Estimation of Multivariate Treatment Effects in Contaminated Randomized Trials

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Outline

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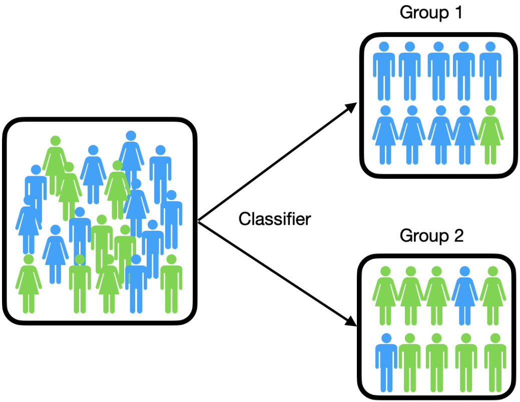
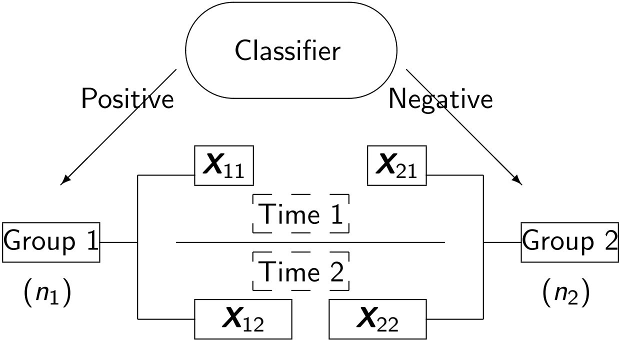


Pre-Post Design



Probabilities of Classification Errors

- Positive Predictive Value (PPV): is the probability $(1 - \varepsilon)$ that a person with a positive test will have the clinical condition of interest.
- Negative Predictive Value (NPV): is the probability $(1 - \delta)$ that a person with a negative test will be free from the clinical condition of interest.
- PPV (NPV) combine sensitivity (specificity) with prevalence information to provide accuracy of a test result.

Probabilities of Classification Errors

- Problem: Not all classifiers are perfect with 100% PPV and NPV.
    - Ignoring these errors will produce **BIASED** results.
        - The expected outcomes are affected by the contamination:

$$
\begin{aligned}
E(\boldsymbol{X}_{11k}) &= (1-\delta_1)\boldsymbol{\mu}_1 + \delta_1\boldsymbol{\mu}_2 \\
E(\boldsymbol{X}_{21k}) &= \delta_2\boldsymbol{\mu}_1 + (1-\delta_2)\boldsymbol{\mu}_2 \\
E(\boldsymbol{X}_{12k}) &= (1-\delta_1)(\boldsymbol{\mu}_1 + \boldsymbol{\tau}_1) + \delta_1(\boldsymbol{\mu}_2 + \boldsymbol{\tau}_2) \\
E(\boldsymbol{X}_{22k}) &= \delta_2(\boldsymbol{\mu}_1 + \boldsymbol{\tau}_1) + (1-\delta_2)(\boldsymbol{\mu}_2 + \boldsymbol{\tau}_2)
\end{aligned}
$$

    - The sample size and the power calculations will produce overly optimistic results.
    - Under-powered studies can fail to detect a significant effect when, in fact, it is present.

Multivariate Normal Model

- The parameter of interest is still

$$\boldsymbol{\Delta} = \boldsymbol{\tau}_1 - \boldsymbol{\tau}_2.$$

- Assume $0 < \delta_1, \delta_2 < 1/2$.
- Let S be the group membership determined by the classifier,

$$\begin{aligned} f(\mathbf{x}|S = s, \boldsymbol{\theta}) =& \{(1 - \delta_1)\phi(\mathbf{x}|\boldsymbol{\eta}_1, \Sigma) + \delta_1\phi(\mathbf{x}|\boldsymbol{\eta}_2, \Sigma)\}I_{\{1\}}(s) \\ &+ \{\delta_2\phi(\mathbf{x}|\boldsymbol{\eta}_1, \Sigma) + (1 - \delta_2)\phi(\mathbf{x}|\boldsymbol{\eta}_2, \Sigma)\}I_{\{2\}}(s), \end{aligned}$$

where $\boldsymbol{\theta} = (\delta_1, \delta_2, \boldsymbol{\eta}_1, \boldsymbol{\eta}_2, \Sigma)$, $\boldsymbol{\eta}_1 = (\boldsymbol{\mu}_1, \boldsymbol{\mu}_1 + \boldsymbol{\tau}_1)^\top$ and $\boldsymbol{\eta}_2 = (\boldsymbol{\mu}_2, \boldsymbol{\mu}_2 + \boldsymbol{\tau}_2)^\top$.

Moment-Based Method (ϵ and δ are Known)

- If ϵ and δ are known,

$$C\mathrm{E}(\overline{\mathbf{Y}}_D - \overline{\mathbf{Y}}_H) = (1-\epsilon-\delta)(\boldsymbol{\tau}_D - \boldsymbol{\tau}_H) = (1-\epsilon-\delta)\boldsymbol{\Delta}.$$

- Thus, an unbiased estimator of $\boldsymbol{\Delta} = \boldsymbol{\tau}_D - \boldsymbol{\tau}_H$ is

$$\widetilde{\boldsymbol{\Delta}} = \frac{1}{1-\epsilon-\delta} C(\overline{\mathbf{Y}}_D - \overline{\mathbf{Y}}_H).$$

The variance of $\widetilde{\boldsymbol{\Delta}}$ is

$$\begin{aligned} Var(\widetilde{\boldsymbol{\Delta}}) = & \frac{1}{(1-\epsilon-\delta)^2} C\Sigma C^\top \left\{ \frac{1}{n_D} + \frac{1}{n_H} \right\} \\ & + \left\{ \frac{\epsilon(1-\epsilon)}{n_D} + \frac{\delta(1-\delta)}{n_H} \right\} \boldsymbol{\Delta}\boldsymbol{\Delta}^\top. \end{aligned}$$

EM-Based Method (ϵ and δ are Unknown)

- Let Z_{ij} be the true group of the jth subject classified in the ith group.
    - Z_{ij} is missing information.
- Via EM algorithm, the MLE of $\boldsymbol{\theta}$ is

$$\widehat{\boldsymbol{\theta}} = \left(\widehat{\delta}_1, \widehat{\delta}_2, \widehat{\boldsymbol{\eta}}_1, \widehat{\boldsymbol{\eta}}_2, \widehat{\Sigma}\right)$$

- Estimate $\boldsymbol{\Delta}$ by $\widehat{\boldsymbol{\Delta}} = C(\widehat{\boldsymbol{\eta}}_1 - \widehat{\boldsymbol{\eta}}_2)$.
- Apply bootstrap to estimate the covariance matrix of $\widehat{\boldsymbol{\Delta}}$, denoted by S_B.

Hybrid Method

- Hybrid estimator of $\mathbf{\Delta}$ is

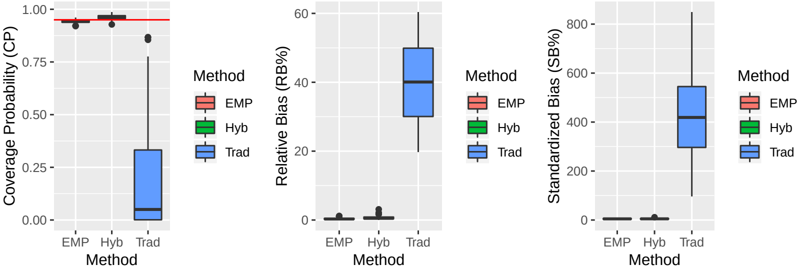
$$\widetilde{\mathbf{\Delta}} = (1 - \widehat{\delta}_1 - \widehat{\delta}_2)^{-1} C \left(\overline{\mathbf{X}}_{1\cdot} - \overline{\mathbf{X}}_{2\cdot}\right)$$

and its variance can be estimated by

$$\widehat{Var(\widetilde{\mathbf{\Delta}})} = \left(1 - \widehat{\delta}_1 - \widehat{\delta}_2\right)^{-2} CSC^{\top}.$$

where $\widehat{\delta}_1$ and $\widehat{\delta}_2$ are EM estimators.

Overall Comparison



(a) Comparison of CP

(b) Comparison of RB%

(c) Comparison of SB%

Figure: Boxplots of CP, RB%, and SB% for all methods.Trad is for the traditional method; Hyb is for the hybrid method; EMP is for the MLE via EM algorithm.

Sample Size Determination

- Hypothesis Test: $H_0 : \mathbf{\Delta} = \mathbf{\Delta}_0$ vs. $H_1 : \mathbf{\Delta} = \mathbf{\Delta}_1$ (s.t. $\mathbf{\Delta}_1 \neq \mathbf{\Delta}_0$).
- For the nominal test size α and power $1 - \beta$, the required sample size of $n = n_D + n_H$, where $n_D/n_H = \pi$ and $0 < \pi < \infty$ can be derived based on test statistic

  $$\widetilde{T} = [C(\overline{\mathbf{Y}}_D - \overline{\mathbf{Y}}_H) - \psi \mathbf{\Delta}_0]^\top \left(CSC^\top \right)^{-1} [C(\overline{\mathbf{Y}}_D - \overline{\mathbf{Y}}_H) - \psi \mathbf{\Delta}_0], \tag{1}$$

  where $C = (-I_p, I_p)$, $S = \frac{1}{n_D}(S_D + \pi S_H)$ and S_D and S_H are the sample covariances of $\mathbf{Y}_{D_i}$ and $\mathbf{Y}_{Hi}$, respectively, and $\psi = 1 - \epsilon - \delta$.

F Approximation

- We have the approximation

$$\widetilde{T} \approx pF \sim pF_{p,f}(n_D \psi^2 (\mathbf{\Delta}_1 - \mathbf{\Delta}_0)^\top \Phi^{-1} (\mathbf{\Delta}_1 - \mathbf{\Delta}_0))$$

  Therefore, to find n_D we need to solve the equation

$$P(T > pF_{p,f_0}(1-\alpha)|H_1) \approx P(F > F_{p,f_0}(1-\alpha)) = 1 - \beta,$$

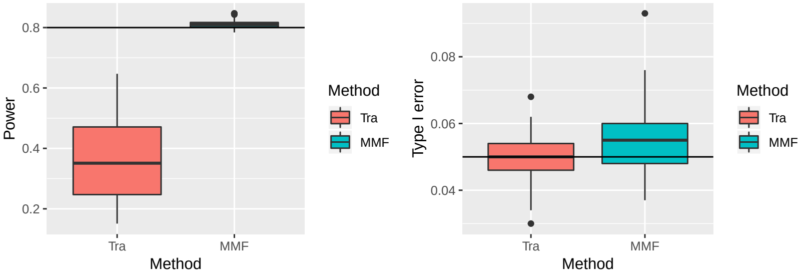
Sample Size

- Due to misclassification rates, the sample size required are larger than the traditional methods.

		ϵ		
δ	Method	0.1	0.2	0.3
0.1	Trad	17	17	17
	F	26	34	47
0.2	Trad	17	17	17
	F	34	48	70
0.3	Trad	17	17	17
	F	47	70	111

Table: Sample size required for parametric setting 1 when $p = 2$. Trad, Traditional method; F, F Approximation

Overall Comparisons



(a) Comparison of power among different methods

(b) Comparison of Type I error among different methods

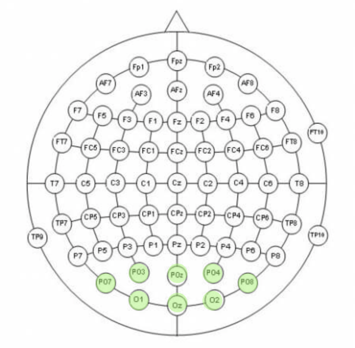
Figure: Boxplots of power and Type I error for all methods. Tra, traditional test that ignores group classification errors; MMF, moment-based test; The sample sizes for MMF are calculated based on F Approximation.

EEG Data: Data Background

- This data was collected to examine Electroencephalograph (EEG) correlates of genetic predisposition to alcohol use disorder.
- 122 subjects: 77 alcohol use disorder (1) and 45 not having alcohol use disorder (2).
- Their baseline brain activities were recorded using EEG.
- After the baseline assessment, a visual stimuli was presented and the brain activities were measured again.

EEG Data: Data Background

- We focus on the activity recorded on EEG electrodes placed at the O1, Oz, O2, PO7, PO3, POz, PO4, and PO8.
- These channels corresponds to the occipital lobe and parietal lobe of the brain.
- They are responsible for visual processing and spatial relationships.



EEG Data: Results and Conclusions

Method	O1	O2	Oz	PO3	PO4	PO7	PO8	POz	p-value
Trad	1.209	0.865	0.205	0.692	0.849	0.797	0.968	0.442	0.660
Hyb	1.514	1.084	0.256	0.867	1.063	0.998	1.212	0.553	0.750
EMP	2.143	1.840	0.637	1.451	1.549	1.368	1.778	0.926	<0.001

Table: Differences in pre and post brain activity ($\mathbf{\Delta}$)

• Trad is traditional estimator that ignores the misclassification probability in diagnostic test;

• Hyb is the hybrid estimator that combines maximum likelihood estimator of ϵ and δ with the moment-based estimator of $\mathbf{\Delta}$;

• EMP is the maximum likelihood estimator of all the parameters via EM algorithm.

Conclusion and Summary

- We should check the diagnostic device's accuracy before applying the traditional method.
- Traditional methods that ignore misclassification errors lead to unacceptably-large bias in estimating treatment effects. We may fail to detect significant differences in treatment effects.
- Sample sizes required from traditional methods are overly optimistic.
- The EM-based methods provide more accurate estimators for misclassification error rates and treatment effects.
- The hybrid method is easy to use and fast to compute.