Introduction à la statistique médicale

Statistical Parametric Mapping short course

Course 2:

General Linear Model, p.1

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GIGA – CRC *In Vivo* Imaging &

GIGA – *In Silico* Medicine

Content

- **Introduction**
- **General Linear Model**
- **Parameter estimation**
- **Improved model**
- **Conclusion**

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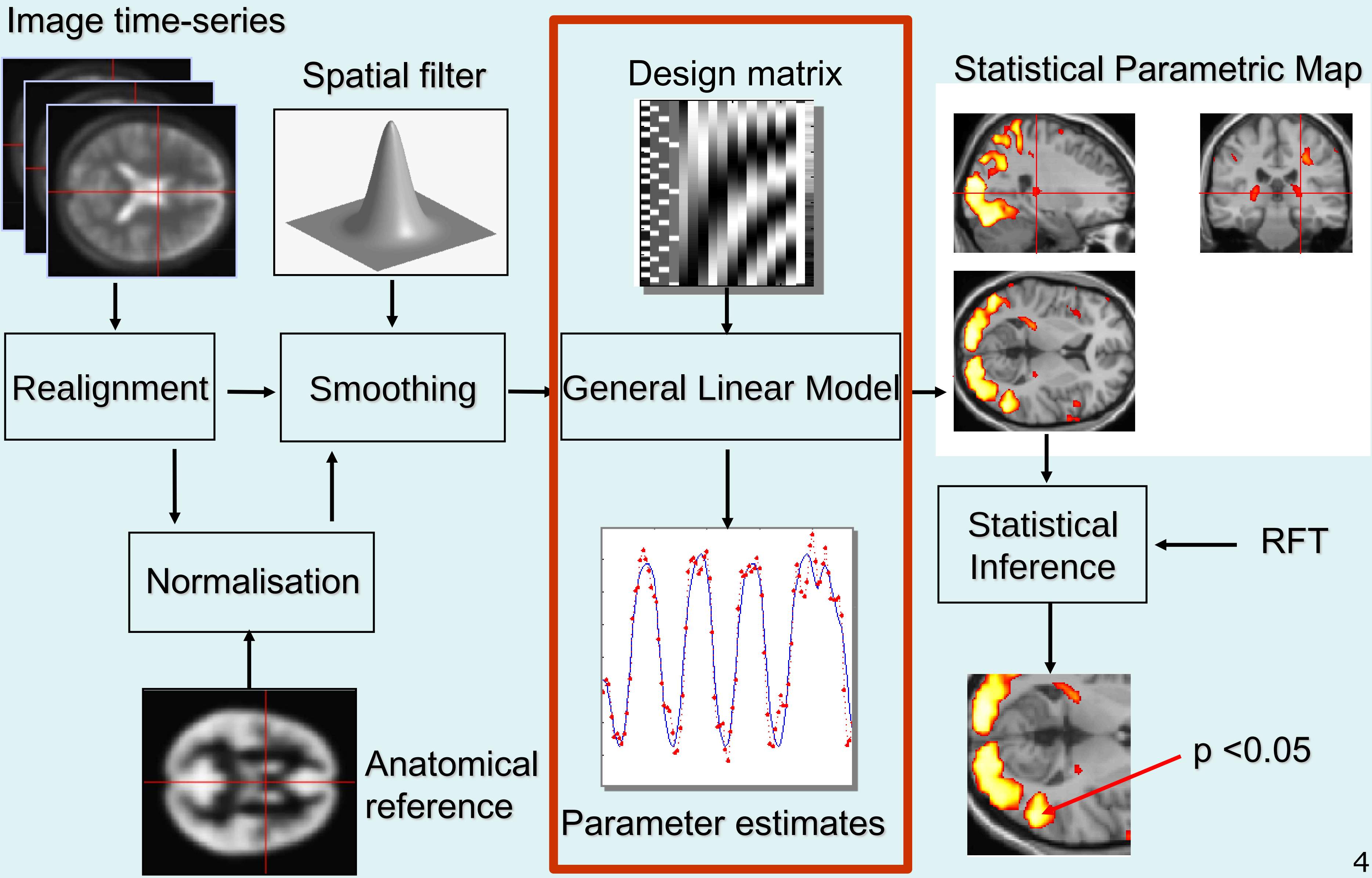
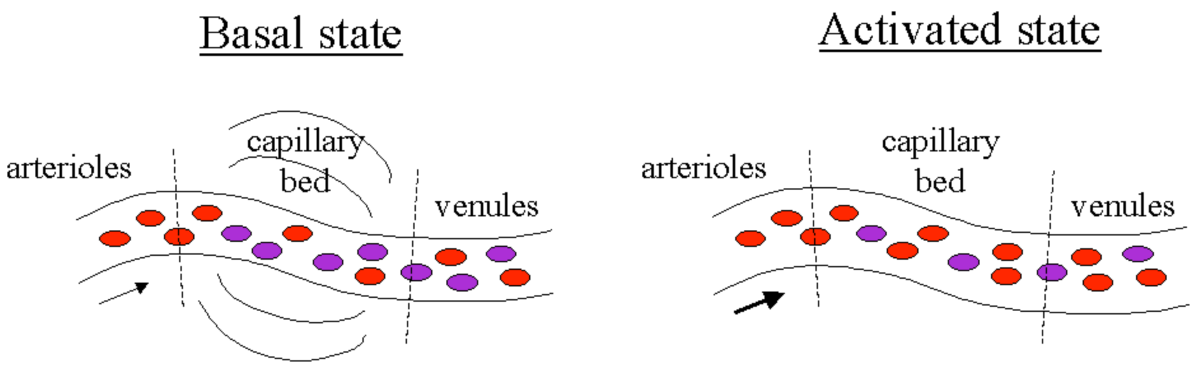
SPM work flow



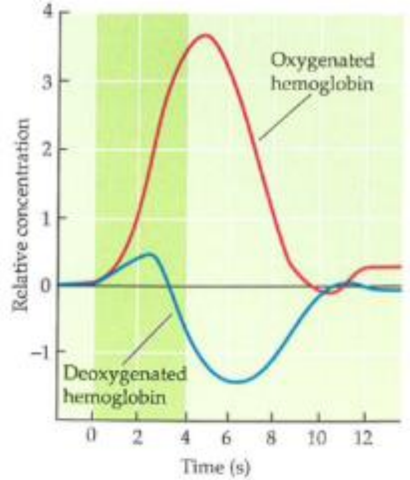
fMRI & BOLD signal



- normal flow
- basal level [Hbr]
- basal CBV
- normal MRI signal

= HbO_2
= Hbr

- increased flow
- decreased [Hbr] (*lower field gradients around vessels*)
- increased CBV
- increased MRI signal (*from lower field gradients*)

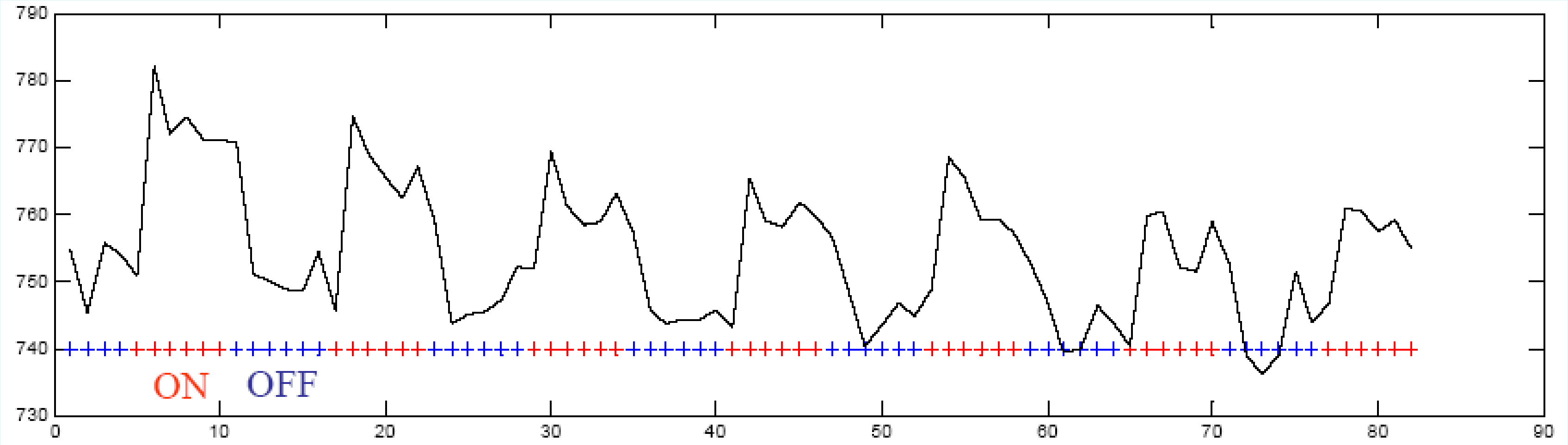


https://www.fil.ion.ucl.ac.uk/spm/course/slides10-zurich/Kerstin_BOLD.pdf

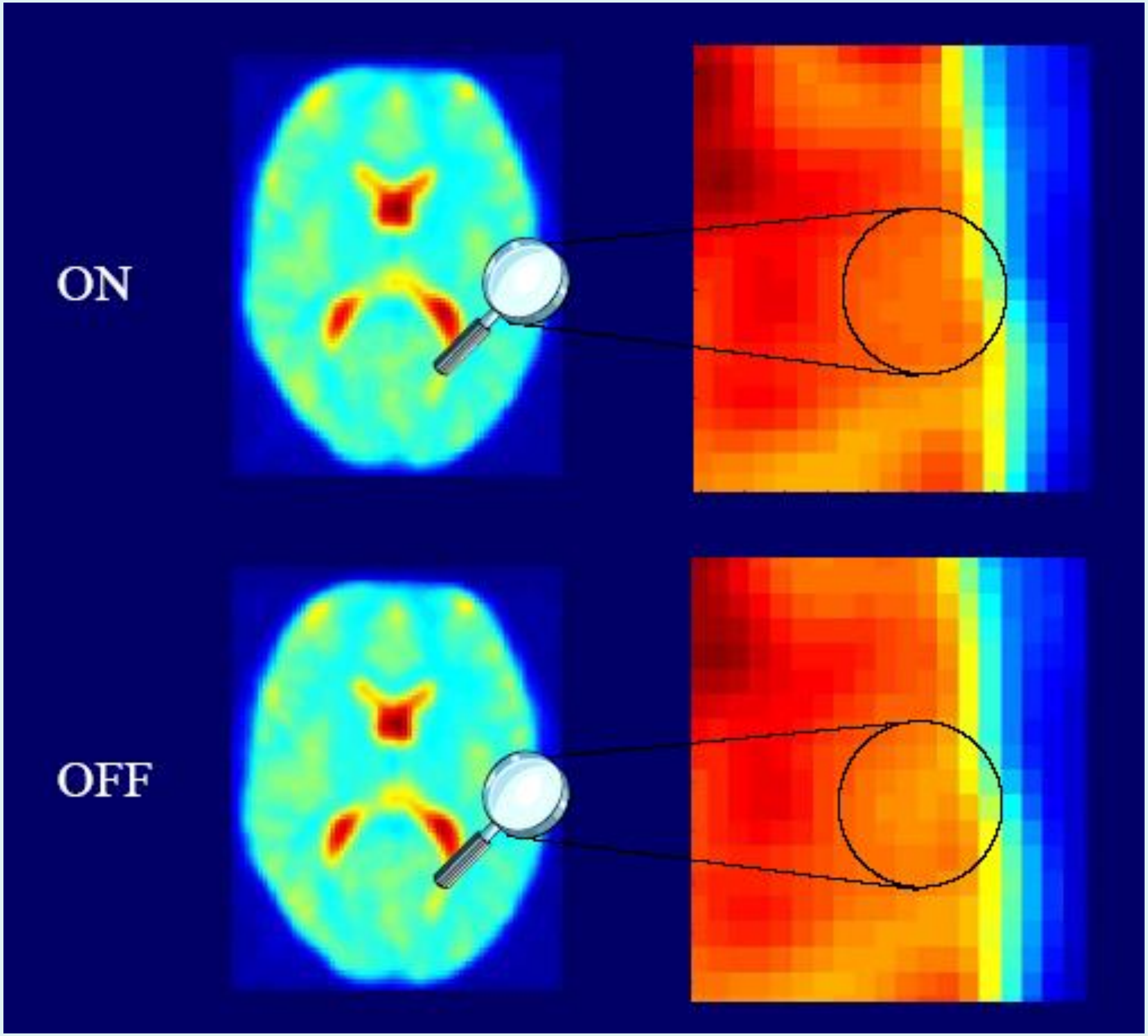
A simple fMRI experiment

Stimuli: passive word listening versus rest

BOLD response in the primary auditory cortex

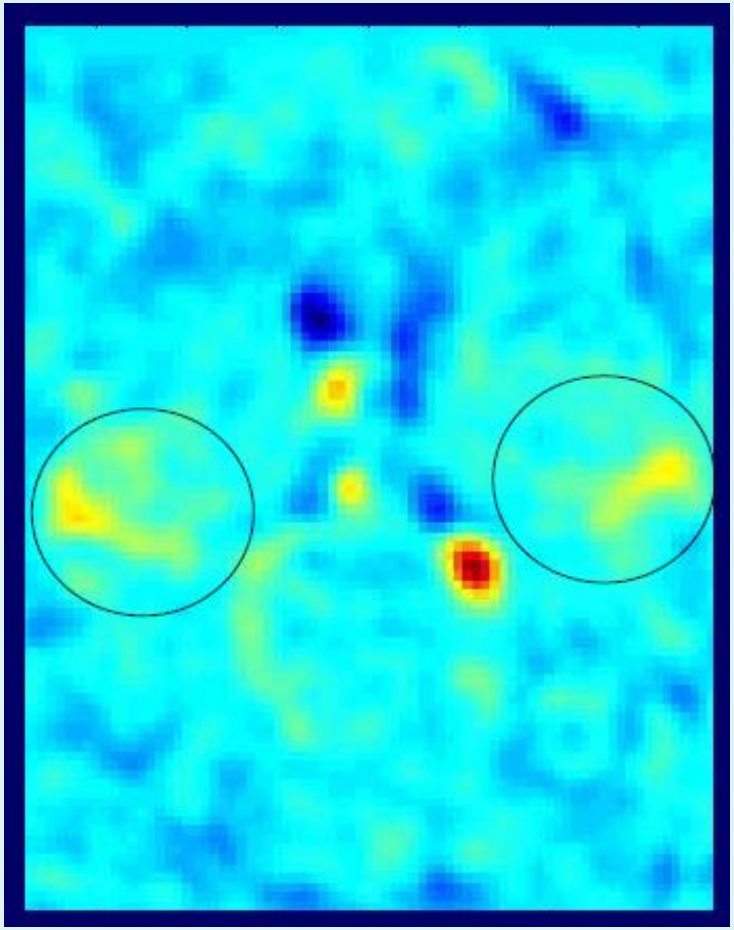


Looking at 2 scans



Looking at 2 scans

ON-OFF, just one scan per condition



Simple *f*MRI example dataset

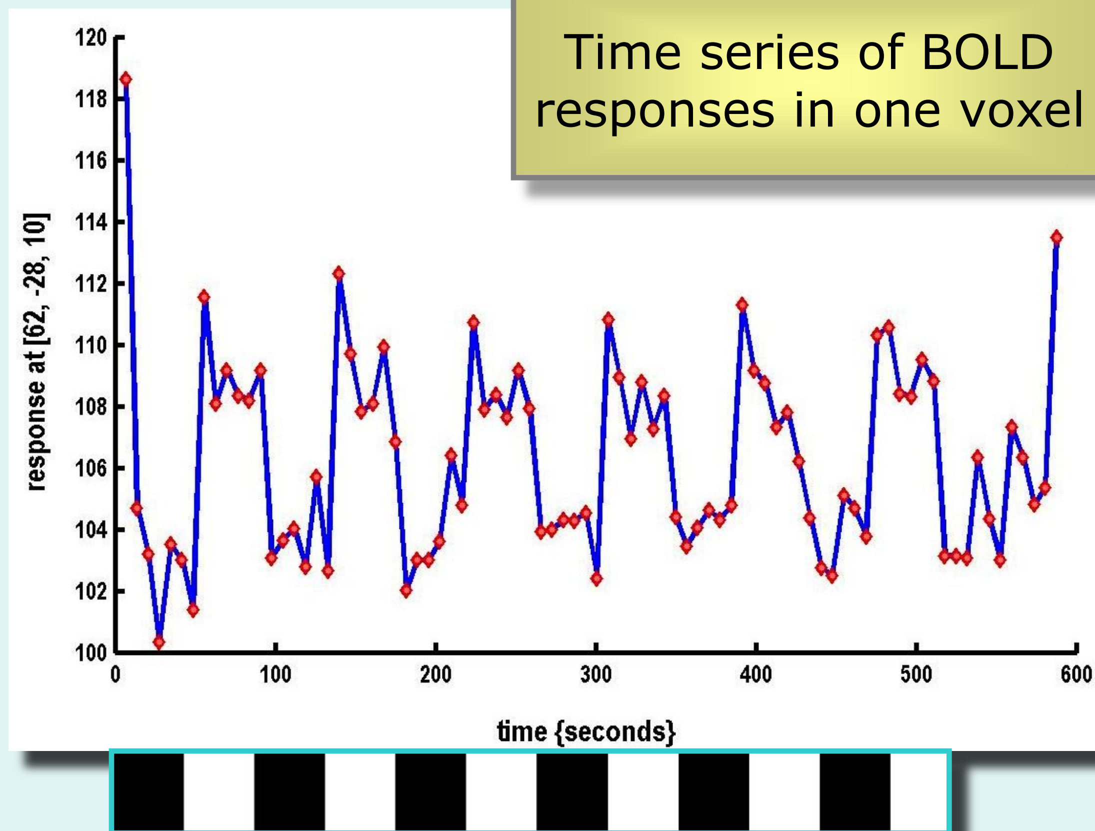
One session, one subject

Passive word listening versus rest

7 cycles of rest and listening

Each epoch 6 scans with 7 sec TR

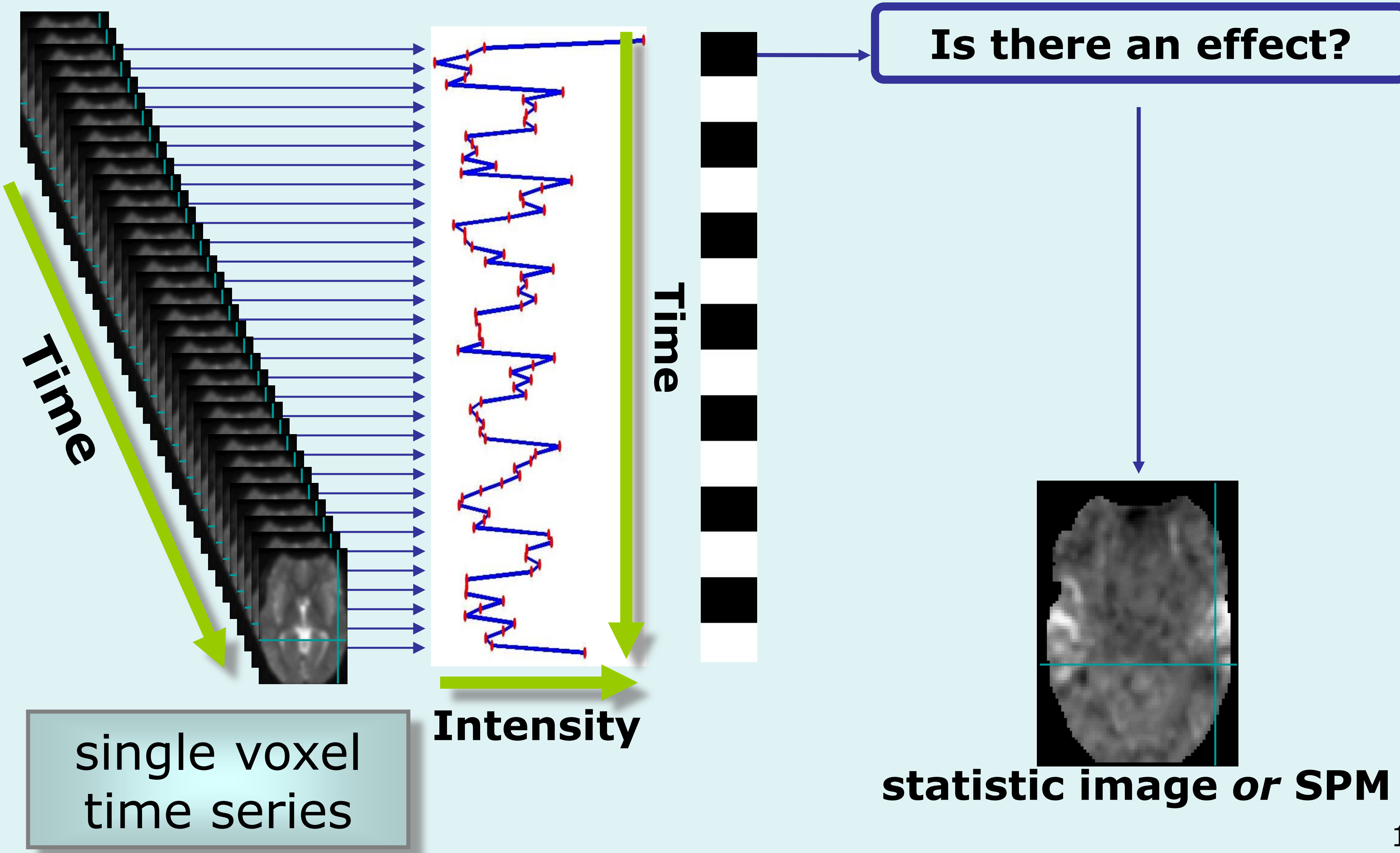
Time series of BOLD responses in one voxel



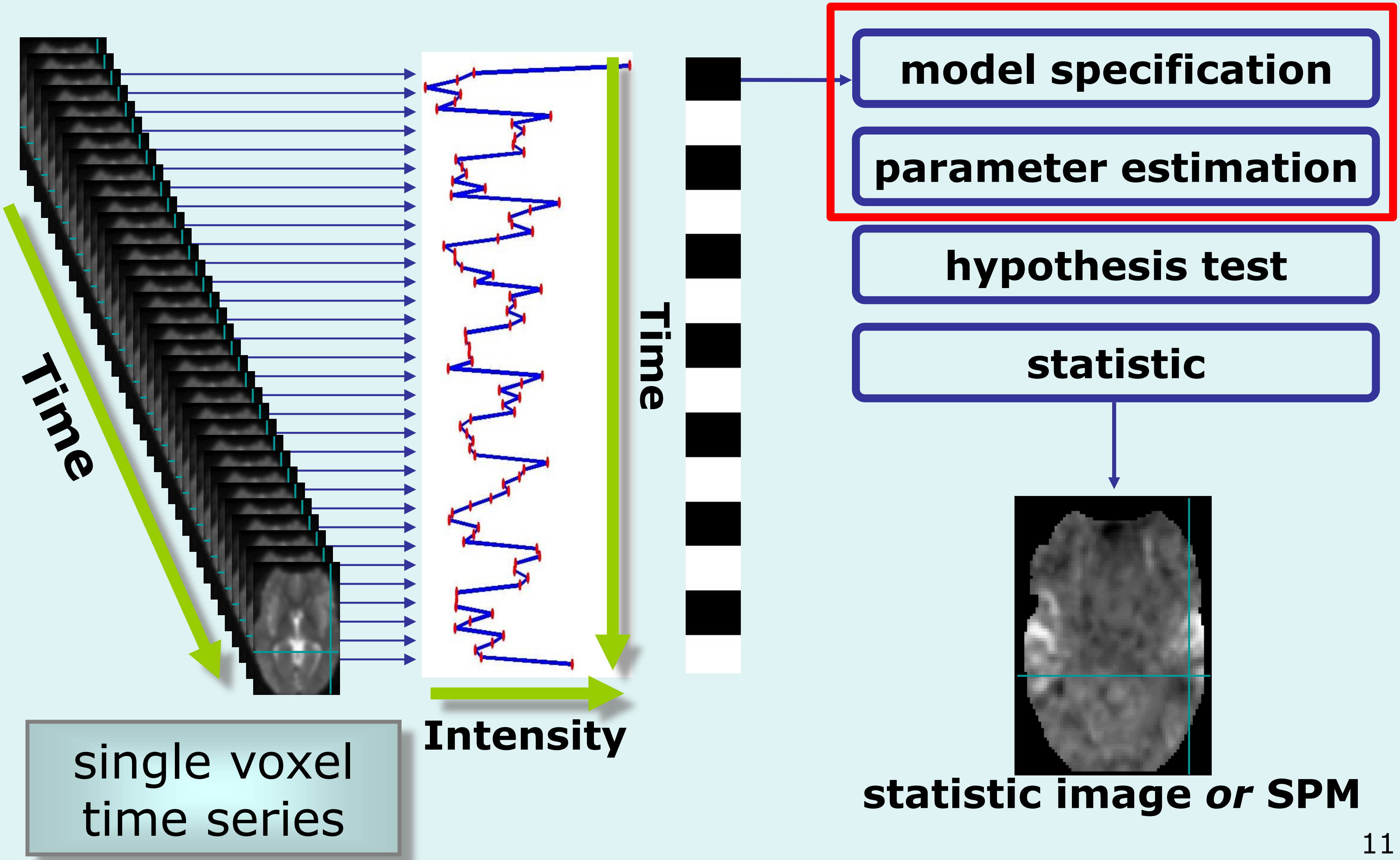
Stimulus function

Question: Is there a change in the BOLD response between listening and rest?

Voxel by voxel statistics



Voxel by voxel statistics



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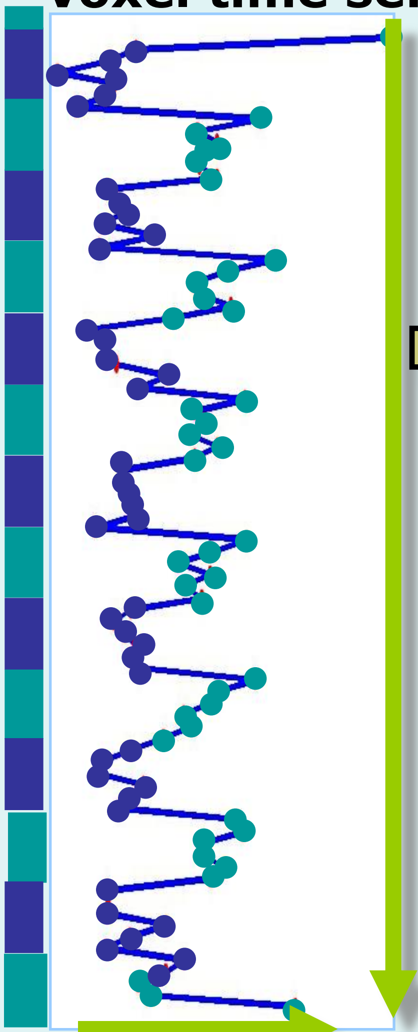
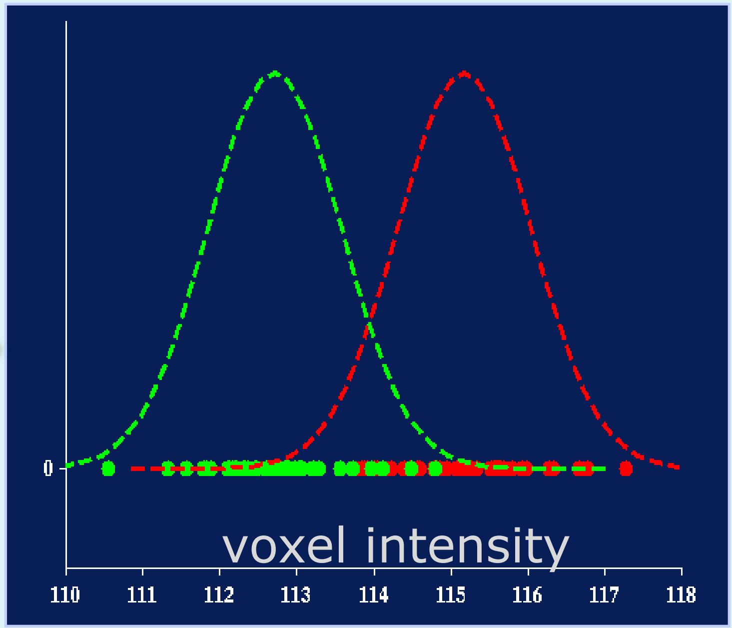
Single voxel, two-sample t-test

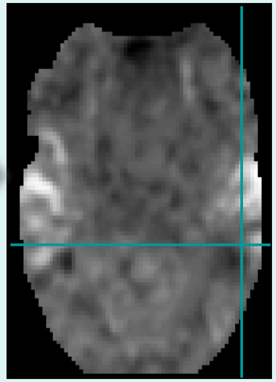
voxel time series



μ_0 μ_1



$$t = \frac{\mu_1 - \mu_0}{\sqrt{\sigma^2\left({}^{1}/_{n_1} + {}^{1}/_{n_0}\right)}}$$

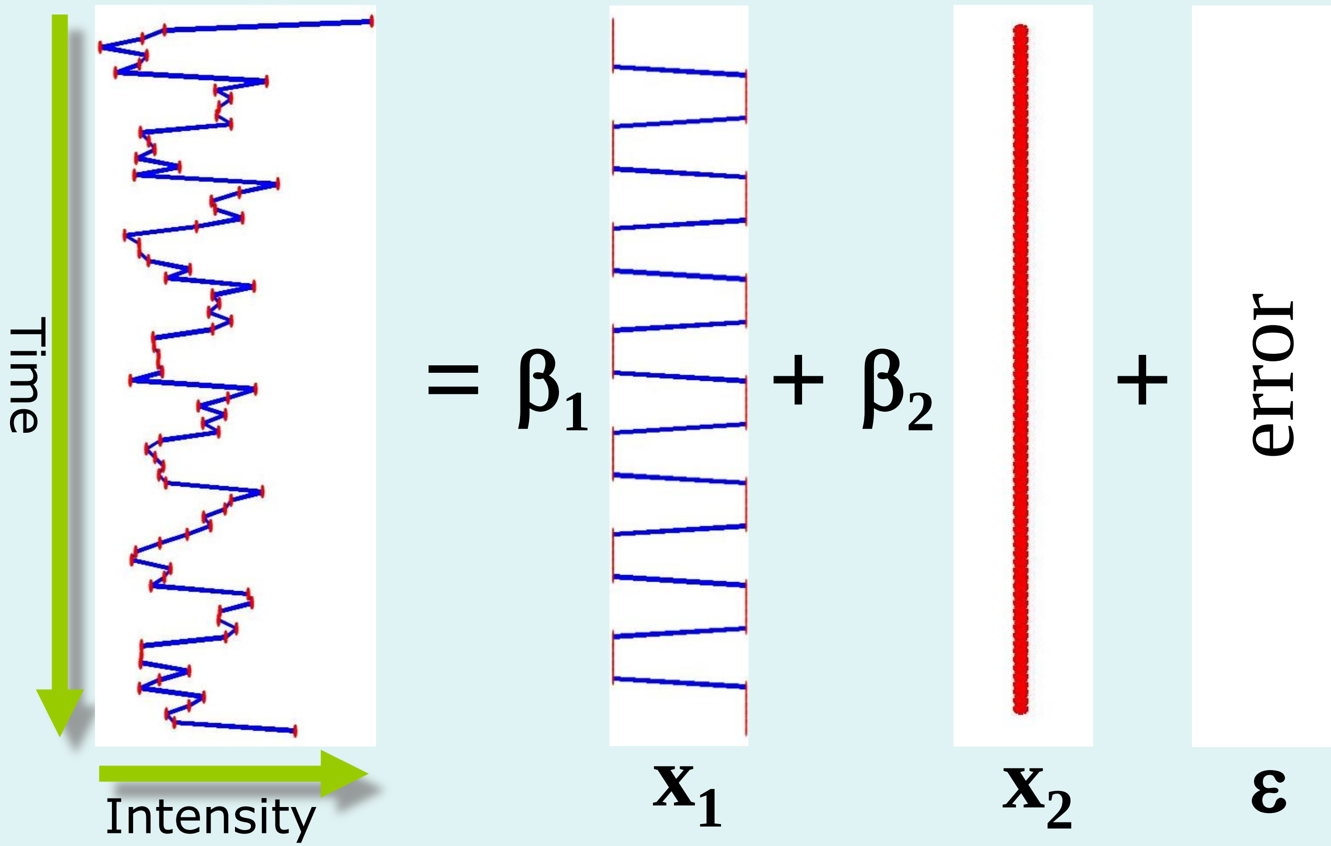


***t*-statistic image**
SPM{*t*}

compares size of effect to its error standard deviation

Question: Is there a change in the BOLD response between listening and rest?

Single voxel, regression model



$\varepsilon \sim N(0, \sigma^2 I)$

(error is normal and independently and identically distributed)

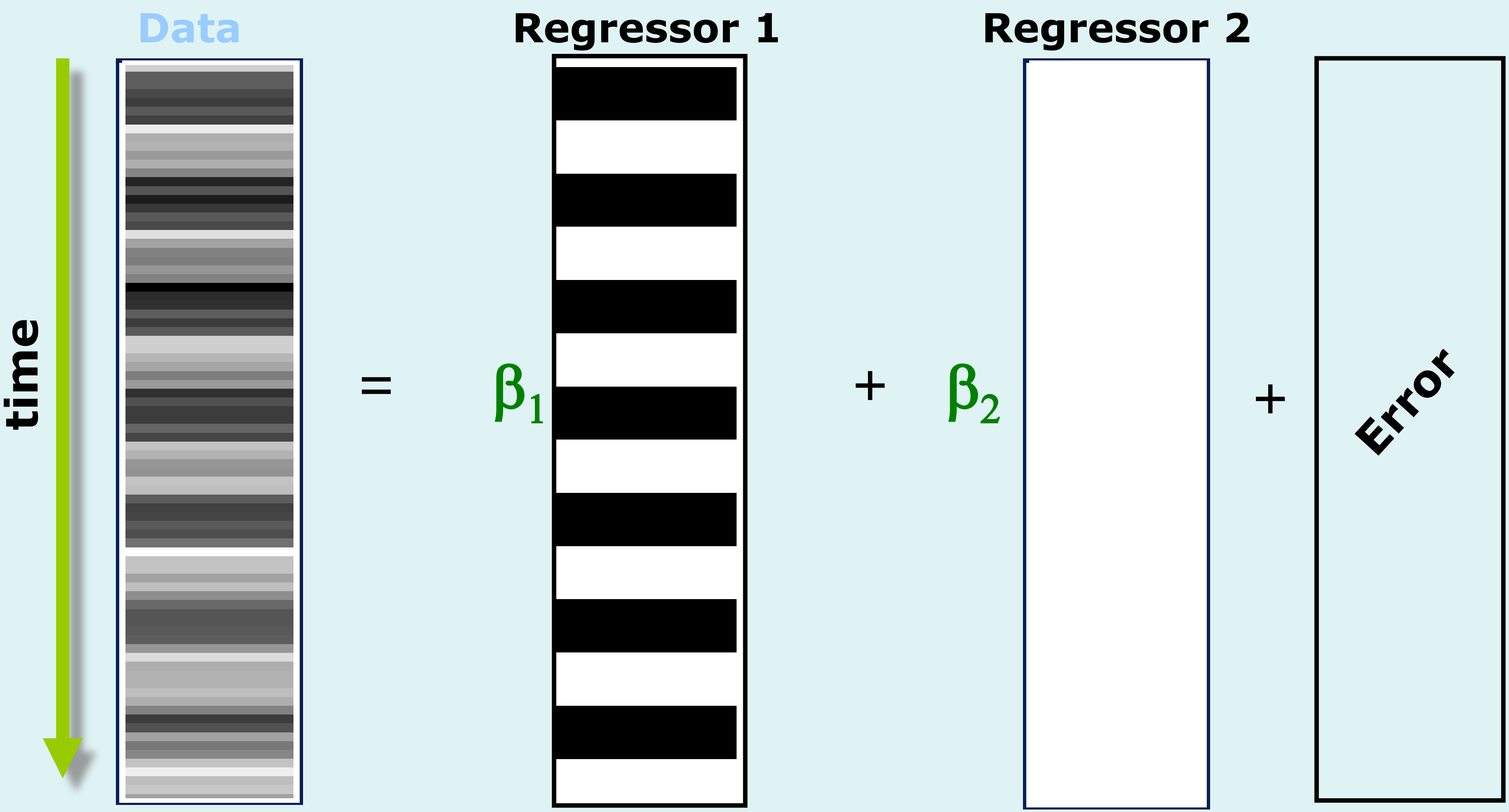
Question: Is there a change in the BOLD response between listening and rest?

Hypothesis test:

$\boldsymbol{\beta_1 = 0}$?

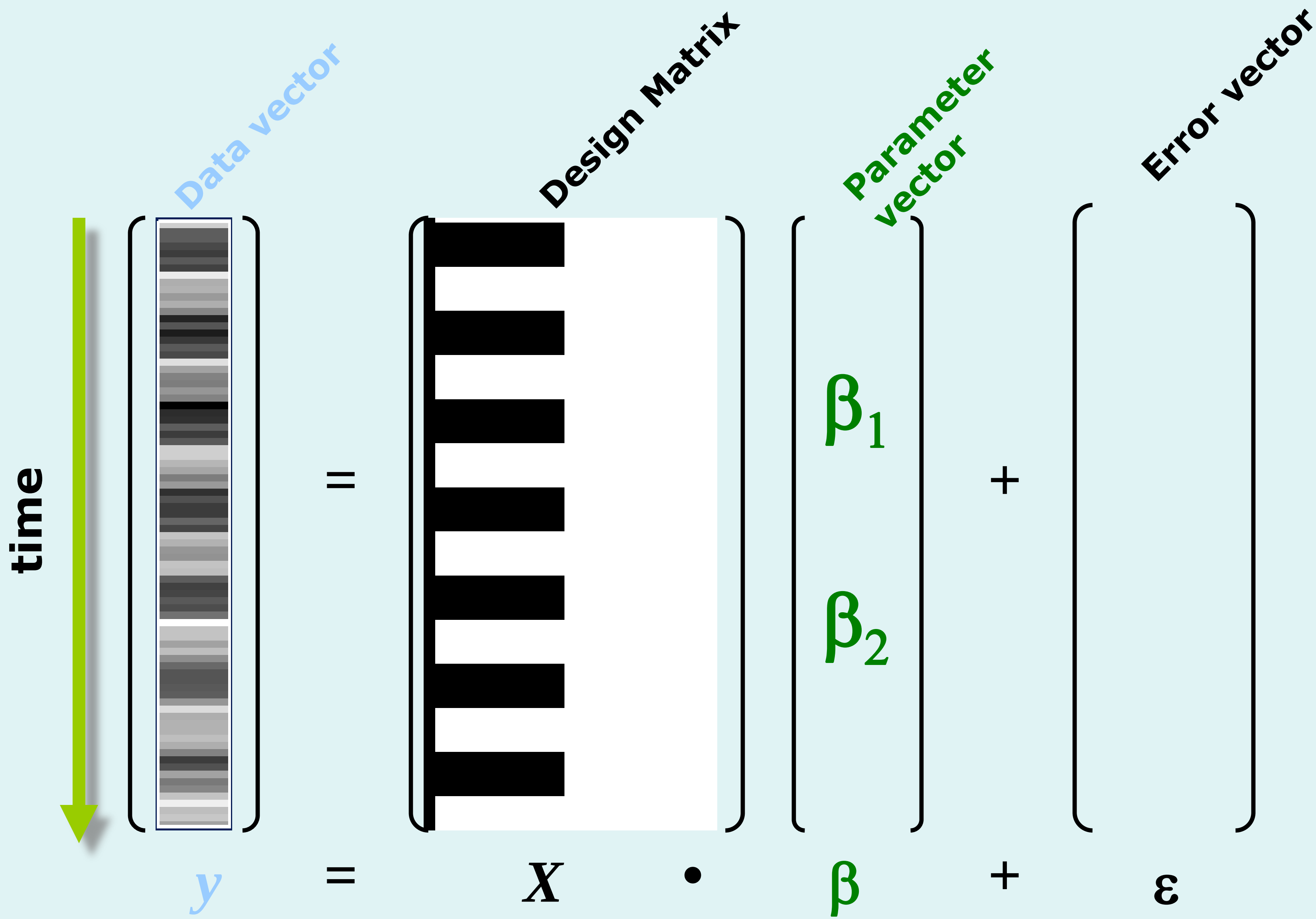
(using t-statistic)

Model as basis functions

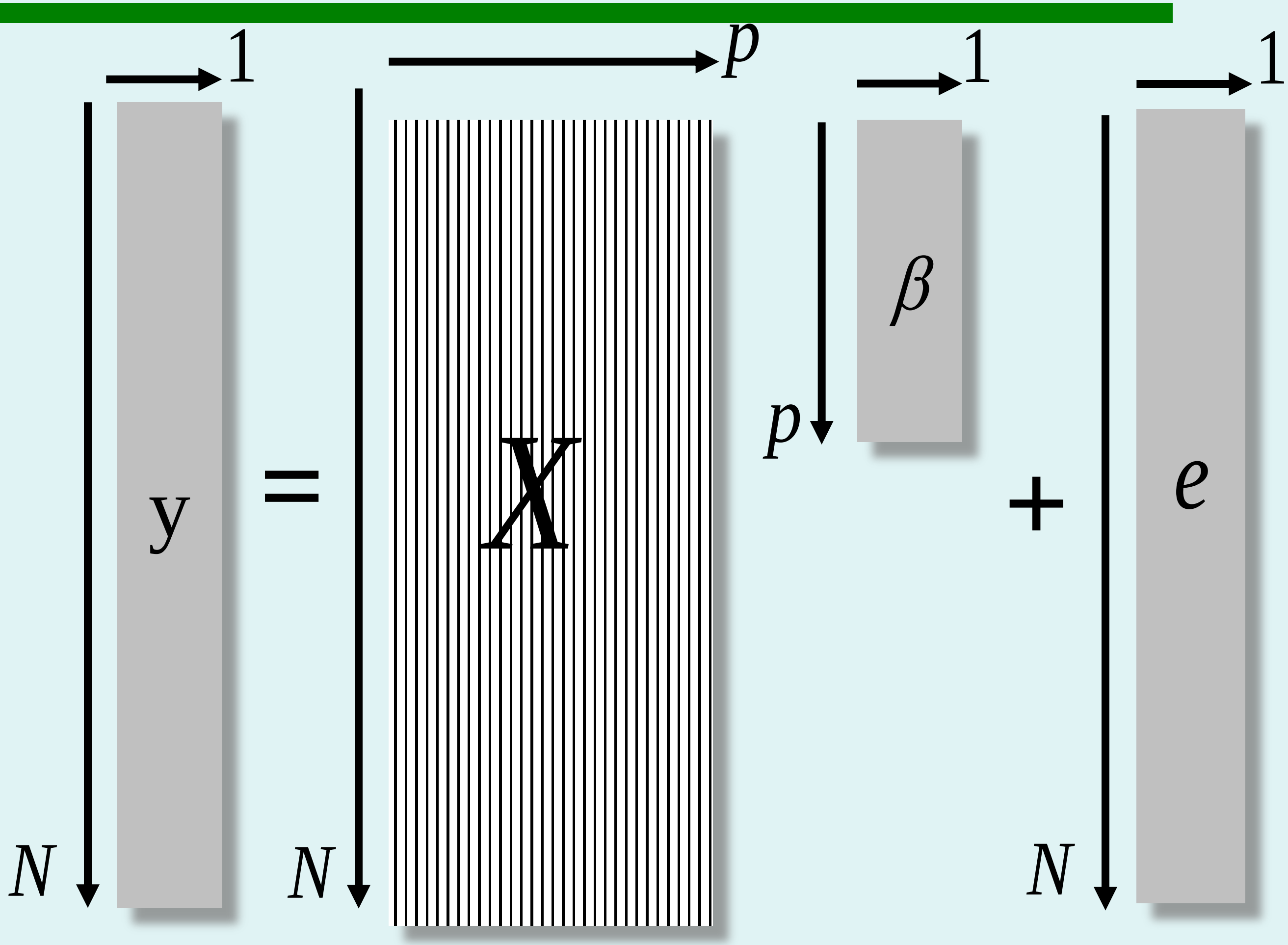


$$y = \beta_1 \cdot X_1 + \beta_2 \cdot X_2 + \varepsilon$$

Design matrix



General Linear Model



$$y = X\beta + e$$

$$e \sim N(0, \sigma^2 I)$$

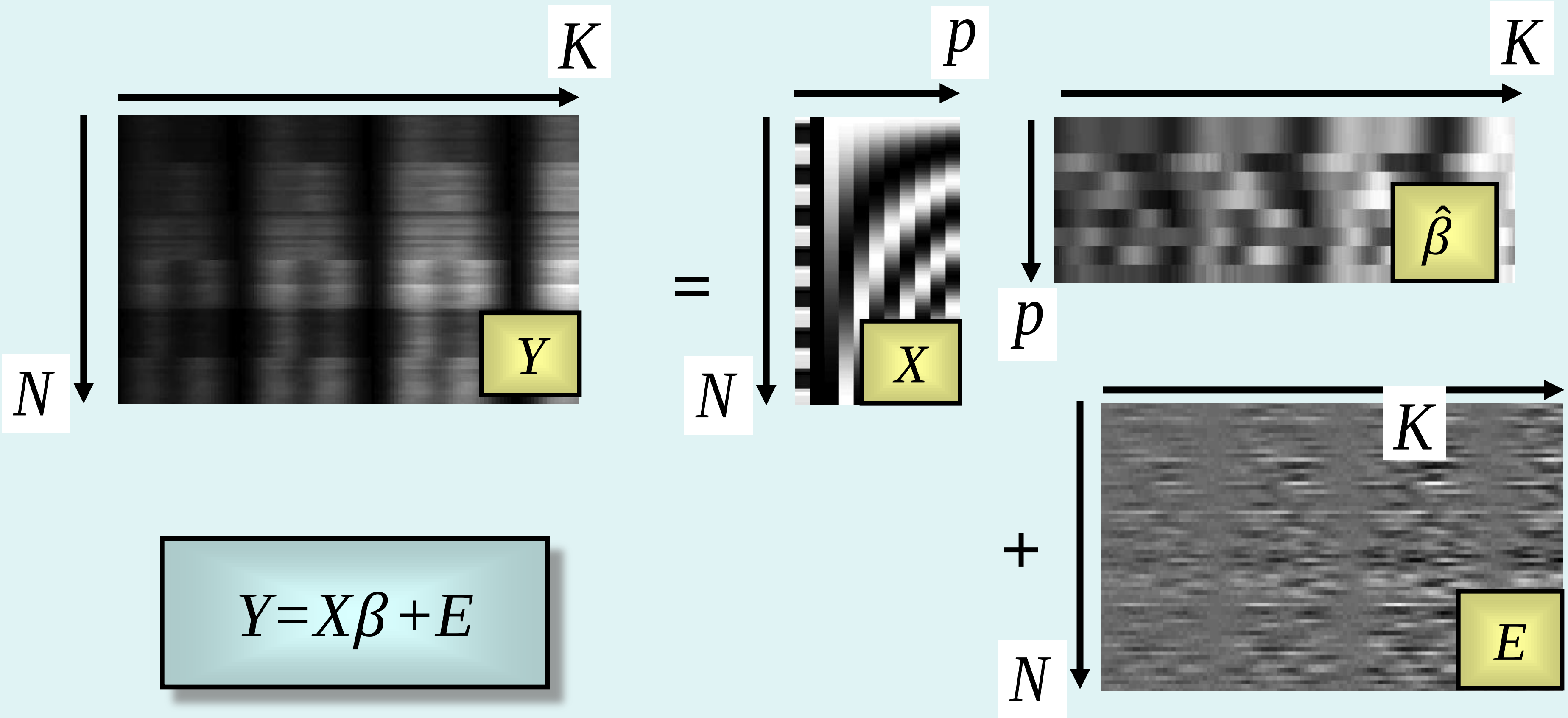
N: number of scans

p: number of regressors

Model is specified by

1. Design matrix **X**
2. Assumptions about **ε**

GLM & Mass univariate approach



$$Y = X\beta + E$$

The design matrix embodies all available knowledge about experimentally controlled factors and potential confounds.

Classical statistics

- parametric
  - one sample *t*-test
  - two sample *t*-test
  - paired *t*-test
  - Anova
  - AnCova
  - correlation
  - linear regression
  - multiple regression
  - *F*-tests
  - etc…

all cases of the

General Linear Model

assume normality

to account for serial correlations:

Generalised Linear Model

- non-parametric?

→ **SnPM**

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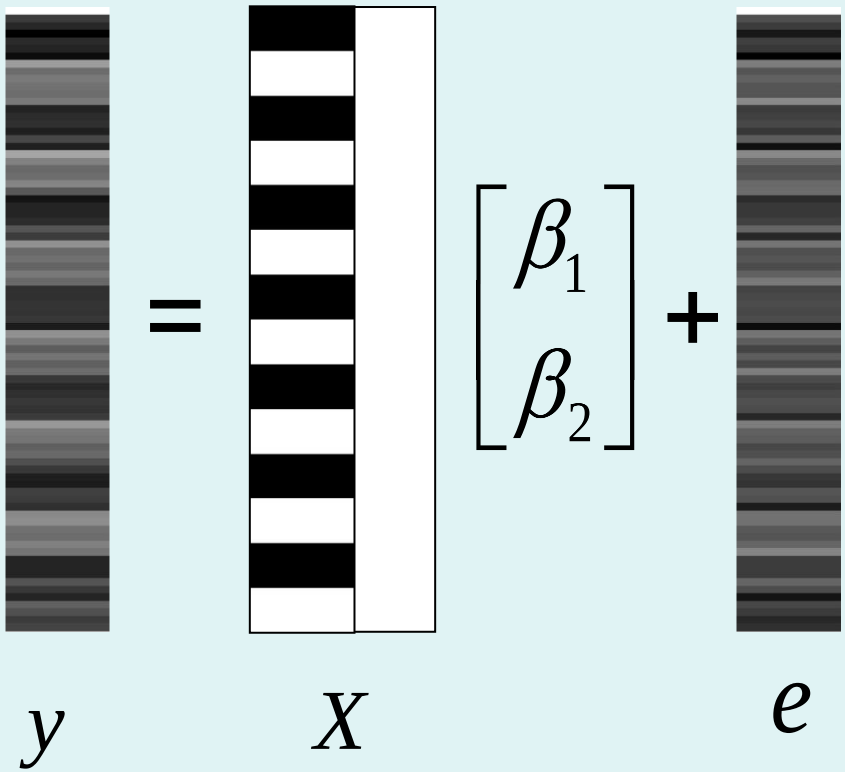
Parameter estimation



$$y = X\beta + e$$

Objective: estimate parameters to minimize

$$\sum_{t=1}^{N} e_t^2$$

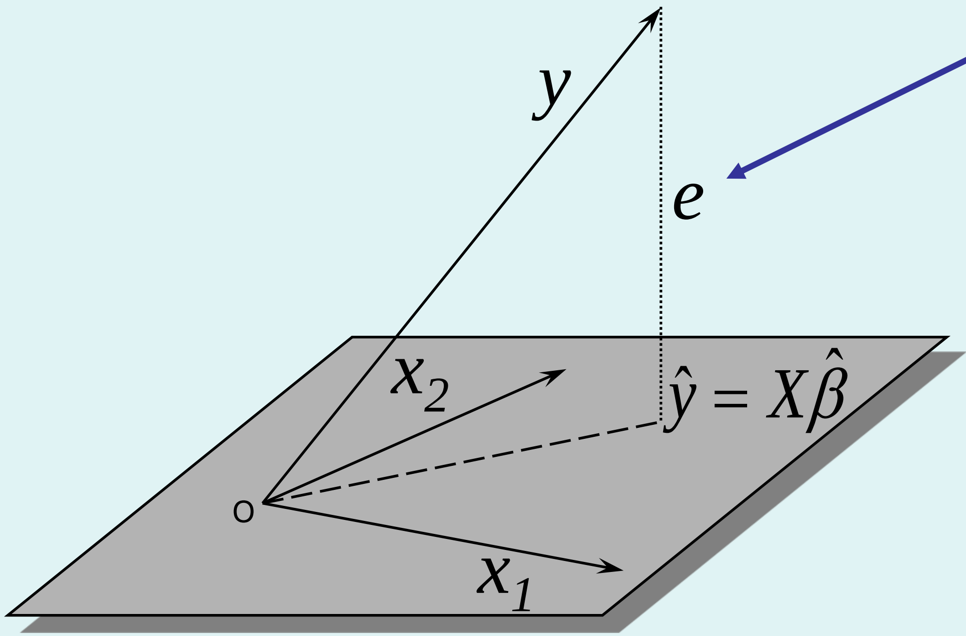
Ordinary least squares estimation (OLS) (assuming i.i.d. error):

$$\hat{\beta} = (X^T X)^{-1} X^T y$$

$$\hat{\beta} \sim N(\beta, \sigma^2 (X^T X)^{-1})$$

Geometric perspective on the GLM

Ordinary Least Squares (OLS)



Smallest errors (shortest error vector) when e is *orthogonal* to X

$$X^T e = 0$$

$$X^T (y - X\hat{\beta}) = 0$$

$$X^T y = X^T X \hat{\beta}$$

$$\hat{\beta} = (X^T X)^{-1} X^T y$$

Design space defined by X

N data points → N dimension space !

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Problems with fMRI time series

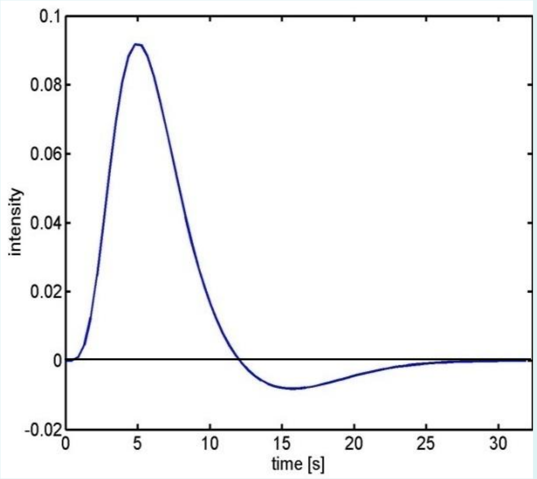
1. The ***BOLD response*** has a delayed and dispersed shape.

2. The BOLD signal includes substantial amounts of ***low-frequency noise*** (e.g. due to scanner drift).

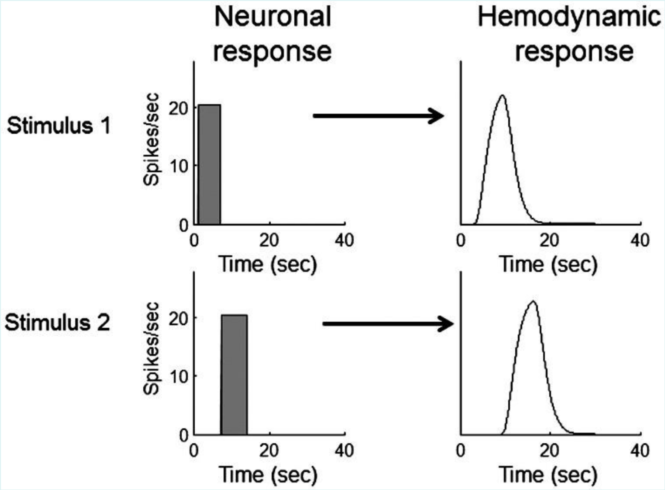
3. Due to breathing, heartbeat & unmodeled neuronal activity, the ***errors are serially correlated***. This violates the assumptions of the noise model in the GLM.

Problem 1: BOLD response

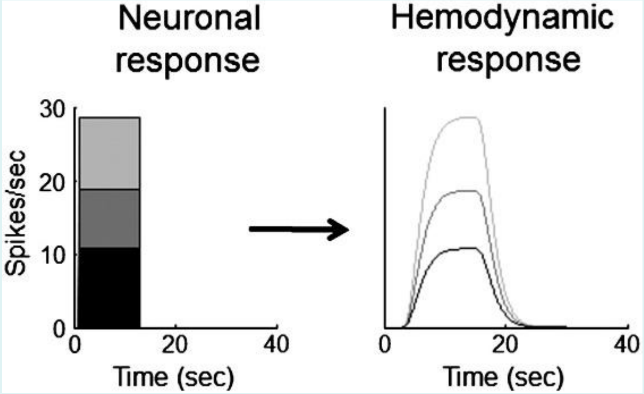
Hemodynamic response function (HRF):



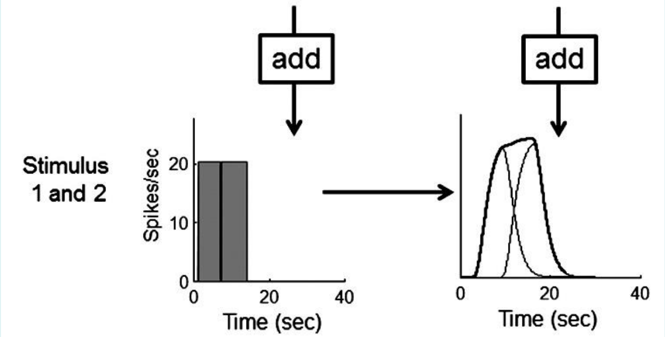
Shift invariance



Scaling



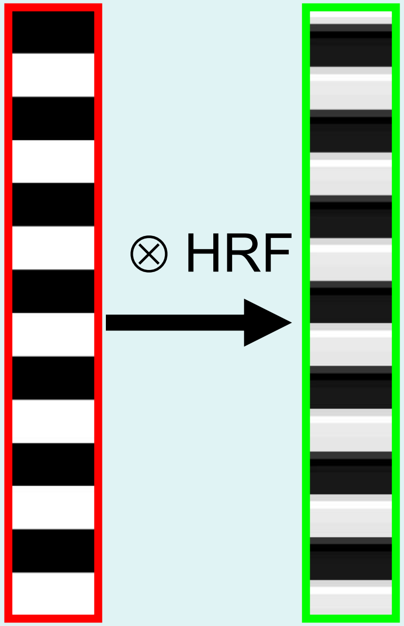
Additivity

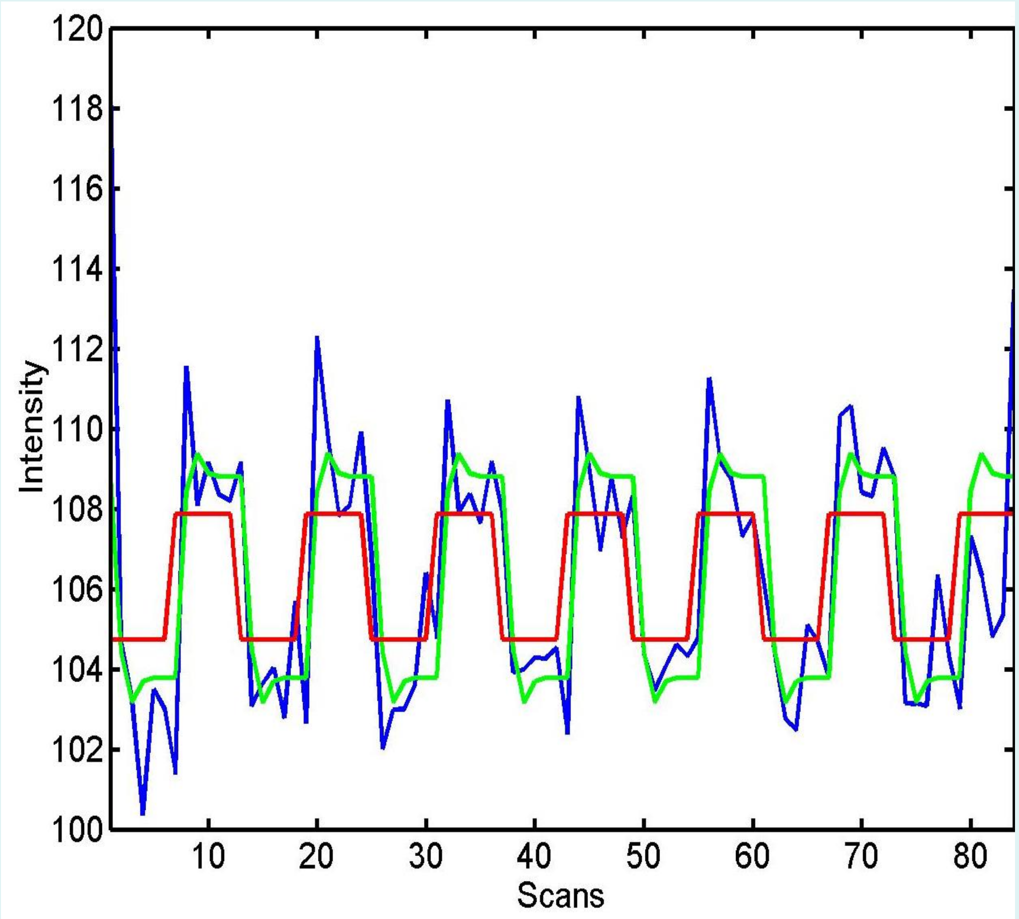


Boynton et al, NeuroImage, 2012.

Solution for the BOLD response

Convolve stimulus function with a canonical hemodynamic response function (HRF):

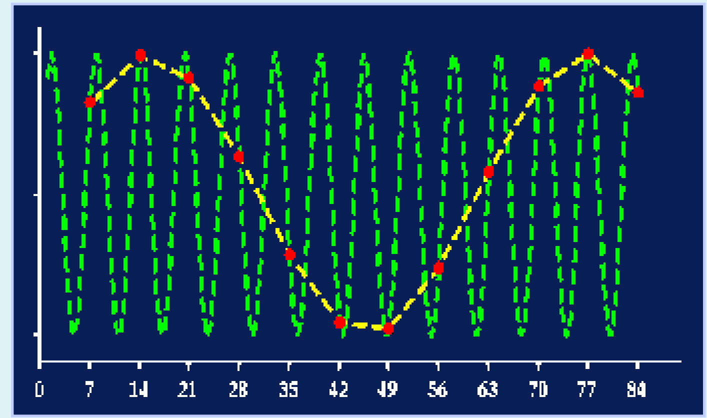


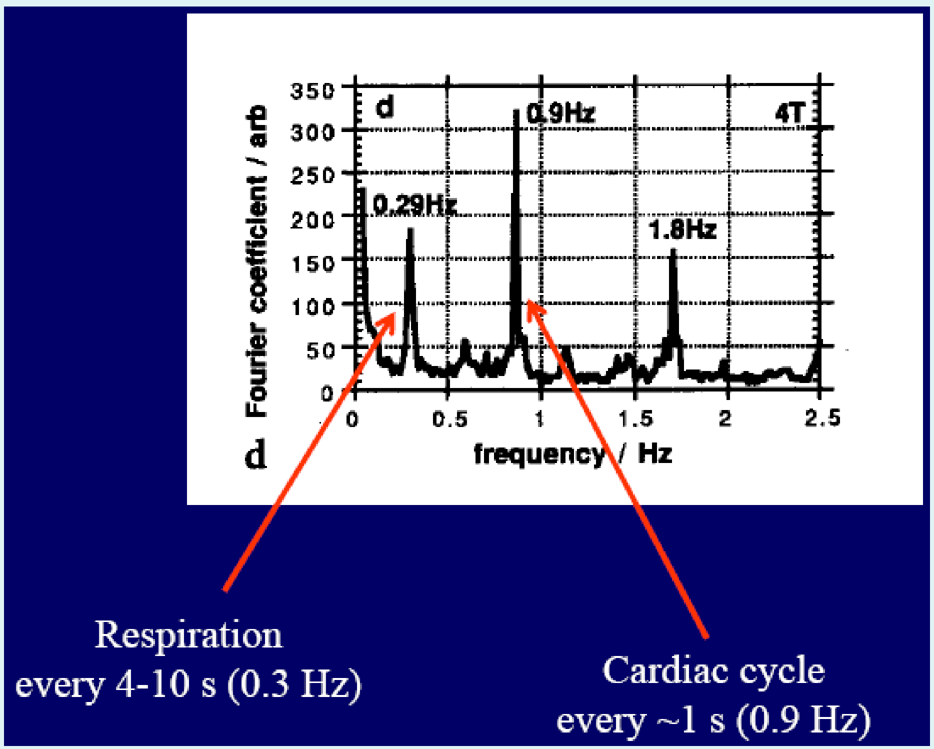


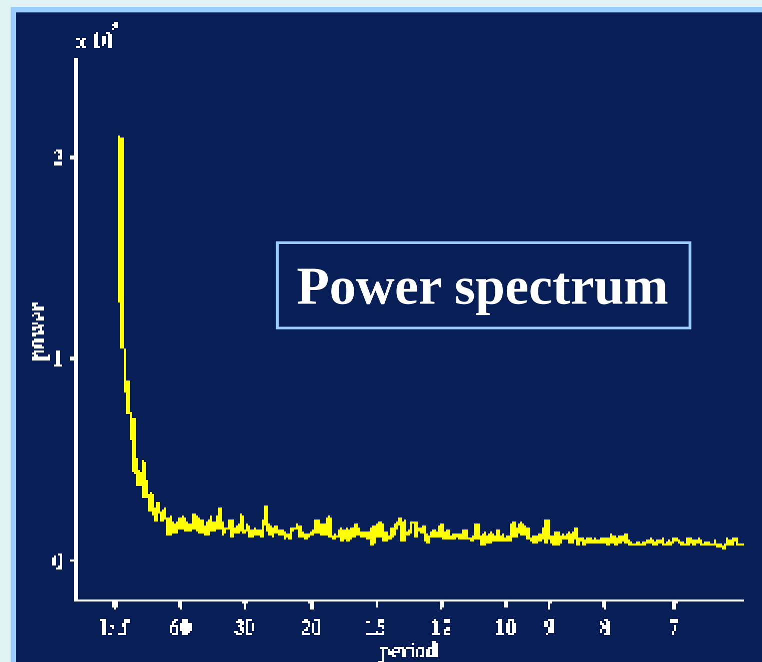
Problem 2: Low frequency noise

- Physiological noise + scanner drift
- Aliased high frequency effects

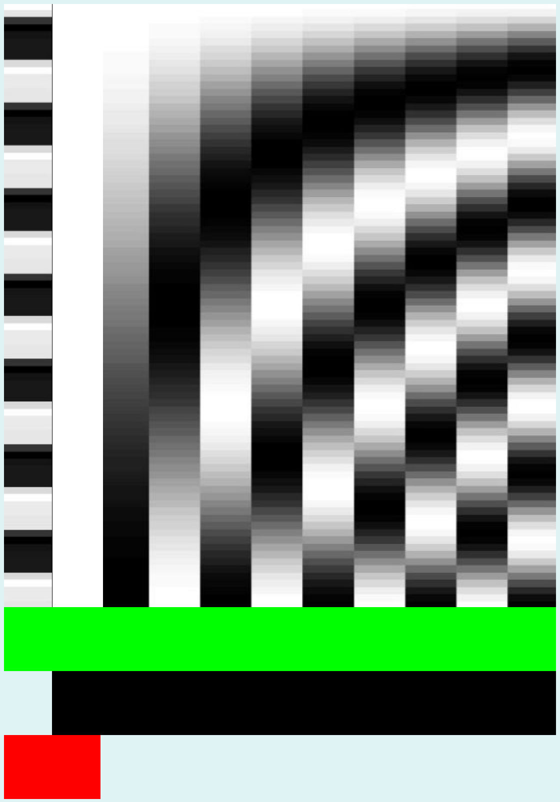
⇒ Power in the low frequencies



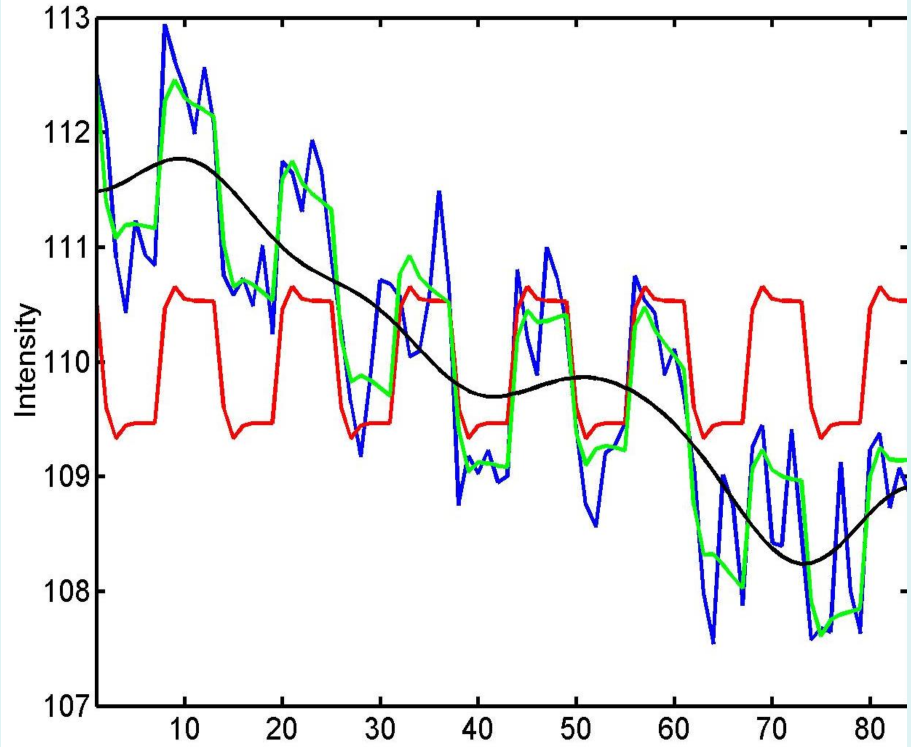




Solution with high pass filtering



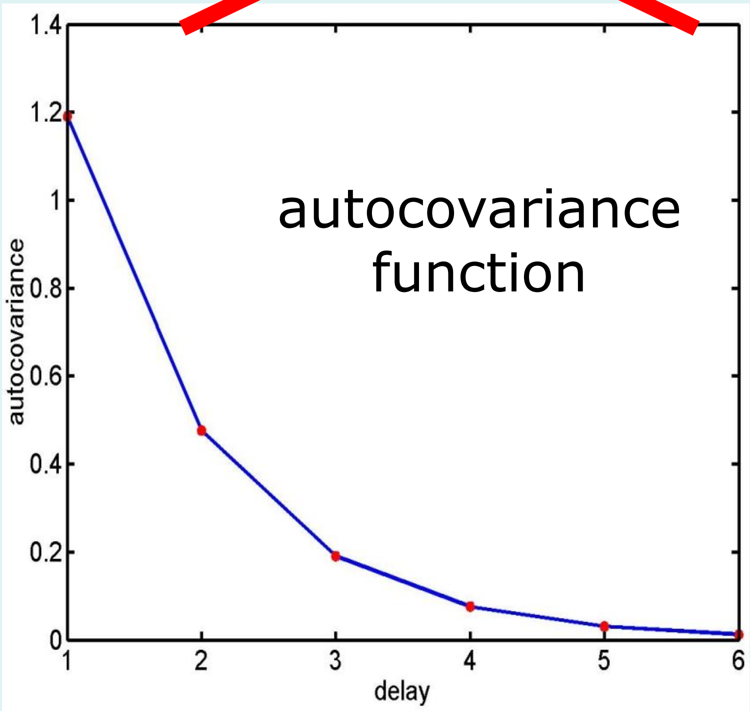
discrete cosine transform (DCT) set

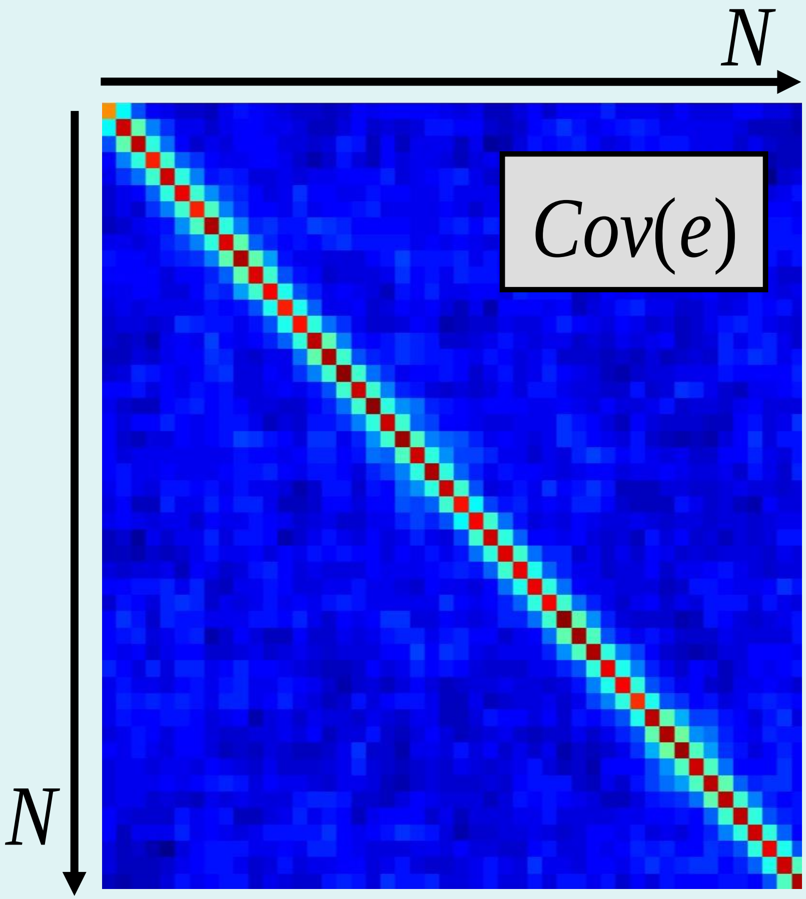


blue =	data
black =	mean + low-frequency drift
green = account	predicted response, taking into low-frequency drift
red = into	predicted response, NOT taking account low-frequency drift

Problem 3: Serial correlations

i.i.d: $e \sim \mathcal{N}(0, \sigma^2 I)$





$e \sim \mathcal{N}(0, \sigma^2 V)$

Solution for serial correlations

$$y = X\beta + e \qquad e \sim \mathcal{N}(0, \sigma^2 V)$$

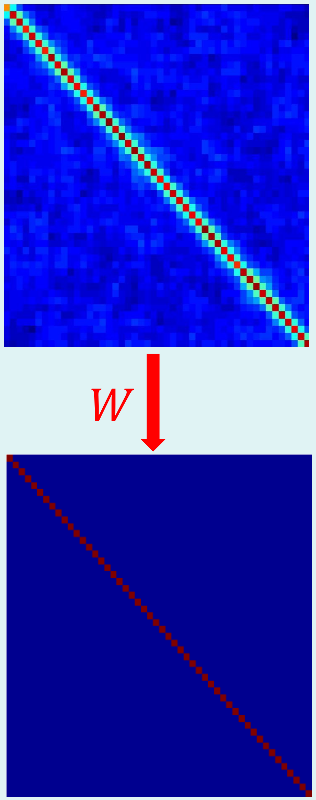
Let $W^T W = V^{-1}$

$$Wy = WX\beta + We \qquad We \sim \mathcal{N}(0, \sigma^2 \underbrace{W^T V W}_{I})$$

$\boldsymbol{y_s}$ $\boldsymbol{X_s}$ $\boldsymbol{e_s}$

Solution : Whitening the data
BUT this requires an estimation of V

V



$W^T V W$

Equivalent to the Weighted Least Square estimator

Multiple covariance components

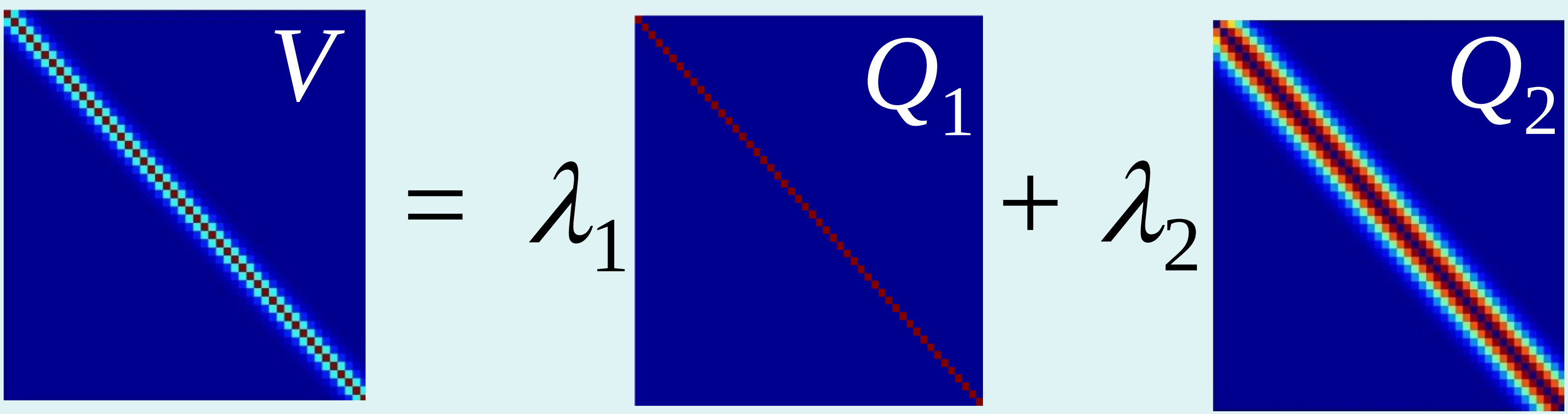
enhanced noise model at voxel *i*

$$e_i \sim N(0, C_i)$$

$$C_i = \sigma_i^2 V$$

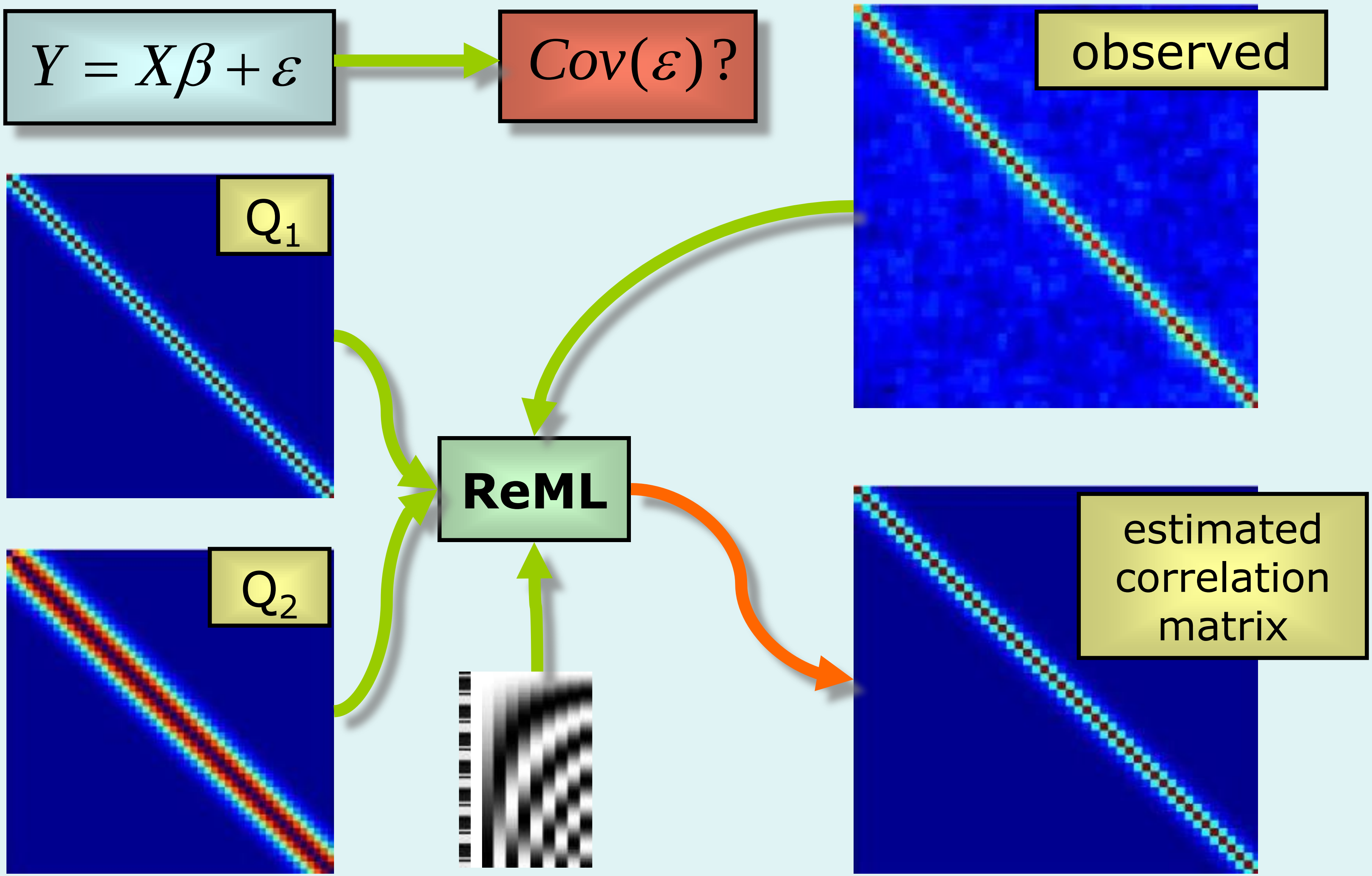
$$V = \sum \lambda_j Q_j$$

error covariance components Q and hyperparameters λ



Estimation of hyperparameters λ with ReML (Restricted Maximum Likelihood).

Restricted Maximul Likelihood



Estimation in SPM

$$y_j = X\theta_j + \varepsilon_j$$

$$\hat{C}_\varepsilon = C\hat{o}v(\varepsilon) = \text{ReML}\Big(\sum_{voxel\ j} y_j y_j^T, X, Q\Big)$$

ReML (pooled estimate)

$$\hat{\theta}_{j,OLS} = X^+ y_j$$

$$\hat{\theta}_{j,ML} = (X^T V^{-1} X)^{-1} X^T V^{-1} y_j$$

Ordinary least-squares

Maximum Likelihood

- 2 passes (first pass for selection of voxels)
- more accurate estimate of V

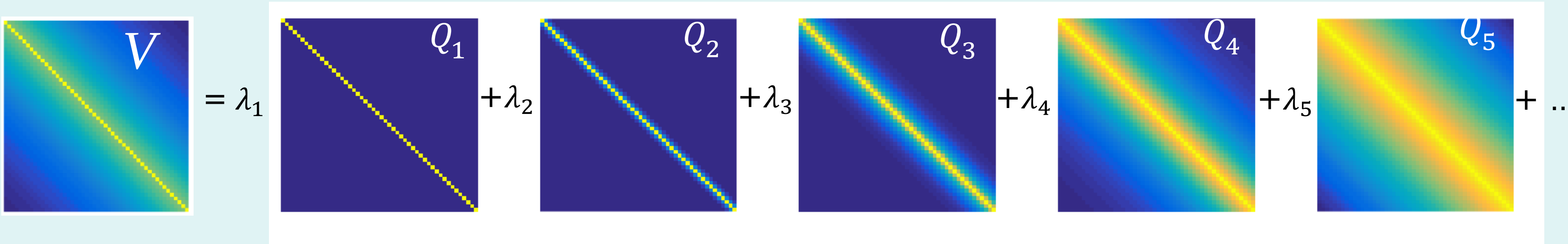
Assume, at voxel j: $C_{\varepsilon,j} = \sigma_j V$

$$t = \frac{c^T\theta}{\text{SE}(c^T\theta)}$$

$$\text{SE}(c^T\theta) = \sqrt{\hat{\sigma}^2 c^T (V^{-1/2}X)^- (V^{-1/2}X)^{-T} c}$$

Limitations

The AR(1)+white noise model may not be enough for short TR (<1.5 s)



The flexibility of the ReML enables the use of any number of components of any shape

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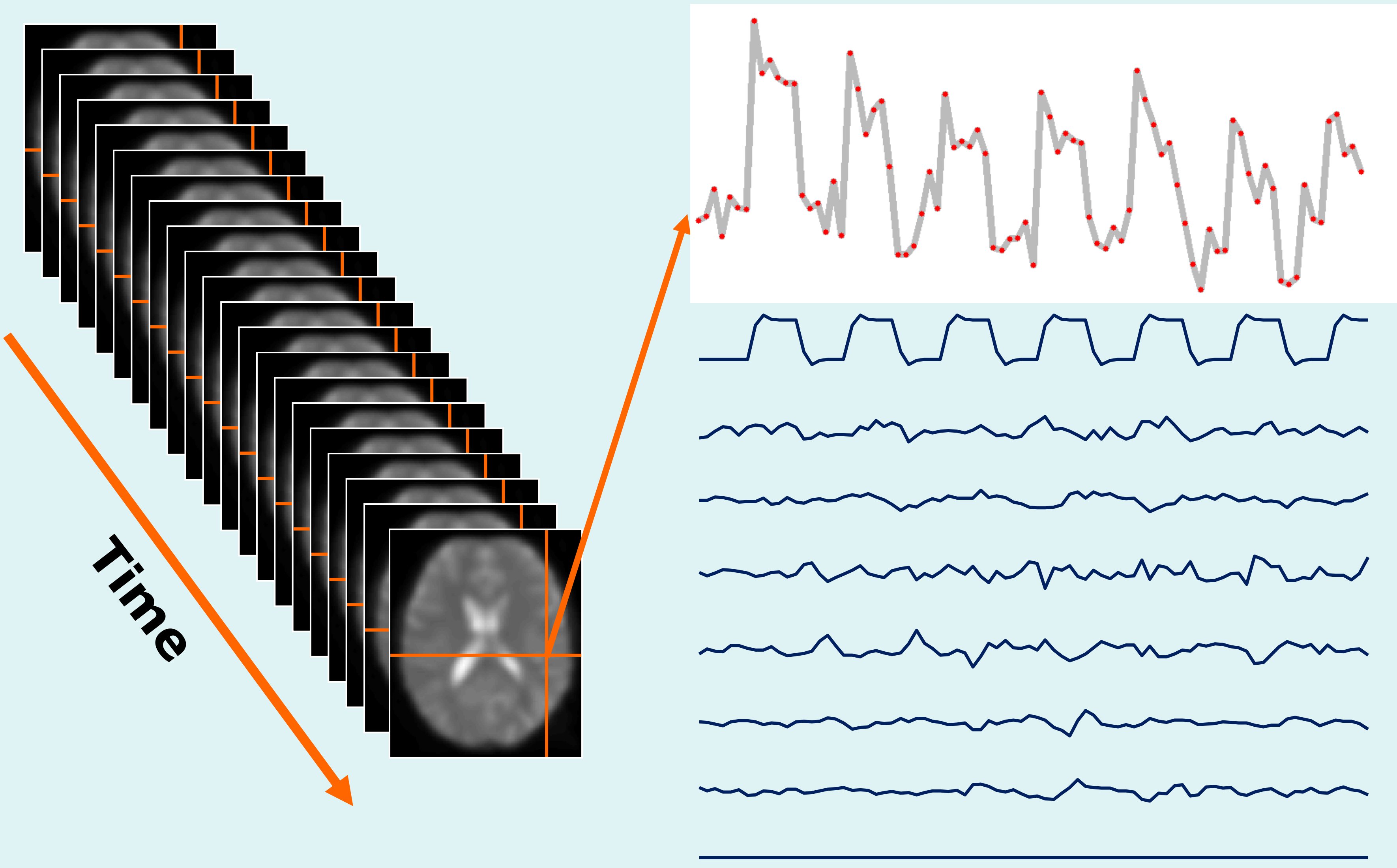
A mass univariate approach

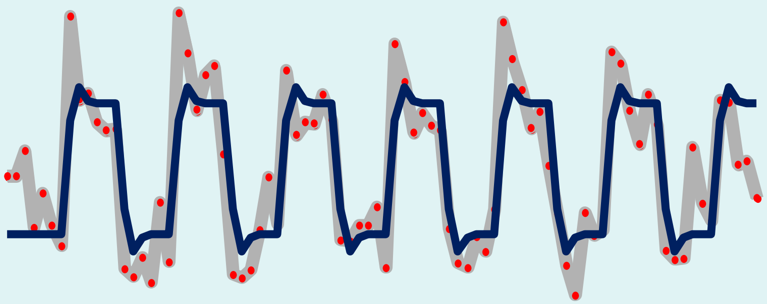


Summary

Mass univariate approach:

- Fit GLMs with
  - design matrix, $\mathbf{X}$,
  - to data at different points in space
  - to estimate local effect sizes, $\boldsymbol{\beta}$
- GLM, a very general approach that accommodates
  - Hemodynamic Response Function
  - Nuisance effects, e.g. high pass filtering
  - Error term covariance, e.g. temporal autocorrelation

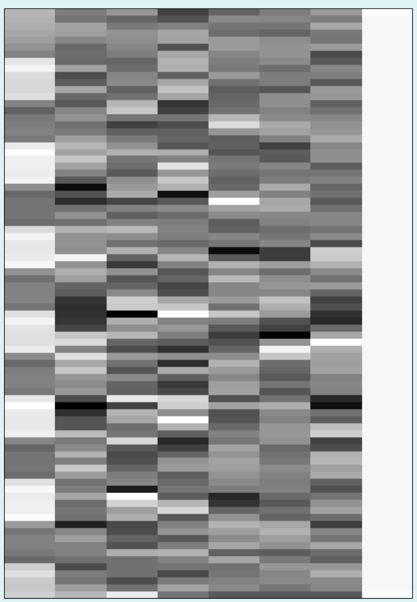
Summary



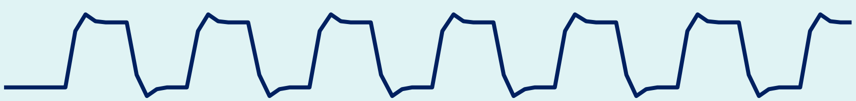
noise assumptions: $\varepsilon \sim N(0, \sigma^2 V)$

Pre-whitening: $X_s = WX \quad y_s = Wy \quad \varepsilon_s = W\varepsilon$

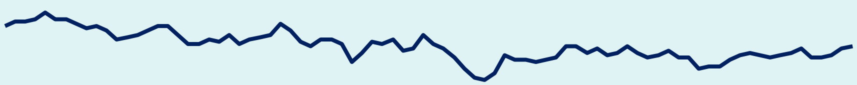
$$\hat{\beta} = (X_s^T X_s)^{-1} X_s^T y_s$$

$y =$  β $+\varepsilon$

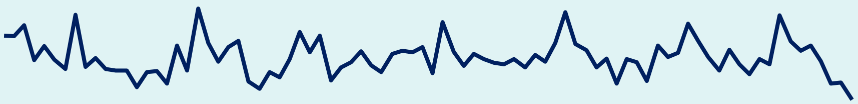
$\hat{\beta}_1 = 3.9831$



$\hat{\beta}_{2-7} = \{0.6871, 1.9598, 1.3902, 166.1007, 76.4770, -64.8189\}$



$\hat{\beta}_8 = 131.0040$

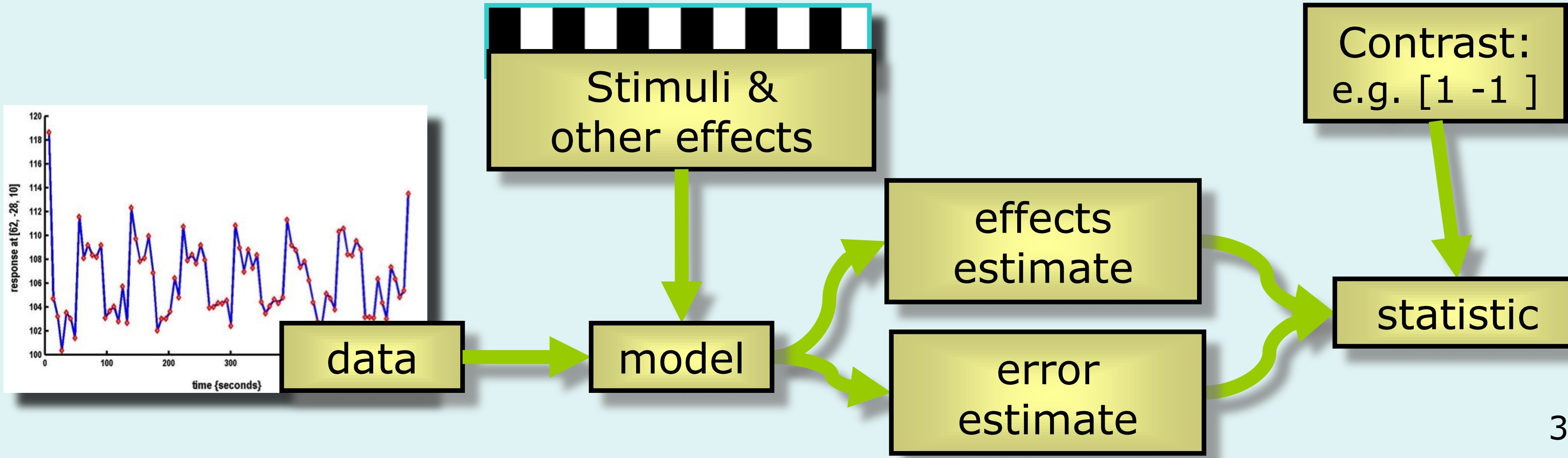
$\widehat{\varepsilon_s} =$ 

$$\hat{\beta} \sim N(\beta, \sigma^2 (X_s^T X_s)^{-1})$$

$$\hat{\sigma}^2 = \frac{\widehat{\varepsilon_s}^T \widehat{\varepsilon_s}}{N-p}$$

Why modelling?

Why?	Make inferences about effects of interest
How?	1. Decompose data into effects and error 2. Form statistic using estimates of effects and error
Model?	Use any available knowledge



References

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- Analysis of fMRI time-series revisited – again, K.J. Worsley and K.J. Friston, NeuroImage, 1995.
- The general linear model and fMRI: Does love last forever?, J.-B. Poline and M. Brett, NeuroImage, 2012.
- Linear systems analysis of the fMRI signal, G.M. Boynton et al, NeuroImage, 2012.