Optimal Treatment Decision Rules in Precision Medicine based on Outcome Trajectories and Biosignatures

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1. Introduction

A pressing challenge in medical research is to identify optimal treatments for individual patients, especially in mental health studies where patients are heterogeneous and traditional statistical analysis cannot effectively identify which treatment option is best for individual patients.

Goals:

- Extract summary information from outcome trajectories, especially when there are missing data
- Develop efficient treatment decision rules (TDRs) using patients' baseline characteristics

2. Average Tangent Slope

Comparing with using the change score (e.g., difference between the first and last observations) as the outcome variable, we proposed a scalar measure: Average Tangent Slope (ATS).

Consider the mixed-effect model:

$$\tilde{\boldsymbol{Y}}_i = \boldsymbol{G}(\boldsymbol{t}_i)(\boldsymbol{\beta} + \boldsymbol{b}_i) + \boldsymbol{\varepsilon}_i \qquad (1)$$

- Observation time points: $\boldsymbol{t}_i = (t_{i1}, \dots, t_{im_i})^\top$;
- Observed outcomes: $\tilde{\boldsymbol{Y}}_i = (\tilde{y}_{i1}, \tilde{y}_{i2}, \dots, \tilde{y}_{im_i})$;
- Design matrix $\boldsymbol{G}(\boldsymbol{t}_i) = (\boldsymbol{g}(t_1), \dots, \boldsymbol{g}(t_{mi}))^\top$ and $\boldsymbol{g}(t) = (g_1(t), \dots, g_p(t))^\top$;
- Fixed effect: $\boldsymbol{\beta}$; Random effect: $\boldsymbol{b}_i \sim N(\boldsymbol{0}, \boldsymbol{D})$.

Average Outcome Function:

$$\mu(t) = \boldsymbol{g}^\top(t)\boldsymbol{\beta} \qquad (2)$$

Average Tangent Slope (ATS):

$$\frac{1}{t_m - t_1}\int_{t_1}^{t_m} \mu'(t)dt = \frac{\mu(t_m) - \mu(t_1)}{t_m - t_1} = \frac{\boldsymbol{g}^\top(t_m) - \boldsymbol{g}^\top(t_1)}{t_m - t_1}\boldsymbol{\beta} \qquad (3)$$

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3. Hypothesis Test

Extend model Eq(1) to K groups (e.g., K = 2):

$$\tilde{\boldsymbol{Y}}_{i,k} = \boldsymbol{G}(\boldsymbol{t}_{i,k})(\boldsymbol{\beta}_k + \boldsymbol{b}_{i,k}) + \boldsymbol{\varepsilon}_{i,k}$$

Hypothesis test can be conducted using ATS as the outcome variable. The test hypothesis is:

$$\mathrm{H}_0: \ E_w^\top(\boldsymbol{g}')(\boldsymbol{\beta}_1 - \boldsymbol{\beta}_2) = 0$$

$$\mathrm{H}_1: \ E_w^\top(\boldsymbol{g}')(\boldsymbol{\beta}_1 - \boldsymbol{\beta}_2) \neq 0$$

The hypothesis can be tested with Wald test, as:

$$\frac{E_w^\top(\boldsymbol{g}')\left(\widehat{\boldsymbol{\beta}}_1 - \widehat{\boldsymbol{\beta}}_2\right)\left(\widehat{\boldsymbol{\beta}}_1 - \widehat{\boldsymbol{\beta}}_2\right)^\top E_w(\boldsymbol{g}') - 0}{\mathrm{Var}\left(E_w^\top(\boldsymbol{g}')(\widehat{\boldsymbol{\beta}}_1 - \widehat{\boldsymbol{\beta}}_2)\right)} \sim \mathscr{X}^2(1) \qquad (4)$$

This test can achieve higher power than using the change score method or ANCOVA.

4. Decision Rules

Identify the treatment decision rule (TDR) with patient's baseline information (biosignatures)

- A collection of baseline covariates measures $\boldsymbol{x} = (x_1, \dots, x_p)'$
- A function d that assigns a treatment decision to a patient based on baseline covariates $\boldsymbol{x} = (x_1, \dots, x_p)'$

$$d: \boldsymbol{x} \to T$$

- A treatment decision
- $T = k$ for treatment k

Mixed-effect model incorporates biosignatures ($\boldsymbol{\alpha}^\top \boldsymbol{x}_{ik}$):

$$\tilde{\boldsymbol{Y}}_{i,k} = \boldsymbol{G}(\boldsymbol{t}_{i,k})\left(\boldsymbol{\beta}_k + \boldsymbol{b}_{i,k} + \boldsymbol{\Gamma}_k(\boldsymbol{\alpha}^\top \boldsymbol{x}_{ik})\right) + \boldsymbol{\varepsilon}_{i,k} \qquad (5)$$

Treatment Decision Rule:

$$d(\boldsymbol{x}^{\text{new}}) = I\Bigg(\frac{\boldsymbol{g}(t_m)^\top - \boldsymbol{g}(t_1)^\top}{t_m - t_1}\left(\widehat{\boldsymbol{\beta}}_2 + \widehat{\boldsymbol{\Gamma}}_2(\widehat{\boldsymbol{\alpha}}^\top \boldsymbol{x}^{\text{new}})\right) > \frac{\boldsymbol{g}(t_m)^\top - \boldsymbol{g}(t_1)^\top}{t_m - t_1}\left(\widehat{\boldsymbol{\beta}}_1 + \widehat{\boldsymbol{\Gamma}}_1(\widehat{\boldsymbol{\alpha}}^\top \boldsymbol{x}^{\text{new}})\right)\Bigg) + 1 \qquad (6)$$

The estimation algorithms of $\boldsymbol{\alpha}$ (subject to $\boldsymbol{\alpha}^\top\boldsymbol{\alpha} = 1$) are based on:

- 1. Kullback-Leibler Divergence: $\widehat{\boldsymbol{\alpha}}_{\text{KL}} = \operatorname{argmax}_{\boldsymbol{\alpha}} \ a_1 + a_2\widehat{\boldsymbol{\mu}}_x^\top\boldsymbol{\alpha} + a_3\boldsymbol{\alpha}^\top(\widehat{\boldsymbol{\mu}}_x\widehat{\boldsymbol{\mu}}_x^\top + \widehat{\boldsymbol{\Sigma}}_x)\boldsymbol{\alpha}$,
- 2. Difference between squared ATS: $\widehat{\boldsymbol{\alpha}}_{\text{ATS}} = \operatorname{argmax}_{\boldsymbol{\alpha}} \ b_1 + b_2\widehat{\boldsymbol{\mu}}_x^\top\boldsymbol{\alpha} + b_3\boldsymbol{\alpha}^\top(\widehat{\boldsymbol{\mu}}_x\widehat{\boldsymbol{\mu}}_x^\top + \widehat{\boldsymbol{\Sigma}}_x)\boldsymbol{\alpha}$,
- 3. Likelihood functions: $\widehat{\boldsymbol{\alpha}}_{\text{ATS}} = \operatorname{argmax}_{\boldsymbol{\alpha}} \ c_1 + \boldsymbol{L}_1^\top\boldsymbol{\alpha} + \boldsymbol{\alpha}^\top\boldsymbol{L}_2\boldsymbol{\alpha}$.

where $a_1, a_2, a_3, b_1, b_2, b_3$ and c_1 are scalar values constructed by $\widehat{\beta}$ and $\widehat{\Gamma}$ and the function $\boldsymbol{g}(t)$

5. Simulation Result 1

The performances for the ATS, WATS, change score and ANCOVA are evaluated through simulation studies. $n = 100$ functional data curves were generated from two populations with the same or different ATSs (to evaluate the tyep I error and power, respectively). The trajectories of the outcome generation functions and the comparisons of performances are shown in Figure 1 and 2.

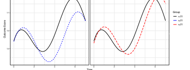

Figure 1: Outcome Trajectories

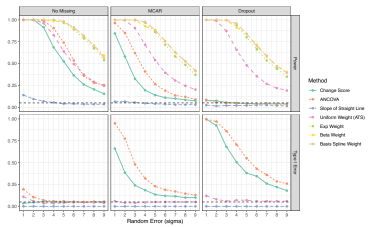

Figure 2: Comparisons of Hypothesis Test Results

6. Simulation Results 2

The Treatment Decision Rules built by the three criteria are compared with the single index models: linear GEM model proposed by Dr. Petkova et al., 2017 and SIMML model developed by Dr. Park et al., 2020.

The three columns present the evaluation of proportion of correct decision (PCD) when: (i) there is no missing data; (ii) data are missing completely at random (MCAR) with a missing rate of 30%; and (iii) subjects drop out the study: 50% of subjects miss their last four assessments.

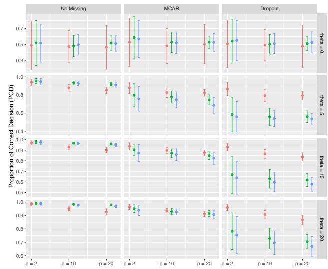

Figure 3: Comparison of Proportion of Correct Decisions

7. Conclusion

- ATS can provide a meaningful scalar summary of a functional trajectory.
- The method has outstanding performances than the other scalar measures and are robust to missing values (MCAR, Dropout)
- Combine baseline characteristics into a single index model and incorporate ATS, we get good estimation of proportion of correction decision, especially when there is missing data

References

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