# Fast and Powerful Multiple Testing Inference in Family-Based Heritability Studies

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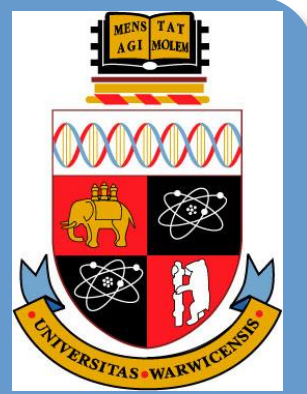
Introduction

Estimation of heritability is essential in imaging genetic studies. Voxel-wise heritability for traits like cortical thickness, fractional anisotropy and BOLD activations have been made practical by genetic analysis tools optimized for imaging research, such as the SOLAR/SOLAReclipse (Kochunov2013). The mass-univariate nature of voxel-wise analyses, however, presents a severe multiple testing problem. In this work we present a fast and powerful permutation test for general pedigree studies that provide traditional, spatial inferences for images, including familywise error corrected voxel- and cluster-level inference.

Methods

Voxel-wise Heritability Estimation:
Heritability estimation is performed using variance component models. In this approach, the phenotype covariance matrix is decomposed into two components, one for the additive genetic effect and one for the combination of individual-specific environmental effects and measurement error $\left(\Sigma = 2\sigma_A^2 \Phi + \sigma_E^2 I\right)$. The parameters are estimated by maximizing the likelihood function under a multivariate normal assumption. An orthogonal transformation (based on the eigenvectors of the kinship matrix) is used to accelerate computation. Hypothesis testing is performed with a likelihood ratio test (LRT).

Permutation Procedures

We propose two permutation tests for heritability inference. The first method is based on the permuting the rows and columns of the kinship covariance matrix, and repeatedly fitting the model and computing the LRT; this provides uncorrected p-values at each voxel and, via the maximum LRT (or maximum cluster-size, based on thresholded LRT images) FWE-corrected p-values. Note that this method requires the iterative optimization of the likelihood function for each permutation, which is computationally intensive.

The second method is based on constructing an auxiliary regression model on squared residuals and the kinship covariance matrix eigenvalues. After orthogonal transformation of the data, the second moment of residuals has a linear relationship with the additive genetic effect and the kinship matrix eigenvalues: $E(e_i^2) = h^2(\lambda_{gi} - 1) + 1$, where e and λ_g are transformed residuals and the kinship matrix eigenvalues respectively (w.l.o.g. we assume data is scaled to unit variance). Based on this expression we fit a regression model, where there is only one unknown parameter (h^2), and the usual regression sum of squares provides a test-statistic.

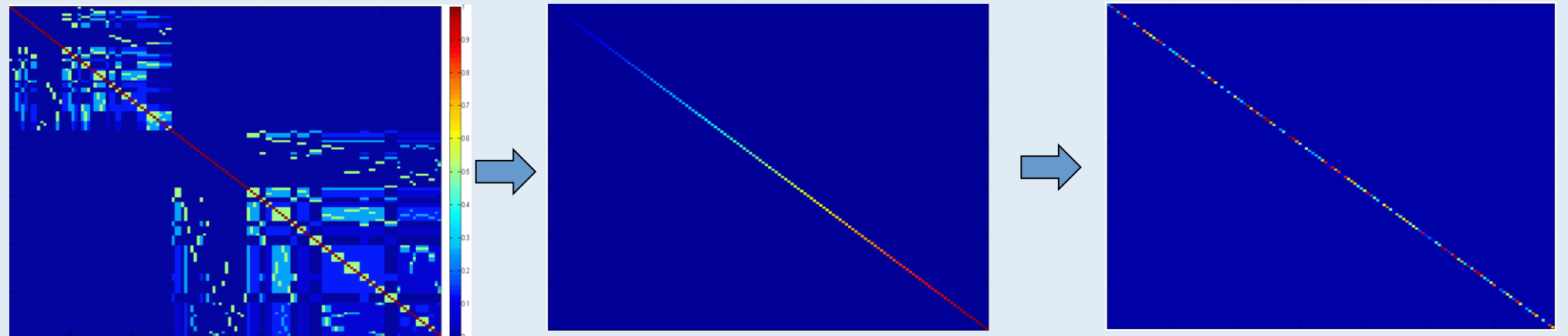## Proposed Permutation framework

Figure 1: Proposed permutation test. First, the data is whitened by orthogonal transformation of the kinship matrix eigenvectors. Under H_0 of zero heritability, the whitened data (i.e. eigenvalues) are homogeneous, and hence can be permuted. The model is refit to the permuted data; we consider both full likelihood-based methods and (fast) auxiliary linear models.

Voxel-Wise and Cluster-Wise Inference Familywise False Positive Error Rate (FWE)
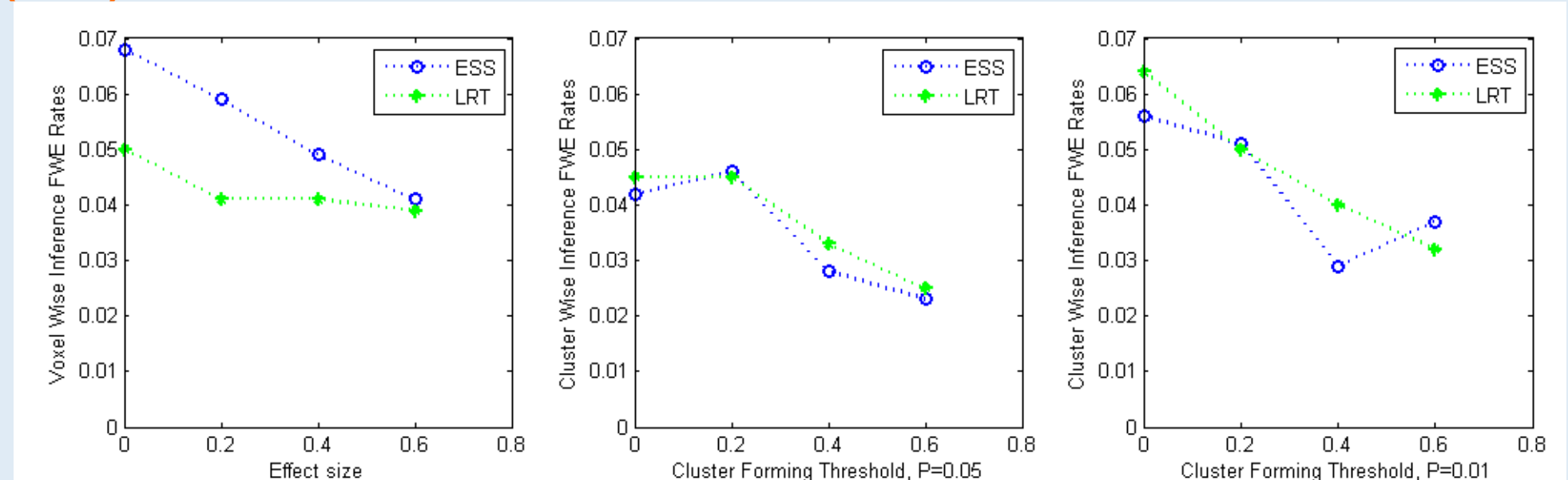

Figure 2: Monte Carlo confidence interval is (0.0365, 0.0635).

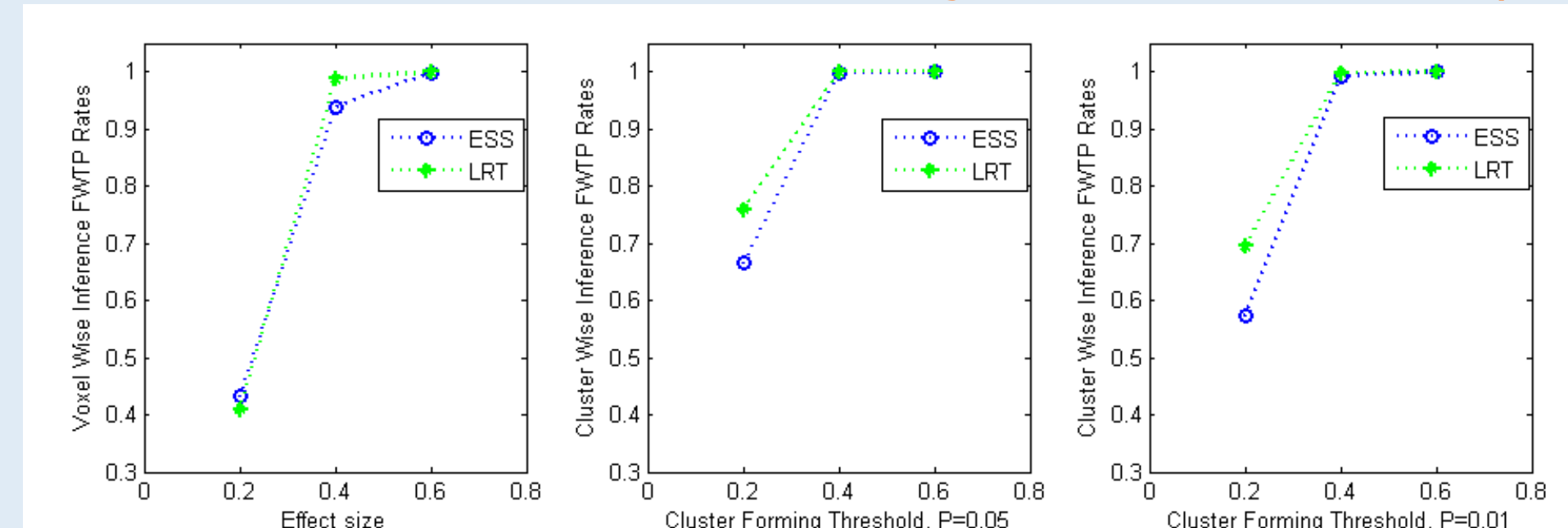## Voxel-wise and Cluster-Wise Inference Familywise True Positive Rate (TPR)

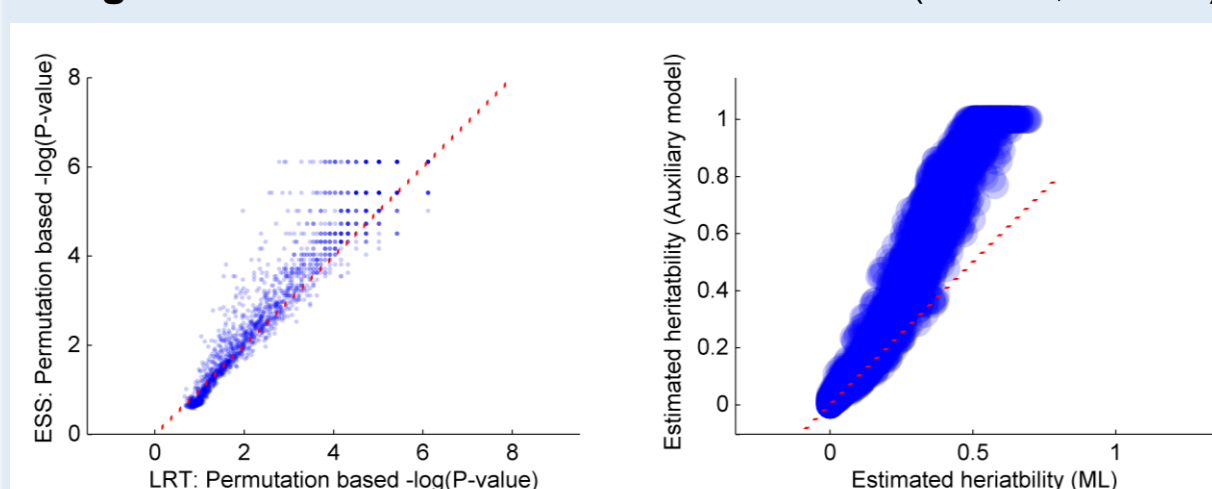**Figure 3:** Monte Carlo confidence interval is (0.0365, 0.0635).

Figure 4: comparing permutation P-values and estimated heritabilities.

Figure 5: Proposed methods applied on FA TBSS data from GOBS study, using 859 subjects in 42 families. The auxiliary model and ML −log10 P-values are quite similar. (red: LRT, green:ESS).

Simulation

Monte Carlo simulation was used to validate the permutation tests cluster size inference for multiple testing error correction in imaging heritability studies. We simulated smooth images of size 64 by 64 containing a circular region of true heritability for two pedigrees, of total 138 subjects. Heritability was varied, h^2 = {0, 0.2, 0.4, 0.6}. 500 permutations were used, and the entire simulation was repeated with 1000 realized datasets.

Results

See figures.

Conclusions

We have developed permutation-based heritability methods for general family data, providing spatial inferences that are useful for brain-imaging. Cluster wise inference based on constructing the auxiliary regression model provides exact control over FWE and has power comparable with LRT.

References
Blangero et al (2013). A kernel of truth: statistical advances in polygenic variance component models for complex human pedigrees. Advances in Genetics, 81:1-31.
Kochunov & Nichols (2013). SOLAR-Eclipse computational tools for imaging genetic and mega-genetic analysis. 19th Annual Meeting OHBM.

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