Clustering Using JIVE with Gaussian Mixtures for Data Integration

Benjamin B. Risk

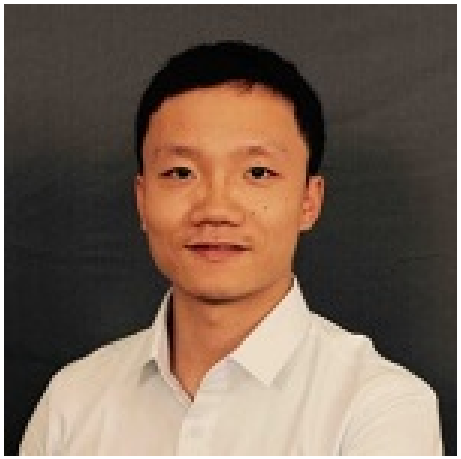
Department of Biostatistics & Bioinformatics
Rollins School of Public Health
Emory University

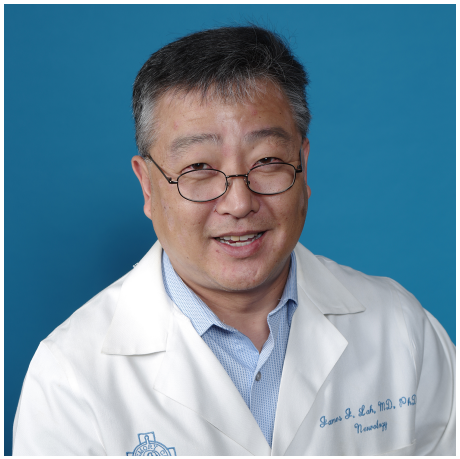
benjamin.risk@emory.edu

github.com/thebrisklab

Joint work

Ganzhong Gavin Tian (Biostatistics, Emory), Raphiel Murden (Biostatistics, Emory), James Lah (Department of Neurology, Emory University School of Medicine), John Hanfelt (Biostatistics, Emory) and Benjamin Risk.






Introduction: AD Prevalence

Alzheimer's Disease (AD):

The most common type of dementia, accounting for 60% – 80% of cases.

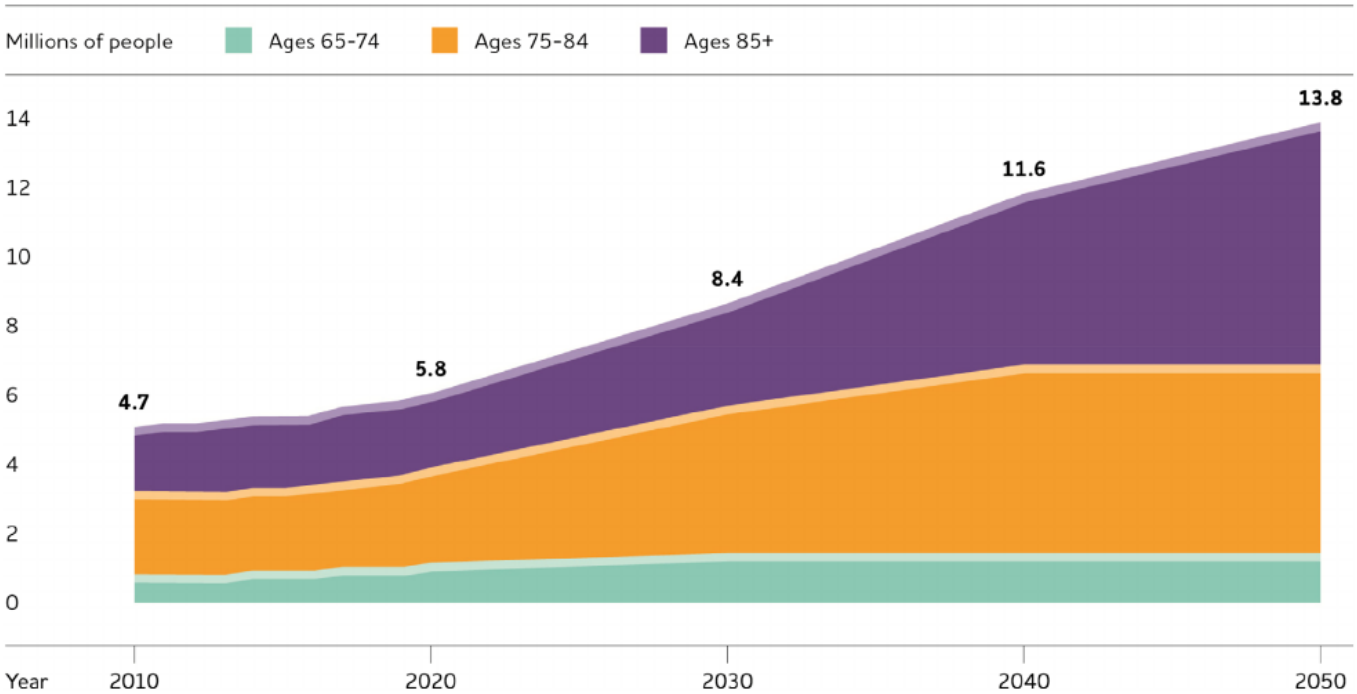


Figure: Projected number of people age 65 and older (total and by age) in the U.S. population with Alzheimer's dementia, 2010 to 2050 (Report, 2020)

Introduction: AD Continuum

Alzheimer's Disease (AD):

Slowly destroys memory, thinking skills, and ability to carry out basic functions.

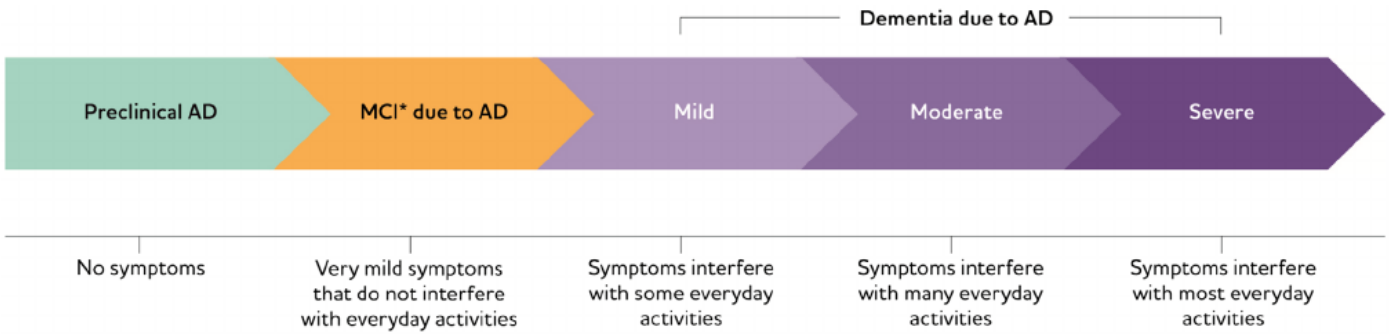


Figure: Alzheimer's disease (AD) continuum. *MCI is the acronym for mild cognitive impairment Report (2020)

.

Preclinical AD: No symptom, but with **measurable bio-marker changes** (E.g.: Cerebrospinal Fluid (CSF) amyloid beta, tau protein, MRI, PET). The mechanism is not fully understood.

Introduction: No gold standard for AD

No definitive diagnosis: A definitive diagnosis of Alzheimer's disease (AD) is only possible from a brain tissue autopsy (Dubois et al., 2007).

Clinical diagnosis: In ADNI, primarily neurocognitive assessment; these days, complicated combination of cognitive exams, brain imaging, CSF biomarkers.

Low amyloid beta and high tau protein CSF biomarker cutoffs are used to inform diagnosis. (Report, 2020; Meyer et al., 2010)).

May be biased because derived from studies dominated by European ancestry (Shin and Doraiswamy, 2016)

Unsupervised methods: Clustering can reveal new insights when gold standard not available (Collins and Huynh, 2014; Meyer et al., 2010). We focus on integrating CSF biomarkers and brain morphometry from MRIs.

Introduction: Finite Mixture Models and Gaussian Mixtures Models

Finite Mixture Models (FMM), have been widely used as a flexible probabilistic clustering framework to solve real-world data-mining and pattern recognition problems (McLachlan and Peel, 2000).

Gaussian Mixture Models (GMM), in particular, due to its simplicity in the modeling & interpretation of the dependence structure among manifest features are widely used in scientific studies (Scrucca et al., 2016).

Integrating multiple datasets of possibly high dimension is challenging. A covariance matrix has to be estimated for each cluster. Can not estimate without additional constraints.

Introduction: Data integration methods

We consider the setting where the same participants are measured in multiple datasets.

Canonical-correlation analysis (CCA) is a popular method to find maximally correlated latent variables from two datasets (Hotelling, 1992).

Recently, methods such as Joint and Individual Variance Explained (JIVE) have been proposed that also extract latent factors unique to each of the datasets (Lock et al., 2013; Feng et al., 2018).

Joint and Individual Clustering (JIC) applies k-means to the joint and individual latent scores to find subgroups (Hellton and Thoresen, 2016).

We develop a statistical model for simultaneous clustering and local dimension reduction from multiple datasets with possibly high dimensions (ADNI dataset with CSF and MRI biomarkers).

Background: Motivation

Probabilistic Principal Component Analysis (PPCA) formulates a probabilistic model for PCA Tipping and Bishop (1999b).

The authors extended PPCA to Mixture of PPCA (MixPPCA) model to perform clustering and local dimension reduction Tipping and Bishop (1999a).

Very recently, Raphiel Murden et al from our research group has developed probabilistic JIVE (ProJIVE) as a statistical model-based extension of JIVE for data integration.

We will propose a **Mixture of Probabilistic JIVE (ProJIVE-Mix)** for simultaneous clustering and local dimension reduction on integrated data, with a computationally feasible EM algorithm for maximum likelihood estimation.

First, background on ProJIVE

Probabilistic JIVE (Murden et al. in prep):

$$\mathbf{y}_{ik} = \boldsymbol{\mu} + \mathbf{W}_{Jk}\boldsymbol{a}_i + \mathbf{W}_{Ik}\boldsymbol{b}_{ik} + \boldsymbol{\epsilon}_{ik}, \;\; i \in \{1, \ldots, n\}, \;\; k \in \{1, \ldots, K\}, \quad (1)$$

$i = 1, \ldots, n$ participant,

$k = 1, \ldots, K$ feature block (dataset),

$\mathbf{W}_{Jk} \in \mathbb{R}^{p_k \times q_J}$ and $\mathbf{W}_{Ik} \in \mathbb{R}^{p_k \times q_k}$ (with $q_J + q_k < p_k$) are full-rank loading matrices,

$\boldsymbol{a}_i \in \mathbb{R}^{q_J}$, $\boldsymbol{b}_{ik} \in \mathbb{R}^{q_k}$ are **joint** and **individual latent scores** for the ith observation, $(\boldsymbol{a}_i^\top, \boldsymbol{b}_{i1}^\top, \boldsymbol{b}_{i2}^\top, \ldots, \boldsymbol{b}_{iK}^\top)^\top \overset{iid}{\sim} \mathcal{N}(\mathbf{0}, \mathbf{I}_{q \times q})$

$\boldsymbol{\epsilon}_{ik} \overset{iid}{\sim} \mathcal{N}(\mathbf{0}, \sigma_k^2 \mathbf{I}_{p_k \times p_k})$ are noise,

$\boldsymbol{\epsilon}_{ik} \perp\!\!\!\perp (\boldsymbol{a}_i^\top, \boldsymbol{b}_{ik}^\top)^\top, \forall k, i.$

ProJIVE: A Generalization of PPCA

(1) can be written as a generalized form of PPCA:

$$\mathbf{y}_i = \begin{pmatrix} \mathbf{y}_{i1} \\ \vdots \\ \mathbf{y}_{iK} \end{pmatrix} = \mathbf{W}\boldsymbol{\theta}_i + \begin{pmatrix} \boldsymbol{\epsilon}_{i1} \\ \vdots \\ \boldsymbol{\epsilon}_{iK} \end{pmatrix} \tag{2}$$

where

$$\boldsymbol{\theta}_i = (\boldsymbol{a}_i^\top, \boldsymbol{b}_{i1}^\top, \boldsymbol{b}_{i2}^\top, \ldots, \boldsymbol{b}_{iK}^\top)^\top \sim \mathcal{N}(\mathbf{0}, \mathbf{I}_{q\times q}), \text{ and } q = q_J + \textstyle\sum_{k=1}^K q_k,$$

$$\mathbf{W} = \begin{pmatrix} \mathbf{W}_{J1} & \mathbf{W}_{I1} & 0 & \ldots & 0 \\ \mathbf{W}_{J2} & 0 & \mathbf{W}_{I2} & \ldots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ \mathbf{W}_{JK} & 0 & 0 & \ldots & \mathbf{W}_{IK} \end{pmatrix} \begin{pmatrix} \boldsymbol{a}_i \\ \boldsymbol{b}_{i1} \\ \boldsymbol{b}_{i2} \\ \ldots \\ \boldsymbol{b}_{iK} \end{pmatrix}$$

Therefore, $\mathbf{y}_i \sim \mathcal{N}(\mathbf{0}, \mathbf{C})$, where $\mathbf{C} = \mathbf{W}\mathbf{W}^\top + \mathbf{D}$,
$\mathbf{D} = diag(\sigma_1^2\mathbf{1}_{p_1}^\top, \sigma_2^2\mathbf{1}_{p_2}^\top, ..., \sigma_K^2\mathbf{1}_{p_K}^\top)$.

Our Model: Mixture of ProJIVE

Extend the ProJIVE model to a **finite mixture model** as:

$$\mathbf{y}_i|g = \begin{pmatrix} \mathbf{y}_{i1}|g \\ \vdots \\ \mathbf{y}_{iK}|g \end{pmatrix} = \boldsymbol{\mu}_g + \mathbf{W}_g\boldsymbol{\theta}_{ig} + \begin{pmatrix} \boldsymbol{\epsilon}_{i1}|g \\ \vdots \\ \boldsymbol{\epsilon}_{iK}|g \end{pmatrix}, \; g \in \{1, \ldots, G\} \quad (3)$$

where $\boldsymbol{\theta}_{ig} = (\boldsymbol{a}_{ig}^\top, \boldsymbol{b}_{i1g}^\top, \boldsymbol{b}_{i2g}^\top, \ldots, \boldsymbol{b}_{iKg}^\top) \sim \mathcal{N}(\mathbf{0}, \mathbf{I}_q)$,

$$\mathbf{W}_g = \begin{pmatrix} \mathbf{W}_{J1g} & \mathbf{W}_{I1g} & 0 & \ldots & 0 \\ \mathbf{W}_{J2g} & 0 & \mathbf{W}_{I2g} & \ldots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ \mathbf{W}_{JKg} & 0 & 0 & \ldots & \mathbf{W}_{IKg} \end{pmatrix} \begin{pmatrix} \boldsymbol{a}_{ig} \\ \boldsymbol{b}_{i1g} \\ \boldsymbol{b}_{i2g} \\ \ldots \\ \boldsymbol{b}_{iKg} \end{pmatrix}$$

Therefore, $\mathbf{y}_i|g \sim \mathcal{N}(\boldsymbol{\mu}_g, \mathbf{C}_g)$, where: $\mathbf{C}_g = \mathbf{W}_g\mathbf{W}_g^\top + \mathbf{D}_g$,
$\mathbf{D}_g = diag(\sigma_{g1}^2\mathbf{1}_{p_1}^\top, \sigma_{g2}^2\mathbf{1}_{p_2}^\top, ..., \sigma_{gK}^2\mathbf{1}_{p_K}^\top)$.

Our Model: Diagram

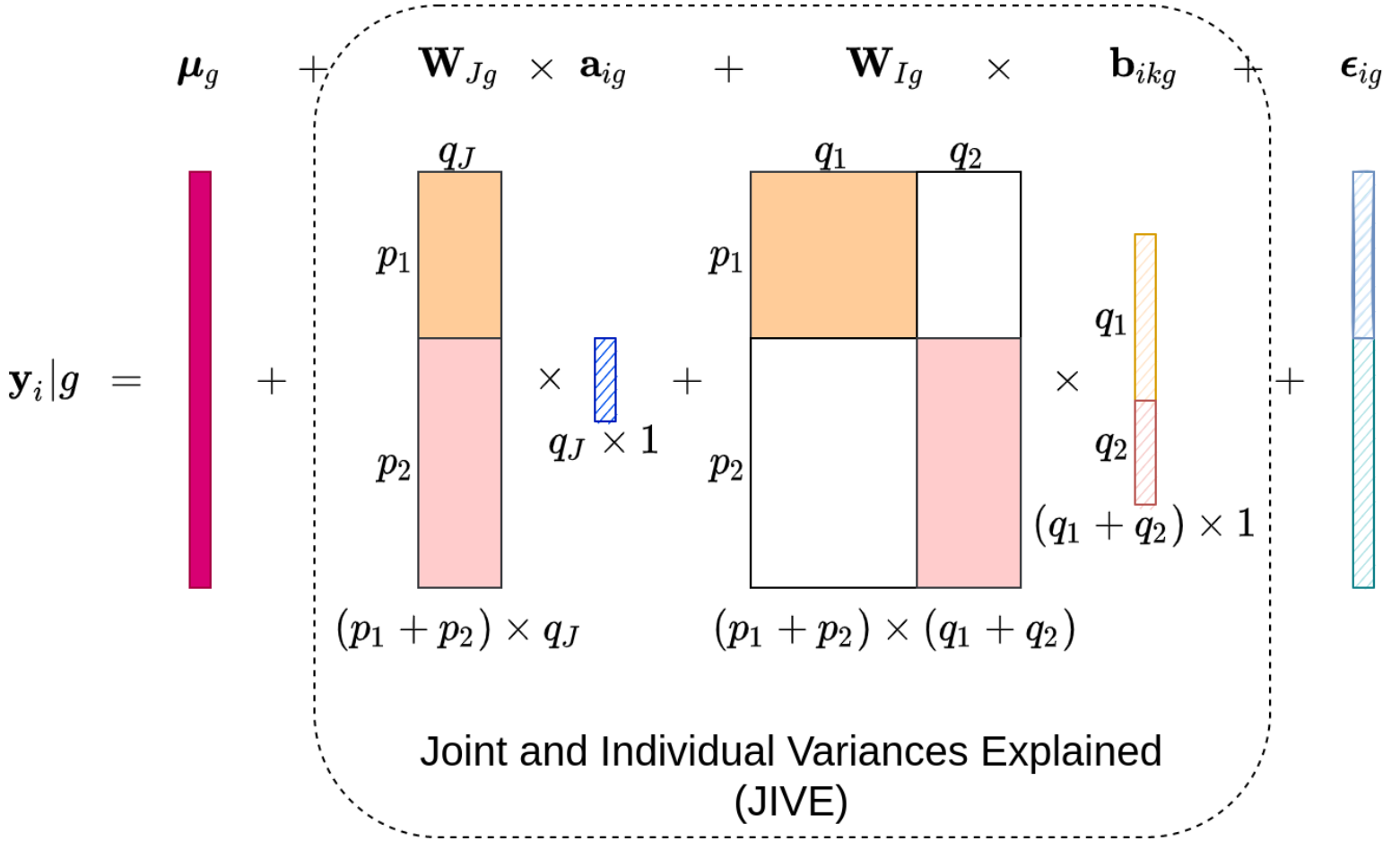


Figure: Diagram of the signal decomposition of $\mathbf{y}_i|g \sim \mathcal{N}(\boldsymbol{\mu}_g, \mathbf{W}_g\mathbf{W}_g^\top + \mathbf{D}_g)$, in an example where we have 2 feature blocks of dimensions p_1 and p_2.

Our model: Likelihood

Assuming latent class indicators $\mathbf{Z}$ and scores $\boldsymbol{\Theta}$ are observed, the complete data log-likelihood function is:

$$\begin{aligned}\ell_c(\mathbf{Y}, \mathbf{Z}, \boldsymbol{\Theta}; \boldsymbol{\Psi}) &= \sum_{i=1}^{n}\sum_{g=1}^{G} z_{ig}\left[\log \omega_g + \log f_g(\mathbf{y}_i, \boldsymbol{\theta}_{ig}; \boldsymbol{\psi}_g)\right] \\ &= \sum_{i=1}^{n}\sum_{g=1}^{G} z_{ig}\{\log \omega_g - \frac{p+q}{2}\log(2\pi) - \frac{1}{2}\log|\mathbf{D}_g| \\ &\quad - \frac{1}{2}[(\mathbf{y}_i - \mathbf{W}_g\boldsymbol{\theta}_{ig} - \boldsymbol{\mu}_g)^\top \mathbf{D}_g^{-1}(\mathbf{y}_i - \mathbf{W}_g\boldsymbol{\theta}_{ig} - \boldsymbol{\mu}_g) \\ &\quad + \boldsymbol{\theta}_{ig}^\top\boldsymbol{\theta}_{ig}]\}\end{aligned} \tag{4}$$

where $f_g(\mathbf{y}_i, \boldsymbol{\theta}_{ig}; \boldsymbol{\psi}_g)$ is the joint multivariate Gaussian density.
$\langle z_{ig}\rangle \equiv \mathbb{E}_{\boldsymbol{\Psi}^{(\nu)}}(z_{ig}|\mathbf{y}_i)$ evaluated at the νth iteration.
$\langle \boldsymbol{\theta}_{ig}\rangle \equiv \mathbb{E}_{\boldsymbol{\Psi}^{(\nu)}}(\boldsymbol{\theta}_{ig}|\mathbf{y}_i)$ and $\langle \boldsymbol{\theta}_{ig}\boldsymbol{\theta}_{ig}^\top\rangle \equiv \mathbb{E}_{\boldsymbol{\Psi}^{(\nu)}}(\boldsymbol{\theta}_{ig}\boldsymbol{\theta}_{ig}^\top|\mathbf{y}_i)$.

Our Model: Likelihood

Taking conditional expectation of the complete data log-likelihood w.r.t both z_{ig} given $\mathbf{y}_i$ and $\boldsymbol{\theta}_{ig}$ given $\mathbf{y}_i$, we have:

$$\begin{aligned}\mathcal{Q}_c(\boldsymbol{\Psi};\boldsymbol{\Psi}^{(\nu)}) \propto \sum_{i=1}^{n}\sum_{g=1}^{G}\langle z_{ig}\rangle \Bigg\{ \log\omega_g - \frac{1}{2}\sum_{k=1}^{K} p_k \log(\sigma^2_{kg}) \\ - \frac{1}{2}\Bigg[\sum_{k=1}^{K}\sigma^{-2}_{kg}(\mathbf{y}_{ik}-\boldsymbol{\mu}_{kg})^\top(\mathbf{y}_{ik}-\boldsymbol{\mu}_{kg}) \\ - 2\sum_{k=1}^{K}\sigma^{-2}_{kg}\langle\boldsymbol{\theta}_{ikg}\rangle^\top\mathbf{W}^\top_{kg}(\mathbf{y}_{ik}-\boldsymbol{\mu}_{kg}) + \mathrm{tr}(\langle\boldsymbol{\theta}_{ig}\boldsymbol{\theta}^\top_{ig}\rangle) \\ + \sum_{k=1}^{K}\sigma^{-2}_{kg}\mathrm{tr}(\mathbf{W}^\top_{kg}\mathbf{W}_{kg}\langle\boldsymbol{\theta}_{ikg}\boldsymbol{\theta}^\top_{ikg}\rangle)\Bigg]\Bigg\}\end{aligned} \tag{5}$$

Where $\boldsymbol{\Psi} = (\pi_1,...,\pi_{G-1},\boldsymbol{\psi}_1,...,\boldsymbol{\psi}_G)$ denote the vector of parameters to be estimated; $\boldsymbol{\psi}_g = (\boldsymbol{\mu}_g, \mathrm{vec}(\mathbf{W}_g), \sigma^2_{g1},...,\sigma^2_{gK})$.

Our Model: EM algorithm E-step

E-step, update the conditional expectations:

$$\langle z_{ig} \rangle \equiv \mathbb{E}_{\boldsymbol{\Psi}^{(\nu)}}(Z_{ig}|\mathbf{y}_i) = \frac{\omega_g^{(\nu)} \phi(\mathbf{y}_i; \boldsymbol{\psi}_g^{(\nu)})}{\sum_{h=1}^{G} \omega_h^{(\nu)} \phi(\mathbf{y}_i; \boldsymbol{\psi}_h^{(\nu)})} \tag{6}$$

$$\langle \boldsymbol{\theta}_{ikg} \rangle \equiv \mathbb{E}_{\boldsymbol{\Psi}^{(\nu)}}(\boldsymbol{\theta}_{ikg}|\mathbf{y}_i) = \mathbf{B}_k \mathbf{M}_g^{(\nu)} \mathbf{W}_g^{(\nu)^\top} \mathbf{D}_g^{(\nu)^{-1}} (\mathbf{y}_i - \boldsymbol{\mu}_g^{(\nu)}) \tag{7}$$

$$\langle \boldsymbol{\theta}_{ikg} \boldsymbol{\theta}_{ikg}^\top \rangle \equiv \mathbb{E}_{\boldsymbol{\Psi}^{(\nu)}}(\boldsymbol{\theta}_{ikg} \boldsymbol{\theta}_{ikg}^\top|\mathbf{y}_i) = \mathbf{B}_k \mathbf{M}_g^{(\nu)} \mathbf{B}_k^\top + \langle \boldsymbol{\theta}_{ikg} \rangle \langle \boldsymbol{\theta}_{ikg} \rangle^\top \tag{8}$$

where $\mathbf{M}_g = (\mathbf{I} - \mathbf{W}_g^\top \mathbf{D}_g \mathbf{W}_g)^{-1}$, is the conditional variances of $\boldsymbol{\theta}_{ig}$ conditioning on $\mathbf{y}_i$, given the gth cluster component; $\mathbf{B}_k$ is a $(q_J + q_k) \times q$ selection matrix such that: $\boldsymbol{\theta}_{ikg} = \begin{pmatrix} \mathbf{a}_{ig} \\ \mathbf{b}_{ikg} \end{pmatrix} = \mathbf{B}_k \boldsymbol{\theta}_{ig}$. Similar, we can define $\mathbf{A}_k$ as a $p_k \times p$ selection matrix such that $\mathbf{y}_{ik} = \mathbf{A}_k \mathbf{y}_i$

Our Model: EM algorithm M-step

M-step, by maximization of $\mathcal{Q}_c(\boldsymbol{\Psi}; \boldsymbol{\Psi}^{(\nu)})$:

$$\omega_g^{(\nu+1)} = \frac{\sum_{i=1}^n \langle z_{ig} \rangle}{n} \tag{9}$$

$$\boldsymbol{\mu}_{kg}^{(\nu+1)} = \mathbf{A}_k \frac{\sum_{i=1}^n \langle z_{ig} \rangle \mathbf{y}_i}{\sum_{i=1}^n \langle z_{ig} \rangle} \tag{10}$$

$$\mathbf{W}_{kg}^{(\nu+1)} = \left\{ \sum_{i=1}^n \langle z_{ig} \rangle (\mathbf{y}_{ik} - \boldsymbol{\mu}_{kg}^{(\nu+1)}) \langle \boldsymbol{\theta}_{ikg} \rangle^\top \right\} \left\{ \sum_{i=1}^n \langle z_{ig} \rangle \langle \boldsymbol{\theta}_{ikg} \boldsymbol{\theta}_{ikg}^\top \rangle \right\}^{-1} \tag{11}$$

$$\begin{aligned} \sigma_{kg}^{2\ (\nu+1)} = \frac{1}{p_k \sum_{i=1}^n \langle z_{ig} \rangle} \sum_{i=1}^n \langle z_{ig} \rangle [& (\mathbf{y}_{ik} - \boldsymbol{\mu}_{kg}{}^{(\nu+1)})^\top (\mathbf{y}_{ik} - \boldsymbol{\mu}_{kg}{}^{(\nu+1)}) \\ & - 2 \langle \boldsymbol{\theta}_{ikg} \rangle^\top \mathbf{W}_{kg}^\top (\mathbf{y}_{ik} - \boldsymbol{\mu}_{kg}{}^{(\nu+1)}) + \mathrm{tr}(\mathbf{W}_{kg}^\top \mathbf{W}_{kg} \langle \boldsymbol{\theta}_{ikg} \boldsymbol{\theta}_{ikg}^\top \rangle)] \end{aligned} \tag{12}$$

Simulation Cases

Simulations generated from ProJIVE-Mix with $q_J = 1,\ q_1 = 1,\ q_2 = 1$, two datasets ($K = 2$) and two clusters ($G = 2$).

		Setting-1 $p_1 = 2, p_2 = 50$ $n = 1{,}000$ $D_B = 1.998$		**Setting-2** $p_1 = 10, p_2 = 250$ $n = 1{,}000$ $D_B = 1.971$		**Setting-3** $p_1 = 50, p_2 = 1{,}250$ $n = 1{,}000$ $D_B = 1.975$	
Data Block		$k = 1$	$k = 2$	$k = 1$	$k = 2$	$k = 1$	$k = 2$
Cluster	$g = 1,\ \omega_1 = 0.3$	0.67(0.67,0.67)	0.31(0.29,0.33)	0.67(0.67,0.67)	0.31(0.29,0.33)	0.67(0.67,0.67)	0.31(0.29,0.333)
	$g = 2,\ \omega_2 = 0.7$	0.86(0.86,0.86)	0.46(0.43,0.48)	0.86(0.86,0.86)	0.46(0.43,0.48)	0.69(0.69,0.69)	0.32(0.30,0.34)

Table: Signal variance (proportions of the features' explainable variances) with differing number of features.

Bhattacharyya distance (D_B): is a distance measuring the overlapping of two distributions. This represents are moderately challenging setting.

Simulation Results

		Setting-1 $p_1 = 2, p_2 = 50$ $n = 1{,}000$ $D_B = 1.998$		**Setting-2** $p_1 = 10, p_2 = 250$ $n = 1{,}000$ $D_B = 1.971$		**Setting-3** $p_1 = 50, p_2 = 1{,}250$ $n = 1{,}000$ $D_B = 1.975$	
Methods	**Train/Test**	df	ARI	df	ARI	df	ARI
ProJIVE-Mix	Training	**317**	**0.884(0.023)**	**1,565**	**0.835(0.022)**	**7,805**	**0.848(0.024)**
	Testing	**317**	**0.888(0.023)**	**1,565**	**0.809(0.027)**	**7,805**	**0.717(0.032)**
MixPPCA	Training	419	0.759(0.048)	2,083	0.650(0.040)	10,403	0.710(0.030)
	Testing	419	0.785(0.034)	2,083	0.602(0.041)	10,403	0.388(0.034)
PCA+GMM	Training	461	0.850(0.027)	1,721	0.692(0.040)	10,301	0.991(0.009)
	Testing	461	0.851(0.024)	1,721	0.655(0.036)	10,301	0.630(0.034)
Full GMM	Training	2,861	0.896(0.026)	68,381	-	1,693,901	-
	Testing	2,861	0.614(0.046)	68,381	-	1,693,901	-
Diag GMM	Training	209	0.568(0.048)	1,041	0.216(0.032)	5,201	0.168(0.029)
	Testing	209	0.577(0.040)	1,041	0.219(0.033)	5,201	0.166(0.023)
JIC.joint	Training	-	0.589(0.038)	-	0.231(0.035)	-	0.284(0.039)
	Testing	-	0.592(0.036)	-	0.231(0.033)	-	0.281(0.035)
K-means	Training	-	0.514(0.045)	-	0.187(0.028)	-	0.149(0.028)
	Testing	-	0.524(0.037)	-	0.191(0.030)	-	0.148(0.022)

Table: ARI measured on a 1,000-point training set and 1,000-point independent **test dataset**, with mean±sd reported in 101 simulations.

Simulation Results

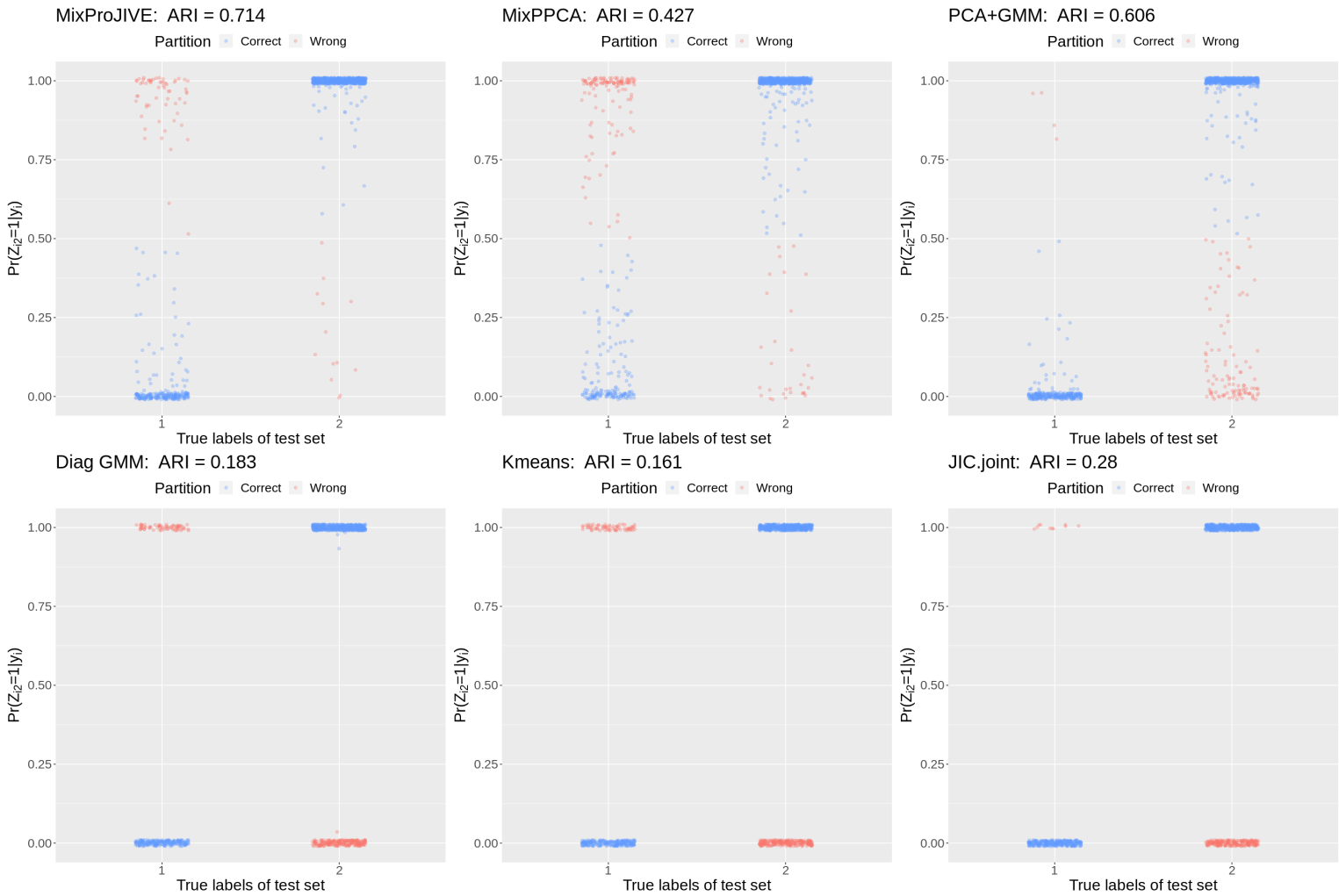


Figure: Scatter plot of posterior probabilities in a 'median' ARI case testing set, under the third simulated setting with high dimensions ($p_1 = 50, p_2 = 1250, n = 1{,}000$).

Real Data Analysis: ADNI CSF+MRI dataset

	Baseline Diagnosis:				
	AD (N = 220)	**MCI (N = 608)**	**CN (N = 360)**	**Total (N = 1,188)**	P-value
Abeta					< 0.001
- Mean (SD)	692.776 (420.054)	1013.824 (549.302)	1354.716 (649.508)	1057.671 (605.693)	
- Range	212.300 - 3139.000	210.900 - 3331.000	203.000 - 3592.000	203.000 - 3592.000	
ttau					< 0.001
- Mean (SD)	368.278 (145.529)	285.022 (128.964)	238.455 (89.113)	286.328 (129.440)	
- Range	133.300 - 851.600	97.890 - 851.800	88.690 - 590.100	88.690 - 851.800	
ptau					< 0.001
- Mean (SD)	36.764 (15.797)	27.665 (14.626)	21.837 (9.106)	27.584 (14.358)	
- Range	10.770 - 94.860	8.210 - 103.000	8.260 - 59.990	8.210 - 103.000	
APOE4					< 0.001
- 0	70 (31.8%)	309 (50.8%)	261 (72.5%)	640 (53.9%)	
- 1	104 (47.3%)	235 (38.7%)	90 (25.0%)	429 (36.1%)	
- 2	46 (20.9%)	64 (10.5%)	9 (2.5%)	119 (10.0%)	
Age					< 0.001
- Mean (SD)	74.519 (8.149)	72.408 (7.514)	73.683 (5.954)	73.185 (7.250)	
- Range	55.600 - 90.300	54.400 - 91.400	56.200 - 89.600	54.400 - 91.400	
Gender					< 0.001
- Female	91 (41.4%)	248 (40.8%)	190 (52.8%)	529 (44.5%)	
- Male	129 (58.6%)	360 (59.2%)	170 (47.2%)	659 (55.5%)	
Edu					< 0.001
- Mean (SD)	15.432 (2.913)	16.079 (2.773)	16.353 (2.628)	16.042 (2.772)	
- Range	4.000 - 20.000	6.000 - 20.000	6.000 - 20.000	4.000 - 20.000	
Race					< 0.001
- Black	4 (1.8%)	15 (2.5%)	22 (6.1%)	41 (3.5%)	
- White	211 (95.9%)	573 (94.2%)	327 (90.8%)	1111 (93.5%)	
- Other	5 (2.3%)	20 (3.3%)	11 (3.1%)	1111 (93.5%)	
Last Diagnosis					< 0.001
- AD	219 (99.5%)	199 (32.7%)	10 (2.8%)	428 (36.0%)	
- MCI	1 (0.5%)	373 (61.3%)	46 (12.8%)	420 (35.4%)	
- CN	0 (0.0%)	36 (5.9%)	304 (84.4%)	340 (28.6%)	

Table: Demographics of TADPOLE ADNI CSF+MRI data ($p_1 = 3, p_2 = 245, n = 1{,}188$) by baseline diagnosis. **Dataset 2: 245 MRI features from Freesurfer (Desikan), cortical thickness, surface area**

Preliminary Results: Model selection

	$\mathbf{G=1}$	$\mathbf{G=2}$	$\mathbf{G=3}$	$\mathbf{G=4}$
$\mathbf{q_J=1, q_1=1, q_2=1}$	698.33	690.13	**686.93**	687.30
$\mathbf{q_J=1, q_1=1, q_2=2}$	684.54	**678.79**	679.39	681.92
$\mathbf{q_J=1, q_1=1, q_2=3}$	677.06	**672.75**	674.35	678.36
$\mathbf{q_J=1, q_1=1, q_2=4}$	670.47	**667.54**	671.25	677.50
$\mathbf{q_J=1, q_1=1, q_2=5}$	665.21	**663.87**	669.39	676.95
$\mathbf{q_J=1, q_1=1, q_2=6}$	**660.22**	661.54	668.29	677.15
$\mathbf{q_J=1, q_1=1, q_2=7}$	**655.97**	659.28	668.31	678.57
$\mathbf{q_J=1, q_1=1, q_2=8}$	**653.19**	658.08	668.32	679.93

Table: Selection of optimal ranks of latent scores and number of mixture components using BIC-ICL on ADNI CSF+MRI data ($p_1 = 3, p_2 = 245, n = 1{,}188$).

The numbers are representing $\times 10^3$.

Preliminary Results: Cluster-1 (AD-like 38.9%)

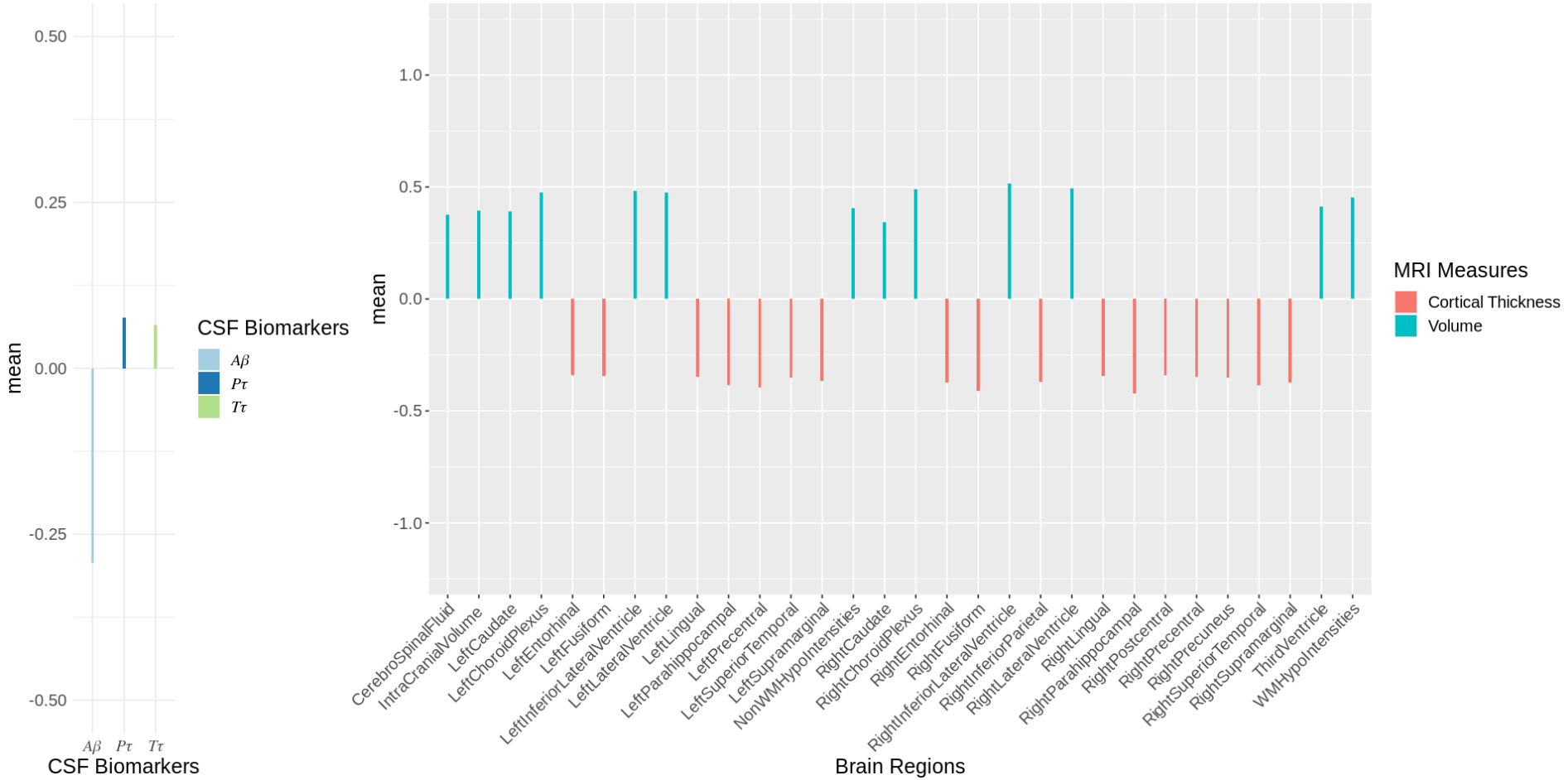


Figure: Mean in cluster 1 of CSF biomarkers and top 30 MRI features ($p_1 = 3, p_2 = 245, n = 1{,}188$).

Preliminary Results: Cluster-2 (non-AD 61.1%)

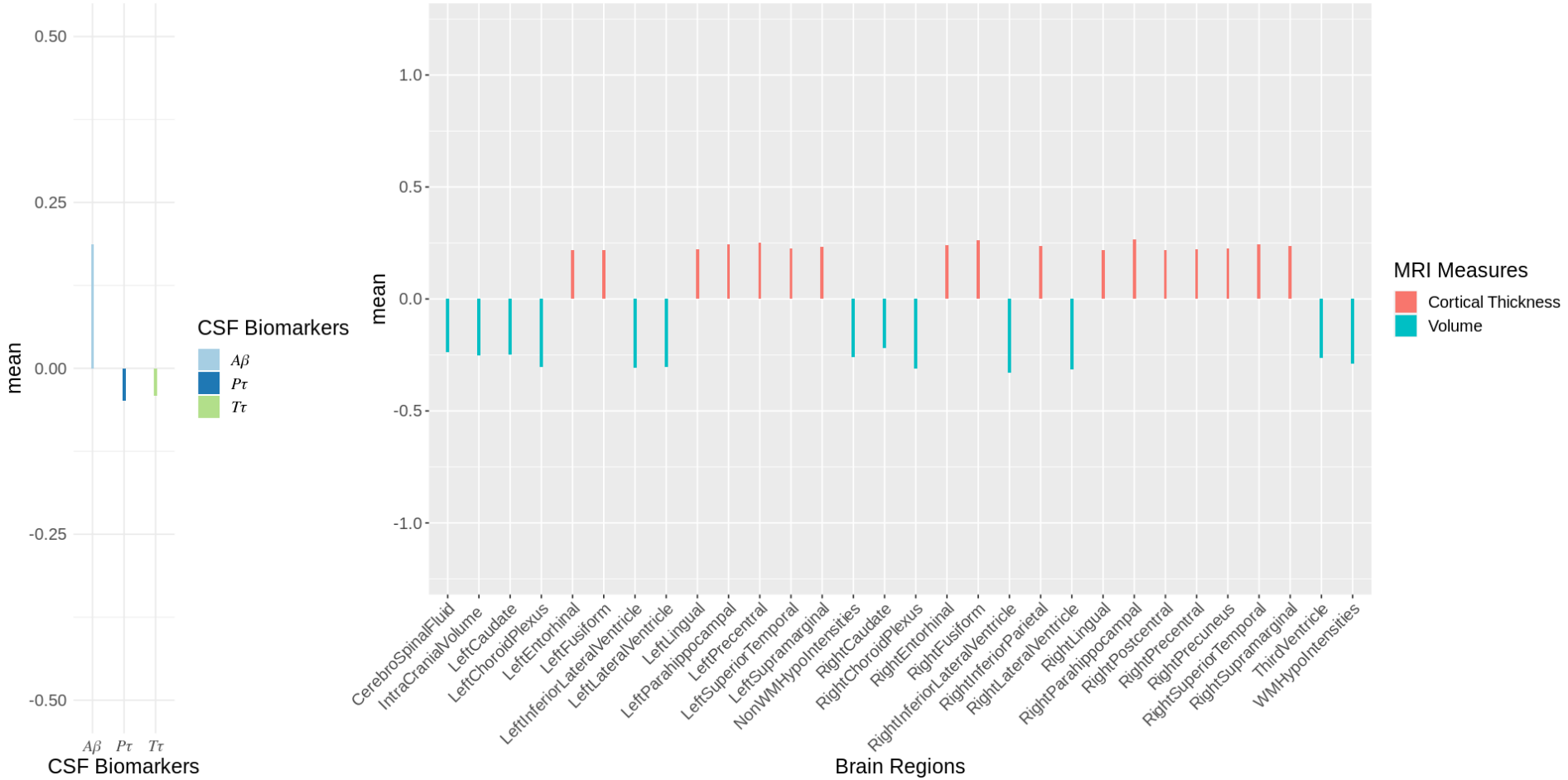


Figure: Mean in cluster 2 of CSF biomarkers and top 30 MRI features ($p_1 = 3, p_2 = 245, n = 1{,}188$).

Preliminary Results: Modeled cluster with $G = 2$, $q_J = 1$, $q_1 = 1$, $q_2 = 5$

Cluster-1: AD-like	**Last Available Diagnosis:**			
	AD	**MCI**	**CN**	**Total**
Baseline Diagnosis:				
AD (%)	134 (100%)	0 (0%)	0 (0%)	134
MCI (%)	100 (43.3%)	126 (54.5%)	5 (2.2%)	231
CN (%)	4 (4.1%)	21 (21.6%)	72 (74.2%)	97
Total (%)	**238 (51.5%)**	**147 (31.8%)**	**77 (16.7%)**	**n = 462**
Cluster-2: Control-like	**Last Available Diagnosis:**			
	AD	**MCI**	**CN**	**Total**
Baseline Diagnosis:				
AD (%)	85 (98.8%)	1 (1.1%)	0 (0%)	86
MCI (%)	99 (26.3%)	247 (65.5%)	31 (8.2%)	377
CN (%)	6 (2.3%)	25 (9.5%)	232 (88.2%)	263
Total (%)	**190 (26.2%)**	**273 (37.6%)**	**263 (36.2%)**	**n = 726**

Table: Hard assign cluster from posterior probabilities. Clusters based on baseline data can inform future conversion: MCI→AD and CN→MCI.

Conclusions

In this study, we:

- **proposed a probabilistic JIVE model with Gaussian mixture for joint clustering from multiple datasets** using an EM algorithm;
- **performed clustering and local feature dimension reduction simultaneously within the clusters**;
- **identified two clusters that tend to align with an AD-like group** with AD related pathology, and a control-like group either with non-AD pathology or are clinical normal;

Limitations and future research:

- model selection is challenging due to trade-off between number of clusters and the rank of the covariance matrices.
- penalized approaches with regularization of the covariance structure may be helpful in data with even higher dimensions.

Acknowledgments

Thank you!

Post doc opportunity available – email me for information!

Data provided by the ADNI Consortium `https://adni.loni.usc.edu/tadpole-challenge-dataset-available/`

BR was supported by R21 AG066970. JH was supported by R01 AG055634 and P50 AG025688. JL was supported by R01 AG070937 and P50 AG025688. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Additional funding for this work was provided by a generous gift from the Goizueta Foundation.

References I

Collins, J. and Huynh, M. (2014). Estimation of diagnostic test accuracy without full verification: a review of latent class methods. *Statistics in medicine*, 33(24):4141.

Dubois, B., Feldman, H. H., Jacova, C., DeKosky, S. T., Barberger-Gateau, P., Cummings, J., Delacourte, A., Galasko, D., Gauthier, S., Jicha, G., Meguro, K., O'Brien, J., Pasquier, F., Robert, P., Rossor, M., Salloway, S., Stern, Y., Visser, P. J., and Scheltens, P. (2007). Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS–ADRDA criteria. *The Lancet Neurology*, 6(8):734–746.

Feng, Q., Jiang, M., Hannig, J., and Marron, J. S. (2018). Angle-based joint and individual variation explained. *Journal of Multivariate Analysis*, 166:241–265.

Hellton, K. H. and Thoresen, M. (2016). Integrative clustering of high-dimensional data with joint and individual clusters. *Biostatistics*, 17(3):537–548.

Hotelling, H. (1992). Relations between two sets of variates. In *Breakthroughs in statistics*, pages 162–190. Springer.

Lock, E. F., Hoadley, K. A., Marron, J. S., and Nobel, A. B. (2013). Joint and individual variation explained (jive) for integrated analysis of multiple data types. *The annals of applied statistics*, 7(1):523.

McLachlan, G. J. and Peel, D. (2000). *Finite mixture models*. Wiley.

Meyer, G. D., Shapiro, F., Vanderstichele, H., Vanmechelen, E., Engelborghs, S., Deyn, P. P. D., Coart, E., Hansson, O., Minthon, L., Zetterberg, H., Blennow, K., Shaw, L., Trojanowski, J. Q., and Initiative, A. D. N. (2010). Diagnosis-Independent Alzheimer Disease Biomarker Signature in Cognitively Normal Elderly People. *Archives of Neurology*, 67(8):949–956.

Report, A. A. (2020). 2020 alzheimer's disease facts and figures. *Alzheimer's and Dementia*, 16.

Scrucca, L., Fop, M., Murphy, T. B., and Raftery, A. E. (2016). mclust 5: clustering, classification and density estimation using Gaussian finite mixture models. *The R Journal*, 8(1):289–317.

Shin, J. and Doraiswamy, P. M. (2016). Underrepresentation of african-americans in alzheimer's trials: a call for affirmative action. *Frontiers in aging neuroscience*, 8:123.

Tipping, M. E. and Bishop, C. M. (1999a). Mixtures of Probabilistic Principal Component Analyzers. *Neural Computation*, 11(2):443–482.

Tipping, M. E. and Bishop, C. M. (1999b). Probabilistic Principal Component Analysis. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*, 61(3):611–622.