BERTChem-DDI : Improved Drug-Drug Interaction Prediction from text using Chemical Structure Information

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Abstract

Traditional biomedical version of embeddings obtained from pre-trained language models have recently shown state-of-the-art results for relation extraction (RE) tasks in the medical domain. In this paper, we explore how to incorporate domain knowledge, available in the form of molecular structure of drugs, for predicting Drug-Drug Interaction from textual corpus. We propose a method, BERTChem-DDI, to efficiently combine drug embeddings obtained from the rich chemical structure of drugs along with off-the-shelf domain-specific BioBERT embedding-based RE architecture. Experiments conducted on the DDIExtraction 2013 corpus clearly indicate that this strategy improves other strong baselines architectures by 3.4% macro F1-score.

1 Introduction

Concurrent administration of two or more drugs to a patient to cure an ailment might lead to positive or negative reaction (side-effect). These kinds of interactions are termed as Drug-Drug Interactions (DDIs). Predicting drug-drug interactions (DDI) is a complex task as it requires to understand the mechanism of action of two interacting drugs. A large number of efforts by the researchers have been witnessed in terms of automatic extraction of DDIs from the textual corpus (Sahu and Anand, 2018), (Liu et al., 2016), (Sun et al., 2019), (Li and Ji, 2019) and predicting unknown DDI from the Knowledge Graph (Purkayastha et al., 2019), (Karim et al., 2019). Automatic extraction of DDI from texts aids in maintaining the databases with high coverage and help the medical experts in their diagnosis and novel experiments.

In parallel to the progress of DDI extraction from the textual corpus, some efforts have been observed recently where the researchers came up with various strategies of augmenting chemical structure information of the drugs (Asada et al., 2018) and textual description of the drugs (Zhu et al., 2020a) to improve Drug-Drug Interaction prediction performance from corpus and Knowledge Graphs.

The DDI Prediction from the textual corpus has been framed by the earlier researchers as relation classification problem. Earlier methods (Sahu and Anand, 2018), (Liu et al., 2016), (Sun et al., 2019), (Li and Ji, 2019) for relation classification are based on CNN or RNN based Neural Networks.

Recently, with the massive success of the pre-trained language models (Devlin et al., 2019), (Yang et al., 2019) in many NLP classification / sequence labeling tasks, we formulate the problem of DDI classification as a relation classification task by leveraging both the entities and sentence-level information. We propose a model that leverages both domain-specific contextual embeddings (BioBERT) (Lee et al., 2019) from the target entities and also external Chemical Structure information of the target entities (drugs). In the recent years, representation learning has played a pivotal role in solving various machine learning tasks. In addition to information of drug entities from the text, we make use of the rich hidden representation obtained from the molecule generation using Variational Auto-Encoder (Gómez-Bombarelli et al., 2018) representation of the drugs to learn the chemical structure representation. During unsupervised learning of chemical structure information of the drugs using Variational AutoEncoder (Kingma and Welling, 2014), we make use of the canonical SMILES representation (Simplified Molecular Input Line Entry System) obtained from the DrugBank (Wishart et al., 2008). We illustrate the overview of the proposed method in Figure 1. Experiments conducted on the DDIExtraction 2013 corpus (Herrero-Zazo et al., 2013) reveals that this method outperforms the existing baseline models and is in line with the new direction of research of fusing various infor-
tion to boost DDI classification performance.

In a nutshell, the major contributions of this work are summarized as follows:

- We propose a method that jointly leverages textual and external Knowledge information to classify relation type between the drug pairs mentioned in the text.
- We show the molecular information from the SMILES encoding using Variational AutoEncoder helps in extracting DDIs from texts.
- Our method achieves new state-of-the-art performance on DDI Extraction 2013 corpus.

2 Methodology

Given a sentence $s$ with target drug entities $d_1$ and $d_2$, the task is to classify the type of relation ($y$) the drugs hold between them, $y \in \{y_1, ..., y_N\}$, where $N$ denotes the number of relation types.

2.1 Text-based Relation Classification

Our model for extracting DDIs from texts is based on the pre-trained BERT-based relation classification model by Roberta. Given a sentence $s$ with drugs $d_1$ and $d_2$, let the final hidden state output from BERT module is $H$. Let the vectors $H_i$ to $H_j$ are the final hidden state vectors from BERT for entity $d_1$, and $H_k$ to $H_m$ the final hidden state vectors from BERT for entity $d_2$. An average operation is applied to obtain the vector representation for each of the drug entities. An activation operation

$$H'_1 = W_1[tanh\left(\frac{1}{j-i+1}\sum_{t=i}^{j} H_t\right)] + b_1 \quad (1)$$

$$H'_2 = W_2[tanh\left(\frac{1}{m-k+1}\sum_{t=k}^{m} H_t\right)] + b_2 \quad (2)$$

We make $W_1$ and $W_2$, $b_1$ and $b_2$ share the same parameters. In other words, we set $W_1 = W_2$ and keep $b_1 = b_2$. For the final hidden state vector of the first token (‘[CLS]’), we also add an activation operation and a fully connected layer, which is formally expressed as:

$$H'_0 = W_0[tanh(H_0)] + b_0 \quad (3)$$

Matrices $W_0$, $W_1$, $W_2$ have the same dimensions, i.e. $W_0 \in R^{d \times d}$, $W_1 \in R^{d \times d}$, $W_2 \in R^{d \times d}$, where $d$ is the hidden state size from BERT.

We concatenate $H'_0$, $H'_1$, and $H'_2$ and then add a fully connected layer and a softmax layer, which can be expressed as:

$$h'' = W_3[concat(H'_0, H'_1, H'_2)] + b_3 \quad (4)$$
\[ y_i' = \text{softmax}(h_i') \] (5)

\[ W_3 \in R^{N \times 3d}, \text{ and } y_i' \text{ is the softmax probability output over } N. \text{ In Equations (1), (2), (3), (4) the bias vectors are } b_0, b_1, b_2, b_3. \text{ We use cross entropy as the loss function. We denote this text-based architecture as BERT-DDI.} \]

### 2.2 Chemical Structure Representation

For the purpose of constructing an encoder from which a continuous latent representation is obtained, molecular representation of drugs has been used as both input and output.

Gómez-Bombarelli et al. (Gómez-Bombarelli et al., 2018) converted the discrete SMILES representations of the drug molecules into a continuous multi-dimensional representation using the unsupervised deep learning algorithm Variational Auto-Encoder (VAE) (Kingma and Welling, 2014). This representation has also been leveraged by (Purkayastha et al., 2019). The input \( x = (x_1, x_2 \ldots \ldots, x_n) \) to VAE is represented by \( x_i \in X \) where \( X = C^* = \{, (), O, F, 1, 2, \ldots, 9 \} \) in the SMILES representation. Each \( x_i \) is a X-dimensional one-hot vector. We denote this VAE architecture used in our experiments as ChemVAE and is explained as follows: As an encoder it uses three 1D convolutional layers, followed by a single fully-connected layer. The decoder uses three layers of GRU networks. The objective of this work is to maximize the probability distribution of generation of SMILES representation of drug molecules with the help of latent representation as presented in equation below:

\[
P(X_{\text{SMILES}}) = \int P(X_{\text{SMILES}}|z)P(z)dz
\] (6)

In equation 6, \( X_{\text{SMILES}} \) denotes the drug molecules, \( z \) represents the latent SMILES representation, \( P(X_{\text{SMILES}}) \) denotes the probability distribution of drug molecules. The ChemVAE model takes SMILES representation of the drugs as input and encodes the drugs into continuous latent representation \( z \). The decoder then samples a string from the probability distribution over characters in the input SMILES representation. Finally, the hidden representation for each of the drug entities is treated as its chemical structure representation from ChemVAE.

### 2.3 BERTChem-DDI

From the sentence \( s \) containing two target drug entities \( d_1 \) and \( d_2 \), we obtain the chemical structure representation of two drugs \( c_1 \) and \( c_2 \) respectively using ChemVAE. We concatenate these two embeddings \( c_1 \) and \( c_2 \) and pass those through a fully connected layer as represented as follows:

\[
chm = W[\text{concat}(c_1, c_2)] + b
\] (7)

\( W \) and \( b \) are the parameters of the fully-connected layer of the chemical structure representation of \( d_1 \) and \( d_2 \). The final layer of BERTChem-DDI model contains the concatenation of all the previous text-based outputs (see Section 2.1) and chemical structure representation as expressed in the equations:

\[
o' = W_3[\text{concat}(H'_0, H'_1, H'_2, chm)] + b_3
\] (8)

\[
y_i' = \text{softmax}(o')
\] (9)

Finally the training optimization is achieved using the cross-entropy loss \( (L_c) \) :

### 3 Experimental Setup

In this section, we explain the dataset and experiments of using ChemVAE and BERTChem-DDI.
3.1 Dataset and pre-processing

We have followed the task setting of Task 9.2 in the DDIExtraction 2013 shared task (Herrero-Zazo et al., 2013) for the evaluation. This data set comprises of documents annotated with drug mentions and five types of interactions: Mechanism, Effect, Advice, Int and Other. The task is a multi-class classification to classify each of the drug pairs in the sentences into one of the types and we evaluate using Precision (P), Recall (R) and F1-score (F1) for each relation type.

During pre-processing, we obtain the DRUG mentions in the corpus and map those into unique DrugBank identifiers. This mention normalization has been performed based on the longest overlap of drug mentions in the DrugBank. This mention normalization has been done for obtaining the corresponding SMILES representation to encode molecular structure information. The dataset statistics of the total drugs and the normalized drugs are enumerated in table 1. We initialize the non-normalized drug representations using pre-trained word2vec trained on PubMED.

3.2 Training Details

We make use of the pre-trained contextual embeddings such as bert-base-cased, scibert-scivocab-uncased (Beltagy et al., 2019) and domain-specific bb v1.0 pubmed pmc and bb v1.0 pubmed as the initialization of the transformer encoder in BERTChem-DDI. We uniformly keep the maximum sequence length as 300, batch size 16, initial learning rate for ADAM optimizer as $2e^{-5}$, drop out 0.1 for all the embedding ablations and trained for 5 epochs. During unsupervised training of ChemVAE with drugs from ZINC (Irwin and Shoichet, 2005), the input SMILES representation has been trimmed to 120. The hidden dimension of ChemVAE encoder is 200 and for the decoder it is 500. Finally, a 292-dimensional representation of the drugs has been ultimately used for initialization of the BERTChem-DDI model’s chemical structure representations of the drugs.

4 Results and Discussion

In this section, we provide a detailed analysis of the various results and findings that we have observed during experimentation. We have demonstrated strong empirical results based on the proposed approach for both text and chemical structure. We further want to understand the specific contributions by the chemical structure component besides the pre-trained BERT and its other domain-specific variants. For this purpose, we refer to our experimental configurations in meaningful ways while enumerating the results.

Ablation of Embeddings on BERT-DDI: During ablation analysis, we observe that the incorporation of domain-specific information in bio bert v.1 pubmed boosts up the predictive performance in terms of macro-F1 score (across all relation types) by 2.3% compared to bert-base-cased. Moreover, the scibert-vocab-cased embeddings due to the scientific details obtained during fine-tuning achieves reasonable boost in performance. bio bert v.1 pubmed based BERT-DDI is thus the best-performing text-based relation classification model. The results are enumerated in Table 4.

**Ablation of Chemical Structure embeddings on BERTChem-DDI:** During empirical analysis of the BERTChem-DDI model, we observe how much performance gain can be achieved by augmenting the chemical structure information. From the results enumerated in terms of macro F1-score on all the relation types in table 3, we observe that the best-performing BERT-DDI model achieves a performance boost of 1.6% after adding chemical structure information in BERTChem-DDI. Probing deeper, we observe that the relation types Mechanism (3.2%) and Advice (2.11%) achieve significant performance improvement over BERT-DDI.

Comparison with the existing baselines: We compare our best-performing model with some of the best-performing existing baselines. Our method achieves the state-of-the-art performance based on the results in Table.

5 Conclusion

In this paper, we develop an approach for DDI relation classification based on pre-trained language model and chemical structure representation of drugs. Experiments on the benchmark DDI dataset further want to understand the specific contributions by the chemical structure component besides the pre-trained BERT and its other domain-specific variants. For this purpose, we refer to our experimental configurations in meaningful ways while enumerating the results.

**Ablation of Embeddings on BERT-DDI:** During ablation analysis, we observe that the incorporation of domain-specific information in bio bert v.1 pubmed boosts up the predictive performance in terms of macro-F1 score (across all relation types) by 2.3% compared to bert-base-cased. Moreover, the scibert-vocab-cased embeddings due to the scientific details obtained during fine-tuning achieves reasonable boost in performance. bio bert v.1 pubmed based BERT-DDI is thus the best-performing text-based relation classification model. The results are enumerated in Table 4.

**Advantage of Chemical Structure embeddings on BERTChem-DDI:** During empirical analysis of the BERTChem-DDI model, we observe how much performance gain can be achieved by augmenting the chemical structure information. From the results enumerated in terms of macro F1-score on all the relation types in table 3, we observe that the best-performing BERT-DDI model achieves a performance boost of 1.6% after adding chemical structure information in BERTChem-DDI. Probing deeper, we observe that the relation types Mechanism (3.2%) and Advice (2.11%) achieve significant performance improvement over BERT-DDI.

**Comparison with the existing baselines:** We compare our best-performing model with some of the best-performing existing baselines. Our method achieves the state-of-the-art performance based on the results in Table.

## Table 4: Ablation of the contextual embeddings.

| Embeddings on BERT-DDI                   | Test set Macro F1 |
|-----------------------------------------|-------------------|
| bert-base-cased                         | 0.806             |
| scibert-scivocab-uncased                | 0.812             |
| bio bert v1.0 pubmed pmc                | 0.818             |
| bio bert v1.1 pubmed                    | 0.822             |

1. http://evexdb.org/pmresources/ngrams/PubMed/
proves the efficacy of our method. Possible directions of further research might be to explore Knowledge Graph based drug representation combined with textual description and other relation specific embeddings obtained from various ontologies.

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