Exploring negation annotations in the DrugDDI Corpus

Behrouz Bokharaeian*, Alberto Diaz*, Mariana Neves†, Virginia Francisco*

*NIL Group, Universidad Complutense de Madrid

behroubo@ucm.es, albertodiaz@fdi.ucm.es, virginia@fdi.ucm.es

†Hasso-Plattner-Institute at the University of Potsdam, Germany

marianalaraneves@gmail.com

Introduction

• The DDI-DrugBank 2013 corpus is a useful resource for investigating relation extraction methods.

• However, one limitation of this corpus is the lack of negation annotations.

• The main goal of this paper is to describe the process for annotating the DDI-DrugBank corpus with negation cues and scopes, to show the correlations between these and the DDI annotations and to demonstrate that negations can be used as features for a DDI detection system.

• Basic experiments have been carried out to show the benefits when considering negations in the DDI task.

DrugDDI 2013 Dataset

	Number	Avg. per document
Documents	730	
Sentences	6,648	9.11
Entities	15,441	21.15
Candidate drug pairs	31,270	42,84 (4.70 per sentence)
Positive interactions (DDIs)	4,672	6.40 (14.94%)
Negative interactions (no DDIs)	26,598	36.44 (85.06%)

Basic statistics of the DDI-DrugBank 2013 corpus

Training	pairs	negative DDIs	positive DDIs	effect	mechanism	advice	int
DrugBank	26005	22217	3788	1535	1257	818	178
Test	pairs	negative DDIs	positive DDIs	effect	mechanism	advice	int
DrugBank	5265	4381	884	298	278	214	94

Statistics of the training and test datasets of the DDI-DrugBank 2013 corpus

Annotating DDI-DrugBank corpus with negation

• All the sentences in the original corpus were annotated, which conforms 6,648 sentences from 730 files.

• For the DDI DrugBank 2013 training dataset, annotations from the NegDrugDDI corpus (Bokharaeain et al. 2013)) have been transferred to the NegDDI-DrugBank 2013 corpus and then reviewed.

• For the DDI DrugBank 2013 test dataset, a first annotation was done with a rule based system (Ballesteros et al. 2012), which follows the BioScope guidelines. The annotation consisted on adding two new tags, the cue and the scope of the negations.

• The pre-annotation automatically obtained was then reviewed by four annotators using the Brat annotation tool.

Examples of negation cue and scope annotations (Brat tool)

```
<sentence id="DDI-DrugBank.d297.s4" text="Concurrent therapy with ORENCIA and TNF antagonists is not recommended.">
    <entity charOffset="24-30" id="DDI-DrugBank.d297.s4.e0" text="ORENCIA" type="brand"/>
    <entity charOffset="36-50" id="DDI-DrugBank.d297.s4.e1" text="TNF antagonists" type="group"/>
    <pair ddi="true" e1="DDI-DrugBank.d297.s4.e0" e2="DDI-DrugBank.d297.s4.e1" id="DDI-DrugBank.d297.s4.p0" type="advise"/>
    <negationtags><xcope> Concurrent therapy with ORENCIA and TNF antagonists is <cue>not</cue>
        recommended</xcope>.</negationtags>
</sentence>
```

The extended unified XML format of a sentence with negation cue in NegDDI-DrugBank corpus.

• The test dataset was split in four parts, one for each annotator, who have manually corrected the automatically generated annotations, whenever necessary, and have added the missing ones. Subsequently, the more experienced annotator reviewed all the annotations to ensure coherence.

• We have performed an analysis on the number of distinct cues in the entire NegDDI-DrugBank 2013 corpus and the number of different problematic annotation that were observed.

Cue	DDI-DrugBank Train	Changes	DDI-DrugBank Test	Changes	DDI-DrugBank	Total	Rate
not	855	266	163	13	1018	279	27.41%
no	439	58	59	1	498	59	11.85%
without	47	8	9	4	56	12	21.43%
neither ... nor ...	14	12	0	0	14	12	85.71%
absence	10	5	3	0	13	5	38.46%
lack	8	1	0	0	8	1	12.50%
cannot	7	4	3	0	10	4	40.00%
Total	1380	354	237	18	1617	372	23.01%

Statistics of the negative cues in the training and test datasets, the changes for each cue during manual checking and the rate of changes, for the NegDDI-DrugBank 2013

Analysis of correlations between negations and DDI annotations

• NegDDI-DrugBank 2013 corpus contains 1,448 sentences with at least one negation scope, which correspond to 21.78% of the sentences. This confirm the statement that negation is frequently used in clinical and biomedical documents, and particularly, in pharmacological documents describing drug activity.

• There is a clear correlation between the DDI type and relative candidate drug positions to negation scope.

• The highest correlation can be seen when both candidate drugs are inside the negation scope and DDI type is advice (78.65% of all advice type cases with negation cue mention a positive DDI).

• Tables show the average of correlations between the DDI type and candidate drug positions. As can be seen there is a significant difference between advice type and the other three DDI types.

Drug1position	Drug2position	DDI	Train	Test	Total	Percentage (%)
inside	inside	false	613	730	1343	93.78
inside	inside	true	39	50	89	6.63
left	left	false	141	1191	1332	89.82
left	left	true	27	124	151	11.34
right	right	false	101	819	920	92.56
right	right	true	12	62	74	8.04
inside	left	false	256	921	1177	92.31
inside	left	true	6	92	98	8.33
inside	right	false	52	437	489	88.43
inside	right	true	7	57	64	13.09

Correlations between DDI and drug positions compared to negation scope

Drug1position	Drug2position	Type	Total	Percentage (%)
inside	inside	advise	70	78.65
left	left	advise	50	33.11
right	right	advise	24	32.43
inside	right	advise	37	57.81
inside	left	advise	66	67.34
inside	inside	effect	4	4.49
left	left	effect	56	37.08
right	right	effect	14	18.91
inside	left	effect	26	26.53
inside	right	effect	15	23.43
inside	inside	mechanism	15	16.85
left	left	mechanism	44	29.13
right	right	mechanism	34	45.94
inside	left	mechanism	6	6.12
inside	right	mechanism	10	15.62
inside	inside	int	0	0
left	left	int	1	0.66
right	right	int	2	2.7
inside	left	int	0	0
inside	right	int	2	3.12

Correlations between positive DDI and drug position compared to negation scope.

Exploring negation features

• We carried out experiments using the version 2.1 of TEES event extraction software tool to verify the effects of the negation annotations in a relation extraction task.

• Experiments were carried out only with the training dataset, i.e., training and testing on the 572 documents dataset, and using the complete corpus i.e., the training dataset of the 2013 edition for training (i.e., 572 documents) and testing on the test dataset of the 2013 edition.

• We get different responses for each of the experiments when considering the negation annotations, nonetheless, both of them positive. When using only the training dataset, the number of true positives does not change much, but TEES returns less false positives.

	true positive	false positive	false negative	precision	recall	F-score
NegDDI-DrugBank Train 2013	225	63	172	78.12	56.67	65.69
NegDDI-DrugBank Tain 2013+Cue	226	54	171	80.71	56.92	66.76
NegDDI-DrugBank Train 2013+Cue+scope	226	53	171	81.00	56.92	66.86
NegDDI-DrugBank 2013	602	173	278	77.67	68.40	72.74
NegDDI-DrugBank 2013+Cue	612	172	271	78.06	69.30	73.42
NegDDI-DrugBank 2013+Cue+Scope	618	175	265	77.93	69.98	73.74

Results obtained from TEES for drug-drug interaction predictions using different configurations

Conclusions and future works

• We have annotated the DDI-DrugBank 2013 corpus with annotations for negation following BioScope guidelines. The extended corpus contains 1,448 sentences with at least one negation scope. This is the 21.78% of the sentences, confirming the tendency of use of negation expressions on biomedical documents.

• We have computed correlations between the DDI and negation annotations present in the corpus. All studied effective factors should be considered as potential features for a machine learning based method or in combination with a rule based system for extracting positive DDI from sentences with negation.

• We plan to continue exploring the effect of features extracted from negation annotations in the DDI task, given the promising results which have been obtained in the preliminary experiments carried out with TEES.

• We plan to extend the annotations to the DDIMedLine 2013 corpus. We expect differences in these annotations due of the language used in scientific publications.