Causal determinants of postoperative length of stay in cardiac surgery using causal graphical learning

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September 18th, 2022

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Motivation

Postoperative length of stay (pLOS) is an important metric in cardiac surgery. Minimizing pLOS is crucial to quality care, linked to improved patient outcomes as well as hospital spending.

To understand how to minimize pLOS, need to identify **causal deteriminants**. Roughly: factors that, if they were manipulated somehow, would shift the pLOS distribution.

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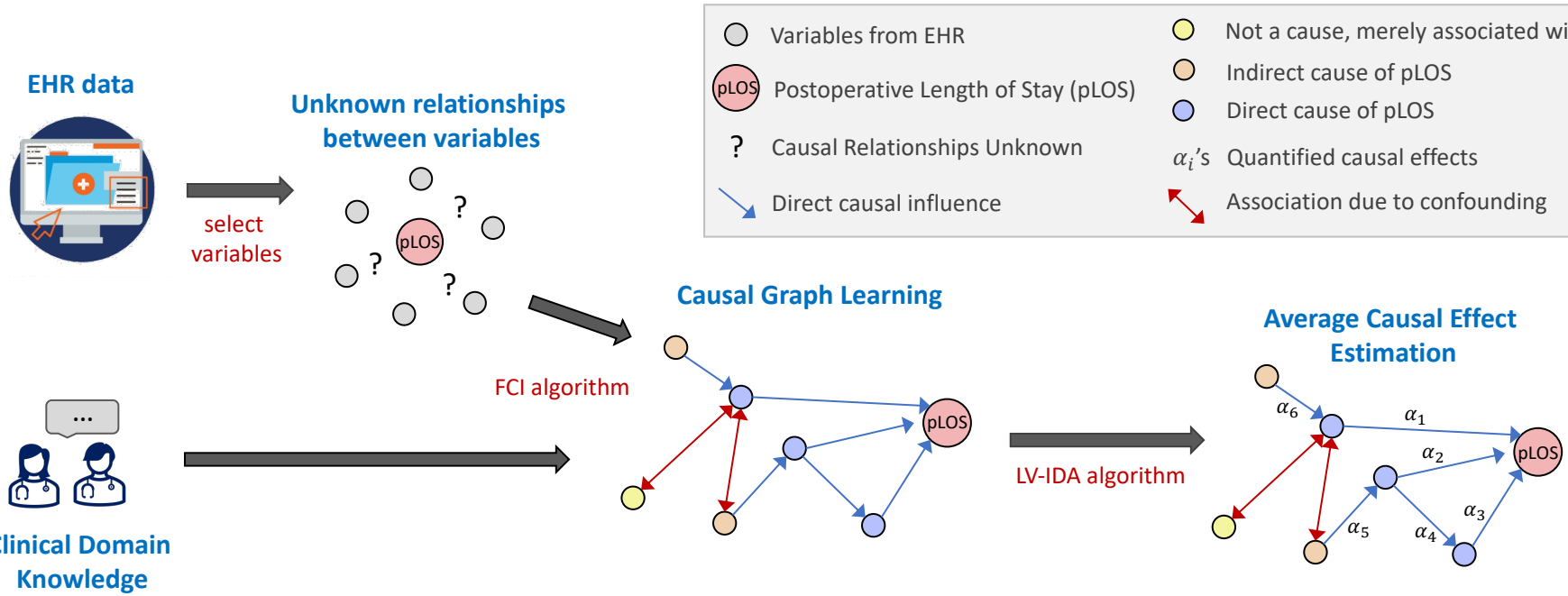
Much research in the area has identified "key variables" that predict pLOS (using linear regression or ML models), but these provide limited insight to guide interventions.

Causal Determinants of Postoperative Length of Stay in Cardiac Surgery



Causal Graphical Learning uncovers true causal relationships and their strengths, leading to actionable insights that can reduce post-operative length of stay.

pLOS: postoperative Length of Stay
EHR: Electronic Health Records
FCI: Fast Causal Inference
LVIDA: Latent Variable Intervention-calculus when the DAG is Absent

EHR data on cardiac surgeries

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- Final sample size was $n = 2610$ patient-visits

Incorporating clinical knowledge

In addition to the selection of variables, we also incorporate clinical knowledge to make the discovery problem easier & more accurate.

Some causal ordering information is known. Ex: baseline patient features (demographics, med history) $\Rightarrow$ intra-op variables $\Rightarrow$ post-op variables $\Rightarrow$ pLOS

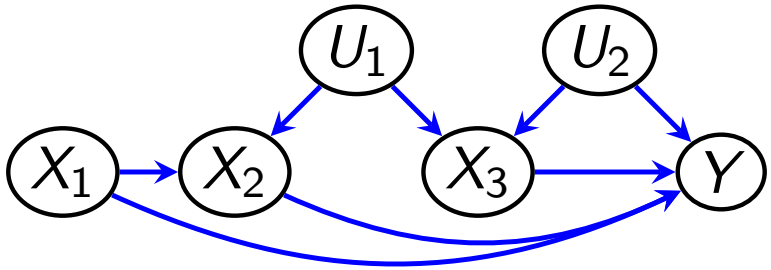
Also know the relative order of a few other variables based on definitions, timing of measurement, clinical experience

Unknowns

Though clinicians have reasonable idea of what factors are relevant, they are quite uncertain about:

- Possible mediation / pathway relationships among the variables: does extubating patient in OR *directly* affect pLOS, or does this effect operate through post-op complications? What mediates the effect of intra-op blood transfusion on pLOS?
- Which variables should we adjust for when estimating the effect of some factor on pLOS? (Confounders vs on the causal pathway)
- What about unmeasured confounders?

Causal DAGs

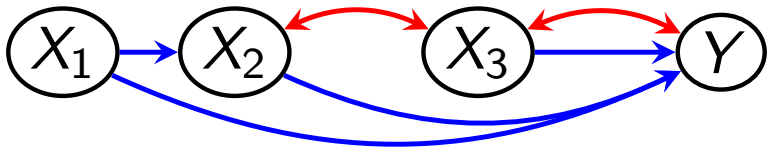


A directed edge in a causal DAG represents "direct" causal influence of one variable on another. Roughly: an **intervention** on some X may **change** the distribution of Y. Missing edges reflect conditional independence.

More formally, may associate a nonparametric SEM or potential outcomes model w/ DAG. (No important difference for our purposes here.)

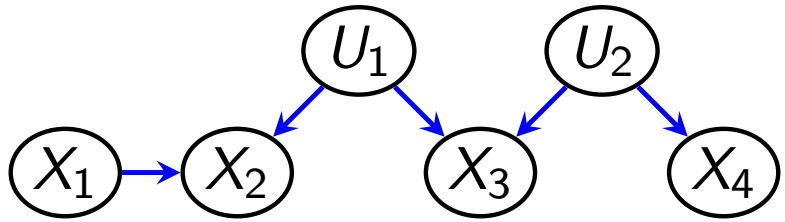
Causal DAGs imply constraints on observed vars

We will assume our data is generated according to some unknown DAG with **arbitrary** latent variables.

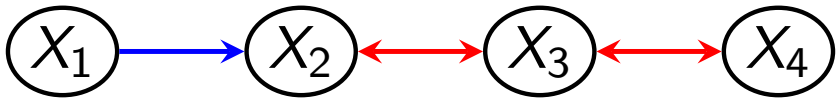


Distinct DAGs (even w/ latents) imply testable conditional independence constraints on the observed variables. We use **constraint-based causal discovery** to narrow down (a set of) causal models consistent with "discovered" constraints.

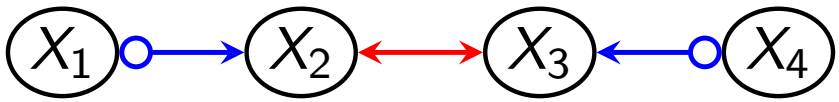
DAGs and PAGs



DAG



MAG (latent projection)



PAG (equivalence class)

PAG learning

A PAG may contain a variety of edges:
$X \to Y$, $X \leftrightarrow Y$, $X \circ\!\!\to Y$, $X \circ\!\!-\!\!\circ Y$.

The classic procedure is the FCI algorithm[1] though there are more recent alternatives.

How does FCI work? (see appendix slides for pseudocode)

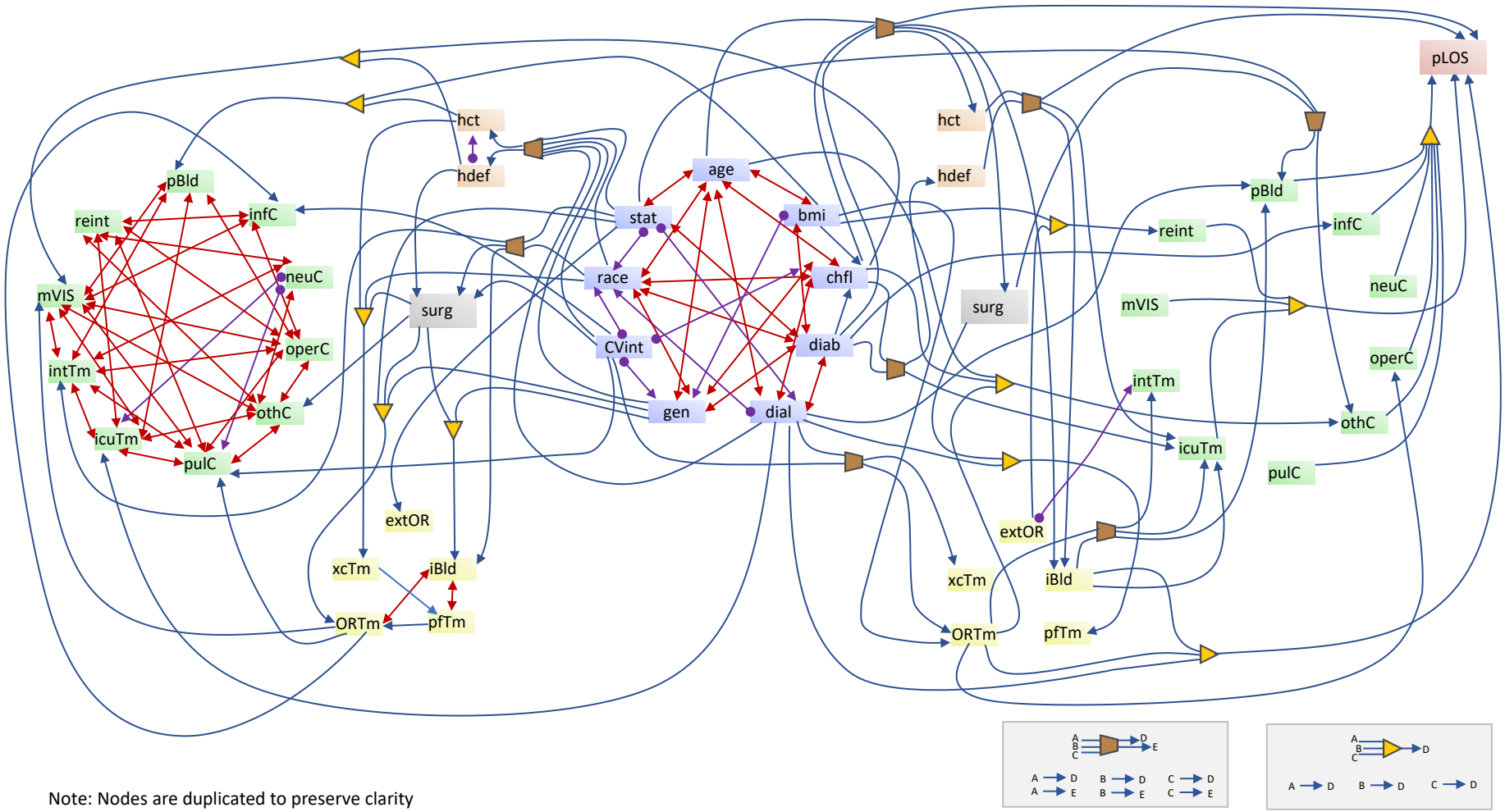
- Begin with a complete graph with only $\circ\!\!-\!\!\circ$ edges btw each vertex.
- Execute a sequence of conditional independence tests. Remove $X_i \circ\!\!-\!\!\circ X_j$ if $X_i \perp\!\!\!\perp X_j | S$.
- Orient colliders $X_i \ast\!\!\to X_k \leftarrow\!\!\ast X_j$ using "collider rule"
- Additional independence tests deal with "inducing paths"
- Additional orientations follow from the acyclicity (ancestrality) assumption

[1] Spirtes et al. (2000), Zhang (2008)

Practical challenges

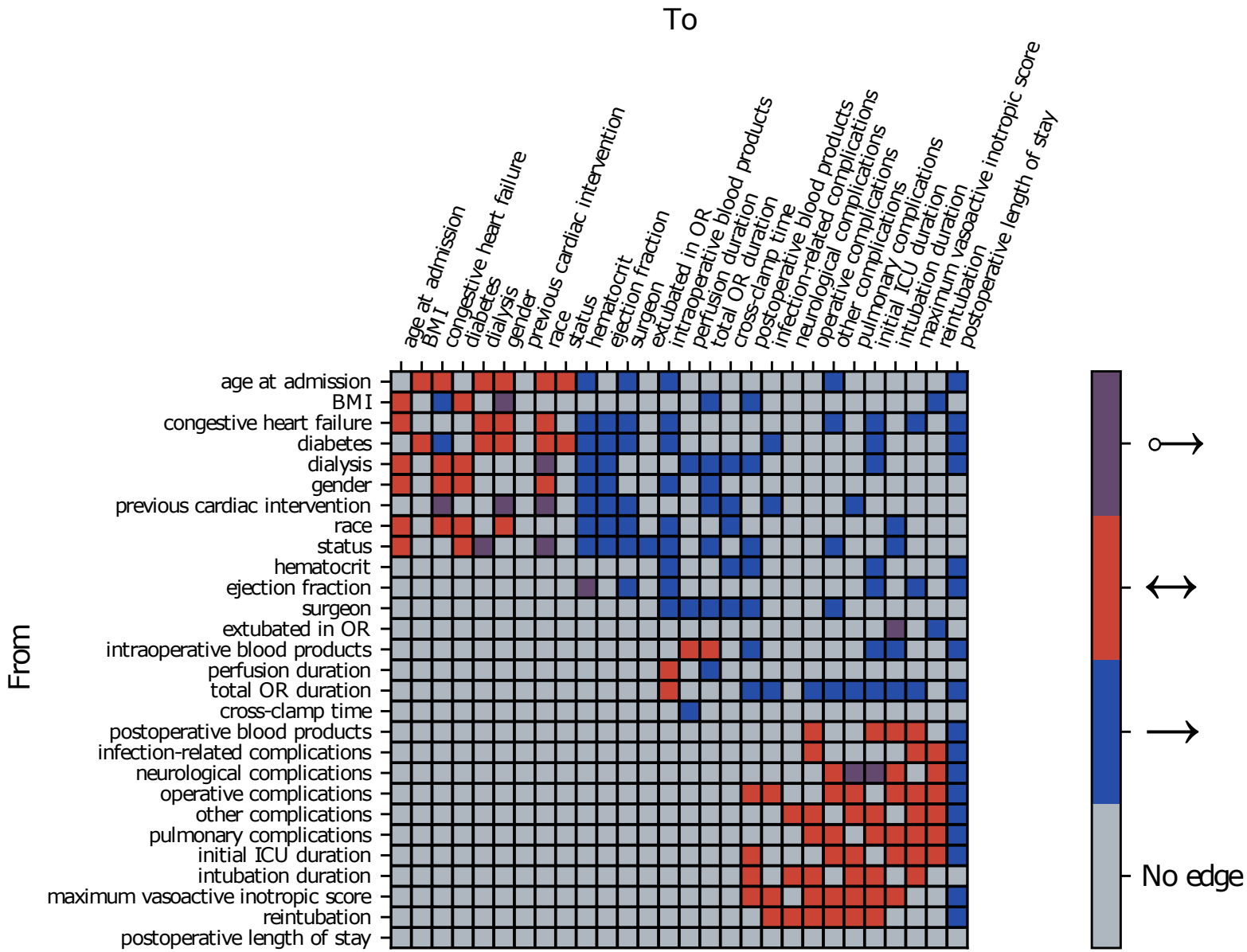
- Incorporate the aforementioned clinical background knowledge
- Data has mixture of continuous and categorical variables – used conditional independence tests based on "degenerate Gaussian" assumption (LRT)
- Limited size of the conditioning set to improve power
- Explored sensitivity of result to independence test significance threshold ("tuning parameter" α)

Results



Note: Nodes are duplicated to preserve clarity

Results


To
age at admission
BMI
congestive heart failure
diabetes
dialysis
gender
previous cardiac intervention
race
status
hematocrit
ejection fraction
surgeon
extubated in OR
intraoperative blood products
perfusion duration
total OR duration
cross-clamp time
postoperative blood products
infection-related complications
neurological complications
operative complications
other complications
pulmonary complications
initial ICU duration
intubation duration
maximum vasoactive inotropic score
reintubation
postoperative length of stay
From
No edge

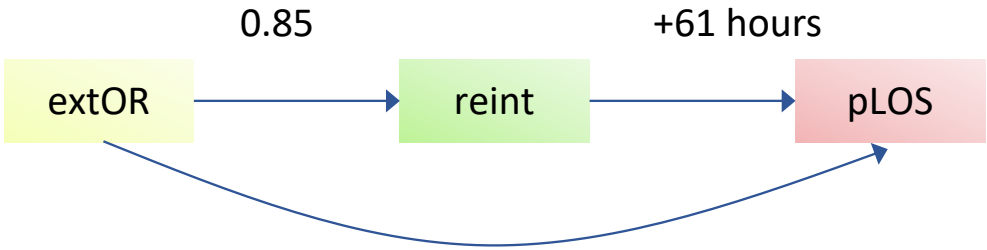
Estimating causal effects

Based on the estimated PAG, we estimate average causal effects (ACEs) of various "exposures" assuming a linear model. NB: linear model is clearly unrealistic here, so only a rough approximation. (Helps to compare with typical linear regression approach.)

Variable	Average Causal Effect (ACE)	Nominal Standard Error of ACE	2.5^{th} percentile	97.5^{th} percentile
Diabetes	†	†	†	†
BMI	†	†	†	†
Perfusion time	†	†	†	†
Neurological complications††	315.23	34.76	247.11	383.35
Preoperative dialysis††	209.35	30.67	149.24	269.45
Infection-related complications	131.48	54.65	24.38	238.59
Pulmonary complications	89.59	17.79	54.73	124.45
Reintubation	61.60	27.45	7.79	115.40
Total OR duration	48.73	2.57	43.69	53.76
Extubation in OR	-47.02	61.17	-166.92	72.88
Status	38.07	9.86	18.75	57.40
Other complications	27.38	8.96	9.82	44.94
Previous cardiac intervention	17.47	11.06	-4.20	39.14
Congestive heart failure	13.06	10.33	-7.19	33.31
Postoperative blood products	10.23	9.13	-7.66	28.13
Gender	7.86	11.03	-13.76	29.49
Intraoperative blood products	-6.26	10.14	-26.13	13.61
Operative complications	5.56	21.91	-37.39	48.51
Hematocrit	-5.22	0.89	-6.97	-3.47
Age at admission	2.21	0.44	1.34	3.07
Ejection fraction†††	-1.34	0.38	-2.09	-0.58
Maximum vasoactive-inotropic score	0.92	0.16	0.61	1.23
Initial ICU hours	0.63	0.07	0.48	0.77
Cross-clamp time	0.40	0.19	0.03	0.77
Initial intubation duration	0.00	0.00	0.00	0.00

Mechanisms of interest

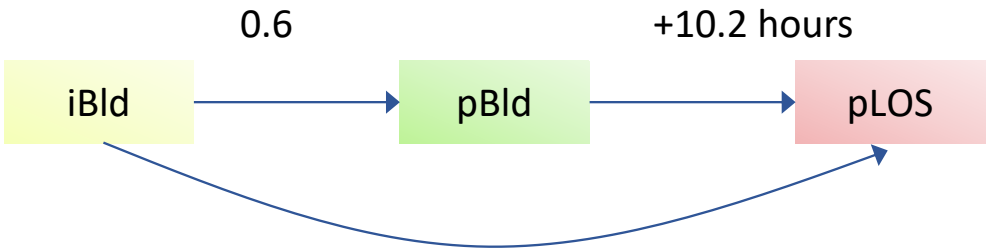
Indirect effect = 0.85 * 61 = +52 hrs



Direct effect = -99 hrs

Overall effect of extOR on pLOS = -47 hrs

Indirect effect = 0.6 * 10.2 = +6.1 hrs



Direct effect = -12.4 hrs

Overall effect of iBld on pLOS = -6.3 hrs

Results (summary)

- Most of the factors identified by clinicians were found to be causal deteriminants of pLOS – but some were only "indirect"
- Estimated causal effects were of different magnitude and sometimes direction compared with naive regression approach
- We identified some possible mechanisms of interest that warrant further study (*very tentative*)
- We hope the approach outlined here will become more normal! Especially for data-driven generation of hypotheses about mechanisms

Methodological challenges/limitations

- Have to make some practical analysis choices/compromises to learn the causal graph and estimate effects *as well as communicate to clinical audience*
- Many of our choices involved unrealistic **parametric** assumptions – more work needed on nonparametric independence tests for mixed continuous/discrete vars
- Our rough mediation analysis was based on linear path analysis – future work should incorporate semiparametric mediation estimators and better incorporate statistical uncertainty

Thank you!

"Causal Determinants of Postoperative Length of Stay in Cardiac Surgery Using Causal Graphical Learning"

J. J. R. Lee, R. Srinivasan, C. S. Ong, D. Alejo, S. Schena, I. Shpitser, M. Sussman, G. J. R. Whitman, and D. Malinsky

Appearing in *Journal of Thoracic and Cardiovascular Surgery*, 2022

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With > 2 variables, some *patterns of independence* may help narrow down the structure (assuming faithfulness).

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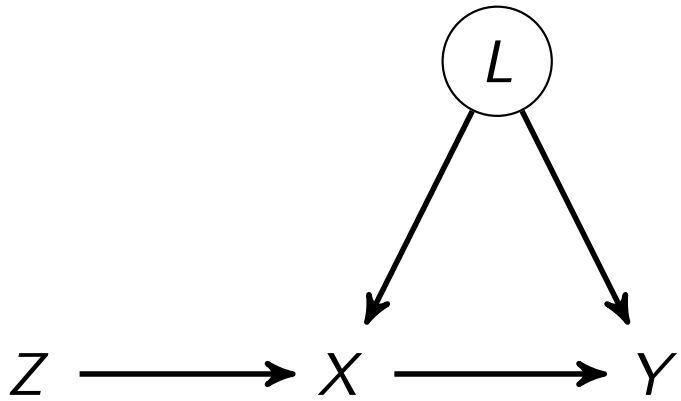
For example:



$\Rightarrow$ Y and Z are **not** independent given X. (Why?)

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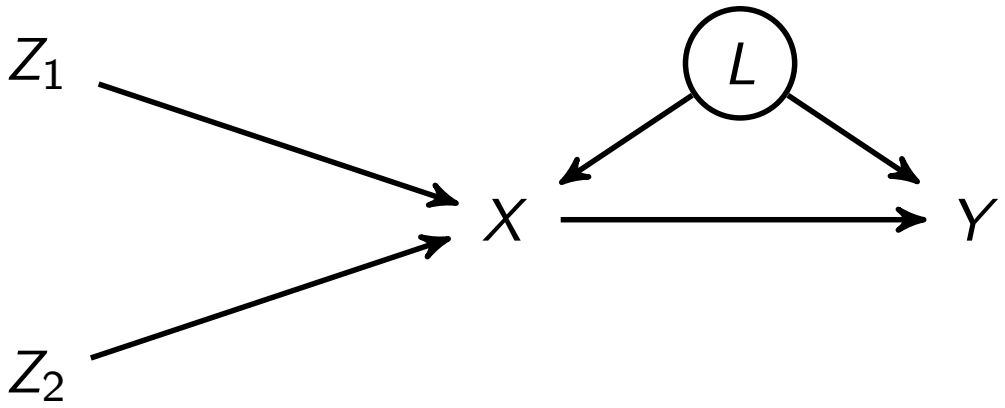
Patterns of independence constraints may rule out latent confounding



$Z_1 \perp\!\!\!\perp Z_2$
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$Y \not\perp\!\!\!\perp \{Z_1, Z_2\}$
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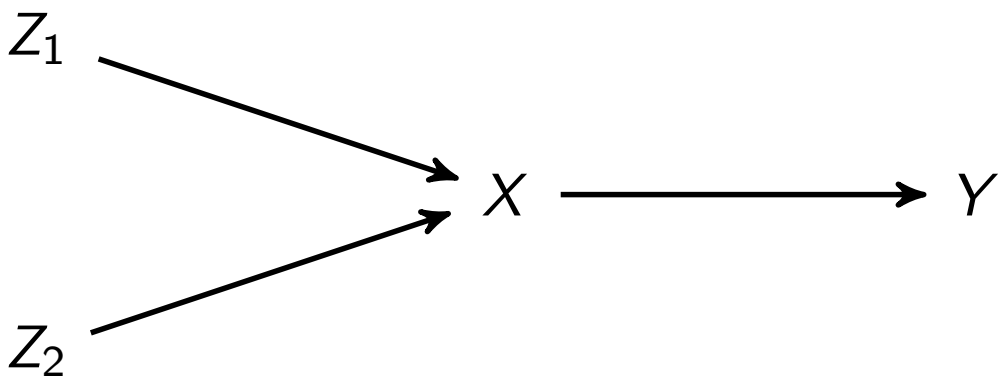

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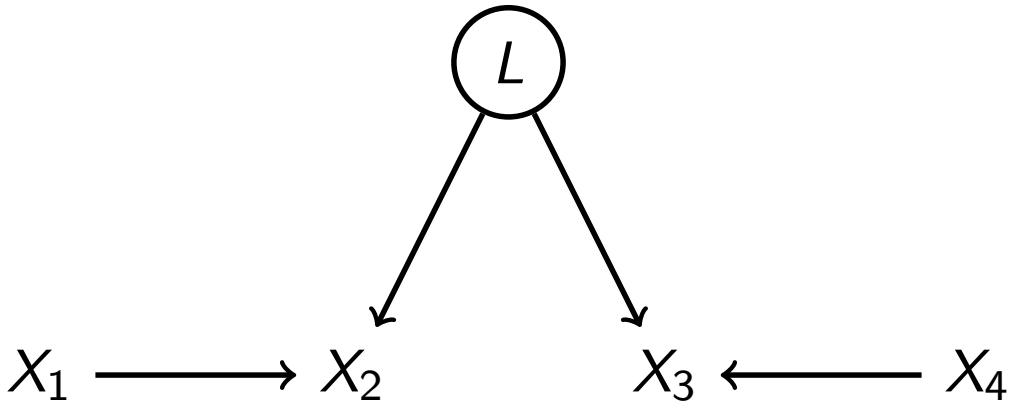
Patterns of independence constraints may also *suggest* latent confounding



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$\Rightarrow$ may represent the independence model with a *mixed* graph

Algorithm 0.1: FCI(TEST, α)

Input: Samples of the vector $X = (X_1, \ldots, X_p)'$
Output: PAG $\mathcal{P}$

1. Form the complete graph $\mathcal{P}$ on vertex set X with $\circ\!\!-\!\!\circ$ edges.
2. $s \leftarrow 0$
3. **repeat**
4. **for all** pairs of adjacent vertices (X_i, X_j) s.t. $|\text{Adj}(X_i, \mathcal{P}) \setminus \{X_j\}| \geq s$ and subsets $X_S \subset \text{Adj}(X_i, \mathcal{P}) \setminus \{X_j\}$ s.t. $|S| = s$
5. **if** $X_i \perp\!\!\!\perp X_j | X_S$ according to (TEST, α) **then** { Delete edge $X_i \circ\!\!-\!\!\circ X_j$ from $\mathcal{P}$. Let $\text{sepset}(X_i, X_j) = \text{sepset}(X_j, X_i) = X_S$.
6. **end**
7. $s \leftarrow s + 1$
8. **until** for each pair of adjacent vertices (X_i, X_j), $|\text{Adj}(X_i, \mathcal{P}) \setminus \{X_j\}| < s$.
9. **for all** triples (X_i, X_k, X_j) s.t. $X_i \in \text{Adj}(X_k, \mathcal{P})$ and $X_j \in \text{Adj}(X_k, \mathcal{P})$ but $X_i \notin \text{Adj}(X_j, \mathcal{P})$, orient $X_i \ast\!\!\rightarrow X_k \leftarrow\!\!\ast X_j$ iff $X_k \notin \text{sepset}(X_i, X_j)$.
10. **for all** pairs (X_i, X_j) adjacent in $\mathcal{P}$ **if** $\exists X_S$ s.t. $X_S \in \text{pds}(X_i, X_j, \mathcal{P})$ or $X_S \in \text{pds}(X_j, X_i, \mathcal{P})$ and $X_i \perp\!\!\!\perp X_j | X_S$ according to (TEST, α) **then** { Delete edge $X_i \ast\!\!-\!\!\ast X_j$ from $\mathcal{P}$. Let $\text{sepset}(X_i, X_j) = \text{sepset}(X_j, X_i) = X_S$.
11. Reorient all edges as $\circ\!\!-\!\!\circ$ and **repeat** step 9.
12. Exhaustively apply orientation rules (R1-R10) in Zhang (2008b) to orient remaining endpoints.
13. **return** $\mathcal{P}$.

Let $X \in \text{pds}(X_i, X_j, \mathcal{G})$ if and only if $X \neq X_i$, $X \neq X_j$, and there is a path π between X_i and X in $\mathcal{G}$ such that for every subpath $\langle X_m, X_l, X_h \rangle$ of π either X_l is a collider on the subpath in $\mathcal{G}$ or $\langle X_m, X_l, X_h \rangle$ is a triangle in $\mathcal{G}$. A *triangle* is a triple $\langle X_m, X_l, X_h \rangle$ where each pair of vertices is adjacent.

Zhang (2008b) refers to "On the completeness of orientation rules for causal discovery in the presence of latent confounders and selection bias," Artificial Intelligence 172: 1873-1896.