The General Linear Model and Statistical Parametric Mapping

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...a voxel by voxel hypothesis testing approach
   → reliably identify regions showing a significant experimental effect of interest

• Key concepts
  • Type I error
    – significance test at each voxel
  • Parametric statistics
    – parametric model for voxel data, test model parameters
  • No exact prior anatomical hypothesis
    – multiple comparisons

• Statistical Parametric Mapping
  • General Linear Model
  • Theory of continuous random fields
Overview…

...a voxel by voxel hypothesis testing approach
→ reliably identify regions showing a significant experimental effect of interest

- The General linear model & Statistical Parametric Mapping
  - General Linear Model
    - models & design matrices
    - model estimation
  - Generalised Linear Model
    - serial correlations
    - variance components
  - Contrasts & Statistic images
    - Statistical Parametric Maps – SPMs
  - Global effects
  - Model selection

- realignment & motion correction
- normalisation
- smoothing
- image data
- kernel
- design matrix
- General Linear Model
  → model fitting
  → statistic image
- Statistical Parametric Map
- corrected p-values
- parameter estimates
- random field theory
Example epoch fMRI activation dataset:
Auditory stimulation

- Single subject
  - RH male
- Conditions
  - Passive word listening
  - Bisyllabic nouns
  - 60wpm
  - against rest
- Epoch fMRI
  - rest & words
  - epochs of 6 scans
  - 42 second epochs
  - 7 BA cycles

Experiment was 8 cycles:
first pair of blocks dropped
→ B A B A B A B A
⇒ last 84 scans of experiment
images 16–99
⇒ ~10 minutes scanning time

Voxel by voxel statistics...

fMRI time series
voxel time series

model specification
parameter estimation
hypothesis
statistic

statistic image or SPM
Voxel statistics...

- **parametric**
  - one sample \( t \)-test
  - two sample \( t \)-test
  - paired \( t \)-test
  - Anova
  - AnCova
  - correlation
  - linear regression
  - multiple regression
  - \( F \)-tests
  - etc...

- **non-parametric?** → SnPM

...e.g. two-sample \( t \)-test?

\[
t = \frac{\bar{Y}_1 - \bar{Y}_0}{\sqrt{\frac{s^2}{n_1} + \frac{s^2}{n_0}}}
\]

- standard \( t \)-test assumes independence
- ignores temporal autocorrelation!

- \( t \)-statistic image
- \( SPM(t) \)
- compares size of effect to its error standard deviation

General Linear Model
- assume normality
- to account for serial correlations:
  - Generalised Linear Model

all cases of the

voxel time series

Image intensity
Regression example...

\[ Y_s = \mu + \alpha f(t) + \varepsilon_s \]

- \( f(t) = 0 \) or \( 1 \)
- \( \varepsilon_s \sim N(0, \sigma^2) \)

- correlation:
  - test \( H_0: \rho = 0 \) equivalent to
  - test \( H_0: \alpha = 0 \)

- two-sample \( t \)-test:
  - test \( H_0: \mu_0 = \mu_1 \) equivalent to
  - test \( H_0: \alpha = 0 \)

\[ t \text{-statistic for } H_0: \alpha = 0 \]

\( \checkmark \) can extend to account for temporal autocorrelation!

…revisited

\[ Y_s = \mu \times 1 + \alpha \times f(t) + \varepsilon_s \]
General Linear Model…

- **fMRI time series**: $Y_1, \ldots, Y_s, \ldots, Y_N$
  - acquired at times $t_1, \ldots, t_s, \ldots, t_N$
- **Model**: Linear combination of basis functions
  \[ Y_s = \beta_1 f^1(t_s) + \ldots + \beta_l f^l(t_s) + \ldots + \beta_L f^L(t_s) + \varepsilon_s \]
- **$f^l(.)$: basis functions**
  - “reference waveforms”
  - dummy variables
- **$\beta_l$: parameters** (fixed effects)
  - amplitudes of basis functions (regression slopes)
- **$\varepsilon_s$: residual errors**
  - $\varepsilon_s \sim N(0, \sigma^2)$
  - identically distributed
  - independent, or serially correlated (Generalised Linear Model $\rightarrow$ GLM)

Design matrix formulation…

\[
Y_s = \beta_1 f^1(t_s) + \ldots + \beta_l f^l(t_s) + \ldots + \beta_L f^L(t_s) + \varepsilon_s \\
Y_1 = \beta_1 f^1(t_1) + \ldots + \beta_L f^L(t_1) + \varepsilon_1 \\
Y_2 = \beta_1 f^1(t_2) + \ldots + \beta_L f^L(t_2) + \varepsilon_2 \\
\vdots \\
Y_N = \beta_1 f^1(t_N) + \ldots + \beta_L f^L(t_N) + \varepsilon_N \\
\]

\[
Y = X \times \beta + \varepsilon
\]

- $X$: data vector
- $\beta$: vector of parameters
- $\varepsilon$: error vector

\[
Y = \begin{bmatrix} Y_1 \\ \vdots \\ Y_N \end{bmatrix} = \begin{bmatrix} f^1(t_1) \ldots f^1(t_N) \\ \vdots \\ f^l(t_1) \ldots f^l(t_N) \\ \vdots \\ f^L(t_1) \ldots f^L(t_N) \end{bmatrix} \begin{bmatrix} \beta_1 \\ \vdots \\ \beta_l \\ \beta_l \\ \beta_K \end{bmatrix} + \begin{bmatrix} \varepsilon_1 \\ \vdots \\ \varepsilon_l \\ \varepsilon_l \\ \varepsilon_N \end{bmatrix}
\]
Box-car regression… (revisited)

\[ Y_s = \mu \times 1 + \alpha \times f(t_s) + \varepsilon_s \]

Box car regression: design matrix…

\[ Y = X \times \beta + \varepsilon \]
Low frequency nuisance effects...

- **Drifts**
  - physical
  - physiological

- **Aliased high frequency effects**
  - cardiac (~1 Hz)
  - respiratory (~0.25 Hz)

- **Discrete cosine transform basis functions**
  - \( r = 1, \ldots, R \)
  - \( R \) \( \leftrightarrow \) cut-off period

\[ f_r(t) = \cos \left( r \frac{\pi}{N} t - t_1 \right) \]

...design matrix

\[
\begin{align*}
Y &= \mathbf{X} \times \mathbf{\beta} + \mathbf{\varepsilon} \\
\end{align*}
\]
Example: a line through 3 points...

**Simple Linear Regression**

\[ Y_i = \alpha x_i + \mu + \epsilon_i \quad i = 1, 2, 3 \]

\[ Y_1 = \alpha x_1 + \mu + \epsilon_1 \]
\[ Y_2 = \alpha x_2 + \mu + \epsilon_2 \]
\[ Y_3 = \alpha x_3 + \mu + \epsilon_3 \]

**Parameter Estimates**
\[ \hat{\mu}, \hat{\alpha} \]

**Fitted Values**
\[ \hat{Y}_1, \hat{Y}_2, \hat{Y}_3 \]

**Residuals**
\[ \epsilon_1, \epsilon_2, \epsilon_3 \]

Geometrical perspective...

\[ Y = \alpha x + \mu + \epsilon \]

\[ Y = \alpha x_1 + \mu x_i + \epsilon \]

\[ Y = \alpha x_2 + \mu x_2 + \epsilon \]

**Design Space**

\[ (a, b, c) \]
Estimation, geometrically…

\[ \hat{Y} = X\hat{\beta} + \varepsilon \]

Estimation, formally…

Consider parameter estimates

\[ \hat{\beta} = (\hat{\beta}_1, \ldots, \hat{\beta}_L)^T \]

Giving fitted values

\[ \hat{Y} = (\hat{Y}_1, \ldots, \hat{Y}_N)^T = X\hat{\beta} \]

Residuals

\[ \varepsilon = (e_1, \ldots, e_N)^T = Y - \hat{Y} = Y - X\hat{\beta} \]

Residual sum of squares

\[ S = \sum_{j=1}^{N} e_j^2 = \varepsilon^T \varepsilon = \sum_{j=1}^{N} \left( Y_j - x_{j1}\hat{\beta}_1 - \ldots - x_{jL}\hat{\beta}_L \right)^2 \]

Minimised when

\[ \frac{\partial S}{\partial \hat{\beta}_k} = 2 \sum_{j=1}^{N} (-x_{jk}) \left( Y_j - x_{j1}\hat{\beta}_1 - \ldots - x_{jL}\hat{\beta}_L \right) = 0 \]

…but this is the \( l \)th row of

\[ X^TY = (X^TX)^{-1}X^TY \]

so the least squares estimates satisfy the normal equations

\[ X^TY = (X^TX)^{-1}X^TY \]
Inference, geometrically...

model:
\[ Y_i = \alpha x_i + \mu + \varepsilon_i \]

null hypothesis:
\( H_0: \alpha = 0 \) (zero slope...)

i.e. does \( x_\alpha \) explain anything? (after \( \mu \))

\[ \varepsilon = (\varepsilon_1, \varepsilon_2, \varepsilon_3)^T \]
Inference, formally...

For any linear compound of the parameter estimates:
\[ \epsilon^T \hat{\beta} \sim N (\epsilon^T \beta, \sigma^2 \epsilon^T(X^TX)^{-1} \epsilon) \]

Further (independently):
\[ \hat{\sigma}^2 = \frac{\epsilon^T \epsilon}{N - p} \sim \sigma^2 \chi^2_{N-p} \]
\[ p = \text{rank}(X) \]

So hypotheses can be assessed using:
\[ \frac{\epsilon^T \hat{\beta} - \epsilon^T \beta}{\sqrt{\hat{\sigma}^2 \epsilon^T(X^TX)^{-1} \epsilon}} \sim t_{N-p} \]
a Student’s t statistic, giving an SPM{t}

Suppose the model can be partitioned…
\[ Y = \left[ X_1 : X_2 \right] \left[ \begin{array}{c} \beta_1 \\ \vdots \\ \beta_2 \end{array} \right] + \epsilon \]
\[ F = \frac{s(\hat{\beta}_1) - s(\hat{\beta}_2)}{p - m} \frac{s(\hat{\beta}_2)}{N - p} \sim F_{p-m,N-p} \]
“Extra sum-of-squares”

Multivariate perspective...

\[ Y = X \beta + \epsilon \]
\[ \hat{\beta} \]
\[ \text{variance} \]
\[ \sigma^2 \]

“Image regression”
fMRI box car example...

\[ Y = X \beta + \varepsilon \]

...fitted
Drifts
- physical
- physiological

Aliased high frequency effects
  e.g.
  - cardiac (~1 Hz)
  - respiratory (~0.25 Hz)

Serial correlations...

\[ Y = X \beta + \epsilon \]
\[ \epsilon \sim N(0, \sigma^2 V) \]

- Intrinsic autocorrelation \( V \)

Problem: Estimate \( \sigma^2 V \) at each voxel and make inference about \( \epsilon^T \beta \)

Model:
Model \( V \) as linear combination of \( m \) variance components
\[ V = \lambda_1 Q_1 + \lambda_2 Q_2 + \ldots + \lambda_m Q_m \]

Assumptions:
- \( V \) is the same at each voxel
- \( \sigma^2 \) is different at each voxel

Example:
For one fMRI session, use 2 variance components. Choice of \( Q_1 \) and \( Q_2 \) motivated by autoregressive model of order 1 plus white noise (AR(1)+wn)
Serial correlations...estimation

**Estimation:**

\( \hat{\beta} = (X^T X)^{-1} X^T Y \) – unbiased, ordinary least squares estimate

Compute sample covariance matrix of data at all activated voxels:

\[ C_Y = \sum_k Y_k Y_k^T / K \]

Important: Data \( Y_k \) must be high-pass filtered.

Model \( C_Y \) as

\[ C_Y = X \beta \beta^T X^T + \sum \lambda_i Q_i \]

and estimate hyperparameters \( \lambda_i \) using Restricted Maximum Likelihood (ReML)

Estimate \( V \) by

\[ V = N \sum \hat{\lambda}_i Q_i / \text{trace}(\sum \hat{\lambda}_i Q_i) \]

Estimate \( \sigma^2 \) at each voxel in the usual way by

\[ \hat{\sigma}^2 = (R V)^T (R V) / \text{trace}(R V) \]

where \( R = I - X (X^T X)^{-1} X \)

Serial correlations...inference

**Inference:**

To test null hypothesis \( c^T \beta = 0 \), compute t-value by dividing size of effect by its standard deviation:

\[ t = \frac{c^T \hat{\beta}}{\text{std}[c^T \beta]} \]

where \( \text{std}[c^T \beta] = \sqrt{\hat{\sigma}^2 c^T (X^T X)^{-1} X} \)

... but \( \text{std}[c^T \beta] \) is not a \( \chi^2 \) variable because of \( V \)

Find approximating \( \chi^2 \) distribution using Satterthwaite approximation:

\[ \text{Var}[\sigma^2] = 2\sigma^4 \text{trace}(R V R V) / \text{trace}(R V)^2 \]

\[ \nu = 2\text{E}[\sigma^2] / \text{Var}[\sigma^2] = \text{trace}(R V)^2 / \text{trace}(R V R V) \]

– effective degrees of freedom


Use t-distribution with \( \nu \) degrees of freedom to compute p-value for \( t \)
Inference — contrasts — SPM\{t\}

Is there an effect of interest after other modelled effects have been taken into account

Contrast — linear combination of parameters: $c^T \beta$

$t$-test $H_0$: $c^T \beta = 0$

$T = \frac{c^T \beta}{\text{variance estimate}}$

Correct variance estimate & degrees of freedom for temporal autocorrelation

Activation: box-car amplitude $> 0$

Inference — $F$-tests — SPM\{F\}

Is there an effect of interest after other modelled effects have been taken into account

Multiple linear hypotheses

$H_0$: $c^T \beta = 0$

$F = \frac{\text{additional variance accounted for by effects of interest}}{\text{error variance estimate}}$

Correct variance estimate & degrees of freedom for temporal autocorrelation

Does HPF basis set model anything?
Conclusions…

General Linear Model

✓ (simple) standard statistical technique
  • temporal autocorrelation – a Generalised Linear Model
✓ single general framework for many statistical analyses
  • flexible modelling ⇐ basis functions
✓ design matrix visually characterizes model
  • fit data with combinations of columns of design matrix
✓ statistical inference: contrasts…
  • t–tests: planned comparisons of the parameters
  • F–tests: general linear hypotheses, model comparison

“Statistical parametric maps in functional imaging: A general linear approach”
Human Brain Mapping 2:189-210

“Analysis of fMRI time series revisited — again” NeuroImage 2:173-181

“To smooth or not to smooth” NeuroImage 12: 196-208

Zarahn E, Aguirre GK, D’Esposito M (1997)


Aguirre GK, Zarahn E, D’Esposito M (1997)


Holmes AP, Friston KJ (1998)

“Generalisability, Random Effects & Population Inference”
NeuroImage 7(4-2/3):S754