

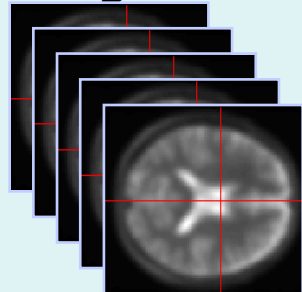
NeuroImaging Data Processing

aka. Statistical Parametric Mapping short course

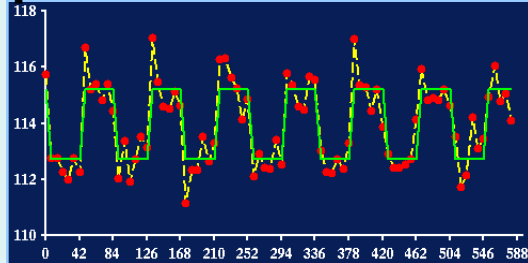
Course 4:

Multiple comparison problem
& levels of inference

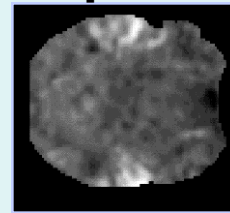
image data



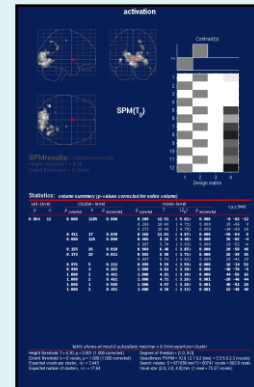
parameter estimates



Statistical
Parametric
Map



corrected p -values



realignment &
motion
correction

General Linear Model

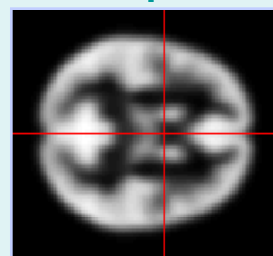
- model fitting
- statistic image

correction for multiple
comparisons

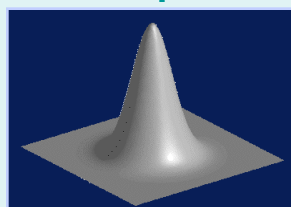
normalisation

smoothing

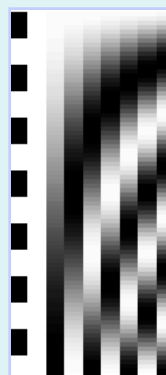
Random effect analysis



anatomical
reference



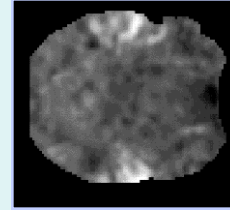
kernel



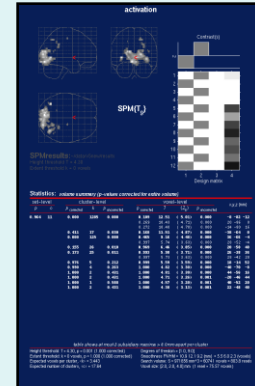
design
matrix

Dynamic causal
modelling,
Functional & effective
connectivity, PPI, ...

Statistical Parametric Map



corrected p -values

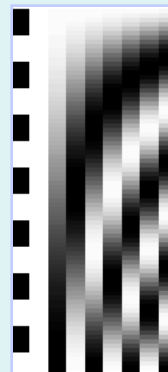


General Linear Model

- model fitting
- statistic image

correction for multiple comparisons

Random effect analysis



design matrix

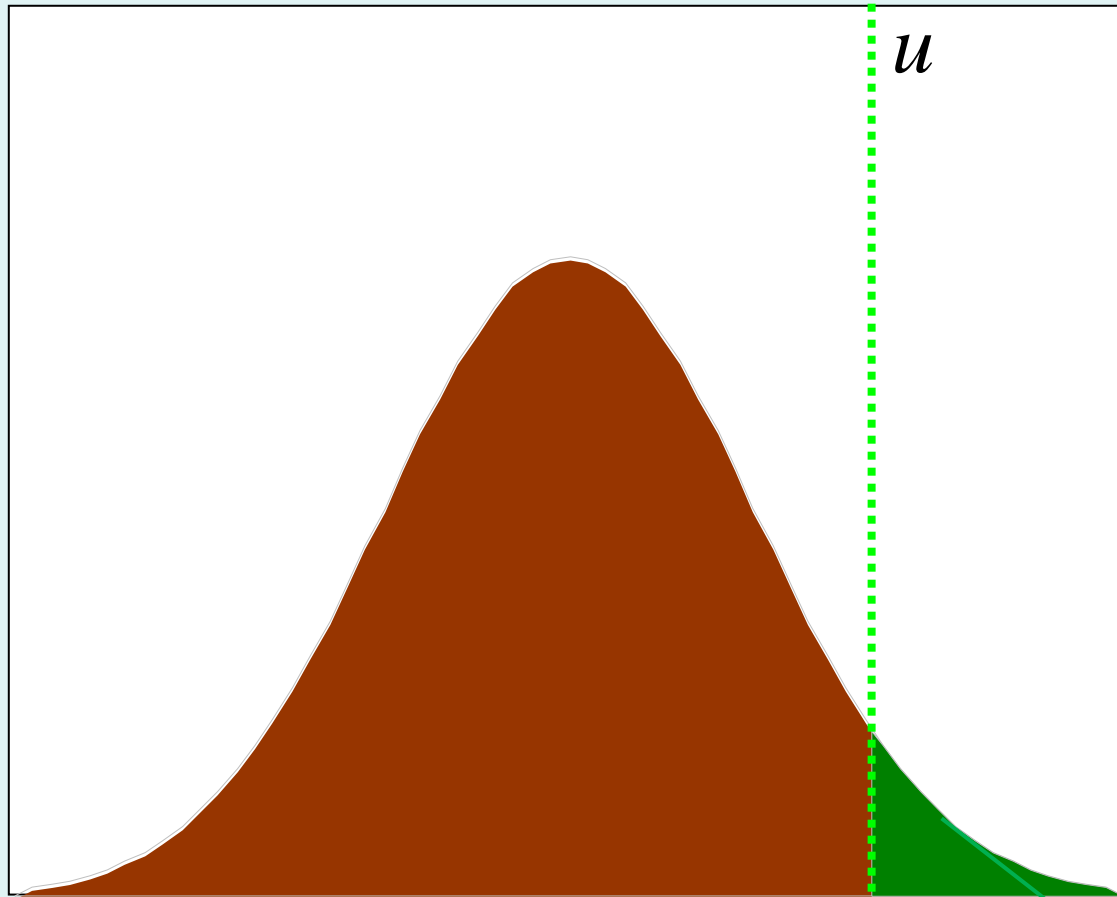
Content

- **Introduction**
- **Family-wise error rate (FWER)**
- **False discovery rate (FDR)**
- **Levels of inference in SPM**
- **Non-parametric permutation test**
- **Conclusion**

Content

- **Introduction**
 - **Single voxel inference**
 - **Multiple comparison problem**
- **Family-wise error rate (FWER)**
- **False discovery rate (FDR)**
- **Levels of inference in SPM**
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Single voxel inference



Null Hypothesis H_0 :
zero activation

Decision rule (*threshold*) u :
determines false positive
rate α

\Rightarrow Choose u to give
acceptable α under H_0

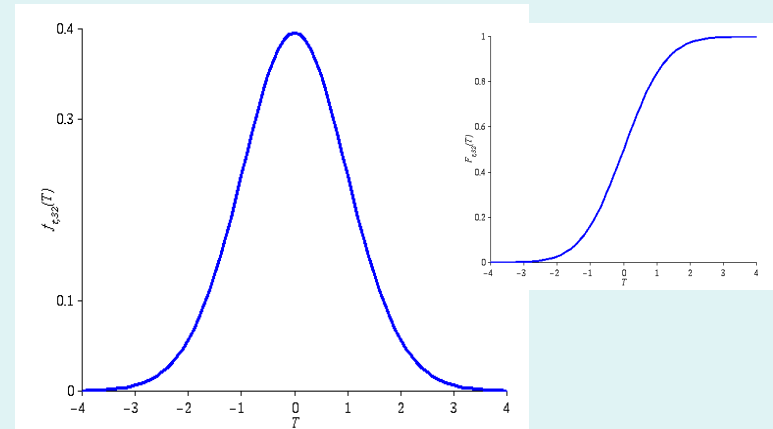
Null distribution of test statistic T

$$\alpha = p(t > u | H_0)$$

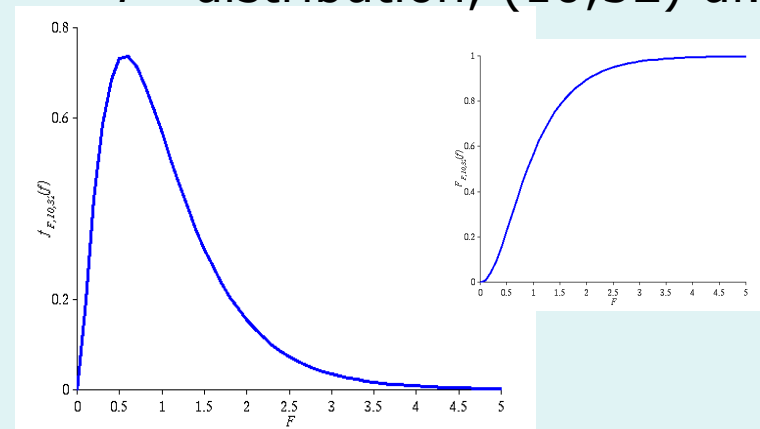
Classical hypothesis testing...

- Null hypothesis H
 - test statistic
 - null distributions
- Hypothesis test
 - control Type I error
 - incorrectly reject H
 - test level α
 - $\Pr(\text{"reject" } H \mid H) \leq \alpha$
- p –value
 - min α at which H rejected
 - $\Pr(T \geq t \mid H)$
 - characterising *"surprise"*

t –distribution, 32 df.



F –distribution, (10,32) df.



Sensitivity & specificity

		ACTION	
		Don't reject	Reject
TRUTH	H_0 true	True Negative	False Positive
	H_0 false	False Negative	True Positive

Sensitivity = $TP / (TP + FN) = \beta$

Specificity = $TN / (TN + FP) = 1 - \alpha$

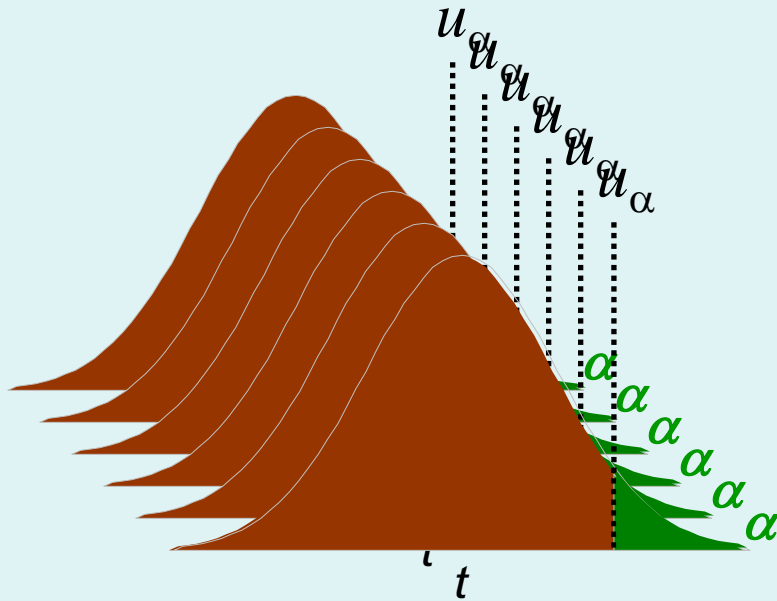
FP = Type I error or 'error'

FN = Type II error

α = p-value/FP rate/error rate/significance level

β = power

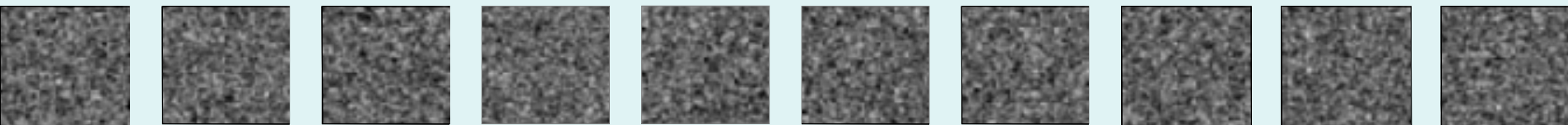
Multiple tests



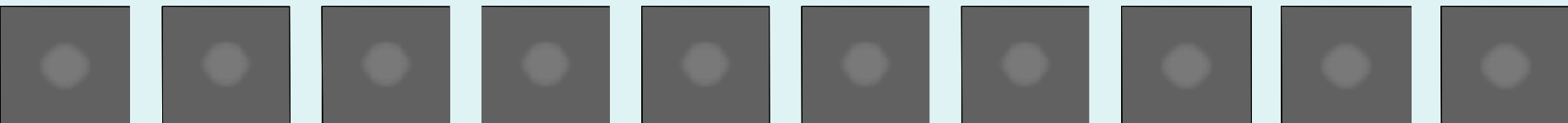
If we have 100000 voxels, $\alpha=0.05$
 \Rightarrow **5000 false positive voxels.**

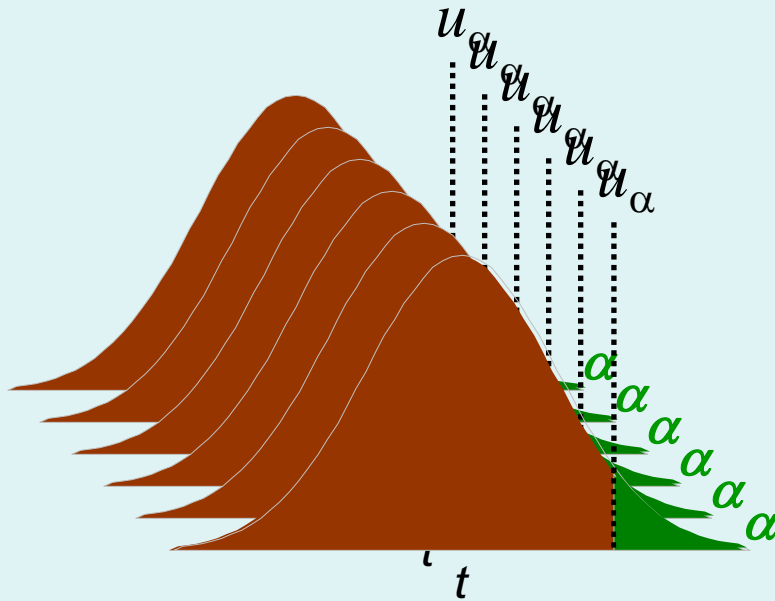
This is clearly undesirable!
Need to define a *null hypothesis* for a collection of tests.

Noise



Signal

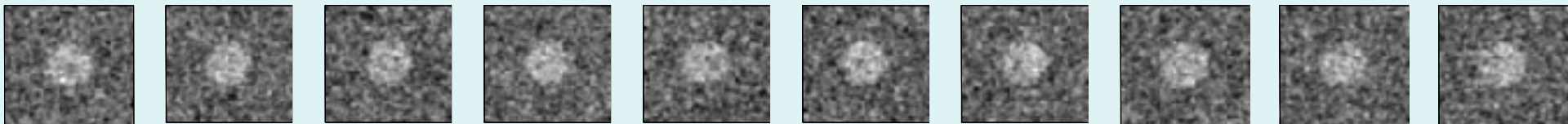




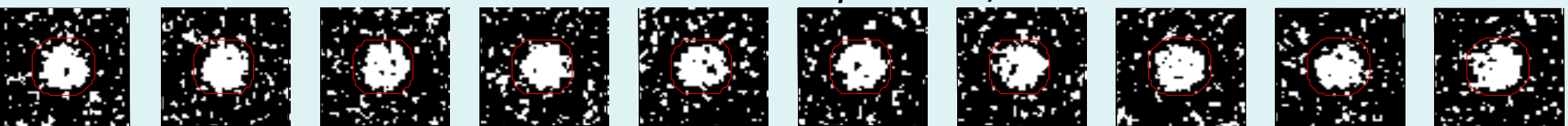
If we have 100000 voxels, $\alpha=0.05$
 \Rightarrow **5000 false positive voxels.**

This is clearly undesirable!
Need to define a *null hypothesis* for
a *collection of tests*.

Noisy data



Use of 'uncorrected' p -value, $\alpha = 0.1$



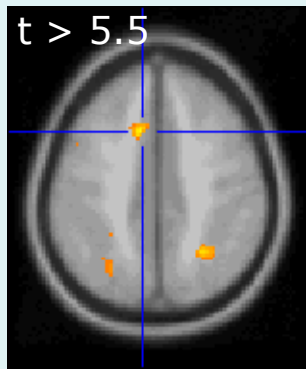
Country	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Denmark	11.3%	11.3%	12.5%	10.8%	11.5%	10.0%	10.7%	11.2%	10.2%	9.5%

Percentage of Null Pixels that are False Positives

Assessing statistics images

Where's the signal?

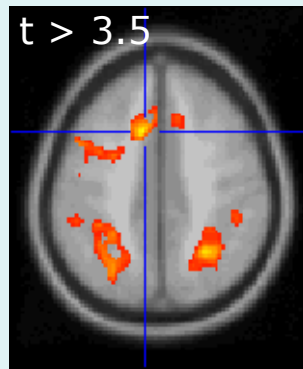
High Threshold



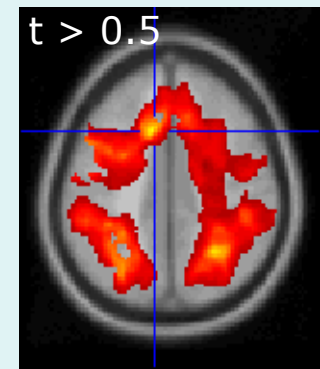
Good Specificity

Poor Power
(risk of false
negatives)

Med. Threshold



Low Threshold



Poor Specificity
(risk of false
positives)

Good Power

Content

- **Introduction**
- **Family-wise error rate (FWER)**
 - **Family-wise Null hypothesis**
 - **Bonferroni correction**
 - **Random Field Theory**
- **False discovery rate (FDR)**
- **Levels of inference in SPM**
- **Non-parametric permutation test**
- **Conclusion**

Family-Wise Null Hypothesis

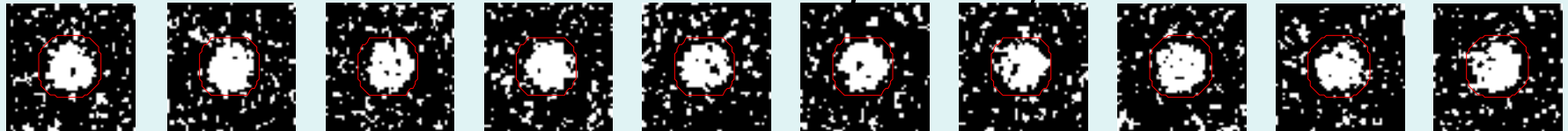
Family-Wise Null Hypothesis:
Activation is zero everywhere

If we reject a voxel null hypothesis at *any* voxel, we reject the family-wise Null hypothesis

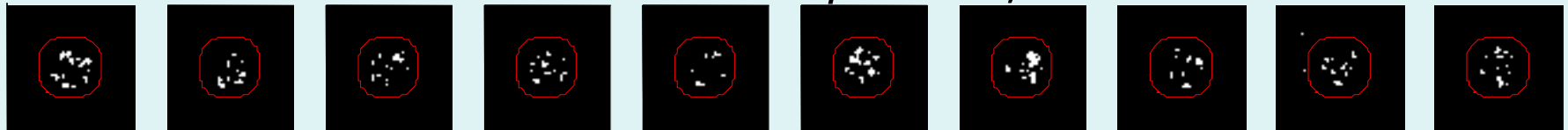
A FP ***anywhere*** in the image gives a **Family Wise Error** (FWE)

Family-Wise Error rate (FWER) = 'corrected' p -value

Use of 'uncorrected' p -value, $\alpha = 0.1$



Use of 'corrected' p -value, $\alpha = 0.1$



FWE

Bonferroni correction

The Family-Wise Error rate (FWER), α_{FWE} , for a family of N tests follows the inequality:

$$\alpha_{FWE} \leq N\alpha$$

where α is the test-wise error rate.

Therefore, to ensure a particular FWER choose:

$$\alpha = \frac{\alpha_{FWE}}{N}$$

This correction does not require the tests to be independent but becomes very stringent if dependence.

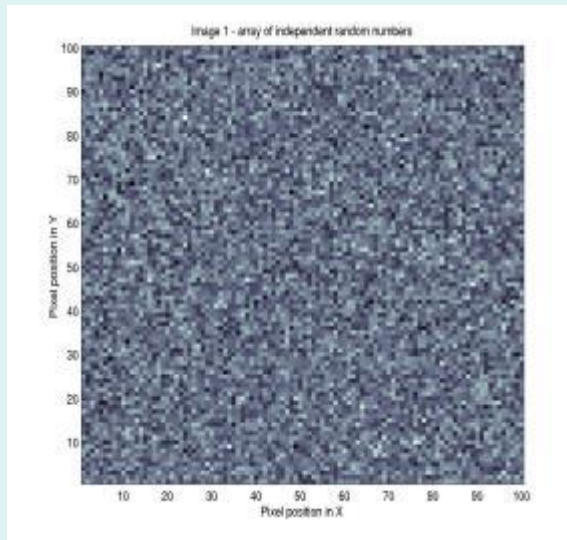
Bonferroni correction, example

- Experiment with $N = 100000$ *independent* voxels and 40 d.f.
 - v = unknown corrected probability threshold,
 - find v such that family-wise error rate $\alpha = 0.05$
- **Bonferroni correction:**
 - probability that all tests are below the threshold,
 - use $v = \alpha / N$
 - here $v = 0.05 / 100000 = 0.0000005$
 \Rightarrow threshold $t = 5.77$
- **Interpretation:**

Bonferroni procedure gives a corrected p-value,
i.e. for a t statistics = 5.77,

 - uncorrected p value = 0.0000005
 - corrected p value = 0.05

Bonferroni & independent observations



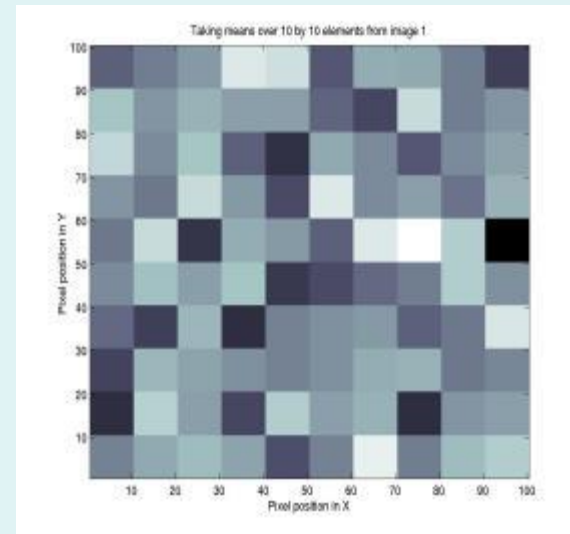
100 by 100 voxels.

10000 independent measures

Fix the $P^{FWE} = 0.05$, z threshold ?

Bonferroni:

$$v = 0.05 / 10000 = 0.000005$$
$$\Rightarrow \text{threshold } z = 4.42$$



100 by 100 voxels.

100 independent measures

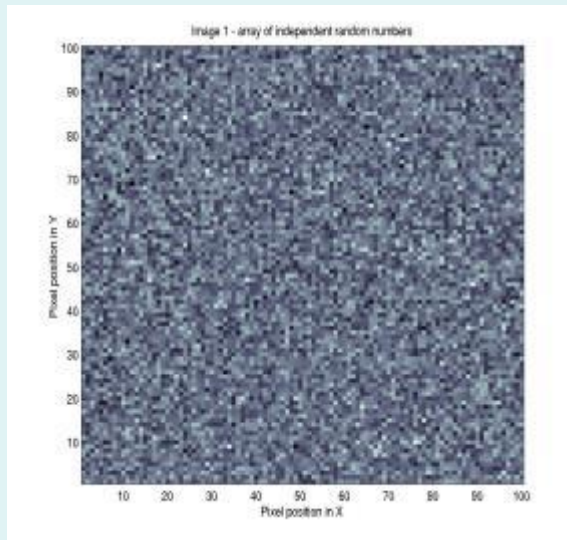
Fix the $P^{FWE} = 0.05$, z threshold ?

Bonferroni:

$$v = 0.05 / 100 = 0.0005$$
$$\Rightarrow \text{threshold } z = 3.29$$

$v = \alpha / n_i$ where n_i is the number of independent observations.

Bonferroni & independent observations



100 by 100 voxels.

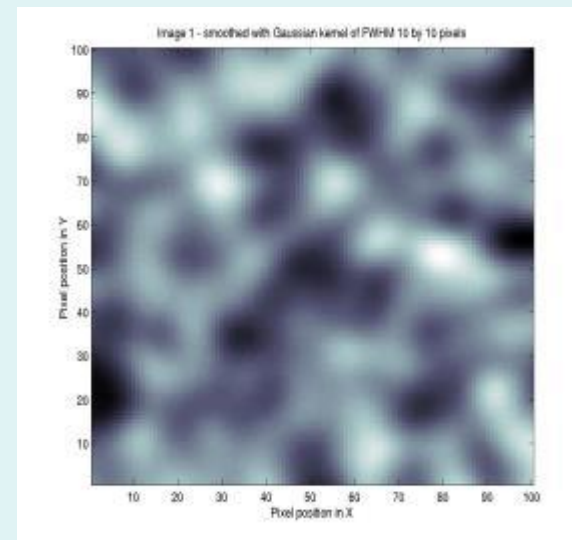
10000 independent measures

Fix the $P^{FWE} = 0.05$, z threshold ?

Bonferroni:

$$v = 0.05 / 10000 = 0.000005$$

$$\Rightarrow \text{threshold } z = 4.42$$

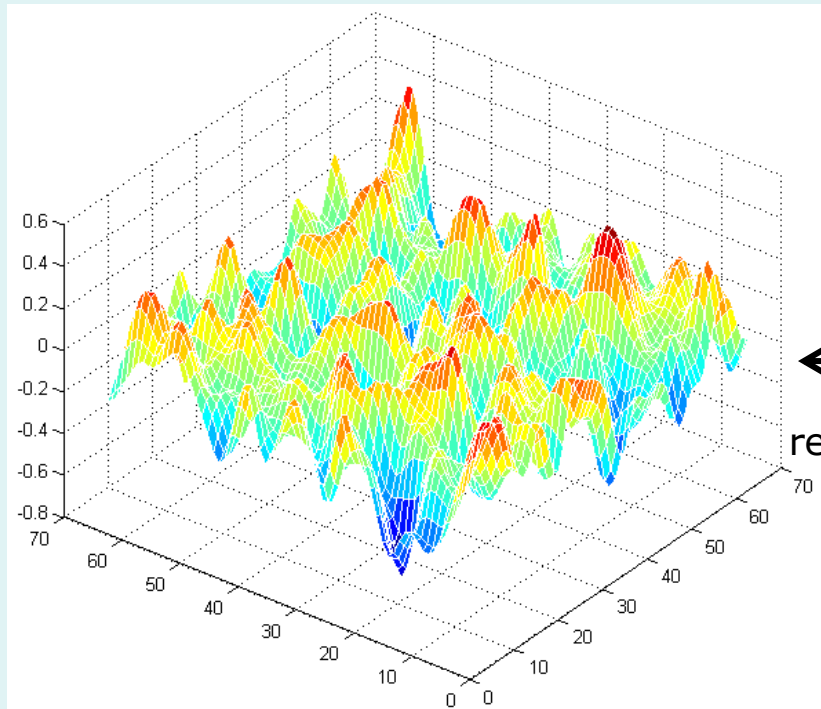


100 by 100 voxels.

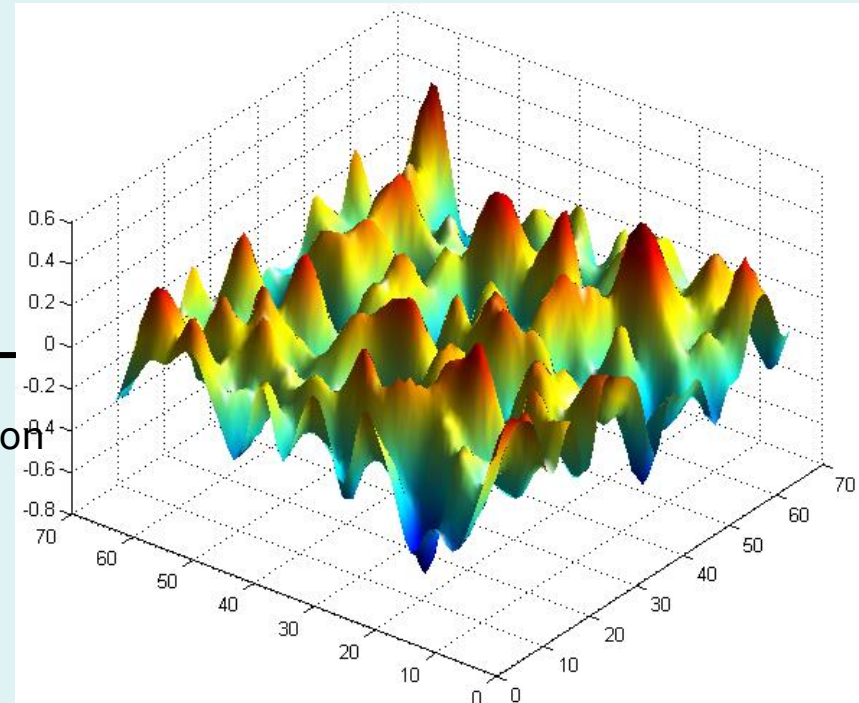
How many independent measures ???

Random Field Theory

- ⇒ Consider a statistic image as a discretisation of a continuous underlying random field.
- ⇒ Use results from continuous **random field theory**.



←
lattice
representation



RFT and Euler Characteristic

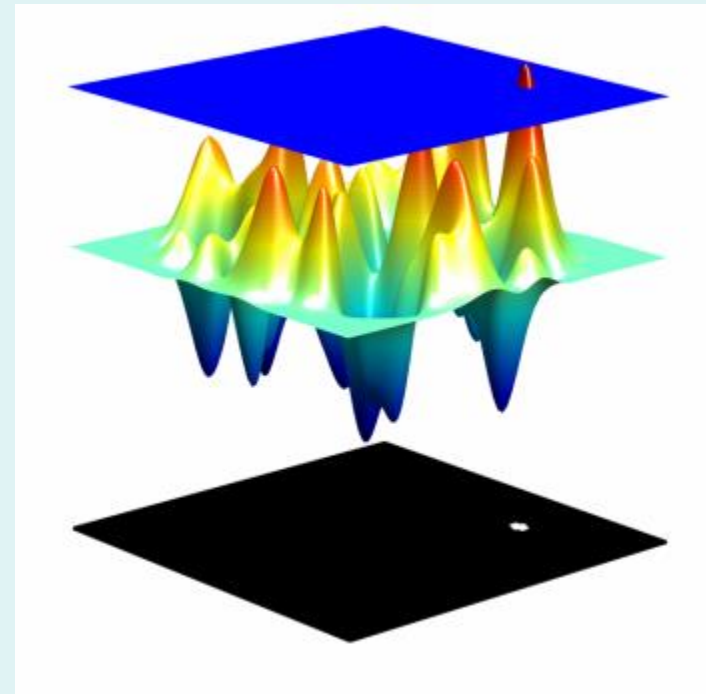
Euler Characteristic χ_u :

- Topological measure

$$\chi_u = \# \text{ blobs} - \# \text{ holes}$$

- at high threshold u :

$$\chi_u = \# \text{ blobs}$$

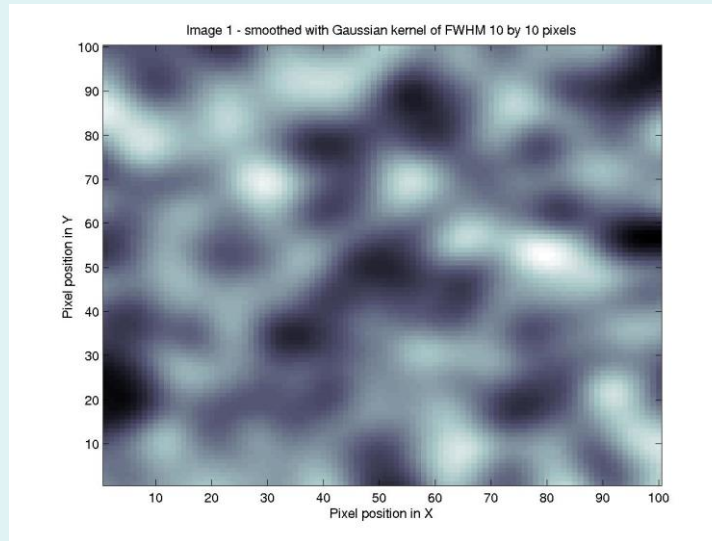
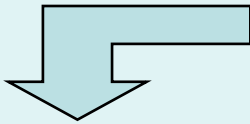


$$\begin{aligned} FWER &= p(FWE) \\ &\approx E[\chi_u] \end{aligned}$$

Euler characteristic...

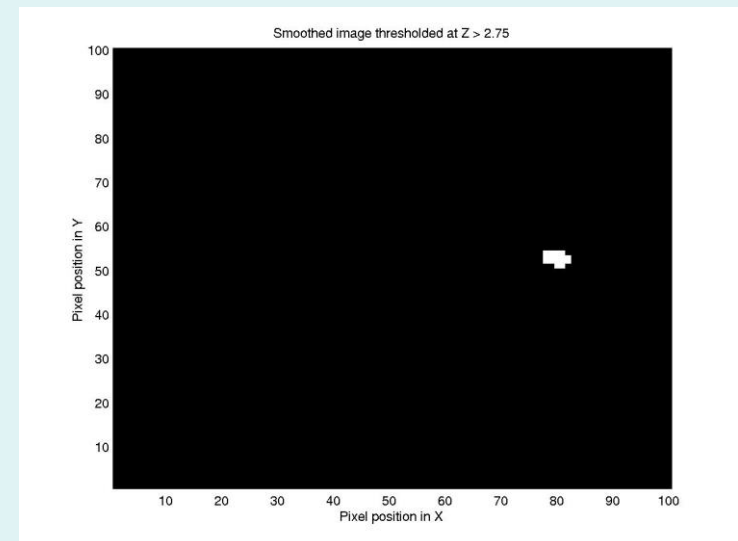
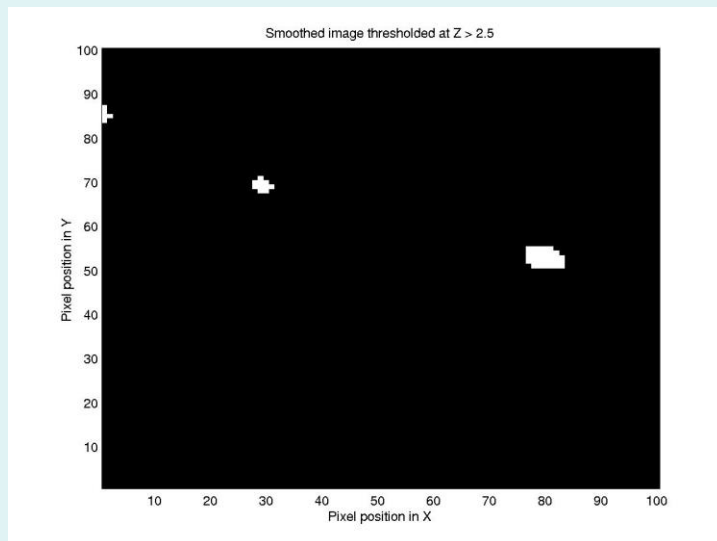
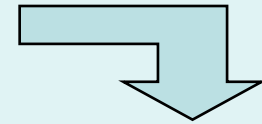
Threshold z-map
at 2.50

EC = 3



Threshold z-map
at 2.75

EC = 1



Expected Euler Characteristic

2D Gaussian Random Field

$$E[\chi_u] = \lambda(\Omega) |\Lambda|^{1/2} u \exp(-u^2/2) / (2\pi)^{3/2}$$

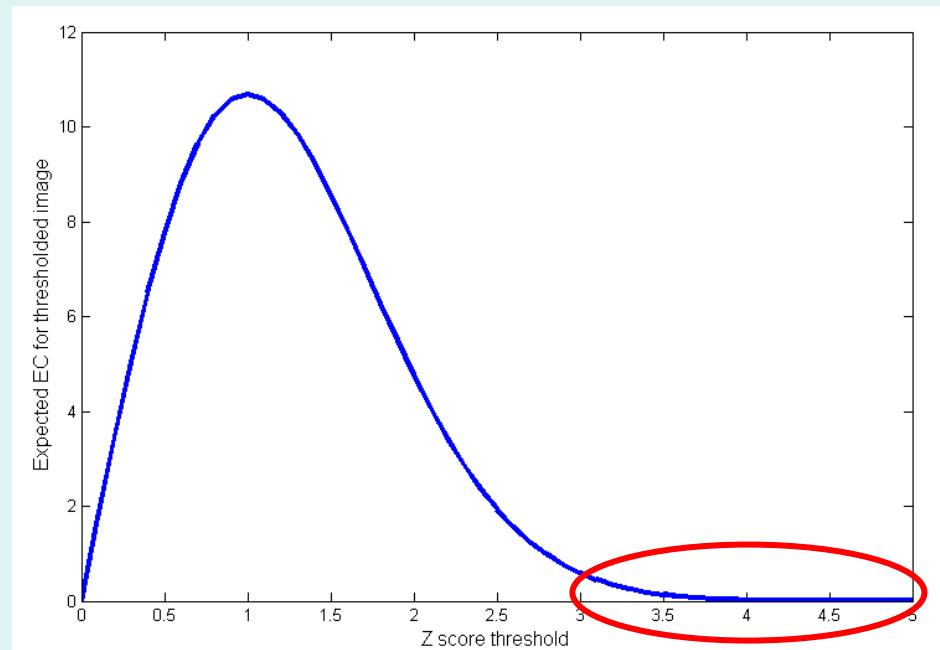
Search volume

Roughness
(1/smoothness)

Threshold

100 x 100 Gaussian Random Field
with FWHM=10 smoothing

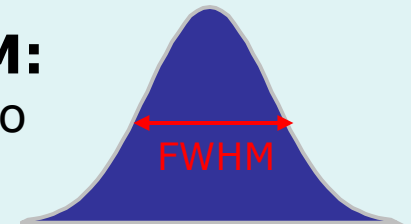
$$\alpha_{FWE} = 0.05 \Rightarrow u_{RFT} = 3.8$$
$$(u_{BONF} = 4.42, u_{uncorr} = 1.64)$$



Smoothness

Smoothness parameterised in terms of FWHM:

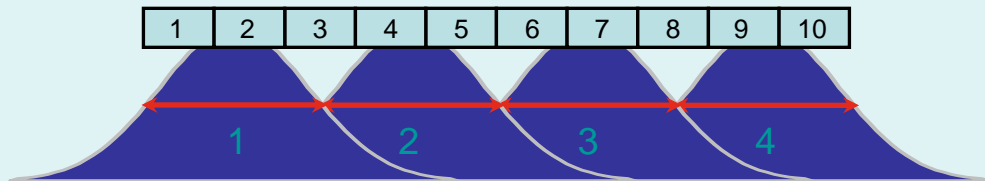
Size of Gaussian kernel required to smooth i.i.d. noise to have same smoothness as observed null (standardized) data.



RESELS (Resolution Elements):

1 RESEL = $FWHM_x FWHM_y FWHM_z$

RESEL Count R = volume of search region in units of smoothness

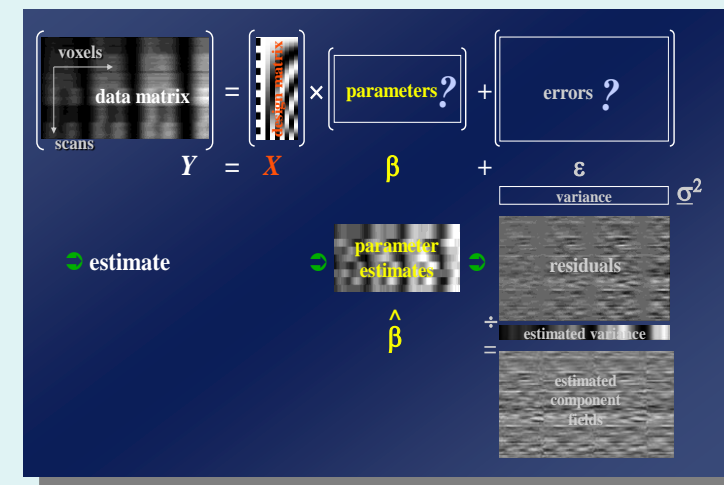


Eg: 10 voxels, 2.5 FWHM, 4 RESELS

The number of resels is similar, but not identical to the number independent observations.

Smoothness estimated from spatial derivatives of standardised residuals:

Yields an RPV image containing local roughness estimation.



RFT intuition

Corrected p -value for statistic value t

$$\begin{aligned} p_c &= p(\max T > t) \\ &\approx E[\chi_t] \\ &\propto \lambda(\Omega) |\Lambda|^{1/2} t \exp(-t^2/2) \end{aligned}$$

- Statistic value t increases ?
 - p_c decreases (better signal)
- Search volume increases ($\lambda(\Omega) \uparrow$) ?
 - p_c increases (more severe correction)
- Smoothness increases ($|\Lambda|^{1/2} \downarrow$) ?
 - p_c decreases (less severe correction)

RFT, unified theory

General form for expected Euler characteristic

- t , F & χ^2 fields
- restricted search regions
- D dimensions

$$E[\chi_u(\Omega)] = \sum_{d=0}^D R_d(\Omega) \rho_d(u)$$

$R_d(\Omega)$: d -dimensional Lipschitz-Killing curvatures of Ω (\approx intrinsic volumes):

– function of dimension,
space Ω and smoothness:

$R_0(\Omega) = \chi(\Omega)$ Euler characteristic of Ω

$R_1(\Omega) =$ resel diameter

$R_2(\Omega) =$ resel surface area

$R_3(\Omega) =$ resel volume

$\rho_d(u)$: d -dimensional EC density of the field

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

E.g. Gaussian RF:

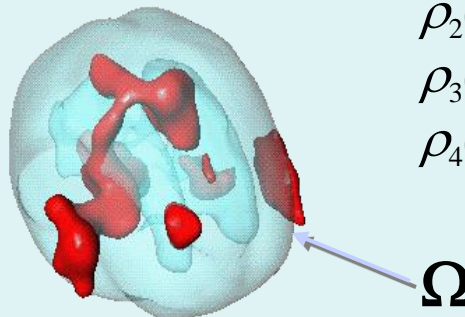
$$\rho_0(u) = 1 - \Phi(u)$$

$$\rho_1(u) = (4 \ln 2)^{1/2} \exp(-u^2/2) / (2\pi)$$

$$\rho_2(u) = (4 \ln 2) u \exp(-u^2/2) / (2\pi)^{3/2}$$

$$\rho_3(u) = (4 \ln 2)^{3/2} (u^2 - 1) \exp(-u^2/2) / (2\pi)^2$$

$$\rho_4(u) = (4 \ln 2)^2 (u^3 - 3u) \exp(-u^2/2) / (2\pi)^{5/2}$$



Estimated component fields

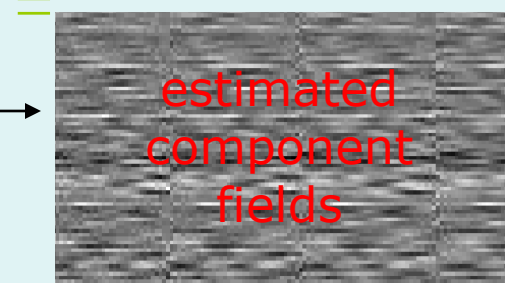
$$\begin{bmatrix} \text{voxels} \\ \text{data matrix} \\ \text{scans} \end{bmatrix} = \begin{bmatrix} \text{design matrix} \end{bmatrix} \times \begin{bmatrix} \text{parameters ?} \end{bmatrix} + \begin{bmatrix} \text{errors ?} \end{bmatrix}$$

$\hat{\beta}$

estimate



\div estimated variance



Each row is an estimated component field →

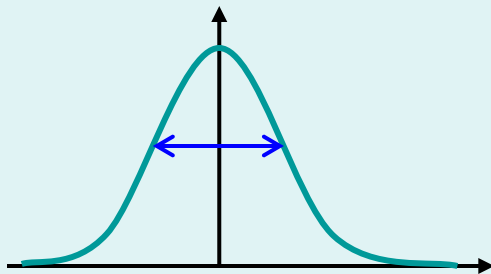
Smoothness, PRF, ResEls...

- Smoothness $\sqrt{|\Lambda|}$

- variance-covariance matrix of partial derivatives (*possibly location dependent*)

$$\Lambda = \begin{pmatrix} \text{var}\left[\frac{\partial e}{\partial x}\right] & \text{cov}\left[\frac{\partial e}{\partial x}, \frac{\partial e}{\partial y}\right] & \text{cov}\left[\frac{\partial e}{\partial x}, \frac{\partial e}{\partial z}\right] \\ \text{cov}\left[\frac{\partial e}{\partial x}, \frac{\partial e}{\partial y}\right] & \text{var}\left[\frac{\partial e}{\partial y}\right] & \text{cov}\left[\frac{\partial e}{\partial y}, \frac{\partial e}{\partial z}\right] \\ \text{cov}\left[\frac{\partial e}{\partial x}, \frac{\partial e}{\partial z}\right] & \text{cov}\left[\frac{\partial e}{\partial y}, \frac{\partial e}{\partial z}\right] & \text{var}\left[\frac{\partial e}{\partial z}\right] \end{pmatrix}$$

- Point Response Function PRF



- Full Width at Half Maximum **FWHM**. Approximate the peak of the Covariance function with a Gaussian

- Gaussian PRF

- Σ – kernel var/cov matrix
- ACF 2Σ
- $\Lambda = (2\Sigma)^{-1}$

$$\Rightarrow \text{FWHM } f = \sigma \sqrt{(8\ln(2))}$$

$$- \Sigma = \begin{pmatrix} f_x & 0 & 0 \\ 0 & f_y & 0 \\ 0 & 0 & f_z \end{pmatrix} \frac{1}{8\ln(2)}$$

ignoring covariances

$$\Rightarrow \sqrt{|\Lambda|} = (4\ln(2))^{3/2} / (f_x \times f_y \times f_z)$$

- Resolution Element (ResEl)

- Resel dimensions ($f_x \times f_y \times f_z$)
- $R_3(\Omega) = \lambda(\Omega) / (f_x \times f_y \times f_z)$

if strictly stationary

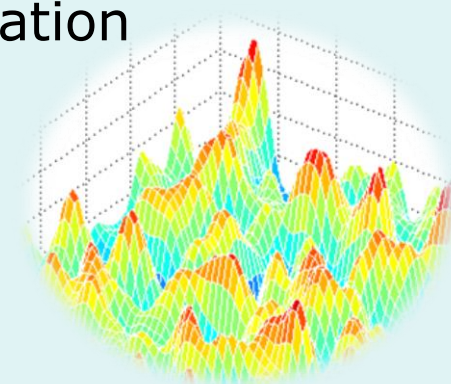
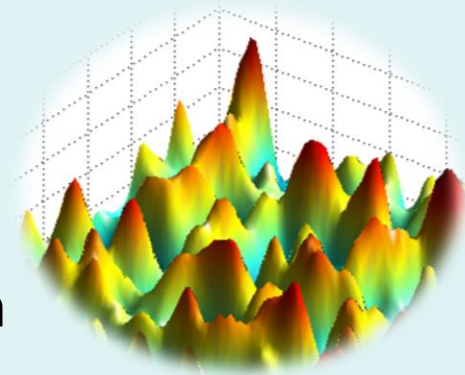
$$E[\chi(A_u)] = R_3(\Omega) (4\ln(2))^{3/2} (u^2 - 1) \exp(-u^2/2) / (2\pi)^2$$

$$\approx R_3(\Omega) (1 - \Phi(u))$$

for high thresholds u

RFT assumptions

- The statistic image is assumed to be a good lattice representation of an underlying random field with a multivariate Gaussian distribution.
- These fields are continuous, with an autocorrelation function twice differentiable at the origin.
- The threshold chosen to define clusters is high enough such that the expected EC is a good approximation to the number of clusters.
- The lattice approximation is reasonable, which implies the smoothness is relatively large compared to the voxel size.
- The errors of the specified statistical model are normally distributed, which implies the model is not misspecified.
- Smoothness of the data is unknown and estimated: very precise estimate by pooling over voxels \Rightarrow stationarity assumption.

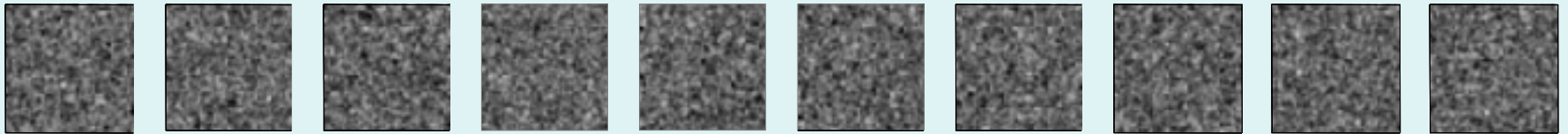


Content

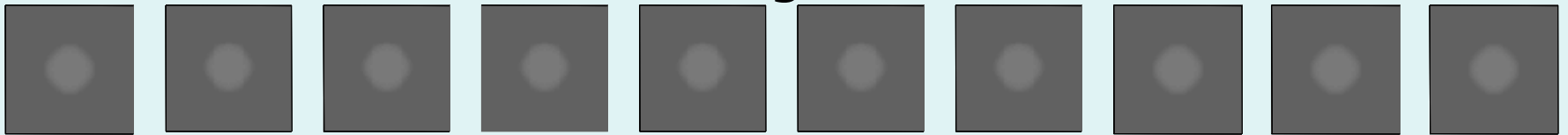
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FDR illustration:

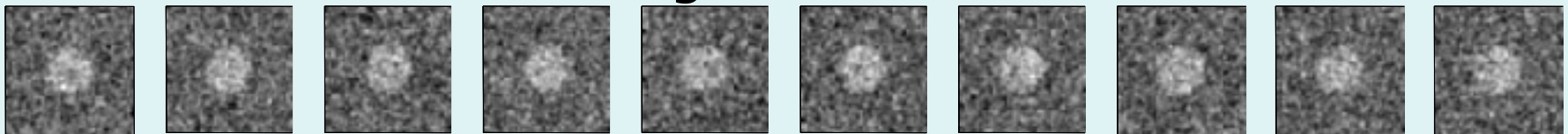
Noise



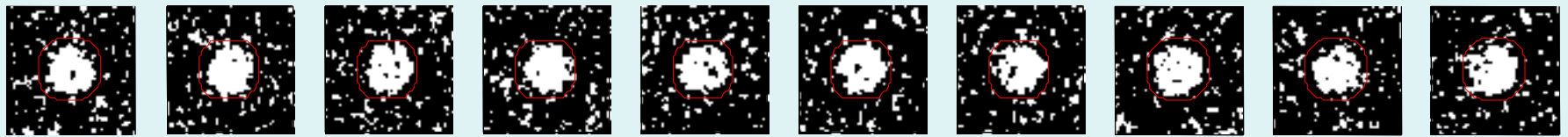
Signal



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%

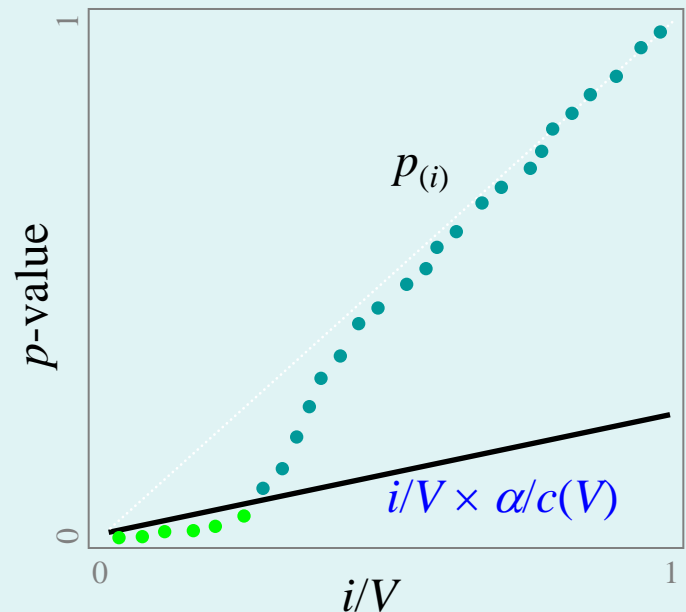
Percentage of Activated Pixels that are False Positives

Benjamini & Hochberg Procedure

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

$$p_{(i)} \leq i/V * \alpha$$

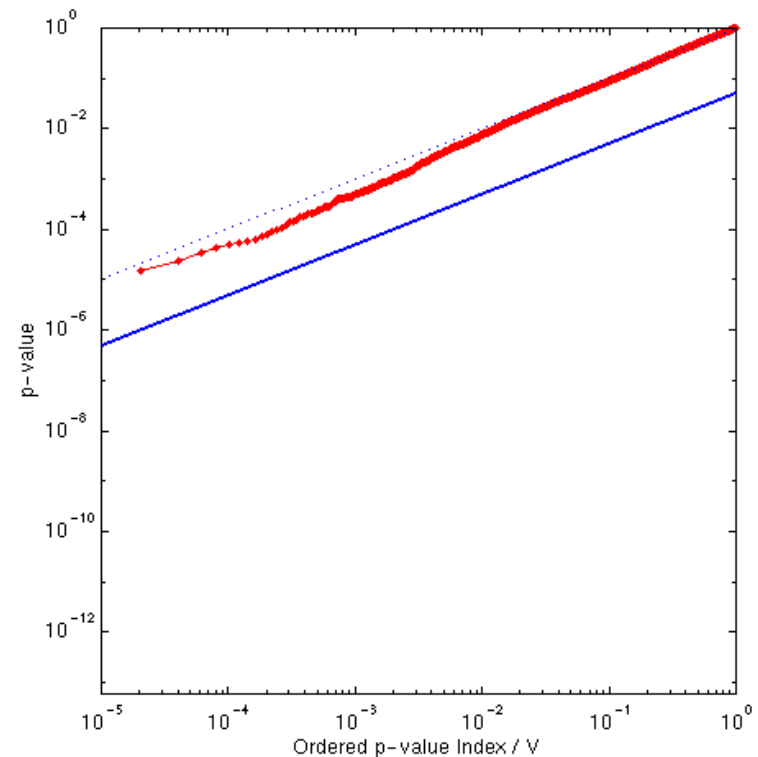
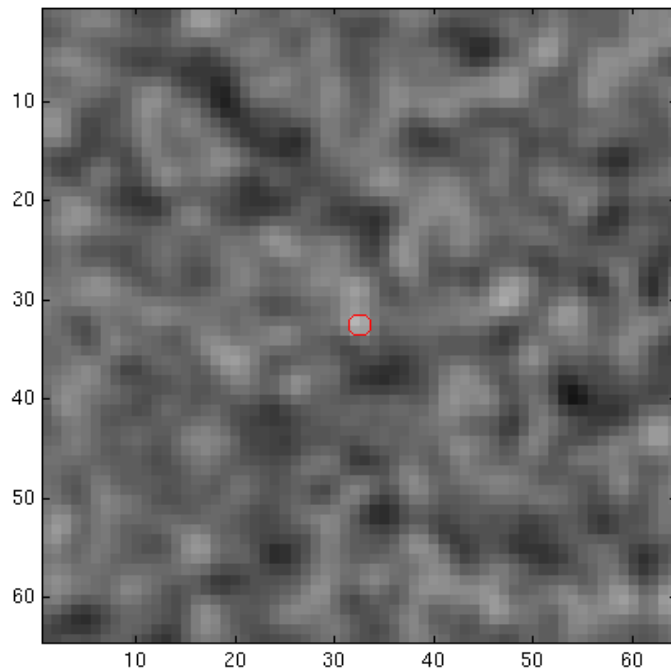
- Reject all hypotheses corresponding to $p_{(1)}, \dots, p_{(r)}$.



B&H: Varying Signal Extent

$p =$

$z =$

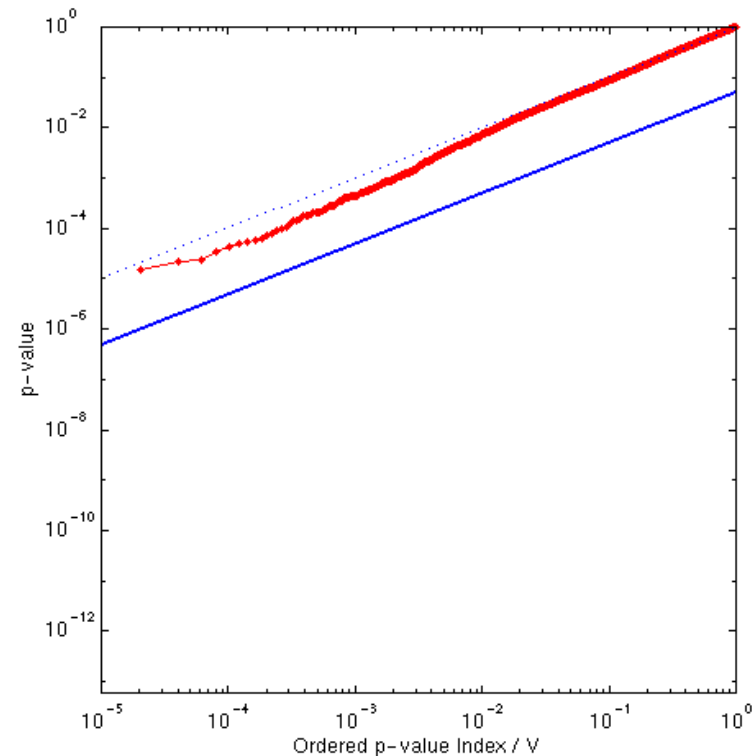
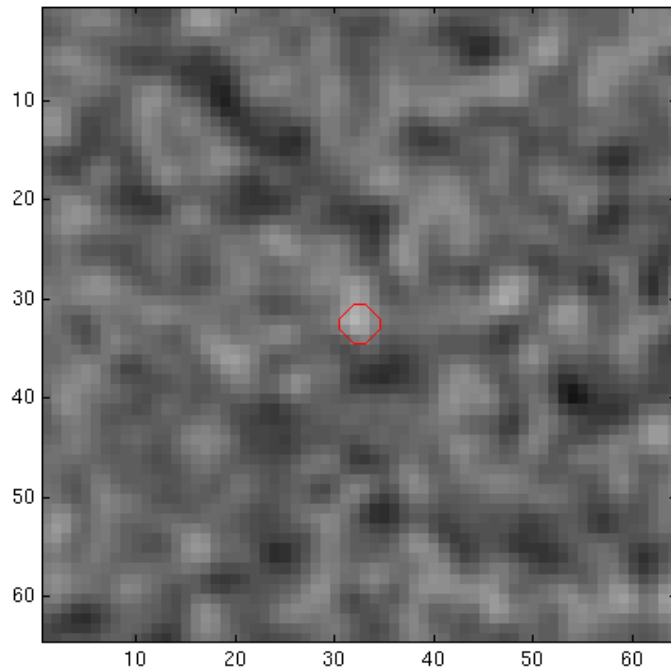


Signal Intensity 3.0 Signal Extent 1.0 Noise Smoothness 3.0

B&H: Varying Signal Extent

$p =$

$z =$

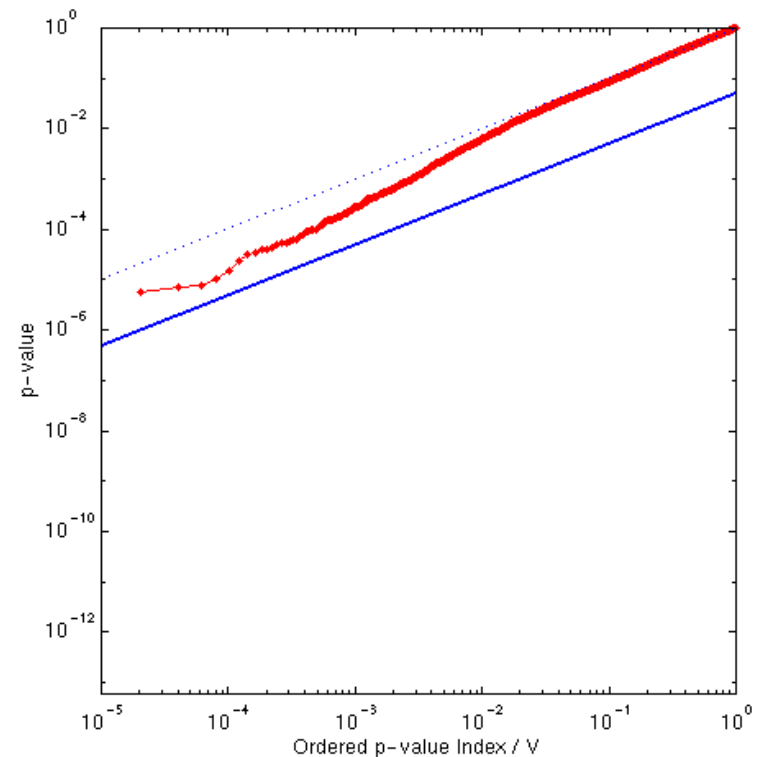
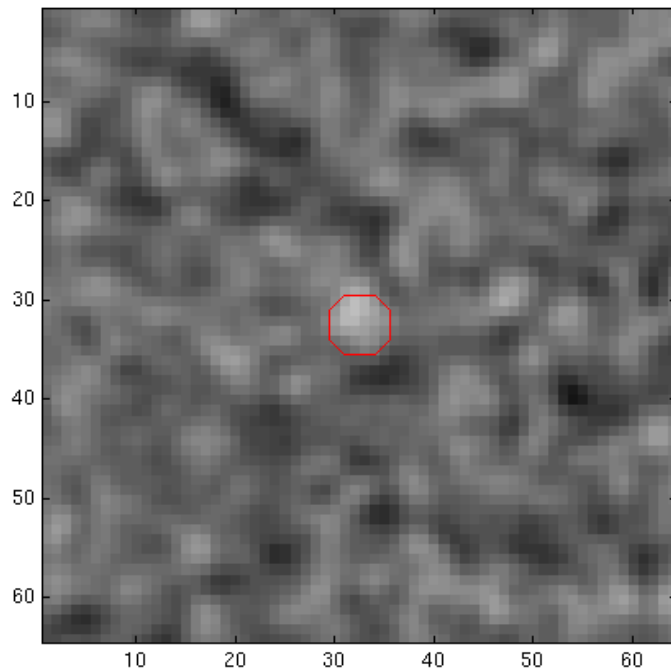


Signal Intensity 3.0 Signal Extent 2.0 Noise Smoothness 3.0

B&H: Varying Signal Extent

$p =$

$z =$

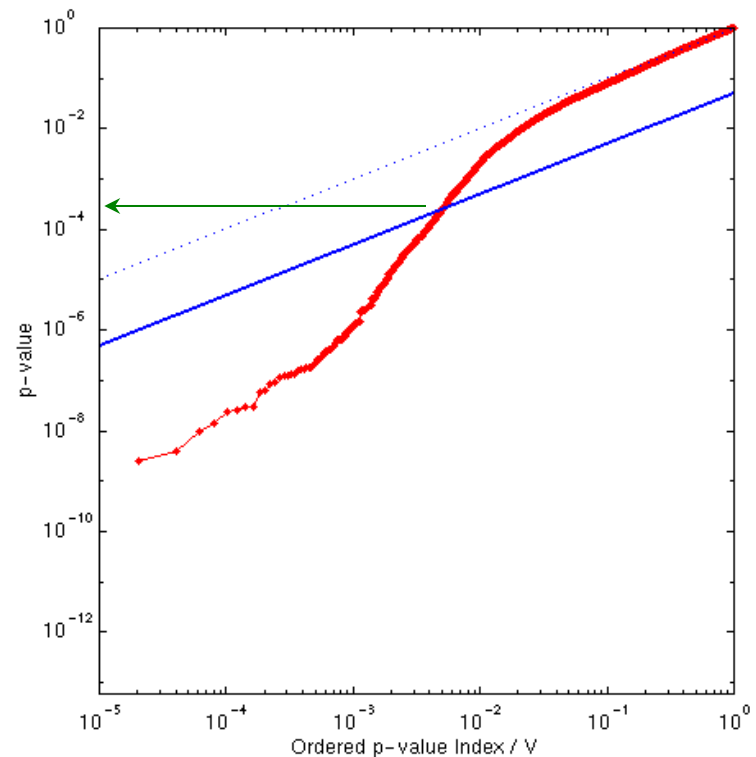
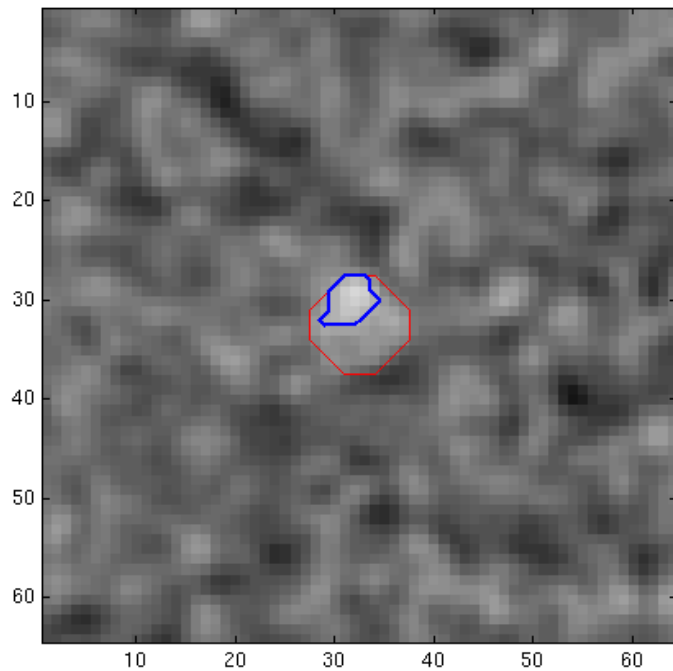


Signal Intensity 3.0 Signal Extent 3.0 Noise Smoothness 3.0

B&H: Varying Signal Extent

$$p = 0.000252$$

$$z = 3.48$$

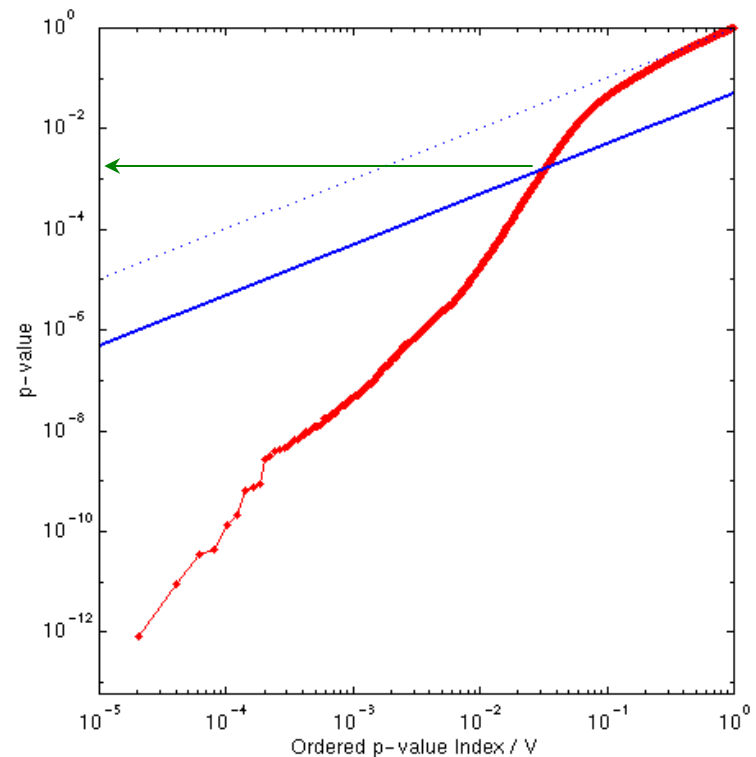
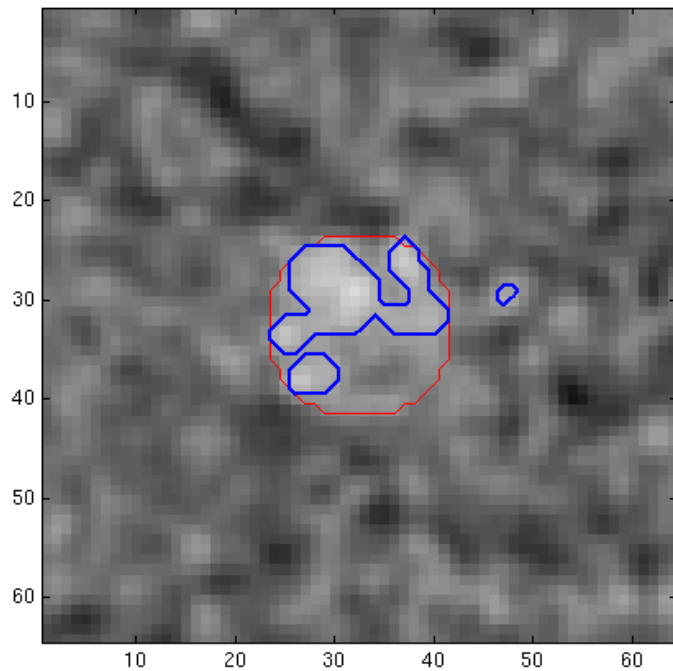


Signal Intensity 3.0 Signal Extent 5.0 Noise Smoothness 3.0

B&H: Varying Signal Extent

$$p = 0.001628$$

$$z = 2.94$$

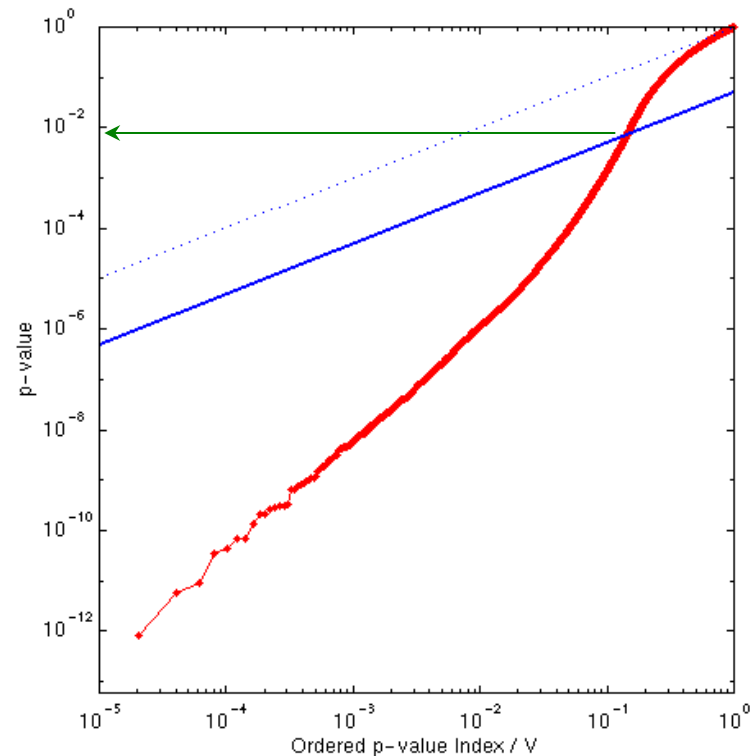
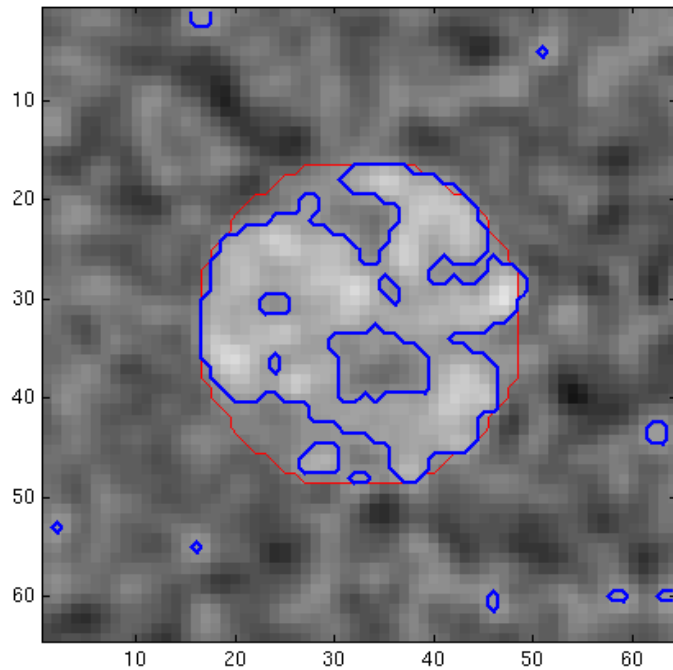


Signal Intensity 3.0 Signal Extent 9.5 Noise Smoothness 3.0

B&H: Varying Signal Extent

$$p = 0.007157$$

$$z = 2.45$$

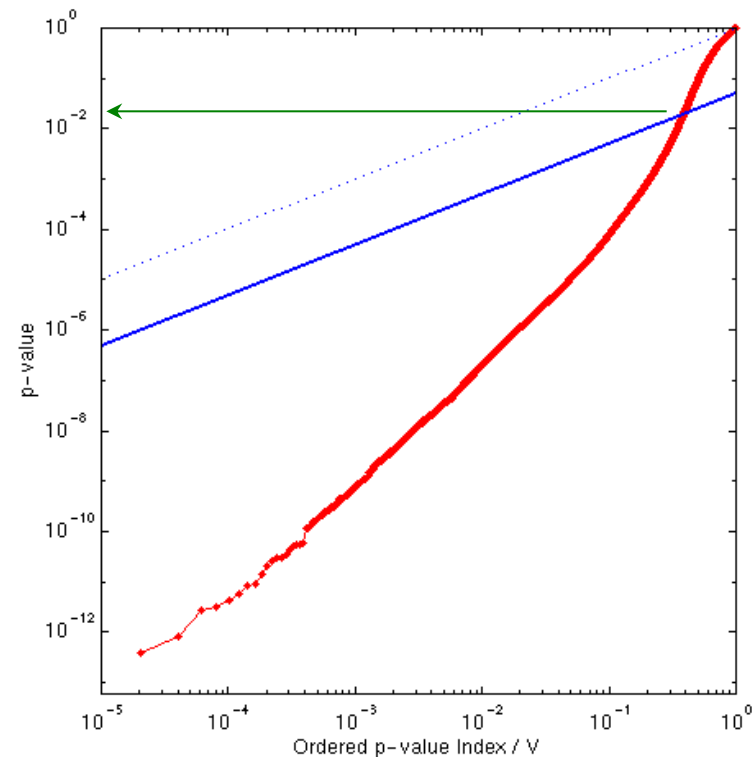
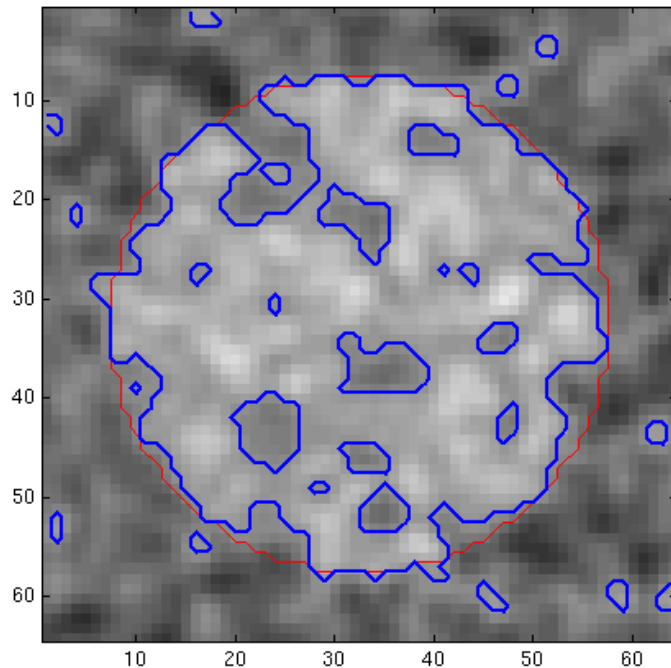


Signal Intensity 3.0 Signal Extent 16.5 Noise Smoothness 3.0

B&H: Varying Signal Extent

$$p = 0.019274$$

$$z = 2.07$$



Signal Intensity 3.0 Signal Extent 25.0 Noise Smoothness 3.0

Benjamini & Hochberg: Properties

- Adaptive
 - Larger the signal, the lower the threshold
 - Larger the signal, the more false positives
 - False positives constant as fraction of rejected tests
 - Not a problem with imaging's sparse signals
- Smoothness OK
 - Smoothing introduces positive correlations

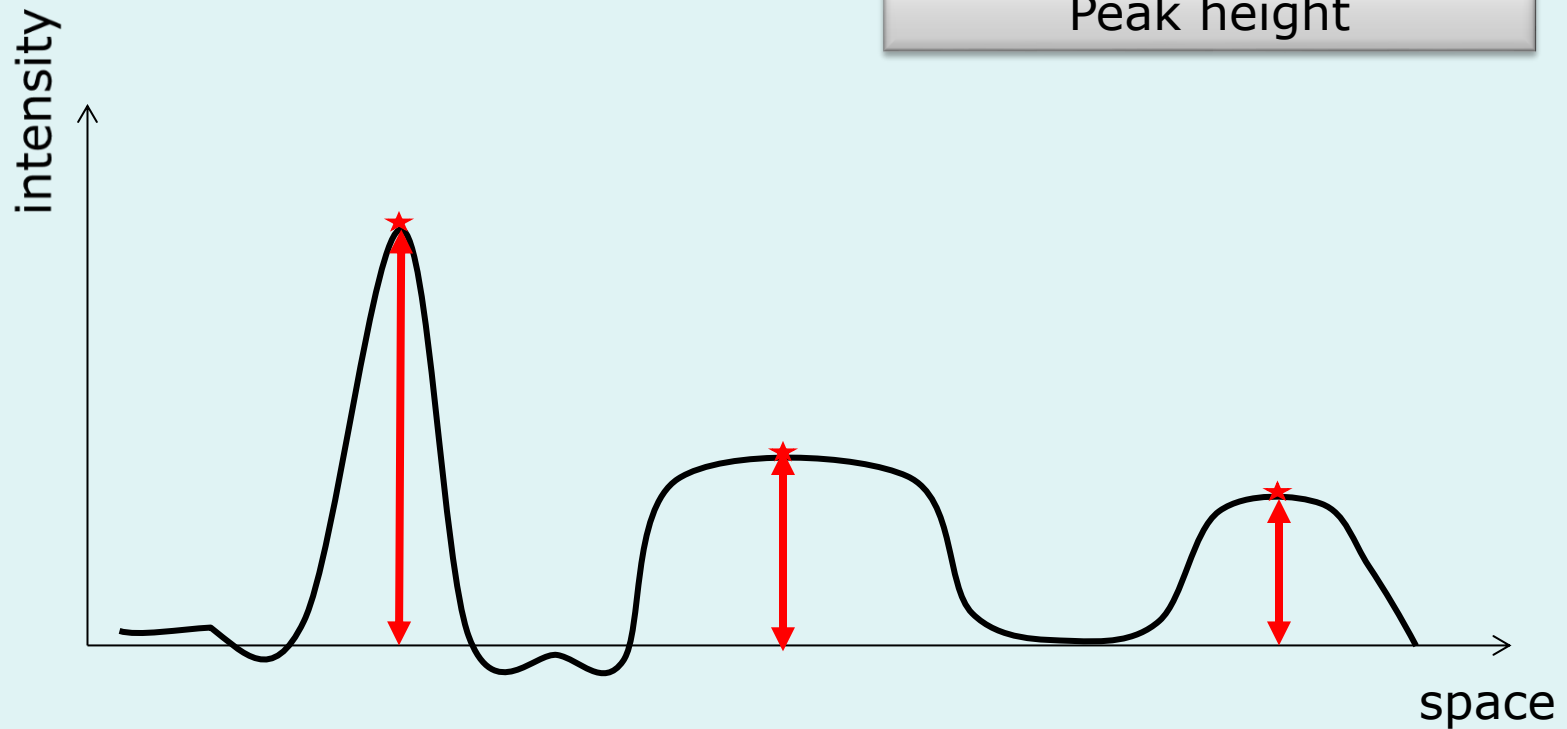
Content

- **Introduction**
- **Family-wise error rate (FWER)**
- **False discovery rate (FDR)**
- **Levels of inference in SPM**
 - **Topological inference**
 - **Small volume correction**
- **Non-parametric permutation test**
- **Conclusion**

Topological inference

Peak level inference

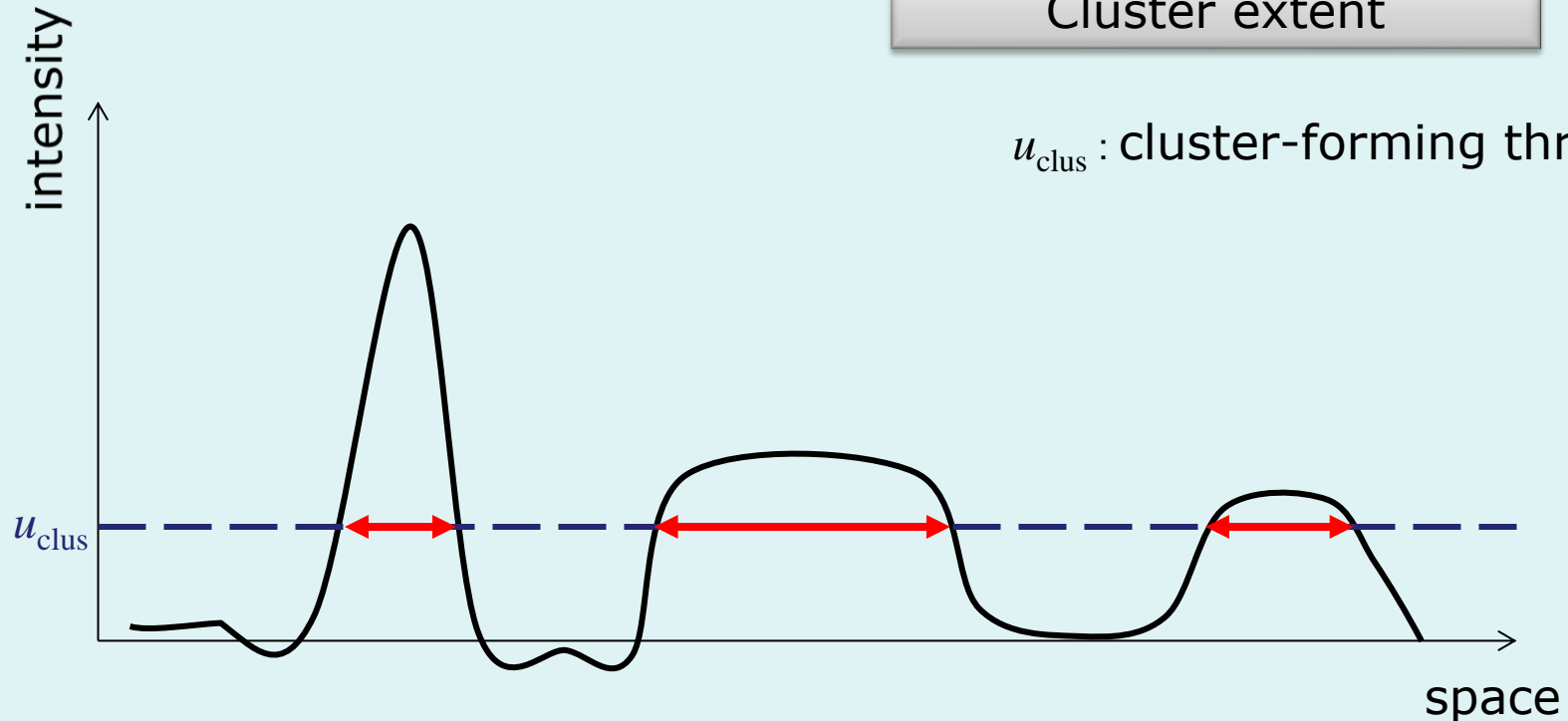
Topological feature:
Peak height



Topological inference

Cluster level inference

Topological feature:
Cluster extent



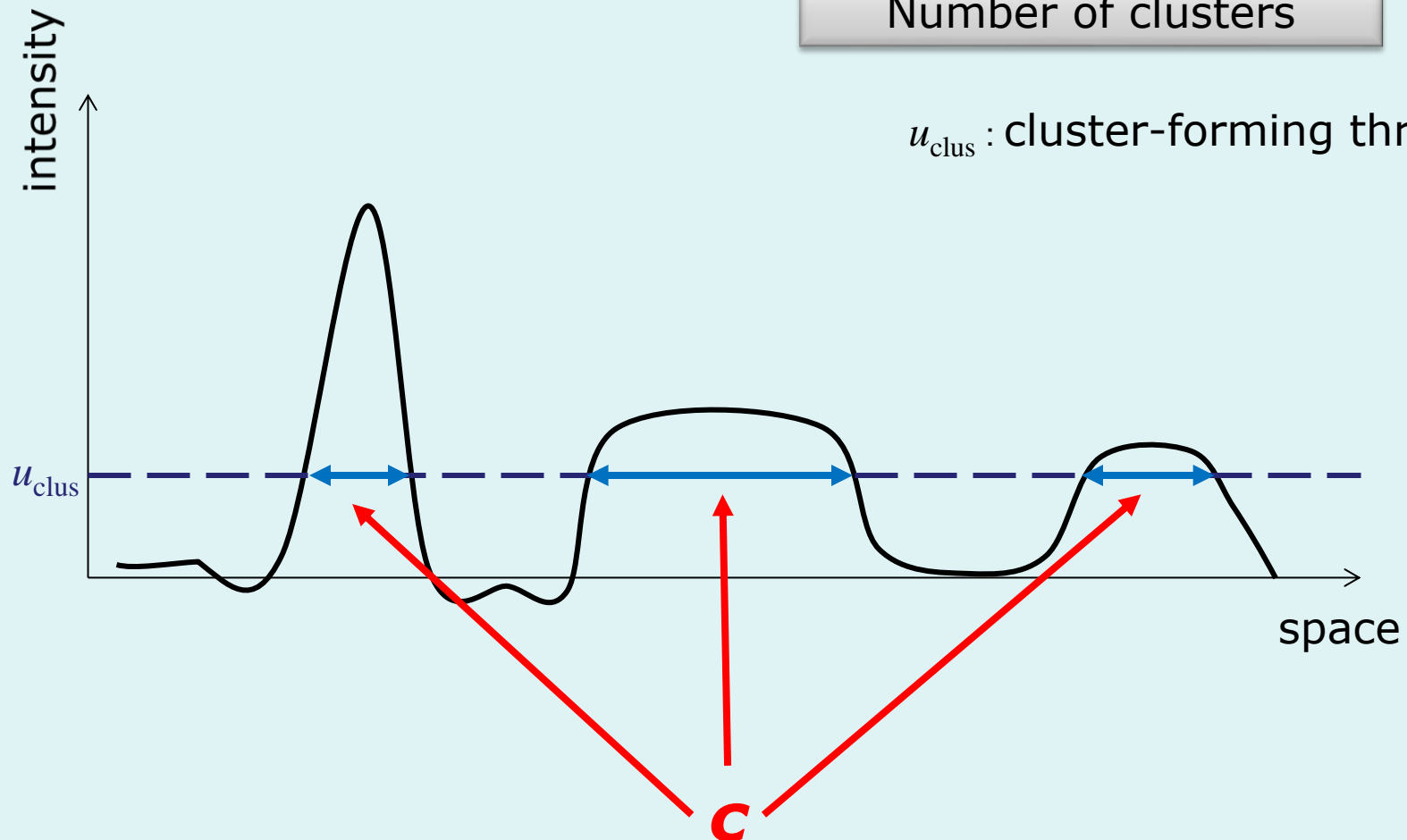
u_{clus} : cluster-forming threshold

You MUST use a sufficiently high cluster-forming threshold u_{clus} , i.e. $p_{\text{unc}} < .001$

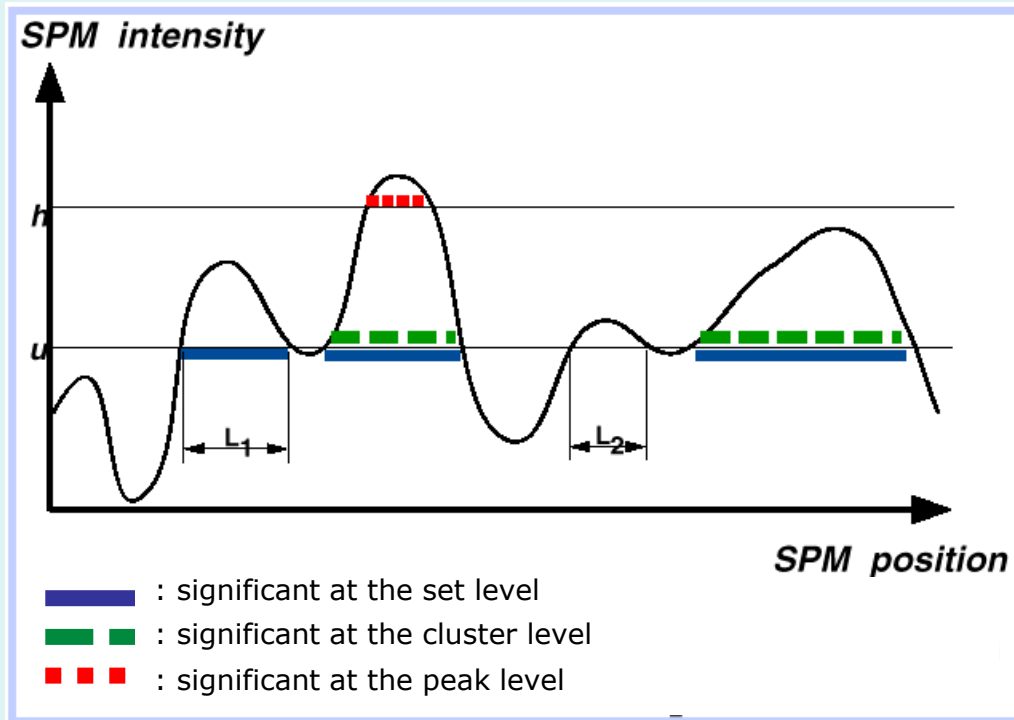
Topological inference

Set level inference

Topological feature:
Number of clusters



Peak, cluster & set level inference



$L_1 >$ spatial extent threshold
 $L_2 <$ spatial extent threshold

Sensitivity

Regional specificity

Peak level test:

height of local maxima

Cluster level test:

spatial extent above u

Set level test:

number of clusters above u



Levels of inference...

Voxel-level

$$P(c \geq 1 \mid n \geq 0, t \geq 4.37) = 0.048 \text{ (corrected)}$$

$$P(t \geq 4.37) = 1 - \Phi\{4.37\} < 0.001 \text{ (uncorrected)}$$

Omnibus

$$P(c \geq 7 \mid n \geq 0, t \geq 3.09) = 0.031$$

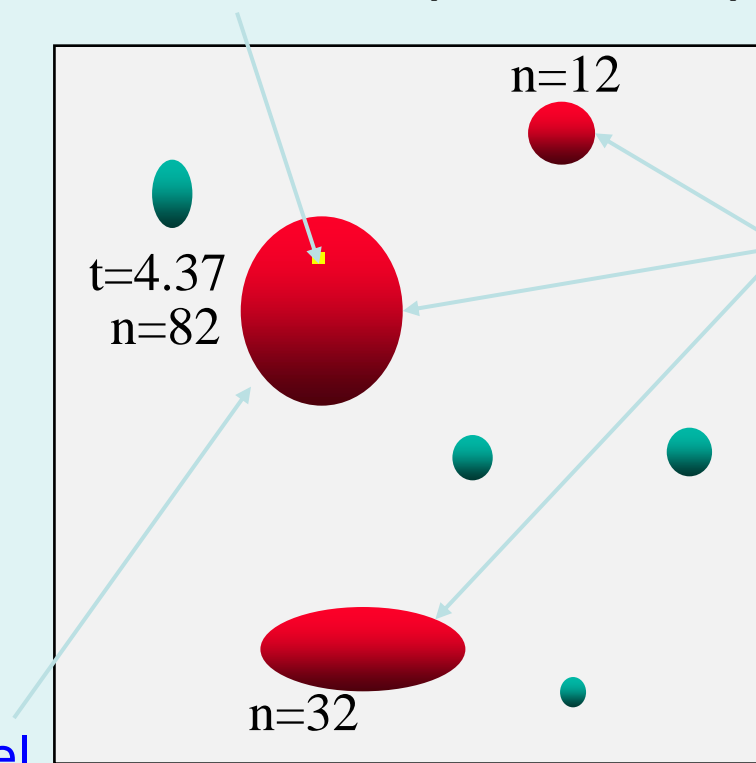
Set-level

$$P(c \geq 3 \mid n \geq 12, t \geq 3.09) = 0.019$$

Cluster-level

$$P(c \geq 1 \mid n \geq 82, t \geq 3.09) = 0.029 \text{ (corrected)}$$

$$P(n \geq 82 \mid t \geq 3.09) = 0.019 \text{ (uncorrected)}$$



Parameters

u	- 3.09
k	- 12 voxels
S	- 32 ³ voxels
<i>FWHM</i>	- 4.7 voxels
D	- 3

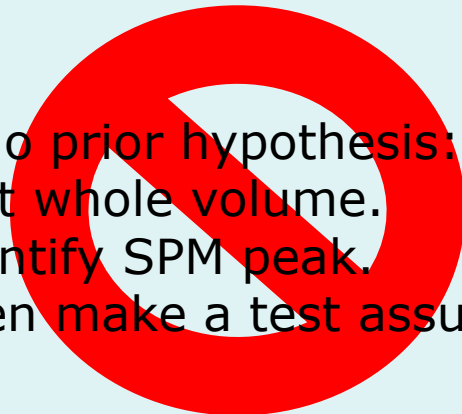
Small volume correction

If one has some *a priori* idea of where an activation should be, one can pre-specify a small search space and make the appropriate correction instead of having to control for the entire search space

- mask defined by (probabilistic) anatomical atlases
- mask defined by separate "functional localisers"
- mask defined by orthogonal contrasts
- search volume around previously reported coordinates

With no prior hypothesis:

1. Test whole volume.
2. Identify SPM peak.
3. Then make a test assuming a single voxel.



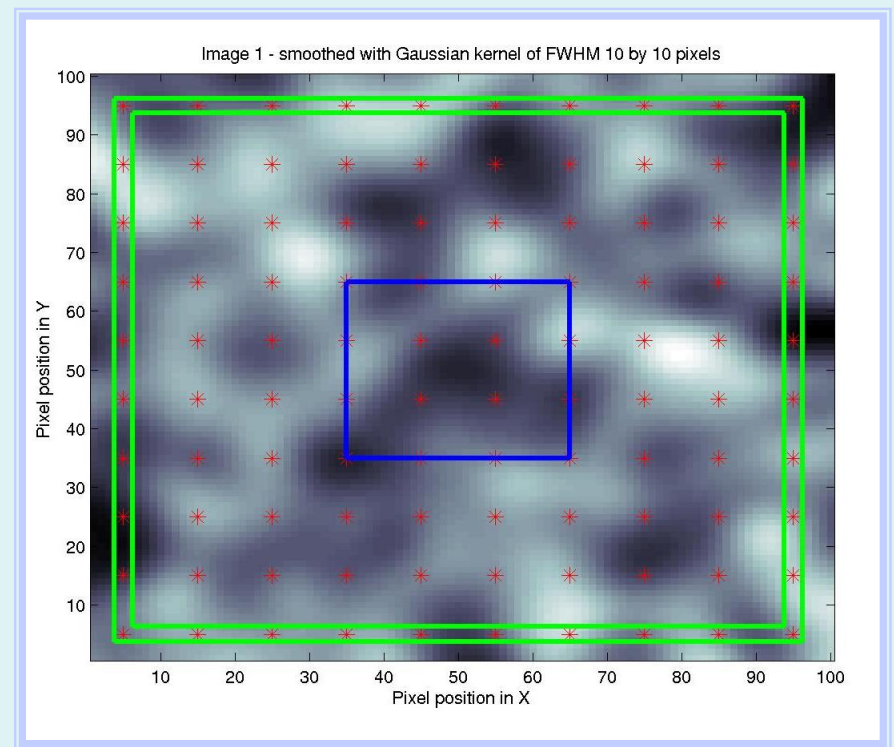
Small Volume Correction

SVC = correction for multiple comparison in a user's defined volume 'of interest'.

Shape and size of volume become important for small or oddly shaped volume !

Example of SVC (900 voxels)

- **compact volume**: samples from maximum 16 resels
- **spread volume**: sample from up to 36 resels
⇒ threshold higher for **spread volume** than **compact volume**.



Small volume correction, topology

TABLE 3. Representative examples of resel counts and critical values.

Search region V	Vol. (cc)	Resel counts				t for $P(M \geq t) =$		
		$R_0(V)$	$R_1(V)$	$R_2(V)$	$R_3(V)$	0.10	0.05	0.01
Single voxel	0	1	0	0	0	1.28	1.64	2.33
Head Of Caudate	7	0	6.18	4.63	0.65	2.75	3.02	3.55
Putamen	12	1	7.32	6.80	1.18	2.89	3.15	3.66
Globus Pallidus	3	0	4.03	2.29	0.24	2.49	2.78	3.35
Thalamus	11	1	4.94	5.14	1.13	2.79	3.05	3.59
Anterior Cingulate Gyrus	9	1	8.20	5.79	0.86	2.86	3.11	3.63
Posterior Cingulate Gyrus	6	1	5.32	3.85	0.58	2.70	2.97	3.51
Cingulate Gyri	15	0	12.89	9.63	1.44	3.03	3.27	3.77
Superior Frontal Gyrus	80	1	15.64	25.69	8.97	3.38	3.60	4.07
Middle Frontal Gyrus	57	1	14.89	21.14	6.23	3.31	3.53	4.00
Inferior Frontal Gyrus	37	1	11.22	14.25	4.06	3.17	3.41	3.89
Precentral Gyrus	32	1	12.30	14.23	3.40	3.16	3.40	3.88
Frontal Gyri	207	1	19.30	53.39	23.63	3.63	3.84	4.28
Occipital Lobe	65	-1	10.68	23.11	7.17	3.32	3.55	4.02
4mm shell	254	2	0.54	207.27	15.88	3.85	4.04	4.45
Whole brain	1294	1	20.43	107.09	153.42	4.05	4.23	4.63

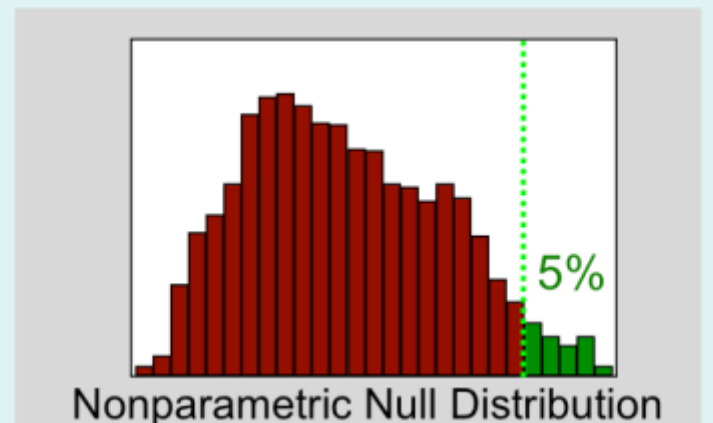
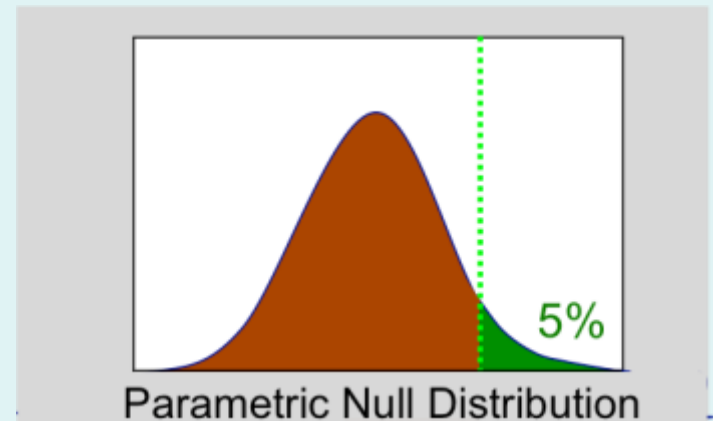
FWHM=20mm

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Non-parametric permutation test

- Parametric methods
 - Assume distribution of statistic under null hypothesis
- 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_0
 - No experimental effect, A & B labels arbitrary
- Statistic
 - Mean difference

Permutation Test : Toy Example

- Under H_0
 - Consider all equivalent relabelings

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

Permutation Test : Toy Example

- Under H_0
 - 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	ABBBA	1.48	BABABA	-9.45	BBBAAA	-4.82

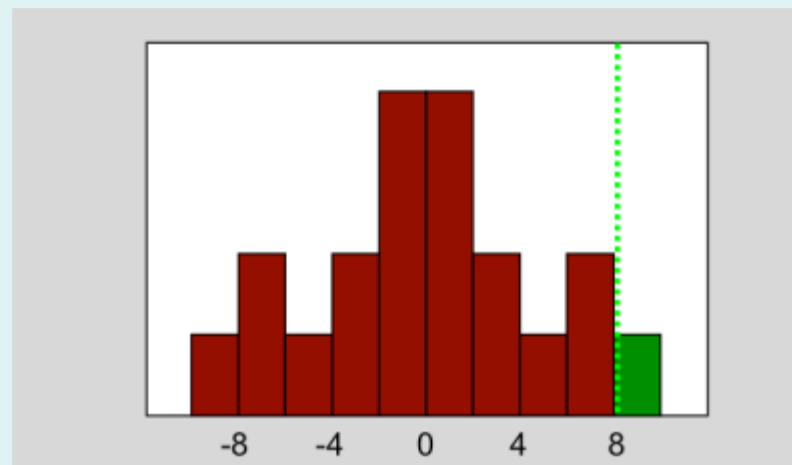
Permutation Test : Toy Example

- Under H_0
 - Consider all equivalent relabelings
 - Compute all possible statistic values
 - Find 95%ile of permutation distribution

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	ABBBA	1.48	BABABA	-9.45	BBBAAA	-4.82

Permutation Test : Toy Example

- Under H_0
 - Consider all equivalent relabelings
 - Compute all possible statistic values
 - Find 95%ile of permutation distribution



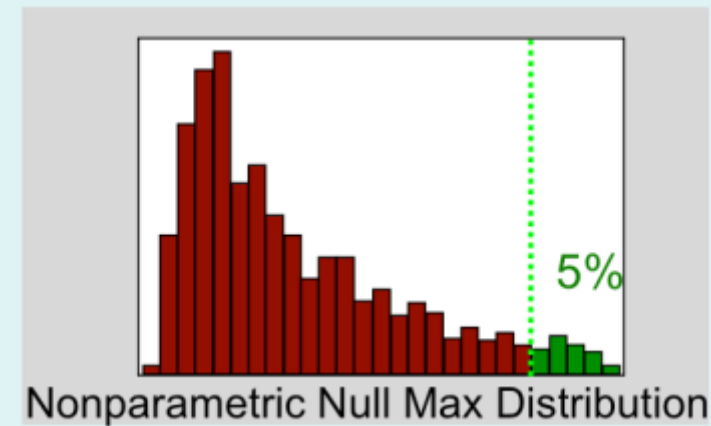
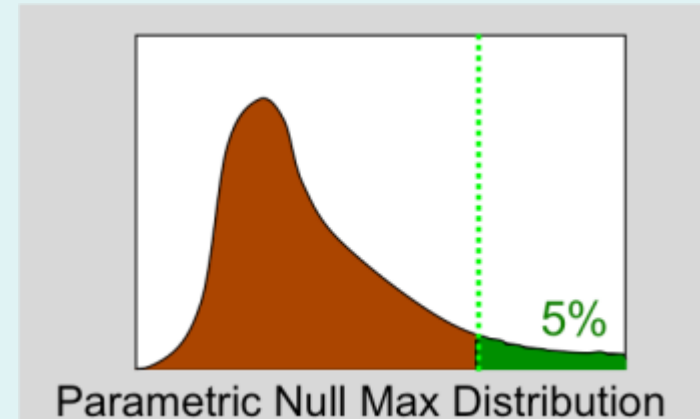
Permutation Test : Toy Example

- Under H_0
 - Consider all equivalent relabelings
 - Compute all possible statistic values
 - Find 95%ile of permutation distribution

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	ABBBA	1.48	BABABA	-9.45	BBBAAA	-4.82

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!



Permutation Test & Exchangeability

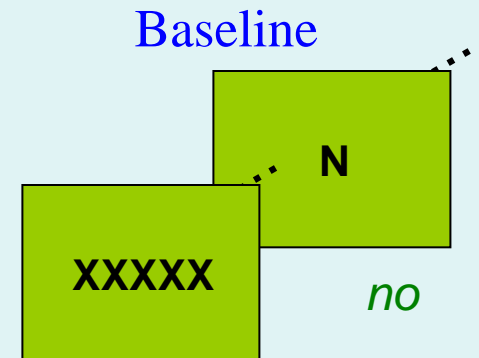
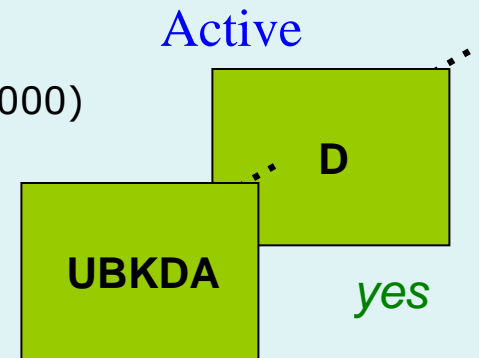
- Exchangeability is fundamental
 - Def: Distribution of the data unperturbed by permutation
 - Under H_0 , exchangeability justifies permuting data
 - Allows us to build permutation distribution
- Subjects are exchangeable
 - Under H_0 , each subject's A/B labels can be flipped
- Are fMRI scans exchangeable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

Permutation Test & Exchangeability

- fMRI scans are *not* exchangeable
 - Permuting disrupts order, temporal autocorrelation
- Intrasubject 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
- Intersubject fMRI permutation test
 - Create difference image for each subject
 - For each permutation, flip sign of some subjects

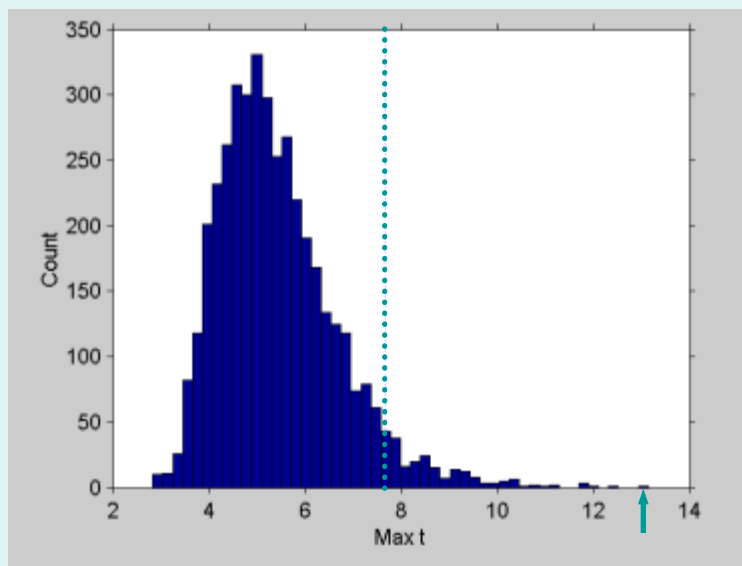
Permutation Test : Example

- 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

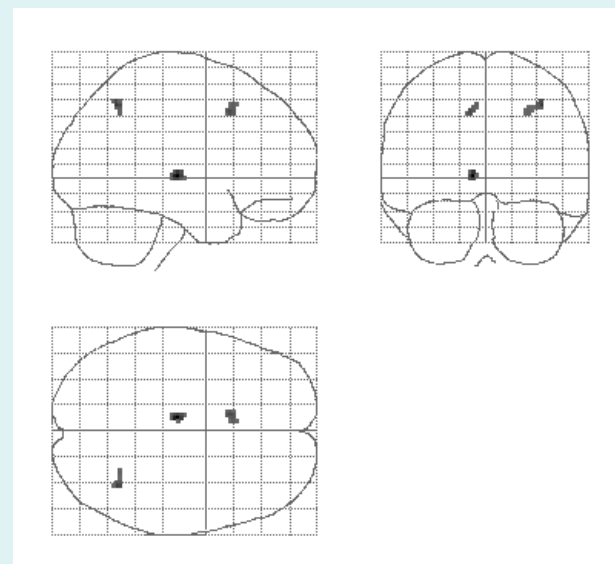


Permutation Test : Example

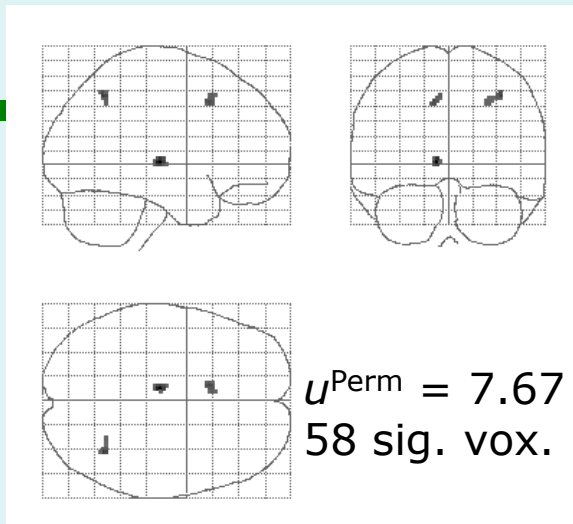
- Permute!
 - $2^{12} = 4,096$ ways to flip 12 A/B labels
 - For each, note maximum of t image



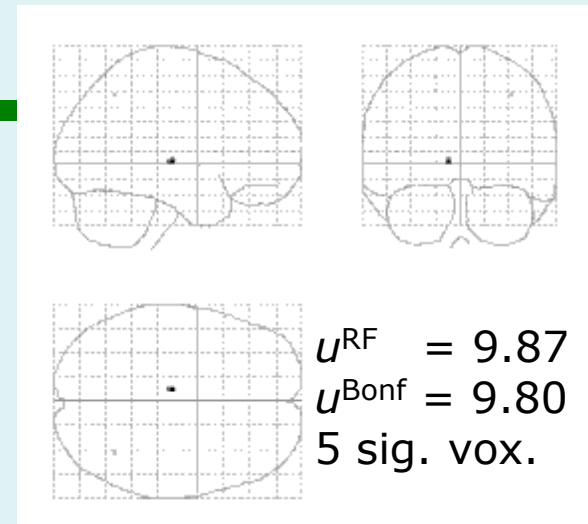
Permutation Distribution
Maximum t



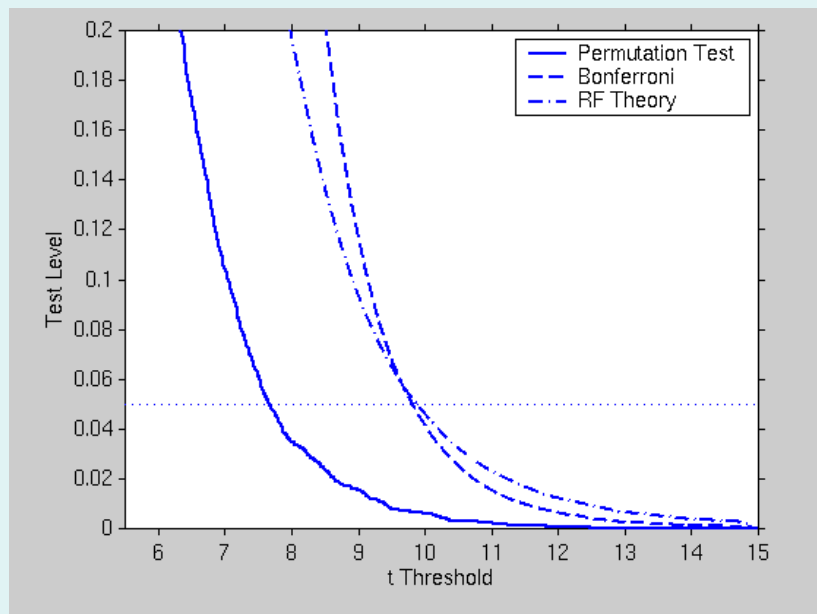
Maximum Intensity Projection
Thresholded t



t_{11} Statistic, Nonparametric Threshold



t_{11} Statistic, RF & Bonf. Threshold



Test Level vs. t_{11} Threshold

- Compare with Bonferroni
 $\alpha = 0.05/110,776$
- Compare with parametric RFT
110,776 $2 \times 2 \times 2$ mm voxels
5.1 \times 5.8 \times 6.9mm FWHM

smoothness
462.9 RESELS

Generalization: RFT vs Bonf. vs Perm.

	df	<i>t</i> Threshold (0.05 Corrected)		
		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.

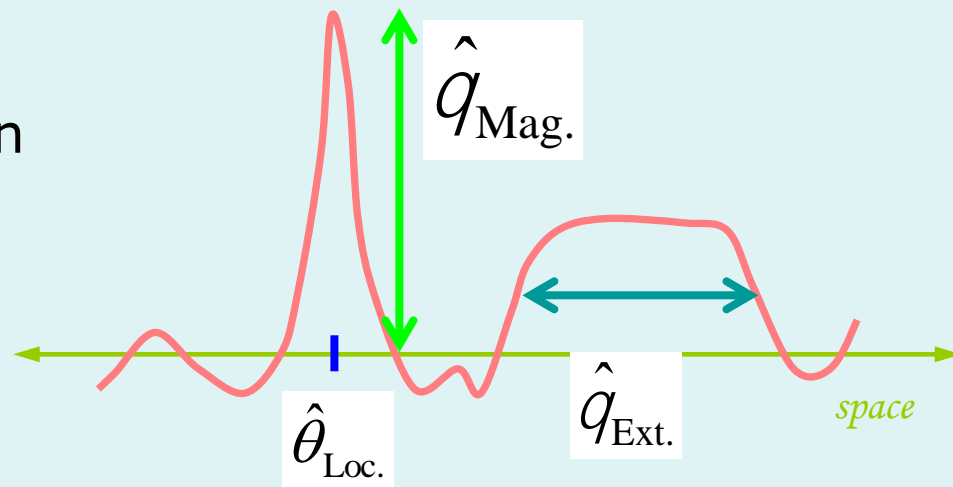
		No. Significant Voxels (0.05 Corrected)		
		<i>t</i>		
	df	RF	Bonf	Perm
Verbal Fluency	4	0	0	0
Location Switching	9	0	0	158
Task Switching	9	4	6	2241
Faces: Main Effect	11	127	371	917
Faces: Interaction	11	0	0	0
Item Recognition	11	5	5	58
Visual Motion	11	626	1260	1480
Emotional Pictures	12	0	0	0
Pain: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

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What we'd like

- Don't threshold, model the signal!
 - Signal **location**?
 - Estimates and CI's on (x,y,z) location
 - Signal **magnitude**?
 - CI's on % change
 - Spatial **extent**?
 - Estimates and CI's on activation volume
 - Robust to choice of cluster definition
- ...but this requires an explicit spatial model



Real-life inference: What we get

- Signal **location**
 - Local maximum – *no inference*
 - Center-of-mass – *no inference*
 - Sensitive to blob-defining-threshold
- Signal **magnitude**
 - Local maximum intensity – P-values (& CI' s)
- Spatial **extent**
 - Cluster volume – P-value, no CI' s
 - Sensitive to blob-defining-threshold

FWER vs. FDR

You **MUST** account for multiplicity
(Otherwise have a fishing expedition)

- FWER
 - Very specific, not very sensitive
- FDR
 - Less specific, more sensitive
(Sociological calibration still underway)

Conclusion

- There is a **multiple testing problem** and corrections *must* be applied on p-values, possibly for the volume of interest only (see SVC).
- Inference is made about **topological features** (peak height, spatial extent, number of clusters). Use results from the **Random Field Theory**. Or **permutation tests**.
- **Control of FWER** (probability of a false positive anywhere in the image) for a space of any dimension and shape.

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Flandin G and Friston KJ. Analysis of family-wise error rates in statistical parametric mapping using random field theory. *Human Brain Mapping*, 2017.

-
- And now a little demo!