Prelim exam

1. Slide 1

   Good morning, everyone! It is my great pleasure for having you here, listening to my prelim presentation.

   My topic is New Methods in Functional data analysis with biostatistical applications.

2. Slide 2

   I will present two of my projects

3. Slide 3

The first one is a functional mixed model for scalar on function regression with application to a functional fMRI study.

4. Slide 4

This project is motivated by a functional magnetic resonance imaging study of thermal pain from Lindquist 2012. The motivation for this study is how the brain activation affects the pain rating.

fMRI measures brain activity by detecting changes associated with blood flow , providing a non-invasive way for the neronal activation study with a certin task

We begin by briefly describing the study, which is performed on 20 participants.

A number of stimuli consisting of thermal stimulations delivered to the participants left forearm, were applied at 2 different levels (high and low) to each participants.
(so each participant will receive both high level stimulus as well as low level stimulus)

The temperature of these painful (high) and non-painful (low) stimuli were determined using a pain calibration task prior to the experiment

After 18 seconds time period of thermal stimulation (either high or low)

a fixation cross was presented for a 14s time period until the words “how painful” appeared on the screen

After 4s of silent contemplation, participants rated the overall pain intensity on a visual analog scale (VAS)

The experiment concluded with 10s of rest
During the course of the experimental trial, each suject’s brain activity was also measured using fMRI

5. Slide 5

Data was extracted from 21 different known pain-responsive brain regions across the brain. We call them regions of interest (ROI). Each time course consisted of 23 equidistant measurements made every 2s, providing a total of 46s of brain activation (ranging from the time of onset of the application of stimuli to the conclusion of pain report)

The same experiment was conducted multiple times on each participant, with the total number of the repetitions ranging from 39 to 48, thereby giving rise to a unbalanced design.

The data observed for each of the ROI has the following form

Y_ij is Pain rating for jth repetition of ith subject
Z_ij is the level of thermal stimuli for jth repetition of ith subject; Z_ij = 1 denote high level, 0 denote low level
W_ijk is the observed fMRI time series data

6. Slide 6
To illustrate the structure of data, figure 1 show the fMRI and the pain rating data for two subjects each with 3 repetitions.
A shows the fmri time series data for suject 1 with 3 visits, solid line is for subject 1
C shows the fmri time series data for subject 2 with 3 visits, dashed line is for subject 2

B shows the pain rating for two subjects along each visits.

7. Slide 7

Objective is to

First: propose a functional mixed model for repeated outcomes, and allow for subject-specific random effect

Second: determine whether the fMRI data of the brain activation affects the pain rating in a unified or subject-specific manner, in other words: the relationship between the brain imaging data and pain rating is subject-specific or not

8. Slides 8

To model the subject-specific random effect of a functional predictor, we propose a novel functional mixed model extending the scalar on function regression for repeated outcomes. We denote this proposed model as FMM

The proposed model is as follows

To make use of the functional predictor, an integration of the functional predictor over the time domain is used

Where alpha is the population intercept

Gamma is the population effect of covariate Z_ij

Gamma_i is the random subject-specific effect of Z_ij, we assume that gamma_i iid normal distributed with 0 mean, and variance sigma_gamma2

beta(t): population effect of functional predictor X_ij(t)

beta_i(t): random subject-specific effect of the functional predictor X_ij(t)

We assume that beta_i(t) are iid random functions following gaussian process over T with mean function 0, and covariance function C(s,t)

E_ij is random errors with distribution N(0, sigma_e2), independent of X_ij(t)

All the random terms (gamma_i, beta_i, e_ij) are mutually independent across subjects and from each other

9. Slides 9

There has been lots of related literatures to our model

Scalar on function regression models are used to relate functional predictors to scalar outcomes,

Standard methods for scalar on function regression (without considering repeated outcomes) has been extensively overviewed in ramsay's book functional data analysis, and also reviewed by Morris

Nonlinear methods: for example , Muller and Yao propose a functional additive model with the underlying functional principal component scores as predictor(with the additive structure on a finite number of PC scores); instead of using the additive structure on a finite number of PC scores, but with additive structure in the function predictor, Mcleans propose a functional generalized additive model, modeling the link-transformed mean response as the integral with respect to t of a bivariate function on functional predicot and time t based on tensor product B-splines with roughness penalty

Standard methods are also extended to data with repeated outcomes, Goldsmith propose a longitudinal penalized regression model to a longitudinal diffusion tensor imaging study; For the same study, Gerthesis propose a Longitudinal Functional Principal Components Analysis based on two levels FPCA which separates the influence of subject- and visit-specific variation in the functional predictors

10.Slides 10
Test for the lack an effect in a functional predictor, has also been well developed in the scalar on function regression literature. For example,

Cardot and others, developed a test using the covariane of scalar response and functional predictor

Mclean and Swihart used the exact likehood ratio tests of zero variance components based on Crainiceanu and Ruppert 2004: Mclean use it in a context of gaussian functional generalized additive model to test the Linearity, interactions in a multivariate additive model or for testing for no effect in the functional linear model. Swihart et al. (2014) use a penalized spline-mixed model for the FLM and use an RLRT for a zero variance component to test the necessity of function effect.

Kong and others extend the classical wald, score, likelihood ratio, F test to functional linear model to test the functional effect

Su and others propose a Wald-type test based on reordering and select PCs using an association-variation index (AVI) for testing the functional effects in FLM.

Slides 11
The current scalar on function regression models only model the effects of the functional predictor as fixed, and do not allow for the random functional effects that are either subject- or outcome- specific; and all the test focus on testing the fixed functional effects and is not directly applicable to simultaneously test a collection of random functional effects.

In stead we propose an equivalent test for testing the covariance function of the random functional effect is zero or not. The test can later be formulated multiple variance components are zero, then the exact likelihood ratio test of zero variance components can be applied.

Recall the observed data at time t_k → W_ijk, we assume that w is a noisy observation of the smooth functional data xij(tk). The model for the functional predictor is as follows:

Since we focus on dimension reduction on x_ij, we do not adopt a more complicated multilevel fPCA as in di and other 2009, and we simply assume that x_ij is independent random functions from gaussian process across subjects and visits

With mean function mu(t), and covariance function K(s,t). Eijk is measurement error that is independent across i,j,k, also independent from true random function X_ij

Our key idea is to formulate FMM into a linear mixed effects model by applying functional principal component analysis (fPCA) to the functional predictor X_ij

12. Slides 12
by Mercer's theorem:
Covariance function can be decomposed as this…

Where phi_k is orthornomal eigenfuncions, with eigenvalues non-increasing eigenvalues

Then by karhunen-loeve expansion, X_ij can be written as a linear combination of the eigenfunctions. With xi_ijk is the independent random scores, with xi_ijk ~ n(0, lambda_k)

13. Slides 13
For model identifiability, we assume that beta(t) can be written as linear combination of eigenfunctions, where theta_k are associated scalar coefficients to be determined; similar for beta_i(t).... Where theta_ik are independent subject-specific random coefficients with distribution N(0, tau_k2), tau_k2 are needed to be determined as well.

Note that the covariance function C(s,t) now equals to …

By plugging in beta(t) and betai(t), it follows that FMM can be rewritten as this…

Note this model has infinitely many parameters and hence can not be fit, a well known problem for scalar on function regression. A standard approach is:

14. Slides 14
Using the truncated number of eigenfunctions for approximating the functional predicor, so that associated scores and parameters for beta(t) and betai(t) are all finite dimensional. Let K be the truncated number of eigenfunctions to be selected, then an approximate and identifiable model is as follows…

Until now, condition on the random scores xi_ijk, this model is a linear mixed model, and can be easily fit using standard mixed effects model software.

15. Slides 15
To convert FMM to LMM, we adopt two steps:
First FPCA on functional predictor, we can obtain the number of PCs, estimated eigenfuctions, estimated eigenvalues, and predicted random scores

We select the K by proportion of variance explain(PVE), but other method such as AIC on the functional predictor (Li and other 2013)

Fpca can be conducted using a number of methods, such as local polynomial methods (yao and other 2005). Here we use the fast covariance estimation (FACE) method in xiao 2016, which is based on penalized splines and is implemented in the r function fpca.face in r package refund

Then, a practical model is as this…. It can be fit in lmer in lme4

We can get the estimated theta_k, prediction of theta_ik
Then bate and betai can be given. Confidence bands for beta and betai can also be constructed, since multivariate normality of thetahat and thetaik

16. Slides 16
Our interest is to access if functional effect is subject-specific or the same across subjects

Recall our proposed FMM,

In other words, it is if betai(t)=0 for all i and all t; versus for some i at some t betai(t) is not 0

Since beta_i is random coefficient functions, test can be formulated in terms of its covariance function.

That is, the covariance function is 0 for all s, t verus not 0 at some s, t

Note: under H0, FMM reduce to a standard scalar on function regression model(FLM)

17. Slides 17
We note that under the truncated model with k selected functional principal components, C(s,t) is this….
Which means, an equivalent test is tau_k==0 for all k against at least one k<=K not 0.

We propose two tests

18. Slides 18
We propose a bonferroni-corrected test by two steps:
First, conduct zeroness test on each tau_k, with constraint of 0 on the rest of them;
Then, a bonferroni correction for simulteneous testing of k hypothesises is used;

19. Slides 19
Another test is equal-variance test.

Following the method in McLean and others which they test the lineartity of bivariate smooth function in the context of FGAM, we make the assumption that
tau_k2===tau_k

And consider the test: tau2==0 versus tau2 is not 0

This test has only one variance component, and referred as equal-variance test

We note that: under the null, this test is equvalent; however, the alternative test is more general than this test; It was noted in McLean's paper that equal variance test could outperform bonferroni-corrected test even when the true variance component are not the same (i.e. this equal variance assumption does not hold)

Both tests involve testing of zeroness on the variance component, and we use the exact likelihood ratio test proposed in Crainniceanu and ruppert.

Recall our practical model for FMM:...

A practical issue with this test is that the standard testing procedure as the likelihood ratio test is not directly applicable to this model, because this model has multiple additive slopes theta_ik. Therefore we need to transform this model under the equal variance assumption to an equivalent model with only one random slope.

20. Slides 20
We first rewrite FMM in terms of matrix form for ith subject:
… pulling all the fixed effect into alpha, with A_i is the random score matric for ith subject

Then, we conduct a singular value decomposition of A_i as this…. where Di is a diagonal matrix of the singular values of Ai
A left multiplication of the U transpose, lead to a the coefficient matrix A_i to a diagonal matrix, therefore additive slopes are transformed to a single random slope. This model can be fit using standard mixed model, and standard lrt can be applied.

21. Slides 21
For the simulation study, each simulation data set consists of I subjects, each have J replicates. Let domain of functional predictor be T=[0,1]

Data are generated as this practical model….
Functional predictor X_ij(t) is generated as follows:
Observed functional predictor Wijk is as this...

The functional predictor has 3 functional principal components
Signal to noise ratio equals either 0 or 3
22. Slides 22
We consider a factorial design with 4 factors:
Number of subject I
Number of replicates per subject J
Signal to noise ratio in the functional data
A total of 24 model conditions are used with random scores being either homo.. Or hetero…
tau^2 measures the level of variation of random subject-specific function effect
Simulate data with tau^2==0 is used to evaluate the performance of the test

Simulate data with multiple values of tau^2 are used to assess the power of tests;
For model estimation, we set tau^2 to be either 0.02, 0.04, 0.08

23. Slides 23
Table 1 illustrate the performance of bonferroni-corrected test and the equal-v.. Test at the 0.05 significance level.

We see that under various model conditions, both tests perform as expected, confirming their validity for testing the proposed hypothesis.

24. Slides 24
Figure 2 illustrate the power of two tests as a function of tau^2 under different model conditions, when the homogeneous variance is used to generate functional predictor.

We see that : 1. Both test has increased power when either # of subjects or # or visits per subject increases; 2. Both tests also have slightly higher power when using smooth (noise-free) functional predictor than noisy functional predictors, as is expected; 3. In all setting we found EV test has higher power than bonfer test, especially when # of subjects are small. This also agree with McLean's finding although their setting is different. 4. It is interesting to note that increasing # of visits seems to result in higher power of the tests than instead increasing the number of subjects.

25. Slides 25

Figure 3 shows the power of two tests as a function of tau^2, when heterogeneous variance is used to generate the random scores.

Finding remains the same, and EV still outperform bonf.

However, under the same model condition and the same tau^2, power of both tests has smaller power in the case of heterogeneous variances. This is reasonable, as the total variation of the random subject-specific functional effects becomes smaller in this case.

25. Slides 25
We compare the proposed FMM with traditional scalar on function regression model (FLM). ie beta_i(t)=0 in FMM, in terms of the estimation accuracy of population effect beta(t), and out-of-sample prediction accuracy of the response. For the former, we use MISE of beta(t) (mean integrated squared error), for the response, we use mean squared error. For each subject in the simulated dataset, we generate 10 new observations in order to evaluate subject-specific prediction accuracy.

Table 2 shows the estimation results for homoge… under 24 model conditions.

1. In each scenario, FMM outperforms FLM in terms of having a smaller MSE for predicting response,
2. and have comparable performance on estimating the fixed population functional effect
3. Both model have slightly better performance with the functional predictor is smooth without noises.
4. As sample size increases, both methods have better performance.

26. Slides 26
This table shows …. When tau2=0.08
Finding is still the same

5. Note that increasing of tau^2 result in worse prediction result for the response in FLM while slightly deteriorating result for FMM, which indicates the better performance of FMM when there is strong subject-level functional effect in the functional predictor.
6. Result for hetero.. Finding remain the same

27. Slides 27
We applied the proposed functional mixed model as well as the EV test to the 21 ROIs, which are the pain responsive brain regions

We found that all ROIs had significant subject-specific functional random effects at the 0.05 level.

28. Slides 28

Figure 4 shows the estimated subject-specific functional effects beta(t)+beta_i(t) from ROI 5 and 10. Red line is for population functional effect beta(t).

The main trend is the same across all ROIs, showing the relatively low though highly diverse signals at the beginning of the trial, followed by a strong positive signal in the middle of the trial, and slightly weaker signal towards the end of trial.

The delayed peak occurring in the time period immediately following the onset of the thermal stimuli (at time 18s) is consistent with the delayed nature of brain hemodynamics, which peaks roughly 6s after peak neuronal activation.

The second peak takes place around the time of the pain reporting, perhaps a contribution of activity during “pain recall”.

We conducted a two cluster analysis on the random functional effects to understand how these effects differ. For ROI 5, it appears that subjects mostly differ during the pain-recall period where the subject ..effect are more pronounced compared to the fixed population effect; ROI 10 demonstrate the heterogeneity of the effects of brain activity during period of the application of the stimuli

28. Slides 28

Figure 5 shows the violin plots of the MSE for response prediction which is first averaged in each subject for FMM and FLM. It shows that MSE at subject level given by FLM has wider spread than FMM in both ROIs.

Also Rsquare of FMM is higher than FLM (here Rsquare is a variance explained by the entire model, including both fixed and random effects using MuMIn::r.squaredGLMM)

29. Slides 29

So in summary, in this project, we proposed functional mixed model to accommodate random functional effects of a functional predictor for scalar on function regression.

FMM outperform traditional scalar on function regression in terms of better prediction of response

Also we proposed a significance test: EV test on random functional effects. Which maintains proper size and has good power.

We applied it to the motivating fMRI study.

The proposed model may also be used when multiple responses are simultaneously modeled with a functional predictor.

Paper of this project has been submitted to Biostatistics.

30. Slides 30

The second project is Fast Covariance Estimation for multivariate functional data

31. Slides 31
Motivating example for this project is Diffusion Tensor imaging study for Multiple Sclerosis.

DTI is a magnetic resonance imaging based modality that traces the diffusion of water in the brain. DTI is used to generate images of the white matter specifically. White matter refer to the central nervous system.
Multiple sclerosis is an autoimmune disease, results in axon demyelination and
lesions in white matter tracts, leads to significant disability in patients.

So the background for this study is to explore the relationship between the white matter tracts in MS patients and the cognitive impairment over time.

corpus callosum (CCA) : connects the left and right sides of the brain
right corticospinal tract (RCST): a white matter motor pathway

the CCA , and RCST tracts are functional, comprised of water diffusivity metrics from diusion tensor imaging on a dense, regular grid of 93 and 55 points, respectively

Several measurements of water diffusion are provided by DTI, including fractional anisotropy, mean/parallel diffusivity.

This data is available in DTI and DTI2 dataset in refund package.

Paced Auditory Serial Addition Test score (PASAT)
which is a commonly used examination of cognitive function affected by MS with scores ranging between 0 and 60, as our scalar outcome. It specifically assesses auditory information processing speed and flexibility, as well as calculation ability. The test result is the number of correct sums given (out of 60 possible). So higher PASAT score, less damage

This study consist of 100 subjects, 66 women and 34 men age between 21~70 years old at first visit, with 2~8 visits per subject, with a median of 3, and were approximately annually. A total of 340 visits were recorded.

Continuous summaries of white
matter tracts, parameterized by distance along the tract and called tract profiles, can be derived from diffusion tensor images.

Continuous summaries of white matter tracts, parameterized by distance along the tract and called tract profiles, can be derived from diffusion tensor images.

35. Slides 35
First column of figure 1: shows mean diffusivity along the rescaled trac profile with two subject, 2 visits for each subject highlighted in red and blue. There are 340 observations in total.
Second column shows the univariate FPCA applied to CCA and RCST seperately.
Third column shows the correlation between the random scores corresponding to the first 3 selected PCs. We can see that 1st PC of CCA has negative correlation with 3rd PC scores of RCST…

mFPCA VS univariate FPCA:

1. Seperate univariate FPCA capture the joint variation indirectly, which make interpretation of FPCA results difficult
2. Univariate FPCA gives correlated scores, which will lead to multicollinearity issues in the subsequent fPC regression
1. first takes correlation among different responses, and could better capture the correlations between functions.
2. Second, an improved correlation estimation will lead to improved FPCA analysis such as inference, and curve prediction in terms of regression on the obtained scores.

36. Slides 36
Suppose observed data has the following form:
….
Yijk is the jth multivariate response observed at time tk for i the subject;
N is the number of subject, p is dimension of response for each subject, m is total length of time grid.

We model the observed y_ijk as this…

u_j(t) is …
X is …
Eink is …. Independ across i, j, k

37. Slides 37
We first review the fundamentals of Multivariate Principal component analysis
Consider a more general random function x(t) observed at time t, which is a p-dimension vector
With mean function …
Covariance function…
Covariance function of j1 and j2 response…

38. Slides 38

Multivariate Mercer theorem gives the decomposition on the covariance function as Follows…

With the kth multivariate eigen function as a p-dimension vector

The orthonormality of the eigenfunctions are defined over the summation across p responses;
(from here we know that mFPCA may not be equvalent to univariate FPCA)

D_k is …
K_j1j2 expressed as

39. Slides 39
Then x(t) has the multivariate KL expansion representation as follows:
…
Xi_k can be represented as … uncorrelated random scores
With 0 mean, covariance dk

40. Slides 40
The objective is to

1. Estimate covariance function K using spline methods
2. Conducted multivariate FPCA

41. Slides 41
Related literature for multivariate functional data consists of
Dense functional data
Sparse functional data

Chiou.. Used a normalized mFPCA by standarlizing the covariance operator
Repeatedly apply point-wise univariate FPCA...

42. Slides 42
Different domain: neoral imaging ADNI study application where data consist of both neoronal function and brain image
Based on KL expansion, estimate cross-covariance using score form univariate FPCA

43. Slides 43
We start by approximating the covariance function using tensor product B splines
Since it is automatic smoother and computationally simple

As follows:
…

b(.) denote the b-spline base
… is a collection of b-spline basis functions
C: number of b-spline basis function
Theta: coefficient matrix

44. Slides 44
Recall our model for observed data, based on multivariate FPCA, can be modeled as this…

Our goal is to estimate the eigenfunction, as well as prediction of random scores xi_ik
We proposed a 5 steps-algorithm…

First, data preprocessing
Smooth the mean function, by univariate smoothing based on P-splines on each response
Then demean observed data
Yj is the j th response of m by n
Then covariance matrix is given as follows….

45. Slides 45
Second step is to smooth each autocovariance matrix Kjj:
Adopting the FACE estimator in xiao , 2016,
The estimator has the following sandwich form:
… can be represented as a tensor product B-splines
Smoother matrix is symmetric matrix of mxm
B is the design matrix of mxc
P is a symmetri c
Can get the estimated smoothing parameter and coefficient matrix

Third step is to smooth each cross-covariance matrix Kj1j2:
As follows…
S_j1 .. obtained from second step
Get coefficient matrix

46. Slides 46
Fourth step is eigen-docomposition

Pool all the estimated coefficent together, and a tensor product Bspline representaion gives a straightforward spectral decompositon based on proposition 1 from Li 2018
The eigen fucntion is given as follows…

Last step:
Prediction on scores and curve prediction
Using projection method (numerical integration)
…