All-Resolutions Inference for brain imaging

Flexible Inference for fMRI Data

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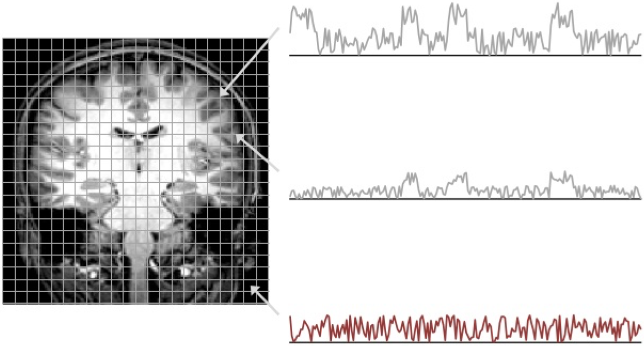
Outline

Volumetric pixels



- fMRI unit of resolution: voxel
- response (BOLD) is measured for every voxel

Go/No-go data

Task

- Go: press a button when you see an happy face ☺
- No-go: hold when you see a neutral face 😐

and vice-versa

High-dimensional data

- $n = 34$ subjects
- $m = 902629$ voxels

Z-score map

- contrast: No-go $>$ Go
- compute the test statistic Z for every voxel

Outline

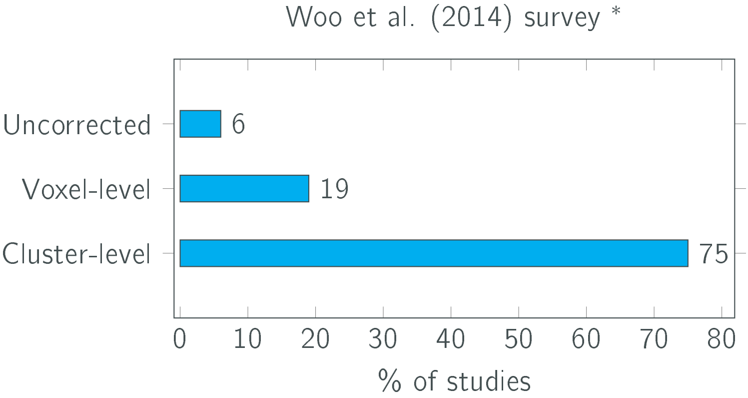
Introduction

Cluster-level Inference

All-Resolutions Inference

Discussion

Most popular approach



* 814 fMRI studies published in 2010 and 2011 from Cerebral Cortex, Nature, Nature Neuroscience, NeuroImage, Neuron, PNAS, and Science

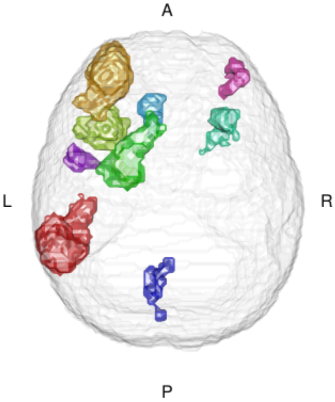
Cluster-level inference

- Cluster-level inference is data-driven: clusters are both defined and tested with the same data
- Issues with circular inference solved by random field theory

1. Cluster definition: specify cluster forming Z-threshold
   e.g. contiguous voxels with $Z > 3.2$
2. Cluster significance: specify RFT α-threshold
   e.g. cluster RFT p-value $< 5\%$ (cluster size $> s_{5\%}$)

Clusters

$\rightarrow$ $Z > 3.2$ and $\alpha = 5\%$ ($s_{5\%} = 161$)
$\leftarrow$ 9 clusters of sizes 2191, 1835, 1400, 698, 421, 304, 245, 232, 187



Low spatial resolution

- Discovering a cluster means that

  "there exists at least one active voxel in the cluster"

  and not that

  "all the voxels in the cluster are active"

- Spatial specificity paradox: the larger the detected cluster, the less information we have on the location of the activation

- No information on the % of activation of each cluster

Low spatial resolution

cluster	*size*	*# active*	*% active*
A	2191	?	?
B	1835	?	?
C	1400	?	?
D	698	?	?
E	421	?	?
F	304	?	?
G	245	?	?
H	232	?	?
I	187	?	?

Notation

- $B = \{1, 2, \ldots, m\}$: brain, collection of m voxels
- $S \subseteq B$: voxel set
- C : cluster (particular case of voxel set)
- $\mathcal{S} = \{S : S \subseteq B\}$ with $|\mathcal{S}| = 2^m$: collection of all voxel sets:
- $A \subseteq B$: (unknown) set of truly active voxels:

Parameter of interest

- $a(S) = |A \cap S|$: # of truly active voxels in S
- $\pi(S) = a(S)/|S|$: % of truly active voxels in S

Cluster null hypothesis

- Given a pre-specified cluster forming Z-threshold, we obtain a collection of clusters $\mathcal{C}$
- Both the number of clusters $|\mathcal{C}|$ and each cluster $C \in \mathcal{C}$ are random quantities, because are determined by the data
- Cluster null hypothesis

$$H_C : \pi(C) = 0$$

- Rejecting H_C implies $\pi(C) > 0$, at least one active voxel in C
- Note that also the null hypotheses are random

Simultaneous confidence bounds

- Simultaneous lower confidence bounds $\bar{\pi}(S)$ for $\pi(S)$ satisfy

$$\mathrm{P}(\text{for all } S \in \mathcal{S} : \bar{\pi}(S) \leq \pi(S)) \geq 1 - \alpha$$

- With probability at least $1 - \alpha$ the lower bound is valid for all S, and therefore for one or more selected S, regardless of how they were selected (after seeing the data, etc.)

All-Resolutions Inference[1]

ARI accounts for 3 layers of circularity:

1. defining clusters
2. testing on clusters
3. testing on voxels within clusters

all with the same data

ARI allows to

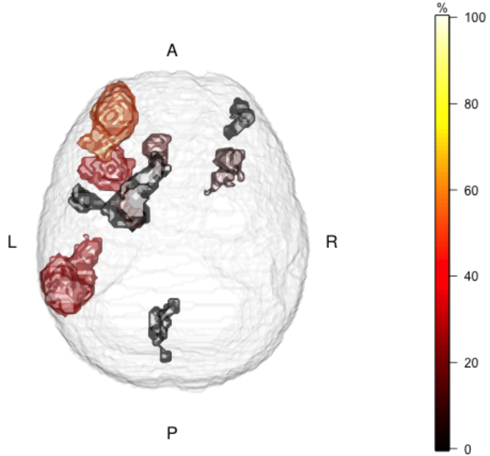
1. quantify the activation of each cluster
2. localize the source of the activation within the cluster: "drill-down" from discovered clusters to sub-clusters

[1] Goeman and Solari (2011) *Statistical Science*

Quantify

cluster	*RFT p-value*	*size*	*# active*	*% active*
A	< .0001	2191	624	29 %
B	< .0001	1835	847	46 %
C	< .0001	1400	454	32 %
D	< .0001	698	0	0 %
E	.0001	421	25	6 %
F	.0034	304	33	11 %
G	.0097	245	0	0 %
H	.0123	232	0	0 %
I	.0291	187	0	0 %

Quantify

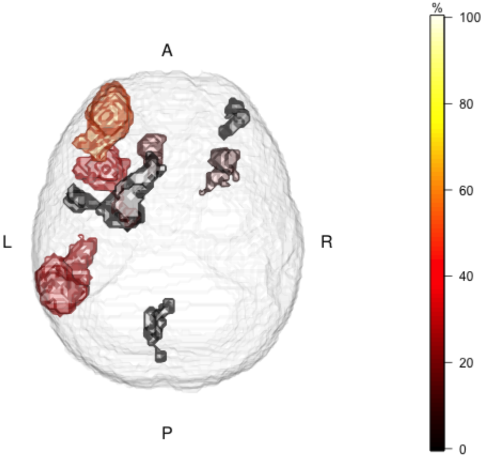


Localize

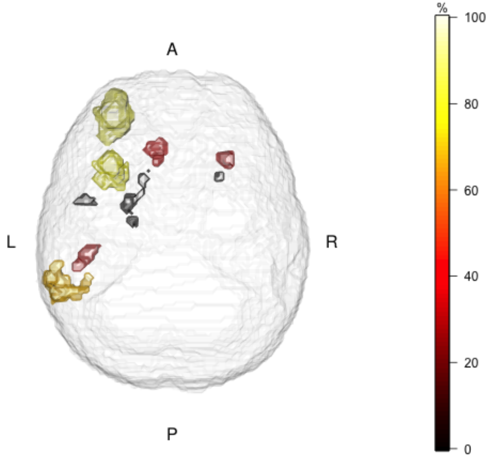
cluster	*threshold*	*RFT p*	*size*	*# active*	*% active*
A	$Z > 3.2$	$< .0001$	2191	624	29 %
1	$Z > 4$	–	405	267	66 %
2	$Z > 4$	–	133	31	23 %
3	$Z > 4$	–	6	0	0 %
B	$Z > 3.2$	$< .0001$	1835	847	46 %
1	$Z > 4$	–	963	826	86 %
C	$Z > 3.2$	$< .0001$	1400	454	32%
1	$Z > 4$	–	583	449	77 %
2	$Z > 4$	–	4	0	0 %
3	$Z > 4$	–	1	0	0 %

⋮

Localize



Localize



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- $A \subseteq B$: (unknown) set of truly active voxels:

- $a(S) = |A \cap S|$: # of truly active voxels in S
- $\pi(S) = a(S)/|S|$: % of truly active voxels in S

All-Resolutions Inference

- Derive simultaneous lower confidence bounds $\bar{\pi}(S)$ for $\pi(S)$:

$$\mathrm{P}(\text{for all } S \in \mathcal{S} : \bar{\pi}(S) \leq \pi(S)) \geq 1 - \alpha$$

- With probability at least $1 - \alpha$ the lower bound is valid for all S, and therefore for one or more selected S, regardless of how they were selected (after seeing the data, etc.)

Simes test

Test the null hypothesis

$$H_S : a(S) = 0$$

with the Simes test

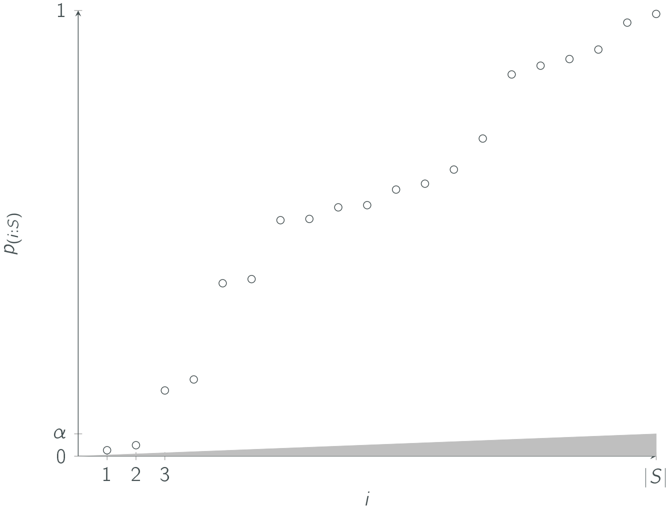
$$p_S = \min_{1 \leq i \leq |S|} \frac{|S|}{i} p_{(i:S)}$$

Reject H_S if $p_S \leq \alpha$

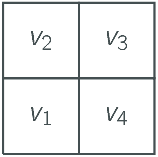
ARI assumption

$\mathrm{P}(p_{B \setminus A} \leq \alpha) \leq \alpha$

Simes inequality



Toy example



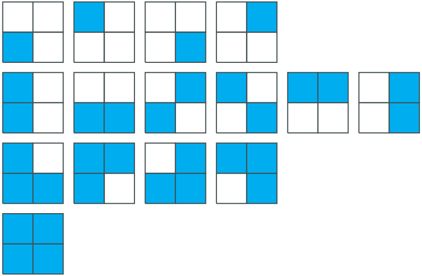
- $p_1 = 0.020$
- $p_2 = 0.026$
- $p_3 = 0.032$
- $p_4 = 0.500$

$|S| = 1$

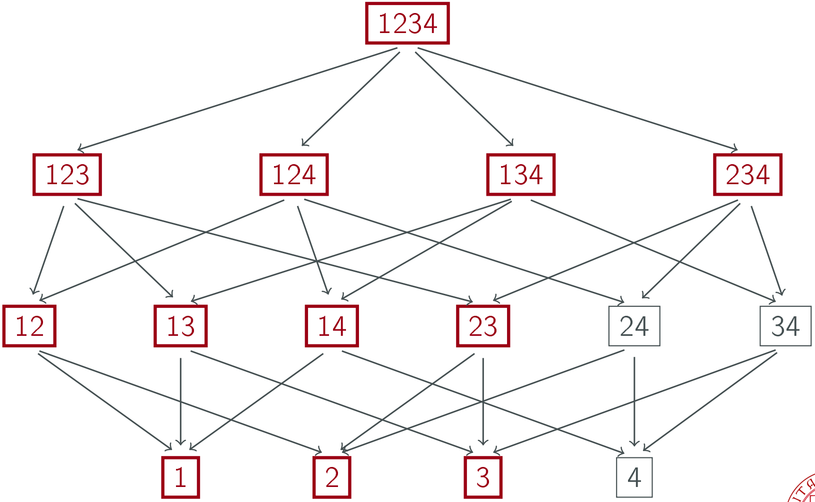
$|S| = 2$

$|S| = 3$

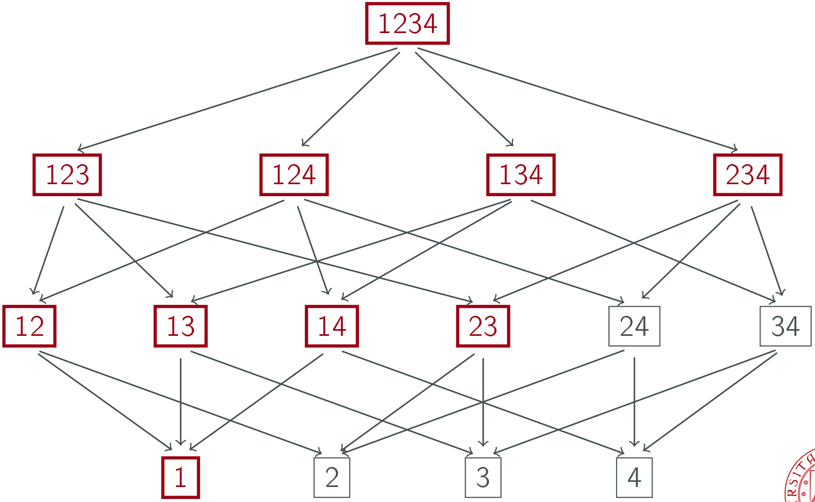
$|S| = 4$



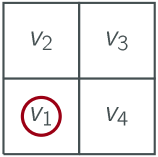
Simes test rejections (local test, raw-p)



Closed testing correction (adjusted-p, multiple testing)



Number of truly active voxels

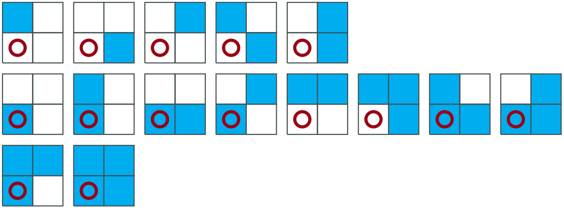


- $p_1 = 0.020$
- $p_2 = 0.026$
- $p_3 = 0.032$
- $p_4 = 0.500$

$a(S) \geq 0$

$a(S) \geq 1$

$a(S) \geq 2$



with statements simultaneously true with probability 95%

Outline

Discussion

- Flexibility of ARI: users can iterate the process of
  1. choosing regions in any way, also after seeing the data
  2. quantify the % of activation
  3. redefine the regions

  without compromising the validity of the inference
- Implemented in C++: take seconds
- Package `hommel` on CRAN.
  Package `ARIbrain` on CRAN implement the method for fMRI data.