

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)
 - SPM2
 - FSL3
- 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)

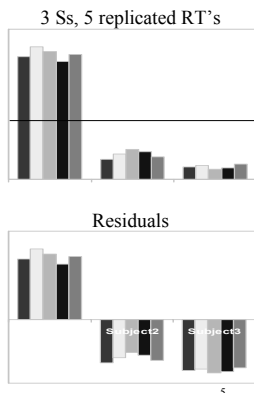
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Random Effects Illustration

- 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 ϵ



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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

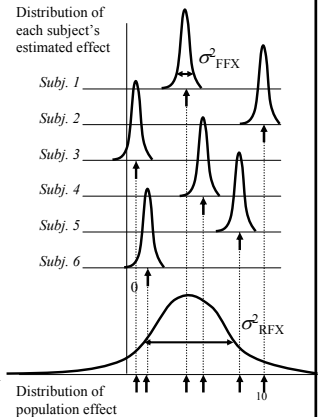


- Response magnitude is *random*
 - Each subject has a different magnitude
 - But note, population mean magnitude is *fixed*
 - Significance based on estimated response relative to sum of measurement error & intersubject variability

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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



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
 - fmirstat - local pooling (smoothing) of $(\sigma_{\text{RFX}}^2)/(\sigma_{\text{FFX}}^2)$
 - SnPM - local pooling (smoothing) of σ_{RFX}^2
 - FSL3 - Bayesian (noninformative) prior on σ_{RFX}^2

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Issues: Efficiency & Power

- Efficiency: $1/(\text{Estimator Variance})$
 - 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 σ_{RFX}^2
 - Usually DF and n yoked, e.g. $\text{DF} = n - p$

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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
 - $\text{FPR} = \alpha$
 - Valid control (possibly conservative)
 - $\text{FPR} \leq \alpha$
- 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)):5754, 1999.
- Holmes *et al.* (SnPM)
 - Permutation inference on summary statistics
 - Nichols & Holmes (2001). Nonparametric Permutation Tests for Functional 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 in neuroimaging: theory. NI 16(2):465-483, 2002
 - Friston *et al.* Classical and Bayesian inference in neuroimaging: variance component estimation in fMRI. NI: 19(2):494-512, 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)
- Procedure
 - Fit GLM for each subject i
 - Compute cb_i , contrast estimate
 - Analyze $\{cb_i\}_i$

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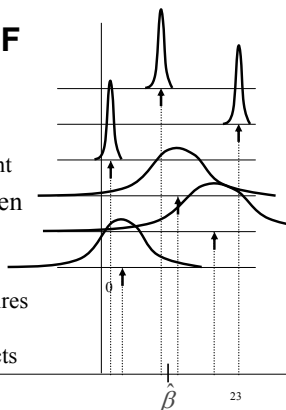
Case Studies: HF Assumptions

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

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Case Studies: HF Efficiency

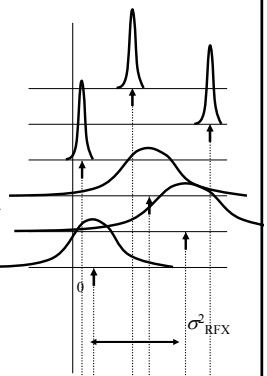
- If assumptions true
 - Optimal, fully efficient
- If σ^2_{FFX} differs between subjects
 - Reduced efficiency
 - Here, optimal $\hat{\beta}$ requires down-weighting the 3 highly variable subjects



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Case Studies: HF Validity

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



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Case Studies: HF Robustness

- Heterogeneity of σ^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 Study: SPM2

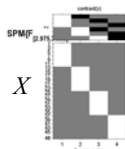
- 1 effect per subject
 - Uses Holmes & Friston approach
- >1 effect per subject
 - Variance basis function approach used...

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SPM2 Notation: iid case

$$y = X\theta + \varepsilon$$

$N \times 1 \quad N \times p \quad p \times 1 \quad N \times 1$



Error covariance
N



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

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Multiple Variance Components

$$y = X\theta + \varepsilon$$

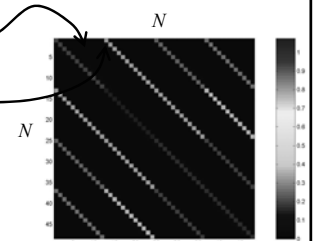
$N \times 1 \quad N \times p \quad p \times 1 \quad N \times 1$

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

Errors can now have different variances and there can be correlations

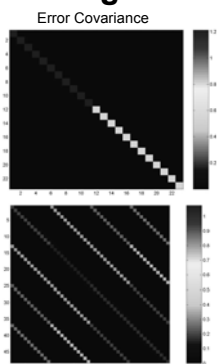
Allows for ‘nonsphericity’

Error covariance



Non-Sphericity Modeling

- Errors are independent but not identical
- Errors are not independent and not identical



Case Study: SPM2

- Assumptions & Limitations
 - assumed to globally homogeneous
 - λ_k 's only estimated from voxels with large F
 - Most realistically, $\text{Cor}(\varepsilon)$ 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 $\text{Cor}(\varepsilon)$ very different from globally assumed
 - Stronger assumptions than Holmes & Friston

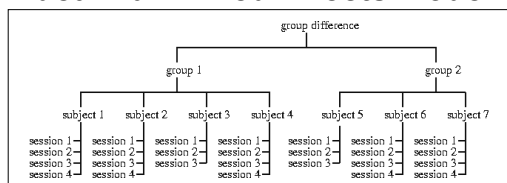
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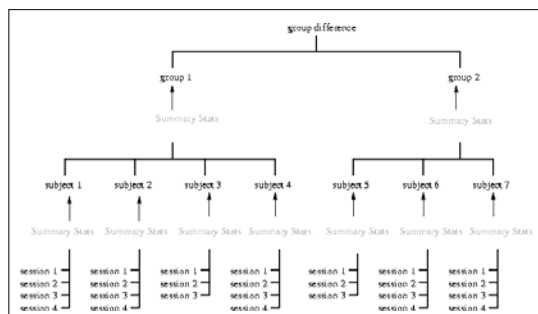
FSL3: Ideal Full Mixed Effects Model



- First-level, combines sessions
- Second-level, combines subjects
- Third-level, combines/compares groups

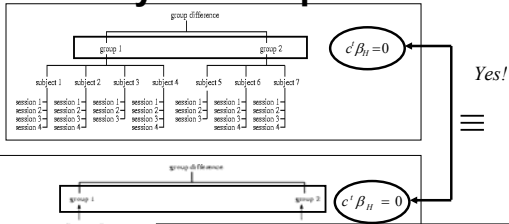
Ideally you'd fit all levels simultaneously, but that's GB's of data!

FSL3: Summary Statistics



... instead, can exact same results be found just with summaries?

Summary Stats Equivalence



Crucially, summary stats here are *not* just estimated effects.

Summary Stats needed for equivalence:

$$\hat{\beta} \quad \text{cov}(\hat{\beta}) \quad \text{dof}$$

Beckmann et al. 2003

Case Study: FSL3's FLAME

- Uses summary-stats model equivalent to full Mixed Effects model
- Doesn't assume intrasubject variance is homogeneous
 - Designs can be unbalanced
 - Subjects measurement error can vary

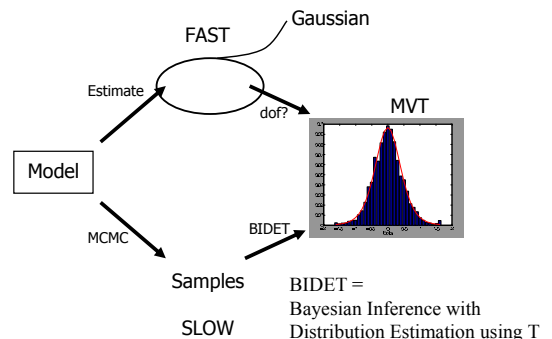
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Case Study: FSL3's FLAME

- Bayesian Estimation
 - Priors, priors, priors
 - Use reference prior
- Final inference on posterior of β
 - $\beta | y$ has Multivariate T distⁿ (MVT) but with unknown *dof*

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Approximating MVTs



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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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