# On Validation and Planning of An Optimal Decision Rule with Application in Healthcare Studies



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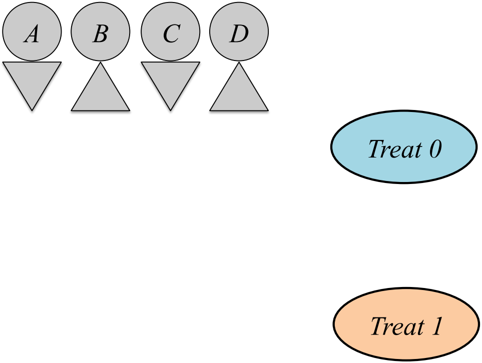
# Motivation

Consider a decision making problem to assign individuals with appropriate treatment options:



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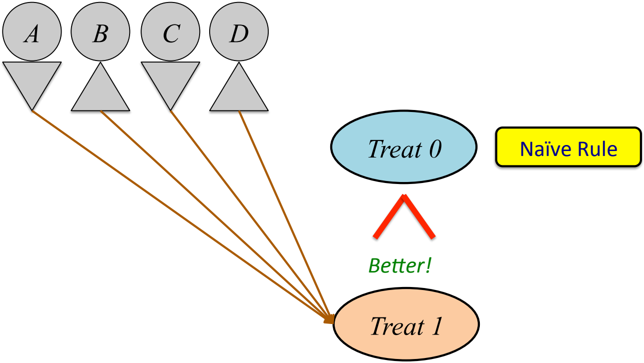
The naïve decision rule is always assigning individuals to a fixed best treatment option:



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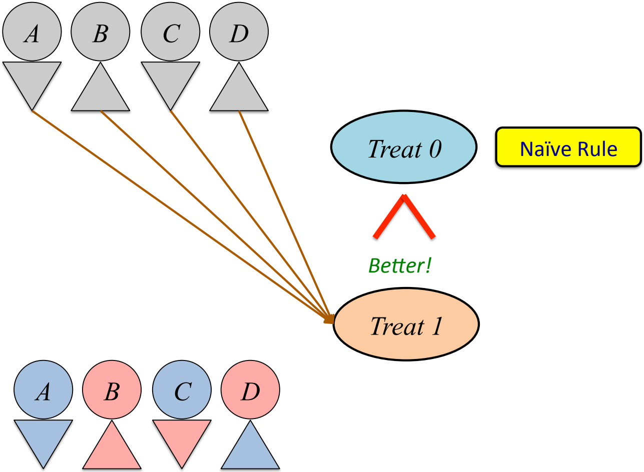
Due to individuals' heterogeneity in outcome to different treatment options, there may not exist a unified best decision.



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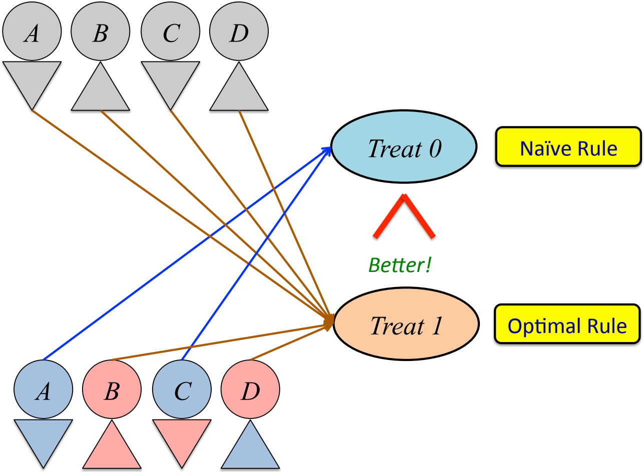
The optimal individualized decision rule (ODR) is to assign individuals with the best treatment option according to their covariates.



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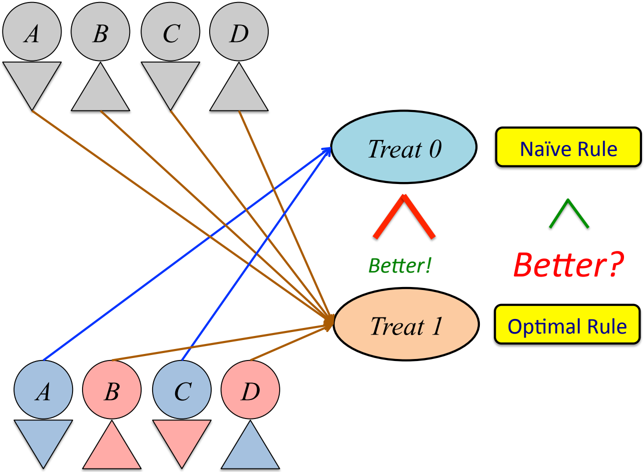
However, no testing procedure is proposed to verify whether these ODRs are significantly better than the naïve decision rule.



# Overview

- Frame a testing procedure for detecting the existence of an ODR that is better than the naïve decision rule under the randomized trials.
- Construct the **test statistic** based on the value difference using the augmented inverse probability weighted (AIPW) method.
- Establish **asymptotic distributions** of the test statistic, and develop its associated **sample size calculation formula**.
- Simulations and a real data application to a schizophrenia clinical trial data to demonstrate the empirical validity of the proposed method.

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# Statistical Framework

- Baseline covariates $X$ is $p \times 1$ vector;
- Treatment $A$ takes 0 or 1 as two treatment options;
- Consider a randomized trial, where the propensity score $\pi = P(A = 1)$ as the likelihood of assignment is known as constant;
- Outcome of interest $Y$;
- Potential outcomes $Y^\star(0)$ and $Y^\star(1)$ are the outcomes that would be observed if a subject receiving treatment 0 or 1, respectively;
- A decision rule is a deterministic function $d(\cdot)$ that maps $X$ to $\{0, 1\}$, relying on a parameter $\beta$ as $d(X, \beta) = I\{g(X)^\top \beta > 0\}$
- Value function under $d(X, \beta)$ is $V(\beta) = E\{Y^\star(d(X, \beta))\}$, where $Y^*(d) = Y^*(0)\{1 - d(X, \beta)\} + Y^*(1)d(X, \beta)$ is the potential outcome under $d(\cdot)$ that would be observed if an individual had received a treatment according to $d(\cdot)$.

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# Optimal Decision Rule and Naïve Decision Rule

- Optimal decision rule (ODR) of interest: $d(X, \beta_0)$, where $\beta_0 = \arg\max_{||\beta||=1} V(\beta)$;
- Value function under the ODR $d(X, \beta_0)$ is $V(\beta_0)$;
- Naïve decision rule: $d(X, \beta) \equiv 1$ and $d(X, \beta) \equiv 0$;
- Values under the two naïve decision rules: $V_1$ and $V_0$, respectively.
- Assume treatment 1 is no worse than treatment 0 on average, i.e. $V_1 \geq V_0$ (easily validated by a two-sample t-test).
- Goal: test whether there exists an ODR that is better than the naïve decision rule in terms of value.

Null and Alternative Hypotheses:

$$H_0: \quad V(\beta_0) = V_1 \quad \text{vs.} \quad H_a: \quad V(\beta_0) > V_1. \tag{1}$$

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# Value Estimator under ODR and Naïve Decision Rule

**AIPW Estimator for $V(\beta)$ under $d(X,\beta)$ (Zhang et al., 2012)**

$$\widehat{V}(\beta) = \frac{1}{n}\sum_{i=1}^{n} \frac{I\{A_i = d(X_i,\beta)\}}{\pi A_i + (1-\pi)(1-A_i)}\{Y_i - \widehat{\mu}(X_i,\beta)\} + \widehat{\mu}(X_i,\beta),$$

where $\widehat{\mu}(X,\beta)$ is an estimator for $\mu(X,\beta) \equiv E\{Y|A = d(X,\beta), X\}$.

- Estimated ODR: $d(X,\widehat{\beta})$, where $\widehat{\beta} = \arg\max_{||\beta||=1} \widehat{V}(\beta)$ (obtained by the direct value search through a global optimization algorithm);
- Estimated value under the estimated ODR for $V(\beta_0)$: $\widehat{V}(\widehat{\beta})$;
- Estimated value for $V_1$ under the naïve decision rule $d(X) \equiv 1$:

$$\widehat{V}^1 = \frac{1}{n}\sum_{i=1}^{n} \frac{A_i}{\pi}\{Y_i - \widehat{\mu}_1(X_i)\} + \widehat{\mu}_1(X_i),$$

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# Test Statistics: Value Difference under Two Rules

- A natural test statistic: $\sqrt{n}\{\widehat{V}(\widehat{\beta}) - \widehat{V}^1\}$.
- Degenerate challenge: asymptotic distribution of $\sqrt{n}\{\widehat{V}(\widehat{\beta}) - \widehat{V}^1\}$ converges in distribution to 0 under the null with regular assumption;
- Modified estimator for $V_1$:

$$\widehat{V}_1 = \frac{1}{n}\sum_{i=1}^{n}\frac{A_i Y_i}{\pi},$$

known as the inverse probability weighted (IPW) estimator of the value function under the naïve decision rule.

- **Test statistic**: (Keep Efficiency of AIPW + Overcome Degeneration)

$$\begin{aligned}\widehat{\Delta}_n &= \sqrt{n}\{\widehat{V}(\widehat{\beta}) - \widehat{V}_1\} \\ &= \frac{1}{\sqrt{n}}\sum_{i=1}^{n}\left[\frac{I\{A_i = d(X_i, \widehat{\beta})\}}{\pi A_i + (1-\pi)(1-A_i)}\{Y_i - \widehat{\mu}(X_i, \widehat{\beta})\} + \widehat{\mu}(X_i, \widehat{\beta}) - \frac{A_i Y_i}{\pi}\right].\end{aligned}$$

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# Asymptotic Distribution of $\widehat{\Delta}_n$ under Null

**Theorem 1**

*Under $H_0$, $\widehat{\Delta}_n$ converges in distribution to a normal random variable with mean 0 and variance*

$$\sigma_0^2 = \frac{1-\pi}{\pi} Var\{E(Y|A=1,X)\}, \text{ as } n \to \infty.$$

**Remark:**

- $\sigma_0^2$ can be consistently estimated by $\widehat{\sigma}_0^2 = \frac{1-\pi}{\pi}\widehat{Var}\{\widehat{\mu}_1(X)\}$.
- At level $\alpha$, **reject the null** hypothesis when $\widehat{\Delta}_n/\widehat{\sigma}_0 \geq z_\alpha$, where $z_\alpha$ is an upper $\alpha$-quantile of the standard normal distribution.
- A two-sided $1-\alpha$ **confidence interval (CI)** for the difference $V(\beta_0) - V_1$ under the null: $\widehat{V}(\widehat{\beta}) - \widehat{V}_1 \pm z_{\alpha/2}\widehat{\sigma}_0/\sqrt{n}$.

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# Asymptotic Distribution of $\widehat{\Delta}_n$ under local alternative

**Theorem 2**

*Under* $H_{a,n}: V(\beta_0) = V_1 + \Delta/\sqrt{n}$, *where* $\Delta > 0$, *we have*

$$\widehat{\Delta}_n = \Delta + \frac{1}{\sqrt{n}} \sum_{i=1}^{n} \phi_i + o_p(1), \text{ where}$$

$$\phi_i = \frac{I\{A_i = d(X_i, \beta_0)\}}{\pi A_i + (1-\pi)(1-A_i)} \{Y_i - \mu(X_i, \beta_0)\} + \mu(X_i, \beta_0) - V(\beta_0) - \left(\frac{A_i}{\pi} Y_i - V_1\right).$$

*It follows that* $\widehat{\Delta}$ *converges in distribution to a random variable with mean* $\Delta$ *and variance* $\sigma_\phi^2 = E(\phi_i^2)$.

**Remark:**

- $\sigma_\phi^2$ can be consistently estimated by $\widehat{\sigma}_\phi^2 = n^{-1} \sum_{i=1}^{n} \widehat{\phi}_i^2$, where $\widehat{\phi}_i = \frac{I\{A_i = d(X_i, \widehat{\beta})\}}{\pi A_i + (1-\pi)(1-A_i)} \{Y_i - \widehat{\mu}(X_i, \widehat{\beta})\} + \widehat{\mu}(X_i, \widehat{\beta}) - \widehat{V}(\widehat{\beta}) - \left(\frac{A_i}{\pi} Y_i - \widehat{V}_1\right).$

# Sample Size Calculation

Detect a pre-specified important difference $\delta_a = V(\beta_0) - V_1$ with a desired power at least $1-\beta$ for a one-sided level-$\alpha$ test:

Set $1 - \Phi\{(z_\alpha \widehat{\sigma}_0 - \Delta)/\widehat{\sigma}_\phi\} = 1 - \beta$, the required sample size as follows

$$n^\star = \frac{(Z_\alpha \sigma_0 + Z_\beta \sigma_\phi)^2}{\delta_a^2}. \tag{2}$$

**Remark:**

- In practice, based on a **pilot study data**, obtain the estimated value difference $\widehat{\delta}_a$, and the variance estimates $\widehat{\sigma}_0^2$ and $\widehat{\sigma}_\phi^2$.
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# Real Data Analysis: Schizophrenia Dataset

- **A randomized trial** to examine the effectiveness of cognitive-behavioral therapy for schizophrenia, measured by the Positive and Negative Syndrome Scale (PANSS);
- Covariates $X = (X_1, X_2)$: $X_1$ is the log duration of untreated psychosis at baseline, and $X_2$ is the PANSS score at the baseline visit.
- Treatment $A$:
  - Treatment as usual (TAU) ($n_0 = 70$);
  - Cognitive-behavioral plus TAU (CBT) ($n_1 = 44$);
  - Supportive counseling plus TAU (SC) ($n_2 = 41$);
- Outcome of interest $Y$: reduction of PANSS score.

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- The proposed test is conducted for comparing two treatments at a time: CBT vs. TAU, SC vs. TAU, and CBT vs. SC;
- **Treatment-specific means** to decide the superior treatment as treatment 1: $\widehat{\mu}_{TAU} = 21.96$, $\widehat{\mu}_{CBT} = 27.34$ and $\widehat{\mu}_{SC} = 28.76$.

| Test Pair | CBT vs. TAU | SC vs. TAU | CBT vs. SC |
|---|---|---|---|
| superior | CBT | SC | SC |
| $\widehat{V}_1$ | 27.34 | 28.76 | 28.76 |
| $\widehat{V}(\widehat{\beta})$ | 30.35 | 33.06 | 34.70 |
| $P$-value | 0.190 | 0.125 | 0.039 |

# Reject Null for Testing Pair: CBT vs. SC

- Individuals with **median** log durations and **median** PANSS score: CBT;
- Patients with **extreme low or high** log durations and PANSS score: SC;
- Consider one-sided test with $\alpha = 0.05$ and a desired power at least $1 - \beta = 90\%$, the **required sample size** to detect a value difference $\widehat{\delta}_a = \widehat{V}(\widehat{\beta}) - \widehat{V}_1$ is $\widehat{n}^\star = 290$.

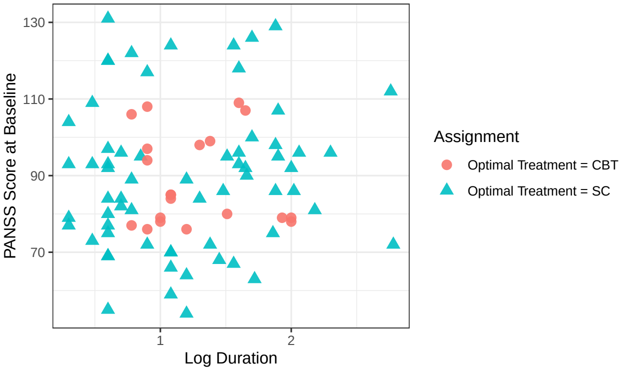


Figure 1: Treatment assignment under the estimated optimal decision rule.

# Contribution

Our proposed testing procedure for detecting the existence of an ODR:

- is a cutting edge work to the **personalized recommendation**;
- is **first work** that forms the hypothesis testing by proposing the non-degenerate value difference of AIPWEs as the test statistic;
- has novel yet effective sample size calculation method, which contributes to the **policy evaluation literature** from a unique angle.
- has clear instruction on the **validation** of a personalized optimal decision making, which has great potential towards developing an automatic decision-making system that is capable of filtering ineffective rules and **planning** the ODR.

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- is **first work** that forms the hypothesis testing by proposing the non-degenerate value difference of AIPWEs as the test statistic;
- has novel yet effective sample size calculation method, which contributes to the **policy evaluation literature** from a unique angle.
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