Multiple testing

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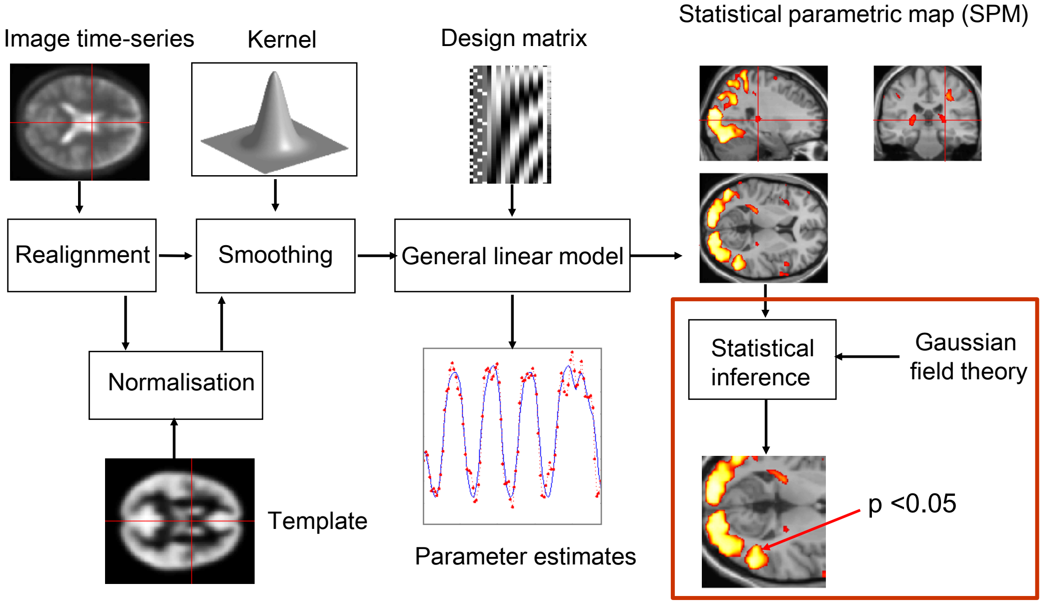
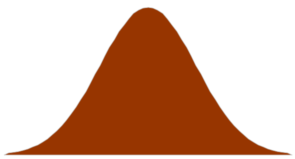
With many thanks for slides & images to:
FIL Methods group

Overview of SPM – Random field theory



Error at a single voxel



t

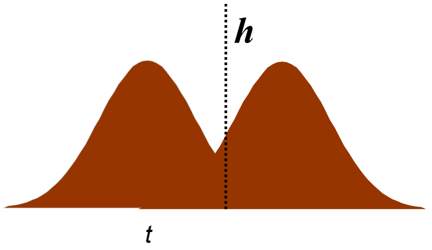
$$t = \frac{\textit{contrast}\text{ of estimated parameters}}{\sqrt{\text{variance estimate}}}$$

Error at a single voxel

t

$$t = \frac{\textit{contrast}\text{ of estimated parameters}}{\sqrt{\text{variance estimate}}}$$

Error at a single voxel

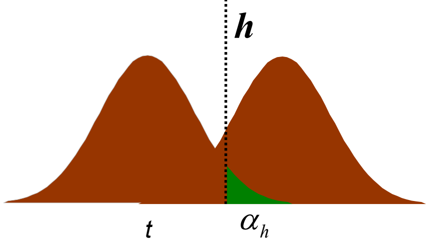


Decision:

H_0 , H_1: zero/non-zero activation

$$t = \frac{\textit{contrast} \text{ of estimated parameters}}{\sqrt{\text{variance estimate}}}$$

Error at a single voxel



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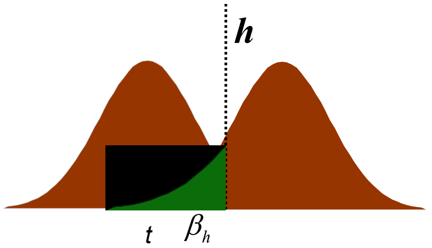
Error at a single voxel



Decision:
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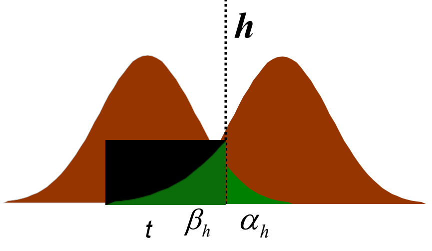
Error at a single voxel



Decision:
H_0 , H_1: zero/non-zero activation

Decision rule (threshold) *h*,
determines related error rates α_h , β_h

Convention: Penalize complexity
Choose *h* to give acceptable α_h under H_0

$$t = \frac{\textbf{\textit{contrast} of estimated parameters}}{\sqrt{\textbf{variance estimate}}}$$

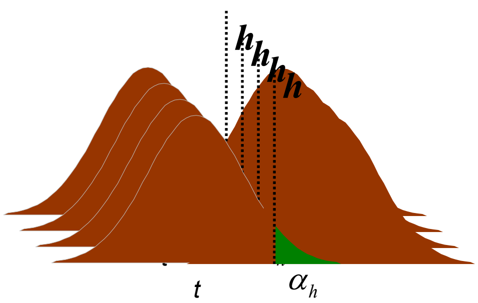
Types of error

		Reality	
		H_0	H_1
Decision	H_1	**False positive (FP)** α_h	**True positive (TP)**
	H_0	**True negative (TN)**	**False negative (FN)** β_h

specificity: 1-α_h
= TN / (TN + FP)
= proportion of actual negatives which are correctly identified

sensitivity (power): 1-β_h
= TP / (TP + FN)
= proportion of actual positives which are correctly identified

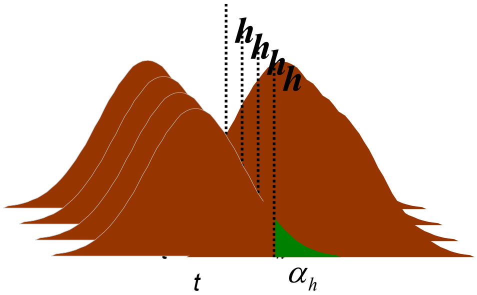
Multiple tests



What is the problem?

$$t = \frac{\textit{contrast}\text{ of estimated parameters}}{\sqrt{\text{variance estimate}}}$$

Multiple tests



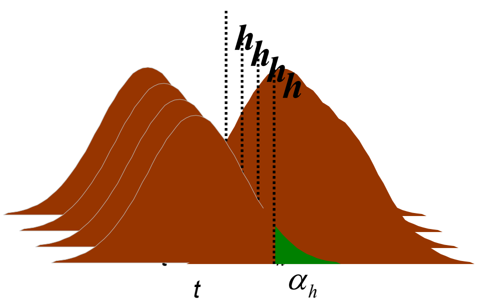
$$t = \frac{\textbf{\textit{contrast}}\textbf{ of estimated parameters}}{\sqrt{\textbf{variance estimate}}}$$

Penalize each independent opportunity for error.

$$p(\ 1\ or\ more\ FP\ ) \ = FWER_h$$

$$E(\ \frac{FP}{All\ positives}\ ) \ = FDR$$

Multiple tests



$$t = \frac{\textbf{\textit{contrast}}\textbf{ of estimated parameters}}{\sqrt{\textbf{variance estimate}}}$$

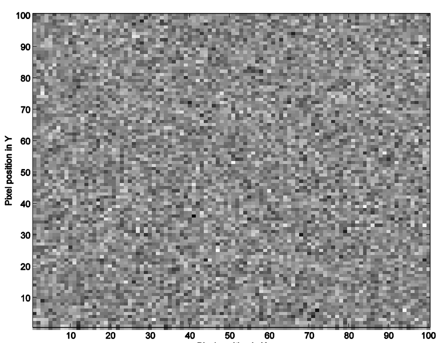
Bonferonni

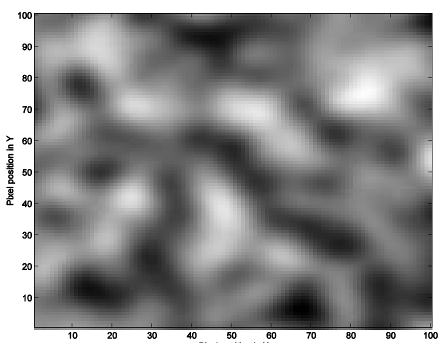
$$FWER_h \le N\alpha_h$$
$$FWER_h / N \le \alpha_h$$

Convention: Choose *h* to limit $FWER_h$
assuming family-wise H_0

Issues

1. Voxels or regions
2. Bonferroni too harsh (insensitive)
   - Unnecessary penalty for sampling resolution (#voxels/volume)
   - Unnecessary penalty for independence





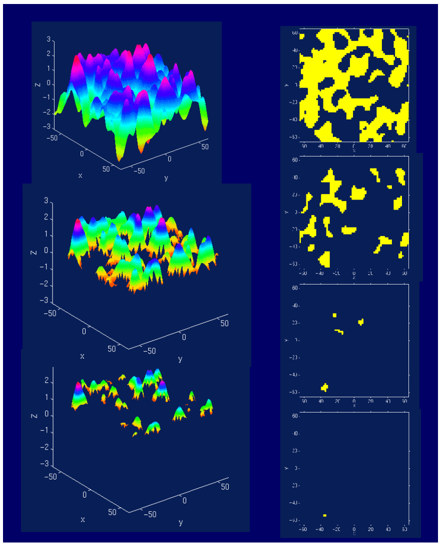
- intrinsic smoothness
  - MRI signals are aquired in k-space (Fourier space); after projection on anatomical space, signals have continuous support
  - diffusion of vasodilatory molecules has extended spatial support
- extrinsic smoothness
  - resampling during preprocessing
  - matched filter theorem
    → deliberate additional smoothing to increase SNR
  - Robustness to between-subject anatomical differences

Acknowledge/estimate dependence
Detect effects in smooth landscape, not voxels

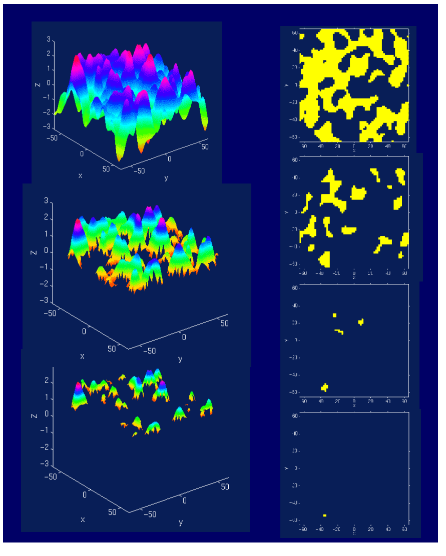
1. Apply high threshold: identify improbably high peaks

2. Apply lower threshold: identify improbably broad peaks

3. Total number of regions?

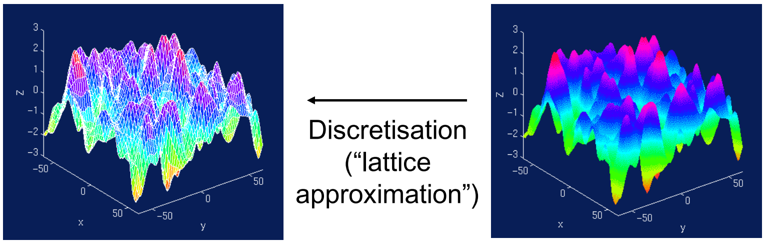


Null distribution?
1. Simulate null experiments
2. Model null experiments



Use continuous random field theory

- image ≈ discretised continuous random field



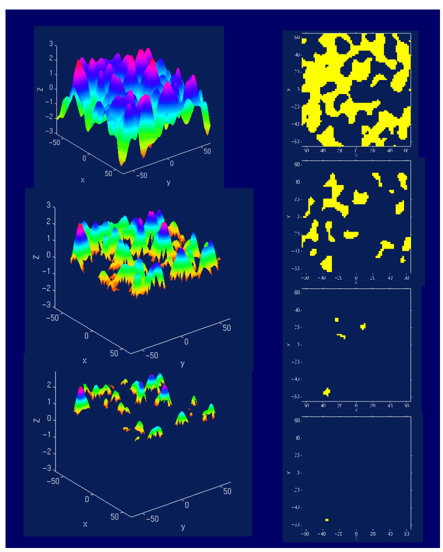
Smoothness quantified: resolution elements ('resels')

- similar, but not identical to # independent observations
- computed from spatial derivatives of the residuals

Euler characteristic

– threshold an image at high h
blobs = N_h

FWER ≈ E [N_h]
= p (blob)



Unified Formula

- General form for expected Euler characteristic
  - χ^2, F, & t fields

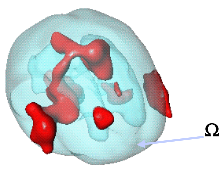
$$E[N_h(\Omega)] = \sum_d R_d(\Omega)\, \rho_d(h)$$

Small volumes: Anatomical atlas, 'functional localisers', orthogonal contrasts, volume around previously reported coordinates…

$R_d(\Omega)$: d-dimensional Minkowski functional of Ω

– function of dimension, space Ω and smoothness:

$R_0(\Omega) = N(\Omega)$ Euler characteristic of
$R_1(\Omega)$ = resel diameter
$R_2(\Omega)$ = resel surface area
$R_3(\Omega)$ = resel volume



$\rho_d(\Omega)$: d-dimensional EC density of $Z(\underline{x})$

– function of dimension and threshold, specific for RF type:

E.g. Gaussian RF:

$$\rho_0(h) = 1 - \Phi(h)$$
$$\rho_1(h) = (4\ln 2)^{1/2} \exp(-h^2/2) / (2\pi)$$
$$\rho_2(h) = (4\ln 2) \exp(-h^2/2) / (2\pi)^{3/2}$$
$$\rho_3(h) = (4\ln 2)^{3/2} (h^2 - 1) \exp(-h^2/2) / (2\pi)^2$$
$$\rho_4(h) = (4\ln 2)^2 (h^3 - 3h) \exp(-h^2/2) / (2\pi)^{5/2}$$

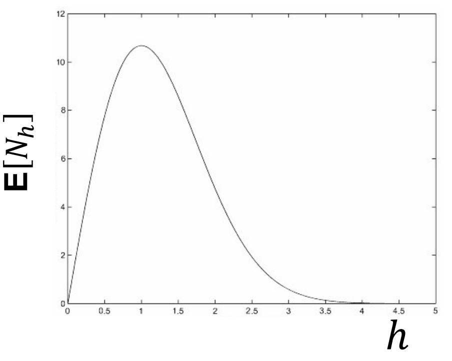
Euler characteristic (EC) for 2D images

$$E[N_h] = R(4\log 2)(2\pi)^{-3/2}\, h \exp(-0.5h^2)$$

R = number of resels
h = threshold

Set h such that $E[N_h] = 0.05$

Example: For 100 resels, $E[N_h]$ = 0.049 for a Z threshold of 3.8. That is, the probability of getting one or more blobs where Z is greater than 3.8, is 0.049.



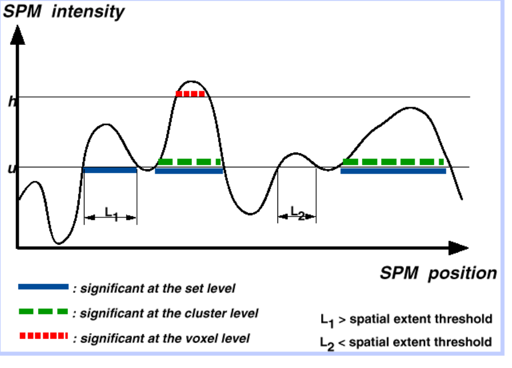
Spatial extent: similar

Voxel, cluster and set level tests

e

u

h



Statistics: *p-values adjusted for search volume*

set-level p	set-level c	cluster-level $p_{FWE-corr}$	cluster-level $q_{FDR-corr}$	cluster-level k_E	cluster-level p_{uncorr}	peak-level $p_{FWE-corr}$	peak-level $q_{FDR-corr}$	peak-level T	peak-level $(Z_{\equiv})$	peak-level p_{uncorr}	mm mm mm
0.000	16	0.000	0.000	138	0.000	0.000	0.000	11.04	7.64	0.000	-34 -70 -28
						0.000	0.009	7.31	5.90	0.000	-44 -74 -24
		0.000	0.000	452	0.000	0.000	0.000	9.82	7.14	0.000	6 16 40
		0.000	0.000	300	0.000	0.000	0.000	9.14	6.84	0.000	44 16 0
						0.041	0.833	5.29	4.64	0.000	38 12 16
		0.000	0.000	173	0.000	0.000	0.009	7.39	5.95	0.000	44 -58 -20
						0.000	0.009	7.35	5.93	0.000	52 -58 -20
						0.002	0.087	6.42	5.38	0.000	50 -66 -24
		0.000	0.000	112	0.000	0.000	0.025	6.93	5.69	0.000	-2 -66 -24
						0.012	0.418	5.73	4.94	0.000	4 -78 -24
						0.014	0.472	5.65	4.89	0.000	2 -86 -28
		0.013	0.374	3	0.257	0.010	0.406	5.77	4.97	0.000	-52 20 4
		0.000	0.019	20	0.008	0.011	0.406	5.76	4.96	0.000	10 -10 8
		0.008	0.263	5	0.148	0.016	0.472	5.63	4.87	0.000	-8 -16 12
		0.000	0.012	24	0.004	0.016	0.472	5.61	4.86	0.000	44 4 28
						0.035	0.736	5.34	4.68	0.000	46 6 20
		0.006	0.231	6	0.116	0.018	0.472	5.59	4.84	0.000	-6 -48 -16
		0.026	0.520	1	0.520	0.021	0.538	5.52	4.80	0.000	-6 -54 -16
		0.026	0.520	1	0.520	0.030	0.713	5.40	4.72	0.000	6 -84 -28

table shows 3 local maxima more than 8.0mm apart

Height threshold: T = 5.21, p = 0.000 (0.050)
Extent threshold: k = 0 voxels, p = 1.000 (0.050)
Expected voxels per cluster, <k> = 2.519
Expected number of clusters, <c> = 0.05
FWEp: 5.213, FDRp: 6.702, FWEc: 1, FDRc: 20

Degrees of freedom = [1.0, 45.0]
FWHM = 9.8 10.6 15.6 mm mm mm; 4.9 5.3 3.9 {voxels}
Volume: 880432 = 55027 voxels = 472.2 resels
Voxel size: 2.0 2.0 4.0 mm mm mm; (resel = 102.26 voxels)
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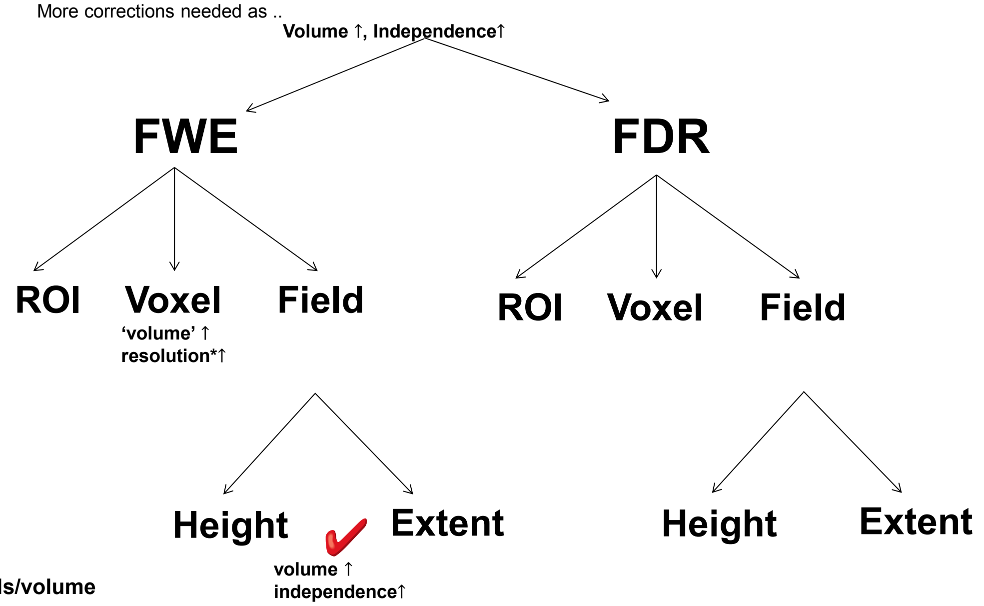
Detect an effect of *unknown* extent & location

There is a multiple testing problem ('voxel' or 'blob' perspective).
More corrections needed as ..



*voxels/volume

Further reading

- Friston KJ, Frith CD, Liddle PF, Frackowiak RS. Comparing functional (PET) images: the assessment of significant change. J Cereb Blood Flow Metab. 1991 Jul;11(4):690-9.
- Genovese CR, Lazar NA, Nichols T. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. Neuroimage. 2002 Apr;15(4):870-8.
- Worsley KJ Marrett S Neelin P Vandal AC Friston KJ Evans AC. A unified statistical approach for determining significant signals in images of cerebral activation. Human Brain Mapping 1996;4:58-73.