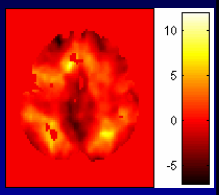
Last week

- Single subject GLM Demo
- Multi-subject GLM

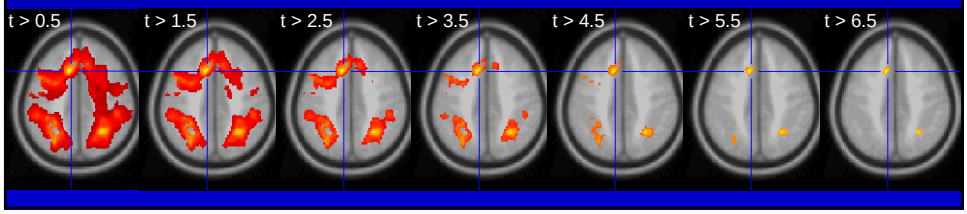
This week

- Multi-subject GLM example
- Thresholding
- Modeling BOLD
  - HRF…deconvolution
  - Derivative boost
  - Balloon model

Multiple Comparisons Problem



- Which of 100,000 voxels are sig.?
  - α=0.05 $\Rightarrow$ 5,000 false positive voxels
- Which of (random number, say) 100 clusters significant?
  - α=0.05 $\Rightarrow$ 5 false positives clusters



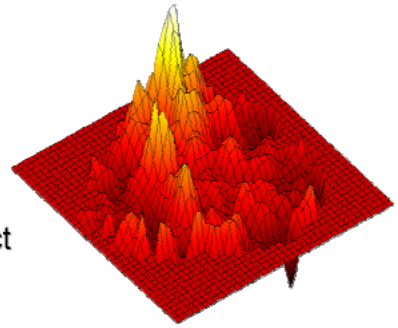
Multiple Comparisons

Standard correction procedure

- Bonferroni correction: $p_{cor} = p_{uncor}/n$
- only appropriate for independent tests
- loss of sensitivity for correlated data sets

Spatial correlation in neuroimaging data

- arbitrary voxel size (< than anatomical structures)
- spatial extent of BOLD effect
- spatial smoothing



Multiple Comparisons

Alternative correction procedures

Theory of Gaussian Random Fields (GRF)

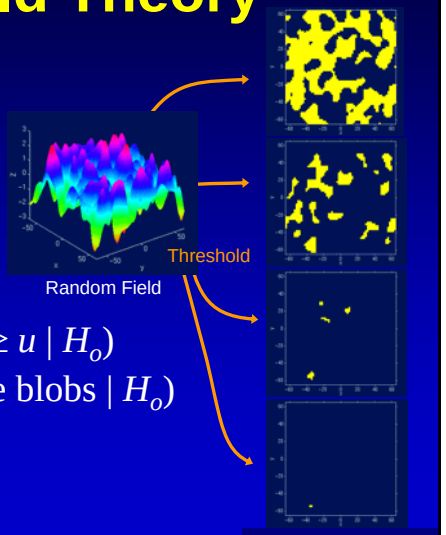
- alternative method to control family wise error rate (FWER)
- estimation of spatial smoothness: resels - independent observations
- Euler characteristic: # of clusters above a given threshold => determine threshold yielding a certain expected EC relative to # of resels
- p_{cor} adaptive to spatial smoothness
- assumes residuals to be multivariate normal
- higher sensitivity than Bonferroni (exception: data sets with extremely low smoothness)

FWER MCP Solutions: Random Field Theory

- Euler Characteristic χ_u
  - Topological Measure
    - #blobs - #holes
  - At high thresholds, just counts blobs
  - FWER = P(Max voxel $\geq u \mid H_o$)
    - = P(One or more blobs $\mid H_o$)
    - $\approx$ P($\chi_u \geq 1 \mid H_o$)
    - $\approx$ E($\chi_u \mid H_o$)

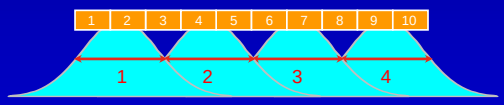
No holes

Never more than 1 blob



Random Field Theory Smoothness Parameterization

- RESELS
  - Resolution Elements
  - 1 RESEL = $FWHM_x \times FWHM_y \times FWHM_z$
  - RESEL Count R
    - $R = \lambda(\Omega) \sqrt{|\Lambda|} = (4\log 2)^{3/2} \lambda(\Omega) \; / \; (FWHM_x \times FWHM_y \times FWHM_z)$
    - Volume of search region in units of smoothness
    - Eg: 10 voxels, 2.5 FWHM 4 RESELS



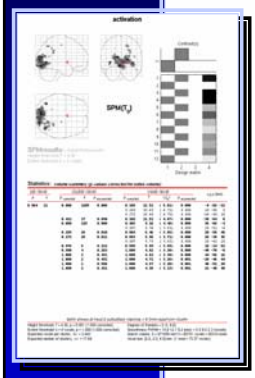
- Beware RESEL misinterpretation
  - RESEL *are not* "number of independent 'things' in the image"
    - See Nichols & Hayasaka, 2003, Stat. Meth. in Med. Res.

Random Field Intuition

- Corrected P-value for voxel value t

$$P^c = \mathrm{P}(\max T > t)$$
$$\approx \mathrm{E}(\chi_t)$$
$$\approx \lambda(\Omega)\,|\Lambda|^{1/2}\,t^2 \exp(-t^2/2)$$

- Statistic value t increases
  - P^c decreases (but only for large t)
- Search volume increases
  - P^c increases (more severe MCP)
- Roughness increases (Smoothness decreases)
  - P^c increases (more severe MCP)



Statistics: *volume summary (p-values corrected for entire volume)*

set-level		cluster-level			voxel-level				x,y,z (mm)
p	c	$p_{corrected}$	k	$p_{uncorrected}$	$p_{corrected}$	T	($Z_=$)	$p_{uncorrected}$	
0.964	**11**	**0.000**	**1285**	**0.000**	**0.109**	**12.51**	**(5.01)**	**0.000**	**-8 -82 -12**
					0.269	10.43	(4.71)	0.000	20 -86 8
					0.272	10.40	(4.70)	0.000	-14 -80 16
		0.411	**17**	**0.030**	**0.168**	**11.51**	**(4.87)**	**0.000**	**-38 -64 0**
		0.000	**125**	**0.000**	**0.465**	**9.16**	**(4.48)**	**0.000**	**36 -66 -4**
					0.997	5.74	(3.63)	0.000	28 -52 -4
		0.155	**26**	**0.010**	**0.969**	**6.46**	**(3.85)**	**0.000**	**20 -58 48**
		0.173	**25**	**0.011**	**0.993**	**5.98**	**(3.71)**	**0.000**	**26 -38 36**
					0.997	5.73	(3.63)	0.000	28 -42 28
		0.976	**5**	**0.212**	**0.999**	**5.59**	**(3.59)**	**0.000**	**18 -14 52**
		0.990	**4**	**0.263**	**1.000**	**4.82**	**(3.30)**	**0.000**	**-40 -70 -8**
		1.000	**2**	**0.431**	**1.000**	**4.81**	**(3.30)**	**0.000**	**44 -56 16**
		1.000	**2**	**0.431**	**1.000**	**4.71**	**(3.26)**	**0.001**	**-20 -46 44**
		1.000	**1**	**0.588**	**1.000**	**4.57**	**(3.20)**	**0.001**	**40 -52 20**
		1.000	**2**	**0.431**	**1.000**	**4.38**	**(3.13)**	**0.001**	**22 -48 40**

table shows at most 3 subsidiary maxima > 8.0mm apart per cluster

Height threshold: T = 4.30, p = 0.001 (1.000 corrected)
Extent threshold: k = 0 voxels, p = 1.000 (1.000 corrected)
Expected voxels per cluster, <k> = 3.443
Expected number of clusters, <c> = 17.64

Degrees of freedom = [1.0, 9.0]
Smoothness FWHM = 10.9 12.1 9.2 {mm} = 5.5 6.0 2.3 {voxels}
Search volume: S = 971856 mm^3 = 60741 voxels = 803.8 resels
Voxel size: [2.0, 2.0, 4.0] mm (1 resel = 75.57 voxels)

Multiple Comparisons

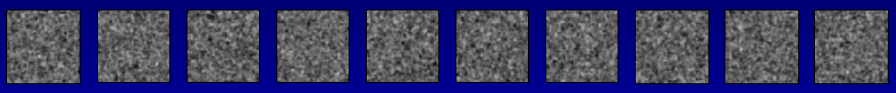
Alternative correction procedures

False Discovery Rate (FDR)

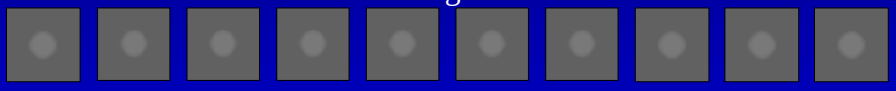
- controls expected # of false positives among all positive results (Benjamini & Hochberg, *JRSS-B* (1995) 57:289-300)
- threshold adaptive to overall effect size

False Discovery Rate Illustration:

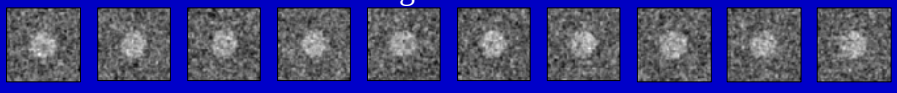
Noise



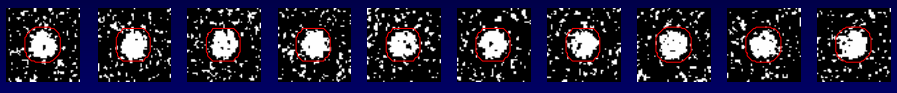
Signal



Signal+Noise



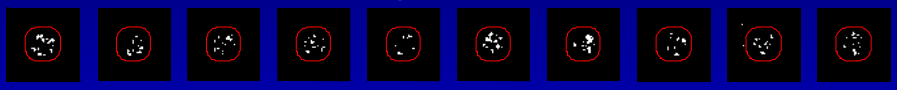
Control of Per Comparison Rate at 10%



11.3% 11.3% 12.5% 10.8% 11.5% 10.0% 10.7% 11.2% 10.2% 9.5%

Percentage of Null Pixels that are False Positives

Control of Familywise Error Rate at 10%



FWE

Occurrence of Familywise Error

Control of False Discovery Rate at 10%

6.7% 10.4% 14.9% 9.3% 16.2% 13.8% 14.0% 10.5% 12.2% 8.7%

Percentage of Activated Pixels that are False Positives

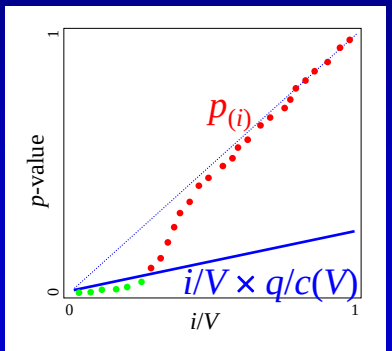
Benjamini & Hochberg Procedure

- Select desired limit q on FDR
- Order p-values, $p_{(1)} \leq p_{(2)} \leq \ \ldots \leq p_{(V)}$
- Let r be largest i such that

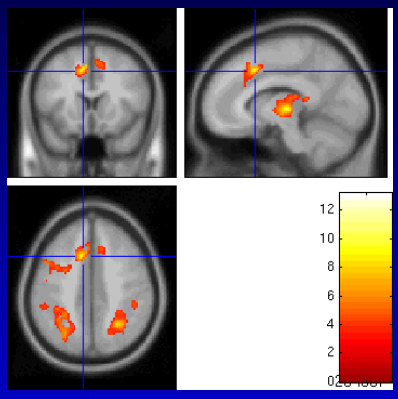
$$p_{(i)} \leq \ i/V \times q/c(V)$$

- Reject all hypotheses corresponding to $p_{(1)}, \ \ldots \ , p_{(r)}$.

JRSS-B (1995) 57:289-300



Real Data: FDR Example



FDR Threshold = 3.83
3,073 voxels
FWER Thresh. = 9.87
7 voxels

Conclusions

- Must account for multiplicity
  - Otherwise have a fishing expedition
- Bonferroni
  - Most specific, least sensitive, assumes independent observations
- FWER
  - Very specific, not very sensitive
- FDR
  - Less specific, more sensitive