Group Modeling for fMRI

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Introduction to fMRI
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Overview

- Mixed effects motivation
- Evaluating mixed effects methods
- Case Studies
  - Summary statistic approach (HF)
  - SnPM
  - SPM2
- Conclusions

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Lexicon

Hierarchical Models

- Mixed Effects Models
- Random Effects (RFX) Models
- Components of Variance

... all the same

... all alluding to multiple sources of variation

(in contrast to fixed effects)

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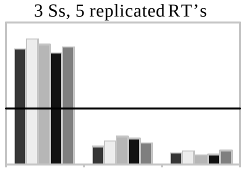
Random Effects Illustration

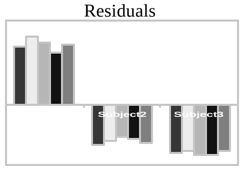
- Standard linear model

  assumes only one source of *iid* random variation
- Consider this RT data
- Here, two sources
  - Within subject var.
  - Between subject var.
  - Causes dependence in *e*

3 Ss, 5 replicated RT's



Residuals



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Fixed Effects

Animation over replications of one subject's experiment

- Only variation is measurement error
- True response magnitude is ***fixed***
  - Significance based on estimated response relative to measurement error variance

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Random/Mixed Effects

Animation over different subjects

- Two sources of variation
  - Measurement error (scan-to-scan var.)
  - Individual differences (subj.-to-subj. var.)
-
  -
  -

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Random/Mixed Effects

Animation over different subjects

- Response magnitude is ***random***
  - Each subject has a different magnitude
  -

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Random/Mixed Effects

Animation over different subjects

- Response magnitude is *random*
  - Each subject has a different magnitude
  - But note, population mean magnitude is ***fixed***
  - Significance based on estimated response relative to sum of measurement error & intersubject variability

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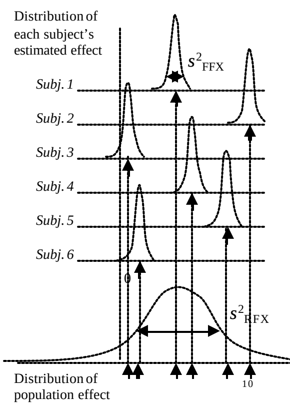
Fixed vs. Random Effects in fMRI

- Fixed Effects
  - Intra-subject variation suggests *all these subjects* different from zero
- Random Effects
  - Intersubject variation suggests *population* not very different from zero



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Fixed vs. Random

- Fixed isn't "wrong," just usually isn't of interest
- Fixed Effects Inference
  - "I can see this effect in this cohort"
- Random Effects Inference
  - "If I were to sample a new cohort from the population I would get the same result"

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Assessing RFX Models Issues to Consider

- Assumptions & Limitations
  - What must I assume?
  - When can I use it
- Efficiency & Power
  - How sensitive is it?
- Validity & Robustness
  - Can I trust the P-values?
  - Are the standard errors correct?
  - If assumptions off, things still OK?

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Issues: Assumptions

- Distributional Assumptions
  - Gaussian? Nonparametric?
- Homogeneous Variance
  - Over subjects?
  - Over conditions?
- Independence
  - Across subjects?
  - Across conditions/repeated measures
  - Note:
    - Nonsphericity = (Heterogeneous Var) or (Dependence)

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Issues: Soft Assumptions Regularization

- Regularization
  - Weakened homogeneity assumption
  - Usually variance/autocorrelation regularized over space
- Examples
  - fmristat - local pooling (smoothing) of (s^2_{RFX})/(s^2_{FFX})
  - SnPM - local pooling (smoothing) of s^2_{RFX}
  - FSL3 - Bayesian (noninformative) prior on s^2_{RFX}

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Issues: Efficiency & Power

- Efficiency: 1/(Estmator Variance)
  - Goes up with *n*
- Power: Chance of detecting effect
  - Goes up with *n*
  - *Also* goes up with degrees of freedom (DF)
    - DF accounts for uncertainty in estimate of s^2_{RFX}
    - Usually DF and *n* yoked, e.g. DF = *n-p*

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Issues: Validity

- Are P-values accurate?
  - I reject my null when $P < 0.05$
    Is my risk of false positives controlled at 5%?
  - "Exact" control
    - FPR = α
  - Valid control (possibly conservative)
    - FPR ≤ α
- Problems when
  - Standard Errors inaccurate
  - Degrees of freedom inaccurate

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Four RFX Approaches in fMRI

- Holmes & Friston (HF)
  - Summary Statistic approach (contrasts only)
  - Holmes & Friston (HBM 1998). Generalisability , Random Effects & Population Inference. NI, 7(4 (2/3)):S754, 1999.
- Holmes *et al.* (SnPM)
  - Permutation inference on summary statistics
  - Nichols & Holmes (2001). Nonparametric Permutation Tests for Fu nctional Neuroimaging: A Primer with Examples. HBM, 15;1-25.
  - Holmes, Blair, Watson & Ford (1996). Nonparametric Analysis of Statistic Images from Functional Mapping Experiments. JCBFM, 16:7-22.
- Friston *et al.* (SPM2)
  - Empirical Bayesian approach
  - Friston et al. Classical and Bayesian inference inneuroimagining : theory. NI 16(2):465-483, 2002
  - Friston et al. Classical and Bayesian inference in neuroimaging: variance component estimation in fMRI. NI: 16(2):484-512, 2002.
- Beckmann et al. & Woolrich et al. (FSL3)
  - Summary Statistics (contrast estimates *and* variance)
  - Beckmann, Jenkinson & Smith. General Multilevel linear modeling for group analysis in fMRI. NI 20(2):1052-1063 (2003)
  - Woolrich , Behrens et al. Multilevel linear modeling for fMRI group analysis using Bayesian inference. NI 21:1732-1747(2004)

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Case Studies: Holmes & Friston

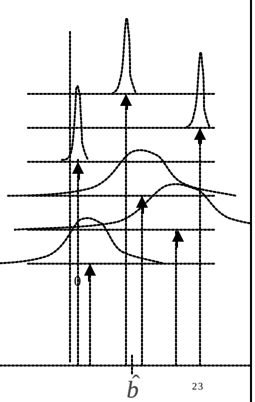
- Unweighted summary statistic approach
- 1- or 2-sample t test on contrast images
  - Intrasubject variance images not used (c.f. FSL)
- Proceedure
  - Fit GLM for each subject *i*
  - Compute cb_i, contrast estimate
  - Analyze $\{cb_i\}_i$

Case Studies: HF Assumptions

- Distribution
  - Normality
  - Independent subjects
- Homogeneous Variance
  - Intrasubject variance homogeneous
    - s^2_{FFX} same for all subjects
  - Balanced designs

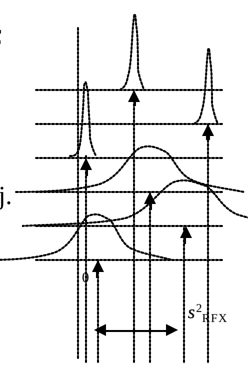
Case Studies: HF Efficiency

- If assumptions true
  - Optimal, fully efficient
- If s^2_{FFX} differs between subjects
  - Reduced efficiency
  - Here, optimal $\hat{b}$ requires down-weighting the 3 highly variable subjects



Case Studies: HF Validity

- If assumptions true
  - Exact P-values
- If s^2_{FFX} differs btw subj.
  - Standard errors OK
    - Est. of s^2_{RFX} unbiased
  - DF not OK
    - Here, 3 Ss dominate
    - DF < 5 = 6-1



Case Studies: HF Robustness

- Heterogeneity of s^2_{FFX} across subjects...
  - How bad is bad?
- Dramatic imbalance *(rough rules of thumb only!)*
  - Some subjects missing 1/2 or more sessions
  - Measured covariates of interest having dramatically different efficiency
    - E.g. Split event related predictor by correct/incorrect
    - One subj 5% trials correct, other subj 80% trials correct
- Dramatic heteroscedasticity
  - A “bad” subject, e.g. head movement, spike artifacts

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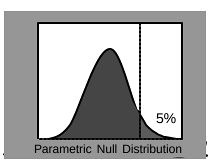
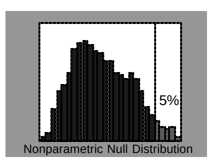
Case Studies: SnPM

- No Gaussian assumption
- Instead, uses data to find empirical distribution





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Case Studies: SnPM Assumptions

- 1-Sample *t* on difference data
  - Under null, differences dist^n symmetric about 0
    - OK if s^2_{FFX} differs btw subjects!
  - Subjects independent
- 2-Sample *t*
  - Under null, dist^n of all data the same
    - Implies s^2_{FFX} must be the same across subjects
  - Subjects independent

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Case Studies: SnPM Efficiency

- Just as with HF...
  - Lower efficiency if heterogeneous variance
  - Efficiency increases with *n*
  - Efficiency increases with DF
    - How to increase DF w/out increasing *n*?
    - Variance smoothing!

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Case Studies: SnPM Validity

- If assumptions true
  - P-values’s exact
- Note on “Scope of inference”
  - SnPM can make inference on population
  - Simply need to assume random sampling of population
    - *Just as with parametric methods!*

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Case Studies: SnPM Robustness

- If data not exchangeable under null
  - Can be invalid, P -values too liberal
  - More typically, valid but conservative

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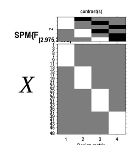
Case Study: SPM2

- 1 effect per subject
  - Uses Holmes & Friston approach
- >1 effect per subject
  - Variance basis function approach used...

SPM2 Notation: iid case

$$\underset{N\times 1}{y} = \underset{N\times p}{X}\ \underset{p\times 1}{q} + \underset{N\times 1}{e}$$

X

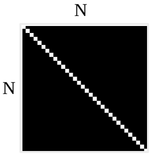


- 12 subjects, 4 conditions
  - Use F-test to find differences btw conditions
- Standard Assumptions
  - Identical distn
  - Independence
  - "Sphericity"... but here not realistic!

Error covariance

N

N



Multiple Variance Components

$$\underset{N\times 1}{y} = \underset{N\times p}{X}\ \underset{p\times 1}{q} + \underset{N\times 1}{e}$$

- 12 subjects, 4 conditions
- Measurements btw subjects uncorrelated
- Measurements w/in subjects correlated

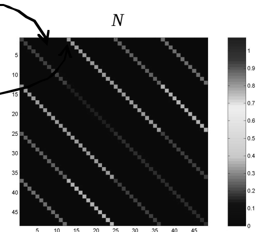
Errors can now have different variances and there can be correlations

Allows for 'nonsphericity'

Error covariance

N

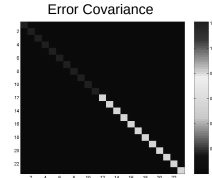
N



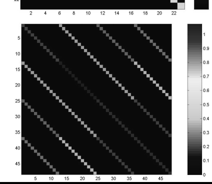
Non-Sphericity Modeling

Error Covariance

– Errors are independent but not identical



– Errors are not independent and not identical



Case Study: SPM2

- Assumptions & Limitations
  - – assumed to globally homogeneous
  - l_k's only estimated from voxels with large F
  - Most realistically, Cor(e) spatially heterogeneous
  - Intrasubject variance assumed homogeneous

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Case Study: SPM2

- Efficiency & Power
  - If assumptions true, fully efficient
- Validity & Robustness
  - P-values could be wrong (over or under) if local Cor(e) very different from globally assumed
  - Stronger assumptions than Holmes & Friston

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Conclusions

- Random Effects crucial for pop. inference
- SPM2
  - Most RFX analyses proceed just like SPM99
  - But nonsphericity modeling can handle multiple contrasts per subject
- FSL
  - Accounts for different intrasubject var.
  - More valid, may be more sensitive
  - Usually will be similar to SPM results

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