Extracting relations from traditional Chinese medicine literature via heterogeneous entity networks

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ABSTRACT

Objective Traditional Chinese medicine (TCM) is a unique and complex medical system that has developed over thousands of years. This article studies the problem of automatically extracting meaningful relations of entities from TCM literature, for the purposes of assisting clinical treatment or poly-pharmacology research and promoting the understanding of TCM in Western countries.

Methods Instead of separately extracting each relation from a single sentence or document, we propose to collectively and globally extract multiple types of relations (eg, herb-syndrome, herb-disease, formula-syndrome, formula-disease, and syndrome-disease relations) from the entire corpus of TCM literature, from the perspective of network mining. In our analysis, we first constructed heterogeneous entity networks from the TCM literature, in which each edge is a candidate relation, then used a heterogeneous factor graph model (HFGM) to simultaneously infer the existence of all the edges. We also employed a semi-supervised learning algorithm estimate the model's parameters.

Results We performed our method to extract relations from a large dataset consisting of more than 100 000 TCM article abstracts. Our results show that the performance of the HFGM at extracting all types of relations from TCM literature was significantly better than a traditional support vector machine (SVM) classifier (increasing the average precision by 11.09%, the recall by 13.83%, and the F1-measure by 12.47% for different types of relations, compared with a traditional SVM classifier).

Conclusion This study exploits the power of collective inference and proposes an HFGM based on heterogeneous entity networks, which significantly improved our ability to extract relations from TCM literature.

Keywords: traditional Chinese medicine, relation extraction, heterogeneous entity networks, collective inference, factor graph model

RESEARCH AND APPLICATIONS

INTRODUCTION

The essential philosophy of traditional Chinese medicine (TCM) is holism, emphasizing the regulation of the integrity of the human body as well as the interaction between individuals and their environment, which provides a distinctive methodology and approach for diagnosing and treating disease.[1] TCM has attracted more and more attention worldwide as an alternative to modern medicine. Hundreds of thousands of TCM researchers have made great efforts to modernize TCM and integrate it with modern medicine. A large number of TCM research articles are published every year. Meanwhile, large-scale analyses of the large body of TCM literature has become an interesting research area in recent years, because such analyses can exploit the collective knowledge of TCM researchers and, in turn, add to the body of medical knowledge.

On the other hand, TCM is a very complex medical system in which multiple types of entities are involved, such as "herb," "formula" (a composition that consists of certain herbs), "symptom," and "syndrome" ("zheng" in Mandarin Chinese, a complex pattern of signs and symptoms, which is used as a holistic summary of a patient's status).[2] Multiple types of intricate relations can exist between these heterogeneous entities, such as composition relations between herbs and formulae, treatment relations between formulae and syndromes, effectiveness relations between herbs and syndromes, and association relations between syndromes and diseases. Establishing these relations is the goal of TCM research. Every researcher contributes his or her discoveries to the TCM knowledge base to form a large-scale, multi-source, and unstructured pool of natural language text data.

In this article, we study the problem of extracting relations from this pool of TCM data. More specifically, given a set of published scientific TCM documents, our goal is to identify all the relations between the instances of different types of entities in those documents. One of the main objectives of relation extraction from TCM literature is to help generate scientific hypotheses and clinical guidelines for practical diagnoses and treatments.[3] Specifically, the knowledge of all TCM researchers (found in the general body of TCM literature) can be integrated into one pool of data, the most significant associations between entities can be extracted from that pool, and these associations can be used to assist clinical treatment or poly-pharmacology research. In addition, the extracted relations may promote the understanding of TCM in Western countries.

Relation extraction from TCM data is somewhat more complicated than relation extraction from biomedical data. The main challenge of relation extraction from TCM data is the complexity of the TCM system itself. Multiple types of interwoven relations can exist between tens of thousands of heterogeneous TCM entities, so it is not advisable to extract a single type of relation independently of the others. Figure 1 gives an example of extracting multiple types of correlated relations between heterogeneous TCM entities. In addition, the vast majority of TCM literature is written in Chinese, a language in which the sentences have no spaces between words and, therefore, word segmentation is needed to automatically divide sentences into words. Errors in word segmentation obstructs feature generation in the relation extraction process.

In this article, we propose a novel approach to relation extraction, to collectively and globally extract relations from the entire corpus

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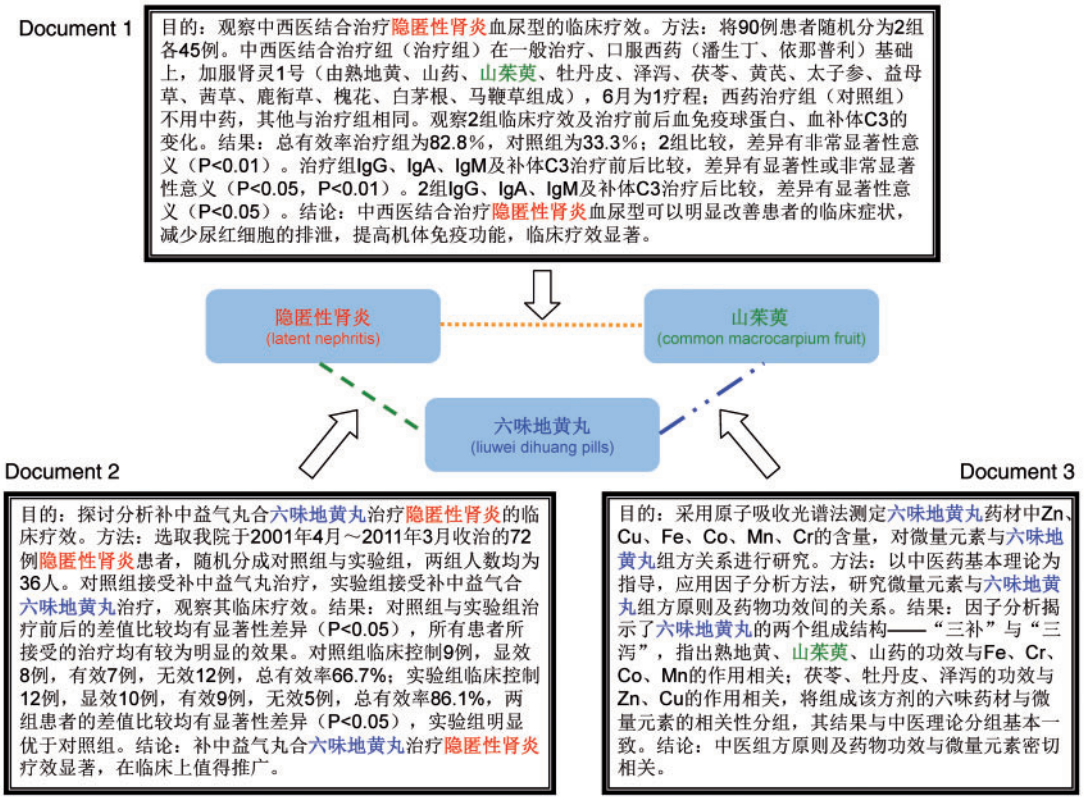
Figure 1: An example of extracting multiple types of correlated relations between heterogeneous traditional Chinese medicine (TCM) entities. Words in red font indicate a disease, words in blue font indicate a formula, and words in green font indicate an herb. The relations extracted from different documents are correlated with one another through their common entities.



of TCM literature from the perspective of network mining. In this approach, we first construct heterogeneous entity networks from the TCM literature. Specifically, we take all types of TCM entities that occur in the literature as nodes and create an edge for each pair of heterogeneous entities co-occurring in the same document. All the edges are treated as candidate relations to be identified. Figure 2 gives a simple example of a heterogeneous TCM network. We then propose a unified graphical model, called the heterogeneous factor graph model (HFGM), to simultaneously infer the labels of all the candidate relations by employing the concept of collective inference.[4,5]

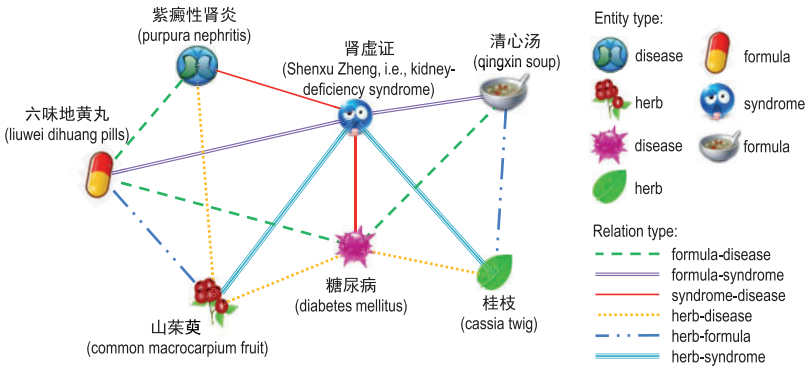
To evaluate the performance of our proposed method, we collected a dataset consisting of more than 100 000 article abstracts from a Chinese publication database and randomly annotated a sample of the relations found therein. We trained and evaluated our HFGM on this partially labelled dataset in a semi-supervised way. Our results demonstrate that our proposed method performs very well at extracting multiple types of relations, including herb-syndrome, herb-disease, formula-syndrome, formula-disease, and syndrome-disease relations.

RELATED WORK

Relation extraction has recently attracted increasing interest in the information extraction community, and many related methods have been successfully applied in the medical field.[6] Compared with open information extraction,[7–9] which tries to find all potentially useful facts and extract as many relations as possible from a large and diverse corpus in which no relation type is specified in advance, medical relation extraction only focuses on deriving the most salient prespecified types of relations from a single domain.

Many techniques have been proposed for biomedical relation extraction, in which a variety of biomedical relations (such as the interactions between proteins, genes, phenotypes, biological targets, and diseases) have been the subject of relation extraction tasks. The simplest method of biomedical relation extraction is to calculate the co-occurring frequency of the entity pairs.[10] This method commonly results in high recall but low precision.[11,12] Other researchers use part-of-speech rules[13] defined by domain experts[14] or derived from an annotated corpus[15] to describe the linguistic patterns of particular relations, a method that exhibits high precision but low recall. Classification-based approaches are also commonly used to identify biomedical relations. Roberts et al.[16] and Rink et al.[17] both describe a supervised classification system for detecting various clinical relations. Bundschus et al.[18] used conditional rand fields to identify disease-treatment and gene-disease relations. Abach and Zweigenbaum[19] propose a hybrid approach that combines patterns defined by domain experts as well as a support vector machine (SVM) classifier for extracting relations between diseases and treatments. Syntactic structures are also thought to assist relation extraction. Miyao et al.[20] performed deep parsing to annotate predicate-argument structures in order to identify and retrieve relational concepts from MEDLINE abstracts. Fundel et al.[21] produced dependency trees and generated syntactic rules to identify gene and protein associations. Similarly, Rinaldi et al.[22] used dependency trees to support the process of querying interactions between genes and proteins.

Figure 2: An example of a simple heterogeneous traditional Chinese medicine (TCM) network. Different icons and line styles indicate different types of TCM entities and candidate relations, respectively, which are closely correlated with one another. Many triadic closures are formed in the network.



Kernel methods have also been employed in the relation extraction process.[23–25]

Related works on relation extraction from the TCM literature are scarce. One of the pioneering works on this subject is a study by Wu et al.,[26] in which the authors used a bootstrapping method to extract syndrome-disease associations from a corpus of data. Based on this study, Zhou et al.[27] developed an integrative data mining system, called MeDisco/3S, to identify relations between syndromes and genes. Fang et al.[28] integrated the association information between entities in both TCM and modern medicine literature into a database system named TCMGeneDIT, in which a co-occurrence-based method and a rule-based method are used to extract different types of relations. In a recent work by Xue et al.,[29] the authors used a TCM integrated database (TCMID), which contains the most comprehensive information on TCM entities and relations to date, and employed co-occurrence to collect relations between herbs, ingredients, and targets from TCM articles published in Chinese.

All the above-mentioned methods assume that the labels of all relations are independently and identically distributed. However, these heterogeneous relations may be dependent on one another, through their common entities. For example, if we have identified one relation between herb A and formula B and another relation between formula B and syndrome C, then it is very likely that there is a relation between herb A and the syndrome C. This is a kind of transitive property among relations. If we can adequately model the widespread dependencies in the literature, it is likely that these dependencies will greatly help us to identify relations. However, the previous methods cannot capture such dependencies.

In this article, we propose a novel HFGM to incorporate all the data gathered from the body of TCM literature into a unified framework, for better identifying TCM relations. A factor graph[30] is a type of probabilistic graphical model that provides an elegant way of representing graphical structure with more emphasis on the factorization of the distribution of data. Many modified factor graph models have been proposed and successfully used in social network analyses, such as those measuring social influence,[31] mining social relationships,[32] inferring social ties,[33,34] and predicting reciprocal interactions.[35]

METHODS

Data Collection and Annotation

We collected abstracts of published articles on TCM from a Chinese publication database, then used four authoritative terminology dictionaries to detect TCM entities in the text of these abstracts. Next, we generated candidate relations between all co-occurring heterogeneous entities. Finally, a sample of relations was labelled by domain experts.

Terminology Dictionaries

Extracting relations from text first requires recognizing instances of the entities. Studying entity recognition is not within the scope of this article. Several relatively complete TCM terminology dictionaries have been published in online TCM databases such as TCMonline and TCMID. TCMonline (http://www.cintcm.com) is the earliest online TCM database system, built by the Institute of Information on Traditional Chinese Medicine at the China Academy of Chinese Medical Science in 1984. TCMID (http://www.megabionet.org/tcmid), which was built by the Institute of Biomedical Sciences at East China Normal University within the last few years, is a comprehensive database that provides information on and bridges the gap between TCM and modern life sciences. We collected dictionaries directly from these databases to detect the instances of entities in TCM literature.

We collected four TCM entity dictionaries by copying and merging the names of the four types of entities from both the TCMonline and TCMID databases: an herb dictionary that contains 8082 herbs, a formula dictionary that contains 39 932 formulae, a syndrome dictionary that contains 2209 syndromes, and a disease dictionary that contains 3316 Medical Subject Headings (MeSH) (http://www.nlm.nih.gov/mesh) disease terms.

TCM Literature

We collected a corpus of data from the China National Knowledge Infrastructure (CNKI) (http://www.cnki.net), which is one of the largest online Chinese publication databases. The collected corpus of data contains the abstracts of all 106 150 papers published in the 114 most popular Chinese TCM journals over the past 5 years, which almost covers all the aspects of TCM research. We used the four terminology dictionaries mentioned above to detect entities that occurred in the corpus of data, and found 3024 herbs, 4957 formulae, 1126 syndromes, and 1650 diseases. We then generated the candidate relations between the co-occurring heterogeneous entity pairs and identified: 11 197 herb-syndrome candidate relations, 11 755 herb-disease candidate relations, 9659 formula-syndrome candidate relations, 7882 formula-disease candidate relations, and 9645

syndrome-disease candidate relations. Note that we did not extract herb-formula relations, because all the formulae in the dictionary are classical TCM formulae, and their relations with herbs have already been well-defined.

Data Annotation

For training and quantitatively evaluating our proposed model, we randomly labelled a small fraction (ie, 10%) of each type of candidate relation. We asked three TCM experts (respectively denoted as Kang, Tang, and Zhan, according to their family names), who specialize in Chinese materia medica and clinical TCM, to annotate the data. For each candidate relation to be labelled, the three domain experts read the corresponding papers' abstracts to identify whether the two end-entities were really related or had just co-occurred by chance. The statistics of our dataset are summarized in Table 1, and the entire dataset is available online at http://arnetminer.org/TCMRelExtr.

We used Kappa statistics to measure inter-annotator agreements. As shown in Table 2, the Cohen's Kappa[36] scores between any two annotators and the Fleiss's Kappa[37] scores among the three annotators are mostly above 0.7, indicating substantial agreement. After that, we employed the majority rule to decide the final label of each candidate relation.

Problem Definition

In this paper, we propose extracting relations in the context of heterogeneous TCM networks. So, we first give the definition of heterogeneous TCM networks, then present the problem formulation.

We use $\tilde{V}$ and $\tilde{E}$ to denote the set of types of TCM entities and relations, respectively. In this paper, we have $\tilde{V} = \{\mathrm{H},\ \mathrm{F},\ \mathrm{S},\ \mathrm{D}\}$ and $\tilde{E} = \{\mathrm{HF},\ \mathrm{HS},\ \mathrm{HD},\ \mathrm{FS},\ \mathrm{FD},\ \mathrm{SD}\}$, where H, F, S, and D represent the entities "herbs," "formulae," "syndromes," and "diseases," respectively, and HF, HS, HD, FS, FD, and SD represent the relations "herb-formula," "herb-syndrome," "herb-disease," "formula-syndrome," "formula-disease," and "syndrome-disease," respectively.

Heterogeneous TCM Networks: Let $V_{\tilde{v}} (\tilde{v} \in \tilde{V})$ be a set of TCM entities of type $\tilde{v}$ and $E_{\tilde{e}} (\tilde{e} \in \tilde{E})$ be a set of TCM relations of type $\tilde{e}$. We define a *heterogeneous TCM network* as a graph $G = (V, E, \mathbf{X})$, where $V = \cup_{\tilde{v} \in \tilde{V}} V_{\tilde{v}}$, $E = \cup_{\tilde{e} \in \tilde{E}} E_{\tilde{e}}$ and $\mathbf{X} = \{\mathbf{X}_{\tilde{e}}\}_{\tilde{e} \in \tilde{E}}$ is a set of attribute matrices. Each $|E_{\tilde{e}}| \times d_{\tilde{e}}$ matrix $\mathbf{X}_{\tilde{e}} \in \mathbf{X}$ is associated with the edges of type $\tilde{e}$, where $d_{\tilde{e}}$ is the number of attributes of type $\tilde{e}$, each row of matrix $\mathbf{X}_{\tilde{e}}$ corresponds to an edge, each column corresponds to an attribute, and an element $\mathbf{x}_{\tilde{e}ik}$ denotes the value of the k-th attribute of edge $e_{\tilde{e}i}$.

TCM Relation Extraction Problem: Given a heterogeneous TCM network, $G = (V, E, \mathbf{X})$, then our objective is to learn a function to predict the label of candidate relations between TCM entities, ie,

$$f : G = (V, E, \mathbf{X}) \rightarrow L$$

Where L is the label space of the problem.

In this work, our goal is to identify the correctness (ie, reliability) of each candidate relation; therefore, we have $L = \{1,\ 0\}$, where the label of 1 means an edge is reliable and 0 means it is unreliable.

Heterogeneous Factor Graph Model

Model Framework

Given a heterogeneous TCM network $G = (V, E, \mathbf{X})$, we use $y_{\tilde{e}i}$ to indicate the label of edge $e_{\tilde{e}i}$ of type $\tilde{e}$. Let $Y_{\tilde{e}} = \{y_{\tilde{e}i}\}$ and $Y = \cup_{\tilde{e} \in \tilde{E}} Y_{\tilde{e}}$. Our objective is to then estimate the values of Y, and we can use a joint posterior probability $P(Y|\mathbf{X}, G)$ to model its distribution. Here, G denotes all forms of network information. This joint probability indicates that the labels of the edges depend not only on the local attributes associated with each edge, but also on the structure of the network.

A factor graph provides a way to factorize the "global" joint probability as a product of "local" factors, each of which depends on a subset of variables in the graph. To represent the dependencies between the labels Y and the attributes $\mathbf{X}$ and the correlations among the labels Y, we can define the following two categories of local factors:

- *Evidence factors*, which are used to capture the dependencies between the labels of edges and their attributes. For instance, an evidence factor $P(y_{\tilde{e}i}|\mathbf{x}_{\tilde{e}i})$ represents the dependency of the label $y_{\tilde{e}i}$ of an edge on its attributes $\mathbf{x}_{\tilde{e}i}$.
- *Compatibility factors*, which are used to capture the compatibility among the labels of edges. We use triadic closures in heterogeneous TCM networks to construct compatibility factors. Triadic closure[38] is one of the fundamental processes of linking information in a network and has been applied in many aspects of social network mining, such as in inferring social ties[34] as well as social roles and statuses.[39] We use $\tilde{C} = \{\mathrm{HFS},\ \mathrm{HFD},\ \mathrm{HSD},\ \mathrm{FDS}\}$ to denote the set of types of triadic closures, where HFS, HFD, HSD, and FDS represent "herb-formula-syndrome" relations, "herb-formula-disease" relations, "herb-syndrome-disease" relations, and "formula-disease-syndrome" relations, respectively. Let $c_{\tilde{c}j}$ be a triadic closure of type $\tilde{c}$ and $Y_{\tilde{c}j}$ its corresponding subset of labels; then, the compatibility factor $P(Y_{\tilde{c}j})$ indicates the correlations among the labels in $Y_{\tilde{c}j}$.

Table 1: Statistics of the Dataset

Relation Type	Number of Unique Candidate Relations		
	Labelled		Unlabelled
	Positive	Negative	
Herb-Syndrome	538	582	10 077
Herb-Disease	534	642	10 579
Formula-Syndrome	392	574	8693
Formula-Disease	377	411	7094
Syndrome-Disease	431	532	8681

Table 2: Inter-annotator Kappa Agreements

Relation Type	Cohen's κ Score			Fleiss's κ Score
	Kang-Tang	Tang-Zhan	Kang-Zhan	Kang-Tang-Zhan
Herb-Syndrome	0.7199	0.7537	0.7236	0.7032
Herb-Disease	0.8271	0.8657	0.7994	0.7789
Formula-Syndrome	0.7983	0.8431	0.8323	0.8264
Formula-Disease	0.6849	0.8176	0.8124	0.7735
Syndrome-Disease	0.7460	0.8867	0.8411	0.8110

Then, the joint probability can be factorized as follows:

$$P(Y|\mathbf{X}, G) = \prod_{\tilde{e}\in\tilde{E}} \prod_{e_{\tilde{e}i}\in E_{\tilde{e}}} P(y_{\tilde{e}i}|\mathbf{x}_{\tilde{e}i}) \prod_{\tilde{c}\in\tilde{C}} \prod_{c_{\tilde{c}j}\in C_{\tilde{c}}} P(Y_{\tilde{c}j}) \quad (1)$$

Where $E_{\tilde{e}}$ is the subset of edges of type $\tilde{e}$, and $C_{\tilde{c}}$ is the subset of triadic closures of type $\tilde{c}$.

The factors $P(y_{\tilde{e}i}|\mathbf{x}_{\tilde{e}i})$ and $P(Y_{\tilde{c}j})$ can be instantiated by exponential-linear functions:

$$P(y_{\tilde{e}i}|\mathbf{x}_{\tilde{e}i}) = \frac{1}{Z_{\tilde{e}i}} \exp\left\{\sum_{m=1}^{d_{\tilde{e}}} \alpha_{\tilde{e}m} f_{\tilde{e}m}(x_{\tilde{e}im}, y_{\tilde{e}i})\right\} = \frac{1}{Z_{\tilde{e}i}} \exp\{\boldsymbol{\alpha}_{\tilde{e}i}^{\mathrm{T}} \mathbf{f}_{\tilde{e}i}\} \quad (2)$$

$$P(Y_{\tilde{c}j}) = \frac{1}{Z_{\tilde{c}j}} \exp\left\{\sum_{n=1}^{d_{\tilde{c}}} \beta_{\tilde{c}n} g_{\tilde{c}n}(Y_{\tilde{c}j})\right\} = \frac{1}{Z_{\tilde{c}j}} \exp\left\{\boldsymbol{\beta}_{\tilde{c}j}^{\mathrm{T}} \mathbf{g}_{\tilde{c}j}\right\} \quad (3)$$

Where $Z_{\tilde{e}i} = \sum_{y'_{\tilde{e}i}} P(y'_{\tilde{e}i}|\mathbf{x}_{\tilde{e}i})$ and $Z_{\tilde{c}j} = \sum_{Y'_{\tilde{c}j}} P(Y'_{\tilde{c}j})$ are local normalization factors; $f_{\tilde{e}m}(x_{\tilde{e}im}, y_{\tilde{e}i})$ is the feature function of the m-th attribute $x_{\tilde{e}im}$ associated with edge $e_{\tilde{e}i}$ of type $\tilde{e}$, $\alpha_{\tilde{e}m}$ is its weight, and $d_{\tilde{e}}$ is the total number of attributes of edges of type $\tilde{e}$. Equation 3 indicates that we define $d_{\tilde{c}}$ feature functions for each triadic closure of type $\tilde{c}$, and $\beta_{\tilde{c}n}$ is the weight of the n-th feature function $g_{\tilde{c}n}(Y_{\tilde{c}j})$.

The joint probability defined in Equation 1 can be rewritten as:

$$\begin{aligned} P_\theta(Y|\mathbf{X}, G) &= \frac{1}{Z} \prod_{\tilde{e}\in\tilde{E}} \prod_{e_{\tilde{e}i}\in E_{\tilde{e}}} \exp\left\{\sum_{m=1}^{d_{\tilde{e}}} \alpha_{\tilde{e}m} f_{\tilde{e}m}(x_{\tilde{e}im}, y_{\tilde{e}i})\right\} \prod_{\tilde{c}\in\tilde{C}} \prod_{c_{\tilde{c}j}\in C_{\tilde{c}}} \exp\left\{\sum_{n=1}^{d_{\tilde{c}}} \beta_{\tilde{c}n} g_{\tilde{c}n}(Y_{\tilde{c}j})\right\} \\ &= \frac{1}{Z} \prod_{\tilde{e}\in\tilde{E}} \prod_{e_{\tilde{e}i}\in E_{\tilde{e}}} \exp\{\boldsymbol{\alpha}_{\tilde{e}i}^{\mathrm{T}} \mathbf{f}_{\tilde{e}i}\} \prod_{\tilde{c}\in\tilde{C}} \prod_{c_{\tilde{c}j}\in C_{\tilde{c}}} \exp\left\{\boldsymbol{\beta}_{\tilde{c}j}^{\mathrm{T}} \mathbf{g}_{\tilde{c}j}\right\} \\ &= \frac{1}{Z} \exp\left\{\sum_{\tilde{e}\in\tilde{E}} \sum_{e_{\tilde{e}i}\in E_{\tilde{e}}} \boldsymbol{\alpha}_{\tilde{e}i}^{\mathrm{T}} \mathbf{f}_{\tilde{e}i}\right\} \exp\left\{\sum_{\tilde{c}\in\tilde{C}} \sum_{c_{\tilde{c}j}\in C_{\tilde{c}}} \boldsymbol{\beta}_{\tilde{c}j}^{\mathrm{T}} \mathbf{g}_{\tilde{c}j}\right\} \\ &= \frac{1}{Z} \exp\{\boldsymbol{\alpha}^{\mathrm{T}} \mathbf{f}\} \exp\{\boldsymbol{\beta}^{\mathrm{T}} \mathbf{g}\} \end{aligned} \quad (4)$$

Where $Z = \prod_{\tilde{e}\in\tilde{E}} \prod_{e_{\tilde{e}i}\in E_{\tilde{e}}} Z_{\tilde{e}i} \prod_{\tilde{c}\in\tilde{C}} \prod_{c_{\tilde{c}j}\in C_{\tilde{c}}} Z_{\tilde{c}j}$ is a global normalization factor and $\theta = (\{\alpha_{\tilde{e}m}\}, \{\beta_{\tilde{c}n}\}) = (\boldsymbol{\alpha}, \boldsymbol{\beta})$ are the parameters to be estimated.

Figure 3 gives the graphical representation of an HFGM. The dotted ellipse at the bottom of the figure encloses the constructed heterogeneous TCM network, in which a node represents a TCM entity of a certain type. The dotted ellipse in the middle of the figure encloses the set of candidate relations, each of which corresponds to an edge in the input network. The dotted ellipse at the top of the figure encloses the factor graph generated from the input network, in which the colored ovals represent variables (labels) corresponding to the candidate relations, and the squares represent factors. The green ovals represent the known labels that are taken as supervised information, while the red ovals represent the unknown labels to be predicted. The black squares represent the evidence factors between variables and their attributes, while the blue squares represent the compatibility factors of triadic closures.

Features in Consideration

In general, the features of evidence factors should be able to reflect prior knowledge of the labels of edges. In this study, we employed three categories of features for evidence factors:

- *Co-occurring frequency*: This is the simplest feature, which represents the instances in which the two end-entities of a relation co-occur in the same document.
- *Lexical context*: Intuitively, the context surrounding the two end-entities is very important for identifying a relation. We used ICTCLAS (Institute of Computing Technology, Chinese Lexical Analysis System; http://ictclas.org) to segment the Chinese documents into words, and took the surrounding words of each entity as features. Six surrounding words were collected for each instance of an entity, three before and three after the instance. After removing the infrequent words, 9784 distinct words remained. We then defined a feature function for each of the words, to indicate the frequency that each word appeared around the two end-entities of a relation.
- *Semantic distance*: Determining the latent semantic relatedness of the two end-entities may also be helpful for identifying a relation. For calculating semantic distance, we first need to represent the semantic meanings of each entity. Distributed vector representations facilitate learning word meanings from large collections of text. Each word is learned as a distinct pattern of continuous values over a single, large vector, with each dimension corresponding to a latent topic. We can then measure the semantic relatedness among words in terms of distances in the resulting vector space. We used word2vec[40] (https://code.google.com/p/word2vec), an efficient tool for computing the vector representations of words by employing deep-learning approaches, to calculate the semantic vectors of TCM entities from our corpus of data, and, with this tool, we generated a 200-dimension vector for each entity. We then defined a feature function on each dimension by using the absolute value of the difference between the values of the dimensions of the two end-entities.

Except for the above three categories of features, syntactic structure (ie, dependency relation) is another type of information that is useful for relation extraction. However, being able to determine syntactic structure requires that the two end-entities co-occur within one single sentence. So, we did not take syntactic structure into account in this study.

The feature functions $\{g_{\tilde{c}n}(Y_{\tilde{c}j})\}$ of compatibility factors should be able to reflect dependencies among the labels of edges. We defined one category of feature functions for compatibility factors based on the transitive property of triadic closures. Figure 4 gives an illustration of the transitive property, in which the labels of three edges form a triad closure. According to the transitive property, we can define the feature function as follows:

$$g(y_1, y_2, y_3) = \begin{cases} -1, & y_1 + y_2 + y_3 = 2 \\ 0, & y_1 + y_2 + y_3 = 0 \text{ or } 1 \\ 1, & y_1 + y_2 + y_3 = 3 \end{cases}$$

Learning and Inferring the HFGM

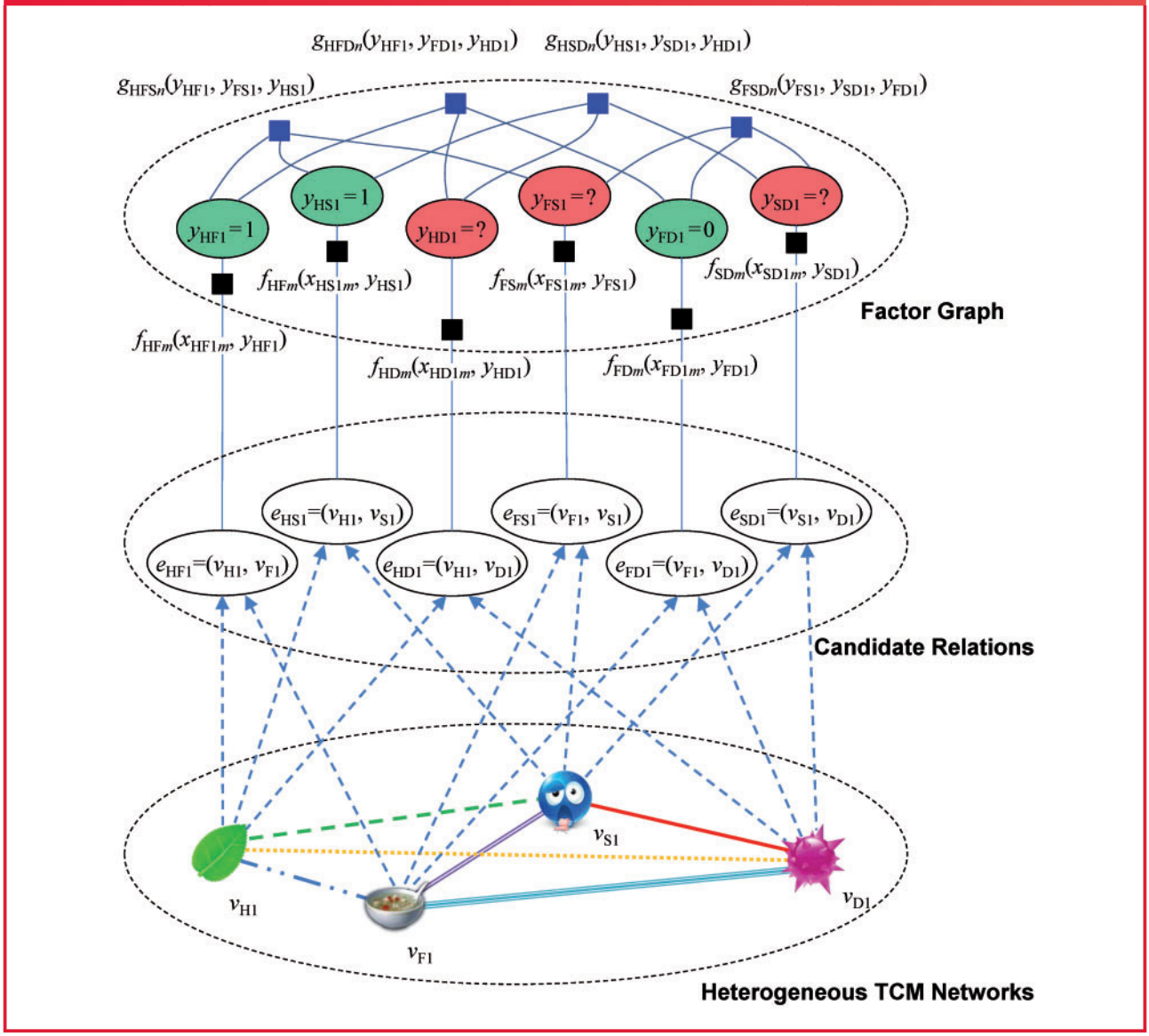
We propose using a semi-supervised learning algorithm to estimate the parameters of the model (see Supplementary Appendix A), which enables us to predict the labels of unknown edges based on the estimated parameters (see Supplementary Appendix B).

RESULTS

We trained and evaluated our proposed HFGM on the dataset we collected and annotated. Five types of relations – herb-syndrome, herb-disease, formula-syndrome, formula-disease, and syndrome-disease – were extracted from the TCM literature we analyzed.

The HFGM model was implemented in C++, and all experiments were conducted on a server running Windows Server 2008, with an Intel Xeon CPU E7-4820 2.00 GHz processor and 256 GB of memory. The entire semi-supervised learning and inference process took about 4.5 h.

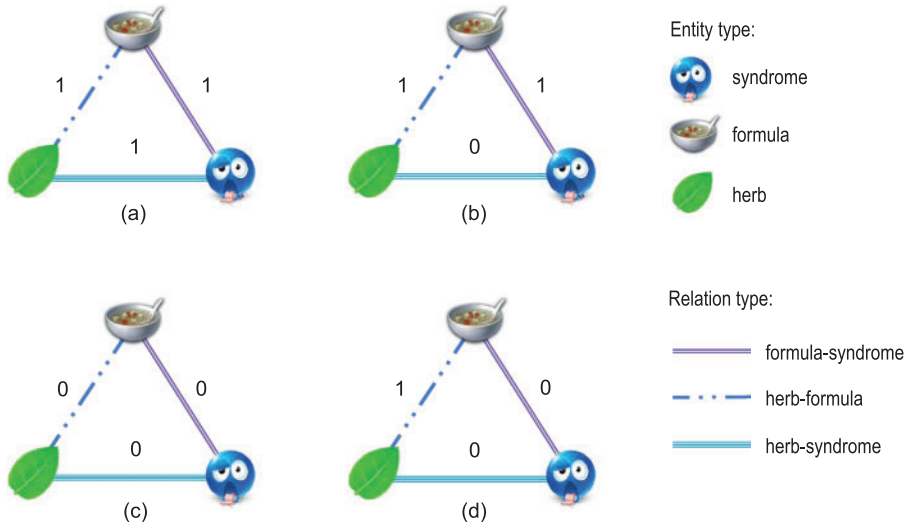
Figure 3: Graphical representation of a heterogeneous factor graph model (HFGM). Here, $v_{\tilde{v}j}$ represents a traditional Chinese medicine (TCM) entity of a certain type $\tilde{v}$ (eg, v_{H1} represents an herb), $e_{\tilde{e}k}$ represents an edge (a candidate relation) of a certain type $\tilde{e}$ (eg, e_{HF1} represents an herb-formula relation), $y_{\tilde{e}k}$ represents the corresponding variable (label) of an edge (eg, y_{HF1} represents the label of the edge e_{HF1}), $f_{\tilde{e}m}(.)$ represents a feature function for evidence factors defined on the observed attributes, and $g_{\tilde{c}n}(.)$ represents a feature function for compatibility factors defined among latent labels. The labels y_{HF1}, y_{HS1}, and y_{FD1} are known in advance and are taken as supervised information, while the labels y_{HD1}, y_{FS1}, and y_{FD1} are unknown and yet-to-be-predicted.



A traditional classification approach was employed as the baseline, in which the co-occurring frequency, lexical context, as well as the aforementioned semantic distance were taken as the classification features. Because the number of features involved in this approach was very large, we used an SVM[41] (www.csie.ntu.edu.tw/∼cjlin/libsvm) as the basic classifier.

In order to let the basic classifier utilize the relations' compatibility information, we also ran an iterative classification algorithm on our relation extraction task. Compared with probabilistic graphical models (eg, factor graph models), iterative classification provides a simple and approximate way of implementing the concept of collective inference, by graphing interdependent variables and taking the inferred neighboring values of a variable as known information to assist with iteratively inferring the variable's value. We designed an iterative SVM classifier in our experiments that takes the results of the basic SVM classifier as the initiate values of all the labels, then iteratively updates the label of each relation by simultaneously using its observed features and inferred neighboring label values, until the labels no longer change. The key challenge of iterative classification is transforming the neighboring label values into regular features in order to capture the labels' compatibility information. In this study, we also defined iterative features based on the transitive property of triadic closures. Specifically, we calculated the numbers of triadic closures with different sums (ie, 0, 1, 2, and 3, as shown in Figure 4) that were formed by each relation with its neighboring relations.

Figure 4: Illustration of the transitive property of triadic closures. (**a**) Complies with the transitive property, because all the three labels are equal to 1; (**b**) violates the transitive property, because only two labels are equal to 1; for (**c**) and (**d**) the transitive property does not apply, because only one label or no labels are equal to 1.



We performed a five-fold cross-validation to evaluate the performance of our model. Table 3 shows the performance of the HFGM as compared with that of two other approaches. Our results show that the HFGM is more efficient at extracting relations from the TCM literature compared with the basic SVM classifier (increasing precision by ~10–12%, recall by ~12–15%, and the F1-measure by ~11–14%, for different types of relations) and the iterative SVM classifier (increasing precision by ~6–8%, recall by ~7–10%, and the F1-measure by ~7–11%, for different types of relations). We performed a *t*-test between the performances of these three approaches with regard to the extraction of different types of relations and found that the difference between them is extremely statistically significant ($P < 0.001$ for all precision, recall, and F1-measures).

FD, formula-disease relation; FS, formula-syndrome relation; HD, herb-disease relation; HFGM, heterogeneous factor graph model; HS, herb-syndrome relation; SD, syndrome-disease relation; SVM, support vector machine; TCM, traditional Chinese medicine.

To further determine the effectiveness of our approach, we plotted receiver operating characteristic curves of the basic SVM and HFGM approaches (as shown in Figure 5), where the *y*-axis represents the rate of predicated positive labels in all the positive samples, and the *x*-axis represents the rate of predicted positive labels in all the negative samples. It is clear that the HFGM significantly outperforms the basic SVM classifier on extracting all types of relations.

DISCUSSION

After performing an in-depth analysis of some specific instances, we found that our HFGM significantly improves the accuracy of relation extraction in the following cases (in which traditional classifiers have difficult identify relations):

- **The context is very short.** For a candidate relation, we took the co-occurring frequency of the two end-entities appearing in the same documents and the frequencies of their surrounding words as the classification features, so if a relation only appears once in a single, short document, then the context information will not be enough to identify the relation.
- **The context contains confusing information.** In some TCM treatment experiments, one or more control groups are used to compare the effectiveness of different treatments, which often misleads traditional classifiers to extract some relations from the control groups that are not actually present.
- **Several different studies are reported on in the same document.** Occasionally, several studies will be covered within a single article or even a single sentence. An example of this would be if an author wrote, "the herb A is curative to the disease B; the herb C is curative to the disease D." In this example, it would be difficult for traditional classifiers to distinguish the correct relations (A–B and C–D) from the incorrect relations (A–C, A–D, B–C, and B–D), which may lead traditional classifiers to extract some incorrect relations from the document.
- **The name of an entity is a polysemous word.** Some Chinese names for TCM entities have other meanings. For instance, the term "太阳" refers to a syndrome called "Tai Yang" in the TCM domain, but it means "the sun" in most contexts, and the term "脱水" refers to dehydration in a medical context, but can also mean "the physical process of dewatering." Such polysemous terms complicate the process of identifying candidate relations.

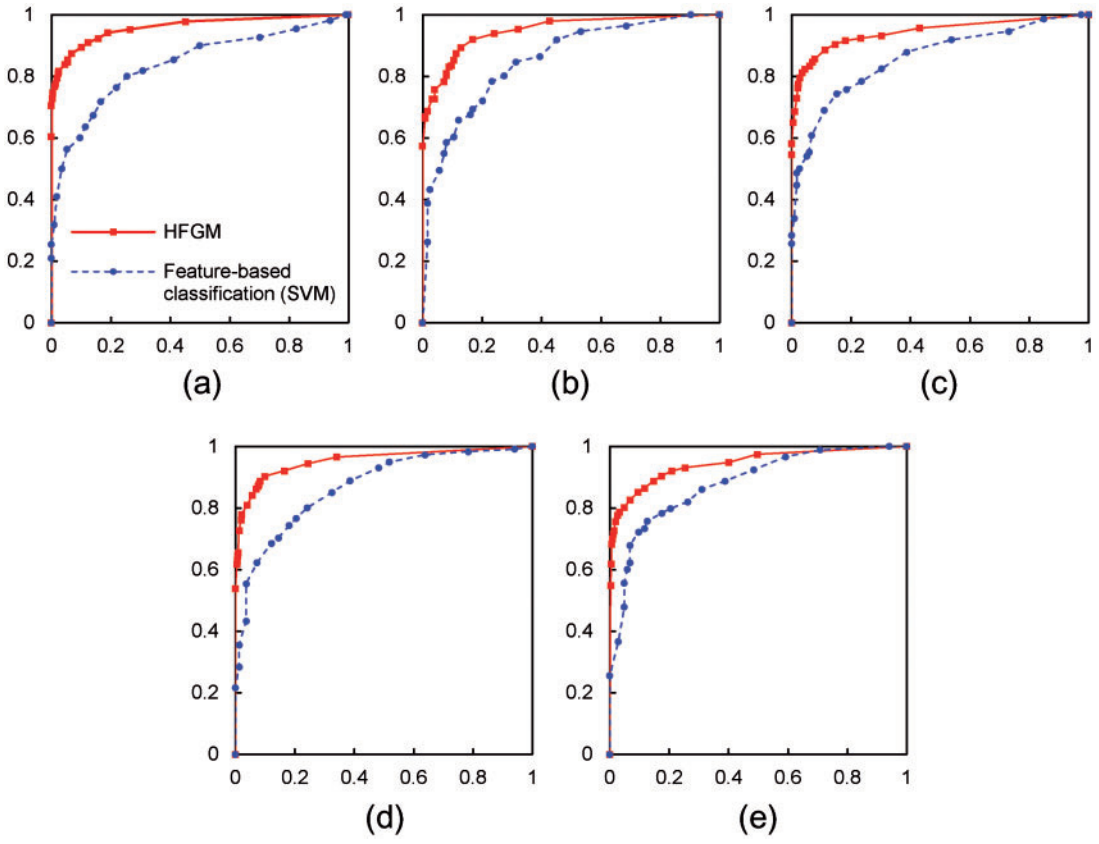
Our HFGM utilizes the correlations between all types of relations to overcome the above difficulties by employing collective inference in the context of heterogeneous entity networks, thus greatly improving the model's ability to extract TCM relations. The effectiveness of the HFGM demonstrates the existence of correlations among different types of relations. In addition, using the transitive property of triadic closures to model the dependencies among the labels of edges in the network is a reasonable and practicable approach.

However, some of our results can be improved upon, and some of the approaches we employ can be expanded upon in the future. Firstly, some other types of important TCM entities, such as

Table 3: Performance of TCM Relation Extraction by Different Approaches (%)

Relation Type		HS	HD	FS	FD	SD	Average
Basic SVM	Precision	78.89	79.13	80.12	81.04	77.72	79.30
	Recall	72.34	74.59	72.32	73.08	73.22	73.15
	F1	75.47	76.79	76.02	76.85	75.40	76.09
Iterative SVM	Precision	83.35 (+4.46)	83.1 (+3.97)	84.33 (+4.21)	85.55 (+4.51)	81.88 (+4.16)	83.54 (+4.24)
	Recall	77.66 (+5.32)	79.51 (+4.92)	77.75 (+5.43)	78.41 (+5.33)	78.34 (+5.12)	78.36 (+5.21)
	F1	80.4 (+4.93)	81.27 (+4.48)	80.91 (+4.89)	81.82 (+4.97)	80.07 (+4.67)	80.87 (+4.78)
HFGM	Precision	90.94 (+12.05)	89.48 (+10.35)	90.81 (+10.69)	91.07 (+10.03)	89.87 (+12.15)	90.39 (+11.09)
	Recall	86.93 (+14.59)	87.34 (+12.75)	85.69 (+13.37)	88.25 (+15.17)	86.87 (+13.65)	86.98 (+13.83)
	F1	88.89 (+13.42)	88.40 (+11.60)	88.18 (+12.16)	89.64 (+12.78)	87.86 (+12.94)	88.56 (+12.47)

Figure 5: Receiver operating characteristic curves of different approaches for extracting (a) herb-syndrome, (b) herb-disease, (c) formula-syndrome, (d) formula-disease, and (e) syndrome-disease relations. The *y*-axis represents the true positive rate and the *x*-axis represents the false positive rate.



symptoms, are not incorporated into our model. This is because there is not a standard or unified terminology glossary for TCM symptoms, so entity recognition techniques are needed to detect the instances of symptom entities in text. If we can bring such entities into our unified model in the future, then more types of relations can be extracted. Secondly, many biomedical discoveries, such as known disease-target and ingredient-target relations or research on the integration of Chinese and Western medicine (eg, established herb-ingredient relations), can be used as prior knowledge in our model and are expected to further improve the model's performance.

Another challenge is that the computational complexity of learning the HFGM is very high, because multiple rounds of approximate

inferences are required over the entire dataset (see Algorithm 1 of the online supplementary data). Consequently, we need to develop efficient learning approaches. Tang et al.[33] has proposed a parallel algorithm to learn factor graph models, which can be used for reference in our future research. In addition, other approximation techniques, such as the pseudolikelihood measure,[42,43] may also be used in our collective inference methods.

Our approach also be directly applied to relation extraction in the field of biomedical text mining. We can construct heterogeneous networks between biomedical entities (eg, proteins, genes, phenotypes, biological targets, diseases, drugs, treatments) gathered from biomedical literature or clinical records, then employ the HFGM to extract biomedical relations in the context of these heterogeneous biomedical networks.

The HFGM model proposed in this article is only suitable for heterogeneous entity networks that contain at least three kinds of entities, because we use triadic closures formed by three kinds of entities to construct compatibility factors in the model.

Another limitation of the current version of our model is that it can only extract one class of relations between the same two types of entities at the same time, because we treat the relation extraction problem as a binary classification problem in this study. For instance, the annotated dataset in this study contains only "herb-treatment-disease" relations, so the learned model also can only extract "herb-treatment-disease" relations. However, if the user wants to extract "herb-hasSideEffect-disease" relations, they may use the data that contains annotated "herb-hasSideEffect-disease" relations to re-train the model.

CONCLUSION

In this article, we examine the problem of automatically extracting meaningful entity relations from TCM literature and propose an HFGM that exploits the power of collective inference in the context of heterogeneous entity networks to simultaneously and globally extract all types of relations (eg, herb-syndrome, herb-disease, formula-syndrome, formula-disease, and syndrome-disease relations) from the entire corpus of TCM data. We propose using a semi-supervised learning algorithm to estimate the parameters of the model. The results of our analysis of a professionally annotated dataset show that our approach is superior to traditional classification methods in extracting multiple types of relations from TCM literature.

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CONTRIBUTORS

The work was a collaboration between all the authors. H.W., X.Z., Q.M., and L.L. constructed the guidelines for data annotation. H.W., M.F.M., W.L., and J.T. designed the methods and experiments. H.W. and J.T. wrote the code and carried out the experiments. H.W., M.F.M., Q.M., and J.T. analyzed the data, interpreted the results, and drafted the paper. All the authors have made valuable contributions to revising and approving the manuscript.

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COMPETING INTERESTS

None.

SUPPLEMENTARY MATERIAL

Supplementary material is available online at http://jamia.oxfordjournals.org/.

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