Universität Zürich UZH

Master Program in Biostatistics www.biostat.uzh.ch
Master Exam

Functional Modeling with Neural Causal Models and Personalized Treatment Effect Estimation

Mike Krähenbühl, Supervisors: Beate Sick, Oliver Dürr

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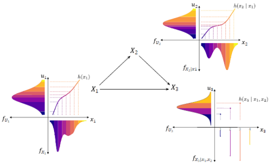
Background

Supervisors:

- Beate Sick, UZH
- Oliver Dürr, HTWG Konstanz

Paper *"Interpretable Neural Causal Models with TRAM-DAGs"* (Sick and Dürr, 2025):

- Framework to model causal relationships
- Based on transformation models
- Rely on (deep) neural networks
- Compromise between interpretability and flexibility



They showed on synthetic data, that TRAM-DAGs can be fitted on observational data and tackle causal queries on all three levels of Pearl's causal hierarchy.

Research Questions

In this presentation:

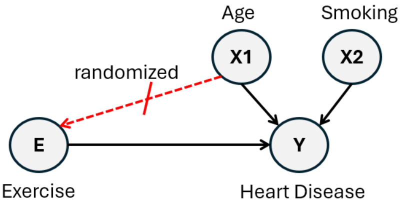
1. TRAM-DAGs
   — How do they work?
2. Individualized Treatment Effect (ITE) estimation
   — Does it work on real data (International Stroke Trial)?
   — When and why does ITE estimation fail (simulation)?
   — How to estimate ITEs with TRAM-DAGs in a complicated graph (simulation)?

TRAM-DAGs

TRAM-DAGs: Motivation

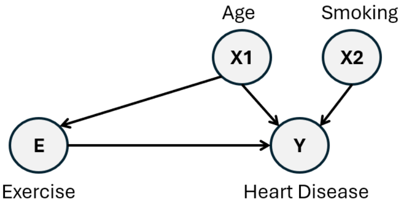
Randomized Controlled Trial:

- Gold standard for estimating causal effect
- Solves problem of confounding



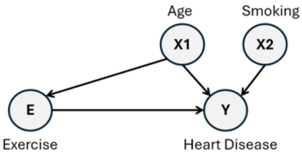
Observational Data:

- Real world, potential confounding
- We assume no unobserved confounding



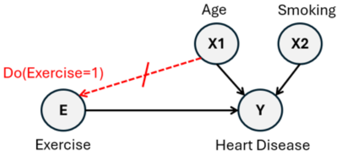
TRAM-DAGs: Motivation

Pearl's causal hierarchy (Pearl, 2009)



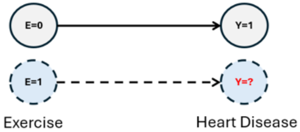
Observational: $P(Y = 1 \mid E = 1)$

"Probability of heart disease given that the person exercises"



Interventional: $P(Y = 1 \mid \mathrm{do}(E = 1))$

"Probability of heart disease if we made people start exercising"



Counterfactual: $P(Y_{(E=1)} = 1 \mid E = 0, Y = 1)$

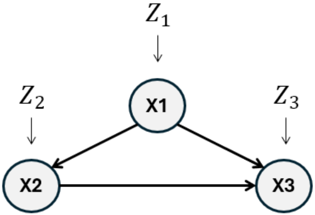
"Would someone who does not exercise and has heart disease still have it if they had exercised?"

TRAM-DAGs: Background

Structural Causal Model: Describes the causal mechanism and probabilistic uncertainty (Pearl, 2009)

- X_i = observed variable
- Z_i = noise distribution
- f_i = deterministic function: $X_i = f_i(Z_i, \mathrm{pa}_i)$

$\rightarrow$ We want a model that estimates $X_i = f_i(Z_i, \mathrm{pa}_i)$ in a flexible and interpretable way!



$$Z \sim F_{Z_1}, Z_2 \sim F_{Z_2}, Z_3 \sim F_{Z_3}$$

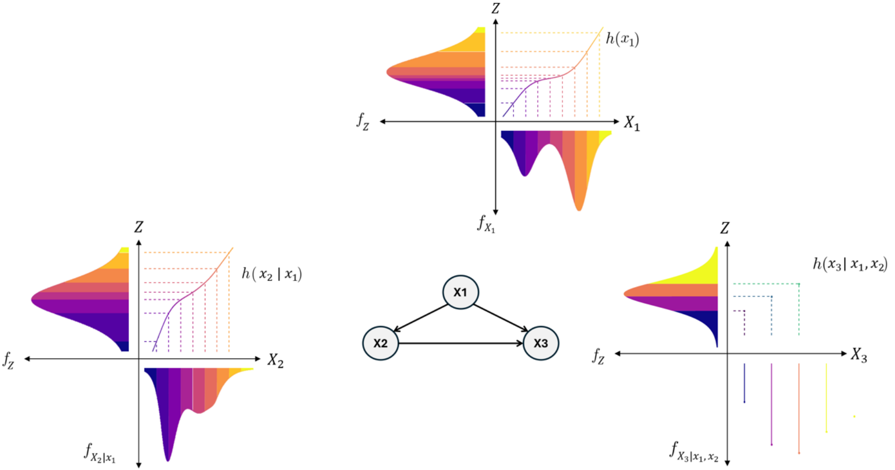
$$X_1 = f_1(Z_1)$$

$$X_2 = f_2(Z_2, X_1)$$

$$X_3 = f_3(Z_3, X_1, X_2)$$

TRAM-DAGs: Background

Proposed framework: TRAM-DAGs (Sick and Dürr, 2025)



TRAM-DAGs: Background

Transformation Models: Flexible distributional regression method (Hothorn et al., 2014)

Continuous $Y \in \mathbb{R}$:

$$F_{Y|\mathbf{X}=\mathbf{x}}(y) = F_Z(h(y) + \mathbf{x}^\top \beta)$$

Discrete $Y \in \{y_1, y_2, \dots, y_K\}$:

$$P(Y \leq y_k \mid \mathbf{X} = \mathbf{x}) = F_Z(\vartheta_k + \mathbf{x}^\top \beta), \quad k = 1, 2, \dots, K-1$$

- F_Z: CDF of the latent distribution (e.g. standard logistic)
- h: Transformation function, monotonically increasing
- $\mathbf{x}$: Predictors

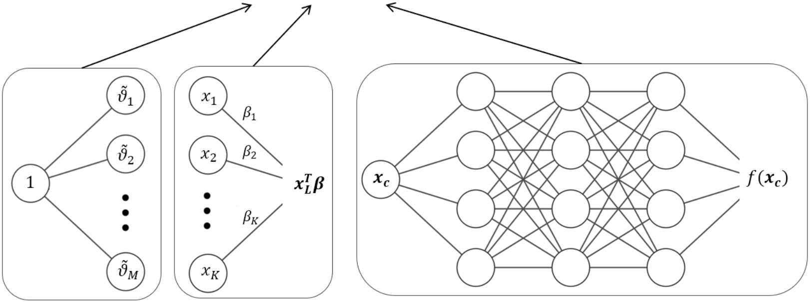
TRAM-DAGs: Background

Extended to Deep TRAMs (Sick et al., 2021)

- Customizable transformation model using neural networks (NNs)
- Minimizing negative log-likelihood (NLL) via NN optimization

Effects of predictors: LS (Linear Shift), CS (Complex Shift), CI (Complex Intercept)

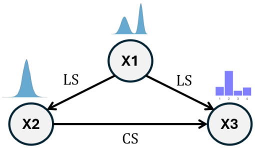
$$h(y|\boldsymbol{x_L}, \boldsymbol{x_C}) = \mathrm{SI} + \mathrm{LS}_{\boldsymbol{x_L}} + \mathrm{CS}_{\boldsymbol{x_C}}$$



TRAM-DAGs: Experiment 1 (simulation)

Setup:

- We have:
  - Observational data (simulated)
  - Predefined DAG
- We want:
  - Estimate $Z_i = h_i(X_i \mid \mathrm{pa}(X_i))$ of each variable i
  - Sample from conditional distributions for causal queries with structural equations $X_i = h_i^{-1}(Z_i \mid \mathrm{pa}(X_i))$



$$X_1 \sim F_z(h(x_1))$$

$$X_2 \sim F_z(h(x_2) + \mathrm{LS}_{x1})$$

$$X_3 \sim F_z(h(x_3) + \mathrm{LS}_{x1} + \mathrm{CS}_{x2})$$

TRAM-DAGs: Experiment 1 (simulation)

Data-generating process (DGP):

X_1: Continuous, bimodal. *Source node* (independent).

X_2: Continuous. Depends on X_1 (linear):

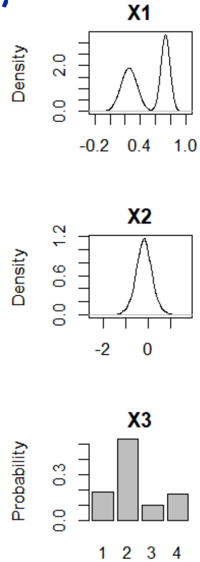
$$\beta_{12} = 2, \quad h_I(X_2) = 5X_2$$

$$\boxed{h(X_2 \mid X_1) = h_I(X_2) + \beta_{12} X_1}$$

X_3: Ordinal. Depends on X_1 (linear) and X_2 (complex):

$$\beta_{13} = 0.2, \quad f(X_2) = 0.5 \cdot \exp(X_2), \quad \vartheta_k \in \{-2,\ 0.42,\ 1.02\}$$

$$\boxed{h(X_{3,k} \mid X_1, X_2) = \vartheta_k + \beta_{13} X_1 + f(X_2)}$$



TRAM-DAGs: Experiment 1 (simulation)

Construct Model: Modular Neural Network

Inputs: Observations + assumed structure

Outputs:

- Simple Intercepts (SI): ϑ
- Linear Shifts (LS): $\beta_{12}X_1$, $\beta_{13}X_2$
- Complex Shift (CS): $f(X_2)$

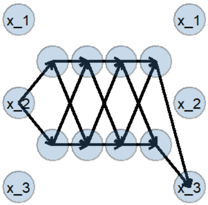
Assemble transformation functions:

$$\boxed{h(X_i \mid \text{pa}(X_i)) = \text{SI} + \text{LS} + \text{CS}}$$

$$h(X_1) = h_I(X_1)$$

$$h(X_2 \mid X_1) = h_I(X_2) + \beta_{12}X_1$$

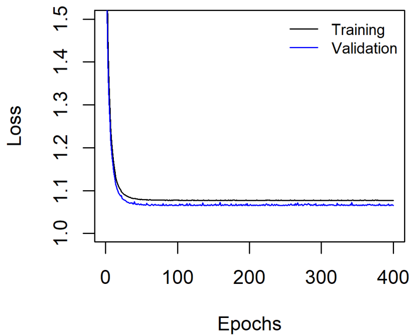
$$h(X_{3,k} \mid X_1, X_2) = \vartheta_k + \beta_{13}X_1 + f(X_2)$$

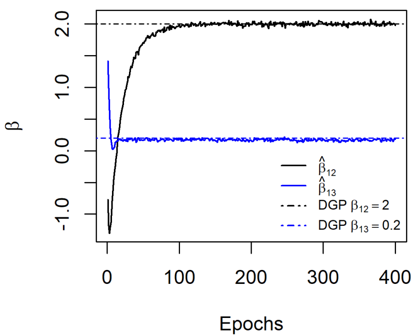


CS_{X_2} on X_3

TRAM-DAGs: Experiment 1 (simulation)

Model fitting: 20,000 training samples, 400 epochs





Sampling from the Fitted TRAM-DAG

Nodes $X_i, i \in \{1, 2, 3\}$**:**

- Sample latent value:

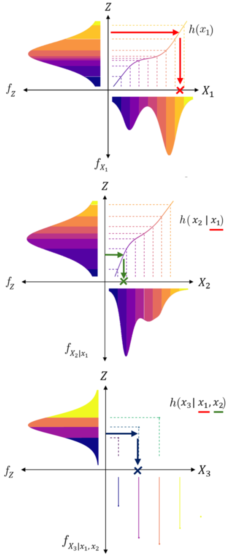
$$z_i \sim F_{Z_i} \quad \text{(e.g., } \texttt{rlogis()} \text{ in R)}$$

- Determine x_i such that:
  - **If X_i is continuous:** Solve for x_i using numerical root-finding:

$$h(x_i \mid \mathrm{pa}(x_i)) - z_i = 0$$

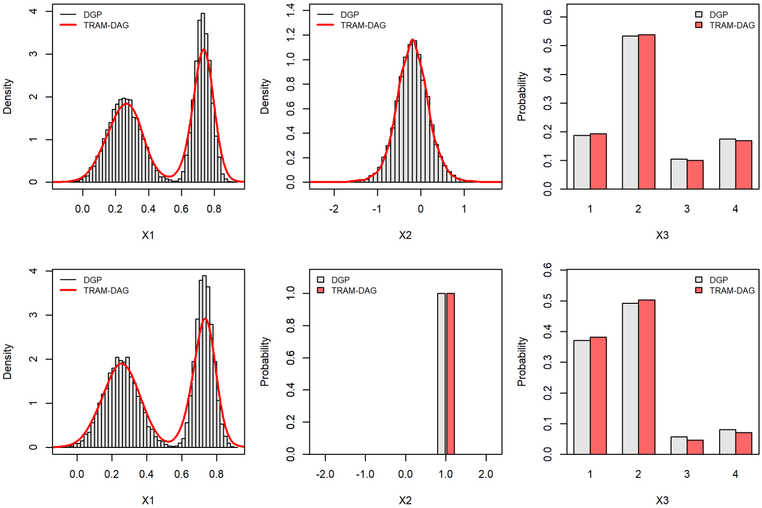
  - **If X_i is ordinal:** find the smallest category x_i such that

$$x_i = \max\left(\{0\} \cup \{x : z_i > h(x \mid \mathrm{pa}(x_i))\}\right) + 1$$



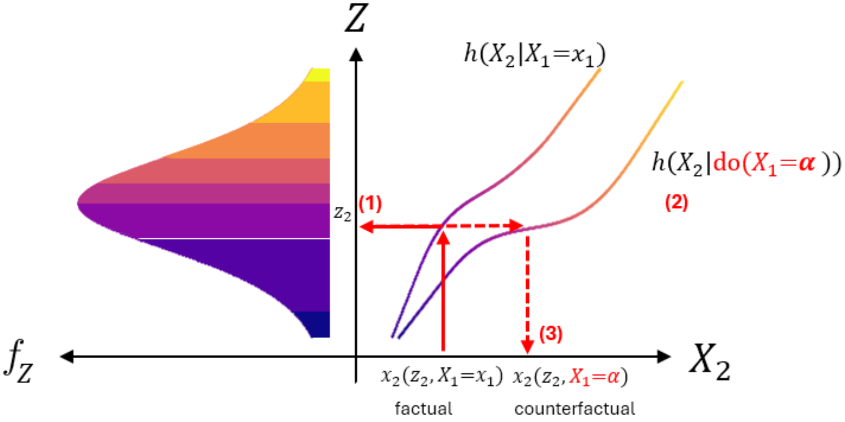
TRAM-DAGs: Experiment 1 (simulation)

Sampled observational and interventional distributions:



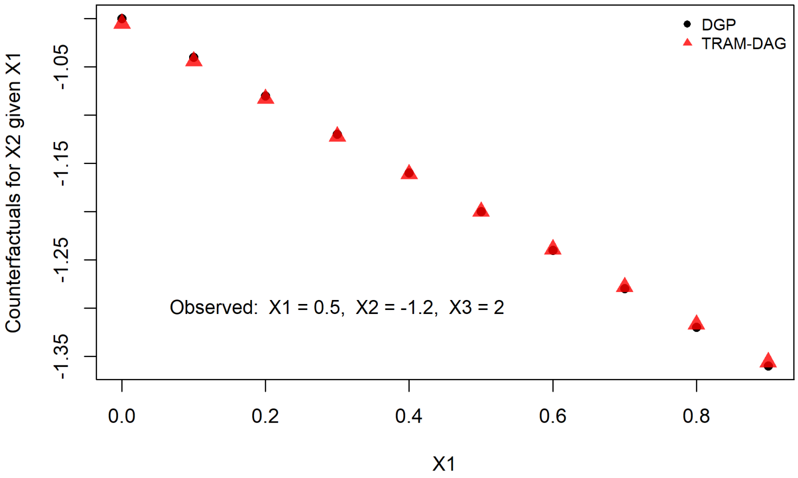
Experiment 1: TRAM-DAGs (simulation)

How to determine a counterfactual value for X_2, given some observation?



Experiment 1: TRAM-DAGs (simulation)

Counterfactuals: Counterfactual value of X_2 under varying X_1



Experiment 1: TRAM-DAGs (simulation)

Discussion: With TRAM-DAGs we can

- estimate the functional form of the edges in the DAG
- customize flexibility and interpretability (SI/CI, LS, CS)
- sample from the fitted model (observational/interventional)
- estimate counterfactuals

Individualized Treatment Effects (ITEs)

Individualized Treatment Effect (ITE): Motivation

Why ITE?

- RCTs estimate the Average Treatment Effect (ATE)
- Individuals may respond differently based on covariates
- Important for personalized medicine, targeted marketing, etc.
- Heterogeneity mostly driven by treatment-covariate interactions

Definition: Difference in potential outcomes (Rubin, 2005)

$$Y_i(1) - Y_i(0)$$

where $Y_i(1)$: outcome if treated, $Y_i(0)$: if not treated

Fundamental problem: We never observe both $Y_i(1)$ and $Y_i(0)$ for the same individual (Holland, 1986)

From Unobservable to Estimable ITE

Goal: Estimate the *individualized treatment effect (ITE)* from observed data (Hoogland et al., 2021).

$$
\begin{aligned}
\mathrm{ITE}(\mathbf{x}_i) &= \mathbb{E}[Y_i(1) - Y_i(0) \mid \mathbf{X} = \mathbf{x}_i] \\
&= \mathbb{E}[Y_i(1) \mid T = 1, \mathbf{X} = \mathbf{x}_i] - \mathbb{E}[Y_i(0) \mid T = 0, \mathbf{X} = \mathbf{x}_i]
\end{aligned}
$$

(by ignorability/exchangeability: no unmeasured confounding)

$$
= \mathbb{E}[Y_i \mid T = 1, \mathbf{X} = \mathbf{x}_i] - \mathbb{E}[Y_i \mid T = 0, \mathbf{X} = \mathbf{x}_i]
$$

(by consistency: observed = potential outcome, e.g. correct label)

Further assumptions:

- **Positivity:** every individual could receive either treatment (e.g. no deterministic assignment)
- **No interference:** one person's treatment doesn't affect another's outcome

Individualized Treatment Effect (ITE): Models

How did we estimate the potential outcomes $\mathbb{E}[Y_i \mid T = t, \mathbf{X} = \mathbf{x}_i]$?

- **T-learner:**
  1. Fit two separate models on treated and control groups
  2. Predict $\mathbb{E}[Y_i \mid \mathbf{X} = \mathbf{x}_i]$ from each model

  - Logistic regression / Random forest (with hyperparameter tuning)

- **S-learner:**
  1. Fit one model on all data with treatment as a feature
  2. Predict $\mathbb{E}[Y_i \mid \mathrm{do}(T = t), \mathbf{X} = \mathbf{x}_i]$ by setting $T = 0$ and $T = 1$

  - TRAM-DAGs (SCM, flexible, interactions, generative)

Experiment 2: ITE on International Stroke Trial (IST)

Background/Motivation: Chen et al. (2025) showed that results of models used for ITE estimation did not generalize to the test set.

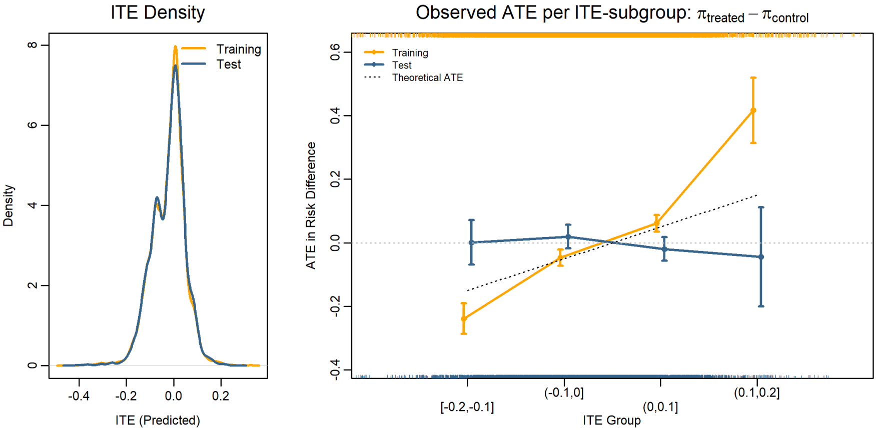
International Stroke Trial (IST):

- Large RCT on stroke patients (19,435 patients, 21 baseline covariates)
- Evaluated the effects of aspirin on stroke patients
- Binary treatment and outcome

Research question: Do we reach similar conclusion as Chen et al. (2025) when estimating ITEs with T-learners (logistic regression, tuned random forest) and S-learner (TRAM-DAGs) on IST dataset.

Experiment 2: ITE on International Stroke Trial (IST)

Results: with T-learner tuned random forest (`comets` package (Kook, 2024)):



Experiment 2: ITE on International Stroke Trial (IST)

Discussion:

- We obtained similar results as Chen et al. (2025)
- Some models suggest a range of ITEs, but these ITEs do not generalize to the test set (no effect)
- We do not know why, since ground truth is unknown

Experiment 3: ITE model robustness in RCTs (simulation)

Motivation: ITE estimation failed on the real-world RCT of the International Stroke Trial (IST). We want to know why.

Research question: What factors contribute to the failure of ITE estimation in causal ML models?

Setup:

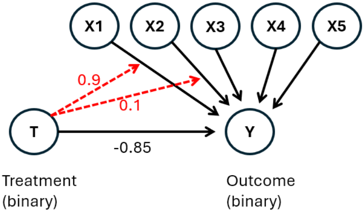
— Simulate different RCT scenarios to understand when ITE estimation fails

— Apply simple model (logistic regression; matching DGP) and non-parametric model (tuned random forest)

Simulation Case 1: Fully Observed

Setup:

- $n = 20{,}000$
- $T \sim \text{Bernoulli}(0.5)$
- $\mathbf{X} = (X_1, \ldots, X_5)^\top \sim \mathcal{N}(\mathbf{0}, \Sigma)$
- $\mathbf{X_{TX}} = (X_1, X_2)^\top$ interaction

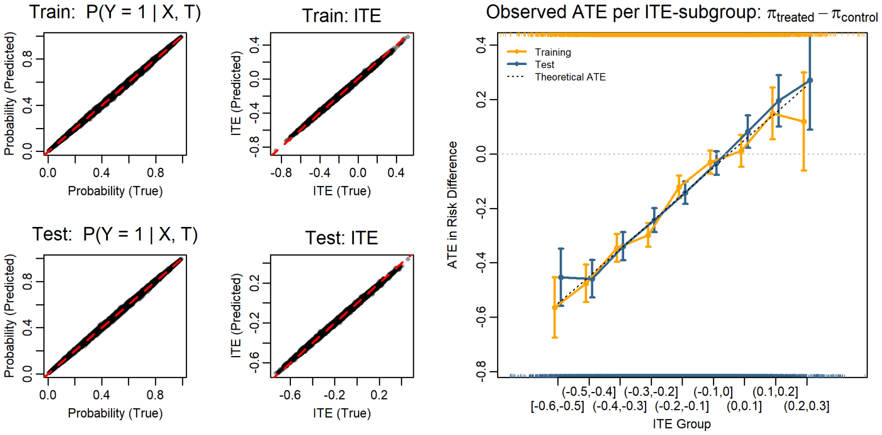


Outcome model:

$$\mathbb{P}(Y = 1 \mid \mathbf{X}, T) = \text{logit}^{-1}\left(\beta_0 + \beta_T T + \boldsymbol{\beta}_X^\top \mathbf{X} + T \cdot \boldsymbol{\beta}_{TX}^\top \mathbf{X_{TX}}\right)$$

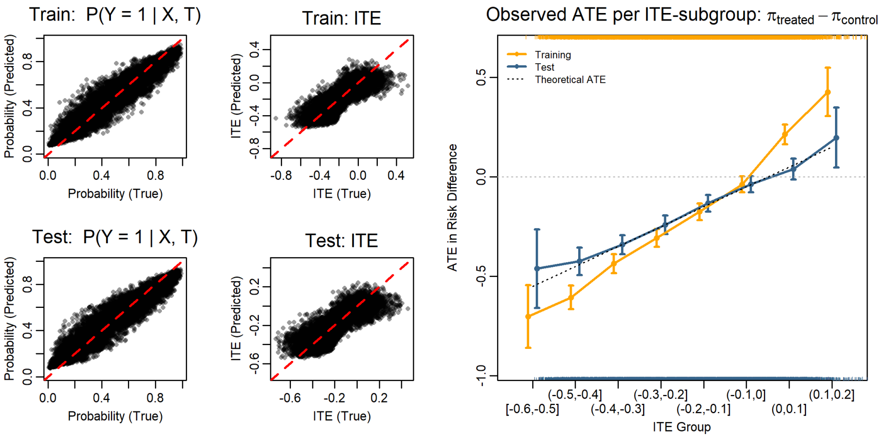
Simulation Case 1: Fully Observed

Results with T-learner logistic regression (glm):



Simulation Case 1: Fully Observed

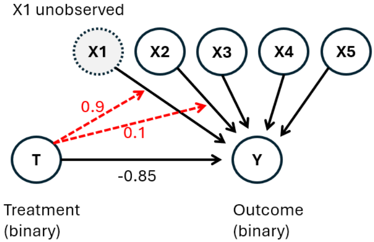
Results with T-learner tuned random forest (`comets` package):



Simulation Case 2: Unobserved Interaction

Setup:

- $n = 20{,}000$
- $T \sim \text{Bernoulli}(0.5)$
- $\mathbf{X} = (X_1, \ldots, X_5)^\top \sim \mathcal{N}(\mathbf{0}, \Sigma)$
- $\mathbf{X_{TX}} = (X_1, X_2)^\top$ interaction



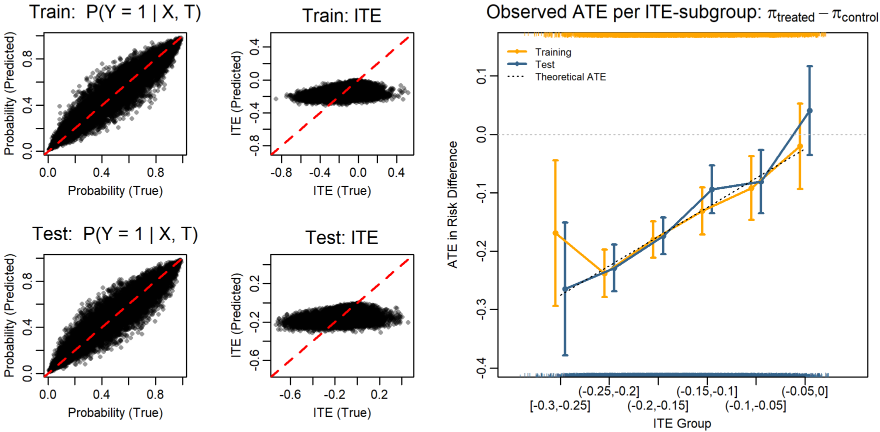
Outcome model:

$$\mathbb{P}(Y = 1 \mid \mathbf{X}, T) = \text{logit}^{-1}\left(\beta_0 + \beta_T T + \boldsymbol{\beta}_X^\top \mathbf{X} + T \cdot \boldsymbol{\beta}_{TX}^\top \mathbf{X_{TX}}\right)$$

Note: Same DGP, but X_1 is not observed!

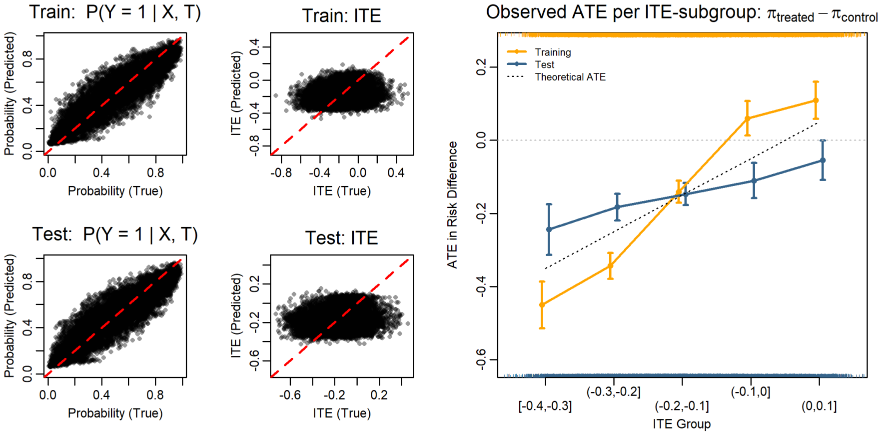
Simulation Case 2: Unobserved Interaction

Results with T-learner logistic regression (glm):



Simulation Case 2: Unobserved Interaction

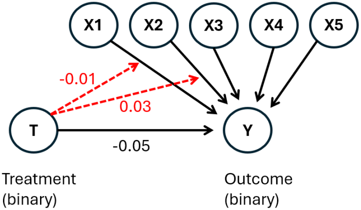
Results with T-learner tuned random forest (`comets` package):



Simulation Case 3: Fully Observed, Small Effects

Setup:

- $n = 20{,}000$
- $T \sim \text{Bernoulli}(0.5)$
- $\mathbf{X} = (X_1, \ldots, X_5)^\top \sim \mathcal{N}(\mathbf{0}, \Sigma)$
- $\mathbf{X_{TX}} = (X_1, X_2)^\top$ interaction



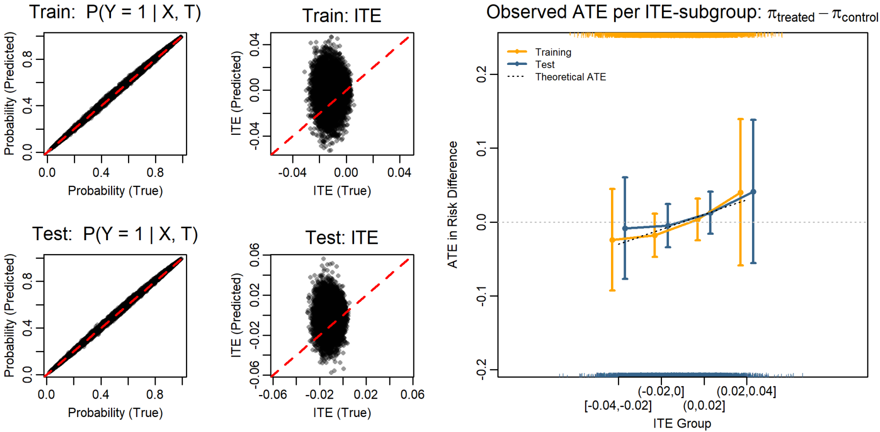
Outcome model:

$$\mathbb{P}(Y = 1 \mid \mathbf{X}, T) = \text{logit}^{-1}\left(\beta_0 + \beta_T T + \boldsymbol{\beta}_X^\top \mathbf{X} + T \cdot \boldsymbol{\beta}_{TX}^\top \mathbf{X_{TX}}\right)$$

Note: Same DGP, but weak treatment effects!

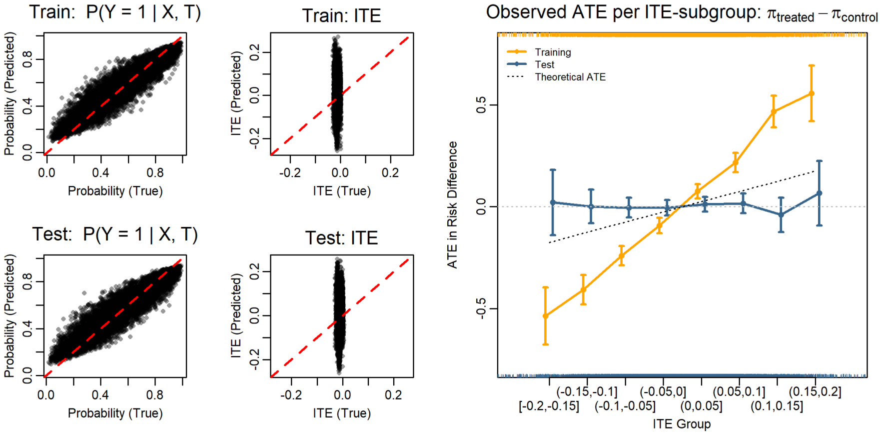
Simulation Case 3: Fully Observed, Small Effects

Results with T-learner logistic regression (glm):



Simulation Case 3: Fully Observed, Small Effects

Results with T-learner Random Forest (`comets` package):

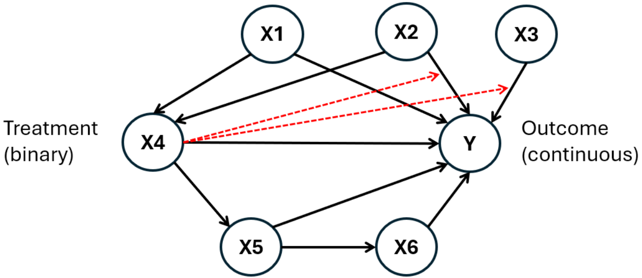


Experiment 3: ITE model robustness in RCTs (simulation)

Discussion:

- When a high predicted treatment effect (ITE) corresponds to a high observed effect in the train set (strong discrimination), but not in the test set, it might be due to **unobserved interaction variables** or **weak treatment effects**.
- This is more likely to occur with complex models, as they tend to overfit when the interaction is not observed.

TRAM-DAGs: Example for ITE estimation

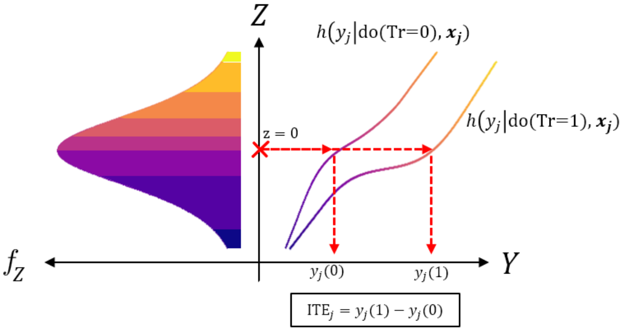


DGP:

- $X5 = h_5^{-1}(\epsilon - 0.8\,X4) \quad \rightarrow$ (depends on treatment)
- $X6 = h_6^{-1}(\epsilon + 0.5\,X5) \quad \rightarrow$ (depends on treatment through X5)
- $Y = h_7^{-1}(\epsilon - \beta_1 X1 - \beta_2 X2 - \beta_3 X3 - \beta_4 X4 - \beta_5 X5 - \beta_6 X6 - Tr \cdot (\beta_{2Tr} X2 + \beta_{3Tr} X3))$

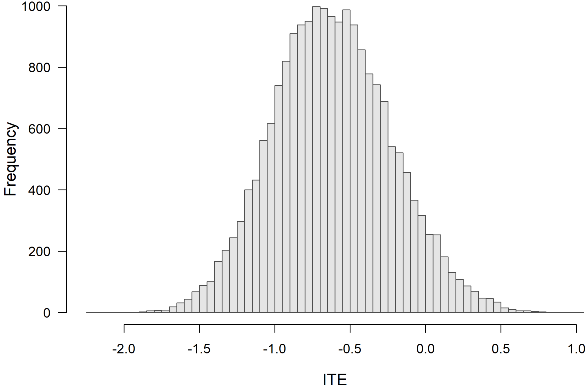
TRAM-DAGs: Example for ITE estimation

$$\text{ITE} = \text{median}(Y \mid \text{do}(T = 1), X) - \text{median}(Y \mid \text{do}(T = 0), X)$$



TRAM-DAGs: Example for ITE estimation

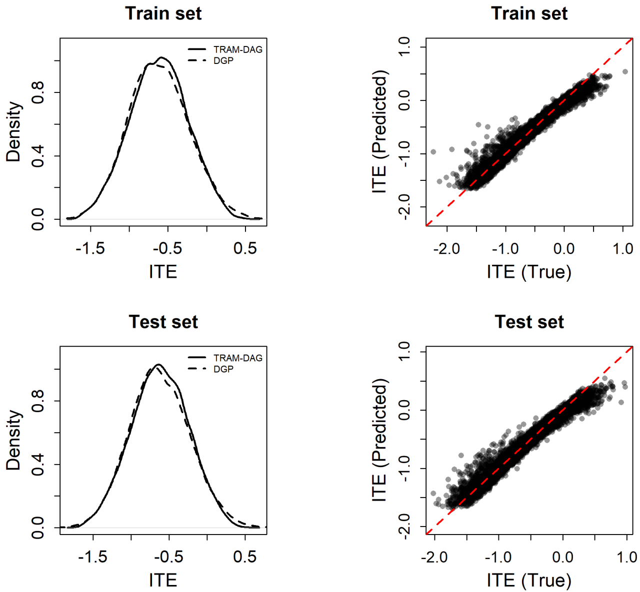
$$\mathrm{ITE} = \mathrm{median}(Y \mid \mathrm{do}(T=1), X) - \mathrm{median}(Y \mid \mathrm{do}(T=0), X)$$



TRAM-DAGs: Estimate Potential Outcomes

1. Estimate each $h_i(X_i \mid \mathrm{pa}(X_i))$ fully flexible (deep-NN / complex intercept)
2. Take the train set or a test set
3. $Z_i = h(X_i \mid pa(X_i))$ gives us the (observed) latent variable for each X_i
4. Determine counterfactuals for X5 and X6 with the (observed) latent variables Z_i
5. Determine medians of potential outcomes $Y(1)$ and $Y(0)$
6. $\mathrm{ITE} = \mathrm{median}(Y(1) \mid X_{tx}) - \mathrm{median}(Y(0) \mid X_{ct})$

TRAM-DAGs: Example for ITE estimation (Results)



Conclusion: Key Findings & Outlook

TRAM-DAGs:

- Flexible and customizable; recovers known causal structure
- Captures interactions between variables

ITE Estimation:

- Calibration is crucial
- Sensitive to missing effect modifiers or weak heterogeneity
- TRAM-DAGs yield unbiased ITEs when DAG is correct and heterogeneity exists

Limitations: Simulations simplify reality; modeling assumptions affect interpretability (e.g., scale of effects)

Recommendations: Apply TRAM-DAGs to real-world data; study ITE estimation under unobserved effect modifiers

Outlook

Findings: TRAM-DAGs

- Customizable; accurately recovers causal relationships in known DAG
- Can model interactions between variables

Findings: Individualized treatment effects (ITE)

- Calibration is important for ITE prediction
- Missing effect modifiers (or weak heterogeneity) are problematic
- TRAM-DAGs estimate unbiased ITEs in complex DAG if fully known and heterogeneity in treatment effects is present

Limitations: Simulations may not represent real-world complexity, TRAM-DAGs require modeling assumptions – for instance, regarding the scale of conditional effects – if interpretability is to be preserved

Recommendations: Apply TRAM-DAGs on real-world data; ITE estimation under unobserved effect modifiers

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