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| Data and text mining  Automatic Discovery of Adverse Drug Reactions through Chinese Social Media  Mengxue Zhang1\*, Meizhuo Zhang2\*, Chen Ge1, Quanyang Liu1, Jiemin Wang2, Jia Wei2\*\*, Kenny Q. Zhu1\*\*  1Dept. CSE, Shanghai Jiao Tong University, 800 Dongchuan Road, Shanghai 200240, China  2R&D Information, AstraZeneca, 199 Liangjing Road, Pudong, Shanghai, 201203, China  \*The authors contributed equally to this work. \*\*Corresponding authors |

Abstract

**Motivation:** Despite tremendous efforts made before the release of every drug, some adverse drug reactions (ADRs) may go undetected and thus, cause harm to both the users and to the pharmaceutical companies. One plausible venue to collect evidence of such ADRs is online social media, where patients and doctors discuss medical conditions and their treatments.

**Results:** We propose a semi-supervised learning framework that detects mentions of medications and colloquial ADR terms and extracts lexicon-syntactic features from natural language text to recognize positive associations between drug use and ADRs. The key contribution is an automatic label generation algorithm, which requires very little manual annotation. With this approach, we discovered a large number of side effects for a variety of popular medicines in real world scenarios.

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# Introduction

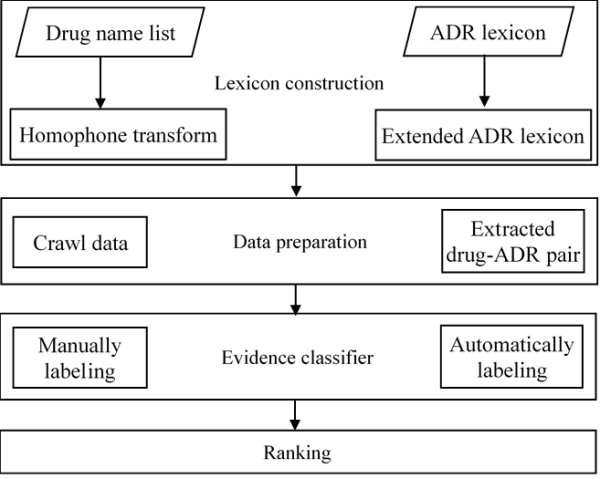
Determination of adverse drug reactions (ADR) is an important part of pharmaceutical research and drug development. Pre-marketing clinical trials are limited by the number of participants, the length of the study and the underlying economic burden for both the pharmaceutical companies and the patients. Some of the new adverse reactions to a drug are learned only when the drug is used in a wide spectrum of patients, with varied ethnicity, underlying diseases and a range of concomitant medication, in a post-launch setting. Furthermore, some reactions take a long time to develop a process which goes well beyond the pre-marketing development cycles of the drugs. For example, Vioxx, developed by Merck & Co, was approved by the FDA in May 1999 as a nonsteroidal anti-inflammatory drug to treat osteoarthritis, acute pain and dysmenorrhea. However, other Merck & Co sponsored studies, which were concluded or commenced after the drug was launched, indicated that it was associated with elevated risk of cardiovascular complications [Bombardier et al. 2000; Bresalier et al. 2005]. In September of 2004, Merck withdrew Vioxx from the market because of concerns about increased risk of heart attack and stroke associated with long-term, high-dosage use. An FDA study estimated that Vioxx could have caused up to 140, 000 cases of serious heart disease in the US since 1999 [Graham et al., 2005]. Regulatory authorities and pharmaceutical companies make tremendous effort in avoiding such incidences by conducting post-launch Phase IV clinical trials. In the United States, drug companies spend up to $12,000 per patient in Phase IV clinical trials, with an average of $5,856[[1]](#footnote-1). Conducting such studies in an “*in silico*” fashion, i.e., collecting ADRs from pre-existing data sources, has become a valid complement, if not an attractive alternative, to costly Phase IV studies.

Recent years saw a growing research interest in mining adverse drug reactions from various data sources. Data sources can be divided into structured data and unstructured text data, and the approaches differ. Structured data primarily includes official adverse event reports collected by health authorities (Harpaz R et al., 2010; Harpaz R et al., 2012; Hahn U et al., 2012; Gurulingappa H et al., 2013). These reports are relatively easy to process due to their strict conformance to the adverse event reporting standards. However, the quantity of such reports is limited. Hence, they cannot catch many infrequent ADRs. Unstructured data so far includes biomedical literature, clinical notes or medical records, and online health discussions. These data sources pose more processing challenges because signals are embedded in natural language, which is inherently ambiguous and noisy. Biomedical literatures such as scientific papers are comparatively easier to mine (Wang et al., 2011; Yang et al., 2012) since the medication and adverse reaction are referred to by their formal names. However, the information therein is not up-to-date and is sometimes biased. Clinical resources were targeted using various methods, such as text mining for identifying ADRs from medicine uses (Warrer et al., 2012), rule-based methods to extract side effects from clinical narratives (Sohn et al., 2011) and retrospective medication orders along with inpatient laboratory results to identify ADRs (Liu et al., 2013). Privacy concerns and access restrictions are the biggest obstacles for its wide adoption. Compared to the above data sources, online social media, especially health discussion forums, provide the most comprehensive and timely information about medication use experiences. The large volume, colloquial use of natural language, spelling and grammatical errors are some of the major challenges in mining ADRs from such data sources.

Existing methods for social media text mining can be categorized into lexicon-based methods, statistical methods, rule-based method, advanced NLP and machine learning approaches (Sarker et al., 2015; Lardon et al., 2015). Most prior studies (Leaman et al. 2010; Yang et al. 2012; Benton et al. 2011; Wu et al. 2013; Ytes and Goharian, 2013; Liu et al., 2014; Jiang et al., 2013; Freifeld et al., 2014; Yeleswarapu et al., 2014) focused on expanding lexicons to find ADRs in text. In these lexicon-based methods, due to the novel adverse reaction phrases on websites, they could not recognize non-regular ADRs that are not contained in the lexicon. Besides, they suffer from poor approximate string matching caused by misspelled words. Some researchers instead utilized statistical (Li 2011; Wu et al 2012; Liu et al 2013), rule (pattern) based methods (Nikfarjam et al. 2011; Benton et al. 2011; Karimi et al. 2011; Yang et al. 2012); or NLP techniques (Sharif et al. 2014; Sarker and Gonzalez 2015). Moreover, a large number of studies have explored machine learning methods for the extraction of ADRs (see Lardon et al. (2015) and Sharker et al. (2015) for a more comprehensive review). These approaches utilize well-studied machine learning methods, and can offer reasonable accuracy. However, they all require large volume of training data during the learning process, a tremendous amount of manual effort.

Although there is substantial previous research on ADRs extraction from English online forums, very limited research was done on Chinese data. To the best of our knowledge, this paper is the first attempt to mine ADRs from three popular social media sites, namely Xunyiwenyao[[2]](#footnote-2), Haodaifu[[3]](#footnote-3) and Sina Weibo[[4]](#footnote-4). Xunyiwenyao and Haodaifu are both online public forums for health-related discussions. Weibo is a Chinese microblogging website where a user can start a new conversation in any topic upon which their friends may respond with comments or forward the discussion to other people.

Figure 1 System framework



Herein, we propose a semi-supervised learning framework requiring very little manual annotations for mining ADRs from Chinese social media. As an alternative to the methods described above, we build a list of commonly misspelled drug names and extend the customized lexicon with colloquial words and adjective modifiers, in order to address the problem of irregular ADR terms and typos. We also focus on distinguishing between indications and ADRs by training a binary classifier, using SVM model. To train the classifier, we introduce an automatic labeling algorithm to generate large amount of training data.

Table 1 ADRs lexicon

|  |  |  |  |
| --- | --- | --- | --- |
| 5’-核苷酸酶下降  (5'-nucleotidase decline) | 各种肝功能分析  (Variety of liver function) | 肝胆系统检查  (Hepatobiliary system check) | 各类检查  (Various types of inspection) |
| 5’-核苷酸酶增加  (5'-nucleotidase increase) | 各种肝功能分析  (Variety of liver function) | 肝胆系统检查  (Hepatobiliary system check) | 各类检查  (Various types of inspection) |
| A型肝炎  (Hepatitis A) | 各种肝脏病毒感染  (Various liver virus infection) | 肝脏及肝胆类疾病  (Liver and hepatobiliary diseases) | 肝胆系统疾病  (Hepatobiliary system diseases) |
| BK病毒感染  (BK virus infection) | 多瘤病毒感染  (Polyomavirus infection) | 传染性病毒感染  (Contagious viral infection) | 感染及侵染类疾病  (Infection and infection diseases) |

# Materials and Methods

Our framework (depicted in Figure 1) is divided into four parts, namely constructing lexica, extracting candidate ADRs, classifying evidences and finally ranking the ADRs.

1. Lexicon construction

We need two lexicons, one for the names of medications of interest; the other for ADRs to be recognized from text.

### Lexicon of medication

We start with a list that contains common names and registered trade names of known drugs. On social media, drug names may be spelled with variation, either by similar characters or homophones. For example, a drug called “耐信(Nexium)”(nài xīn in Chinese phonetic alphabet) may be misspelled as “奈信”(nài xìn), “乃信”(nǎi xìn) and so on. To solve this problem, we expand each correct character in a drug name to several commonly misspelled characters in Chinese according to the Chinese phonetic alphabet. For example, “耐” is extended to “奈” or “乃”, while “信” is extended to “心”, “新” and so on. However, if “耐信” is transformed to “耐心”, which is a commonly used Chinese word, many irrelevant posts containing “耐心” maybe returned. Thus common Chinese words which are clearly not drug names are filtered out. After this kind of expansion, we obtain a total of 110779 different drug names for 79 drugs of interest. The list of all these 79 drugs of interest could be found in the appendix A.

### Basic ADR lexicon

The basic ADR lexicon comes from four sources: The NCI Common Terminology Criteria for Adverse Events (CTCAE) (Trotti et al., 2003), Sougou Pinyin ADRs lexicon[[5]](#footnote-5) , MedDRA(The Medical Dictionary for Regulatory Activities) (Brown *et al.*, 1999) and the ADR database by Ye et al (Ye et al., 2014). CTCAE contains formal terms of the ADRs used for adverse event reporting to regulatory agencies. Sougou ADRs is utilized particularly for colloquial terms. Both CTCAE and Sougou ADRs are available in Chinese. The ADRs database coversmore than 6000 ADRs in English. It was translated into Chinese by Google Translate[[6]](#footnote-6). In addition, classification of these terms is very important. Because some words have the same or similar meaning, their results can be merged in the following analysis steps. For example, “体重减少” (loss of weight) is the same as “体重下降” (drop in weight). If we classify both words in the same category, their result can be directly added and we get one total result for later discussion. Finally, based on MedDRA’s category, we classify all the words into structured lexicon which has four levels. The lowest level contains ADR words from the three data sources. The three upper levels are custom categories in MedDRA. In the table 1, the first column in the left is the fourth level and the next three columns are the upper levels in MedDRA.



Translation:

Title: Why my two legs are swollen in recent months

Content:

Description of disease (Onset, Main symptom, Change):

Why my two legs are swollen in recent months

The previous treatment and its effect:

I eat hypertension pill every day. Glycemic Index:7.9

The help needed:

Want to know the causing reason.

Related examination: blood sugar

Figure 2 Question posted on Xunyiwenyao website

### Extended ADR lexicon

To improve the ability to match colloquial terms in online discussion, we further expand our basic ADR lexicon by adding variations of the terms. For example, when a person has a headache, he or she may say “头痛(headache)” or “头有点痛(got a little headache)”, the latter of which is a slight variation with a degree modifier between an organ name and symptom word such as “痛” (pain), and is added to our extended lexicon.

There is a variety of such degree modifiers. We adopt a data-driven approach to mine such degree modifiers by pattern-matching an organ name, up to 5 characters and a symptom word, for example “头(head)XXXXX 痛(pain)”, from online discussion corpus. The algorithm to extend ADR lexicon is presented briefly as follows.

**Algorithm: extend ADR lexicon**

// Construct regular expression patterns

for each term in basic ADRs do

if term contains organ then

construct a regular pattern

// Discover degree words

for each line in all data do

if line match a pattern then

count one for this word

// Extend lexicon

for each term in lexicon do

if term contains organ then

for each word in words list do

insert word into term to generate a new term

1. Data Sources and Data preparation

This section describes three Chinese social media and how we extract evidences of ADRs for drugs from them. We discuss Weibo separately because the nature of posts on Weibo is substantially different from Xunyiwenyao and Haodaifu.

### Chinese social media

Xunyiwenyao was established in 2004. In 2014, there are over 80,000,000 registered accounts, over 20,000,000 daily independent, which earned it the number one ranking in the medical and health service industry 2 The discussion forum contains 14 categories and 64,050 discussion threads on average, every day. Each discussion thread starts with a patient’s question, which is followed by responses from multiple doctors or other patients (see Figure 2).

Haodaifu was launched in 2006 3. Its physician-patient interactive forum is the largest in China, with over 501,000 registered healthcare professionals. It contains 29 categories and 18,632,602 discussion threads until now. The format of the discussion is similar to Xunyiwenyao.

Weibo was established in 2009. By 2016, it has over 297,000,000 subscribers and 132,000,000 daily users[[7]](#footnote-7). The number of posts each day is around 100, 000,000 [[8]](#footnote-8). Weibo messages are terse and informal. The quality of such messages is lower than the first two data sources while the quantity is much larger.

### 

### Issues with Weibo posts

We have mentioned that the discussion volume of Weibo is higher than the other two, but the quality is poorer because:

* A doctor would post a message on Weibo after answering a question in Xunyiwenyao or Haodaifu, and which is already contained in the crawled data so it’s redundant;
* When users comment and forward a message, it rarely contains a complete sentence, which means it’s highly dependent on the original message and makes it harder to processing;
* Very few messages are really about ADRs. For example, there are 7734 messages about Betaloc that we crawled from Weibo, but only 1323 messages contain both Betaloc and a condition;
* There is lots of noise, such as commercial advertisements. In the previous example, out of 1323 messages containing both Betaloc and a condition, only 36% of the messages are really experience reports from the patients who have taken Betaloc.

In a consequence, we do not use the data from Weibo. We only use the combination of data from “Xunyiwenyao” and “Haodaifu” to find the potential ADRs for the 46 drugs of interest.

### Extraction of evidences

First, we preprocess all the user posts from three websites. If one post contains a drug name of interest, this post is considered as an “effective” target. All sentences in “effective” posts are segmented by ICTCLAS (Zhang et al., 2003), a Chinese word segmentation tool.

With the ADR lexicon, we can detect candidate ADR terms from the effective posts. However, when a drug name X is mentioned in a post, the user may not actually have taken that drug. Similarly, when an ADR term is mentioned, the user may not actually have the symptom, or the symptom may not be the result of taking X. Therefore, given a pair of a drug name and an ADR, we need to determine whether the ADR is truly the consequence of taking the drug, given the context of the pair in the post. Because of that a drug-ADR pair that is too far away from each other in the text is not reliable, the context is defined as one or more consecutive sentences where the distance between drug and ADR is less than 55 Chinese words (including punctuations but excluding spaces). We ensure that each context contain one drug-ADR pair.

We define a context as a positive evidence if the candidate ADR in the context is a real ADR. while the other cases belong to the negative sentence. The following are two contexts showing a positive evidence and a negative evidence:

* 服用易瑞沙后头痛，眼睛复视，模糊 (After taking Iressa, had a headache, eye diplopia and blurred vision)
* 吃的是奥美拉唑，克拉霉素，阿莫西林，吗丁啉等药，咳嗽有所减少 (After taking Omeprazole, Clarithromycin, Amoxicillin, Domperidone and other drugs, cough lessened)

### Data set

We have crawled user messages posted between January 2011 to April 2015 on Haodaifu and Xunyiwenyao. These messages mentioned 79 drugs, which treat 11 types of diseases. Table 2 summarizes the diseases and the number of corresponding drugs. In total, 456,753 posts were crawled.

After preprocessing these posts, we obtain 302,180 sentences where a drug-ADR pair is revealed. We first manually label 1200 sentences which contains 600 positive evidences and 600 negative evidences. Then we divide them into training set, tuning set and test set. Finally, we get a training set with 300 positive evidences and 300 negative evidences, a tuning set with 200 positive evidences and 200 negative evidences and a test set with 100 positive evidences and 100 negative evidences.

Table 2 List of diseases and number of drugs studied

|  |  |  |  |
| --- | --- | --- | --- |
| **Diseases** | **Number of drugs** | **Diseases** | **Number of drugs** |
| Hypertension | 29 | Hyperacidity | 2 |
| Diabetes | 18 | Lung cancer | 1 |
| Asthma | 15 | Rhinitis | 1 |
| Statins | 9 | Schizophrenia | 1 |
| Breast cancer | 1 | Acute coronary syndrome | 1 |
| Anesthesia | 1 |

1. Evidence Classifier

Given a drug name and a medical condition, identified by the extended lexicon, as well as their context in the original text, the problem of evidence classification is to determine whether the medical condition is actually an ADR resulting from the drug. Next we present a method to train such an evidence classifier. In particular, we show how to produce large amount of training data by automatic labeling.

### Building the training set

A supervised classifier requires labeled training data. However, manual labeling on user discussion posts can’t scale up because of the large amount of informal use of language and colloquial terms. Fortunately, information in the package insert of the drugs, e.g., the indications and the known side effects of the drug, can be used to automatically generate labeled data.

Our first and simple idea is to regard a pair of drug and medical condition as true if the medical condition is listed as a side effect in the package insert of the drug. Conversely, we regard the pair as false if the medical condition is listed as an indication of the drug. All other pairs are discarded from labeled data set. However, this approach is not perfect. For example, “头晕(dizzyness)” is a known ADR for Betaloc, but sometimes in the real discussion it serves as an indication:

* 突然感到头晕心慌,坐卧不安,去医院检查血压160.100心电图心动过速160次,开了倍他乐克 (Suddenly I felt dizzy, flustered, and restless, my blood pressure was at 160/100; tachycardia electrocardiogram was at 160 times. Consequently I was given Betaloc)

Similarly, “房颤(atrial fibrillation)” is an indication for Betaloc, but sometimes it is reported as if it’s a side effect:

* 后根据医嘱，可达龙减至1/4片每天，加服倍他乐克缓释片一片。一段时间后出现房颤 (According to the doctor’s advice, Cordarone was reduced to 1/4 tablets per day, plus one tablet of Betaloc (slow release). Atrial fibrillation occurred after a period of time)

Because the actual situation arising from patients’ experience may be more complicated than specified on the inserts, we adopt a semi-supervised approach instead. We firstly use our 600 manual labelling data to train a simple SVM classifier and use it to predict all the sentences in the corpus. The features used are discussed in *Features extraction* section below. If the classifier predicts a sentence to be positive, and the medical condition is a known ADR for the drug according to the packet insert, we add this sentence into the new positive training set. If a sentence is predicted to be negative, and the condition in that sentence is a known indication of the drug, then we add this sentence into the negative training set. We will ignore those sentences where the prediction of classifier and the conclusion of the packet insert are different. The new training set also contains our original 600 manual labeling data.

With little manual effort, we have now obtained a much larger set (called semi-supervised data) of positive and negative training data --- 12,238 training instances in total. By manual validation, the accuracy of such automatic labeling is 82%.

### Features extraction

Our main evidence classifier extracts the following features, after parsing the evidence sentences into dependency trees (Chang et al., 2009):

1. Verbs before the drugs, e.g. “服用(take)” in “服用倍他乐克(take *Betaloc*)”;
2. Verbs before the conditions, e.g. “感到(feel)” in “感到头晕(feel dizzy)”;
3. Verbs after the conditions, e.g. “好转(improved)” in “头疼好转(headache improved)”;
4. Preposition, conjunction and noun of locality, e.g. “因为(because of)” in “因为头疼(because of headaches)” and “后(after)” in “服用倍他乐克后(after taking *Betaloc*)”;
5. Punctuations that surround drugs and conditions;
6. The number of other drugs and other conditions between the drug and condition of interest;
7. A Boolean value that indicates whether condition appears in front of the drug or not.

The verbs are hard to extract without parsing the sentences. They often occur along with modifiers in the Chinese language. For example, “头疼好转(headaches improved)” would often be expressed as “头疼稍微好转(headaches improved a little bit)”, and with the dependency tree we can extract “好转(improved)” from it easily. The set of features described above are used in both the initial and the final classifier. However, with more training data, the final classifier can better distinguish unseen tokens.

It’s worth noting that all these seven features are independent with the name of drug and ADR.

### Overall flow

We choose SVM as our primary classifier, because our feature vectors are high-dimensional (many different words). The overall process of our method is:

* Manually label small amount of seed data ***S***;
* Train an initial SVM classifier ***M’*** from ***S***;
* Use ***M’*** and package inserts to generate more training data ***T***;
* Train the final SVM classifier ***M*** from ***T***.

### Bootstrapping of automatically labeling

The above method uses the package inserts the initial classifier ***M’*** to generate more training data. One interesting thought is to use that newly obtained classifier ***M*** to label even more training data, and thus build a newer classifier. This process can go on iteratively until no more new training data is obtained. We will show the results of this in Section 3. The training data obtained at the final iteration is called semi-supervised data and will be used to train our SVM classifier and the other baseline classifiers (see section 2.4).

1. Baseline extraction techniques

### Pattern-based method

Beside the above semi-supervised learning method, we have also tried a naïve pattern-based classifier as a baseline. We extract preposition, conjunction and noun of locality from sentences as patterns from training data generated by package inserts. Each pattern has a weight, which is its frequency of occurrence; a negative pattern extracted from negative examples will have a negative weight. For example, below are two patterns we extracted and their weight:

* drug ... 后 ... adr ... 20
* adr ... 后 ... drug ... -3

For a new sentence that can be matched to several patterns, the score is the sum of these patterns. Then a classifier is built based on the score: if the score is greater than 0, it’s positive; otherwise negative.

### HMM-based classifier

We train a HMM classifier based on the method in the paper of SampathKumar et al. (Sampathkumar et al., 2014). Particularly, comparing to original HMM paper where the sentences to be classified may not contain a drug-ADR pair, our task is more challenging because we firstly ensure a drug-ADR pair in all sentences and then make the classification.

We train two HMM classifiers in all. One classifier is only trained with 600 manually-labeled data and another classifier is trained with the semi-supervised data by using the packet insert.

### CRF-based classifier

We train a CRF-based classifier by using the method which was referred in the paper of Nikfarjam et al. (Nikfarjam et al., 2015). We also use two kind of data to train the two CRF-based classifiers: one with 600 manually-labeled data and another with semi-supervised data.

Both the HMM and CRF classifiers were slightly modified to adapt to the Chinese input. For example we use ICTCLAS to segment and POS to tag the input sentences.

1. Ranking

For each drug, there are many candidate ADRs. We are interested in ADRs of high confidence. One way of ranking the ADRs of a drug is by the number of its appearances in positive evidence posts. This doesn’t work well because, most discussions about a drug involves the indications of the drug. For example, discussion about *Betaloc* would naturally include a lot of occurrences of the term “hypertension” and the absolute number of such mentions is very large. Although our classifier could arrive at a high accuracy, there still exists a number of sentences which contains “hypertension” as ADR and are also mistakenly predicted to be positive sentence. Consequently, “hypertension” would be ranked highly as an ADR of *Betaloc*. To solve this problem, we rank the ADRs according to the frequency of the positive evidences minus that of the negative evidences. This approach effectively lowers the rankings of the indications of a drug, but promotes real ADRs.

Table 3 The effectiveness of classification features.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| SVM Features | positive pairs | negative pairs | R | P | F1 | accuracy |
| All | 184/200 | 148/200 | 0.92 | 0.74 | **0.820** | **0.83** |
| All – verbs before drugs (feature 1) | 175/200 | 152/200 | 0.875 | 0.76 | 0.813 | 0.818 |
| All – verbs before conditions (feature 2) | 184/200 | 147/200 | 0.92 | 0.735 | 0.817 | 0.828 |
| All – verbs after conditions (feature 3) | 175/200 | **153**/200 | 0.875 | **0.765** | 0.816 | 0.82 |
| All – preposition, conjunction and noun of locality (feature 4) | **187**/200 | 144/200 | **0.935** | 0.72 | 0.814 | 0.828 |
| All – punctuations (feature 5) | 169/200 | 131/200 | 0.845 | 0.655 | 0.738\* | 0.75 |
| All – number of other drugs and other conditions (feature 6) | 180/200 | 141/200 | 0.9 | 0.705 | 0.791\* | 0.803 |
| All – Boolean value (feature 7) | 173/200 | 146/200 | 0.865 | 0.73 | 0.792\* | 0.798 |

# Results

We divide our evaluation into six parts. Firstly, we run the automatically labeling algorithm iteratively and show the change of the performance. Secondly, we will examine the importance of different features in the SVM classifier. Thirdly, we compare the accuracy of our final classifier with other several baseline classifiers (HMM, CRF and pattern-based), the difference caused by the difference training set will also be shown. Fourthly, we evaluate the effect of enlarging the drug and ADR lexica. Finally, we evaluate the accuracy of discovered ADRs with the help of drug package inserts, and show the top-ten discovered ADRs of several drugs, as verification and supplement for the known ADRs in the package inserts.

## Impact of the iteration

Figure 3 shows the accuracies and F1-scores on the tuning set after each iteration, using the bootstrapping approach in Section 2.3. The result at iteration 0 is obtained using only the manually labeled data. After each iteration, the training set will enlarge, however the speed of growth becomes slow in each iteration and drops to 0 at 15th iteration. By using the tuning set which contains 400 manually labeled data (200 positive + 200 negative) to calculate the f1-score and accuracy of our SVM classifier in each iteration, we observe quick convergence: the two values keep constant after 9th iteration.

Table 4 Performance of various classifier

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Methods | positive pairs | negative pairs | recall | precision | F1-score |
| Manual labels (Pattern-based) | 24/100 | 97/100 | 0.24 | 0.889 | 0.378 |
| Semi-supervised (Pattern-based) | 76/100 | 89/100 | 0.76 | 0.874 | 0.813 |
| Manual labels (HMM) | 62/100 | 85/100 | 0.62 | 0.805 | 0.700 |
| Semi-supervised labels (HMM) | 87/100 | 54/100 | 0.87 | 0.654 | 0.747 |
| Manual labels (CRF) | 86/100 | 75/100 | 0.86 | 0.775 | 0.815 |
| Semi-supervised labels (CRF) | 98/100 | 34/100 | 0.98 | 0.598 | 0.742 |
| Manual labels (SVM) | 68/100 | 87/100 | 0.68 | 0.840 | 0.752 |
| Auto labels from inserts (SVM) | 86/100 | 58/100 | 0.81 | 0.698 | 0.75 |
| Semi-supervised labels (SVM) | 86/100 | 79/100 | 0.86 | 0.804 | **0.831** |

***Manual labels****: use the manually labeled training set with 300 positive instances and 300 negative instances*

***Semi-supervised labels****: use the training data that we obtained after the 5th iteration.*

***Auto labels from insert****: use the training data that we obtained according to the packet insert directly without help of the manually labeled data. If the symptom in the sentence is ADR according to the packet insert, it will be added into positive training set. Inversely, if the symptom in the sentence is indication according to the packet insert, it will be added into negative training set.*

The biggest improvement of performance comes from the 0th iteration to the 1st iteration since the most knowledge is acquired in the first round of bootstrapping. The gain in accuracy and f1-score saturates after a peak is reached at the 5th iteration. We therefore use the training data obtained at that time to train our final SVM classifier and other baseline classifiers.

Figure 3 F1-score and accuracy of the new SVM classifier at each iteration

## The effectiveness of classification features

To examine the contribution of each feature of our SVM classifier, we use the previous tuning set which contains 400 manually labeled sentences to performed leave-one-out feature experiments on the tuning set. The result is shown in Table 3.

We find that each feature does the contribution for the performance of the classifier. Among all the features, feature 5, 6, 7 are the most important ones.

Table 5 Enlarging data set through homophone transform and ADR extension

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | 倍他乐克  (Betaloc) | 耐信  (Nexium) | 拜唐苹  (Glucobay) | 氨茶碱  (Aminophylline) | All 79 drugs |
| official name | 24073 | 6521 | 530 | 7493 | 158695 |
| homophone | 13177 | 6369 | 1611 | 2388 | 143485 |
| total | 37250 | 12890 | 2141 | 9881 | 302180 |
| % increase | 64.6% | 50.6% | 24.8% | 75.8% | 52.5% |

## Drug-ADR association

According to the previous research, we use the training data obtained at the 5th iteration and all the features to train our SVM classifier. To make the comparison with several baseline classifiers, another 200 manually-labeled test data (100 positive + 100 negative), which are different from the previous tuning set, is chosen to check the performance of the various classifier. The result is shown in Table 4.

The pattern-based classifier depends a lot on the size of the training data set. More training data could help it to recognize more patterns of a positive sentence. In consequence, the performance improves a lot when using semi-supervised labels.

The HMM-based classifier emphasizes on the structure of sentences. The performance improved if the structure in training set and testing set is standard. Therefore, when we use the manually-labeled data to train the HMM classifier, the small size of training data set results in a low precision. It can be also seen that the percentage of true positives is inversely correlated with the percentage of true negatives. This means a classifier is biased to produce either more positive labels or more negative labels. A good classifier, such as the one trained with the semi-supervised labels manages to strike a balance between the two biases and produce a better overall F1-score.

CRF-based classifier use the sequence labeling with word embedding cluster features, which reduce the effect of the training set’s size. However, this kind of classifier also depends on the grammatical form of a sentence. When training set enlarges, the structure of negative instances becomes various and do not have a regular form, which leads to a bad performance of the CRF classifier.

In short, both the HMM and CRF concentrate more on the information of the single word itself and its limited surrounding words. However, SVM focus on the features of the whole sentence.

The semi-supervised data, which is doubly verified by the primary SVM classifier and package inserts, may not have a very standard form (e.g., some sentences do not have the causal keyword but have a lot of noisy words between the ADR and its associated drug). For those user posts, which do not have a standard form, SVM performs clearly better because of its global view, and HMM doesn’t perform as well because it requires sentences in their standard form.

Figure 4 End-to-end rankings’ AveP

## Homophone transformation and extended ADR lexicon

As shown in the table 5, our data set, measured by the number of sentences containing at least one of the 4 selected drugs and an ADR, is enlarged significantly after homophone transformation.

Among all the 302,180 sentences which contains a (drug, ADR) pair, there are totally 1,328 sentences where the candidate ADR contains an adverb of degree and can only be extracted by using the extended ADR lexicon. Although 1,328 is not large compared to 302,180, extended ADR lexicon could also help us to enlarge the data set to find more potential ADRs.

## End-to-end ranking

By using the ranking method which is referred in section 2.5, our system returns a ranked list of possible ADRs when given a drug. We evaluate the end-to-end performance of the system by the Average Precision (AveP) according to the package insert of the drug：

where *P(k)* is the precision at cut-off k in the list, *rel(k)* is an indicator function equaling 1 if the item at rank *k* is a relevant document, 0 otherwise.[[9]](#footnote-9)

We expect the true ADR of a drug to rank high in the list while the true indication ranks lower in the list. The ground truth we use here is the known ADRs and known indications of four random-sampled drugs according to the packet inserts. Figure 4 shows the results of the four previous randomly chosen drugs, 倍他乐克(Betaloc), 耐信(Nexium), 拜唐苹(Glucobay) and 氨茶碱(Aminophylline). We also calculate the weighted average of *AveP* for all the 79 drugs.

From Figure 4, we can see that AveP(ADR) is much larger than AveP(Indication), which means that most of ADRs that our classifier discovers are already included in the packet insert. Besides, the known indications are not in our returned ADR list or ranked very low in our list.

Together with Table 5, which gives the sizes of the datasets for four drugs, we learn that more data helps to increase the ADR prediction accuracy.

## Top-ten discovered ADRs

Table 6 Top 10 discovered ADRs for 4 common drugs

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **药物**  **(Drugs)** | **倍他乐克**  **(Betaloc)** | **耐信**  **(Nexium)** | **拜唐苹**  **(Glucobay)** | **氨茶碱**  **(Aminophylline)** |
| 副作用(ADRs) | 咳嗽(2.45%)  (Cough) | 咳嗽(1.77%)  (Cough) | 不适(3.31%)  (Discomfort) | 咳嗽(51.39%)  (Cough) |
| 紧张(2.06%)  (Nervous) | 头晕(1.09%)  (Dizziness) | 无力(2.18%)  (Acratia) | 头晕(0.69%)  (Dizziness) |
| 不适(4.04%)  (Discomfort) | 不适(2.30%)  (Discomfort) | 发热(1.48%)  (Fever) | 恶心(0.57%)  (Nausea) |
| 心悸(2.82%)  (Palpitation) | 紧张(0.32%)  (Nervous) | 头晕(2.70%)  (Dizziness) | 心悸(0.26%)  (Palpitation) |
| 头晕(5.52%)  (Dizziness) | 便秘(0.85%)  (Constipation) | 乏力(1.31%)  (Weak) | 呕吐(1.13%)  (Emesis) |
| 疲劳(0.67%)  (Fatigue) | 疲劳(0.16%)  (Fatigue) | 瘙痒(0.87%)  (Itching) | 心动过速(0.19%)  (Tachycardia) |
| 头痛(1.32%)  (Headache) | 失眠(0.50%)  (Insomnia) | 腹泻(1.13%)  (Diarrhea) | 心律失常(0.26%)  (Arrhythmia) |
| 恶心(0.89%)  (Nausea) | 头痛(0.36%)  (Headache) | 低血糖(3.14%)  (Hypoglycemia) | 打鼾(0.22%)  (Snore) |
| 便秘(0.16%)  (Constipation) | 心悸(0.11%)  (Palpitation) | 虚弱(0.52%)  (Asthenia) | 抽搐(0.22%)  (Tic) |
| 瘙痒(0.14%)  (Itching) | 皮肤过敏(0.12%)  (Skin allergy) | 咳嗽(0.61%)  (Cough) | 紧张(0.12%)  (Nervous) |

Table 6 shows the top-ten discovered ADRs for 4 aforementioned drugs. The number in the parentheses after an ADR indicates the percentage of posts discussing a drug and reporting that ADR (formula). ADRs which don’t have direct match in the package inserts (therefore potentially new discoveries) are marked in red.

In Table 6, we discovered many ADRs that are already included in the package inserts. Although these ADRs are known, the frequency statistics can be valuable for: i) verifying ADRs listed in the package inserts; ii) studying the relative frequency between the ADRs. For example, the frequency of *Fatigue* and *Constipation* of Betaloc in package insert are both larger than 1%, but they are 0.67% and 0.16% respectively in our result.

There are also a number of ADRs without direct match in the manuals. These fall into several cases:

*Synonyms of the known ADRs* (e.g., “疲乏(Exhaustion)” is a synonym of “疲劳(Fatigue)” for “耐信(Nexium) ”. While they are synonyms, the ADRs listed in package inserts are often some terminologies and the colloquial synonyms can help patients understand them easily.

*Specialization of the known ADRs* (e.g., “呕吐(Emesis)” is a specialization of the symptom “不适 (Discomfort)” for “倍他乐克 (Betaloc)”). Some ADRs from package inserts are very general terms. Our results give the insight of what specific symptoms are actually encountered by the patients.

# Conclusion

We have proposed an effective framework for extracting and analyzing ADRs from Chinese online social media. It uses a lexicon-based method to extract ADRs from the data followed by a binary classifier to identify the positive evidences. In this framework, we introduce a data-driven algorithm to extend the drug and ADR lexica. In order to build the evidence classifier, we propose an automatic labeling algorithm to produce large amounts of labeled sentences. Completely relying on the information from the package inserts produces training data that is too noisy. Our tradeoff is a semi-supervised approach where we manually label a small set, then use these data and package inserts collectively to generate more training data. This algorithm proves to be highly effective.

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**Appendix A List of Drugs Studied**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Category** | **Drug Name** | **English Name** | **Manufactor** | **Total Num of posts** |
| 鼻炎(Rhinitis) | 雷诺考特 | Rhinocort | AstraZeneca | 8164 |
| 肺癌(Lung Cancer) | 易瑞沙 | Iressa | AstraZeneca | 16481 |
| 高血压  (Hypertension) | 倍他乐克 | Betaloc | AstraZeneca | 37250 |
| 波依定 | Plendil | AstraZeneca | 7089 |
| 颉沙坦 | Valsartan | Norvatis | 2468 |
| 乌拉地尔 | urapidil | Nycomed GmbH | 151 |
| 替米沙坦 | Telmisartan | Boehringer Ingelheim | 1949 |
| 瑞泰 | Tritace | Sanofi-Aventis | 380 |
| 雅施达 | Acertil | LES LABORATOIRES SERVIER | 1133 |
| 科素亚 | Cozaar | Merck Sharp & Dohme Limited | 2853 |
| 海捷亚 | Hyzaar | Merck Sharp & Dohme Limited | 613 |
| 赖诺普利 | lisinopril | AstraZeneca UK Limited | 287 |
| 再宁平 | Zanidip | Recordati S.P.A. | 75 |
| 乐息平 | Lacipil | GLAXOSMITHKLINE | 693 |
| 马来酸伊索拉定 | Gaslon N | Nippon Shinyaku Co.,Ltd. | 29 |
| 安博维 | APROVEL | Sanofi Pharma Bristol-Myers Squibb SNC | 2522 |
| 寿比山 | Indapamide | Servier | 1773 |
| 达爽 | Tanatril | 天津田边制药有限公司 | 386 |
| 蒙诺 | Monopril | 中美上海施贵宝制药有限公司 | 1222 |
| 多沙唑嗪 | Cardura XL | Pfizer Pharma GmbH | 229 |
| 合心爽 | Altiazem | 天津田边制药有限公司 | 1522 |
| 卡维地洛片 | Carvedilol | ROCHE S.P.A. | 562 |
| 必洛斯 | Blopress | Takeda Pharmaceutical Company Limited | 523 |
| 康忻 | Concor | Merck Serono GmbH | 3104 |
| 贝尼地平 | Coniel | Kyowa Hakko Kirin Co.,Ltd. | 180 |
| 阿替洛尔 | Atenolol | AMRI India Pvt. Ltd. | 877 |
| 尼群地平 | Nitrendipine | Alvogen Malta Operations Ltd | 874 |
| 阿尔马尔 | Almarl | Dainippon Sumitomo Pharma Co., Ltd. | 901 |
| 络活喜 | Norvasc | Pfizer Australia Pty Limited | 4636 |
| 锐思力 | Rasilez | Novartis Pharma Schweiz AG | 2 |
| 特拉唑嗪 | Terazosin | Abbott | 1316 |
| 他汀类药物  (Statins) | 可定 | Crestor | AstraZeneca | 2179 |
| 阿伐他汀 | Lipitor | Pfizer Ireland Pharmaceuticals | 134 |
| 辛伐他汀 | Simvastatin Tablets | Merck Sharp &amp; Dohme (Australia) Pty. Ltd. | 1140 |
| 普伐他汀 | Pravastatin | 华北制药股份有限公司 | 110 |
| 洛伐他汀 | Lovastation | AstraZeneca | 751 |
| 氟伐他汀 | Fluvastatin | Novartis | 267 |
| 葆至能 | VYTORIN | MSP Singapore Company,LLC | 7 |
| 匹伐他汀 | LIVALO KOWA | Kowa Company, Ltd. | 57 |
| 氨氯地平阿托伐他汀 | Amlodipine Besylate and Atorvastatin Calcium Tablets | Pfizer Inc. | 85 |
| 胃酸过多  (GERD) | 洛赛克 | Losec | AstraZeneca | 41957 |
| 耐信 | Nexium | AstraZeneca | 12890 |
| 急性冠脉综合征  (Acute coronary) | 倍林达 | BRILINTA | AstraZeneca | 179 |
| 精神分裂  (Schizophrenia) | 思瑞康 | Seroquel | AstraZeneca | 10859 |
| 麻醉(Sedation) | 得普利麻 | Diprivan | AstraZeneca | 578 |
| 乳腺癌  (Breast Cancer) | 瑞宁得 | ARIMIDEX | AstraZeneca | 1915 |
| 糖尿病  (Diabetes) | 安立泽 | Onglyza | Bristol-Myers Squibb Company | 269 |
| 百泌达 | BYETTA | Eli Lilly Nederland B.V. | 198 |
| 伏格列波糖 | Voglibose | Ranbaxy Laboratories Limited | 419 |
| 维格列汀 | Galvus | Novartis Europharm Ltd. | 114 |
| 捷诺维 | JANUVIA | Merck Sharp &amp; Dohme (Australia) Pty Ltd | 208 |
| 罗格列酮 | Avandamet | GlaxoSmithKline | 449 |
| 瑞格列奈片 | NovoNorm | Novo Nordisk A/S | 1157 |
| 吡格列酮 | Actos | Takeda Pharmaceutical Company Limited | 822 |
| 赛尼可 | Xenical | Roche Pharma(Schweiz) Ltd | 993 |
| 那格列奈片 | Nateglinide Tablet | 北京诺华制药有限公司 | 273 |
| 诺和力 | Victoza | Novo Nordisk A/S | 59 |
| 长秀霖 | Basalin | 甘李药业股份有限公司 | 530 |
| 来得时 | LANTUS | Sanofi-Aventis Deutschland GmbH | 1719 |
| 诺和锐 | NovoRapid FlexPen | Novo Nordisk A/S | 1337 |
| 格列吡嗪控释片 | Glucotrol XL | Pfizer Inc. | 224 |
| 格列美脲片 | Amaryl | Sanofi-Aventis Deutschland GmbH | 771 |
| 达美康 | Diamicron MR | Les Laboratoires Servier | 1675 |
| 拜唐苹 | Glucobay | Bayer Vital GmbH | 2141 |
| 哮喘  (Asthma) | 普米克 | Pulmicort | AstraZeneca | 10621 |
| 信必可 | Symbicort | AstraZeneca | 8349 |
| 安可来 | ACCOLATE | AstraZeneca UK Limited | 14 |
| 氨茶碱 | Aminophylline | Sannova Co | 9881 |
| 沙丁胺醇 | Salbutamol | EugenPharm Inc, USA | 4028 |
| 美普清 | Meptin | 中国大冢制药有限公司 | 4252 |
| 吡嘧司特钾 | Pemirolast Potassium Tablets | 河北医科大学制药厂 | 216 |
| 盐酸奥洛他定 | Allelock | Kyowa Hakko Kirin Co.,Ltd. | 1414 |
| 顺尔宁 | Singulair | Merck Sharp &amp; Dohme Australia Pty Ltd | 54621 |
| 阿乐迈 | Alomide | s.a. ALCON-COUVREUR n.v. | 108 |
| 奥克斯都保 | Oxis Turbuhaler | AstraZeneca AB | 609 |
| 舒利迭 | Seretide | Glaxo Wellcome UK Limited | 19147 |
| 依匹斯汀 | Alesion | Nippon Boehringer Ingelheim Co.,Ltd. | 296 |
| 阿米迪 | Amiaid | Nitto Denko Corporation | 1601 |
| 帮备 | Bambec | AstraZeneca | 313 |
| **Total** |  | | | **302180** |

1. https://www.cuttingedgeinfo.com/2011/us-phase-iv-budgets/ [↑](#footnote-ref-1)
2. http://club.xywy.com/ [↑](#footnote-ref-2)
3. http://www.haodf.com/ [↑](#footnote-ref-3)
4. http://weibo.com [↑](#footnote-ref-4)
5. Sogou Pinyin is a Chinese input method, and there are many lexicons available. And the interested one is the ADRs lexicon: <http://pinyin.sogou.com/dict/detail/index/644> . [↑](#footnote-ref-5)
6. https://translate.google.com/ [↑](#footnote-ref-6)
7. http://www.businessofapps.com/sina-weibo-revenue-and-statistics/ [↑](#footnote-ref-7)
8. www.useit.com.cn/thread-14392-1-1.html [↑](#footnote-ref-8)
9. AveP is defined at <https://en.wikipedia.org/wiki/Information_retrieval> [↑](#footnote-ref-9)