A general empirical null for voxelwise FDR inference in neuroimaging

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PURPOSE

To improve false discovery rate inference in group imaging studies by estimating the null distribution from the data itself.

BACKGROUND

- Voxel wise comparisons in group imaging studies lead to a multiple comparisons problem.
- Number of subjects is usually small, but number of tests is usually large.
- False discovery rate (FDR) control is an attractive alternative to family wise error rate (FWER) control.

METHODS

Mixture model:

$$f(t) = p_0 f_0(t) + (1-p_0) f_A(t)$$

Null density (f_0) — Alternative density (f_A)

Empirical null:

- Normal family $N(\mu,\sigma^2)$: $f_0(z) \propto e^{-(z-\mu)^2/(2\sigma^2)}$

$$\Rightarrow \log[p_0 f_0(z)] = -\frac{1}{2}\left(\frac{z-\mu}{\sigma}\right)^2 + \text{const.}$$

Estimate μ_0, σ_0^2 by Poisson regression ($z_{min} < z < z_{max}$):

$$\log \hat{f}(z) \approx a_0 + a_1 z + a_2 z^2$$

- Scaled χ_2 family $s\chi_2(\nu)$: $f_0(u) \propto \left(\frac{u}{s}\right)^{\nu/2-1} e^{-u/(2s)}$

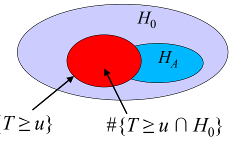
$$\Rightarrow \log[p_0 f_0(u)] = \left(\frac{\nu}{2}-1\right)\log u - \frac{u}{2s} + \text{const.}$$

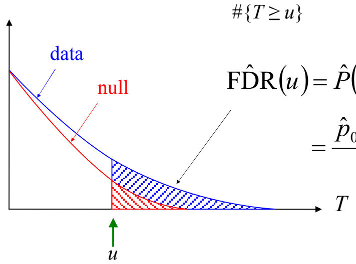
Estimate s, ν by Poisson regression ($u < u_{max}$):

$$\log \hat{f}(u) \approx a_0 + a_1 u + a_2 \log u$$

False discovery rate:

- Empirical Bayes estimate:

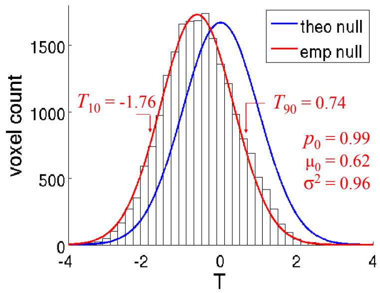




$$\hat{\text{FDR}}(u) = \hat{P}(H_0 | T \geq u) = \frac{\hat{p}_0 \hat{P}(T \geq u | H_0)}{\hat{P}(T \geq u)}$$

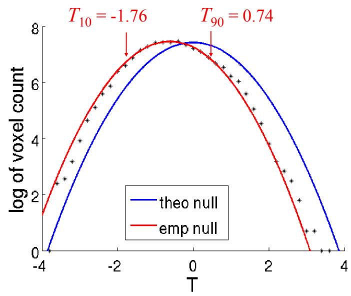
DATA EXAMPLE

- Source Deutsch et al.: DTI study of reading ability, 2 groups, 6 subjects in each group.
- FA test:



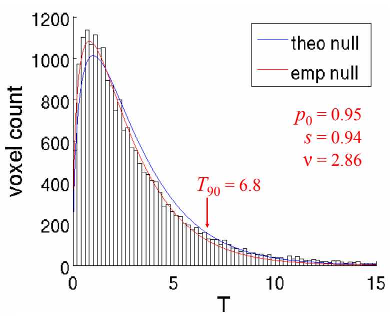
Histogram of $t(10)$ statistics transformed to normal scale

Empirical null corrects shift in histogram.

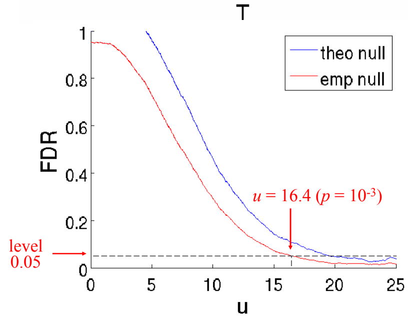


Histogram in log-scale

- Tensor eigenvector test (Schwartzman et al. 2006):

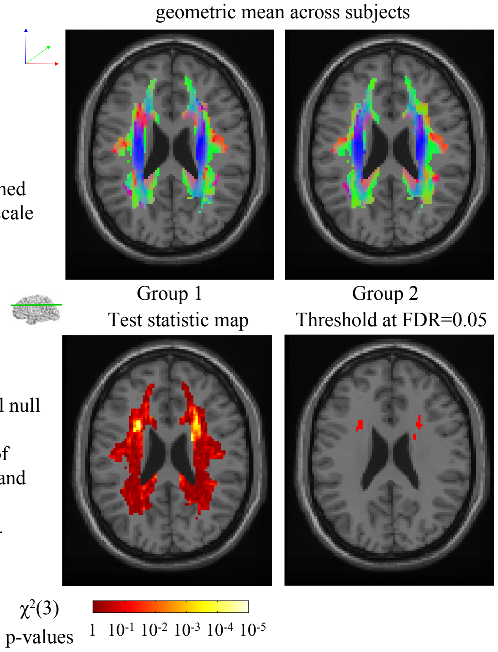


$F(3,60)$ statistics transformed to $\chi^2(3)$ scale



Empirical null corrects degrees of freedom and improves detection.

Principal diffusion direction of matrix geometric mean across subjects



CONCLUSIONS

- Using the correct null distribution is crucial for statistical inference.
- Inference can be made more accurate by fitting an empirical null to the data histogram.
- The empirical null proposed here can handle:
  - One- and two-sided tests.
  - Normal, t, χ^2, F distributions and exponential families in general.

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References

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