Screening for Partial Conjunction Hypotheses

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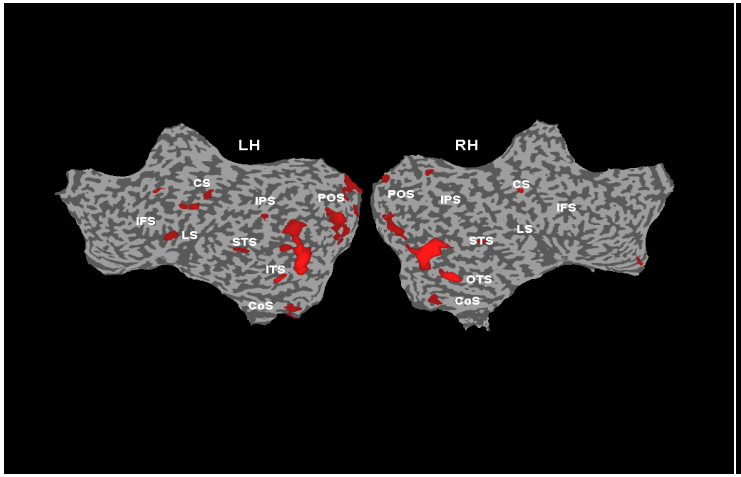
An fMRI Vision Experiment

The brain activity is measured in tens of thousands of brain locations while the subject views 4 visual stimuli:
(i) faces (ii) houses (iii) common man-made objects and (iv) geometric patterns.

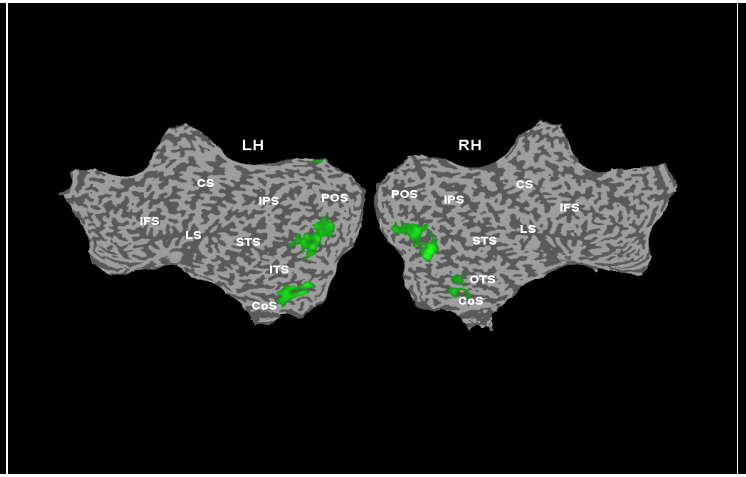
How to find the regions that were more active during most of (i)-(iii) than (iv)?

For each contrast, used the BH procedure to control the FDR at the 0.05 level.

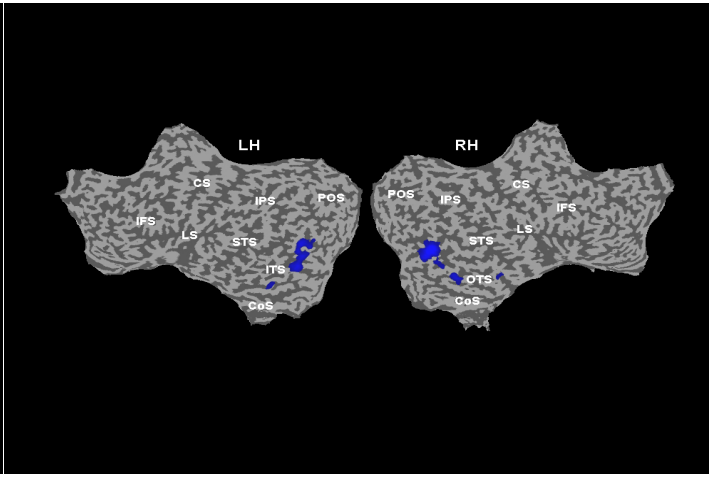
a) Faces vs. Patterns



b) Houses vs. Patterns



c) Objects vs. Patterns



The FDR level of the conjunction of maps may be as high as 1.

Combining Maps

Two possibilities:

1. Threshold each map at an FDR level $q' < q$.

   complicated and conservative

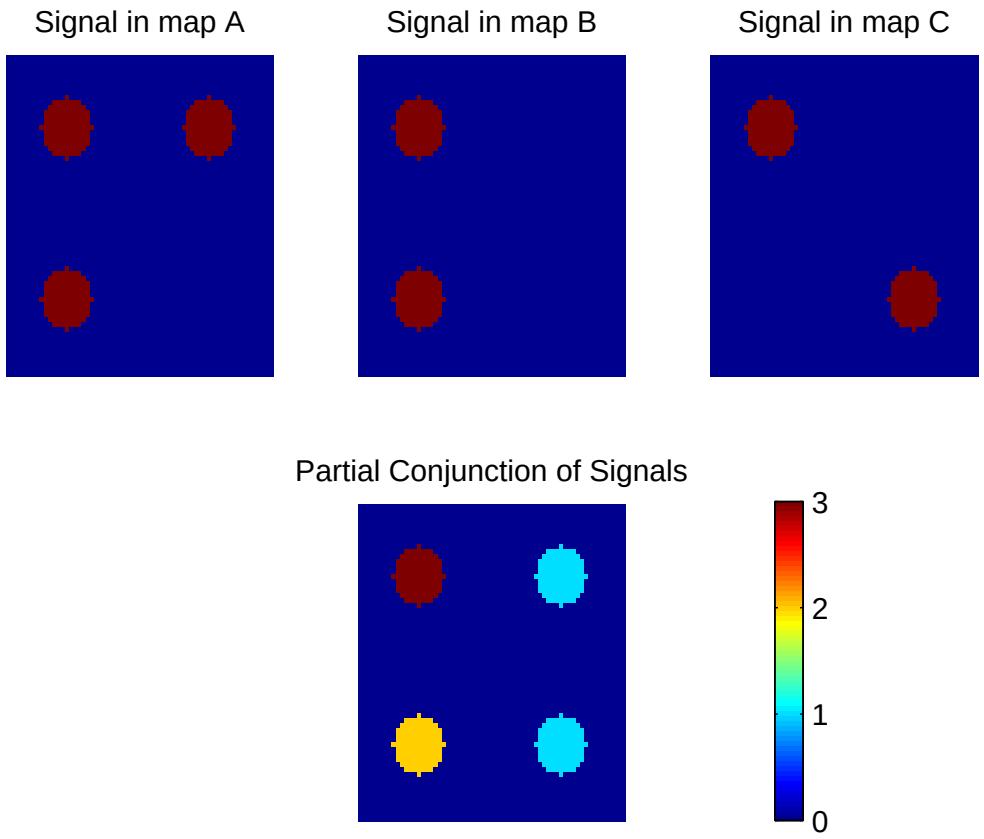
2. Combine the p-values in each location into a pooled p-value and threshold the resulting p-value map at an FDR level q.

   simple and powerful

Source 1 $\quad \ldots \quad$ Source n

$$\begin{bmatrix} p_{11} \\ \vdots \\ p_{i1} \\ \vdots \\ p_{M1} \end{bmatrix} \quad \ldots \quad \begin{bmatrix} p_{1n} \\ \vdots \\ p_{in} \\ \vdots \\ p_{Mn} \end{bmatrix}$$

The Scientific Statement when Combining Maps



In which locations the null hypothesis is false in at least one map? at least two maps? all maps?

The Partial Conjunction Hypothesis Test

Have n hypotheses at location i ($i = 1, \ldots, M$) :

$H_{1i}^{u/n}$: At least u alternatives are true

versus

$H_{0i}^{u/n}$:At most $u-1$ alternatives are true (i.e. at least $n-u+1$ nulls are true)

Extreme cases:

1. $H_{0i}^{n/n}$ is the **Conjunction Null**: At least one null hypothesis is true.

   $H_{1i}^{n/n}$ is the **Conjunction Alternative**: All alternatives are true .

   Difficult to reject in practice when screening a large # of conjunction nulls.

2. $H_{0i}^{1/n}$ is the **Global Null**: All null hypotheses are true.

   $H_{1i}^{1/n}$ is the **Global Alternative**: At least one alternative is true.

   Often too general to be scientifically meaningful.

Existing Methods for Combining P-values

- For testing $H_{0i}^{n/n}$: the maximum p-value $p_i^{n/n} = p_{i(n)} \leq \alpha$.
- For testing $H_{0i}^{1/n}$:
  1. For independent p-values, Fisher's combining method (among others):

$$p_i^{1/n} = P(\chi^2_{2n} \geq -2\sum_{j=1}^{n} \log p_{ij}) \leq \alpha$$

  2. For PRDS p-values (e.g. all treatments compared to the same control), Simes test: $p_{i(1)} \leq \ldots \leq p_{i(n)}$, Reject $H_{0i}^{1/n}$ if $\exists \quad j \quad s.t. \quad p_{i(j)} \leq \frac{j}{n}\alpha \iff$

$$p_i^{1/n} = \min_{j=1,\ldots,n} \{\frac{n}{j} p_{i(j)}\} \leq \alpha$$

  3. For dependent p-values, Bonferroni's test:
     Reject $H_{0i}^{1/n}$ if $\exists\, j \;\; p_{i(j)} \leq \frac{1}{n}\alpha \iff$

$$p_i^{1/n} = np_{i(1)} \leq \alpha$$

PRDS property : $P(p_v \in A, v = 1, \ldots, V | p_v = x)$ is non-decreasing in x for any increasing set A and any $p_v \in I_0$, where I_0 is the set of null hypotheses.

Our Generalizations

1. For testing the partial conjunction null $H_{0i}^{u/n}, \quad 1 \leq u \leq n$, we generalize the combining methods to derive valid p-values, in the sense that

   $p_i^{u/n} \overset{H_{0i}^{u/n}}{\sim} U(0,1)$ or $\underset{\text{st}}{\succ} U(0,1)$.

2. Screen these valid p-values across locations while controlling for the FDR.

Combining p-Values under Independence

The p-value for testing $H_{0i}^{u/n}$ motivated by the Fisher method

$$p_i^{u/n} = P(\chi^2_{2(n-u+1)} \geq -2\sum_{j=u}^{n} \log p_{i(j)})$$

If the p-values are 0.5, 0.022, 0.01 then

$$\begin{aligned} p_i^{1/3} &= P(\chi^2_6 \geq -2(log(0.5) + log(0.022) + log(0.01))) = 0.0057 \\ p_i^{2/3} &= P(\chi^2_4 \geq -2(log(0.5) + log(0.022))) = 0.061 \\ p_i^{3/3} &= 0.5 \end{aligned}$$

Theorem. If the set of null p-values at location i are independent , then $p_i^{u/n}$ is a valid p-value for testing $H_{0i}^{u/n}$.

Sufficient Conditions for Valid Combining Methods

The pooled p-value for testing $H_{0i}^{u/n}$ will be valid if:

1. The combining function $p_i^{u/n} = f(p_{i1}, \ldots, p_{in})$ is increasing in $p_{ij}\ \forall\ j = 1, \ldots, n$.

   The stochastically smallest p-value under the null is $f(U_1, \ldots, U_{n-u+1}, 0, \ldots, 0), \quad U_j \sim U(0,1) \quad j = 1, \ldots, n-u+1$.

2. The combining function combines only the $n-u+1$ largest p-values.

3. The combining function is a valid one for testing $H_{0i}^{1/(n-u+1)}$.

   Then

$$f(U_1, \ldots, U_{n-u+1}, 0, \ldots, 0) \sim U(0,1) \text{ or } \underset{\text{st}}{\succ} U(0,1)$$

Combining p-Values under Dependence

For testing $H_{0i}^{u/n}$:

- The pooled p-value motivated by the Simes method

$$p_i^{u/n} = \min_{j=1,\ldots n-u+1} \{ \frac{(n-u+1)}{j} p_{i(u-1+j)} \}$$

Theorem. If the set of null p-values at location i are independent or satisfy the PRDS property, then $p_i^{u/n}$ is a valid p-value for testing $H_{0i}^{u/n}$.

- The pooled p-value motivated by the Bonferroni method is

$$p_i^{u/n} = (n-u+1) p_{i(u)}$$

Theorem. $p_i^{u/n}$ is a valid p-value for testing $H_{0i}^{u/n}$.

Screening for Partial Conjunction Hypotheses

1. Specify the scientifically appropriate u for testing the partial conjunction null $H_{0i}^{u/n}$.

2. For every location i combine the largest $n-u+1$ p-values into a single valid p-value $p_i^{u/n}$.

3. Use an FDR controlling procedure on the pooled location p-values $\{p_i^{u/n} : i = 1, \ldots, M\}$.

Do the FDR controlling procedures control the FDR?

This depends on the dependency **within** the map of pooled p-values.

If p-values **within** every map are

1. independent then the pooled p-values are independent

   $\Longrightarrow$ use any FDR controlling procedure.

2. PRDS then the pooled p-values are PRDS in the extreme null configuration if pooled using the method motivated by Fisher (conjecture: Simes and Bonferroni)

   $\Longrightarrow$ use the BH procedure.

3. locally dependent then the pooled p-values are locally dependent

   $\Longrightarrow$ use any asymptotically valid FDR controlling procedure.

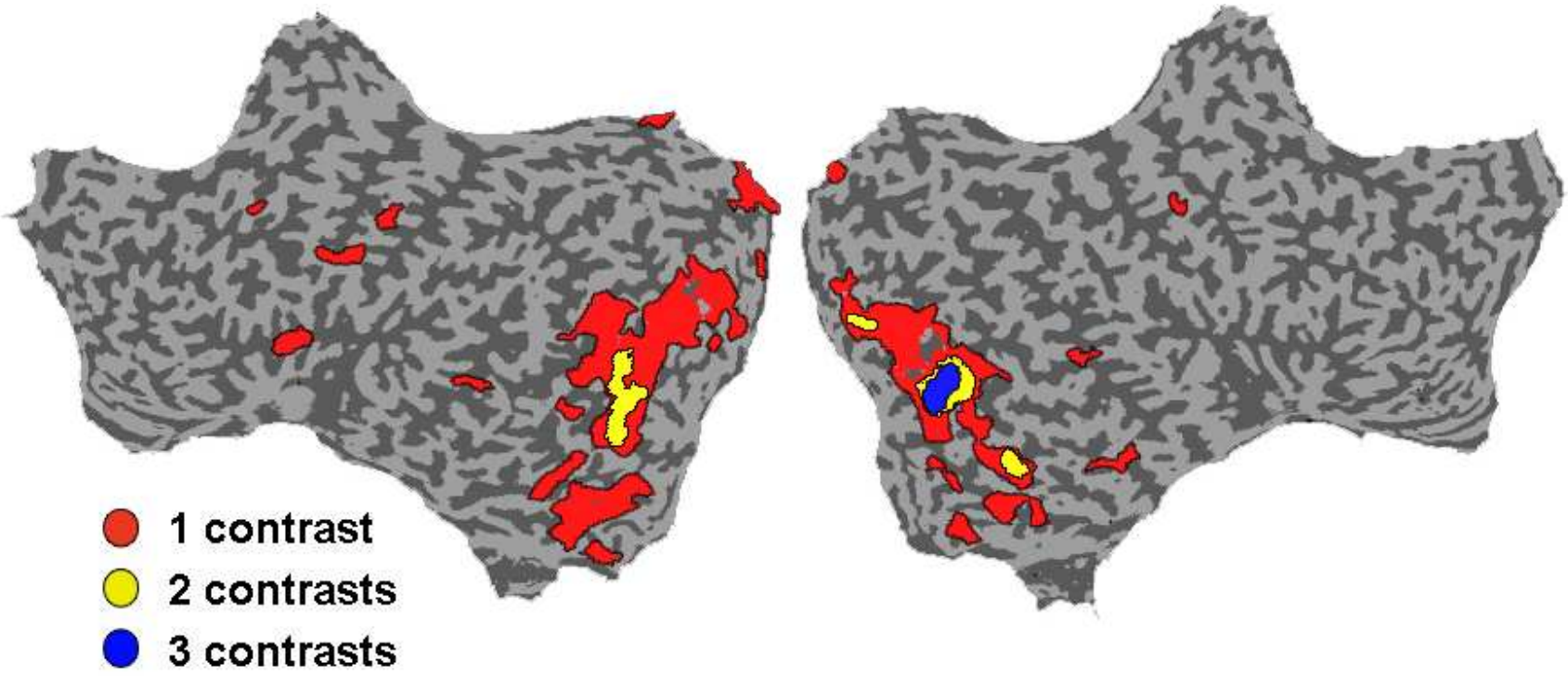
Application to the fMRI Vision Experiment

Experiment: Subject views 4 visual stimuli (1) faces (2) houses (3) common man-made objects and (4) geometric patterns.

Goal: to find the regions that were more active during the (1)-(3) than (4).

Method: Pooled p-values using Simes, BH procedure at level 0.05.

Results: Regions that were found to react to: all 3 contrasts are colored in blue; at least 2 contrasts are colored in blue or yellow; at least 1 contrast are colored in blue, yellow or red.



Application to Microarray Meta-Analysis

- The expression level of thousands of genes are simultaneously measured.
- Have several experiments (labs) that examine the same problem.

  How to identify genes that are consistently differentially expressed in most experiments?

	Microarray 1	...	Microarray n
gene 1	p_{11}		p_{1n}
⋮	⋮		⋮
gene i	p_{i1}	...	p_{in}
⋮	⋮		⋮
gene M	p_{M1}		p_{Mn}

Microarray Data Example

Data: Three ChIP-chip genome-wide TF binding datasets.

Goal: Meta-analysis for the protein Swi4.

Methods:

1. Screening for partial conjunctions:
   Pooled p-values using Fisher, BH procedure at level 0.05.

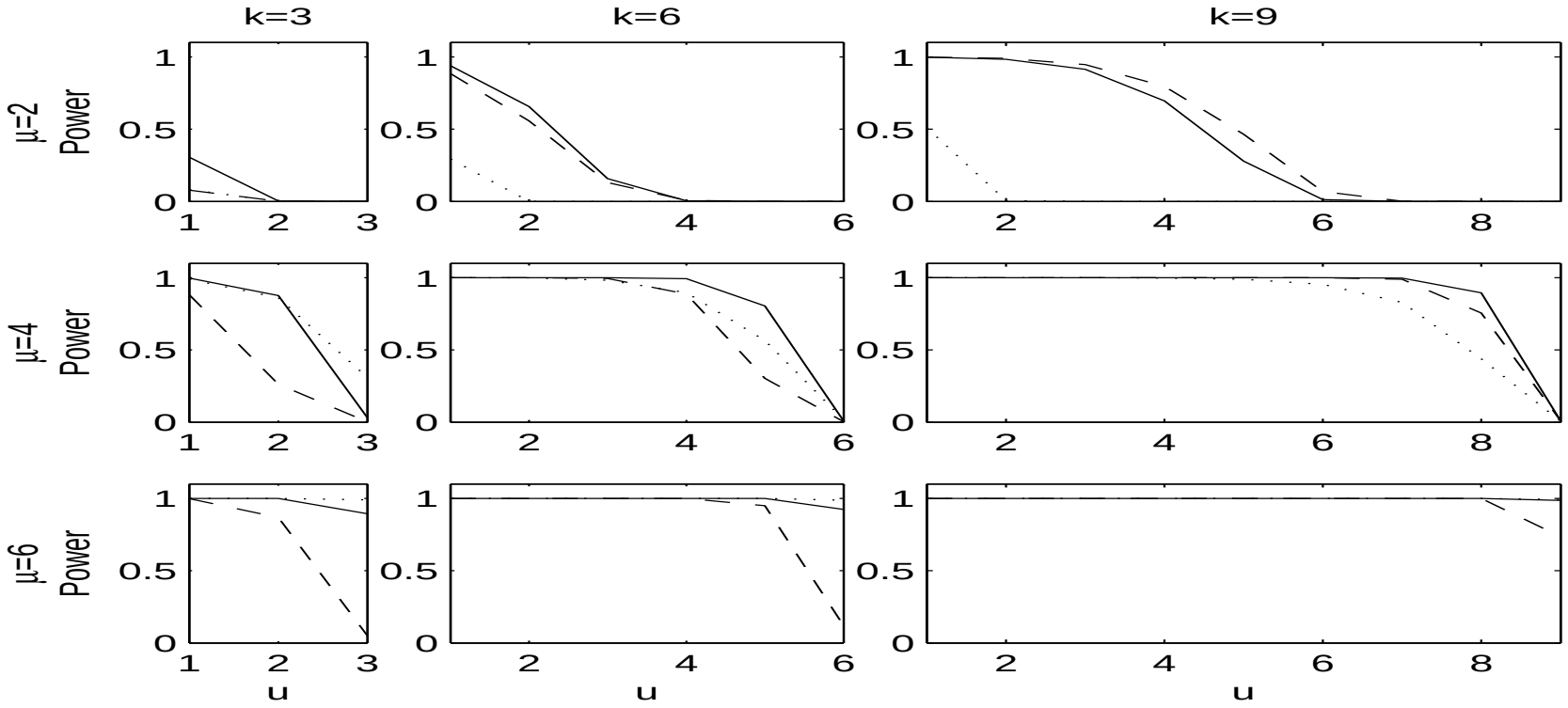
2. Naive: Threshold each map with the BH procedure at level 0.05, then combine the threshold maps. The Naive method does not control the FDR.

Results: Number of significant genes for swi4

	All 3	At least 2	At least 1
Screening for partial conjunctions	73	176	305
Naive method	78	121	161

A Simulation Example: Combine 10 Maps

Power as a function of u for the pooled p-value motivated by Simes (blue) and by Fisher (black), for testing $H_{0i}^{u/10} : k(i) < u$, $i = 1, \ldots, 1000$ using the BH procedure at level 0.05.
(setting: 100 locations had a signal size μ in k repetitions).



Supp: The BH Procedure

1. For every hypothesis $v,\ v \in \{1, \ldots, V\}$, compute a p-value.
2. Sort the p-values $p_{(1)} \leq \ldots \leq p_{(V)}$.
3. Let $k = max\{j : p_{(j)} \leq (j/V)q\}$.

   Reject all voxels corresponding to the k smallest p-values.

[Benjamini and Yekutieli, 2001] show that $\mathrm{FDR} \leq \mathrm{q}$ for p-values that are independent as well as PRDS.

PRDS property : $P(p_v \in A, v = 1, \ldots, V | p_v = x)$ is non-decreasing in x for any increasing set A and any $p_v \in I_0$, where I_0 is the set of null hypotheses.

Bibliography

[Benjamini and Hochberg, 1995] Benjamini, Y. and Hochberg, Y. (1995). Controlling the false discovery rate - a practical and powerful approach to multiple testing. *J. Roy. Stat. Soc. B Met.*, 57 (1):289–300.

[Benjamini and Yekutieli, 2001] Benjamini, Y. and Yekutieli, Y. (2001). The control of the false discovery rate in multiple testing under dependency. *The Annals of Statistics*, 29 (4):1165–1188.