Nonparametric Thresholding Methods
(FWE inference w/ SnPM)

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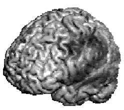


USA SPM Course
April 8, 2005

Overview

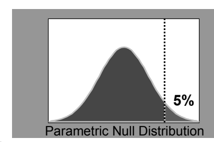
- Multiple Comparisons Problem
  - Which of my 100,000 voxels are “active”?
- SnPM
  - Permutation test to find threshold
  - Control chance of any false positives (FWER)

Nonparametric Inference: Permutation Test

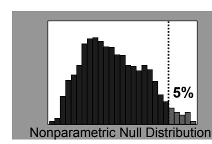
- Assumptions
  - Null Hypothesis Exchangeability
- Method
  - Compute statistic t
  - Resample data (without replacement), compute t^*
  - $\{t^*\}$ permutation distribution of test statistic
  - P-value = $\#\{\ t^* > t\ \}\ /\ \#\{\ t^*\ \}$
- Theory
  - Given data and H_0, each t^* has equal probability
  - Still can assume data randomly drawn from population

Nonparametric Inference

- Parametric methods
  - Assume distribution of statistic under null hypothesis
  - Needed to find P-values, u_α



- Nonparametric methods
  - Use *data* to find distribution of statistic under null hypothesis
  - Any statistic!



Permutation Test Toy Example

- Data from V1 voxel in visual stim. experiment
  A: Active, flashing checkerboard   B: Baseline, fixation
  6 blocks, ABABAB   Just consider block averages...

A	B	A	B	A	B
103.00	90.48	99.93	87.83	99.76	96.06

- Null hypothesis H_o
  - No experimental effect, A & B labels arbitrary
- Statistic
  - Mean difference

Permutation Test Toy Example

- Under H_o
  - Consider all equivalent relabelings

AAABBB	ABABAB	BAAABB	BABBAA
AABABB	ABABBA	BAABAB	BBAAAB
AABBAB	ABBAAB	BAABBA	BBAABA
AABBBA	ABBABA	BABAAB	BBABAA
ABAABB	ABBBAA	BABABA	BBBAAA

Permutation Test
Toy Example

- Under H_o
  - Consider all equivalent relabelings
  - Compute all possible statistic values

AAABBB	4.82	ABABAB	9.45	BAAABB	-1.48	BABBAA	-6.86
AABABB	-3.25	ABABBA	6.97	BAABAB	1.10	BBAAAB	3.15
AABBAB	-0.67	ABBAAB	1.38	BAABBA	-1.38	BBAABA	0.67
AABBBA	-3.15	ABBABA	-1.10	BABAAB	-6.97	BBABAA	3.25
ABAABB	6.86	ABBBAA	1.48	BABABA	-9.45	BBBAAA	-4.82

Permutation Test
Toy Example

- Under H_o
  - Consider all equivalent relabelings
  - Compute all possible statistic values
  - Find 95%ile of permutation distribution

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Permutation Test
Toy Example

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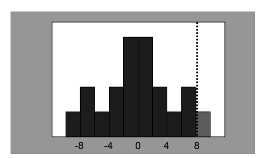


Permutation Test
Strengths

- Requires only assumption of exchangeability
  - Under Ho, distribution unperturbed by permutation
  - Allows us to build permutation distribution
- Subjects are exchangeable
  - Under Ho, each subject’s A/B labels can be flipped
- fMRI scans not exchangeable under Ho
  - Due to temporal autocorrelation

Permutation Test
Limitations

- Computational Intensity
  - Analysis repeated for each relabeling
  - Not so bad on modern hardware
    - No analysis discussed below took more than 3 hours
- Implementation Generality
  - Each experimental design type needs unique code to generate permutations
    - Not so bad for population inference with t-tests

MCP Solutions: Measuring False Positives

- Familywise Error Rate (FWER)
  - Familywise Error
    - Existence of one or more false positives
  - FWER is probability of familywise error
- False Discovery Rate (FDR)
  - R voxels declared active, V falsely so
    - Observed false discovery rate: V/R
  - FDR = E(V/R)

FWER MCP Solutions

- Bonferroni
- Maximum Distribution Methods
  - Random Field Theory
  - Permutation

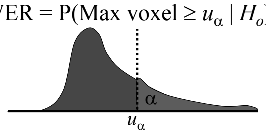
FWER MCP Solutions: Controlling FWER w/ Max

- FWER & distribution of maximum

$$\begin{aligned}\text{FWER} &= \text{P(FWE)} \\ &= \text{P(One or more voxels} \geq u \mid H_o) \\ &= \text{P(Max voxel} \geq u \mid H_o)\end{aligned}$$

- $100(1-\alpha)$%ile of max dist^n controls FWER

$$\text{FWER} = \text{P(Max voxel} \geq u_\alpha \mid H_o) \leq \alpha$$

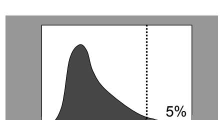


FWER MCP Solutions

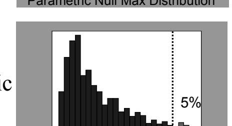
- Bonferroni
- Maximum Distribution Methods
  - Random Field Theory
  - Permutation

Controlling FWER: Permutation Test

- Parametric methods
  - Assume distribution of *max* statistic under null hypothesis
- Nonparametric methods
  - Use *data* to find distribution of *max* statistic under null hypothesis
  - Again, any max statistic!



Parametric Null Max Distribution



Nonparametric Null Max Distribution

Permutation Test & Exchangeability

- Exchangeability is fundamental
  - Def: Distribution of the data unperturbed by permutation
  - Under H_0, exchangeability justifies permuting data
  - Allows us to build permutation distribution
- Subjects are exchangeable
  - Under Ho, each subject's A/B labels can be flipped
- Are fMRI scans exchangeable under Ho?
  - If no signal, can we permute over time?

Permutation Test & Exchangeability

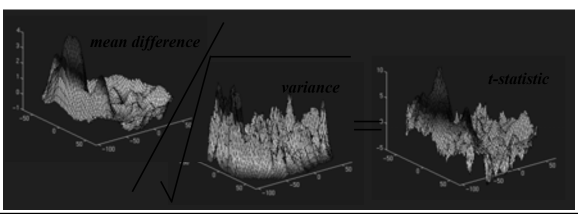
- fMRI scans are not exchangeable
  - Permuting disrupts order, temporal autocorrelation
- *Intra*subject fMRI permutation test
  - Must decorrelate data, model before permuting
  - What is correlation structure?
    - Usually must use parametric model of correlation
  - E.g. Use wavelets to decorrelate
    - Bullmore et al 2001, HBM 12:61-78
- *Inter*subject fMRI permutation test
  - Create difference image for each subject
  - For each permutation, flip sign of some subjects

Permutation Test Other Statistics

- Collect max distribution
  - To find threshold that controls FWER
- Consider smoothed variance *t* statistic
  - To regularize low-df variance estimate

Permutation Test Smoothed Variance *t*

- Collect max distribution
  - To find threshold that controls FWER
- Consider smoothed variance *t* statistic



Permutation Test Smoothed Variance *t*

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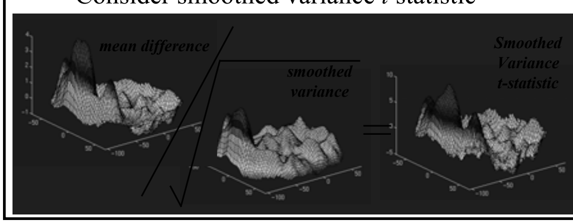
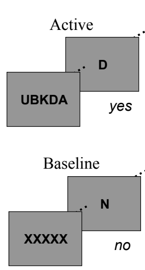


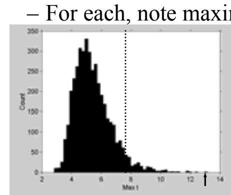
Permutation Test Example

- fMRI Study of Working Memory
  - 12 subjects, block design Marshuetz et al (2000)
  - Item Recognition
    - Active: View five letters, 2s pause, view probe letter, respond
    - Baseline: View XXXXX, 2s pause, view Y or N, respond
- Second Level RFX
  - Difference image, A-B constructed for each subject
  - One sample, smoothed variance *t* test

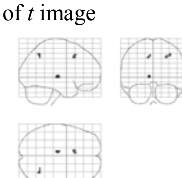


Permutation Test Example

- Permute!
  - 2^{12} = 4,096 ways to flip 12 A/B labels
  - For each, note maximum of *t* image



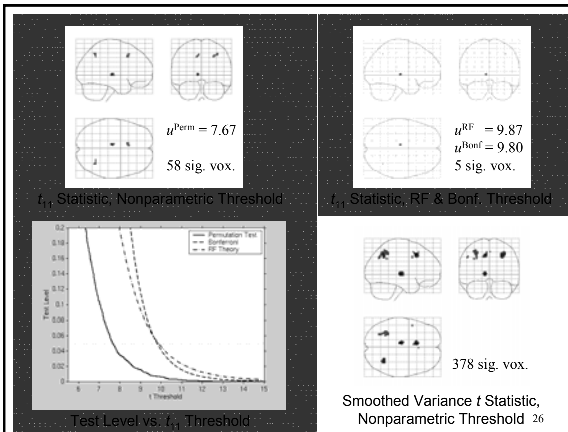
Permutation Distribution Maximum *t*



Maximum Intensity Projection Thresholded *t*

Permutation Test Example

- Compare with Bonferroni
  - $\alpha = 0.05/110{,}776$
- Compare with parametric RFT
  - 110,776 $2\times2\times2$mm voxels
  - $5.1\times5.8\times6.9$mm FWHM smoothness
  - 462.9 RESELs



Does this Generalize? RFT vs Bonf. vs Perm.

		t Threshold (0.05 Corrected)		
	df	RF	Bonf	Perm
Verbal Fluency	4	4701.32	42.59	10.14
Location Switching	9	11.17	9.07	5.83
Task Switching	9	10.79	10.35	5.10
Faces: Main Effect	11	10.43	9.07	7.92
Faces: Interaction	11	10.70	9.07	8.26
Item Recognition	11	9.87	9.80	7.67
Visual Motion	11	11.07	8.92	8.40
Emotional Pictures	12	8.48	8.41	7.15
Pain: Warning	22	5.93	6.05	4.99
Pain: Anticipation	22	5.87	6.05	5.05

RFT vs Bonf. vs Perm.

		No. Significant Voxels (0.05 Corrected)			
			t		SmVar t
	df	RF	Bonf	Perm	Perm
Verbal Fluency	4	0	0	0	0
Location Switching	9	0	0	158	354
Task Switching	9	4	6	2241	3447
Faces: Main Effect	11	127	371	917	4088
Faces: Interaction	11	0	0	0	0
Item Recognition	11	5	5	58	378
Visual Motion	11	626	1260	1480	4064
Emotional Pictures	12	0	0	0	7
Pain: Warning	22	127	116	221	347
Pain: Anticipation	22	74	55	182	402

Conclusions

- t random field results conservative for
  - Low df & smoothness
  - 9 df & ≤12 voxel FWHM; 19 df & < 10 voxel FWHM
    (based on Monte Carlo simulations, not shown)
- Bonferroni not so bad for low smoothness
- Nonparametric methods perform well overall

Monte Carlo Evaluations

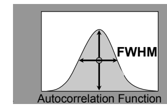
- What's going wrong?
  - Normality assumptions?
  - Smoothness assumptions?
- Use Monte Carlo Simulations
  - Normality strictly true
  - Compare over range of smoothness, df
- Previous work
  - Gaussian (Z) image results well-validated
  - t image results hardly validated at all!

Monte Carlo Evaluations Challenges

- Accurately simulating *t* images
  - Cannot directly simulate smooth *t* images
  - Need to simulate ν smooth Gaussian images
    - (ν = degrees of freedom)
- Accounting for all sources of variability
  - Most M.C. evaluations use known smoothness
  - Smoothness not known
  - We estimated it residual images

Monte Carlo Evaluations

- Simulated One Sample T test
  - 32x32x32 Images (32767 voxels)
  - Smoothness: 0, 1.5, 3, 6,12 FWHM
  - Degrees of Freedom: 9, 19, 29
  - Realizations: 3000

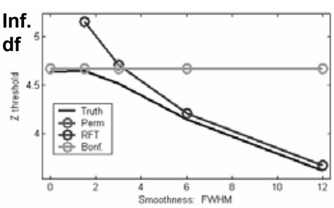


- Permutation
  - 100 relabelings
  - Threshold: 95%ile of permutation dist^n of maximum
- Random Field
  - Threshold: $\{ u : E(\chi_u \mid H_o) = 0.05 \}$
- Also Gaussian

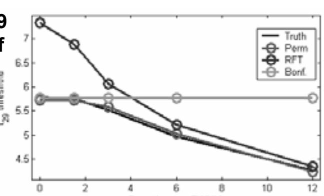
Familywise Error Thresholds

- RFT valid but conservative
- Gaussian not so bad (FWHM >3)
- t_{29} somewhat worse

Inf. df



29 df



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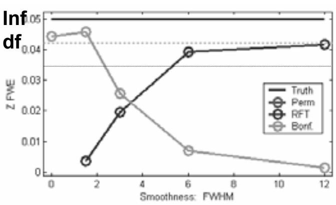
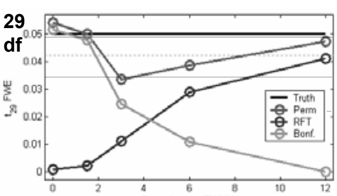
Familywise Rejection Rates

- Need > 6 voxel FWHM

Inf df



29 df



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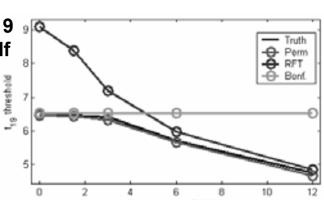
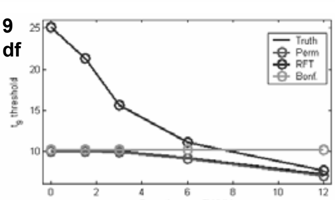
Familywise Error Thresholds

- RF & Perm adapt to smoothness
- Perm & Truth close
- Bonferroni close to truth for low smoothness

19 df



9 df



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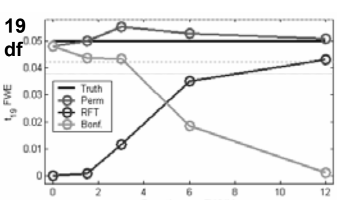
Familywise Rejection Rates

- Bonf good on low df, smoothness
- Bonf bad for high smoothness
- RF only good for high df, high smoothness
- Perm exact

19 df



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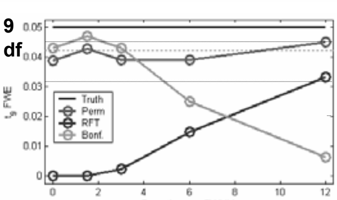

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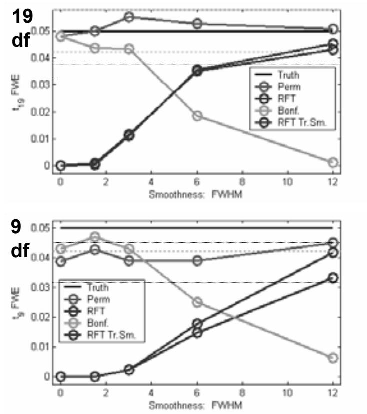
Familywise Rejection Rates

- Smoothness estimation is not (sole) problem

19 df

9 df



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Performance Summary

- Bonferroni
  - Not adaptive to smoothness
  - Not so conservative for low smoothness
- Random Field
  - Adaptive
  - Conservative for low smoothness & df
- Permutation
  - Adaptive (Exact)

Understanding Performance Differences

- RFT Troubles
  - Multivariate Normality assumption
    - True by simulation
  - Smoothness estimation
    - Not much impact
  - Smoothness
    - You need lots, more at low df
  - High threshold assumption
    - Doesn't improve for α_0 less than 0.05 (not shown)

HighThr

Conclusions

- *t* random field results conservative for
  - Low df & smoothness
  - 9 df & ≤12 voxel FWHM; 19 df & < 10 voxel FWHM
- Bonferroni surprisingly satisfactory for low smoothness
- Nonparametric methods perform well overall
- More data and simulations needed
  - Need guidelines as to when RF is useful
  - Better understand what assumption/approximation fails

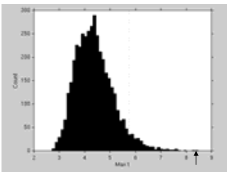
References

- TE Nichols and AP Holmes.
  Nonparametric Permutation Tests for Functional Neuroimaging: A Primer with Examples.
  Human Brain Mapping, 15:1-25, 2002.
- http://www.sph.umich.edu/~nichols

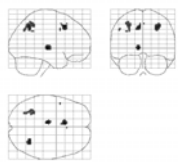
Data ThrRslt MC ThrRslt MC P Rslt EstSmCf

Permutation Test Example

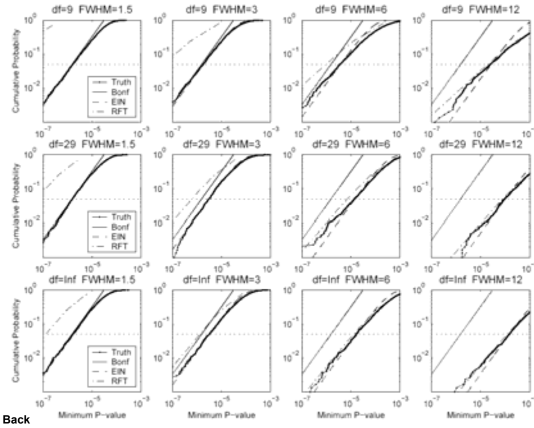
- Permute!
  - 2^{12} = 4,096 ways to flip A/B labels
  - For each, note max of smoothed variance t image



Permutation Distribution
Max Smoothed Variance t



Maximum Intensity Projection
Threshold Sm. Var. t



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