Estimation of Treatment Effects for Multiple Outcomes by Using Weighting Approach

Yuki Shintaro, Kensuke Tanioka, Hiroshi Yadohisa

Doshisha University

1. Introduction

Background

Randomized controlled trials and observational studies are conducted to test the efficacy of a treatment, and here we are dealing specifically with two-arm comparison. The characteristics that would render the test therapy more effective than the control therapy (called subgroups) are detected by estimating the treatment effect and identifying interactions between treatments and covariates.

Chen et al. (2017) systematically summarized methods for modeling the interaction between treatments and covariates and proposed the Weighting Approach (WA) as a general framework. Although this method estimates the treatment effect on a single outcome.

Randomized controlled trials often have multiple outcomes of interest, such as primary and secondary endpoints. Simultaneously, observational studies are conducted to discover new clinical hypotheses; therefore, it is natural to consider multiple outcomes.

Problems and Solutions

Problems:

(i) When using the WA by Chen et al. (2017) with multiple outcomes, the correlation structure between each outcome cannot be considered.

(ii) The relationship between multiple outcomes and explanatory variables becomes difficult, and the resulting difficulty in interpreting subgroups may be problematic.

Overcoming these problems:

(i) We extend the loss function of the WA to handle multiple outcomes.

(ii) We introduce latent variables into the treatment effects to discover and interpret subgroups.

2. Proposed method

Extension of WA to multiple continuous outcomes

1) We define the loss function $M_C(\boldsymbol{y}, \boldsymbol{v})$ as below.

Let $\boldsymbol{\Sigma} \in \mathbb{R}^{p\times p}$ be the covariance matrix of multiple outcomes,

$$M_C(\boldsymbol{y}, \boldsymbol{v}) = \frac{1}{2}(\boldsymbol{y}-\boldsymbol{v})'\boldsymbol{\Sigma}^{-1}(\boldsymbol{y}-\boldsymbol{v}) \qquad \boldsymbol{y}, \boldsymbol{v} \in \mathbb{R}^p$$

2) Corresponding propensity score weighted empirical loss function:

$$L_{WC}(\boldsymbol{f}_C) = \frac{1}{n}\sum_{i=1}^{n} \frac{M_C(\boldsymbol{Y}_i, T_i \boldsymbol{f}_C(\boldsymbol{x}_i))}{T_i\pi(\boldsymbol{x}_i) + (1-T_i)/2}$$

For subject i,

Random variable corresponding to multiple outcome: $\boldsymbol{Y}_i \in \mathbb{R}^p$

Covariates: $\boldsymbol{x}_i \in \mathbb{R}^m$

Personalized benefit scoring system: $\boldsymbol{f}_C(\boldsymbol{x}_i) : \mathbb{R}^m \to \mathbb{R}^p$

Let T_i be a random variable, as follows:

$$T_i = \begin{cases} 1 & \text{(If subject } i \text{ is allocated test group)} \\ -1 & \text{(If subject } i \text{ is allocated control group)} \end{cases}$$

Propensity score: $P(T_i = 1|\boldsymbol{x}_i) = \pi(\boldsymbol{x}_i)$

Theorem: Let $\boldsymbol{f}_C^*(\boldsymbol{x}_i)$ be the $\boldsymbol{f}_C(\boldsymbol{x}_i)$ that minimizes $\mathbb{E}[L_{WC}(\boldsymbol{f}_C)|\boldsymbol{x}_i]$.

Then it holds that $2\boldsymbol{f}_C^*(\boldsymbol{x}_i) = \mathbb{E}[\boldsymbol{Y}_i^{(1)} - \boldsymbol{Y}_i^{(-1)}|\boldsymbol{x}_i]$

Heterogeneous treatment effect (HTE) for multiple outcome

Introducing latent variables into the treatment effects

Let the function of treatment effects to be a linear function, i.e., $\boldsymbol{f}_C(\boldsymbol{x}_i) = \boldsymbol{\Gamma}'\boldsymbol{x}_i/2$, where $\boldsymbol{\Gamma} = (\gamma_1, \gamma_2, \cdots, \gamma_p) \in \mathbb{R}^{m\times p}$ is the regression coefficient matrix. In addition, we introduce latent variables into this function so that $\boldsymbol{f}_C(\boldsymbol{x}_i) = \boldsymbol{\Gamma}^{*'}\boldsymbol{A}'\boldsymbol{x}_i/2$ subject to $\boldsymbol{A}'\boldsymbol{A} = \boldsymbol{I}_d$.

$\boldsymbol{A} = (\boldsymbol{a}_1, \boldsymbol{a}_2, \cdots, \boldsymbol{a}_d) \in \mathbb{R}^{m\times d}$ is loading matrix with column orthogonal constraint, and $d \leq m$. $\boldsymbol{\Gamma}^* = (\gamma_1^*, \gamma_2^*, \cdots, \gamma_p^*) \in \mathbb{R}^{d\times p}$ is the coefficient matrix for latent variables $\boldsymbol{A}'\boldsymbol{x}_i$.

3. Proposed method

Objective function of the proposed method

Objective function (using the framework of Kawano et al. (2018)):

$$\min_{\boldsymbol{A},\boldsymbol{B},\boldsymbol{\Gamma}^*,\boldsymbol{\Sigma}} \left\{ L_{WC}(\boldsymbol{f}_C) + \omega\|\boldsymbol{X} - \boldsymbol{X}\boldsymbol{A}\boldsymbol{B}'\|_F^2 + \lambda_a \sum_{k=1}^{d}\|\boldsymbol{a}_k\|_1 + \lambda_{\gamma^*}\sum_{l=1}^{p}\|\gamma_l^*\|_1 \right\}$$

Estimation of HTE — Dimensional reduction — Lasso penalty (Tibshirani, 1996)

subject to $\boldsymbol{B}'\boldsymbol{B} = \boldsymbol{I}$

Regularization parameters: $\lambda_a, \lambda_{\gamma^*} (\geq 0)$, Positive tuning parameter: ω

The first term of this objective function is the empirical weighted loss function that estimates the treatment effects with a linear function, and the second term is the loss function of PCA, the others are the Lasso penalty terms.

We use the Lasso estimate $\boldsymbol{A}$ and $\boldsymbol{\Gamma}^*$ to ease the interpretation of latent variables and their influence on treatment effects.

4. Application

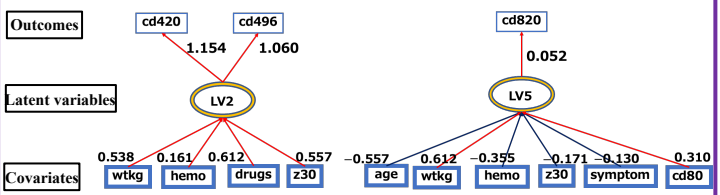
Data description

We applied the proposed method to ACTG175 data. This dataset is available in the package **speff2trial** for R. Here we define the test therapy as combination therapy with zidovudine and didanosine (n=332), and the control therapy as monotherapy with zidovudine (n=318).

Outcomes: cd420, cd496, cd820 **Covariates**: age, wtkg, hemo, homo, drugs, karnof, oprior, z30, zprior, race, gender, str2, symptom, cd40, cd80

Results

Here we assume that the number of latent variables is five. The tuning parameter ω is set to 0.1, $\lambda_a, \lambda_{\gamma^*}$ is selected by five-fold cross-validation. The visualization of the estimated $\boldsymbol{A}$ and $\boldsymbol{\Gamma}^*$ is shown below. For the visualization, all coefficients that are not estimated to be zero are listed.



LV2 is a component such that combination therapy has a greater effect on CD4 cells. LV5 is a component such that combination therapy has a greater effect on CD8 cells. Here, we describe the covariates that contribute to these components. (+) means positive coefficients and (−) means negative coefficients.

LV2(+): "wtkg", "hemo", "drugs", "z30"; **LV5(+)**: "wtkg", "cd80"; **LV5(−)**: "age", "hemo", "karnof", "oprior", "z30", "symptom"

We found the subgroup in which test therapy was more effective in treatment effect of **CD4 cells** compared to control therapy:

Participants with • obesity • zidovudine use in the 30 days prior to treatment initiation • hemophilia • history of intravenous drug use

In the same way, for **CD8 cells**:

Participants with • obesity • large CD8 T cell count at baseline • younger • no hemophilia • no zidovudine use in the 30 days prior to treatment initiation • no symptomatic

Validate "zidovudine use in the 30 days prior to treatment initiation", the subgroup obtained for CD4 cells:

For subjects who received <4 weeks of prior zidovudine therapy, combination therapy significantly increased CD4 cells through 72 weeks compared with zidovudine monotherapy (Schooley et al, 1996).

Chen, S., Tian, L., Cai, T., and Yu, M. (2017). A general statistical framework for subgroup identification and comparative treatment scoring. *Biometrics*, **73** (4), 1199-1209.

Kawano, S., Fujisawa, H., Takada, T. and Shiroishi, T. (2018). Sparse principal component regression for generalized linear models. *Computational Statistics and Data Analysis*, **124**, 180-196.

Tibshirani, R. (1996). Regression shrinkage and selection via the lasso. *Journal of the Royal Statistical Society: Series B (Methodological)*, **58** (1), 267-288.