Exact Voxelwise Inference using Random Field Theory

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1. Introduction - Overview

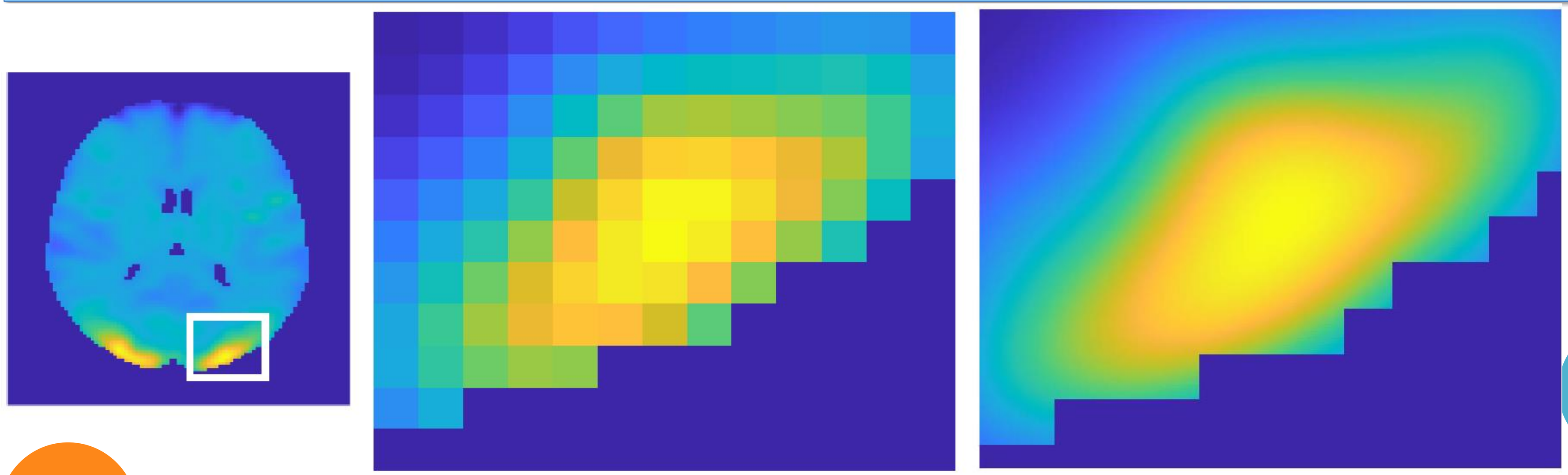
Random Field Theory (RFT) is a computationally efficient means of analysing neuroimaging data that has been widely applied to control false positives via cluster, peak and voxel level inference (Worsley et al. (1992), Worsley et al. (1996), Friston et al. (1994), Chumbley and Friston (2009)). However it has historically relied on a number of key assumptions. We propose improved RFT methods which drop a number of these assumptions and provide exact (instead of conservative) false positive rate control for voxelwise inference.

2. Introduction – Voxelwise Inference

For a mass univariate analysis producing a test-statistic image T taking values on the brain $S \subset \mathbb{R}^3$, the **FWER** (family wise error rate) is the probability of at least one false discovery, $\mathbb{P}(\max_{s\in S} T(s) > u)$, which we seek to control at a level α (typically 0.05). Let $M_u(T)$ be the number of local maxima of T above a threshold u, then

$$\mathbb{P}\left(\max_{s\in S} T(s) > u\right) = \mathbb{P}(M_u(T) \geq 1) \leq \mathbb{E}[M_u(T)].$$

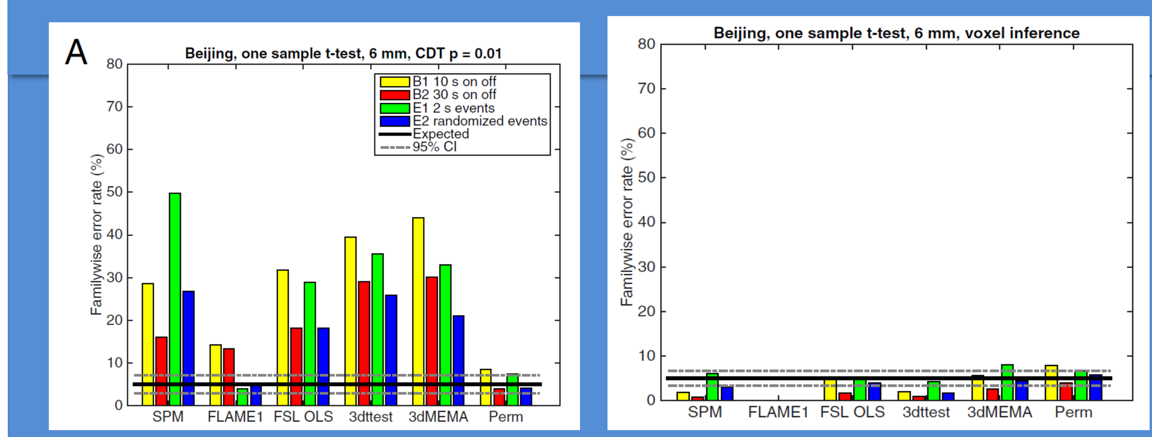
Closed form expressions for $\mathbb{E}[M_u(T)]$ exist (see box 6) which allow us to choose the threshold u to control the FWER.



3. Introduction – Cluster Failure

Eklund et al (2016) demonstrated that standard RFT inference methods do not correctly control false positive rates due to a number of their assumptions being violated. They tested clusterwise and voxelwise RFT inference[a] on null (resting state) data using different software (FSL, SPM and AFNI). They processed this data using different pre-processing settings including block (B1, B2 below) and event related (E1, E2 below) designs. They showed that clusterwise RFT had inflated false positive rates above the desired 5% rate (see below, left) but found the opposite problem for voxelwise RFT (below, right).

[a]Note that clusterwise RFT seeks to control the false positive rate over clusters whereas voxelwise RFT seeks to control it over voxels as described in box 2.



12. Talk

See
https://sjdavenport.github.io/talks/ohbm2020
for a short video talk discussing these results.

4. Introduction – RFT Assumptions

Voxelwise inference typically makes many fewer assumptions than clusterwise inference. To be valid it has historically required that the data is Gaussian, stationary and sufficiently smooth. Gaussianity is usually reasonable in neuroimaging settings such as fMRI and VBM. However non-stationarity and sufficient smoothness are not and the failure of these, especially non-stationarity, is in large part responsible for cluster failure. We will show that both of these key assumptions can be dropped.

5. Methods – Convolution Fields

Traditional RFT typically makes the assumption that the applied smoothing is high. This is required in order to provide good estimates of the smoothness of the data and to correctly infer on the distribution of the maximum. However RFT inference can be made to work at any (non-zero) applied smoothness. To see this, suppose the data is smoothed with a kernel K. Given data $X_n : S \to \mathbb{R}$ for each subject $n = 1, \ldots, N$ (corresponding to our pre-processed unsmoothed fMRI data) on a lattice L, for $s \in S$ we define convolution random fields to be

$$Y_n(s) = \sum_{l\in L} K(s-l)X(l)$$

and define $T(s)$ to be the test-statistic arising from these fields. This defines a continuous field defined at all $s \in S$ (not just the lattice points): see above for an example. Using convolution fields we can perform exact inference using RFT.

6. Methods – Non Stationarity

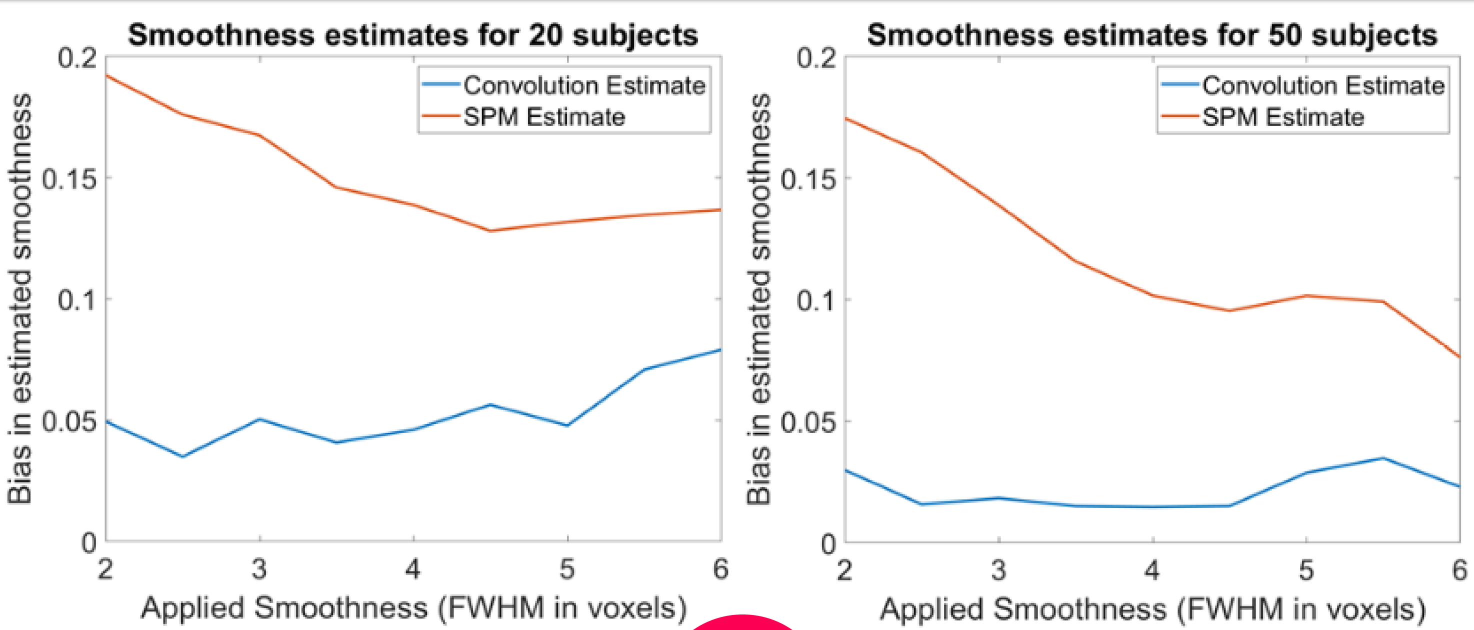
RFT has historically required stationarity (Worsley 1992). Revolutionary work (Taylor 2006) extended RFT to allow for non-stationarity. They showed that above high thresholds u (a very reasonable assumption for voxelwise inference) the expected number of maxima can be written as

$$\mathbb{E}[M_u] = \sum_{d=0}^{D} \mathcal{L}_d \rho_d(u)$$

where ρ_d are known functions and $\mathcal{L}_d$ are constants (to be estimated) which depend on the shape of the brain and the smoothness of the data. This result is a generalization (to non-stationarity) of the results used by Worsley. Our work implements this in 3D for use in brain imaging. This approach allows us to drop the stationarity assumption and, combined with convolution fields, allows exact control of the false positive rate for any applied smoothness.

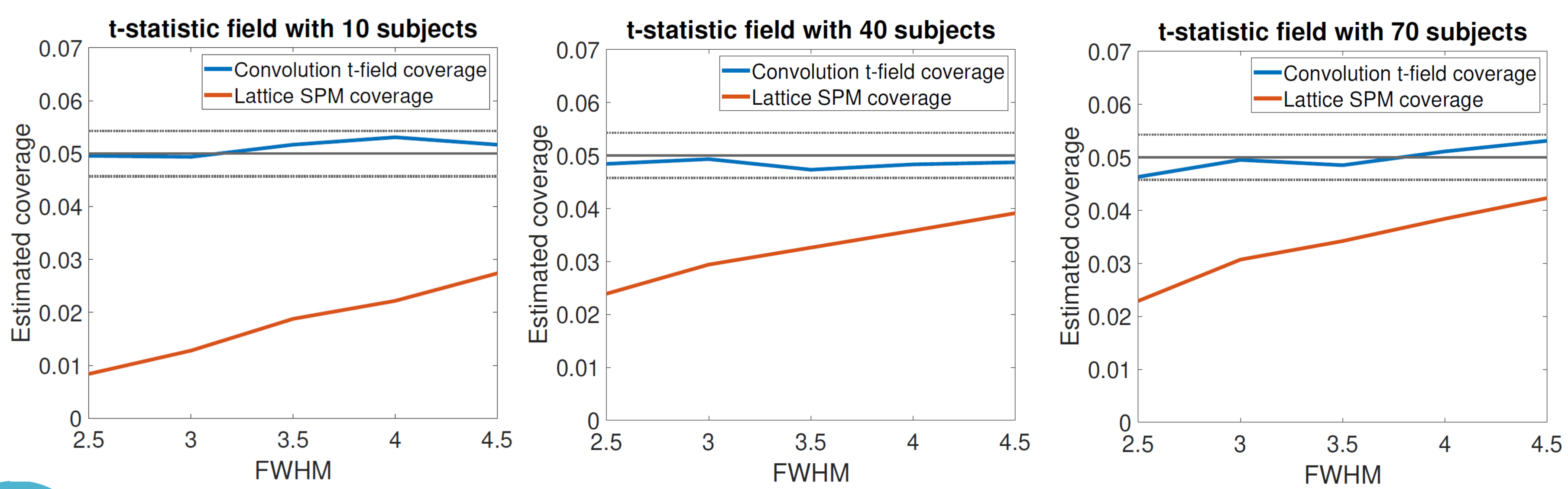
7. Results – FWHM estimation

FWHM estimation under the historical RFT framework has always been biased, as documented by Kiebel (1999). This bias arises because derivatives are estimated discretely. Using convolution fields the derivatives can be computed exactly allowing estimates of the smoothness that are significantly less biased (see below). To make these plots we generated 1000 random fields, of dimension 90 by 90 by 90, by smoothing iid Gaussian data on a lattice with an isotropic Gaussian kernel with specified FWHM. We then estimated the smoothness at the centre using SPM and convolution fields.



8. Results – False Positive Control

The graphs below demonstrate the false positive rate control that results from using voxelwise RFT. Coverage is estimated, in a non-stationary 2D t-statistic scenario with varying levels of applied smoothness and numbers of subjects, using 10000 simulations for each setting. The false positive rates are exactly controlled at the 5% level. Contrast this with the lattice SPM implementations which control the false positive much more stringently and are thus much less powerful. SPM implementations also do not correctly account for non-stationarity and so are not valid for use in fMRI data analyses.



9. Discussion

In this work we have demonstrated that voxelwise RFT perfectly controls the false positive rates to the nominal level. We are in the process of validating this using null, i.e. resting-state data, to ensure that false positive rates are correctly controlled. We have discussed here how the two main assumptions of current RFT implementations (non-stationarity and smoothness) can be completely dispensed with allowing for a robust theory. Our RFT implementations run significantly faster than the main other method used in the field (permutation testing) so have the potential to save huge amounts of computational time. This is especially important in the Biobank era where large numbers of subjects mean that non-parametric methods are infeasible.

10. RFTtoolbox

Software to implement these methods is available online at https://sjdavenport.github.io/software
A detailed matlab tutorial is available.

11. References

Chumbley and Friston 2009, Topological FDR for neuroimaging.
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