The General Linear Model (GLM)

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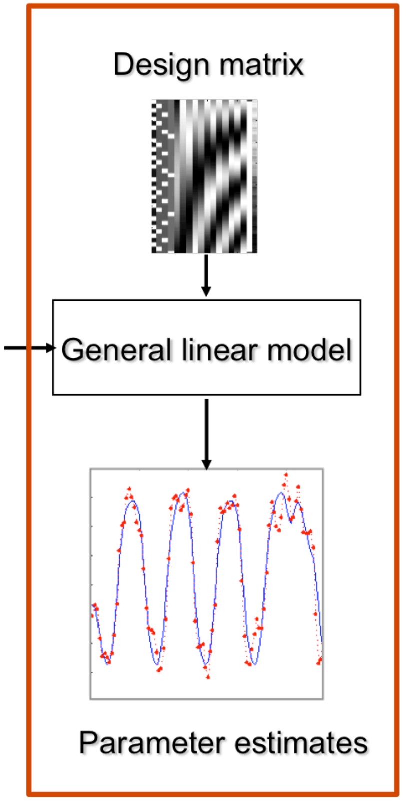


With many thanks for slides & images to:

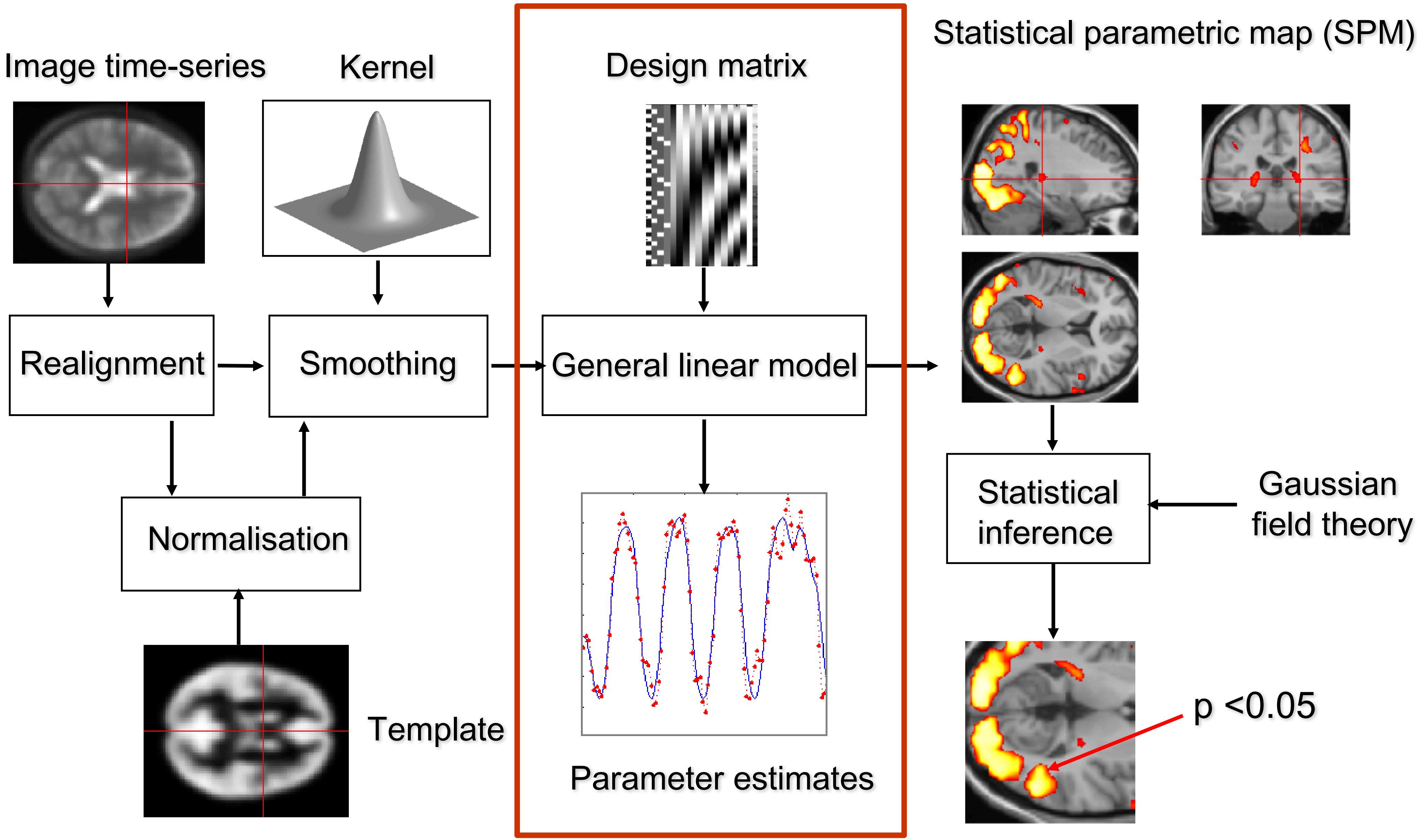
FIL Methods group, Virginia Flanagin and Klaas Enno Stephan

Translational Neuromodeling Unit

University of Zurich[UZH]

ETH
Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

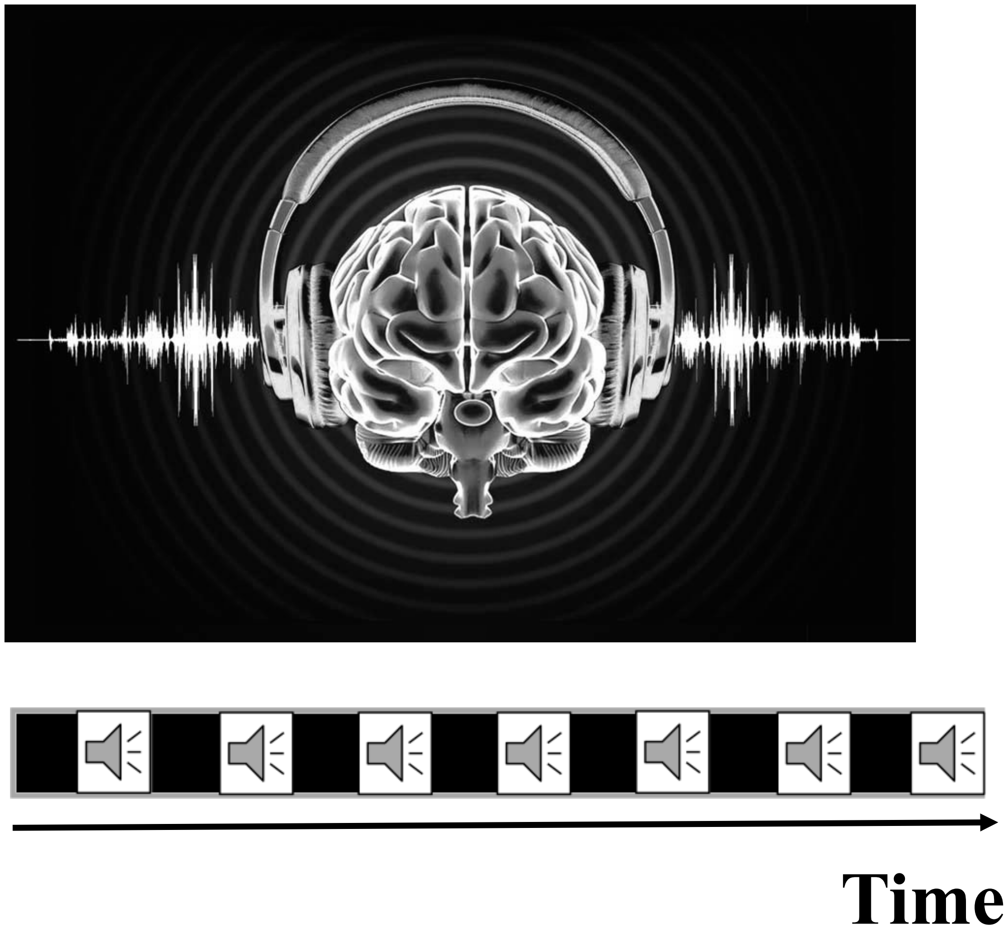
Overview of SPM

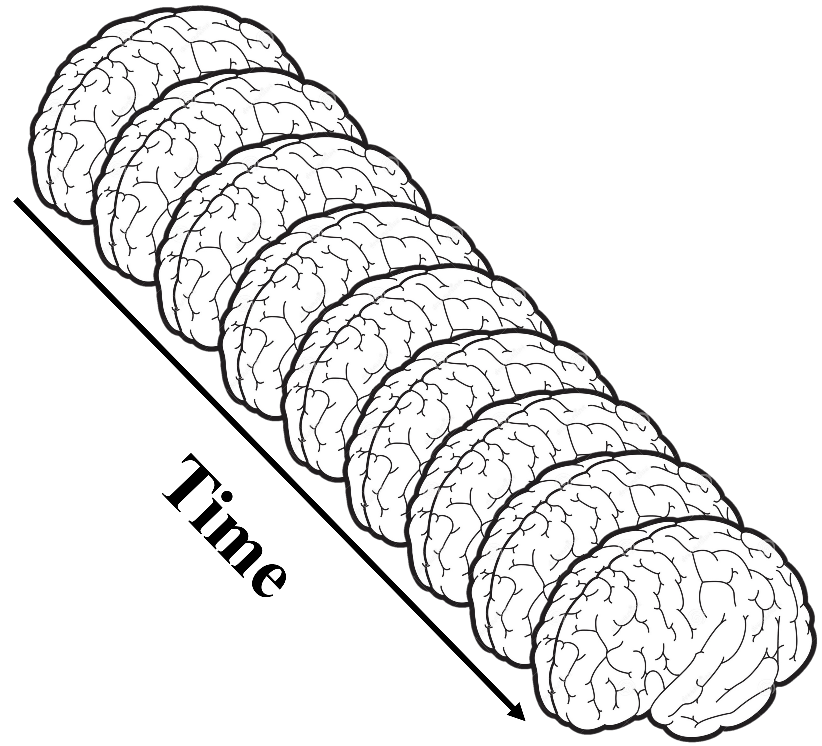


Research Question:

Where in the brain do we represent listening to sounds?

Image a very simple experiment…





SINGLE VOXEL TIME SERIES…

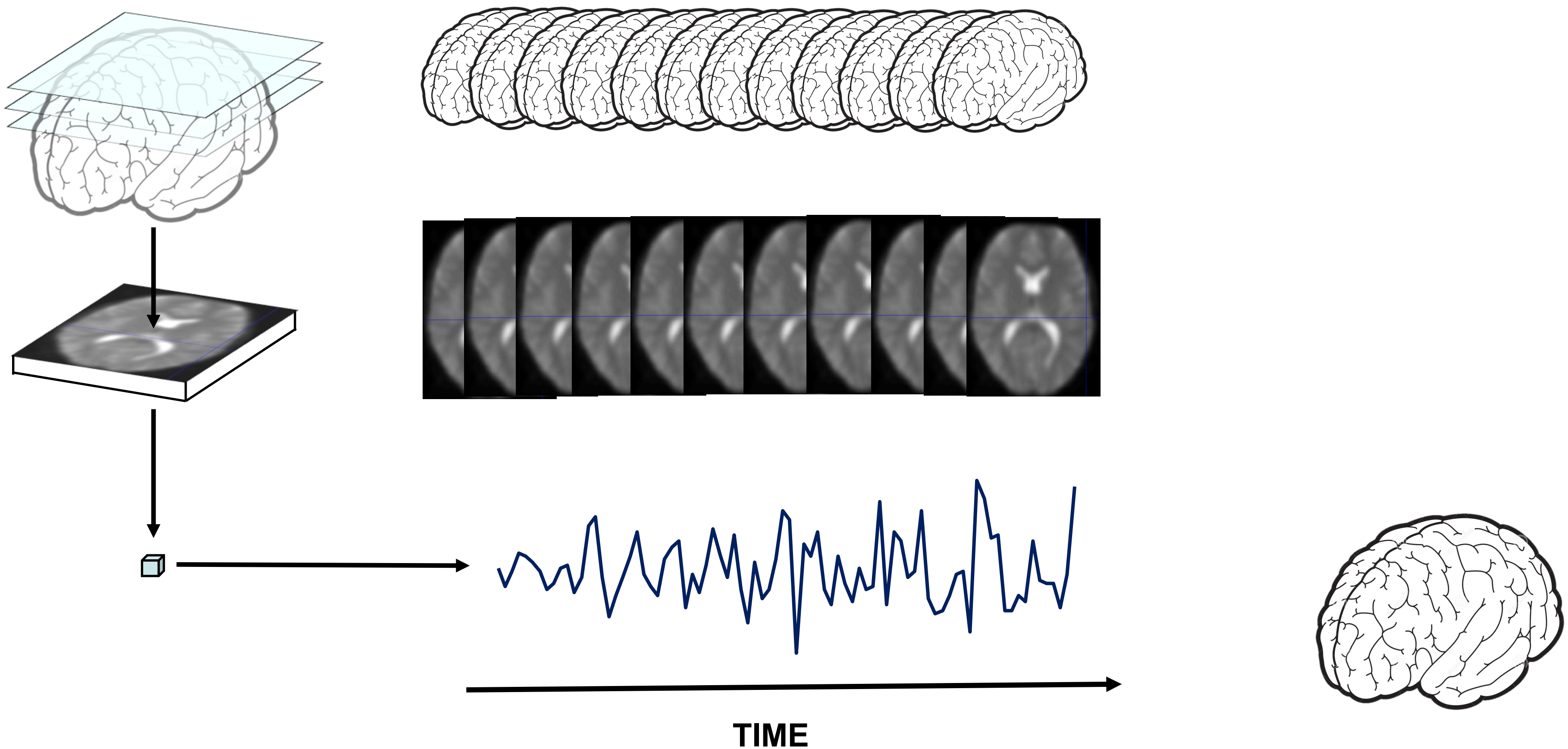


Image a very simple experiment…

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

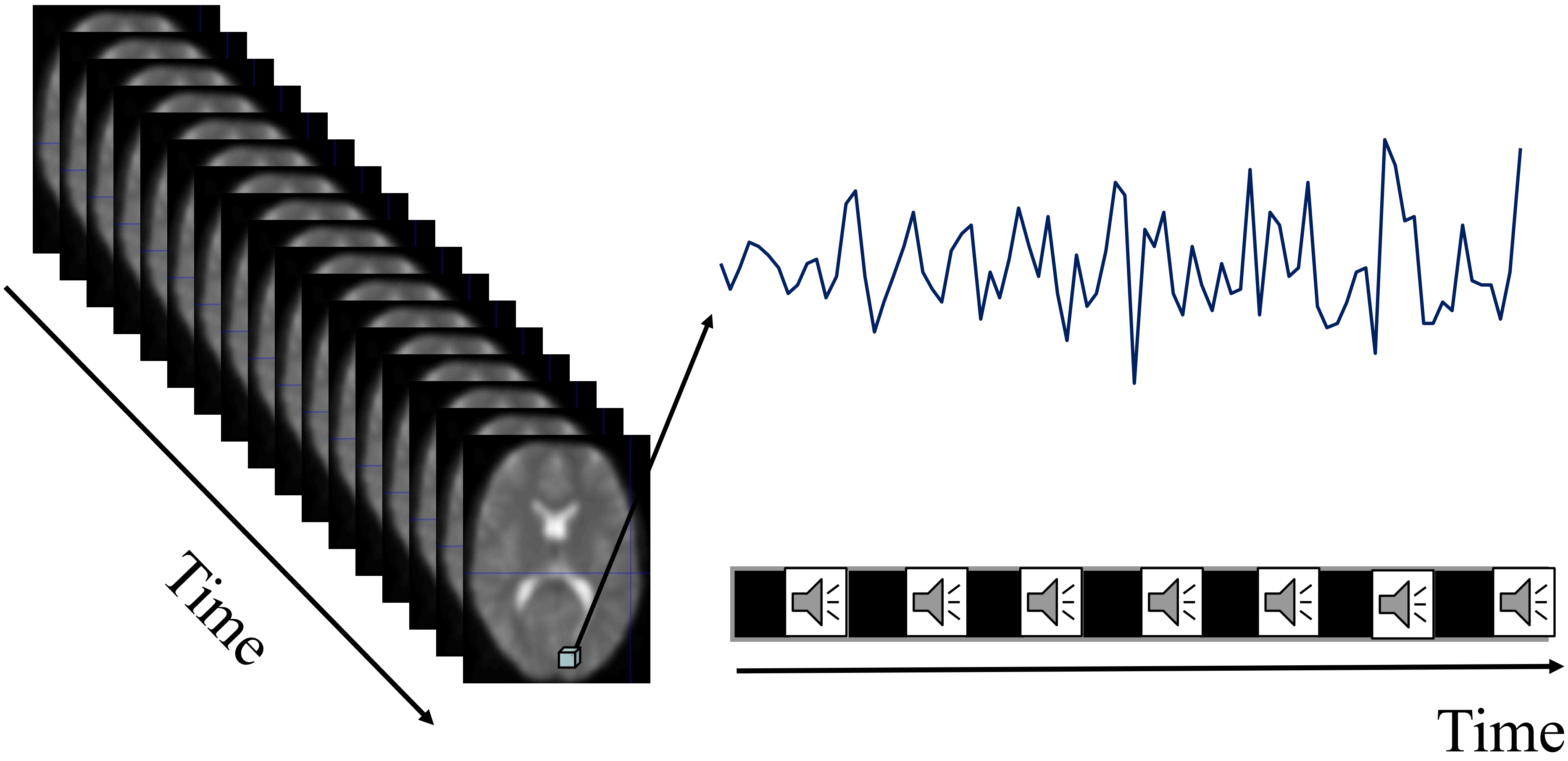
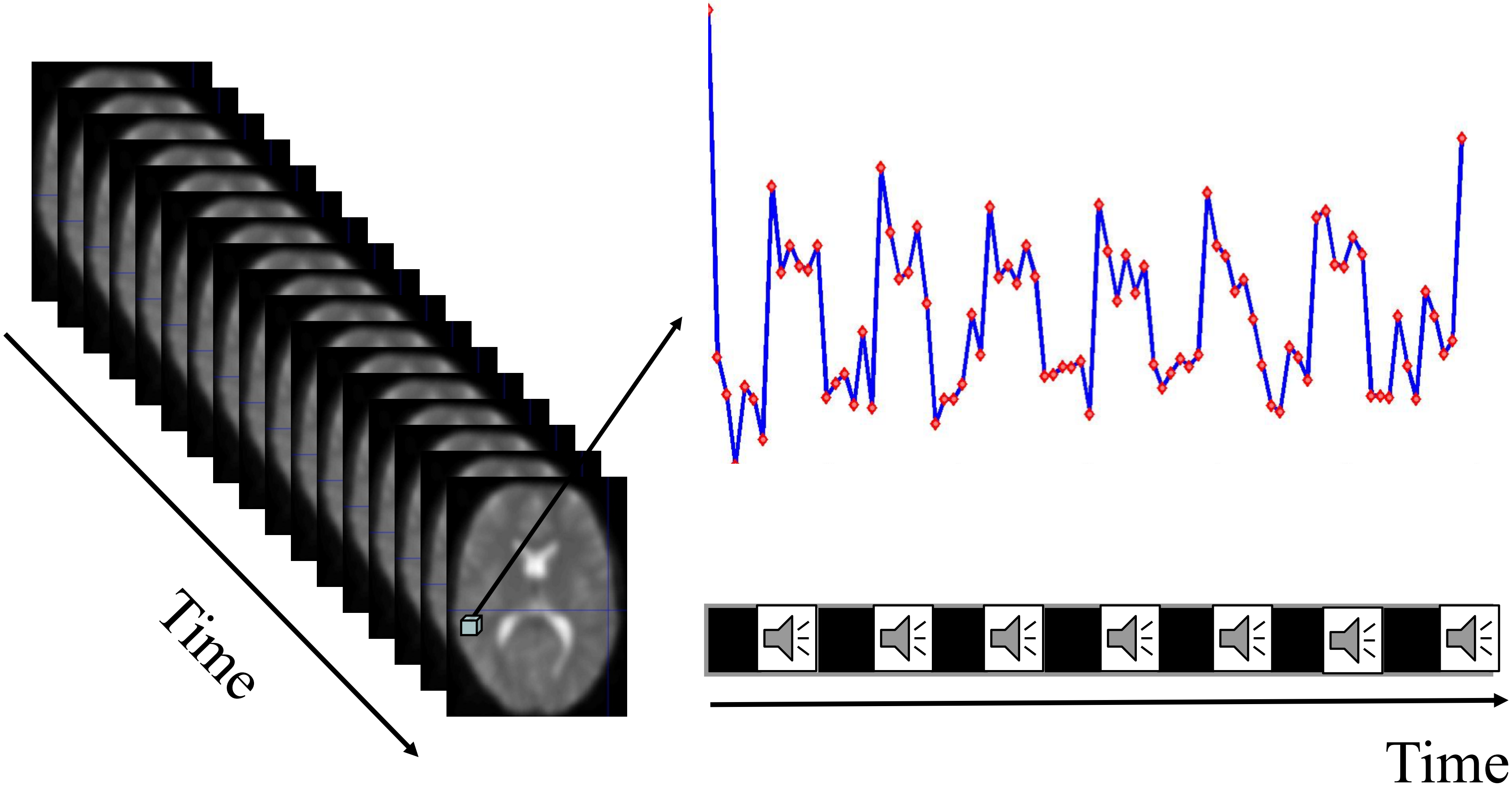
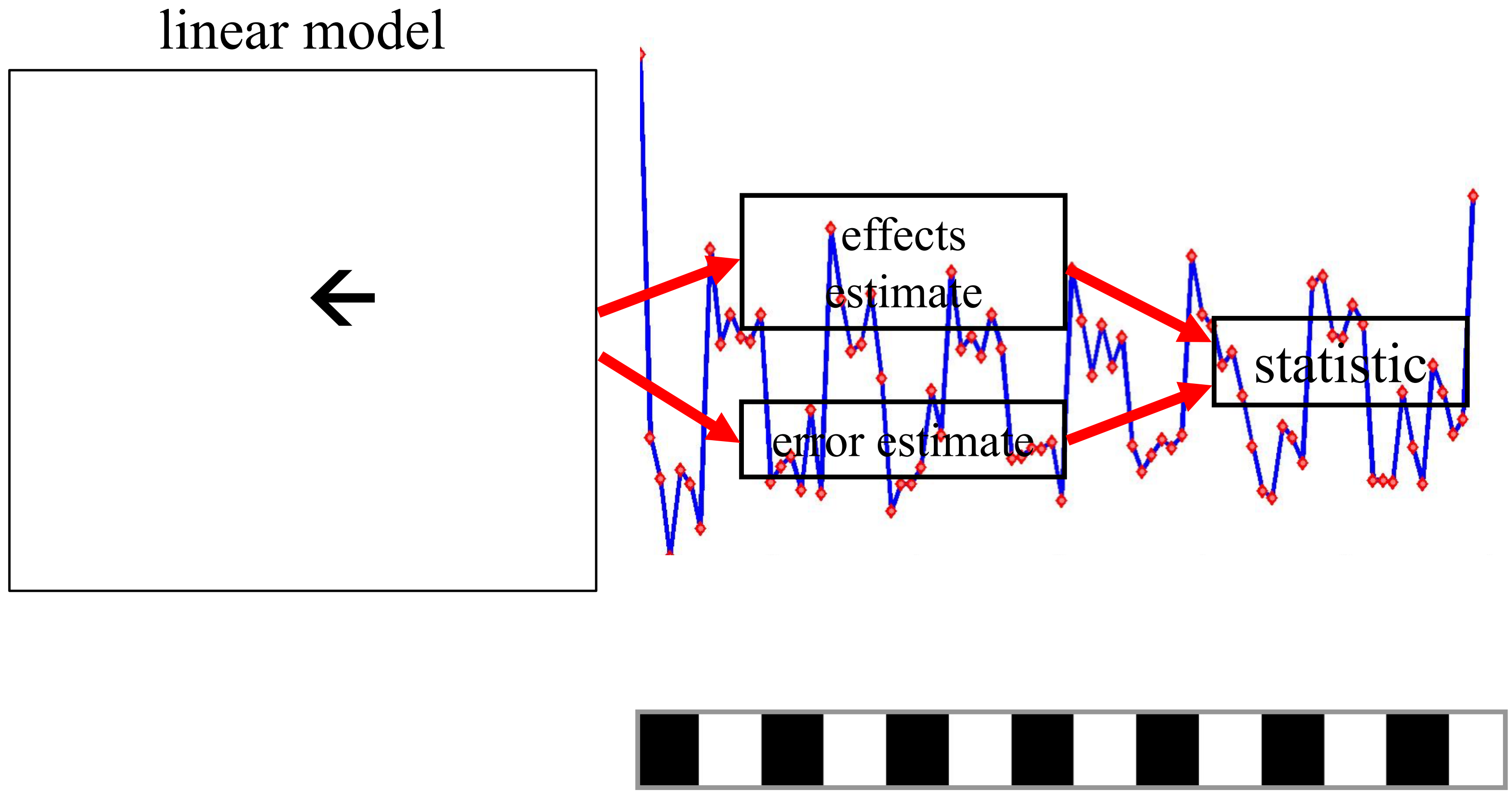


Image a very simple experiment…

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

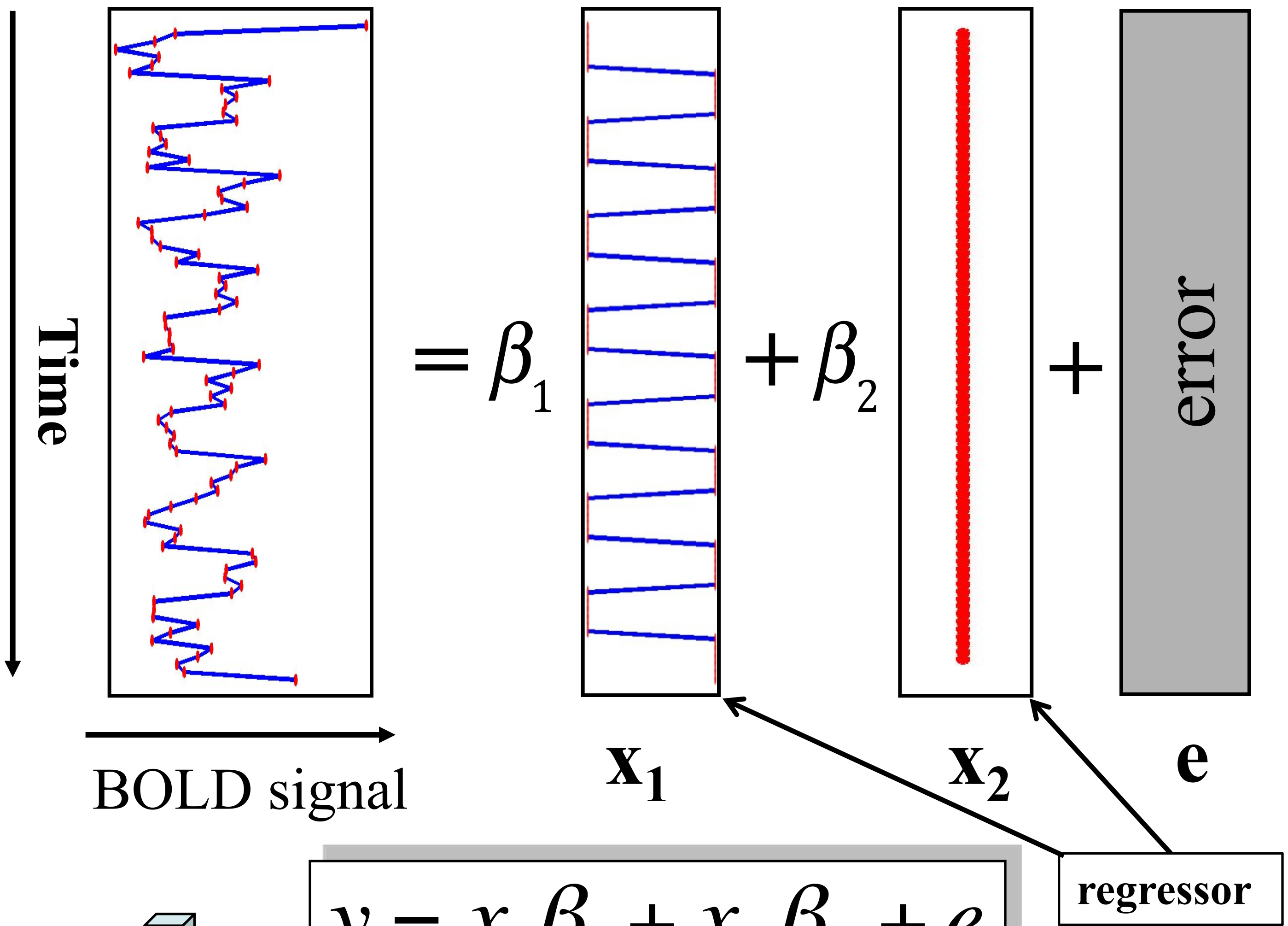


You need a model of your data…



Explain your data…

as a combination of experimental manipulation, confounds and errors

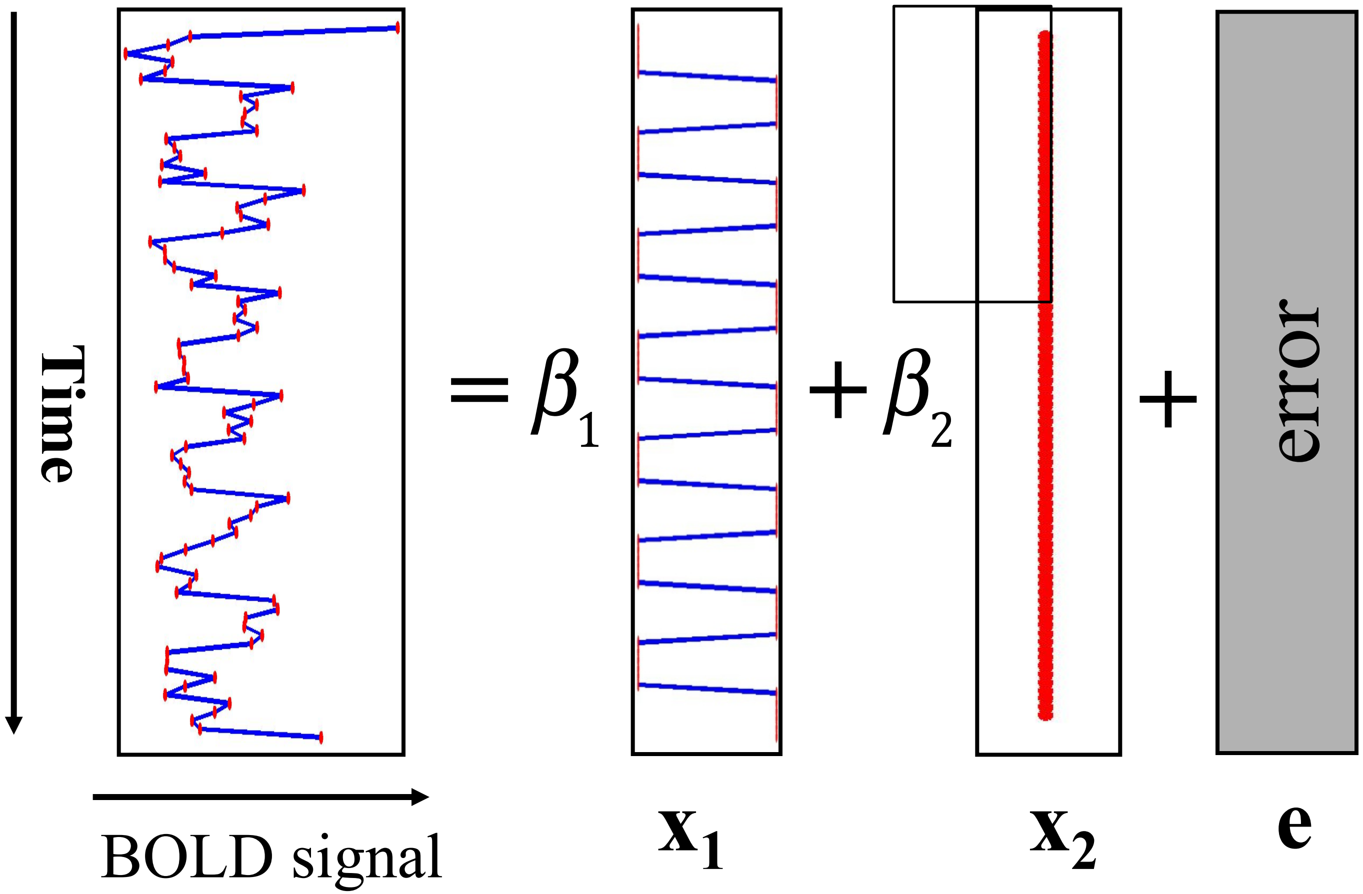


Single voxel regression model:

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

Explain your data…

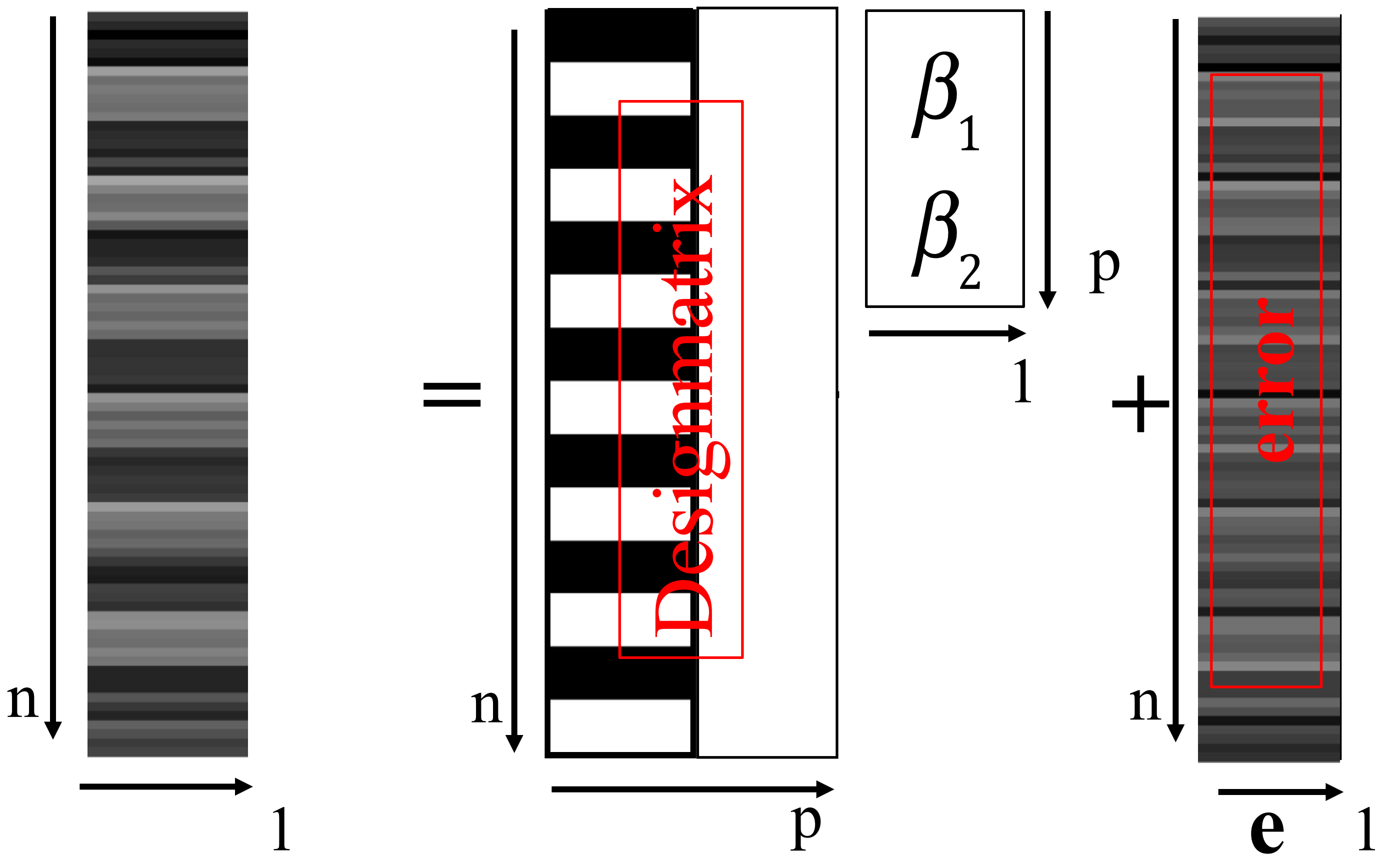
as a combination of experimental manipulation,confounds and errors



Single voxel regression model:

$$y = X\beta + e$$

The black and white version in SPM



$$y = X\beta + e$$

n: number of scans
p: number of regressors

Model assumptions

Designmatrix

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

error

You want to estimate your parameters such that you minimize:

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

This can be done using an **Ordinary least squares** estimation (OLS) assuming an i.i.d. error

error

GLM assumes identical and independently distributed errors

i.i.d. = error covariance is a scalar multiple of the identity matrix $e \approx N(0,\sigma^2 I)$

$$Cov(e) = \begin{array}{cc} & \begin{array}{cc} \mathbf{t1} & \mathbf{t2} \end{array} \\ & \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix} \begin{array}{c} \mathbf{t1} \\ \mathbf{t2} \end{array} \end{array}$$

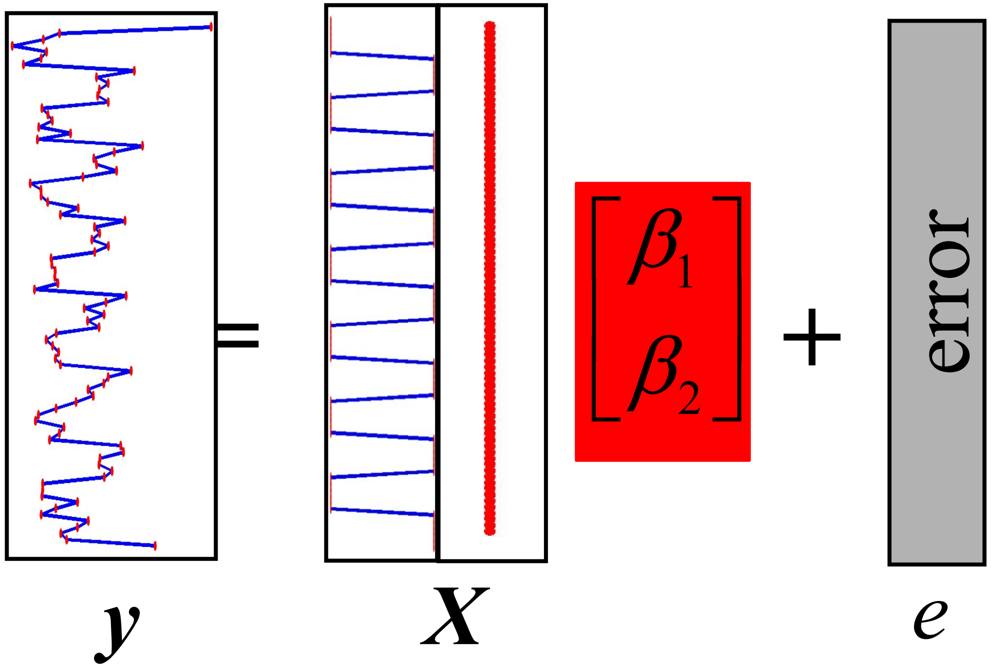
non-identity

$$Cov(e) = \begin{bmatrix} 4 & 0 \\ 0 & 1 \end{bmatrix}$$

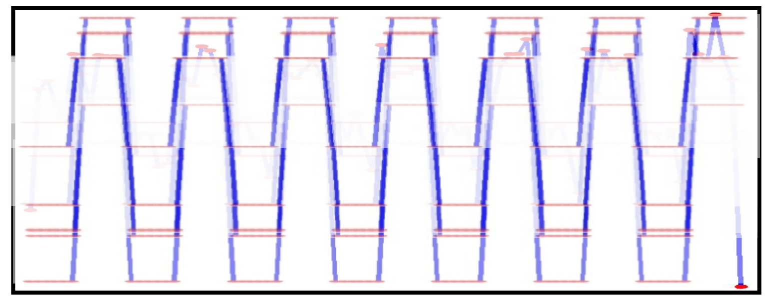
non-independence

$$Cov(e) = \begin{bmatrix} 2 & 1 \\ 1 & 2 \end{bmatrix}$$

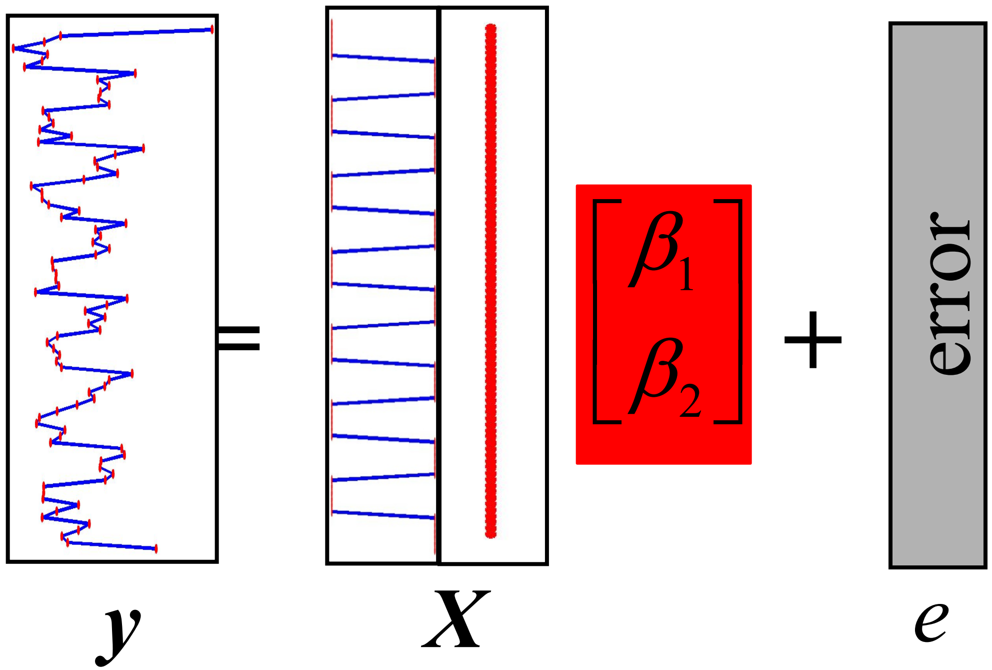
How to fit the model and estimate the parameters?



„Option 1“: Per hand



How to fit the model and estimate the parameters?



OLS (Ordinary Least Squares)

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

Data predicted by our model

$$e = y - \hat{y}$$

Error between predicted and actual data

$$e = y - X\hat{\beta}$$

Goal is to determine the betas such that we minimize the quadratic error

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

OLS (Ordinary Least Squares)

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

The goal is to minimize the quadratic error between data and model

OLS (Ordinary Least Squares)

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

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

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OLS (Ordinary Least Squares)

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The goal is to minimize the quadratic error between data and model

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

This is a scalar and the transpose of a scalar is a scalar ☺

$$e^T e = y^T y \boxed{- y^T X\hat{\beta}} - \hat{\beta}^T X^T y + \hat{\beta}^T X^T X\hat{\beta}$$

OLS (Ordinary Least Squares)

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

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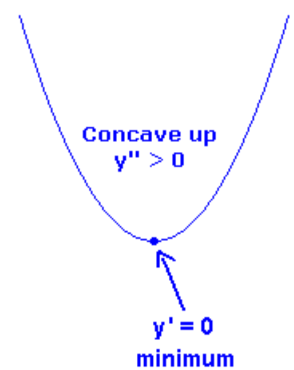
This is a scalar and the transpose of a scalar is a scalar ☺

$$e^T e = y^T y - 2\hat{\beta}^T X^T y + \hat{\beta}^T X^T X\hat{\beta}$$

$$\frac{\partial e^T e}{\partial \hat{\beta}} = -2X^T y + 2X^T X\hat{\beta}$$

$$0 = -2X^T y + 2X^T X\hat{\beta}$$

You find the extremum of a function by taking its derivative and setting it to zero



OLS (Ordinary Least Squares)

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

The goal is to minimize the quadratic error between data and model

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

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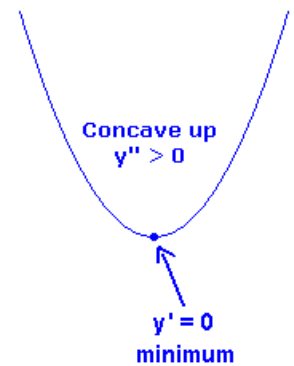
You find the extremum of a function by taking its derivative and setting it to zero

$$0 = -2X^T y + 2X^T X\hat{\beta}$$

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

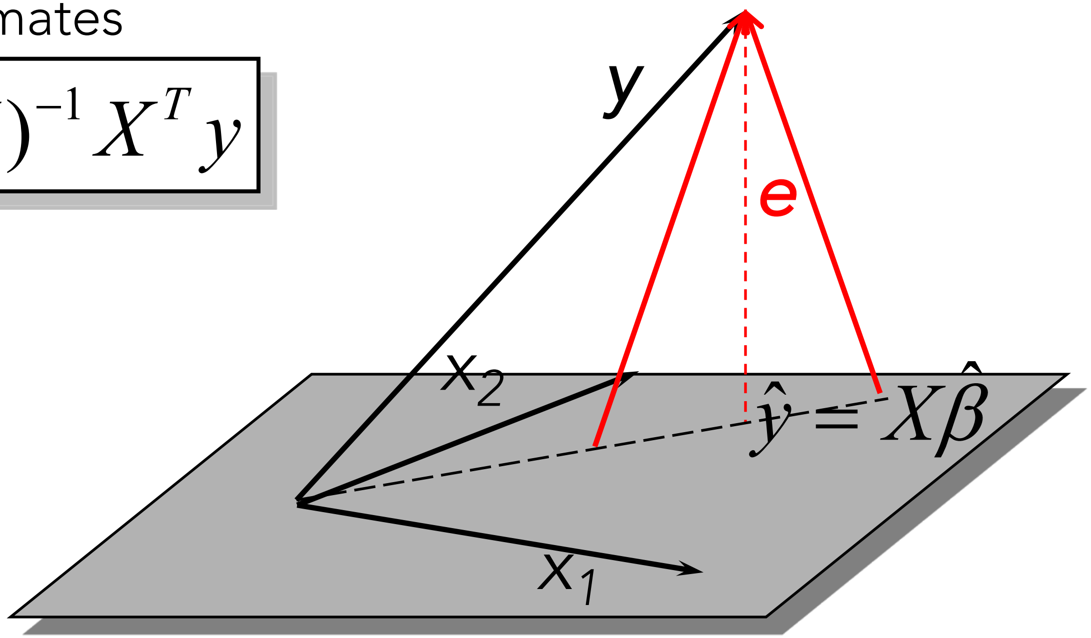
SOLUTION: OLS of the Parameters



A geometric perspective on the GLM

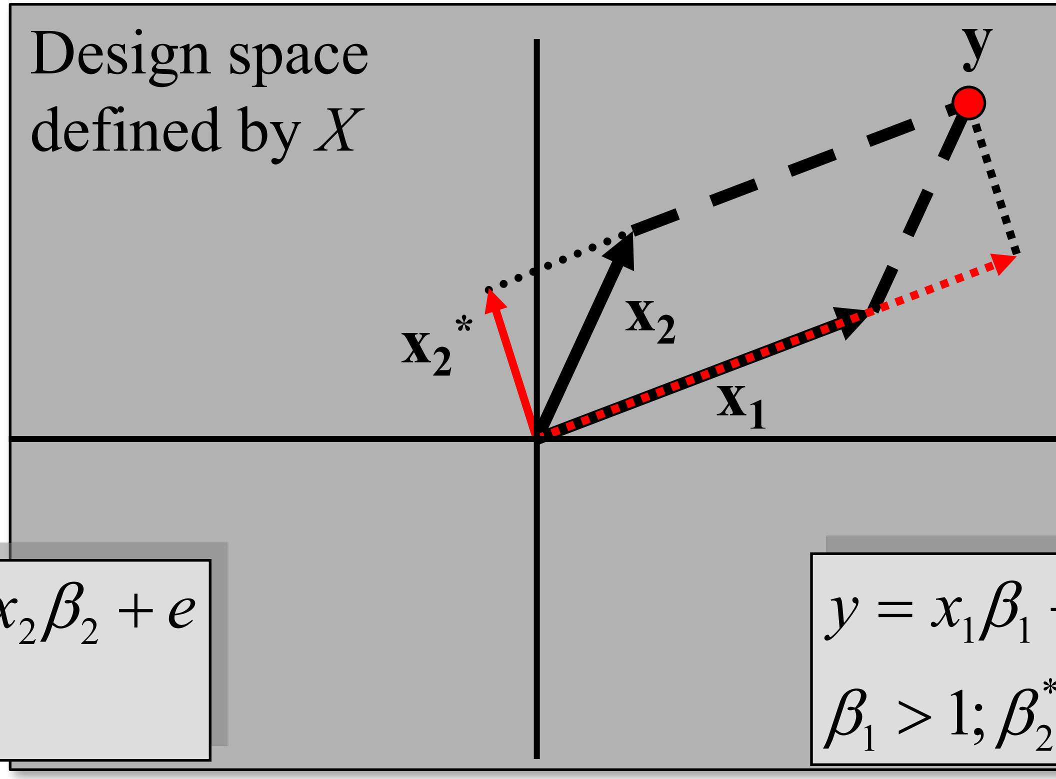
OLS estimates

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



Design space
defined by *X*

Correlated and orthogonal regressors



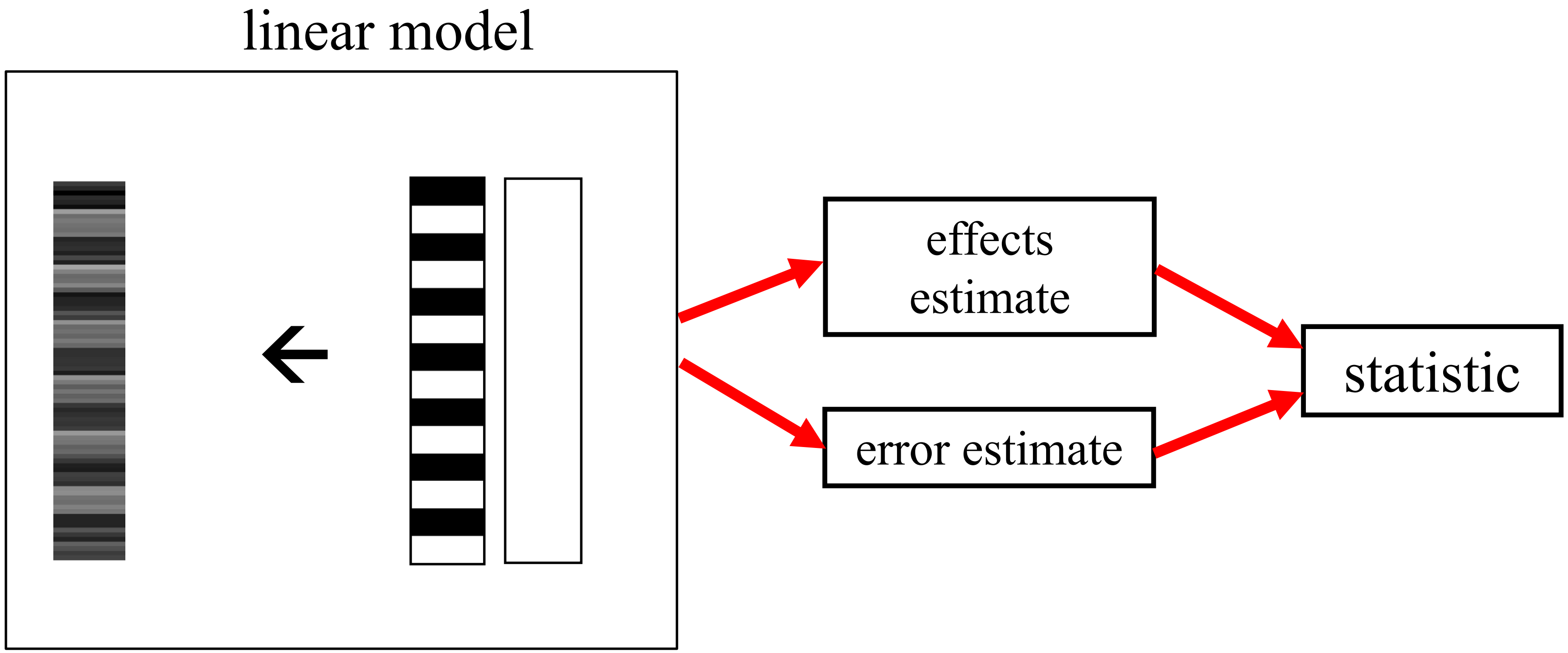
$$y = x_1\beta_1 + x_2\beta_2 + e$$
$$\beta_1 = \beta_2 = 1$$

$$y = x_1\beta_1 + x_2^*\beta_2^* + e$$
$$\beta_1 > 1; \beta_2^* = 1$$

Correlated regressors = explained variance is shared between regressors

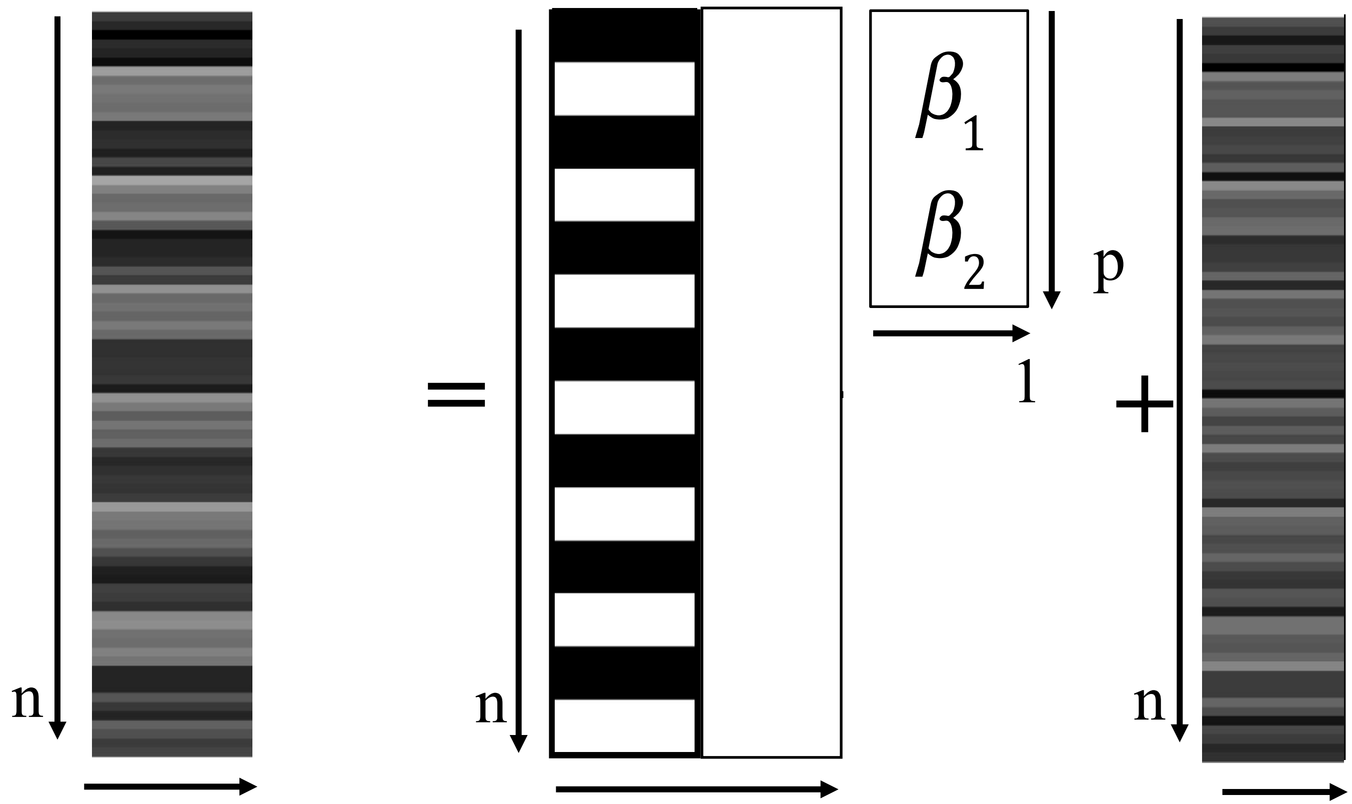
When x_2 is orthogonalized with regard to x_1, only the parameter estimate for x_1 changes, not that for x_2!

We are nearly there…

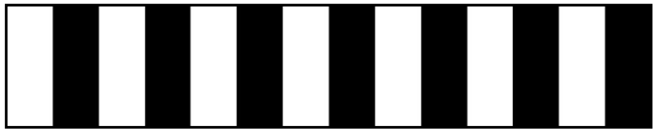


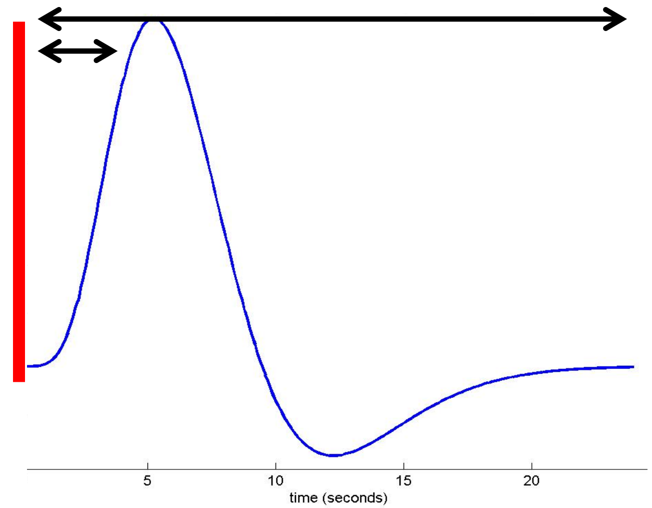
…but we are dealing with fMRI data

What are the problems?



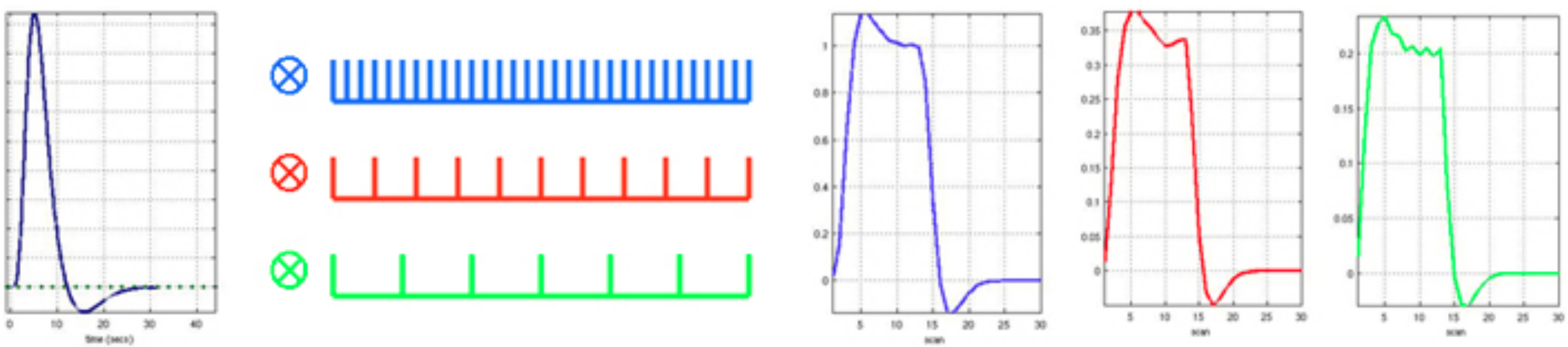
Problem 1: Shape of BOLD response





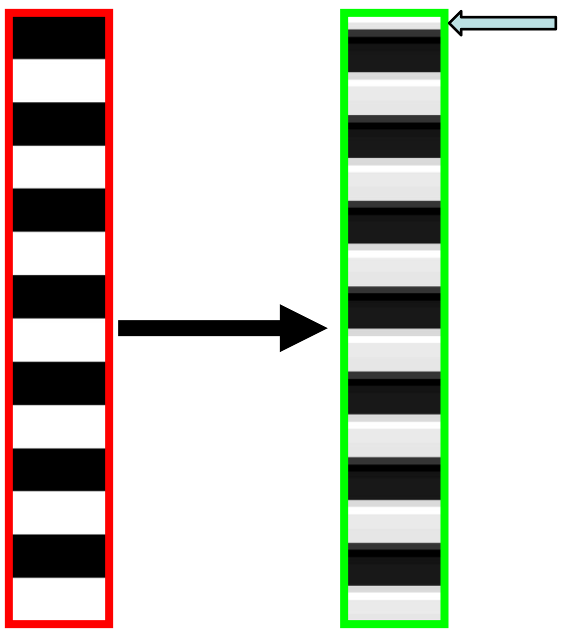
$$f \otimes g(t) = \int_{0} f(\tau)g(t-\tau)d\tau$$

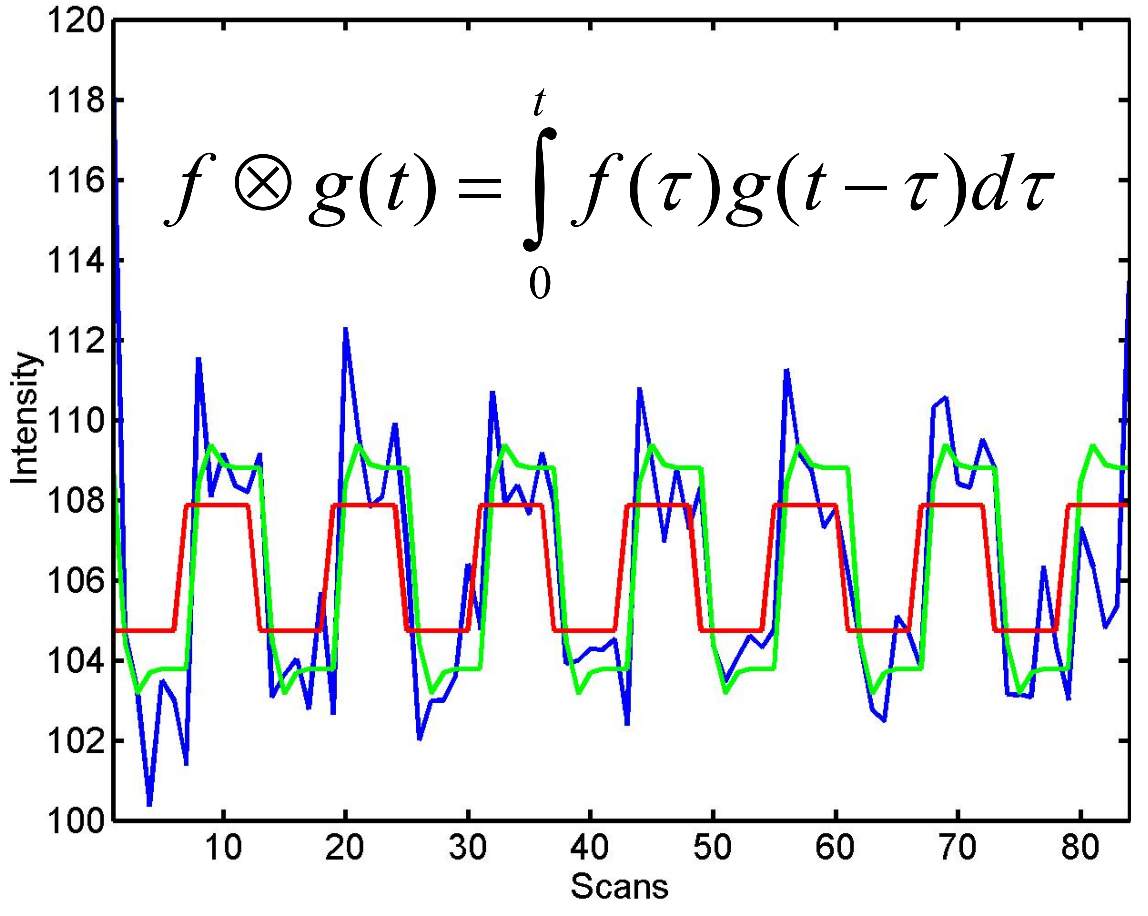
The response of a linear time-invariant (LTI) system is the convolution of the input with the system's response to an impulse (delta function).



Solution: Convolution model of the BOLD response

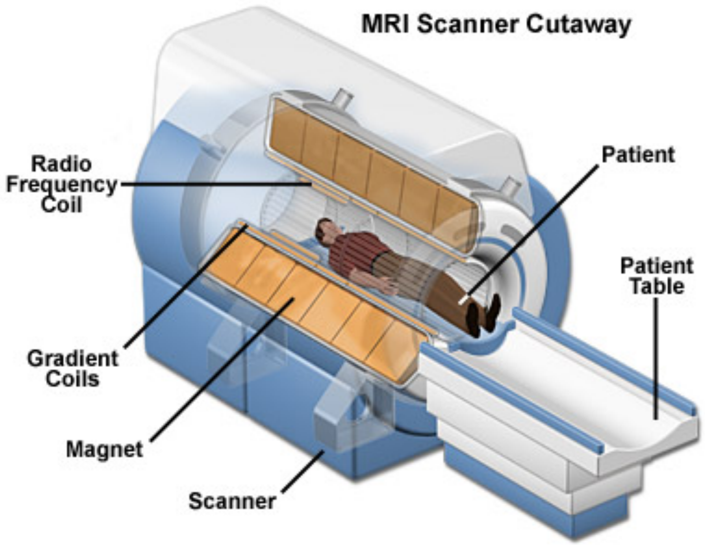
expected BOLD response
= input function x impulse response function (HRF)

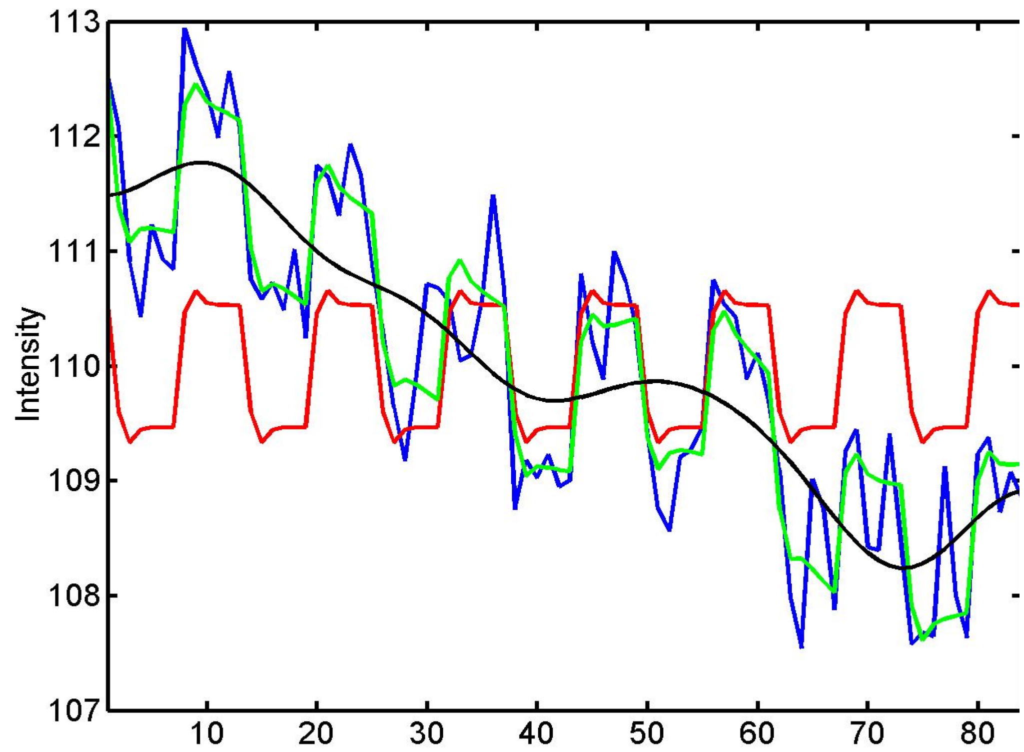




blue = data
green = predicted response, taking convolved with HRF
red = predicted response, NOT taking into account the HRF

Problem 2: Low frequency noise





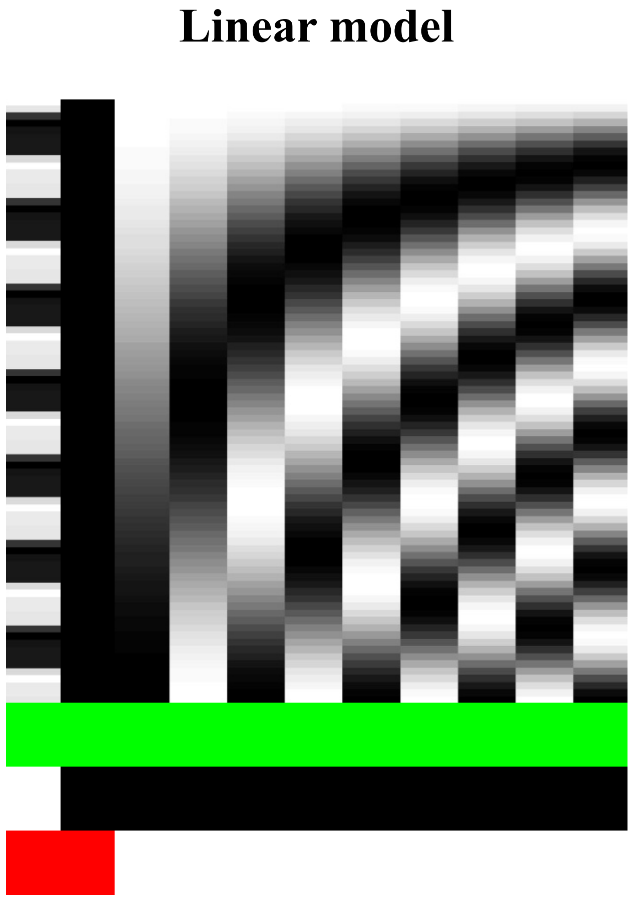
blue = data

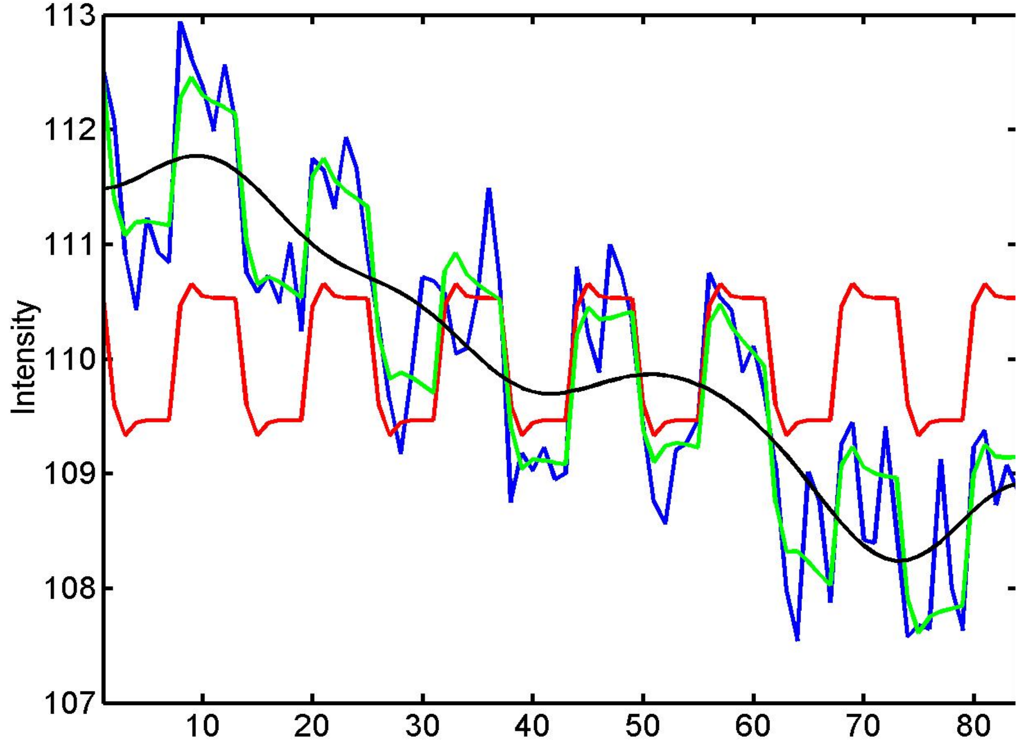
black = mean + low-frequency drift

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

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

Problem 2: Low frequency noise





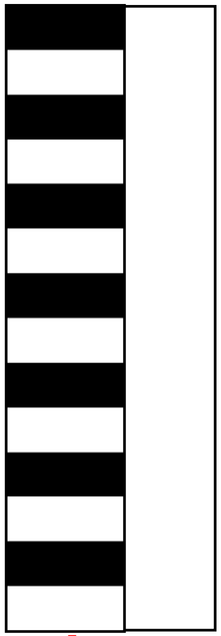
blue = data

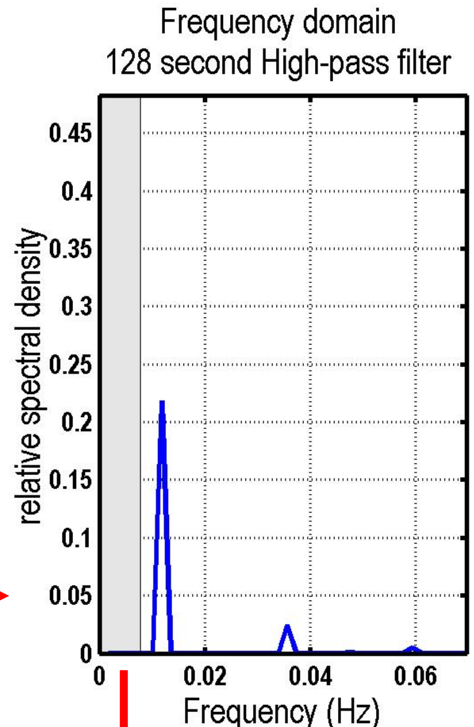
black = mean + low-frequency drift

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

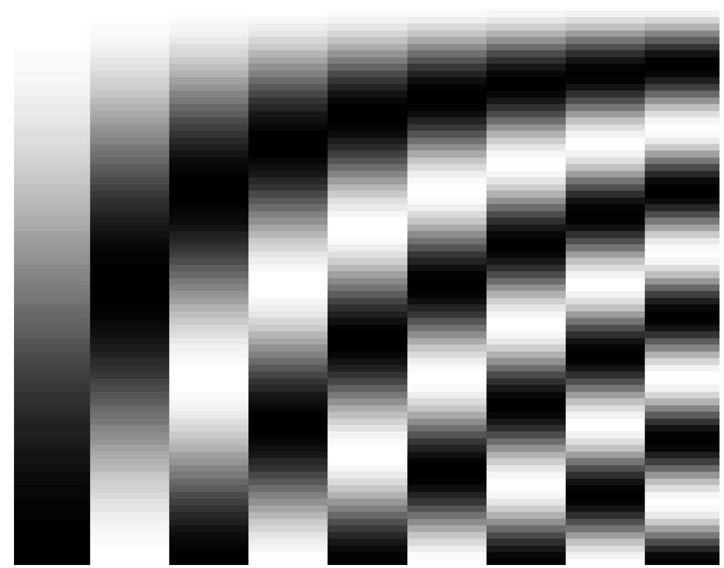
red = predicted response, NOT taking into account low-frequency drift

Solution 2: High pass filtering





discrete cosine transform (DCT) set



Problem 3: Serial correlations

i.i.d

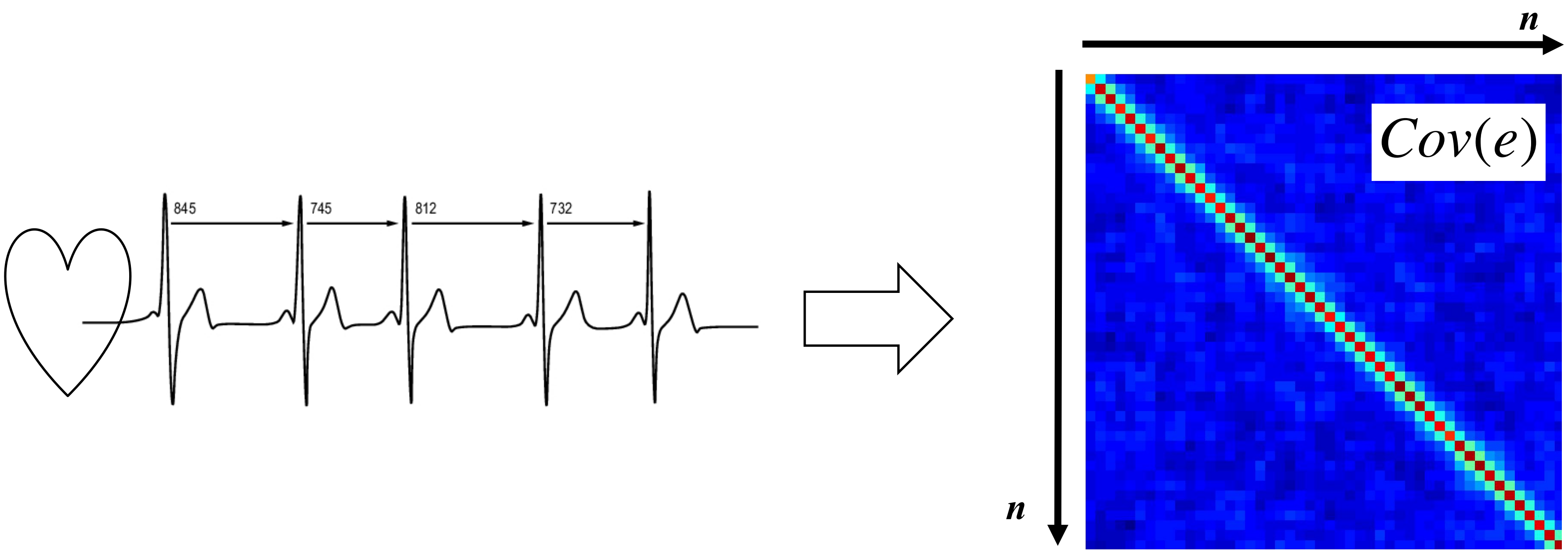
$$Cov(e) = \begin{array}{c@{}c} & \begin{array}{cc} \mathbf{t1} & \mathbf{t2} \end{array} \\ & \left[\begin{array}{cc} 1 & 0 \\ 0 & 1 \end{array}\right] \begin{array}{c} \mathbf{t1} \\ \mathbf{t2} \end{array} \end{array}$$

non-identity

$$Cov(e) = \begin{bmatrix} 4 & 0 \\ 0 & 1 \end{bmatrix}$$

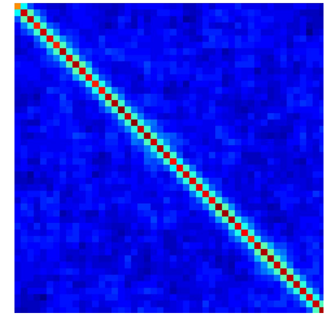
non-independence

$$Cov(e) = \begin{bmatrix} 2 & 1 \\ 1 & 2 \end{bmatrix}$$



n: number of scans

Problem 3: Serial correlations



- Transform the signal into a space where the error is iid

$$\boxed{Wy = WX\beta + \overbrace{We}^{\text{This is i.i.d}}}$$

- *Pre-whitening*:

  1. Use an enhanced noise model with multiple error covariance components, i.e. e ~ $N(0,\sigma^2 V)$ instead of e ~ $N(0, \sigma^2 I)$.

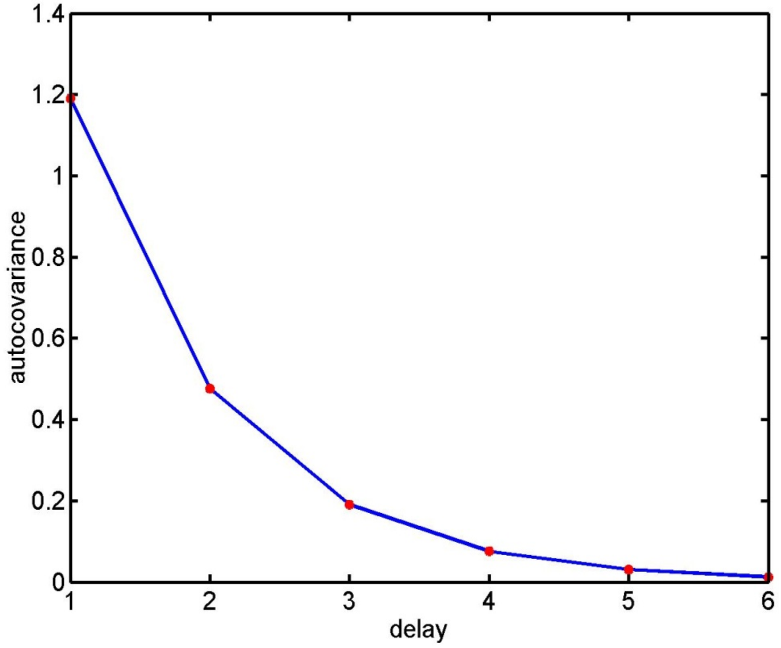
  2. Use estimated serial correlation to specify filter matrix *W* for whitening the data.

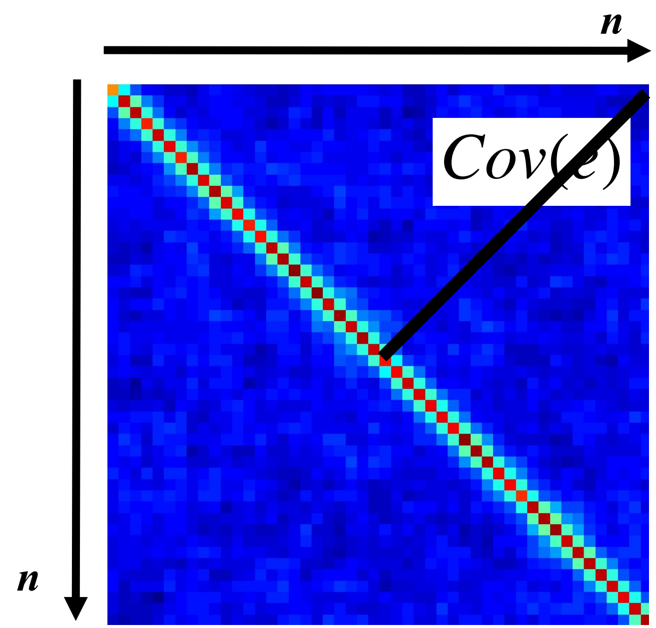
Problem 3: How to find W → Model the noise

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

1st order autoregressive process: AR(1)

autocovariance
function





n: number of scans

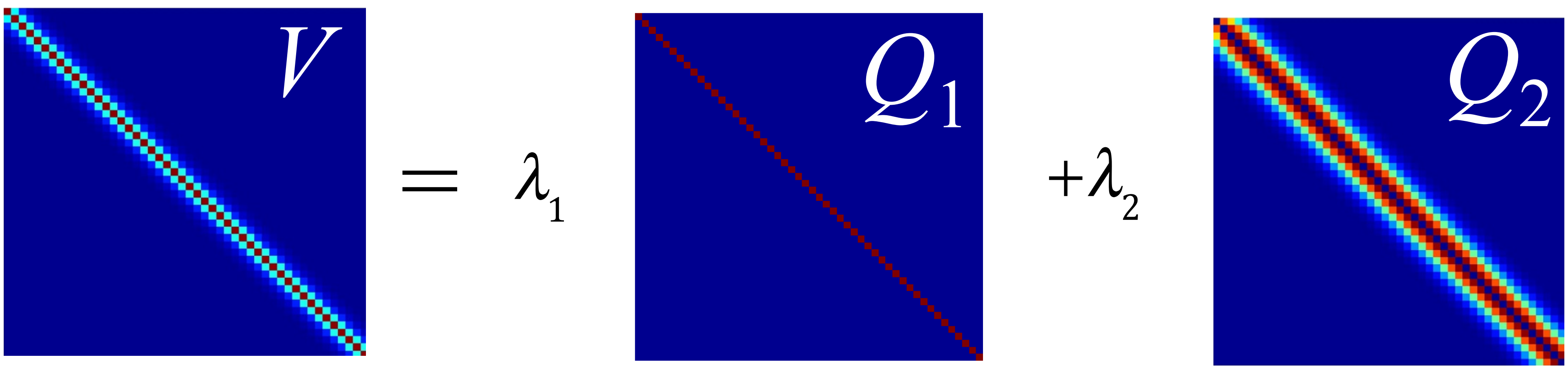
Model the noise: Multiple covariance components

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

enhanced noise model

$$V \propto Cov(e)$$
$$V = \sum \lambda_i Q_i$$

error covariance components Q and hyperparameters



Estimation of hyperparameters with EM (expectation maximisation) or ReML (restricted maximum likelihood).

How do we define W ?

- Enhanced noise model

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

- Remember linear transform for Gaussians

$$x \sim N(\mu, \sigma^2), y = ax$$
$$\Rightarrow y \sim N(a\mu, a^2\sigma^2)$$

- Choose W such that error covariance becomes spherical

$$We \sim N(0, \sigma^2 W^2 V)$$
$$\Rightarrow W^2 V = I$$
$$\Rightarrow W = V^{-1/2}$$

- **Conclusion: W is a simple function of V**

$$Wy = WX\beta + We \longrightarrow y_s = X_s\beta + e_s$$

We are there…

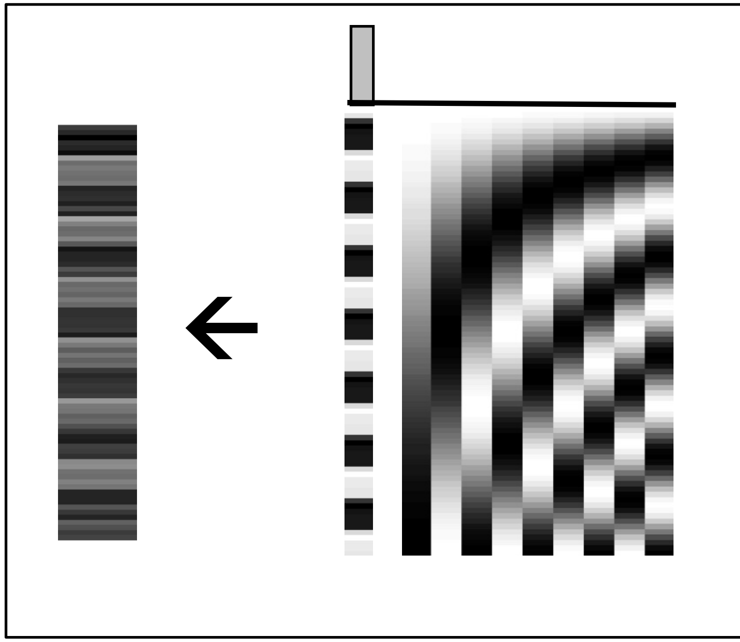
- the GLM models the effect of your experimental manipulation on the acquired data
- GLM includes all known experimental effects and confounds
- estimates effects an errors on a voxel-by-voxel basis

Because we are dealing with fMRI data there are a number of problems we need to take care of:

- Convolution with a canonical HRF
- High-pass filtering to account for low-frequency drifts
- Estimation of multiple variance components (e.g. to account for serial correlations)

We are there…

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



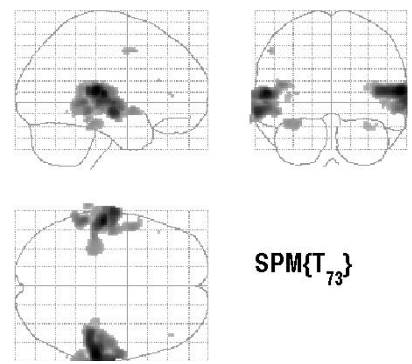
effects estimate

error estimate

statistic

Null hypothesis: $\beta_1 = 0$

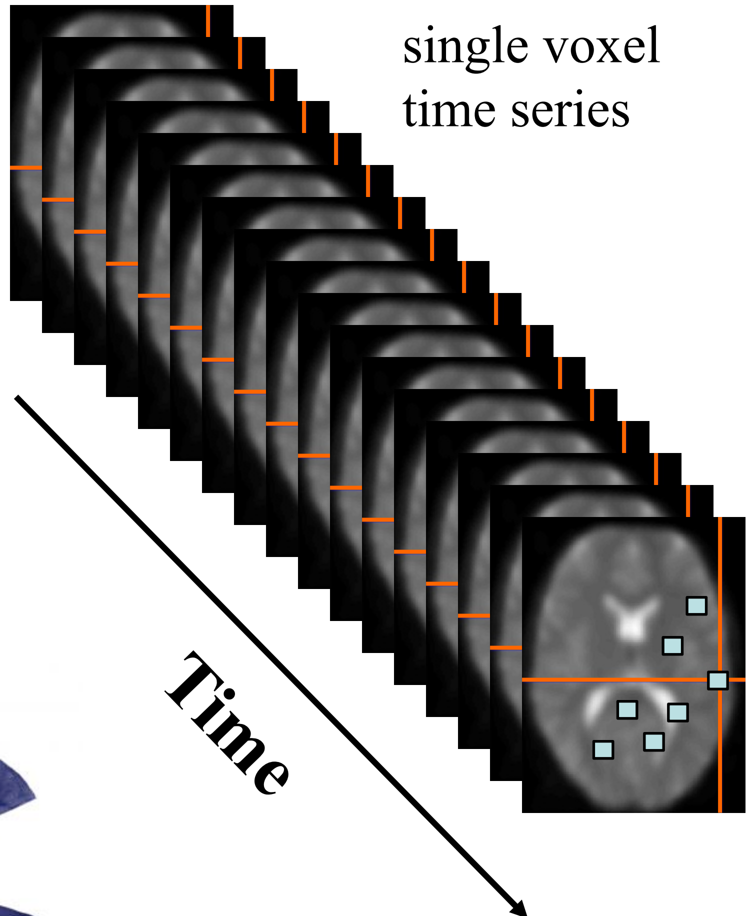
$$t = \frac{c^T \hat{\beta}}{Std(c^T \hat{\beta})}$$



SPM{T_{73}}

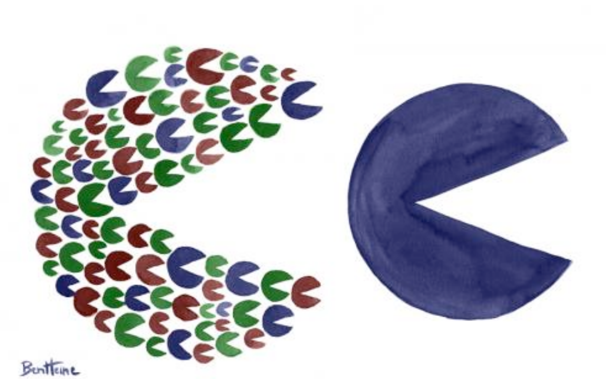
So far we have looked at a single voxel…

- Mass-univariate approach: GLM applied to > 100,000 voxels
- Threshold of p<0.05 more than 5000 voxels significant by chance!



single voxel time series

- Massive problem with multiple comparisons!
- Solution: Gaussian random field theory



Outlook: further challenges

- correction for multiple comparisons
- variability in the HRF across voxels
- limitations of frequentist statistics
- GLM ignores interactions among voxels

Thank you for listening!

- **Friston, Ashburner, Kiebel, Nichols, Penny (2007)**
  ***Statistical Parametric Mapping: The Analysis of Functional Brain Images*.**
  Elsevier.

- Christensen R (1996) *Plane Answers to Complex Questions: The Theory of Linear Models*. Springer.

- Friston KJ et al. (1995) Statistical parametric maps in functional imaging: a general linear approach. *Human Brain Mapping* 2: 189-210.