AFNI: Population-Level Modeling

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Three subsections

- Part 1 - Overview, perspectives and concepts
- Part 2 - Basic modeling approaches
- Part 3 - Advanced modeling approaches

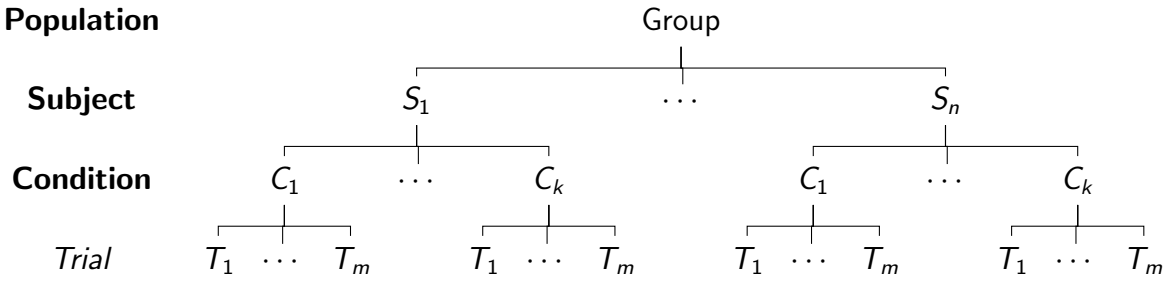
Themes

- Modeling considerations
  - Spatial unit: voxel, surface node or ROI level
  - Input data: effect estimates with/without uncertainty
  - Data reduction: trial- vs condition-level effects
  - BOLD response: presumed vs estimated HDR
  - Handling quantitative variables: linear vs nonlinear
  - Interaction: homogeneity vs heterogeneity
- Model types
  - Conventional: Student's *t*, GLM, AN(C)OVA, LME
  - Adventurous: Bayes, multilevel smoothing splines
- Focus
  - Model vs effects of interest or no interest
  - Estimation (full results) vs inference (dichotomization)

Program list

Spatial Unit	Program	Model
voxel, node, ROI	3dttest++	t-tests, GLM
	3dMEMA	effect + t-stat as input
	3dMVM	GLM, AN(C)OVA
	3dLME	simple LME
	3dLMEr	LME, test-rest reliability
massively univariate	3dMSS	multilevel smoothing splines
	3dICC	intra-class correlation
	3dISC	inter-subject correlation
ROI	RBA	region-based analysis
Bayesian multilevel	MBA	matrix-based analysis

Data hierarchy



Why population-level modeling?

- Ideal but impractical: one model that incorporates everything
- Two-stage methodology
  - Splitting
    - Subject level: time series regression with GLS
    - Population level
  - Good but challenging: subject-level effect estimates with reliability (e.g. std dev)
  - Common: subject-level effect estimates only; ignoring reliability
- Generalizability: part of scientific endeavor
  - Prior assumption: cross-subject variability $\sim \mathcal{N}(0, \sigma^2)$
  - Equally applicable to trials? Aggregation vs cross-trial variability

Perspectives of population-level modeling

- Data structure
  - Categorical variables: factors
  - Quantitative variables
  - Within- or between-subject? Crossed or nested?
- Effects of interest vs no interest
  - Interest: contrasts (A vs B), simple effects (A, B)
  - No interest
    - No-love treatment (nuisance variables): "covariates"
    - Additive effects w/o interactions
    - No mention in publications
- Model structure
  - Student's t, GLM, AN(C)OVA, LME, MSS, BML
- Multiple testing adjustment
  - Voxel-wise vs ROI-based

Some concepts

- Factors: within- vs between-subjects
  - Between-subjects (patient vs control): independence
  - Within-subject (positive vs negative): relatedness (e.g. variance-covariance)
- Factors: fixed- vs random-effect
  - Fixed: constant; effects of interest (e.g., positive vs negative)
  - Random: sample size; exchangeable (e.g., subjects, trials); generalizeability
  - Clear dichotomy: conventional statistics
- Model structure
  - Student's t, GLM, AN(C)OVA, LME, MSS, BML
- Multiple testing adjustment
  - Overfitting: assuming no commonality
  - Voxel-wise vs ROI-based

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Student's t-test

- One-sample: 3dttest++
  - Data at each spatial unit: $y_i,\ i = 1, 2, ..., n$
  - Special GLM with 2 parameters: $y_i \sim \mathcal{N}(m, \sigma^2)$
  - Estimation
    - $\widehat{m} = \frac{1}{n}\sum_{i=1}^{n} y_i,\ \widehat{\sigma} = \frac{1}{n-1}\sum_{i=1}^{n}(y_i - \widehat{m})^2$
    - Uncertainty interval: $(\widehat{m} - 2\widehat{\sigma},\ \widehat{m} + 2\widehat{\sigma})$
  - Inference - imprimatur: $t(n-1)$-statistic; p-value
- Paired: 3dttest++ -paired
  - 1 group with 2 conditions - data at each spatial unit: $(y_{i1}, y_{i2}),\ i = 1, 2, ..., n$
  - Reducing to one-sample: $y_{i1} - y_{i2} \sim \mathcal{N}(m, \sigma^2)$
- Two-sample: extension of one-sample; special univariate GLM
- Handling missing voxel values: -zskip

Univariate GLM

- ≥ 1 groups; ≥ 0 quantitative variables
- AN(C)OVA without within-subject variables
- Data at each spatial unit: $(y_i, x_{i1}, ...)$, $i = 1, 2, ..., n$
- Formulation: $y_i \sim \mathcal{N}(a + b_1 x_{i1} + ..., \sigma^2)$
- Effects of interest: $a, b_1, ...$
- When an explanatory variable x is quantitative
  - Centering: not needed for x effect; crucial for some effects
  - Linearity assumption: too strong?
- Special GLMs
  - Two-sample t-test
  - AN(C)OVA w/o within-subject variables
- programs: 3dttest++, 3dMVM

Multivariate GLM

- AN(C)OVA with ≥ 1 within-subject factors
  - Extension of paired t-test
  - ≥ 1 groups, ≥ 0 quantitative variables (between-, not within-, subject)
- No quantitative within-subject variables
  - Yes, go with LME
- Data at each spatial unit: $\boldsymbol{y}$
- Formulation: $\boldsymbol{Y} \sim \mathcal{N}(\boldsymbol{X}\boldsymbol{\beta}, \boldsymbol{\Sigma})$
- Problematic approach via univariate GLM: popular
- When an explanatory variable x is quantitative
  - Centering: not needed for x effect; crucial for some effects
  - Linearity assumption: too strong?

Multivariate GLM (cont.)

- Special cases: Student's t, univariate GLM
- Omnibus inferences through F-statistic
  - Main effect - overall assessment about the differences among levels of a factor: emotion valences (positive, negative, neutral)
  - Interaction - overall assessment about the relationship between $\geq$2 explanatory variables: group (patients, controls) and emotion (positive, negative, neutral)
- Effect partitioning
  - contrasts: positive vs negative
  - simple effects: positive
- Programs: 3dMVM, 3dLME, 3dLMEr

LME

- ≥ 1 within-subject variables; multivariate GLM: a special case
- Differentiation of fixed and random effects
  - Fixed: population effects (groups, tasks, slopes)
  - Random: lower-level effects (cross-subject, cross-trial, cross-family)
- Data at each spatial unit: $\boldsymbol{y}$
- Hierarchical or multilevel structure
- Complex random effects
  - ≥ 2 levels: cross- and within-subject; cross- and within-family
  - Crossed random-effects structure: subject + trial
- Formulation: $\boldsymbol{Y} \sim \mathcal{N}(\boldsymbol{X}\boldsymbol{\beta} + \boldsymbol{Z}\boldsymbol{b}, \boldsymbol{\Sigma})$
  - Fixed effects $\boldsymbol{\beta}$
  - Random effects $\boldsymbol{b} \sim \mathcal{N}(\boldsymbol{0}, \boldsymbol{R})$: Varying intercept, varying slope

LME (cont.)

- When an explanatory variable x is quantitative
  - Centering: not needed for x effect; crucial for some effects
  - Linearity: too strong?
- Specialities
  - Relatedness among varying effects: within-subject quantitative variables
  - Missing data: missing at random
  - Complex random effects: crossed structure; ICC; ISC
- When an explanatory variable x is quantitative
  - Centering: not needed for x effect; crucial for some effects
  - Linearity: too strong?
- Special cases: paired t-test and within-subject AN(C)OVA
- programs: 3dLME, 3dLMEr
- Gaussianity, point estimate, measurement error and numerical issues.

Accounting for effect uncertainty

- Uncertainty of subject-level effect estimates
  - Largely ignored in the field
  - Impact: mostly (not always) negligible
- Incorporation of uncertainty in response variable
  - Weighting: differentiation based on reliability
  - Similar to meta analysis
  - Program: 3dMEMA
  - Input: effect estimate (β) and t-statistic from each subject
  - Applicability: similar to 3dttest++
  - Missing data at voxel level: -missing_data 0

Handling quantitative predictors

- Quantitative predictors
  - Examples: age, RT, gray-matter volume, ...
  - Types: between-subject, within-subject
  - Longitudinal vs cross-sectional
- Linearity
  - Popular, easy implementation
  - Between-subject predictor: 3dttest++ 3dMEMA, 3dMVM, 3dLME, 3dLMEr
  - Within-subject predictor: 3dLME, 3dLMEr
- Nonlinearity
  - Polynomials: difficulty with order selection and model validation
  - Smoothing splines: adaptive and flexible
  - Program: 3dMSS

Estimating hemodynamic response

- Presumed HDR
  - Convenient, popular
  - Large variations across regions, tasks, subjects, groups
  - Inflexibility, lackluster fitting, compromised detection
- Estimating HDR
  - Subject level: tent, cubic splines
  - Population level: smooth splines
  - Programs: 3dMVM, 3dMSS

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Accounting for cross-trial variability

- Subjects: samples for population
  - Representatives from a hypothetical pool
  - Each subject's effects expressed in the model
  - Generalizability - reason for various models: GLM, AN(C)OVA, LME
- How about trials?
  - Representatives from a hypothetical pool of experimental condition
  - Subject level: one regressor per condition
  - Cross-trial variability: fully ignored!
  - Consequences: loss of generalizability legitimacy; distortion of effect estimates and statistical evidence
- Better approach: modeling trials
  - Subject level: estimate trial effects
  - Population level: accounting for cross-trial effects (e.g., 3dLMEr)

Inter-subject correlation analysis

- Naturalistic scanning
  - Task-related FMRI: too far-fetched from real life experience
  - Movie watching, speech/music listening
- ISC analysis
  - Data structure complexity: n subjects leads to $\frac{1}{2}n(n-1)$ ISC pairs
  - How to disentangle the hierarchical structure? LME
  - Program: 3dISC

$n = 5$ subjects: 10 ISC pairs

	z_{21}	z_{31}	z_{41}	z_{51}	z_{32}	z_{42}	z_{52}	z_{43}	z_{53}	z_{54}
z_{21}	1	ρ	ρ	ρ	ρ	ρ	ρ	0	0	0
z_{31}	ρ	1	ρ	ρ	ρ	0	0	ρ	ρ	0
z_{41}	ρ	ρ	1	ρ	0	ρ	0	ρ	0	ρ
z_{51}	ρ	ρ	ρ	1	0	0	ρ	0	ρ	ρ
z_{32}	ρ	ρ	0	0	1	ρ	ρ	ρ	ρ	0
z_{42}	ρ	0	ρ	0	ρ	1	ρ	ρ	0	ρ
z_{52}	ρ	0	0	ρ	ρ	ρ	1	0	ρ	ρ
z_{43}	0	ρ	ρ	0	ρ	ρ	0	1	ρ	ρ
z_{53}	0	ρ	0	ρ	ρ	0	ρ	ρ	1	ρ
z_{54}	0	0	ρ	ρ	0	ρ	ρ	ρ	ρ	1

Test-retest reliability

- Intra-class correlation (ICC)
  - Same conditions repeated with the same subjects
  - How repeatable or consistent of subjects' BOLD response across repetitions?
  - ICC computation: ANOVA, LME
  - Program: 3dICC
  - Poor ICC: strong effects (e.g., Stroop, Flanker) in behavior measure and FMRI
- Modeling problem with classical ICC
  - Reliability: subject-level metric
  - Not suited for data with multiple trials
  - Cross-trial variability not accounted for
- New modeling framework
  - Subject level: obtain trial-level effects
  - Population level: disentangle trial-level effects
  - LME approach: not ideal (3dLMEr)
  - Bayesian multilevel (BML): TRR

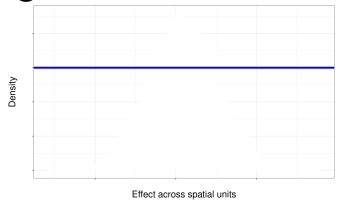
Handling multiplicity

- Massively univariate analysis
  - Treat each spatial unit as an isolated entity: no commonality with peers
  - As many models as spatial units
  - Staple methodology over 30 years in neuroimaging
  - Intuitive and straightforward
- Multiple testing adjustment: two approaches
  - Leverage among neighboring spatial units
  - Cluster-based adjustment
    - 3dttest++ -Clustsim
    - Other programs (e.g., 3dMVM, 3dLME, 3dLMEr): 3dClustSim
  - Permutation-based adjustment: 3dttest++ -ETAC

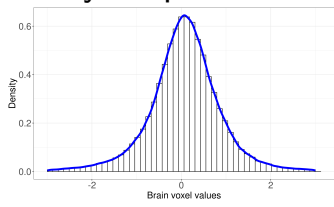
Handling multiplicity (cont.)

- Problems
  - Overfitting
  - Information waste
  - Heavy penalty
  - Dichotomization
  - Discrimination against anatomically small regions
  - Vulnerability to data manipulations

Ignorant information across brain

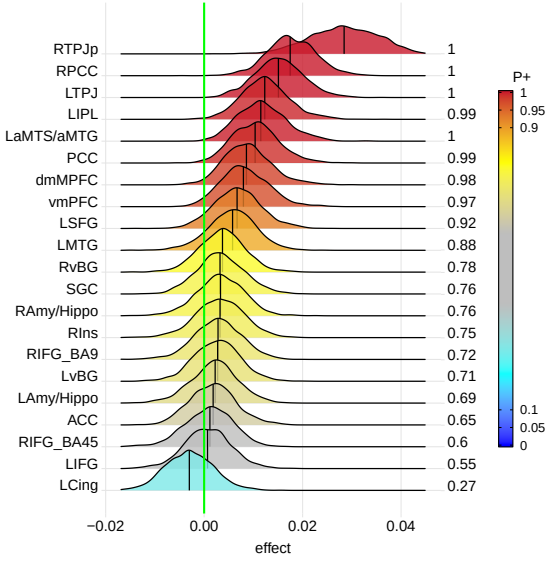


Really no prior knowledge?



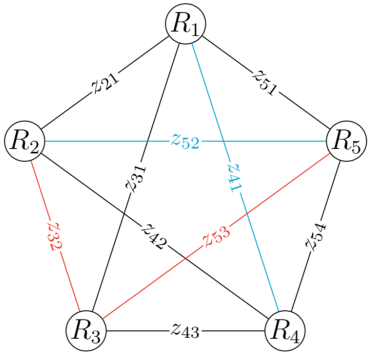
Region-based analysis

- One model integrating all ROIs: Bayesian multilevel model (BML)
  - Multiplicity dissolved
  - Likely high efficiency
  - Transparency: full results
  - Region specificity
  - No dichotomization
  - No discrimination against anatomically small regions
  - Less vulnerability to data manipulations
- Program: RBA



Matrix-based analysis

- Complexity of data structure
  - Conventional: massively univarate analysis + multiplicity
  - Hierarchical structure: BML
  - Multiplicity dissolved
- Program: MBA



$$\boldsymbol{P}^{(5)} = \begin{array}{c} \\ z_{21} \\ z_{31} \\ z_{41} \\ z_{51} \\ z_{32} \\ z_{42} \\ z_{52} \\ z_{43} \\ z_{53} \\ z_{54} \end{array} \begin{array}{c} \begin{array}{cccccccccc} z_{21} & z_{31} & z_{41} & z_{51} & z_{32} & z_{42} & z_{52} & z_{43} & z_{53} & z_{54} \end{array} \\ \begin{pmatrix} 1 & \rho & \rho & \rho & \rho & \rho & \rho & 0 & 0 & 0 \\ \rho & 1 & \rho & \rho & \rho & 0 & 0 & \rho & \rho & 0 \\ \rho & \rho & 1 & \rho & 0 & \rho & 0 & \rho & 0 & \rho \\ \rho & \rho & \rho & 1 & 0 & 0 & \rho & 0 & \rho & \rho \\ \rho & \rho & 0 & 0 & 1 & \rho & \rho & \rho & \rho & 0 \\ \rho & 0 & \rho & 0 & \rho & 1 & \rho & \rho & 0 & \rho \\ \rho & 0 & 0 & \rho & \rho & \rho & 1 & 0 & \rho & \rho \\ 0 & \rho & \rho & 0 & \rho & \rho & 0 & 1 & \rho & \rho \\ 0 & \rho & 0 & \rho & \rho & 0 & \rho & \rho & 1 & \rho \\ 0 & 0 & \rho & \rho & 0 & \rho & \rho & \rho & \rho & 1 \end{pmatrix} \end{array}$$

Matrix-based analysis (cont.)

- BML applied to a matrix dataset