Adverse Drug Reaction Detection in Clinical Notes

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Introduction

Electronic Health Records (EHR) are summaries of patient's health, documented and reviewed by doctors and hospital staff.

Electronic Health Records are both Structured (e.g. Structured Diagnostic notes) and Natural Text documents (e.g. Progress Reports).

Raw text EHRs (**Clinical Notes**) contain richer information about patient health than structured records.

Introduction

Extracting medical events from Clinical Notes provides information for surveillance of adverse side effects.

Deep Learning accelerate the extraction of adverse events from large number of Clinical Notes.

Support the doctor's decisions during the prescription of medications in real-time Pharmacovigilance.

WORKFLOW

DATASET

Named Entity Recognition (NER)

- Deep Learning approach

Relation Extraction

- Identification of ADE-Drug relation

Raw Clinical Text **>>** **Predicted Entities [Drug], [ADE]** **>>** **Entity Relations [Drug] caused [ADE]**

Adverse Drug Reaction Detection in Clinical Notes

Named Entity Recognition (NER) to classify named entities in specific categories of medical context, and Relation Extraction between the entities.

"*the patient has internal bleeding …* "

[Event]

ADE (Adverse Drug Event) refers to any adverse event occurring at the time a drug is used, whether or not it is identified as a cause of the event

"*the patient has internal bleeding … warfarin*"

[ADE] **[Drug]**

1. Named Entity Recognition

ADR (Adverse Drug Reaction) is an Adverse Drug Event caused by a drug (Relation ADE-Drug)

2. Relation Extraction

"*the patient has internal bleeding secondary to warfarin*"

[ADE] <<< ADR >>> [Drug]

NER Methods for ADE recognition

Long Short-Term Memory (LSTM): RNN (Recurrent Neural Network) model that is efficient in learning long term label dependencies between entities in sequences [1], like the dependency between Drugs and ADEs.

Additionally capturing the correlations between adjacent labels can help in sequence labeling problems (Lample et al., 2016).

Conditional Random Fields (CRF): probabilistic model that have been used for sequence labeling tasks due to their ability to model the dependencies in the outputs of a sequence (Laerty et al., 2001).

Therefore, we used a combination of **LSTM and CRF** models (BiLSTM-CRF) for Named Entity Recognition.

John Laerty, Andrew McCallum, and Fernando CN Pereira. Conditional random Fields: Probabilistic models for segmenting and labeling sequence data. 2001

Dataset

MADE dataset [1] has manually annotations of ADE, drugs, *Other Signs Symptoms and Diseases* (SSLIF), etc, named medical entities used in NER task of **MADE Challenge** [13].

Challenge focused on extracting fine grained structured information related to Drug Safety [21].

-Unstructured EHRs (natural text medical) from 21 different patients (Cancer domain).

-79003 annotations with **9 Named Entity** types (+None), about 14% of annotations (average) for test dataset.

Annotations	Training	Test
ADE	1509	431
SSLIF	**34056**	**5328**
drug	13507	2395
indication	3168	636
frequency	4148	658
duration	**765**	**133**
route	2278	389
dosage	4893	801
severity	3374	534
Total Ann.	67698	11305
Nb files	876	213

Imbalance probl. between entities

Events

Attributes

Full dataset:
= 79003 Annot.
= 1089 Docum.

Average 800 Words/Document approx.

[1] Jagannatha, Abhyuday et al. "Structured prediction models for RNN based sequence labeling in clinical text." *Proceedings of the Conference on Empirical Methods in Natural Language Processing*. 2016.

[13] Hong Yu, Abhyuday Jagannatha, Feifan Liu, and Weisong Liu. 2018. NLP Challenges for Detecting **D**rug and **A**dverse **D**rug **E**vents from Electronic Health Records. Hosted by University of Massachusetts Lowell. https://bio-nlp.org/index.php/announcements/39-nlp-challenges

Annotations of Clinical Notes

SEVERITY INDICATION

Patient A with moderate hypothyroidism.

ROUTE DRUG DOSAGE FREQUENCY DURATION

He will take an oral tablet of levothyroxine 5mg every day for 12 weeks.

ADE DRUG

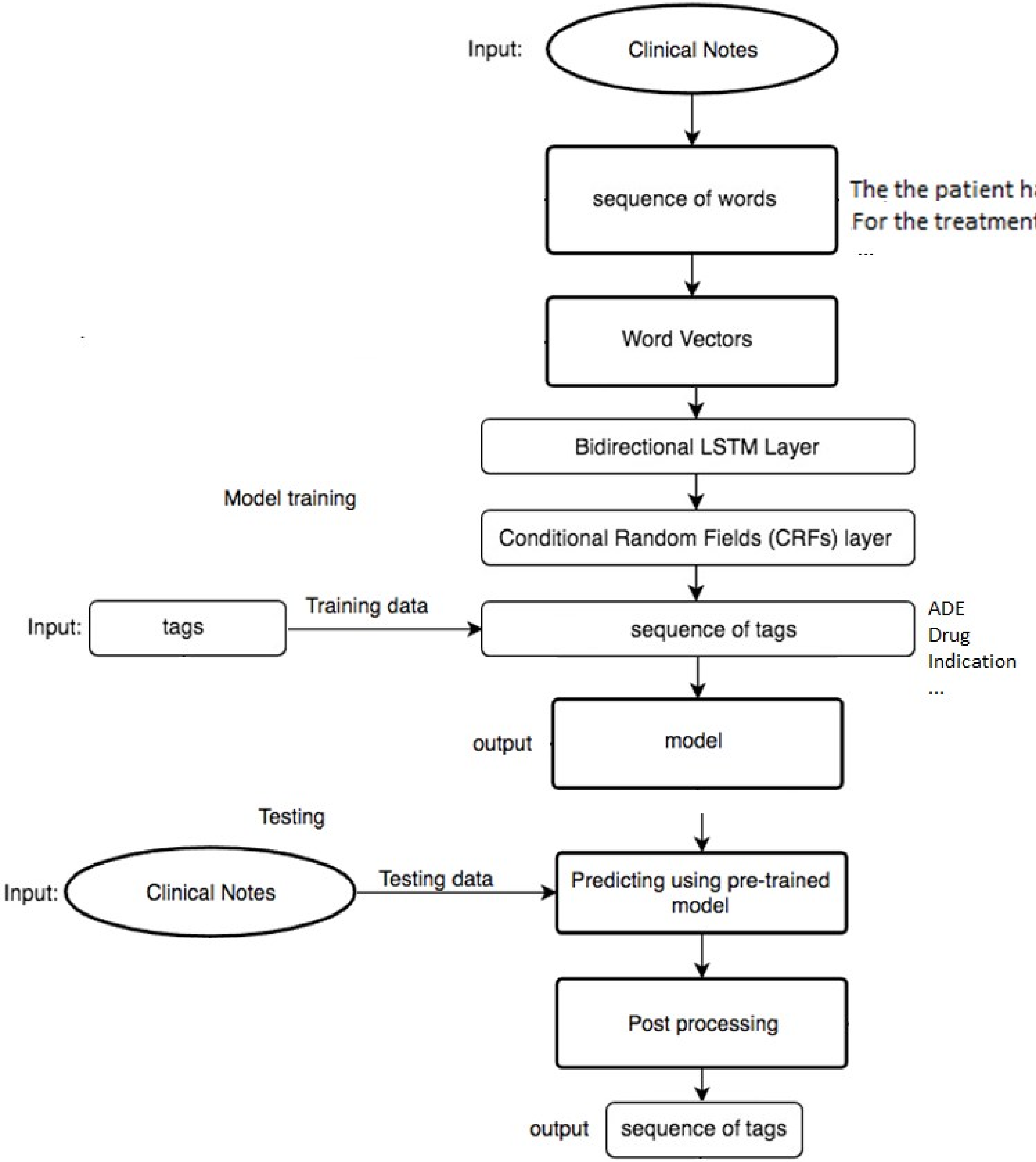
Patient B has significant peripheral neuropathy secondary to Velcade.

SSLIF SSLIF

He complains about fatigue and dry skin.

Training inputs: Text and tags

[21] Hong Yu, Abhyuday Jagannatha, Feifan Liu, and Weisong Liu. 2018. NLP Challenges for Detecting **D**rug and **A**dverse **D**rug **E**vents from Electronic Health Records. Hosted by University of Massachusetts Lowell. https://bio-nlp.org/index.php/announcements/39-nlp-challenges



- **Word Vectors:**

  Pre-trained Word embedding + Character embedding

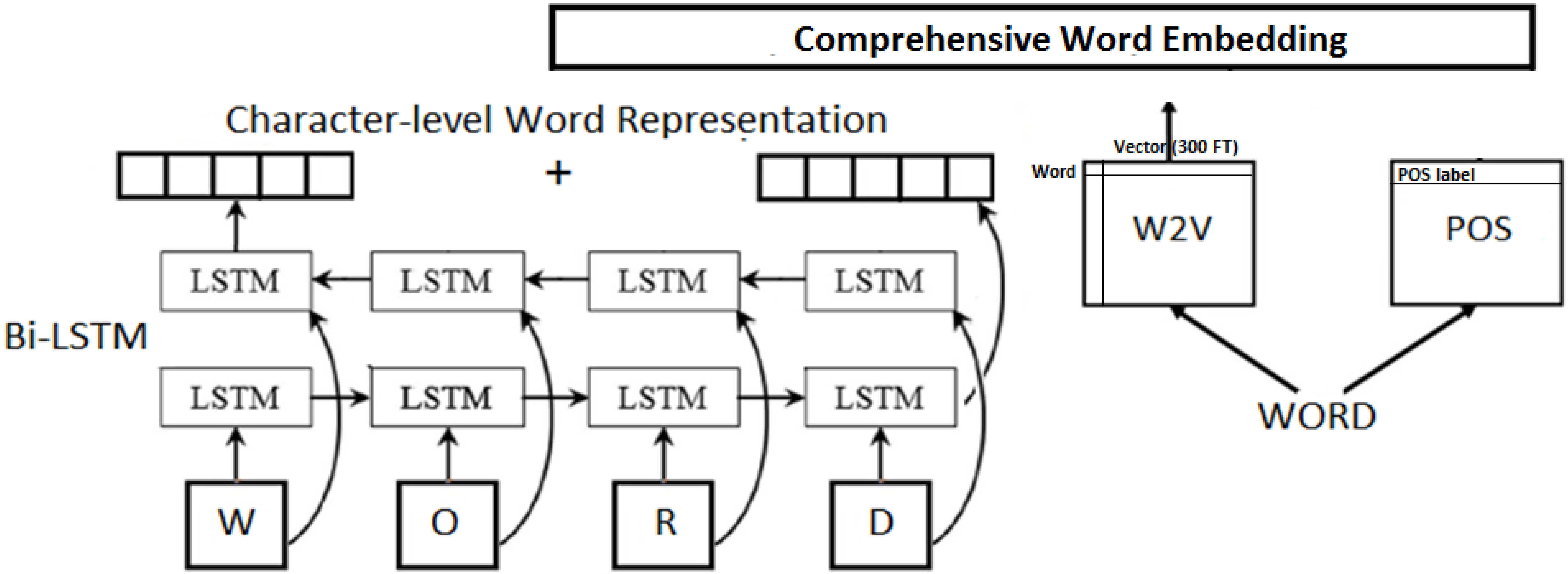
- **Deep learning model training**

  Training and validation sets

- **Post processing**

  Convert to BIO format the predicted tags for evaluation versus true tags

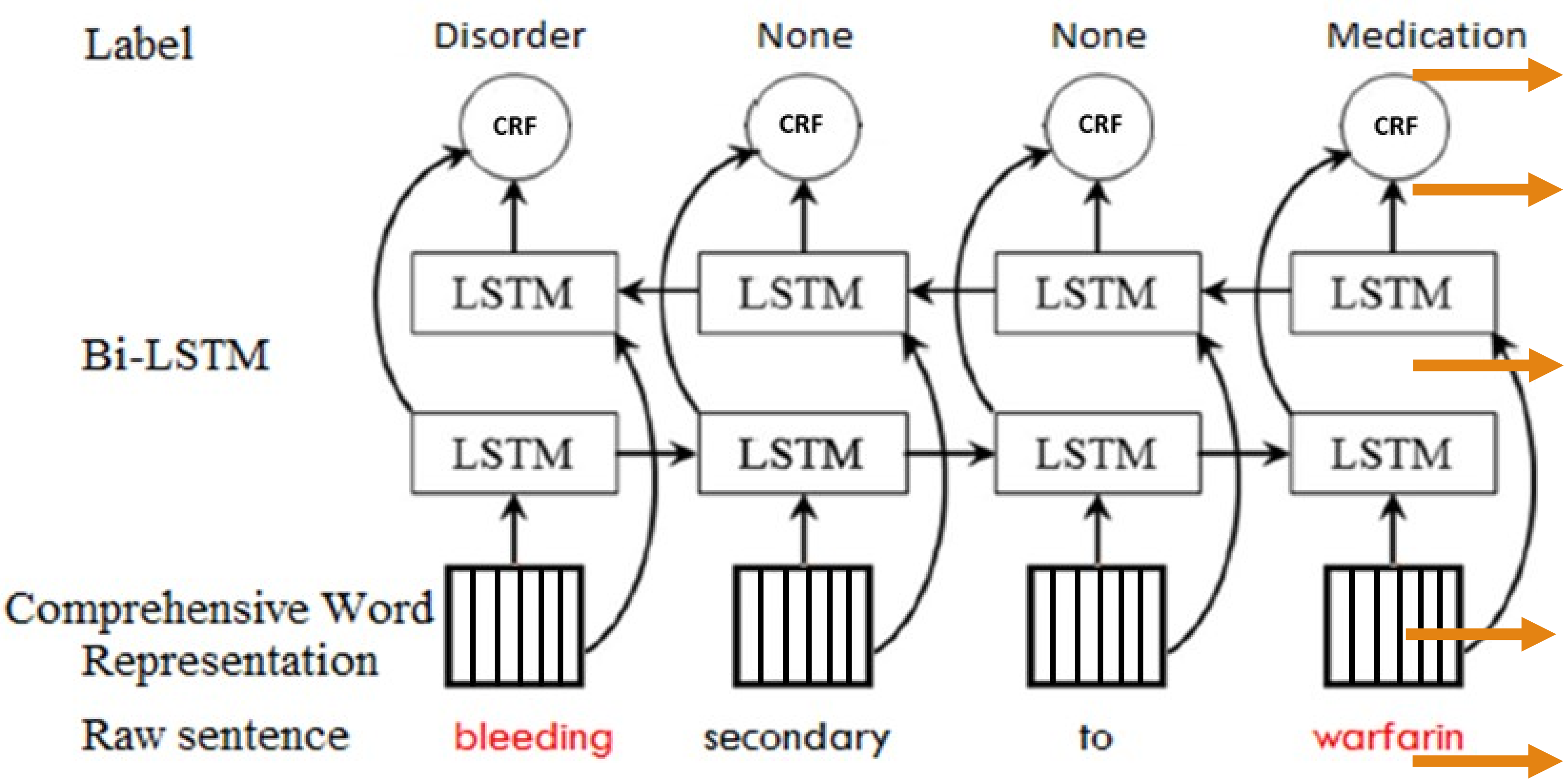
Word Vector



-Prefix and Suffix information
e.g. Drugs like Clonazepam and Lorazepam

-W2V [FT] pre-trained with Skip-Gram, but W2V has Out-of-vocabulary problem due to rare words (e.g. Drug's names)

LSTM+CRF network



True Label

CRF layer

Sequence of hidden states

Hidden cells: 100 each direction

W2V(FT)+Char(LSTM) +POS

Length: 60 words

[11] Liu, Z., Yang, M., Wang, X., Chen, Q., Tang, B., Wang, Z., & Xu, H. (2017). Entity recognition from clinical texts via recurrent neural network. *BMC medical informatics and decision making*, *17*(2), 67.

Results

Performances of models for NER task in MADE Challenge (Test dataset).

Model	Recall	Precision	F1
W2V[1]+Char(LSTM)+POS + **LSTM**	0,720	0,681	0,700
W2V(FT)+Char(LSTM)+POS + **LSTM**	0,748	0,716	0,732
W2V(rd)+ **LSTM**	0,651	0,612	0,631
W2V(rd)+ **LSTM + CRF**	0,663	0,700	0,681
W2V(FT)+ **LSTM**	0,708	0,724	0,724
W2V(FT)+ **LSTM + CRF**	**0,773**	**0,803**	**0,788**

Parameters: Batch size 32, Sequence length 70, 200 LSTM cells, initial learning rate 0.01 using Adagrad, epoch 500

Model	Team	F1
W2V+Char(LSTM) + **LSTM**+CRF	1st Worcester Polytechnic Institute	**0.8290**

[1] Hong Yu, Abhyuday Jagannatha, Feifan Liu, and Weisong Liu. 2018. NLP Challenges for Detecting Drug and Adverse Drug Events from Electronic Health Records. https://bio-nlp.org/index.php/announcements/39-nlp-challenges

Performance by category

Performance (F1) of LSTM models with Test dataset

Entity Category	W2V(rd) LSTM	W2V(FT) LSTM	W2V(rd) LSTM+CRF	W2V(FT) LSTM+CRF	1.Worcester LSTM+CRF	% total Ann.
Drug	0,822	0,867	0,818	**0,875**	0,90	20,0
Indication	0,393	0,457	0,417	0,603	0,64	4,7
Frequency	0	0,656	0,673	0,764	0,84	6,1
Severity	0,485	0,690	0,457	0,781	0,81	5,0
Dose	0,727	0,771	0,739	0,809	0,88	7,2
Duration	0,517	0,568	0,483	0,686	0,77	1,1
Route	0,856	0,868	0,837	0,903	**0,92**	3,4
ADE	**0**	**0,360**	**0,397**	**0,401**	**0,64**	2,2
SSLIF	0,692	0,714	0,682	0,788	0,84	50,3
Overall	0,631	0,724	0,681	**0,788**	0,829	

The performance for ADE and Duration entities is lower than other categories (Imbalance problem due to training with low samples in some categories)

Conclusions

Network good to recognize medical entities on clinical notes, with Character-level features extracted by LSTM, which was used in conjunction with word representations as a comprehensive word representation.

It does not allow the LSTM alone to reach the best performance achieved for the task. Then we improved the performance using CRF in the inference layer.

However we still got low accuracy for annotations with low number of samples (like ADE), therefore we will add an additional technique to give more weight to specific type of annotations.

WORKFLOW

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Raw Clinical Text >> **Predicted Entities [Drug], [ADE]** >> **Entity Relations [Drug] caused [ADE]**

Relation Extraction (Ongoing work)

Supervised Learning approach for Relation Extraction with annotated data (MADE Challenge, task 2 [13]):

1. Random Forest

2. Neural Networks (LSTM)

3. Support Vector Machines (SVM)

Type of relation between 2 annotations (entities), e.g. “Adverse” between Drug and ADE (Adverse Drug Event)

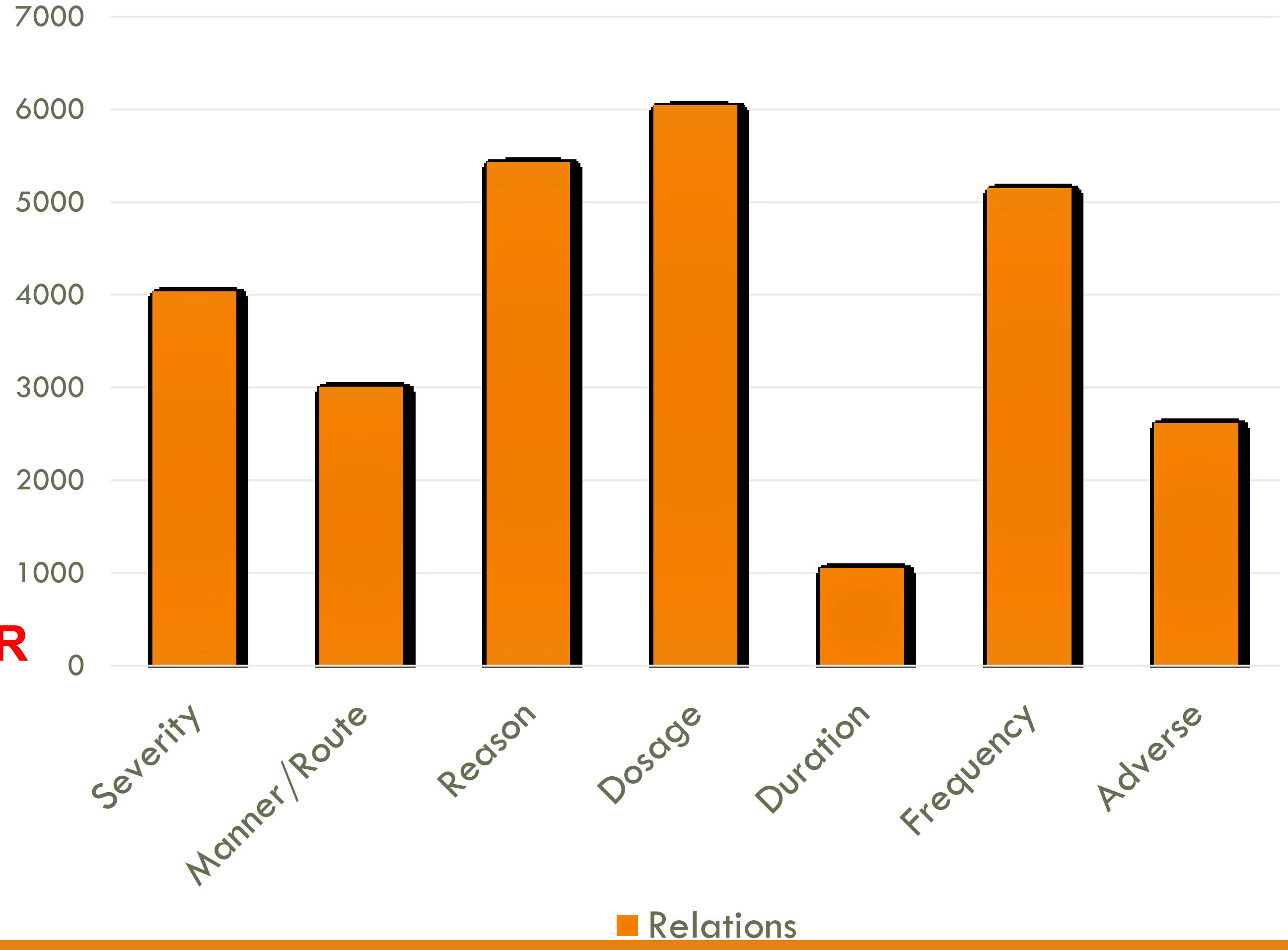
[13] Yu, H., Jagannatha, A., Liu, F., Liu, W.: NLP Challenges for Detecting Drug and Adverse Drug Events from Electronic Health Records (https://bio-nlp.org/index.php/announcements/39-nlp-challenges) (2018).

Dataset

Types of Relations

- Drug given for **Reason** (Indication)
- Drug has **Dosage**
- Drug has **Frequency**
- Drug has **Duration**
- Drug has **Manner/Route**
- Drug caused ADE (**Adverse** Drug Event) **=ADR**
- Sign/Symptom(SSD) has **Severity**

Total relations: 27328



Example of Relations

Training dataset has 17630 (76.1%) are intra-sentential relations and 5535 (23.9%) are inter-sentential.

Relation Type	Example
DOSAGE	Velcade 20mg orally once daily
REASON	He is on prophylactic acyclovir theraphy
FREQUENCY	Velcade 20mg orally once daily
SEVERITY	He has mild renal insufficiency
MANNER/ROUTE	Velcade 20mg orally once daily
ADVERSE (ADR)	He has significant peripheral neuropathy secondary to Velcade
DURATION	Velcade 20mg orally once daily for two weeks

Annotation

- Source

- Target

Build possible relations

- For learning build only common combinations between entities of each note, and also restrict the number of lines between both entities (source and target).

Attributes

Events

	Drug	ADE	Reason	SSD	Severity	Frequency	Duration	Route	Dosage
Drug	---								
ADE		---							
Reason			---						
SSD				---					

Build possible relations

Restrict to pairs within a fixed number of sentences. Example limited to 3 sentences:

> ***The patient is being treated for lymphoma. The patient received one cycle of fludarabine. He is on Velcade 2 weeks out of each month.*** *The patient is currently on thalidomide 100 mg a day. He has significant peripheral neuropathy secondary to Velcade.*

Possible pairs for ***lymphoma***:

REASON-DRUG: ***lymphoma***→fludarabine
REASON-DRUG: ***lymphoma***→Velcade

Possible pairs for ***Velcade (from sentence 5)***:

DRUG-ADE: ***Velcade***→neuropathy

- Source
- Target

Future Work

Design rules to handle entities of low number of samples in training data.

Task-Specific Embeddings for clinical notes: specialized W2V from medical corpus to reduce Out-of vocabulary problem (words that do not appear in the training data but appear in test data).

Additional features like ICD10 codes to create more specific word representations.

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Thank You!

Adverse Drug Reaction Detec
Clinical Notes

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