Data and text mining

Using drug descriptions and molecular structures for drug–drug interaction extraction from literature

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Abstract

Motivation: Neural methods to extract drug–drug interactions (DDIs) from literature require a large number of annotations. In this study, we propose a novel method to effectively utilize external drug database information as well as information from large-scale plain text for DDI extraction. Specifically, we focus on drug description and molecular structure information as the drug database information.

Results: We evaluated our approach on the DDIExtraction 2013 shared task dataset. We obtained the following results. First, large-scale raw text information can greatly improve the performance of extracting DDIs when combined with the existing model and it shows the state-of-the-art performance. Second, each of drug description and molecular structure information is helpful to further improve the DDI performance for some specific DDI types. Finally, the simultaneous use of the drug description and molecular structure information can significantly improve the performance on all the DDI types. We showed that the plain text, the drug description information and molecular structure information are complementary and their effective combination is essential for the improvement.

Availability and implementation: Our code is available at https://github.com/tticoin/DESC_MOL-DDIE.

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1 Introduction

When two or more drugs are administered to a patient at the same time, the effects of the drugs may be enhanced or weakened, which may also cause side effects. These kinds of interactions are called drug–drug interactions (DDIs). DDIs are reported in biomedical articles on a daily basis. Several drug databases, such as DrugBank (Wishart et al., 2018), Therapeutic Target DB (Wang et al., 2019) and PharmGKB (Whirl-Carrillo et al., 2012), have been provided to integrate drug information including DDI information for researchers and professionals; however, not all interactions are registered in the databases, and valuable outcomes are still buried in biomedical articles. Therefore, automatic DDI extraction from biomedical literature is demanded.

Deep neural network-based DDI extraction methods have recently drawn a considerable attention because of their high performance. The methods require a large amount of text that is annotated by biomedical experts. Since the annotation efforts are costly and time-consuming, it is unrealistic to prepare a sufficient amount of annotated data. In addition, it is difficult to learn how to extract DDIs from text only with the limited amount of annotated text because deep understanding of DDI interaction descriptions often requires domain knowledge on drugs. Various drug information, such as detailed descriptions and molecular structure information of drugs, are registered in drug databases. Furthermore, models pre-trained on large-scale raw text show significant improvements in various natural language processing tasks (Devlin et al., 2019). Effective use of such external information is necessary to reduce the reliance on annotated text.

In this study, we propose a method to utilize such external drug information in drug database DrugBank as well as large-scale raw text information for the extraction of DDIs from text. We focus on DrugBank because DDIExtraction 2013 shared task dataset is created based on the DrugBank database. We leave the incorporation of other databases for our future work. Specifically, we utilize the description and molecular structure information of drugs in the database. We also incorporate the information from large-scale raw texts by using a Bidirectional Encoder Representations from Transformers (BERT) model (Devlin et al., 2019) pre-trained on large-scale raw text.

We illustrate the overview of the proposed method in Figure 1. For our baseline model, we employ the convolutional neural network (CNN)-based DDI extraction model (Asada et al., 2018) that receives an input sentence with a target drug pair and classifies the pair into a specific DDI type. We enrich the input sentence using SciBERT (Beltagy et al., 2019), which is a BERT model trained on large-scale biomedical and computer science text. We obtain the drug description representation of the target drugs using SciBERT and the molecular structure representation of the target drugs using molecular graph neural network (GNN) model proposed by
Tsubaki et al. (2019). We combine these drug description and molecular structure representation with the enriched input sentence representation and classify the target drug pair into a specific DDI type.

We evaluated our method on the DDIExtraction 2013 shared task dataset (Segura-Bedmar et al., 2013). Experimental results show that SciBERT boosts the performance of the baseline model. As a result, the performance is already strong enough and better than the previously reported performance. We show the drug database information is complementary to the large-scale pre-trained information, and the simultaneous use of drug description and drug molecular structure information can enhance the performance of DDI extraction from texts with SciBERT.

This article is a substantial extension of our work in ACL 2018 (Asada et al., 2018) and we have following extensions:

- We replaced the token representation from word2vec to contextualized vectors obtained by SciBERT. As a result, we remarkably improved the performance of the baseline with the state-of-the-art performance.
- We employed the neural molecular GNN (Tsubaki et al., 2019) that considers relatively large fragments of atoms and better represents molecular structures.
- We used drug descriptions registered in the drug database and we show drug description information is useful for extracting DDIs from corpus for some DDI types.
- We found the large-scale pre-training information, drug description and drug molecular structure are complementary and their effective combination can largely improve the DDI extraction performance.

2 Related work

Various neural DDI extraction methods have been recently proposed using CNNs and recurrent neural networks since Liu et al. (2016) tackled the DDI extraction using the neural network-based method and outperformed various feature-based methods.

Especially in recent years, contextualized embeddings-based methods have been drawn a great attention (Peng et al., 2019). Contextualized embeddings are pre-trained by a deep transformers-based method (Peng et al., 2019) on large-scale text corpora. SciBERT is a model of the unsupervised pre-training method BERT (Devlin et al., 2019), and it is pre-trained on a large multi-domain scientific corpus of Semantic Scholar (Ammar et al., 2018). SciBERT achieved the state-of-the-art performance on several tasks in the biomedical domain, even compared with the bio-specific BioBERT (Peng et al., 2019) model.

Several GNNs have been proposed for quantum chemistry, such as Duvenaud et al. (2015). In predicting drug properties, GNNs convert the molecular graph of a drug into a fixed-sized vector by aggregating the representation of atom nodes in the drug. Atoms in the drug are represented as nodes and bonds as edges. Tsubaki et al. (2019) proposed GNNs for molecular graphs, which takes subgraphs of the drug molecular graph as input, instead of single atoms. No GNN-based methods have been applied to the extraction of DDIs except for our previous work (Asada et al., 2018).

3 DDI extraction

In this study, we propose a novel method to utilize drug database information for DDI extraction from text. We obtain the representation of input sentences by pre-trained contextualized embeddings, i.e., BERT, and CNNs. We link the mentions of target drugs to the drug entries in a drug database and acquire the description and
m_{ij} = f(W^{sent}_i \odot z_i + b^{sent}), \quad (3)

where \( \odot \) is an element-wise product, \( b^{sent} \) is a bias term and \( f(\cdot) \) is a GELU (Hendrycks and Gimpel, 2016) function (we chose the GELU activation function from ReLU, eLU, SeLU and GELU based on the results in our preliminary experiment). We define a weight tensor for convolution as \( W^{sent} \in \mathbb{R}^{d \times (2d) \times k} \). We represent the \( i \)-th column of \( W^{sent} \) as \( W^{sent}_i \), \( k \) is a window size. We depict the tensor \( W^{sent} \) as a red box in the left part of Figure 1A. We then employ max-pooling to convert the output of each filter in the convolution layer into a fixed-size vector as follows:

\[ b^{sent} = \max_i m_{ij}. \quad (4) \]

### 3.3 Drug description representation

Similarly to the input sentences, the description sentences of a drug mention are converted to the real-valued fixed-size vector by BERT and CNN. We directly use the wordpiece embeddings by BERT without word position embeddings to prepare the input to the convolution layer. We define a convolution weight tensor \( W^{desc} \in \mathbb{R}^{d \times (2d) \times k} \) and bias \( b^{desc} \) for description. Convolution and max-pooling are employed in the same way as the processing of the input sentences and we obtain the description representations \( b^{desc} \) and \( b^{desc2} \) of drug mentions \( m_1 \) and \( m_2 \), respectively.

### 3.4 Molecular structure representation

We represent the molecular graph structures of drugs using GNNs. GNNs convey a drug molecule graph \( G \) into a fixed-size vector \( b^g \). We represent atoms as nodes and bonds as edges in the graph. We employ the neural molecular GNN method proposed by Tsubaki et al. (2019). The molecular GNN method uses relatively large fragments referred to as \( r \)-radius subgraphs or molecular fingerprints to represent atoms with their contexts in the graph. The molecular GNN adopts fingerprint vectors as atom vectors, initializes the vectors randomly and updates them considering the graph structure of a molecule. We define the vector of the \( i \)-th atom in a drug molecule as \( b_i \), and its set of neighboring atoms as \( N_i \). The vector \( b_i \) is updated in the \( i \)-th step as follows:

\[ b_i = b_i^{t-1} + \sum_{j \in N_i} f(W^{hidden}_{\text{hidden}} b_{j}^{t-1} + b_{j}^{\text{hidden}}), \quad (5) \]

where \( f(\cdot) \) denotes a ReLU function. The drug molecular vector is obtained by summing up all the atom vectors and then the resulting vectors are fed into a linear layer.

\[ b^{mol} = f(W_{\text{output}} \sum_{i=1}^{M} b_{i}^{t} + b_{\text{output}}). \quad (6) \]

where \( M \) is the number of fingerprints. Figure 2 shows how the molecular GNN model extracts fingerprints including \( \beta \)-lactam (\( b_1 \)) from penicillin drug \( (r = 2) \) and update fingerprint vectors.

We obtain the molecular structure representations \( b^{mol1} \) and \( b^{mol2} \) of drug mentions \( m_1 \) and \( m_2 \), respectively.

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**Table 1. An example of preprocessing**

| Mention1   | Mention2   | Preprocessed input sentence |
|------------|------------|----------------------------|
| S-ketamine | Itraconazole | Exposure to oral DRUG1 is unaffected by DRUG2 but greatly increased by DRUGOTHER. |
| S-ketamine | Ticlopidine | Exposure to oral DRUG1 is unaffected by DRUGOTHER but greatly increased by DRUG2. |
| Itraconazole | Ticlopidine | Exposure to oral DRUGOTHER is unaffected by DRUG1 but greatly increased by DRUG2. |

Note: The input sentence contains three target drug pairs.
3.5 DDI extraction using database information

When we use the drug description information for DDI extraction, we concatenate the input sentence representation and two description representations as in Equation (7):

$$b = [b^{\text{sent}}, b^{\text{desc}}_1, b^{\text{desc}}_2].$$

Similarly, two molecular structure representations are concatenated with the input sentence representation as in Equation (8):

$$b = [b^{\text{sent}}, b^{\text{mol}}_1, b^{\text{mol}}_2].$$

We use the resulting vector as the input to the prediction layer. We convert $b$ into prediction scores using a weight matrix $W^{\text{pred}} \in \mathbb{R}^{d_p \times d_s}$:

$$s = W^{\text{pred}} b,$$

where $s = [s_1, \ldots, s_C]$ and $o$ is the number of DDI types. We convert $s$ into the probability of possible interactions $p$ by a softmax function:

$$p = [p_1, \ldots, p_o], p_i = \frac{\exp(s_i)}{\sum_{j=1}^{o} \exp(s_j)}.$$  

We illustrate the DDI extraction using drug description information and drug molecular structure information in Figure 1B and C, respectively.

3.6 Training

The loss function $L$ is defined as in Equation (11) using $p$ in Equation (10) when the gold type distribution $y$ is given, $y$ is a one-hot vector where the probability of the gold label is 1 and the other probabilities are 0.

$$L = - \sum y \log p.$$  

3.7 Ensemble

We employ an ensemble technique to combine the prediction from different models. Specifically, we simply sum up the prediction scores from different models for the ensemble after each of the models is trained separately. For instance, when we combine the prediction of the model with the description information and that with the molecular structure information, we sum up the prediction scores in Equation (9) as follows:

$$s = s^{\text{desc}} + s^{\text{mol}}.$$  

4 Experimental settings

In this section, we explain the DDI extraction task settings, drug database preprocessing, drug mention linking and hyper-parameter settings.

4.1 DDI extraction task settings

We followed the DDIExtraction-2013 shared task (SemEval-2013 Task 9.2) (Segura-Bedmar et al., 2013). This dataset is composed of documents annotated with drug mentions and their interactions. The dataset consists of two parts: MEDLINE and DrugBank. MEDLINE consists of abstracts in MEDLINE/PubMed articles, while DrugBank consists of the texts of drug interactions in the FDA label reference of DrugBank.

The task defines the following four interaction labels.

- **Mechanism**: this type is assigned when a pharmacokinetic mechanism is described in an input sentence.
- **Effect**: this type is assigned when the effect of the DDI is described.
- **Advice**: this is assigned when a recommendation or advice regarding the concomitant use of two drugs is described.
- **Int (Interaction)**: this type is assigned when the sentence simply states that an interaction occurs and does not provide any detailed information about the interaction.

A more detailed DDI type classification is directed to the annotation guidelines (https://www.cs.york.ac.uk/semeval-2013/task9/data/uploads/annotation_guidelines_ddi_corpus.pdf).

The statistics of the dataset with the official data split is shown in Table 2. Approximately 77% of the DDI corpus documents were randomly selected for the training dataset and rest were used for the test dataset by the official task organizers. This shows that the pairs with no interaction (negative pairs) are much more than the pairs with interactions (positive pairs).

We evaluated the performance with precision ($P$), recall ($R$) and F-score ($F$) on each interaction type as well as micro-averaged precision, recall and F-score on all the interaction types. While a macro-averaged metric is calculated by first calculating the metric for each type and then taking the average, a micro-averaged metric is calculated by directly calculating the metric for all the types.

4.2 DrugBank preprocessing

DrugBank is a freely available drug database containing more than 10,000 drugs. Each drug is given sentences describing its characteristics and efficacy. We show the first sentence of the drug description of Salbutamol as an example: Salbutamol is a short-acting, selective beta2-adrenergic receptor agonist used in the treatment of asthma and COPD. DrugBank also contains drug molecular structure information. Structure information is registered in SMILES string encoding.

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![Fig. 2. Illustration of molecular fingerprints. This figure shows the extraction of several fingerprint subgraphs from a molecular structure when radius is 2.](image-url)
To obtain the graph of a drug molecule, we took as input the SMILES string encoding of the molecule from DrugBank and then converted it into the graph structure using RDKit (Landrum, 2020). We extracted fingerprints from the graph using preprocessing scripts provided by Tsubaki et al. (2019).

### 4.3 Drug mention linking

We linked mentions in the corpus to DrugBank entries by relaxed string matching. In particular, we lowercased each mention and the following items in the DrugBank entries, and we chose the entry that includes an item showing the most overlap with the mention.

- **Name**: Headword of the drug entry
- **Brand**: Brand names from different manufacturers
- **Product**: The final commercial preparation of the drug
- **Synonym**: Synonyms of the drug
- **ATC-code**: Codes for hierarchical drug classification.

For the ATC code, the same code can be assigned to multiple drugs, so we use only ATC codes that are assigned to single drugs for mention linking. Also, for synonyms, we linked mentions and synonyms by exact string matching instead of relaxed string matching to avoid the matching with very short strings (e.g. abbreviations). With this linking, 90.50% and 91.10% of drug mentions in the SemEval-2013 train and test dataset matched the DrugBank entries. **Figure 3** shows how the linking is performed. The input sentence contains two mentions ‘noregestrel’ and ‘norethindrone’. We performed string matching to link these mentions to DrugBank entries. As a result, the mention ‘noregestrel’ matched the Name item and the mention ‘norethindrone’ matched the Product item.

#### 4.4 Training settings

We followed the training settings for the fine-tuning of BERT on the GLUE tasks (Devlin et al., 2019) except for the following two points. First, we employed the AdamW optimizer (Loshchilov and Hutter, 2019) instead of Adam optimizer. Second, we employed mixed-precision training (Le Gallo et al., 2018) for the memory efficiency.

We applied dropout to the input of the convolution layer for regularization. Word position embeddings are initialized with random values drawn from a uniform distribution between $-10^{-3}$ and $10^{-3}$. We set the description and molecular structure vectors of unmatched entities to zero vectors. Tables 3 and 4 show hyperparameters for CNNs and GNNs. We used the same hyperparameters as the GLUE tasks in Devlin et al. (2019) for the BERT layer. In the DDIEXtraction 2013 shared task, the official development dataset is not provided; thus we prepared a development dataset from the official training dataset to choose the other hyperparameters. In order to train the model on the same setting as other existing models (Asada et al., 2018; Liu et al., 2016; Peng et al., 2019), the development dataset is included in the entire training dataset for training the model. We used the entire training dataset for training the model to evaluate the performance on the test set. For GNNs, we show the results with different radii 0, 1 and 2 for molecular fingerprints. Note that, GNNs with a radius of 0 means no molecular fingerprints, which assigns vectors to atoms.

## 5 Results

Table 5 shows the performance of DDIs extraction models including the proposed models with different settings and the state-of-the-art models. We can see that the baseline text-only model (SciBERT CNN) using SciBERT is powerful. SciBERT improved the performance of the model without SciBERT (word2vec CNN) by 11.04% points in the micro $F$-score. With this improvement, the model with SciBERT has achieved the state-of-the-art performance when we compare it with the state-of-the-art models in the top rows of the table. When we omitted the CNNs from the baseline model (SciBERT Linear), we used the first special token [CLS] as the aggregated representation of the sentence and we fed the embedding of [CLS] into the linear classifier layer. The performance slightly dropped with this omission but the difference is negligible. This indicates the BERT model is powerful enough to capture the similar information as CNNs.

We observe additional increase of the micro $F$-score by using drug description and molecular structure information as shown in the bottom part of the table. This shows the large-scale raw text information from SciBERT and the database information are complementary, and they are both useful for extracting DDIs from text. For CNNs, GNNs with molecular fingerprints (radius = 1 or 2) show better performance than CNNs without them (radius = 0), and GNNs with the radius of 1 show the highest performance. When comparing the description and molecular structure information, the micro $F$-score with molecular structure information (radius = 1) is slightly higher than one with the description information (+Desc), but their difference is not significant and the superiority depends on how to represent the molecular structure information, i.e. molecular fingerprints. We leave the search of the better representations for future work. The improvement by the ensemble model of description and the molecular structure information is statistically significant when compared with the baseline model ($P < 0.005$, McNemar test). We used the scikit-learn (Pedregosa et al., 2011) Python library for evaluating the statistical significance.

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**Table 3. Hyper-parameters for CNNs**

| Parameter                  | Value |
|----------------------------|-------|
| Word embedding size $d_w$  | 768   |
| Initial learning rate      | 5e-5  |
| Number of fine-tuning epochs | 3     |
| L2 weight decay            | 0.01  |
| Dropout rate               | 0.1   |
| Mini-batch size            | 32    |
| Word position embedding size $d_p$ | 10  |
| Convolution window size $k$ | 5     |
| Convolution filter size $d_d$ | 768  |
| Convolution window size for description | 3 |
| Convolution filter size for description | 20 |

**Table 4. Hyper-parameters for GNNs**

| Parameter                  | Value |
|----------------------------|-------|
| Molecular embedding size $d_m$ | 50    |
| Number of hidden layer $L$  | 5     |
| Radius                     | 1     |
Table 5. Evaluation on DDI extraction from texts on the test set

| Method                          | P    | R    | F (%) |
|---------------------------------|------|------|-------|
| Liu et al. (2016)               | 75.29| 60.37| 67.01 |
| BioBERT (Peng et al., 2019)     | —    | —    | 78.8  |
| (Asada et al., 2018)            | 71.97| 68.44| 70.16 |
| Text-only (word2vec CNN)        | 80.28| 81.92| 81.09 |
| Text-only (SciBERT linear)      | 83.10| 80.38| 81.72 |
| + Desc                          | 84.05| 81.81| 82.91 |
| + Mol (radius = 0)              | 83.29| 82.02| 82.65 |
| + Mol (radius = 1)              | 83.57| 82.12| 82.84 |
| + Mol (radius = 2)              | 83.66| 81.10| 82.36 |
| + Desc + Mol (radius = 1)       | 85.36| 82.83| 84.08 |
| + Desc + Mol (radius = 0,1,2)   | 84.51| 82.53| 83.51 |
| + Mol (radius = 0,1,2)          | 84.69| 82.53| 83.60 |

Note: We defined Text-only (SciBERT CNN) model as our baseline model. The best score is shown in bold.

Table 6. Evaluation on DDI extraction from texts on the development set

| Method                          | P    | R    | F (%) |
|---------------------------------|------|------|-------|
| Text-only (SciBERT CNN)         | 83.55| 80.19| 81.84 |
| + Desc                          | 83.19| 82.31| 82.75 |
| + Mol (radius = 0)              | 83.73| 81.25| 82.47 |
| + Mol (radius = 1)              | 82.85| 83.90| 83.37 |
| + Mol (radius = 2)              | 82.88| 83.58| 83.23 |
| + Desc + Mol (radius = 1)       | 84.59| 84.32| 84.46 |

Table 7. Performance on individual DDI types in F-scores

| DDI type          | Mech. | Effect | Adv. | Int. (%) |
|-------------------|-------|--------|------|----------|
| Text-only         | 86.18 | 79.12  | 88.34| 55.94    |
| + Desc            | 87.62 | 81.08  | 87.05| 60.27    |
| + Mol (radius = 0)| 84.65 | 81.20  | 90.67| 55.71    |
| + Mol (radius = 1)| 86.33 | 80.48  | 92.07| 49.25    |
| + Mol (radius = 2)| 84.02 | 82.24  | 88.58| 37.34    |
| + Desc + Mol (radius = 1)| 87.61| 82.05 | 90.79| 58.74    |

Note: The best score for each type is shown in bold and the scores lower than the baseline model are shown with underlines.

Table 8. Individual F-scores on 5-fold cross-validated training dataset

| Method                          | DDI type          |
|---------------------------------|-------------------|
|                                | Mech. | Effect | Adv. | Int. (%) |
| Fold 1 Text-only               | 84.60 | 86.38  | 85.80| 68.29    |
| + Desc                         | 82.55 | 81.82  | 85.23| 64.37    |
| + Mol (radius = 1)             | 84.55 | 84.62  | 84.53| 71.05    |
| + Desc + Mol (radius = 1)      | 86.13 | 85.46  | 86.69| 67.47    |
| Fold 2 Text-only               | 83.46 | 83.26  | 78.80| 81.48    |
| + Desc                         | 84.15 | 82.52  | 81.99| 79.01    |
| + Mol (radius = 1)             | 82.26 | 83.45  | 81.64| 76.54    |
| + Desc + Mol (radius = 1)      | 84.29 | 83.38  | 82.64| 79.01    |
| Fold 3 Text-only               | 84.91 | 59.21  | 76.54| 91.43    |
| + Desc                         | 83.40 | 88.31  | 73.53| 91.67    |
| + Mol (radius = 1)             | 84.43 | 86.24  | 75.24| 94.44    |
| + Desc + Mol (radius = 1)      | 86.09 | 87.25  | 76.22| 92.96    |
| Fold 4 Text-only               | 76.81 | 51.56  | 78.01| 79.45    |
| + Desc                         | 77.54 | 82.47  | 79.65| 81.16    |
| + Mol (radius = 1)             | 78.17 | 84.03  | 77.34| 76.92    |
| + Desc + Mol (radius = 1)      | 77.35 | 85.15  | 79.40| 83.33    |
| Fold 5 Text-only               | 81.97 | 81.76  | 89.51| 76.54    |
| + Desc                         | 84.95 | 83.02  | 87.73| 81.48    |
| + Mol (radius = 1)             | 86.09 | 83.74  | 87.23| 73.33    |
| + Desc + Mol (radius = 1)      | 86.26 | 84.91  | 88.34| 75.00    |
| Average Text-only              | 82.34 | 76.99  | 81.67| 79.07    |
| + Desc                         | 83.09 | 84.39  | 81.27| 78.09    |
| + Mol (radius = 1)             | 82.47 | 83.57  | 81.60| 78.97    |
| + Desc + Mol (radius = 1)      | 84.01 | 85.20  | 82.70| 78.99    |

Note: We used the micro-averaged F-score to calculate the average of the folds. The best score for each type is shown in bold and the scores lower than the baseline model are shown with underlines.

Table 9. Comparisons of F-scores on different parts of the test set

| Method                          | MEDLINE | DrugBank | Overall (%) |
|---------------------------------|---------|----------|-------------|
| Text-only (SciBERT CNN)         | 74.57   | 82.44    | 81.72       |
| + Desc                          | 74.41   | 83.75    | 82.91       |
| + Mol (radius = 0)              | 75.00   | 83.41    | 82.65       |
| + Mol (radius = 1)              | 73.98   | 83.71    | 82.84       |
| + Mol (radius = 2)              | 74.57   | 83.15    | 82.36       |
| + Desc + Mol (radius = 1)       | 78.16   | 84.67    | 84.08       |

Note: The model shows higher performance than the baseline model on all types. We cross-validated the training dataset using 5-fold cross-validation and we further analyzed the performance on individual DDI types. Table 8 shows the F-scores for folds of cross-validated training dataset. We used the micro-averaged F-score to calculate the average of the folds. The models with individual information show higher performance than the baseline model on Mechanism and Int., while they show comparable or lower performance than the baseline model on other labels. Although the changes in performance are inconsistent for the DDI types and folds, the model with the ensemble technique shows higher performance than the models with individual information on average. As a result, the model with the ensemble technique improves the F-scores on average for all the types except for Int., where our model performs on par with the baseline model. These results show that the
6 Discussion

6.1 Pre-training of GNNs and CNNs on DrugBank

To investigate the further use of DrugBank information, we verify if the DrugBank DDI labels can improve the DDI extraction performance. Specifically, we pre-trained GNNs for molecular structure information and CNNs for description information on DrugBank DDI labels. Many drug pairs have information of interactions, so this pre-training needs no additional annotations.

We extracted 50,000 interacting (positive) pairs from DrugBank. We note that, unlike the DDIExtraction 2013 shared task dataset, DrugBank only contains the information of interacting pairs; there are no detailed labels and no information for non-interacting (negative) pairs. We thus generated the same number of pseudo-negative pairs by randomly pairing drugs and removing those in positive pairs. To avoid overestimation of the performance, we deleted drug pairs mentioned in the test set of the test corpus in preparing the pairs. We split positive and negative pairs into 4:1 for train and test data, and we evaluated the classification accuracy using only the molecular information or only the description.

We first show the performance of the accuracy of binary classification on DrugBank DDI pairs in Table 10. The performance is surprisingly high, although the accuracy is evaluated on automatically generated negative instances. Overall, both drug description and molecular structure information can capture DDI information in DrugBank. In detail, the accuracy with drug description information is higher than that with molecular structure information. For molecular structure information, GNN with the radius of 2 shows the best performance. The difference in accuracy between radius 0 and 2 is 21.78% points, and this large difference shows the importance of capturing molecular fingerprints for DDI.

We pre-trained CNNs and GNNs using the DrugBank interaction labels including the pseudo-negative labels and fine-tuned them on the DDIExtraction 2013 dataset. Table 11 shows the comparison of the F-scores with or without pre-training. Unfortunately, for all the settings, the models with pre-training show lower performance than those without pre-training. This may be because the labels in the DDI extraction tasks are annotated depending on the context of the pairs and the labels can be inconsistent with labels in DrugBank and because the pseudo-negative examples are used in training instead of the real negative examples.

6.2 Can DrugBank information alone extract DDIs from texts?

To further investigate how the contextual information is important in the DDI task, we verified whether the textual DDI can be extracted only from the drug information in DrugBank without using the input sentence. We simply omitted the input sentence representation $h_{\text{sent}}$ from Equations (7) and (8) and trained the DDI extraction models, but the F-scores were quite low (<5%) for both models. This result shows that we cannot extract DDI relation from texts only with the description and molecular structure information. This indicates that DDI extraction from texts greatly depends on the context information around drug mention pairs and our models on the database information serve as a supplement to the textual CNN model.

6.3 Error analysis

Figure 4 shows F-scores for different sentence lengths on the 5-fold cross-validated training dataset. We used the micro-averaged F-score to calculate the average of the folds.

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**Table 10. Accuracy of binary classification on the DrugBank pairs**

| Description | SciBERT | GNN (radius = 0) | GNN (radius = 1) | GNN (radius = 2) |
|-------------|---------|-----------------|-----------------|-----------------|
| Accuracy (%) | 91.05   | 67.58           | 82.21           | 89.36           |

**Table 11. Evaluation on DDI extraction from texts with or without pre-training of GNNs for the molecular structure and CNNs for the description**

| Methods                          | P     | R     | F (%) |
|----------------------------------|-------|-------|-------|
| w/ pre-training                  |       |       |       |
| + Desc                           | 84.62 | 79.26 | 81.85 |
| + Mol (radius = 0)               | 82.69 | 81.00 | 81.83 |
| + Mol (radius = 1)               | 84.51 | 80.28 | 82.34 |
| + Mol (radius = 2)               | 82.36 | 80.28 | 81.74 |
| w/o pre-training                 |       |       |       |
| + Desc                           | 84.05 | 81.81 | 82.91 |
| + Mol (radius = 0)               | 83.29 | 82.02 | 82.65 |
| + Mol (radius = 1)               | 83.57 | 82.12 | 82.84 |
| + Mol (radius = 2)               | 83.66 | 81.10 | 82.36 |

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Fig. 4. F-scores for different sentence lengths on the 5-fold cross-validated training dataset. We used the micro-averaged F-score to calculate the average of the folds.
7 Conclusions

We proposed a novel neural method for DDI extraction from text using large-scale raw text information and drug database information, especially the drug descriptions and the drug molecular structure information. The results show that the large-scale raw text information with SciBERT greatly improves the performance of DDI extraction from text on the dataset of the DDIExtraction 2013 shared task. In addition, either of the drug description and the molecular structure information can further improve the performance for specific DDI types, and their simultaneous use can improve the performance on all the DDI types.

Our future work includes investigating other information registered in DrugBank and other drug databases. In addition, we will seek the way to build a model that can effectively utilize multiple items in drug databases and combine the textual and drug database information.

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