Combining randomized and observational data

Toward new clinical evidence?

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Senior Researcher

Inria

Missing values, causal inference

Erwan Scornet

Associate professor

École Polytechnique

Random forests, missing values

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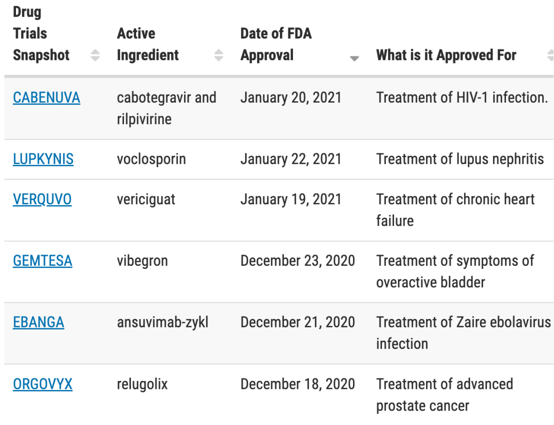
Co-founder of scikit-learn,

Machine-Learning

Current practice: Randomized Controlled Trials (RCTs for short)

A longstanding presence of RCTs . . . now being **the** gold-standard

For e.g. in the 16^{th} century a cross-over trial has been documented about rhubarb's effect. **Source: The Conversation - Wellcome Collection, CC BY**



Drug Trials Snapshot	Active Ingredient	Date of FDA Approval	What is it Approved For
CABENUVA	cabotegravir and rilpivirine	January 20, 2021	Treatment of HIV-1 infection.
LUPKYNIS	voclosporin	January 22, 2021	Treatment of lupus nephritis
VERQUVO	vericiguat	January 19, 2021	Treatment of chronic heart failure
GEMTESA	vibegron	December 23, 2020	Treatment of symptoms of overactive bladder
EBANGA	ansuvimab-zykl	December 21, 2020	Treatment of Zaire ebolavirus infection
ORGOVYX	relugolix	December 18, 2020	Treatment of advanced prostate cancer

Recently approved drugs by the Food and Drug Administration (FDA), all with their corresponding RCT snapshot and information. **Source:** `www.fda.gov`

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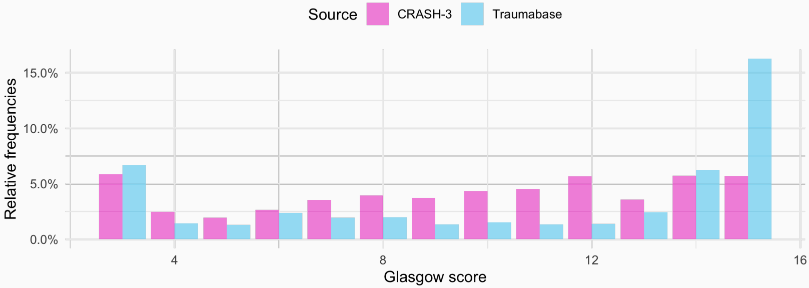

Source: CRASH3 data trial and Traumabase cohort data comparing patients suffering from Traumatic Brain Injuries, and in particular their Glasgow score (severity of the trauma).

Introduction to the notations

Using the potential outcome framework[1], we denote

- 💊 A the treatment,
- 🩺 X the covariates,
- 🌡️ Y the **observed** outcome.

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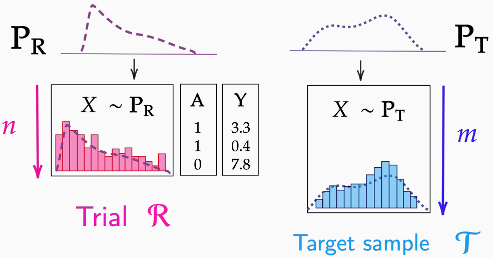

A	Y
1	3.3
1	0.4
0	7.8

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What if we only use the trial to estimate the Average Treatment Effect (ATE)?

Compute ATE averaging over the trial sample:

$$\hat{\tau}_{\mathrm{HT},n} = \frac{1}{n} \sum_{i \in \mathcal{R}} \left(\frac{Y_i A_i}{\pi} - \frac{Y_i (1 - A_i)}{1 - \pi} \right),$$

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$$p_{\mathrm{R}}(x) \neq p_{\mathrm{T}}(x) \Rightarrow \quad \underbrace{\tau_{\mathrm{R}} := \mathbb{E}_{\mathrm{R}}[Y^{(1)} - Y^{(0)}]}_{\text{ATE in the RCT}} \neq \underbrace{\mathbb{E}_{\mathrm{T}}[Y^{(1)} - Y^{(0)}] := \tau}_{\text{Target ATE}}$$

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Re-weighting the trial's data?

$$\hat{\tau}_{\mathrm{IPSW}} := \frac{1}{n}\sum_{i\in\mathcal{R}} w(X_i)\underbrace{\left(\frac{Y_iA_i}{\pi} - \frac{Y_i(1-A_i)}{1-\pi}\right)}_{\text{Horvitz-Thomson.}}$$

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$\Longrightarrow$ *Inverse Propensity Sampling Weighting* (IPSW) - Stuart et al. 2010.

Generalization's *causal* assumptions.

Re-weight, so that the trial follows the target sample's distribution,

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Which assumptions?

Transportability

$$\forall x \in \mathcal{X},\ \mathbb{P}_{\mathrm{R}}(Y^{(1)} - Y^{(0)} \mid X = x) = \mathbb{P}_{\mathrm{T}}(Y^{(1)} - Y^{(0)} \mid X = x).$$

i.e. Needed covariates to re-weight correspond to shifted treatment effect modifier covariates (along the absolute scale).

Support inclusion

$$\text{supp}(P_T(X)) \subset \text{supp}(P_R(X))$$

i.e. Each individuals in the target population has to be represented in the trial.

State-of-the-art and open practical questions

State-of-the-art

- Re-weighting can be found back in the early 2000's;
  $\Longrightarrow$ see books in epidemiology, under the name *standardization*
- But the idea of relying on an external representative sample is recent;
  $\Longrightarrow$ in particular seminal articles can be found in the early 2010's[2] and is getting more and more popular[3]
- Since, other approaches than IPSW have been proposed
  $\Longrightarrow$ outcome-modeling (G-formula), balancing, doubly-robust approaches, . . .

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- Which covariates should we use?

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For the rest of the work, we assume X is composed of categorical covariates

$\Longrightarrow$ for e.g. gender, smoking status, Glasgow score, insurance status, . . .

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Theoretical guarantees of IPSW with oracle weights

$$\hat{\tau}^{*}_{\pi,\text{T, R},n} = \frac{1}{n}\sum_{i\in\mathcal{R}} \overset{\text{True (or oracle) probabilities}}{\boxed{\frac{p_{\text{T}}(X_i)}{p_{\text{R}}(X_i)}}} \; Y_i \left(\frac{A_i}{\pi} - \frac{1-A_i}{1-\pi}\right),$$

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Properties

$$\mathbb{E}\left[\hat{\tau}^*_{\pi,\mathrm{T},\mathrm{R},n}\right] = \tau, \text{ and } \textbf{Var}\left[\hat{\tau}^*_{\pi,\mathrm{T},\mathrm{R},n}\right] = \frac{V_{\mathrm{oracle}}}{n},$$

where

$$V_{\mathrm{oracle}} := \textbf{Var}_{\mathrm{R}}\left[\frac{p_{\mathrm{T}}(X)}{p_{\mathrm{R}}(X)}\tau(X)\right] + \mathbb{E}_{\mathrm{R}}\left[\left(\frac{p_{\mathrm{T}}(X)}{p_{\mathrm{R}}(X)}\right)^2 V_{\mathrm{HT}}(X)\right].$$

$\tau(x)$ being the effect of treatment on strata $X = x$.

How do we estimate weights in practice?

$$\hat{\tau}^{*}_{\pi,\mathrm{T},n} = \frac{1}{n}\sum_{i\in\mathcal{R}} \frac{p_{\mathrm{T}}(X_i)}{\boxed{\hat{p}_{\mathrm{R},n}(X_i)}} Y_i\left(\frac{A_i}{\pi} - \frac{1-A_i}{1-\pi}\right),$$

Estimated with $\mathcal{R}$

Estimation is intuitive, and corresponds to how many times the specific combinaison of category x appears in the trial, that is

$$\hat{p}_{\mathrm{R},n}(x) := \frac{1}{n}\sum_{i\in\mathcal{R}} 1_{X_i=x}$$

Theoretical guarantees of IPSW with completely estimated weights

$$\hat{\tau}_{\pi,n,m} = \frac{1}{n}\sum_{i\in\mathcal{R}} \frac{\overset{\text{Estimated with } \mathcal{T}}{\boxed{\hat{p}_{\mathrm{T},m}(X_i)}}}{\underset{\text{Estimated with } \mathcal{R}}{\boxed{\hat{p}_{\mathrm{R},n}(X_i)}}}\; Y_i \left(\frac{A_i}{\pi} - \frac{1-A_i}{1-\pi}\right),$$

Asymptotic properties

Letting $\lim\limits_{n,m\to\infty} m/n = \lambda \in [0,\infty]$,

$$\lim_{n,m\to\infty} \min(n,m)\,\mathrm{Var}\left[\hat{\tau}_{\pi,n,m}\right] = \min(1,\lambda)\left(\frac{\mathrm{Var}\left[\tau(X)\right]}{\lambda} + V_{so}\right).$$

Variance depends on the size of the two data sets, n and m

What if also estimating π?

$$\hat{\tau}^*_{n,m} = \frac{1}{n}\sum_{i\in\mathcal{R}} \frac{\hat{p}_{\mathrm{T},m}(X_i)}{\hat{p}_{\mathrm{R},n}(X_i)} \quad Y_i \left(\frac{Y_iA_i}{\hat{\pi}_n(x)} - \frac{Y_i(1-A_i)}{1-\hat{\pi}_n(x)} \right) ,$$

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where

$$\tilde{V}_{so} \leq V_{so}.$$

Variance is smaller if also estimating π with the data

💡 This phenomenon is the same as the Difference-in-Means having better precision than the Horvitz-Thomson on a trial.

Impact of additional covariates: for the worse

Covariates needed to generalize are,

- Treatment effect modifier
  a covariate along which the treatment effect is modulated;
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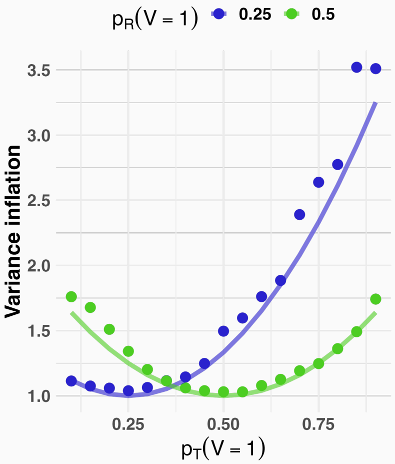

Plot showing the impact of adding a non-necessary covariates *V* when generalizing. Plain lines are the theory, and dots the simulations

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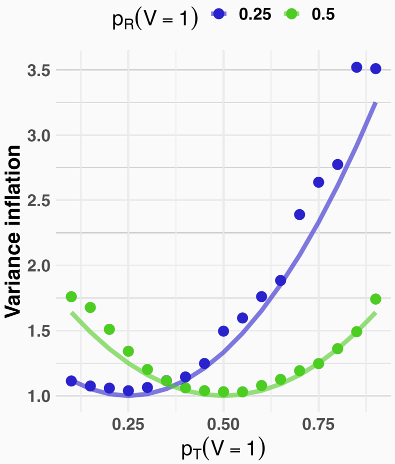

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(i) Including non-necessary covariates can seriously damage precision!

Impact of additional covariates: for the worse, and the better

What happen if a non-shifted covariate, known to be treatment effect modifier, is added?

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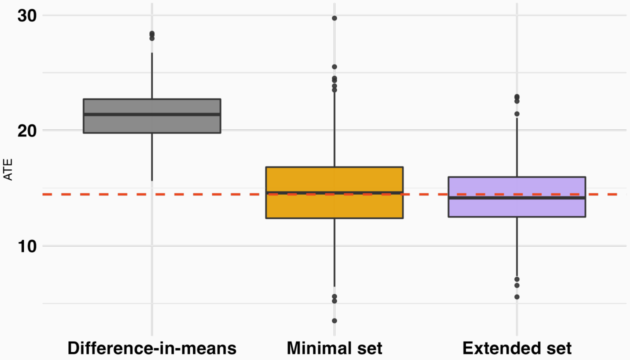

(ii) Adding a non-shifted, but treatment effect modifiers covariate, in the adjustment set improves precision.

Semi-synthetic simulation

- All the results are illustrated on semi-synthetic simulations;
- Build from two large clinical data bases, reflecting a real-world situation
  - CRASH3 $\sim$ 9 000 individuals.
  - Traumabase $\sim$ 30 000 individuals.
- The outcome is the only synthetic part,

$$Y := f(\texttt{GCS}, \texttt{Gender}) + A\,\tau(\texttt{TTT}, \texttt{Blood Pressure}) + \epsilon_{\texttt{TTT}},$$

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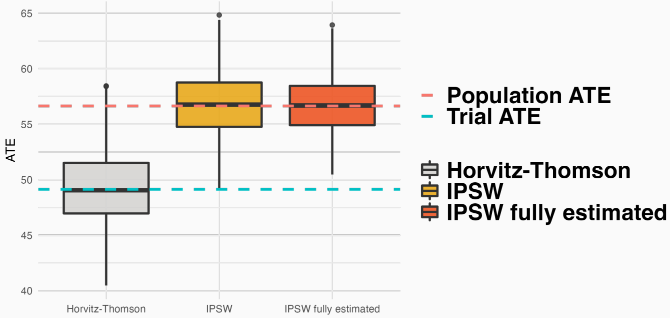

More in the main paper,

- Different asymptotic regimes,
- The re-weighted trial has not necessarily larger variance,
- Effect of adding non-necessary covariates.

Conclusion

Main idea:

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In this talk:

- New theoretical properties for an intuitive method i.e. trial re-weighting
- Alongside with clear and important guidelines for users about **covariate selection**.

  $\Longrightarrow$ *Physicians and epidemiologists have an important role to play in selecting a limited number of covariates when generalizing trial's findings!*

Theoretical guarantees of IPSW with semi-oracle (= so) weights

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Estimated with $\mathcal{R}$

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🤔 Estimating $p_{\mathrm{R}}(x)$ is more efficient than taking the oracle probability (counter-intuitive!)