Development of Complex Curricula for Molecular Bionics and Infobionics Programs within a consortial* framework**

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**Molekuláris bionika és Infobionika Szakok tananyagának komplex fejlesztése konzorciumi keretben

***A projekt az Európai Unió támogatásával, az Európai Szociális Alap társfinanszírozásával valósul meg.

BIOMEDICAL IMAGING

(Orvosbiológiai képalkotás)

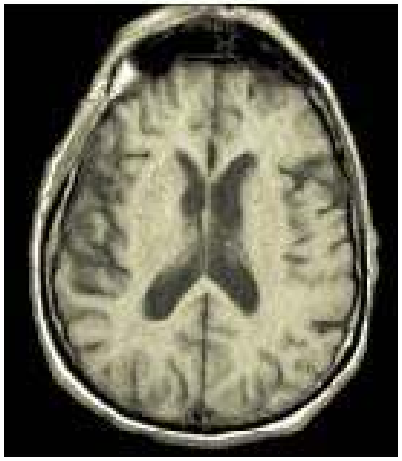
fMRI – Data Processing and Basic Analysis

(fMRI – Adatfeldolgozás és elemzés)

ÉVA BANKÓ, VIKTOR GÁL

Acquired Data

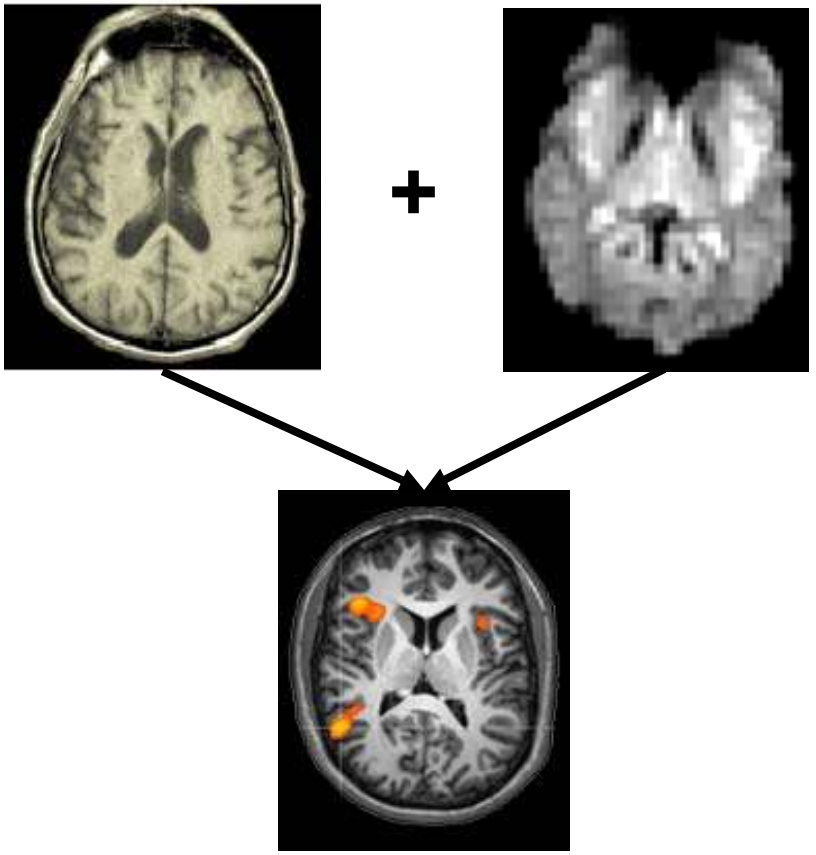
- 3D T1 anatomy
  - 1×1×1 mm resolution



- 4D T2* EPI images
  - 3D timeseries collected at each TR (1-2 s)
  - ~4×3.5×3.5 mm resolution

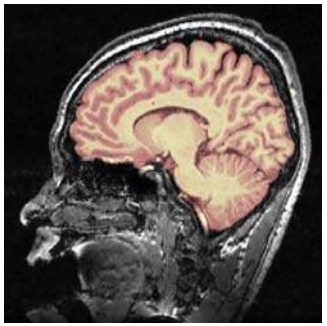
Preprocessing and Processing Steps

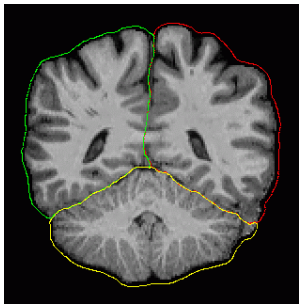
- Anatomical images
  - Intensity normalization
  - Skull-stripping
  - 3D reconstruction
  - Normalization (MNI or Talairach)
- Functional images
  - Coregistration
  - 3D motion correction
  - Slice-time correction
  - Smoothing
  - Defining ROIs
  - Regression analysis

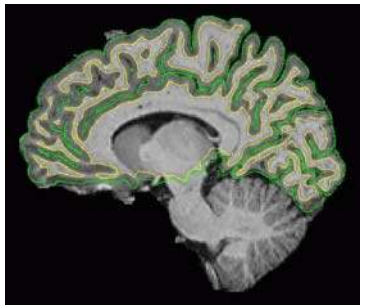


Anatomical Preprocessing I.

- Intensity normalization
  - make white matter (WM) homogenous to aid segmentation
- Skull-stripping
  - remove all non-brain tissues
  - caveat: shouldn't accidentally remove grey matter (GM)
- Segmentation
  - separate hemispheres, then separate GM from WM, so analysis can be restricted to GM

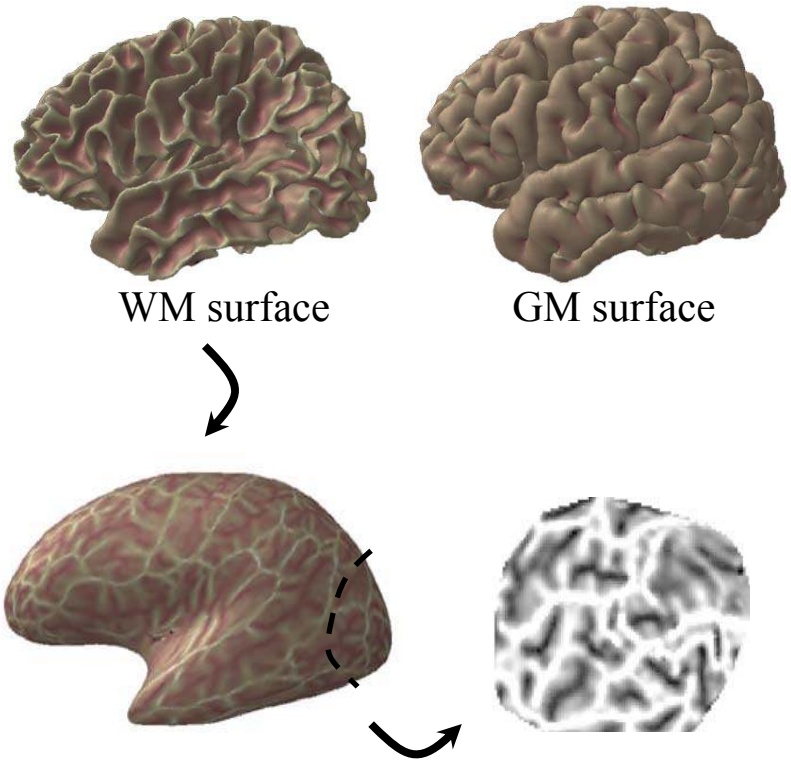






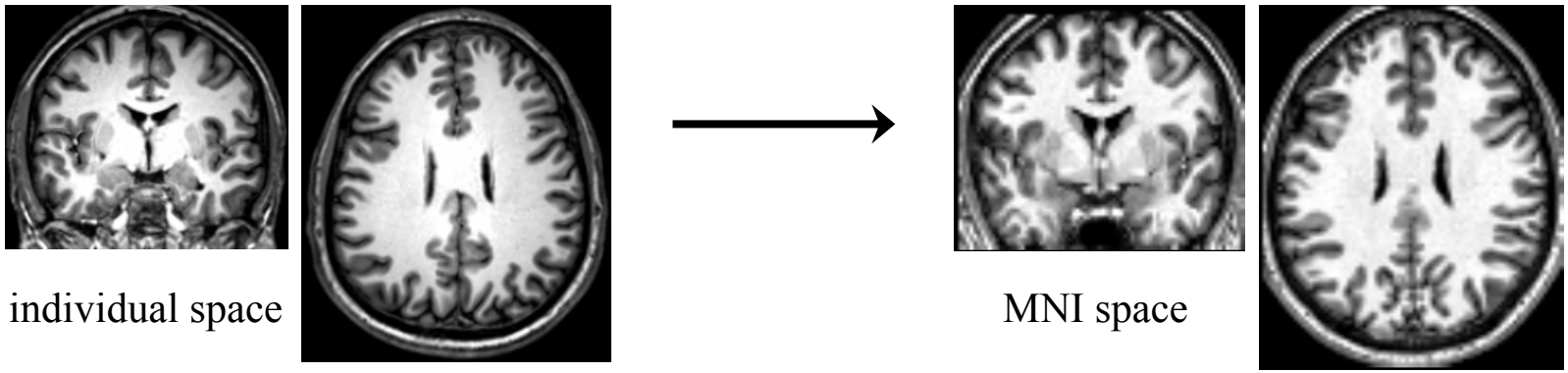
Anatomical Preprocessing II.

- Surface creation
  - make surfaces out of the segmented GM and WM
- Inflation
  - inflate WM surface to better visualize activations in sulci
- Flattening
  - cut a patch and flatten or cut at predefined sulci to flatten the whole brain



Anatomical Preprocessing III.

- Normalization
  - transform each individual brain into a standard space by predefined algorithms so 2nd-level (group-level) analysis can be performed
  - standard spaces:
    - Talairach space based on one post-mortem brain
    - Montreal Neurological Institute (MNI) space based on a large series of MRI scans on normal controls

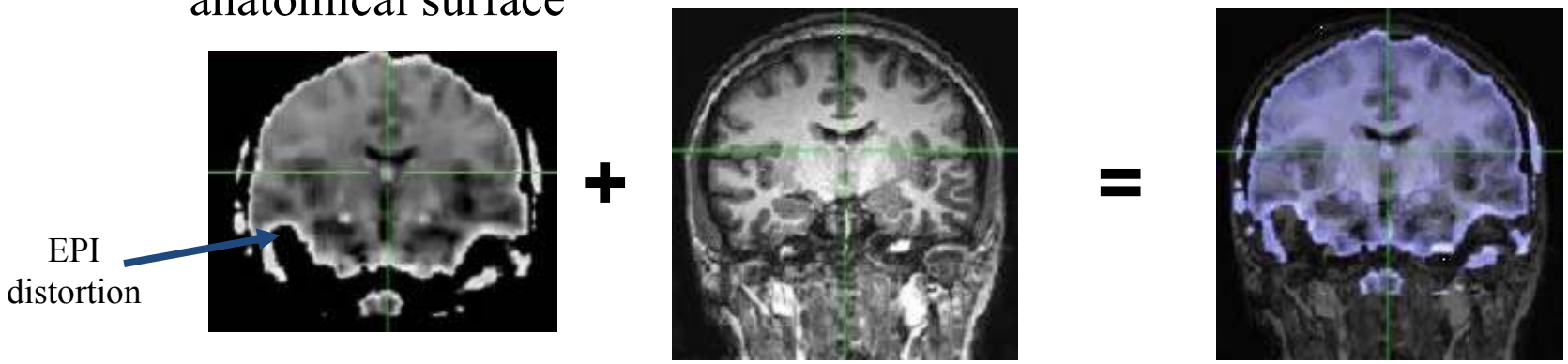


individual space

MNI space

Functional Preprocessing I.

- Coregistration
  - 3D anatomy and the functional images are acquired in a different space; moreover the EPI sequence distorts the brain in the neighborhood of cavities
  - a linear (or non-linear) warping algorithm is required to register both in the same space so statistical activations can be projected to the anatomical surface



Functional Preprocessing II.

- 3D Motion correction
  - align all functional images to a reference image (usually the first image or the image in the middle of the scan) since their location could have slightly changed due to subject motion and all statistical analyses assume that the location of a given voxel within the brain does not change over time
- Slice-timing correction
  - with a continuous descending EPI sequence, the bottom slice is acquired a TR later than the slice on the top, so there is a shift in the onset of the haemodynamic function. One solution to this problem is to interpolate the data during preprocessing as if the slices were acquired simultaneously
- Smoothing
  - spatially smoothing each of the images improves the signal-to-noise ratio (SNR), but will reduce the resolution in each image

Statistical Analysis of Functional Images I.

- Aims:
  - find and describe the effect of stimulation if there is any
- Based on the spatial complexity of the signal, there are:
  - one-dimensional methods
    - doing the statistics separately on a voxel-by-voxel basis (classic GLM regression method)
    - averaging the time course of predefined voxels in a certain area (region-of-interest: ROI) and doing the statistics on that (increases signal-to-noise ratio (SNR)
  - multi-dimensional (multi-variate) methods
    - finding patterns in time *and* space

Statistical Analysis of Functional Images II.

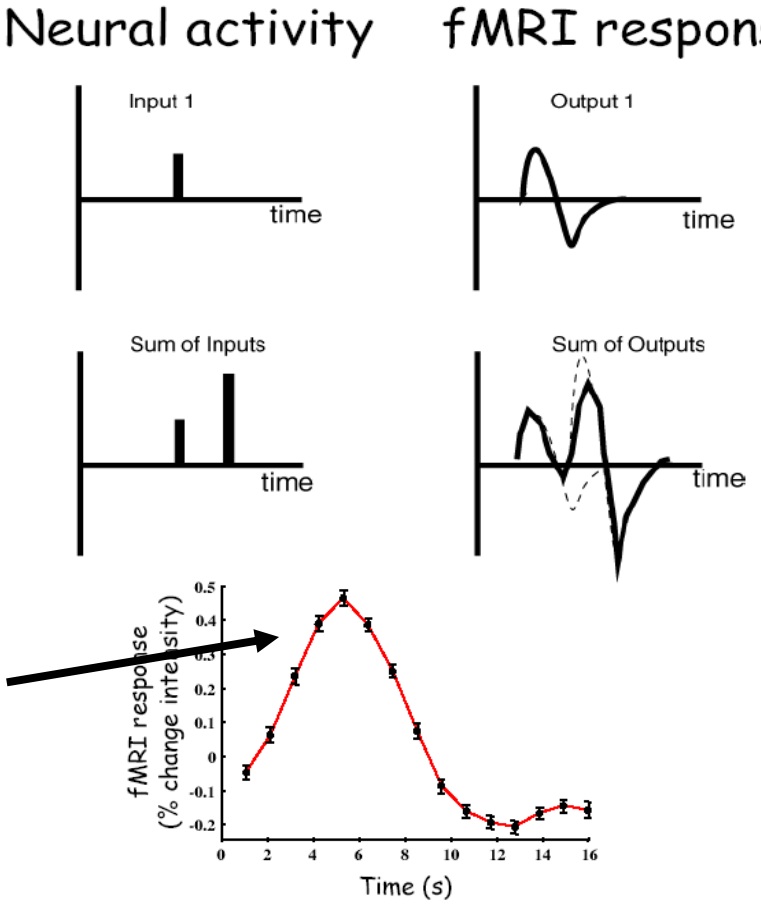
- Fitting models to the data:
  - find models that describe the signal and the noise and evaluate the fit
- Parametric models:
  - linear correlation
  - t-tests
  - event-related averaging
  - general linear models (GLM)
- Non-parametric models
  - bootstrap
  - Monte-Carlo simulations
  - multi-variate models

Statistical Analysis of Functional Images III.

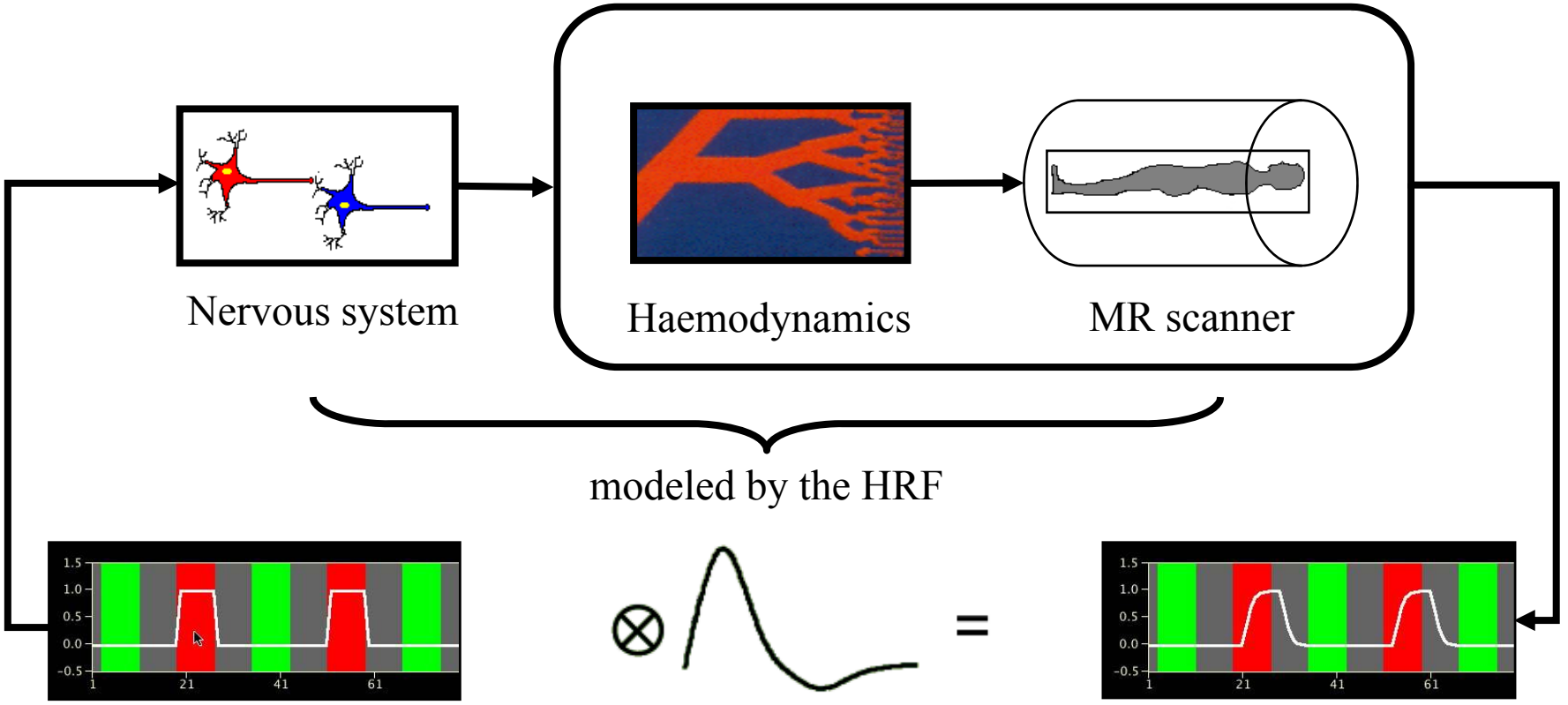
- Noise integration into models
  - models should take noise into account either as a separate term
  - there are models devoted to noise estimation (nuisance variability models) such as time autocorrelation or drift
- Univariate models treating each voxel separately need to be statistically corrected for
  - correction for the multiple comparison problem
- Group-level statistics model the population not particular individuals
  - Random effects models

Linear Transform Hypothesis

- It is assumed that the processes from neuronal firing to BOLD response constitute a time-invariant linear system, so the fMRI signal is approximately proportion to a measure of local neural activity, averaged over a spatial extent of several millimeters and over a time of several seconds.
- *Haemodynamic impulse response function*: (HIRF or HRF) the measurable fMRI signal for a brief stimulus presentation

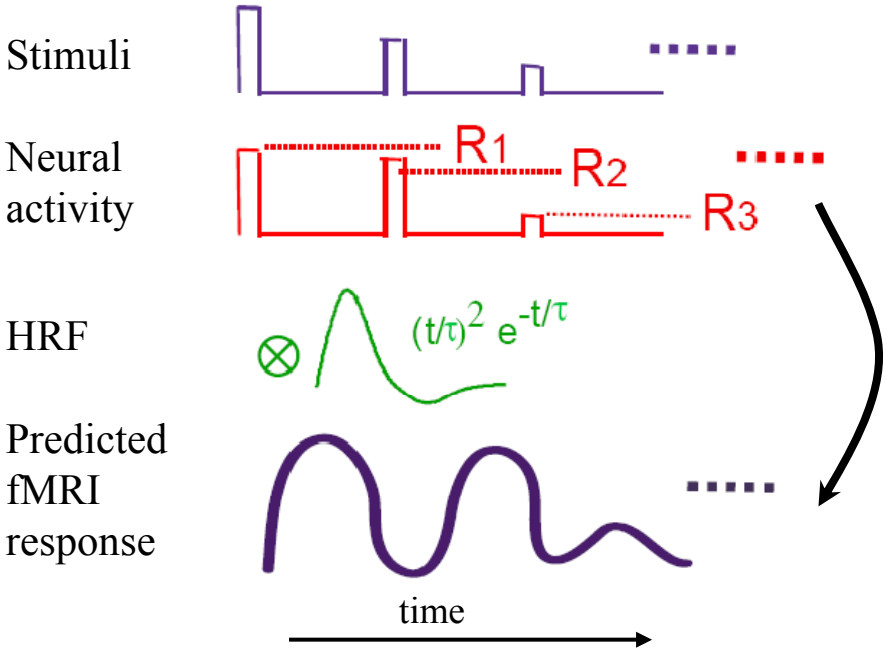


Haemodynamic Response Function

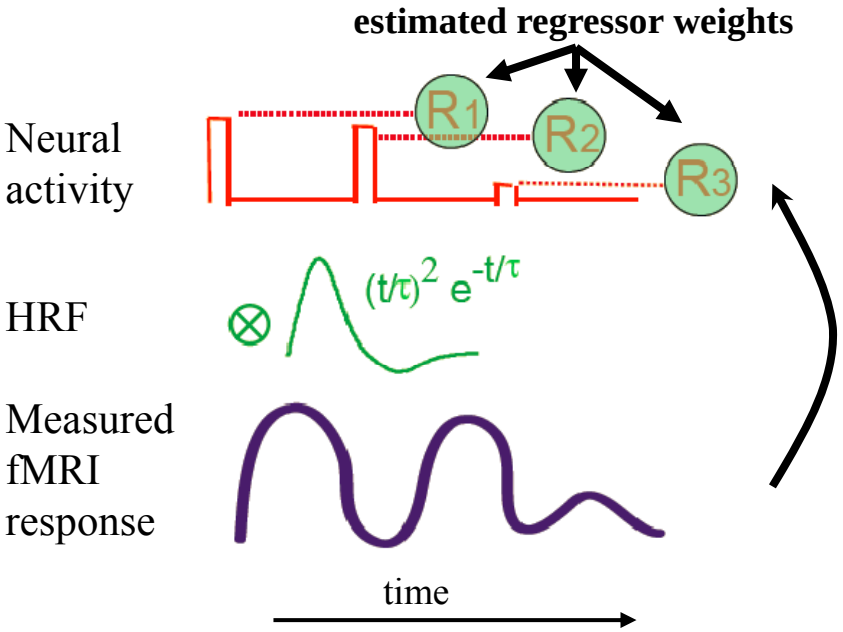


Model of Cortical Activity and Haemodynamic Impulse

fMRI responses from cortical activity



Estimating cortical activity from fMRI responses



General Linear Model Approach

- in the case of continuous signal:

$$y(t) = x_1(t) * h_1(t) + \cdots + x_N(t) * h_N(t) + n(t)$$

y(t): measured fMRI response
x(t): input signal (i.e. the sum of time-shifted Dirac delta functions)
h(t): HRF
n(t): noise
N: number of event types in the experiment

- in the case of discrete signal:

$$y = X_1 h_1 + \cdots + X_N h_N + n$$

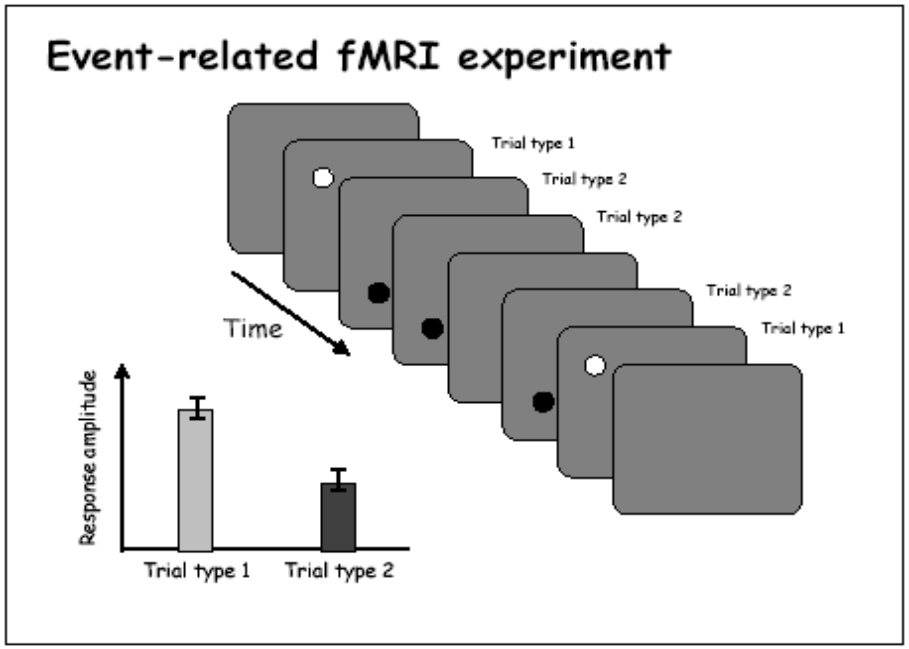
$$y = Xh + n$$

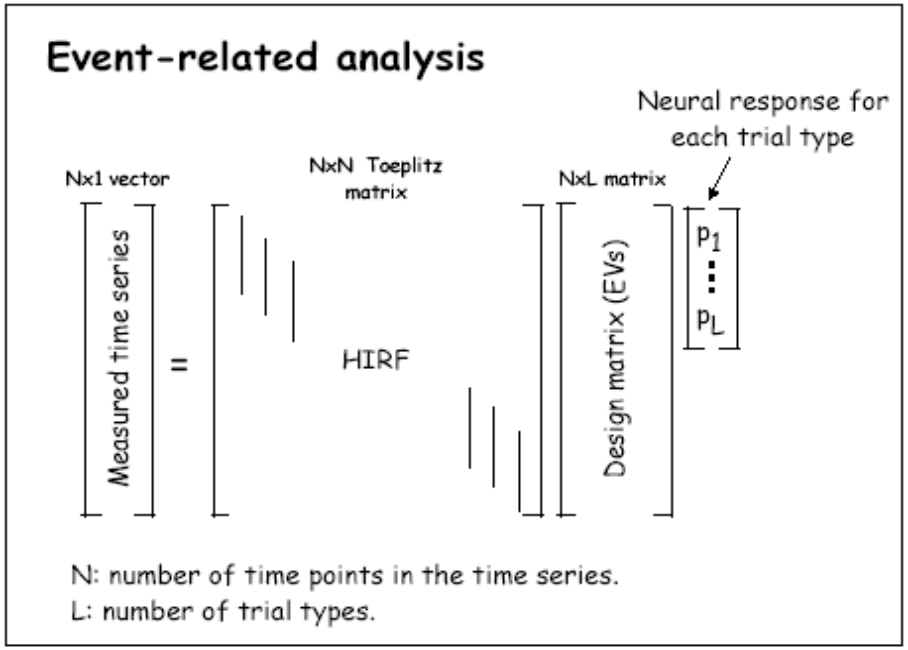
y: measured fMRI response
X: convolution (design) matrix
h: HRF vector

if X = [X1 X2 .. Xn]
h = [h1
:
hN]

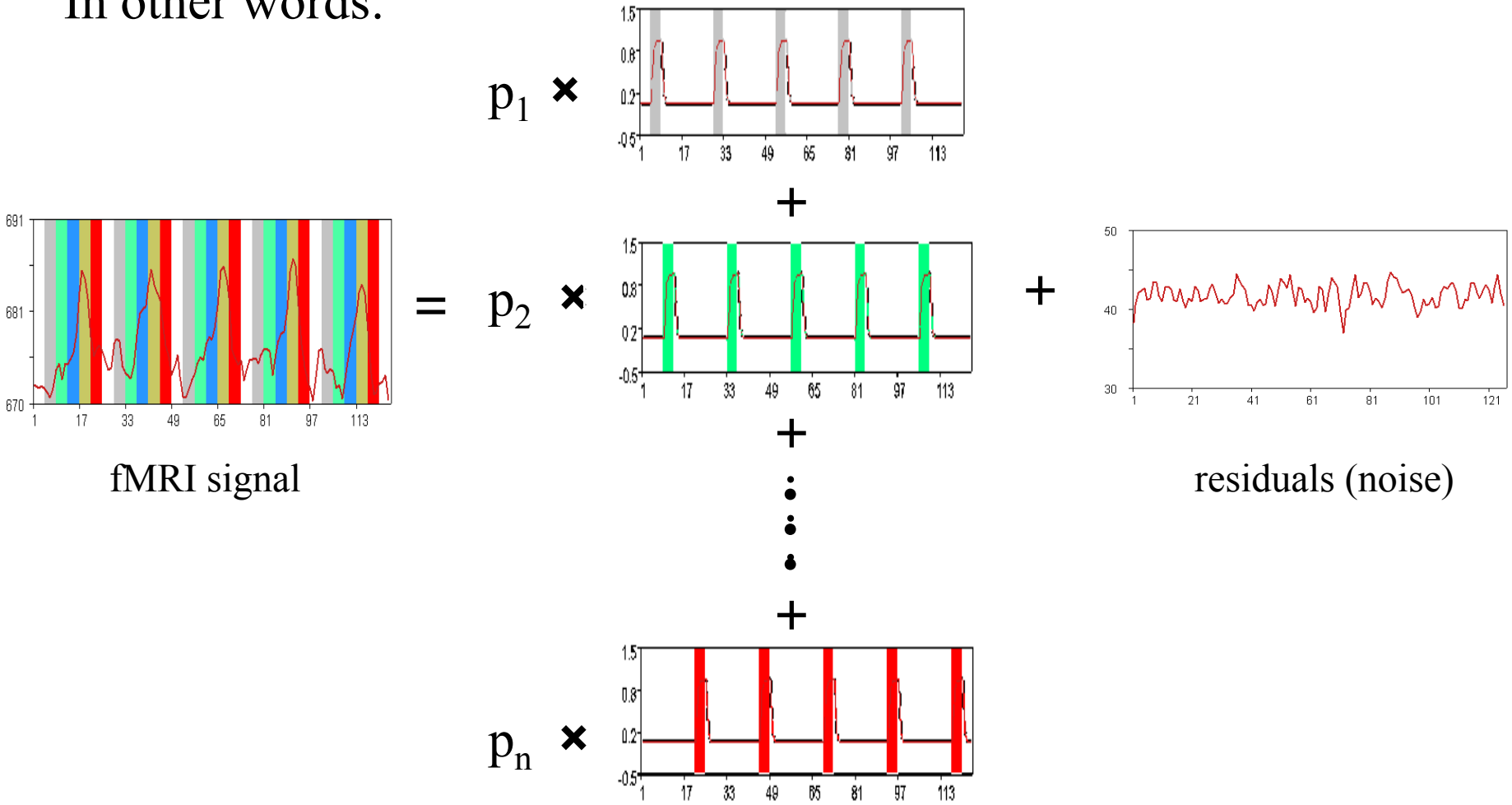
y = Xhp or y = **X**p where ***X*** is the convolution of the known design matrix with the assumed HRF

p: the amplitude of the neural response / weight of the regressor / beta parameter



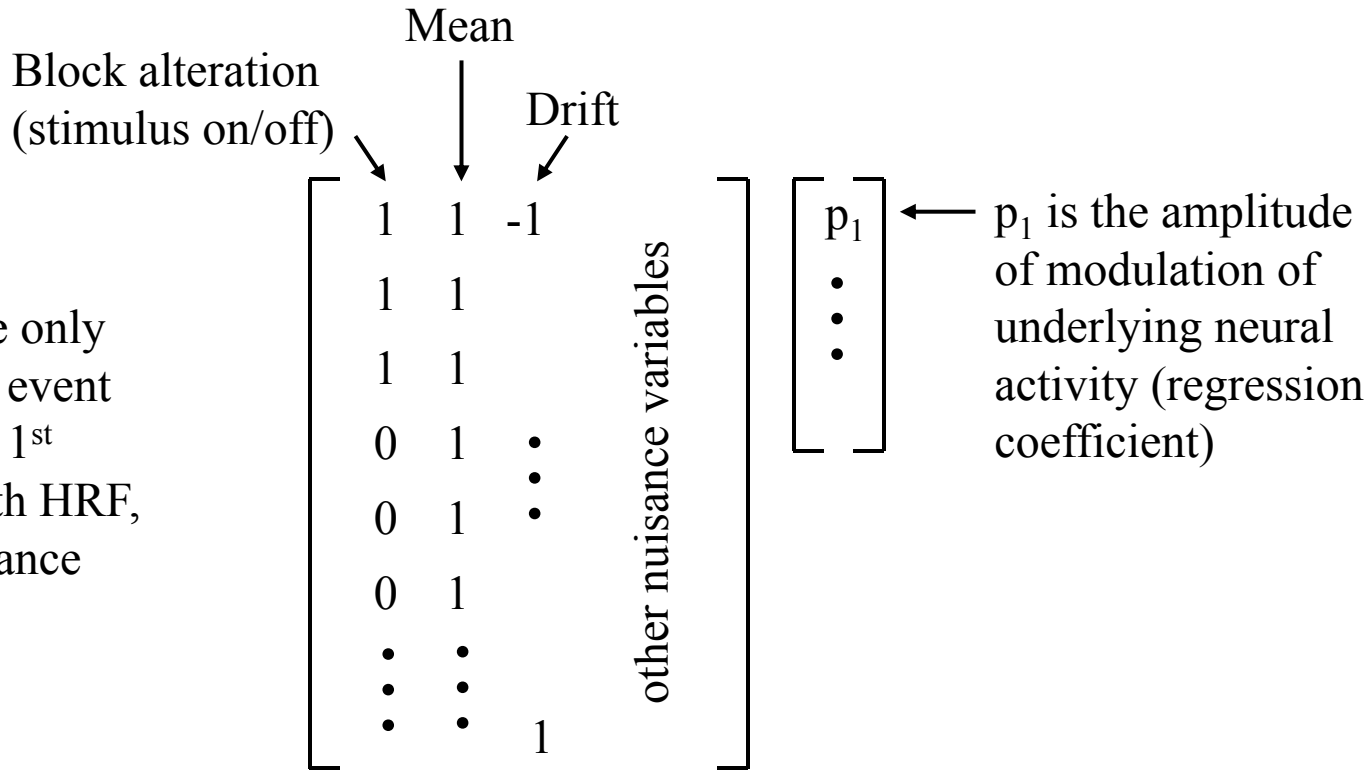


In other words:



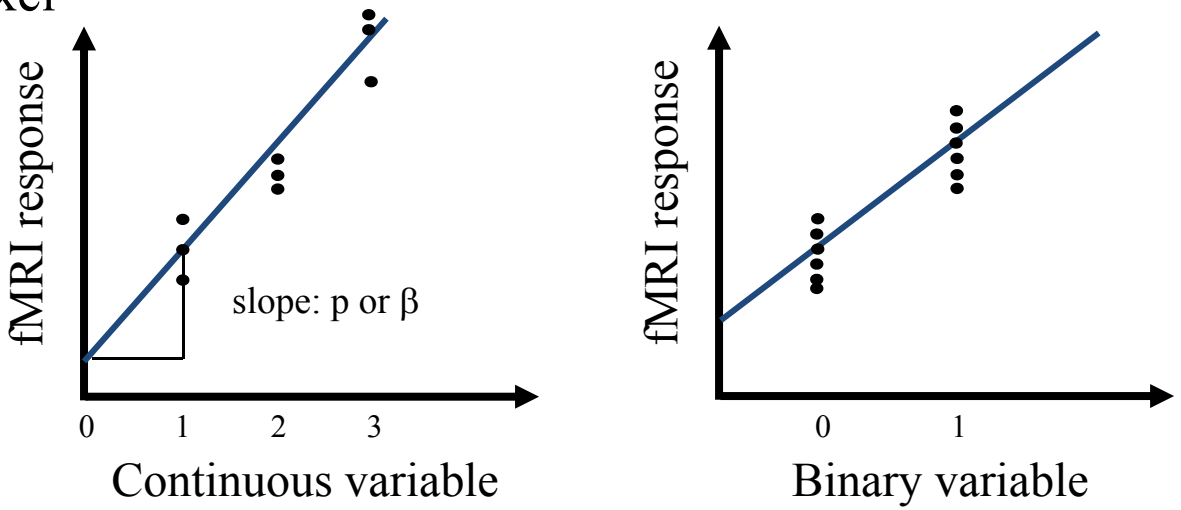
Design Matrix

- in a simple case (block design, one type of event only)



What is *p* (regression coefficient)?

- p or beta (β) is the slope of the regression line that relates the values of the experimental variable to the measured fMRI response to the variable in a given voxel



- Continuous regressor –also called a covariate – contain quantifying exp. variable (e.g. stimulus contrast), while a binary regressor contain distinguishable exp. conditions (e.g. on/off)

To solve, find p to satisfy

$$\vec{y} = X\,\vec{p}$$

p is the product of the measured signal *y* with the pseudoinverse of ***X*** ($\mathbf{X}^{\#}$)

$$\vec{p}_{opt} = X^{\#}\,\vec{y}$$

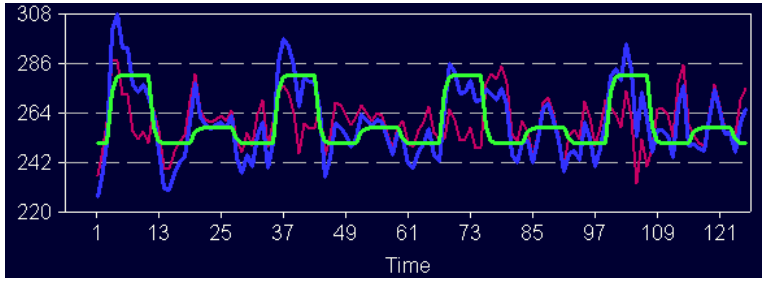
$$X^{\#} = (X^{T}X)^{-1}X^{T}$$

- Advantages:
  - estimation can be done even with superposing fMRI responses
  - noise is accommodated in the model
- Limitations:
  - each event type is estimated with a single *p* parameter
  - GLM approach assumes that the shape of the HRF is identical (canonical HRF) to each event type and at every area in the cortex

Steps in a GLM Analysis

- Defining the regressors (i.e. the design matrix) to model:
  - presentation time, or properties of the stimuli
  - noise parameters (drift, head motion)
  - behavior (performance) of the subjects
- Model fitting
  - determine the regressor coefficients (e.g. by least-squares estimation)
  - estimate the goodness of fit by determining the residuals (the difference between the actual measured signal and the predicted signal)
- Visualization
  - residual variance maps to visualize goodness of fit
  - t-maps to visualize the contrast between two regressors
  - bar diagrams of regressor coefficients (beta values) extracted from a cortical area (ROI analysis)

GLM Summary



Model

$$y = X * p + \varepsilon$$

Observed data:	Design matrix:	Parameters:	Error:
y is the fMRI (BOLD) signal at various time points at a single voxel (GLM treats each voxel as a separate column vector of data).	Several components which explain the observed data, i.e. the BOLD time series for the voxel convolved with the shape of the expected BOLD response over time (HRF). Includes timing info: onset and duration vectors, other regressors, e.g. realignment parameters.	Define the contribution of each component of the design matrix to the value of ***y***. Estimated so as to minimize the error ***ε***, i.e. least sums of squares.	Difference between the observed data, ***y*** and that predicted by the model, ***Xp***. Not assumed to be spherical in fMRI.

Goodness of fit

- it can be quantified how much the model accounts for the variance in the measured data:

$$r^2 = 1 - \frac{\mathrm{var}[data - model]}{\mathrm{var}[data]}$$

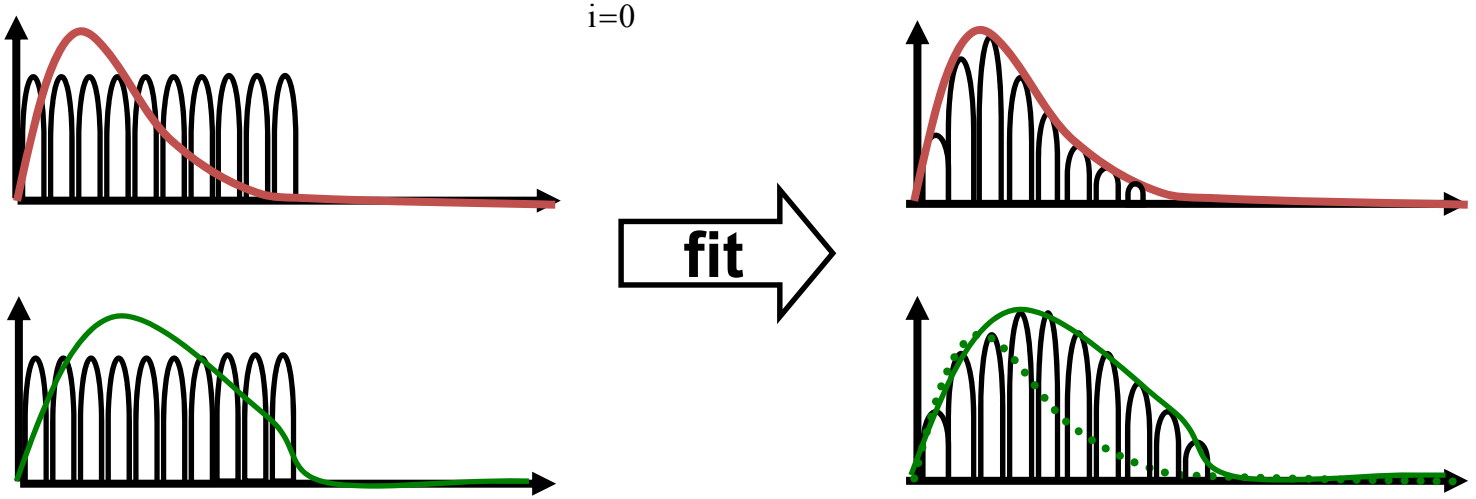
- crucial to determine how well the given parameter estimate describes the fMRI response in that specific condition (or it is just a result of a noisy data)
- a statistical test is needed that does not depend on the perfect fit of the model → *randomization test* (similar to bootstrapping the data)

Finite Impulse Response (FIR) Filter

… an alternate way to estimate the underlying HRF

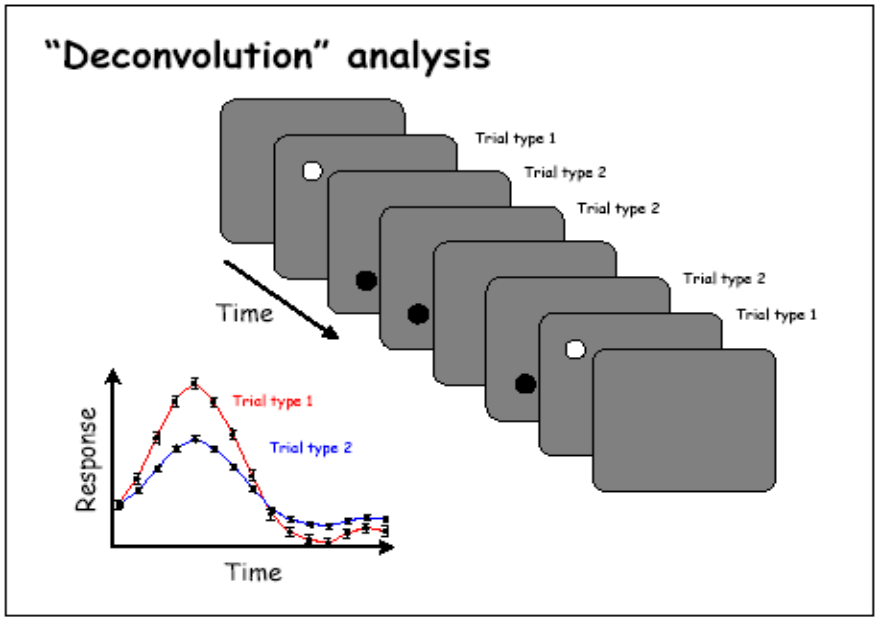
- fits data with many finite impluse responses
- however, it is sensitive to overfitting: to fit to the noise in that particular dataset/condition

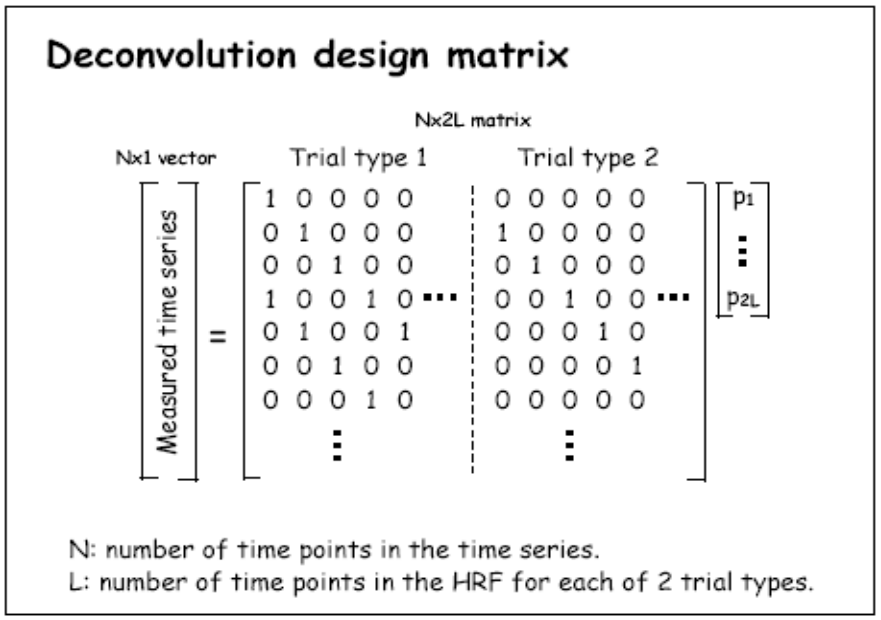
$$y(n) = \sum_{i=0}^{N} b_i \delta(n-i) + \varepsilon$$



Deconvolution Analysis based on FIR model

$$y = Xh$$





- instead of estimating one parameter per condition, the aim is to estimate the whole HRF seperately for each condition
- therefore, it can only done reliably when the number of conditions is low

HRF optimization

To solve, find vector *h* to satisfy

$$y = Xh$$

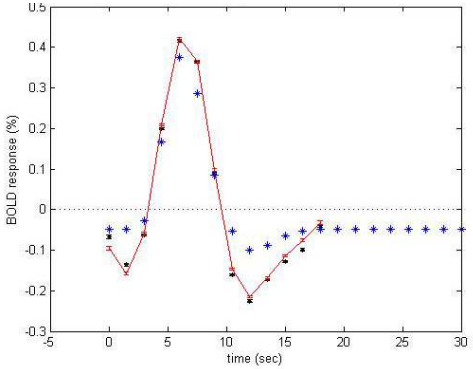
- h can be obtained via „deconvolution” analysis using a non-linear regression method:
  - start out with a canonical HRF, convolve it with the design matrix to get an estimated signal (model)
  - compare measured signal to model and calculate the least-squares error

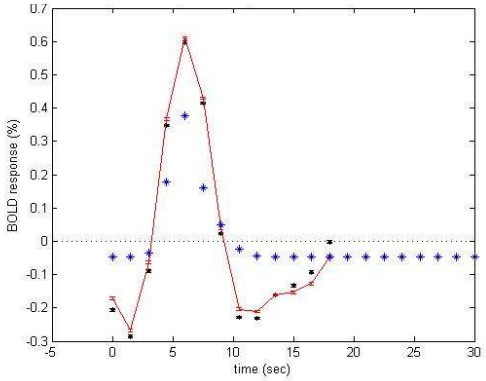
$$R^2 = \sum_{i=1}^{n} [y_i - f(x_i, \alpha_1, \alpha_2, \ldots, \alpha_n)]$$

  - change the parameters of the HRF to minimize the error

HRF can slightly differ between subjects and areas

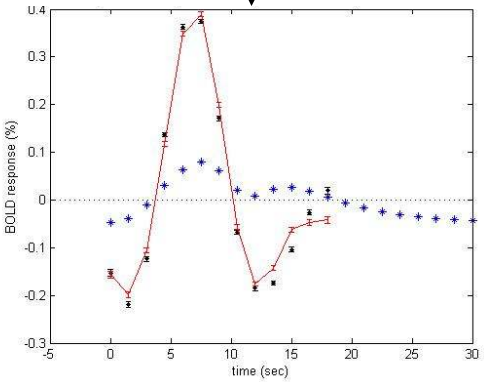
Subj 1 – V1





Subj 1 – V4

- measured signal
- fitted HRF

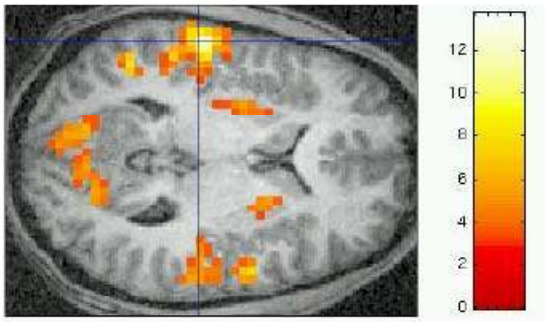


Subj 2 – V4

Why bother to estimate HRF anyway?

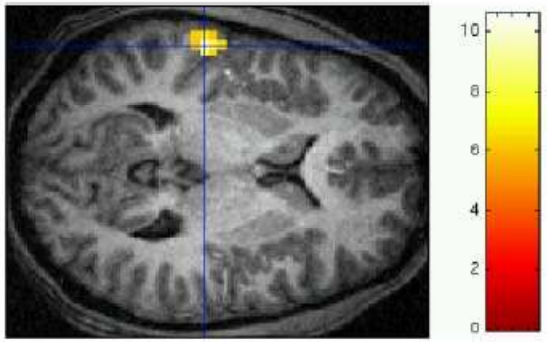
- better sensitivity → improved detection

GLM built using HRF estimate →



more sensible:
bilateral activation
in Heschel gyrus for
(sound-silence)

GLM built upon canonical HRF →

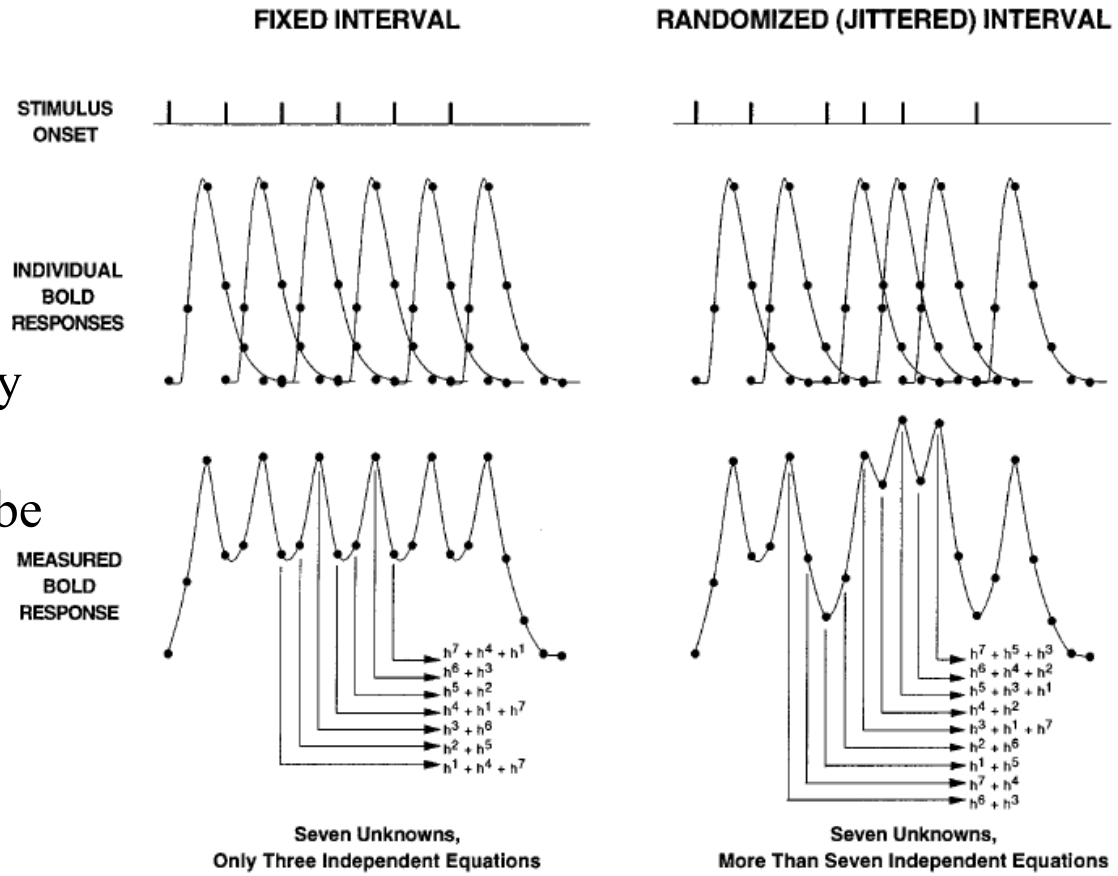


(Ciuciu et al., 2002, 1st Int. Symp. on Biological Imaging)

BUT in order to do so…

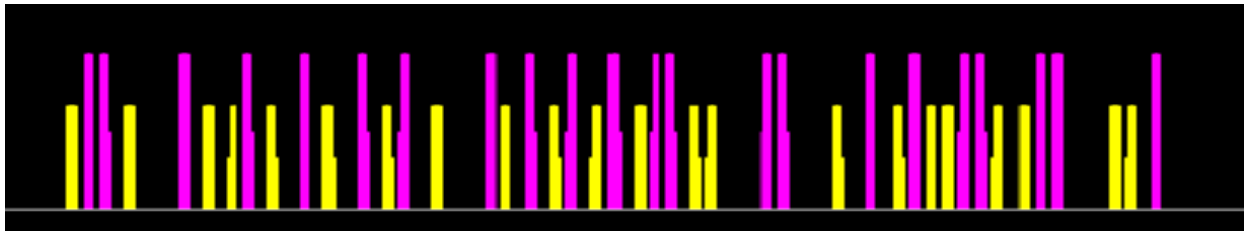
- reasonable SNR is needed
- the design needs to be efficient and random (i.e. jittered intervals and randomized event order) so that the event are linearly independent
- the design matrix needs to be invertible to solve for the parameters

(applies to all experiments)

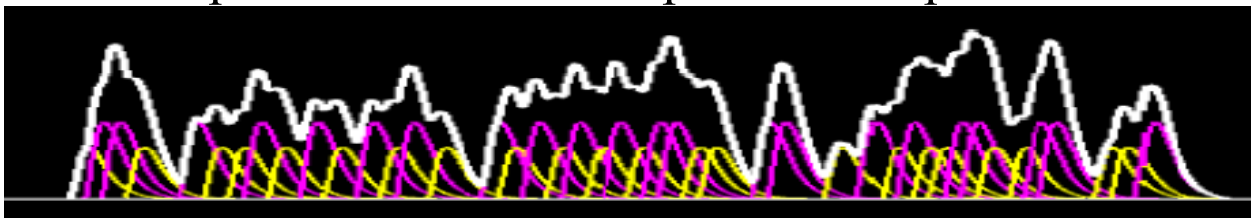


An example…

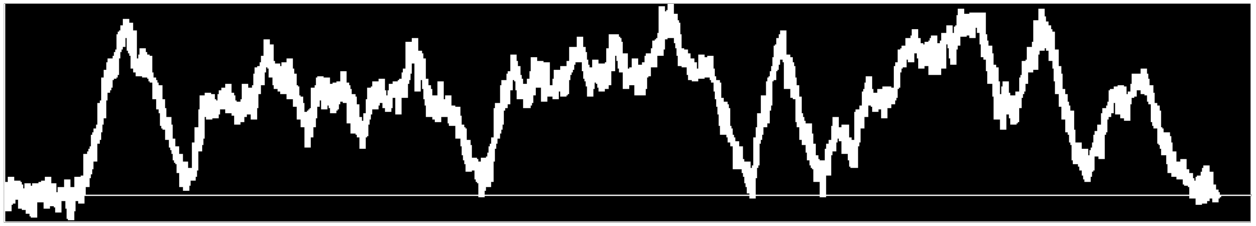
Event (stimulus) sequence



Model: separate and summed up BOLD responses



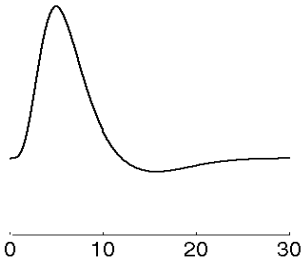
Measured BOLD signal

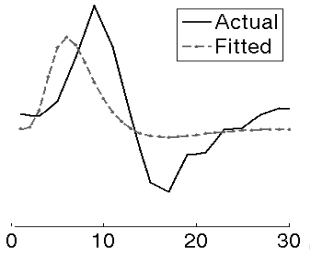


The ultimate goal is to model the data the best possible way

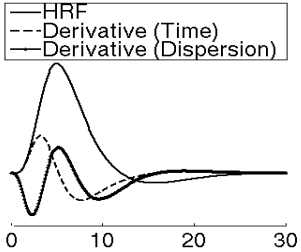
Basis Functions

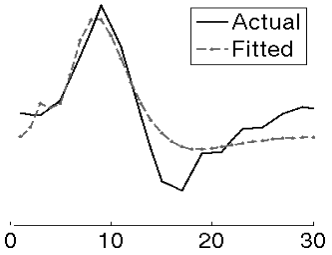
Single HRF



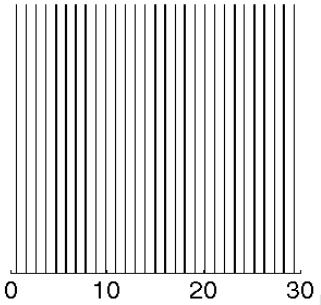


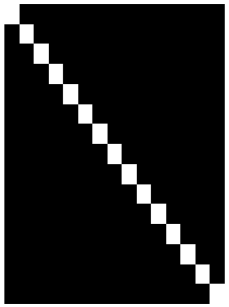
HRF + derivatives

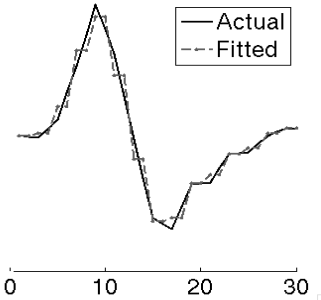




Finite Impulse Response (FIR)





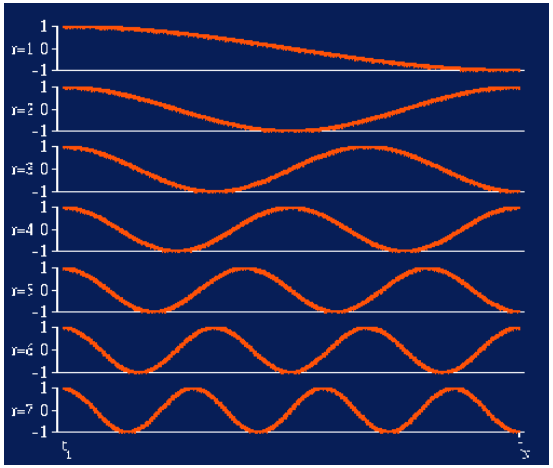


Time (s)

Modeling Noise - "Nuisance Variability"

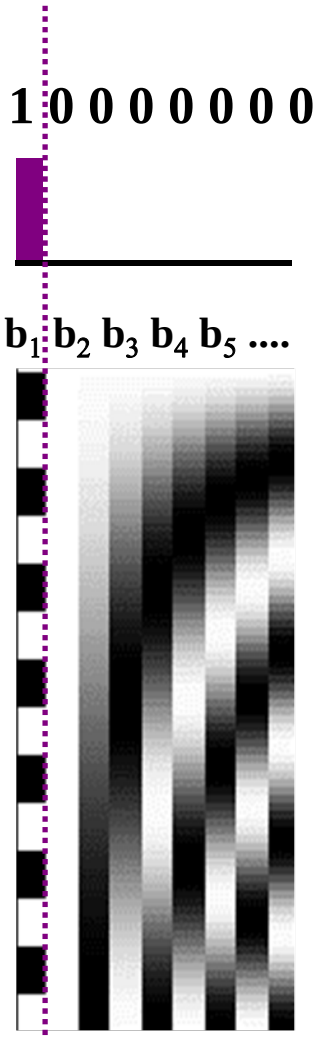
- if not modeled:
  - specificity decreases (due to underestimating variance and increasing the number of false positives)
- types:
  - drift (slow change):
    - can be linear or quadratic
    - denoising: discrete cosine transform (DCT)
  - autocorrelation:
    - fast, periodic autoregressive signals
    - elimination: AR(1): old + new noise

ARMA(1,1): AR + a series of independent white noise



DCT base functions

Parametric maps



F-test

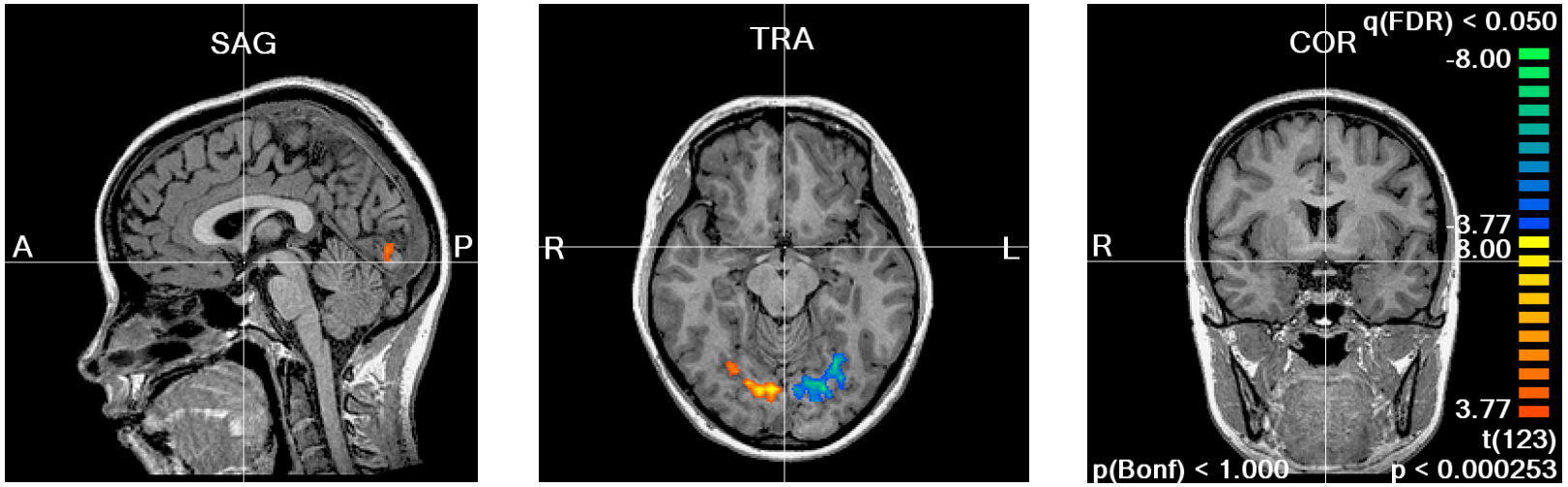
- compare the residuals with and without including one of the explanatory variables to see if it accounts for a statistically significant portion of the variance of the data. The ratio of the variance estimates follows the F distribution.

T-test

- define contrast (*c*) as a linear combination of parameter estimates and divide by their variance
  (e.g. $c=1*b_1 + 0*b_2 + 0*b_3 + \ldots$)

T-test example

$c=1*b_1+ -1*b_2$



Experimental Design

- Block design
  - a sequence of longer periods of a fixed type of stimulation and rest intervals
  - simple, robust, high SNR
  - unnatural, rigid frame for doing experiments
- Event-related design (fast or slow)
  - similar to EEG experiments
  - requires more complex statistics
  - yields smaller SNR therefore requires more repetition
  - more flexible, natural experimental frame
  - event spacing needs to be jittered and event sequence randomized