BMI 210-768 /STAT 932-621

Statistical Methods for Medical Image Analysis

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Lecture 2

Image Segmentation
Gaussian Mixture Models
Statistical analysis on binary images
Gaussian Kernel Smoothing
Voxel-based Morphometry
ROI volumetry

• This is a traditional approach

• Region of interest (ROI) volumetry measures volume of a segmented region of interest (ROI). It provides a single scalar measure of the ROI.
Example: Hippocampal volumetry

1. Manually/automatically segment hippocampus
2. Count the number of masked voxels
3. #number of voxel x volume of voxel

This is a really old technique that is still in wide use.
Imaging in a patient 2·5 h after a major left-hemisphere stroke

A: Diffusion-weighted MR image shows a large hyperintense left basal ganglia/hemispheric lesion.

B: Gradient echo image shows a mass lesion with few signs of haemorrhage-specific features on the medial border (dark areas due to haemosiderin).

C: CT immediately afterwards clearly shows an intracerebral haemorrhage with extension into the left lateral ventricle.

Warlow et al. 2003 Nancet 362:1211-1224
A stroke patient with dysphagia (difficulty in swallowing)

Manual segmentation in DWI

Dong-Eog Kim, Dongguk university hospital, Korea
Group 0: patients with dysphagia who got better (n1=58)

Group 1: patients with dysphagia who didn’t get better (n2=23)
MATLAB DEMO
Bernoulli random variable

\[ P(X = 1) = p \]
\[ P(X = 0) = 1 - p \]
\[ P(X = x) = (1 - p)^{1-x} p^x \]

See an additional reading note lecture.02.binarydata.pdf
Binomial random variable

$n$ independent identically distributed Bernoulli random variables

$$X_1, X_2, \cdots, X_n$$

$$X = X_1 + X_2 + \cdots + X_n$$

Binomial distribution
Central limit theorem for binomial

For binomial distribution $X$,

$$\frac{X - np}{\sqrt{np(1-p)}} \rightarrow N(0,1)$$

standard normal
Given $n$ binary experiments, we observe $pn$ number of activations. $p$ fraction/proportion is activated. Test the statistical significance of this event.

The larger the value of $p$, it is likely that the event is statistically significant. We will quantify this probabilistically.

The proportion of activation is modeled as Bernoulli($p$).
Inference on binary outcomes

Formal statistical inference framework:
A more complicated inference procedure is just a complicated version of this example.

1. Null and alternate hypotheses:

\[ H_0 : p = p_0 \text{ vs. } H_1 : p > p_0 \]

2. Test statistic:

\[ Y = \frac{X_1 + X_2 + \cdots + X_n}{n} \]

\[ E(Y) = p, V(Y) = \frac{p(1-p)}{n} \]

Unbiased estimator
**p-value**

\[ p\text{-value: } P(Y > p') \]

where \( p' \) is the observed proportion

If the \( p \)-value is small, it is likely that \( p' \) is already large. The smallness of \( p \)-value determines the significance of the event.

For sufficiently large sample size, 

\[ Z = \frac{Y - E(Y)}{\sqrt{V(Y)}} \rightarrow N(0, 1) \]

Under the null hypothesis, 

\[ p\text{-value} = P \left( Z > \frac{p' - p_0}{\sqrt{p_0(1-p_0)/n}} \right) \]
HOMEWORK 1

Using group 0 images only, determine pixels that are statistically significant.

Hint:
Read lecture.02.binarydata.pdf
Perform one sample test by letting $p_0=0.5$

Due: 2 weeks from now. Send your solution through email. There can be many solutions and no need to follow suggested hint. It’s just a suggestion.

Group 0: patients with dysphagia who got better (n1=58)
Limitation

The inference is based on the asymptotic normality of binomial distribution.

*Limitation:* it only works for large sample size. Most imaging studies have small sample sizes.
QUESTION

The above inference procedure only works for $0 < p_0 < 1$.

What will you do when $p_0 = 0$?
This may not be signal. Most likely an artifact.
How neuroimaging people fixed this problem?
Voxel-based morphometry (VBM)

- A new approach (Ashburner & Friston, 2000)
- No ROI segmentation required.
- Anatomical difference is characterized at each voxel.
- Works for small sample size
Advantages of VBM

• It does not require \textit{a priori} knowledge of the ROI to perform the morphological analysis (Davatzikos, 1999; Ashburner and Friston, 2000; Chung et al., 2001).

• No need for time consuming either manual or automatic segmentation of ROI.

• Anatomical differences can be detected at a voxel level within ROI itself giving additional localization power that ROI-based approaches lack.
Introduction to VBM

- Fully automated image analysis technique allowing identification of regional differences in gray matter (GM) and white matter (WM) between populations without a prior ROI.

VBM procedures

• Normalize structural MRIs to the standard SPM template
• Segment the normalized images into white and gray matter and cerebrospinal fluid (CSF) based on a Gaussian mixture model (Ashburner and Friston, 1997, 2000).
• The final output: the probability of each voxel belonging to a particular tissue type. This probability is usually referred to as the gray/white matter density.
**VBM pipeline**

1. **Pre-processing**
   - T1 Weighted MRI
   - Image normalization
     - MNI template or SPM template
   - Segmentation
     - Tissue segmentation
   - Gaussian kernel smoothing
     - Tissue density
   - General linear model
     - Removing effect of nuisance covariates
   - Random field theory
     - Multiple comparison correction
Pre-processing for VBM

Source: John Ashburner
Smoothing

Before convolution

Convolved with a circle

Convolved with a Gaussian
Examples of four subjects

Warped Grey Matter Density

12mm FWHM Smoothened Version
Tissue density in voxel-based morphometry

**Binary masks:** 0 or 1

**Gaussian kernel smoothing**

**Probability map** [0, 1]

Gray matter  White matter
Ashburner proposed to use logit transform on smoothed density map

\[ \text{logit}(p) : p \rightarrow \frac{1}{2} \log\left( \frac{p}{1 - p} \right) \]

But it is not really necessary since Gaussian kernel smoothing will make data more Gaussian.

Checking images follow Gaussian? QQ-plot, KS-test etc.
Statistical Parametric Mapping…

voxel by voxel
Linear model

\( \alpha_{k1} \)

\( \alpha_{k2} \)

group 1

group 2

\[ \left( \text{parameter estimate} - \frac{1}{\text{standard error}} \right) \]

\( \text{statistic image or SPM} \)
SPM results

**Statistics:** volume summary (p-values corrected for entire volume)

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<th>p</th>
<th>c</th>
<th>k</th>
<th>p_corrected</th>
<th>p_uncorrected</th>
<th>T</th>
<th>(Z)</th>
<th>x, y, z (mm)</th>
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Height threshold T = 4.30
Extent threshold k = 0 voxels
Real Example: 2D version of VBM

$m=12$ normal controls

$n=16$ autistic subjects

See Chung et al. 2004 NeuroImage
Pre-processing
Nonlinear image registration
(Normalization)

Each subject undergoes this process to reduce positional variability.

300 subjects MNI template
White matter segmentation

Normalized image → Segmentation of midsagittal corpus callosum region

Segmentation is done by Gaussian mixture model
2D Gaussian kernel smoothing on white matter density map.
Average of 12 normalized mid sagittal segmented images showing well defined corpus callosum. This is our template.
White matter concentration difference

- autism

- control

- Compute the sample mean at each voxel.
- Is the density difference statistically significant?
White matter variability difference

autism

control
T-statistic map with equal variance assumption
But the two sample t test doesn’t seem to be right. There may be possible age effect so it is necessary to remove the age effect. How?

**General linear model (GLM), linear regression**

\[
density = \lambda_1 + \lambda_2 \text{age} + \beta_1 \text{group} + e
\]

\[H_0 : \beta_1 = 0 \ vs. \ H_1 : \beta_1 \neq 0\]
Computing the sum of squared errors (residuals) requires the least squares estimation (LSE) of unknown parameters.
\textit{p}-value map for $t$-test on cortical thickness difference

\textbf{Decrease:} left superior temporal sulcus, left occipital-temporal gyrus, right orbital prefrontal

\textbf{Increase:} left superior temporal gyrus, left middle temporal gyrus, left and right postcentral sulci
$p$-value map for $F$-test removing age effect

Decrease: left superior temporal sulcus
left occipital-temporal gyrus
right orbital prefrontal
It is better to remove the age effect in anatomical data especially for developmental age range.
How to validate VBM framework?
This is not a permutation test although it looks like it.

Randomly permute 16 autism and 12 controls to generate 14 autism and 14 controls. Our two sample t-test should not detect anything except possible random occurrences.

Above all three random permutations, p-value > 0.3679
Lecture 3

Volume to surface
Jacobian determinants
Tensor-based morphometry (TBM)

Read
http://www.stat.wisc.edu/~mchung/papers/CVPR/CVPR.pdf