Overview

- Explicit vs Implicit Spatial Modeling
- Multiple Comparisons Problem
- Random Field Theory for MCP
- Nonparametric Permutation Test for MCP

Spatial Modeling: Spatial vs Temporal

- fMRI data is fundamentally spatiotemporal
- Yet we usually fit temporal models, one voxel at time
- Spatial modeling harder
  - *And you though temporal was hard!?*
  - Have replicates over time
  - Not so over space

Spatial Modeling: What do we want?

- We want to find the signal
  - Where is it?
  - How big is it?
- Explicit Model
  - Each blob parameterized
    - x,y,z location
    - Volume
  - Standard errors & confidence intervals on location, volume

Spatial Modeling: What do we get?

- Sorry
  - While naive estimates available...
    - Location of local maximum
    - Volume above a threshold
  - ... no standard errors
- What is available?
  - Implicit Models

Spatial Modeling: Implicit Models

- Implicit Spatial Models
  - Fit temporal model at every voxel
    - No information shared across space
  - Create statistic at each voxel
    - GLM & contrast
  - Create p-values based on statistic image
- Want to find the signal?
  - All this approach tells you
    - "Is this blob/voxel real?", i.e.
    - "Is this blob larger than expected by chance?"
    - "Is this voxel more intense than expected by chance?"

Spatial Modeling: Overview

- Create statistic images
- Test null hypothesis at each voxel
- Apply two thresholds
  - Primary, arbitrary intensity threshold
    - Defines clusters
  - Cluster size threshold
  - Secondary, corrected intensity threshold
    - Defines individually significant voxels

Spatial Modeling: "Scopes of Inference"

- SPM's framework on inference
- Define Clusters
  - ⇀ Use intensity *and* cluster size threshold
- Consider 4 "levels"
  - ⇀ Average, Set, Cluster, & Voxel
- Each has successively greater spatial specificity
  - ⇀ Though successively less sensitivity

Spatial Modeling: "Scopes of Inference"

- Average
  - ⇀ Assesses $\bar{F}$, average of F image
  - ⇀ Small p-value rejects $\mathcal{H}_0$: No activation anywhere
    - – No localization power
- Set
  - ⇀ Assesses c, number of clusters
    - – Given intensity & cluster size threshold
  - ⇀ Small p-value rejects $\mathcal{H}_0$: No activation anywhere
    - – No localization power

Spatial Modeling: "Scopes of Inference"

- Cluster
  - ⇀ Assesses k, number of voxels in a cluster
    - – Given intensity threshold
  - ⇀ Small p-value rejects $\mathcal{H}_0$: No activation in vicinity
    - – Localization to cluster
    - – However, can't point to particular voxel
- Voxel
  - ⇀ Assesses z or t or F statistic at a voxel
  - ⇀ Small p-value rejects $\mathcal{H}_0$: No activation here
    - – Localization to precise voxel

Spatial Modeling: Overview

- What secondary threshold?
  - ⇀ Usual $\alpha = 0.05$ threshold?
  - ⇀ Yields 5% false positive rate
  - ⇀ Yet we're performing 100,000 tests!
  - ⇀ 5,000 false positives OK?
- Rest of today is on voxel-level inference

Multiple Comparisons: Overview

- Multiple comparisons problem
  - ⇀ Usual threshold produces too many false positives
- What to control?
  - ⇀ Control *per-voxel* false positive rate
    - – That is, do nothing
  - ⇀ Control *FamilyWise false positive Error* rate (FWE)
    - – FWE one or more false positives, anywhere
    - – FWER is chance of getting *any* false positive
- Adjust threshold to control FWER

MCP: Bonferroni

- Usual approach to MCP
- Use α/S as critical value instead of α
  - ⇀ S = Number of tests
- Controls FWER

MCP: Bonferroni

- Math

$$\begin{aligned}\text{FWER} = \mathsf{P}(\text{FWE}) &= \mathsf{P}(\cup_{i=1}^{S}\{T_i > t_{\alpha/S}\}|\mathcal{H}_0) \\ &\leq \sum_{i=1}^{S}\mathsf{P}(\{T_i > t_{\alpha/S}\}|\mathcal{H}_0) \\ &= \sum_{i=1}^{S}\alpha/S \\ &= \alpha\end{aligned}$$

⇀ Where $\mathcal{H}_0$ is the joint null hypothesis
"Null hypothesis true everywhere"
"No signal anywhere"

⇀ t_α is upper tail critical value

MCP: Bonferroni

- But it's an *inequality*, not equality
  - ⇀ Conservative
  - ⇀ For correlated data, very conservative
    - – Data spatially smooth due to acquisition or smoothing
- Bonferroni doesn't account for smoothness
  - ⇀ Same threshold for independence and total correlation

MCP: FWE & Maximum Statistic

- Important connection between FWE & Maximum
- Maximum searching over space
  - ⇀ Just has each voxel has null dist^n
  - ⇀ So does the maximal statistic

D:t.Mt

- Define m_α as upper tail critical value on distribution of maximum
  - ⇀ Tail integral above m_α on max dist^n is α
  - ⇀ Just like t_α above

MCP: FWE & Maximum Statistic

- Using m_α as a threshold controls FWER!

$$\begin{aligned}\mathsf{P}(\text{FWE}) &= \mathsf{P}(\cup_{i=1}^{S}\{T_i > m_\alpha\}|\mathcal{H}_0) \\ &= \mathsf{P}(\max_{i=1}^{S} T_i > m_\alpha|\mathcal{H}_0) \\ &= \alpha\end{aligned}$$

⇀ Only way any T_i can be above m_α is if maximum is above m_α

MCP: FWE & Maximum Statistic

- If we can find the distribution for the max statistic we're done!
- Two approaches
  - ⇀ Random field theory
  - ⇀ Nonparametric permutation approach

RFT: That spells Random Field Theory

- Random Field is statistical process
  - ⇀ Ocean surface
  - ⇀ Temperature map of USA
  - ⇀ A brain image
- Rich theory available for continuous random fields
  - ⇀ But we have discretely sampled "lattice" data
  - ⇀ Smooth image data approximates continuous random field
  - ⇀ First assumption (of many)

RFT: Getting at the Max with the Euler Characteristic

- Euler (say "oiler") Characteristic (EC)
  - ⇀ Take continuous random field
  - ⇀ Threshold it at level u
  - ⇀ EC = #blobs - #holes   N:Wor92
- At high thresholds, no holes
  - ⇀ EC then just counts blobs
- At very high thresholds
  - ⇀ EC is just zero or one
  - ⇀ Either one or no blobs

RFT: Getting at the Max with the Euler Characteristic

- Expected EC
  - ⇀ Mean or average
  - ⇀ By definition

    $\mathsf{E}(EC) = \sum_k k\mathsf{P}(EC = k)$
- For high thresholds, expected EC is just what we want!

$$\begin{aligned} \mathsf{E}(EC) &= \sum_k k\mathsf{P}(EC = k) \\ &= 0\mathsf{P}(EC = 0) + 1\mathsf{P}(EC = 1) + 2\mathsf{P}(EC = 2) + \cdots \\ &\approx \mathsf{P}(EC = 1) \\ &= \mathsf{P}(\text{“Maximum is above threshold } u\text{”}) \end{aligned}$$

RFT: Getting at the Max with the Euler Characteristic

- Want expected EC for a null statistic image
- This will approximate the probability
  - ⇀ $\mathsf{P}\{\max_i T_i > u\}$
    - – The FWER α for threshold u
    - – Equivalently, the corrected p-value if u is a statistic value of interest

RFT: Corrected p-values with Expected EC

- So we can obtain p-values using
  - ⇀ $\mathsf{P}\{\max_{i=1}^S T_i > u\} \approx \mathsf{E}(EC_u)$
- Expected EC formula for Gaussian random field
  - ⇀

    $\mathsf{E}(EC_u) = (\text{RESELs})(u^2 - 1)\exp(-u^2/2)/(2\pi)^2(4\log(2))^{3/2}$
  - ⇀ Where

    u is the threshold

    RESELs is the RESolution ELement
- RESEL is search volume in units of resolution

RFT: RESELs

- Smoothness described in terms of FHWM
  - ⇀ FWHM = Full Width at Half Maximum   D:fwhm
- RESEL formula

$$\text{RESEL} = \frac{S}{f_x f_y f_z}$$

  - ⇀ Where

    S is search volume, in mm^3

    f_x, f_y, f_z is FWHM smoothness in mm in x, y, & z

RFT: Intuition

- Get a feel for corrected p-values!
- Say I observe a statistic with value u

$$\mathsf{P}\{\max_{i=1}^{S} T_i > u\} \approx \mathsf{E}(EC_u) = (\text{RESELs})(u^2 - 1)exp(-u^2/2)\cdots$$

All other things equal...

- ... as u increases
  - ⇀ Corrected p-values go ____, i.e. ____ significance
    - – Hint: As u gets higher, can ignore u^2 term
- ... as number of RESELS increases
  - ⇀ Corrected p-values go ____, i.e. ____ significance

RFT: Intuition

- ... as search volume S increases
  - ⇀ Corrected p-values go ____, i.e. ____ significance
  - ⇀ Remember RESEL $= \frac{S}{f_x f_y f_z}$
- ... as resolution f increases
  - ⇀ Corrected p-values go ____, i.e. ____ significance
  - ⇀ Remember RESEL $= \frac{S}{f_x f_y f_z}$
  - ⇀ Remember resolution is measured in FHWM, so bigger f means [sharper | fuzzier] statistic images

RFT: Assumptions

- Raw image data are multivariate Gaussian
  - ⇀ Can check Normality at each voxel
  - ⇀ Impossible to check multivariate Normality for every pair of voxels
- Smoothness
  - ⇀ Images are sufficiently smooth to approximate continuous field
    - – Rule of thumb: FWHM 2-3 times voxel size
  - ⇀ Insufficient smoothness results in
    - – Conservative voxel-wise p-values
    - – Liberal cluster-size p-values

RFT: Assumptions

- Stationarity
  - ⇀ Smoothness the same *everywhere*
  - ⇀ Assumption needed for cluster size p-values
  - ⇀ *Not* needed for voxel size p-values

RFT: Details

- Above results only for *Gaussian* images
  - ⇀ We never have Gaussian/Normal data, because we have to estimate σ^2 with $\hat{\sigma}^2$
- (More complicated) Results exist for t, F, χ^2, etc.
  - ⇀ General idea and intuition is the same
- See references in Petersson *et al.* on the website for details

Spatial Modeling & MCP: Quiz

I-1 Explain the difference bewteen explicit and implicit spatial modeling.

I-2 Describe what constitutes a Familywise Error.

I-3 Fill in the blank: I examine 20 statistic images, each thresholded such that Familywise Error Rate is controlled at 5%. On average, I expect that only _____ of these 20 thresholded statistic images will have any false positive voxels.

I-4 All other things equal, increasing smoothness (i.e. increasing FWHM) has what impact on corrected p-values?

I-5 If I decrease my smoothness (decrease FWHM), in order to have the same FWER, how do I have to change my threshold?