Extracting Scalar Measures from Functional Data with Missingness

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Introduction

- In RCTs, it is often of interest to estimate the effect of various treatments on the outcome.
- Patients outcomes are collected at different time points (Longitudinal).
- The longitudinal structures are often ignored. "Change Score" are usually used as the measurement.
- Functional data are often hard to compare since the outcomes are trajectories.
- In functional data analysis, we want to get a scalar value to represent the trajectory.
- In Precision medicine, how could we make a treatment decision rule (TDR) when the outcomes are curves.

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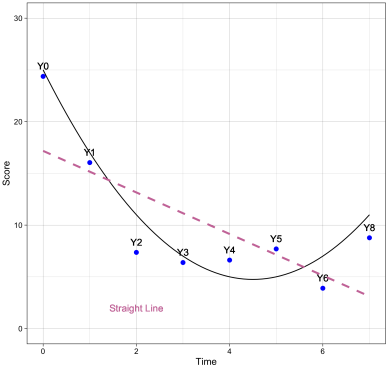
Scalar Outcome from a Functional Trajectory

Figure: An Example Trajectory



Longitudinal Outcomes

- Y_i: Observed outcomes
- Trajectory: Outcome generation function

Extract a scalar

- Last observed outcome: Y_8
- Change Score: $Y_8 - Y_1$ or $\frac{Y_8 - Y_1}{t_8 - t_1}$
- Slope of straight line

Target:

- Avoid the drawbacks
- Looking for a scalar measure: utilize the shape information and capture the features accurately.

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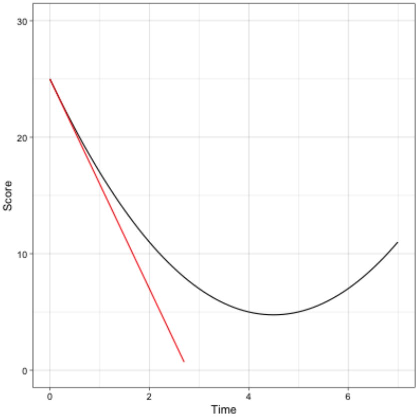
Average Tangent Slope

Average rate of change (average derivative)



Consider the mixed-effect model:

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

- Observation time points: $\boldsymbol{t}_i = (t_{i1}, \ldots, t_{im_i})^{\mathsf{T}}$;
- Observed outcomes: $\tilde{\boldsymbol{Y}}_i = (\tilde{y}_{i1}, \tilde{y}_{i2}, \ldots, \tilde{y}_{im_i})$;
- Design matrix $\boldsymbol{G}(\boldsymbol{t}_i) = (\boldsymbol{g}(t_1), \ldots, \boldsymbol{g}(t_{mi}))^{\mathsf{T}}$ and $\boldsymbol{g}(t) = \left(g_1(t), \ldots, g_p(t)\right)^{\mathsf{T}}$;
- Fixed effect: $\boldsymbol{\beta}$; Random effect: $\boldsymbol{b}_i \sim N(\boldsymbol{0}, \boldsymbol{D})$; Random error: $\boldsymbol{\varepsilon}_i \sim N(\boldsymbol{0}, \sigma^2 \boldsymbol{I})$

Average Outcome Function:

$$\mu(t) = \boldsymbol{g}^{\mathsf{T}}(t)\boldsymbol{\beta} \tag{2}$$

Average Tangent Slope (ATS) [Tarpey et al., 2021]:

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

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Example: Quadratic Trajectory

For example, if the outcome trajectory is quadratic in a longitudinal study, the design matrix $\boldsymbol{G}(\cdot)$ is constructed with the time function $\boldsymbol{g}(t) = (1, t, t^2)^{\mathsf{T}}$:

$$\boldsymbol{G}(\boldsymbol{t}_i) = \begin{pmatrix} 1 & t_1 & t_1^2 \\ \vdots & \vdots & \vdots \\ 1 & t_{m_i} & t_{m_i}^2 \end{pmatrix} \tag{4}$$

the average outcome trajectory function:

$$\mu(t) = \beta_0 + \beta_1 t + \beta_2 t^2 \tag{5}$$

The ATS is:

$$\frac{1}{t_m - t_1} \int_{t_1}^{t_m} \mu'(t) dt = \beta_1 + \beta_2 (t_1 + t_m) \tag{6}$$

The ATS estimator:

$$\frac{1}{t_m - t_1} \int_{t_1}^{t_m} \mu'(t) dt = \hat{\beta}_1 + \hat{\beta}_2 (t_1 + t_m) \tag{7}$$

Properties of ATS estimator

- ***Result 1:*** Both ATS estimator and Change Score Estimator are unbiased for the trajectory information when there is no missing data.
- ***Result 2:*** The ATS Estimator has smaller variance than Change Score Estimator.
- ***Result 3:*** When there is missing data, the ATS Formula Estimator is still unbiased while the Change Score Estimator is biased.
- ***Result 4:*** When there is missing data, the variances of the ATS Formula Estimator is inflated.

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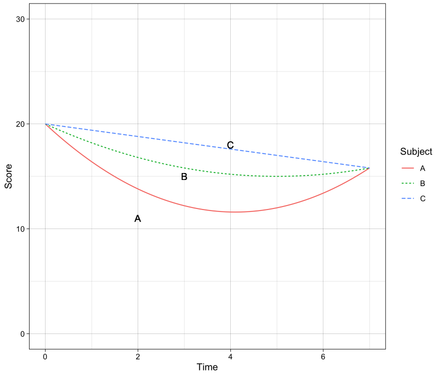
Weighted Average Tangent Slope



ATS

$$\frac{1}{t_m - t_1} \int_{t_1}^{t_m} \mu'(t)dt = \frac{\mu(t_m) - \mu(t_1)}{t_m - t_1} \quad (8)$$

WATS

$$\int_{t_1}^{t_m} w(t)\mu'(t)dt \quad (9)$$

where $\int_{t_1}^{t_m} w(t)dt = 1.$

Q: How can we find the weight function?

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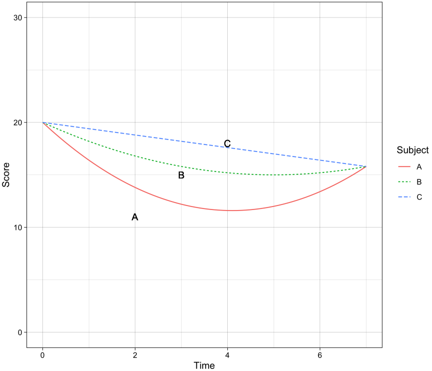

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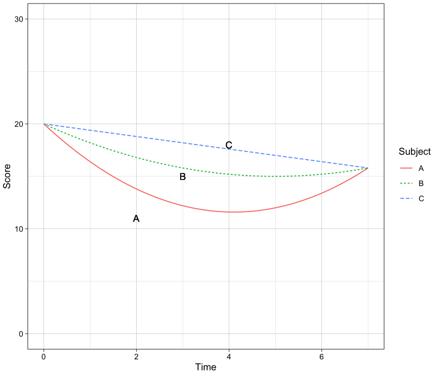

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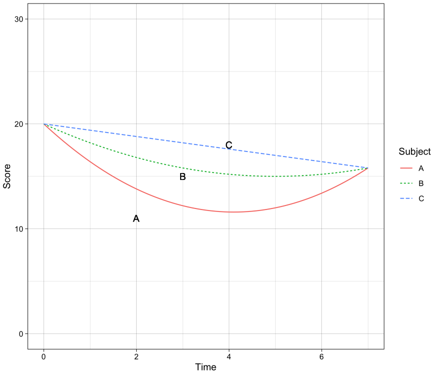

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Selection of Weight Function $w(t)$

Define $E_w(\boldsymbol{g}') = \left(\int_{t_1}^{t_m} w(t)g_1'(t)dt, \ldots, \int_{t_1}^{t_m} w(t)g_p'(t)dt\right)^{\mathsf{T}}$,

$$\text{WATS} = \int_{t_1}^{t_m} w(t)\mu'(t)dt = E_w^{\mathsf{T}}(\boldsymbol{g}')\boldsymbol{\beta} \tag{10}$$

Selection of $w(t)$:

- Arbitrary function
- Exponential function: $w(t) = h_1 \exp(\alpha_1 t + \alpha_2 t^2)$
- Beta distribution: $w(t) = h_2 \left(\frac{t-t_1}{t_m-t_1}\right)^{\gamma_1-1} \left(\frac{t_m-t}{t_m-t_1}\right)^{\gamma_2-1}$
- Basis spline weight function: $w(t) = \boldsymbol{b}_w^{\mathsf{T}}(t)\boldsymbol{q}\boldsymbol{q}^{\mathsf{T}}\boldsymbol{b}_w(t)$

Parameters: $h_1, h_2, \alpha_1, \alpha_2, \gamma_1, \gamma_2$

$\boldsymbol{q}$: coefficients for basis function $\boldsymbol{b}_w(t)$

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Hypothesis Test

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

$$\tilde{\boldsymbol{Y}}_{i,k} = \boldsymbol{G}(\boldsymbol{t}_{i,k})(\boldsymbol{\beta}_k + \boldsymbol{b}_{i,k}) + \boldsymbol{\varepsilon}_{i,k} \tag{11}$$

Hypothesis:

$$\begin{aligned} \mathrm{H}_0 &: E_w^{\mathsf{T}}(\boldsymbol{g}')(\boldsymbol{\beta}_1 - \boldsymbol{\beta}_2) = 0 \\ \mathrm{H}_1 &: E_w^{\mathsf{T}}(\boldsymbol{g}')(\boldsymbol{\beta}_1 - \boldsymbol{\beta}_2) \neq 0 \end{aligned} \tag{12}$$

Wald Test statistic:

$$\frac{E_w^{\mathsf{T}}(\boldsymbol{g}')\left(\widehat{\boldsymbol{\beta}}_1 - \widehat{\boldsymbol{\beta}}_2\right)\left(\widehat{\boldsymbol{\beta}}_1 - \widehat{\boldsymbol{\beta}}_2\right)^{\mathsf{T}} E_w(\boldsymbol{g}') - 0}{\mathrm{Var}\left(E_w^{\mathsf{T}}(\boldsymbol{g}')(\widehat{\boldsymbol{\beta}}_1 - \widehat{\boldsymbol{\beta}}_2)\right)} \sim \mathscr{X}^2(1) \tag{13}$$

Objective function:

$$\widehat{w(t)} = \underset{w(t)}{\operatorname{argmax}} \frac{E_w^{\mathsf{T}}(\boldsymbol{g}')\left(\widehat{\boldsymbol{\beta}}_1 - \widehat{\boldsymbol{\beta}}_2\right)\left(\widehat{\boldsymbol{\beta}}_1 - \widehat{\boldsymbol{\beta}}_2\right)^{\mathsf{T}} E_w(\boldsymbol{g}')}{E_w^{\mathsf{T}}(\boldsymbol{g}')\left(\mathrm{Cov}(\widehat{\boldsymbol{\beta}}_1) + \mathrm{Cov}(\widehat{\boldsymbol{\beta}}_1)\right) E_w(\boldsymbol{g}')} \tag{14}$$

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Optimization:

- 1. Choose the basis functions $\boldsymbol{g}(t)$ (any basis functions should be able to get the same result)
- 2. Fit the mixed effect model and get estimations of $\widehat{\boldsymbol{\beta}}_k$
- 3. Estimate the variance of $\widehat{\boldsymbol{\beta}}_k$ with $(\sum_{i=1}^{n} \boldsymbol{g}(t_i)^{\mathsf{T}} \widehat{\boldsymbol{V}}_{ki}^{-1} \boldsymbol{g}(t_i))^{-1}$, and $\widehat{\boldsymbol{V}}_{ki} = \boldsymbol{g}(t_i)\widehat{\boldsymbol{D}}\boldsymbol{g}(t_i)^{\mathsf{T}} + \hat{\sigma}^2 \boldsymbol{I}$, where $\widehat{\boldsymbol{D}}$ is the estimated covariance matrix.
- 4. Solve the generalized Rayleigh Quotient and get the estimated $\widehat{E_w(\boldsymbol{g}')}$
- 5. Plug the $\widehat{E_w(\boldsymbol{g}')}$ back in Eq(14) and get the estimated $\widehat{\mathsf{WATS}}_k$

$$\widehat{\mathsf{WATS}}_k = \widehat{E_w(\boldsymbol{g}')}^{\mathsf{T}} \widehat{\boldsymbol{\beta}}_k$$

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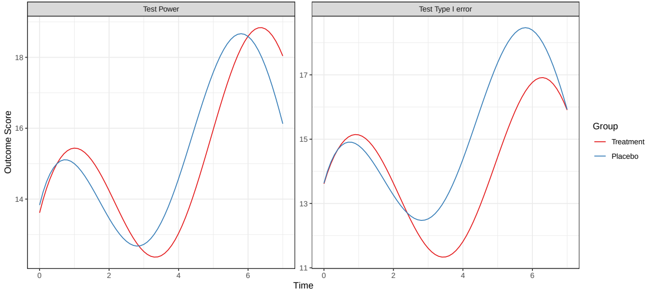
Simulation Study

Figure: Outcome Trajectories



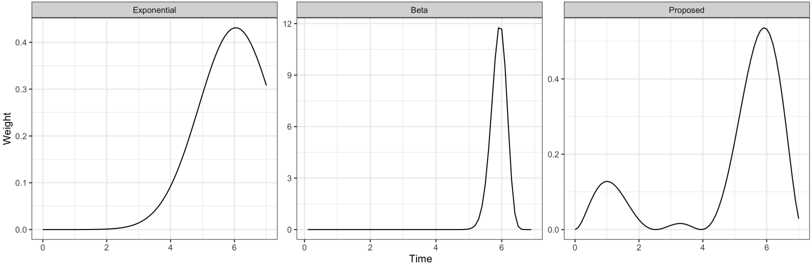
- $n = 100$ in each group (K = 2)
- $\boldsymbol{t} = (0, 1, ..., 7)^{\mathsf{T}}$, week 0 to week 7
- Random error $\varepsilon_1, \varepsilon_2 \sim N(0, \sigma^2)$, $\sigma \in \{1, 2, .., 10\}$
- Missingness: MCAR (30%);
- Missingness: Dropout: 50% subjects droped out at week 4.

Simulation Study

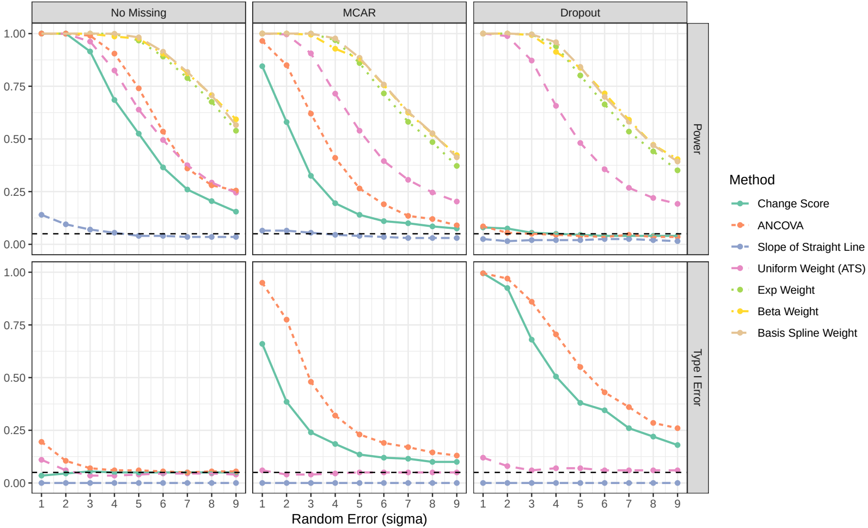
Methods Comparison:

- ATS estimator,
- WATS: exponential weight, beta weight, and weight function with basis function,
- Change Score, Slope of linear straight line, ANCOVA with adjustment of baseline outcomes.

Figure: Weight Functions



Comparison of Power and Type I Error



Treatment Decision Rules based on ATS

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

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

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

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

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Single Index Models

Single-index: $w = \boldsymbol{\alpha}^\mathsf{T}\boldsymbol{x}$.

Generated Effect Modifier model [Petkova et al., 2017]

$$y_k = \boldsymbol{x}(\boldsymbol{\gamma}_k \otimes \boldsymbol{\alpha}) + \varepsilon_k$$

- Choose $\boldsymbol{\alpha}$ that maximizes the statistical significance of modifying or interaction effect

Single index model with multiple links model [Park et al., 2020]

$$y_k = g_k(\boldsymbol{\alpha}_k^\mathsf{T}\boldsymbol{x}) + \varepsilon_k$$

- Nonlinear link function
- Flexible methods for determining composite variables

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

$$\tilde{\boldsymbol{Y}}_{i,k} = \boldsymbol{G}(\boldsymbol{t}_{i,k})\Big(\boldsymbol{\beta}_k + \boldsymbol{b}_{i,k} + \boldsymbol{\Gamma}_k(\boldsymbol{\alpha}^\top \boldsymbol{x}_{ik})\Big) + \boldsymbol{\varepsilon}_{i,k} \tag{15}$$

The averaged outcome function given biosignatures:

$$\mu_k(t|\boldsymbol{\alpha}^\top \boldsymbol{x}) = \boldsymbol{g}(t)^\top \left(\boldsymbol{\beta}_k + \boldsymbol{\Gamma}_k(\boldsymbol{\alpha}^\top \boldsymbol{x})\right) \tag{16}$$

Conditional ATS:

$$\text{ATS}_k(\boldsymbol{\alpha}^\top \boldsymbol{x}) = \frac{1}{t_m - t_1}\int_{t_1}^{t_m} \mu_k'(t|\boldsymbol{\alpha}^\top \boldsymbol{x})dt = \frac{\boldsymbol{g}(t_m)^\top - \boldsymbol{g}(t_1)^\top}{t_m - t_1}\Big(\boldsymbol{\beta}_k + \boldsymbol{\Gamma}_k(\boldsymbol{\alpha}^\top \boldsymbol{x})\Big) \tag{17}$$

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Optimizing the TDRs: Maximize the differences of ATS among groups

$$\int \Big(\text{ATS}_2(u) - \text{ATS}_1(u)\Big)^2 f_u(u)du$$
$$= b_1 + b_2 \boldsymbol{\mu}_x^\top \boldsymbol{\alpha} + b_3 \boldsymbol{\alpha}^\top (\boldsymbol{\mu}_x \boldsymbol{\mu}_x^\top + \boldsymbol{\Sigma}_x)\boldsymbol{\alpha} \quad (18)$$

where

- $b_1 = (\boldsymbol{\beta}_1^\top - \boldsymbol{\beta}_2^\top) \frac{\boldsymbol{g}(t_m) - \boldsymbol{g}(t_1)}{t_m - t_1} \frac{\boldsymbol{g}^\top(t_m) - \boldsymbol{g}^\top(t_1)}{t_m - t_1} (\boldsymbol{\beta}_1 - \boldsymbol{\beta}_2)$
- $b_2 = 2(\boldsymbol{\beta}_1^\top - \boldsymbol{\beta}_2^\top) \frac{\boldsymbol{g}(t_m) - \boldsymbol{g}(t_1)}{t_m - t_1} \frac{\boldsymbol{g}^\top(t_m) - \boldsymbol{g}^\top(t_1)}{t_m - t_1} (\boldsymbol{\Gamma}_1 - \boldsymbol{\Gamma}_2)$
- $b_3 = (\boldsymbol{\Gamma}_1^\top - \boldsymbol{\Gamma}_2^\top) \frac{\boldsymbol{g}(t_m) - \boldsymbol{g}(t_1)}{t_m - t_1} \frac{\boldsymbol{g}^\top(t_m) - \boldsymbol{g}^\top(t_1)}{t_m - t_1} (\boldsymbol{\Gamma}_1 - \boldsymbol{\Gamma}_2)$

Objective Function:

$$\widehat{\boldsymbol{\alpha}} = \underset{\boldsymbol{\alpha}}{\text{argmax}} \int \Big(\widehat{\text{ATS}}_2(u) - \widehat{\text{ATS}}_1(u)\Big)^2 f_u(u)du$$
$$= \underset{\boldsymbol{\alpha}}{\text{argmax}}\; b_1(\boldsymbol{\alpha}) + b_2(\boldsymbol{\alpha}) \widehat{\boldsymbol{\mu}}_x^\top \boldsymbol{\alpha} + b_3(\boldsymbol{\alpha}) \boldsymbol{\alpha}^\top (\widehat{\boldsymbol{\mu}}_x \widehat{\boldsymbol{\mu}}_x^\top + \widehat{\boldsymbol{\Sigma}}_x)\boldsymbol{\alpha} \quad (19)$$

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Optimizing the TDRs: Maximize the differences of ATS among groups

$$\int \Big(\text{ATS}_2(u) - \text{ATS}_1(u)\Big)^2 f_u(u)du \\ = b_1 + b_2\boldsymbol{\mu}_x^{\top}\boldsymbol{\alpha} + b_3\boldsymbol{\alpha}^{\top}(\boldsymbol{\mu}_x\boldsymbol{\mu}_x^{\top} + \boldsymbol{\Sigma}_x)\boldsymbol{\alpha} \tag{18}$$

where

- $b_1 = (\boldsymbol{\beta}_1^{\top} - \boldsymbol{\beta}_2^{\top})\frac{\boldsymbol{g}(t_m)-\boldsymbol{g}(t_1)}{t_m-t_1}\frac{\boldsymbol{g}^{\top}(t_m)-\boldsymbol{g}^{\top}(t_1)}{t_m-t_1}(\boldsymbol{\beta}_1 - \boldsymbol{\beta}_2)$
- $b_2 = 2(\boldsymbol{\beta}_1^{\top} - \boldsymbol{\beta}_2^{\top})\frac{\boldsymbol{g}(t_m)-\boldsymbol{g}(t_1)}{t_m-t_1}\frac{\boldsymbol{g}^{\top}(t_m)-\boldsymbol{g}^{\top}(t_1)}{t_m-t_1}(\boldsymbol{\Gamma}_1 - \boldsymbol{\Gamma}_2)$
- $b_3 = (\boldsymbol{\Gamma}_1^{\top} - \boldsymbol{\Gamma}_2^{\top})\frac{\boldsymbol{g}(t_m)-\boldsymbol{g}(t_1)}{t_m-t_1}\frac{\boldsymbol{g}^{\top}(t_m)-\boldsymbol{g}^{\top}(t_1)}{t_m-t_1}(\boldsymbol{\Gamma}_1 - \boldsymbol{\Gamma}_2)$

Objective Function:

$$\widehat{\boldsymbol{\alpha}} = \underset{\boldsymbol{\alpha}}{\text{argmax}} \int \Big(\widehat{\text{ATS}}_2(u) - \widehat{\text{ATS}}_1(u)\Big)^2 f_u(u)du \\ = \underset{\boldsymbol{\alpha}}{\text{argmax}}\; b_1(\boldsymbol{\alpha}) + b_2(\boldsymbol{\alpha})\widehat{\boldsymbol{\mu}}_x^{\top}\boldsymbol{\alpha} + b_3(\boldsymbol{\alpha})\boldsymbol{\alpha}^{\top}(\widehat{\boldsymbol{\mu}}_x\widehat{\boldsymbol{\mu}}_x^{\top} + \widehat{\boldsymbol{\Sigma}}_x)\boldsymbol{\alpha} \tag{19}$$

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Treatment Decision Rule:

$$d(\boldsymbol{x}^{\text{new}}) = I\Big(\frac{\boldsymbol{g}(t_m)^{\mathsf{T}} - \boldsymbol{g}(t_1)^{\mathsf{T}}}{t_m - t_1}\big(\widehat{\boldsymbol{\beta}}_2 + \widehat{\boldsymbol{\Gamma}}_2(\widehat{\boldsymbol{\alpha}}^{\mathsf{T}}\boldsymbol{x}^{\text{new}})\big) > \frac{\boldsymbol{g}(t_m)^{\mathsf{T}} - \boldsymbol{g}(t_1)^{\mathsf{T}}}{t_m - t_1}\big(\widehat{\boldsymbol{\beta}}_1 + \widehat{\boldsymbol{\Gamma}}_1(\widehat{\boldsymbol{\alpha}}^{\mathsf{T}}\boldsymbol{x}^{\text{new}})\big)\Big) + 1 \quad (20)$$

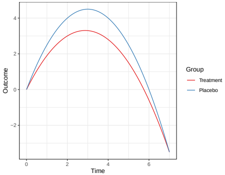
Simulation Study

- $n = 100$, $\boldsymbol{t} = (0, 1, ..., 7)^\mathsf{T}$
- $\boldsymbol{\beta}_1 = (0, 3, -0.5)^\mathsf{T}, \boldsymbol{\beta}_2 = (0, 2.3, -0.4)^\mathsf{T}$
- $\boldsymbol{\Gamma}_1 = (0, \cos(\frac{\theta}{180}\pi), \sin(\frac{\theta}{180}\pi))^\mathsf{T}$
- $\boldsymbol{\Gamma}_2 = (0, \cos(\frac{\theta}{180}\pi), -\sin(\frac{\theta}{180}\pi))^\mathsf{T}$,
- $\theta \in \{0, 5, 10, 20\}$
- Random effect $\boldsymbol{\gamma}_{1,i} \sim N(\mathbf{0}, \boldsymbol{D}_1)$, $\boldsymbol{\gamma}_{2,i} \sim N(\mathbf{0}, \boldsymbol{D}_2)$, where

$$\boldsymbol{D}_1 = \boldsymbol{D}_2 = \begin{pmatrix} 8 & 3 & -0.4 \\ 3 & 1.5 & -0.16 \\ -0.4 & -0.16 & 0.03 \end{pmatrix}$$

- Missingness: MCAR (30 %); Dropout: 50% dropout at week 2.

Figure: Outcome Trajectory




No Missing
MCAR
Dropout
theta = 0
theta = 5
theta = 10
theta = 20
Proportion of Correct Decision (PCD)
p = 2
p = 10
p = 20
Method
ATS
LinGEM
SIMML

Summary

- Average tangent slope can provide a meaningful scalar summary of a functional trajectory.
- The weighted average tangent slope allows additional flexibility in extracting a scalar summary statistic.
- Both methods have outstanding performances than the other scalar measures and are robust to missing values (MCAR, Dropout)
- In precision medicine, the ATS and WATS can help the derivation of the optimal treatment decision.
- 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

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Thank you!

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