Simulation Study of Automated Thickness Analyzing Machine (ATAM)[Change the name if you want]

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Background and Motivation

Several diseases have been found to be related to white matter loss in brain, such as Autism (Vidal 2006) and ADHD (Luders 2009). Here, we measure white matter loss based the thickness of the mid-sagittal slice of the corpus callosum (CC), the largest white matter structure in brain.

Our objective: To analyze the link between white matter thickness along the CC, and Expanded Disability Status Scale (EDSS) score in patients with multiple sclerosis (MS). Specifically, if there are regions of the CC that are predictive of EDSS score, we want to find out where they are.

Today we'll present a simulation study on our proposed method.

Figure : CC 3D rendering and mid-sagittal slice
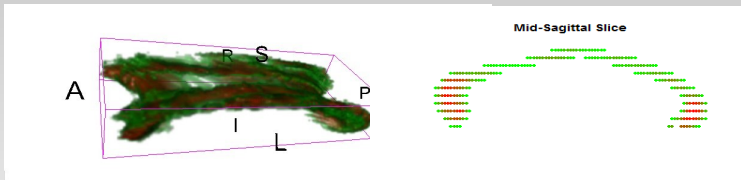
176 patients with MS(Multiple Sclerosis), 466 scans.
Color indicates corresponding FA.

Pipeline

1. Obtain the center curve (principal curve) of the target data cloud.
2. Measure the thickness.
3. Regress the thickness function on a scalar outcome.
4. Hypothesis testing.

Simulation Settings

For ease of computation, we first generate Y_i, $(i = 1, 2, ... I)$ and then generate I shapes with features of the ith shape determined by the value of Y_i.
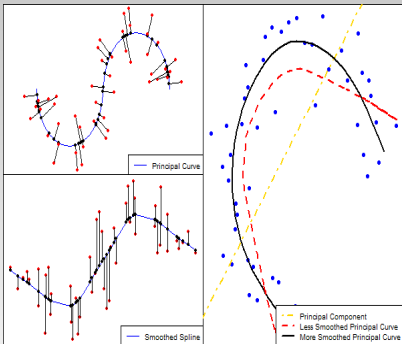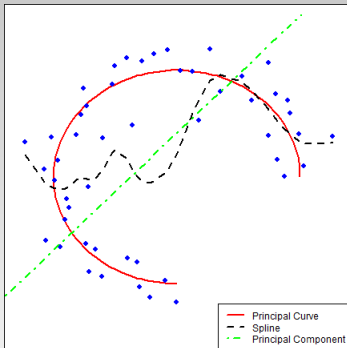
- Case 1: I=300, response $Y_i \sim$ Possion$(\lambda = 3)$. Thickness of image$_i$ within $(\frac{\pi}{3}, \frac{3\pi}{4})$ and $(\frac{5\pi}{4}, \frac{7\pi}{4})$ is related to Y_i.

- Case 2: I=300, response $Y_i \sim$ Possion$(\lambda = 3)$. Thickness of image$_i$ in the vertical bar is related to Y_i.
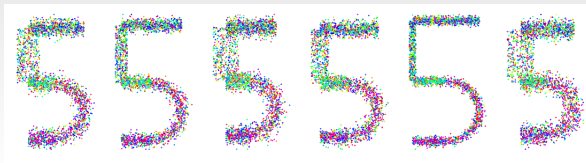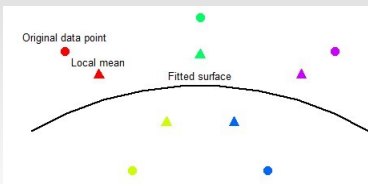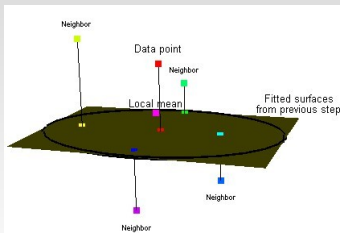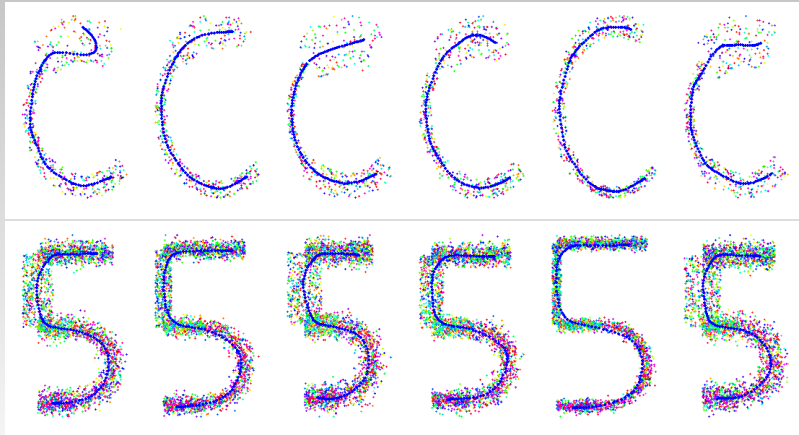
Principal curve

Principal Curve Algorithm

1. **The Projection Step.** The points are projected onto the curve of the previous iteration.

2. **The Conditional Expectation Step.** For each data point $\mathbf{x}^{(i)}$, we calculate a locally average $\bar{\mathbf{x}}^{(i)}$.

3. **The Smoothing Step.** Fitting a fast TPS using all the local average data point $\bar{\mathbf{x}}^{(i)}$, obtain f^{new}.
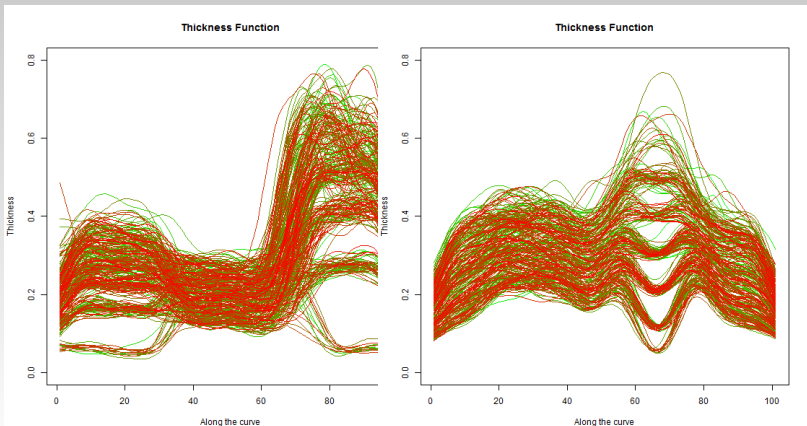
Principal curve fitting result

Obtaining Thickness along the principal curve

- $\text{Thick}^*(t) = \text{Quantile}\left(\{2 \times \text{dist}_{t_j}, \left||t_j - t\right| \leq .02\}\ 0.95\right)$
- Fit a smooth spline of all $\text{Spline}(\text{Thick}^*(.) \longrightarrow \text{Thick}(.))$

Regression Notation

Y_i = Outcome (simulated EDSS score)

$X_i(t)$ = The thickness function along the track of the structure

$\beta(t)$ = Function representing effect of thickness on outcome, at different points.
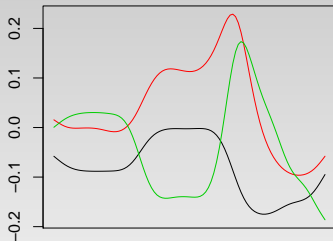
$t \in [0, 1]$.

$$Y_i \sim Poisson(\theta_i)$$

$$\theta_i = \beta_0 + \int_0^1 X_i(t)\beta(t)dt$$

Regression Notation
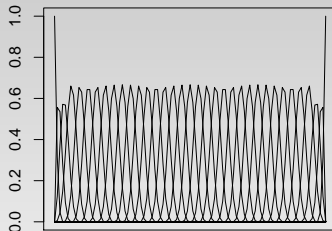
Estimate the functions $X_i(t)$ and $\beta(t)$ using basis functions.

For X, we'll use it's principle components. For β, we'll use a b-spline basis.

Principle Components for X

b–spline basis for β

$$X_i(t) \approx \sum_{k=1}^{K_x} \xi_{ik} \Psi_k(t) \qquad \qquad \beta(t) \approx \sum_{l=1}^{K_\beta} \beta_l \varphi_l(t)$$

Regression Notation

$$\int_0^1 X_i(t)\beta(t)dt \approx \int_0^1 \left(\sum_{k \in \{A\}} \xi_{ik}\Psi_k(t) \right) \left(\sum_{j \in \{B\}} \beta_l\varphi_l(t) \right) dt$$

$$= \int_0^1 \left(\sum_{(k,j) \in \{A\} \times \{B\}} \xi_{ik}\Psi_k(t)\varphi_l(t)\beta_l \right) dt$$

$$= \sum_{(k,j) \in \{A\} \times \{B\}} \xi_{ik} \left(\int_0^1 \Psi_k(t)\varphi_l(t)dt \right) \beta_l$$

$$=: \xi_i \mathbf{J} \beta^T$$

- Where $\xi_i = [\xi_{i1}, ..\xi_{iK_X}]^T$, $\beta = [\beta_1, ...\beta_{K_\beta}]^T$, and $\mathbf{J}$ is a $K_x \times K_\beta$ matrix with $(i,j)^{th}$ element equal to $\int_0^1 \Psi_i(t)\varphi_j(t)dt$.
- For this project we'll assume $\xi_i \mathbf{J}$ is fixed, and will put a penalty prior on β.

Full Model

$$Y_i \sim Poisson(\theta_i)$$
$$\theta_i = \beta_0 + \xi_i \mathbf{J}\beta^T$$
$$\beta_0, \beta_1 \sim N(0, 100)$$
$$\beta_j \sim N(\beta_{j-1}, 1/\tau_\beta)$$
$$\tau_\beta \sim \Gamma(.001, .001)$$

This could be made to account for measurement error by letting:
$W_i(t) = \sum_{k=1}^{K_x} \xi_{ik} \Psi_k(t) + \epsilon_i(t)$, and assigning priors for $\epsilon_i(t)$ and ξ_{ik}.
Fit this in WinBUGS. [1]

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[1](Crainiceanu and Goldsmith 2010; Brezger, Kneib, and Lang 2005; Lang and Brezger 2004;
Goldsmith, Feder, Crainiceanu, Caffo, and Reich, 2010)

Hypothesis Testing
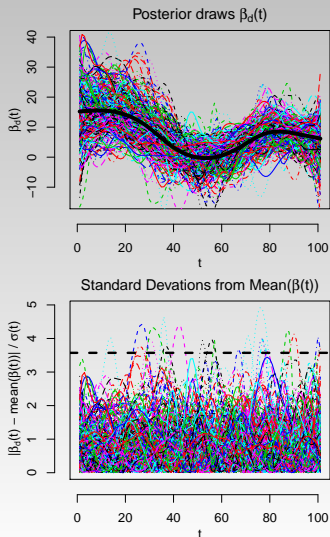
Given draws $(\beta_d(t))$ from the posterior:

- Credible intervals give the range along the curve where 95% of the points will fall
  - To estimate this, we need the quantiles for $\beta_d(t)$.
- Credible bands give the area within which 95% of the curves will be completely contained
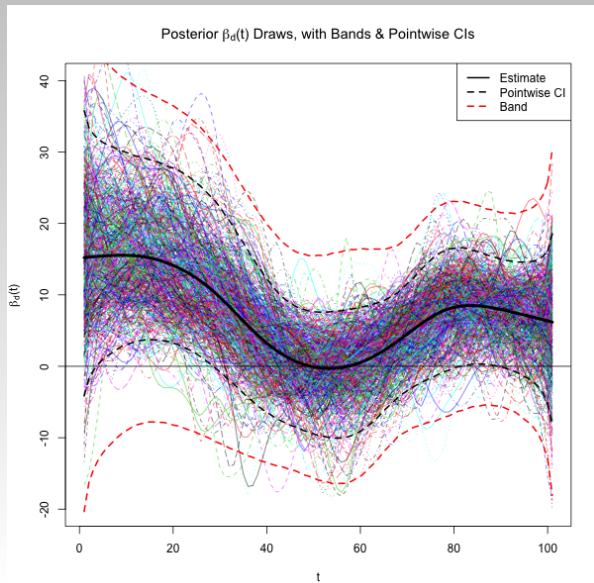 - Roughly speaking, we'd need the quantiles for each curve's largest deviation from the mean curve.

Posterior draws $\beta_d(t)$

Covariance Matrix for $\beta_d(t)$
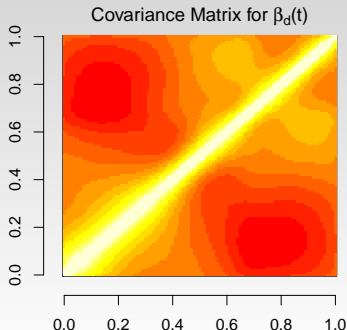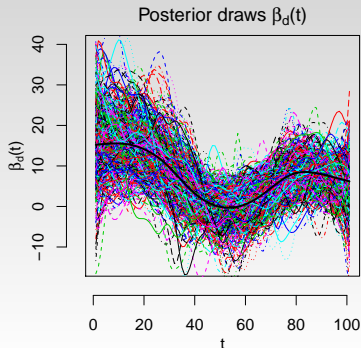
Hypothesis Testing

Let:

- $\hat{\beta}(t) = mean(\beta_d(t))$

- $\sigma(t)^2 = var(\beta_d(t))$

- $S_d(t) = \frac{|\beta_d(t) - \hat{\beta}(t)|}{\sigma(t)}$
  - Assume $P(S_d(t) > s)$ is constant over t, given s

- $m_d = max_t \{S_d(t)\}$

- $q(m_d, .95)$ is the 95% quantile of m_d across d.

- Reconstruct credible bands using $\hat{\beta}(t) \pm q(m_d, .95)\sigma(t)$.


Posterior draws β_d(t)

Standard Devations from Mean(β(t))

Credible Intervals & Bands - C Shape

Posterior $\beta_d(t)$ Draws, with Bands & Pointwise CIs

Comparison to a Bonferroni

- Pointwise intervals above are calculated above using the ($.5\alpha$) & (1-$.5/alpha$) quantiles at each point t (with $\alpha = .05$).
- We could also create a confidence band using a Bonferroni style adjustment, using the ($.5\alpha/100$) and $(1 - \frac{.5\alpha}{100})$

Credible Intervals & Bands - C Shape

Posterior $\beta_d(t)$ Draws, with Bands & Pointwise CIs
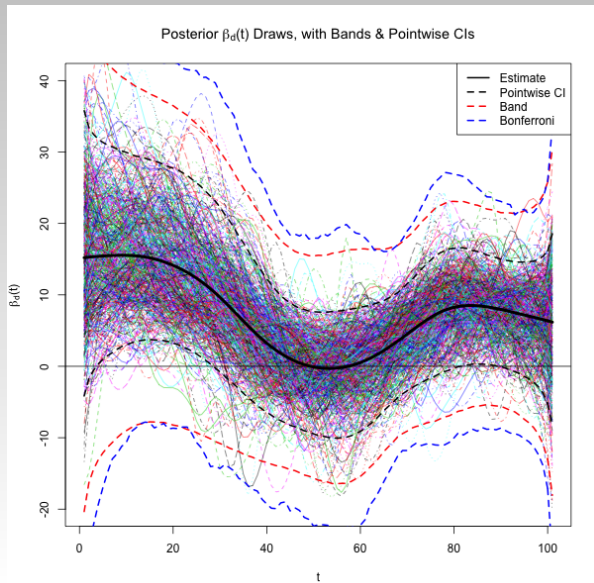
Credible Intervals & Bands - 5 Shape
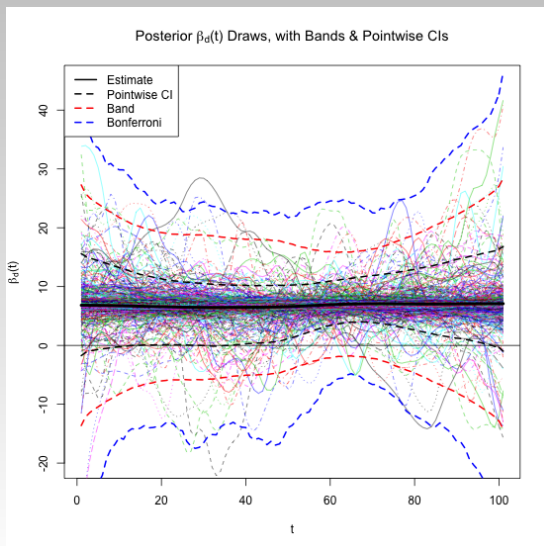
Discussion

- The credible band never rises above zero, but several points are pointwise significant. These could be the subject of future tests if they were real data.

- Principle curve procedure sometimes doesn't work so well at the end points, it they are too thick.

- Results are slightly sensitive to number of splines chosen.