



Inverse problems in functional brain imaging

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1: CEA/NeuroSpin/LNAO

2: IFR49

The logo for NeuroSpin, featuring the word "NeuroSpin" in a stylized font with a green circle containing a white dot.

The logo for LNAO, featuring a stylized brain and the letters "LNAO" in a bold, serif font.

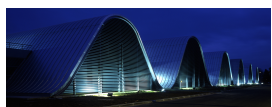
The logo for IFR 49, featuring a stylized head profile with a colorful brain scan image and the text "IFR 49" below it.

July 24, 2009

GDR -ISIS Summer school -Peyresq

Outline

- Introduction to functional brain imaging
 - Magneto/Electro-encephalography
 - functional MRI
- Mapping brain activity
 - GLM framework (Statistical Parametric Mapping)
 - Spatial regularization [VB optimization]
- Probe brain dynamics in fMRI
 - FIR modeling
 - Temporal regularization [EM/SAEM algorithms]
- Joint detection-estimation
 - Unify both questions
 - Spatio-temporal regularization [MCMC methods]





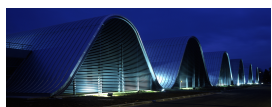
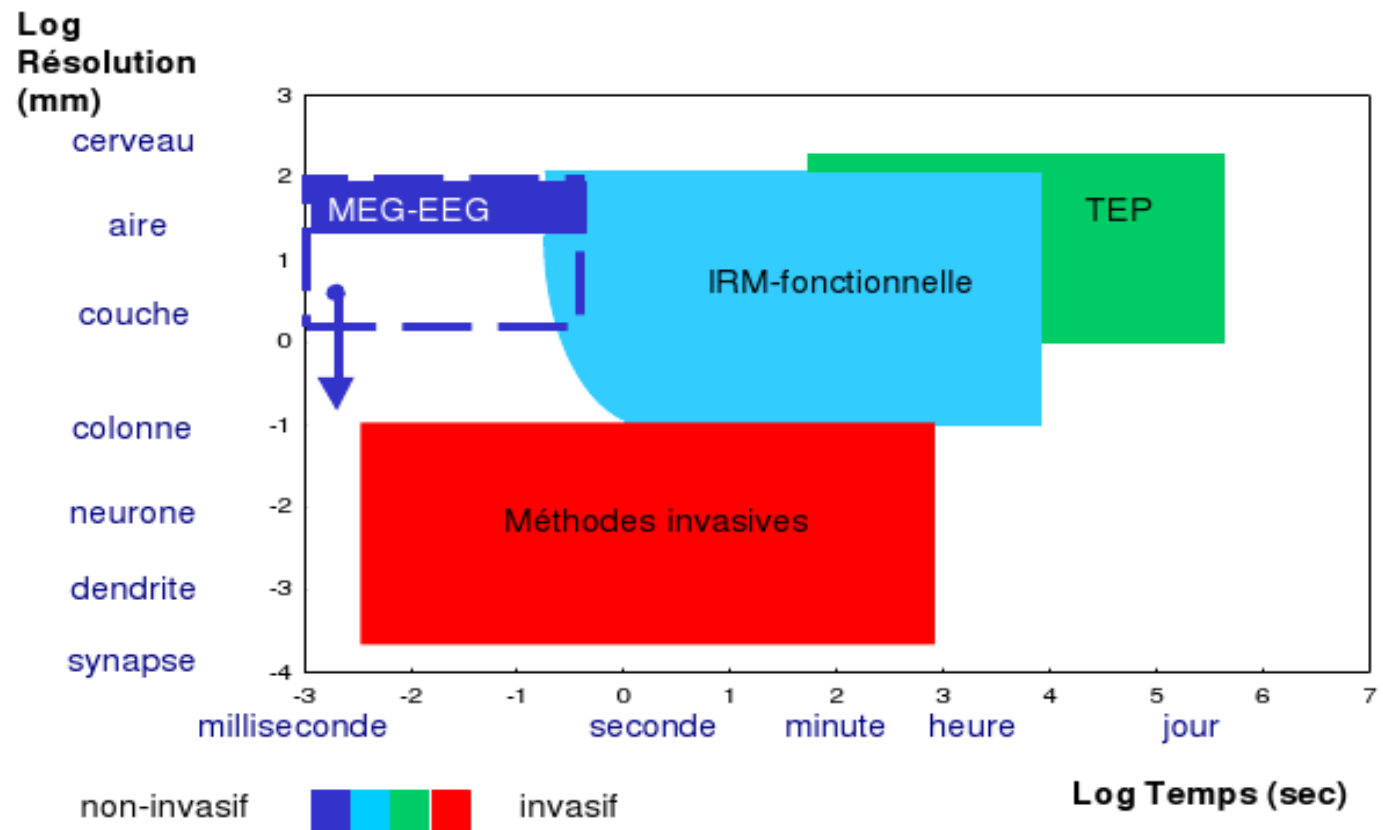
Functional brain imaging

Imagerie Fonctionnelle Cérébrale

- Etude du cerveau en action
- Nombreuses applications cliniques et en Sciences Cognitives
- À l'interface entre les Sciences de la Vie et les Sciences pour l'Ingénieur

Techniques

■ Où et Quand ?

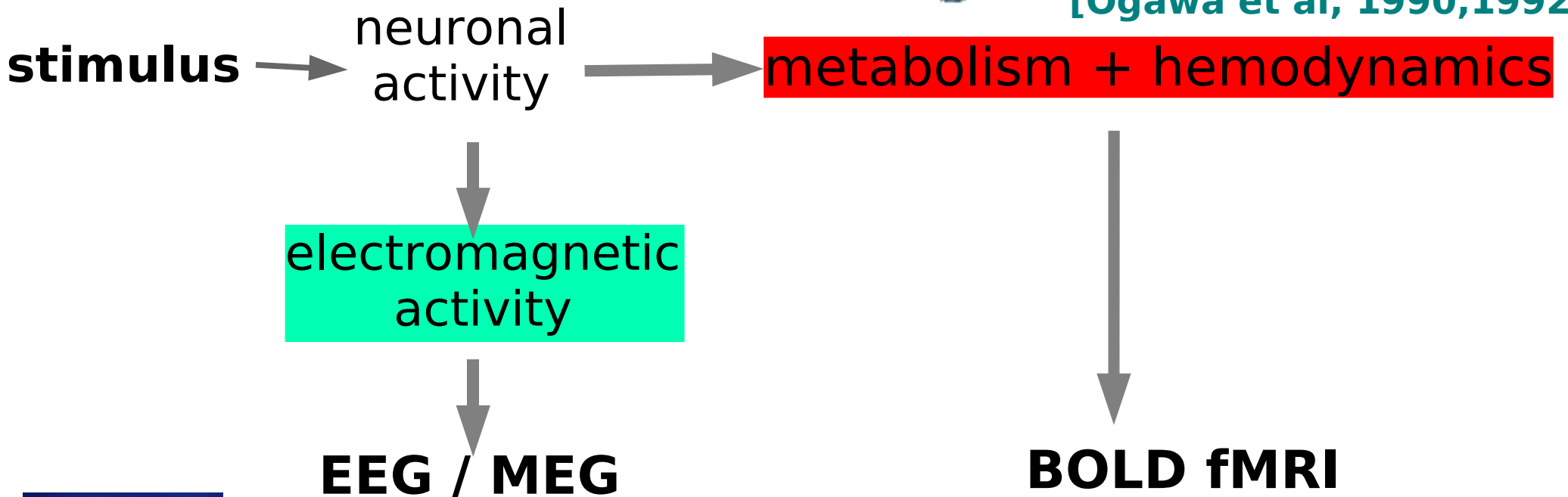


Functional brain imaging

Probe brain dynamics
non-invasively

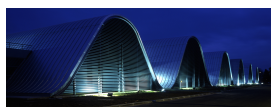


[Ogawa et al, 1990,1992]



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MEG/EEG

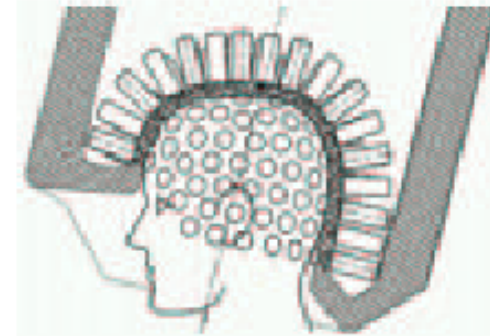
Électroencéphalographie (EEG)

Activité électrique neuronale

Résolution temporelle : $\sim 1\text{ms}$



Magnétoencéphalographie (MEG)



EEG : mesure du potentiel électrique

Ordre de grandeur : qq $\mu\text{-volts}$

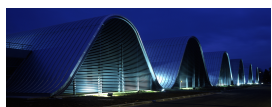
Capteurs : électrodes

MEG : mesure du champ magnétique

Ordre de grandeur : 10^{-13} Tesla

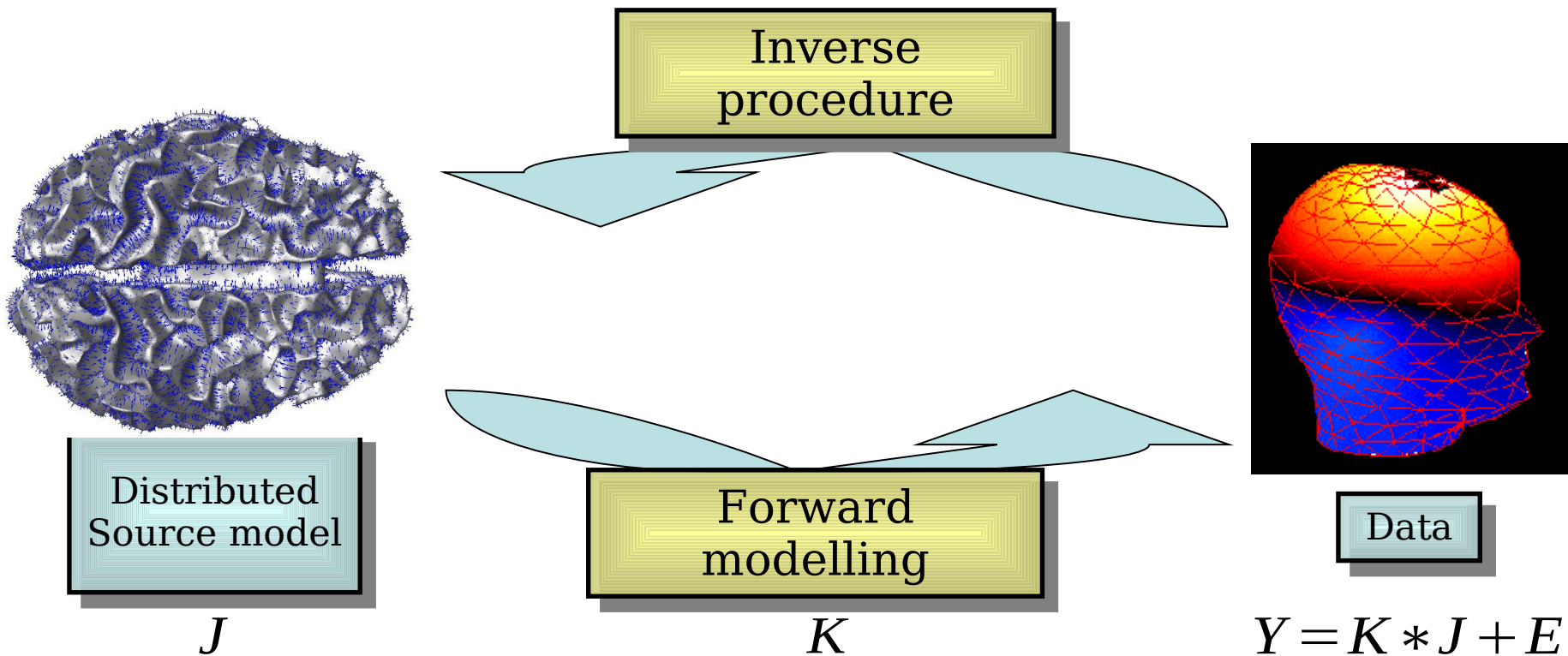
Capteurs SQUID couplés à des bobines

Posthumous honor to Line Garnero





MEG/EEG source reconstruction



$$Y = KJ + E$$

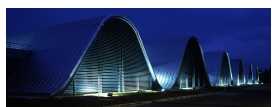
[nxt] [nxp|pxt] [nxt]

n : number of sensors
p : number of dipoles
t : number of time samples

- under-determined system
- priors required

Bayesian
framework

[Mattout et al., Neuroimage, 2006]





MEG/EEG source reconstruction



$$p(J|Y) \propto p(Y|J) p(J)$$

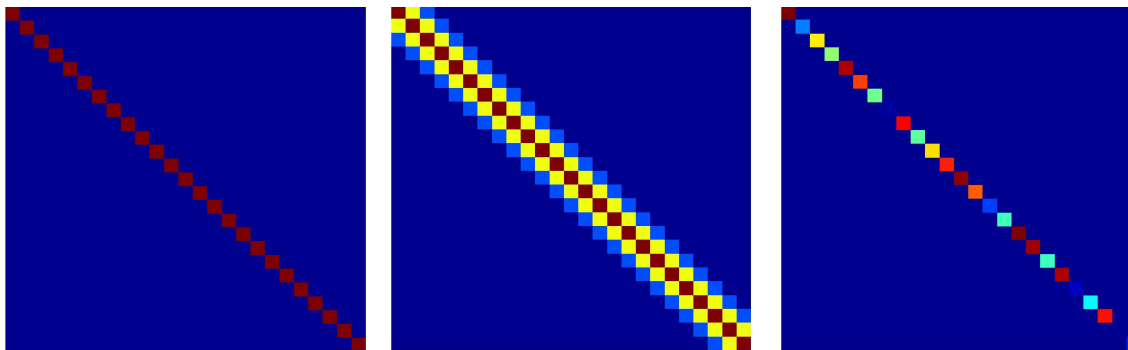
$$U_{MAP}(J) = \underbrace{\|C_e^{-1/2}(Y - KJ)\|^2}_{\text{likelihood}} + \underbrace{\lambda \|WJ\|^2}_{\text{WMN prior}}$$



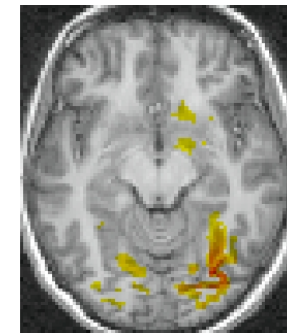
$$p(J) \sim N(0, C_j) \quad C_{j-1} = \lambda W^T W$$

2-level hierarchical model:

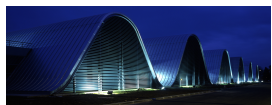
$$\begin{aligned} Y &= KJ + E_1 & E_1 &\sim N(0, C_e) \\ J &= 0 + E_2 & E_2 &\sim N(0, C_p) \end{aligned}$$



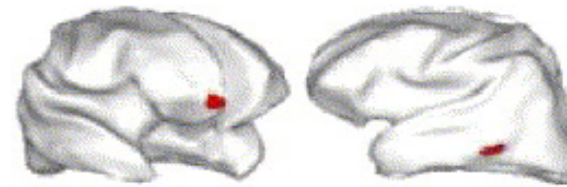
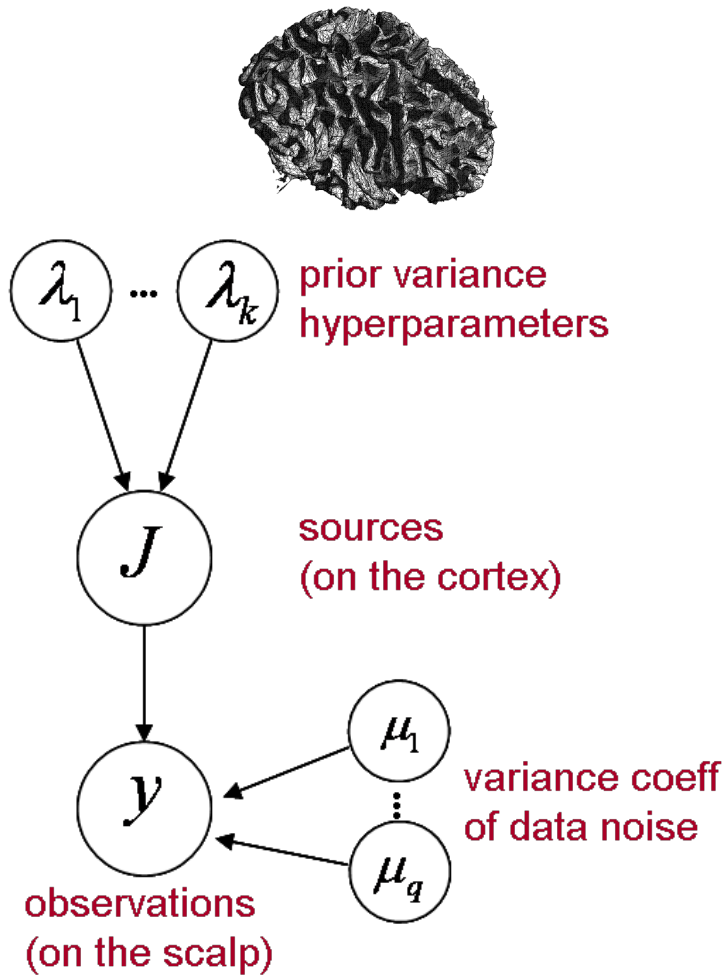
minimum norm smoothness prior functional prior



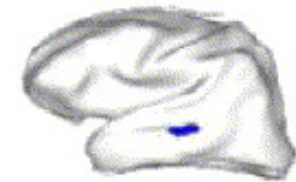
[Mattout et al., Neuroimage, 2006]



MEG/EEG source reconstruction



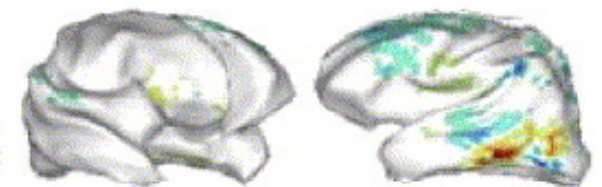
(a) Source locations



(b) Invalid prior location



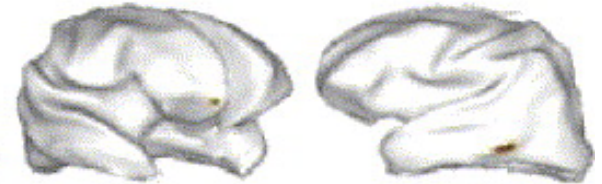
(c) WMN solution under the smoothness prior



(d) ReML solution under the smoothness prior

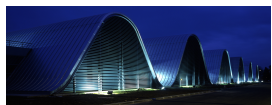


(e) ReML solution under the smoothness and valid priors



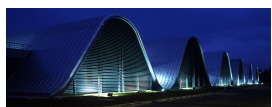
(f) ReML solution under the smoothness, valid and invalid priors

[Mattout et al., Neuroimage, 2006]



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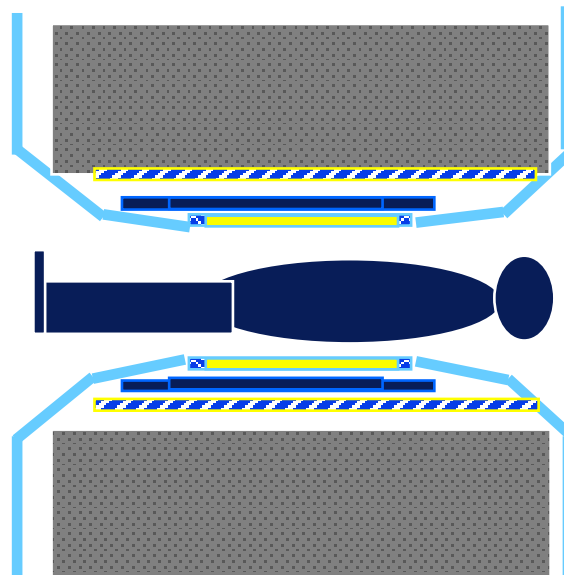
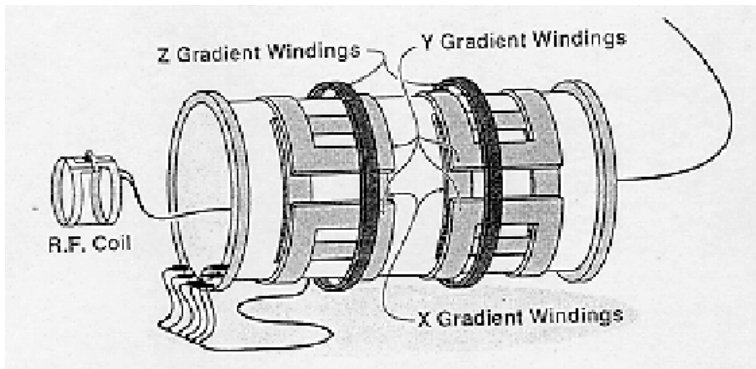


Magnetic Resonance Imaging



⇒ High magnetic field

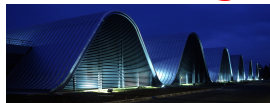
3T



⇒ Émetteur/récepteur RF



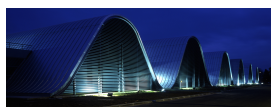
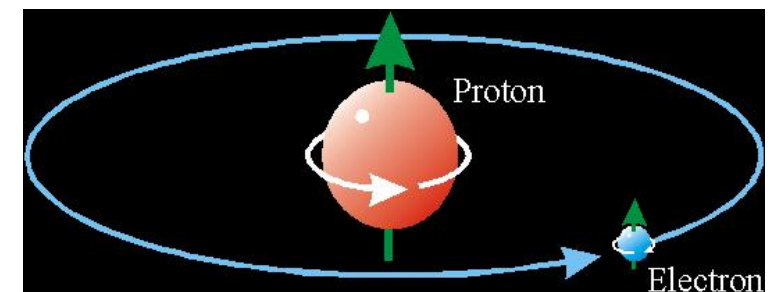
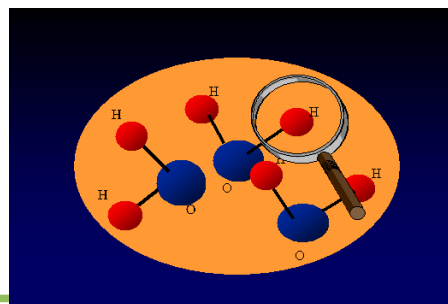
⇒ Auxiliary coils: the « gradients »



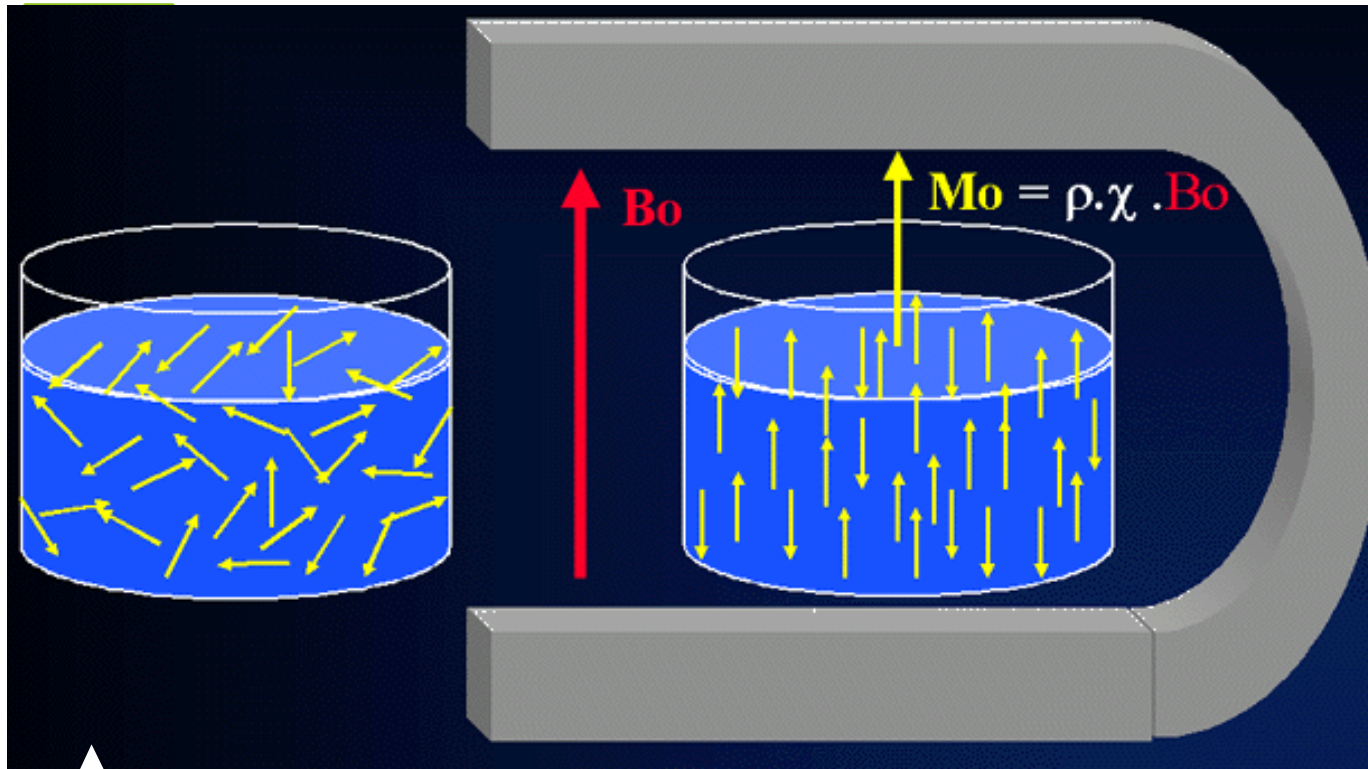
Atomes en RMN

Éléments	Abondance biologique	Eléments Utilisé en RMN	Symbole	Abondance dans le corps humain
Hydrogen (H)	0.63	Hydrogen	^1H	99.985
Sodium (Na)	0.00041		^2H	0.015
Phosphorus (P)	0.0024	Carbon	^{13}C	1.11
Carbon (C)	0.094	Nitrogen	^{14}N	99.63
Oxygen (O)	0.26		^{15}N	0.37
Calcium (Ca)	0.0022	Sodium	^{23}Na	100
Nitrogen (N)	0.015	Phosphorus	^{31}P	100
		Potassium	^{39}K	93.1
		Calcium	^{43}Ca	0.145

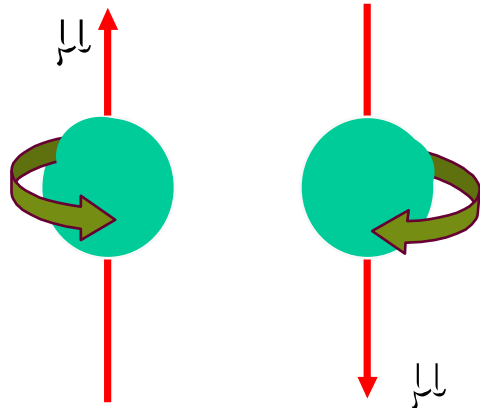
Choix des **protons des atomes d'hydrogène** de l'eau pour l'imagerie



Choix de l'aimant statique



Alignement des moments magnétiques suivant 2 directions:

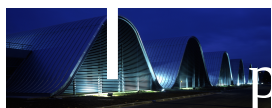


- direction parallèle: orientation dans la direction de B_0
- direction antiparallèle: orientation dans la direction opposée à B_0

Mouvement de précession

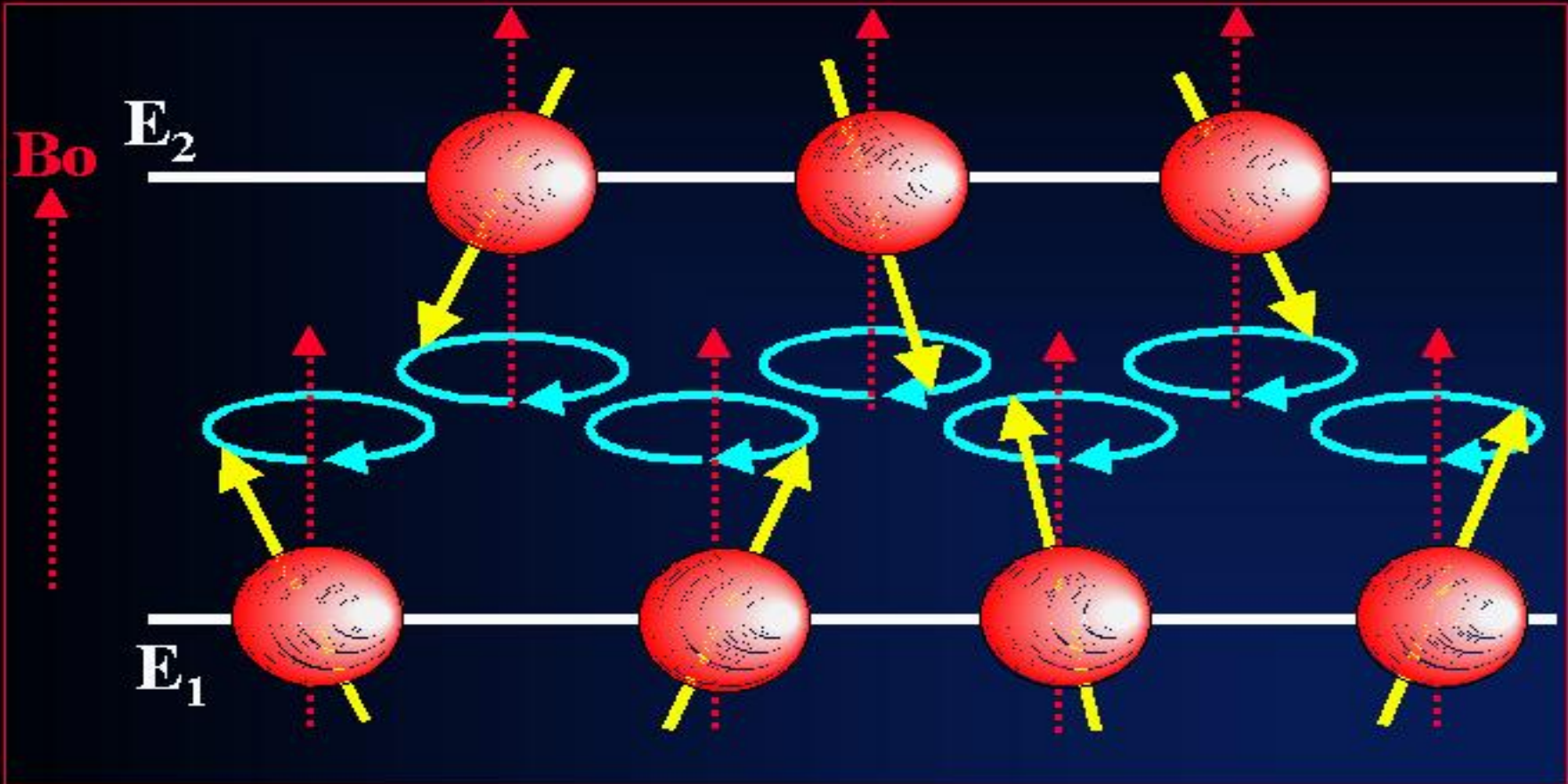
$$\omega = \gamma B$$

Pour les protons 42.58 MHz/T



Spins des protons

Les deux états d'énergie magnétique du noyau d'Hydrogène



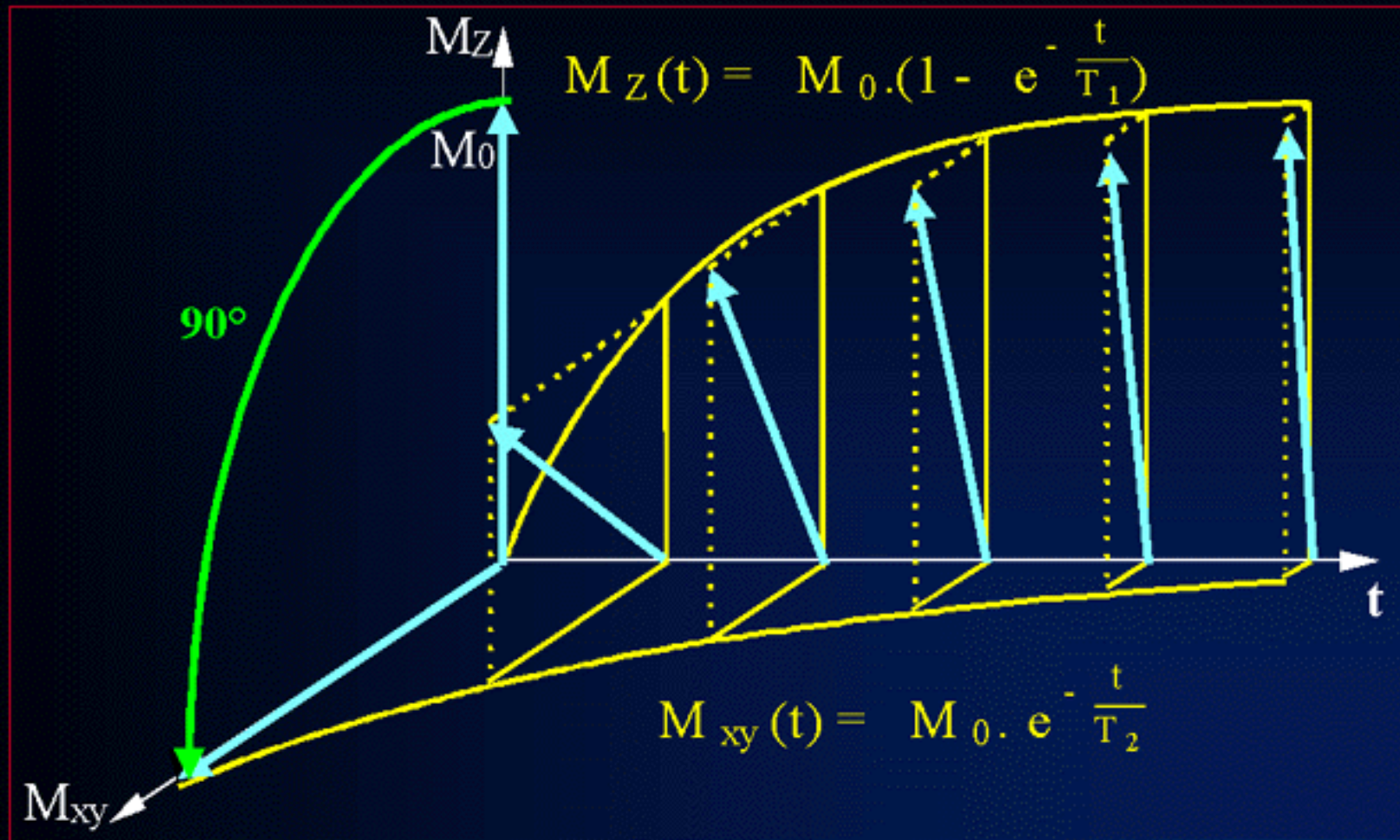
en présence d'un champ magnétique B_0



Phénomène de RMN

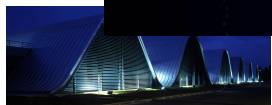
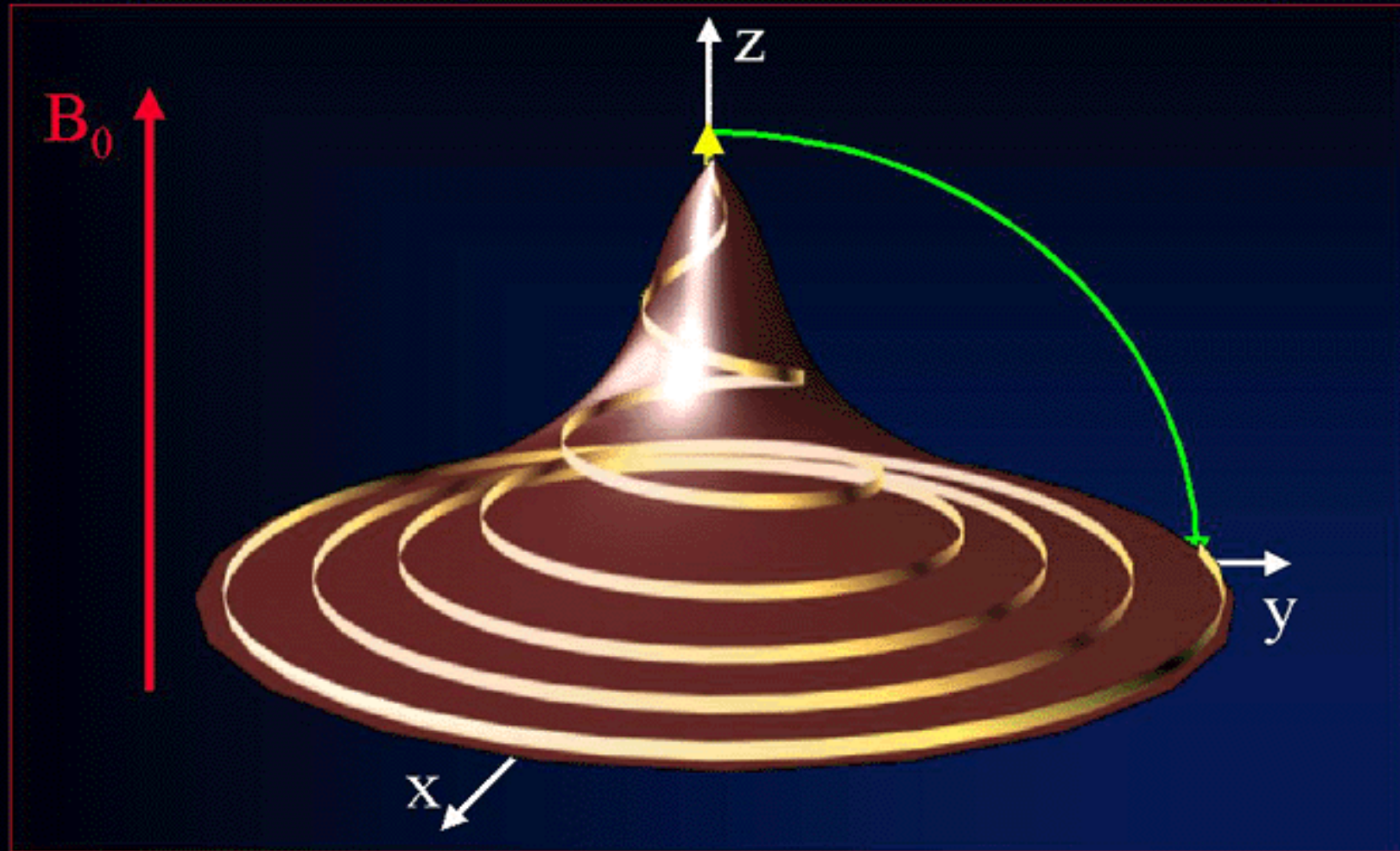


Relaxation



Phénomène de RMN

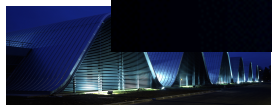
Retour à l'Equilibre de l'Aimantation Nucléaire



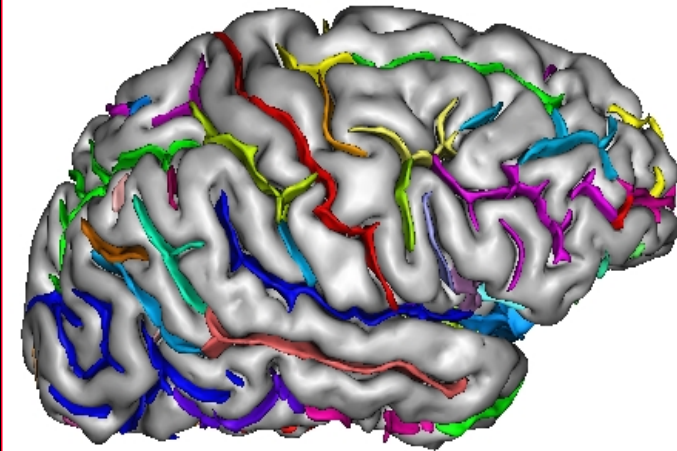
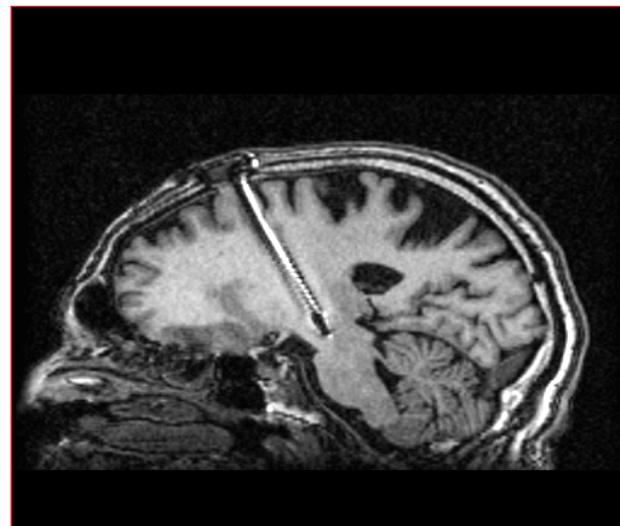
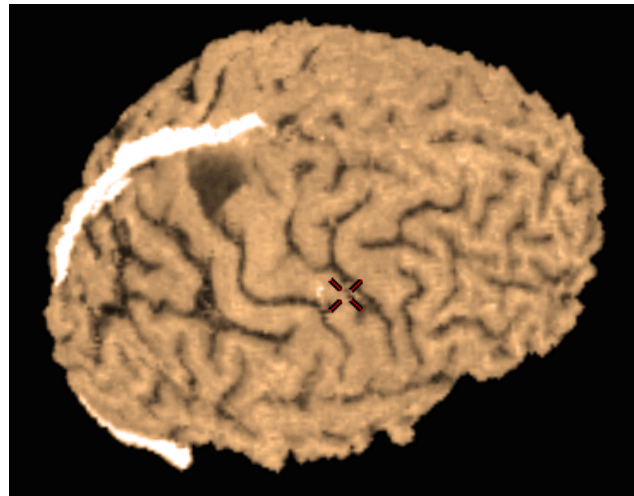
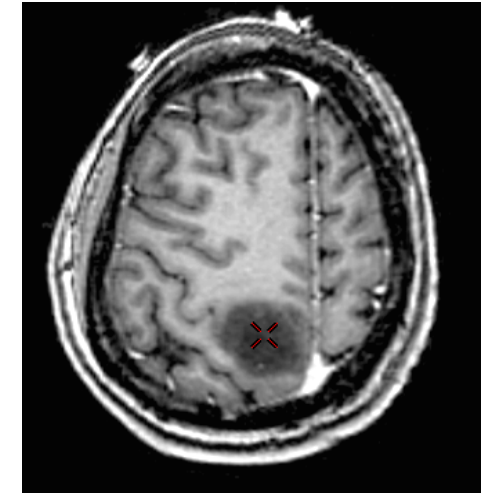
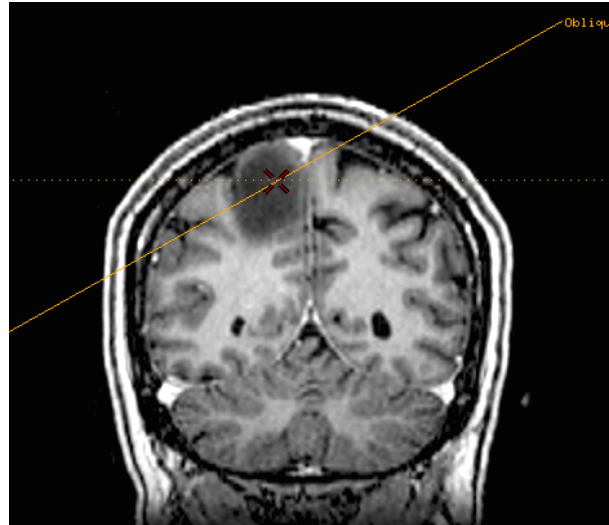
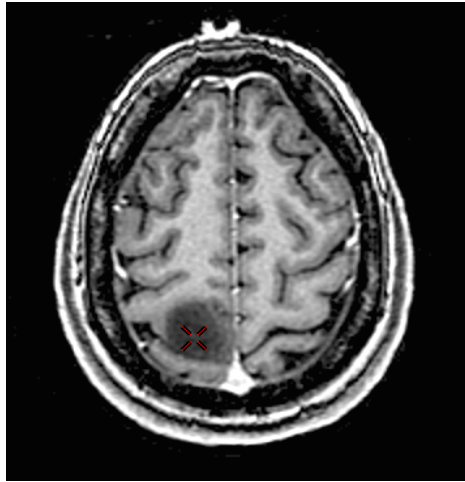
Temps de relaxation

Ordres de Grandeurs des Temps de Relaxation à 1,5 T

Temps de Relaxation Tissus Humains	T1	T2
Liquide Céphalo-rachidien	2500 ms	2000 ms
Substance Grise	900 ms	90 ms
Substance Blanche	750 ms	80 ms
Graisse	300 ms	40 ms



Anatomical MRI



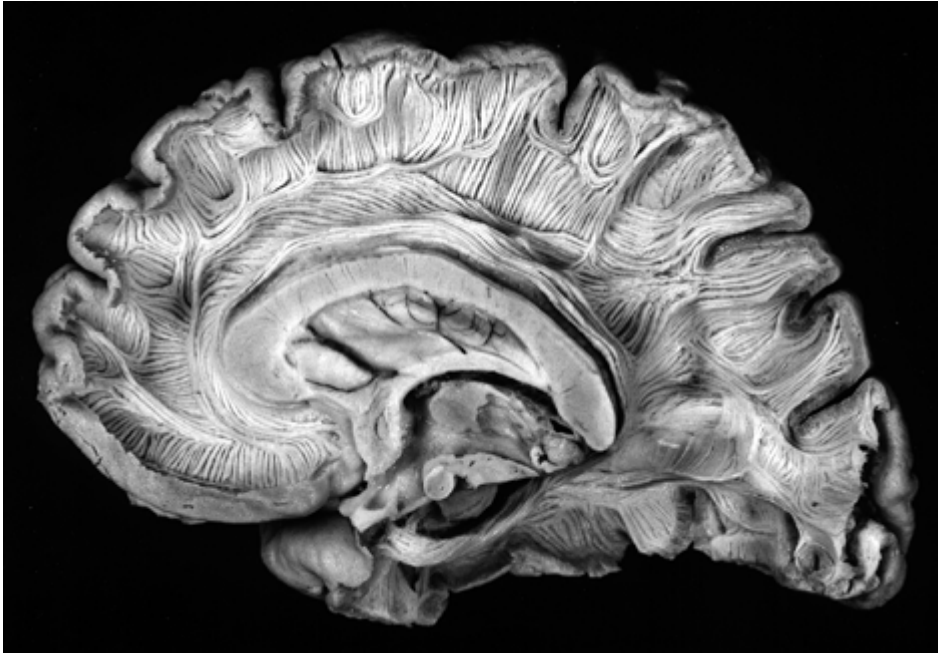
Brain tumor

Post-op checking

Sulci recognition



diffusion MRI



[Virtual Hospital, 1998]



[Elkouby, 2005]

- ✗ *in vivo* imaging of the water brownian motion
- ✗ Get access to the structural connectivity

Mouvement brownien
[Einstein, 1905]

Spectro diffusion
[Stejskal-Tanner, 1965]

IRM de diffusion
[Le Bihan, 1986]

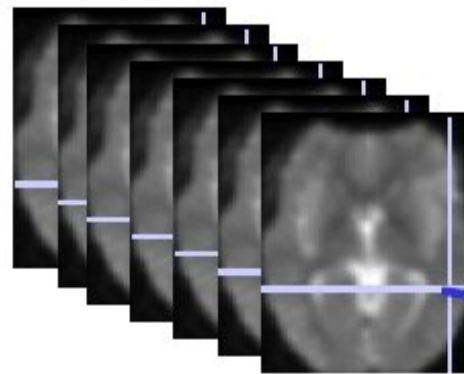
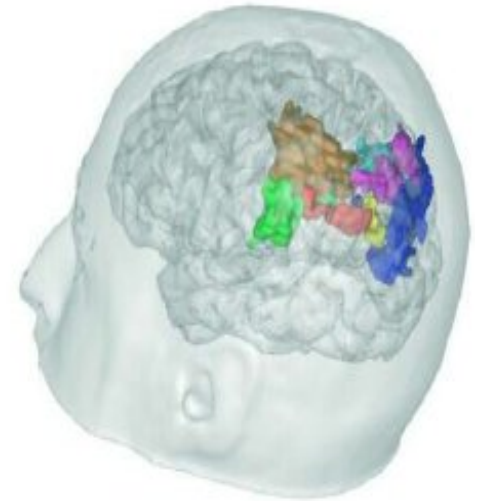
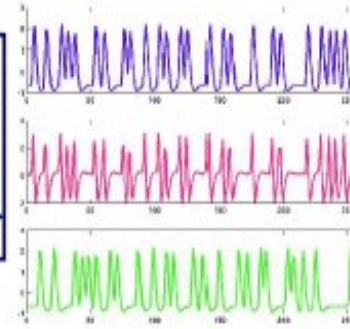


Functional MRI

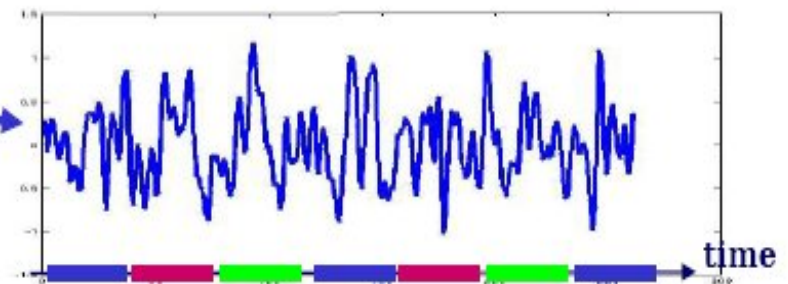
Neuronal activation



Experimental Paradigm



64x64x32x1000



Measured 4D signal :

BOLD = Blood Oxygenation Level Dependent signal

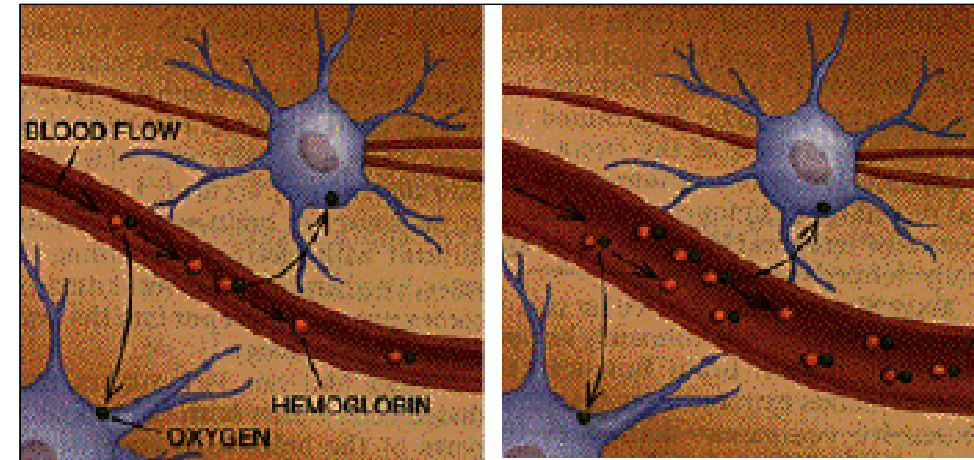


Le signal BOLD

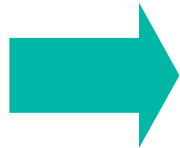
[Ogawa et al, 1990,1992]

Produit de contraste intrinsèque :
 Oxyhémoglobine (HbO₂) : diamagnétique
 Désoxyhémoglobine (Hb) : paramagnétique

Détectable en IRMf

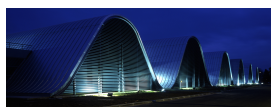
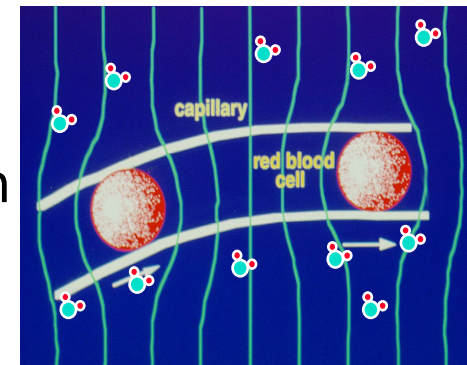


Activation
 cérébrale



Légère augmentation de la consommation
 O₂, accompagnée d'un fort afflux de sang
 oxygéné

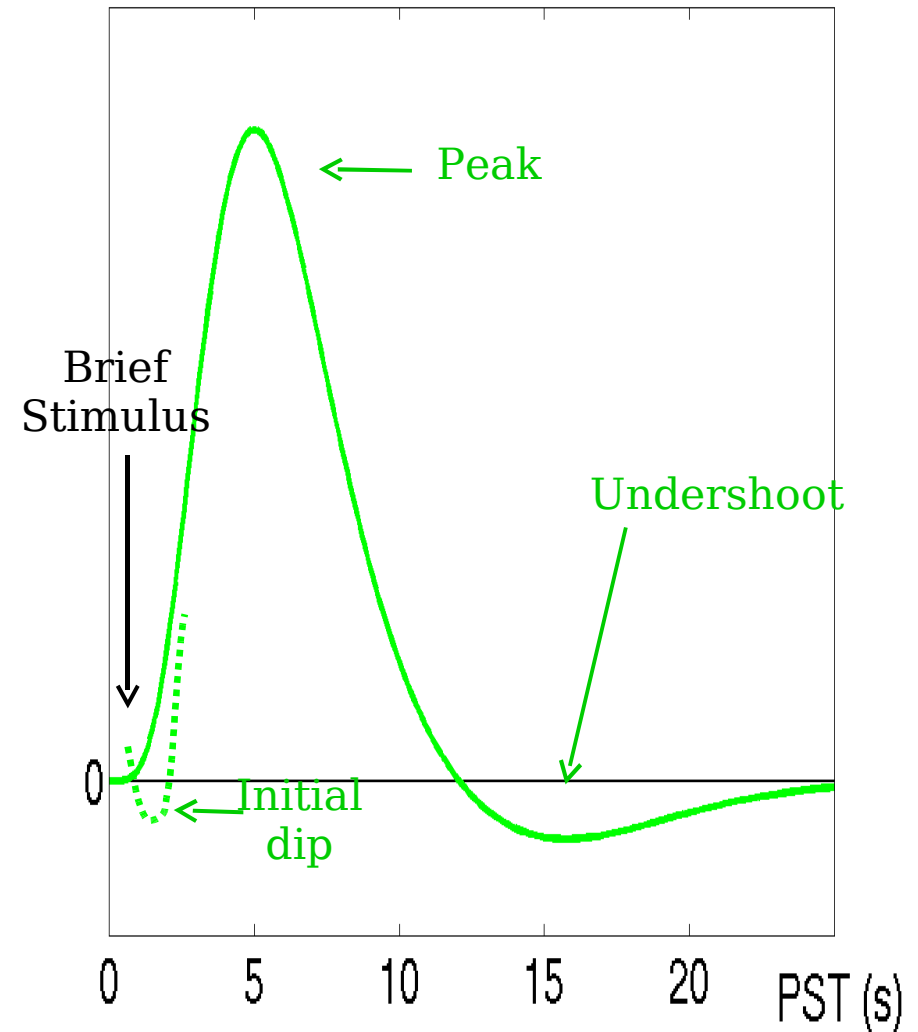
Conséquence : augmentation de la concentration
 en sang oxygéné (HbO₂) des vaisseaux proches
 des neurones actifs





Hemodynamic Response Function

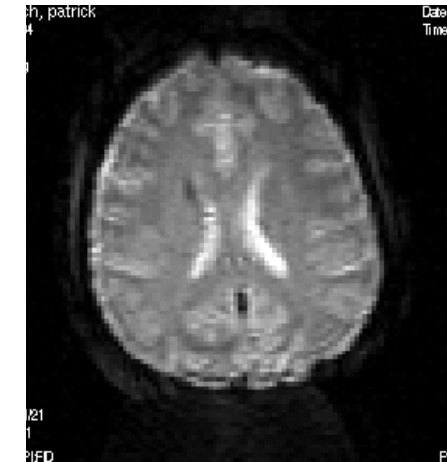
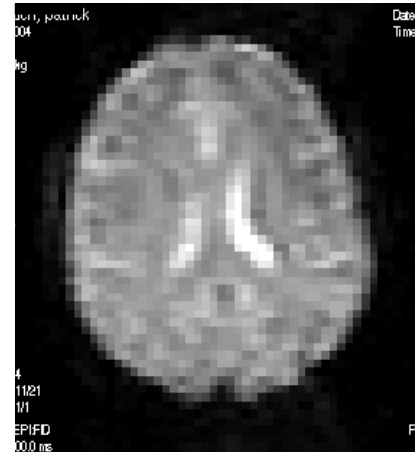
- Function of blood oxygenation, flow, volume [Buxton et al. 98]
- Peak (max. oxygenation) 4-6s poststimulus;
- Baseline after 20-30s
- Initial undershoot can be observed [Malonek & Grinvald. 96]
- ... but differences across: other regions [Schacter et al. 97]
- individuals [Aguirre et al. 98]



The truth about fMRI data

64x64 Pixels ~ 3 x 3 mm

128x128 Pixels ~ 1.5 x 1.5mm

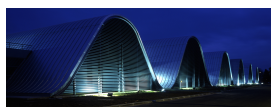
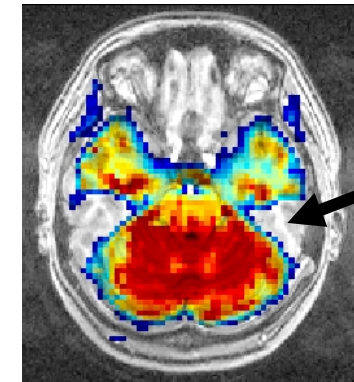
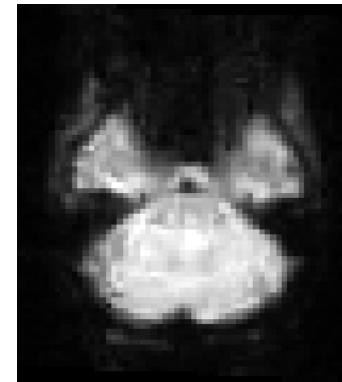
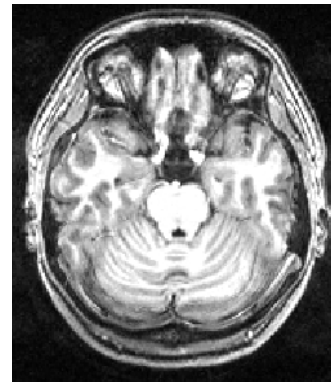


I. They are distorted

II. They are noisy

III. They don't have signal everywhere in the brain

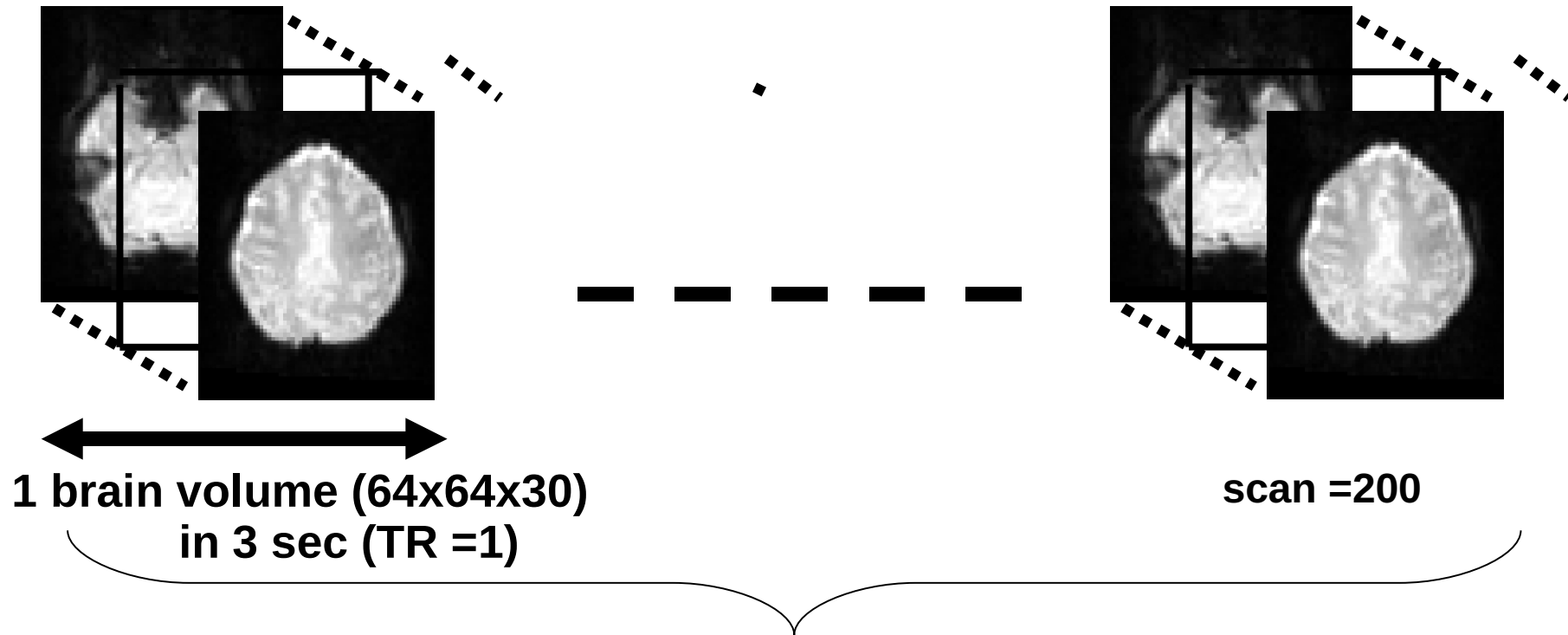
IV. They depend on many parameters: $T2^*$, B_0 , TE, ...



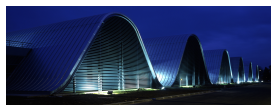


The truth about fMRI data

V. They are big ... and are getting bigger

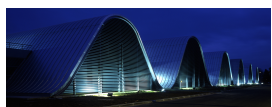


This is ONE run; often 3-8 runs X 15 subjects
6D Data (~20 Go)



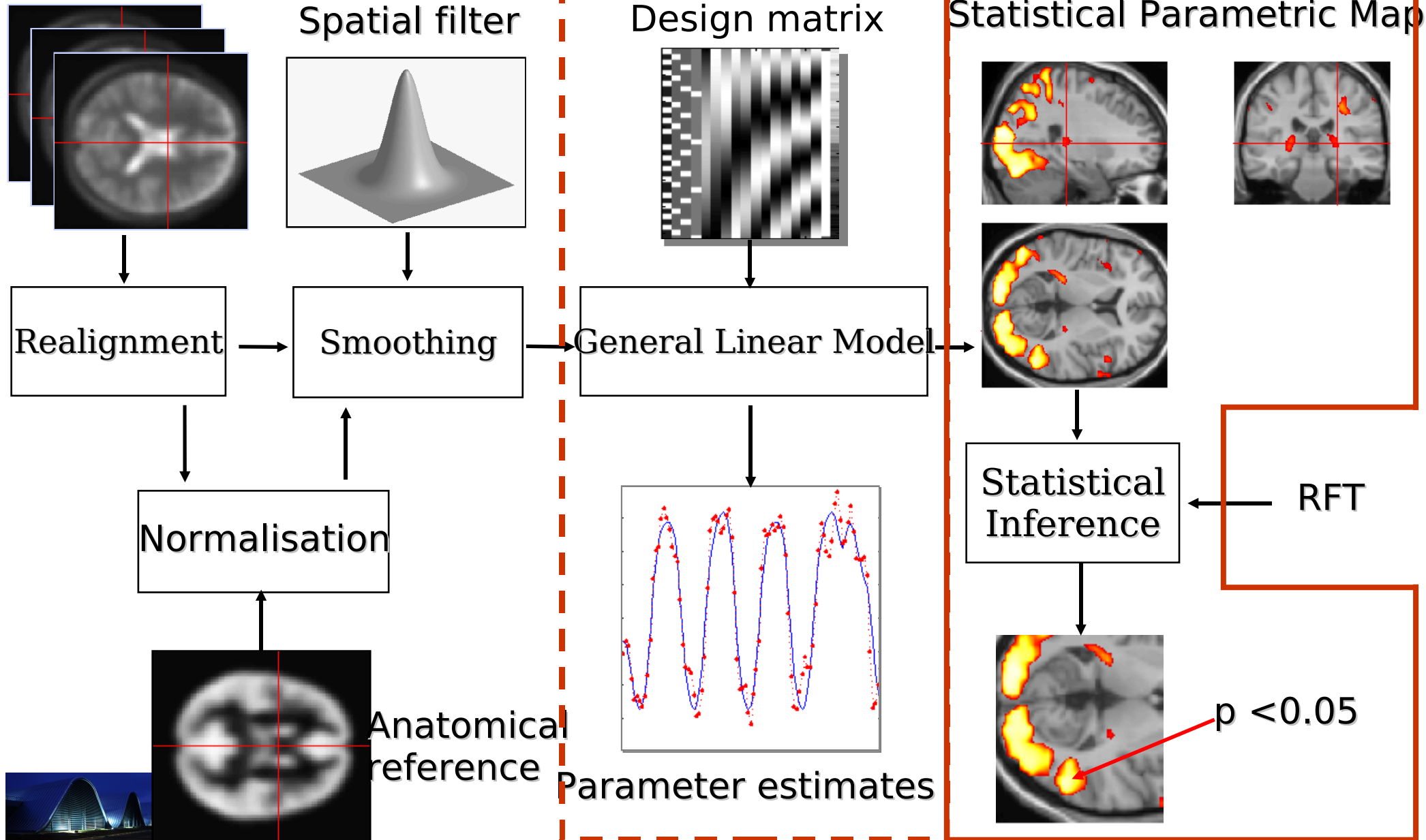
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fMRI processing pipeline

Image time-series



fMRI example

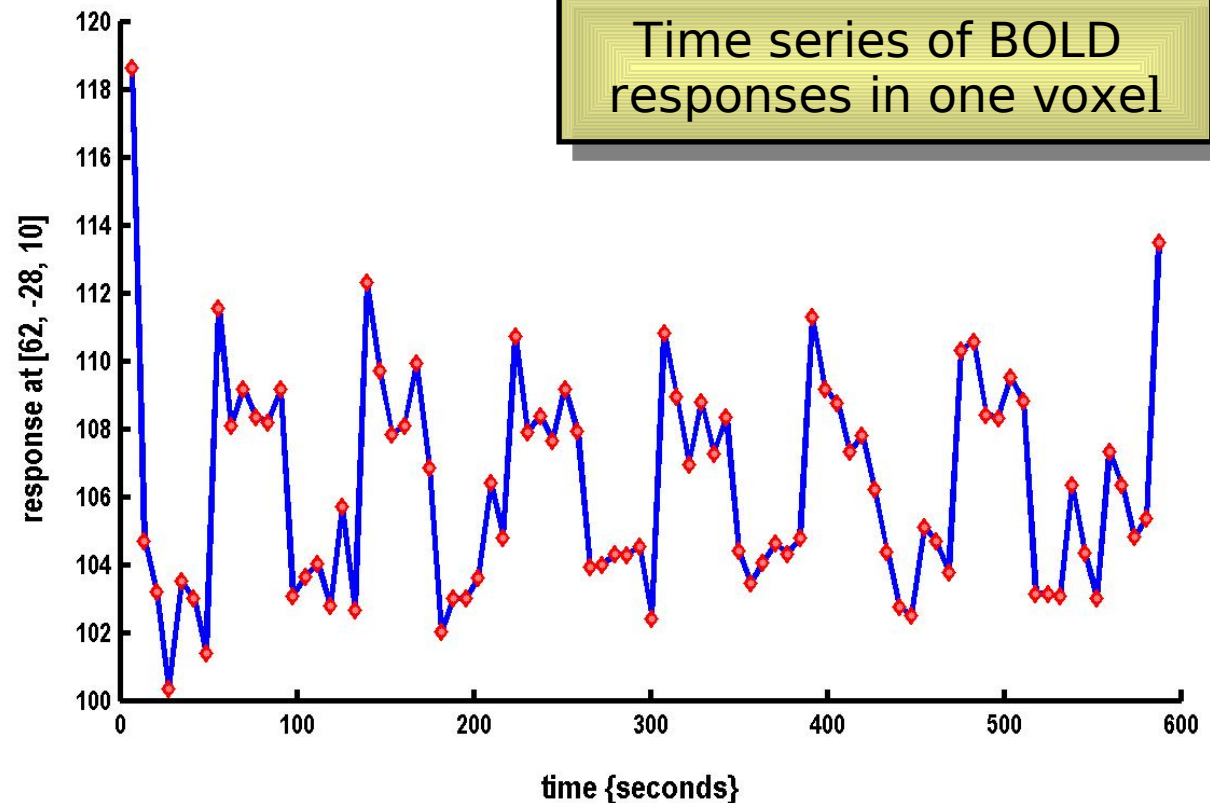


One session

Passive word listening
versus rest

7 cycles of
rest and listening

Each epoch 6 scans
with 7 sec TR



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

Stimulus function



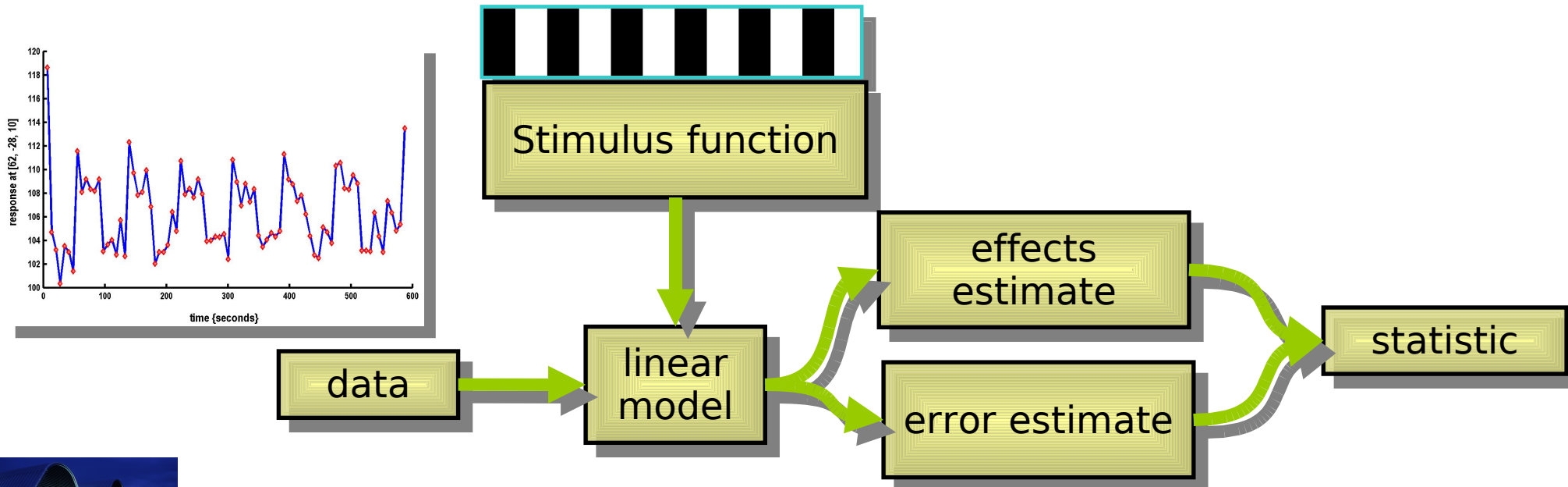
Why modelling?

Why?

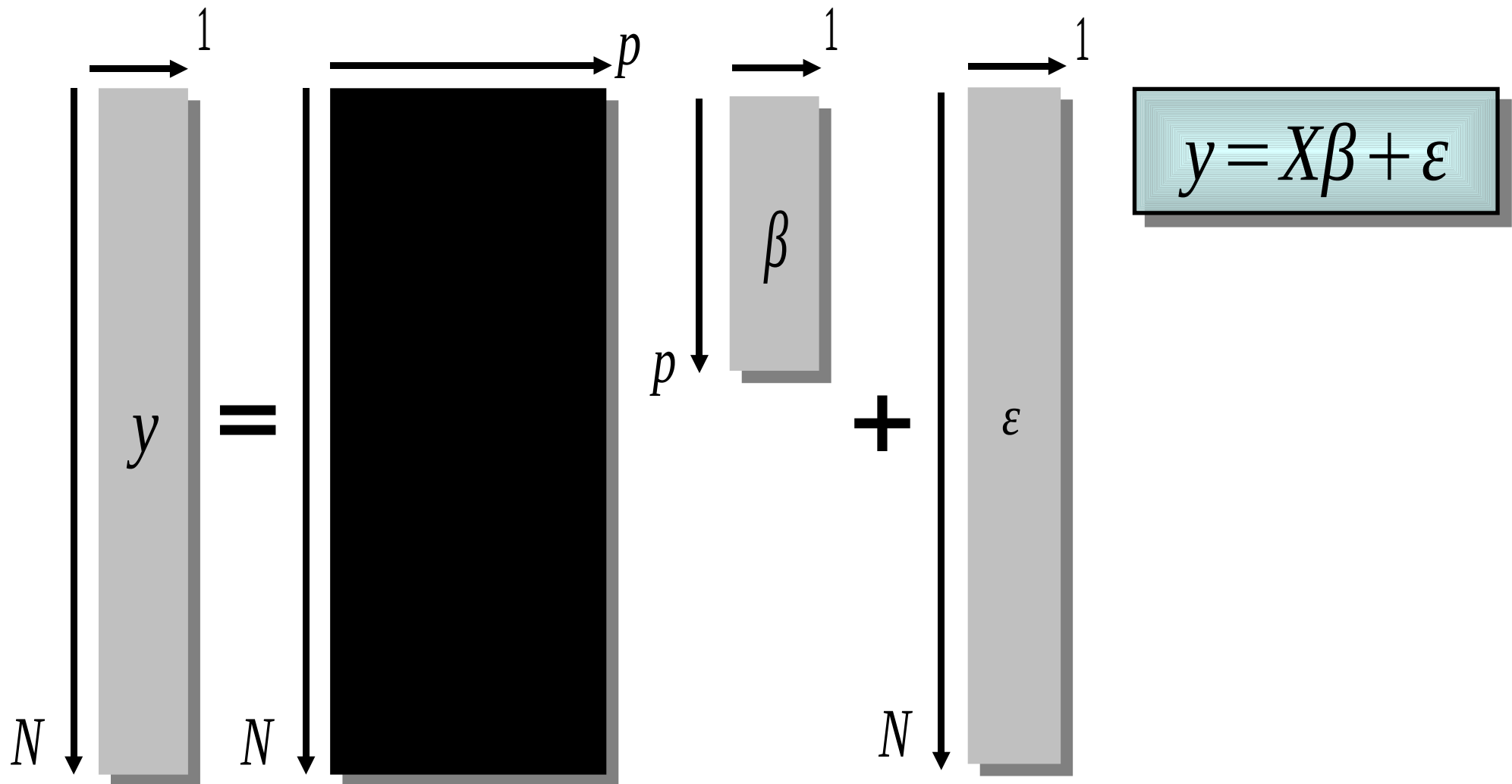
Make inferences about effects of interest

How?

1. Decompose data into effects and error
2. Form statistic using estimates of effects and error



General Linear Model



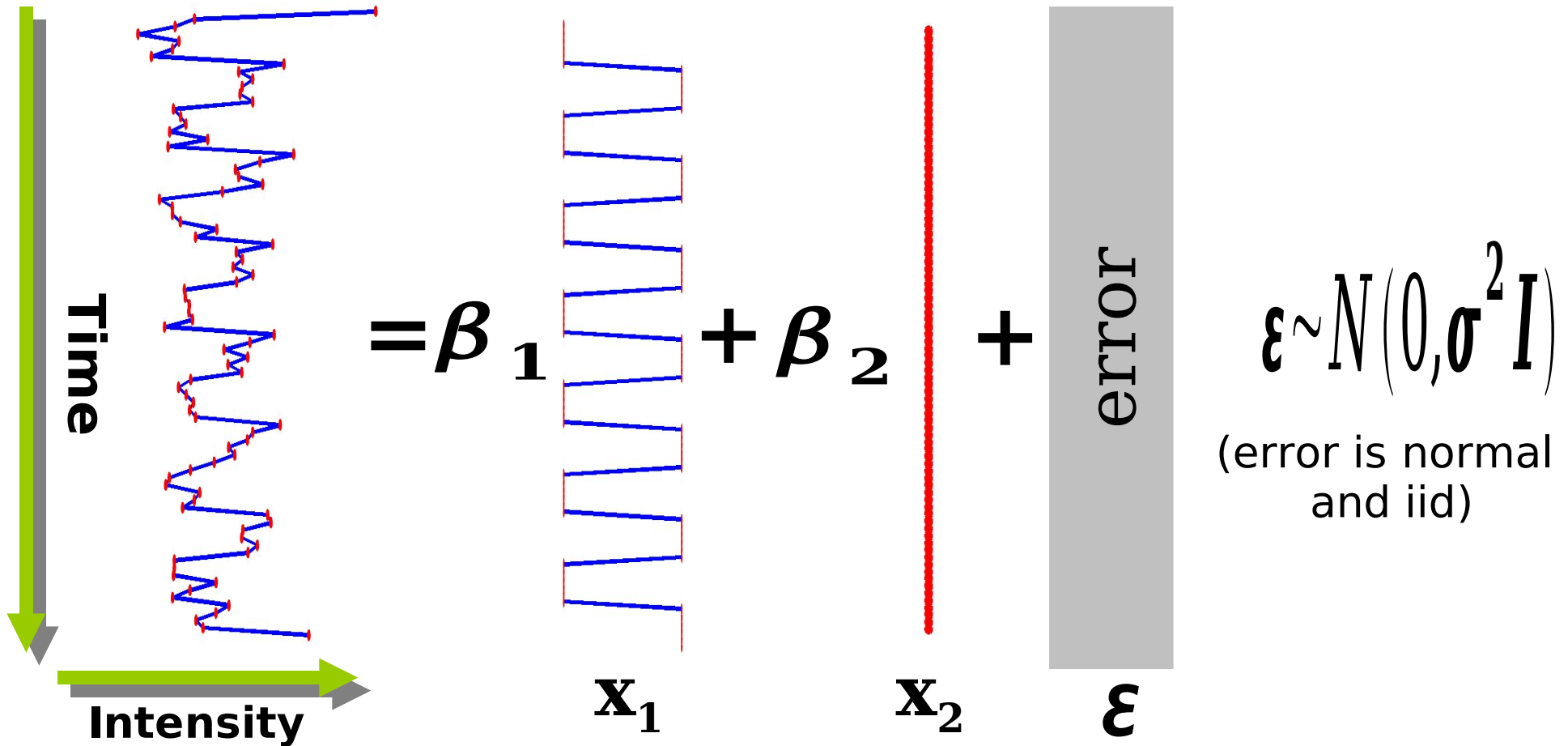
N : number of scans
 p : number of regressors

Model is specified by

- Design matrix X
- Assumptions about ε

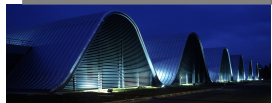


General Linear Model



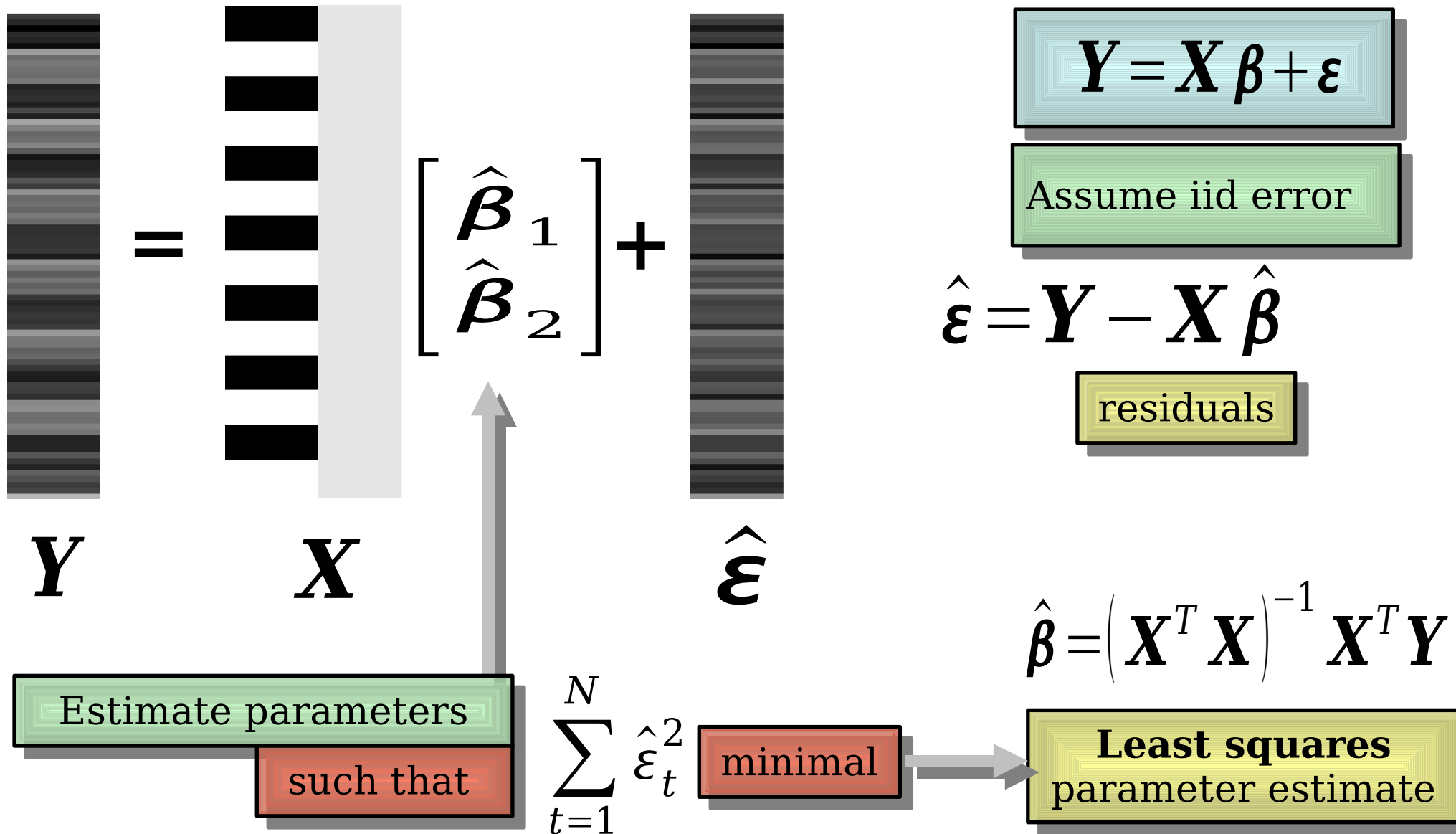
Question: Is there a change in the BOLD response between listening and rest?

Hypothesis test: $\beta_1 = 0$?
(using t-statistic)

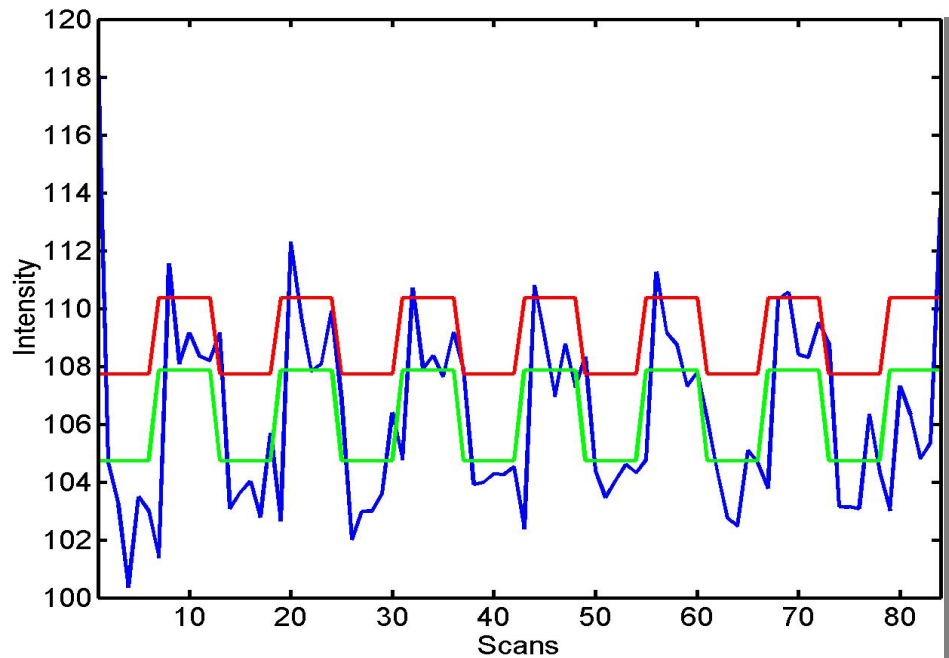


Parameter estimation

cea



Estimation, example



$$Y = X\beta + \varepsilon$$

Assume iid error

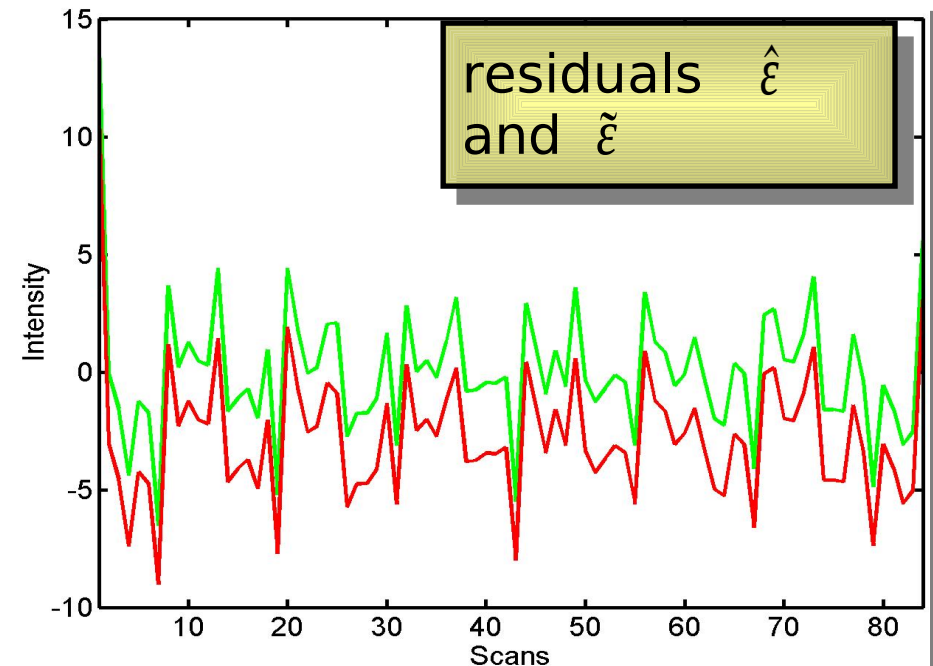
$$\hat{\beta} = (X^T X)^{-1} X^T Y$$

Least squares
estimate

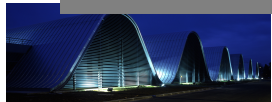
$$\hat{\beta} = \begin{bmatrix} 3.15 \\ 104.74 \end{bmatrix}$$

Another
estimate

$$\tilde{\beta} = \begin{bmatrix} 2.65 \\ 107.74 \end{bmatrix}$$

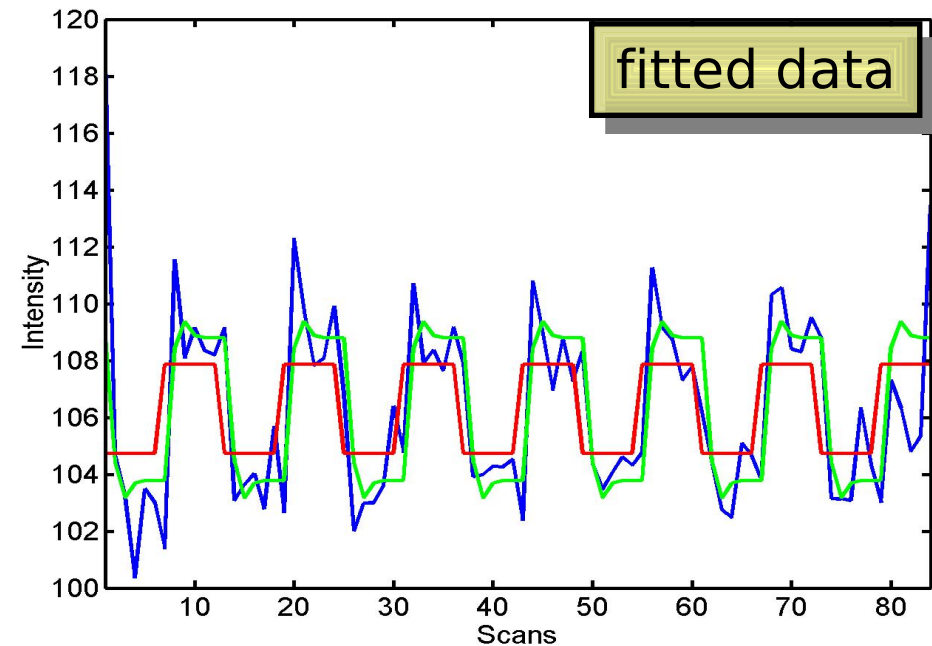
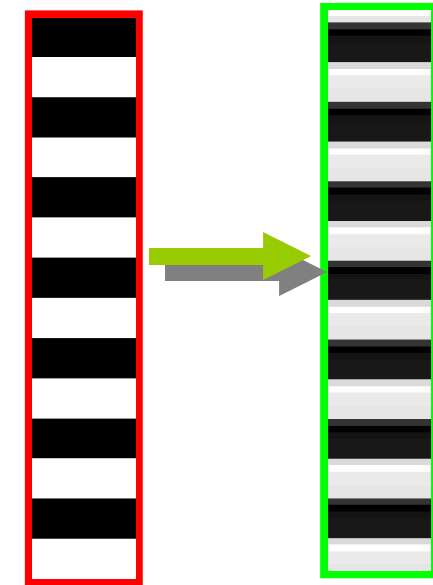
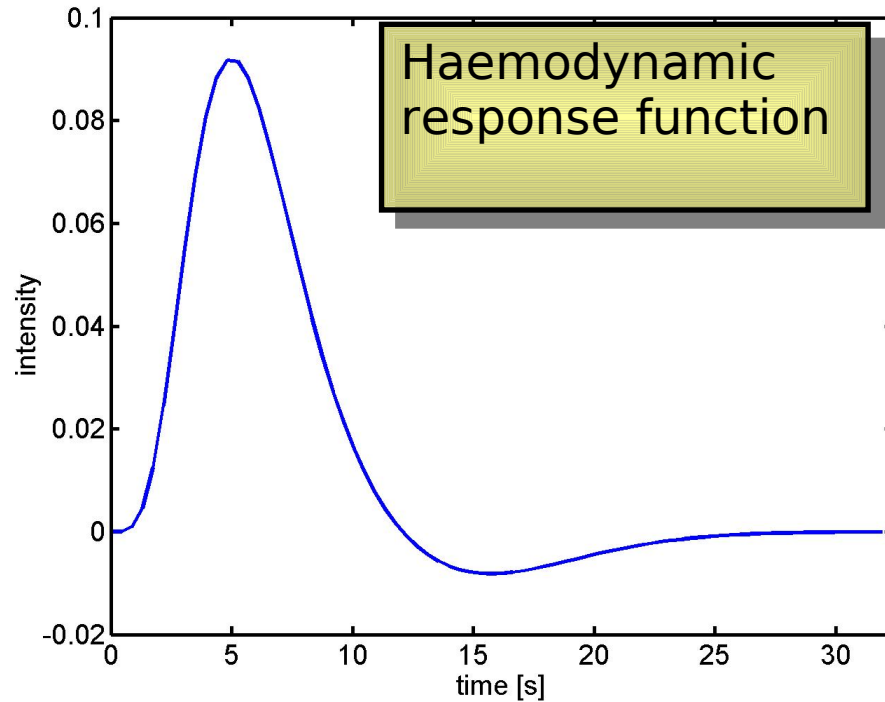


residuals $\hat{\varepsilon}$
and $\tilde{\varepsilon}$



Improved model

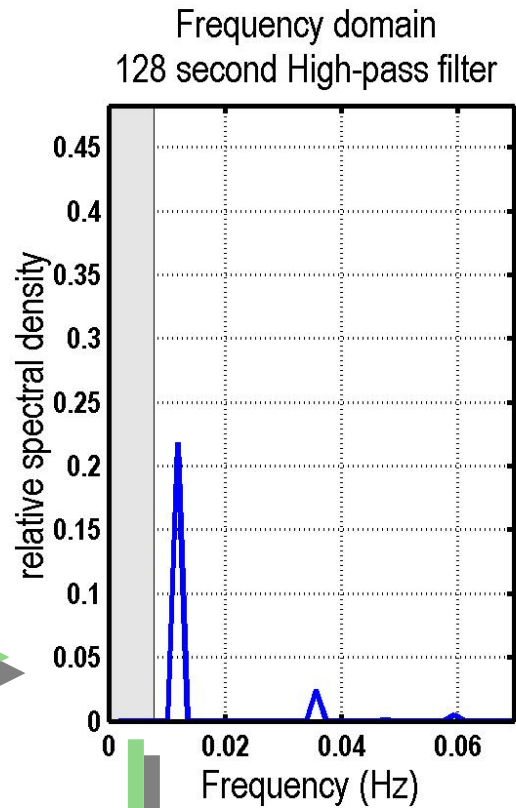
Convolve stimulus function with model of BOLD response



High-pass filtering



$$Y = X\beta + \varepsilon$$

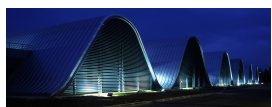
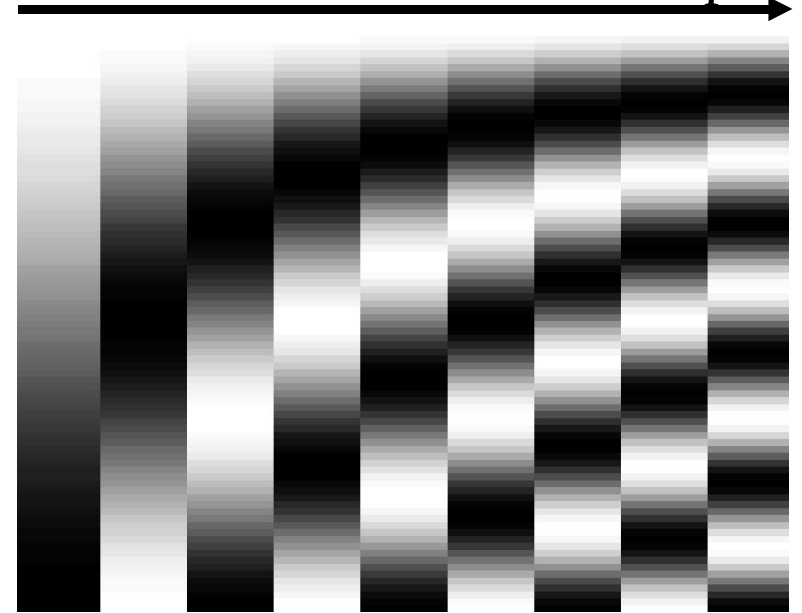


High-pass filter
implemented by
modelling low
frequencies

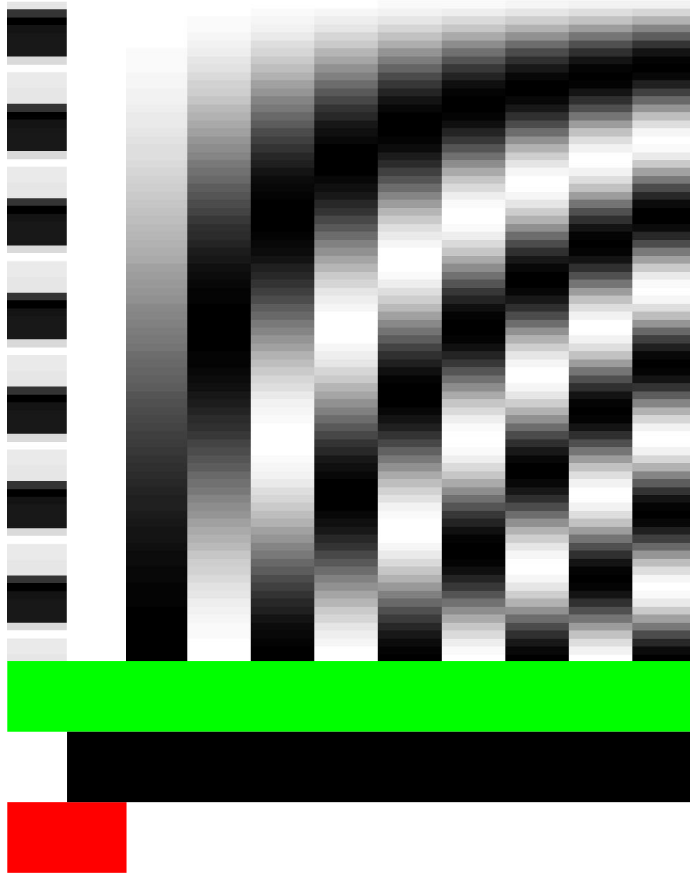
p

discrete cosine
transform set

N

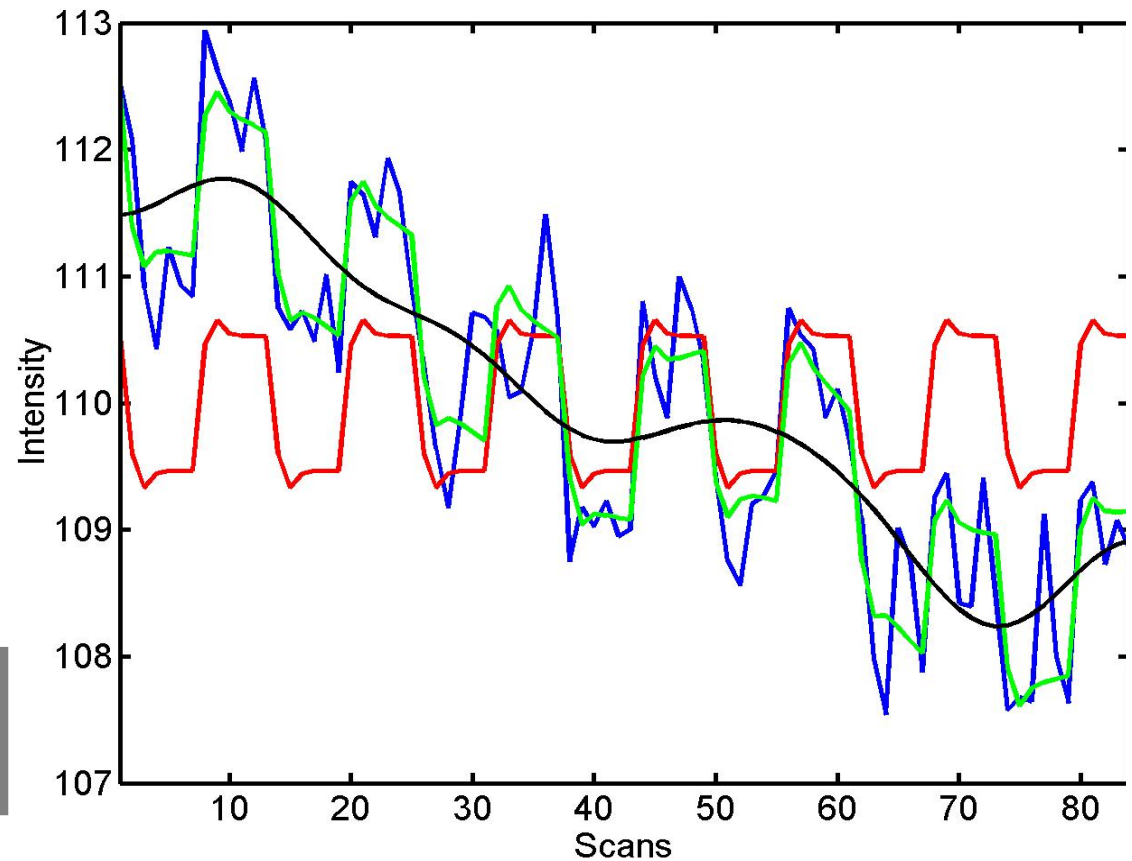


High-pass filtering



$$Y = X\beta + \varepsilon$$

the data and three different models



Error covariance matrix

$$Y = X\beta + \varepsilon$$

$$\text{Cov}(\varepsilon)$$

i.i.d.

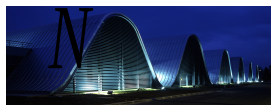
AR(1)

 N

$$V_{ij} = \sigma^2 \frac{a^{|i-j|}}{1-a^2}$$

sampled error
covariance matrix

Serial correlations

 N 

Maximum likelihood solution

- Least Mahalanobis distance (Gaussian assumption)

- Assume V is known up to a scalar factor: $V = \sigma^2 W$

- The ML effect estimator minimizes the Mahalanobis distance

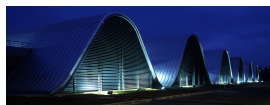
$$d_{maha}^2 = (Y - X\beta)^t W^{-1} (Y - X\beta) = \|W^{-\frac{1}{2}}(Y - X\beta)\|^2$$

- To see this, note that:

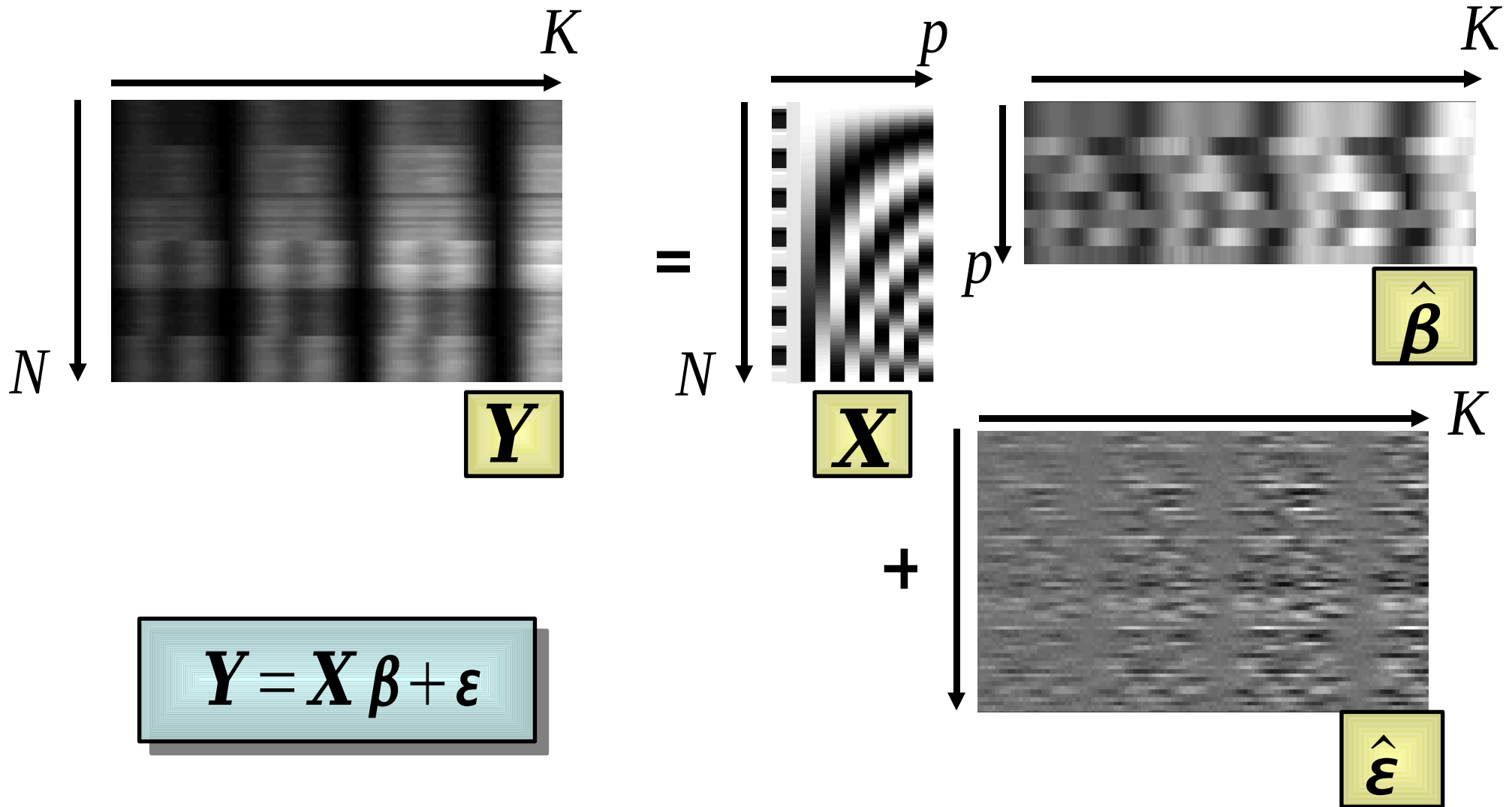
$$W^{-\frac{1}{2}} Y = W^{-\frac{1}{2}} X\beta + \sigma^2 N(0, I_n)$$

- Therefore, only need to pre-whiten the data and the design matrix

$$Y \leftarrow W^{-\frac{1}{2}} Y, \quad X \leftarrow W^{-\frac{1}{2}} X$$



Mass-univariate approach

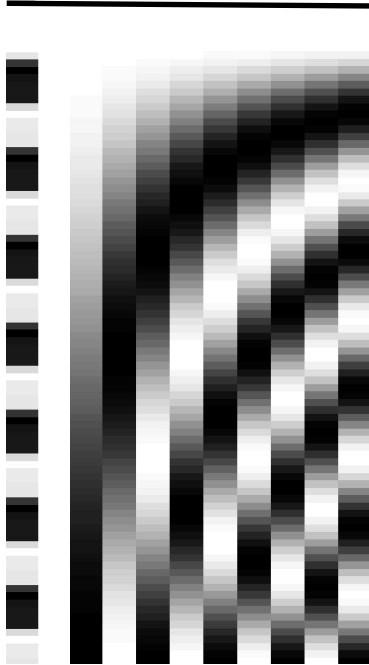


Inference - t-statistic



$$Y = X\beta + \varepsilon$$

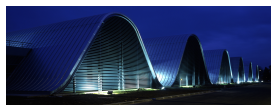
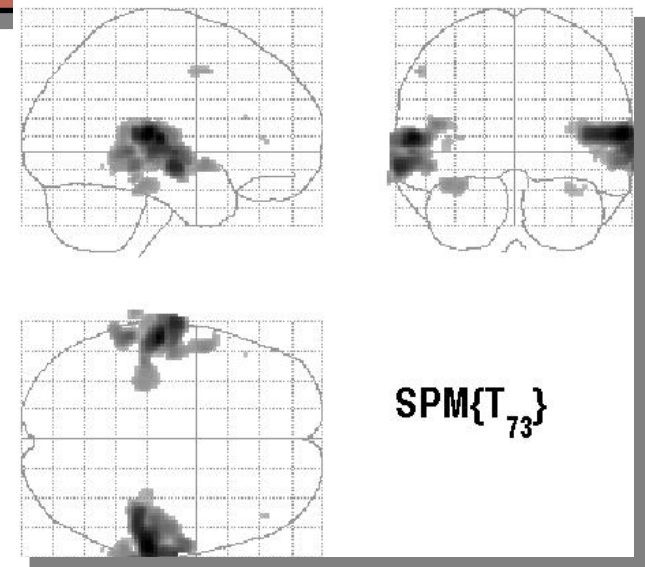
$$c = \begin{matrix} +1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{matrix}$$



boxcar parameter > 0 ?

Null hypothesis: $\beta_1 = 0$

$$t = \frac{c^t \hat{\beta}}{\sqrt{\text{Var}(c^t \hat{\beta})}}$$



t-statistic - Computations

$$Y = X\beta + \varepsilon$$

$\hat{\beta}$ least squares estimates

$$c = +1000000000000$$

$$t = \frac{c^t \hat{\beta}}{\sqrt{\text{Var}(c^t \hat{\beta})}}$$

$$\text{Var}(c^t \hat{\beta}) = \hat{\sigma}^2 c^t X V X^{-t} c$$



X

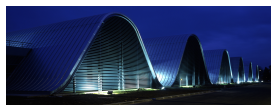
$$\hat{\sigma}^2 = \frac{\sum_{t=1}^N (y_t - [X\hat{\beta}]_t)}{df}$$

compute **df** using Satterthwaite approximation



V

ReML



Hypothesis Testing



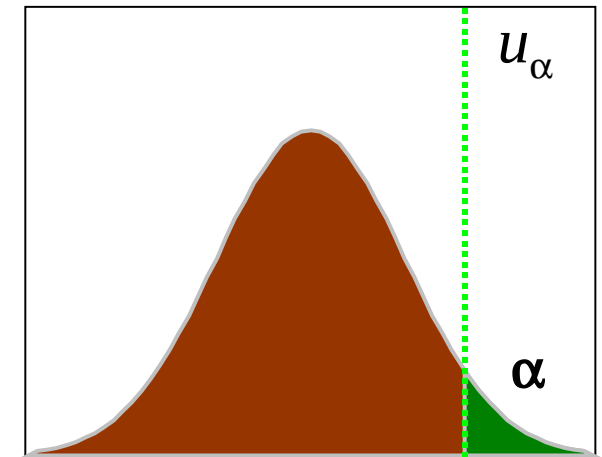
□ **Type I Error α :**

Acceptable *false positive rate* α .

Level \Rightarrow threshold u_α

Threshold u_α controls the false positive rate

$$\alpha = p(T > u_\alpha | H_0)$$



Null Distribution of T

Observation of test statistic t , a realisation of T

□ **P-value:**

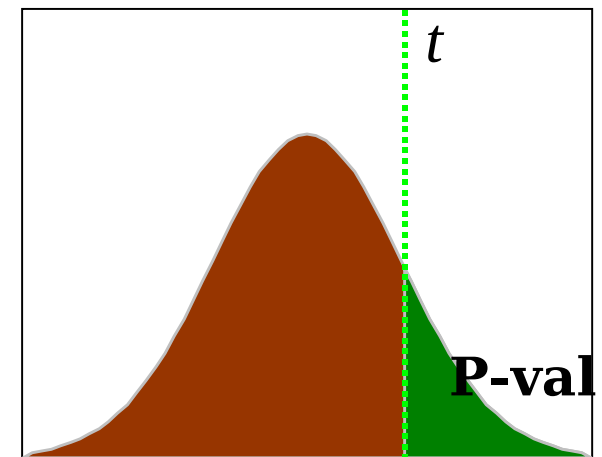
A *p-value* summarises evidence against H_0 .

This is the change of observing value more extreme than t under the null hypothesis.

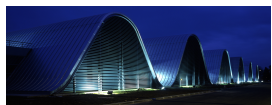
$$p(T > t | H_0)$$

□ **The conclusion about the hypothesis:**

We reject the null hypothesis in favour of the alternative hypothesis if $t > u_\alpha$

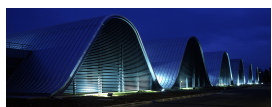
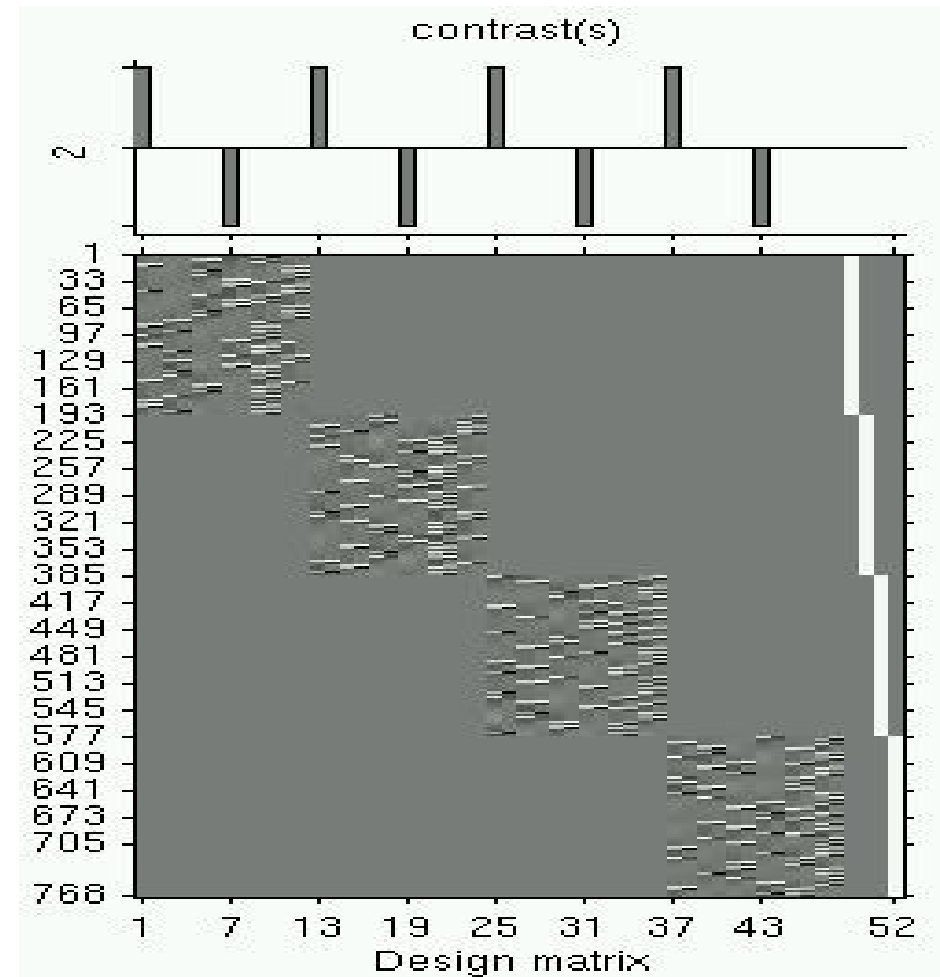
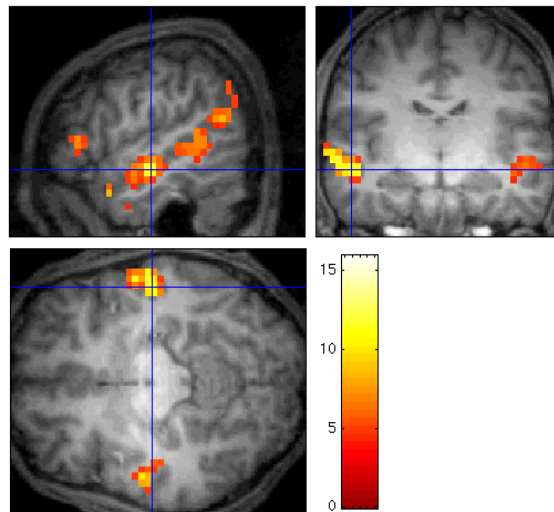
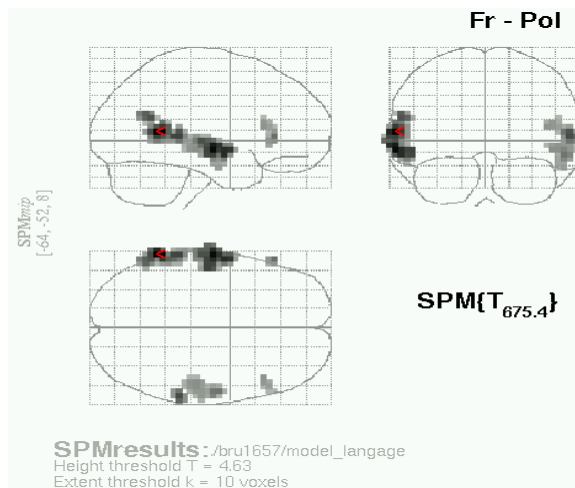


Null Distribution of T



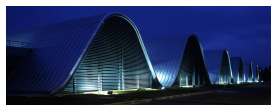
Example of fMRI model

- A language comprehension study [Pallier et al, 2002]



Part I - Mapping brain activity

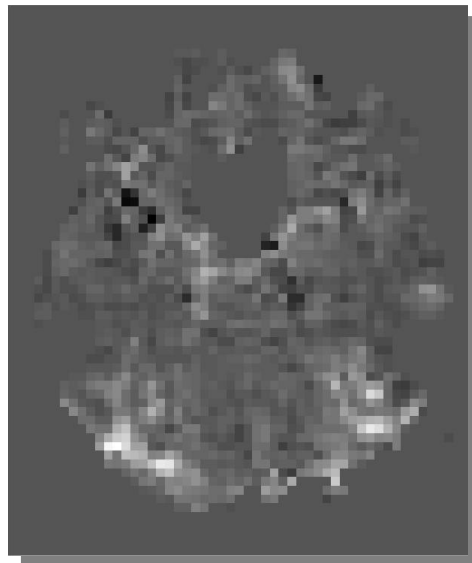
- A) A tour about the GLM framework
- B) What kind of regularization?
- C) Numerical Bayesian inference methods



Experimental evidence

Even without applied spatial smoothing, activation maps (and maps of eg. AR coefficients) have spatial structure.

Contrast

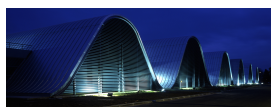


AR(1)



- ⇒ Definition of a spatial prior via Gaussian Markov Random Field
- ⇒ Automatic spatial regularisation of Regression coefficients and AR coefficients

Bayesian fMRI



Bayesian fMRI

General Linear Model:

$$Y = X\beta + \varepsilon$$

with $\varepsilon \propto N(0, C_\varepsilon)$

What are the priors?

- In “*classical*” SPM, no (flat) priors
- In “*full*” Bayes, priors might be from theoretical arguments or from independent data
- In “*empirical*” Bayes, priors derive from the same data, assuming a hierarchical model for generation of the data

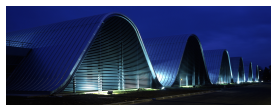
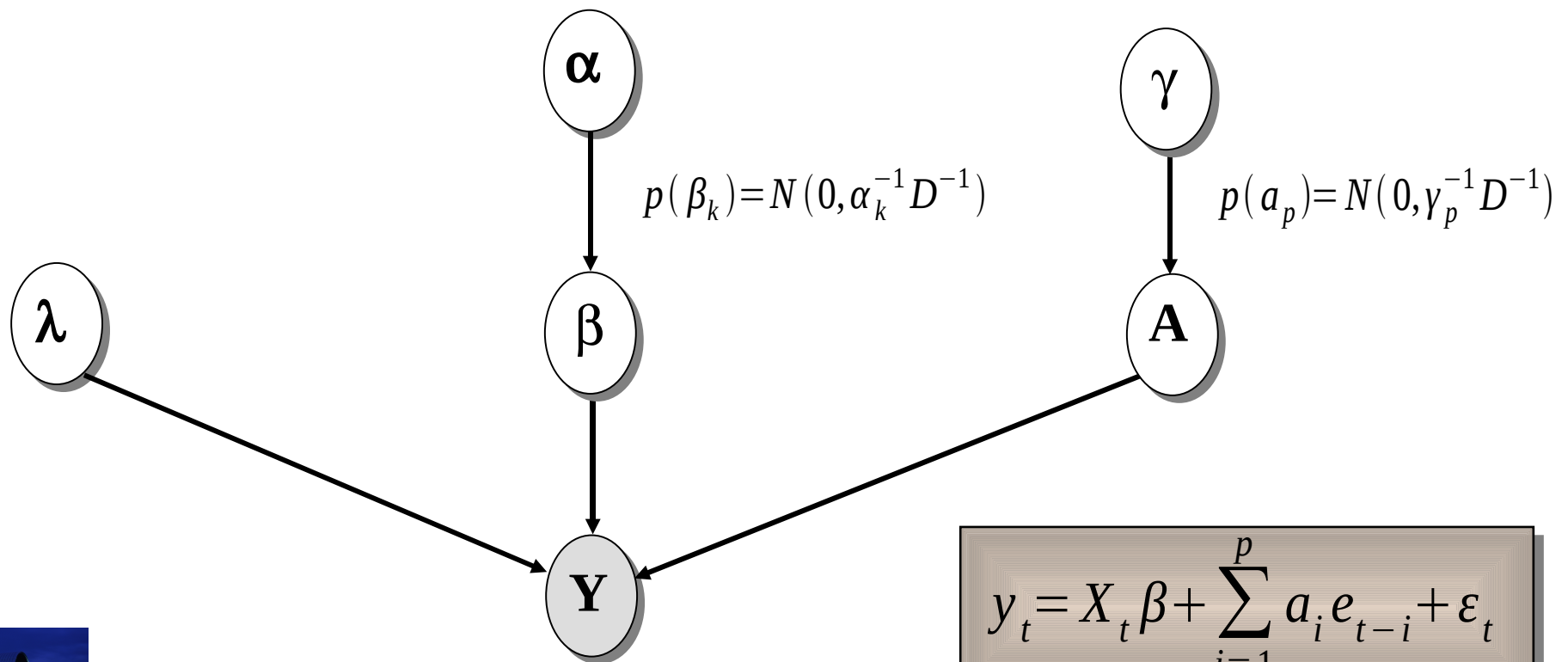
↳ Parameters of one level can be made priors on distribution of parameters at lower level



The generative model

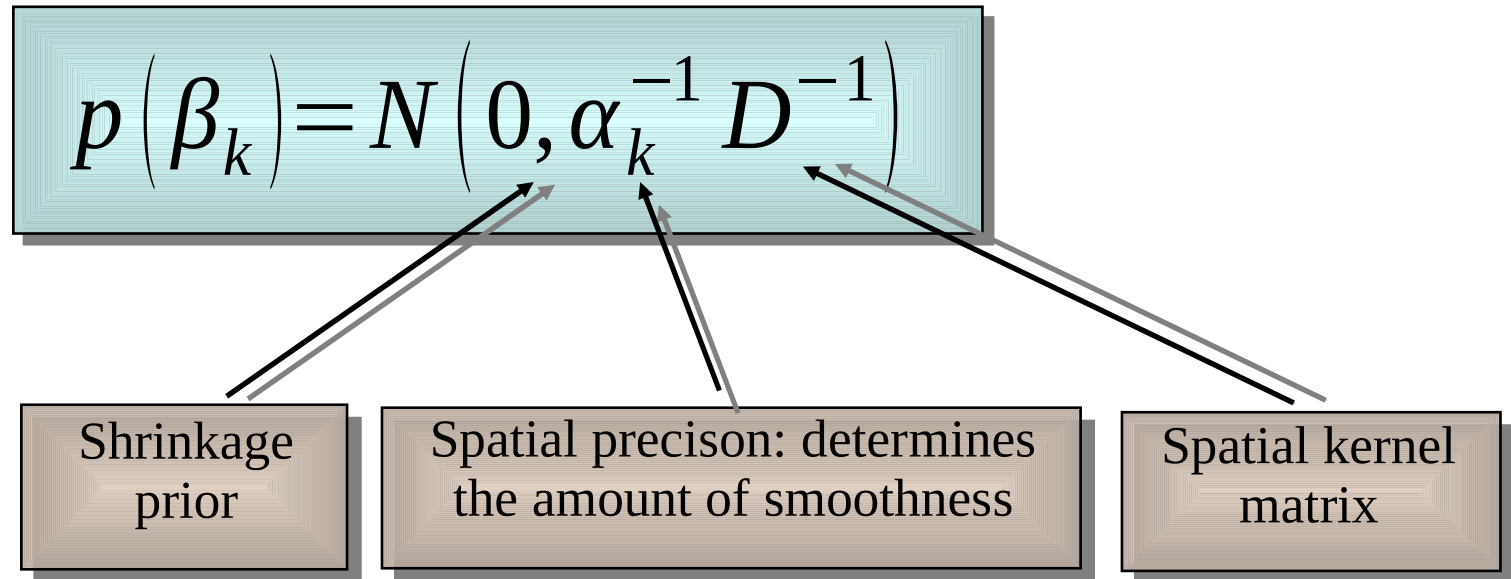
General Linear Model with Auto-Regressive error terms (GLM-AR):

$$Y = X\beta + E \text{ where } E \text{ is an AR}(p)$$



Spatial prior

Over the regression coefficients: [Penny et al, NeuroImage, 2003, 2005]

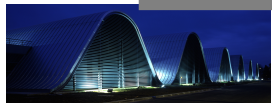


Gaussian Markov Random Field priors D

$$D = \begin{bmatrix} 1 & & & & \\ & 1 & & & \\ & & \ddots & & \\ & & & d_{ij} & \\ & & & d_{ji} & 1 \\ & & & & & 1 \end{bmatrix}$$

$\left\{ \begin{array}{l} 1 \text{ on diagonal elements } d_{ii} \\ d_{ij} > 0 \text{ if voxels } i \text{ and } j \text{ are neighbors.} \\ 0 \text{ elsewhere} \end{array} \right.$

Same prior on the AR coefficients.



Prior, Likelihood and posterior

The prior:

$$p(\beta, A, \lambda, \alpha, \gamma) = \left(\prod_k p(\beta_k | \alpha_k) p(\alpha_k | q_1, q_2) \right) \left(\prod_p p(a_p | \gamma_p) p(\gamma_p | r_1, r_2) \right) \left(\prod_n p(\lambda_n | u_1, u_2) \right)$$

The likelihood:

$$p(Y | \beta, A, \lambda) = \prod_n p(y_n | \beta_n, a_n, \lambda_n)$$

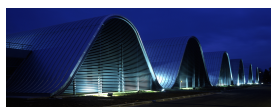
The posterior?

$$p(\beta | Y) ?$$

The posterior over β doesn't factorise over k or n .

⇒ Exact inference requires sampling techniques

⇒ Variational approximation achievable at lower cost



Part I - Mapping brain activity

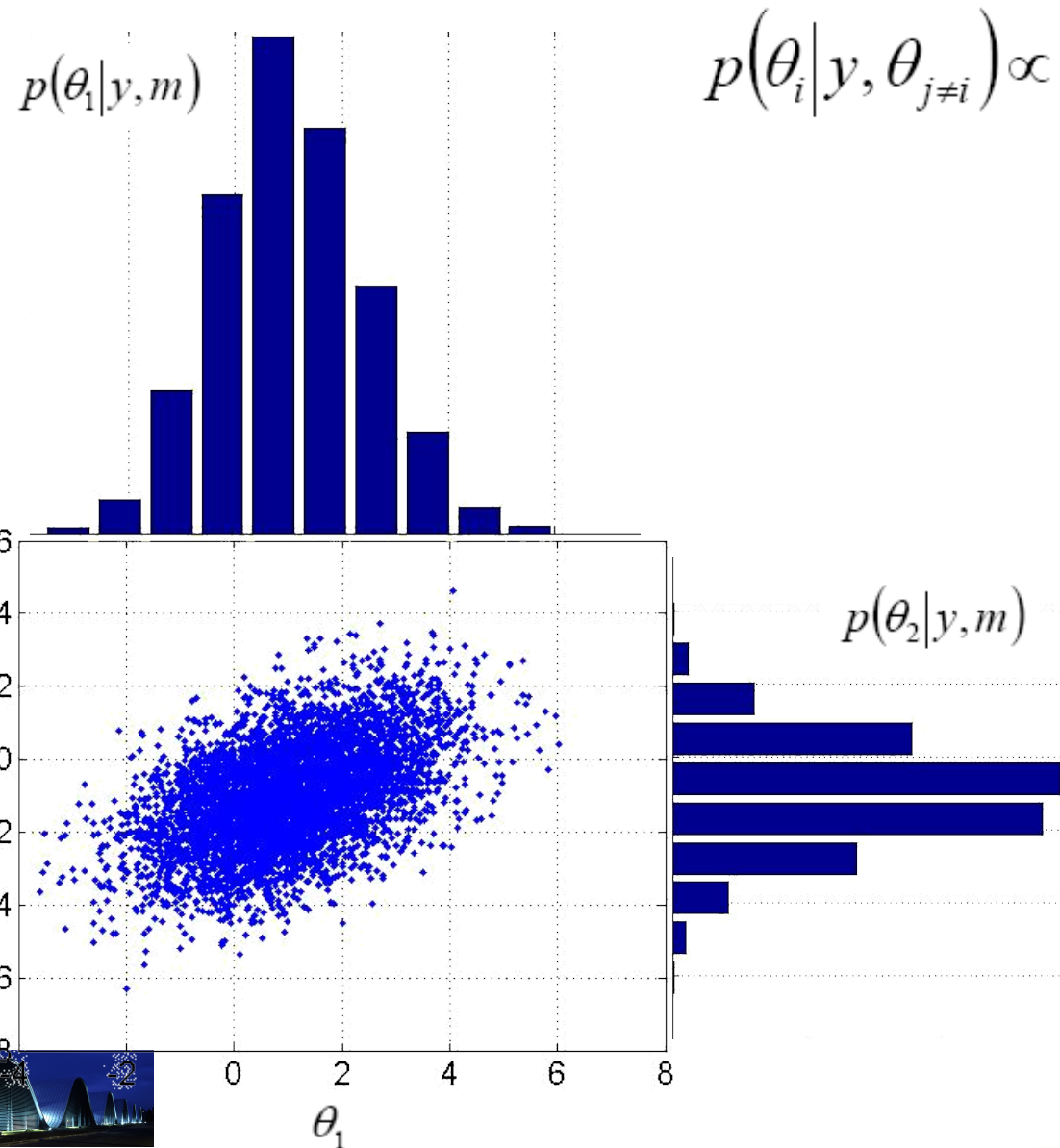
- A) A tour about the GLM framework
- B) What kind of regularization?
- C) Numerical Bayesian inference methods



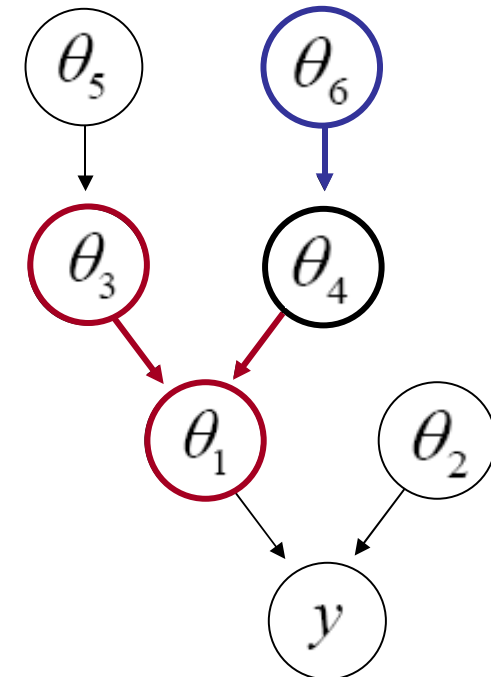
Sampling methods



MCMC example: Gibbs sampling



$$p(\theta_i|y, \theta_{j \neq i}) \propto \underbrace{p(\theta_i|par(\theta_i))}_{\text{blue underline}} \underbrace{\prod_{j=ch(i)} p(\theta_j|par(\theta_j))}_{\text{red underline}}$$



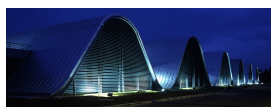
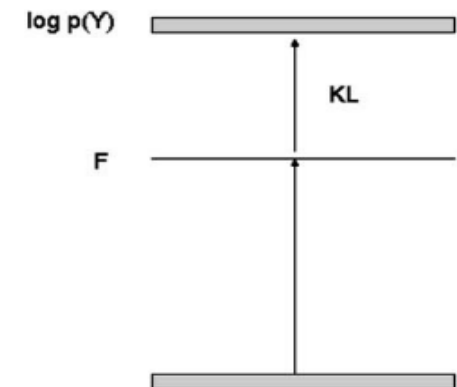
Variational Bayes

- Central quantity of Bayesian learning $p(\boldsymbol{\theta} | \mathbf{Y})$ with $\boldsymbol{\theta} = \{\beta, A, \lambda\}$
- Log-evidence of the model or integrated likelihood

$$\begin{aligned}
 \forall \text{ pdf } q, \log p(\mathbf{Y}) &= \int q(\boldsymbol{\theta} | \mathbf{Y}) \log p(\mathbf{Y}) d\boldsymbol{\theta} \\
 &= \int q(\boldsymbol{\theta} | \mathbf{Y}) \log \frac{p(\mathbf{Y}, \boldsymbol{\theta})}{p(\boldsymbol{\theta} | \mathbf{Y})} d\boldsymbol{\theta} \\
 &= \int q(\boldsymbol{\theta} | \mathbf{Y}) \log \left[\frac{q(\boldsymbol{\theta} | \mathbf{Y}) p(\mathbf{Y}, \boldsymbol{\theta})}{p(\boldsymbol{\theta} | \mathbf{Y}) q(\boldsymbol{\theta} | \mathbf{Y})} \right] d\boldsymbol{\theta} \\
 &= \int q(\boldsymbol{\theta} | \mathbf{Y}) \log \frac{p(\boldsymbol{\theta}, \mathbf{Y})}{q(\boldsymbol{\theta} | \mathbf{Y})} d\boldsymbol{\theta} + \int q(\boldsymbol{\theta} | \mathbf{Y}) \log \frac{q(\boldsymbol{\theta} | \mathbf{Y})}{p(\boldsymbol{\theta} | \mathbf{Y})} d\boldsymbol{\theta} \\
 &= \mathcal{F} + D(q || p_{\boldsymbol{\theta} | \mathbf{Y}})
 \end{aligned}$$

- \mathcal{F} is a lower bound of the model evidence

$$\log p(\mathbf{Y}) = \mathcal{F} \iff q(\boldsymbol{\theta} | \mathbf{Y}) = p(\boldsymbol{\theta} | \mathbf{Y})$$



Variational Bayes (cont'd)

- Aim of VB : maximize \mathcal{F}
 - Make the approximate posterior $q(\boldsymbol{\theta} | \mathbf{Y})$ as close as possible to the true posterior $p(\boldsymbol{\theta} | \mathbf{Y})$
- Practical efficient algorithm:
 - Ensure tractability of integrals in \mathcal{F}
 - Generic procedure: mean-field approximation

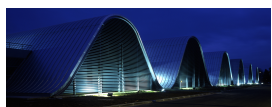
$$q(\boldsymbol{\theta} | \mathbf{Y}) = \prod_i q(\theta_i | \mathbf{Y})$$

θ_i = i th group of parameters

- Maximizers of \mathcal{F} **[Lappalainen and Miskin, 2000]**

$$q(\theta_i | \mathbf{Y}) = \frac{\exp[I(\theta_i)]}{\int \exp[I(\theta_i)] d\theta_i}$$

$$\text{with } I(\theta_i) = \int q(\boldsymbol{\theta}^{\setminus i} | \mathbf{Y}) \log p(\mathbf{Y}, \boldsymbol{\theta}) d\boldsymbol{\theta}^{\setminus i}$$



Variational Bayes (exemple)

Approximate posteriors that allows for *factorisation*

$$q(\beta, A, \lambda, \alpha, \gamma) = \left(\prod_k q(\alpha_k | Y) \right) \left(\prod_p q(\gamma_p | Y) \right) \left(\prod_n q(\beta_n | Y) q(a_n | Y) q(\lambda_n | Y) \right)$$

Variational Bayes Algorithm

Initialisation

While ($\Delta F > \text{tol}$)

 Update Suff. Stats. for β

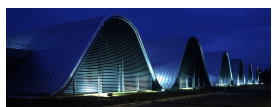
 Update Suff. Stats. for A

 Update Suff. Stats. for λ

 Update Suff. Stats. for α

 Update Suff. Stats. for γ

End



Variational Bayes (exemple)

Approximate posteriors that allows for *factorisation*

$$q(\beta, A, \lambda, \alpha, \gamma) = \left(\prod_k q(\alpha_k | Y) \right) \left(\prod_p q(\gamma_p | Y) \right) \left(\prod_n q(\beta_n | Y) q(a_n | Y) q(\lambda_n | Y) \right)$$

Regression coefficients

$$q(\mathbf{w}_n) = N(\mathbf{w}_n; \hat{\mathbf{w}}_n, \hat{\Sigma}_n)$$

$$\hat{\mathbf{w}}_n = \hat{\Sigma}_n (\bar{\lambda}_n \tilde{\mathbf{b}}_n^T + \mathbf{r}_n)$$

$$\hat{\Sigma}_n = (\bar{\lambda}_n \tilde{\mathbf{A}}_n + \mathbf{B}_{nn})^{-1}$$

$$\mathbf{B} = \mathbf{H} (\text{diag}(\bar{\alpha}) \otimes \mathbf{S}^T \mathbf{S}) \mathbf{H}^T$$

$$\mathbf{r}_n = - \sum_{i=1, i \neq n}^N \mathbf{B}_{ni} \hat{\mathbf{w}}_i$$

AR coefficients

$$q(\mathbf{a}_n) = N(\mathbf{a}_n; \mathbf{m}_n, \mathbf{V}_n)$$

$$\mathbf{V}_n = (\bar{\lambda}_n \tilde{\mathbf{C}}_n + \beta \mathbf{I}_p)^{-1}$$

$$\mathbf{m}_n = \bar{\lambda}_n \tilde{\mathbf{D}}_n \mathbf{V}_n$$

Spatial precisions

$$q(\alpha) = \prod_{k=1}^K q(\alpha_k)$$

$$q(\alpha_k) = Ga(\alpha_k; g_k, h_k)$$

$$\frac{1}{g_k} = \frac{1}{2} \left[\text{Tr}(\hat{\Sigma}_k \mathbf{S}^T \mathbf{S}) + \hat{\mathbf{w}}_k^T \mathbf{S}^T \mathbf{S} \hat{\mathbf{w}}_k \right] + \frac{1}{q_1}$$

$$h_k = \frac{N}{2} + q_2$$

$$\bar{\alpha}_k = g_k h_k$$

Observation noise

$$q(\lambda_n) = Ga(\lambda_n; b_n, c_n)$$

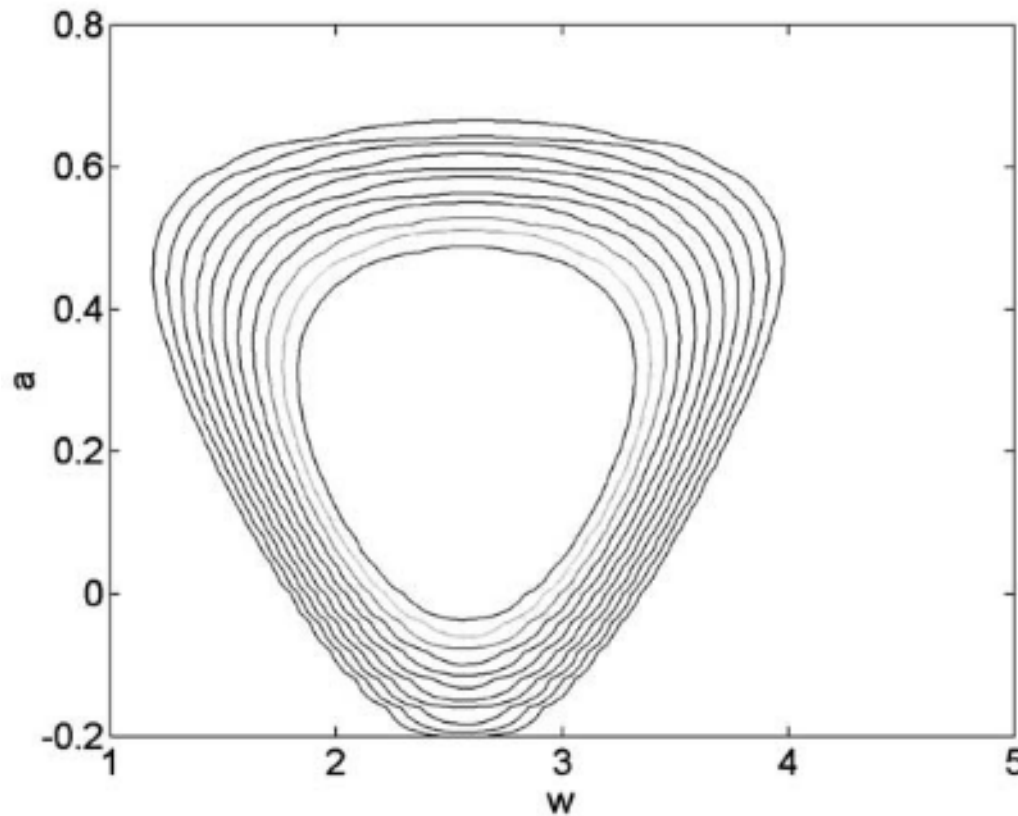
$$\frac{1}{b_n} = \frac{\tilde{G}_n}{2} + \frac{1}{u_1}$$

$$c_n = \frac{T}{2} + u_2$$

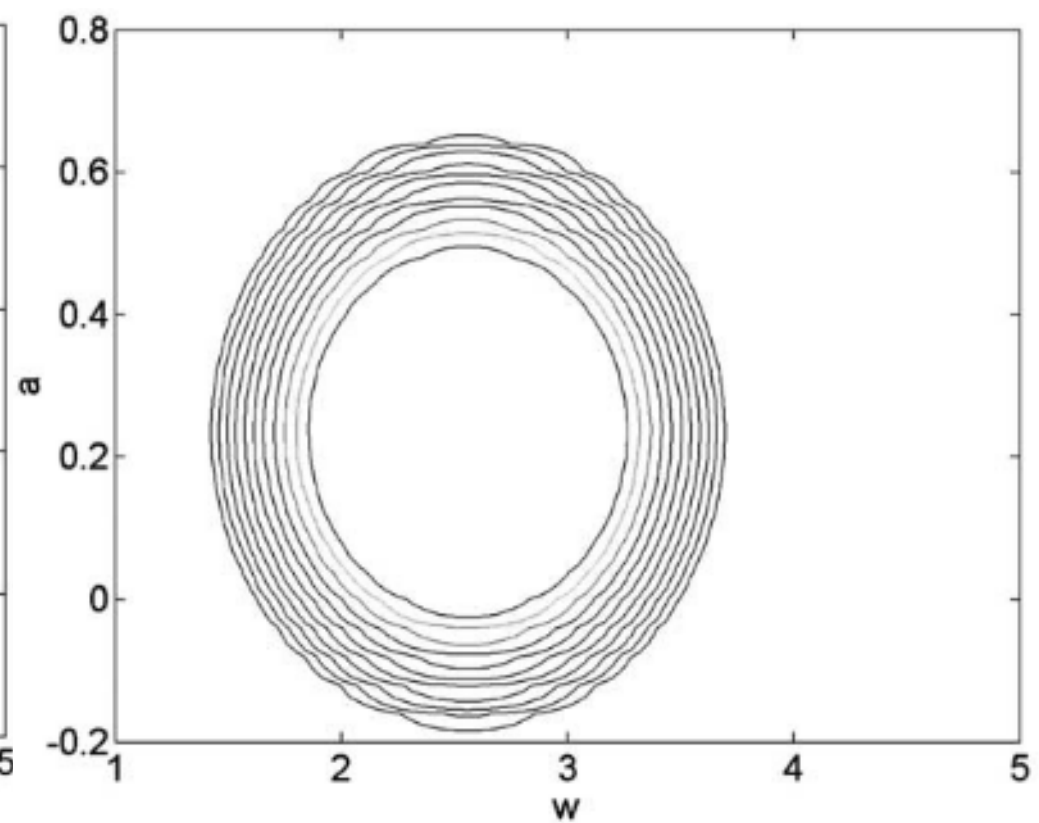


VB: approximation effect

iso-levels of the posterior $p(\theta | Y)$



iso-levels of the posterior $q(\theta | Y)$



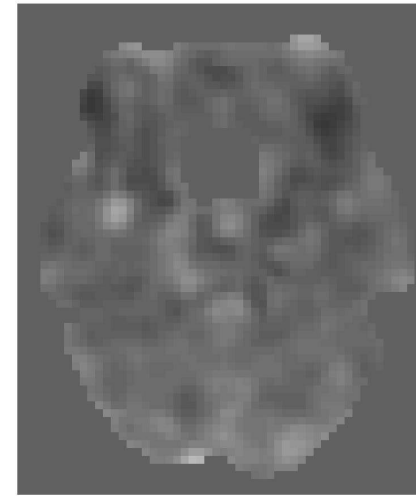
Accurate mode approximation

Error hidden in the **higher order** moments



Event-related fMRI

Familiar vs.
unfamiliar faces



Smoothing



Global prior

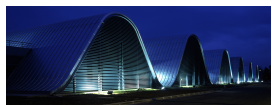


Spatial Prior



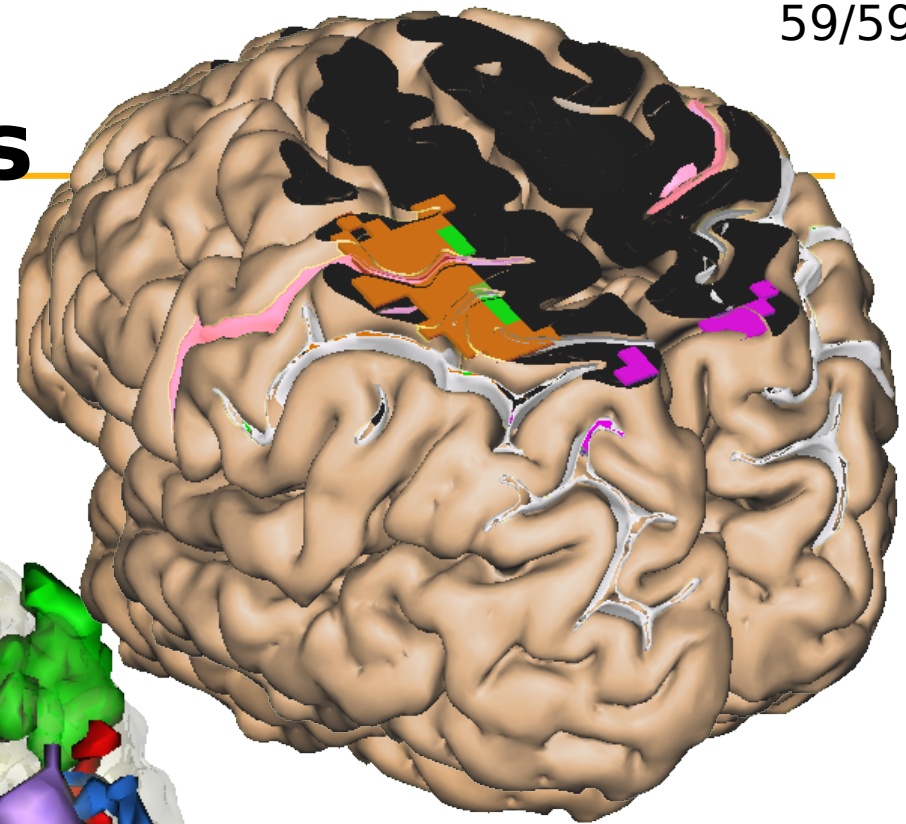
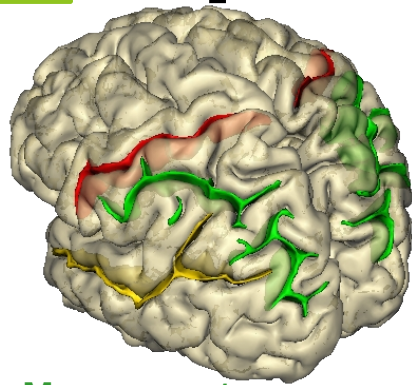
Summary

- Activation detection in fMRI
 - Preprocessings
 - A whole brain model of the BOLD signal
 - Statistical tests
- Bayesian gain
 - Don't smooth the data
 - Prefer spatial regularization





Mapping of the parietal circuits



Mouvements de la main droite

Saisie manuelle

Calcul seul

Calcul et Langage

Langage seul

Tâches Visuo-Spatiales (saisie, pointage, Attention, saccades)

Attention et Saccades

Saccades Seules

