Latent Gaussian Mixture Models for Nationwide Kidney Transplant Center Evaluation

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Outline

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1 Introduction

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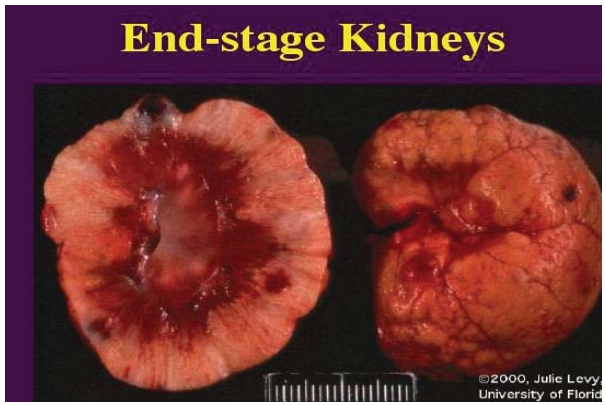
Introduction

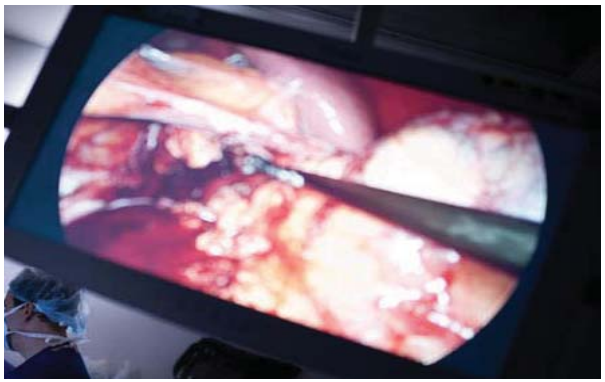
End Stage Renal Disease (ESRD)



- K idneys are functioning below 10 percent of their normal function.
- Progressive and Costly
  - Total patients: 620,000.
  - New cases: 120,000 a year.
  - Total cost per year: $50.0 billion.

Introduction

Kidney Transplantation



- The most desired and cost-effective modality of renal replacement therapy.
- Conducted at 296 transplant centers nationwide.

Evaluation of Quality of Care

- Practice patterns vary across transplant centers.
- Variation reflects the differential practice preferences of physicians, surgeons, therapists, dietitians, etc. from a specific center.
- Important to evaluate transplant centers for quality improvement.
- Post-transplant survival is an important indicator for quality of care delivered by transplant centers.

Data Information

- Data are obtained from the Organ Procurement and Transplantation Network (OPTN)
- All adult transplant patients with the transplant date between January 1987 and December 2008.
- 269,386 patients from 296 transplant centers.
- **X**: demographics of patients (age, gender, BMI), donor information (cold ischemic time).
- Y: 5 year survival status (1 = death, -1=survive) .
- The overall failure rate within 5 years of transplantation is 27.59%.

Model

Generalized linear mixed model

Y_{ik}: observed outcome for the kth patient from the ith center; $\boldsymbol{X}_{ik}$ is a subject-specific covariate.

$$f(Y_{ik}|\boldsymbol{X}_{ik}, \gamma_i; \beta, \varphi) = \exp\left\{\frac{Y_{ik}\xi_{ik} + b(\xi_{ik})}{a(\varphi)} + d(Y_{ik}, \varphi)\right\}.$$

- $\xi_{ik} = \boldsymbol{X}_{ik}^T\boldsymbol{\beta} + \gamma_i$.
- γ_i: effect for center i.
- We use logistic link in our application.

Fixed Effects Models

- Fixed effects provide more precise estimation of true effects for centers with extreme values.
- Variation is large for centers with fewer patients.

Generalized Linear Mixed Effects Models (GLMM)

- Some policy researchers advocate modeling the center effects as Gaussian random effects.
- Most GLMM literature assumes Gaussian random effects.
  - Ignores the heterogeneity among the medical providers.
  - Estimates are shrunk toward the overall mean, and are biased.

Our Proposal: Finite Gaussian Mixture Models

- Allow subgroup (cluster) structures among the centers.
- Model center effects using a finite Gaussian mixture model.
- A compromise between the random effects and fixed effects models.
  - Reduce to the random effects model when there is only one component in the mixture distribution.
  - Become the fixed effects model if each transplant center is a cluster.
- Gaussian mixture models are weakly identifiable with unbounded Fisher information.
- Limited work on GLMM with finite Gaussian mixture random effects.
- Extend recent work by Chen et al. (2012) and Kasahara and Shimotsu (2015) to make inference on the latent Gaussian mixture model.

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Gaussian mixture random effects with C components

Assume transplant centers belong to C subpopulations

- $\gamma_i \sim \sum_{c=1}^{C} \pi_c N(\mu_c, \sigma_c^2)$.
- $\pi_c \in (0, 1]$ is the weight for subpopulation c, $\sum_{c=1}^{C} \pi_c = 1$.
- $\boldsymbol{\theta}_\gamma = (\mu_1, \ldots, \mu_C, \sigma_1, \ldots, \sigma_C, \pi_1, \ldots, \pi_C)^T$ is the collection of parameters in $g(\gamma)$.

Latent Random Vector

- Define $\boldsymbol{L}_i = (L_{i1}, \ldots, L_{iC})^T$ as a latent random vector of subpopulation memberships.
- $L_{ic} = 1$ if γ_i belongs to component c and $L_{ic} = 0$ otherwise.
- $\boldsymbol{L}_i \sim \text{Multinomial}(\pi_1, \ldots, \pi_C)$.

Log Complete Likelihood

Log complete likelihood

$$\ell_{comp}(\boldsymbol{\theta}; \mathbf{Y}, \mathbf{X}, \boldsymbol{\gamma}, \mathbf{L}) = \sum_{i=1}^{n} \ell_{i,comp}(\boldsymbol{\theta}; Y_i, X_i, \gamma_i, L_i),$$

- $\ell_{i,comp}(\boldsymbol{\theta}; Y_i, X_i, \gamma_i, L_i) = \log f(\boldsymbol{Y}_i | \boldsymbol{X}_i, \gamma_i; \boldsymbol{\theta}_y) + \sum_{c=1}^{C} L_{ic} \log\{\pi_c f_c(\gamma_i | \mu_c, \sigma_c)\}$.
- $\boldsymbol{\gamma} = (\gamma_1, \ldots, \gamma_n)^T$.

Penalized complete data likelihood

Penalized complete data likelihood

$$\ell_{pen}(\boldsymbol{\theta}; \mathbf{Y}, \mathbf{X}, \gamma, \mathbf{L}) = \ell_{comp}(\boldsymbol{\theta}; \mathbf{Y}, \mathbf{X}, \gamma, \mathbf{L}) + \sum_c p_n(\sigma_c^2; \hat{\sigma}_{c,pilot}^2).$$

- Penalty proposed by Chen and Li (2009)

$$p_n(\sigma^2; \hat{\sigma}_{pilot}^2) = -a_n(\hat{\sigma}_{pilot}^2/\sigma^2 + \log(\sigma^2/\hat{\sigma}_{pilot}^2) - 1),$$

- $\hat{\sigma}_{pilot}^2$ is an initial estimate for the variance of γ and $a_n = o_p(n^{1/4})$.
- The penalty prevents any σ_c^2 from converging to 0.

EM Algorithm

- E-step: calculate a conditional expectation of the complete log-likelihood at the t-th iteration:

$$E\left[\ell_{i,comp}(\boldsymbol{\theta}; Y_i, \boldsymbol{X}_i, \gamma_i, L_i) | Y_i, \boldsymbol{X}_i, \boldsymbol{\theta}^{(t-1)}\right]$$

- M-step: maximize with respect to $\boldsymbol{\theta}$.

Parameter Space and Its Closure

- The parameter space for a model with exactly C components is

$$\Theta_C = \{\boldsymbol{\theta} \mid \boldsymbol{\beta} \in \mathbb{R}^p, \sum_{c=1}^{C} \pi_c = 1, 0 < \pi_c < 1, \mu_1 < \mu_2 < \cdots < \mu_C, \sigma_c > 0, c = 1, 2, \ldots, C\}.$$

- The closure of Θ_C is

$$\bar{\Theta}_C = \{\mid \boldsymbol{\beta} \in \mathbb{R}^p, \sum_{c=1}^{C} \pi_c = 1, 0 \leq \pi_c \leq 1, \mu_1 \leq \mu_2 \leq \cdots \leq \mu_C, \sigma_c \geq 0, \ c = 1, 2, \ldots, C\},$$

  which also includes the over-fitted models, i.e models with less than C components.

Consistency of Estimators

- Parameterization in $\bar{\Theta}_C$ is not unique.
- Let $\boldsymbol{\theta}_0 \in \bar{\Theta}_C$ be the true parameter, define the equivalent class of $\boldsymbol{\theta}_0$

$$\mathbb{F} = \left\{ \boldsymbol{\theta} \in \bar{\Theta}_C;\ \int_{-\infty}^{(\mathbf{x}',\mathbf{y}')} f(\mathbf{x},\mathbf{y}|\boldsymbol{\theta}) d\mu(\mathbf{x},\mathbf{y}) = \int_{-\infty}^{(\mathbf{x}',\mathbf{y}')} f(\mathbf{x},\mathbf{y},|\boldsymbol{\theta}_0) d\mu(\mathbf{x},\mathbf{y}) \text{ for any } (\mathbf{x}',\mathbf{y}') \right\}.$$

Proposition

Under suitable assumptions, $\widehat{\boldsymbol{\theta}}_C$ is consistent in the sense $\inf_{\boldsymbol{\theta}^* \in \mathbb{F}} \|\widehat{\boldsymbol{\theta}}_C - \boldsymbol{\theta}^*\| \to 0$ in probability

Detect Number of Components: Locally Restricted Alternative Space

- Test $H_0 : C_0 = C$ sequentially for $C = 1, 2, \ldots$ and stop when fail to reject a hypothesis.
- A Bonferroni procedure can be used to control the family-wise error rate.
- With non-identifiability, the regular asymptotic theory for likelihood ratio tests does not apply.
- Most importance one is the homogeneity hypothesis $H_0 : C_0 = 1$ vs $H_1 : C_0 = 2$.
- We use a locally restricted likelihood ratio test similar to those Chen et al. (2012) and Kasahara and Shimotsu (2015).

Homogeneity test

- Test $H_0 : C_0 = 1$ vs $H_1 : C_0 = 2$.
- The null model is not unique under the alternative hypothesis.
- For any $\tau \in (0, 0.5]$, define a restricted parameter space

$$\bar{\Theta}_2(\tau) = \{\boldsymbol{\theta} \in \bar{\Theta}_2 \mid \pi_1 = \tau, \pi_2 = 1 - \tau\},$$

- In $\bar{\Theta}_2(\tau)$, the null model is uniquely parameterized by $\boldsymbol{\theta}_{\gamma,0}(\tau) = (\mu_\gamma, \mu_\gamma, \sigma_\gamma, \sigma_\gamma, \tau, 1-\tau)^{\mathrm{T}}$.
- Restricted alternative estimator $\widehat{\boldsymbol{\theta}}_{full}(\tau) = \arg\max_{\boldsymbol{\theta} \in \bar{\Theta}_2(\tau)} \ell_{pen}(\boldsymbol{\theta})$.

Proposition

Under $H_0 : C_0 = 1$ for any fixed $\tau \in (0, 0.5]$, $\widehat{\boldsymbol{\beta}}_{full}(\tau) - \boldsymbol{\beta}_0 = O_p(n^{-1/2})$, and $\widehat{\boldsymbol{\theta}}_{\gamma,full}(\tau) - \boldsymbol{\theta}_{\gamma,0}(\tau) = O_p(n^{-1/4})$.

Locally Restricted Likelihood Ratio Test

- Let the reduced model estimator be $\widehat{\boldsymbol{\theta}}_{red} = \arg\max_{\boldsymbol{\theta} \in \bar{\Theta}_1} \ell_{pen}(\boldsymbol{\theta})$.
- Let $\mathcal{T} = (0, 0.5]$, define the test statistic $\widetilde{T}_1 = \max_{\tau \in \boldsymbol{\mathcal{T}}} T_1(\tau)$, where $T_1(\tau) = 2[l_n\{\widehat{\boldsymbol{\theta}}_{full}(\tau)\} - l_n(\widehat{\boldsymbol{\theta}}_{red})]$ and

$$l_n(\boldsymbol{\theta}; \mathbf{Y}, \mathbf{X}) = \sum_{i=1}^{n} \log \int \left\{ \prod_{k=1}^{n_i} f(Y_{ik} | \mathbf{X}_{ik}, \gamma_i; \boldsymbol{\theta}_y) g(\gamma_i | \boldsymbol{\theta}_\gamma) \right\} d\gamma_i.$$

Proposition

Under $H_0 : C_0 = 1$ and suitable assumptions, $\widetilde{T}_1 \xrightarrow{d} \chi^2(2)$ as $n \to \infty$.

Test for $H_0 : C_0 = C$ vs $H_1 : C_0 = C + 1$ for $C \geq 2$

- Reduced model estimator is $\widehat{\boldsymbol{\theta}}_{red} = \arg\max_{\boldsymbol{\theta} \in \bar{\Theta}_C} l_{pen}(\boldsymbol{\theta})$
- Take turns to test if the cth component of the mixture can be further split into two.
- Define non-overlapping intervals $D_1, \ldots, D_C$ such that $\mu_{c,0} \in D_c$. For a fixed $\tau \in (0, 0.5]$ and $c \in \{1, \ldots, C\}$, define neighborhoods in $\bar{\Theta}_{C+1}$

$$\begin{aligned} \mathcal{N}_{C+1}(c, \tau) \quad = \quad \{\boldsymbol{\theta} \in \bar{\Theta}_{C+1} \mid \tfrac{\pi_c}{\pi_c + \pi_{c+1}} = \tau; \quad & \mu_{c'} \in D_{c'} \text{ for } c' < c; \\ & \mu_c, \mu_{c+1} \in D_c; \quad \mu_{c'} \in D_{c'-1} \text{ for } c' > c+1\}. \end{aligned}$$

- $\widehat{\boldsymbol{\theta}}_{full}(c, \tau) = \arg\max_{\boldsymbol{\theta} \in \mathcal{N}_{C+1}(c,\tau)} l_{pen}(\boldsymbol{\theta})$.

Proposition

Under $H_0 : C_0 = C$, for any fixed $\tau \in (0, 0.5]$,

$$\begin{aligned} \widehat{\mu}_{c,full}(c, \tau) - \mu_{c,0} &= O_p(n^{-1/4}), \quad \widehat{\mu}_{c+1,full}(c, \tau) - \mu_{c,0} = O_p(n^{-1/4}), \\ \widehat{\sigma}_{c,full}(c, \tau) - \sigma_{c,0} &= O_p(n^{-1/4}), \quad \widehat{\sigma}_{c+1,full}(c, \tau) - \sigma_{c,0} = O_p(n^{-1/4}), \end{aligned}$$

and all other estimators converge to the true values in a root-n rate.

Test for $H_0 : C_0 = C$ vs $H_1 : C_0 = C + 1$ for $C \geq 2$ (cont.)

- For a fixed $\tau \in (0, 0.5]$, define $T_C(\tau) = \max_{c \in \{1,2,\ldots,C\}} T_C(c, \tau)$, where $T_C(c, \tau) = 2[l_n\{\widehat{\boldsymbol{\theta}}_{full}(c, \tau)\} - l_n(\widehat{\boldsymbol{\theta}}_{red})]$.
- Let $\mathcal{T}$ be any subset of $(0, 0.5]$, define $\widetilde{T}_C = \max_{\tau \in \mathcal{T}} T_C(\tau)$.

Proposition

The asymptotic distribution for $\widetilde{T}_C$ is that of the maximum of C correlated χ^2_2 random variables.

- We use a simulation procedure to approximate the asymptotic distribution of $\widetilde{T}_C$, where the correlations between the χ^2 variables are computed using the theoretical expression.

Transplant center evaluation

- Following Efron (2004), identify the "empirical null" distribution of γ as a subset of components in the mixture density, $g_0(\gamma|\boldsymbol{\theta}_\gamma) = \sum_{c\in\mathcal{C}_0} \pi_c f_c(\gamma|\mu_c, \sigma_c) / \sum_{c\in\mathcal{C}_0} \pi_c$ where $\mathcal{C}_0 \subset \{1, 2, \ldots, C\}$.
- For each transplant center i, test if it belongs to one of the components in $\mathcal{C}_0$, or $H_{i0} : \sum_{c\in\mathcal{C}_0} L_{ic} = 1$, $i = 1, \ldots, n$.
- Suppose $\mathcal{C}_0$ consists of centers of average performance, then center i is considered "interesting" (either outperforming or underperforming) if H_{i0} is rejected.

Transplant center evaluation (cont.)

- We address this multiple hypothesis testing problem using local FDR

$$\begin{aligned} lFDR_i &= P(\textstyle\sum_{c\in\mathcal{C}_0} L_{ic} = 1 | \boldsymbol{X}_i, \boldsymbol{Y}_i) \\ &= \frac{\sum_{c\in\mathcal{C}_0} \pi_c \int f(\boldsymbol{Y}_i|\boldsymbol{X}_i, \gamma; \boldsymbol{\beta}) f_c(\gamma|\mu_c, \sigma_c) d\gamma}{\int f(\boldsymbol{Y}_i|\boldsymbol{X}_i, \gamma; \boldsymbol{\beta}) g(\gamma|\boldsymbol{\theta}_\gamma) d\gamma}. \end{aligned}$$

- **Benjamini-Hochberg** procedure: Let $lFDR_{(1)} \leq lFDR_{(2)} \leq \cdots \leq lFDR_{(n)}$ be the ranked lFDR values. For any $\alpha > 0$, let $k = \max_i\{\frac{1}{i}\sum_{j=1}^{i} lFDR_{(j)} \leq \alpha\}$ and our FDR control procedure is to reject all H_{i0} with the rank of $lFDR_i$ less or equal to k.

Transplant center evaluation (cont.)

- We address this multiple hypothesis testing problem using local FDR

$$\begin{aligned} lFDR_i &= P(\textstyle\sum_{c\in\mathcal{C}_0} L_{ic} = 1 | \boldsymbol{X}_i, \boldsymbol{Y}_i) \\ &= \frac{\sum_{c\in\mathcal{C}_0} \pi_c \int f(\boldsymbol{Y}_i|\boldsymbol{X}_i, \gamma; \boldsymbol{\beta}) f_c(\gamma|\mu_c, \sigma_c) d\gamma}{\int f(\boldsymbol{Y}_i|\boldsymbol{X}_i, \gamma; \boldsymbol{\beta}) g(\gamma|\boldsymbol{\theta}_\gamma) d\gamma}. \end{aligned}$$

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Proposition

Under the latent Gaussian mixture model, the above procedure controls FDR at level α.

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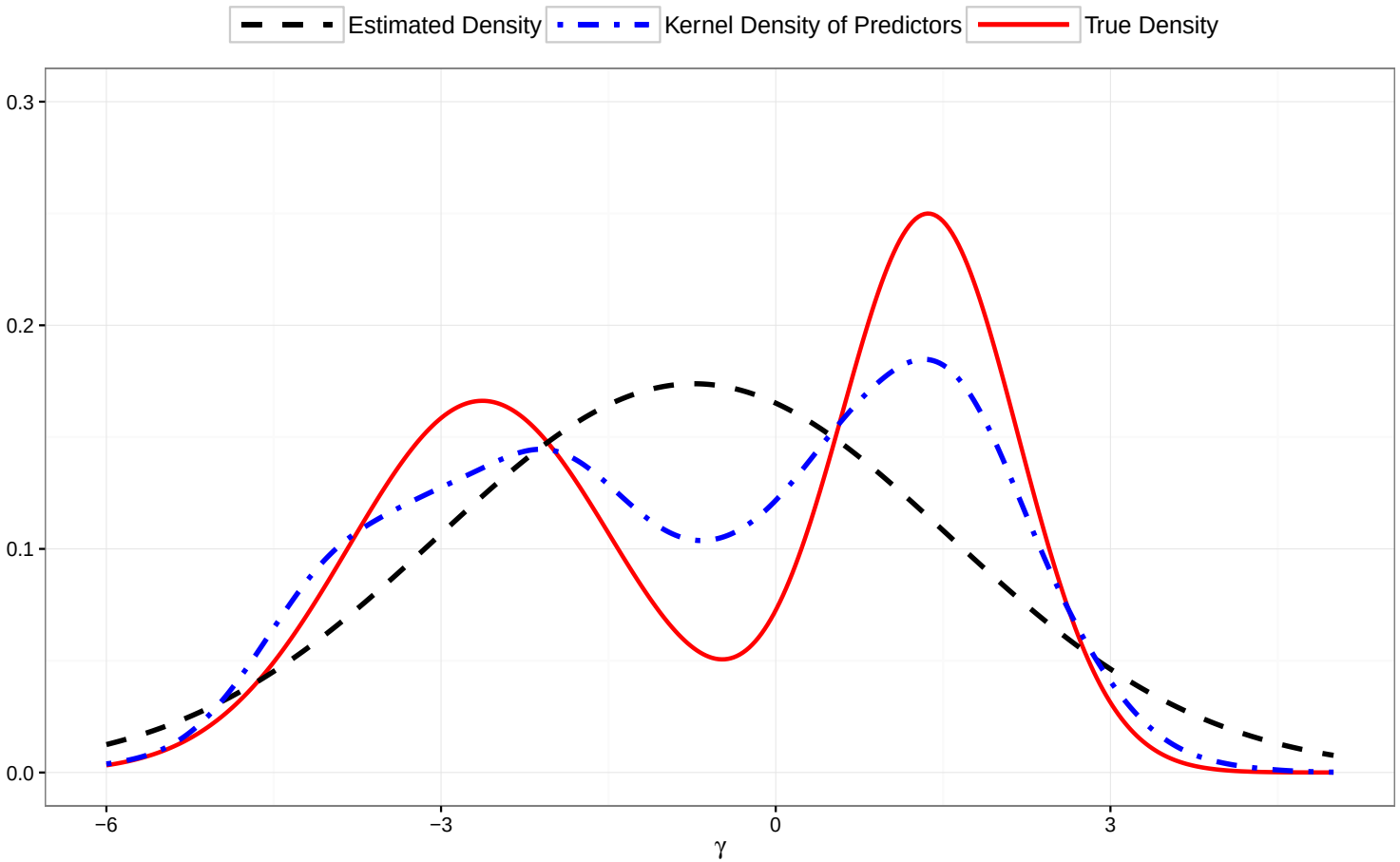
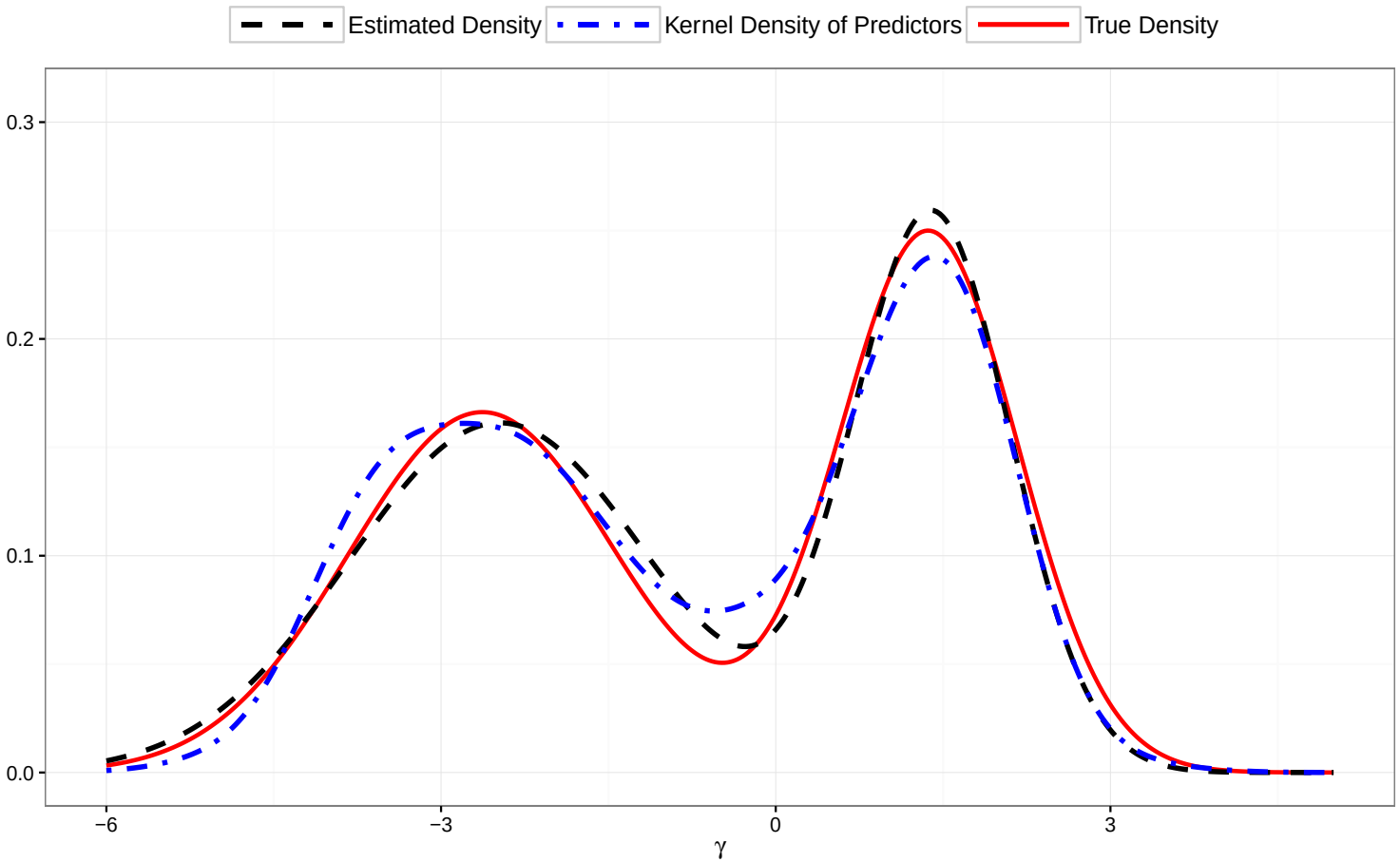
Simulation Setup

- We use the same number of centers as in real data.
- Roughly 1/10 of the number subject per center.
- Y_{ik} are generated from logistic regression model and γ_i are generated from various finite Gaussian mixture models.

Assume One Component

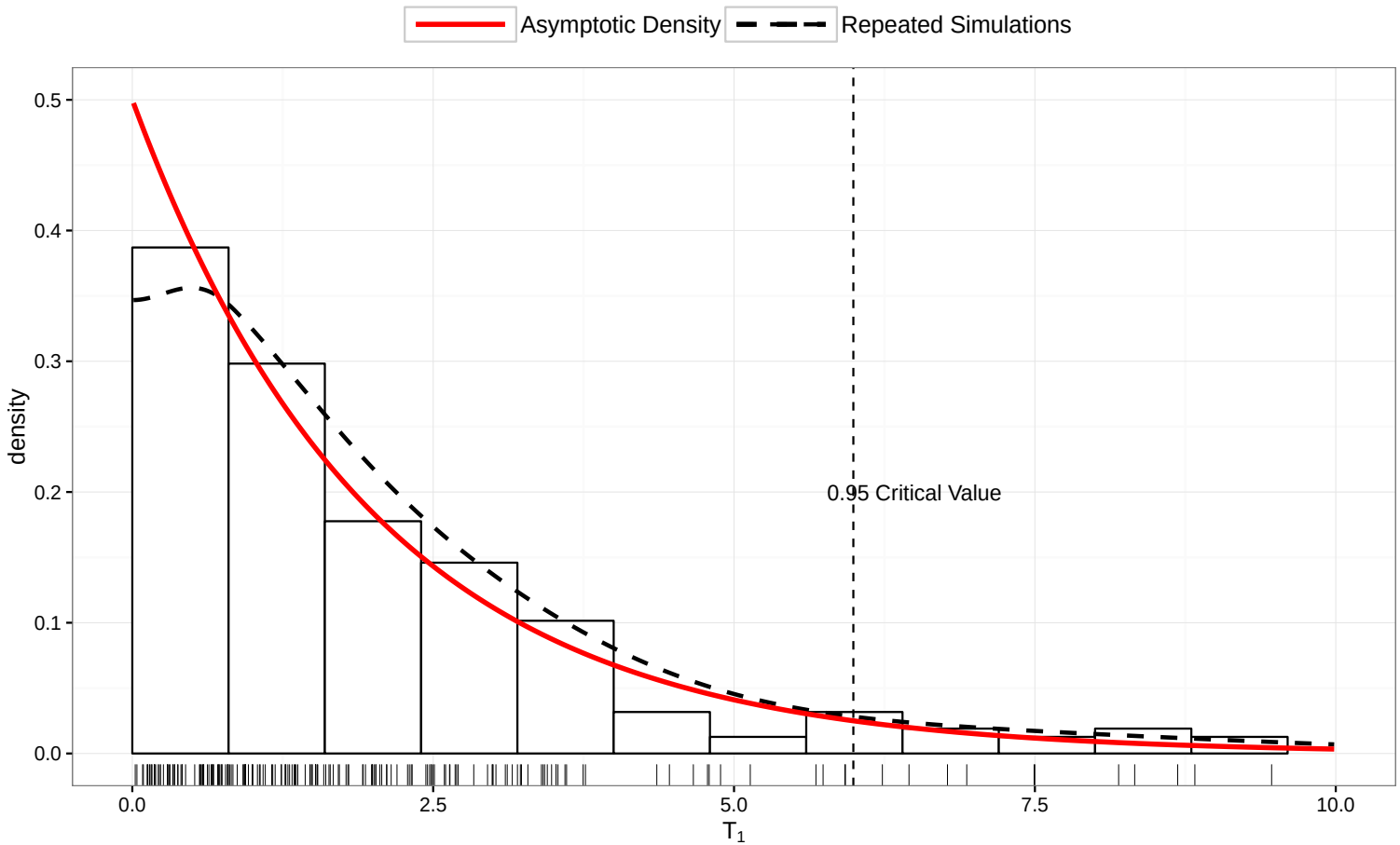


Assume Two Components



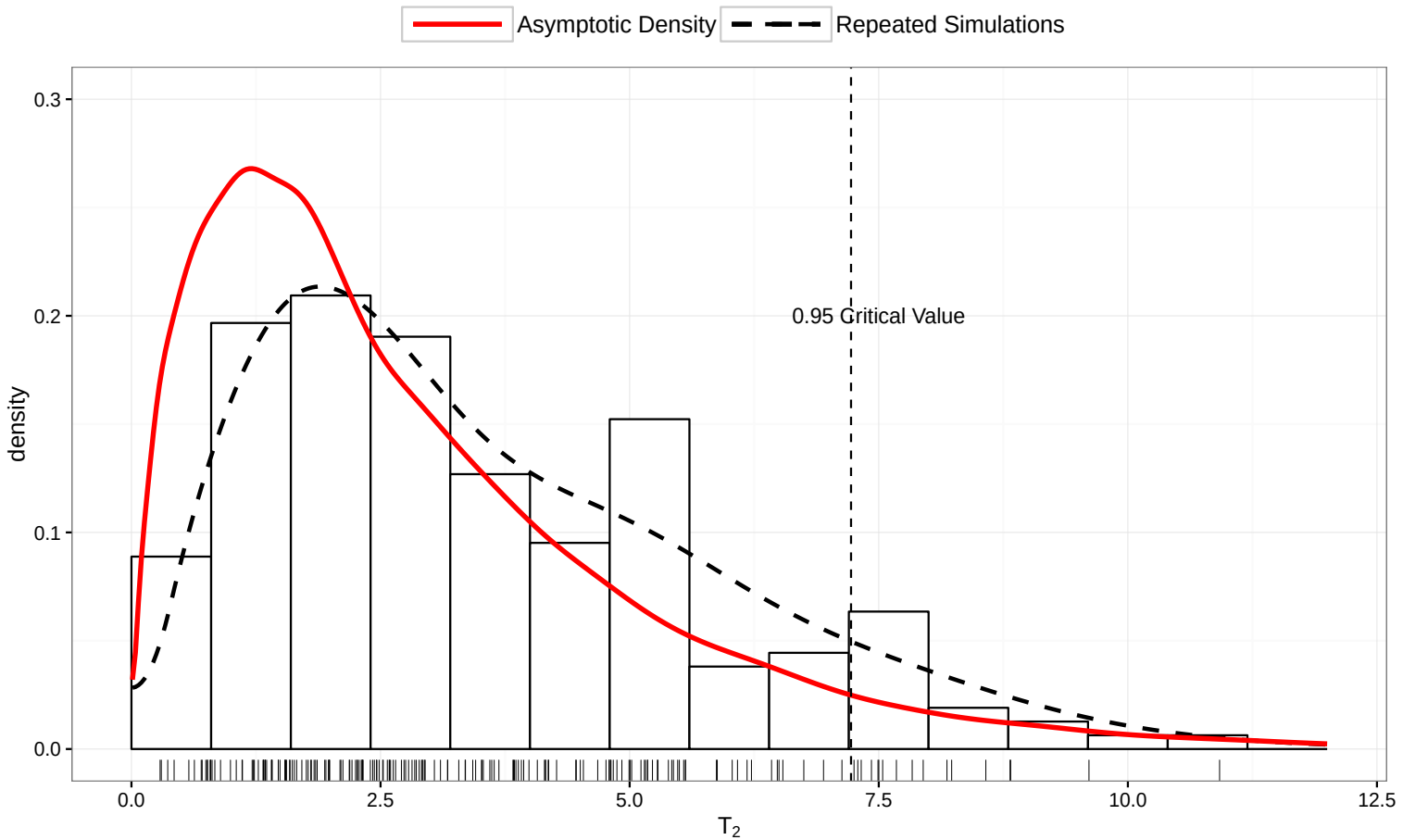
Asymptotic Distribution

Theoretical vs. empirical distribution of $\widetilde{T}_1$ when $H_0 : C = 1$ is true.



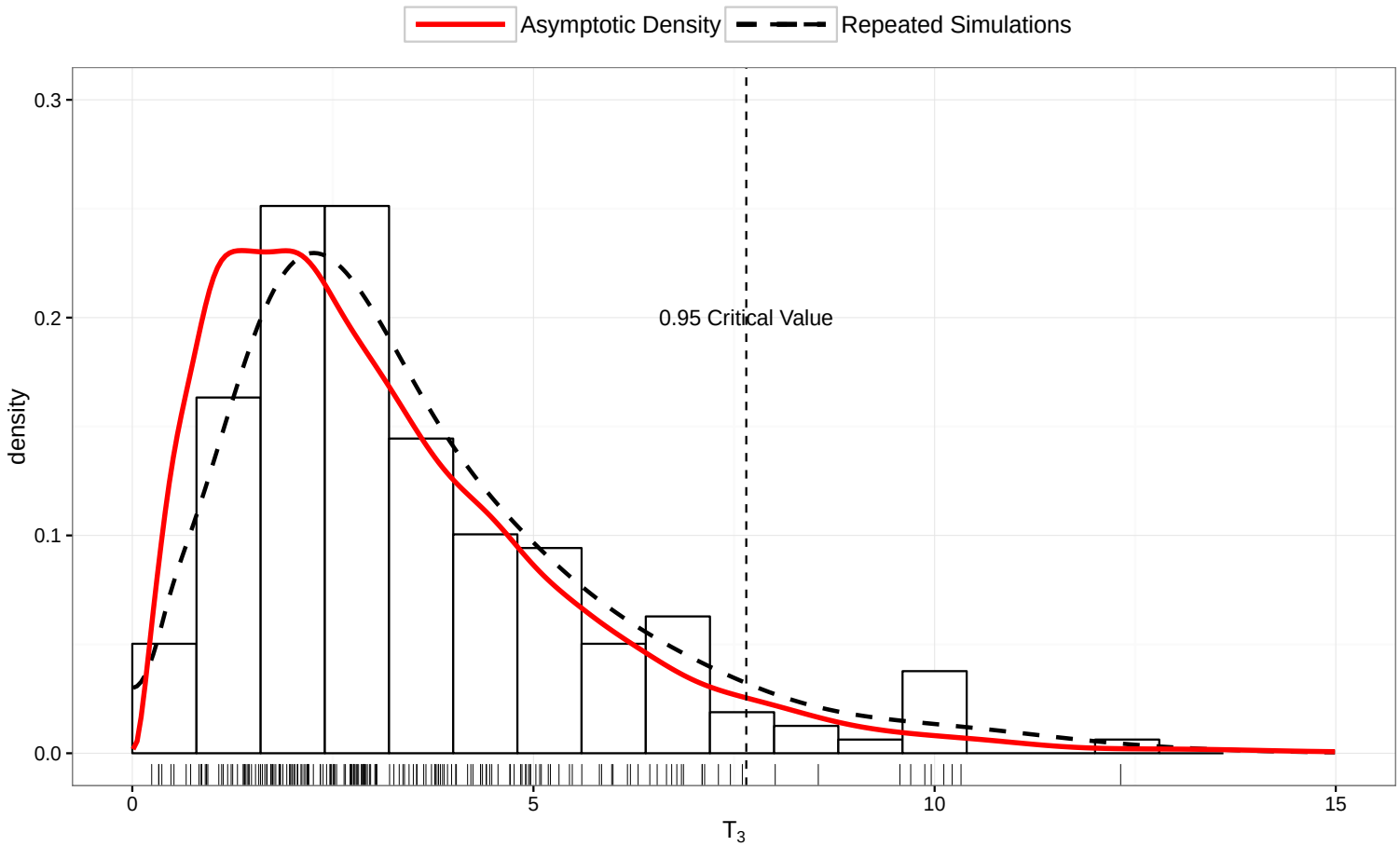
Asymptotic Distribution

Theoretical vs. empirical distribution of $\widetilde{T}_2$ when $H_0 : C = 2$ is true.



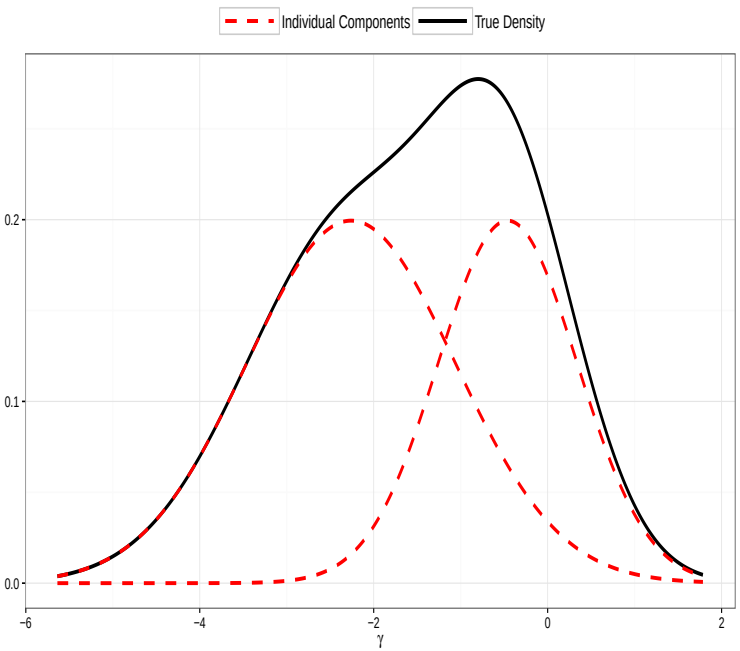
Asymptotic Distribution

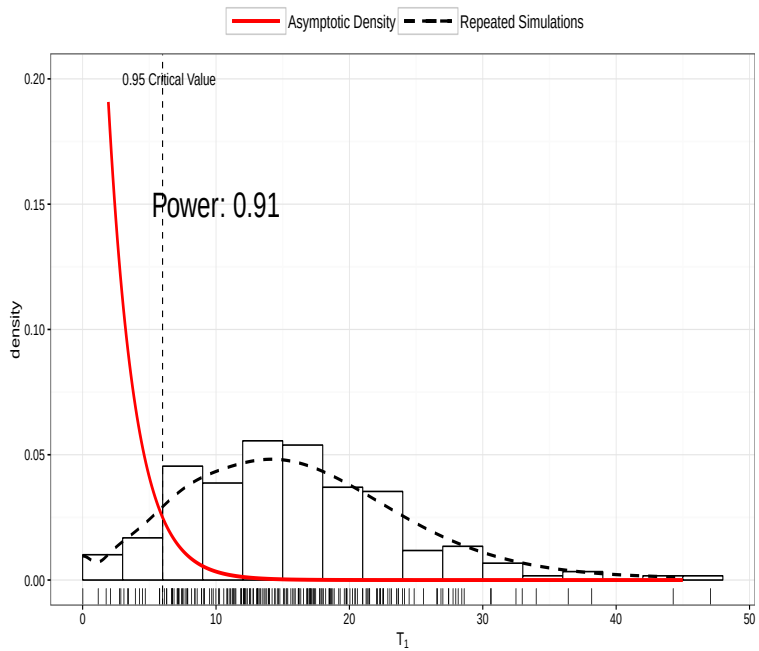
Theoretical vs. empirical distribution of $\widetilde{T}_3$ when $H_0 : C = 3$ is true.



Power

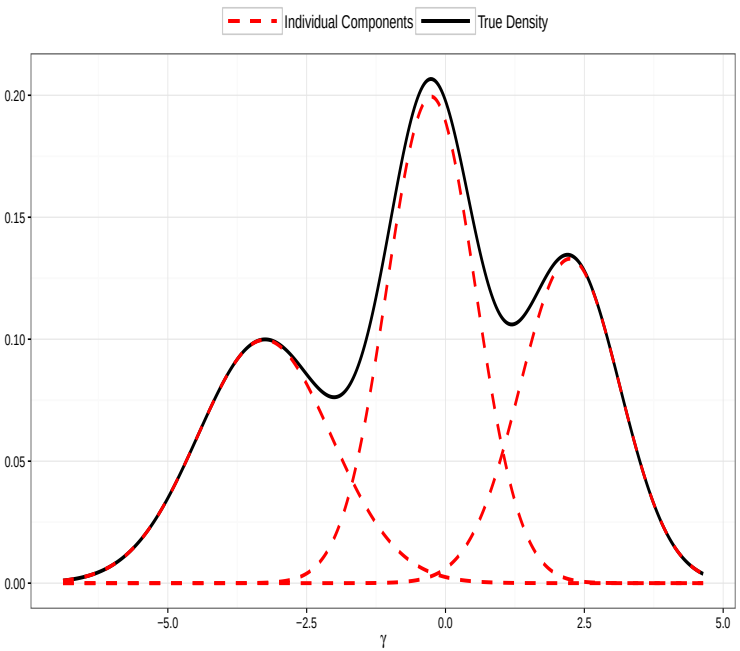
Testing $H_0 : C = 1$ when the true distribution is a 2-component mixture.

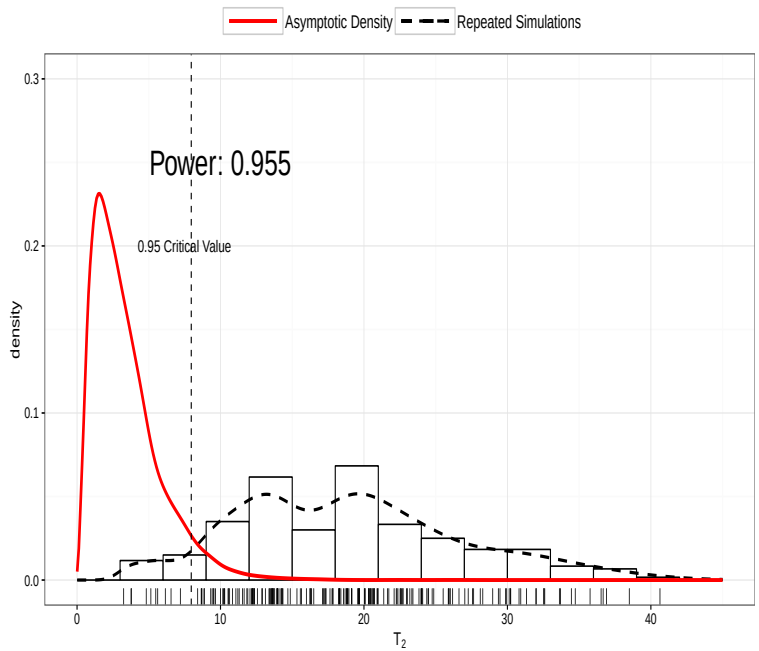




Power

Testing $H_0 : C = 2$ when the true distribution is a 3-component mixture.





Model selection: BIC vs. Sequential test

- Sequential test procedure with $\alpha = 0.05$ vs. a Naive BIC.
- For the 2-component mixture model, BIC picks the correct model 39% of the time (usually underfit).
- For the 3-component model, BIC chooses the correct number of components 50.5% of the time.
- The sequential test chooses the correct number of components 88.5% and 86% of the time for the two models.

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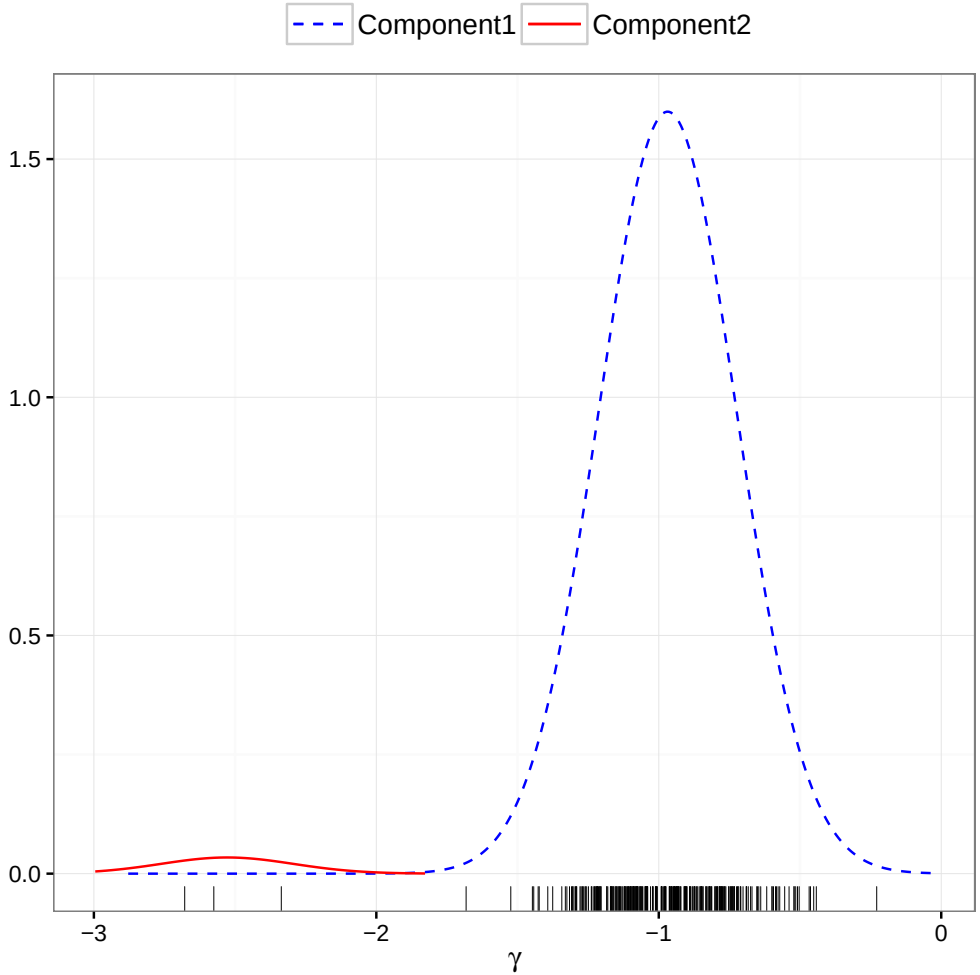
A Cohort of Patients from United Network for Organ Sharing

- Transplant patients with the transplant date between January 1987 and December 2008.
- $N = 269,386$ patients from 296 transplant centers.
- **X**: demographics of patients, donor information.
  - Age, gender (1=male, 0=female), BMI and cold ischemic time.
- **Y**: 5 year survival status (1=death and -1=survival).
  - The overall failure rate within 5 years of transplantation is 27.59%.

Data Analysis



Data Analysis (Cont.)

- The density for the predicted center effects is left skewed with a minor mixture component on the left tail.
- Three transplant centers in the small component are flagged as performing significantly better than the majority.

Characteristics of flagged centers

Center id	lFDR	$\hat{\gamma}$	Sample Size	Survival Rate
#287	0.0013	-2.6784	114	0.973
#10	0.0061	-2.5753	125	0.944
#28	0.0736	-2.3364	120	0.841

Data Analysis (Cont.)

Fixed effects estimation

	Estimate	Std. Error	z-value	p-value
cold ischemic time	0.019503	0.0003048	63.9869	<1e-99
age	0.007112	0.0002117	33.5890	<1e-99
sex	0.030928	0.0094616	3.2688	0.0011
BMI (22,25]	0.077860	0.0154998	5.0232	<1e-6
BMI (25,30]	0.120536	0.0129628	9.2986	<1e-19
BMI 30+	0.225015	0.0148196	15.1836	<1e-51

- The longer the cold ischemic time, the older the patient at transplantation, the higher the post-transplantation death rate.
- Males and patients with high BMI have higher death rates.
- We also included indicator for time periods when the surgery was performed. 5-year death rate is decaying over time due to new technology used in surgery and recovery.

Summary

- Model transplant center effects by using finite Gaussian mixture random effects.
- Study likelihood ratio tests to determine the number of components in the Gaussian mixture distribution.
- The fitted mixture model provides a convenient means of classifying transplant centers.

Thank You!