Scalable Causal Structure Learning via Amortized Conditional Independence Testing

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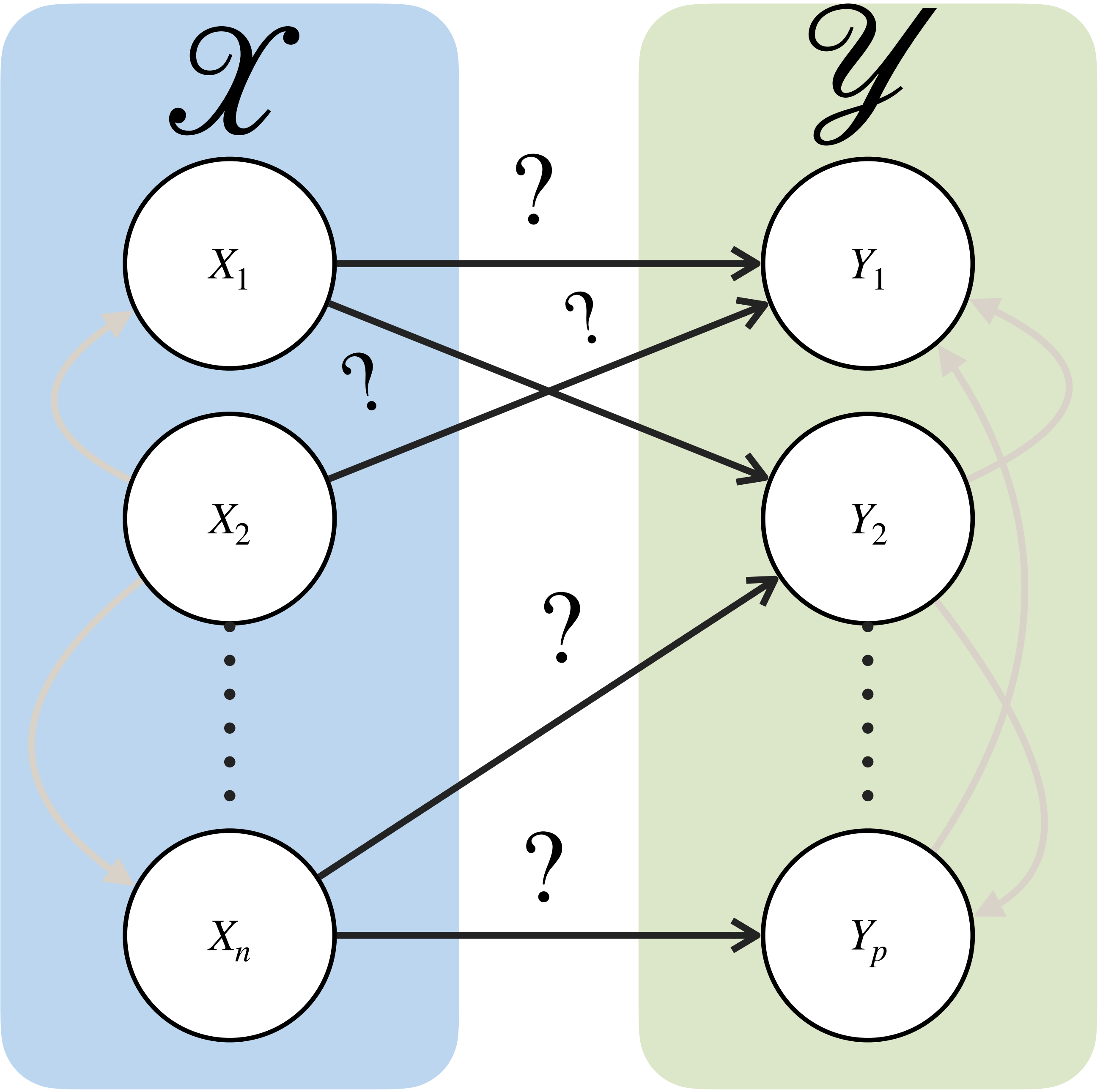
Consider a causal graph with two sets of nodes, $\mathscr{X}$ and $\mathscr{Y}$

Assume that $\mathscr{X}$ predates $\mathscr{Y}$

Key Question: Which edges exist between $\mathscr{X}$ and $\mathscr{Y}$?

The arrow of time implies that…

- No edge can be directed from $\mathscr{X}$ to $\mathscr{Y}$
- Edges between nodes in the same set can be oriented in any direction



A first step is to reduce the question to one of conditional independence relations

Assume the graph…

- satisfies the global directed Markov property
- is d-separation faithful
- does not contain latent confounders

$X_j \to Y_k$ is absent $\Longleftrightarrow$ $\exists S \subseteq Y_{-k}$ such that $X_j \perp Y_k \,|\, S, X_{-j}$

$X_j \to Y_k$ is present $\Longleftrightarrow$ $X_j \not\perp Y_k \,|\, S, X_{-j}$ for all $S \subseteq Y_{-k}$

Our goal is to learn edge-specific p-values for the graph

Key Inequality $p_{X_j \to Y_k} \leq \max_{S \subseteq Y_{-k}} p_{X_j \perp Y_k | S, X_{-j}}$

Exhaustive querying of all CI relationships is valid but may not be computationally feasible for even moderately sized graphs…

Prior work on causal discovery either…

- Searches for a graph (e.g. by maximizing a score function) but does not produce p-values with frequentist guarantees
- Outputs edge-specific p-values but only under the assumption of zero Type II error (i.e. no erroneous edge deletions) [Strobl et al., 2019]

We tackle this problem in two steps

1. **Find a function $T_{X_j,Y_k}(\,\cdot\,)$ that takes in S as an input and outputs a statistic for the hypothesis** $X_j \perp Y_k \,|\, S, X_{-j}$
2. **Use discrete optimization to find** $\hat{S} :=$ **arg** $\min_{S \subseteq Y_{-k}} T_{X_j,Y_k}(S)$

Shah and Peters [2018]

Generalized Covariance Measure

Target Estimand: $\mathbb{E}\left[\mathbb{E}[X_jY_k \,|\, S, X_{-j}] - \mathbb{E}[X_j \,|\, S, X_{-j}]\mathbb{E}[Y_k \,|\, S, X_{-j}]\right]$

(expected conditional covariance)

Inputs: Flexible ML estimates

$\hat{X}_j$ **targeting** $\mathbb{E}\left[X_j \,|\, S, X_{-j}\right]$

$\hat{Y}_k$ **targeting** $\mathbb{E}\left[Y_k \,|\, S, X_{-j}\right]$

Test statistic

Let $R_i = \left(X_j^i - \widehat{X}_j^i\right)\left(Y_k^i - \hat{Y}_k^i\right)$

If ML estimates converge sufficiently fast, then under the null (and appropriate regularity conditions),

$$T_{X_j,Y_k}^{(n)} := \frac{\sqrt{n} \cdot \frac{1}{n}\sum_{i=1}^{n} R_i}{\left(\frac{1}{n}\sum_{i=1}^{n} R_i^2 - \left(\frac{1}{n}\sum_{r=1}^{n} R_r\right)^2\right)^{1/2}} \approx N(0,1)$$

(won't have power against alternatives that are dependent but with 0 expected conditional covariance)

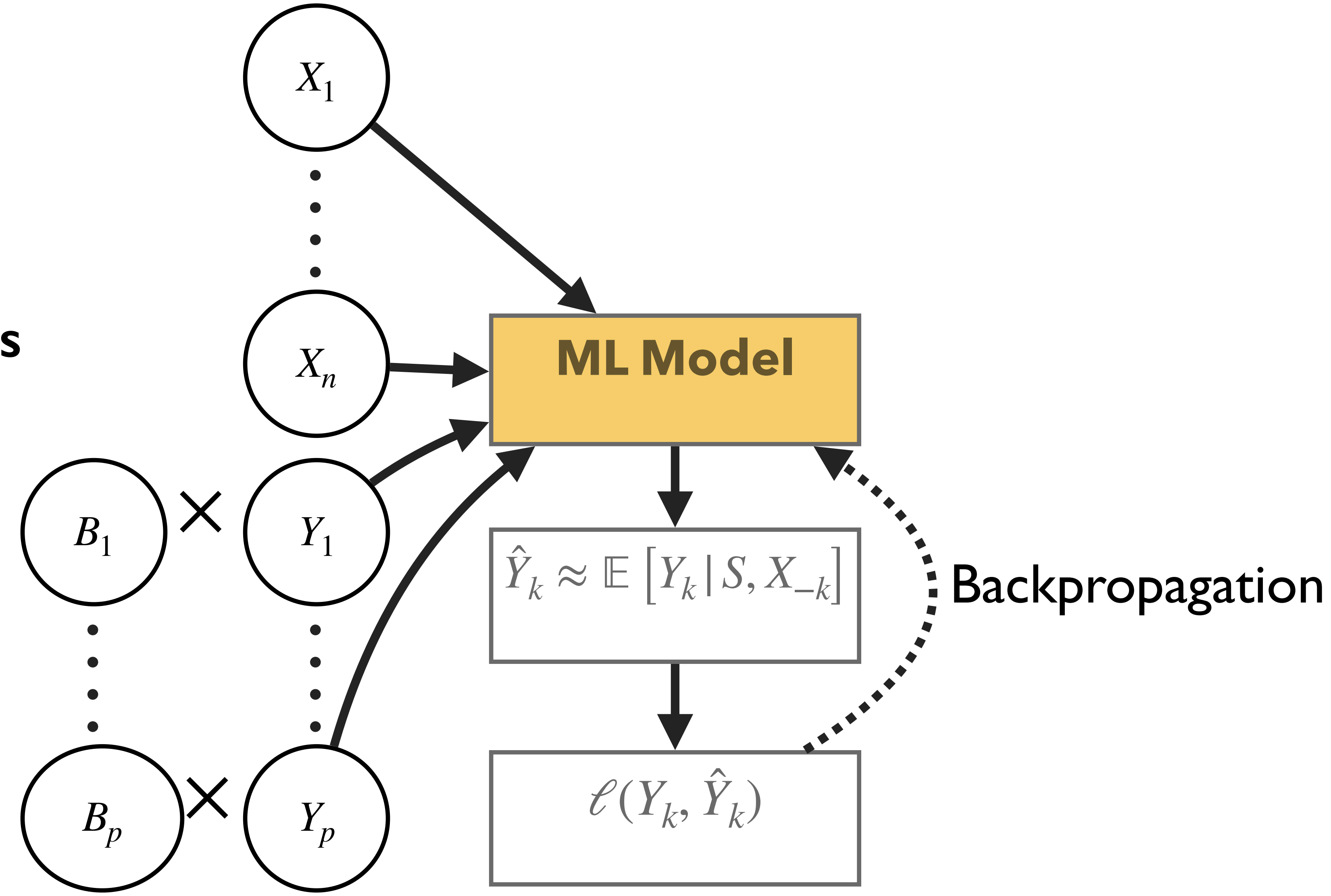
Using the GCM converts the CI testing problem to one of conditional mean estimation

Desiderata: train models $\hat{X}_j(\cdot)$ and $\hat{Y}_k(\cdot)$ that target $\mathbb{E}\left[X_j \mid S, X_{-j}\right]$ **and** $\mathbb{E}\left[Y_k \mid S, X_{-j}\right]$

Intuitively, we need to "hide" some pieces of information during training to mask out $Y_k \notin S$

During training, sample masks $B_k \sim$ Ber(p)

$S := \{Y_k$ **s.t.** $B_k = 1\}$



When using model, manually let $B_k = 1$ for all $Y_k \in S$ (given arbitrary choice of S)

Training process mimics process of an end user arbitrarily evaluating different conditioning subsets

Jang et al. [2017]

Gumbel-Softmax Optimization

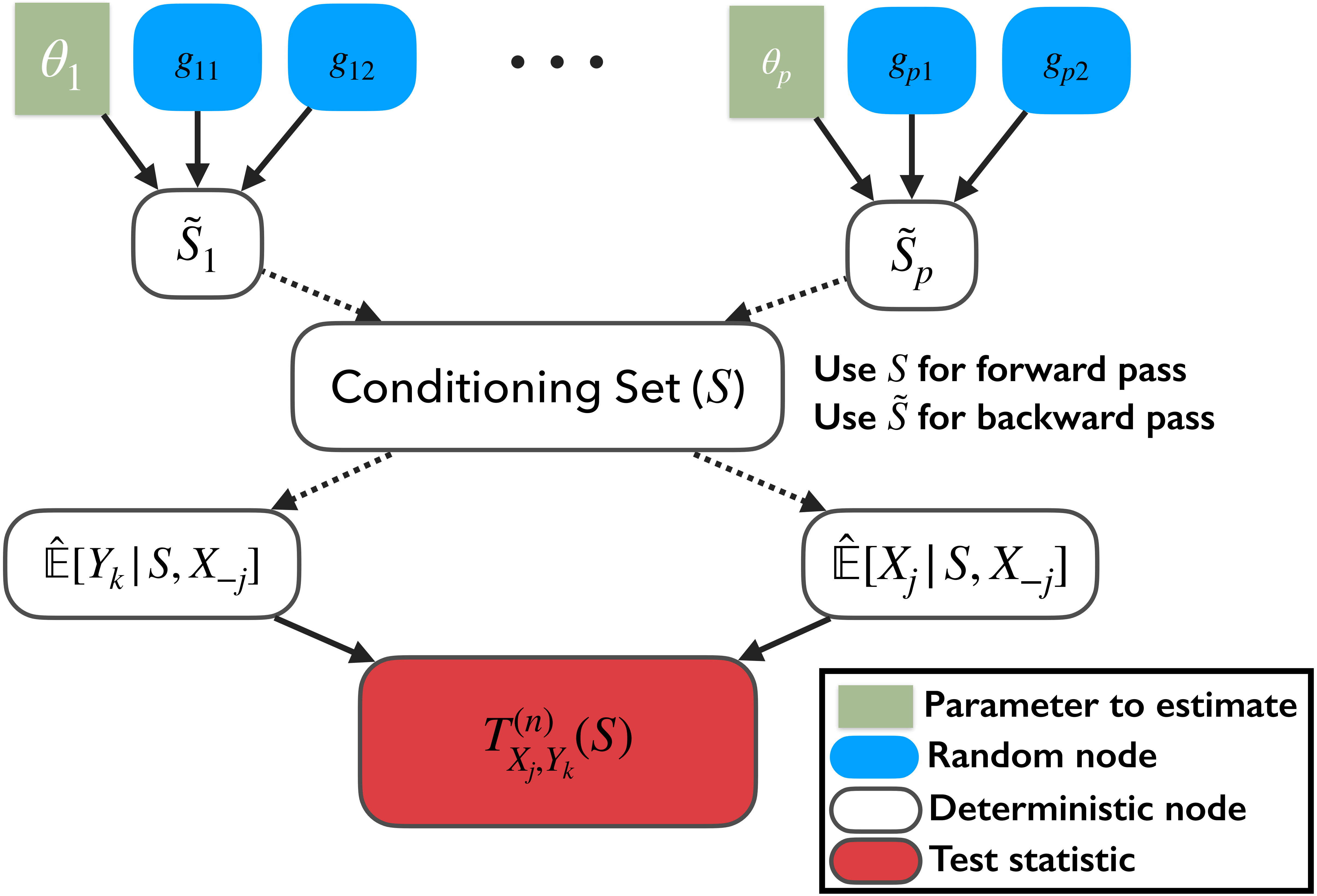
Desiderata: Learn $\arg \min_{\theta_1,\ldots,\theta_p} \mathbb{E}\left[T_n(S)\right]$ **where** $1_{Y_k \in S} \sim \text{Ber}(\theta_k)$

To enable back propagation, we replace $\frac{\partial T_n}{\partial S} \approx \frac{\partial T_n}{\partial \tilde{S}}$ **where** $\tilde{S}$ **is a continuous relaxation of** S

$$\tilde{S}_i = \frac{\exp\left((\log \theta_i + g_{i1})/\tau\right)}{\exp\left((\log \theta_i + g_{i1})/\tau\right) + \exp\left(\left(\log(1-\theta_i) + g_{i2}\right)/\tau\right)} \qquad g_{i1}, g_{i2} \sim \text{Gumbel}(0,1)$$

$\tau \to 0$ approximates a discrete distribution

We can now learn the conditioning set with gradient descent



Use S for forward pass
Use $\tilde{S}$ for backward pass

🟩 Parameter to estimate
🟦 Random node
□ Deterministic node
🟥 Test statistic

Results

We consider a cancer dataset as a motivating example

Dataset [Nguyen et al., 2022] $n = 22{,}352$ patients where

- $\mathscr{X}$ contains binary variables indicating whether certain mutations are contained in the primary tumor site
- $\mathscr{Y}$ contains binary variables indicating whether metastases have developed in secondary locations

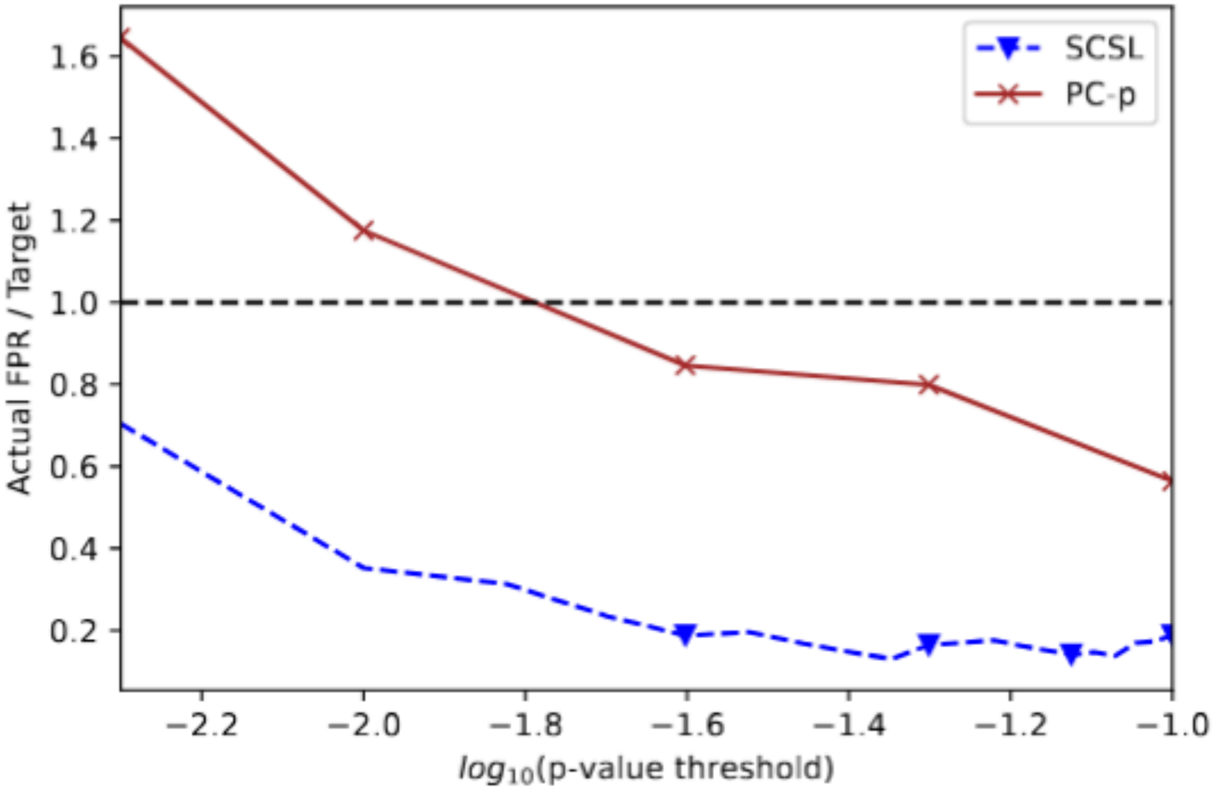
Discovering connections of the form $X_j \rightarrow Y_k$ allow us to proactively screen at-risk patients and better understand the progression of the disease.

We test using semi-synthetic data…

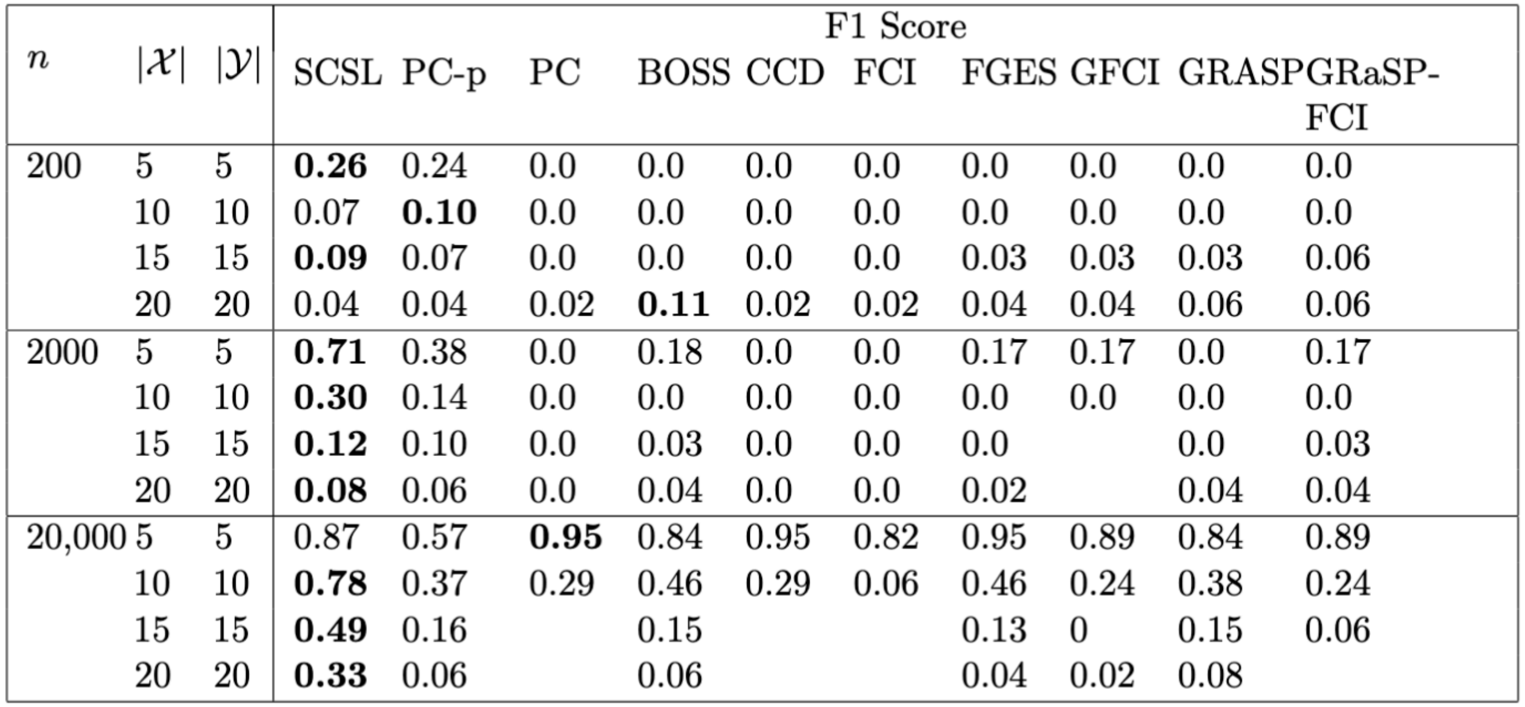
1. Posit a logistic model $\mathscr{P}$ relating $\mathscr{X}$ and $\mathscr{Y}$.
2. For reach patient, we calculate $\pi_i := \mathscr{P}(\mathscr{Y}_i \,|\, \mathscr{X}_i)$ as the likelihood of this row under the assumed model.
3. Construct new dataset by sampling Cat$(\pi_1, \ldots \pi_n)$.
4. This preserves marginal distributions of $\mathscr{X}$ and $\mathscr{Y}$ while providing ground truth knowledge of causal relationship

SCSL controls Type I error and has high power

The only other causal discovery method that produces p-values has inflated type I error, while SCSL is conservative.



SCSL also often has improved performance even when compared to methods not designed for frequentist error control…

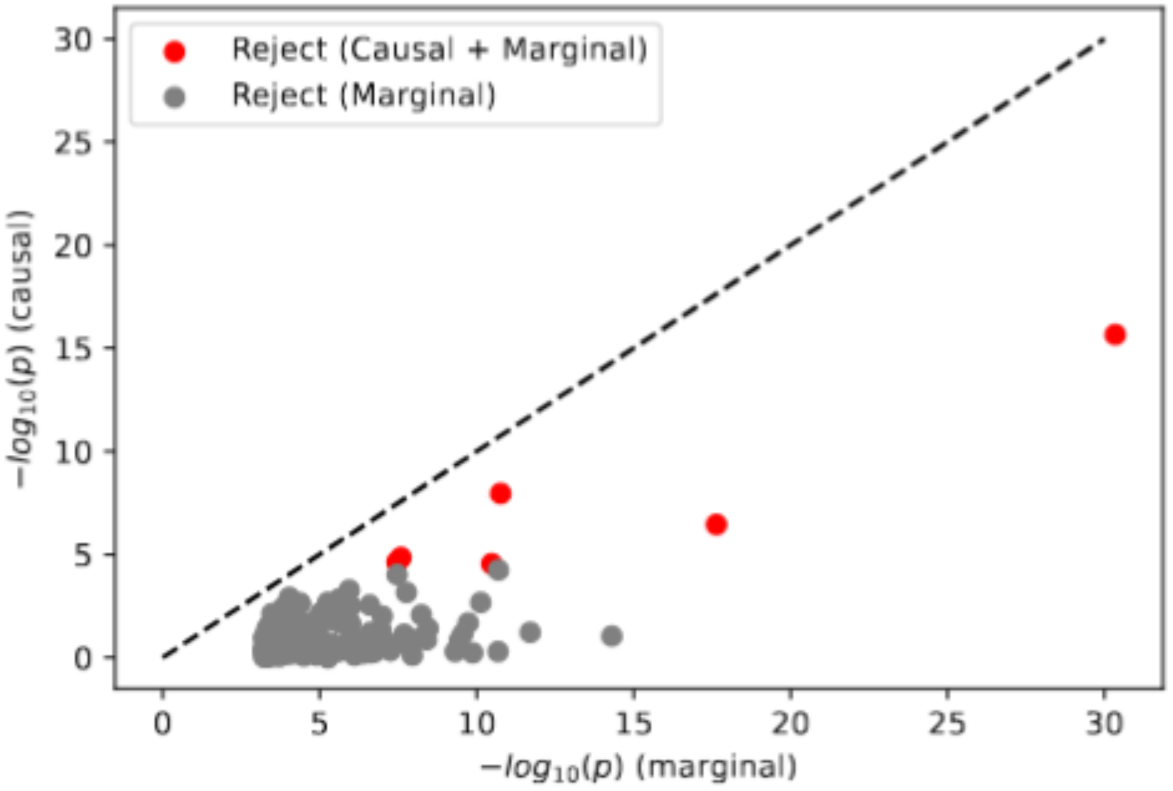


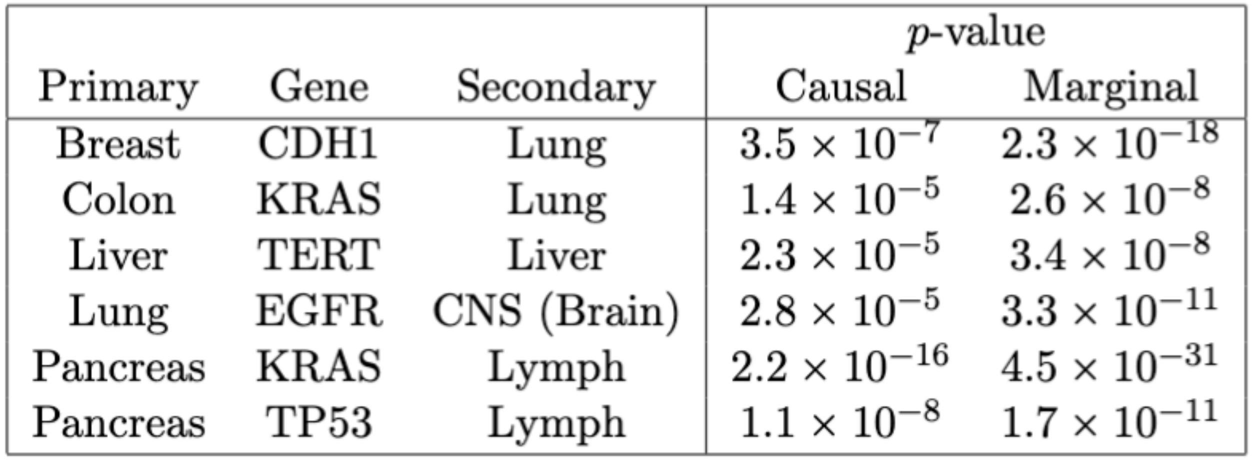
n	$\lvert\mathcal{X}\rvert$	$\lvert\mathcal{Y}\rvert$	F1 Score									
			SCSL	PC-p	PC	BOSS	CCD	FCI	FGES	GFCI	GRASP	GRaSP-FCI
200	5	5	**0.26**	0.24	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	10	10	0.07	**0.10**	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	15	15	**0.09**	0.07	0.0	0.0	0.0	0.0	0.03	0.03	0.03	0.06
	20	20	0.04	0.04	0.02	**0.11**	0.02	0.02	0.04	0.04	0.06	0.06
2000	5	5	**0.71**	0.38	0.0	0.18	0.0	0.0	0.17	0.17	0.0	0.17
	10	10	**0.30**	0.14	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	15	15	**0.12**	0.10	0.0	0.03	0.0	0.0	0.0		0.0	0.03
	20	20	**0.08**	0.06	0.0	0.04	0.0	0.0	0.02		0.04	0.04
20,000	5	5	0.87	0.57	**0.95**	0.84	0.95	0.82	0.95	0.89	0.84	0.89
	10	10	**0.78**	0.37	0.29	0.46	0.29	0.06	0.46	0.24	0.38	0.24
	15	15	**0.49**	0.16		0.15			0.13	0	0.15	0.06
	20	20	**0.33**	0.06		0.06			0.04	0.02	0.08	

On real data, the method reveals interesting connections between mutations and metastases

In the original study, 161 discoveries were identified using associative p-values with a Benjamini-Hochberg (BH) adjustment

Only 6 discoveries remain when substituting causal p-values with the same BH adjustment.





Primary	Gene	Secondary	p-value Causal	 Marginal
Breast	CDH1	Lung	3.5×10^{-7}	2.3×10^{-18}
Colon	KRAS	Lung	1.4×10^{-5}	2.6×10^{-8}
Liver	TERT	Liver	2.3×10^{-5}	3.4×10^{-8}
Lung	EGFR	CNS (Brain)	2.8×10^{-5}	3.3×10^{-11}
Pancreas	KRAS	Lymph	2.2×10^{-16}	4.5×10^{-31}
Pancreas	TP53	Lymph	1.1×10^{-8}	1.7×10^{-11}

Thank you!