Detecting Adverse Drug Reaction in Drug Labels using a Cascaded Sequence Labeling Approach

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Introduction

- TAC 2017 ADR Challenge
  - Adverse Drug Reaction Extraction from Drug Labels
- We participated in all four tasks
  - Task 1 – Extract mentions of *AdverseReactions* and modifier concepts (i.e., *Severity*, *Factor*, *DrugClass*, *Negation*, and *Animal)*
  - Task 2 – Identify the relations between *AdverseReactions* and their modifier concepts (i.e., *Negated*, *Hypothetical*, and *Effect*)
  - Task 3 – Identify positive *AdverseReaction* mentions in the labels
  - Task 4 – Map recognized positive AdverseReaction to *MedDRA PT*(s) and *LLT*(s).

Data Sets

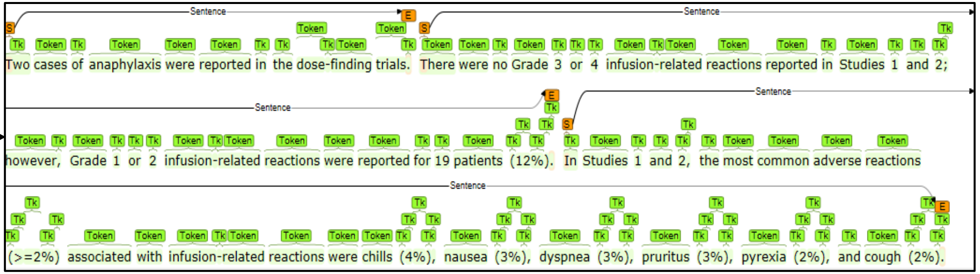
	#drug labels	Usage
Training	101	Developing models and optimizing parameters
Development	2,208	Training word embeddings and rule development
Test	99	Testing

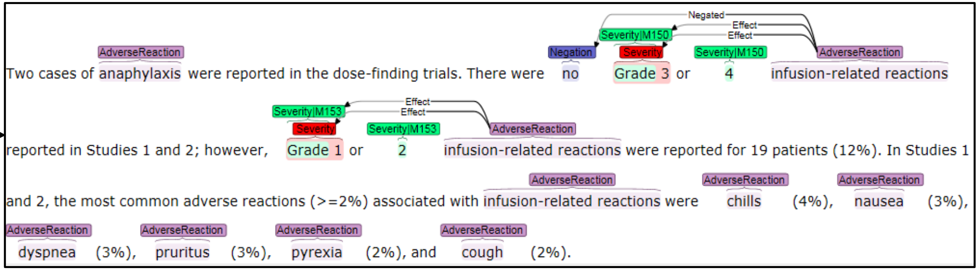
Pre-processing and baseline approaches

CLAMP
Clinical Language Annotation, Modeling, and Processing Toolkit

- Sentence Boundary Detection
- Tokenization
- POS Tagging
- Entity Recognition
- Entity Normalization
- Visualization

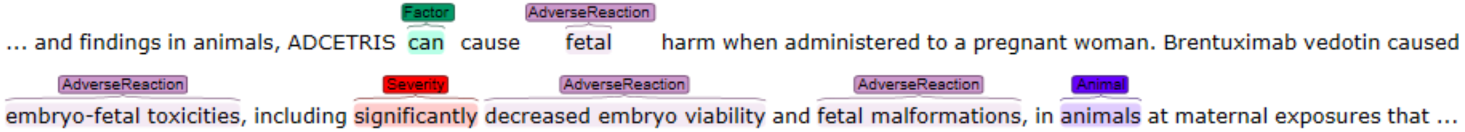
Two cases of anaphylaxis were reported in the dose-finding trials. There were no Grade 3 or 4 infusion-related reactions reported in Studies 1 and 2; however, Grade 1 or 2 infusion-related reactions were reported for 19 patients (12%). In Studies 1 and 2, the most common adverse reactions (>=2%) associated with infusion-related reactions were chills (4%), nausea (3%), dyspnea (3%), pruritus (3%), pyrexia (2%), and cough (2%).



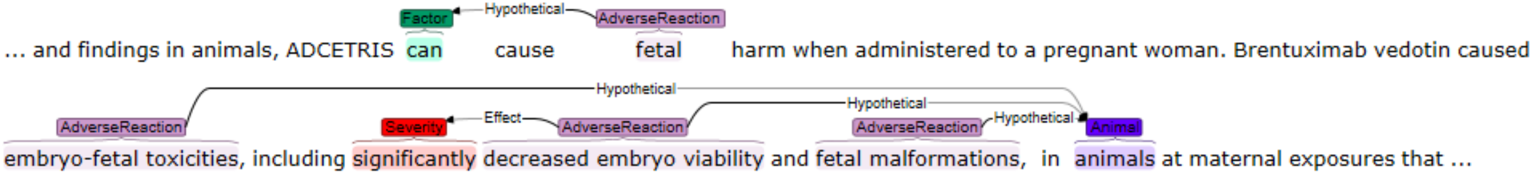


Task 1&2: Extract *AdverseReactions*, related mentions, and their relations

- Task 1: Named Entity Recognition

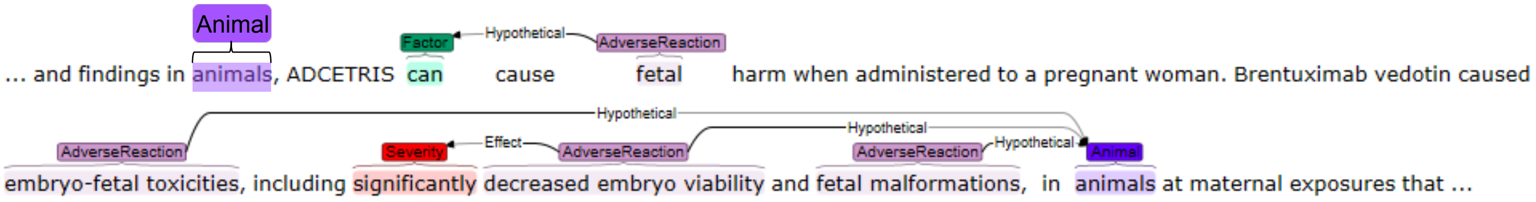


- Task 2: Relation Extraction



Identified Issues – related mention recognition

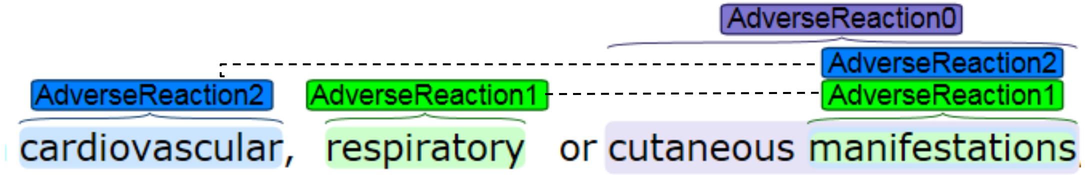
- A related mention is not annotated in the gold standard if it is not associated with any *AdverseReaction*



- **Issue 1**: Cannot train a machine-learning based NER system directly
- **Issue 2**: Missing some negative relation samples, thus making it difficult for the traditional relation classification approach, which requires for both positive and negative candidates for training

Identified Issue – Disjoint/overlapping entities

- Example of disjoint entities



- **Issue**: Cannot handle disjoint entities using the traditional NER approaches
  - Basic assumptions for a machine learning-based NER system
    - entities do not overlap with one another
    - each entity consists of contiguous words

Our approach - Cascaded Sequence Labeling Models

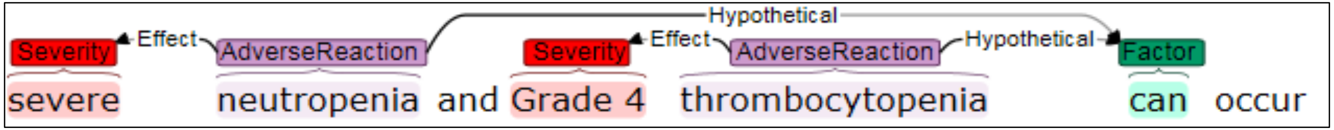
- Model 1 – Sequence labeling model for AdverseReaction only

- Model 2 – Recognize both related mentions and their relations to the target AdverseReaction mentions at the same time, using one sequence labeling model

Model 1 – AdverseReaction NER

- Train 1st sequence labeling model, recognize AdverseReaction only

Gold



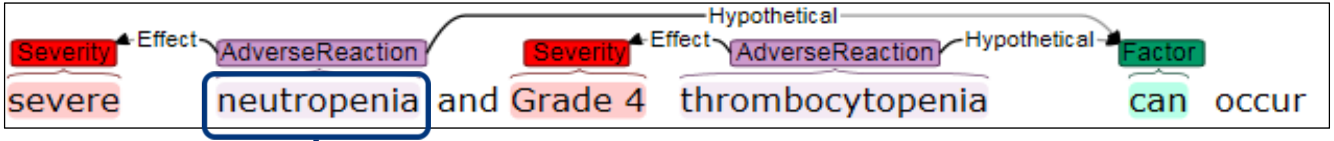
Label	O	B-AdverseReaction	O	O	O	B-AdverseReaction	O	O
Word	severe	neutropenia	and	Grade	4	thrombocytopenia	can	occur

1st Sequence Labeling Model

Model 2 – Related mentions and relations

- Train 2nd sequence labeling model, focus on modifier concepts and their relations with AdverseReactions together

Gold



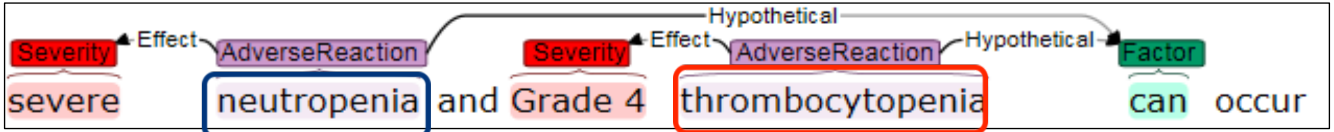
Label	B-Severity	O	O	O	O	O	B-Factor	O
Word	severe	neutropenia	and	Grade	4	thrombocytopenia	can	occur
Target ADR	O	B-T-ADR	O	O	O	B-O-ADR	O	O

Sample 1

Model 2 – Related mentions and relations

- Train 2nd sequence labeling model, focus on modifier concepts and their relations with AdverseReactions

Gold



Sample 1

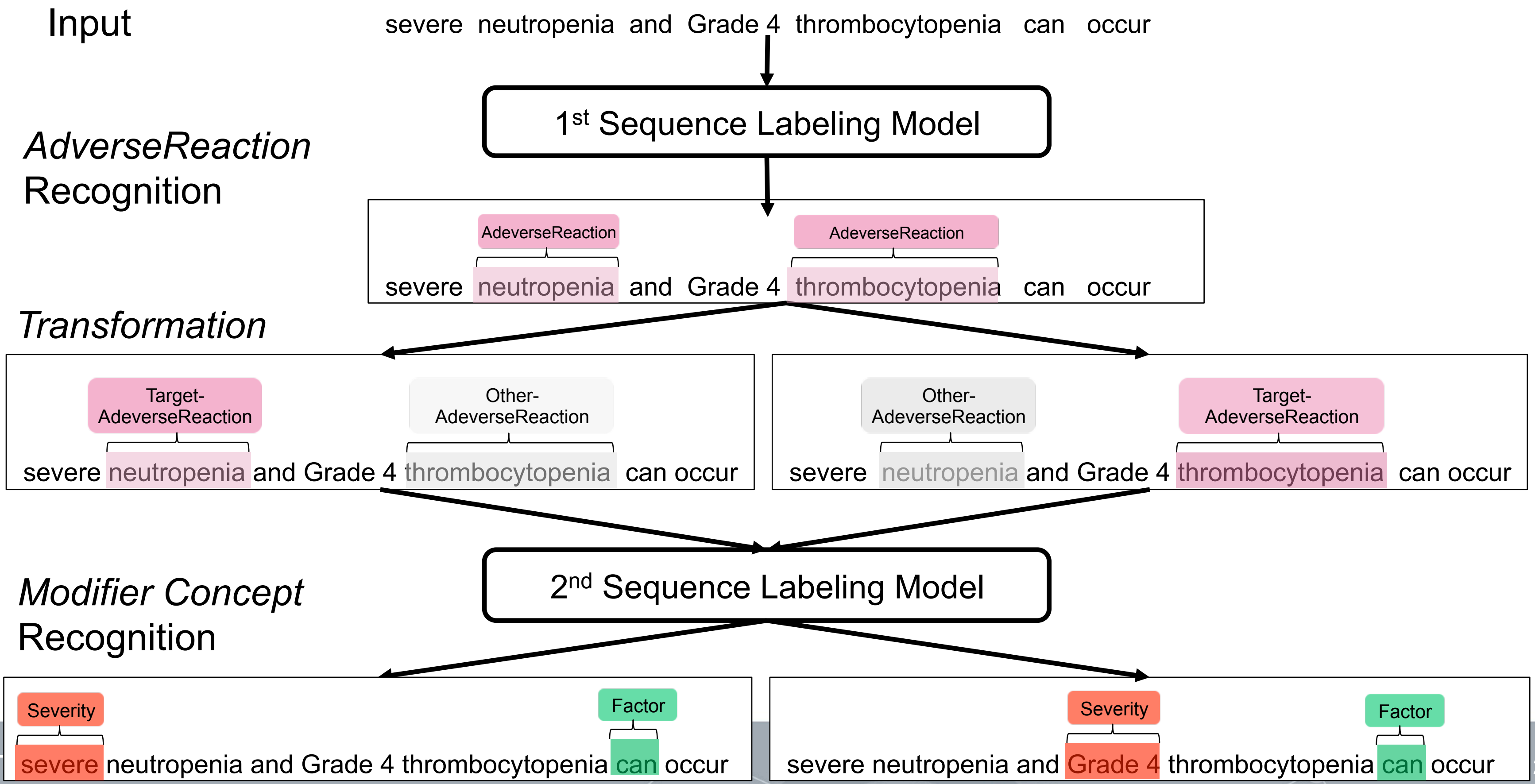
Label	B-Severity	O	O	O	O	O	B-Factor	O
Word	severe	neutropenia	and	Grade	4	thrombocytopenia	can	occur
Target ADR	O	B-T-ADR	O	O	O	B-O-ADR	O	O

Sample 2

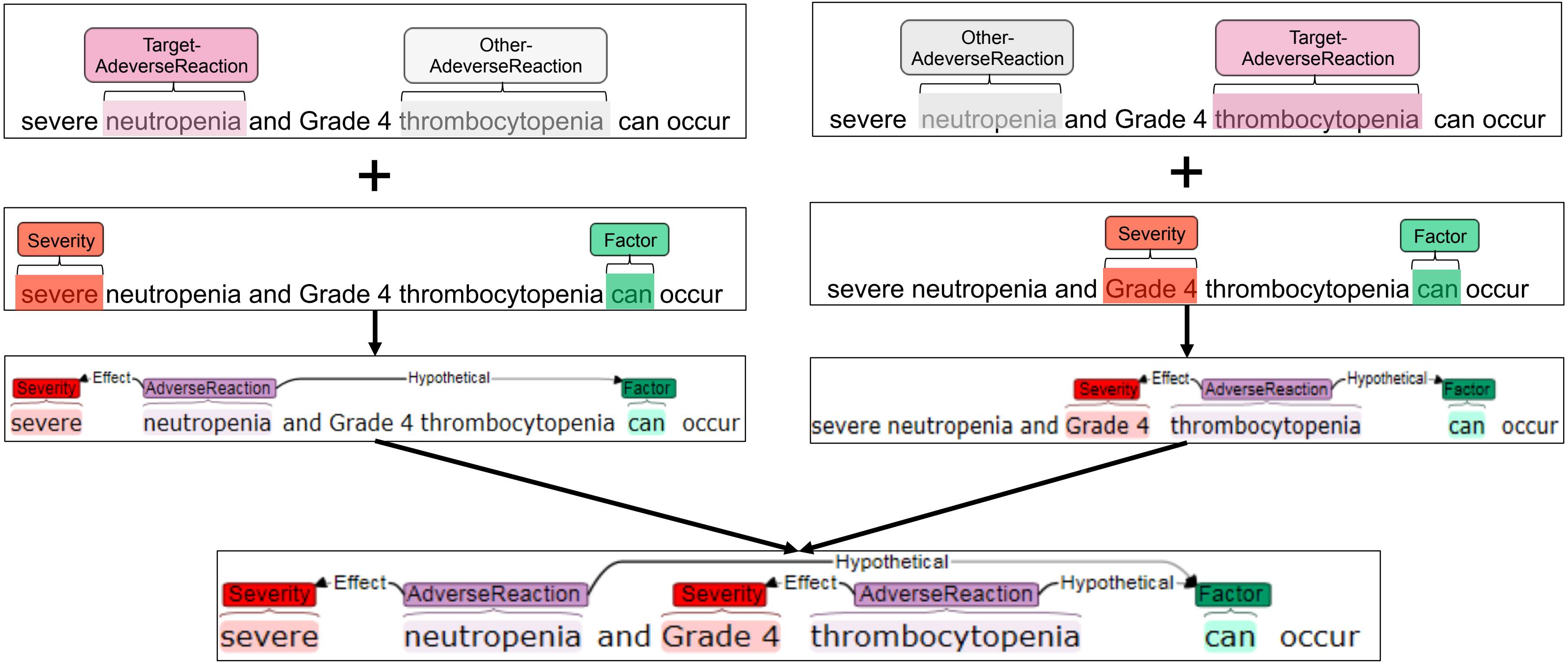
Label	O	O	O	B-Severity	I-Severity	O	B-Factor	O
Word	severe	neutropenia	and	Grade	4	thrombocytopenia	can	occur
Target ADR	O	B-O-ADR	O	O	O	B-T-ADR	O	O

2nd Sequence Labeling Model

Predict with Cascaded Sequence Labeling Models



Predict with Cascaded Sequence Labeling Models

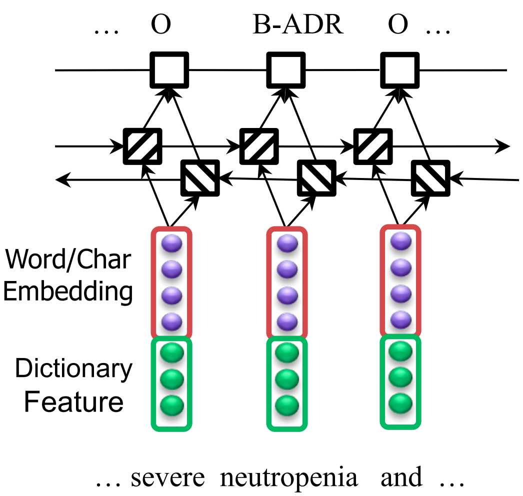


Sequence Labeling Models

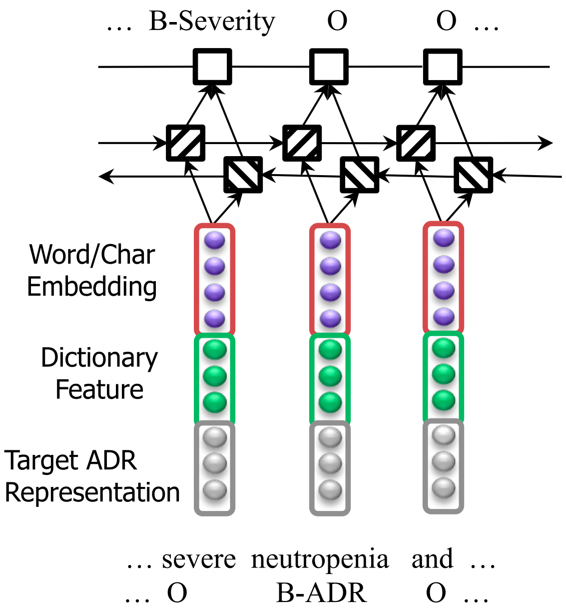
- Conditional Random Fields (CRF)
  - Linear-Chain CRF (Lafferty et al., 2001)
- Recurrent Neural Network (RNN)
  - LSTM-CRF: a bidirectional LSTM with a conditional random field layer above it (Lafferty et al., 2016)
    - Input layer: word embeddings + character embeddings
  - LSTM-CRF(Dict)
    - Use B-/I-/O to represent dictionary lookup results, initiate with random values
    - Input layer: word embeddings + character embeddings +dictionary features

LSTM-CRF(Dict)

1st model for *AdverseReaction* recognition



2nd model for modifier concepts and relation extraction



Our approach for disjoint entities

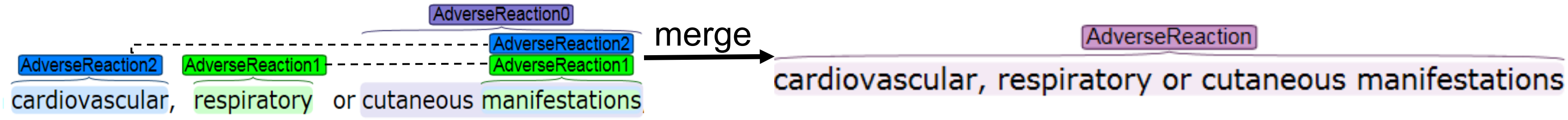
- Step 1 - Merge qualified disjoint entities into *pseudo* continuous entities

- Step 2 - Training NER models using *pseudo* continuous entities

- Step 3 - Split detected continuous entities using rules

Merge and Train disjoint entities

- Merge qualified entities in gold standard
  - Discard, if
    - cross sentences, or
    - more than 3 segments, or
    - more than 5 tokens between two segments
  - Merge others



- Train NER models using ‘continuous’ entities

Split continuous entities

- Detect candidates
  - has more than 4 tokens, or
  - contain any of 'and', 'or', '/', ',', or '('
- Split using rules
  - Regular expression rules
    - *((grade|stage)\s+\d)\s*(?:and|or|\-|\/)\s*(\d) →group(1)|group(2)+group(3)*
    - E.g. **'Grade 3 and 4'** → ***'Grade 3 '*** *and* ***'Grade … 4'***
  - Dictionary–based rules
    - Dictionary(~3000 pairs):<infections, viral>, <infections, protozoal>, <increase in, AST> etc.
      - Started from Training data, and
      - enriched with MedDRA terms
    - E.g. **viral, or protozoal infections '** → **'viral … infections'** and **'protozoal infections'**

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Task 3 - Identify Positive *AdverseReactions*

- An AdverseReaction is positive if:

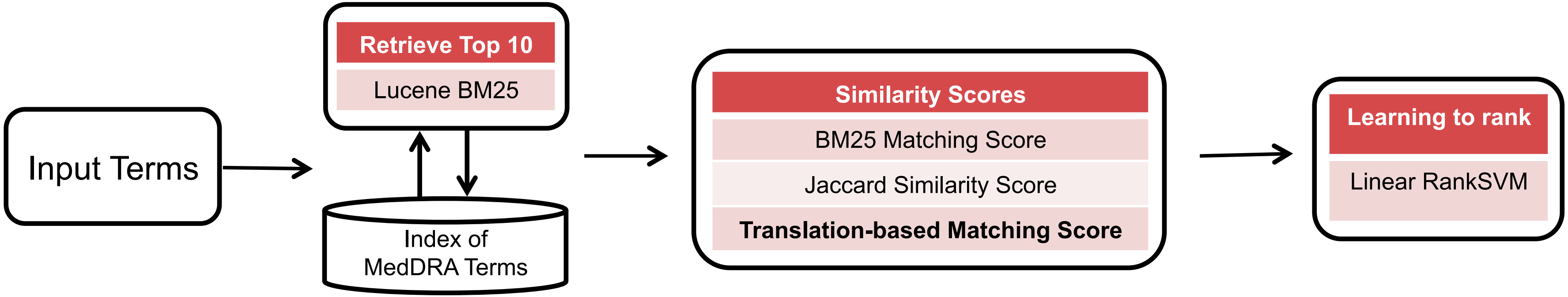
  the *AdverseReaction* is not negated

  AND

  the *AdverseReaction* is not related by a *Hypothetical* relation to a *DrugClass* or *Animal*

Task 4 Link AdverseReactions to MedDRA codes

- Work flow for MedDRA encoding



"elevations, lipids"

Top 10 Concepts
Lipids
Lipid proteinosis
…
Lipid increased

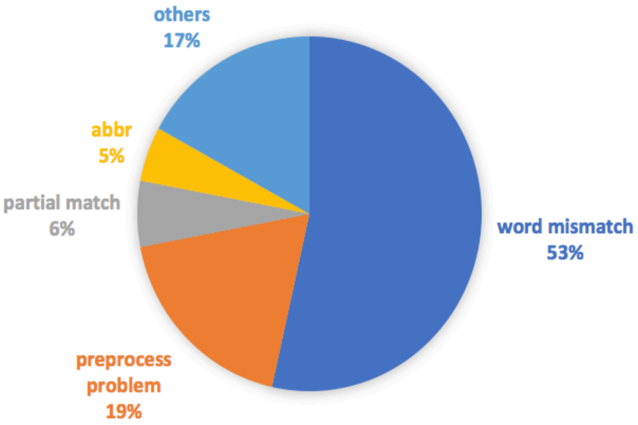
Top 10 Concepts	BM25	Jaccard	TransLM
Lipids	11.12	0.5	-1.95
Lipid proteinosis	8.93	0.5	-5.74
…			
Lipid increased	8.93	0.5	-0.76

Top 10 Concepts	score
Lipids	0.73
Lipid proteinosis	0.63
…	
Lipid increased	**0.98**

Translation-based similarity

- Motivation --- Word mismatch problem

Mention	Elevations, lipids
Simple Match	lipids
Ground-truth	lipids increased



- Machine translation model
  - Word-to-word translation probability
  - t = increased, w = elevations, $p(w|t)$ = 0.6142

Train the word-to-word translation probabilities

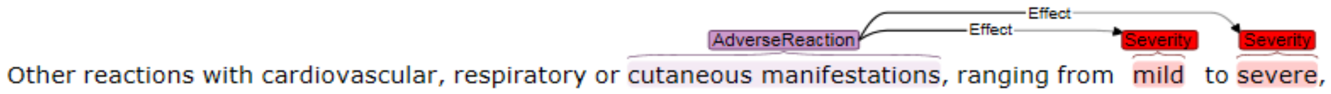
- Prepare parallel corpus
  - From MedDRA, construct 53,368 mapping pairs <Low Level Term, Preferred Term>, e.g.
    - <Diseases of nail, Nail disorder>
    - <Bilirubin elevated, Blood bilirubin increased>
  - From Training Data, construct 7,045 mapping pairs <Mention, Mapped MedDRA Term>, e.g.
    - <alt elevations, ALT increased>
    - <cardiovascular disease, cardiovascular disorder>
- Train word-to-word translation probability with IBM Model 1(Brown et al., 1993)

$$P(t|s) = \frac{\epsilon}{(l+1)^m} \prod_{j=1}^{m} \sum_{i=0}^{l} p(t_j \mid s_i)$$

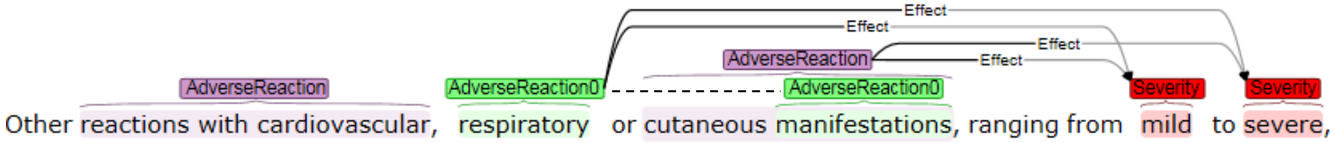
We use GIZA++ toolkit to train the translation probabilities

Submissions

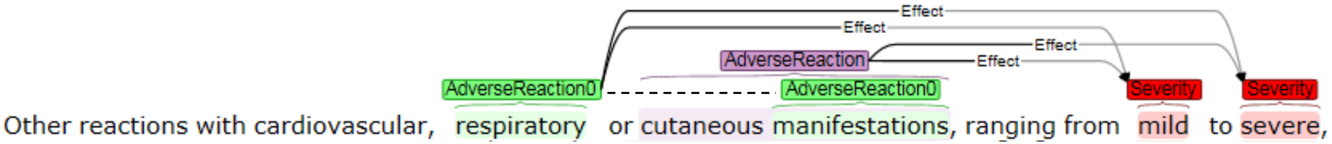
- Run 1: discarded all disjoint *AdverseReactions*, for higher precision



- Run 2: use “merge → predict → split” strategy, for higher recall



- Run 3: combine Run 1 and Run 2, for higher F1



Results of submissions

- The performances of the three runs of our system on all tasks

Run	Task 1			Task 2			Task 3			Task 4		
	+type			Full(+type)			Macro-			Macro-		
	P	R	F1	P	R	F1	P	R	F1	P	R	F1
1	**83.78**	79.74	81.71	**51.67**	44.45	47.79	**82.61**	81.88	81.65	**84.04**	86.67	84.79
2	80.22	**84.40**	82.26	46.24	**48.32**	47.26	78.77	**85.62**	81.39	80.83	**89.90**	84.53
3	82.54	82.42	**82.48**	50.24	47.82	**49.00**	80.69	85.05	**82.19**	83.02	89.06	**85.33**

Results- 1st model to recognize AdverseReactions

- CRF vs. RNN on **non-disjoint AdverseReactions**
  - Training data set
  - 5-fold cross validation
  - Exact match

Model	Precision	Recall	F1-measure
CRF	88.05	77.60	82.50
LSTM-CRF	84.21	80.29	82.21
LSTM-CRF(Dict)	**85.03**	**82.01**	**83.34**

Results- 1st model to recognize AdverseReactions

- CRF vs. RNN, **merged disjoint AdverseReactions**
  - Training data set
  - 5-fold cross validation
  - Exact match

Model	Precision	Recall	F1-measure
CRF	87.7	83.8	85.7
LSTM-CRF	85.4	87.8	86.6
LSTM-CRF(Dict)	**86.7**	**90.0**	**88.3**

Results- 2nd model to recognize related mentions and relations to AdverseReaction

- CRF vs. RNN
  - Training data set, merged disjoint AdverseReactions
  - 5-fold cross validation
  - Gold AdverseReactions
  - Exact match

Model	Mentions	Modifier Extraction			Relation Extraction		
	Type/To Entity	P	R	F1	P	R	F1
CRF	Animal	0.830	0.886	0.857	0.739	0.718	0.729
	DrugClass	0.603	0.281	0.384	0.593	0.263	**0.364**
	Factor	0.747	0.681	0.712	0.711	0.625	0.665
	Negation	0.833	0.561	0.671	0.789	0.504	0.615
	Severity	0.881	0.698	0.779	0.788	0.625	0.697
LSTM - CRF (Dict)	Animal	0.884	0.864	**0.874**	0.815	0.746	**0.779**
	DrugClass	0.528	0.305	**0.387**	0.547	0.272	**0.363**
	Factor	0.720	0.771	**0.745**	0.669	0.744	**0.704**
	Negation	0.716	0.643	**0.677**	0.689	0.597	**0.640**
	Severity	0.787	0.793	**0.790**	0.721	0.749	**0.735**

Results of MedDRA encoding

- Performances of different normalization methods
  - Training data set
  - 5-fold cross validation

	Macro-P	Macro-R	Macro-F1	%impr BM25
cTakes	88.39	75.55	81.28	
MetaMap	90.99	86.79	88.76	
BM25	87.82	90.56	89.11	
TransLM (MedDRA)	90.64	92.57	91.53	2.72
TransLM (MedDRA+TrainData)	93.09	94.42	93.70	5.15
Learning to Rank	93.18	94.58	93.83	5.30

Discussion

- A cascaded sequence labeling model for entity and relation extraction
  - Reasonable performance
  - Need further investigation to compare it with traditional relation classification methods
- RNN for entity and relation extraction
  - Better performance than CRF?
  - Knowledge/dictionary helps, worth further investigation
- Disjoint entities
  - What are the best strategies?
- Linking to MedDRA
  - Translation-based similarity methods

Acknowledgement

- Grants
  - NLM 2R01LM010681-05
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  - Jingqi Wang M.S
  - Qiang Wei M.S.
  - Hua Xu Ph.D.

Thank you!

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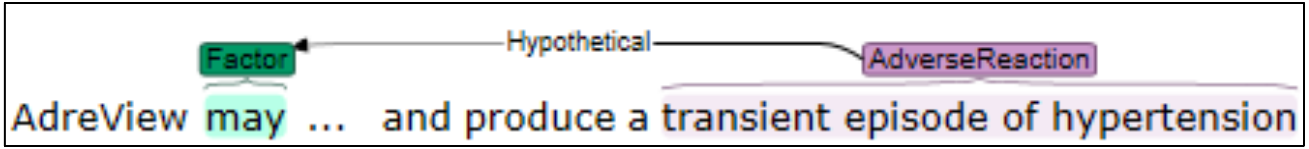
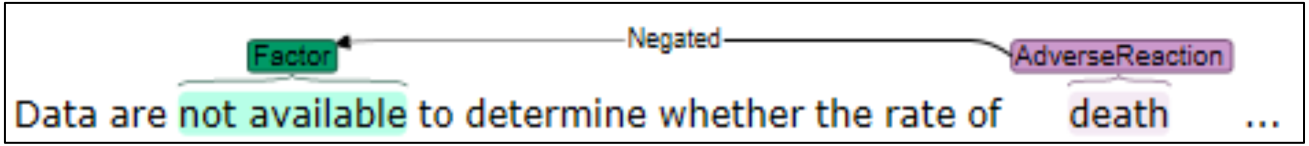
Detect Relation Type for <*Factor*, *AdverseReaction*>

- Limitation of the Cascaded Sequence Labeling-based Approach
  - Cannot classify the relation type of a <modifier, AdverseReaction> pair



Factor that speculates about the drug's relation with an *AdverseReaction*



Factor that negates an *AdverseReaction*

- Rule-based Post-processing
  - Negated: *Factor* is one of *placebo, too small, other than, not available, no trial, etc.*
  - Hypothetical: *Factor* is none of above