

# VALID INFERENCE FOR GROUP-ANALYSIS OF FUNCTIONALLY ALIGNED FMRI IMAGES

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CON40 - IMAGE ANALYSIS AND VISUAL METHODS



**Multi-subjects** fMRI studies permit to compare studies across subjects, to generalize and to validate the results.

The anatomical and functional structure of brains vary across subjects even in response to identical sensory inputs.



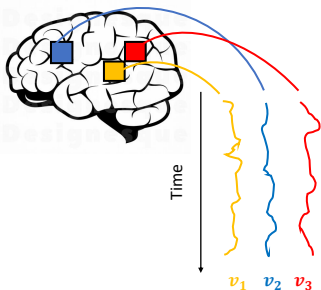
ALIGNMENT STEP

- **Anatomical Alignment** (MNI normalization) <sup>1</sup>;
- **Functional Alignment.**

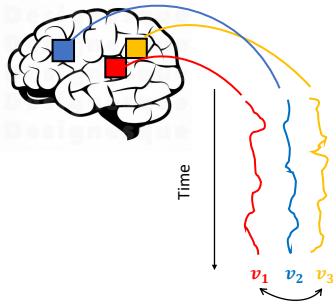
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<sup>1</sup>Jenkinson, M. and Smith, S., Medical image analysis (2001)

Subject 1



Subject 2



We can assume that the neural activities in different brains are **noisy rotations of a common space.**

Analyzing group activation means performing roughly 200,000 statistical tests equal to the number of voxels → **multiple testing problem**.

We propose a method that simultaneously

- resolves the **functional misalignment**;
- **gains power** in group analysis inference without affecting the type I error.

The functional alignment is done by the **ProMises**<sup>2</sup> (von Mises-Fisher-Procrustes) model



sorts the null hypotheses based on a priori information independent from the test statistics → **valid inference**.

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<sup>2</sup>Andreella, A. and Finos, L., Psychometrika (2022).

Let  $n$  time points,  $m$  voxels and  $i = 1, \dots, N$  subjects:

$$\mathbf{X}_i = \alpha_i (\mathbf{M} + \mathbf{E}_i) \mathbf{R}_i^\top$$

where

- $\{\mathbf{X}_i \in \mathbb{R}^{n \times m}\}_{i=1, \dots, N}$  represent the matrices to be aligned;
  - $\mathbf{M} \in \mathbb{R}^{n \times m}$  is the configuration reference matrix;
  - $\vec{\mathbf{E}}_i \sim \mathcal{N}_{nm}(\vec{\mathbf{0}}, \boldsymbol{\Sigma}_m \otimes \boldsymbol{\Sigma}_n)$ ;
  - $\{\mathbf{R}_i \in \mathcal{O}(m)\}_{i=1, \dots, N}$  **orthogonal matrix parameter**, and  $\alpha_i \in \mathbb{R}_{>0}$  scaling parameter.
- $\mathbf{R}_i \sim$  **von Mises-Fisher**<sup>3</sup> distribution with **location parameter**  $\mathbf{F} \in \mathbb{R}^{m \times m}$  and **concentration parameter**  $k \in \mathbb{R}_{>0}$ , i.e.,

$$f(\mathbf{R}_i) = C \exp(k \operatorname{tr}(\mathbf{F}^\top \mathbf{R}_i))$$

<sup>3</sup>Downs, T. D., Biometrika (1972).

## Theorem

Let the singular value decomposition of  $\mathbf{X}_i^\top \boldsymbol{\Sigma}_n^{-1} \mathbf{M} \boldsymbol{\Sigma}_m^{-1} + k\mathbf{F}$  be  $\mathbf{U}_i \mathbf{D}_i \mathbf{V}_i^\top$ , then the ProMises model returns:

1.  $\hat{\mathbf{R}}_i$  equals  $\mathbf{U}_i \mathbf{V}_i^\top$ ;
2.  $\hat{\alpha}_{i\hat{\mathbf{R}}_i}$  equals  $\frac{\|\mathbf{X}_i \hat{\mathbf{R}}_i\|_F^2}{\text{Tr}(\mathbf{D}_i)}$ .

- The von Mises-Fisher distribution is **conjugate**<sup>4</sup> to the matrix normal distribution, with location parameter:

$$\mathbf{X}_i^\top \boldsymbol{\Sigma}_n^{-1} \mathbf{M} \boldsymbol{\Sigma}_m^{-1} + k\mathbf{F}.$$

<sup>4</sup>Green, P. J. and Mardia, K. V., Biometrika (2006).

Let consider a given voxel  $k$ , where  $k = 1, \dots, m$  for each subject  $i$ :

$$\mathbf{X}_i = \mathbf{D}\mathbf{B}_i + \mathbf{Z}\mathbf{G}_i + \mathbf{E}_i$$

where

- $\mathbf{D} \in \mathbb{R}^{n \times p}$  and  $\mathbf{Z} \in \mathbb{R}^{n \times q}$  are fixed matrices;
- $\mathbf{B}_i \in \mathbb{R}^{p \times m}$ ,  $\mathbf{G}_i \in \mathbb{R}^{q \times m}$  and  $\mathbf{B}_i = \mathbf{B} + \mathbf{U}_i$ ,  $\mathbf{G}_i = \mathbf{G} + \mathbf{g}_i$  with  $\mathbf{B}$  is the true matrix of **fixed effects of interest**,  $\mathbf{G}$  of fixed nuisance effects;
- $[\mathbf{U}_i^T | \mathbf{g}_i^T] \sim \mathcal{MN}(\mathbf{0}, \boldsymbol{\Sigma}_m, \boldsymbol{\Sigma}_{pq})$  is the matrix of random effects.

We have now a set of  $N$  matrices  $\{\hat{\mathbf{B}}_1, \dots, \hat{\mathbf{B}}_N; \hat{\mathbf{B}}_i \in \mathbb{R}^{p \times m}\}$  (e.g., describing the difference between the neural activation during two stimuli recorded in the voxel  $k \in \{1, \dots, m\}$  of the subject  $i$ ).

### One-sample t-test

$$T = \frac{\hat{\mu}}{\hat{\sigma}/\sqrt{N}} \quad (1)$$

- $\hat{\mu} = \sum_{i=1}^N \hat{\mathbf{B}}_i / N$  is the sample mean between-subjects with  $\hat{\mu} \in \mathbb{R}^{p \times m}$ ;
- $\hat{\sigma} = \frac{1}{N-1} \sum_{i=1}^N (\hat{\mathbf{B}}_i - \hat{\mu})^2$  is the sample variance between-subjects with  $\hat{\sigma} \in \mathbb{R}^{p \times m}$ .

One local test  $T_k$  for each  $H_0^k: \mu_k = 0$  vs the two-sided alternative hypothesis  $\rightarrow$  **one  $T_k$  for each  $k$  voxel.**



## Theorem

Let consider the  $p$ -values  $p_k$  related to the statistical test  $T_k$ , where  $k \in M = \{1, \dots, m\}$ . If the ProMises model is valid, then:

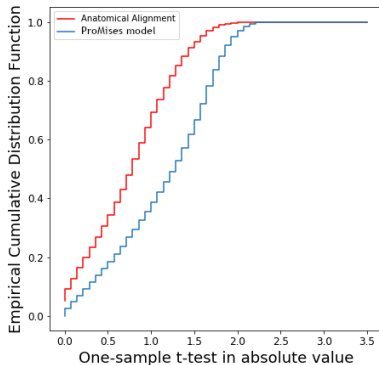
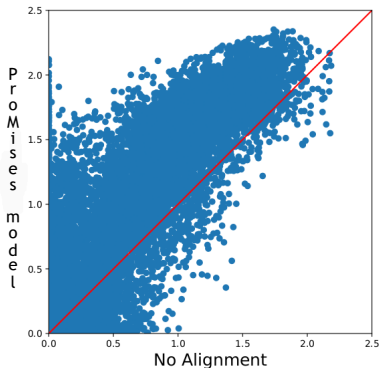
$$\Pr(p_k \leq \alpha \mid \hat{\mathbf{R}}_j, \hat{\alpha}_j) = \alpha, \quad \forall k \in S$$

where  $S \subseteq M$  is the set of true null hypotheses, and  $\alpha$  is the significance level.

The information involved in the estimation of  $\mathbf{R}_j$  and  $\mathbf{B}_j$  are orthogonal under  $H_0$ .

- We align the images of 18 subjects passively listening to vocal, i.e., speech, and non-vocal sounds.
- After the  $X_i$  matrices' alignment, **the one-sample t-test** was performed to study the significance of the group's mean activation concerning the difference between the neural activation during the two stimuli.
- The inferential analysis is performed on the **superior temporal gyrus**. The ProMises model is compared with **raw data** (i.e., anatomical alignment only).

# INFERENCE ANALYSIS - AUDITORY DATA



Using data functionally aligned, we have tests **85.85%** higher than those returned by using raw data, with baseline 50%.

- We proved the **validity of the inference** in functionally aligned data;
- Alignment reduces the intra-subject variability and localizes the signal → more **powerful inference**;
- One sample t-tests at the group level using data aligned by the ProMises model illustrate **higher absolute values** than the one-sample t-tests computed using raw data.

The method is implemented as

- Python module: `ProMisesModel`;
- R package: `alignProMises`

on my GitHub profile <https://github.com/angeella>.