UNIVERSITÀ DEGLI STUDI DI UDINE

Spatial Statistical Inference in Functional Magnetic Resonance Imaging (fMRI) data

Examining the performace of a trend surface model

Divya Brundavanam

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bdivya@umich.edu

Overview

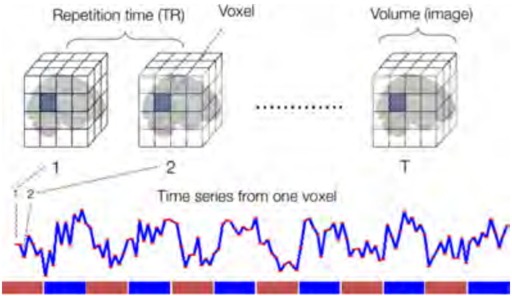
1 Functional Magnetic Resonance Imaging (fMRI) data

- Nature
- Modeling and Assumptions

2 Performance of an alternative approach

Neuroimaging to study the brain

- Non-invasive real-time study of the brain - Structural and Functional
- Several existing techniques: PET, fMRI, CT, EEG, MEG
- Methods to analyze the outputs of these techniques



Dimensionality

200,000 voxels for a 3T scanner

100-2000 images/subject

10-40 subjects/population inference study

Haemodynamic Reponse Function (HRF)
Blood oxygen level dependent (BOLD) signal

The predicted response

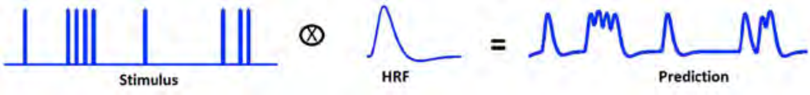


Figure: Obtaining the predicted response at a voxel. Source: FSL Course (http://fsl.fmrib.ox.ac.uk/fslcourse/)

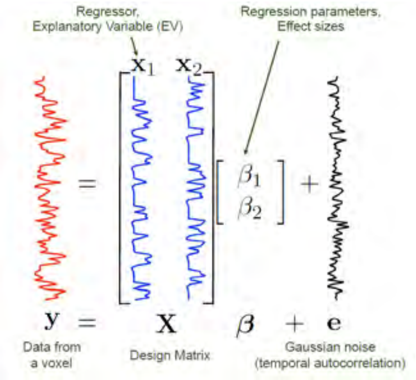


Figure: The GLM framework at each voxel. Source: FSL Course (http://fsl.fmrib.ox.ac.uk/fslcourse/)

Modeling fMRI data
Contrast maps

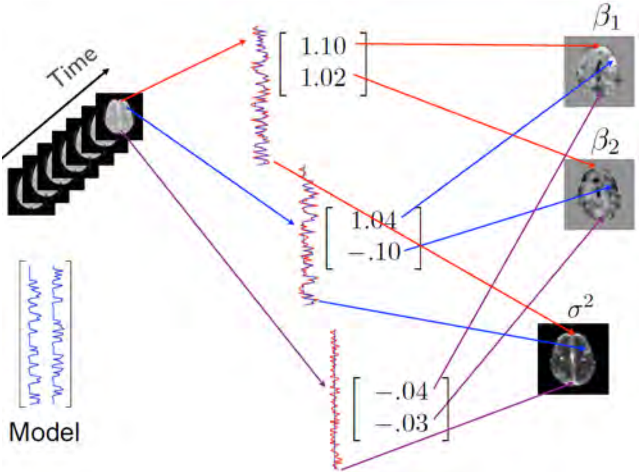


Figure: Generation of contrast maps. Source: FSL Course (http://fsl.fmrib.ox.ac.uk/fslcourse/)

Modeling fMRI data

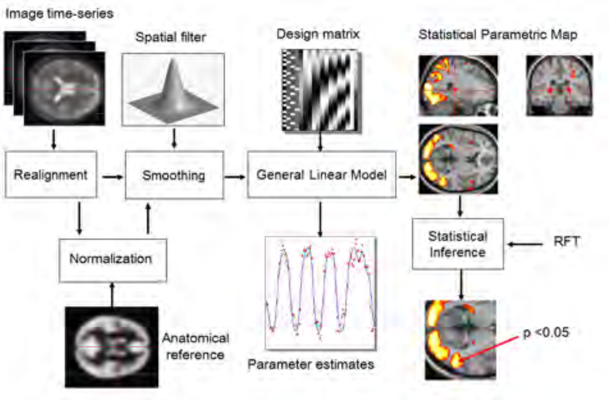


Figure: Typical steps for image processing (Source: Karl Friston, SPM workshop (May 2011))

What features to infer on?

- Voxel
- Clusters

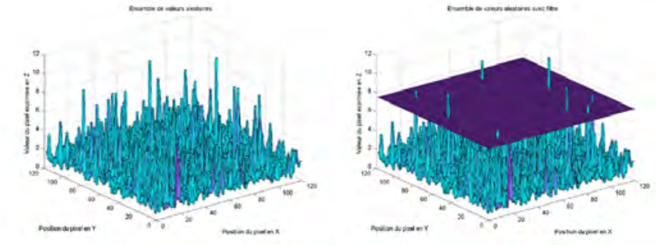


Figure: Choosing an appropriate threshold for inference. (Source: Presentation, RFT for Dummies - Part 1 (2009), Lea Firmin and Anna Jafarpour)

Hypothesis testing in neuroimaging: Multiple testing problem

Measures of error:

- Familywise Error Rate (FWE)
  - Bonferroni correction

$$\alpha_{corr} = \alpha_{FWE}/(n_{\text{Tests}})$$

  - Random Field theory

$$p^{vox}(t) \approx R\frac{(4\ln(2))^{3/2}}{((2\pi)^2)}e^{(-t^2/2)}(t^2-1)$$

No. of Resels $R = V/(FWHM_x FWHM_y FWHM_z)$

  - Permutation testing

RFT assumptions:

- Spatial smoothness of fMRI signal is constant across the brain
- the autocorrelation function is a squared exponential

Eklund et al: Real resting-state data and random task group analyses to compute empirical family-wise error rates for the fMRI software packages SPM,FSL, and AFNI

- High false-positive rates in established methods for cluster-wise inference
- spatial autocorrelation in the data violates the assumption squared exponential assumption of RFT

An alternative approach

A trend surface model proposed by Heurtas et. al. (2017) employing the instantaneous connectivity parcellation (ICP) (van Oort et al 2016).

Instantaneous Correlation Parcellation
(van Oort et al. 2016)

- Top-down parcellation
- Known large-scale ROI → *functionally homogenous* sub-regions based on temporal signature

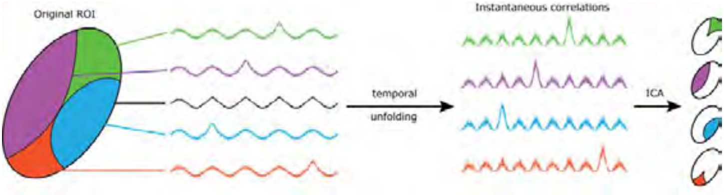


Figure: Simulated time courses using simple sinusoid, transients and Gaussian noise, as presented in Van Oort et al. "Human brain parcellation using time courses of instantaneous correlations" NeuroImage (2017)

- Basis functions: subnetworks obtained from ICP
- Find a linearly weighted sum of these basis functions

$$\mathbf{y}_s = \sum_{m=1}^{M} \mathbf{w}_m \phi_m(\mathbf{x}) + \epsilon_s \tag{1}$$

where
- M is the total no. of basis functions, $\epsilon_s \sim N(0, \beta^{-1})$, β is the noise precision
- $\mathbf{w}_s = [w_{1,s}, \ldots, w_{M,s}]^T$ is an M dimensional weight vector of regression coefficients

$$p(\mathbf{Y}, \boldsymbol{\Phi}, \mathbf{W}, \boldsymbol{\Lambda}_\alpha, \beta \mid \theta_\beta, \theta_\alpha) = p(\beta \mid \theta_\beta) p(\boldsymbol{\Lambda}_\alpha \mid \theta_\alpha) \prod_{s=1}^{S} p(\mathbf{y}_s \mid \mathbf{X}, \beta, \mathbf{w_s}) p(\mathbf{w_s} \mid \boldsymbol{\Lambda}_\alpha) \tag{2}$$

- $\boldsymbol{\Phi}$ is a $V \times M$ matrix of basis functions and $\mathbf{Y}$ is a $V \times S$ matrix of the neuroimaging data for all subjects.
- $\mathbf{W} = [\mathbf{w}_1, \ldots, \mathbf{w}_N]$ is an $M \times S$ weight matrix, with prior $p(\mathbf{w}_s \mid \alpha) = \mathcal{N}(\mathbf{w}_s \mid \mathbf{0}, \boldsymbol{\Lambda}_\alpha^{-1})$. $\boldsymbol{\Lambda}_\alpha$ is the precision matrix with $\alpha = [\alpha_1, \ldots, \alpha_m]^T$ as hyperparameters.

- The precision matrix is assigned a Wishart prior $p(\mathbf{\Lambda}_\alpha \mid \theta_\alpha) = \mathrm{Wish}(\mathbf{\Lambda}_\alpha \mid N, \mathbf{P})$, N is degrees of freedom and $\mathbf{P}$ is the precision of the prior.

- The noise precision has a Gamma prior $p(\beta \mid \theta_\beta) = \mathrm{Gamma}(\beta \mid a, b)$ where a, b are the shape coefficients.

- Spatial correlations between basis functions by allowing off-diagonal entries in $\mathbf{\Lambda}_\alpha$

Data Analysis
The Data

1. Resting state fMRI data (used as null data) from the 1000 Functional Connectomes project - Cambridge dataset
   - 198 healthy controls (75 M,123 F), 18–30 y.o.
   - 3T scanner, 119 time points, $72 \times 72 \times 47$ voxels
2. Task fMRI data from the Human Connectome Project (500 Subjects release)
   - 100+ unrelated healthy subjects
   - 3T scanner
   - Four tasks: Working memory, Gambling, Emotion and Language tasks

Results: Specificity

Specificity of the TSM

How well does TSM detect false positives?

- Randomized box-design: ~ 6 % false positive rate

Results: Specificity

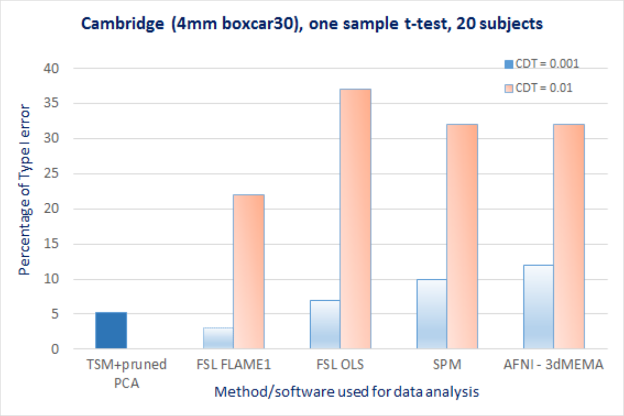


Figure: False positive rate from the TSM using pruned principle components, in comparison with results obtained by Eklund et al. (2016) for the softwares FSL, SPM and AFNI for cluster defining threshold (CDT) values of p=0.001 and p=0.01

Results: Sensitivity

Sensitivity of the TSM

How well does TSM detect task activation?

- 1000 groups of N=20 subjects selected randomly (without replacement) from 100+ subjects in each of the four tasks from the Human Connectome Project task fMRI data
- One sample t-test; random group shows significant result if atleast one parcel is significant (FWE)
- An ICP parcel that is significant in atleast 50% of random group analysis is considered to be activated

Results: Sensitivity

Sensitivity of TSM: Working Memory task

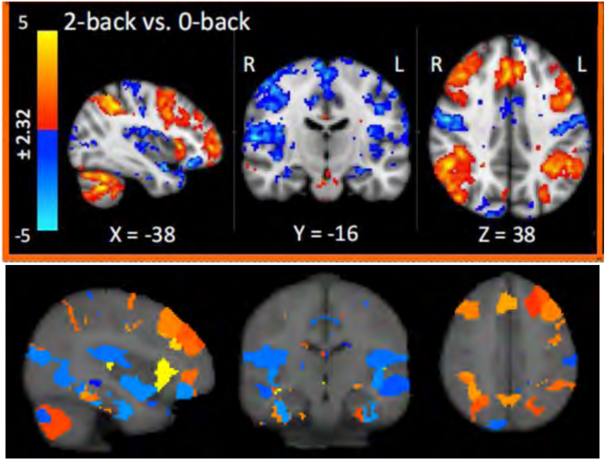


Figure: Brain activation under the Working Memory task from Barch et al. (2014) (top) and that obtained using TSM (bottom)

Results: Sensitivity
Sensitivity of TSM: Gambling task

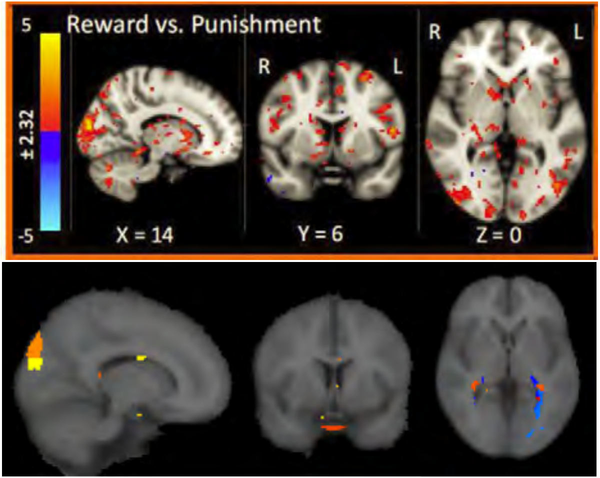


Figure: Brain activation under the Gambling task from Barch et al. (2014) (top) and that obtained using TSM (bottom)

Results: Sensitivity

Sensitivity of TSM: Emotion task

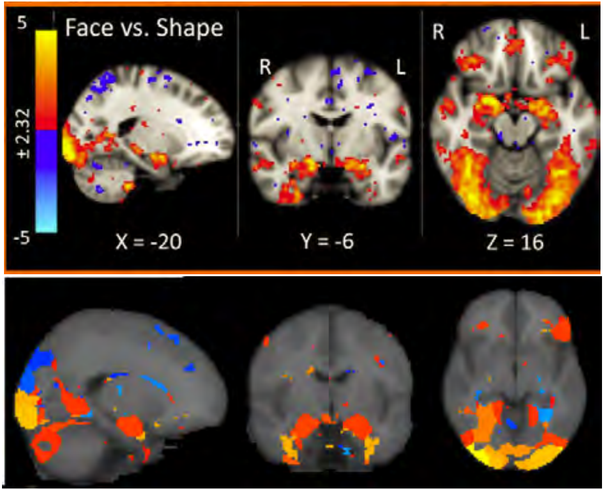


Figure: Brain activation under the Emotion task from Barch et al. (2014) (top) and that obtained using TSM (bottom)

Conclusion

The TSM fills an existing need for statistical methods that tackle spatial structure of neuroimaging data, and provides the following advantages:

- Abstracts away the voxels
- Cleaner biological interpretation
- Much fewer basis functions than voxels $\implies$ highly reduced no. of parameters and hence correction for multiple comparisons
- No commitment to a specific scale of parcellation $\implies$ applicable to areas requiring high resolution imaging

Conclusion

TSM provides good specificity and sensitivity, thereby providing a good alternative to currently popular methods of fMRI data analysis and inference.

Key References

1. Barch et al. "Function in the human connectome: task-fMRI and individual differences in behavior Neuroimage 80, 169189 (2013)
2. Beckmann et al. "General multilevel linear modeling for group analysis in fmri". NeuroImage, 20(2):1052–1063 (2003)
3. Eklund et al. "Cluster failure: why fMRI inferences for spatial extent have inflated false-positive rates." Proceedings of the National Academy of Sciences (2016): 201602413.
4. Huertas et al. "Spatial model using multiscale functional parcels" NeuroImage (2017), 10.1016/j.neuroimage.2017.08.009.
5. Van Oort et al. "Human brain parcellation using time courses of instantaneous correlations" NeuroImage (2017), http://dx.doi.org/10.1016/j.neuroimage.2017.07.027

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Thank you!