Using the Literature to Identify Confounding Variables for Performing Pharmacovigilance with Clinical Notes

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Overview

- **Motivation**
- **Background**
  - Confounding
  - Causal Modeling
  - Literature-Based Discovery
- **Data and Methods**
- **Results and Discussion**
- **Current/Future Work**

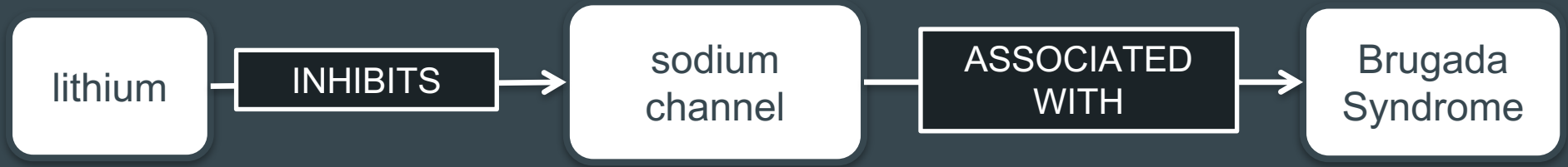
Motivation

- **Adverse drug events** (ADEs): 807K events and 124K deaths in 2014 (FAERS)
- **Pharmacovigilance**: ***FDA approval is not the end***
- **Spontaneous Reporting Systems** (SRSs) (e.g., FAERS, EudraVigilance)
  - Underreporting, lack of context, inaccuracy, **Botsis, 2015; Hersh et al., 2013**
- **Electronic Health Records** (EHR)
- **Confounding** introduces bias in between predictor and outcome of interest
- **Prior Approaches**
  - Meta-analysis, **Harpaz et al, 2013**, lasso shrinkage regression, **Li et al, 2014, 2015**
- **Why causal modeling and discovery?**
  - We wish to know the direction of influence, not merely correlation
  - X→Y : X “CAUSES” Y

Literature-Based Confounder Discovery

- **Literature Based Discovery** *("LBD")*
  - **Swanson et al., 1986** (Raynaud's syndrome and fish oil)
  - **Hristovski et al., 2006** (Discovery Patterns ["DPs"])
  - **Kilicoglu et al., 2012** (SemMedDB)
  - **Shang et al., 2014** (DPs for Pharmacovigilance)

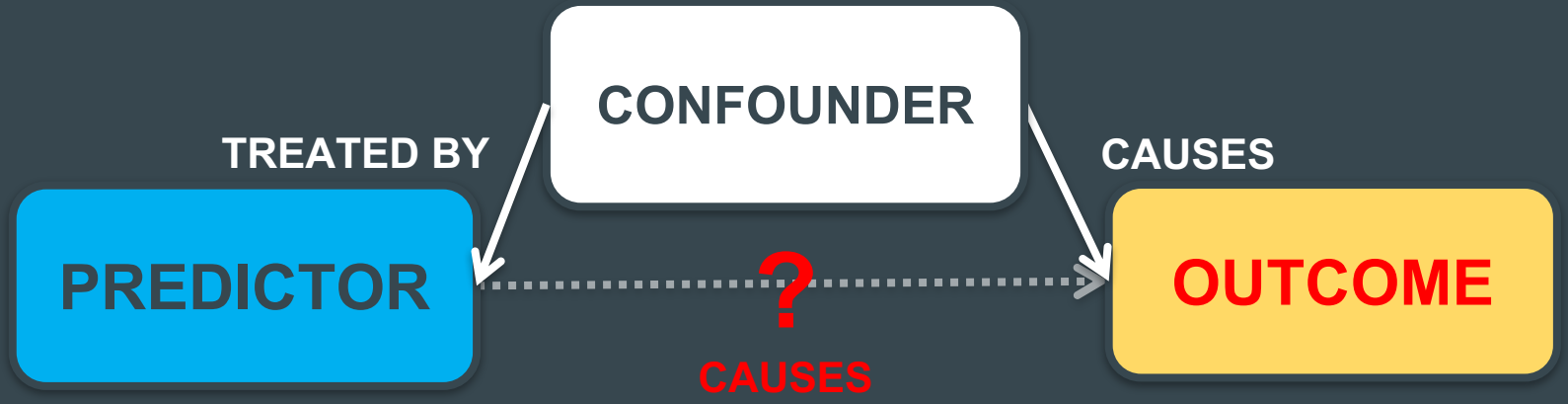
DPs: relational constraints that help discover meaningful implicit relationships.



Hypothesis

Hypothesis: Predictions from literature-informed causal models will be more accurate than those from unadjusted statistical correlation.

Goal: Improve detection of drug safety signals in clinical notes.



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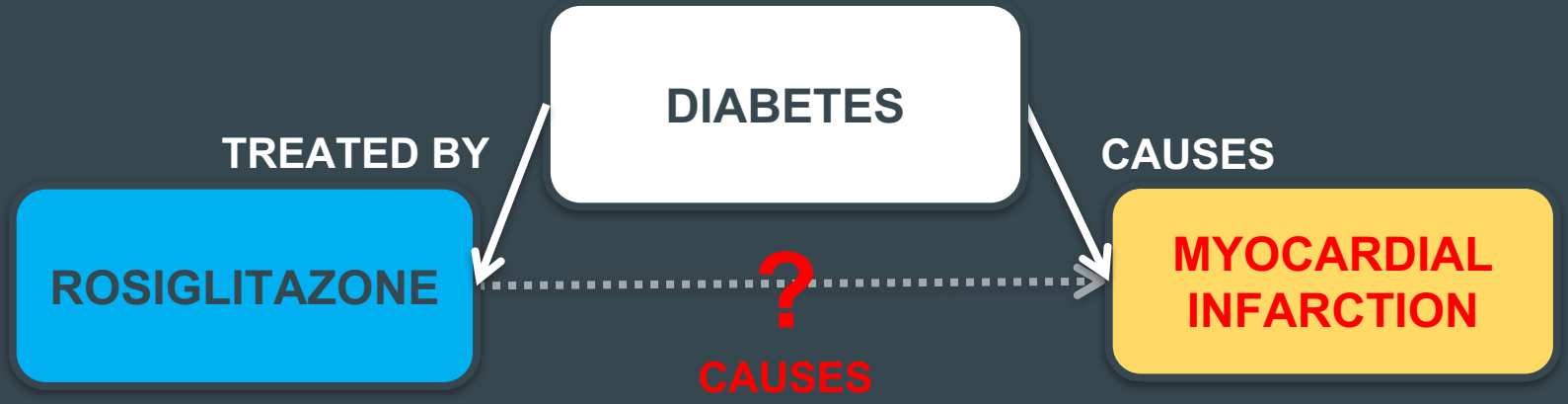

Data and Knowledge

- **Data**
  - Curated reference set - 399 drug-ADE pairs, **Ryan et al., 2013**
  - UT Clinical Data Warehouse subset ~2.2M outpatient notes (~364k patients)
  - Processed notes with MedLEE, **Friedman et al., 1995** → ~ 33K UMLS concepts
- **Knowledge**
  - **SemMedDB:** ~70M predications extracted from MEDLINE as triple stores
  - **EpiphaNet LBD system** (http://epiphanet.uth.tmc.edu), **Cohen et al., 2010**
- **Reference standard**
  - 165 positive and 234 negative examples of drug ADE pairs, **Ryan et al., 2013**
  - Acute kidney injury; acute liver injury; gastrointestinal bleed; myocardial infarction

Method

- Identify confounders - query EpiphaNet backend
  Discovery Pattern: drug TREATS x; x CAUSES ADE
- Test confounders using observational clinical data using FGeS in TETRAD, **Ramsey, 2015**
- Combinatorial expansion of all unique sets of confounders

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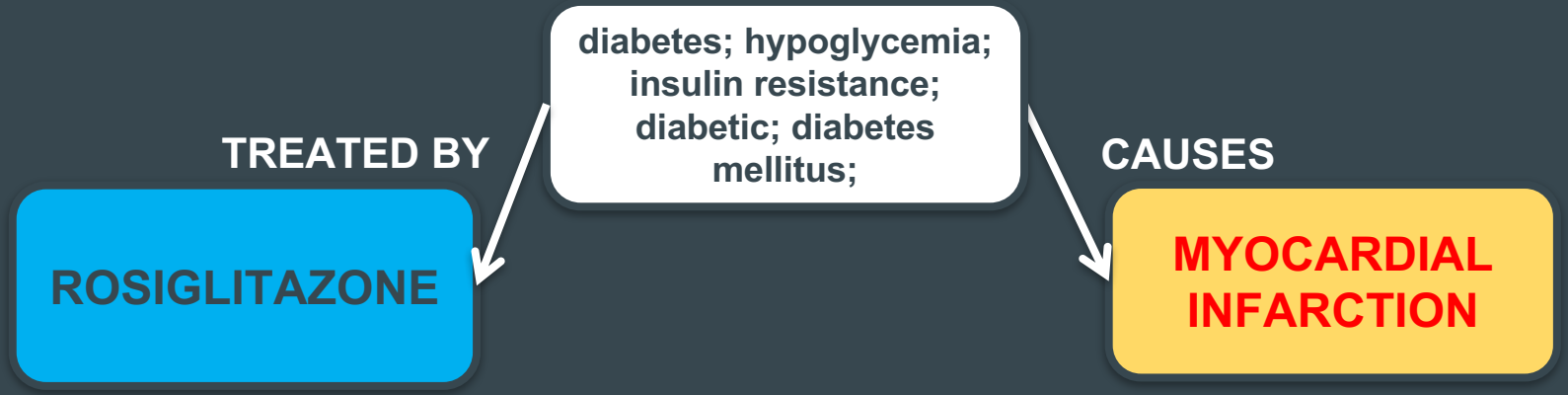
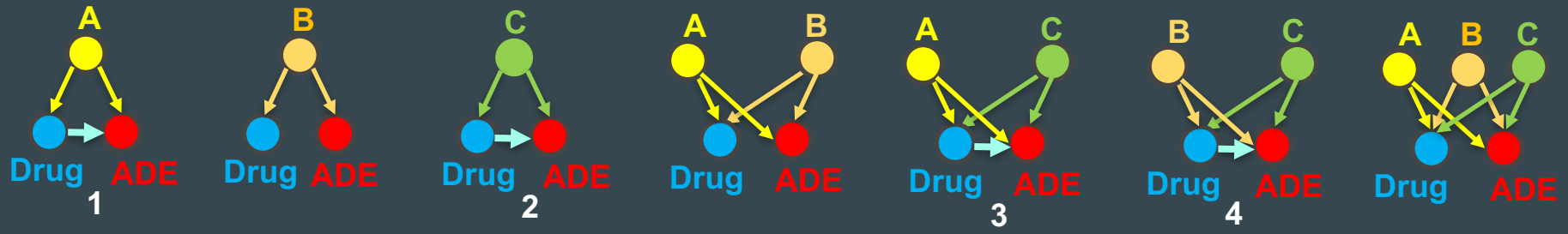


Combinatorial Expansion

- A continuous value is required in order to calculate AUC using “ground truth” in reference dataset, **Ryan et al., 2013**
- Say we have a set of confounders { **A**, **B**, **C** } that we wish to include in a model. We identify all unique permutations (order does not matter).
  { [**A**], [**B**], [**C**], [**A**, **B**], [**A**, **C**], [**B**, **C**], [**A**, **B**, **C**] }
- To calculate score for this set of confounders given 4 directed edges, the score would be **4 / 7 = 0.5714**



ADE	RESULTS	
	Baseline AUC (unadjusted logistic regression)	Causal model AUC
Gastrointestinal Bleeding	0.5643	0.6912
Acute Kidney Injury	0.5547	0.6598
Acute Liver Injury	0.4957	0.5449
Acute Myocardial Infarction	0.4946	0.56
Overall	0.504	0.5704

Discussion

- **Findings**
  - LBD was able to identify confounders in the EHR
  - Improvements of 0.10-0.13 when baseline is above noise

- **Limitations**
  - Improvements only evident when there is already decent “signal”
  - co-medications would have been helpful
  - Performance is not on par with meta-analysis, Li et al., 2015, Harpaz et al., 2017

What is next?

- **Future Work**
  - Replace combinatorial expansion procedure with ***parameter estimation***
  - Incorporate more procedures to reject unhelpful covariates
  - Identify and incorporate ***co-medication*** confounders

Thank you!

The End

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