposed for solving this problem. These approaches mainly use text-mining techniques to discover non-specified relationships between two concepts.

We have presented an approach based on semantic web techniques to discover the association of pairs of specified relationships, which we call relationship associations. These relationship associations could help researchers generate scientific hypotheses and also assist in the creation of semantic graphs describing scientific documents in a computer-interpretable way.

We first reviewed our preliminary work for creating semantic graphs using an ontology developed from a subset of the MeSH vocabulary. Then, we described the process of extracting relationship associations from those semantic graphs. First, we generate triple queries from the semantic graphs and calculate their frequencies of occurrence by matching them with the set of semantic graphs using logical and rule-based inference. Next, we generate association queries from the triple queries whose frequencies of occurrence are larger than a specified threshold. We remove association queries that specify the same semantic relationships and match the remaining association queries with the set of semantic graphs to get their frequencies of occurrence. Finally, we convert the association queries whose frequencies exceed the given threshold to relationship associations expressed in natural language.

We discussed the results of an experiment to apply the approach to a set of 392 semantic graphs based on papers from MEDLINE. The relationship

associations that were created from these semantic graphs were examined and several interesting ones were identified.

The relationship association extraction method presented here can be used in other knowledge domains. In future work, we plan to apply the method to extract relationship associations from a set of semantic graphs that have been created to express failure events in the field of engineering.

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