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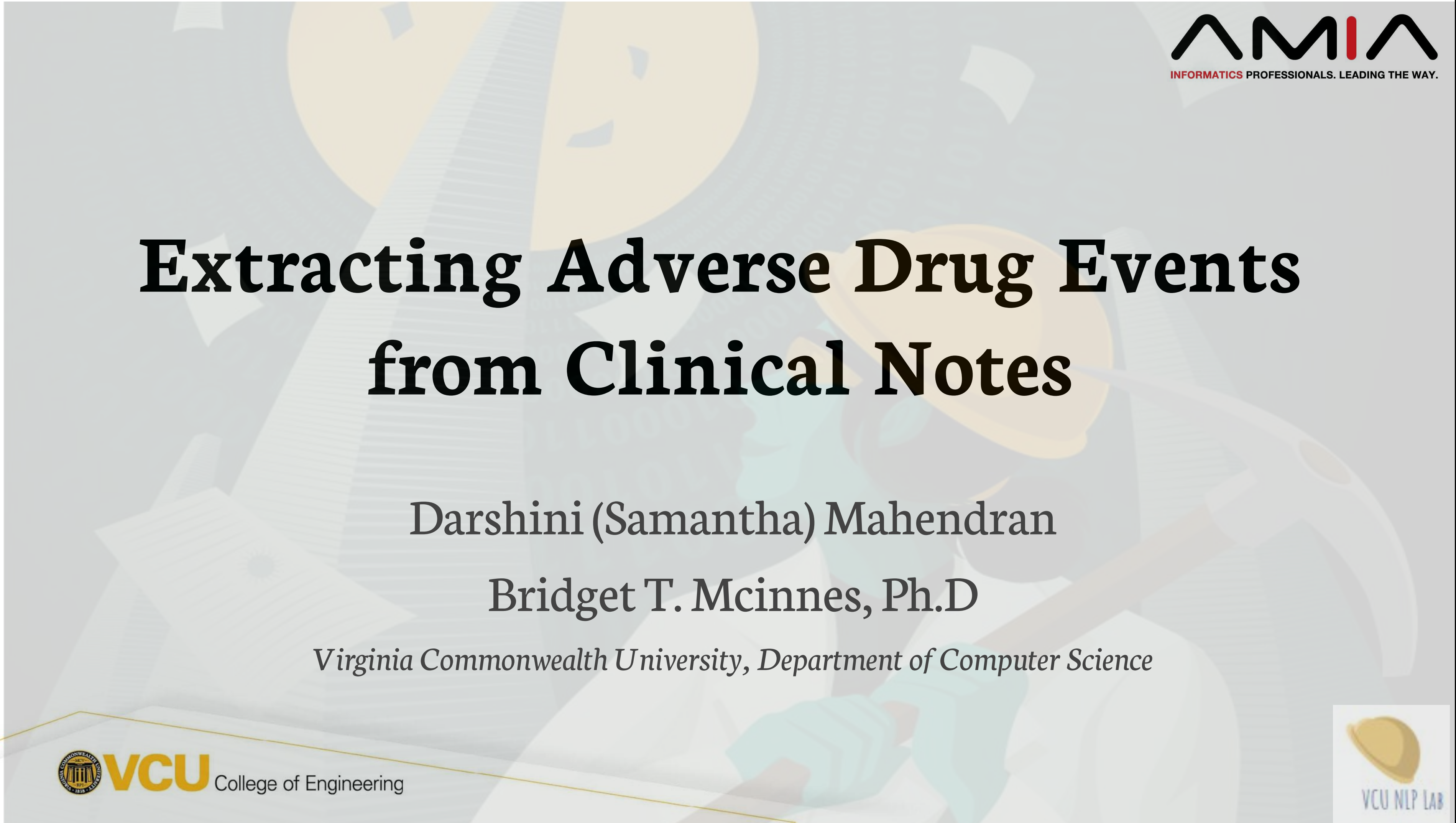

Extracting Adverse Drug Events from Clinical Notes

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Outline

1. Introduction
2. Data
3. Methodology
4. Results and Analysis
5. Conclusion

Introduction

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What is Adverse drug events (ADE)?

- ADEs are unintended incidents that involve the taking of a medication (unwanted effect caused by the administration of a drug)

- Includes overdoses, allergic reactions, drug interactions, and medication errors

- Often Lead to hospitalization, and account for an estimated 12% of all emergency room visits

- Conditions caused by undiscovered ADEs, increase costs and risks further and impact patient economically and mentally

The challenge

- Quickly identifying ADEs in large, can increase both safety and quality of patient health care
- Require information about not just the drug itself, but attributes describing the drug (e.g. strength, dosage) and why the drug was initially being taken (e.g. reason)
- Processing information manually from scientific publications and clinical narratives is challenging

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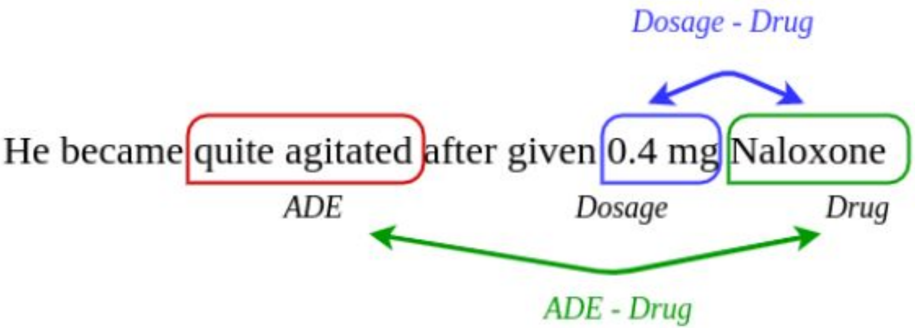
Data

Data: n2c2 (2018)

Includes adverse drug events (ADE), drug related attributes and drug related relations from clinical records



Dosage - Drug

He became quite agitated after given 0.4 mg Naloxone

ADE

Dosage

Drug

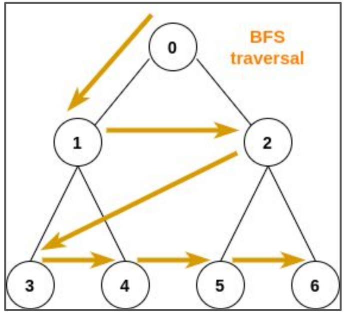
ADE - Drug

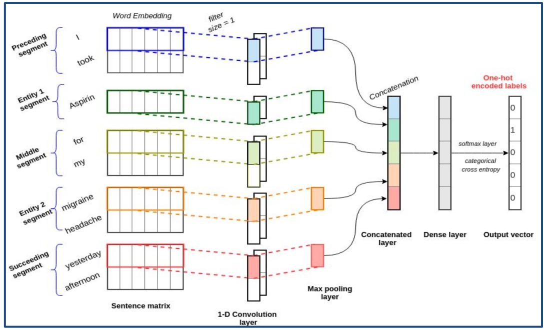
Relation	# train	# test
Drug-Strength	6702	4244
Drug-Duration	643	426
Drug-Route	5538	3546
Drug-Form	6654	4374
Drug-ADE	1107	733
Drug-Dosage	4225	2695
Drug-Reason	5169	3410
Drug-Frequency	6310	4034

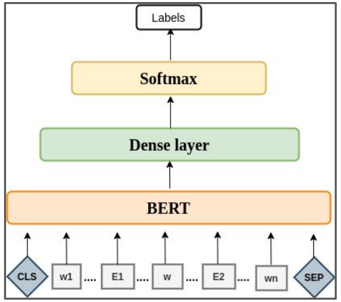
Methodology

Method

- ***RelEx*** - a ***Rel***ation ***Ex***traction Framework based on Python for RE
- Utilize three approaches for clinical RE:
  - Rule-based approach
    - Left-only traversal
    - Left-Right (bounded & unbounded)
  - Deep learning-based approach
    - Sentence CNN
    - Segment CNN
  - BERT-based approach
    - BERT - cased/uncased
    - Bio-BERT
    - Clinical -BERT



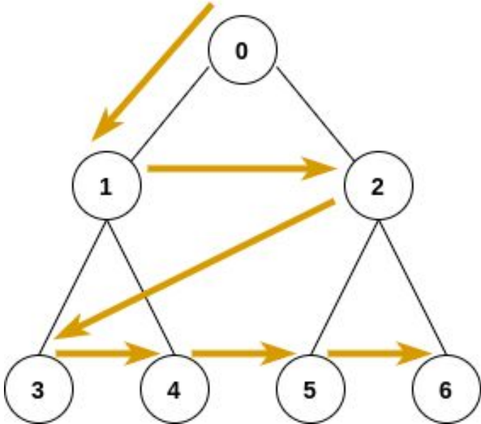




Our system can be found here: https://github.com/NLPatVCU/RelEx, https://github.com/SamMahen/RelEx-BERT

Rule-based approach

- Utilizes co-location information to determine whether a relation exists between two entities
- Graph-based algorithm is used for traversal
- Different traversal techniques are applied and best traversal technique for each relation type is determined
  - ○ traverse left side only
  - ○ traverse right side only
  - ○ traverse left first then right
  - ○ traverse right first then left



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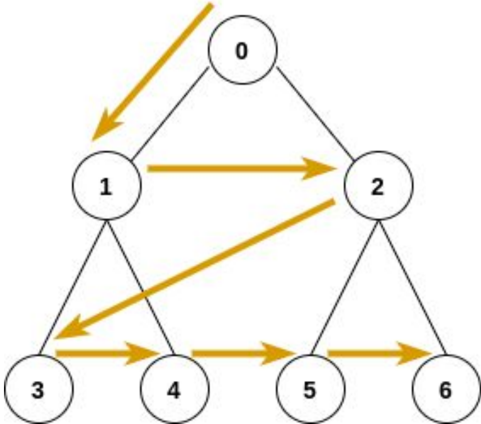

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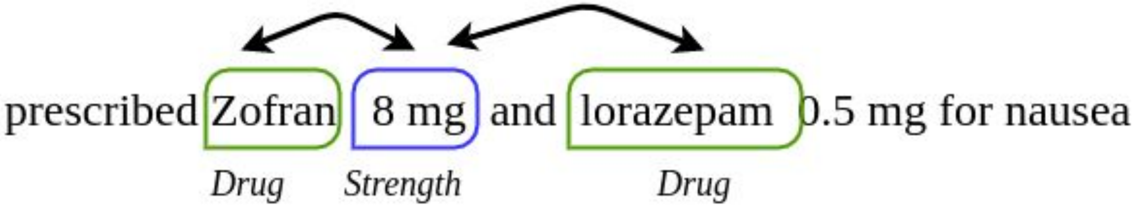

prescribed Zofran 8 mg and lorazepam 0.5 mg for nausea

Drug *Strength* *Drug*

Rule-based approach

- Different traversal techniques are applied and best traversal technique for each relation type is determined
  - ○ traverse left side only
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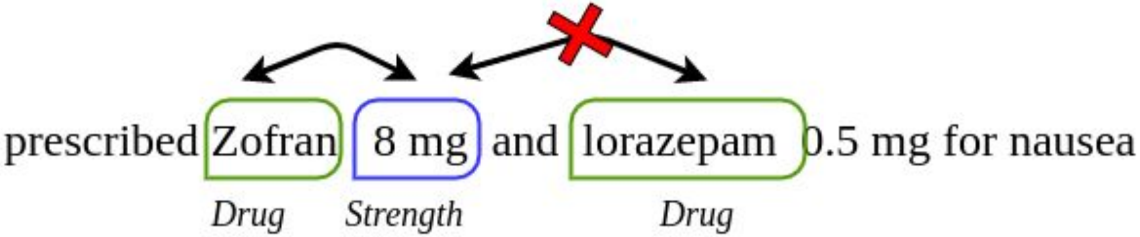
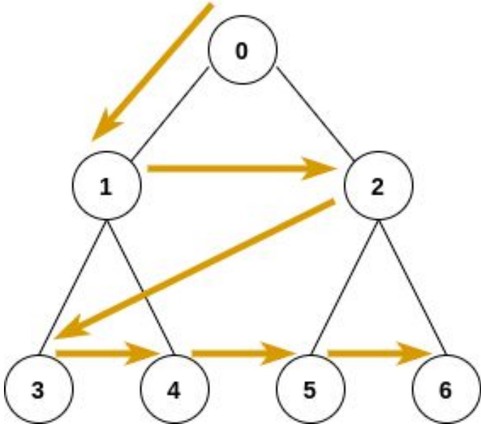


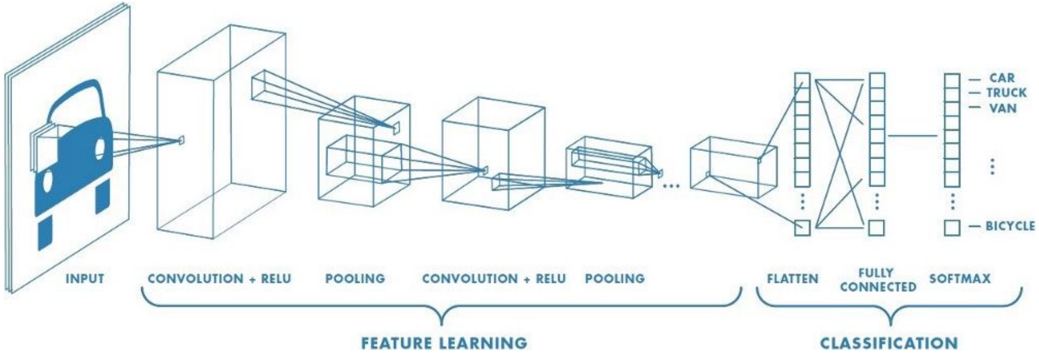
Rule-based approach

- Different traversal techniques are applied and best traversal technique for each relation type is determined
    - traverse left side only
    - traverse left first then right
- Conduct traversals in two modes:
    - bounded - limiting traversal to only a single relation per relation class
    - unbounded - allows a entity to be linked to multiple other entity classes with same relation



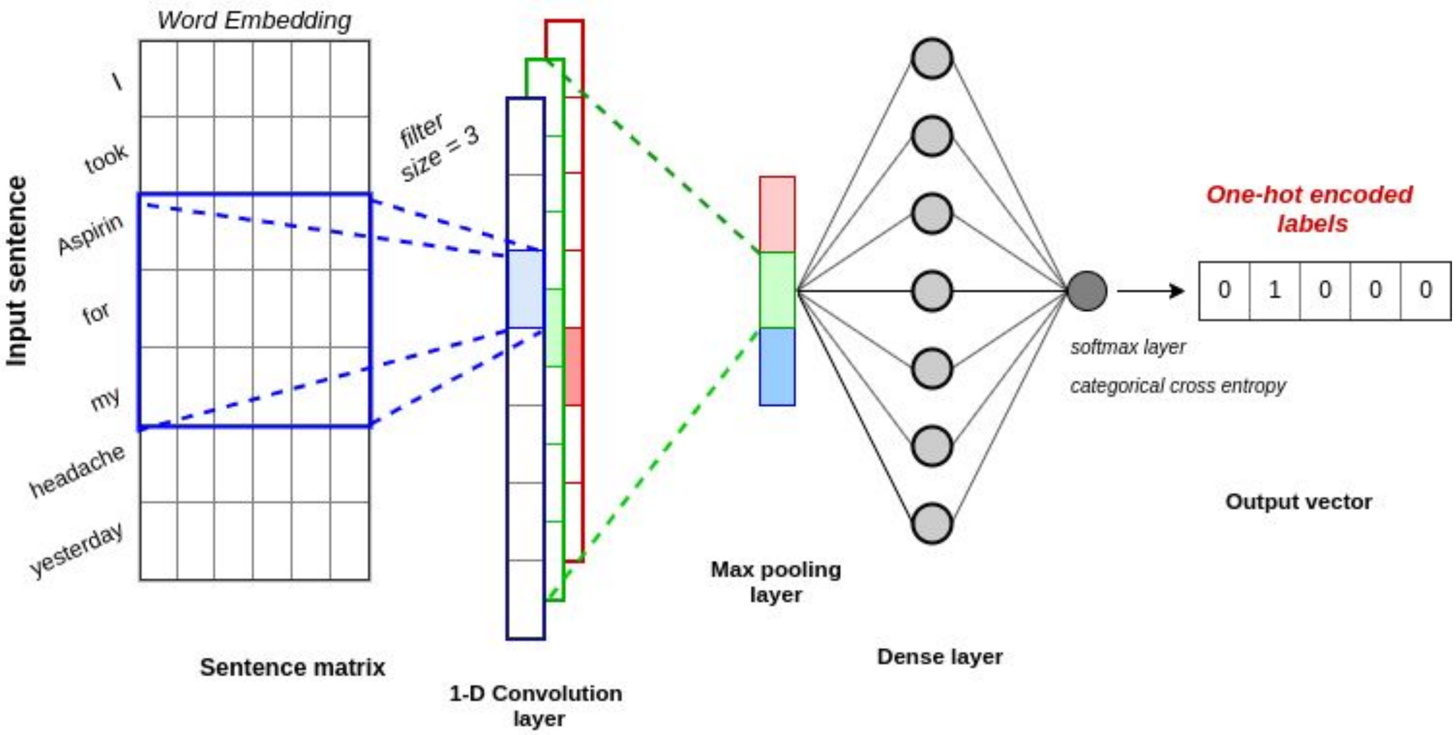
Deep learning-based approach

- Use Convolutional Neural Networks (CNN) in our approaches
- CNN - class of deep neural networks (NN), works well with data that consists of hidden patterns or complex relations among entities
- Our deep learning-based approach includes two CNN architectures:
  - Sentence-CNN
  - Segment-CNN



https://towardsdatascience.com/a-comprehensive-guide-to-convolutional-neural-networks-the-eli5-way-3bd2b1164a53

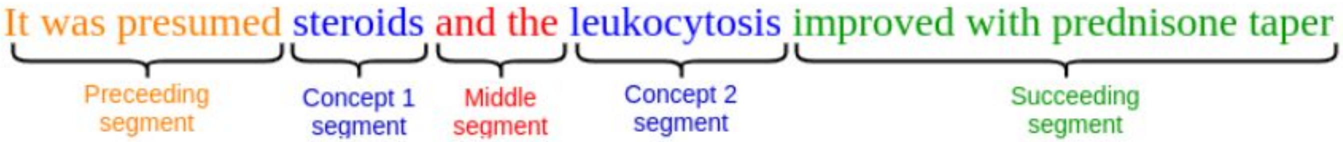
Sentence CNN



Segment CNN

- Different segments play different role in determining the relation class

- Divide the sentence 5 into segments based on the position of the entities in the sentence
  - preceding - tokenized words before the first entity
  - entity 1 - tokenized words in the first entity
  - middle - tokenized words between the two entities
  - entity 2 - tokenized words in the second entity
  - succeeding - tokenized words after the second entity



It was presumed steroids and the leukocytosis improved with prednisone taper

Preceeding segment

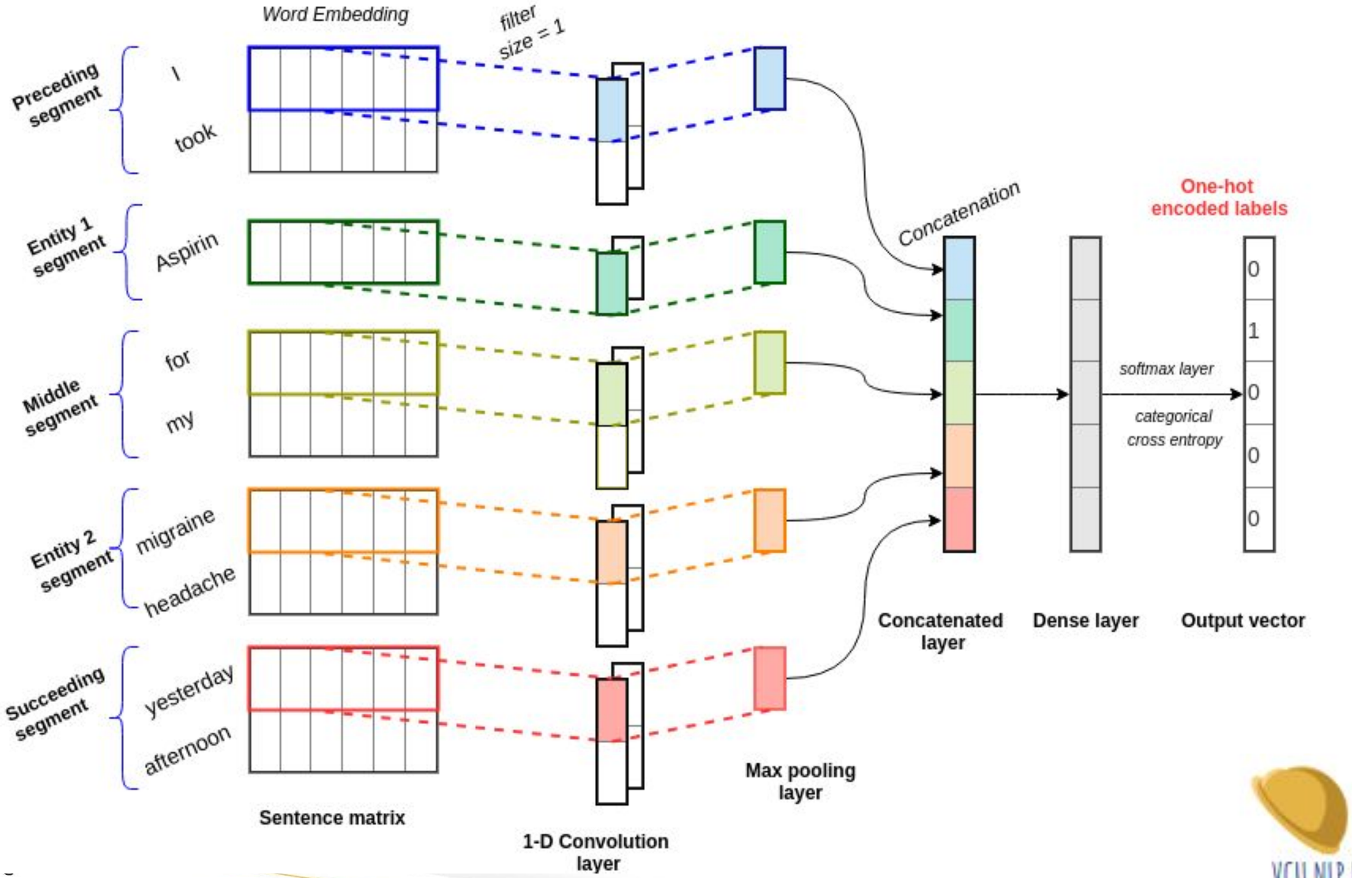
Concept 1 segment

Middle segment

Concept 2 segment

Succeeding segment

Segment CNN

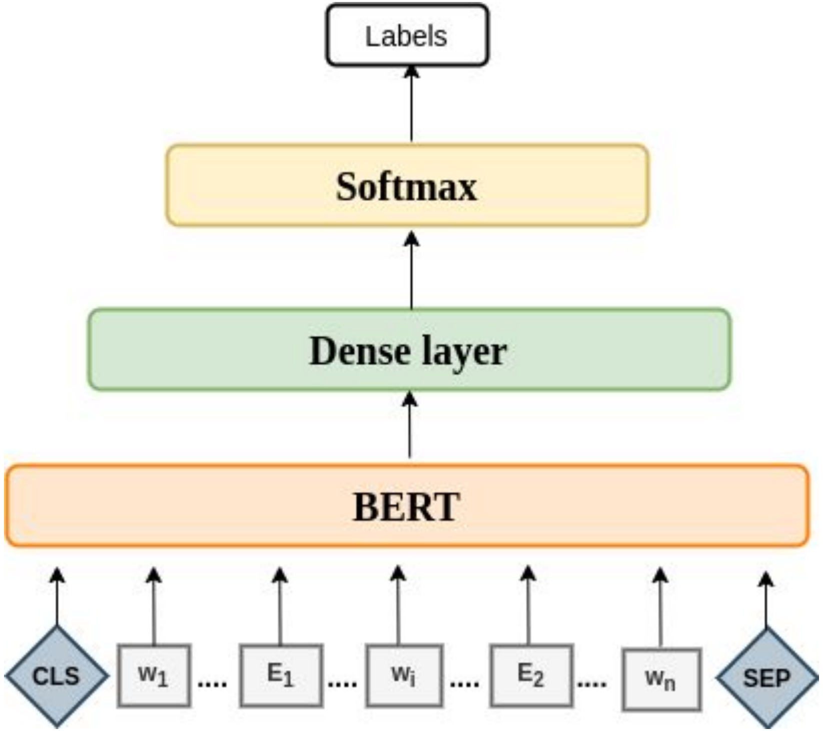

Word Embedding
filter size = 1
Preceding segment
I
took
Entity 1 segment
Aspirin
Middle segment
for
my
Entity 2 segment
migraine
headache
Succeeding segment
yesterday
afternoon
Sentence matrix
1-D Convolution layer
Max pooling layer
Concatenation
One-hot encoded labels
softmax layer
categorical cross entropy
0
1
0
0
0
Concatenated layer
Dense layer
Output vector

Bidirectional Encoder Representations from Transformers (BERT)

- Introduced by Google in 2018
- BERT embeddings - Context-based representation of a token is generated based on the surrounding words in the text.
- Pre-trained BERT models we used:
  - BERT (uncased)
  - BERT (cased)

    trained on English data: BookCorpus (800M words) & Wikipedia (2500Mwords)
  - BioBERT - *general BERT, trained over research articles from PubMed abstracts*
  - Clinical BERT - *BioBERT, further fine-tuned over MIMIC-III*

BERT-based approach



Evaluation criteria

- Precision (P) - Ratio between correctly predicted mentions over total set of predicted mentions for a specific entity
- Recall (R) - Ratio of correctly predicted mentions over actual number of mentions
- F-1 score (F) - Harmonic mean between precision and recall
- System performance is reported by,
  - Micro average - calculates metrics globally by counting total true positives, false negatives, and false positives

Results & Analysis

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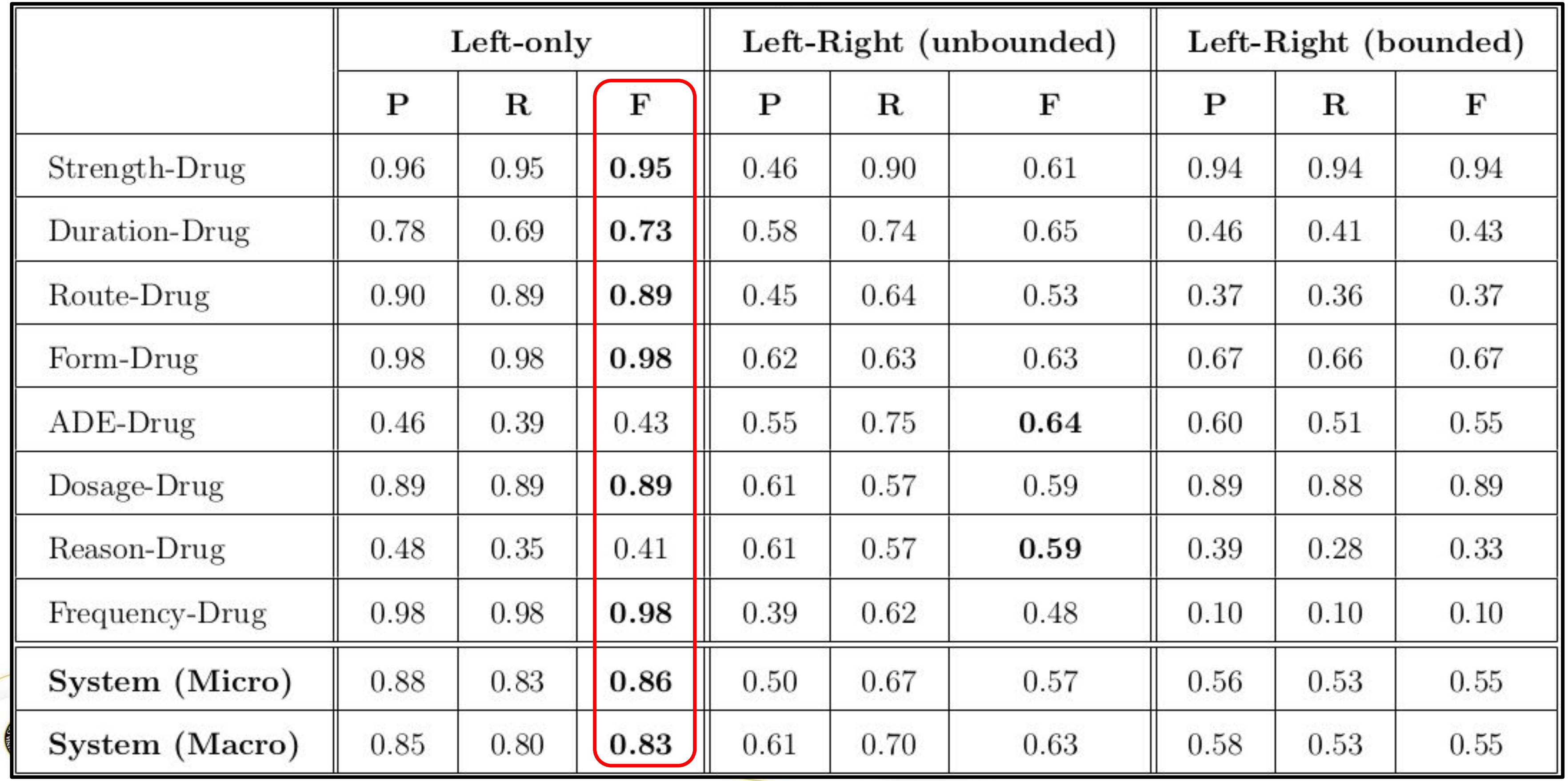
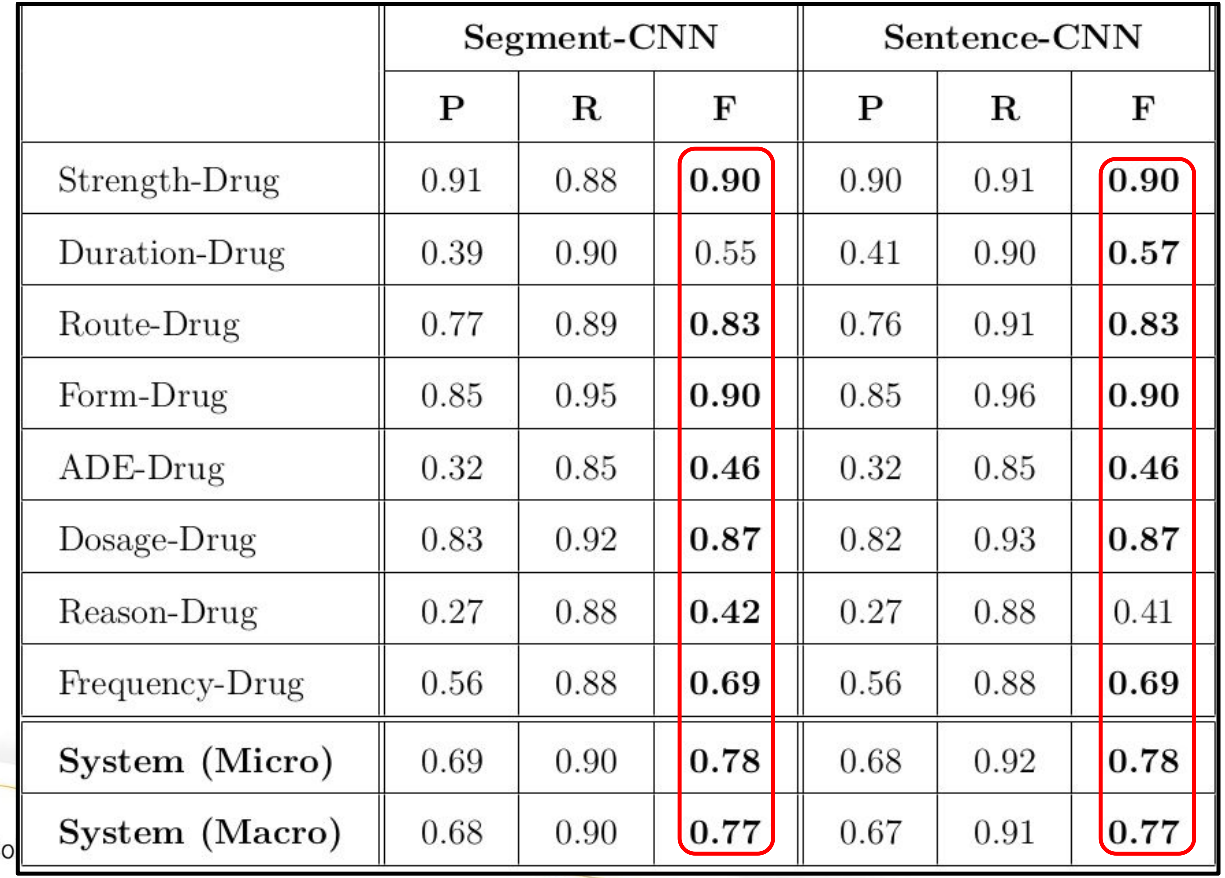
Results: Rule-based



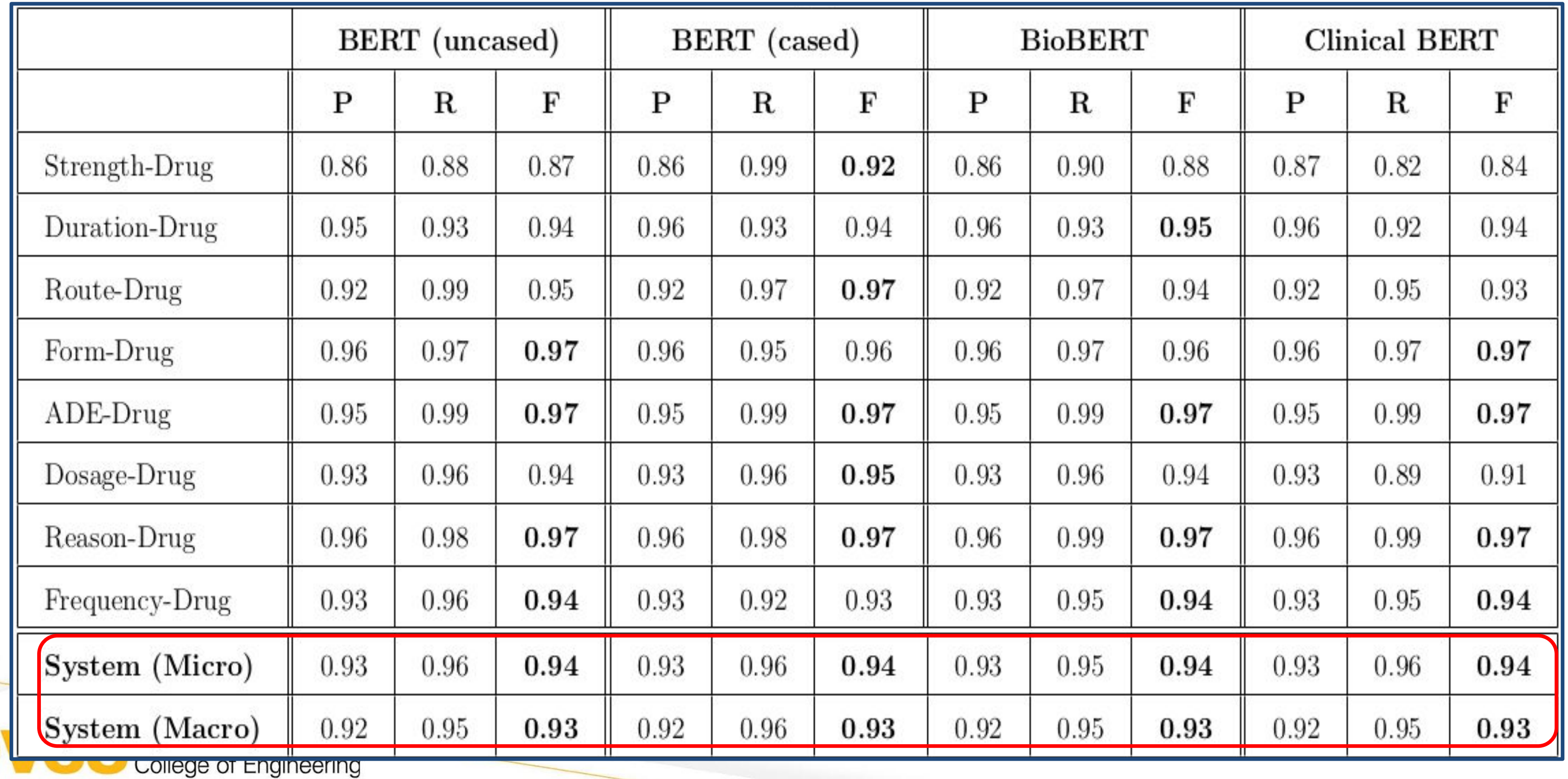
	Left-only			Left-Right (unbounded)			Left-Right (bounded)		
	P	**R**	**F**	**P**	**R**	**F**	**P**	**R**	**F**
Strength-Drug	0.96	0.95	**0.95**	0.46	0.90	0.61	0.94	0.94	0.94
Duration-Drug	0.78	0.69	**0.73**	0.58	0.74	0.65	0.46	0.41	0.43
Route-Drug	0.90	0.89	**0.89**	0.45	0.64	0.53	0.37	0.36	0.37
Form-Drug	0.98	0.98	**0.98**	0.62	0.63	0.63	0.67	0.66	0.67
ADE-Drug	0.46	0.39	0.43	0.55	0.75	**0.64**	0.60	0.51	0.55
Dosage-Drug	0.89	0.89	**0.89**	0.61	0.57	0.59	0.89	0.88	0.89
Reason-Drug	0.48	0.35	0.41	0.61	0.57	**0.59**	0.39	0.28	0.33
Frequency-Drug	0.98	0.98	**0.98**	0.39	0.62	0.48	0.10	0.10	0.10
System (Micro)	0.88	0.83	**0.86**	0.50	0.67	0.57	0.56	0.53	0.55
System (Macro)	0.85	0.80	**0.83**	0.61	0.70	0.63	0.58	0.53	0.55

Results: Deep Learning-based



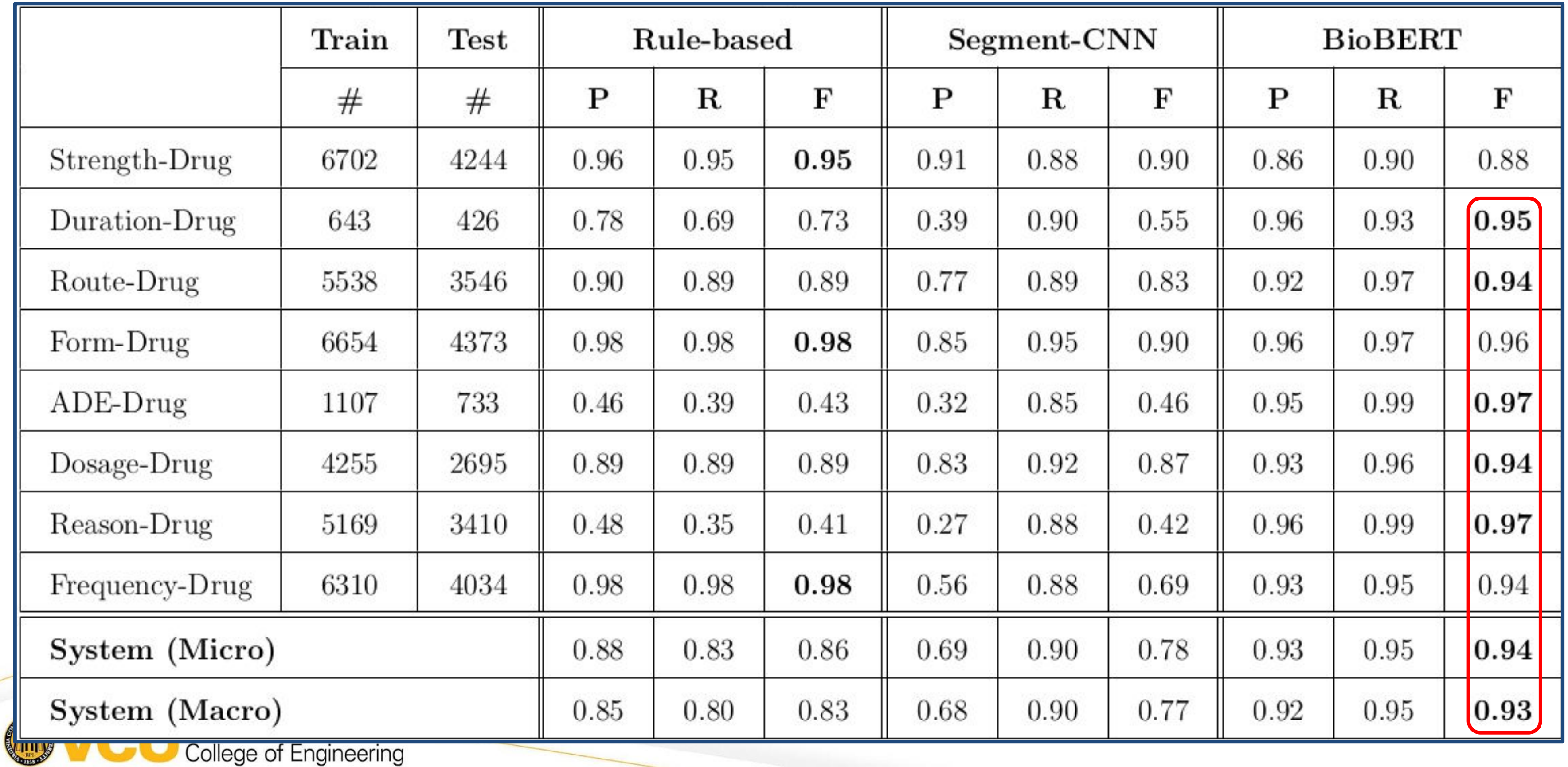
	Segment-CNN			Sentence-CNN		
	P	**R**	**F**	**P**	**R**	**F**
Strength-Drug	0.91	0.88	**0.90**	0.90	0.91	**0.90**
Duration-Drug	0.39	0.90	0.55	0.41	0.90	**0.57**
Route-Drug	0.77	0.89	**0.83**	0.76	0.91	**0.83**
Form-Drug	0.85	0.95	**0.90**	0.85	0.96	**0.90**
ADE-Drug	0.32	0.85	**0.46**	0.32	0.85	**0.46**
Dosage-Drug	0.83	0.92	**0.87**	0.82	0.93	**0.87**
Reason-Drug	0.27	0.88	**0.42**	0.27	0.88	0.41
Frequency-Drug	0.56	0.88	**0.69**	0.56	0.88	**0.69**
System (Micro)	0.69	0.90	**0.78**	0.68	0.92	**0.78**
System (Macro)	0.68	0.90	**0.77**	0.67	0.91	**0.77**

Results: BERT-based



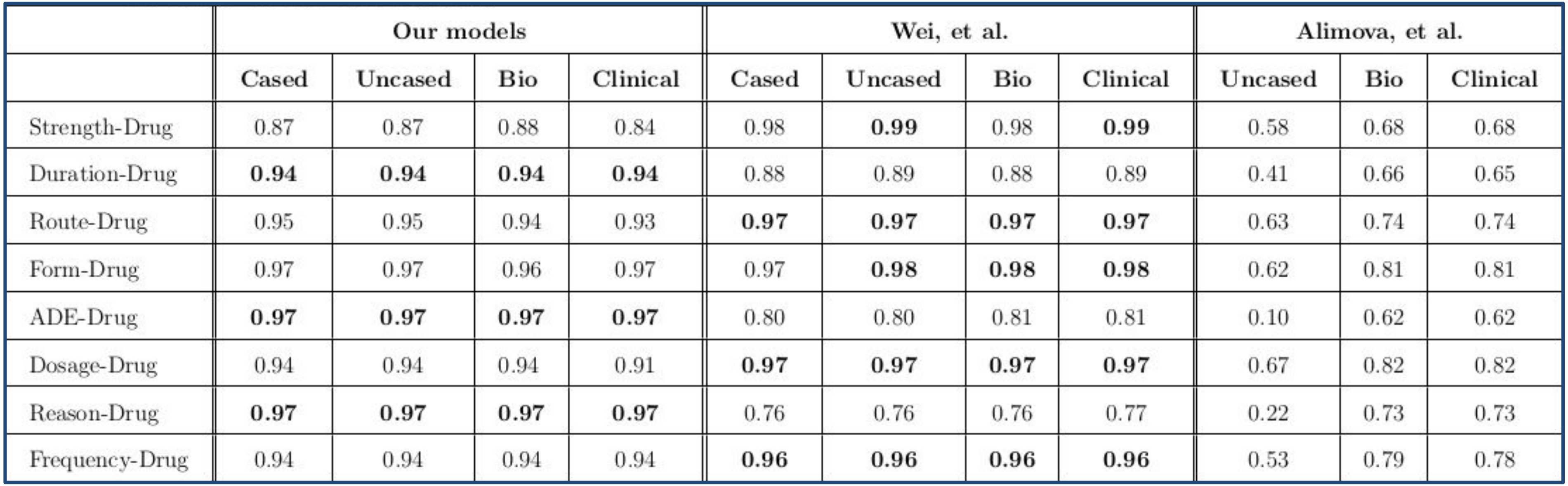
	BERT (uncased)			BERT (cased)			BioBERT			Clinical BERT		
	P	R	F	P	R	F	P	R	F	P	R	F
Strength-Drug	0.86	0.88	0.87	0.86	0.99	**0.92**	0.86	0.90	0.88	0.87	0.82	0.84
Duration-Drug	0.95	0.93	0.94	0.96	0.93	0.94	0.96	0.93	**0.95**	0.96	0.92	0.94
Route-Drug	0.92	0.99	0.95	0.92	0.97	**0.97**	0.92	0.97	0.94	0.92	0.95	0.93
Form-Drug	0.96	0.97	**0.97**	0.96	0.95	0.96	0.96	0.97	0.96	0.96	0.97	**0.97**
ADE-Drug	0.95	0.99	**0.97**	0.95	0.99	**0.97**	0.95	0.99	**0.97**	0.95	0.99	**0.97**
Dosage-Drug	0.93	0.96	0.94	0.93	0.96	**0.95**	0.93	0.96	0.94	0.93	0.89	0.91
Reason-Drug	0.96	0.98	**0.97**	0.96	0.98	**0.97**	0.96	0.99	**0.97**	0.96	0.99	**0.97**
Frequency-Drug	0.93	0.96	**0.94**	0.93	0.92	0.93	0.93	0.95	**0.94**	0.93	0.95	**0.94**
System (Micro)	0.93	0.96	**0.94**	0.93	0.96	**0.94**	0.93	0.95	**0.94**	0.93	0.96	**0.94**
System (Macro)	0.92	0.95	**0.93**	0.92	0.96	**0.93**	0.92	0.95	**0.93**	0.92	0.95	**0.93**

Results: Comparison across our approaches



	Train	Test	Rule-based			Segment-CNN			BioBERT		
	#	#	P	R	F	P	R	F	P	R	F
Strength-Drug	6702	4244	0.96	0.95	**0.95**	0.91	0.88	0.90	0.86	0.90	0.88
Duration-Drug	643	426	0.78	0.69	0.73	0.39	0.90	0.55	0.96	0.93	**0.95**
Route-Drug	5538	3546	0.90	0.89	0.89	0.77	0.89	0.83	0.92	0.97	**0.94**
Form-Drug	6654	4373	0.98	0.98	**0.98**	0.85	0.95	0.90	0.96	0.97	0.96
ADE-Drug	1107	733	0.46	0.39	0.43	0.32	0.85	0.46	0.95	0.99	**0.97**
Dosage-Drug	4255	2695	0.89	0.89	0.89	0.83	0.92	0.87	0.93	0.96	**0.94**
Reason-Drug	5169	3410	0.48	0.35	0.41	0.27	0.88	0.42	0.96	0.99	**0.97**
Frequency-Drug	6310	4034	0.98	0.98	**0.98**	0.56	0.88	0.69	0.93	0.95	0.94
System (Micro)			0.88	0.83	0.86	0.69	0.90	0.78	0.93	0.95	**0.94**
System (Macro)			0.85	0.80	0.83	0.68	0.90	0.77	0.92	0.95	**0.93**

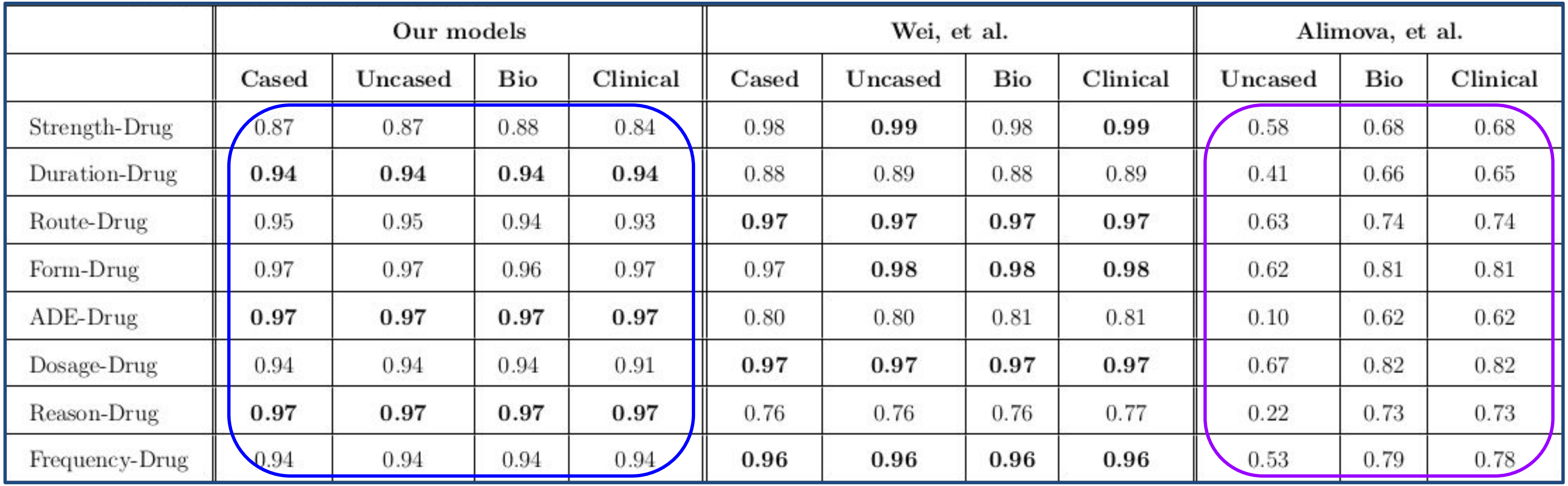
Results: Comparison with state-of-art



	Our models				Wei, et al.				Alimova, et al.		
	Cased	Uncased	Bio	Clinical	Cased	Uncased	Bio	Clinical	Uncased	Bio	Clinical
Strength-Drug	0.87	0.87	0.88	0.84	0.98	**0.99**	0.98	**0.99**	0.58	0.68	0.68
Duration-Drug	**0.94**	**0.94**	**0.94**	**0.94**	0.88	0.89	0.88	0.89	0.41	0.66	0.65
Route-Drug	0.95	0.95	0.94	0.93	**0.97**	**0.97**	**0.97**	**0.97**	0.63	0.74	0.74
Form-Drug	0.97	0.97	0.96	0.97	0.97	**0.98**	**0.98**	**0.98**	0.62	0.81	0.81
ADE-Drug	**0.97**	**0.97**	**0.97**	**0.97**	0.80	0.80	0.81	0.81	0.10	0.62	0.62
Dosage-Drug	0.94	0.94	0.94	0.91	**0.97**	**0.97**	**0.97**	**0.97**	0.67	0.82	0.82
Reason-Drug	**0.97**	**0.97**	**0.97**	**0.97**	0.76	0.76	0.76	0.77	0.22	0.73	0.73
Frequency-Drug	0.94	0.94	0.94	0.94	**0.96**	**0.96**	**0.96**	**0.96**	0.53	0.79	0.78

Wei, et al. - Relation Extraction from Clinical Narratives Using Pre-trained Language Models
Alimova, et al. - Multiple features for clinical relation extraction: A machine learning approach

Results: Comparison with state-of-art



	Our models				Wei, et al.				Alimova, et al.		
	Cased	Uncased	Bio	Clinical	Cased	Uncased	Bio	Clinical	Uncased	Bio	Clinical
Strength-Drug	0.87	0.87	0.88	0.84	0.98	**0.99**	0.98	**0.99**	0.58	0.68	0.68
Duration-Drug	**0.94**	**0.94**	**0.94**	**0.94**	0.88	0.89	0.88	0.89	0.41	0.66	0.65
Route-Drug	0.95	0.95	0.94	0.93	**0.97**	**0.97**	**0.97**	**0.97**	0.63	0.74	0.74
Form-Drug	0.97	0.97	0.96	0.97	0.97	**0.98**	**0.98**	**0.98**	0.62	0.81	0.81
ADE-Drug	**0.97**	**0.97**	**0.97**	**0.97**	0.80	0.80	0.81	0.81	0.10	0.62	0.62
Dosage-Drug	0.94	0.94	0.94	0.91	**0.97**	**0.97**	**0.97**	**0.97**	0.67	0.82	0.82
Reason-Drug	**0.97**	**0.97**	**0.97**	**0.97**	0.76	0.76	0.76	0.77	0.22	0.73	0.73
Frequency-Drug	0.94	0.94	0.94	0.94	**0.96**	**0.96**	**0.96**	**0.96**	0.53	0.79	0.78

Wei, et al. - Relation Extraction from Clinical Narratives Using Pre-trained Language Models
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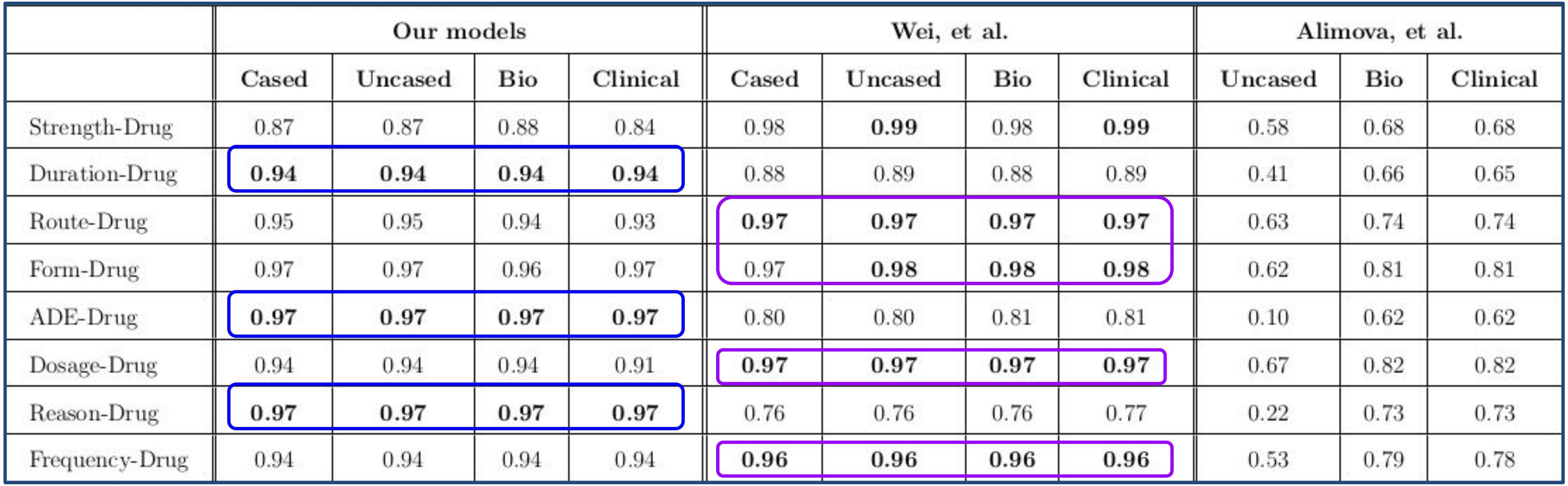
Results: Comparison with state-of-art



	Our models				Wei, et al.				Alimova, et al.		
	Cased	Uncased	Bio	Clinical	Cased	Uncased	Bio	Clinical	Uncased	Bio	Clinical
Strength-Drug	0.87	0.87	0.88	0.84	0.98	**0.99**	0.98	**0.99**	0.58	0.68	0.68
Duration-Drug	**0.94**	**0.94**	**0.94**	**0.94**	0.88	0.89	0.88	0.89	0.41	0.66	0.65
Route-Drug	0.95	0.95	0.94	0.93	**0.97**	**0.97**	**0.97**	**0.97**	0.63	0.74	0.74
Form-Drug	0.97	0.97	0.96	0.97	0.97	**0.98**	**0.98**	**0.98**	0.62	0.81	0.81
ADE-Drug	**0.97**	**0.97**	**0.97**	**0.97**	0.80	0.80	0.81	0.81	0.10	0.62	0.62
Dosage-Drug	0.94	0.94	0.94	0.91	**0.97**	**0.97**	**0.97**	**0.97**	0.67	0.82	0.82
Reason-Drug	**0.97**	**0.97**	**0.97**	**0.97**	0.76	0.76	0.76	0.77	0.22	0.73	0.73
Frequency-Drug	0.94	0.94	0.94	0.94	**0.96**	**0.96**	**0.96**	**0.96**	0.53	0.79	0.78

Wei, et al. - Relation Extraction from Clinical Narratives Using Pre-trained Language Models
Alimova, et al. - Multiple features for clinical relation extraction: A machine learning approach

Conclusions

1. Explored a rule-based, deep learning-based, and contextualized language model-based approaches for ADE extraction.
2. BERT-based approach outperformed other models overall and obtained state-of-the-art performance
3. However, co-location information is sufficient to identify many relations -
   a. Rule-based approach obtained a higher Precision and Recall for certain relations, for e.g. Strength-Drug, Form-Drug, Frequency-Drug (order of entities play a vital role)

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Feature Representation

Word2Vec

- Trained over MIMIC - III (Medical Information Mart for Intensive Care)
  - Experimented: 200d, 300d, 400d
- Performed well with *Segment - CNN*

GloVe

- Trained over Wikipedia (2014) and Gigaword 5
  - Experimented: 100d, 200d, 300d
- Performed well with *Sentence - CNN*

Results - Analysis

- Ambiguity between the terms ADE and Reason reduces the overall performance
- Performance is low for Drug-ADE (mostly) and Drug - Reason is the ambiguity between the terms
- Most ADE relations are categorized as Drug - Reason relations
- Experiment - Convert ADE and Reason labels to a common term (Symptom) to increase the overall performance

hyper parameter tuning

dataset	relation types	Sentence CNN (Single label)	Sentence CNN (Multi label)	Segment CNN
i2b2 - 2010	Pr-Tr	Glove 200d	Glove 300d	MIMIC 200d
	Pr-Te	Glove 200d	Glove 300d	MIMIC 200d
	Pr-Pr	MIMIC 200d	Glove 300d	MIMIC 300d
n2c2 - 2018	All	Glove 200d	Glove 200d	MIMIC 200d

* *binary classification*

() no of classes

Overall Conclusions

- Rule-based approach is applicable for relations with consistent positional information
- Deep learning-based approaches are applicable for labeled data with many training instances
- BERT-based approaches utilize contextualized word embeddings and they perform better than approaches that use non-contextualized word embeddings

t-test & p values

dataset	relation types	t-test	p value	Statistically significant
i2b2 - 2010	Pr-Tr	1.57	0.15	no
	Pr-Te	-2.97	0.02	yes
n2c2 - 2018	All	-95.22	1.65 e-13	yes

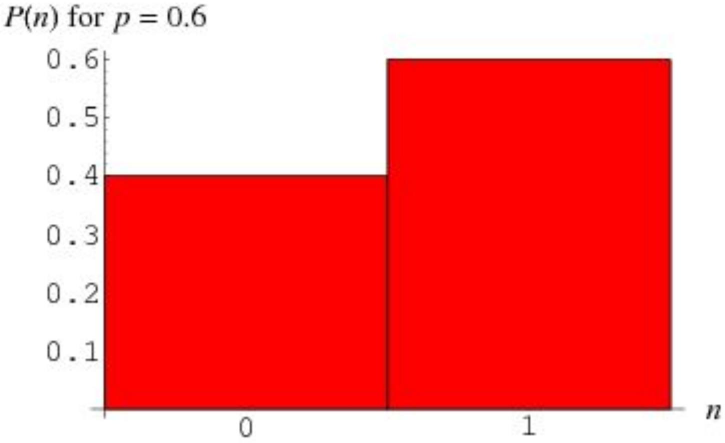
* *binary classification*
() no of classes

Experimental details

- Keras 2.3
- Spacy 2.1.3
- Hyper parameters that are tuned:
  - word embeddings (MIMIC III, GloVe)
  - embedding dimensions(100d, 200d, 300d, 400d)
  - sliding window (2, 3, 5)
  - optimizers (Adam, RMSProp)
  - loss (categorical cross entropy, binary cross entropy)

Bernoulli distribution

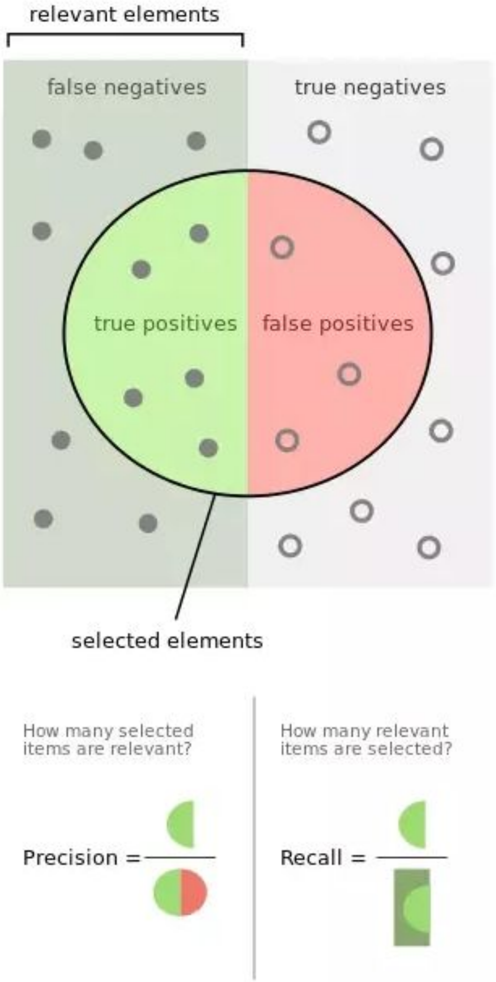
The Bernoulli distribution is a discrete distribution having two possible outcomes labelled by and in which ("success") occurs with probability and ("failure") occurs with probability , where . It therefore has probability density function. (1)



Precision and Recall

$$\text{Precision} = \frac{True\ Positive}{True\ Positive + False\ Positive}$$

$$\text{Recall} = \frac{True\ Positive}{True\ Positive + False\ Negative}$$



Softmax

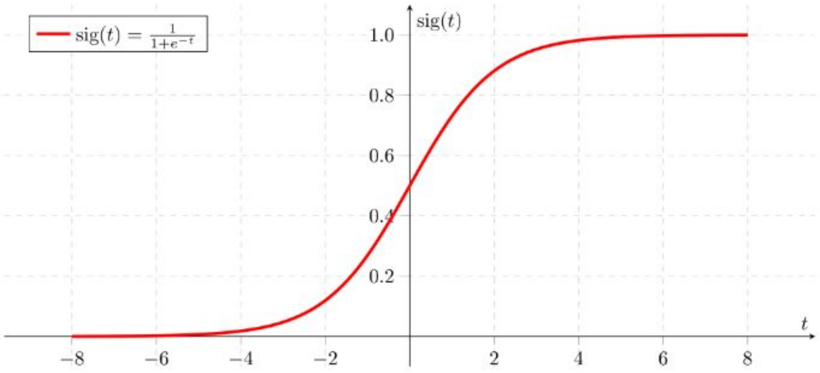
- Softmax calculates the probabilities distribution of the event over ‘n’ different events. (will calculate the probabilities of each target class over all possible target classes).

- Output probabilities range will be 0 to 1, and the sum of all the probabilities will be equal to one.

- If the softmax function used for multi-classification model it returns the probabilities of each class and the target class will have the high probability.

Sigmoid

- Sigmoid function take any range real number and returns the output value which falls in the range of 0 to 1
- When we’re building a classifier for a problem with more than one right answer, we apply a sigmoid function to each element of the raw output independently
- Unlike softmax which gives a probability distribution around n classes, sigmoid functions allow for independent probabilities.

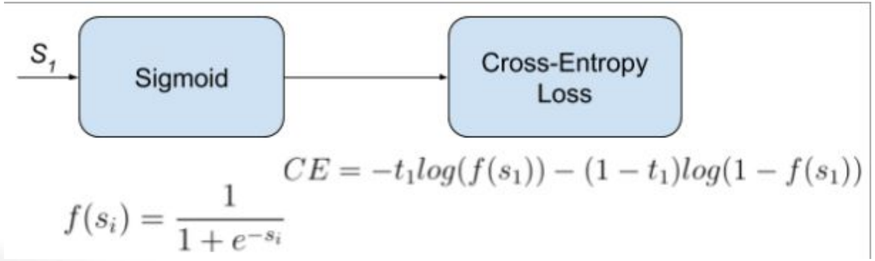


Binary Cross-Entropy Loss

It is a Sigmoid activation plus a Cross-Entropy loss.

Unlike Softmax loss it is independent for each vector component (class), i.e. the loss computed for every CNN output vector component is not affected by other component values.

That’s why it is used for multi-label classification

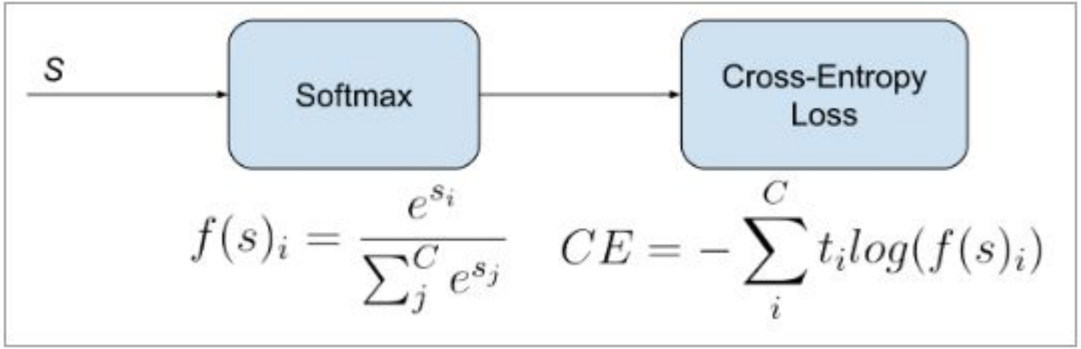


$$CE = -t_1 log(f(s_1)) - (1 - t_1) log(1 - f(s_1))$$

$$f(s_i) = \frac{1}{1 + e^{-s_i}}$$

Categorical Cross-Entropy Loss

- It is a Softmax activation plus a Cross-Entropy loss.
- If we use this loss, we will train a CNN to output a probability over the n classes for each image.
- It is used for multi-class classification.



$$f(s)_i = \frac{e^{s_i}}{\sum_j^C e^{s_j}} \qquad CE = -\sum_i^C t_i log(f(s)_i)$$