An Ontology-Based Artificial Intelligence Model for Medicine Side-Effect Prediction: Taking Traditional Chinese Medicine as An Example

Zeheng Wang1*, Kun Lu2, Jun Cao3, Yuanzhe Yao1*, Liang Li1, Runyu Liu1, Zhiyuan Liu1, Jing Yan4

1. School of Information and Software Engineering, University of Electronic Science and Technology of China, Chengdu, 610054, People’s Republic of China
2. Walter-Brendel-Centre for Experimental Medicine, Ludwig Maximilian University of Munich, 81377, Germany
3. Faculty of Medicine, University of New South Wales, Sydney, NSW2052, Australia
4. The First Clinical Medical College, Zhejiang Chinese Medicine University, Hangzhou, 310006, People’s Republic of China

* Corresponding authors: zenwang@outlook.com (Z. Wang) and yzyao@tsinghua.edu.cn (Y. Yao)
Email address: lu.kun@campus.lmu.de (K. Lun) and j.cao@neura.edu.au (J. Cao)

Abstract

In this work, an ontology-based model for AI-assisted medicine side-effect (SE) prediction is developed, where three main components, including the drug model, the treatment model, and the AI-assisted prediction model, of proposed model are presented. To validate the proposed model, an ANN structure is established and trained by two hundred and forty-two TCM prescriptions that are gathered and classified from the most famous ancient TCM book and more than one thousand SE reports, in which two ontology-based attributions, hot and cold, are simply introduced to evaluate whether the prediction will cause a SE or not. The results preliminarily reveal that it is a relationship between the ontology-based attributions and the corresponding indicator that can be learnt by AI for predicting the SE, which suggests the proposed model has a potential in AI-assisted SE prediction. However, it should be noted that, the proposed model highly depends on the sufficient clinic data, and hereby, much deeper exploration is important for enhancing the accuracy of the prediction.

1. Introduction

Artificial intelligence is a modern technology that is utilized in various fields of medicine [1–3]. At the meantime, Chinese Traditional Medicine (TCM) is now widely considered as a promising alternative medicine for complementary treatment in cancers or chronic diseases due to the effective methodology practically developed by generations of doctors for almost 4000 years [4]. Based on previous verification, it is undeniable that there are many correlations between the TCM syndromes and western diseases, turning out novel approaches for enhancing the treatment efficiency and developing medicines regarding with TCM methodologies [5]. Unfortunately, hindered by the remarkable gap between the modern informatics and the fundament of TCM: antient Chinese philosophy, such correlations are still too elusive to be formulated precisely.

Therefore, recently, in order to figure out the deep connection between modern science and TCM, the research combining TCM with AI for valid knowledge acquisition and mining attracts extremely
attention, and hereby, leading to many profound works, such as ontology information system design [6], latent tree models design [7], TCM warehouse for AI application [8], and digital knowledge graph development [2]. On the other hand, researchers face, however, many difficulties in setting up AI for TCM in terms of directly interpreting TCM semantic system (almost recorded by ancient Chinese doctrines) into structured database. Because in this way, considerable workload must be undertaken by limited numbers of experts who are proficient in both AI and TCM to translate the TCM terminologies and then formulate the modern model thereof. In contrast, as shown in Fig. 1, the digestion of using TCM methodology in dealing with issues of modern science, new medicine design for example, is relatively lacking and thus of significant worth to explore.

Fig. 1. The development based on modern science and the TCM-based ontology

In this paper, an ontology-based model is developed to train AI for drug side-effect (SE) prediction, in which the methodology of TCM including syndromes differentiation is applied to determine the ontology-based attributions and optimize the AI components, and consequently, form a novel scheme of effectively predicting the medicine’s attribution. Here, limited by the shortage of accurate clinic experiment data of modern medicine, TCM data in famous ancient books are used to verify the model which shows a tremendous potential in medicine discovery.

2. Methodology

2.1. The ontology-based drug model

The artificial intelligence model proposed in this paper is based on Ontology that considers the essence of a certain entity as a combination of several fundamental attributions with corresponding values and relationships. Such attributions are not only the definite properties which are already completely recognized by researchers, but also the latent properties including unknown information and relationships. For example, as shown in Fig.2, each drug has certain attributions including the definite ones and latent others, which are all involved in a certain prescription with sufficient records of clinical effects. In addition, assuming our prepared ontology system is complete and exclusive, a new drug or prescription which contains attributions we have already recorded can be depicted easily in the ontology-based semantic system, where we could focus on the superficial relationship between such attributions and effects caused. In other words, we avoid figuring out the ingredient and other deeper properties of each attribution in the new drug literally, and hereby, the attribution-effect pair is crucial and could be easily converted into an AI scheme such as artificial neural network (ANN) to
handle the prediction of the treatment procedures. Moreover, the proposed ontology-based attribution model could be revised by more accurate clinic records automatically with AI assistance due to the intentionally fuzzy and dynamic defined latent attributions.

![Fig. 2. Ontology-based drug model and latent attributions thereof](image)

### 2.2. The ontology-based treatment model

![Fig. 3. Ontology-based treatment model concerning the attribution-indicator relationships](image)

Based on the proposed drug model, it can be depicted as Fig. 3 that the model of the treatment procedure via a certain prescription which contains several drugs including the attributions of known ingredients and the latent attributions. As shown in Fig. 3, the latent attributions own the capability of influencing the group of indicators with different unknown path and efficiency. In another word, in this model, the final results of the treatment procedure that is defined as the positive or negative change of the corresponding indicator are the comprehensive synthesis of the effects given by various latent attributions. Therefore, this procedure could be interpreted into a TCM-based semantic entities: attribution-indicator pairs performing the effects. It should be noted that the different attributions maybe dominate in influencing the same indicator. Furthermore, the model is compatible with the known ingredients or explored attributions and the effects thereof.
2.3. AI assisted prediction model

Based on the drug/prescription and treatment models aforementioned, as illustrated in Fig. 4, the SE prediction of new drug X is realized by comprehensive consideration of the involved ontology-based latent attributions with their influential factors (IFs) revised by sufficient medicines’ clinic records that contain, for instance, the attribution 3 and X, where the revision procedure could be undertaken by AI scheme such as ANN. Also, the same AI scheme could predict the SE with the trained pattern.

It should be noted that the IFs must be linked with the corresponding attributions and indicators which means the trained model is consisted of IFs-indicator vectors but not the isolated IFs as the input. In this way, the ontology-based model that the latent attributions with corresponding IFs influence a certain indicator is established. Next, we will generate an AI scheme to validate our proposed model by determining two latent attributions which are hot and cold of the prescription, and a simple indicator: whether the prescription causes SE or not when this prescription is used in a right way.

Fig. 4. The network for training AI using proposed models

3. Experiment detail

Fig. 5. The SE prediction procedure of proposed model
According to the analysis in section 2, it is the key of establishing the proposed model that determines the attributions and obtains the IFs-indicator vectors. However, owning to the lack of related theory, generating the attributions directly, comprehensively, and exclusively is very hard. Therefore, we follow the theory of TCM which has the advantage in matured ontology-based semantic system that can determine the attributions spontaneously. For example, hot and cold are two main attributions catalogized by TCM theory, where all the drugs contain one out of these two attributions, leading to a charming approach for determining the latent attributions of western drugs in the same way.

As shown in Fig. 5, after the identification of the attributions and indicators, we should establish and train the AI model. Here, we gathered the detailed data, including 150 effective prescriptions, the dosages thereof and the corresponding indicators, from a famous antient TCM book *Shanghanzabinglun* (Treatise on Cold Pathogenic and Miscellaneous Diseases) which is considered as the origin of practical TCM prescription in clinic. In addition, as concluded before, according to the practice identification by antient TCM doctors and the TCM standards published by Chinese government [9,10], we labeled two ontology-based attributions that are hot and cold for describing the drugs’ fundamental property which is the first step of conducting the prediction as depicted in Fig. 5. Thereafter, we assigned the IFs of each attribution equaling to the total dosage of the drugs which own the corresponding attribution in the prescription. Since in the ontology-based labeling procedure a drug must belong to one certain catalogue out of the two in total, using the summarized dosage to represent the IFs is reasonable, however, it needs more verification in research. In addition, it should be noted that some prescriptions do not contain any drugs (for example some pure chemical ingredients) associated with hot or cold, where these drugs could be considered as neutral ones and not affiliated with the two attributions mentioned before.

![Fig. 6. The frequency counts of the hot/cold IF (counts) in the book](image)

As shown in Fig. 6(a), 242 effective prescriptions are dotted regarding with the normalized total dosage, where the x-axis and y-axis in the figure represent the total hot dosage and the total cold dosage respectively that are considered as the IF factors of the prescription. According to our best knowledge, owning to there are no reports indicating the 150 prescriptions gathered here of the book *Shanhanzabinglun*, we consider the prescriptions of that book are the safe prescriptions. In contrast, we gathered 92 unsafe prescriptions reported to frequently cause SE when they are used in a right way.

The distribution of the percentages of the safe prescriptions and the unsafe prescriptions feature a huge difference in terms of whether the dosage is stronger than 500, which suggests the reported unsafe prescriptions own the characteristics that can be assorted from the safe prescriptions. Therefore, we try to use ANN to build a simple classifier to predict which prescription has the potential of causing SE.

The schematic scheme of the prediction is shown in Fig. 7, where the ANN’s input layer and output layer both contains two units for receiving the dosage vectors and yielding the SE prediction.
vectors, respectively. To train the ANN model, we prepared and washed 150 hot/cold dosage data as the safe prescription from the book *Shanhanzabinglun* and 92 reported prescriptions that frequently causes SE [11–16]. Thereafter, we randomly choose 10 safe prescriptions and 10 prescriptions frequently causing SE for the test dataset to evaluate the proposed prediction scheme.

![Diagram](image)

**Fig. 7.** The schematic structure of the ANN and the dataflow

### 4. Result and discussion

The accuracy of training and validation versus the train epochs are shown in Fig. 8, where the training accuracy shows an inclining trend initially and a weak fluctuation thereafter, meanwhile, the validation accuracy shows relatively huge shocks compared with training one. This suggests that the dataset is not saturate to form a mature ANN for the prediction. Nevertheless, the accuracy is acceptable for validating our proposed model.

Thus, we use this ANN for testing and extract the detail of testing results, which is listed in Table 1. The prediction results with a total accuracy of 0.65 illustrate an acceptable determination that whether the prescription will cause SE.

Hence, the proposed ontology-based SE prediction model is initially verified by the ANN. However, in this procedure we did not revise the IFs as planed due to the lack of the dataset, resulting in a weak prediction accuracy. Furthermore, the determination of the attributions is relatively broad. In another word, the attribution space may be classified into more detailed catalogue such as hot, warm, neutral, cool, and cold. In this way, the ANN could learn more features of the dataset and give more precise predictions. Besides, according to other factors such as different length of treatment, it is of great significance that IFs should be evaluated with a weight vector or even tensor, which will influence the results of prescriptions and should be studied in next stage.
Fig. 8. The prediction accuracy of the proposed ANN versus the epochs

Table 1. The detailed results of one prediction test

| Total hot dosage | Total cold dosage | Label | Prediction |
|------------------|-------------------|-------|------------|
| 3150             | 150               | 1     | 1          |
| 600              | 750               | 1     | 0          |
| 156              | 192               | 1     | 0          |
| 0                | 2400              | 1     | 1          |
| 256              | 312               | 1     | 0          |
| 135.6            | 46.8              | 0     | 0          |
| 31.2             | 93.6              | 0     | 0          |
| 74.4             | 62.4              | 0     | 0          |
| 78               | 281               | 0     | 0          |
| 42               | 15                | 0     | 0          |
| 423.56           | 46.8              | 0     | 0          |
| 20               | 4                 | 0     | 0          |
| 91.2             | 62.4              | 0     | 0          |
| 4                | 12                | 0     | 0          |
| 502.9            | 78                | 0     | 0          |
| 425              | 750               | 1     | 0          |
| 190              | 280               | 1     | 0          |
| 618              | 184               | 1     | 1          |
| 100              | 585               | 1     | 0          |
| 2000             | 2000              | 1     | 0          |

Total accuracy: 0.65
5. Conclusion

An ontology-based model for AI-assisted medicine side effect prediction is proposed in this paper. The drug, treatment, and prediction models are established and verified by ANN, in which a simplified scheme containing latent attributions and corresponding indicators with IFs is investigated preliminarily. Clinic data coming from both TCM prescriptions of a famous ancient TCM book and unsafe prescriptions reported is adopted to train the ANN, thereafter, predict SE. The success of predicting whether a prescription will cause SE by the help of two kinds of attributions, hot and cold, demonstrates the simplicity and effectiveness of this work, which could be further improved as a powerful tool to predict more side effect syndrome.

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