Hypothesis Generation with AGATHA

Accelerate Scientific Discovery with Deep Learning

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Motivation: Drug Discovery

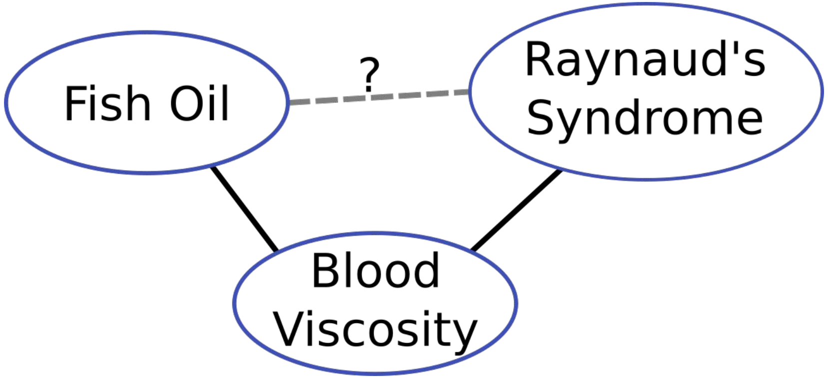
- Solution strategy:
  - Identify ~1000 target substances
  - Determine ~10 candidates
  - Conduct ~1 human trial
- Challenges:
  - Expensive early investment
  - Uncertain results

Available Data

- National Library of Medicine provides public databases
- MEDLINE contains nearly 30 million biomedical abstracts
- Data available through PubMed
- New papers per-year is increasing!
    - Nearly 1 million last year
    - New paper every 35 sec

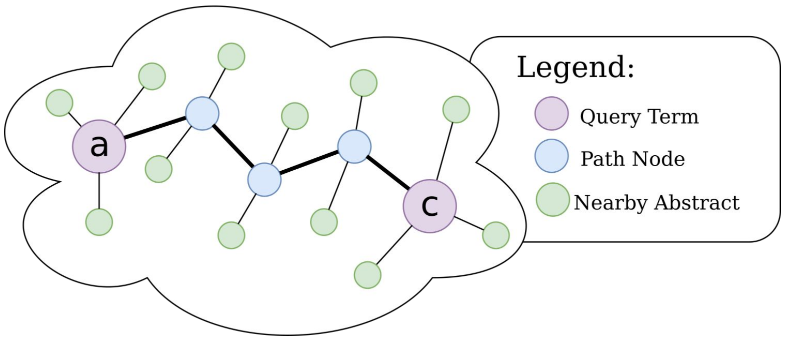
Background: ARROWSMITH (1986)

- Pattern:
  - Given two terms: A, C
  - Find words related to A
  - Find words related to C
  - Find overlap
- Key Limitations:
  - Only simple connections
  - Biased to incremental results

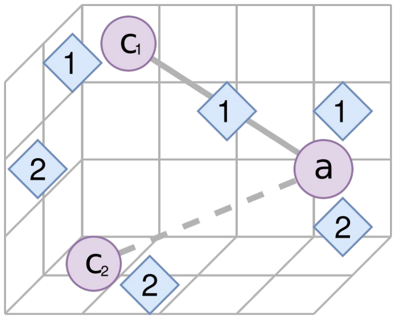


Background: MOLIERE (2017)

- Our first hypothesis generation system
- Process:
  - Construct semantic network
  - Shortest path queries
  - Topic modeling
  - Heuristic analysis
- Limitations:
  - Minutes per query
  - Heuristic analysis



Shortest Path Query

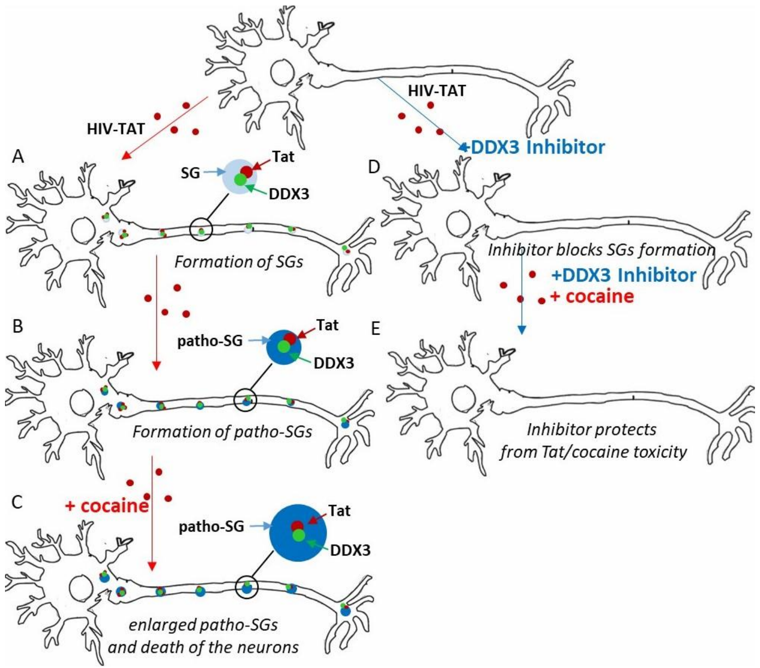


Topic Model Heuristic Analysis

Moliere: Automatic biomedical hypothesis generation system
Sybrandt, Shtutman, Safro
KDD'17

Success with HIV-Associated Dementia

- Moliere ranked 40,000 genes
- DDX3 ranked highly
- Confirmed in laboratory



Inhibition of the DDX3 prevents HIV-1 Tat and cocaine-induced neurotoxicity by targeting microglia activation

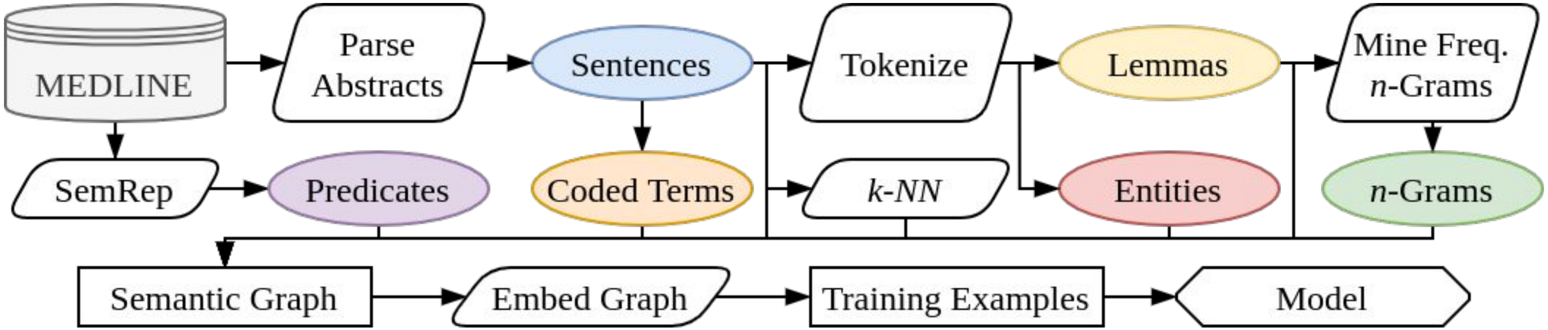
Aksenovam, Sybrandt, Chu, Sikirzhytski, Ji, Odhiambo, Lucius, Turner, Broude, Pena, Lizzaraga, Zhu, Safro, Wyatt, Shtutman

JNP'19

Agatha

- Process:
    - Parse MEDLINE
    - Construct semantic network
    - Train embedding & model
    - Validate through ranking
- Intuition:
    - Remove heuristics
    - Add data-driven insights
    - Speed up hypothesis queries

Agatha Pipeline Summary



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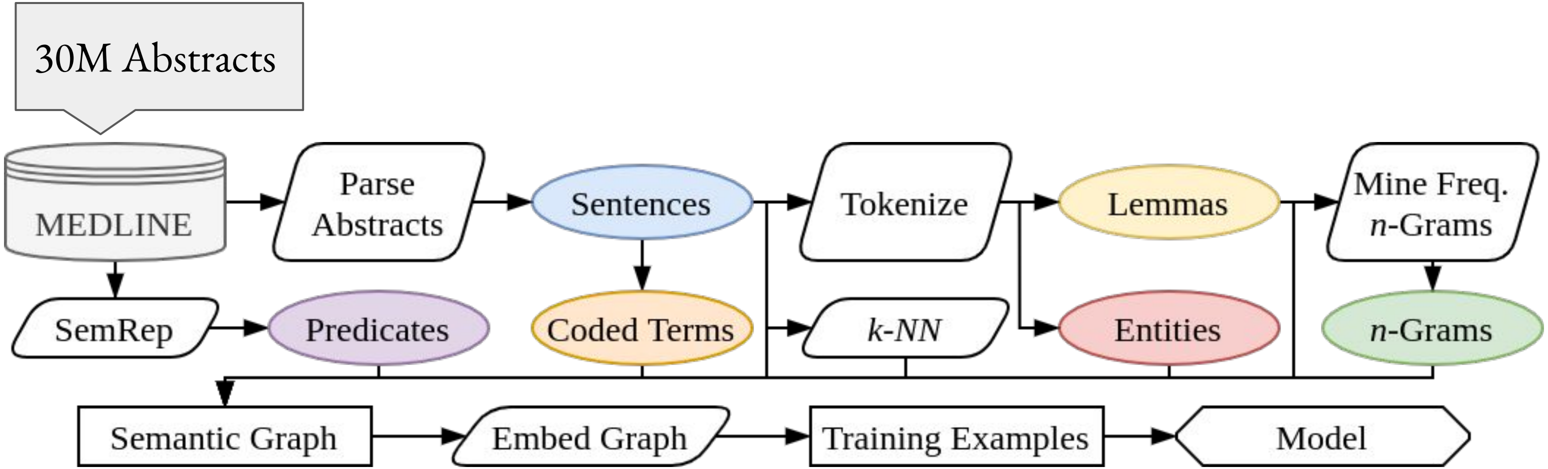

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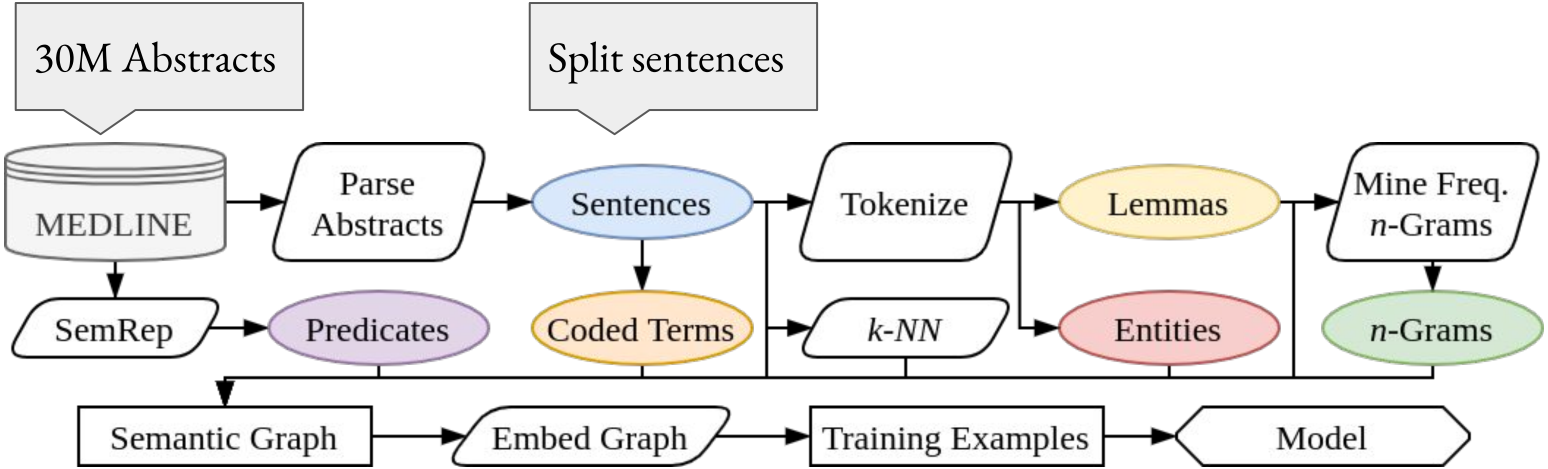

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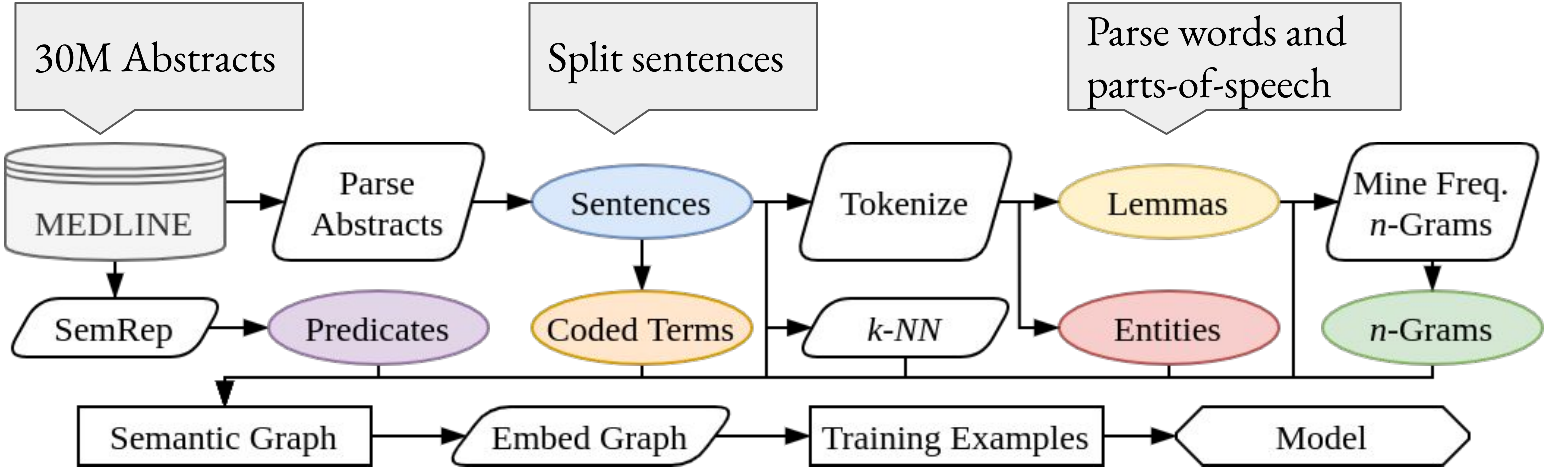

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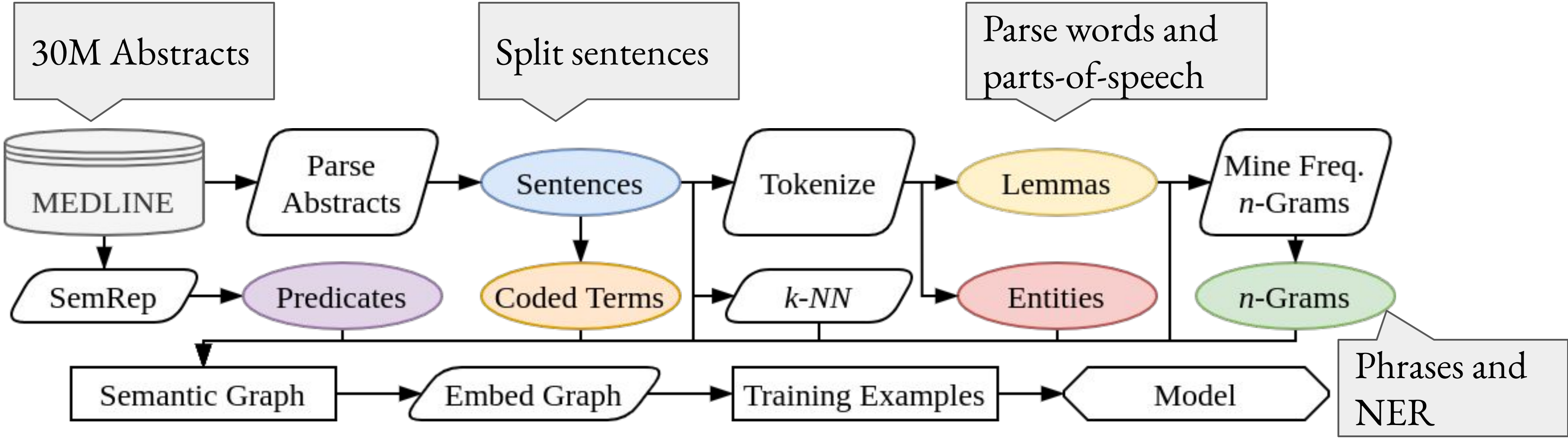

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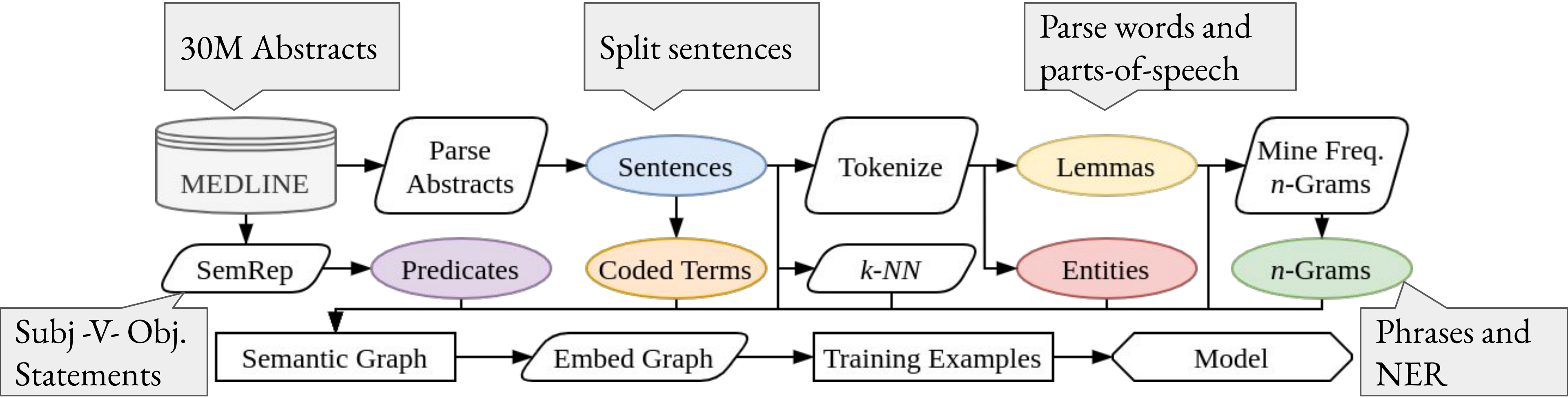
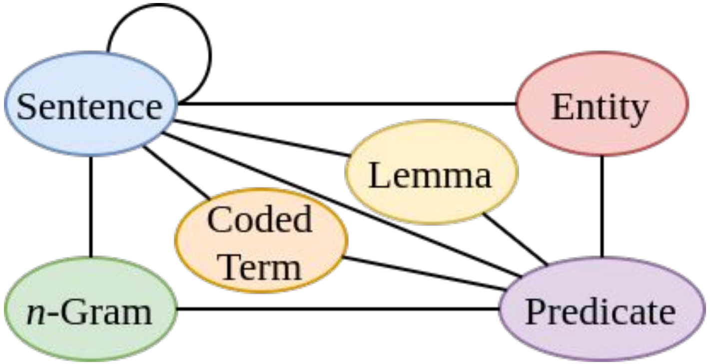


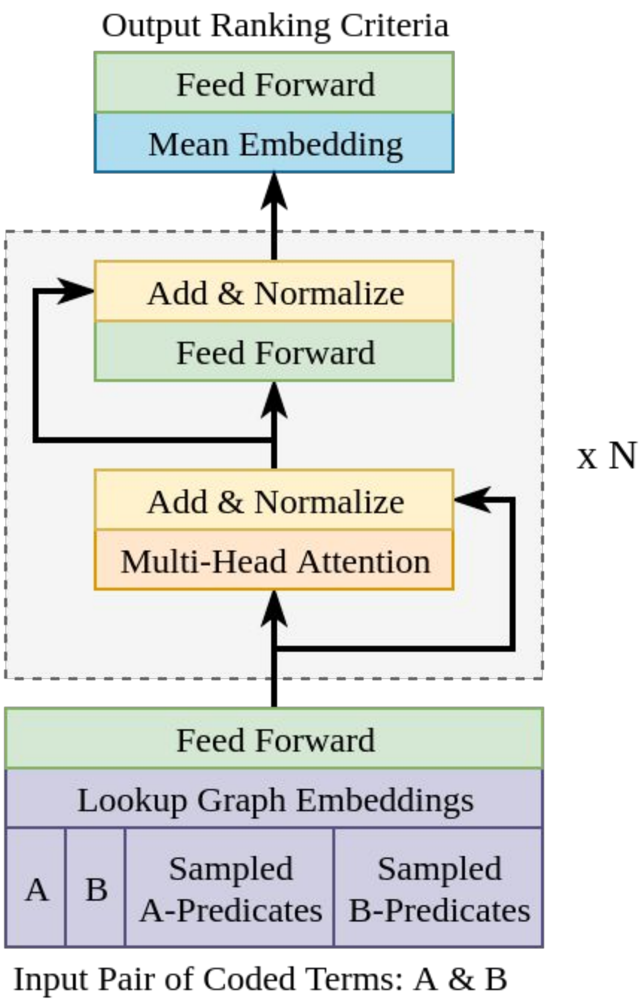
Semantic Graph

- Sentences:
  - Connected by nearest-neighbors
  - Edges to contained elements
- Predicates
  - Edges to info supplied by SemMedDB
- Size:
  - 2015 Release:
    - 188 M. Nodes
  - 2020 Release:
    - 270 M. Nodes



Agatha Deep Learning Model

- Goal: train a transformer encoder to accept two query terms and produce ranking criteria
- Objective: Margin Ranking Loss
- Model: Transformer Encoder
- Graph Embedding



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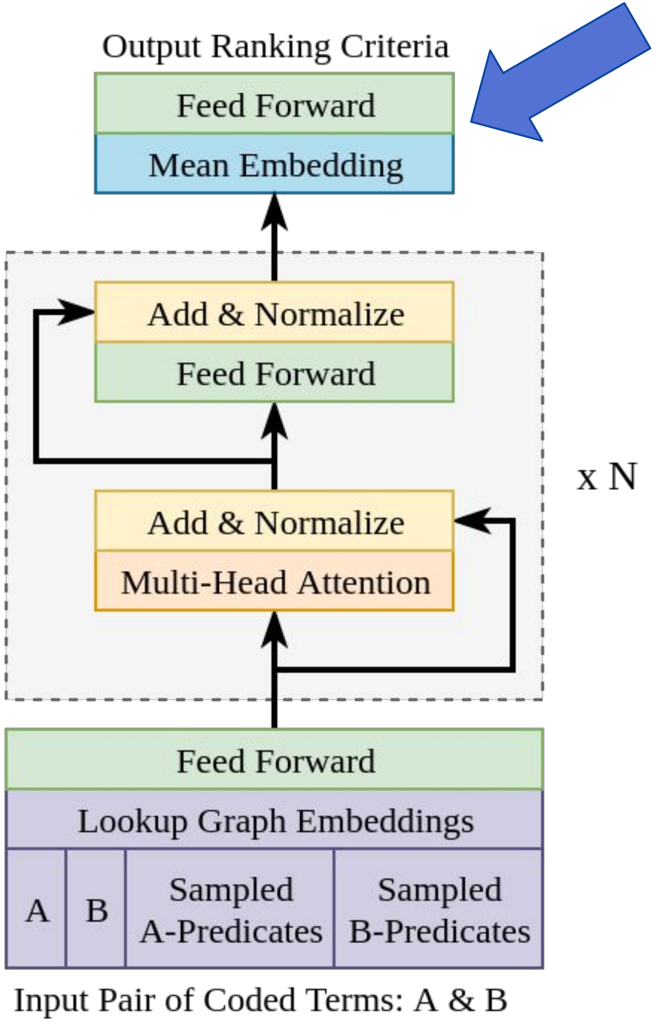

Predicate Modeling Objective

$$\mathcal{L}(\alpha, \beta) = \sum_{i=0}^{n} L\left(\mathrm{PS}_{\alpha\beta}, \mathrm{Nscr}_{\alpha\beta}^{(i)}\right) + \sum_{j=0}^{n'} L\left(\mathrm{PS}_{\alpha\beta}, \mathrm{Nswp}_{\alpha\beta}^{(j)}\right)$$

$$\text{where } L(p, n) = \max\left(0, m - \mathcal{H}(p) + \mathcal{H}(n)\right)$$

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Loss associated with two connected terms

Predicate Modeling Objective

Positive Sample

Negative Sample (Scramble)

Negative Sample (Swap)

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Loss associated with two connected terms

margin ranking loss

margin

Model output

Predicate Formulation

$$\mathrm{PS}_{\alpha\beta} = \left\{\alpha, \beta, \gamma_1^{(\alpha)}, \ldots, \gamma_s^{(\alpha)}, \gamma_1^{(\beta)}, \ldots, \gamma_s^{(\beta)}\right\}$$

where $\gamma_i^{(\alpha)} \sim \{\Gamma(\alpha) - \Gamma(\beta)\}$, and $\gamma_i^{(\beta)} \sim \{\Gamma(\beta) - \Gamma(\alpha)\}$

Predicate Formulation

Set containing two terms and other associated predicates

$$\mathrm{PS}_{\alpha\beta} = \left\{\alpha, \beta, \gamma_1^{(\alpha)}, \ldots, \gamma_s^{(\alpha)}, \gamma_1^{(\beta)}, \ldots, \gamma_s^{(\beta)}\right\}$$

where $\gamma_i^{(\alpha)} \sim \{\Gamma(\alpha) - \Gamma(\beta)\}$, and $\gamma_i^{(\beta)} \sim \{\Gamma(\beta) - \Gamma(\alpha)\}$

Set of predicates using a given term

Sampled predicate

Negative Samples

- Scramble (easy):

$$\begin{aligned}\mathrm{NScr}_{\alpha\beta} &= \{x, y, \gamma_1, \ldots, \gamma_{2s}\}\\ &\text{where } x, y \sim T,\\ &\text{and } \gamma_i \sim P,\\ &\text{s.t. } \Gamma(x) \cap \Gamma(y) = \emptyset\end{aligned}$$

- Swap (hard):

$$\begin{aligned}\mathrm{NSwp}_{\alpha\beta} &= \left\{x, y, \gamma_1^{(x)}, \ldots, \gamma_s^{(x)}, \gamma_1^{(y)}, \ldots, \gamma_s^{(y)}\right\}\\ &\text{where } x, y \sim T,\\ &\text{and } \gamma_i^{(x)} \sim \{\Gamma(x) - \Gamma(y)\},\\ &\text{and } \gamma_i^{(y)} \sim \{\Gamma(y) - \Gamma(x)\},\\ &\text{s.t. } \Gamma(x) \cap \Gamma(y) = \emptyset\end{aligned}$$

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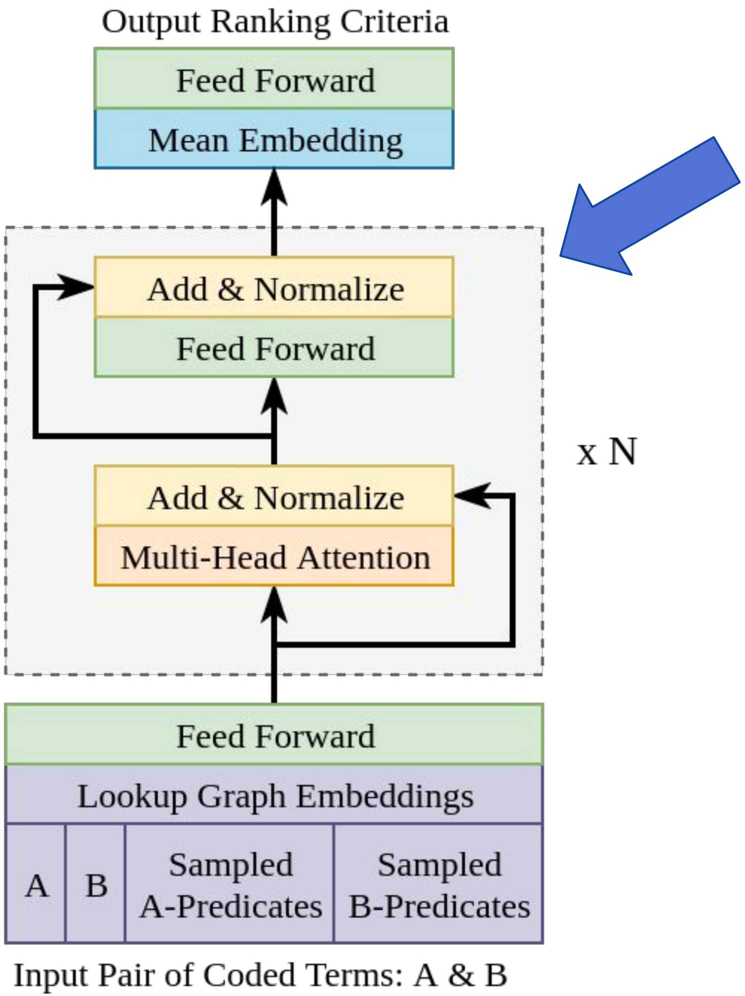


Model Formalism

- Prediction Model:

$$\mathcal{H}(X) = \text{sigmoid}(\mathcal{M}W)$$

$$\mathcal{M} = \frac{1}{|X|} \sum_{x_i \in X} E_N(FF(e(x_i)))$$

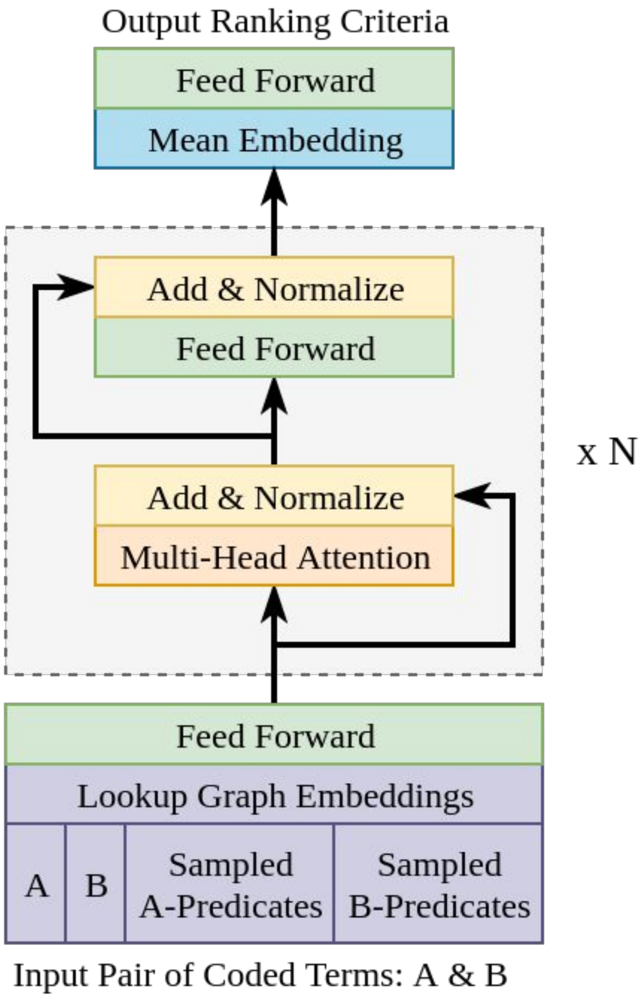
$$E_{i+1}(x) = \mathcal{E}(E_i(x)), \text{ and } E_0(x) = x$$

- Encoder Block:

$$\mathcal{E}(X) = \text{LayerNorm}(FF(\alpha) + \alpha)$$

$$\text{where } FF(Y) = \max(0, YW)\,W'$$

$$\text{and } \alpha = \text{LayerNorm}(\text{MultiHead}(X) + X)$$



Predicate Modeling

- Attention: learned weighted averages

$$\mathrm{Attention}(Q, K, V) = \mathrm{softmax}\left(\frac{QK^{\intercal}}{\sqrt{d_k}}\right)V$$

Predicate Modeling

- Attention: learned weighted averages

Think: if key matches query

$$\mathrm{Attention}(Q, K, V) = \mathrm{softmax}\left(\frac{QK^\top}{\sqrt{d_k}}\right)V$$

... then add in value

Predicate Modeling

- Attention: learned weighted averages

$$\text{Attention}(Q, K, V) = \text{softmax}\left(\frac{QK^\intercal}{\sqrt{d_k}}\right)V$$

- Multi Head Self Attention:

$$\text{MultiHead}(X) = [h_1; \ldots; h_k]W^{(4)}$$
$$\text{where } h_i = \text{Attention}\left(XW_i^{(1)}, XW_i^{(2)}, XW_i^{(3)}\right)$$

Predicate Modeling

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Compute multiple times and merge

$$\text{where } h_i = \text{Attention}\left(XW_i^{(1)}, XW_i^{(2)}, XW_i^{(3)}\right)$$

Derive Q, K, and V from X

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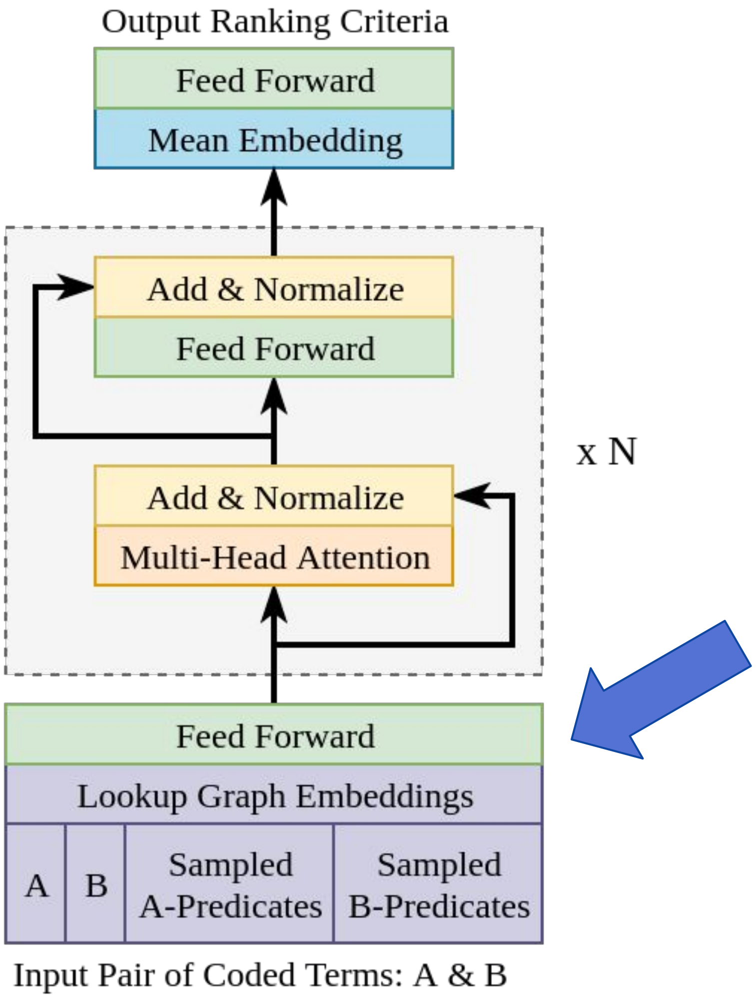

Graph Embedding Objective

- PyTorch-BigGraph (PTBG) distributed embedding
- Produce embedding per node in network
- Trained separate from Agatha ranking model
- Minimizes Softmax Loss:
  - Positive probability close to 1
  - All negative probabilities close to 0

$$\text{GraphLoss}_{ij} = -s(ij) + \log \sum_{n=0}^{100} \exp\left(s\left(x_n^{(ij)} y_n^{(ij)}\right)\right)$$

Similarity assoc. w/ existing edge

Similarity assoc. w/ absent edge

Graph Embedding

- Similarity measure:
  - biased transformed dot product of nodes
  - includes typed translation

$$s(ij) = e(i)_1 + e(j)_1 + T_1^{(t_i t_j)} + \sum_{k=2}^{N} e(i)_k \left(e(j)_k + T_k^{(t_i t_j)} \right)$$

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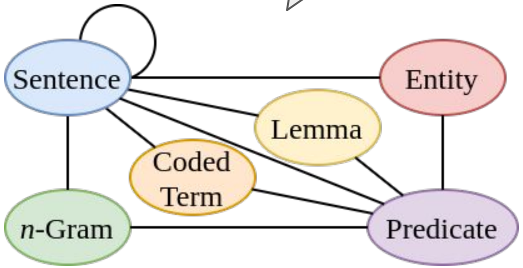
Estimated sim.
btwn. i and j

Graph Embedding

Each is a type



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T translates between types

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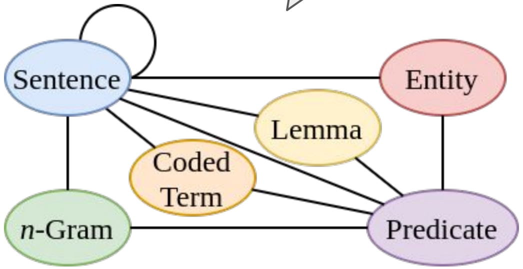

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Translated dot product

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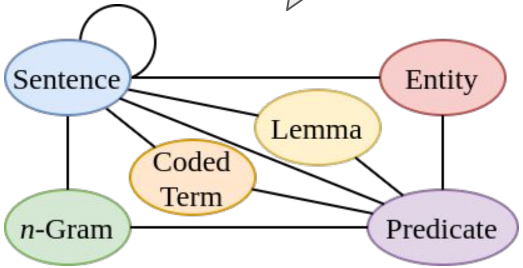

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Estimated sim. btwn. i and j

First dim. is bias

Translated dot product

T translates between types

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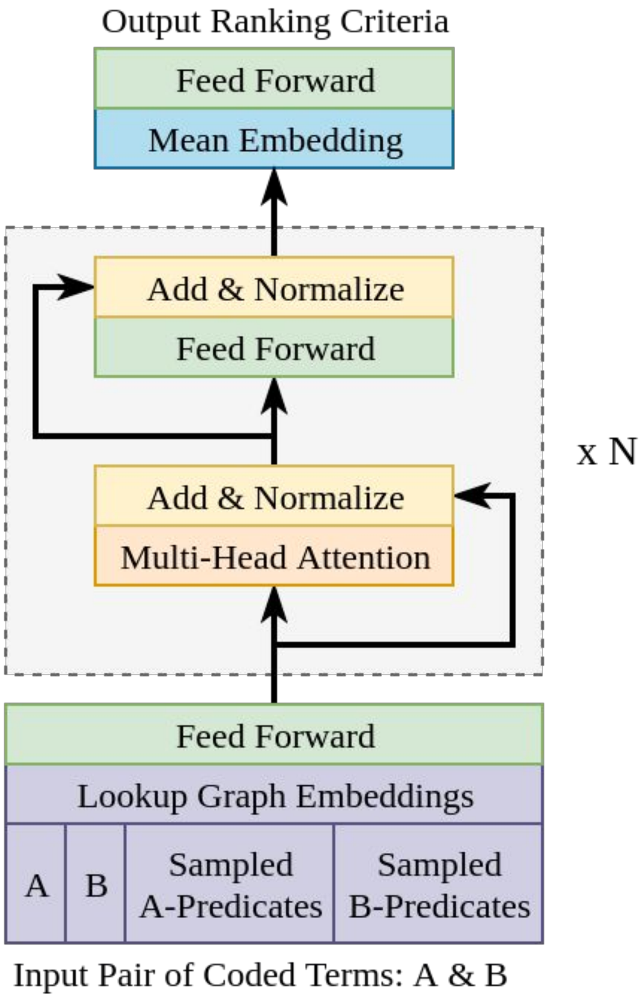

How to Validate

- Challenge: looking for novel information
- Existing methods:
  - Recreate 7 experiments from early 90's
  - Domain-specific statistics
  - Expert interpretation
  - Publish in medicine
- Complications:
  - Too narrow: Only specific domains
  - Too slow: Human in the loop
  - Too small: Datasets of <10 hypotheses

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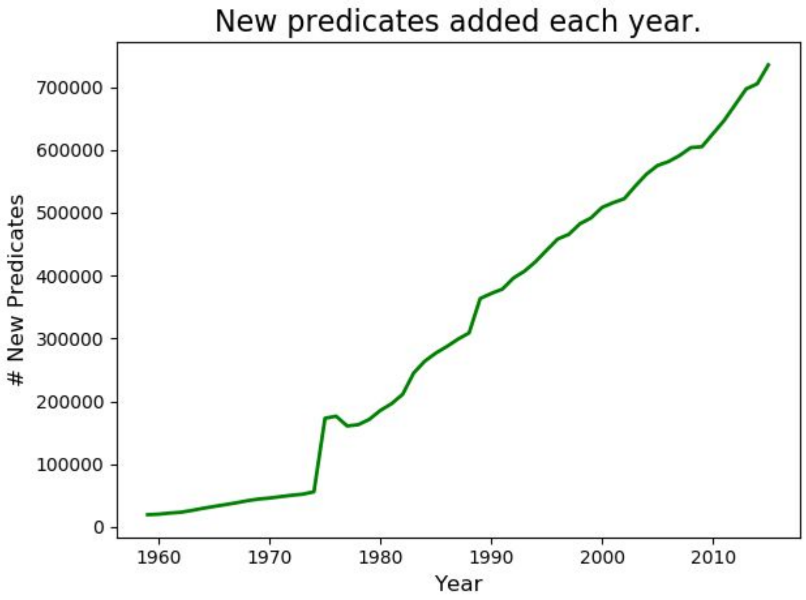
Large-scale validation of hypothesis generation systems via candidate ranking
Sybrandt, Shtutman, Safro

BigData'18

Validation via Ranking

- Drug discovery is ranking
- Positive test set
  - Recently introduced predicates
- Negative test set
  - Never introduced predicates
- Perform temporal holdout

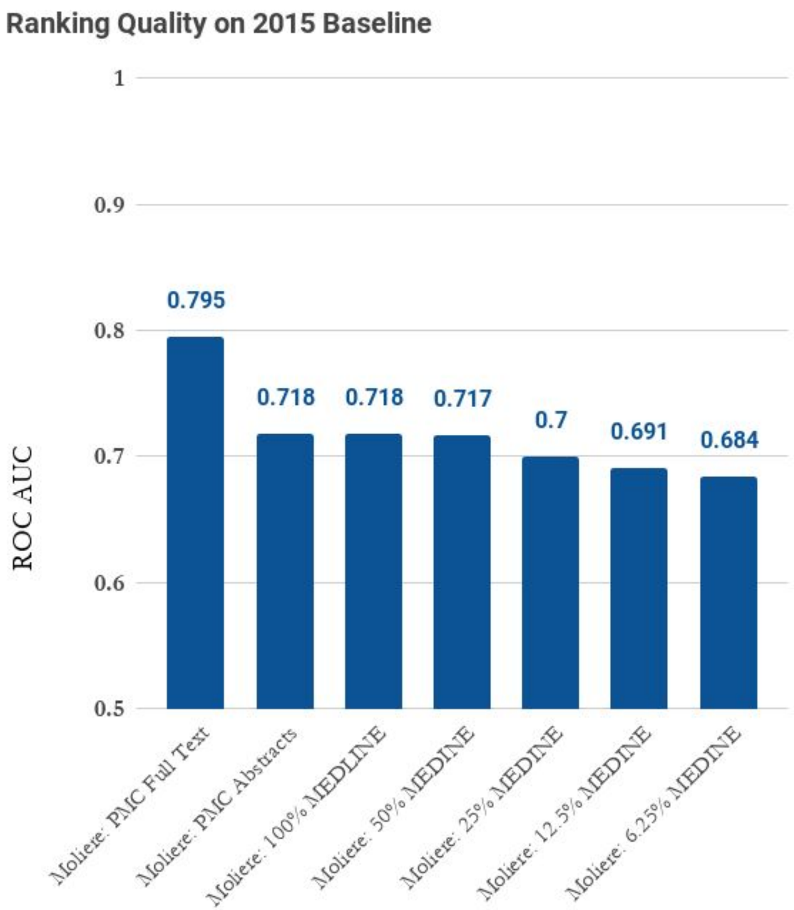


Moliere Baseline

- Train on data before 2015
- Explore different training datasets
- Rank recent predicates with heuristic criteria
- Found that full text papers outperform abstracts by 10%

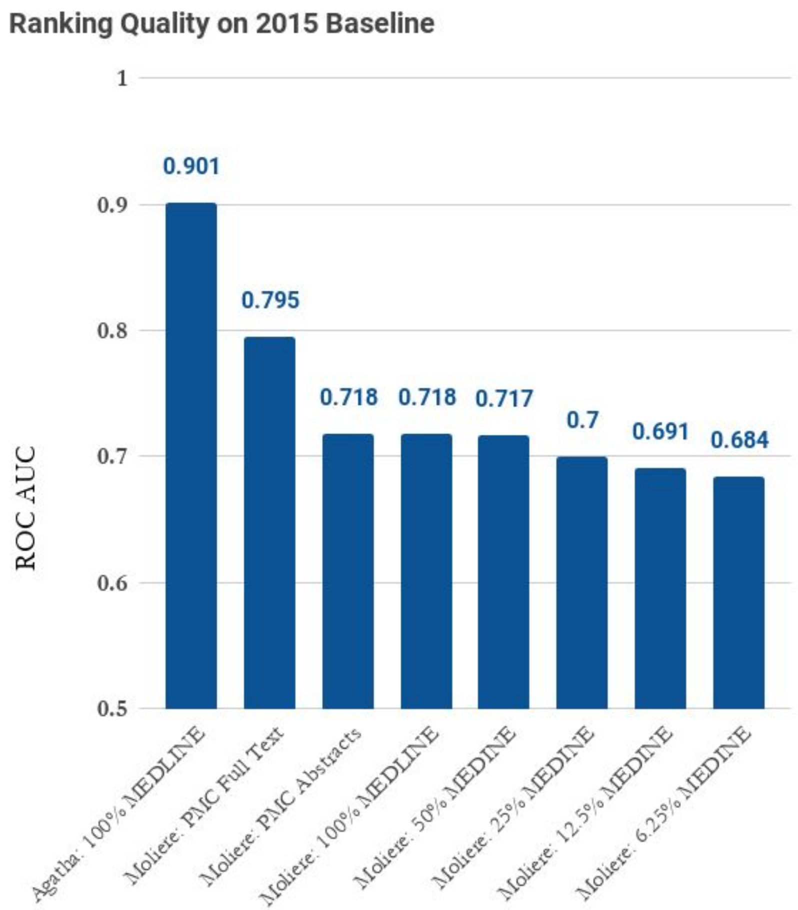
Are abstracts enough for hypothesis generation?
Sybrandt, Carrabba, Herzog, Safro

BigData'18



Agatha performance on Moliere Benchmark

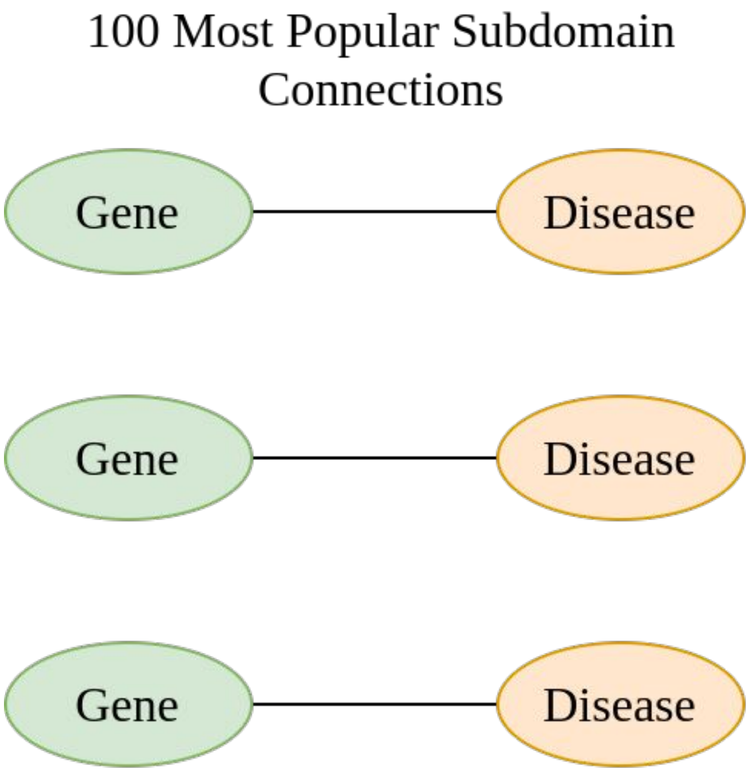
- Trained on same holdout as Moliere experiments (2015)
  - Used only abstracts
- Same set of predicates
- 100's queries per minute

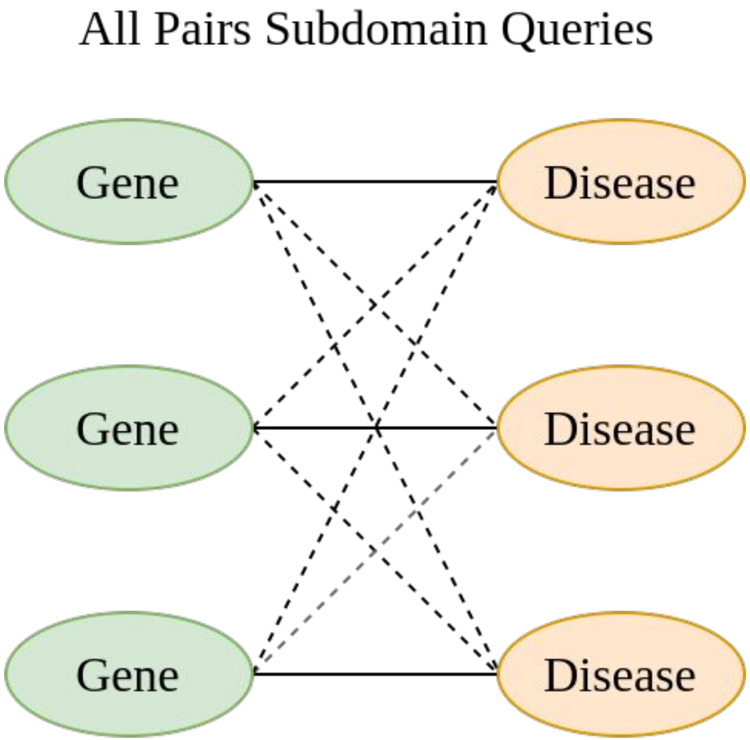


Beyond the Moliere Benchmark

- Moliere benchmark had significant issues
  - Balanced classes
  - Non-representative negative samples
- New validation task
  - Subdomain all-pairs recommendation
- Procedure:
  - Identify popular types of predicates
  - Find 100 most popular new findings within each predicate type
  - Predict all pairs of queries within popular entities
  - Rank
  - Compute recommendation system metrics

All Pairs Recommendation Example





Gene to Cell Function

Top 100 predicates of this type.

- Area under curves:
  - PR: 0.44
  - ROC: 0.62
- Top ranked predicate is positive
- Half of the top-10 are positive
- Each one-to-many query on average:
  - Positive result within first two

Gene to Neoplastic Process

Top 100 predicates of this type.

- Area under curves:
  - PR: 0.34
  - ROC: 0.65
- Second ranked predicate is positive
- Half of the top-10 are positive
- Each one-to-many query on average:
  - Positive result within first two

Try it yourself

```python
# Its now incredibly easy to run your own
# Hypothesis Generation Queries!
import torch
agatha_data_dir = "..."
model = torch.load(f"{agatha_data_dir}/model.pt")
model.set_data_root(agatha_data_dir)
model.init()
# Now you can rank arbitrary UMLS term pairs!
# Keywords: Cancer(C0006826), Tobacco(C0040329)
model.predict_from_terms([("C0006826", "C0040329")])
>>> [0.78358984]
# Check us out at github.com/jsybrandt/agatha
```

In Summary

- Agatha:
  - Deep learning model built on graph embeddings and the transformer
  - Ranks user queries
  - High quality recommendation
- Learn more:
  - Email: jsybran@clemson.edu
  - Project: sybrandt.com/2020/agatha
  - Github: github.com/jsybrandt/agatha