ADDI

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ADDI: Recommending alternatives for drug–drug interactions with negative health effects

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ABSTRACT

Investigating the interactions among various drugs is an indispensable issue in the field of computational biology. Scientific literature represents a rich source for the retrieval of knowledge about the interactions between drugs. Predicting drug–drug interaction (DDI) types will help biologists to evade hazardous drug interactions and support them in discovering potential alternatives that increase therapeutic efficacy and reduce toxicity. In this paper, we propose a general-purpose method called ADDI (standing for Alternative Drug–Drug Interaction) that applies deep learning on PubMed abstracts to predict interaction types among drugs. As an application, ADDI recommends alternatives for drug–drug interactions (DDIs) which have Negative Health Effects Types (NHETs). ADDI clearly outperforms state-of-the-art methods, on average by 13%, with respect to accuracy by using only the textual content of the online PubMed papers. Additionally, manual evaluation of ADDI indicates high precision in recommending alternatives for DDIs with NHETs.

1. Introduction

Lately, discovering interactions among drugs attracted a lot of attention [1–8]. Biological literature is a rich source of knowledge for discovering interactions among drugs [9–14] and this gives computational text mining approaches an important role in current drug studies [15–17]. The intended effect of a drug can be changed with the simultaneous use of another drug [18]. There are varied definitions for drug-interaction with respect to different perspectives/vocabularies/etc. Some definitions for drug interactions are:

- "A drug interaction is a change in the action or side effects of a drug caused by concomitant administration with a food, beverage, supplement, or another drug" [19].
- "A drug interaction has occurred when the administration of one drug alters the clinical effects of another. The result may be an increase or decrease in either the beneficial or harmful effects of the second agent" [20].
- "A drug interaction can be defined as an interaction between a drug and another substance that prevents the drug from performing as expected" [21].
- "One drug can affect the activity of another when they are administered together, which can cause adverse drug reactions or sometimes improve therapeutic effects" [22].
- "A drug interaction occurs when a substance affects the activity of a drug, either increasing or decreasing its efficacy, or, alternatively, a new effect is observed that is not observed with just the drug alone" [23].

Understanding types of DDIs is essential to recommend alternatives that decrease unexpected adverse drug events (ADEs) and increase synergistic advantages [24–26].

Available computational methods for predicting DDIs are usually based on structural and other similarities or drug–target associations [27–34]. In the following, we refer to selected representatives of these related approaches. Cheng et al. [35] generated a drug–drug network by quantifying the relationships between drug targets and disease proteins in the human protein–protein interactome to predict clinically useful drug combinations for specific diseases. Rohani and Eslahchi [32] proposed a neural network-based method for DDI prediction that applied the neural network model with similarity selection and fusion methods to increase the accuracy of predicting DDIs. Qian et al. [36] constructed a gradient boosting-based classifier to predict adverse DDIs using genetic interactions between the gene targets of two drugs. They discovered that adversely interacting drug targets are more likely to have more synergistic genetic interactions than non-interacting drugs targets. Karim et al. [37] combined a convolutional

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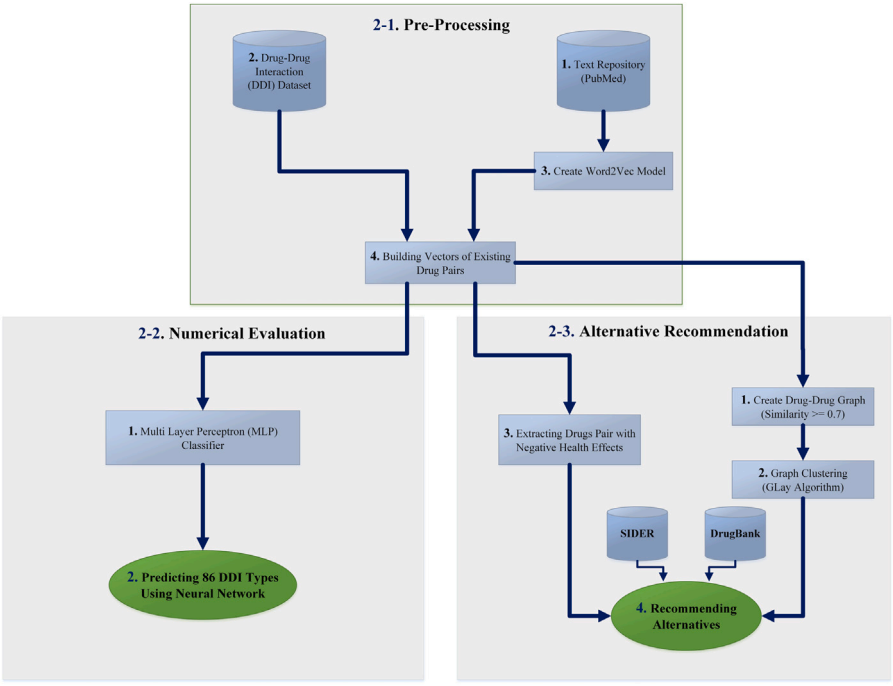

Fig. 1. Overview of ADDI method.

neural network (CNN) and a long short-term memory (LSTM) network to predict DDIs in multiple data sources that are integrated using Knowledge Graphs. They embed the nodes in the graph applying various embedding approaches. Ryu et al. [24] proposed a computational framework, DeepDDI, that takes chemical structural information of two drugs as inputs and accurately predicts relevant DDI types for the input drug pair.

The main drawback of previous methods for predicting DDIs is that they require detailed drug information such as the chemical structure of drugs, drug targets or side effects as input, which are often error-prone and costly and time-consuming to provide. As an alternative to these methods, there are methods that exploit text-mining to extract DDIs using less information. Huang et al. used LSTM and POS embedding to extract features from the text in order to predict DDIs [38]. Zhao et al. proposed a syntax convolutional neural network (SCNN) based DDI extraction method [39]. Lim et al. used PubMed-and-PMC-w2v and LSTM to extract DDIs [40]. Shi et al. used matrix factorization to predict drug–drug interactions (DDIs) [41]. They used drug-binding proteins. Zheng et al. proposed a method called DDI-PULearn that predicted DDIs using SVM and KNN algorithms as well as using the PCA feature reduction method [42]. All of these text-mining approaches apply pre-trained models on only one kind of text input and are limited in their extension capacity. In this paper, we propose an expandable method called ADDI (Alternative Drug–Drug Interactions) that uses online text resources such as PubMed to predict interaction types among drugs. ADDI applies a word-embedding technique known as Word2vec [43,44] on 29 million PubMed paper abstracts [45] to extract drug embeddings. ADDI uses a neural network that receives drug embeddings as input to predict DDI types as output. Additionally, ADDI creates a drug–drug network. ADDI applies a clustering algorithm to recommend alternatives for DDIs which have negative health effects types (NHETs). The key contribution of this paper is:

– ADDI is the first and still informative method in combining most recent advanced deep learning-based text mining approaches with graph mining approaches for the task of recommending novel alternatives for drug pairs with negative health effects. Additionally, compared to the state-of-the-art methods, ADDI produces more accurate results by using less amount of information (only online PubMed texts) as input data. The manual evaluation of recommended alternatives indicates the predictive power of ADDI.

Table 1
Parameters configuration of Word2Vec.

Parameter	Setting
Model	CBOW
min-count	5
dim	200
samp	1e−4
win	8

The structure of this paper is as follows: ADDI is described in detail in Section 2. The empirical results are presented in Section 3 and discussed in Section 4. Section 5 summarizes major insights and proposes promising directions for future research.

2. ADDI

The basic idea underlying ADDI is to apply deep learning to discover DDI types and to recommend alternatives for interactions with negative health effects. The main steps of ADDI are shown in Fig. 1, and the following subsections will discuss each main step in detail.

2.1. Pre-processing

Pre-processing consists of the following four sub-steps through which the input data are polished and integrated so that they can be further processed in the subsequent main steps "Numerical Evaluation" and "Application":

1. ADDI is a general method that works on textual data that contains relevant information about drugs and DDIs. For this purpose, ADDI employed two datasets in the experimental analysis described in Section 3. As a text repository containing drug information, ADDI uses the PubMed dataset which contains all

Table 2
14 DDI types known as Negative Health Effects.

Index	Negative Health Effects
1	Cardiotoxicity
2	Central neurotoxicity
3	Hepatotoxicity
4	Nephrotoxicity
5	Neurotoxicity
6	Ototoxicity
7	Hypersensitivity
8	Adverse effects
9	Bleeding
10	Heart failure
11	Hyperkalemia
12	Hypertension
13	Hypotension
14	QTc prolongation

the information regarding PubMed papers, such as title, abstract, authors' name, year of publication, etc. ADDI extract abstracts of all papers in the PubMed dataset. This resulted in a repository of 30 GB data, which we made available in [46]. ADDI constructs word2vec embedding for each drug term using the PubMed dataset. These embeddings are considered as input features of multilayer perceptron (MLP) network [47] (discussed later in Section 2.2).

2. ADDI requires data that comprises DDIs. For the experiments reported in Section 3, ADDI used the drug–drug interaction (DDI) dataset described in [24], which contains 192,284 DDIs representing 86 DDI types. Each DDI represents a zero–one feature $DDI_{i,j}^{t_k}$ indicating whether DDI type t_k existed between two drugs d_i and d_j. These features are used in the output layer of the MLP network (discussed later in Section 2.2). The list of all 86 DDI types is available at [48,49]. DDI types describe changes in pharmacological effects and the risk of adverse drug events as a result of the interaction between two drugs in pairs [24]. For instance, one drug may alter the pharmacokinetics of another. Among the 86 DDI types, 14 DDI types are known to be classed as "Negative Health Effects" (see Table 2). The drug pairs having "negative health effects" are those which are described with "the increased risk or severity of adverse effects" and explicit expression such as "cardiotoxic activity", "nephrotoxic activity", and "the increased risk or severity of bleeding".
3. ADDI applies Word2Vec [44,50] on the PubMed dataset to describe each drug term in PubMed. Word2Vec is a two-layer neural network that processes text by describing each word in the text with a small vector. Word2vec takes as its input a text corpus and produces a set of feature vectors that represent words in that corpus [50]. CBOW and Skip-gram are two Word2vec models. Skip-gram and CBOW are more efficient in the case of smaller and larger volumes of training data, respectively [43]. When running ADDI with 30GB of data (which is considered as a high volume of data), we expected that CBOW would discover more DDIs than skip-gram. The configuration of Word2Vec is shown in Table 1. The minimum count (min-count) specifies the minimum number of occurrences needed for a word to be included in the word vectors. The vector dimension (dim) is the learned word vector size. High-frequency words usually provide little information. Sub-sampling (samp) is the process of diminishing frequent word occurrences (words with a frequency above a certain threshold) in order to increase training speed. The context window size (win) denotes the range of words to be included as the target word context [51–53]. The values used in our experiments for these parameters are shown in Table 1 and have been chosen according to best practices described in the literature [44,51,54–58].

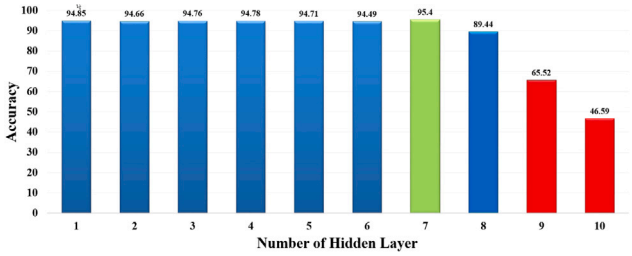

Fig. 2. Accuracy of MLP network in varied hidden layers. Accuracy maximizes when the number of hidden layers equals 7. MLP network overfits when the number of hidden layers exceeds 8.

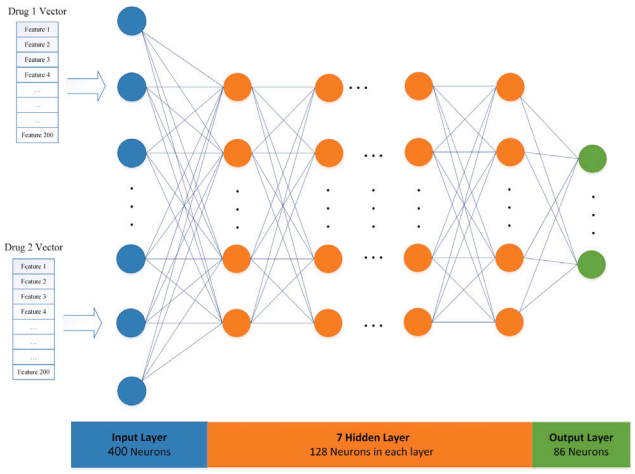

Fig. 3. An illustration of the MLP neural network used by the ADDI method.

4. ADDI predicts DDIs using drug embeddings extracted by Word2Vec from our text repository (For each drug term (d_i) in PubMed dataset, Word2vec extracts a vector ($\overrightarrow{W2V}(d_i)$)). Therefore, from all the DDIs in the DDI dataset, we only considered the DDIs in which the involved drugs exist in our Word2Vec model.

2.2. Numerical evaluation

ADDI utilizes neural networks [59,60] to predict the type of interaction among drug pairs. These networks consist of multiple layers of simple processing units called neurons, where each such unit generates an output signal based its input signals according to some activation function. Neural networks have been shown in various domains to be extremely powerful pattern recognition tools [59,60].

1. Specifically, for the experiments reported here, Multilayer Perceptrons (MLP) was used [47]. This is a class of feedforward artificial neural network that has the following architecture:
   - The input layer contains 400 neurons (200 dimensions $\overrightarrow{W2V}(d_i)$ + 200 dimensions $\overrightarrow{W2V}(d_j)$).
   - The output layer contains 86 neurons, one for each of the 86 DDI types in the DDI dataset (see Section 2.1).
   - Neurons' activation functions, Sigmoid [61] and Softmax [62], are used in the hidden layers and in the output layer, respectively.
   - To determine the number of hidden layers, we examined the MLP network with a varied range of hidden layers, calculating accuracy using a 10-fold cross validation. As shown in Fig. 2, the MLP network reaches its best accuracy when the number of hidden layers equals 7. It was also observed that with more

Table 3
The result of ADDI compared to state-of-the-art methods.

Methods	Type	Accuracy
ADDI	Text-mining	**95.4%**
Ryu et al. [24]	Chemical structures	92.4%
Huang et al. [38]	Text-mining	69%
Zhao et al. [39]	Text-mining	68.9%
Lim et al. [40]	Text-mining	83.8%
Shi et al. [41]	Text-mining	90%
Zheng et al. [42]	Text-mining	90.4%

than 8 layers, the MLP network overfits to the training data and produced a worse result.
An illustration of the MLP neural network is shown in Fig. 3. The network consists of an input layer with 400 neurons, seven hidden layers each having 128 neurons, and output layer with 86 neurons.

2. ADDI utilizes the MLP neural network to predict DDIs and employs 10-fold cross-validation for evaluation and comparing itself with previous methods.

2.3. Alternative recommendation

ADDI recommends alternatives for drug pairs with negative health effects by executing the following four steps:

1. For all (d_i, d_j), ADDI uses the cosine similarity between $\overrightarrow{W2V}(d_i)$ and $\overrightarrow{W2V}(d_j)$ to calculate their semantic similarity (see Formula (1)):

$$SemSim(d_i, d_j) = \frac{\overrightarrow{W2V}(d_i) \cdot \overrightarrow{W2V}(d_j)}{\|\overrightarrow{W2V}(d_i)\| \times \|\overrightarrow{W2V}(d_j)\|} \quad (1)$$

where $\overrightarrow{W2V}(d_i) \cdot \overrightarrow{W2V}(d_j)$ is the dot product of the Word2Vec vectors of d_i and d_j and $\|\overrightarrow{W2V}(d_i)\|$ stands for the magnitude of that vector. $SemSim(d_i, d_j)$ indicates the semantic similarity of two drugs d_i and d_j with respect to their Word2Vec models. ADDI considers only the most informative discovered interactions between drug pairs by pruning the interactions with semantic similarity values less than γ_1. More precisely, an interaction between two drugs d_i and d_j ($DDI(d_i, d_j)$) is pruned if $SemSim(d_i, d_j) < \gamma_1$ (see Formula (2)):

$$\text{Pruning}(DDI(d_i, d_j)) = \begin{cases} \text{remove}(DDI(d_i, d_j)), & \text{if } SemSim(d_i, d_j) < \gamma_1 \\ \text{keep}(DDI(d_i, d_j)), & \text{otherwise} \end{cases} \quad (2)$$

For the experiments reported here, $\gamma_1 = 0.7$ was chosen. In our studies, we found that $\gamma_1 = 0.7$ is high enough to exclude most irrelevant interactions and low enough to prevent loss of possibly relevant interactions.
ADDI constructs a graph $G(V, E)$ of the DDIs in which each node $v_i \in V$ represents a drug d_i and each edge $e_{ij} \in E$ indicates that the semantic similarity (see Formula (1)) between the interacting drugs d_i and d_j is greater than 0.7.

2. ADDI applies the Glay algorithm [63] to cluster the graph of DDIs. This algorithm partitions the graph G into m non-overlapping clusters $c_1, \ldots, c_m$. If d_i is the member of cluster c_k ($1 \le k \le m$) then $CoMemCluster(d_i)$ returns the set of drugs belonging to same cluster as drug d_i. Formally this is expressed by Formula (3)

$$CoMemCluster(d_i) = \bigcup_{d_j \in D} \left(cluster(d_i) = cluster(d_j)\right) \quad (3)$$

where D is the set of all drugs and $cluster(d_i)$ returns the index of cluster of d_i. $CoMemCluster(d_i)$ indicates a set of drugs that are in the same cluster of drug d_i and accordingly, are contextually similar to each other with respect to their appearance in the biological text repository.

3. Among the 86 DDI types in DDI dataset, 14 DDI types are known to be of the "Negative Health Effects" type (see Table 2). ADDI extracts 180 drug pairs with these 14 DDI types in order to recommend alternatives. In the rest of this paper, we refer to these 14 DDI types with Negative Health Effects as "NHETs".
4. ADDI uses the result of clustering to reduce the search space for recommending alternative drugs. For this purpose, if an interaction between drugs d_i and d_j is among the NHETs then ADDI aims to discover all alternative drugs $d_{i'}$ for drug d_i that fulfill the following three conditions:

(1) $d_{i'} \in CoMemCluster(d_i)$
(2) $d_{i'}$, individually, does not have negative health effects (ADDI uses the SIDER dataset[1] to consider each drug's side-effect individually and exclude drugs that cause negative health effects. SIDER contains information on marketed medicines and their recorded adverse drug reactions.)
(3) $DDITypes(d_{i'}, d_j) \notin$ NHETs (To eliminate drug pairs that have NHETs, ADDI utilizes DrugBank dataset.[2] The DrugBank database is a unique bioinformatics and cheminformatics resource that combines detailed drug data with comprehensive drug target information.)
where $DDITypes(d_{i'}, d_j)$ is interaction type between two drugs $d_{i'}$ and d_j. In other words, ADDI examines the drugs that are in the same cluster as d_i, looking for all drugs $d_{i'}$ that do not have negative health effects individually and in combination with drug d_j. In exactly the same way ADDI aims to discover all alternative drugs $d_{j'}$ for d_j that have no negative effects with drug d_i.
For all discovered alternative drugs $d_{i'}$ and $d_{j'}$, ADDI calculates the semantic similarities $SemSim(d_i, d_{i'})$ and $SemSim(d_j, d_{j'})$, respectively. In a last step, ADDI is looking for *(i)* $d_{i'}^{MaxSim}$ as an alternative for d_i so that $SemSim(d_i, X)$ is highest for $X = d_{i'}^{MaxSim}$ and *(ii)* $d_{j'}^{MaxSim}$ as an alternative for d_j so that $SemSim(d_j, Y)$ is highest for $Y = d_{j'}^{MaxSim}$. Finally, ADDI recommends three alternatives for $DDI(d_i, d_j)$:

(1) $DDI(d_{i'}^{MaxSim}, d_j)$
(2) $DDI(d_i, d_{j'}^{MaxSim})$
(3) $DDI(d_{i'}^{MaxSim}, d_{j'}^{MaxSim})$ where $DDITypes(d_{i'}^{MaxSim}, d_{j'}^{MaxSim}) \notin$ NHETs.

Among all the drugs $d_{i'}$ that 1- Are in the same cluster of drug d_i and 2- Have no negative health effect in interacting with drug d_j, $DDI(d_{i'}^{MaxSim}, d_j)$ returns $d_{i'}^{MaxSim}$ that have the maximum contextual similarity with drug d_i. In other words, $DDI(d_{i'}^{MaxSim}, d_j)$ returns an alternative drug that is biologically very similar to drug d_i and can replace drug d_i and more importantly, does not have negative health effect interaction with drug d_j. In some cases, It is better to replace both drug d_i and drug d_j in the drug combination. Among all the drugs $d_{i'}$ in the same cluster as d_i and among all the drugs $d_{j'}$ in the same cluster of drug d_j, $DDI(d_{i'}^{MaxSim}, d_{j'}^{MaxSim})$ recommends drug pair $(d_{i'}, d_{j'})$ with the maximum contextual similarity as an alternative recommendation for drug pair (d_i, d_j).

3. Empirical results

In the following subsections, we first evaluate the predicted DDI types and then demonstrate the ability of ADDI to recommend alternatives for DDIs with NHETs.

[1] http://sideeffects.embl.de/.
[2] https://www.drugbank.ca/.

Table 4
99 DDIs with NHE-type and their alternatives.

Index	d_1	d_2	$d_{1'}^{MaxSim}$	$d_{2'}^{MaxSim}$	$SemSim(d_1, d_{1'}^{MaxSim})$	$SemSim(d_2, d_{2'}^{MaxSim})$	NHETs
1	dofetilide	escitalopram	flecainide	agomelatine	0.769	0.704	QTc prolongation
2	ibutilide	escitalopram	flecainide	agomelatine	0.76	0.704	QTc prolongation
3	sotalol	escitalopram	flecainide	agomelatine	0.803	0.704	QTc prolongation
4	ibutilide	lopinavir	dofetilide	amprenavir	0.759	0.733	QTc prolongation
5	dofetilide	disopyramide	flecainide	aprindine	0.769	0.794	QTc prolongation
6	dofetilide	thioridazine	flecainide	chlorpromazine	0.769	0.711	QTc prolongation
7	ibutilide	amiodarone	flecainide	flecainide	0.76	0.755	QTc prolongation
8	dofetilide	ibutilide	flecainide	flecainide	0.769	0.76	QTc prolongation
9	dofetilide	sotalol	flecainide	flecainide	0.769	0.803	QTc prolongation
10	ibutilide	sotalol	flecainide	flecainide	0.76	0.803	QTc prolongation
11	dofetilide	pimozide	flecainide	fluphenazine	0.769	0.713	QTc prolongation
12	ibutilide	pimozide	flecainide	fluphenazine	0.76	0.713	QTc prolongation
13	sotalol	pimozide	flecainide	fluphenazine	0.803	0.713	QTc prolongation
14	dofetilide	zuclopenthixol	flecainide	fluphenazine	0.769	0.73	QTc prolongation
15	ibutilide	zuclopenthixol	flecainide	fluphenazine	0.76	0.73	QTc prolongation
16	sotalol	zuclopenthixol	flecainide	fluphenazine	0.803	0.73	QTc prolongation
17	dofetilide	quinidine	flecainide	mexiletine	0.769	0.732	QTc prolongation
18	ibutilide	quinidine	flecainide	mexiletine	0.76	0.732	QTc prolongation
19	sotalol	quinidine	flecainide	mexiletine	0.803	0.732	QTc prolongation
20	dofetilide	flupentixol	mexiletine	perphenazine	0.704	0.779	QTc prolongation
21	sotalol	flupentixol	mexiletine	perphenazine	0.734	0.779	QTc prolongation
22	ibutilide	nilotinib	flecainide	ponatinib	0.76	0.771	QTc prolongation
23	sotalol	nilotinib	flecainide	ponatinib	0.803	0.771	QTc prolongation
24	dofetilide	citalopram	flecainide	reboxetine	0.769	0.731	QTc prolongation
25	sotalol	lopinavir	dofetilide	ritonavir	0.796	0.748	QTc prolongation
26	dofetilide	iloperidone	flecainide	sertindole	0.769	0.753	QTc prolongation
27	ibutilide	iloperidone	flecainide	sertindole	0.76	0.753	QTc prolongation
28	sotalol	iloperidone	flecainide	sertindole	0.803	0.753	QTc prolongation
29	dofetilide	cisapride	flecainide	tegaserod	0.769	0.725	QTc prolongation
30	ibutilide	cisapride	flecainide	tegaserod	0.76	0.725	QTc prolongation
31	sotalol	cisapride	flecainide	tegaserod	0.803	0.725	QTc prolongation
32	ibutilide	asenapine	dronedarone	vilazodone	0.704	0.718	QTc prolongation
33	dofetilide	asenapine	mexiletine	vilazodone	0.704	0.718	QTc prolongation
34	sotalol	asenapine	mexiletine	vilazodone	0.734	0.718	QTc prolongation
35	vemurafenib	minaprine	erlotinib	amineptine	0.729	0.727	QTc prolongation
36	vemurafenib	dapiprazole	erlotinib	apraclonidine	0.729	0.772	QTc prolongation
37	vemurafenib	gatifloxacin	erlotinib	besifloxacin	0.729	0.723	QTc prolongation
38	vemurafenib	pirbuterol	erlotinib	bitolterol	0.729	0.757	QTc prolongation
39	vemurafenib	domperidone	erlotinib	cisapride	0.729	0.726	QTc prolongation
40	vemurafenib	paroxetine	erlotinib	clomipramine	0.729	0.78	QTc prolongation
41	vemurafenib	flecainide	erlotinib	dofetilide	0.729	0.769	QTc prolongation
42	vemurafenib	sotalol	erlotinib	dofetilide	0.729	0.796	QTc prolongation
43	vemurafenib	milnacipran	erlotinib	duloxetine	0.729	0.769	QTc prolongation
44	vemurafenib	amoxapine	erlotinib	maprotiline	0.729	0.796	QTc prolongation
45	vemurafenib	isocarboxazid	erlotinib	maprotiline	0.729	0.707	QTc prolongation
46	vemurafenib	phenelzine	erlotinib	maprotiline	0.729	0.714	QTc prolongation
47	vemurafenib	protriptyline	erlotinib	maprotiline	0.729	0.772	QTc prolongation
48	vemurafenib	prochlorperazine	erlotinib	metoclopramide	0.729	0.735	QTc prolongation
49	vemurafenib	fluconazole	erlotinib	micafungin	0.729	0.718	QTc prolongation
50	vemurafenib	clotrimazole	erlotinib	miconazole	0.729	0.752	QTc prolongation
51	vemurafenib	econazole	erlotinib	miconazole	0.729	0.811	QTc prolongation
52	vemurafenib	sertaconazole	erlotinib	miconazole	0.729	0.76	QTc prolongation
53	vemurafenib	moclobemide	erlotinib	nefazodone	0.729	0.787	QTc prolongation
54	vemurafenib	tranylcypromine	erlotinib	pargyline	0.729	0.731	QTc prolongation
55	vemurafenib	fluphenazine	erlotinib	perphenazine	0.729	0.806	QTc prolongation
56	vemurafenib	molindone	erlotinib	perphenazine	0.729	0.763	QTc prolongation
57	vemurafenib	zuclopenthixol	erlotinib	perphenazine	0.729	0.725	QTc prolongation
58	vemurafenib	nalbuphine	erlotinib	pethidine	0.729	0.732	QTc prolongation
59	vemurafenib	mesoridazine	erlotinib	promazine	0.729	0.75	QTc prolongation

(*continued on next page*)

3.1. Predicting DDI types

ADDI accepts the Word2Vec of two drugs as an input of a neural network (as described in Section 2.2) and predicts the interaction types of two input drugs as an output of the neural network. We made the structure of the MLP algorithm available at [49]. Comparing ADDI to state-of-the-art methods, ADDI outperforms those methods with respect to accuracy (see Table 3). Accuracy is defined as (see Formula (4)):

$$Accuracy = \frac{\text{Number of Correct (Predicted) DDIs}}{\text{Number of existed DDIs (in Dataset)}} \quad (4)$$

This is remarkable because ADDI succeeded in outperforming both text mining-based [38–40] and non-text mining-based [24] approaches. In particular, compared to Ryu et al. [24], which receives chemical structures of two drugs as input, ADDI generates an equally accurate (and even slightly better) result with significantly less information — it only uses the information available online in the PubMed dataset.

3.2. Recommending alternatives

A key feature of ADDI is its ability to recommend alternatives for DDIs with NHETs. As described in Section 2, this ability is based on

Table 4 (*continued*).

Index	d_1	d_2	$d_{1'}$	$d_{2'}$	$SemSim(d_1, d_{1'})$	$SemSim(d_2, d_{2'})$	NHETs
60	vemurafenib	triflupromazine	erlotinib	promazine	0.729	0.834	QTc prolongation
61	vemurafenib	remoxipride	erlotinib	sertindole	0.729	0.743	QTc prolongation
62	vemurafenib	dezocine	erlotinib	sufentanil	0.729	0.721	QTc prolongation
63	vemurafenib	remifentanil	erlotinib	sufentanil	0.729	0.784	QTc prolongation
64	vemurafenib	progabide	erlotinib	tiagabine	0.729	0.753	QTc prolongation
65	vemurafenib	terconazole	erlotinib	tioconazole	0.729	0.735	QTc prolongation
66	vemurafenib	bifonazole	erlotinib	tolnaftate	0.729	0.825	QTc prolongation
67	vemurafenib	oxiconazole	erlotinib	tolnaftate	0.729	0.778	QTc prolongation
68	vemurafenib	agomelatine	erlotinib	vortioxetine	0.729	0.74	QTc prolongation
69	flupentixol	lopinavir	perphenazine	amprenavir	0.779	0.733	QTc prolongation
70	disopyramide	ibutilide	aprindine	flecainide	0.794	0.76	QTc prolongation
71	citalopram	sotalol	clomipramine	flecainide	0.773	0.803	QTc prolongation
72	citalopram	ibutilide	reboxetine	flecainide	0.731	0.76	QTc prolongation
73	disopyramide	zuclopenthixol	aprindine	fluphenazine	0.794	0.73	QTc prolongation
74	rasagiline	methyldopa	entacapone	hydralazine	0.751	0.708	Hypertension
75	selegiline	methyldopa	entacapone	hydralazine	0.761	0.708	Hypertension
76	isocarboxazid	methyldopa	maprotiline	hydralazine	0.707	0.708	Hypertension
77	minaprine	methyldopa	maprotiline	hydralazine	0.717	0.708	Hypertension
78	phenelzine	methyldopa	maprotiline	hydralazine	0.714	0.708	Hypertension
79	tranylcypromine	methyldopa	maprotiline	hydralazine	0.728	0.708	Hypertension
80	moclobemide	methyldopa	nefazodone	hydralazine	0.787	0.708	Hypertension
81	pargyline	methyldopa	nialamide	hydralazine	0.798	0.708	Hypertension
82	quinidine	asenapine	mexiletine	lurasidone	0.732	0.817	QTc prolongation
83	moclobemide	atomoxetine	nefazodone	methylphenidate	0.787	0.795	Central neurotoxicity
84	disopyramide	quinidine	aprindine	mexiletine	0.794	0.732	QTc prolongation
85	cisapride	quinidine	domperidone	mexiletine	0.726	0.732	QTc prolongation
86	flupentixol	quinidine	perphenazine	mexiletine	0.779	0.732	QTc prolongation
87	disopyramide	flupentixol	aprindine	perphenazine	0.794	0.779	QTc prolongation
88	cisapride	flupentixol	tegaserod	perphenazine	0.725	0.779	QTc prolongation
89	cisapride	zuclopenthixol	tegaserod	perphenazine	0.725	0.725	QTc prolongation
90	flupentixol	nilotinib	perphenazine	ponatinib	0.779	0.771	QTc prolongation
91	disopyramide	iloperidone	aprindine	sertindole	0.794	0.753	QTc prolongation
92	cisapride	iloperidone	tegaserod	sertindole	0.725	0.753	QTc prolongation
93	amiloride	tacrolimus	bumetanide	sirolimus	0.761	0.74	Hyperkalemia
94	triamterene	tacrolimus	chlorothiazide	sirolimus	0.806	0.74	Hyperkalemia
95	disopyramide	pimozide	aprindine	sulpiride	0.794	0.738	QTc prolongation
96	disopyramide	cisapride	aprindine	tegaserod	0.794	0.725	QTc prolongation
97	disopyramide	asenapine	aprindine	vilazodone	0.794	0.718	QTc prolongation
98	cisapride	asenapine	tegaserod	vilazodone	0.725	0.718	QTc prolongation
99	teniposide	vincristine	fotemustine	vinblastine	0.705	0.788	Neurotoxicity

the application of the Glay Algorithm on the drug–drug network to partition it into clusters of mostly related drugs. As a result of applying the Glay clustering algorithm on the pruned DDI graph, 110 clusters with an average member size 8 and an average clustering coefficient of 0.445 are generated. We made the result of this clustering available on GitHub [49].

ADDI uses the result of clustering to recommend alternatives (for details see Section 2.3). As a result, ADDI discovered 99 out of 180 DDIs with NHETs that fulfill all constraints regarding recommending alternatives. The 99 DDIs with NHETs, together with their alternatives, are shown in Table 4 and are also available at [49]. We used SIDER to exclude drugs which have the same side effect as an NHET. In Table 4, different colors represent the common drug classes, each of which is shown in Table 5.

Table 5
Common drug classes with colors selected to display them in Table 4.

Common drug classes
Class Ia antyarithmic
Class Ib antyarrithmic
Calss Ic antyarithmic
Class III antyarithmic
Antipsichotic
Antidepressant
Parkinson
Gastrokinetic agent
Opioid pain relif
Antibiotic/antimicotic
HIV/AIDS
Kinase inhibitor
Chemotherapeutic
Diuretic
Other

4. Discussion

A more detailed look into Table 4 shows that most of the NHETs are QTc prolongations. QTc prolongation is a known side effect of many drug groups, including Class Ia and Class III antiarrhythmics, antipsychotics, and kinase inhibitors [64,65]. It can lead to life-threatening torsade de points tachycardia. Class Ia antiarrhythmics are sodium channel blockers that lengthen the heart's action potential leading to QT interval elongation [66]. Class III antiarrhythmics lengthen the hearth's action potential as well as making the repolarisation longer through inhibiting the potassium channels. These antiarrhythmics treat ventricular tachycardias. ADDI suggested using various type Ib and Ic antiarrhythmics, such as using flecainide (Ib) or mexiletine (Ic). Class Ib drugs shorten the action potential of the hearth; meanwhile, Ic type of drugs do not change it; only make the depolarization slower [66]. Flecainide is indicated for use in atrial fibrillation and supraventricular tachycardias, but clinical trials suggested it's use in catecholaminergic polymorphic ventricular tachycardia, a genetic heart disease [67]. Mexiletine is used as well for the treatment of ventricular tachycardias. In the case of antipsychotics [68] and antidepressants [69], many such drugs can have QT interval elongation effects. ADDI suggested avoiding such drugs e.g., lurasidone instead asenapine (line 82) or clomipramine instead of citalopram (line 71). In the case of any antiarrhythmic treatments with depression or psychosis, ADDI can be a useful tool to find alternative drugs for patients. In the case of the B-RAF

inhibitor vemurafenib, ADDI suggested the EGFR inhibitor erlotinib. Vemurafenib is used in B-RAF mutant melanoma treatment [70]. Targeting EGFR besides B-RAF can increase the sensitivity of the tumors to vemurafenib [71], but erlotinib cannot replace vemurafenib.

Among the NHETs, besides QT elongation, are hypertension, hyperkalemia, and neurotoxicity. In the case of hypertension, ADDI suggested the use of hydrazidine instead of methyldopa. Both methyldopa and hydralazine are used primarily in hypertonic crisis and preeclampsia. The potential hypertonia causing interaction between methyldopa and monoamine oxidase inhibitor antidepressants starts from the inhibition of the methyldopa metabolizing monoamine oxidase. Methyldopa can form dopamine and noradrenaline, which causes hypertension [72]. This is the exact opposite of the desired therapeutic outcome. ADDI was able to find this DDI and suggest better alternatives e.g., the tetracyclic antidepressant maprotiline instead of the monoaminoxidase inhibitor minaprine.

In this case, the semantic similarity was inadequate for a replacement drug. In the case of hyperkalemia, ADDI suggested the use of loop (bumetanide) or thiazide (chlorothiazide) diuretics instead of the potassium-sparing diuretics amiloride and triamterene [73].

In the case of Neurotoxicity, ADDI suggested the use of the topoisomerase blocker teniposide [74] and the vinca alkaloid vincristine the use of fotemustine, a guanine alkylating agent [75] and vinblastine another vinca alkaloid [76] instead. Vincristine can exist at higher concentration into the central neuron system compared to vinblastine in rats [77]. Such chemotherapeutic regimes and a combination of them need careful evaluation. ADDI can flag the chemotherapeutic agents with major NHETs to consider alternatives, e.g., in the case of vincristine and vinblastine.

In conclusion, ADDI was able to recommend various therapeutic considerations, e.g., in the case of diuretics or antipsychotics, however the therapeutic indications overwrite the recommendations like in the case of vemurafenib. ADDI was able to find such NHETs where none of the drugs individually have the side effect as in the case of monoamine-oxidase inhibitors and methyldopa. After finding this NHET, ADDI recommended alternative drugs to avoid discovered NHET. In the case of antiarrhythmics, the drugs' side effect and the desired effect match, so to avoid a potentially fatal side effect, proper dosage is required. Nonetheless, ADDI recommendations of the use of non-QT intervals or increasing antidepressants, or antipsychotics in combination with antiarrhythmics can be a useful tool for flagging life-threatening NHETs.

5. Conclusions and future work

Recently, the use of Drug–Drug Interactions (DDIs) to recommend alternative drugs has attracted much attention. To the best of our knowledge, there is no method available to use online text resources for this purpose. In this paper we proposed ADDI as such a method. ADDI applies Word2vec on text resources to extract drug embeddings and uses deep learning to predict DDI types. For the empirical results presented here, 29 million PubMed paper abstracts [45] were used as ADDI's text input. The experimental results show that, in terms of accuracy, ADDI outperforms the state-of-the-art methods by 13% on average, and it does so by using online text resources only. ADDI generates a drug–drug network and uses a clustering algorithm to recommend plausible alternatives for DDIs with negative health effects.

Regarding future research induced by our work, we see three particularly important and very promising directions for refinement and extension of our approach. First, to consider additional data available for drugs (such as chemical data and side effects) as input of ADDI that can be represented by a vector for predicting DDIs. Second, to extend ADDI towards detecting drug combinations (i.e., synergistic or antagonistic interactions) in the drug–drug interactions network. Third, to use the DDI network proposed by ADDI to discover novel relationships among drug side-effects. The main hypothesis to be evaluated is to check if two connected drugs in DDI network share same set of side-effects. We are currently focussing on the use of additional data.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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