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# Single concatenated input is better than indenpendent multiple-input for CNNs to predict chemical-induced disease relation from literature

Dang Thanh Hai*, Bui Manh Thang

*Bingo Biomedical Informatics Lab, Faculty of Information Technology, VNU University of Engineering and Technology, Hanoi, Vietnam*

**Abstract**

Chemical compounds (drugs) and diseases are among top searched keywords on the PubMed database of biomedical literature by biomedical researchers all over the world (according to a study in 2009). Working with PubMed is essential for researchers to get insights into drugs' side effects (chemical-induced disease relations (CDR)), which is essential for drug safety and toxicity. It is, however, a catastrophic burden for them as PubMed is a huge database of unstructured texts, growing steadily very fast (~28 millions scientific articles currently, approximately two deposited per minute). As a result, biomedical text mining has been empirically demonstrated its great implications in biomedical research communities. Biomedical text has its own distinct challenging properties, attracting much attetion from natural language processing communities. A large-scale study recently in 2018 showed that incorporating information into indenpendent multiple-input layers outperforms concatenating them into a single input layer (for biLSTM), producing better performance when compared to state-of-the-art CDR classifying models. This paper demonstrates that for a CNN it is vice-versa, in which concatenation is better for CDR classification. To this end, we develop a CNN based model with multiple input concatenated for CDR classification. Experimental results on the benchmark dataset demonstrate its outperformance over other recent state-of-the-art CDR classification models.

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*Keywords:* .

## 1. Introduction

Drug manufacturing is an extremely expensive and time-consuming process [1]. It requires approximated 14 years, with a total cost of about $1 billion, for a specific drug to be available in the pharmaceutical market [2]. Nevertheless, even when being in clinical uses for a while, side effects of many drugs are still unknown to scientists and/or clinical doctors [3]. Understanding drugs' side effects is essential for drug safety and toxicity. All these facts explain why chemical compounds (drugs) and diseases are among top searched keywords on PubMed by biomedical researchers all over the world (according to [4]). PubMed is a huge database of biomedical literature, currently with ~28 millions scientific articles, and is growing steadily very fast (approximate two ones added per minute).

Working with such a huge amount of unstructured textual documents in PubMed is a catastrophic burden for biomedical researchers. It can be, however, accelerated with the

* Corresponding author. E-mail.: hai.dang@vnu.edu.vn

application of biomedical text mining, hereby for drug (chemical) - disease relation prediction, in particular. Biomedical text mining has been empirically demonstrated its great implications in biomedical research communities [5-7].

Biomedical text has its own distinct challenging properties, attracting much attetion from natural language processing communities [8, 9]. In 2004, an annual challenge, called BioCreative (Critical Assessment of Information Extraction systems in Biology) was launched for biomedical text mining researchers. In 2016, researchers from NCBI organized the chemical disease relationship extraction task for the challenge [10].

To date, almost all proposed models are only for prediction of relationships between chemicals and diseases that appear within a sentence (intra-sentence relationships) [11]. We note that those models that produce the state-of-the-art performance are mainly based on deep neural architechtures [12-14], such as recurrent neural networks (RNN) like bi-directional long short-term memory (biLSTM) in [15] and convolutional neural networks (CNN) in [16-18].

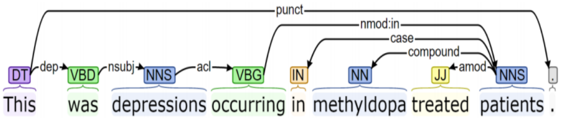
Recently, Le et al. developed a biLSTM based intra-sentence biomedical relation prediction model that incorporates various informative linguistic properties in an independent multiple-layer manner [19]. Their experimental results demonstrate that incorporating information into indenpendent multiple-input layers outperforms concatenating them into a single input layer (for biLSTM), producing better performance when compared to relevant state-of-the-art models. To the best of our knowledge, there is currently no study confirming whether it is still hold true for a CNN-based intra-sentence chemical disease relationship prediction model by far. To this end, this paper proposes a model for prediction of intra-sentence chemical disease relations in biomedical text using CNN with concatenation of multiple layers for encoding different linguistic properties as input.

The rest of this paper is organized as follows. Section 2 describes the proposed method in detail. Experimental results are discussed in section 3. Finally, section 4 concludes this paper.

## 2. Method

Given a preprocessed and tokenized sentence containing two entity types of interest (i.e. chemical and disease), our model first extracts the shortest dependency path (SDP) (on the dependency tree) between such two entities. The SDP contains tokens (together with dependency relations between them) that are important for understanding the semantic connection between two entities (see Figure 1 for an example of the SDP).

Figure 1. Dependency tree for an example sentence. The shortest dependency path between two entities (i.e. *depression* and *methyldopa*) goes through the tokens "*occurring*" and "*patients*".



Each token $t$ on a SDP is encoded with the embedding $e^t$ by concatenating three embeddings of equal dimension $d$ (i.e. $e^w+e^{pt}+e^{ps}$), which represent important linguistic information, including its token itself ($e^w$), part of speech (POS) ($e^{pt}$) and its position ($e^{ps}$). Two former partial embeddings are fine-tuned during the model training. Position embeddings are indexed by distance pairs $[d^l\%5, d^r\%5]$, where $d^l$ and $d^r$ are distances from a token to the left and the right entity, respectively.

For each dependency relation ($r$) on the SDP, its embedding has the dimension of $3*d$, and is randomly initialized and fine-tuned as the model's parameters during training.

To this end, each SDP is embedded into the $R^{NxD}$ space (see Figure 2), where $N$ is the number of all tokens and dependency relations on the SDP and $D=3*d$. The embedded SDP will be fed as input into a conventional convolutional neural network (CNN [20]) for being classified if there is or not a predefined relation (i.e. chemical-induced disease relation) between two entities.

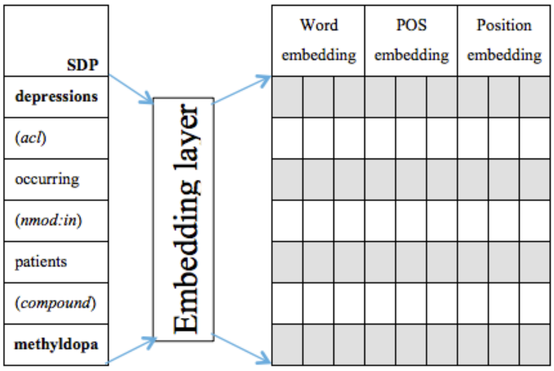


Figure 2. Embedding by concatenation mechanism of the Shortest Dependency Path (SDP) from the example in Figure 1.

### 2.1. Multiple-channel embedding

For multi-channel embedding, instead of concatenating three partial embeddings of each token on a SDP we maintain three independent embedding channels for them. Channels for relations on the SDP are identical embeddings. As a result, SDPs are embedded into $R^{nxdxc}$, where n is the number of all tokens and dependency relations between them, $d$ is the dimension number of embeddings, and $c=3$ is the number of embedding channels.

To calculate feature maps for CNN we follow the scheme in the work of Kim 2014 [21]. Each CNN's filter *f_i* is slided along each embedding channel (*c*) independently, creating a corresponding feature map fm_i_c. The max pooling operator is then applied on those created feature maps on all channels (three in our case) to create a feature value for filter *f_i* (Figure 3).

### 2.2. Hyper-parameters

The model's hyper-parameters are empirically set as follows:

- Filter size: *n* x *d*, where *d* is the embedding dimension (300 in our experiments), *n* is a number of consecutive elements (tokens/POS tags, relations) on SDPs.
- Number of filters: 32 filters of the size 2 x 300, 128 of 3 x 300, 32 of 4 x 300, 96 of 5 x 300.
- Number of hidden layers: 2.
- Number of units at each layer: 128.
- The number of training epochs: 100
- Patience for early stopping: 10
- Optimizer: Adam

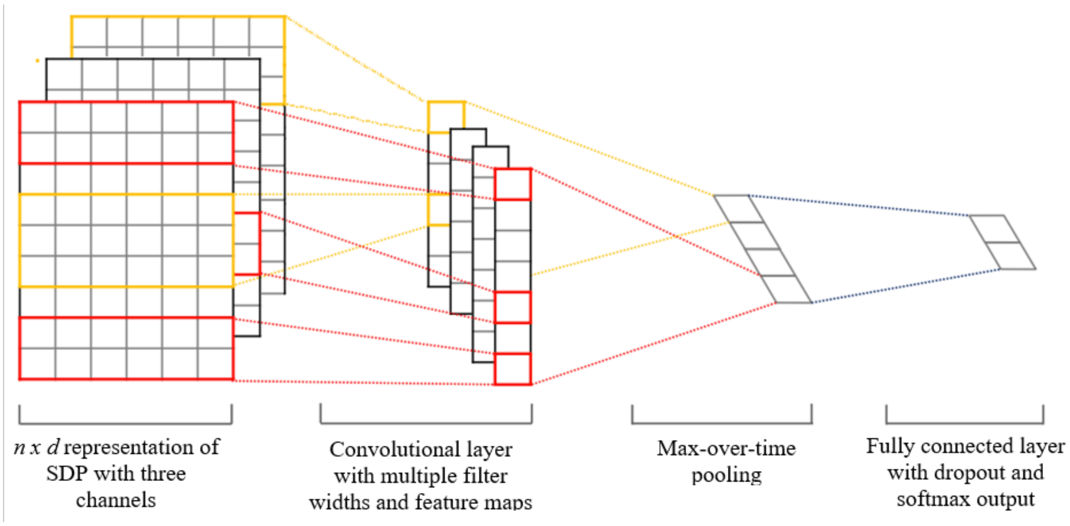

*n* x *d* representation of SDP with three channels
Convolutional layer with multiple filter widths and feature maps
Max-over-time pooling
Fully connected layer with dropout and softmax output

Figure 3. Model architecture with three-channel embedding as an input for an SDP.

## 3. Experimental results

### *3.1. Dataset*

Our experiments are conducted on the Bio Creative V data [10]. It's an annotated text corpus that consists of human annotations for chemicals, diseases and their chemical-induced-disease (CID) relation at the abstract level. The dataset contains 1500 PubMed articles divided into three subsets for training, development and testing. In 1500 articles, most were selected from the CTD data set (accounting for 1400/1500 articles). The remaining 100 articles in the test set are completely different articles, which are carefully selected. All these data is manually curated. The detail information is shown in Table 1.

*Table 1. Statistics on BioCreative V CDR dataset [10].*

| **Dataset** | **Articles** | **Chemical** | | **Disease** | | **CID** |
|---|---|---|---|---|---|---|
| | | **Mention** | **ID** | **Mention** | **ID** | |
| **Training** | 500 | 5203 | 1467 | 4182 | 1965 | 1038 |
| **Development** | 500 | 5347 | 1507 | 4244 | 1865 | 1012 |
| **Test** | 500 | 5385 | 1435 | 4424 | 1988 | 1066 |

### *3.2. Model evaluation*

We merge the training and development subsets of the BioCreative V CDR into a single training dataset, which is then divided into the new training and validation/development data with a ratio 85%:15%. To stop training process at the right time, we use the early stop technique on F1-score on the new validation data.

The entire text will be passed through a sentence splitter. Then based on the name of the disease, the name of the chemical has been marked from the previous step, we filter out all the sentences containing at least one pair of chemical-disease entities. With all the sentences found, we can classify the relation for each pair of chemical-disease entities. We perform model training and evaluating 15 times on the new training and development set, the averaged F1 on the test set is chosen as the final evaluation result across the entire dataset to make sure that the model can work well with strange samples.

Finally, the models that achieve the best results based on the sentence level will be applied to the problem on the abstract level to compare with other very recent state-of-the-art methods.

### *3.3. Results and Comparison*

Experiment results show that the model achieves the averaged F1 of 57.1% (Precision of 55.6% and Recall of 58.6%) at the abstract level. Compared with its variant that does not use dependency relations, we observe a big outperformance of about 2.6% at F1, which is very significant (see Table 2). It indicates that dependency relations contain much information for relation extraction. In the meanwhile, POS tag and position information are also very useful when contributing 0.9% of the F1 improvement to the final performance of the model.

*Table 2. Performance of our model with different linguistic information used as input.*

| Information used | Precision | Recall | F1 |
|---|---|---|---|
| Tokens only | 53.7 | 55.4 | 54.5 |
| Token, Dependency (depRE) | 55.7 | 56.8 | 56.2 |
| Tokens, DepRE and POS tags | 55.7 | 57.5 | 56.6 |
| **Tokens, depRE, POS and Position** | **55.6** | **58.6** | **57.0** |

Compared with recent state-of-the-art models such as MASS [19], ASM [22], and the tree kernel based model [23], our model performs better (Table 3). Ours and MASS only exploit intra-sentence information (namely SDPs, POS and positions), ignoring prediction for cross-sentence relations, while the other two incorporate cross-sentence information. We note that cross-sentence relations account for 30% of all relations in the CDR dataset. This probably explains why ASM could achieve better recall (67.4%) than our model (58.6%).

*Table 3. Performance of our model in comparison with other state-of-the-art models.*

| **Model** | **Relations** | **Precision** | **Recall** | **F1** |
|---|---|---|---|---|
| Zhou et al., 2016 | Intra- and inter-sentence | **64.9** | 49.2 | 56.0 |
| Panyam et al., 2018 | Intra- and inter-sentence | 49.0 | **67.4** | 56.8 |
| Le et al., 2018 | Intra-sentence | 58.9 | 54.9 | 56.9 |
| Our model | Intra-sentence | 55.6 | 58.6 | **57.0** |

## 4. Conclusion

This paper experimentally demonstrates that CNNs perform better prediction of abstract-level chemical-induced disease relations in biomedical literature when using concatenated input embedding channels rather than independent multiple channels. It is vice versa for BiLSTM when multiple independent channels give better performance, as shown in a recent large-scale related study [Le et al., 2018]. To this end, this paper present a model for prediction of chemical-induced disease relations in biomedical text based on a CNN with concatenated input embeddings. Experimental results on the benchmark dataset show that our model outperforms three recent state-of-the-art related models.

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