Bayesian Wavelet-Based Functional Mixed Models

Jeffrey S. Morris

UT M.D. Anderson Cancer Center

Raymond J. Carroll

Texas A&M University

Functional Data Analysis

- **Functional Data:**
  - **Ideal units of observation: curves**
  - **Observed data: curves sampled on fine grid**
- **Increasingly encountered in scientific research**
- **FDA (Ramsay & Silverman, 1997)**

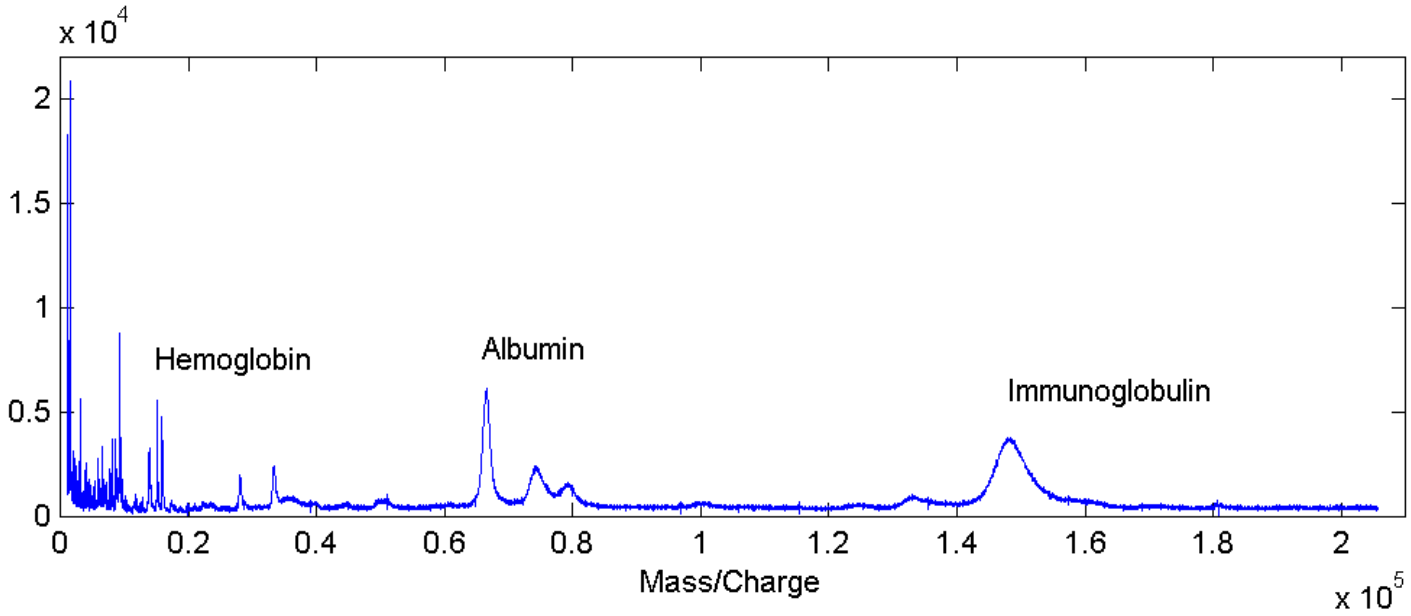
2 issues with functional data

1. **Regularization: exploiting the assumed smoothness or regularity between measurements within a curve**
2. **Replication: combining information across N curves**

Example: Mass Spectrometry Proteomics

- **Central dogma: DNA → mRNA → protein**
- **Microarrays: measure expression levels of 10,000s of genes in sample (amount of mRNA)**
- **Proteomics: look at proteins in sample.**
  - **Gaining increased attention in research**
    - **Proteins more biologically relevant than mRNA**
    - **Can use readily available fluids (e.g. blood, urine)**
  - **MALDI-TOF: mass spectrometry instrument that can see 100s or 1000s of proteins in sample**

Sample MALDI-TOF Spectrum



- **MALDI-TOF Spectrum: observed function**
- **$g(t)$ = intensity of spectrum at m/z value t**
- **Intensity at peak (roughly) estimates the abundance of some protein with molecular weight of t Daltons**

Example: Mouse proteomics study

- 16 nude mice had 1 of 2 cancer cell lines injected into 1 of 2 organs (lung or brain)
- Cell lines:
  - A375P: human melanoma, low metastatic potential
  - PC3MM2: human prostate, highly metastatic
- Blood Serum extracted from each mouse – placed on 2 MALDI plates
- Samples run at 2 different laser intensities (low/ high)
- Total of 32 spectra (observed functions), 2 per mouse
- Sampled on equally-spaced grid of roughly 24,000
  - Downsampled to grid of size 2000

Example: Mouse proteomics study

- **Goal:**

  Find proteins differentially expressed by:
  - **Host organ site (lung/brain)**
  - **Donor cell line (A375P/PC3MM2)**
  - **Organ-by-cell line interaction**
- **Combine information across laser intensities:**

  Requires us to include in modeling:
  - **Functional laser intensity effect**
  - **Random effect functions to account for correlation between spectra from same mouse**

Linear Mixed Models

Linear Mixed Model (Laird and Ware, 1982):

$$\underset{N\times 1}{Y} = \underset{N\times p}{X}\overbrace{\beta}^{p\times 1} + \underset{N\times m}{Z}\overbrace{u}^{m\times 1} + \underset{N\times 1}{e}$$

$$u \sim N(0, \overbrace{P}^{m\times m})$$

$$e \sim N(0, \underbrace{R}_{N\times N})$$

- **Fixed effects** part, $X\beta$, accommodate a broad class of mean structures, including main effects, interactions, and linear coefficients.
- **Random effects** part, Zu, provide a convenient mechanism for modeling correlation among the N observations.
- Marginally, $Y \sim N(X\beta, ZPZ'+R)$

Functional Mixed Model (FMM)

Suppose we observe a sample of N curves, $Y_i(t)$, $i=1, \ldots, N$, on a compact set $\mathcal{T}$

$$\underbrace{Y(t)}_{N \text{ functions}} = \overbrace{X}^{N\times p}\ \underbrace{B(t)}_{p \text{ functions}} + \overbrace{Z}^{N\times m}\ \underbrace{U(t)}_{m \text{ functions}} + \underbrace{E(t)}_{N \text{ functions}}$$

$$U(t) \sim MGP(P, Q)$$
$$E(t) \sim MGP(R, S)$$

- **DEFN: $U(t) \sim MGP(P,Q)$ implies the rows of $P^{-1/2}U(t)$ are ind. mean zero Gaussian Processes with covariance surface $Q(t_1,t_2)$.**
  - **Functional generalization of Matrix Normal (Dawid, 1981).**
  - **Implies $\text{Cov}\{U_i(t_1), U_j(t_2)\} = P_{ij} * Q(t_1,t_2)$**
- **P and R are covariance matrices (between-curve)**
- **$Q(t_1,t_2)$ and $S(t_1,t_2)$ are covariance surfaces on $\mathcal{T}\times\mathcal{T}$**

Discrete Version of FMM

Suppose each observed curve is sampled on a common equally-spaced grid of length *T*.

$$\underbrace{Y}_{N\times \mathrm{T}} = \overbrace{X}^{N\times p}\ \underbrace{B}_{p\times \mathrm{T}} + \overbrace{Z}^{N\times m}\ \underbrace{U}_{m\times \mathrm{T}} + \underbrace{E}_{N\times \mathrm{T}}$$

$$U \sim MN(P,Q)$$
$$E \sim MN(R,S)$$

- ***U* and *E* follow the Matrix Normal distn.**
  - ***U*~MN(*P*,*Q*) implies Cov{U_{ij}, $U_{i'j'}$}=$P_{ii'}$*$Q_{jj'}$**
- ***P* and *R* are covariance matrices ($m \times m$ & $N \times N$)**
- ***Q* and *S* are within-curve covariance matrices ($T \times T$)**

Functional Mixed Models

- **Key feature of FMM: Does not require specification of parametric form for curves**
- **Most existing literature for nonparametrically modeling functional data is based on kernels or splines.**
- **Kernels/splines may not work well for spatially heterogeneous data**

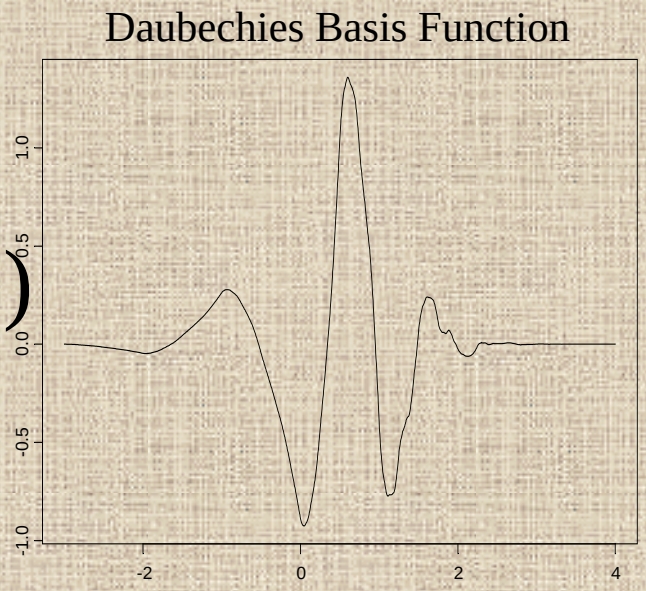
Introduction to Wavelets

- Wavelets: **families of orthonormal basis functions**

$$g(t) = \sum_{j,k \in \Im} d_{jk} \psi_{jk}(t)$$

$$\psi_{jk}(t) = 2^{-j/2} \psi(2^{-j/2} t - k)$$

$$d_{jk} = \int g(t) \psi_{jk}(t) dt$$

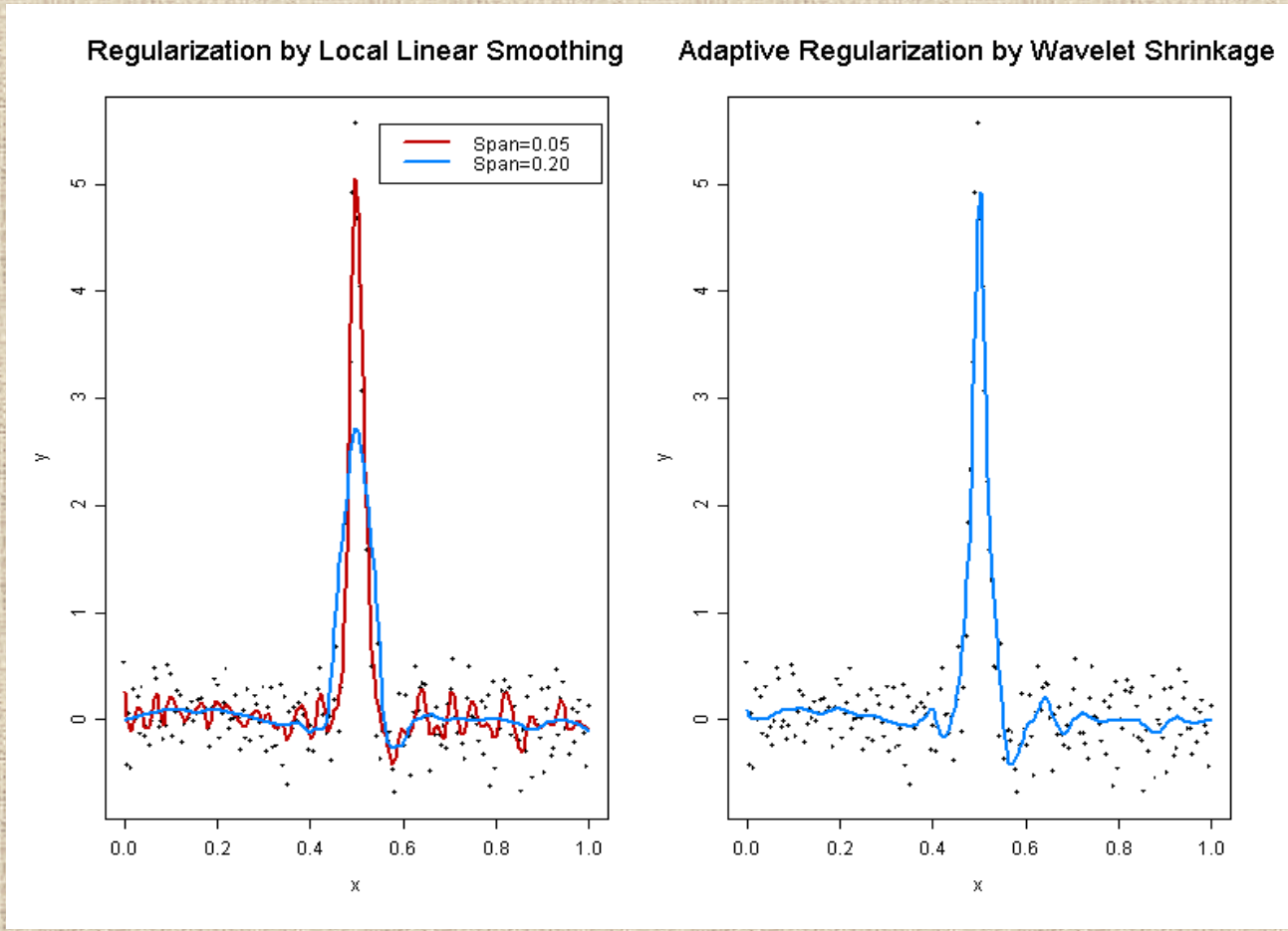


- Discrete Wavelet Transform (DWT): **fast algorithm {O(*T*)} for obtaining empirical wavelet coefficients for curves sampled on equally-spaced grid of length *T*.**

Wavelet Regression

- **Useful properties of wavelets:**
  - **Whitening property**
  - **Compact support**
  - **Parsimonious representation**
- **Wavelet Regression – 3 step process**
  1. **Project data into wavelet space**
  2. **Threshold/shrink coefficients**
  3. **Project back to data space**
- **Yields *adaptively regularized* nonparametric estimates**

Adaptive Regularization



Wavelet-Based Hierarchical Functional Models

- **Most existing wavelet regression methods for single function case**
- **Morris, Vannucci, Brown, and Carroll (2003)**
  - **Bayesian wavelet-based method for estimating mean function for functional data from nested design.**
  - **Extends wavelet regression to hierarchical functional context.**
- **Goal: Develop Bayesian wavelet-based methodology for much more general setting of functional mixed models.**

Wavelet-Based FMM:

General Approach

1. **Project observed functions** Y **into wavelet space.**
2. **Fit FMM in wavelet space.**

   (Use MCMC to get posterior samples)
3. **Project wavelet-space estimates (posterior samples) back to data space.**

Wavelet-Based FMM:

General Approach

1. **Project observed functions Y into wavelet space.**
2. **Fit FMM in wavelet space**
   (Use MCMC to get posterior samples)
3. **Project wavelet-space estimates (posterior samples) back to data space.**

Wavelet-Based FMM

1. Project observed functions Y to wavelet space

- **Apply DWT to rows of Y to get wavelet coefficients corresponding to each observed function**

$$\underbrace{D}_{N\times T} = \underbrace{Y}_{N\times T}\ \underbrace{W'}_{T\times T}$$

- **Projects the observed curves into the space spanned by the wavelet bases.**

Wavelet-Based FMM:

General Approach

1. **Project** observed functions Y **into wavelet space.**
2. **Fit FMM** in wavelet space

   (Use MCMC to get posterior samples)

3. **Project** wavelet-space estimates (posterior samples) **back to data space.**

Projecting FMM to Wavelet Space

$$\underbrace{Y}_{N\times \mathrm{T}} = \overbrace{X}^{N\times p}\ \underbrace{B}_{p\times \mathrm{T}} + \overbrace{Z}^{N\times m}\ \underbrace{U}_{m\times \mathrm{T}} + \underbrace{E}_{N\times \mathrm{T}}$$

$$U \sim MN(P,Q)$$
$$E \sim MN(R,S)$$

Projecting FMM to Wavelet Space

$$\underbrace{Y}_{N\times \mathrm{T}}\ \overbrace{\mathbf{W'}}^{\mathbf{T}\times\mathbf{T}} = \overbrace{X}^{N\times p}\ \underbrace{B}_{p\times \mathrm{T}}\ \overbrace{\mathbf{W'}}^{\mathbf{T}\times\mathbf{T}} + \overbrace{Z}^{N\times m}\ \underbrace{U}_{m\times \mathrm{T}}\ \overbrace{\mathbf{W'}}^{\mathbf{T}\times\mathbf{T}} + \underbrace{E}_{N\times \mathrm{T}}\ \overbrace{\mathbf{W'}}^{\mathbf{T}\times\mathbf{T}}$$

$$U\mathbf{W'} \sim MN(P, \mathbf{W}Q\mathbf{W'})$$

$$E\mathbf{W'} \sim MN(R, \mathbf{W}S\mathbf{W'})$$

Projecting FMM to Wavelet Space

$$\underbrace{D}_{N\times \mathrm{T}} = \overbrace{X}^{N\times p}\ \underbrace{B^{*}}_{p\times \mathrm{T}} + \overbrace{Z}^{N\times m}\ \underbrace{U^{*}}_{m\times \mathrm{T}} + \underbrace{E^{*}}_{N\times \mathrm{T}}$$

$$U^{*} \sim MN(P, Q^{*})$$
$$E^{*} \sim MN(R, S^{*})$$

Wavelet Space FMM

D : empirical wavelet coefficients for observed curves

Row *i* contains wavelet coefficients for observed curve *i*

Each column double-indexed by wavelet scale *j* and location *k*

$$\underbrace{D}_{N\times \mathrm{T}} = \overbrace{X}^{N\times p}\ \underbrace{B^*}_{p\times \mathrm{T}} + \overbrace{Z}^{N\times m}\ \underbrace{U^*}_{m\times \mathrm{T}} + \underbrace{E^*}_{N\times \mathrm{T}}$$

$$U^* \sim MN(P, Q^*)$$
$$E^* \sim MN(R, S^*)$$

- ***B*=BW'*** **&** ***U*=UW'*** **: Rows contain wavelet coefficients for the fixed and random effect functions,**
- ***E*=EW'*** **is the matrix of residuals**
- ***Q*=WQW'*** **and** ***S*=WSW'*** **model the covariance structure between wavelet coefficients for a given function.**
- ***P, Q*, R*** **and** ***S**** **are typically too large to estimate in an unstructured fashion.**

Covariance Assumptions

- **We choose parametric structures for P and R to model the covariance structure between the curves.**
  - **Based on the experimental design**
  - **As in linear mixed models.**
- **We assume the between-wavelet covariance matrices Q^* and S^* are diagonal.**
  - **Assume wavelet coefficients within given function independent**
  - **Heuristically justified by whitening property of DWT**
  - **Common assumption in wavelet regression**
  - **Is parsimonious in wavelet space (T parameters), yet leads to flexible class of covariance structures in data space**

Wavelet Space Model

$$\underbrace{D}_{N\times \mathrm{T}} = \overbrace{X}^{N\times p}\ \underbrace{B^{*}}_{p\times \mathrm{T}} + \overbrace{Z}^{N\times m}\ \underbrace{U^{*}}_{m\times \mathrm{T}} + \underbrace{E^{*}}_{N\times \mathrm{T}}$$

$$U^{*} \sim MN(P, Q^{*})$$
$$E^{*} \sim MN(R, S^{*})$$

Model Each Column Separately

$$\underbrace{d_{jk}}_{N\times 1} = \overbrace{X}^{N\times p}\underbrace{B^{*}_{jk}}_{p\times 1} + \overbrace{Z}^{N\times m}\underbrace{U^{*}_{jk}}_{m\times 1} + \underbrace{E^{*}_{jk}}_{N\times 1}$$

$$U^{*}_{jk} \sim N(0, P\cdot Q^{*}_{jk})$$

$$E^{*}_{jk} \sim N(0, R\cdot S^{*}_{jk})$$

Single Wavelet Coefficient Model

- **Independence assumption allows us to fit wavelet-space model one column at a time.**
  - **i.e., we have a series of *T* (scalar) mixed models, with the only shared parameters being the between-curve covariance parameters in *P* and *R*.**
- **In principal, we could fit this model using standard mixed models software.**
- **However, fitting this model without additional mechanism for regularization would result in rough, noisy estimates of the *p* fixed effects functions $B_i(t)$**

Prior Assumptions

Mixture prior on β_{ijk}^*:

$$\beta_{ijk}^* = \gamma_{ijk}^* N(0, \tau_{ij}) + (1 - \gamma_{ijk}^*)\delta_0$$

$$\gamma_{ijk}^* = \text{Bernoulli}(\pi_{ij})$$

- **Nonlinearly shrinks β_{ijk}^* towards 0, leading to adaptively regularized estimates of $B_i(t)$.**
- **τ_{ij} & π_{ij} are regularization parameters**
  - **Can be estimated from the data using empirical Bayes**
  - **Extend Clyde&George (1999) to functional mixed model**

Model Fitting

- **MCMC to obtain posterior samples of model quantities**
  - **Work with marginal likelihood; U* integrated out;**
- **Let Ω be a vector containing ALL covariance parameters (i.e. for *P*, *Q**, *R*, and *S**).**

MCMC Steps

1. **Sample from $f(B^*|D,\Omega)$:**

   Mixture of normals and point masses at 0 for each *i,j,k*.

2. **Sample from $f(\Omega|D,B^*)$:**

   Metropolis-Hastings steps for each *j,k*

3. **If desired, sample from $f(U^*|D,B^*,\Omega)$:**

   Multivariate normal

Wavelet-Based FMM:

General Approach

1. **Project observed functions Y into wavelet space.**
2. **Fit FMM in wavelet space**
   (Use MCMC to get posterior samples)
3. **Project wavelet-space estimates (posterior samples) back to data space.**

Wavelet-Based FMM

3. Project wavelet-space estimates (posterior samples) back to data space.

- **Apply IDWT to posterior samples of *B** to get posterior samples of fixed effect functions $B_i(t)$ for $i=1,\ldots, p$, on grid t.**
  - **B=B*W**
- **Posterior samples of *U(t)*, *P*, *Q*, *R*, and *S* are also available, if desired.**
- **Can be used for Bayesian inference/prediction**

Example: Model

Let $Y(t)$ be the $N=32$ MALDI spectra, preprocessed.

$$Y(t) = XB(t) + ZU(t) + E$$

- **$X=\{1, X_{organ}, X_{cell\text{-}line}, X_{int}, X_{laser}\}$, where**
  X_{organ}=1 for lung, -1 brain. $X_{cell\text{-}line}$=1 for A375P, -1 for PC3MM2
  $X_{int} = X_{organ} * X_{cell\text{-}line}$ X_{laser}=1 for low laser intensity, -1 high.

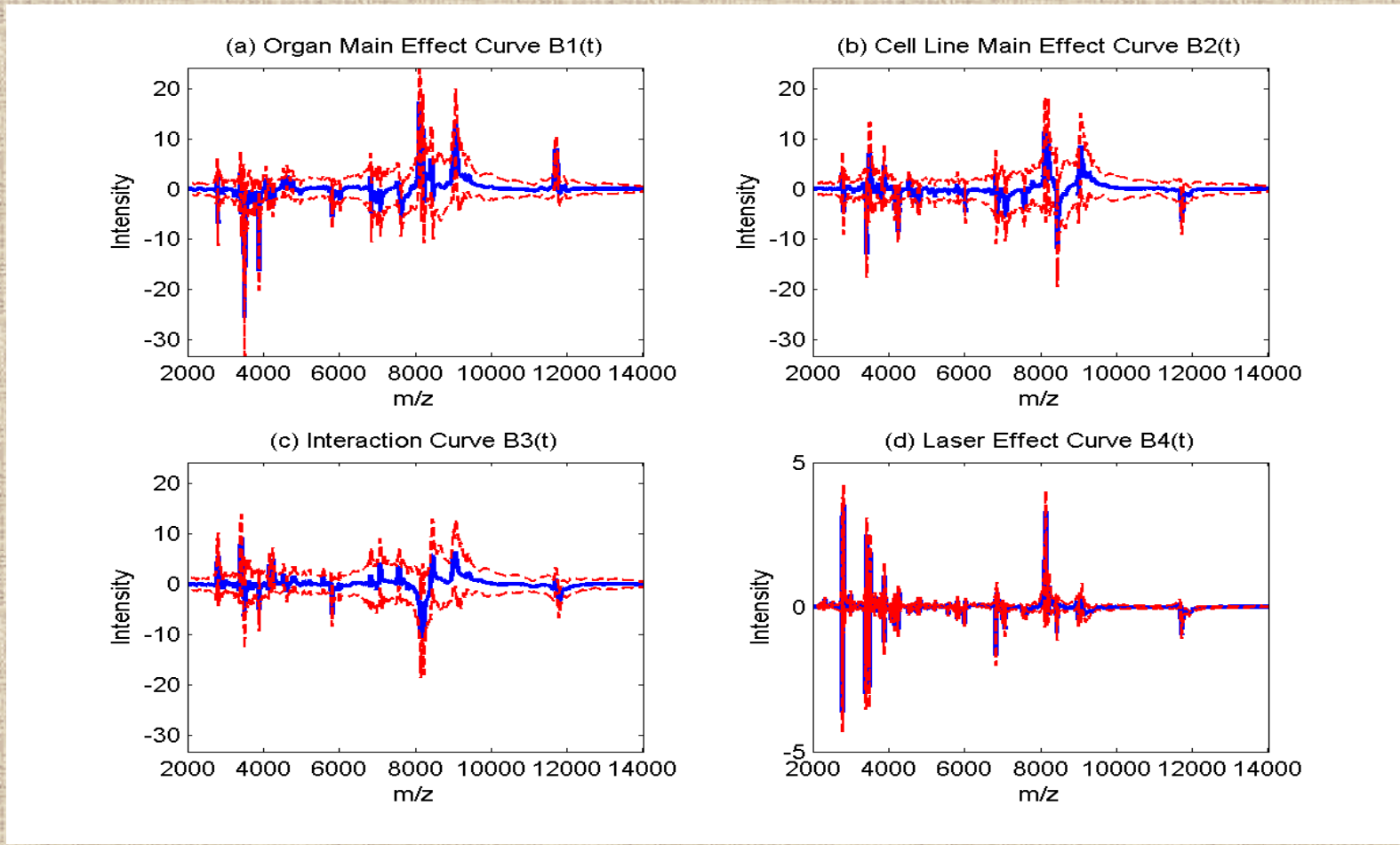
- **$B(t)=\{B_0(t), B_1(t), B_2(t), B_3(t), B_4(t)\}$, where**
  $B_0(t)$ = overall mean **spectrum** **$B_1(t)$** = organ main effect **function**
  $B_2(t)$ = cell-line main effect **$B_3(t)$** = org x cell-line int **function**
  $B_4(t)$ = laser intensity effect **function**

- **$Z=1_2 \otimes I_{16}$, and $U(t)=\{U_1(t), \ldots, U_{16}(t)\}$ are** mouse random effect **functions.**

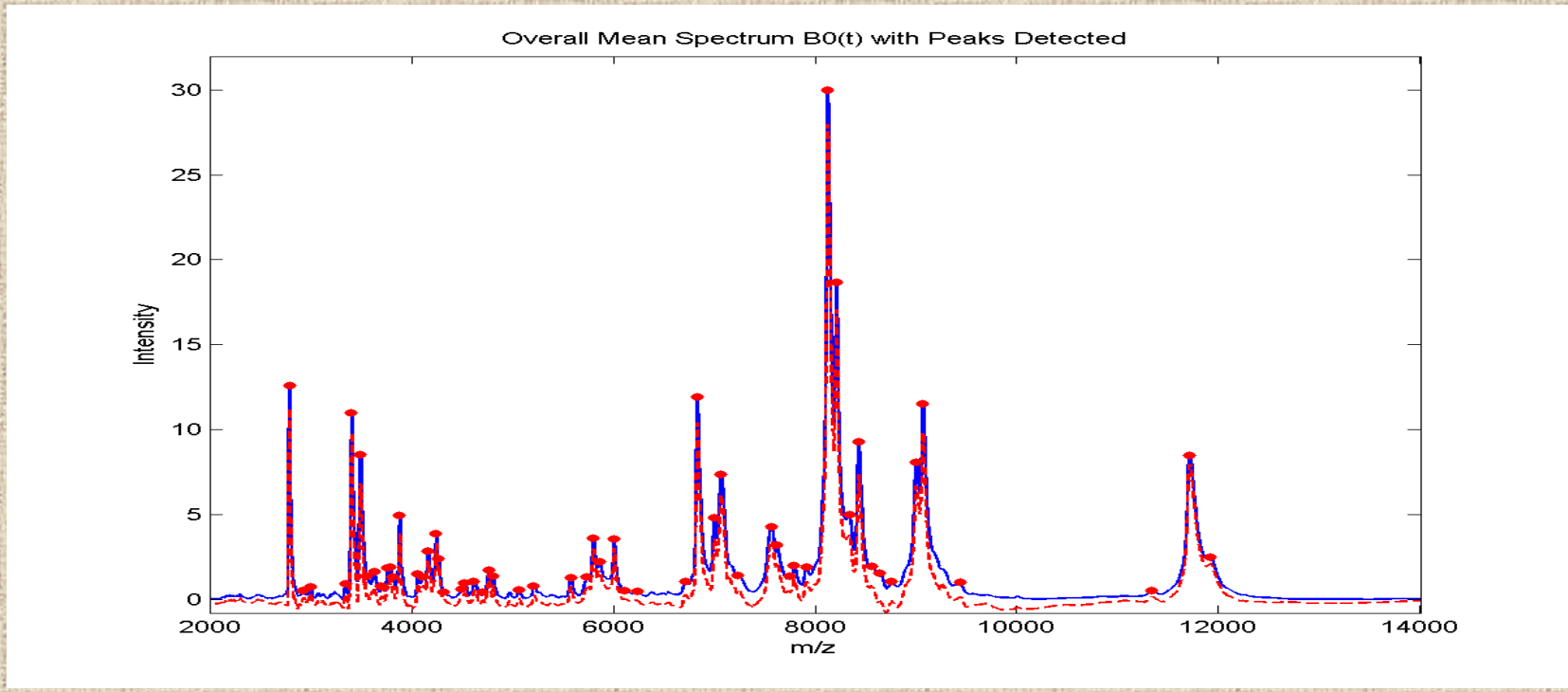
Example: Model Fitting

- **Daubechies 8 wavelet basis, J=11 levels**
- **Empirical Bayes procedure used to estimate regularization parameters π_{ij} and τ_{ij} from data.**
- **Burn-in 1000; 20,000 MCMC samples; thin=10**
- **Took 7hr 53min on Win2000 P-IV 2.8GHz 2GB RAM**
  - **That is Matlab code; C++ code takes ~2 hours.**
- **Trace plots indicated good convergence properties**
- **Metropolis Hastings acceptance probabilities good:**
  - **Range of (0.04, 0.53)**
  - **(10^{th},50^{th},90^{th}) percentiles of (0.20, 0.29, 0.50)**

Example: Results



Example: Peak detection



- **We first did "peak detection"**
  Local maxima in posterior mean (denoised) estimate of $B_0(t)$ with High posterior probability of nonzero mean; $\Pr\{B_0(t)>0|Y\}\geq 0.95$
- **Using this criterion, we found 58 peaks**
- **We restrict inference to values of *t* at peaks**

Example: Flagged peaks

Detecting 'significant' peaks: (assoc. w/ organ,cl,int)

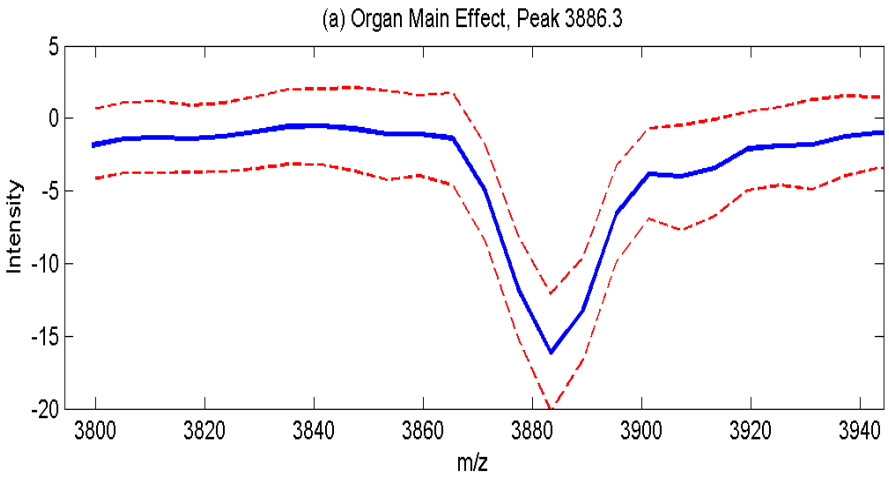
For each *t* at a peak, compute $p_i(t)=\min[\Pr\{B_i(t)>0\},\Pr\{B_i(t)<0\}]$

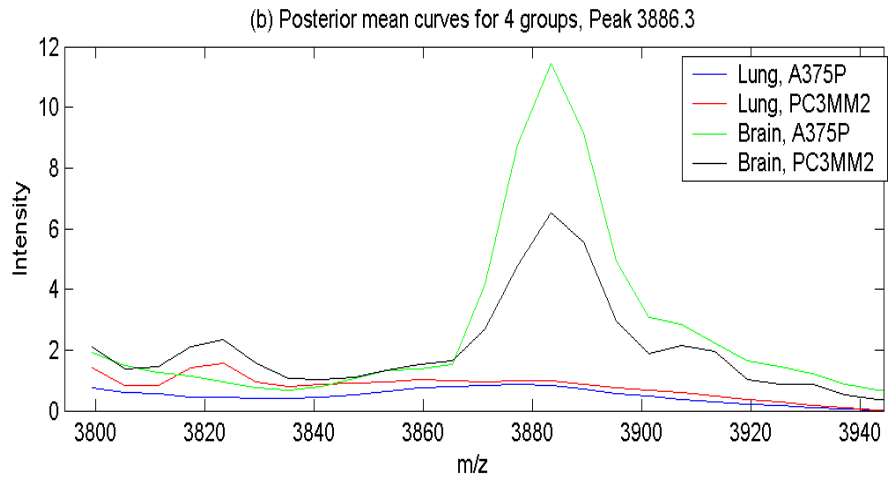
Flag any peak for which $p_i(t)$ is very small. (<0.05/58=0.00086)

Using this criterion, we flagged 9 peaks as interesting

m/z	Effect	*p*	Comment
3412.6	int.	<0.0005	PC3MM2>A375P for brain-injected only
3496.6	organ	<0.0005	Only expressed in brain-injected mice
3886.3	organ	<0.0005	Only expressed in brain-injected mice
4168.2	int.	0.0005	PC3MM2>A375P in brain-injected only
4252.1	int.	<0.0005	PC3MM2>A375P in brain-injected only
4270.1	cell line	<0.0005	PC3MM2>A375P
5805.3	int.	<0.0005	brain>lung only for mice given A375P cell-line
6015.2	cell line	<0.0005	PC3MM2>A375P
11721	cell line	<0.0005	PC3MM2>A375P
11721	organ	<0.0005	lung>brain

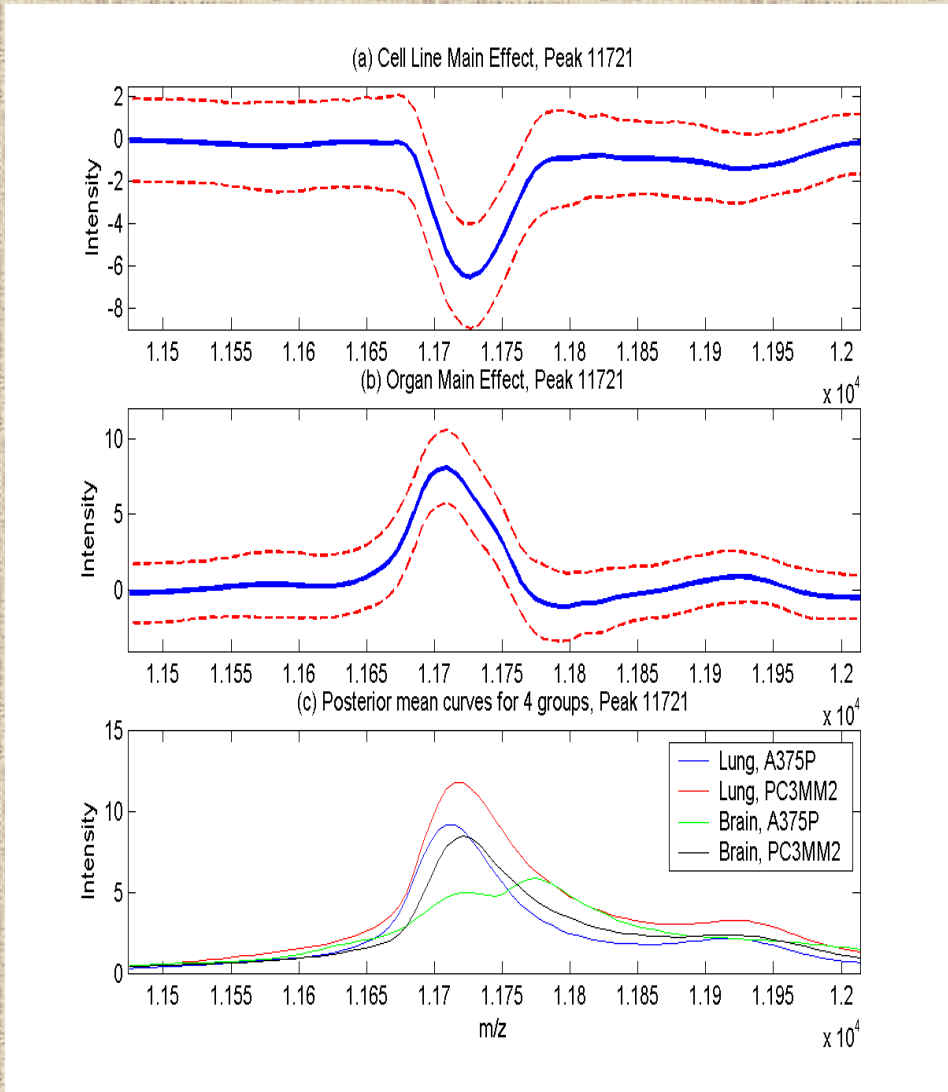
Example: Results





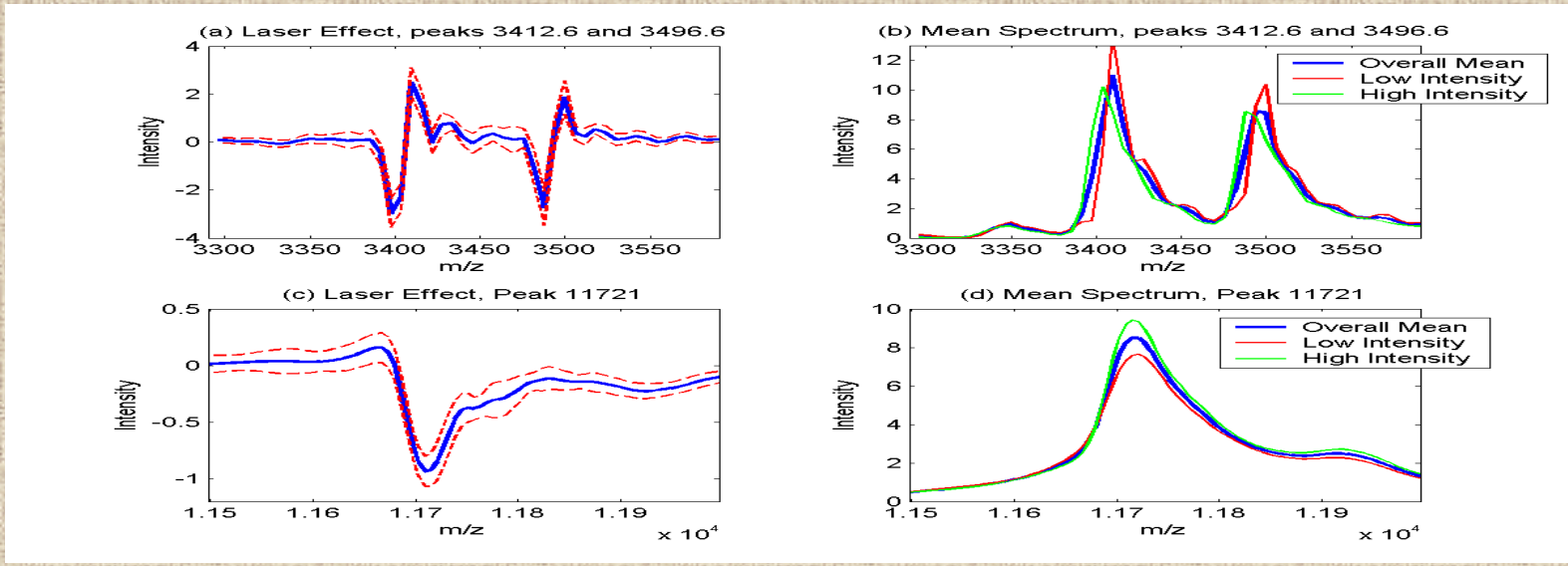
- **Specific to brain-injected mice**
- **May be CGRP-II (3882.34 Dal), peptide in mouse proteome that dilates blood vessels in brain**
- **Host response to tumor implanted in brain?**

Example: Results



- **Higher in mice injected with metastatic (PC3-MM2) cell line**
- **May be MTS1 (11721.43 Dalt), metastatic cell protein in mouse proteome.**
- **Also higher in lung-injected mice than brain-injected mice**

Example: Results



- **Laser intensity effect adjusts for:**
  - **Offsets in m/z scale**
  - **Shifts in intensities**
- **Important proof of principle that "linear" functional term can be used to adjust for functional effects of nuisance factors**

Discussion

- **Introduced unified modeling approach for FDA**
  - **Applied here to MALDI-TOF, but method is general.**
- **Method based on mixed models; is FLEXIBLE**
  - **Accommodates a wide range of experimental designs**
  - **Addresses large number of research questions**
- **Posterior samples allow Bayesian inference and prediction**
  - **Posterior credible intervals; pointwise or joint**
  - **Predictive distributions for future sampled curves**
  - **Predictive probabilities for group membership of new curves**
  - **Bayesian functional inference can be done via Bayes Factors**
- **Since a unified modeling approach is used, all sources of variability in the model propagated throughout inference.**

Discussion

- **Since functions adaptively regularized using wavelet shrinkage, the method is appropriate for spatially heterogeneous functional data.**
- **Approach is Bayesian. The only informative priors to elicit are regularization parameters, which can be estimated from data using empirical Bayes.**
- **Method generalizes to higher dimensional functions, e.g. image data, space/time (fixed domain) data.**
- **We used wavelet bases, but approach can be generalized to other orthogonal basis functions.**
- **Difficult to develop unified statistical modeling approach for replicated functional data, but worth the effort.**

Acknowledgements

- **Thanks to Phil Brown, Marina Vannucci, Louise Ryan, Kevin Coombes, Keith Baggerly, Yuan Ji, and Simon Lunagomez for useful discussions regarding this work.**
- **Thanks to Josh Fidler, Stan Hamilton, and Nancy Shih for the data used in this work**
- **Thanks to Dick Herrick for assistance in optimizing the code for the method.**