FDP control in multivariate linear models using the bootstrap

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Notation and general framework

Random Fields on a lattice

Definition

Given $D, L \in \mathbb{N}$ and a finite set $\mathcal{V} \subset \mathbb{R}^D$, we define a **random field** on $\mathcal{V}$ to be a random function $f : \mathcal{V} \to \mathbb{R}^L$. We will say that f has **dimension** L.

Definition

Given functions $\mu : \mathcal{V} \to \mathbb{R}^L$ and $\mathfrak{c} : \mathcal{V} \times \mathcal{V} \to \mathbb{R}$ we write $f \sim \mathcal{G}(\mu, \mathfrak{c})$ if f is a random field on $\mathcal{V}$ with mean μ and covariance $\mathfrak{c}(u, v) = \mathrm{cov}(f(u), f(v))$ and such that $\mathrm{vec}(f)$ has a multivariate Gaussian distribution.

Linear Model

Suppose that we observe random fields $y_i : \mathcal{V} \to \mathbb{R}$, for $1 \leq i \leq n$ and some number of subjects n. At each voxel we assume that

$$Y_n(v) = X_n\beta(v) + E_n(v)$$

- $Y_n(v) = [y_1(v), \dots, y_n(v)]^T$: the response at each $v \in \mathcal{V}$
- $\beta : \mathcal{V} \to \mathbb{R}^p$: vector of parameters
- X_n: design matrix (which is itself random)
- $E_n = [\epsilon_1, \dots, \epsilon_n]^T$ - the noise - is an n-dimensional random field. We will assume that $(\epsilon_m)_{m\in\mathbb{N}}$ is an i.i.d sequence.

Testing contrasts

Then given contrasts, $c_1, \dots, c_L \in \mathbb{R}^p$ for some number of contrasts $L \in \mathbb{N}$, we are interested in testing the null hypotheses:

$$H_{0,l}(v) : c_l^T \beta(v) = 0$$

for $1 \leq l \leq L$ and each $v \in \mathcal{V}$.
We can test these using the t-statistic:

$$T_{n,l}(v) = \frac{c_l^T \hat{\beta}_n(v)}{\sqrt{\hat{\sigma}_n(v)^2 c_l^T (X_n^T X_n)^{-1} c_l}}. \tag{1}$$

Obtaining p-values

For $n \in \mathbb{N}$, $1 \leq l \leq L$ and $v \in \mathcal{V}$ we can define p-values,

$$p_{n,l}(v) = 2(1 - \Phi_{n-r_n}(|T_{n,l}(v)|)) \tag{2}$$

where Φ_{n-r_n} is the CDF of a t-statistic with $n - r_n$ degrees of freedom.

- These are asymptotically valid
- Under an additional assumption of Gaussianity they are valid in the finite sample

Simultaneous coverage

- Let $\mathcal{H} = \{(l, v) : 1 \leq l \leq L \text{ and } v \in \mathcal{V}\}$ and $m = |\mathcal{H}|$.
- For $H \subseteq \mathcal{H}$, let $|H|$ denote the number of elements within H.
- let $\mathcal{N} \subset \mathcal{H}$ index the null hypotheses.

Given $0 < \alpha < 1$ we want,

$$V : \{H : H \subset \mathcal{H}\} \to \mathbb{N}$$

such that

$$\mathbb{P}(|S \cap \mathcal{N}| \leq V(S), \ \forall S \subset \mathcal{H}) \geq 1 - \alpha. \tag{3}$$

If (3) holds then, with probability $1 - \alpha$, simultaneously over all $S \subset \mathcal{H}$, $V(S)$ provides a upper bound on the number of false positives within S.

Joint Error Rate (JER)

Define the **joint error rate (JER)** of the collection $(R_k)_{1\leq k\leq K} \subset \mathcal{H}$

$$\text{JER}((R_k(\lambda))_{1\leq k\leq K}) := \mathbb{P}(|R_k \cap \mathcal{N}| > k-1, \text{ some } 1 \leq k \leq K) \tag{4}$$

(Blanchard, Neuvial, Roquain, et al., 2020) showed that if

$$\text{JER}((R_k)_{1\leq k\leq K}) \leq \alpha$$

then the bound $\overline{V}_\alpha : \{H : H \subset \mathcal{H}\} \to \mathbb{R}$, sending $S \subset \mathcal{H}$ to

$$\overline{V}_\alpha(S) = \min_{1\leq k\leq K}(|S \setminus R_k| + k - 1) \wedge |S|, \tag{5}$$

satisfies (3) and thus provides an α-level bound over the number of false positives within each chosen rejection set.

Template Families

Let $K \in \mathbb{N}$ and suppose we have a set of, strictly increasing and continuous template functions

$$t_k : [0,1] \to \mathbb{R} \tag{6}$$

for each $1 \leq k \leq K$. Given $n \in \mathbb{N}$, define

$$R_k(\lambda) = \{(l, v) \in \mathcal{H} : p_{n,l}(v) \leq t_k(\lambda)\},$$

for each $\lambda \in [0,1]$. We will refer to the collection $(R_k(\lambda))_{1 \leq k \leq K}$ as the canonical reference family. The simplest example is the linear template family i.e. $t_k(\lambda) = \frac{\lambda k}{K}$.

Controlling the JER

Let $p^n_{(k:\mathcal{N})}$ be the kth smallest p-value in the set $\{p_{n,l}(v) : (l, v) \in \mathcal{N}\}$ (and set $p^n_{(k:\mathcal{N})} = 1$ if $k > |\mathcal{N}|$).

Claim

For each $\lambda \in [0, 1]$,

$$JER((R_k(\lambda))_{1\leq k\leq K}) = \mathbb{P}\left(\min_{1\leq k\leq K\wedge|\mathcal{H}|} t_k^{-1}(p^n_{(k:\mathcal{N})}) \leq \lambda \right).$$

Bootstrapping in the Linear Model

Bootstrapping

Let

$$\hat{E}_n = Y_n - X_n\hat{\beta}_n = (I_n - X_n(X_n^TX_n)^{-1}X_n^T)E_n.$$

where I_n is the $n \times n$ identity matrix and

$$\hat{\beta}_n = (X_n^TX_n)^{-1}X_n^TY_n = \beta + (X_n^TX_n)^{-1}X_n^TE_n.$$

Given $B \in \mathbb{N}$ for each $1 \leq b \leq B$, conditional on the data, $\hat{\epsilon}_1^b, \dots, \hat{\epsilon}_n^b$ are chosen independently with replacement from $\left\{\hat{E}_{n,1}, \dots, \hat{E}_{n,n}\right\}$ resulting in a combined random field $E_n^b = [\hat{\epsilon}_1^b, \dots, \hat{\epsilon}_n^b]^T$. Let

$$Y_n^b = X_n\hat{\beta}_n + E_n^b$$

and let

$$\hat{\beta}_n^b = (X_n^TX_n)^{-1}X_n^TY_n^b$$

be the bootstrapped parameter estimates.

Assumptions

Assumption

- (a) For $n \in \mathbb{N}$, $X_n = [x_1, \dots, x_n]^T$ for a sequence of i.i.d vectors $(x_n)_{n\in\mathbb{N}}$ whose multivariate density is bounded above and that $\mathbb{E}(||x_1||^{5/2}) < \infty$.
- (b) Assume that $\mathrm{var}(\epsilon_1(v)) < \infty$ for all $v \in \mathcal{V}$ and that $(x_m)_{m\in\mathbb{N}}$ and $(\epsilon_m)_{m\in\mathbb{N}}$ are independent.

CLT for $\hat{\beta}_n^b$

Theorem

(Bootstrap convergence.) Suppose that $(X_m)_{m\in\mathbb{N}}$ *and* $(\epsilon_m)_{m\in\mathbb{N}}$ *satisfy Assumption 1. Then conditional on* $(X_m, Y_m)_{m\in\mathbb{N}}$*, for almost every sequence* $(X_m, Y_m)_{m\in\mathbb{N}}$*, for each* $1 \leq b \leq B$*,*

$$\sqrt{n}(\hat{\beta}_n^b - \hat{\beta}_n) \xrightarrow{d} \mathcal{G}(0, \mathfrak{c}_\epsilon \Sigma_X^{-1}).$$

- (Freedman, 1981) proved a version of this in 1D based on convergence in the Mallows metric using ideas from (Bickel & Freedman, 1981).
- (Eck, 2018) extended this proof to the multivariate case.
- We have a (substantially simpler) proof based on the Lindeberg CLT which has not to our knowledge been written down before.

Convergence of the bootstrapped t-statistics

Theorem

(Bootstrap test-statistic convergence.) Suppose that $(X_m)_{m\in\mathbb{N}}$ *and* $(\epsilon_m)_{m\in\mathbb{N}}$ *satisfy Assumption 1 and, for each* $1 \leq b \leq B$, *let* $T_n^b : \mathcal{V} \rightarrow \mathbb{R}$ *be the* L*-dimensional random field on* $\mathcal{V}$ *such that, for* $1 \leq l \leq L$,

$$T_{n,l}^b = \frac{c_l^T(\hat{\beta}_n^b - \hat{\beta}_n)}{\hat{\sigma}_n^b\sqrt{c_l^T(X_n^TX_n)^{-1}c_l}}.$$

Then conditional on $(X_m, Y_m)_{m\in\mathbb{N}}$, *for almost every sequence* $(X_m, Y_m)_{m\in\mathbb{N}}$, *for each* $1 \leq b \leq B$,

$$T_n^b \xrightarrow{d} \mathcal{G}(0, \mathfrak{c}')$$

as $n \rightarrow \infty$. *In particular it follows that*

$$T_n^b|_{\mathcal{N}} \xrightarrow{d} \mathcal{G}(0, \mathfrak{c}')|_{\mathcal{N}}.$$

JER Control in the Linear Model

Bootstrapped quantile

Let $f_n : \left\{ g : \mathcal{V} \rightarrow \mathbb{R}^L \right\} \rightarrow \mathbb{R}$ send

$$T \mapsto \min_{1 \leq k \leq K \wedge |\mathcal{N}|} t_k^{-1}(p^n_{(k:\mathcal{N})}(T))$$

For each $n, B \in \mathbb{N}$ and $0 < \alpha < 1$, define the α-quantile of the bootstrapped distribution of $f_n(T_n)$ as

$$\lambda^*_{\alpha,n,B} = \inf \left\{ \lambda : \frac{1}{B} \sum_{b=1}^{B} 1 \left[f_n(T_n^b) \leq \lambda \right] \geq \alpha \right\}.$$

Main Result

Theorem

Assume Assumption 1 holds and that $r_n = o(n)$.

Then,

$$\lim_{n\to\infty}\lim_{B\to\infty} JER\Big((R_k(\lambda^*_{\alpha,n,B}))_{1\leq k\leq K}\Big) = \lim_{n\to\infty}\lim_{B\to\infty}\mathbb{P}\left(\min_{1\leq k\leq K\wedge|\mathcal{H}|} t_k^{-1}(p^n_{(k:\mathcal{N})}) \leq \lambda^*_{\alpha,n,B}\right) = \lim_{n\to\infty}\lim_{B\to\infty}\mathbb{P}\Big(f_n(T_n)\leq \lambda^*_{\alpha,n,B}\Big) = \alpha$$

I.e. the joint error rate is asymptotically bounded at a level α.

Iterating a step down version of this procedure is available.

Simes Bound

Under PRDS, for $0 < \alpha < 1$, the Simes inequality implies that

$$\mathbb{P}\left(\exists k \in \{1, \dots, m\} : p^n_{(k:\mathcal{N})} < \frac{\alpha k}{m}\right) \leq \frac{\alpha|\mathcal{N}|}{m}.$$

Thus defining the linear template family as $t_k(x) = \frac{xk}{m}$, it follows that

$$\text{JER} = \mathbb{P}\left(\min_{1 \leq k \leq K \wedge |\mathcal{H}|} t_k^{-1}(p^n_{(k:\mathcal{N})}) \leq \alpha\right) \leq \alpha.$$

Thus $\overline{V}_\alpha$ (constructed using the sets $R_k(\alpha)$) is a valid post-hoc bound.

- This works best under independence as then the inequality becomes exact.
- PRDS may not hold (especially in the contrast cases);

ARI

(Rosenblatt, Finos, Weeda, Solari, & Goeman, 2018) introduced a version of this that estimates $|\mathcal{N}|$ using the hommel value h. It can be shown that under PRDS,

$$\text{JER} = \mathbb{P}\left(\min_{1 \leq k \leq K \wedge |\mathcal{H}|} t_k^{-1}(p^n_{(k:\mathcal{N})}) \leq \frac{\alpha m}{h} \right) \leq \alpha.$$

- The $\overline{V}_{\frac{\alpha m}{h}}$ (constructed using the sets $R_k(\frac{\alpha m}{h})$) is thus a valid post-hoc bound.
- Known as All Resolutions Inference or (ARI)
- It's the step down version of the Simes bound

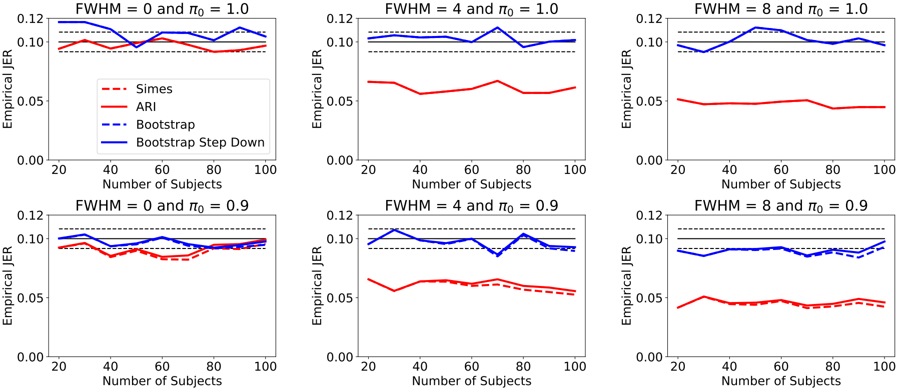
Results

Simulation description

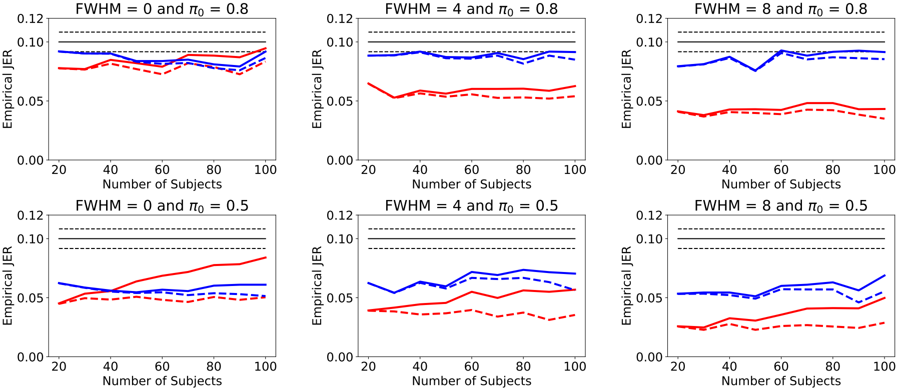
We ran 2D simulations to test the performance of the methods.

- 50×50 GRFs smoothed with FWHM $= 0, 4, 8$
- $N = \{20, 30, \ldots, 100\}$ subjects
- randomly divided the subjects into 3 groups
- tested the difference between the first and the second and between the second and the third group at each pixel
- Randomly assigned a proportion $\pi_0 \in \{0.5, 0.8, 0.9, 1\}$ of the contrasts to have non-zero mean 1.
- Compared the parametric and bootstrap methods.
- Bootstrap uses 100 bootstraps

Empirical JER



Empirical JER - continued



Power - definition

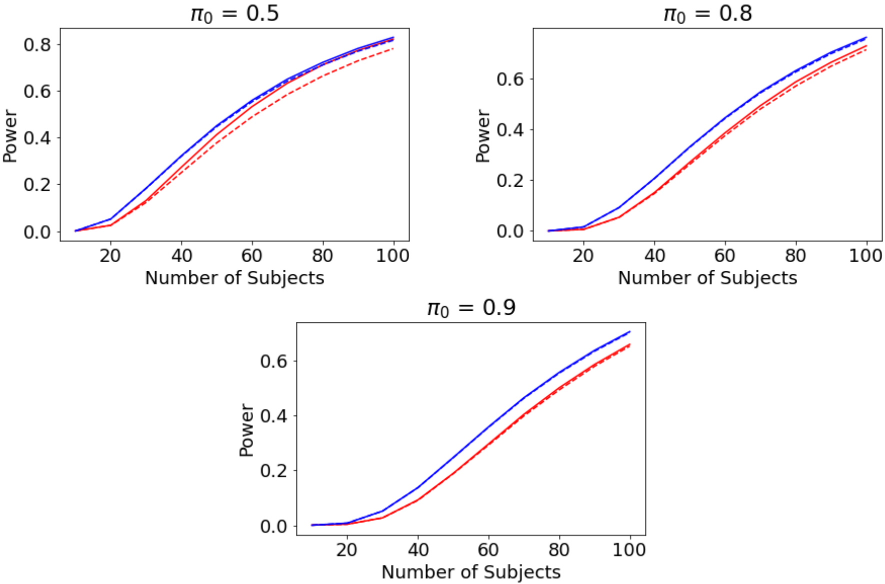
Given a set $R \subset \mathcal{H}$, define

$$\mathrm{Pow}(R) := \mathbb{E}\left[\frac{|R| - \overline{V}(R)}{|R \cap (\mathcal{H} \setminus \mathcal{N})|} \middle| |R \cap (\mathcal{H} \setminus \mathcal{N})| > 0 \right]$$

we take $R = \mathcal{H}$ (in this talk).

- This is a measure of the bounds on the true discovery proportion and so serves as a measure of power.
- Same notion of power as that of (Blanchard et al., 2020).
- Consider the same simulation setting where the FWHM $= 4$

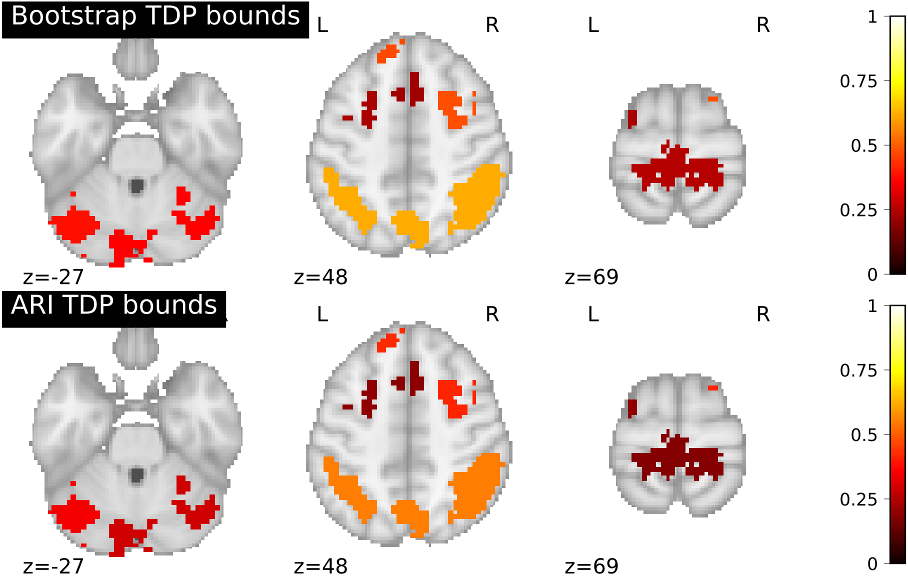
Power - Results (In the FWHM = 4 setting)



fMRI data model

- fMRI data from 365 unrelated subjects from the HCP
- Subjects take a test the results of which are measured numerically.
- They also perform a working memory task
- At each voxel we fit a linear model of the fMRI data against: Age, Sex, Height, Weight, BMI, Blood pressure and the intelligence measure
- Test contrasts for Sex and intelligence

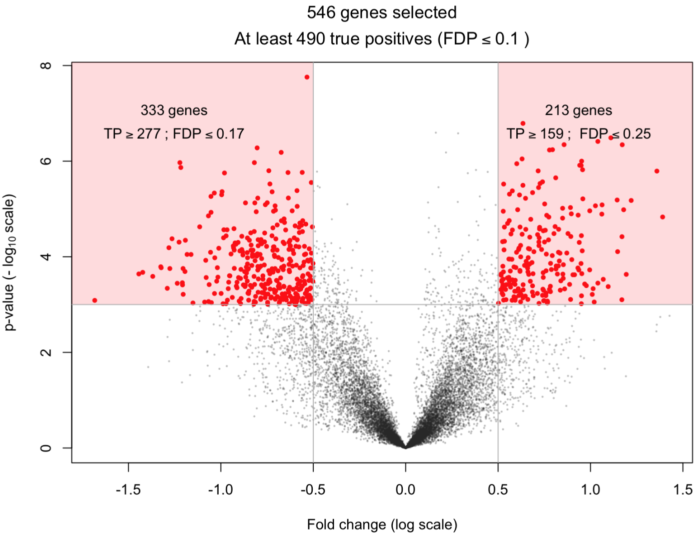
fMRI data analysis



Transcriptomic data analysis

- Have genetics data from 135 subjects
- 12531 genes
- run a regression against some controlled covariates and lung function and considered a single contrast for lung function.

Volcano plot



Conclusions

- Using resampling approaches allows for large power gains when doing inference under dependence.
- Recommend using it over ARI in most cases
- The method is flexible and extends to other settings. I.e. other bootstrap settings.
- Code for implementation is available at github.com/sjdavenport/pyperm
- Pre-print available on arxiv (and from my website).

Bibliography

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