An Unsupervised Text Mining Method for Relation Extraction from Biomedical Literature

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Abstract

The wealth of interaction information provided in biomedical articles motivated the implementation of text mining approaches to automatically extract biomedical relations. This paper presents an unsupervised method based on pattern clustering and sentence parsing to deal with biomedical relation extraction. Pattern clustering algorithm is based on Polynomial Kernel method, which identifies interaction words from unlabeled data; these interaction words are then used in relation extraction between entity pairs. Dependency parsing and phrase structure parsing are combined for relation extraction. Based on the semi-supervised KNN algorithm, we extend the proposed unsupervised approach to a semi-supervised approach by combining pattern clustering, dependency parsing and phrase structure parsing rules. We evaluated the approaches on two different tasks: (1) Protein–protein interactions extraction, and (2) Gene–suicide association extraction. The evaluation of task (1) on the benchmark dataset (Almed corpus) showed that our proposed unsupervised approach outperformed three supervised methods. The three supervised methods are rule based, SVM based, and Kernel based separately. The proposed semi-supervised approach is superior to the existing semi-supervised methods. The evaluation on gene–suicide association extraction on a smaller dataset from Genetic Association Database and a larger dataset from publicly available PubMed showed that the proposed unsupervised and semi-supervised methods achieved much higher F-scores than co-occurrence based method.

Introduction

Because biomedical relations play an important role in biological processes, the study of interactions in the life sciences domain has captured considerable interest. Much effort is currently spent on extracting useful biomedical relationships such as protein–protein interactions or gene–disease associations.

Biomedical relation extraction techniques basically include two branches: interaction database based methods and text mining methods. Interaction database based methods rely on the availability of interaction databases, such as MINT [1], IntAct [2], BIND [3], and SwissProt [4], which predict interactions between entities using sequence, structural, or evolutionary information. Although these databases host a large collection of manually extracted interactions from the literature, manually curated databases require considerable effort and time with the rapid increasing of biomedical literature.

Since most biological facts are available in the free text of biomedical articles, the wealth of interaction information provided in biomedical articles motivated the implementation of text mining approaches to automatically extract biomedical relations. Text mining approaches to relation extraction have shown an evolution from simple systems that rely solely on co-occurrence statistics [5] to complex systems utilizing syntactic analysis or dependency parsing [6–8], and machine learning algorithms [9–12]. However, most of this research has concentrated on supervised methods requiring large amounts of labeled data. Such annotated resources are expensive to create because the annotation of relations is considerably complicated.

Open Information Extraction started as an effort to approach relation extraction in an unsupervised way by learning regularities and patterns from the web. The Open Information Extraction systems [13–15] do not need any manual data or rules, but the relational facts they extract are not disambiguated to entities and relations [16]. As a result, they are hard to be applied in biomedical domain. In addition, Unsupervised Semantic Parsing [17] aims at clustering entity mentions and relation surface forms, and thus generating a semantic representation of the texts on which inference may be used. Some techniques that have been used are Markov Random Fields and Bayesian generative models. These approaches are quite powerful but have very high computational requirements [18].

In this paper, we propose a novel approach for relation extraction. We identify interaction words using polynomial kernel
based pattern clustering, which can identify interaction words efficiently in an unsupervised way. The extracted interaction words are combined with phrase structure parsing and dependency parsing for relation extraction, which make full use of both full and partial sentence structure information. Based on the semi-supervised KNN algorithm, we also extend the proposed unsupervised approach to a semi-supervised approach.

In evaluation, we compare the proposed method with several state-of-the-art methods (including supervised and semi-supervised approaches, which used labeled data or manually compiled word list) using a standard biomedical relation corpus. The experimental results demonstrate the effectiveness of our approach. After that, we employ the proposed approach to predict gene–suicide associations, and show that it achieves much higher F-score than co-occurrence based method.

**Method**

Interaction words identification using pattern clustering

Based on the observation that quite a few biomedical relations can be inferred by interaction words (e.g., IL-6 activates human gp130; BDNF may play a role in suicidal behavior), in this section, we present an unsupervised approach for interaction words identification using pattern clustering.

**Interaction pattern extraction.** Windows of limited size around the entities can provide useful clues to identify the roles of the entities within a relation. If two biological entities are co-mentioned in a sentence within certain window, we extract the words between the two biological entities as a candidate pattern. A candidate pattern will be further processed by a filtering process, which filters stopwords, most common words such as “the”, “a”, “that”, and nonenglish words such as numbers or Greek symbols. Any biological entity name contained within a candidate pattern would also be filtered out. In addition, patterns with negation words (“no”, “not”, “neither”) are pruned.

**Interaction words identification.** Kernel methods (KMs) are a class of algorithms for pattern analysis, which had been well used in many applications. In this work, we employ KM based interaction pattern clustering for interaction words identification.

KMs approach the problem by mapping the data into a high dimensional feature space. In that space, a variety of methods can be used to find relations in the data [19]. In this work, an interaction pattern polynomial kernel (PK) is generated for pattern clustering. In the basic vector-space model, interaction patterns are represented by a matrix \( D \), whose columns are indexed by the patterns and rows are indexed by the terms.

A pattern \( p \) is represented by a row vector, see equation (1).

\[
\phi(p) = (tf(t_1, p), \ldots, tf(t_N, p)) \in \mathbb{R}^N
\]  

(1)

where \( tf(t_i, p) \) is the frequency of term \( i \) appeared in pattern \( p \). The corresponding kernel is given by the inner product between the feature vectors, see equation (2) and (3).

\[
K = D^T D
\]  

(2)

\[
k(p_1, p_2) = \langle \phi(p_1), \phi(p_2) \rangle = \sum_{j=1}^{N} tf(t_j, p_1) tf(t_j, p_2)
\]  

(3)

With the basic kernel, for degree \( d \) polynomials, the derived polynomial kernel (PK) is defined by equation (4).

\[
k(p_1, p_2) = (\phi(p_1))^T \phi(p_2) + c^d
\]  

(4)

where \( c \geq 0 \) is a constant trading off the influence of higher-order versus lower-order terms in the polynomial. The inner product \( \phi(p_1)^T \phi(p_2) \) between pattern \( p_1 \) and \( p_2 \) denotes their similarity value.

Based on the definition of polynomial kernel (PK), we can get a PK matrix, and pattern similarities are used to cluster interaction patterns. The pseudo-code of the proposed PK based interaction pattern clustering algorithm is presented in Algorithm 1.

Algorithm 1 first sorts the set of patterns \( \{Pat\} \) in the descending order of total frequency (Line 1). After sorting, the most common patterns in the corpus appear at the beginning of \( Pat \), whereas rare instances are shifted to the end. PoP function (Line 4) returns and removes the first pattern from \( Pat \). Assign function (Line 5) measures the similarity between the vector \( p \) that corresponds to pattern \( p \) and each cluster \( c_i \). Similarity between \( p \) and \( c_i \) is measured by function \( Avgsim = \frac{\sum_{p \in c_i} sim(p, r)}{|c_i|} \), where \( sim(p, r) \) is the similarity between vectors \( p \) and \( c_i \). \( |c_i| \) is the number of elements in cluster \( c_i \). \( Avgsim \) computes the average similarity between \( p \) and each vector \( v \in c_i \) (Line 13).

**Algorithm 1.** PK based interaction pattern clustering algorithm.

**Input:** pattern set \( \{Pat\} \), interaction pattern PK matrix \( K \), threshold \( \theta \)

**Output:** pattern clusters \( \{CPat\} \), interaction pattern PK matrix \( K \), threshold \( \theta \)

1: Sort \( \{Pat\} \)
2: \( \{CPat\} = \{\} \)
3: while \( \{Pat\} \neq \{\} \) do
4: \( p = \text{Pop}(\{Pat\}) \)
5: \( \text{Assign}(p, \{CPat\}, \theta) \)
6: end while
7: return \( \{CPat\} \)
8: function \( \text{Assign}(x, C, \theta) \)
9: \( c* = \{\} \)
10: \( \text{max} = -\infty \)
11: for cluster \( c_i \in C \) do
12: \( sim = \text{Avgsim}(x, c_i) \)
13: if \( sim > \text{max} \)
14: \( \text{max} = sim \)
15: \( c* = c_i \)
16: end if
17: end for
18: if \( \text{max} > \theta \) then
19: \( c* = c* \cup \{x\} \)
20: else
21: \( C = C \cup \{x\} \)
22: end if
23: return \( \{CPat\} \)

If the similarity between \( p \) and the most similar cluster \( c* \) is greater than the threshold \( \theta \), then we merge \( p \) to \( c* \). Otherwise, we form a new cluster that contains \( p \) and append it to \( \{CPat\} \). The while-loop (Line 3) is repeated until the pattern set \( \{Pat\} \) is empty.

Algorithm 1 has a threshold \( \theta \), which indirectly specify the number of clusters. We determine \( \theta \) heuristically based on the similarity score distribution of the interaction pattern PK matrix. Specifically, we first define \( n \) similarity score increment intervals: \([0, t_1], \ldots, [t_{n-1}, t_n]\) \( t_n \) is the max similarity in the PK matrix). We then count the pattern numbers in each interval. When there is a
significant drop of pattern number in the current interval (no more than 20 percent of the previous interval), we use that lower limit of the current interval as our threshold θ.

As most of interaction words are verbs and nouns, we employ the Stanford POS tagging tool [http://nlp.stanford.edu/software/tagger.shtml] to do the POS tagging for patterns and select the verbs which occur more than one times in each cluster. We then normalize the verbs (e.g., activated—activate) and extend interaction words from verbs to nouns (e.g., associate—association) by the SPECIALIST NLP Tools [http://lexsrv3.nlm.nih.gov/Specialist/Home/index.html] to extend the coverage.

Relation extraction using interaction words and sentence parsing

As stated previously, most of interaction words are verbs and nouns, and because the dependency grammar (DG) views the verb as the structural center of all clause structure, dependency grammar is very fit for relation extraction, and a lot of previous studies extract biomedical relations are based on dependency parsing [7] [20–21]. However, dependency parse cannot treat non-local dependencies, and thus rules acquired from the constructions are partial. In addition, one challenge posed by the biological domain is that current systems for parsing do not perform as well on the biomedical narrative as on the newspaper corpus on which they were originally trained [22].

In this work, we combine dependency parsing and phrase structure parsing for relation extraction.

Dependency parsing for relation extraction. We assume that if two biological entities are in a relation this should be reflected in their dependencies with the same interaction word. Biomedical dependencies are simply a specific case of dependencies that we would find with a dependency parser.

In the dependency grammar, a syntactic relation between two words \( w_1 \) and \( w_2 \) can be described as \( (w_1, w_2) \) depends on \( w_2 \) (or \( w_1 \)). Qiu defined two categories (direct and indirect dependency) to summarize all possible dependencies between two words in sentences [23].

Based on the definition of direct and indirect dependency, we define dependency distance (\( dd \)) between two words \( w_1 \) and \( w_2 \) by equation (5).

\[
\begin{align*}
dd(w_1, w_2) &= \\
&= \begin{cases} 
1 & \text{if there is a direct dependency between } w_1 \text{ and } w_2; \\
\text{dependency_numer} + 1 & \text{if there is an indirect dependency between } w_1 \text{ and } w_2; \\
+ \infty & \text{otherwise}
\end{cases} \\
&= \begin{cases} 
1 & \text{if there is a direct dependency between } w_1 \text{ and } w_2; \\
\text{dependency_numer} + 1 & \text{if there is an indirect dependency between } w_1 \text{ and } w_2; \\
+ \infty & \text{otherwise}
\end{cases}
\end{align*}
\]

Equation (5) ignores dependency direction. Both \( w_1 \) depends on \( w_2 \) and \( w_2 \) depends on \( w_1 \) are considered equal. Some examples are given in Figure 1.

Figure 1 (1) illustrates the dependency distance (\( dd \)) between two words \( w_1 \) and \( w_2 \) equal to one. Figure 1 (2) shows that both \( w_1 \) and \( w_2 \) have direct dependencies with word \( A \), and the dependency distance (\( dd \)) between two words \( w_1 \) and \( w_2 \) is equal to 2. Figure 1 (3) shows that both \( w_1 \) and \( w_2 \) have direct or indirect dependencies with word \( A \), and the dependency distance (\( dd \)) between two words \( w_1 \) and \( w_2 \) is above 2.

Figure 2 shows the dependency tree we obtained for the sentence ‘Recombinant neuregulin-2beta induces the tyrosine phosphorylation of ErbB2, ErbB3 and ErbB4 in cell line express all of these erbb family receptor.’

Based on this dependency tree, we can get the dependency distance (\( dd \)) between two words. For instance, there is a direct dependency between ‘ErbB2’ and ‘ErbB3’, therefore, \( dd(’ErbB2’, ’ErbB3’) = 1 \); there is an indirect dependency ‘induces—phosphorylation—of—ErbB2’ between ‘induces’ and ‘ErbB2’, and the dependency number between them is three, therefore \( dd(’induces’, ’ErbB2’) = 3 \).

Figure 2. The dependency tree of the sentence ‘Recombinant neuregulin-2beta induces the tyrosine phosphorylation of ErbB2, ErbB3 and ErbB4 in cell line express all of these erbb family receptor.’ where words are assigned with word positions (number appended to words), dependency types (italic) appended to edges. Words marked in bold indicate gene/protein names. Words in rectangle indicate interaction words.

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For long and complex sentences, the dependency distance between entity node and interaction word node may above four. For instance, in the dependency tree of the sentence ‘A double point mutation in the activation domain of p53 impaired the ability of this domain to activate transcription and its ability to interact with both TAFII40 and TAFII60,’ the derived dependency path from ‘p53’ to ‘interact’ is ‘p53—of—domain—in—mutation—impaired—to—transcription—ability—interact.’ Because $d_d('p53','interact')>4$, the relations (p53, TAFII40) and (p53, TAFII60) cannot be detected by dependency rules. We apply phrase structure parsing rules to extract the relations that cannot be identified by dependency rules.

Phrase structure parsing for relation extraction

Phrase structure grammars identify syntactic rather than semantic relations of dependency grammars. Phrase structure parsing is full parsing, which takes into account the full sentence structure. Combined with the interaction characteristics between biological entities, we focus on the type of NP+VP structure, shown by Figure 3.

Figure 3 illustrates that $w_1$ is in an NP structure, $w_2$ is in a VP structure, and the NP node and VP node have the same parent node. NP+VP structure is able to catch both full and partial sentence structure information. When the NP and VP nodes are the separate direct parents of $w_1$ and $w_2$, the NP+VP structure represents a partial sentence structure, while when the NP and VP nodes are the separate indirect parents of $w_1$ and $w_2$, the NP+VP structure represents a wider range structure. When P node is the root node, NP+VP structure represents a full sentence structure.

Because current systems for biomedical narrative parsing are not as reliable as those on newspaper corpora, another benefit that we combine dependency parsing and phrase structure parsing is that two different parsers can compensate for each other from the view of system accuracy.

![Diagram of NP+VP phrase structure between $w_1$ and $w_2$.](https://example.com/diagram.png)

**Table 1. The extracted paths and relations from the dependency tree (Fig. 2) by Rule RD1.**

| No. | Path | Relation |
|-----|------|----------|
| 1   | neuregulin-2beta—induces—phosphorylation—of—ErbB2 | (neuregulin-2beta, ErbB2) |
| 2   | neuregulin-2beta—induces—phosphorylation—of—ErbB2—ErbB3 | (neuregulin-2beta, ErbB3) |
| 3   | neuregulin-2beta—induces—phosphorylation—of—ErbB2—ErbB4 | (neuregulin-2beta, ErbB4) |
| 4   | ErbB3—ErbB2—of—phosphorylation—induces—phosphorylation—of—ErbB2 | (ErbB3, ErbB2) |
| 5   | ErbB4—ErbB2—of—phosphorylation—induces—phosphorylation—of—ErbB2 | (ErbB4, ErbB2) |
| 6   | ErbB3—ErbB2—of—phosphorylation—induces—phosphorylation—of—ErbB2—ErbB4 | (ErbB3, ErbB4) |

*Words marked in bold indicate the focused entities. Italic words indicate interaction words.*

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We employ Stanford PCFG phrase structure parsing [24]. The extraction rules based on phrase structure parsing are given as follows.

**Rules**

1. **RP1:** Entity1 and entity2 have a NP+VP phrase structure.
2. **RP2:** There is an interaction word A in the VP structure of the NP+VP structure in RP1.

Rules RP1 and RP2 applied on the sentence ‘A double point mutation in the activation domain of p53 impaired the ability of this domain to activate transcription and its ability to interact with both TAFII40 and TAFII60’ extract the relations (p53, TAFII40) and (p53, TAFII60) that were not be identified by dependency rules.

**Results and Discussion**

**Evaluation on protein–protein interactions extraction**

We use AImed corpus as the benchmark dataset for protein–protein interactions extraction. AImed corpus is manually developed by Bunescu et al. for protein–protein interaction and protein name recognition [25], which has been used for many protein interaction extraction systems [22] [26-30]. AImed corpus consists of 225 Medline abstracts: 200 are known to describe interactions between human proteins, while the other 25 do not refer to any interaction. There are 4084 protein references and around 1000 tagged interactions in this dataset. The corpus and the experimental data can be downloaded from our website (http://a1-www.is.tokushima-u.ac.jp/member/ren/Projects/Unsupervised-biomedical-relation-extraction.htm#userconsent#).

We compare the following four methods on the task of retrieving protein interactions from AImed. The performances are measured using the standard evaluation measures of precision ($p$), recall ($r$) and F-score ($F$), $F = 2pr/(p + r)$. We adopt the evaluation methodology of One Answer per Occurrence in the Document – OAOD (each individual occurrence of a protein interaction has to be extracted from the document) [28].

- **Yakushiji et al., 2005** [26]: This is a rule based method where linguistic rules were extracted from a relatively small annotated corpus. They demonstrated that their rule extraction method is better than manual-made extraction rules or rules generalized by machine learning techniques.
- **Mitsumori et al., 2006** [27]: This is a machine learning method. They applied support vector machines (SVMs) to extract protein-protein interaction. An annotated corpus was used for model training.
- **Bunescu et al., 2006** [22]: This is a kernel based method, which used three types of subsequence patterns to assert relationships between two entities. This is a supervised machine learning method.
This is a kernel-based machine learning method, which combined global and local context features. This is a supervised machine learning method and solely on shallow linguistic information.

Miwa et al., 2009 [29]: This is a kernel-based machine learning method, which combined several different layers of information from a sentence and its syntactic structures by using several parsers. This is a supervised machine learning method.

Erkan et al., 2007 [30]: This approach is based on the analysis of the paths between two protein names in the dependency parse trees of the sentences. The best performance is achieved by transductive SVM algorithm with edit distance similarity. This is a semi-supervised method.

Our proposed I (unsupervised): This is a clustering based method, which combines dependency and phrase structure parsing for relation extraction. This is an unsupervised method. In the step of interaction pattern extraction, the window of candidate pattern extraction is set 10 words. The parameters of the polynomial kernel (PK) are $c = 0$, $d = 0.5$ (equation 4). In Algorithm 1, the parameter threshold $\theta = 4$ is set by a heuristical method.

Our proposed II (semi-supervised): This approach combines our proposed I (unsupervised) approach and a semi-supervised KNN (K-Nearest Neighbor) algorithm [30]. In the semi-supervised KNN algorithm, the similarity between two instances is measured by edit-distance that proposed by Erkan et al., 2007 [30]. The semi-supervised KNN algorithm is used for instance classification firstly, and then the interaction words identified by our proposed pattern clustering method and the rules based on dependency parsing (RD1, RD2) and phrase structure parsing (RP1, RP2,) are applied for correcting errors in KNN classification. The parameter of the KNN algorithm is $K = 11$. The number of training sentences is 500.

Table 2 shows the results comparison on precision (p), recall (r), and F-score (f) respectively of these approaches.

### Evaluation on gene–suicide association extraction

Determining gene-disease associations will enhance the development of new techniques for prevention, diagnosis and treatment of diseases. As the identification of new disease genes based on biomedical experiments require considerable effort and time, increasing attention is being paid to identifying gene–disease associations by mining the amount of biomedical literature.

Suicide receives increasing attention around the world, with many countries developing national strategies for prevention. Hawton and Heeringen analyzed several risk factors for suicide, in which genetic loading is considered one of the most important factors [31]. Costanza et al. present the latest neurobiological findings that have been shown to be implicated in suicide completers [32].

In comparison to other diseases, biomedical experiments for finding suicide related genes are much harder to conduct. Many existing databases maintain only a few records on suicide and its related genes. In one of the most well-known gene–disease association databases, Online Mendelian Inheritance in Man (OMIM [33]), suicide has not been recorded and does not have a MIM code. Many other gene-disease databases (DisGeNET [34],

### Table 3. Results comparison with different linguistic parsing and rules.

| Suicide related gene list | Method                  | Dataset I |          |          | Dataset II |          |          |
|--------------------------|-------------------------|-----------|----------|----------|------------|----------|----------|
|                          |                         | P         | R        | F        | P          | R        | F        |
| GAD gene list            | Co-occurrence           | 54.40     | 100.00   | 70.50    | 14.90      | 95.10    | 25.70    |
|                          | Our proposed (Unsupervised) | 71.10     | 86.50    | 78.00    | 25.60      | 56.10    | 35.10    |
|                          | Our proposed (Semi-supervised) | 75.35     | 90.06    | 82.05    | 29.55      | 67.12    | 41.03    |
| GeneCards                | Co-occurrence           | 54.29     | 96.50    | 69.49    | 24.67      | 82.03    | 37.93    |
|                          | Our proposed (Unsupervised) | 63.46     | 91.67    | 75.00    | 28.37      | 76.62    | 42.18    |
|                          | Our proposed (Semi-supervised) | 67.80     | 94.66    | 79.01    | 33.28      | 81.12    | 47.20    |
In this paper we address the problem of biomedical relation extraction based on pattern clustering and sentence parsing. We evaluated our approach on two different tasks. The first task concentrates on protein–protein interactions extraction. Our approach identified interaction words using unsupervised pattern clustering. This is the difference between our approach and the existing methods that used labeled data.

We used two databases to get suicide related gene list.

(1) GAD gene list. It contains 52 suicide related genes, whose “Assoc?YorN” labels in GAD are null or “Y” in GAD database. The disease phenotype has been annotated by one of phenotypes in the set of {“Suicide”, “Suicide, Attempted”, “bipolar disorder suicide”, “depressed suicide”, “depressive disorder, major sui”, “schizoaffective disorder, alco”, “suicidal ideation”}.

(2) GeneCards gene list. It contains 362 suicide related genes, which are obtained by querying “suicide” in GeneCards database [38].

Text preprocessing. Sentences in abstracts are split by GENIA Sentence Splitter (http://www.genecards.org/index.php?path=/Search/keywored/suicide/0/500/score/desc), which is reported to have an F-score of 99.7 on 200 unseen GENIA abstracts. Gene and protein names are identified by GENIA Tagger (http://www.nactem.ac.uk/GENIA/tagger/) which is reported to have an overall F-score of 71.37% on named entity recognition performance. To normalize the gene names tagged by GENIA Tagger, we use the HUGO Gene Nomenclature Committee (HGNC) database (http://www.genenames.org/cgi-bin/hgnc_stats), which contains 84,584 genes (including gene synonyms). We combined each tagged gene name with its corresponding approved gene symbol.

Results. Table 3 shows the experimental results on the two datasets. The baseline method is co-occurrence based method.

Discussion. In this paper we address the problem of biomedical relation extraction based on pattern clustering and sentence parsing. We evaluated our approach on two different tasks. The first task concentrates on protein–protein interactions extraction. Our approach identified interaction words using unsupervised pattern clustering. This is the difference between our approach and the existing methods that used labeled data.

From Table 4, we can see that our proposed unsupervised approach has 21.7%, 7.4% and 0.9% improvement in F-score over Yakushiji et al. (2005)’s rule based method, Mitsumori et al. (2006)’s SVM based method, and Bunescu et al. (2006)’s Kernel based method. All of the three methods are supervised. Our proposed semi-supervised approach has 0.9% improvement in F-score over Erkan et al., 2007’s semi-supervised method, and superior to other supervised methods except for Miwa et al., 2009’s method.

In semi-supervised KNN algorithm, each data instance (labeled or unlabeled) is a node that is connected to its K nearest neighbor nodes. We experiment different K values to compare the F-scores with varying sizes of train. The sentences in AIMed dataset were firstly partitioned into labeled and unlabeled sentence randomly based on the ratio of labeled and unlabeled sentence number (from 1:5 to 1:1). The results are the averages over 10 such random runs.

Figure 4 shows the F-score curves by using semi-supervised KNN algorithm on the AIMed dataset with varying sizes of training data with different K values.

Figure 4 shows that the best F-scores were obtained when $K=11$ on the average. Based on this result, we compared the semi-supervised KNN algorithm and our proposed semi-supervised approach which combined semi-supervised KNN, pattern clustering, dependency parsing and phrase structure parsing. The parameter of the KNN algorithm is $K=11$.  

Table 4. The extracted interaction words of protein–protein interaction from AIMed.

| Interaction words (from AIMed corpus) |
|--------------------------------------|
| Bind, induce, activate, associate, mediate, block, interact, contain, phosphorylate |

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Figure 4. The F-score curves on the Almed corpus with varying sizes of training data with different K values.

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Figure 5. The F-score curves by using semi-supervised KNN algorithm and the proposed semi-supervised approach on the AIMed dataset with varying sizes of training data.

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Figure 5 shows the F-score curves by using semi-supervised KNN algorithm and the proposed semi-supervised approach on the AImed dataset with varying sizes of training data. In the proposed semi-supervised approach, the semi-supervised KNN algorithm was used for instance classification firstly, and then the interaction words identified by our proposed pattern clustering method and the rules based on dependency parsing (RD1, RD2) and phrase structure parsing (RP1, RP2) were applied for correcting errors in KNN classification.

In Figure 5, ‘Semi-supervised KNN+Drules’ means the approach combined with semi-supervised KNN, pattern clustering, and dependency parsing rules. ‘Semi-supervised KNN+Drules+Prules’ means the approach combined with semi-supervised KNN, pattern clustering, dependency parsing rules, and phrase structure parsing rules. We find that the proposed semi-supervised approach improved the performance of the semi-supervised KNN algorithm greatly. Both dependency parsing rules and phrase structure parsing rules contribute to improving the performance.

Table 4 lists the extracted protein–protein interaction words from AImed dataset by the polynomial kernel (PK) based pattern clustering method, which includes nine interaction verbs.

Based on the identified interaction words, we combined dependency parsing and phrase structure parsing for relation extraction. Table 5 compares the performances of relation extraction with different linguistic rules.

From Table 5, we can find that dependency parsing can achieve higher recall, while phrase structure parsing can achieve higher precision. Their combination took the best aspects of each, which achieved higher F-score than either of them. When comparing with previous rule based approaches, the rules defined in our approach are much simpler and easier to implement.

The second task focused on gene–suicide association extraction. Table 6 lists the extracted interaction verbs of gene-suicide relation from Dataset I and Dataset II.

From Table 6, we can find that the interaction verbs of gene–suicide relation and of protein–protein interaction are quite different. Based on these interaction verbs, we used the rules based on dependency parsing and phrase structure parsing for gene-suicide relation extraction. As shown in Table 2, when GAD gene list was matched against, our proposed method outperformed co-occurrence based method significantly; the F-scores obtained by the unsupervised method are improved about 7.5% and 9.4% separately on the two datasets; the F-scores obtained by the semi-supervised method are improved about 11.6% and 15.3% separately on the two datasets; when GeneCards gene list was matched against, our proposed unsupervised method outperformed co-occurrence based method about 5.5% and 4.3% separately on the two datasets; our proposed semi-supervised method outperformed co-occurrence based method about 9.5% and 9.3% separately on the two datasets. However we have to admit that being able to match the list of suicide-related genes present in databases does not equate to finding the appropriate relations within a document, which is one of the limitations of the evaluation approach.

### Conclusions

We have presented a novel approach to extract biomedical relations based on pattern clustering and sentence parsing. Compared to prior work, our approach does not require labeled relation dataset or manually compiled word list. The combination of dependency parsing and phrase structure parsing takes the best aspects of each, and achieved higher F-score than either of them. The linguistic rules defined in our approach are quite general and easy to implement in different biomedical relation extraction tasks, including protein–protein interactions, gene-disease association, etc. Based on the semi-supervised KNN algorithm, we extended the proposed unsupervised approach to a semi-supervised approach by combining pattern clustering, dependency parsing and phrase structure parsing rules.

We evaluated our approaches on two tasks. The first is protein–protein interactions extraction. The evaluation on the benchmark dataset (AImed corpus) showed that our proposed unsupervised approach outperformed three supervised methods. The three supervised methods are rule based, SVM based, and Kernel based separately. The proposed semi-supervised approach has 0.9% improvement in F-score over Erkan et al., 2007’s semi-supervised approach.

| Parsing type                                                                 | Linguistic rules | P     | R     | F     |
|------------------------------------------------------------------------------|------------------|-------|-------|-------|
| Dependency parsing                                                          | RD1              | 34.28 | 75.70 | 47.19 |
|                                                                              | RD1+RD2          | 38.32 | 72.74 | 50.20 |
| Phrase structure parsing                                                     | RP1+RP2          | 49.90 | 39.57 | 44.14 |
| Dependency parsing + phrase structure parsing                                | RD1+RD2+RP1+RP2  | 44.80 | 71.40 | 55.10 |

Table 6. The extracted interaction verbs of gene-suicide relation from Dataset I and Dataset II.

| Interaction words           | Dataset I | Dataset II |
|----------------------------|-----------|------------|
|                           | Associate, complete, control, increase, consider, homozygote, attempt, suggest, bear, repeat, carry, compare, classify, play, modify, find, indicate, influence, depress, affect, implicate, act, monitor | Attempt, associate, commit, program, increase, compare, complete, message, consider, influence, know, show, use, involve, link, carry, measure, obtain, confer, play, homozygote, implicate, assess, find, function, express, result, combine, contain, act, distinguish, decrease, admit, adopt, report, depress, take, identify, incur, load, risk, indicate, include, reduce, construct, live, confirm, announce, investigate, control, set, prevent, cingulate, liberate, suggest, monitor, hospitalize |

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method, which obtained the best result on Almed corpus among the existing semi-supervised methods.

The experiments also showed that the combination of dependency parsing and phrase structure parsing took the best aspects of each, and achieved higher F-score than either of them. When comparing with previous rule based approaches, the rules defined in our approach are much simpler and easier to implement.

We also evaluated our approaches on gene–suicide association extraction. They achieved much higher F-score than co-occurrence based method on a smaller dataset from Genetic Association Database (GAD) and a larger dataset from publicly available PubMed.

Author Contributions
Conceived and designed the experiments: CQ FR. Performed the experiments: CQ MW. Analyzed the data: CQ MW. Contributed reagents/materials/analysis tools: CQ. Wrote the paper: CQ MW.

References
1. Zanzoni A, Montecchi-Palazzi L, Quondam M X (2002) Mint: A molecular interaction database. FEBS Letters 513: 135–140.
2. Kerren S, Aranda B, Breuza L (2002) The InAct molecular interaction database in 2012. Nucleic Acids Research 40: 841–846.
3. Rader GD, Donaldson I, Wolting C (2003) Bind—the biomolecular interaction network database. Nucleic Acids Research 31: 248–250.
4. Bairisch A, Ag威尔er R (2008) The swiss-prot protein sequence database and its supplement trembl in 2000. Nucleic Acids Research 28: 45–48.
5. Chen ES, Hripesk a G, Xia H (2008) Automated acquisition of disease-drug knowledge from biomedical and clinical documents: An initial study. Journal of the American Medical Informatics Association 15: 87–90.
6. Rinaldi F, Schneider G, Kaljurand K (2007) Mining of relations between proteins over biomedical scientific literature using a deep-linguistic approach. Artificial Intelligence in Medicine 39: 127–136.
7. Funke J, Kuffner R, Zimmer R (2007) RelEx—Relation extraction using dependency parse trees. Bioinformatics 23: 363–371.
8. Miyao Y, Ohta T, Masuda K (2006) Semantic retrieval for the accurate identification of relational concepts in mass text bases. Proceedings of the 21st International Conference on Computational Linguistics and the 44th Annual Meeting of the Association for Computational Linguistics 1017–1024.
9. Roberts A, Gaizauskas R, Hepple M (2008) Extracting clinical relationships from patient narratives. Proceedings of the Workshop on Current Trends in Biomedical Natural Language Processing 10–16.
10. Rink B, Harabadju S, Roberts K (2011) Automatic extraction of relations between medical concepts in clinical texts. Journal of the American Medical Informatics Association 18: 594–600.
11. Bundschus M, Dejori M, Stetter M (2008) Extraction of semantic biomedical relations from text using conditional random fields. BMC Bioinformatics 9: 207–220.
12. Ananiadou S, Pyyaloa S, Tsujii J, Kell DB (2010) Event extraction for systems biology by text mining the literature. Trends in Biotechnology 28: 381–390.
13. Sekine S (2006) On-demand information extraction. Proceedings of the COLING/ACL on Main conference poster sessions 731–738.
14. Banko M, Cafarella MJ, Soderland S, Broadhead M, Etzioni O (2007) Open information extraction from the web. Proceedings of the 20th international joint conference on Artificial intelligence 2670–2676.
15. Bellegarda DT, Matsuo Y, Ishizuka M (2010) Relational duality: Unsupervised biomedical relation extraction by leveraging multiple kernels and parsers. International journal of medical informatics 78:12: e39–e46.
16. Banko M, Cafarella MJ, Soderland S, Broadhead M, Etzioni O (2007) Open information extraction from the web. Proceedings of the 20th international joint conference on Artificial intelligence 2670–2676.
17. Titov I, Klein N (2011) A bayesian model for unsupervised semantic parsing. Proceedings of the 49th Annual Meeting of the Association for Computational Linguistics 34–59.
18. Yao L, Haghihi A, Riedel S, Mccallum A (2011) Structured relation discovery using generative models. Proceedings of Empirical Methods in Natural Language Processing 1456–1466.
19. Bie T, Cristianini N (2004) Kernel Methods for Exploratory Pattern Analysis: A Demonstration on Text Data, Structural, syntactic, and statistical pattern recognition 3138: 16–29.
20. Erkan G (2007) Semi-supervised classification for extracting protein interaction sentences using dependency parsing. Proceedings of the Joint Conference on Empirical Methods in Natural Language Processing and Computational Natural Language Learning (EMNLP-CoNLL) 228–237.
21. Oygur A, Yu T, Erkan G, Radev DR (2008) Identifying gene-disease associations using centrality on a literature mined gene–interaction network. Bioinformatics 24: 217–225.
22. Bunesec R, Mooney RJ (2006) Subsequence Kernels for Relation Extraction. Advances in Neural Information Processing Systems 18: 171–178.
23. Qin G, Liu B, Bu J, Chen C (2011) Opinion Word Expansion and Target Extraction through Double Propagation. Computational Linguistics 37: 9–27.
24. Klein D, Manning CD (2003) Accurate Unlexicalized Parsing. Proceedings of the 41st Meeting of the Association for Computational Linguistics 423–430.
25. Bunesec R, Ge R, Kate RJ, Marcotte EM (2005) Comparative experiments on learning information extractors for proteins and their interactions. Artificial Intelligence in Medicine 33: 139–155.
26. Yakushiji A, Miyao Y, Tateisi Y (2005) Biomedical information extraction with predicate argument structure patterns. Proceedings of the Eleventh Annual Meeting of the Association for Natural Language Processing 93–96.
27. Mitsumori T, Murata M, Fukuda Y (2006) Extracting protein-protein interaction information from biomedical text with svm. IEICE Transactions on Information and Systems 89: 2464–2466.
28. Giuliano C, Alberti L, Lorenza R (2006) Exploiting Shallow Linguistic Information for Relation Extraction from Biomedical Literature. Proceedings of the 11th Conference of the European Chapter of the Association for Computational Linguistics 401–408.
29. Miyao Y, Sereca R, Miyaoa Y, Tsujii J (2009) Protein-protein interaction extraction by leveraging multiple kernels and parsers. International journal of medical informatics 78:12: e39–e46.
30. Erkan G, Oygur A, Radev DR (2007) Semi-Supervised Classification for Extracting Protein Interaction Sentences using Dependency Parsing. Proceedings of EMNLP-CoNLL 228–237.
31. Hawton K, Heeringen K (2009) Suicide. Lancet 373: 1372–1381.
32. Costanza A, D’Ortu I, Perroud N, Harper R (2013) Neurobiology of suicide: do biomarkers exist? Int J Legal Med 128: 75–82.
33. Online Mendelian inheritance in man, OMIM (TM). McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD). Available: http://www.ncbi.nlm.nih.gov/omim/Accessed 10 June 2013.
34. DisGeNET. Available: http://db.imim.es/DisGeNET/web/v02/home/ Accessed 10 June 2013.
35. KEGG DISEASE. Available: http://www.genome.jp/kegg/disease/ Accessed 10 June 2013.
36. The Human Gene Mutation Database. http://www.hgmd.cf.ac.uk/ac/index.php Accessed 10 June 2013.