The General Linear Model

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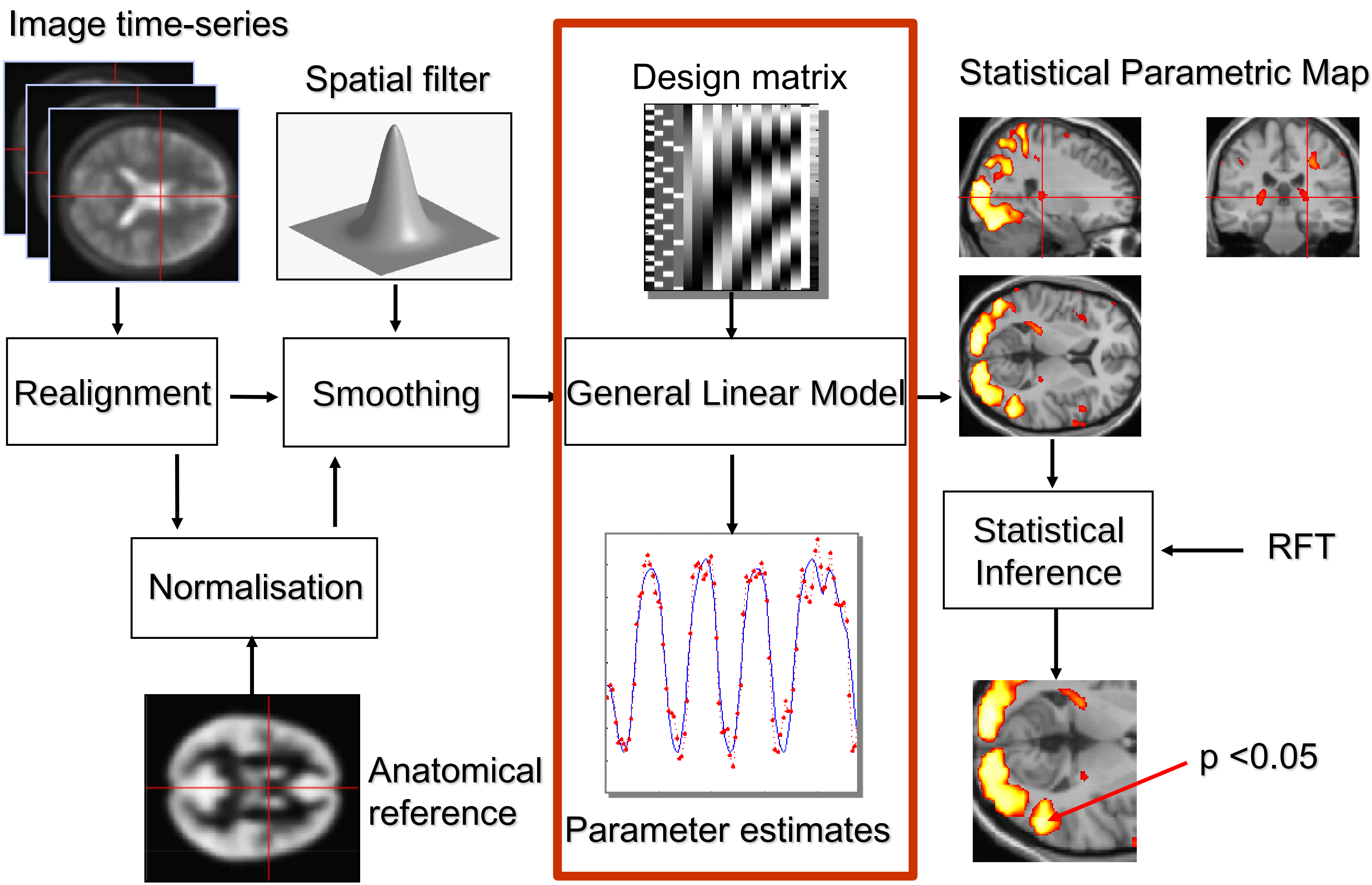


Image time-series
Spatial filter
Design matrix
Statistical Parametric Map
Realignment
Smoothing
General Linear Model
Normalisation
Statistical Inference
RFT
Anatomical reference
Parameter estimates
p <0.05

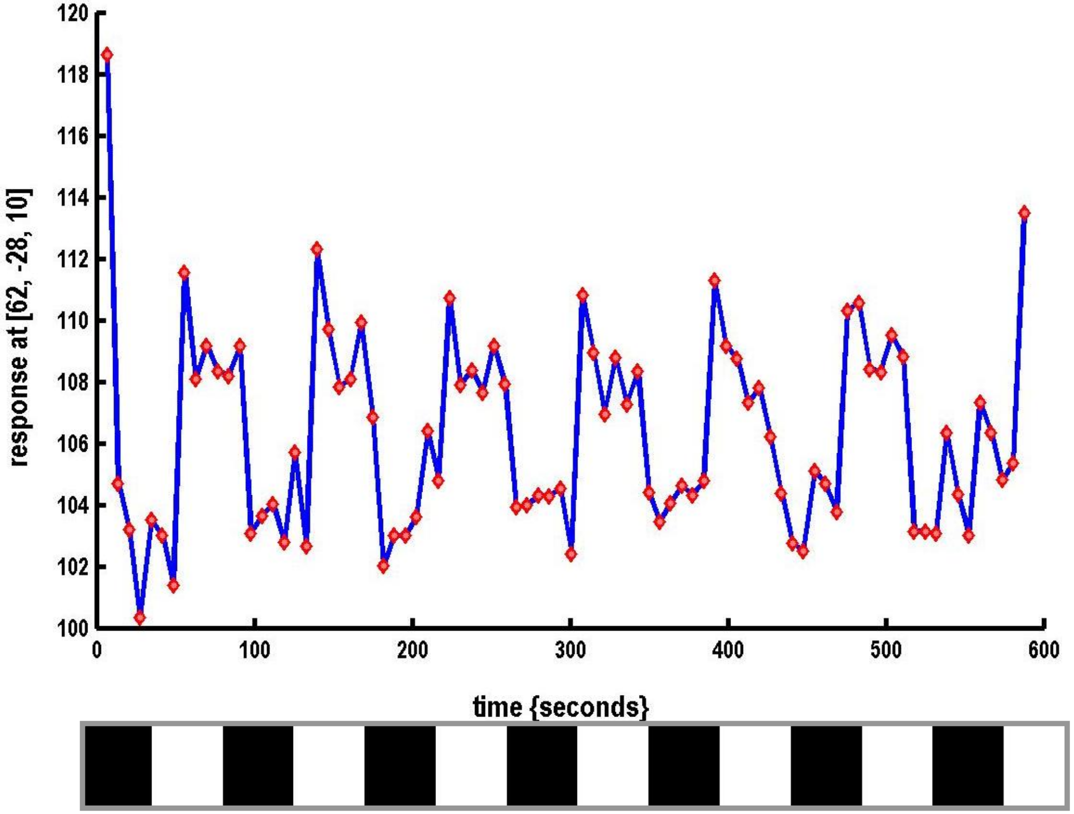
A very simple fMRI experiment

One session

Passive word listening versus rest

7 cycles of rest and listening

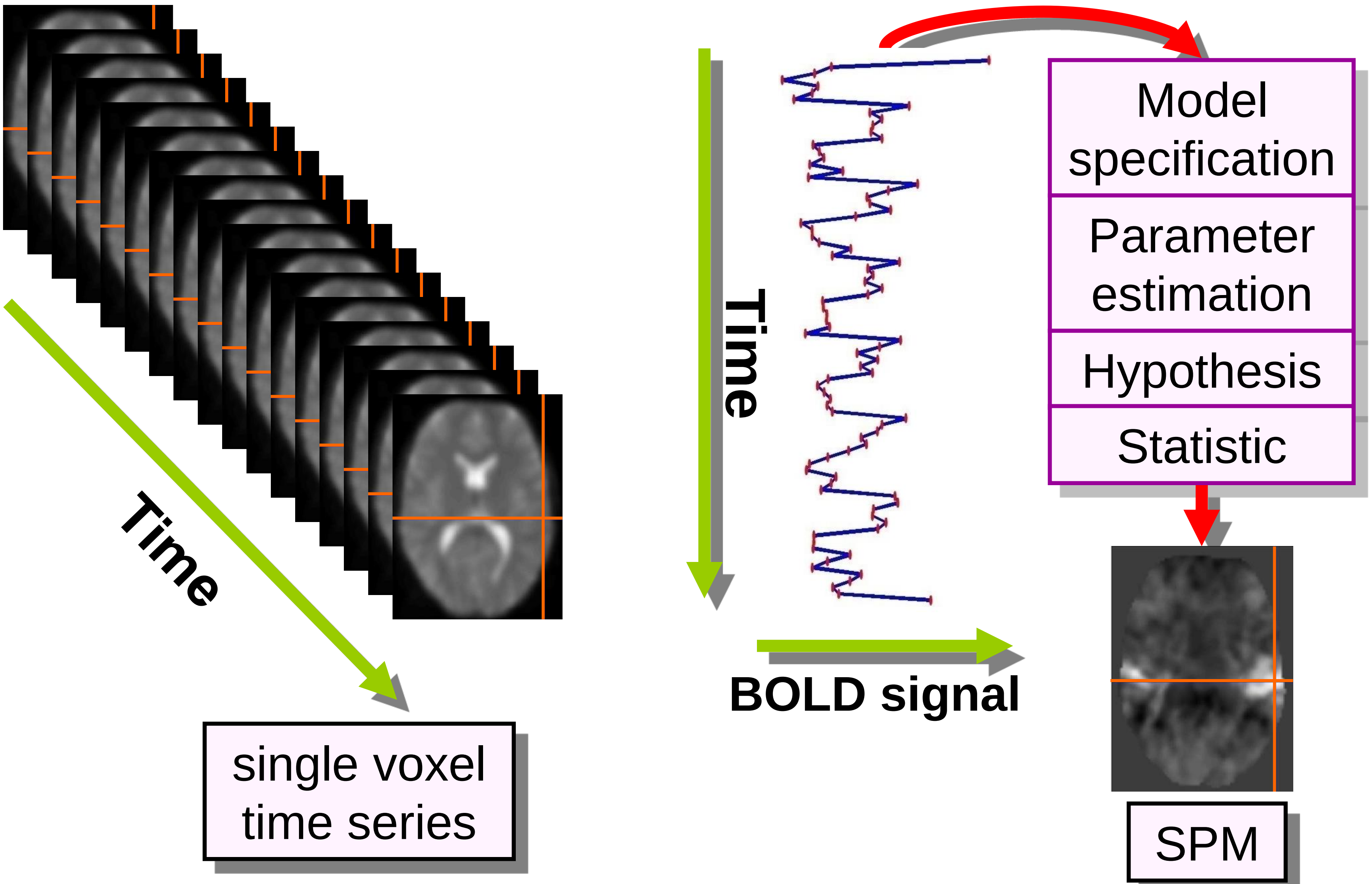
Blocks of 6 scans with 7 sec TR



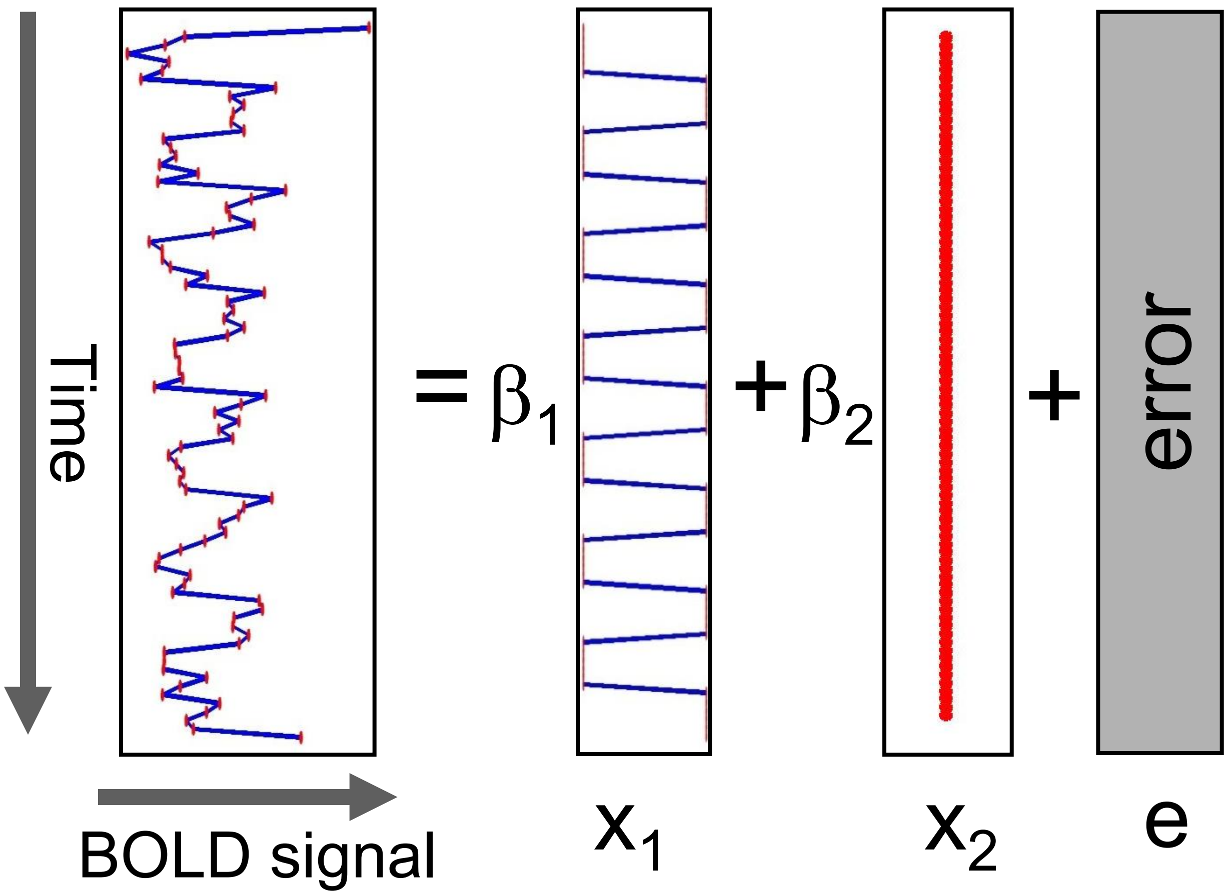
Stimulus function

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

Voxel-wise time series analysis

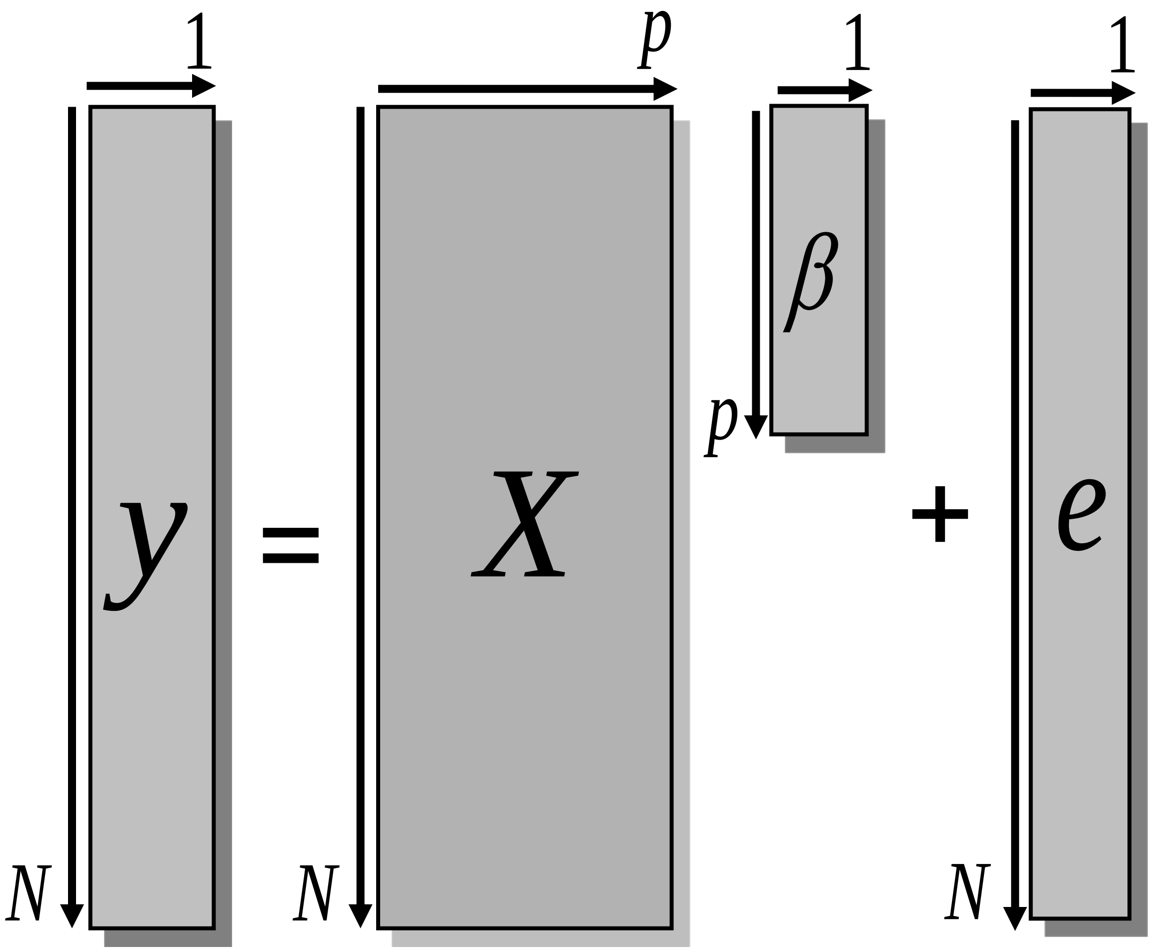


Single voxel regression model



$$y = x_1\beta_1 + x_2\beta_2 + e$$

Mass-univariate analysis: voxel-wise GLM



$$y = X\beta + e$$

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

Model is specified by
1. Design matrix X
2. Assumptions about e

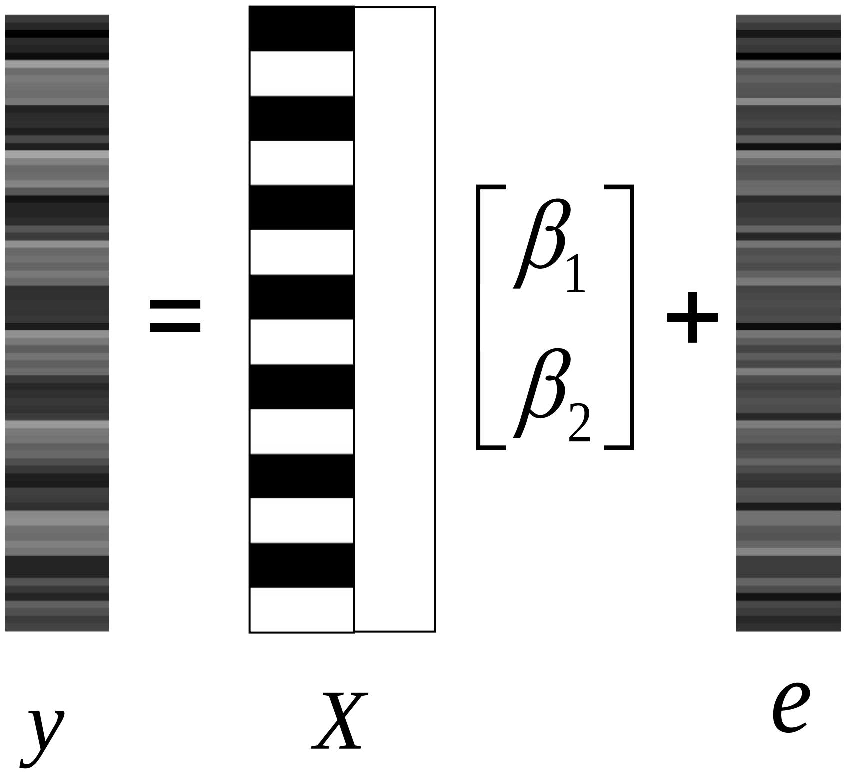
N: number of scans
p: number of regressors

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

General Linear Model (GLM):
A flexible framework for parametric analyses

- one sample *t*-test
- two sample *t*-test
- paired *t*-test
- Analysis of Variance (ANOVA)
- Analysis of Covariance (ANCoVA)
- correlation
- linear regression
- multiple regression

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):

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

Problems of this model with fMRI time series

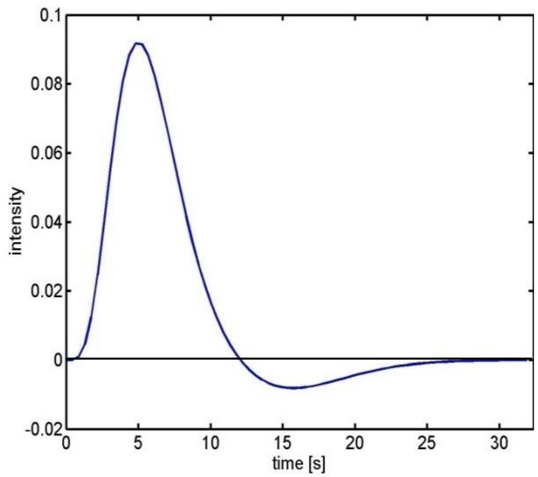
1. The **BOLD** ***response*** has a delayed and dispersed shape.

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):



Linear time-invariant (LTI) system:

$$u(t) \longrightarrow \boxed{hrf(t)} \longrightarrow x(t)$$

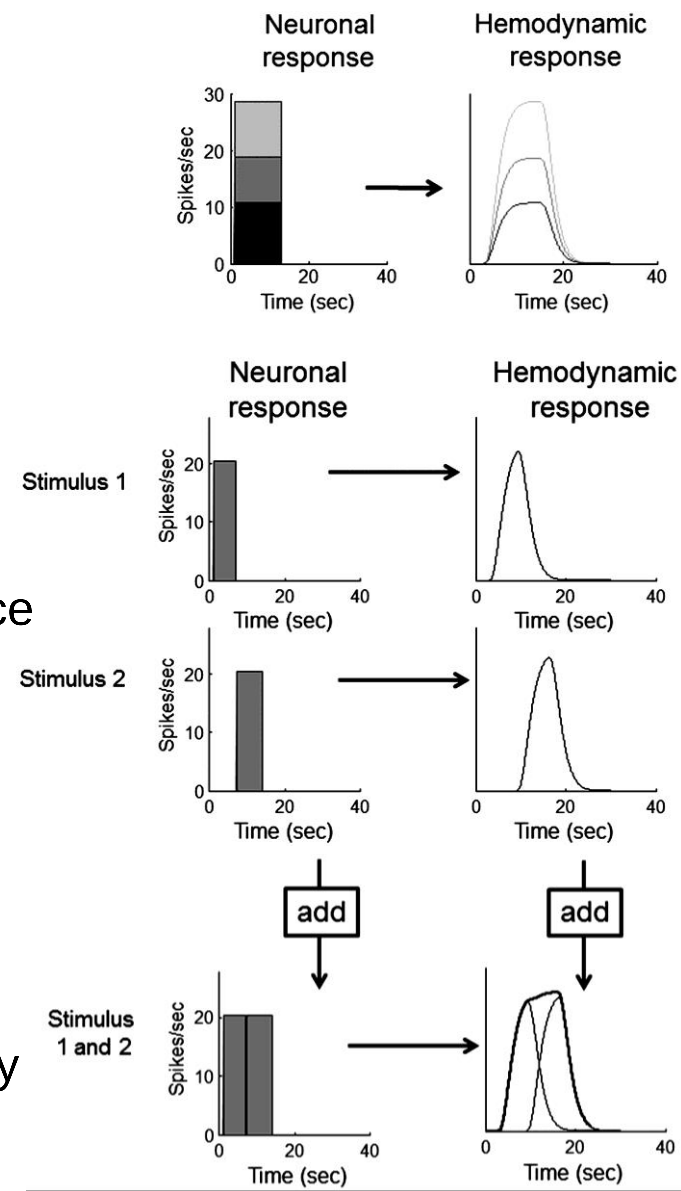
Convolution operator:

$$
\begin{aligned}
x(t) &= u(t) * hrf(t) \\
&= \int_0^t u(\tau)hrf(t-\tau)d\tau
\end{aligned}
$$

Scaling

Shift invariance

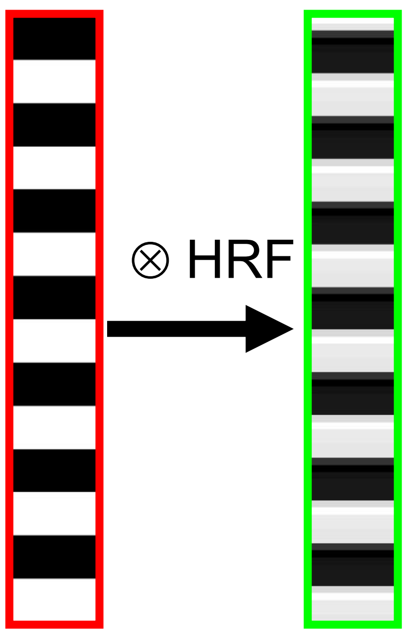
Additivity

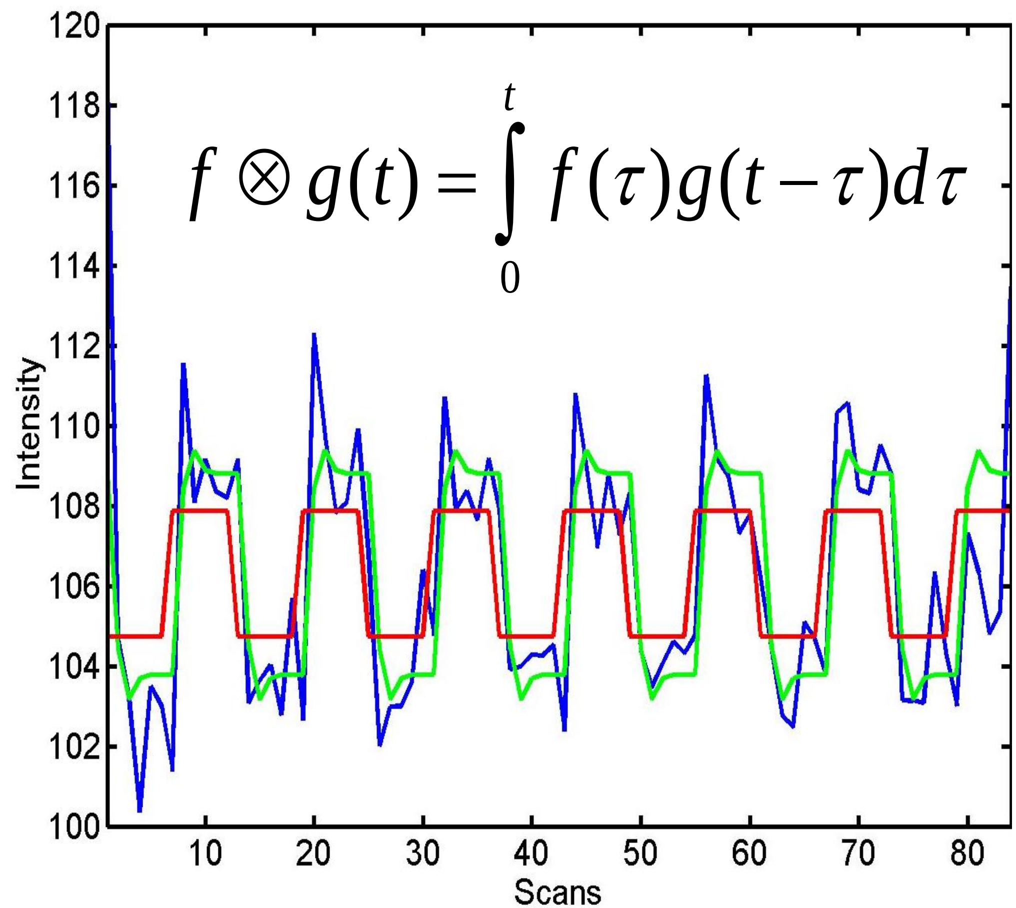


Boynton et al, NeuroImage, 2012.

Convolution model of the BOLD response

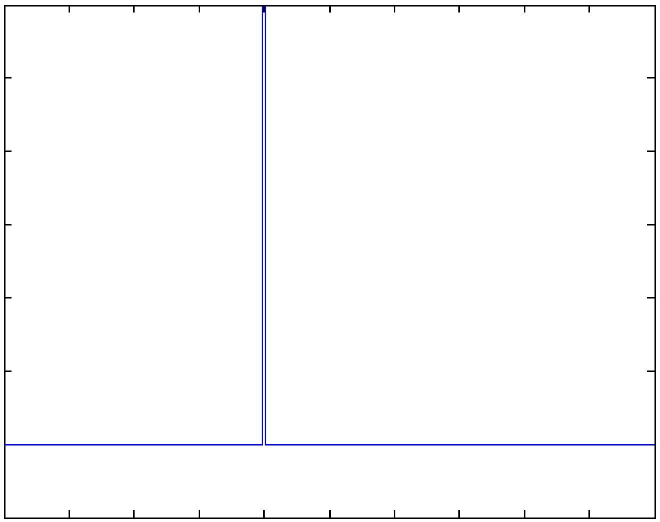
Convolve stimulus function with a canonical hemodynamic response function (HRF):

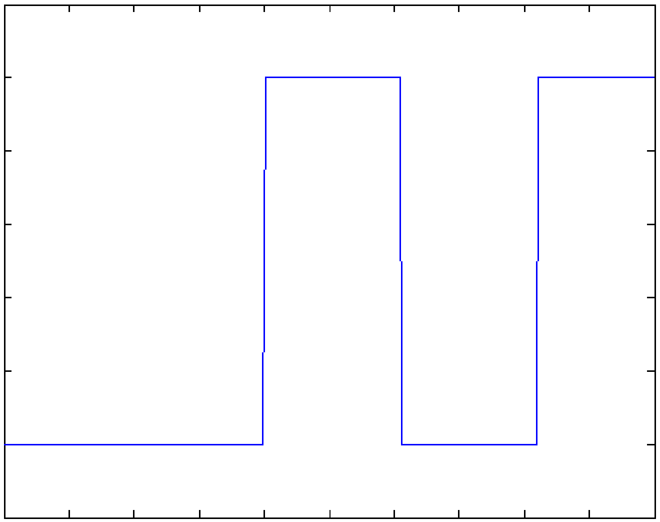


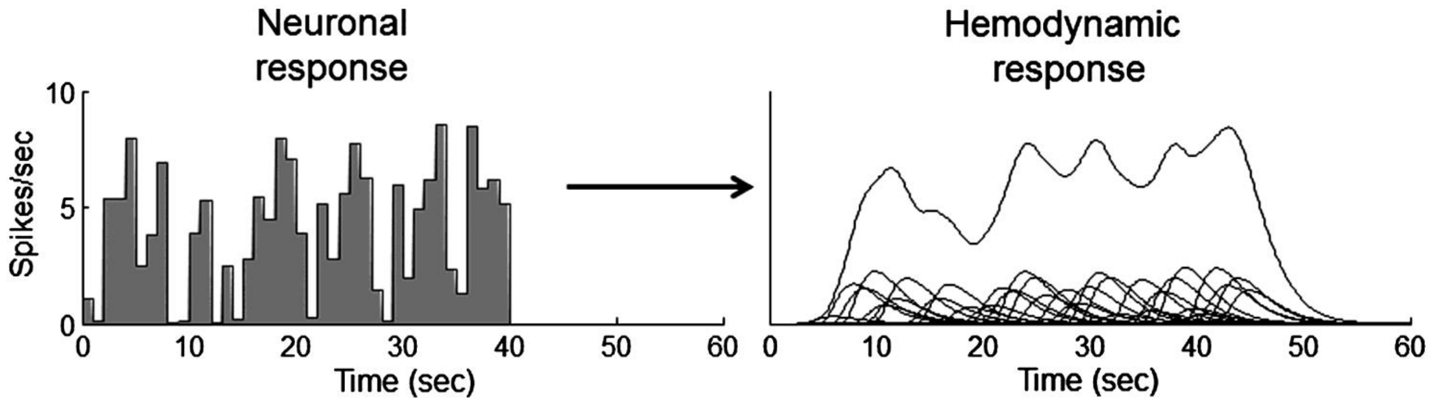


$$f \otimes g(t) = \int_0^t f(\tau) g(t-\tau) d\tau$$

Problem 1: BOLD response
Solution: Convolution model

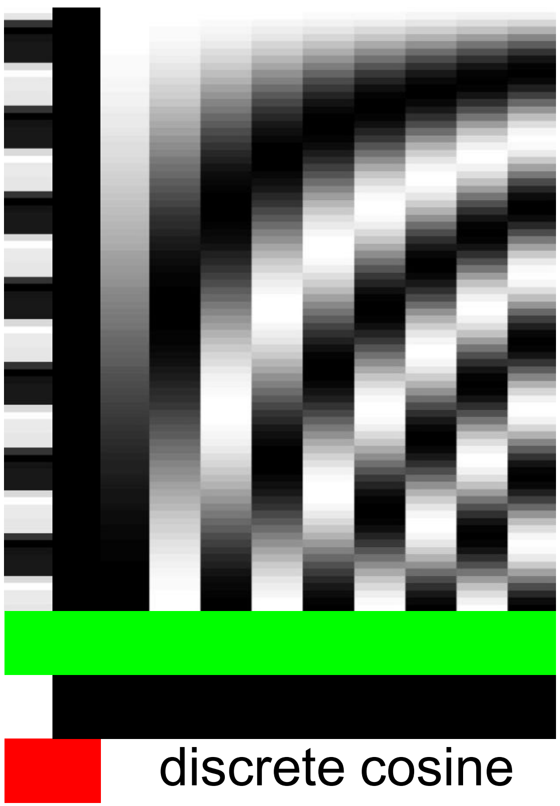




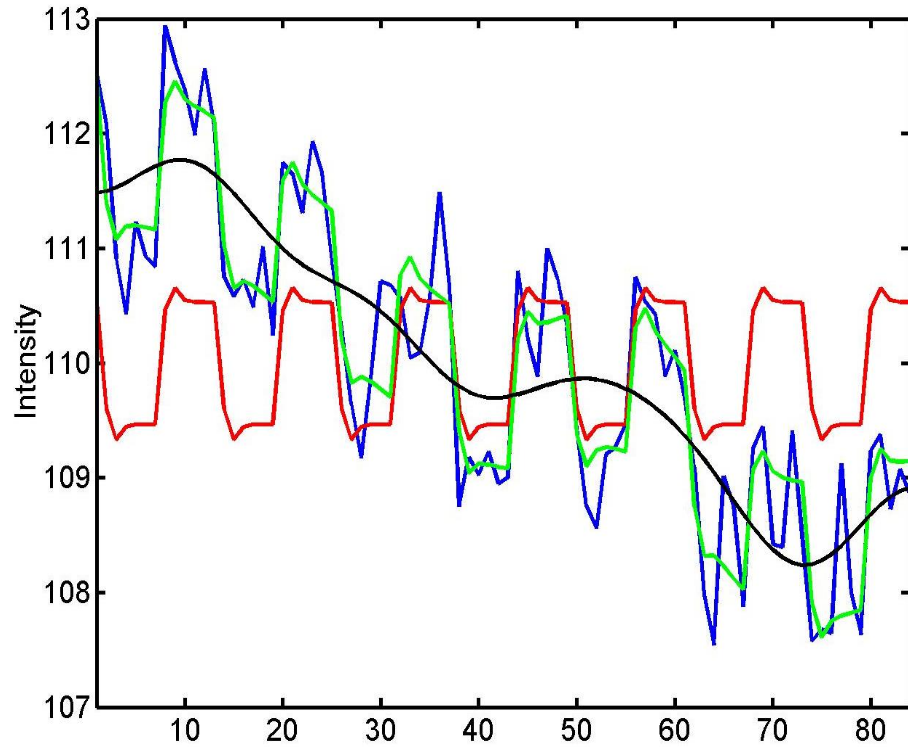


Problem 2: Low-frequency noise

Solution: High pass filtering



discrete cosine transform (DCT) set



blue = data

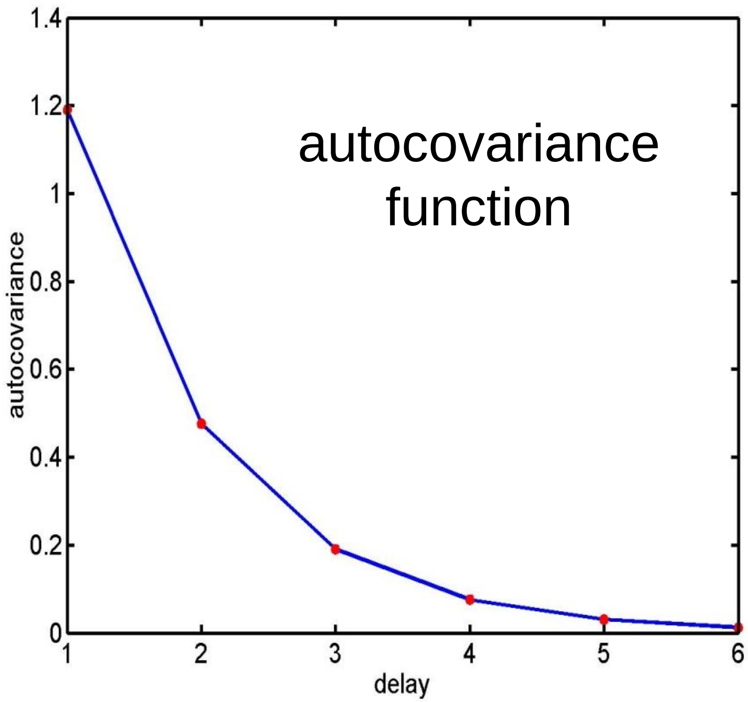
black = mean + low-frequency drift

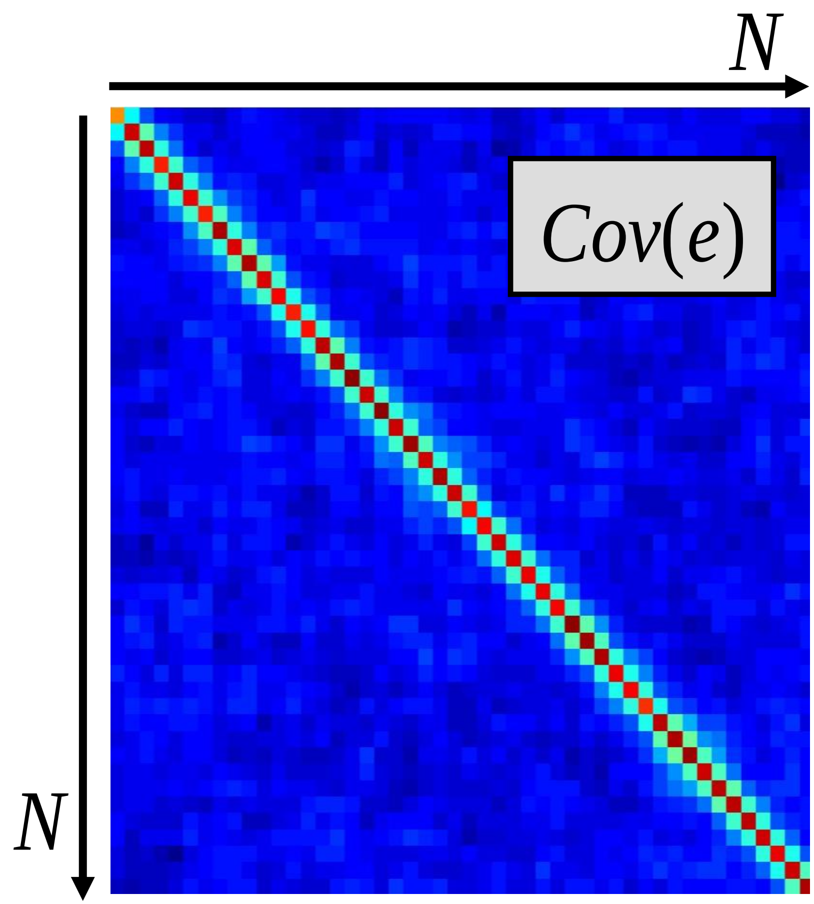
green = predicted response, taking into account low-frequency drift

red = predicted response, NOT taking into account low-frequency drift

Problem 3: Serial correlations

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





✓ $e_t = ae_{t-1} + \varepsilon_t$ with $\varepsilon_t \sim N(0,\sigma^2)$

Multiple covariance components

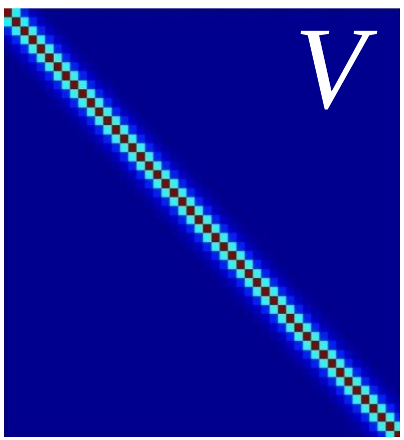
enhanced noise model at voxel *i*

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

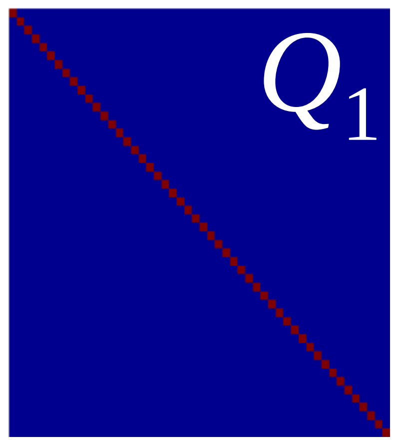
$$C_i = \sigma_i^2 V$$

$$V = \sum \lambda_j Q_j$$

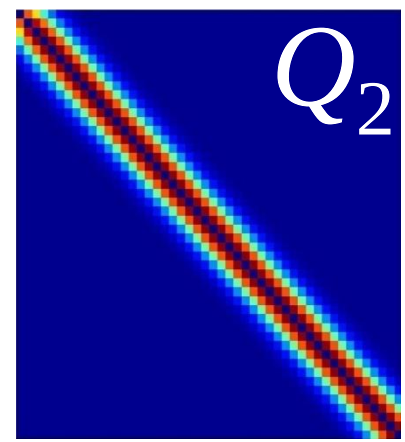
error covariance components Q
and hyperparameters λ



$= \lambda_1$



$+ \lambda_2$



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

Weighted Least Squares (WLS):

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

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

Then

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

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

where

$$X_s = WX \,, \; y_s = Wy$$

WLS equivalent to OLS on whitened data and design

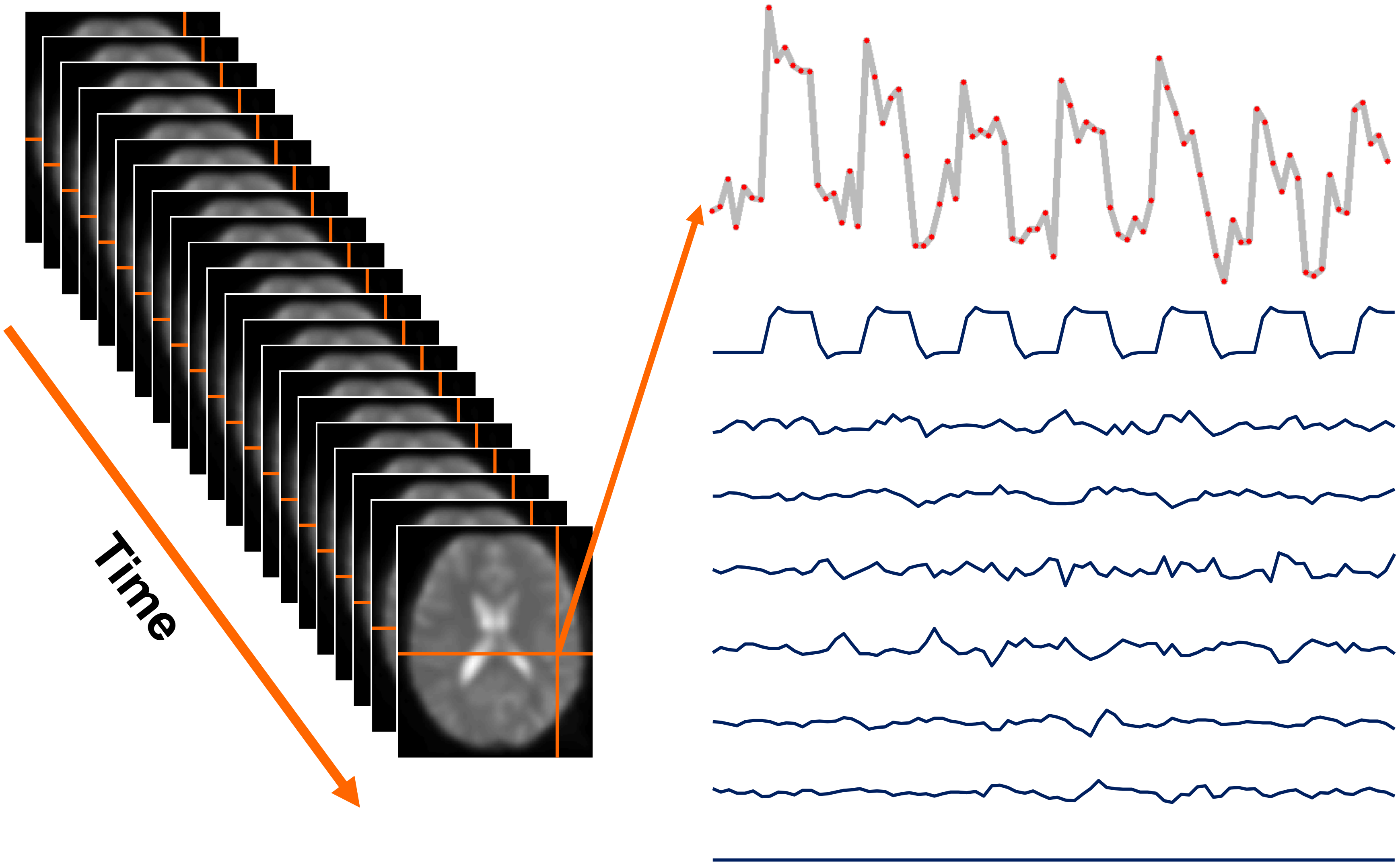
Summary

- Mass-univariate approach.
- Fit GLMs with design matrix, X, to data at different points in space to estimate local effect sizes, β
- GLM is a very general approach
- Hemodynamic Response Function
- High pass filtering
- Temporal autocorrelation

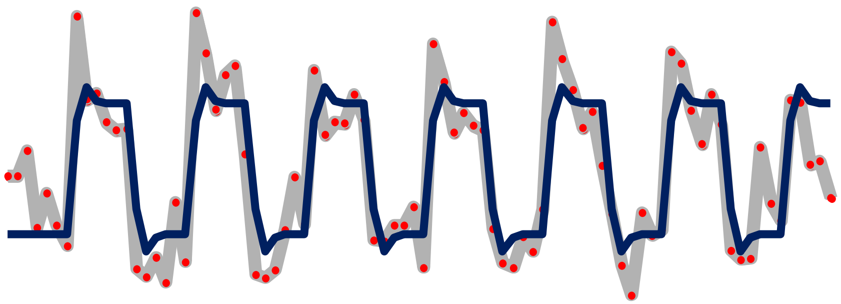
References

- **Statistical parametric maps in functional imaging: a general linear approach**, *K.J. Friston et al*, Human Brain Mapping, 1995.
- **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.

A mass-univariate approach



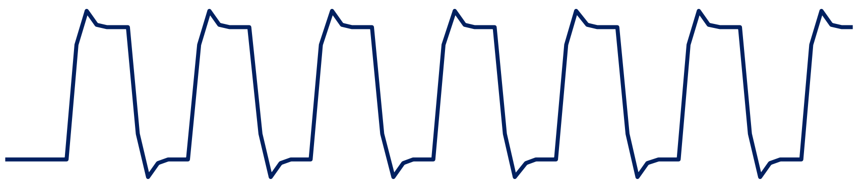
Estimation of the parameters



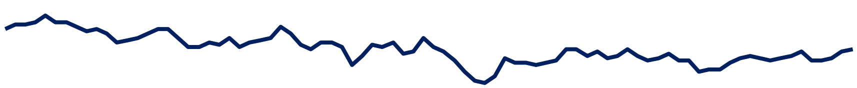
noise assumptions: $\varepsilon \sim N(0, \sigma^2 V)$

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

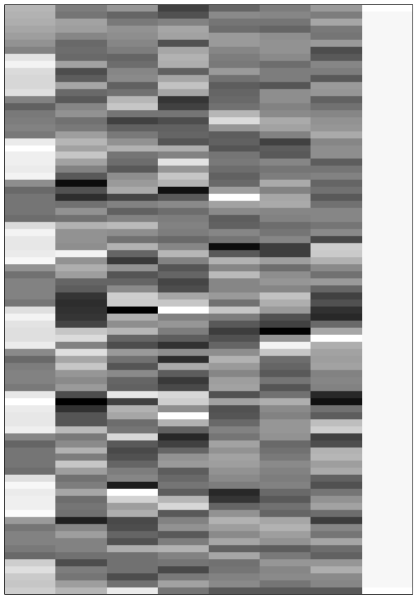
$\hat{\beta}_1 = 3.9831$



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



$\hat{\beta}_8 = 131.0040$

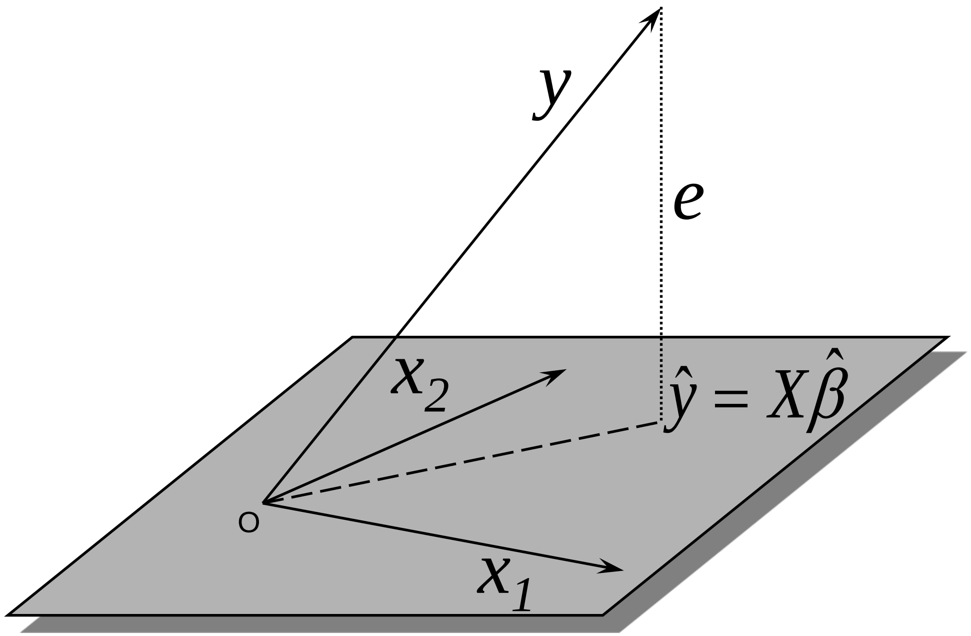
$y =$  β $+\varepsilon$

$\hat{\varepsilon} =$ 

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

$$\boxed{\hat{\sigma}^2 = \frac{\hat{\varepsilon}^T \hat{\varepsilon}}{N-p}}$$

A geometric perspective on the GLM



Design space defined by X

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

$$X^T e = 0$$

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

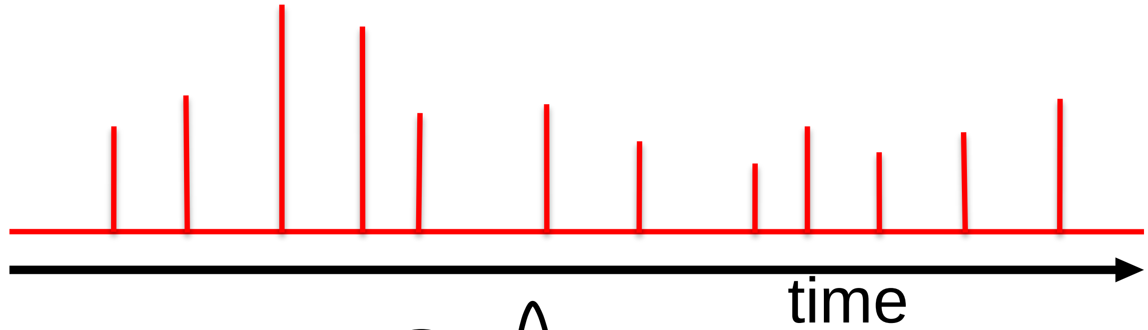
$$X^T y = X^T X\hat{\beta}$$

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

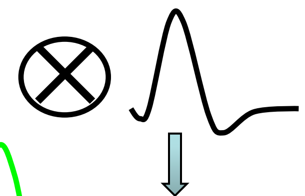
Ordinary Least Squares (OLS)

Fluctuation of a hidden variable over time:

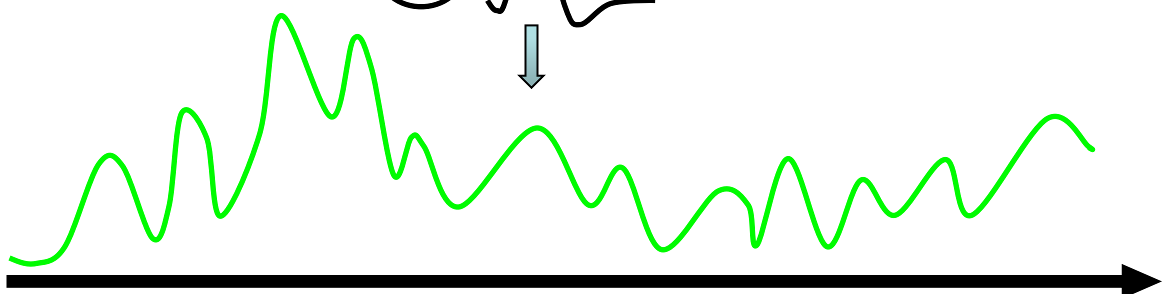
e.g. **subjective value of a food stimulus**



Convolution with the hrf function



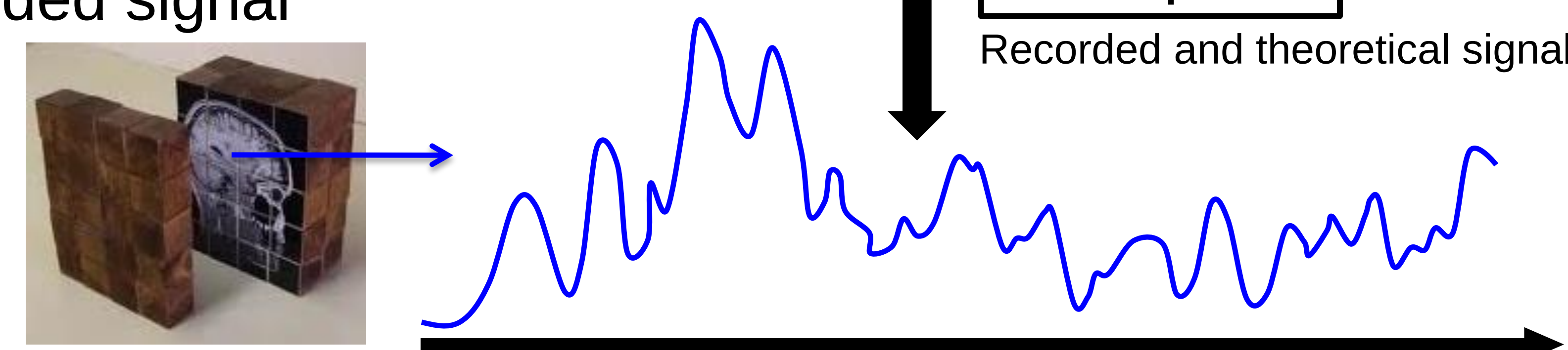
Theoretical signal



Compare

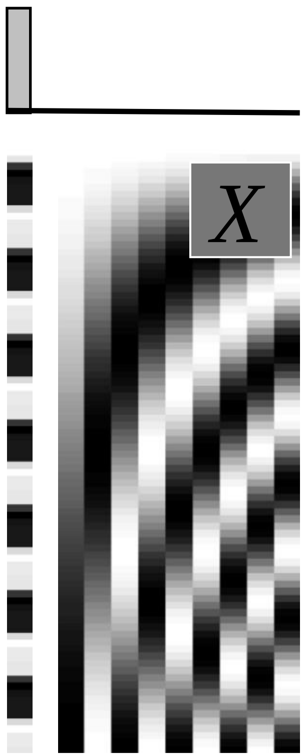
Recorded and theoretical signals

Recorded signal



Contrasts & statistical parametric maps

c = 1 0 0 0 0 0 0 0 0 0 0



Q: activation during listening ?

Null hypothesis: $\beta_1 = 0$

$$t = \frac{c^T \hat{\beta}}{Std(c^T \hat{\beta})}$$