Machine Learning for Estimating Individualized Treatment Effect from Real World Data for Use in Health Technology Assessment

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Introduction

Average treatment effects (ATE) are at the heart of clinical and policy decision making, used to derive incremental cost-effectiveness ratio and incremental net benefits.

More nuanced decision-making accounting for heterogeneity in treatment effect may yield greater population health gains [1-3].

Clinicians and payers have focused more on considerations at the subgroup- and individual levels.

Patients and clinicians want to know what the outcomes of a treatment is for them, not for an average individual.

From ATE to ITE

The individualized treatment effect (ITE) for individual i with a vector of individual-specific predictors $X = x_i$ can be defined as:

$$ITE(x_i) = E[Y_i^{a=1}|X = x_i] - E[Y_i^{a=0}|X = x_i]$$

The $ATE(E[Y_i^{a=1}] - E[Y_i^{a=0}])$ is equal to the average of the $ITEs(E[Y_i^{a=1} - Y_i^{a=0}])$.

Identification Assumptions of ITE are the same as ATE, including **consistency**, **conditional exchangeability**, **positivity**, **no interference**.

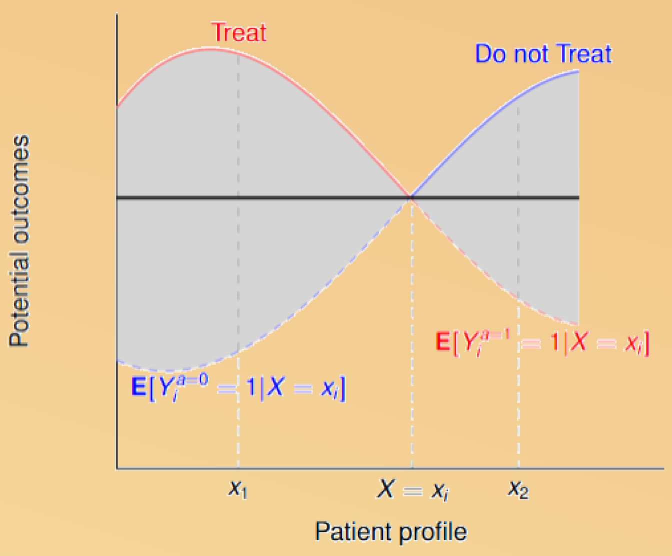

Figure 1: Optimal treatment strategy based on potential outcomes

Challenges in Estimating ITE

1. **What Data Is Required for ITE Estimation?**

ITE is essentially a highly conditional average treatment effect and can be realistically derived from large, well-designed, real-world studies.

2. **Why use machine learning (ML) to Estimate ITE?**

ML identify potential subgroups and select covariates (NICE real-world evidence framework June 2022). ML flexibly model complex interactions between treatment and high-dimensional individual characteristics. ML are not substitutes for content knowledge and clinicians' opinions.

3. **Uncertainty Quantification** makes ML more trustworthy and facilitate safer and more consistent treatment decisions.

4. **Parameters** focus on TTE outcome, baseline risk, related measures of treatment effect, HRQoL and costs.

Risk of Bias in Causal Inference

- General to All Observational Studies
  1. Selection Bias
  2. Confounding
  3. Collider Bias
  4. Measurement Error
- Specific to Longitudinal Analysis
  1. Loss to Follow-Up
  2. Exposure Affected Time-varying Confounding
  3. Immortal Time Bias

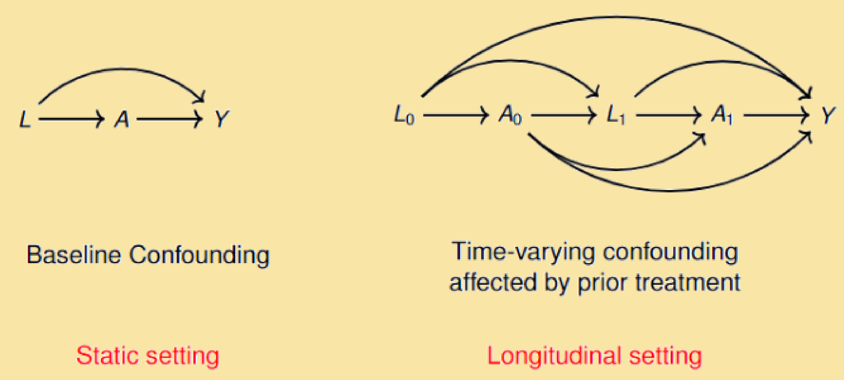

Figure 2: Confounding

Summarize ML Algorithms

We **extract data** based on:

- the available data (cross-sectional or longitudinal);
- the outcome of interest (continuous, binary or TTE);
- whether handle observed or unobserved confounders;
- whether quantify uncertainties of treatment effects or predicted outcomes;
- software implementation (R, Python or Stata).

ML Methods to Estimate ITE in Static Setting

Most ML methods:

- are designed for binary or continuous outcomes, require large samples;
- handle baseline confounding, assume no hidden confounding;
- not quantify uncertainty of both the predicted outcomes and treatment.

Table 1: Methods to Estimate ITE in Static Settings

Method	Confounding	Outcome	Uncertainty	Software
Bayesian Additive Regression Trees, Bayesian Causal Forest	Observed	Continuous, Binary	Counterfactual, Treatment Effect	R: BART, bartCause, bcf
Causal Forest, Causal Multi-task Gaussian Processes, Non-stationary Gaussian Processes	Observed, Unobserved	Continuous, Binary	Counterfactual, Treatment Effect	R: randomForestSRC, grf, BayesTree, causalForest
Virtual Twins Random Forests(VT), VT interaction, Counterfactual Random Forest (RF), counterfactual synthetic RF, Bivariate RF	Observed	Continuous, Binary	Counterfactual, Treatment Effect	R: aVirtualTwins, model4you
Balancing Neural Network	Observed	Continuous, Binary	No	No
Treatment-Agnostic Representation Network	Observed	Continuous, Binary	Treatment Effect	Python: cfrnet
Local Similarity Preserved Individual Treatment Effect	Observed	Continuous, Binary	No	Python: SITE
Deep Counterfactual Networks with Propensity-Dropout	Observed	Continuous, Binary	Treatment Effect	Python: DCN-PD
Multi-Task Deep Learning and K-Nearest Nighbours	Observed	Continuous, Binary	No	Python: CNN
Generative Adversarial Nets for inference of Individualised Treatment Effects	Observed	Continuous, Binary	Counterfactual	Python: GANITE
Person-Centered Treatment Effects Using a Local Instrumental Variables	Observed, Unobserved	Continuous, Binary	Counterfactual, Treatment Effect	Stata: petiv
Counterfactual Survival Analysis	Observed	TTE	Counterfactual, Treatment Effect	Python: CSA
SurvITE	Observed	TTE	No	Python: SurvITE
Cox Proportional Hazards Deep Neural Network	No	TTE	Counterfactual	Python: DeepSurv
Non-Parametric Accelerated Failure Time	Observed	TTE	Counterfactual, Treatment Effect	R: AFTrees
Non-Parametric Bayesian Additive Regression Trees within the framework of accelerated failure time mode	Observed	TTE	Counterfactual, Treatment Effect	R: AFT-BART-NP
Random Survival Forests	Observed	TTE	Treatment Effect	No
Causal Survival Forest	Observed	TTE	Treatment Effect	R: grf
Deep Multi-task Gaussian Processes	Observed	TTE	Counterfactual, Treatment Effect	Python: DMGP

ML Methods to Estimate ITE in Longitudinal Setting

In chronic conditions, treatments are sustained over time and dynamic treatment regimes may be of interest.

Table 2: Methods to Estimate ITE in Longitudinal Settings

Method	Baseline confounding	Time-varying confounding	Outcome	Uncertainty	Software
Bayesian Non-parametric	Observed	Observed	Continuous	Counterfactual	No
Bayesian Treatment Response Curves	No	No	Continuous	Counterfactual	No
Counterfactual Gaussian Process	Observed	Observed	Continuous	Counterfactual	No
Recurrent Marginal Structural Networks	Observed	Observed	Continuous, Binary	No	Python: RMSN
Counterfactual Recurrent Network	Observed	Observed	Continuous, Binary	No	Python: CRN
Deep Sequential Weighting	Observed, Unobserved	Observed, Unobserved	Continuous	No	Python: DSW
SyncTwin	Observed	Observed	Continuous	No	Python: synth_control
Time Series Deconfounder	Observed, Unobserved	Observed, Unobserved	Continuous, Binary	No	Python: Time Series Deconfounder
Causal Dynamic Survival model	Observed	No	TTE	Counterfactual, Treatment Effect	Python: CDS

ML Methods to Estimate ITE for TTE Outcomes

Survival model should account for potential bias from:

- non-randomised treatment assignment (confounding),
- informative censoring,
- event-induced covariate shift [17].

Modeling competing risks is another challenge.

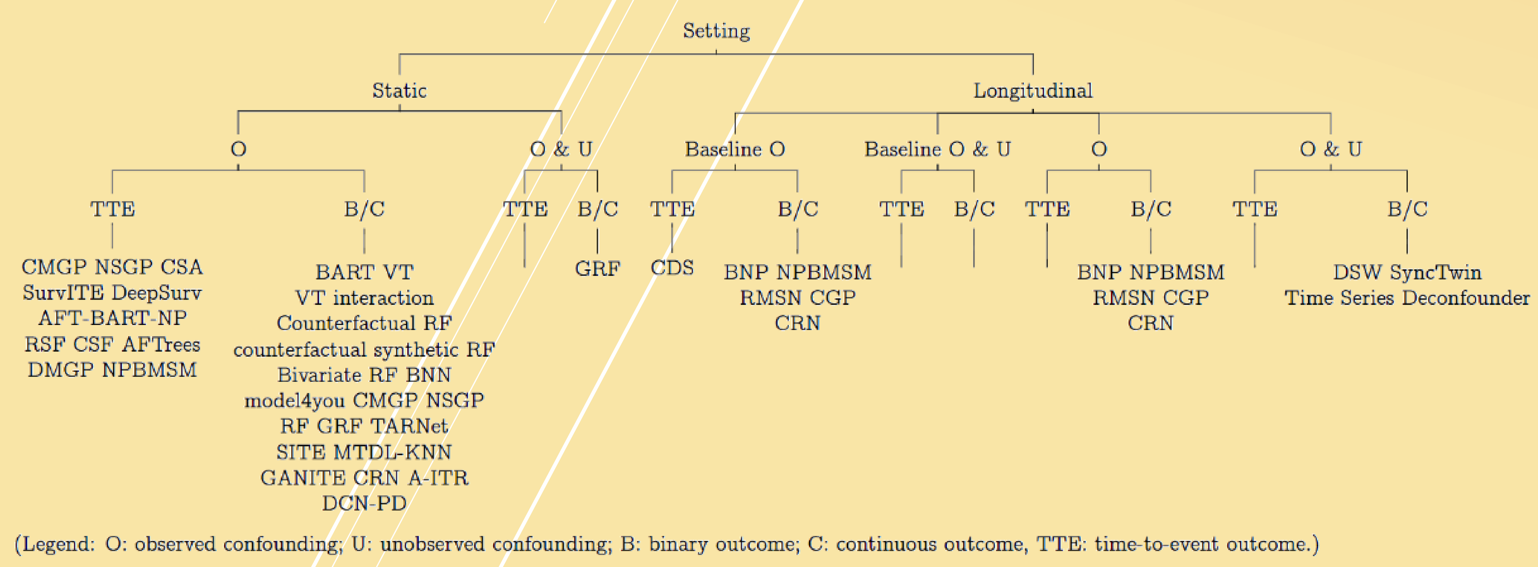

Figure 3: A taxonomy of statistical and machine learning individualized treatment effects estimation methods for use in HTA

Conclusions and Discussions

1. Most ML for ITE estimation can handle **confounding at baseline** but **not time-varying or hidden confounding**.
2. ML accounting for time-varying confounding are developed mostly for use with **continuous or binary outcomes**.
3. Most ML methods do **not quantify uncertainty** of treatment effects estimates or predicted outcomes, especially in longitudinal settings.
4. Modeling **assumptions** should be properly assessed before making causal conclusions.
5. No ML can estimate **ITE for TTE outcomes AND account for time-varying confounders**.

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(note: The full reference list is available upon request).

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HTx Next Generation Health Technology Assessment

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