Biomedical Named Entity Recognition and Information Extraction with PubTator

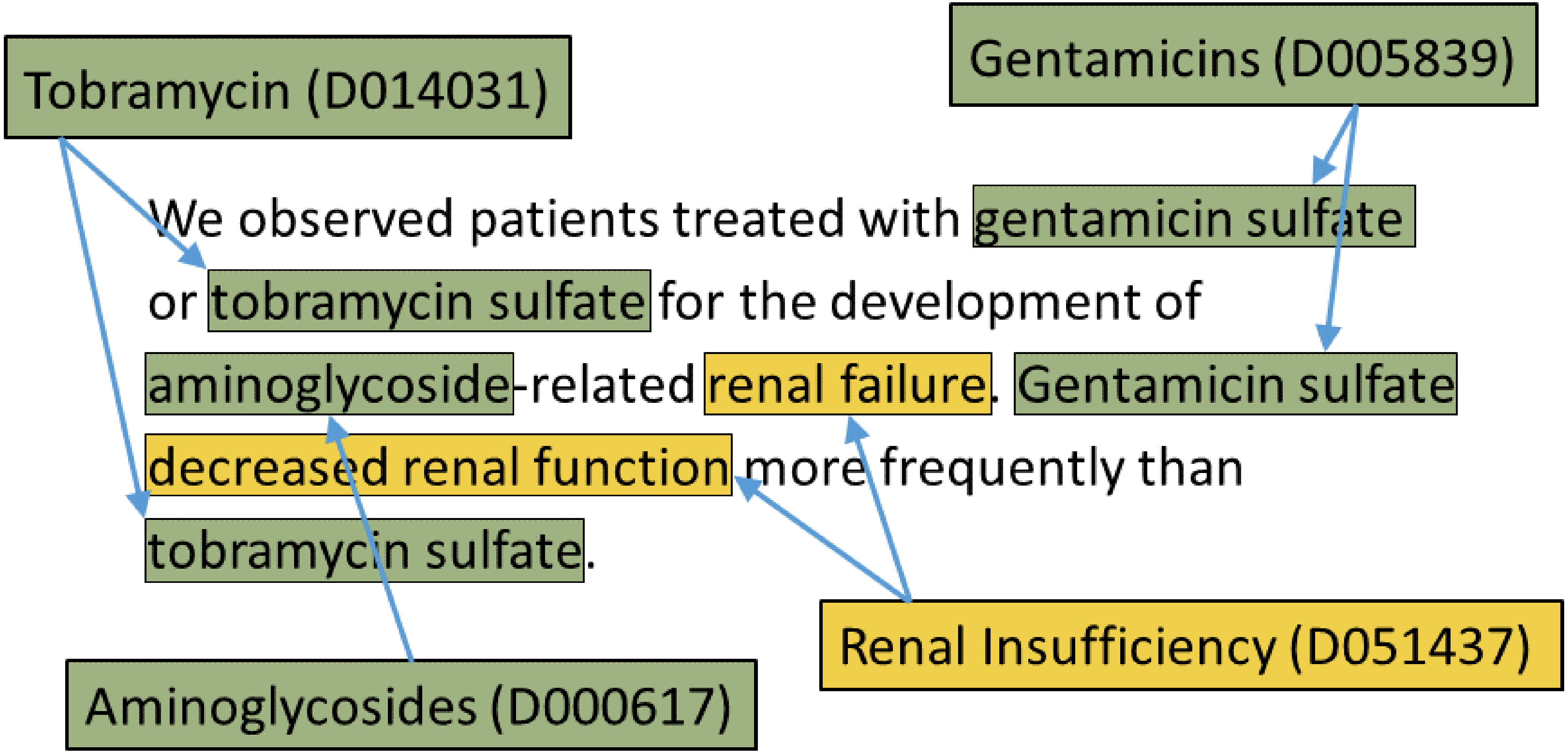
Robert Leaman & Shankai Yan

May 10, 2019

U.S. National Library of Medicine

NCBI

Named Entities: Recognition and Normalization



Challenge: name variation

Pattern	Disease Examples
Neoclassical	Nephropathy
Eponyms	Schwartz-Jampel syndrome
Anatomy	breast cancer
Symptoms	cat-eye syndrome
Causative agent	staph infection
Biomolecular etiology	G6PD deficiency
Heredity	X-linked agammaglobulinemia
Traditional	pica, founder

Pattern	Gene Examples
Phenotype appearance	White swiss cheese
Function	Heat shock protein 60 Calmodulin suppressor of p53
Pop culture	Sonic hedgehog I'm Not Dead Yet ken and barbie
Creative	Cheap date

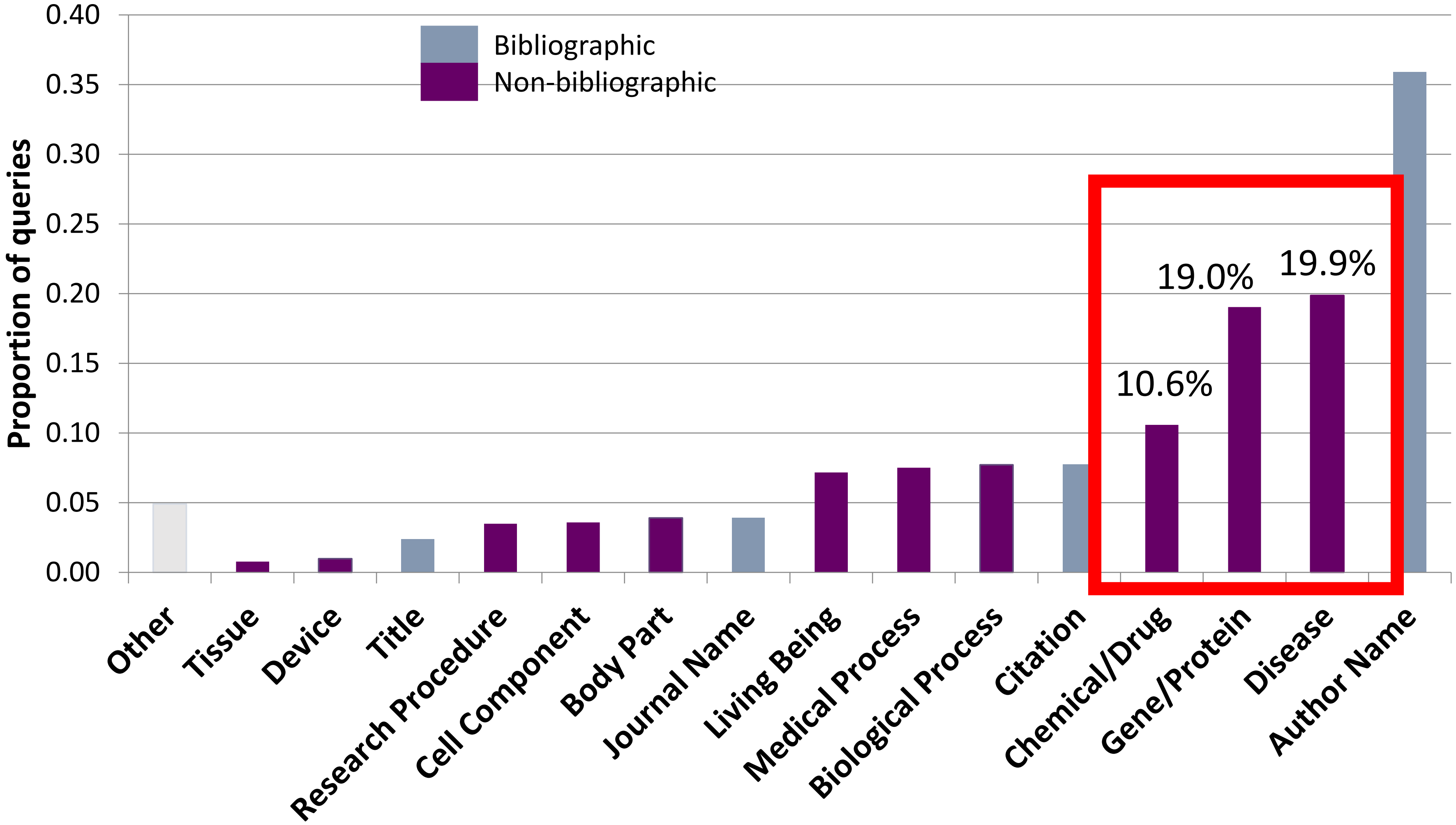
Challenge: phrase variation

Mention Text	Concept name (MeSH/OMIM ID)
bipolar affective disorder	Bipolar disorder (D001714)
immunodeficiency disease	Immunological deficiency syndrome (D007153)
colon carcinoma	Colon cancer (D003110)
anaemia	Anemia (D000740)
pharungitis [sic]	Pharyngitis (D10612)
oral cleft	Cleft lip (D002971)
asthmatic	Asthma (D001249)
absence of functional C7	C7 deficiency (OMIM:610102)
widening of the vestibular aqueduct	Dilated vestibular aqueduct (OMIM:600791)

Challenge: ambiguity

Mention Text	Analysis
THE	English article or gene name?
White	Color or gene name?
founder	Horse disease or creator?
HD	HD gene or Huntington Disease?
P50	Human: NFKB1, CD40, or ARHGEF7?
kaliotoxin	Polypeptide: protein or chemical?
Zinc finger protein	Not anatomy, maybe not zinc
Acute Coronary Syndrome	“Acute” part of name, not modifier

Most searched topics in PubMed



Neveol, Dogan, Lu, Semi-automatic semantic annotation of PubMed queries:
A study on quality, efficiency, satisfaction, *Journal of Biomedical Informatics*, 2010

Key entity types

Disease	• diabetes mellitus; DM; type 2 diabetes
Genomic variation	• c.77A>C; c.77A->C; A77C; AC
Gene/Protein	• TP53; tumor protein p53; p53; BCC7; LFS1
Species	• Arabidopsis thaliana; thale-cress; AT
Chemical/Drug	• Aspirin; 2-(Acetyloxy)benzoic Acid; Acetysal
Cell line	• HEK293; 293 cells; human embryonic kidney 293

Our NER tools

Disease	• TaggerOne: 83.70%
Genomic variation	• tmVar 2.0: 86.24%
Gene/Protein	• GNormPlus: 86.70%
Species	• SR4GN 86.00%
Chemical/Drug	• TaggerOne: 89.50%
Cell line	• TaggerOne: 83.10%

- Freely available & open source
- High Performance
- Novel NLP techniques
- BioC format compatible for improved interoperability

All numbers are F1 scores

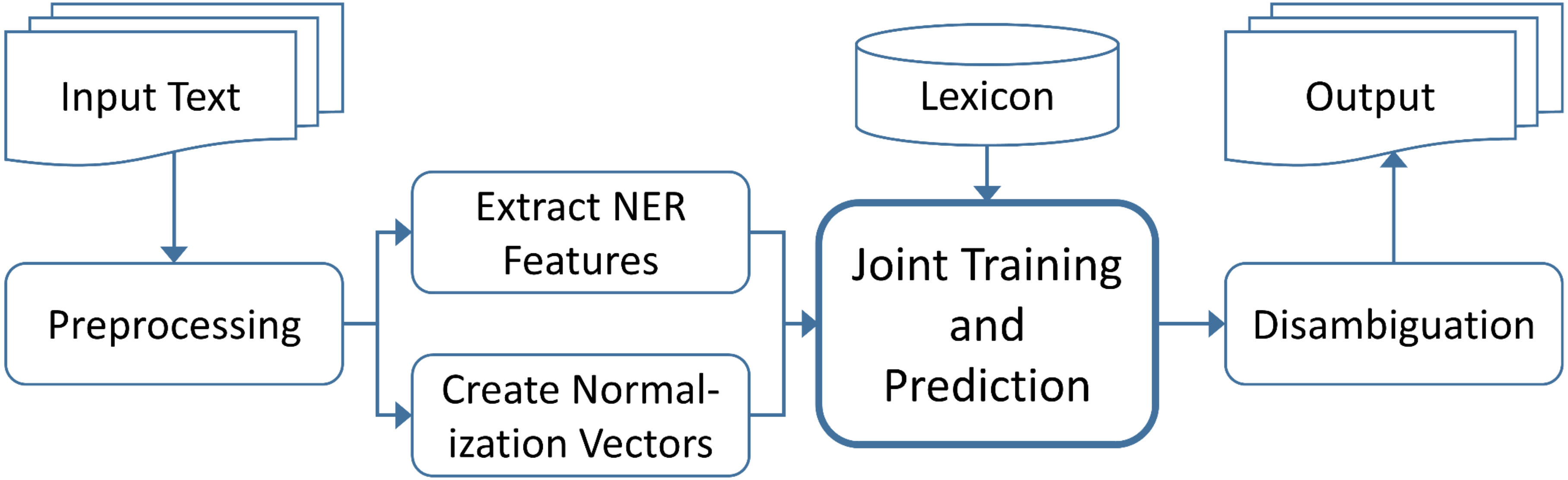
Fundamental methods

- Dictionary based
  - Straightforward, efficient
  - Difficult to find new entities or different variations
- Rule based
  - Can find new entities
  - Rules created manually
  - Adaptation requires system modification
- Machine learning based
  - Can find new entities
  - Learns from examples; needs training data
  - Adaptation requires new training data

Most systems are hybrids

TaggerOne: joint NER and normalization

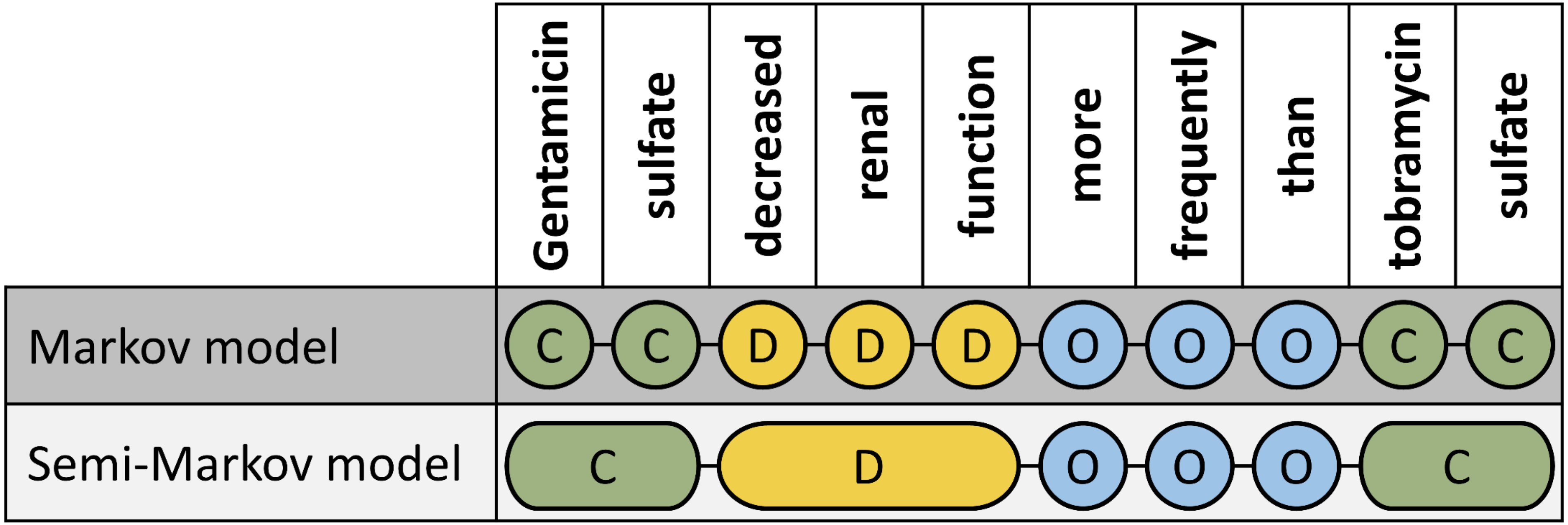
- Hypothesis: simultaneous normalization improves NER performance
- NER: rich feature approach
- Normalization score used as a feature in NER scoring



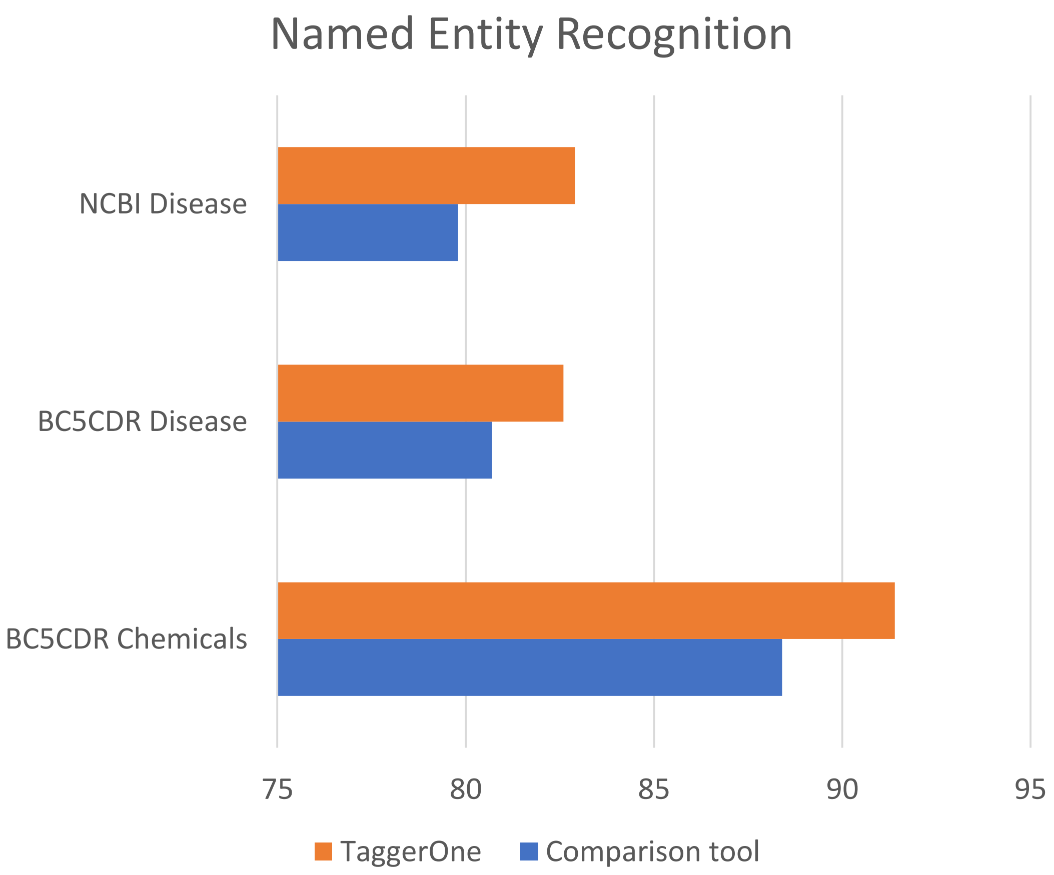
Leaman, Robert, and Zhiyong Lu. "TaggerOne: joint named entity recognition and normalization with semi-Markov Models." Bioinformatics 32.18 (2016): 2839-2846.

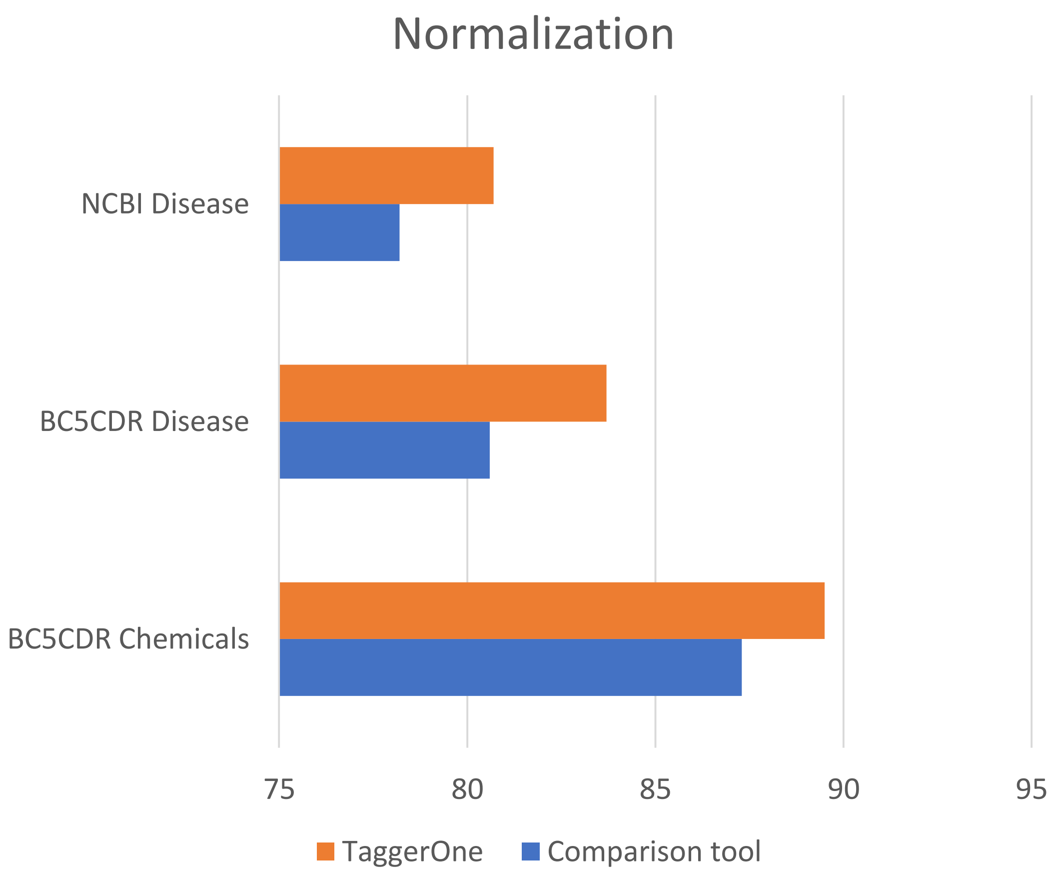
TaggerOne: joint NER and normalization

- Normalization: learns mapping from mention text to concept names



TaggerOne - results





Multiple resources enrich the lexicon

- Different organization, coverage & granularity
- Example: Hodgkin's Lymphoma
  - MeSH: 1 concept
  - OMIM: 3 concepts (inheritance)
  - UMLS: 7 (histopathology & demographics)
  - OrphaNet: 8 (histopathology)
  - Disease Ontology: 49 (histopathology & anatomical site)

Integrating lexical resources

- Method: use agreement between resources to learn the accuracy of each
- Model: predicted accuracy → expected pairwise agreements
- Training: observed agreement → updated accuracy prediction

Vocabulary added	NCBI Disease	BC5 CDR
+ Disease Ontology	+ 0.0%	+ 1.1%
+ MONDO	- 0.5%	+ 1.7%
+ PharmGKB	+ 1.8%	+ 2.3%
+ probable synonyms	+ 3.7%	+ 7.2%

PubTator

https://www.ncbi.nlm.nih.gov/research/pubtator/

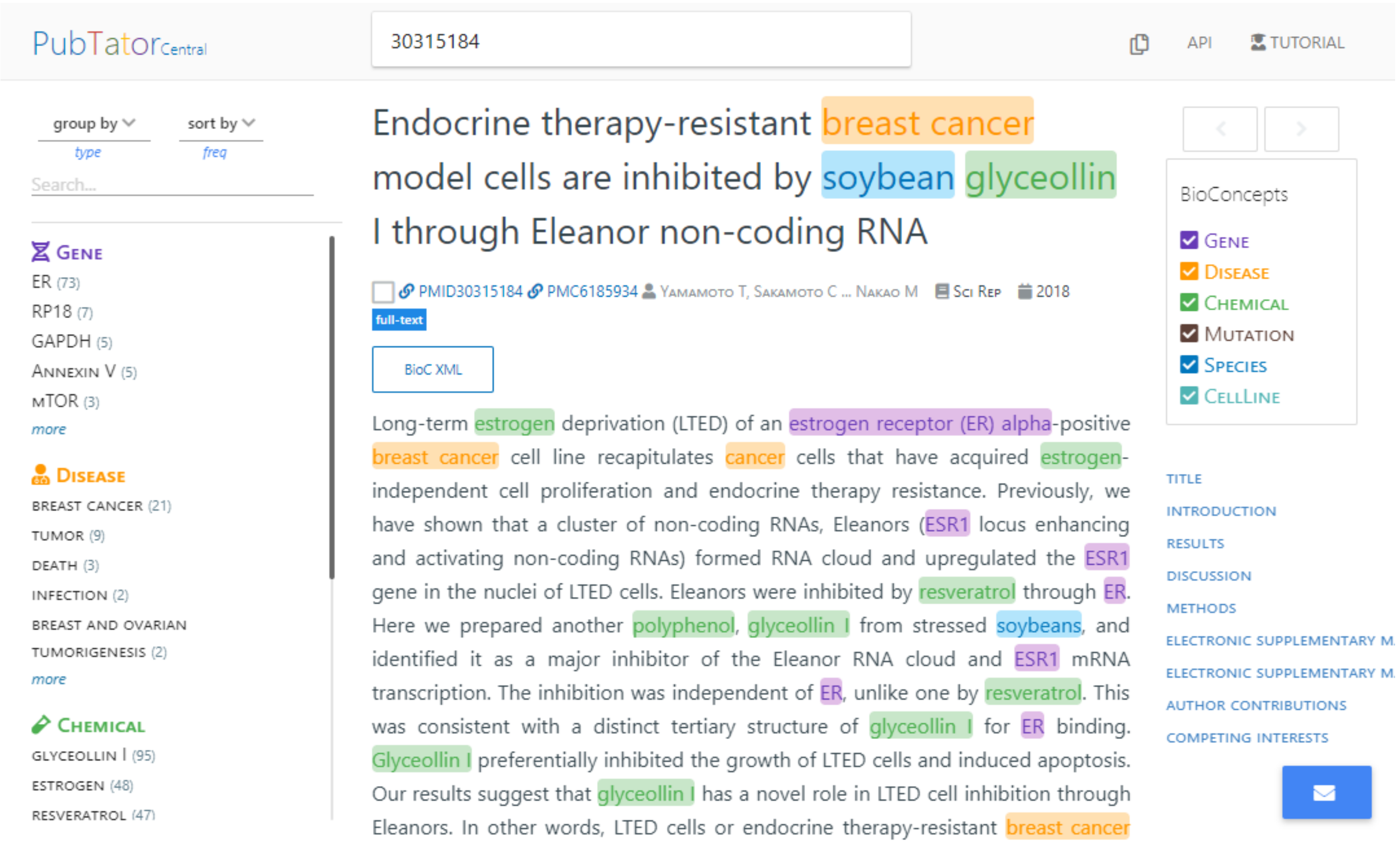
- Biomedical concept annotations
  - Genes/proteins, Genetic variants, Diseases, Chemicals, Species, Cell lines
  - New deep-learning based disambiguation
- PubMed abstracts & PMC Text Mining subset
  - Immediately available
  - Daily updates
- Web service: freely available, no installation

- Wei, Chih-Hsuan, Hung-Yu Kao, and Zhiyong Lu. "PubTator: a web-based text mining tool for assisting biocuration." Nucleic acids research 41.W1 (2013): W518-W522.
- Wei, C.H., Allot, A., Leaman, L. and Lu, Z. “PubTator Central: Automated Concept Annotation for Biomedical Full Text Articles" Nucleic Acids Research, *In press*.

PubTator

https://www.ncbi.nlm.nih.gov/research/pubtator/

- Online interface
  - Search
  - Visualize
  - Create collections
- RESTful service
- bulk FTP download



PubTator: RESTful API

[https://www.ncbi.nlm.nih.gov/research/pubtator-api/publications/export/**[Format]**?**[Type]**=**[Identifiers]**&concepts=**[Bioconcepts]**](https://www.ncbi.nlm.nih.gov/research/pubtator-api/publications/export/)

Formats:
- pubtator
- biocxml
- biocjson

List of PMIDs or PMCIDs:
- pmids=28483577
- pmcids=PMC6207735
- pmids=28483577,28483598

List of concept types:

gene, disease, chemical, species, mutation, cellline (optional)

28483577|t|Formoterol and fluticasone propionate combination improves histone deacetylation and anti-inflammatory activities in bronchial epithelial cells exposed to cigarette smoke.
28483577|a|The addition of long-acting beta2-agonists (LABAs) to corticosteroids improves asthma control. Cigarette smoke exposure, increasing oxidative stress, may negatively affect corticosteroid responses. The anti-inflammatory effects of formoterol (FO) and fluticasone propionate (FP) in human bronchial epithelial cells exposed to cigarette smoke extracts (CSE) are unknown. The present study provides compelling evidences that FP combined with FO may contribute to revert some processes related to steroid resistance induced by oxidative stress due to cigarette smoke exposure increasing the anti-inflammatory effects of FP.

28483577	921	926	HDAC3	Gene	8841
28483577	931	936	HDAC2	Gene	3066
28483577	1009	1013	IL-8	Gene	3576
28483577	1015	1020	TNF-a	Gene	7124
28483577	1022	1027	IL-1b	Gene	3553
28483577	1245	1250	HDAC3	Gene	8841
28483577	1264	1269	HDAC2	Gene	3066

Other tools

- MetaMap & MetaMap lite: identifies UMLS concepts

  Aronson, Alan R. "Effective mapping of biomedical text to the UMLS Metathesaurus: the MetaMap program." Proceedings of the AMIA Symposium. American Medical Informatics Association, 2001.

  Demner-Fushman, Dina, Willie J. Rogers, and Alan R. Aronson. "MetaMap Lite: an evaluation of a new Java implementation of MetaMap." Journal of the American Medical Informatics Association 24.4 (2017): 841-844.

- cTAKES: framework based on UIMA to build pipeline systems

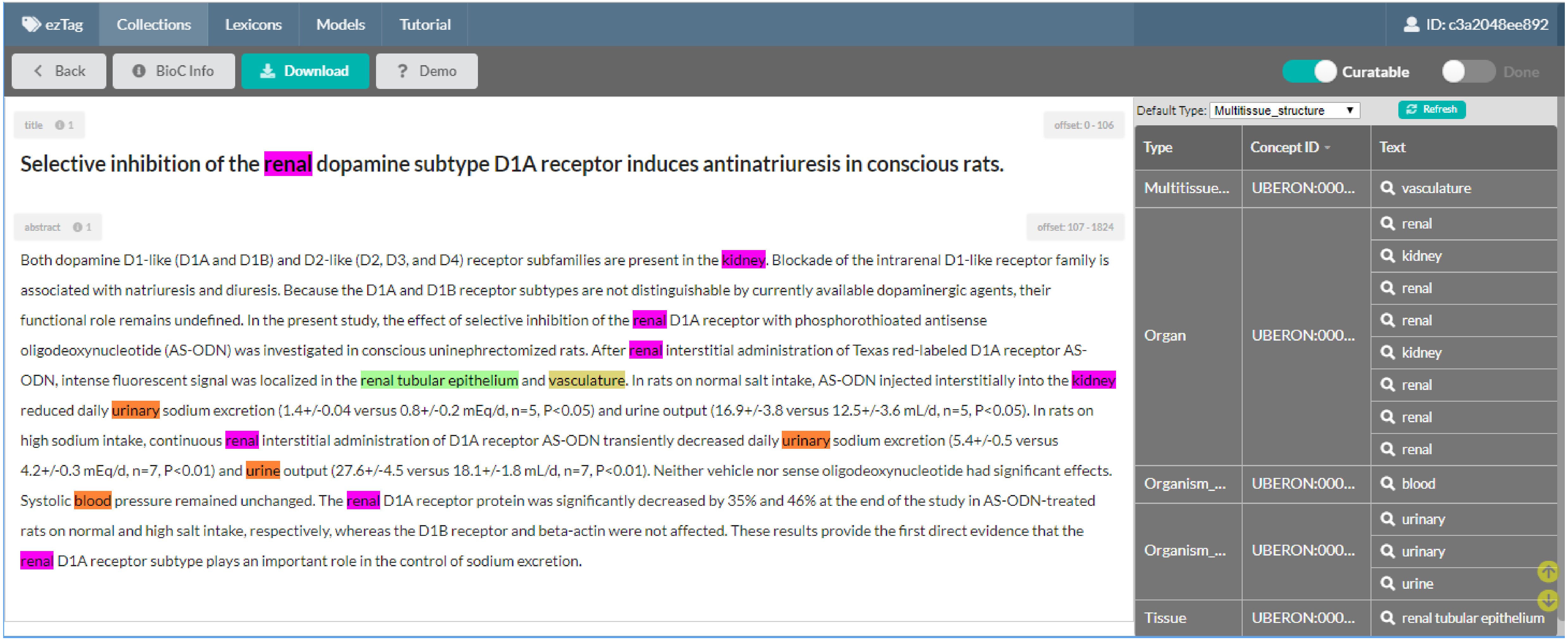
  Savova, Guergana K., et al. "Mayo clinical Text Analysis and Knowledge Extraction System (cTAKES): architecture, component evaluation and applications." Journal of the American Medical Informatics Association 17.5 (2010): 507-513.

- Web services: BeCAS and Thalia

  Nunes, Tiago, et al. "BeCAS: biomedical concept recognition services and visualization." Bioinformatics 29.15 (2013): 1915-1916.

  Soto, A.J., Przybyła, P. and Ananiadou, S. (2018) Thalia: Semantic search engine for biomedical abstracts. Bioinformatics, bty871

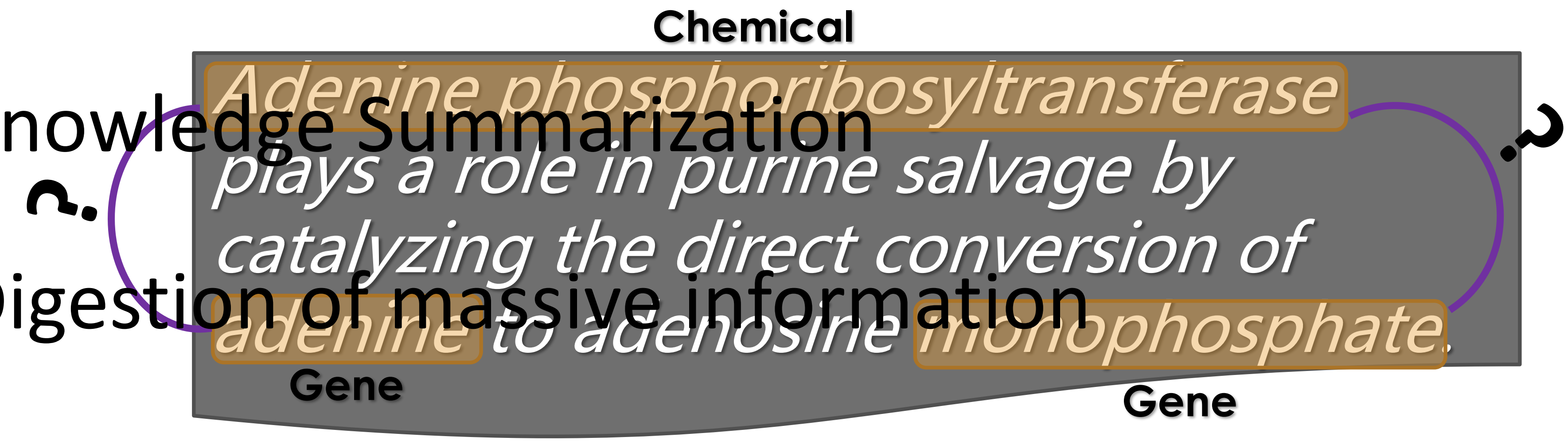
ezTag: interactive annotation https://eztag.biocrator.org/



Kwon, Dongseop, et al. "ezTag: tagging biomedical concepts via interactive learning." *Nucleic acids research* 46.W1 (2018): W523-W529.

What and why?

- Information Extraction after NER



- Knowledge Summarization
- Digestion of massive information
- Much less costly and less time-consuming

What kinds of information do we expect?

- Protein Interaction (e.g. signal transduction)
- Drug Interaction (e.g. side effect using aspirin and warfarin)
- Gene Disease Association (e.g. PARKx and Parkinson's Disease)
- Drug Gene Interaction (e.g. druggable genes)
- Genotype Phenotype Association

Which data resource do we use?

Biomedical Literature

PubMed PMC

Clinical Notes

MIMIC i2b2

Shared Tasks

BioCreative

DDIExtraction

BioNLP-ST

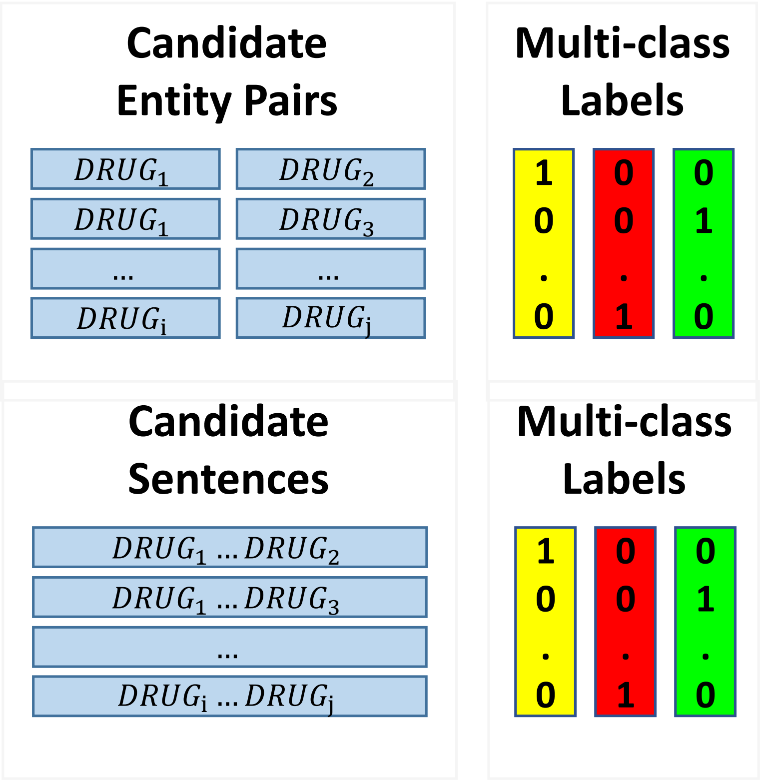
i2b2

Problems

- **Pair-wise entities classification**

Fenfluramine may increase slightly the effect of antihypertensive drugs, e.g., guanethidine, methyldopa, reserpine.

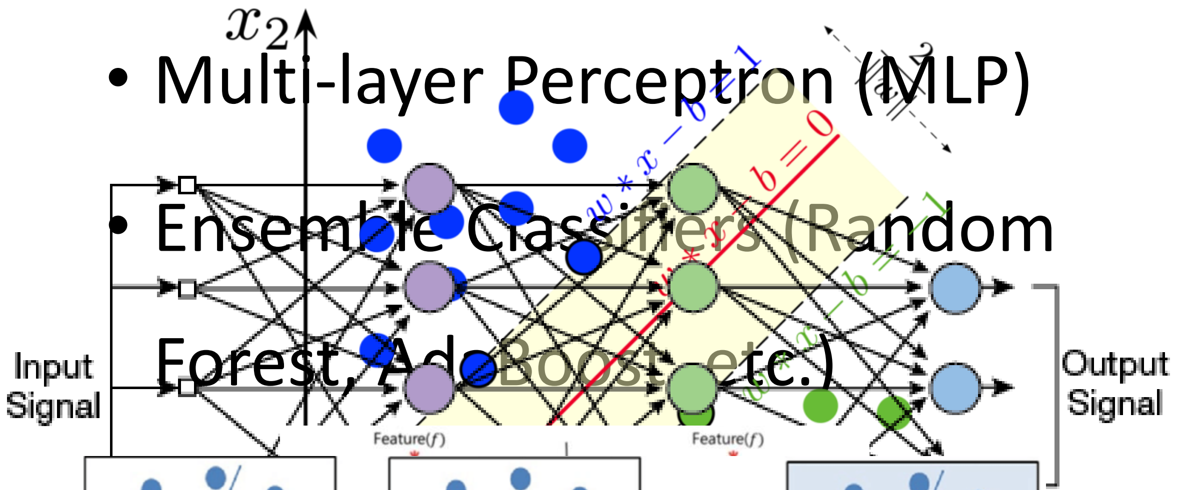
DRUG1 (Fenfluramine), **DRUG2** (antihypertensive drugs), **DRUG3** (guanethidine), **DRUG4** (methyldopa), **DRUG5** (reserpine)

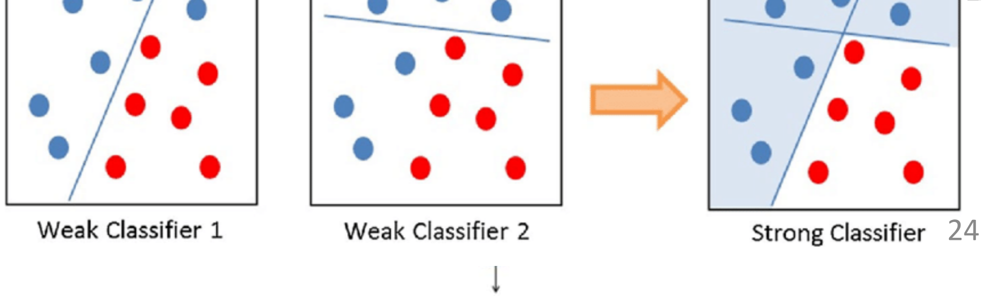


Traditional Machine Learning Methods

- Handcrafted Features
  - Tokens
  - Part-of-speech (NP, VVP, etc.)
  - Entity type
  - Grammatical function tag (SBJ,OBJ,ADV, etc.)
  - Distance in the parse tree

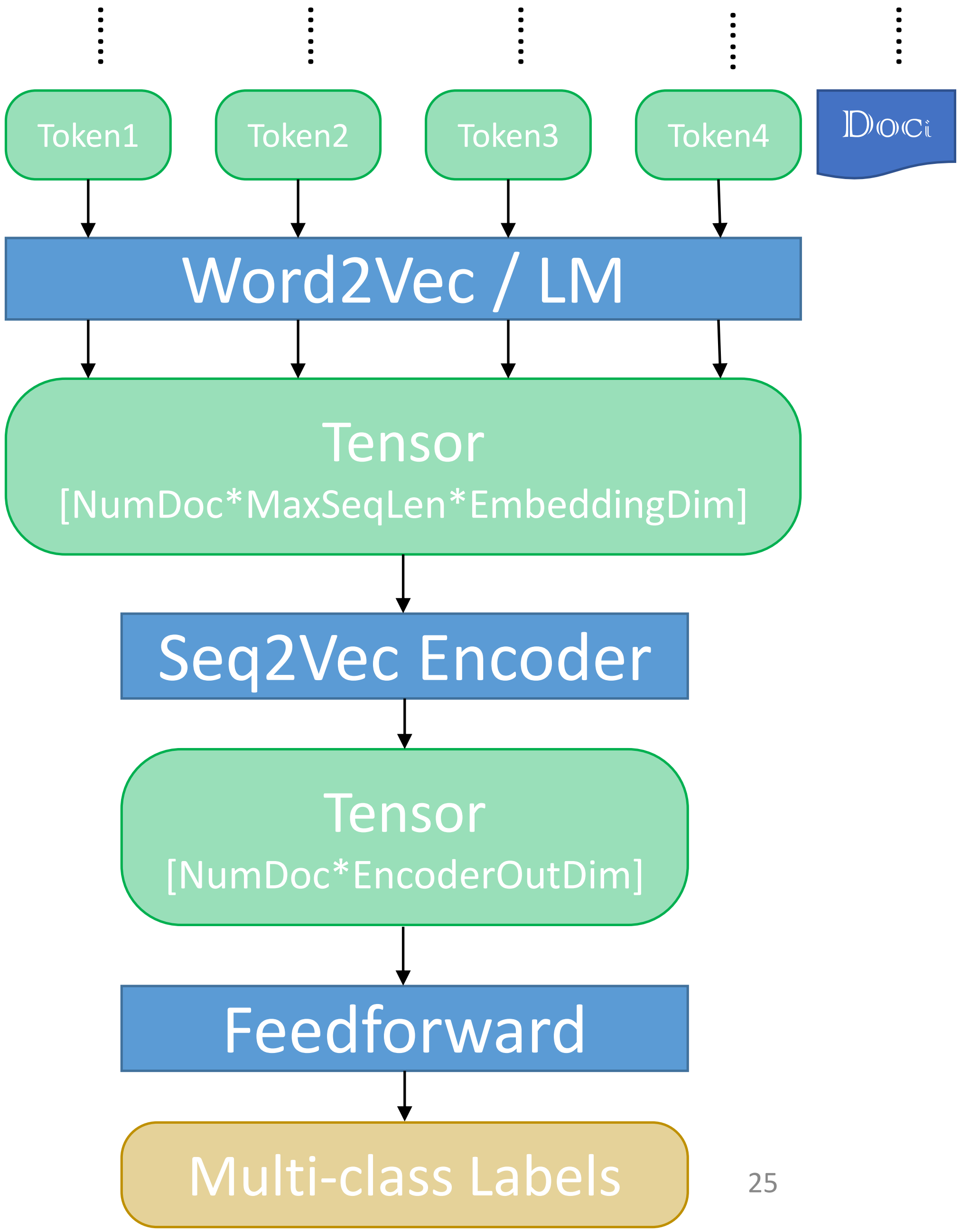
- Classical ML models
  - Support Vector Machine (SVM)
  - Multi-layer Perceptron (MLP)
  - Ensemble Classifiers (Random Forest, AdaBoost, etc.)





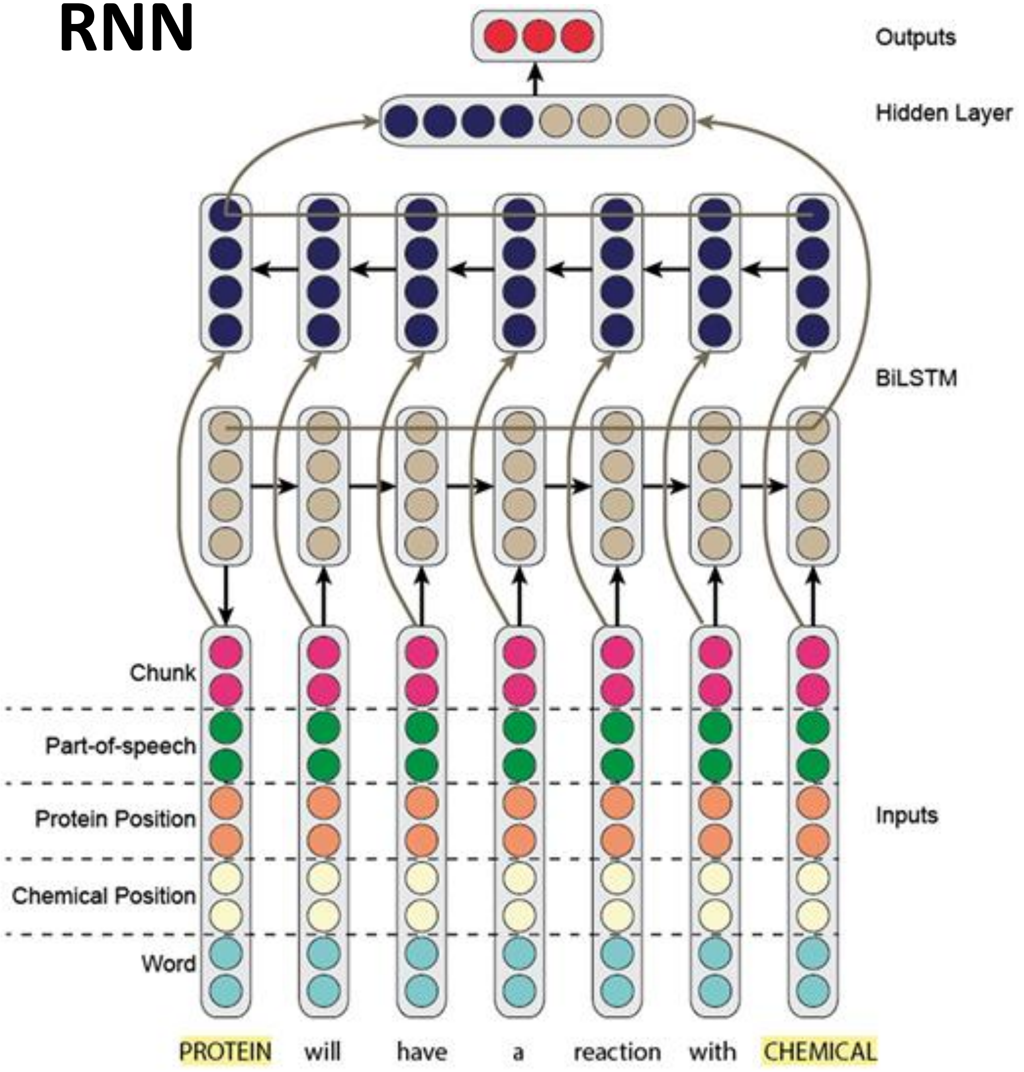
Deep Learning Methods

- Word Embedding (cbow,skipgram,fastText,glove) or Language Model (ELMo, GPT, BERT)
- Sequence to Vector Encoder
  - Bag of Embedding (average or sum)
  - RNN (e.g. LSTM, GRU)
  - CNN
- Classifier:
  - Feedforward Layer
  - Linear Layer

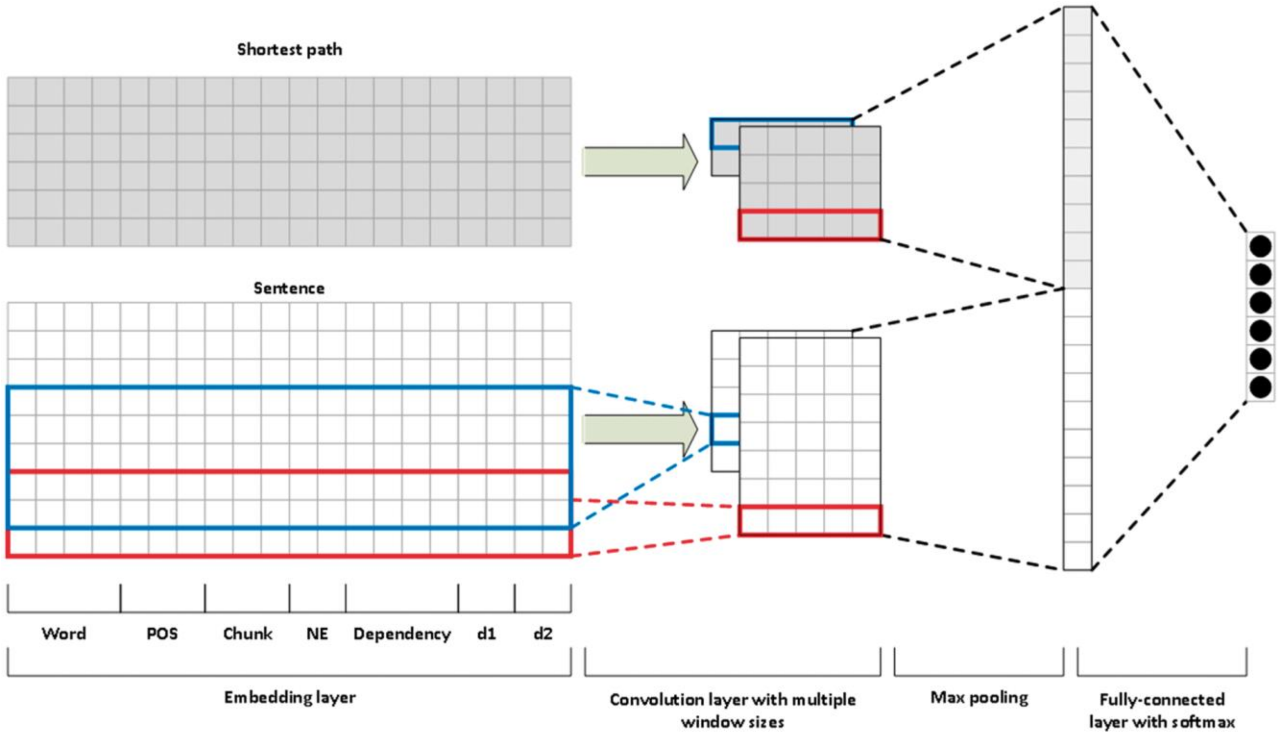


Example for Deep Learning

RNN



CNN



Peng, Yifan, et al. "Extracting chemical–protein relations with ensembles of SVM and deep learning models." *Database* 2018 (2018).

Traditional ML v.s. Deep Learning

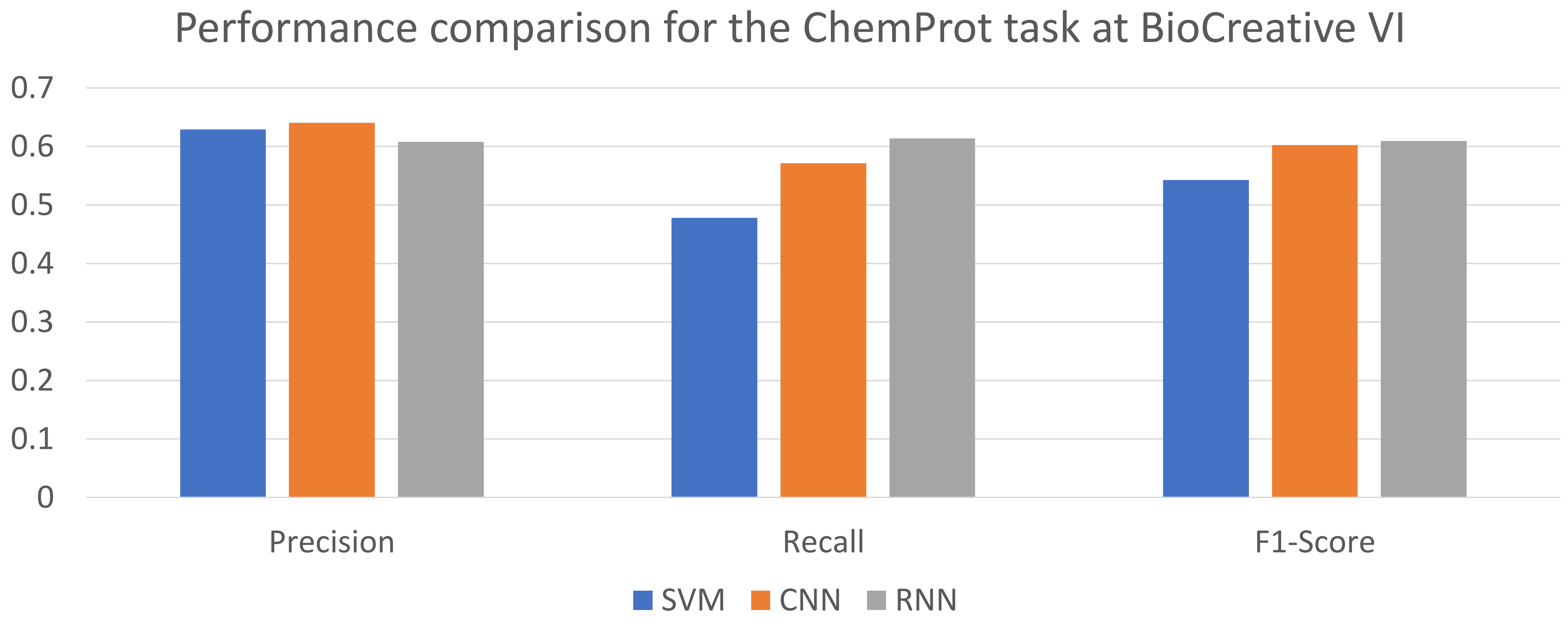
Traditional ML

- Hand crafted features
- Simple logic of the methodology
- Computationally efficient (CPU)
- Decent performance

Deep Learning

- Automatic feature extractions
- Complicated architecture
- Require more computations (GPU)
- Improved excellent performance

Traditional ML v.s. Deep Learning



Peng, Yifan, et al. "Extracting chemical–protein relations with ensembles of SVM and deep learning models." *Database* 2018 (2018).

Challenges

- Limited Annotations
- Complex Relation Extraction
  - Biomedical event (trigger detection, argument recognition, event prediction)
  - Multiple level event
  - Nesting relationships
- Complex Interaction/Regulation/Association Network

Future Directions

- General relation extraction model
- Clinical relation extraction from electronic health record
- Large-scale complex relation extraction
- Transfer learning

Acknowledgements

- Zhiyong Lu
- Chih-Hsuan Wei
- Alexis Allot
- Rezarta Islamaj
- Dongseop Kwon
- Sun Kim
- Yifan Peng
- Qinyu Cheng

NCBI

NIH U.S. National Library of Medicine

NIH Intramural Research Program
Our Research Changes Lives

Thank You!