



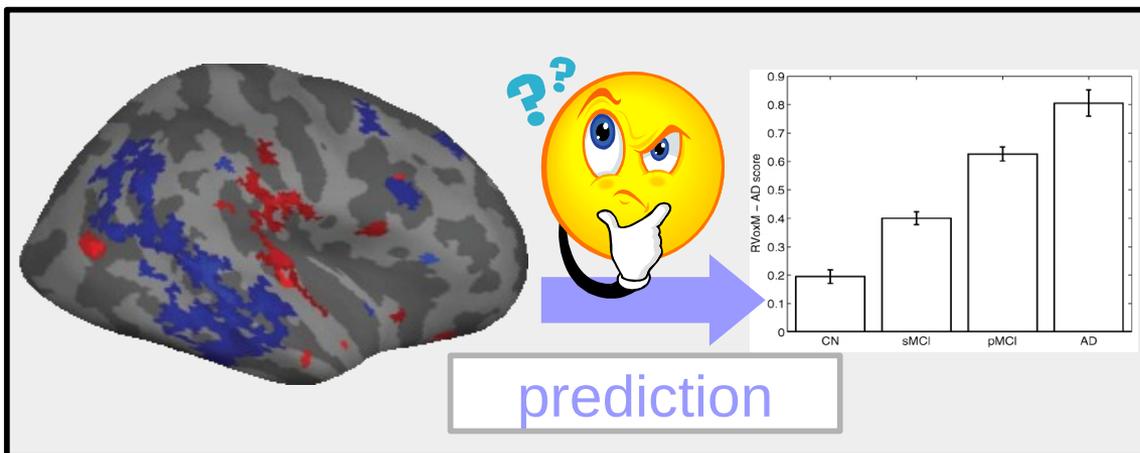
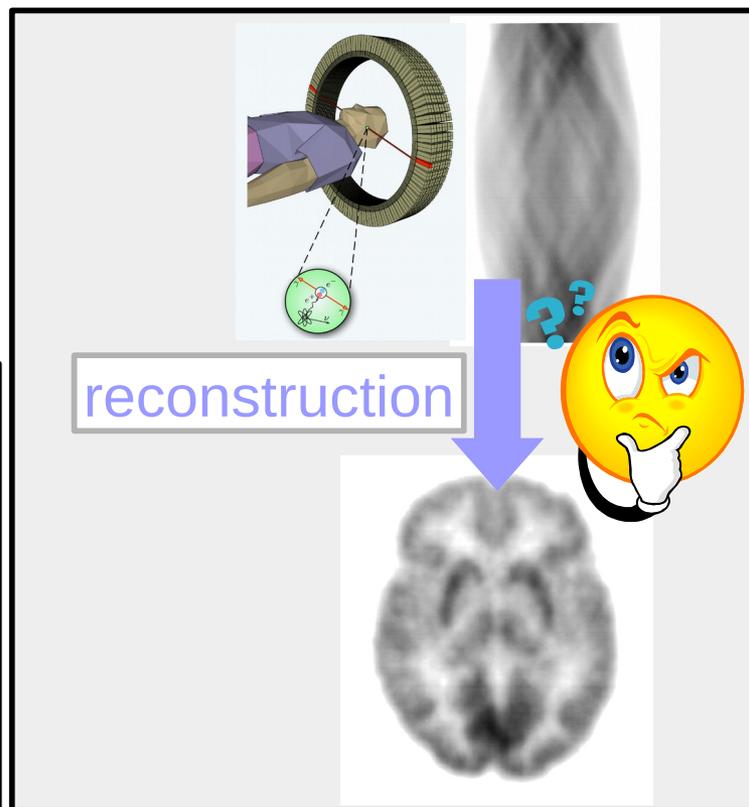
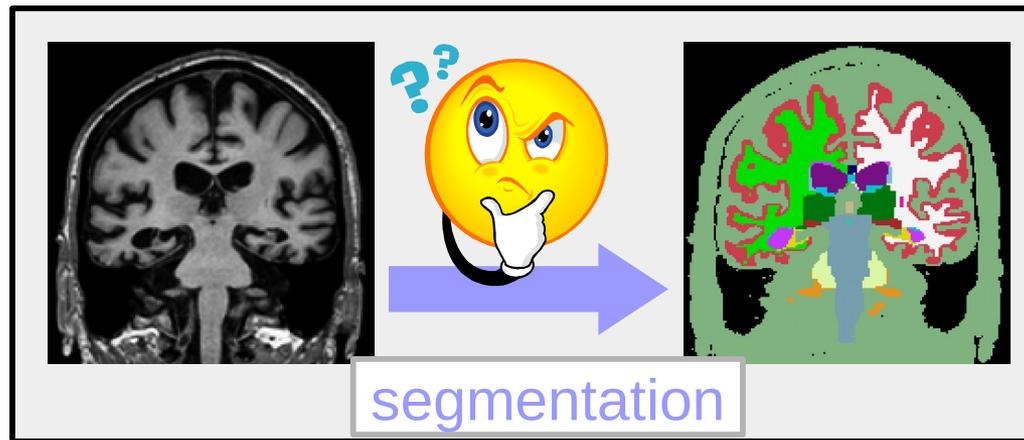
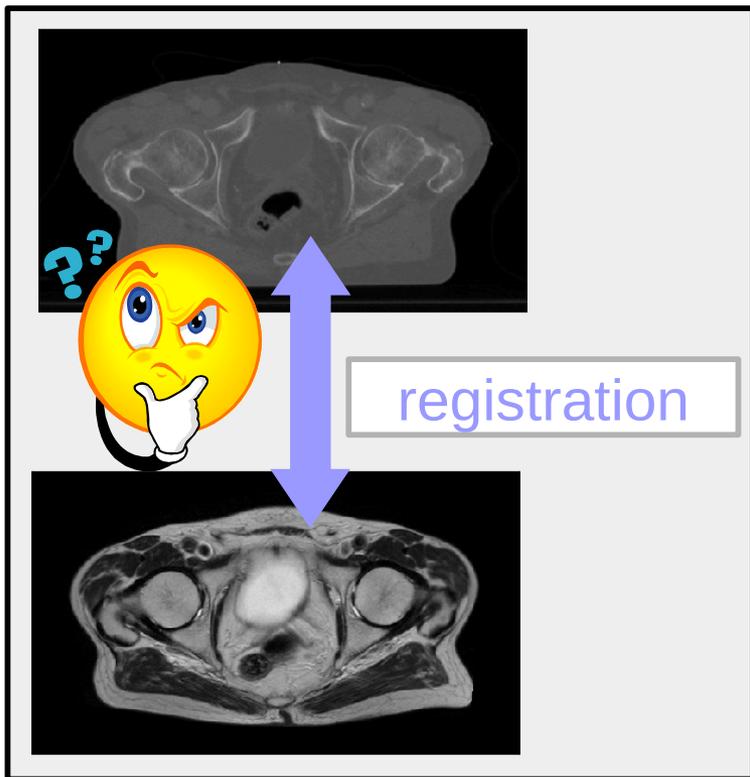
# Medical Image Analysis

Course 22525

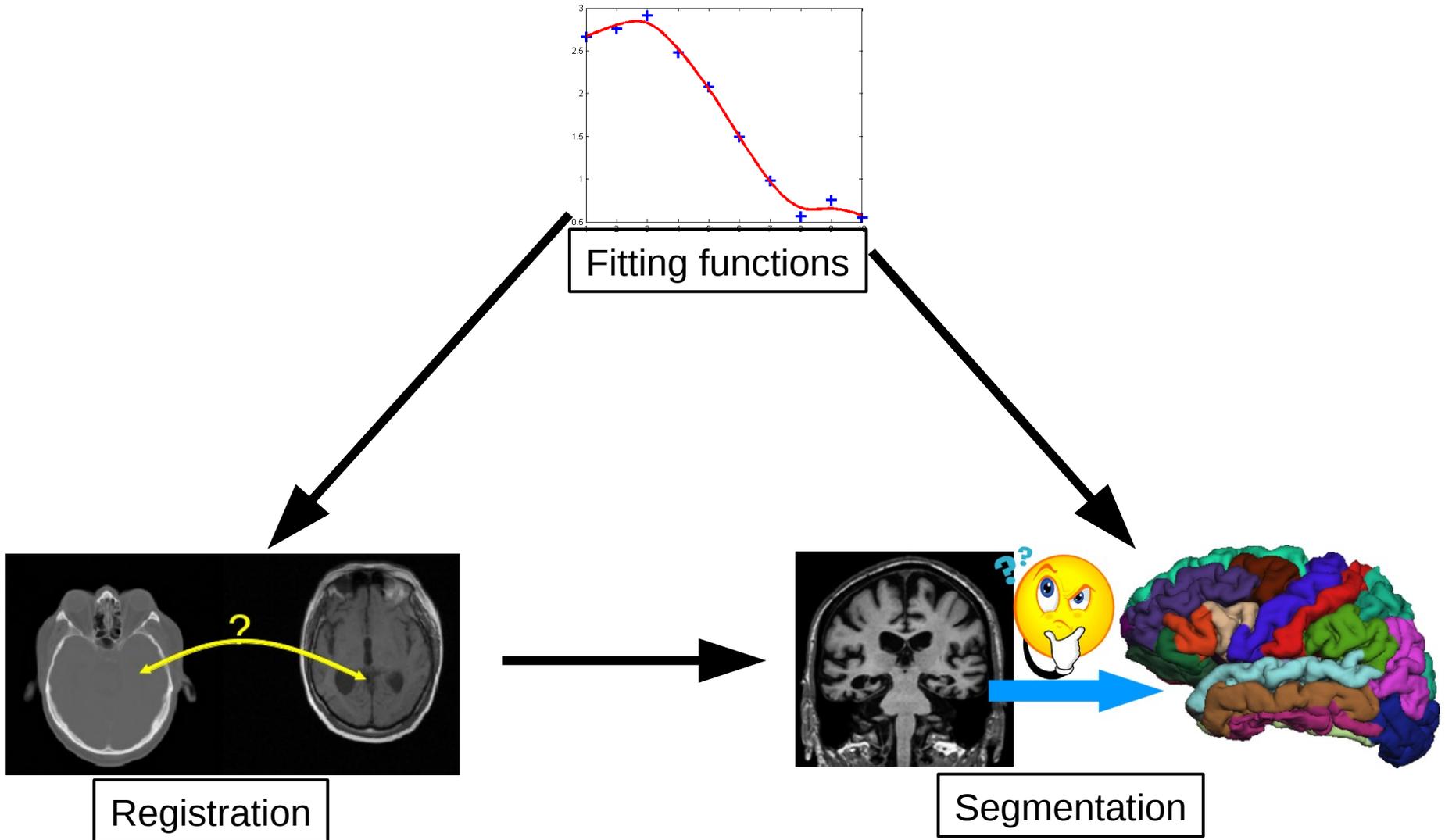
**Koen Van Leemput**

DTU HealthTech

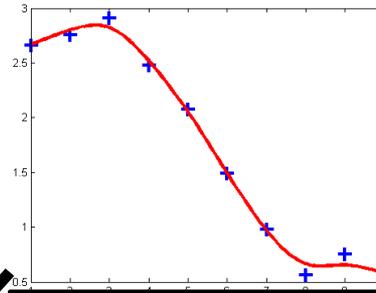
Technical University of Denmark



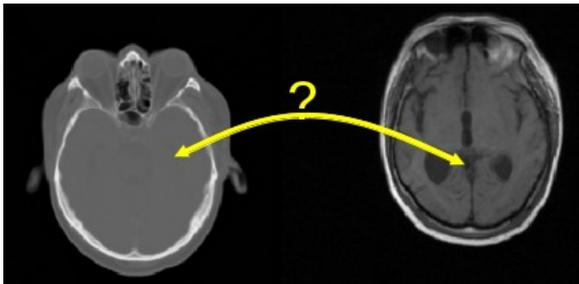
# Course structure



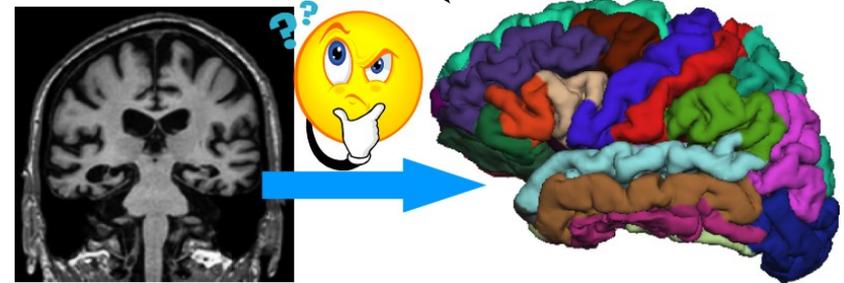
# Course structure



Fitting functions



Registration



Segmentation

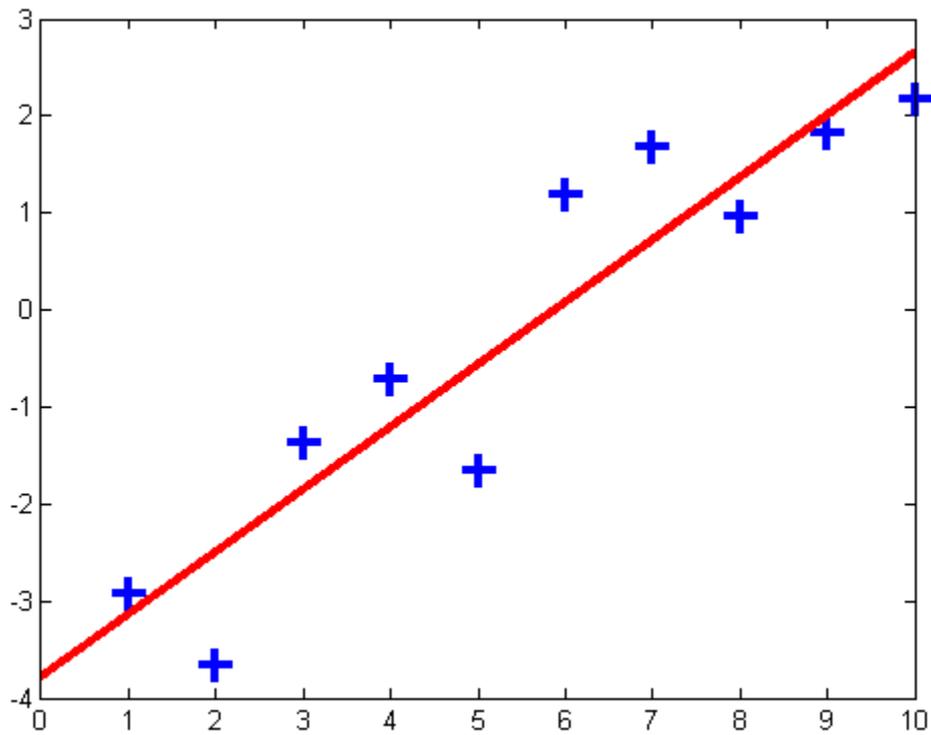
# Linear regression

Input:  $\mathbf{x}_i = (x_{i1}, x_{i2}, \dots, x_{ip})^T \in \mathbb{R}^p$

Observations:  $\{\mathbf{x}_i, y_i\}_{i=1}^N$

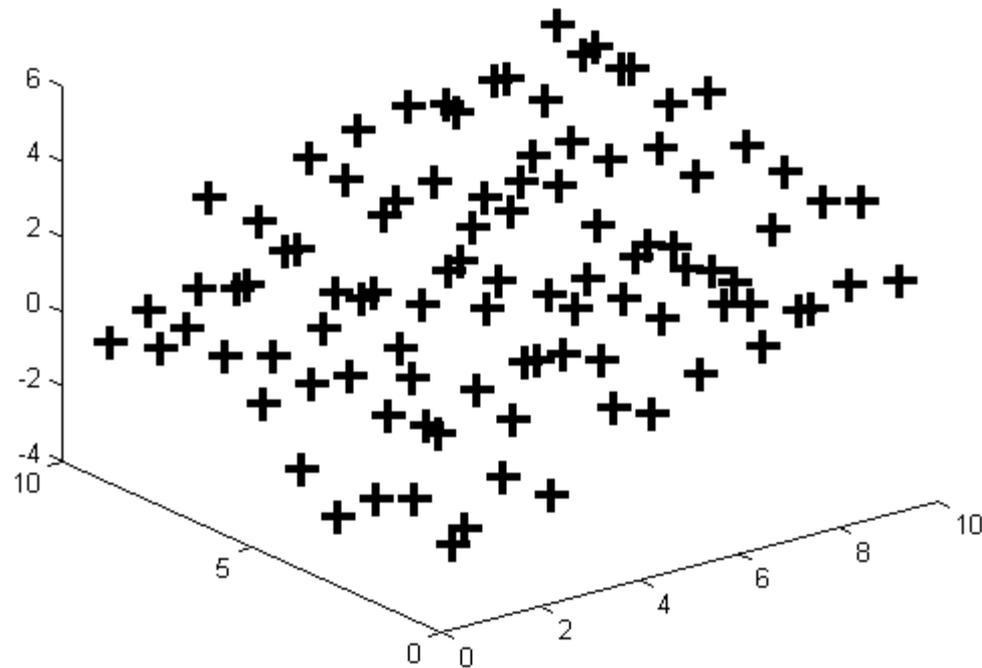
Linear regression model:  $f(\mathbf{x}_i) = \beta_0 + \sum_{j=1}^p x_{ij}\beta_j$

# Example



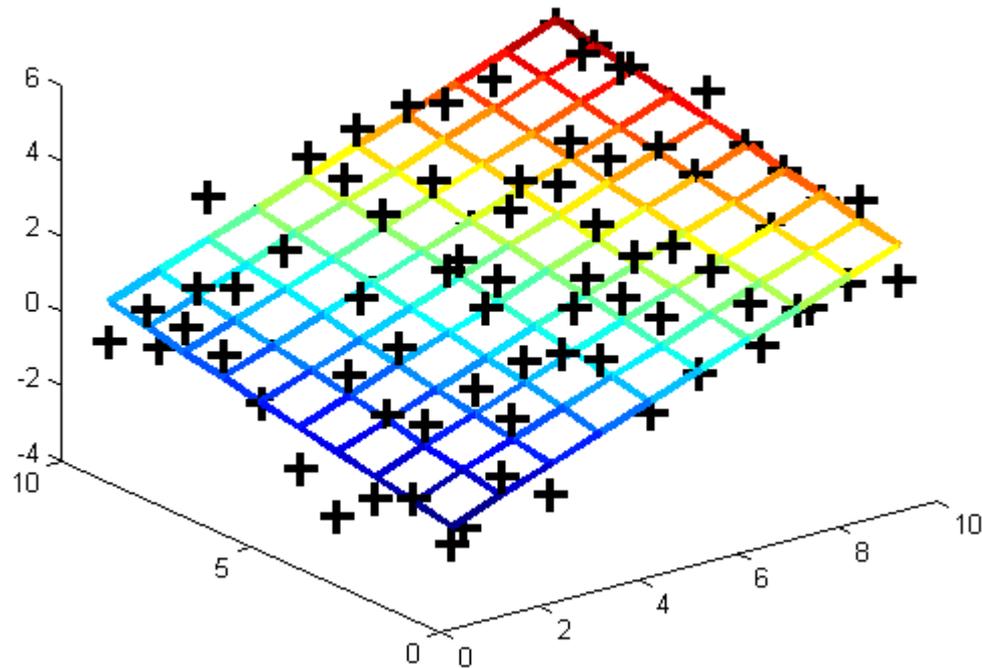
$$f(\mathbf{x}): \mathbf{x} \in \mathbb{R}$$

# Example



$$f(\mathbf{x}) : \mathbf{x} \in \mathbb{R}^2$$

# Example



$$f(\mathbf{x}) : \mathbf{x} \in \mathbb{R}^2$$

# Linear regression

Find parameter vector  $\boldsymbol{\beta} = (\beta_0, \beta_1, \dots, \beta_p)^\top$  that minimizes

$$\text{RSS}(\boldsymbol{\beta}) = \sum_{i=1}^N (y_i - f(\mathbf{x}_i))^2 = \sum_{i=1}^N (y_i - \beta_0 - \sum_{j=1}^p x_{ij}\beta_j)^2$$

Matrix notation:

$$\text{RSS} = (\mathbf{y} - \mathbf{X}\boldsymbol{\beta})^\top (\mathbf{y} - \mathbf{X}\boldsymbol{\beta})$$

$$\mathbf{X} = \begin{pmatrix} 1 & x_{11} & x_{12} & \cdots & x_{1p} \\ 1 & x_{21} & x_{22} & \cdots & x_{2p} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 1 & x_{N1} & x_{N2} & \cdots & x_{Np} \end{pmatrix} \quad \mathbf{y} = (y_1, y_2, \dots, y_N)^\top$$

# Linear regression

$$\text{RSS} = (\mathbf{y} - \mathbf{X}\boldsymbol{\beta})^T (\mathbf{y} - \mathbf{X}\boldsymbol{\beta})$$

$$\frac{\partial \text{RSS}}{\partial \boldsymbol{\beta}} = -2\mathbf{X}^T (\mathbf{y} - \mathbf{X}\boldsymbol{\beta})$$

Minimum found at:  $\mathbf{X}^T (\mathbf{y} - \mathbf{X}\boldsymbol{\beta}) = 0$

# Linear regression

$$\mathbf{X}^T(\mathbf{y} - \mathbf{X}\boldsymbol{\beta}) = 0 \quad \longrightarrow \quad \hat{\boldsymbol{\beta}} = (\mathbf{X}^T\mathbf{X})^{-1}\mathbf{X}^T\mathbf{y}$$

The predicted values at the training points are

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

$\mathbf{H} = \mathbf{X}(\mathbf{X}^T\mathbf{X})^{-1}\mathbf{X}^T$  is called the “hat” matrix

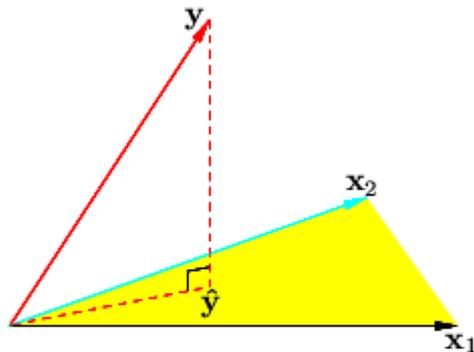


Figure 3.2: *The  $N$ -dimensional geometry of least squares regression with two predictors. The outcome vector  $\mathbf{y}$  is orthogonally projected onto the hyperplane spanned by the input vectors  $\mathbf{x}_1$  and  $\mathbf{x}_2$ . The projection  $\hat{\mathbf{y}}$  represents the vector of the least squares predictions*

Residuals are orthogonal to column space of  $\mathbf{X}$

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

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

$\mathbf{H}$  computes this projection.

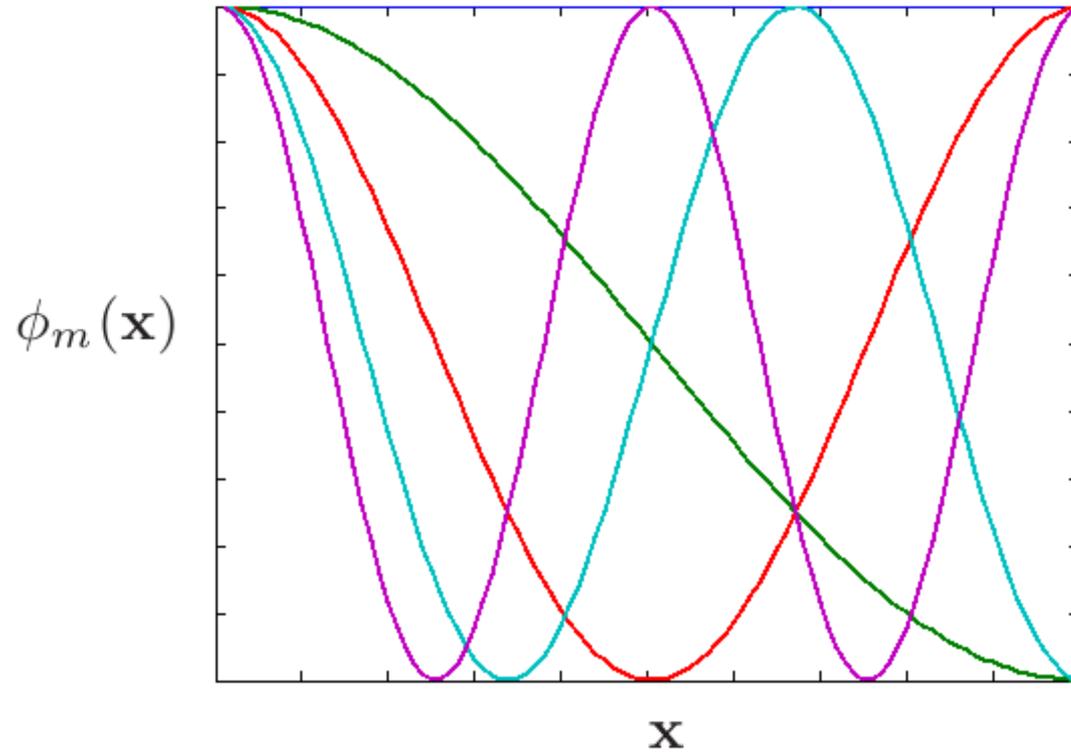
# Linear basis function models

Models so far linear in both parameters  $\beta$  **and** input variables  $x_{ip}$

More flexible models:  $f(\mathbf{x}) = \sum_{m=1}^M \beta_m \phi_m(\mathbf{x})$

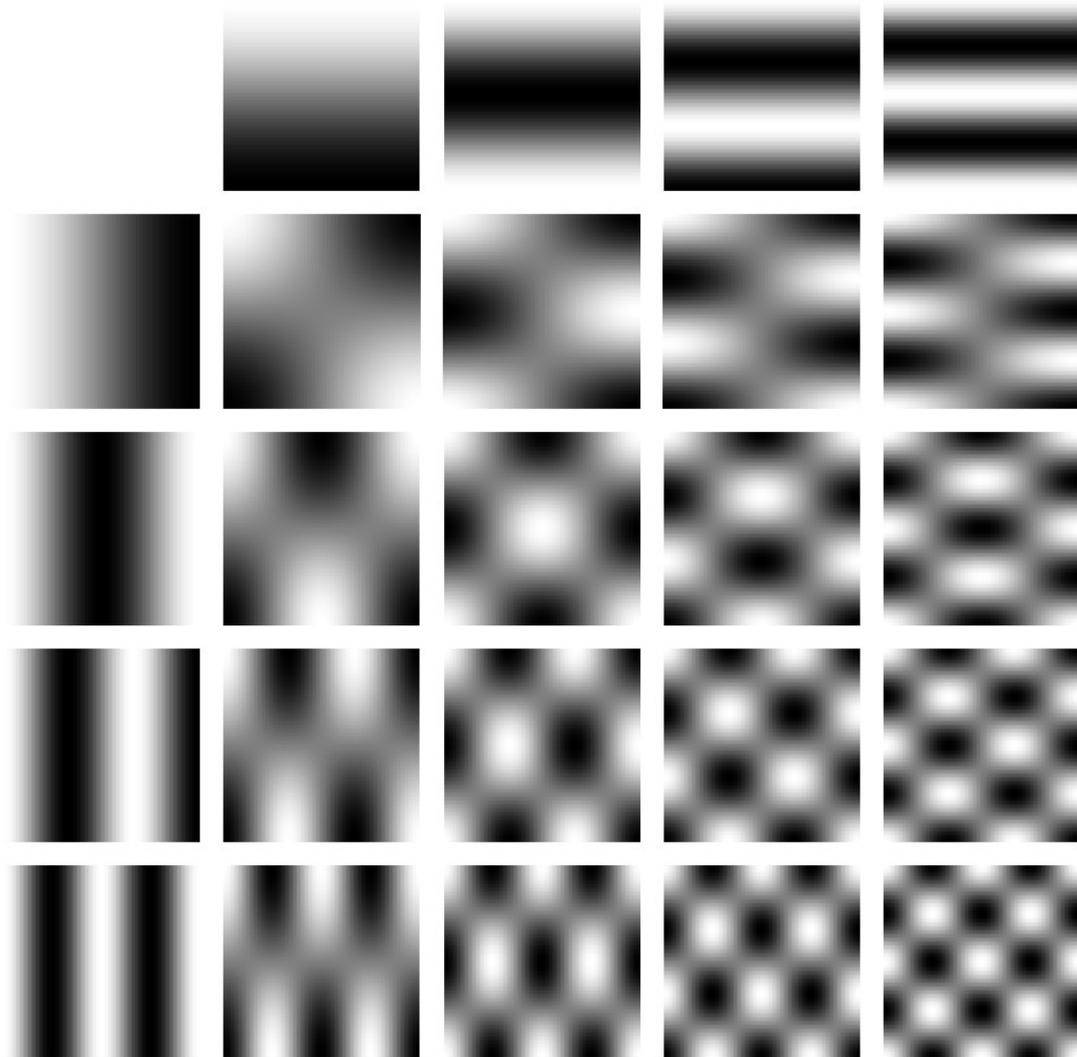
$\phi_m(\mathbf{x})$  are *basis functions*: non-linear, smooth functions of  $\mathbf{x}$

# Example: cosines (1D)

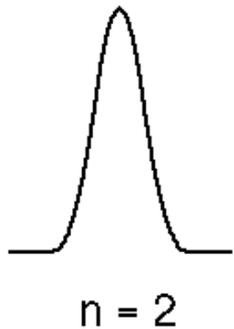
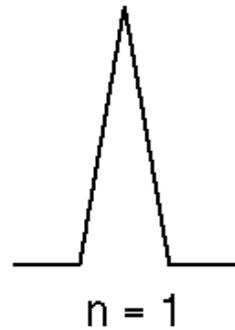
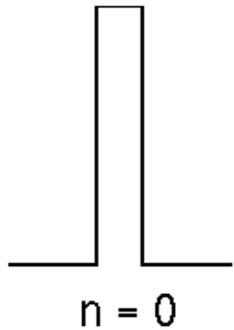


# Example: cosines (2D)

$\phi_m(\mathbf{x})$

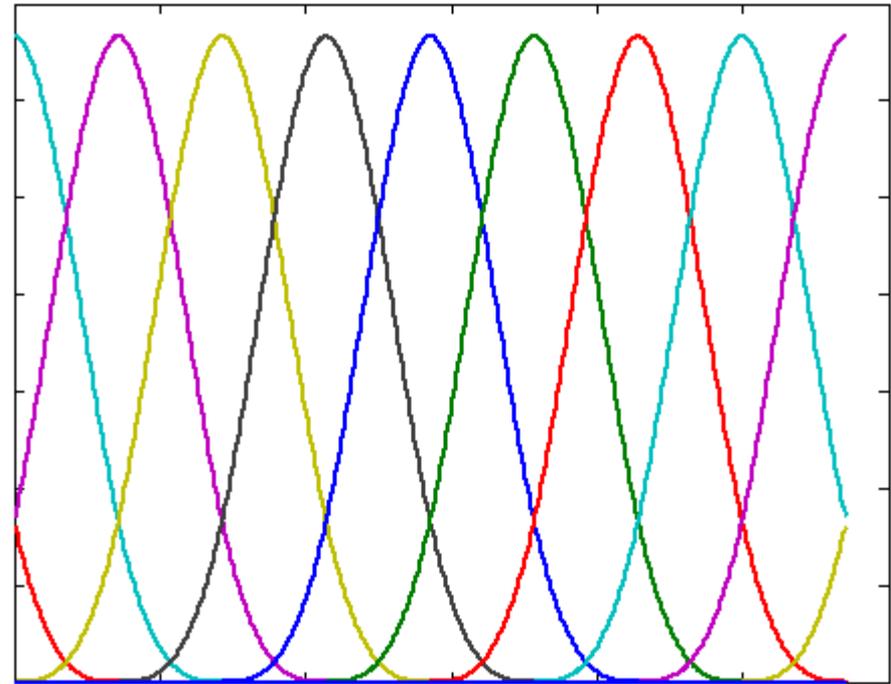


# Example: B-splines (1D)



$$B_0(x) = \begin{cases} 1, & -\frac{1}{2} \leq x \leq \frac{1}{2} \\ \frac{1}{2}, & |x| = \frac{1}{2} \\ 0, & \text{otherwise} \end{cases}$$

$$B_n(x) = \underbrace{B_0 * B_0 \dots B_0(x)}_{(n+1) \text{ times}}$$



$\phi_m(\mathbf{x})$

# Linear basis function models

Minimize: 
$$\sum_{i=1}^N (y_i - f(\mathbf{x}_i))^2 = (\mathbf{y} - \Phi\boldsymbol{\beta})^T (\mathbf{y} - \Phi\boldsymbol{\beta})$$

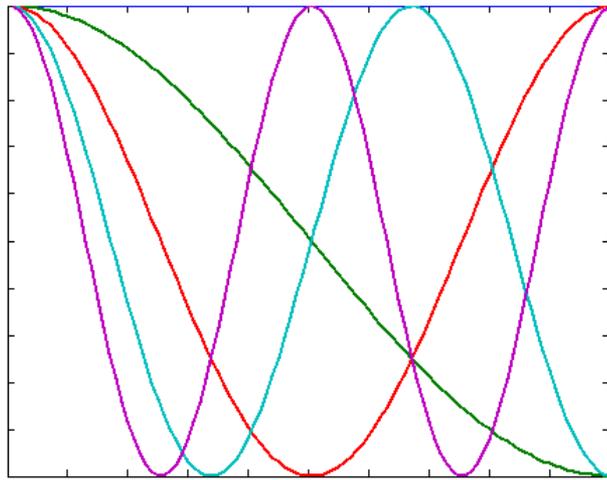
$$\Phi = \begin{pmatrix} \phi_1(\mathbf{x}_1) & \phi_2(\mathbf{x}_1) & \cdots & \phi_M(\mathbf{x}_1) \\ \phi_1(\mathbf{x}_2) & \phi_2(\mathbf{x}_2) & \cdots & \phi_M(\mathbf{x}_2) \\ \vdots & \vdots & \ddots & \vdots \\ \phi_1(\mathbf{x}_N) & \phi_2(\mathbf{x}_N) & \cdots & \phi_M(\mathbf{x}_N) \end{pmatrix}$$

Non-linear in input variables, but still linear in parameters!

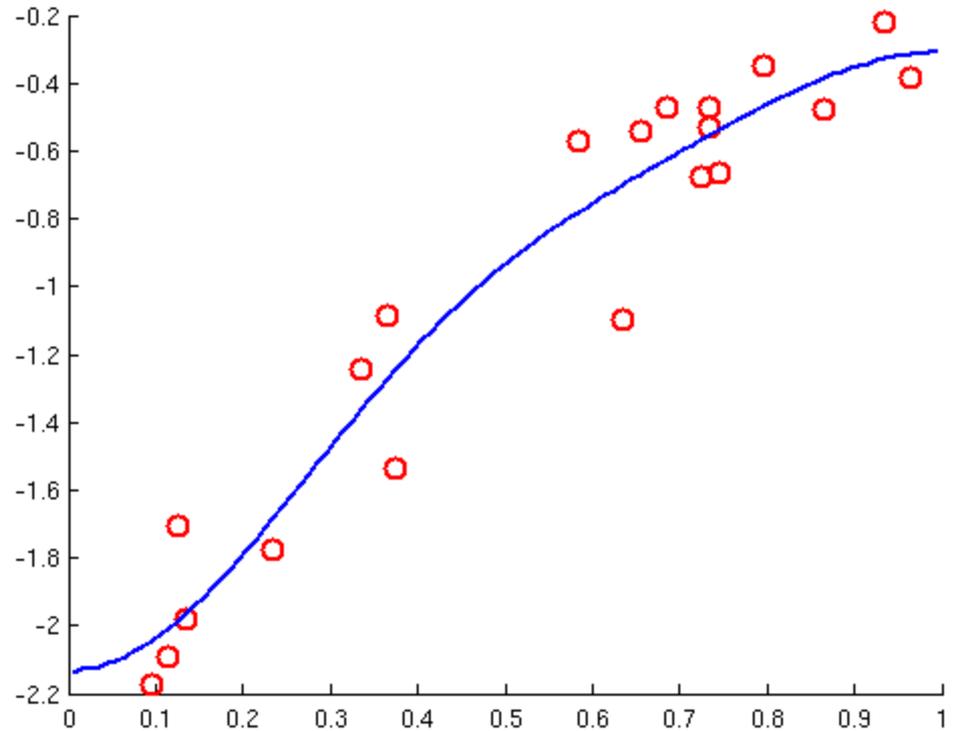
Solution (set gradient to zero): 
$$\hat{\boldsymbol{\beta}} = (\Phi^T \Phi)^{-1} \Phi^T \mathbf{y}$$

Predicted values at training points: 
$$\hat{\mathbf{y}} = \Phi \hat{\boldsymbol{\beta}} = \Phi (\Phi^T \Phi)^{-1} \Phi^T \mathbf{y}$$

# Linear basis function models



$\phi_m(\mathbf{x})$



# Regularization

Minimize:  $(\mathbf{y} - \Phi\boldsymbol{\beta})^T(\mathbf{y} - \Phi\boldsymbol{\beta}) + \lambda\boldsymbol{\beta}^T\Theta\boldsymbol{\beta}$

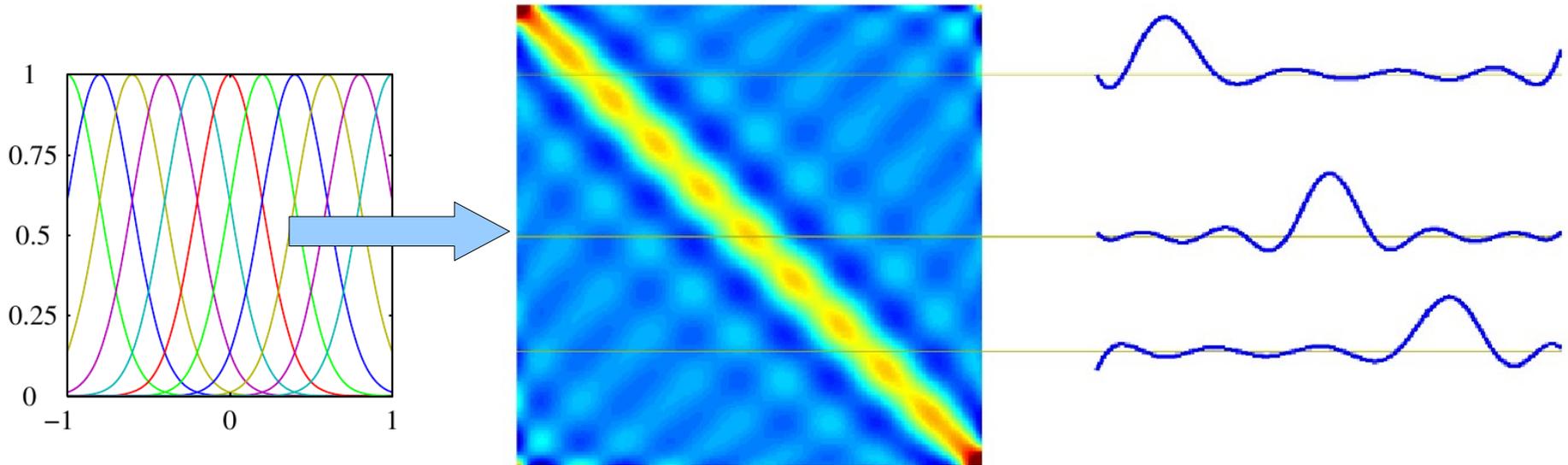
$\Theta$  is a  $M \times M$  positive-semidefinite matrix that penalizes certain  $\boldsymbol{\beta}$

Solution (set gradient to zero):  $\hat{\boldsymbol{\beta}} = (\Phi^T\Phi + \lambda\Theta)^{-1}\Phi^T\mathbf{y}$

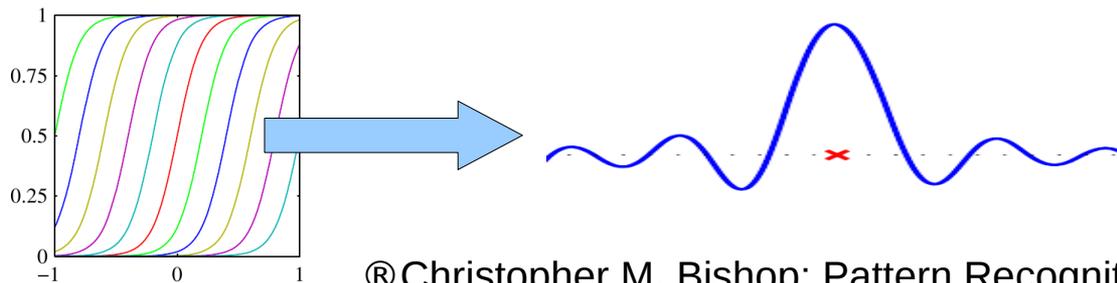
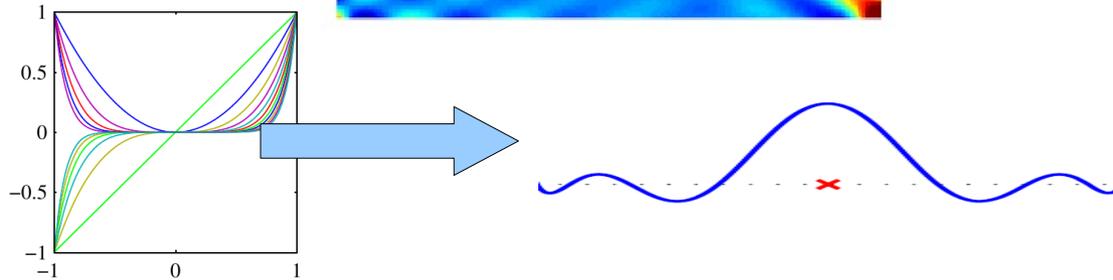
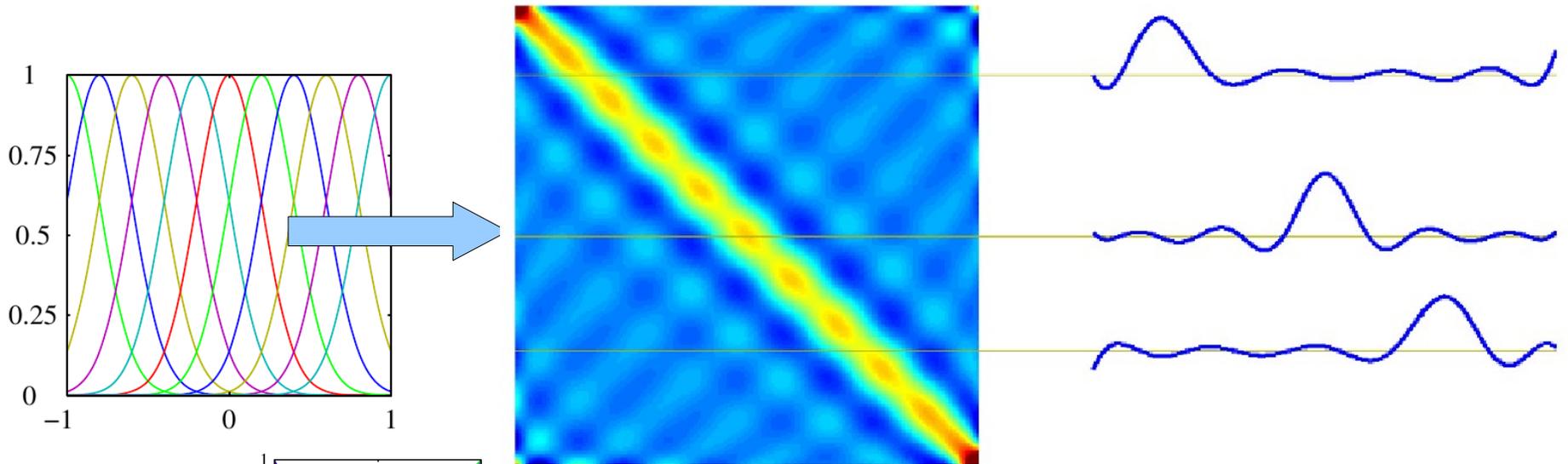
Predicted values at training points:  $\hat{\mathbf{y}} = \Phi(\Phi^T\Phi + \lambda\Theta)^{-1}\Phi^T\mathbf{y}$

$$\text{tr}(\Phi(\Phi^T\Phi + \lambda\Theta)^{-1}\Phi^T) = \textit{effective degrees of freedom} \\ \leq \text{number of parameters } M$$

# Meaning of $\hat{y} = \Phi(\Phi^T \Phi + \lambda \Theta)^{-1} \Phi^T y$



# Meaning of $\hat{y} = \Phi(\Phi^T \Phi + \lambda \Theta)^{-1} \Phi^T y$



## Please discuss in your buzz group

"buzzGroup\_questions.pdf"

in DTU Learn

(<https://learn.inside.dtu.dk>)

We have seen that approximating a  $N$ -dimensional measurement vector  $\mathbf{y}$  with a regression model  $\Phi\beta$ , where  $\Phi$  is a  $N \times M$  matrix of  $M$  basis functions stored in its columns, and  $\beta$  is a  $M$ -dimensional parameter vector, can be obtained by minimizing

$$\|\mathbf{y} - \Phi\beta\|^2 + \lambda\beta^T\Theta\beta,$$

where  $\Theta$  is a regularization matrix and  $\lambda$  is a regularization strength.

Here we will consider the special case where there is no regularization (e.g.,  $\lambda$  is set to zero), so that the regression problem reduces to minimizing

$$\|\mathbf{y} - \Phi\beta\|^2.$$

As we have seen, the solution to this problem is given by

$$\hat{\beta} = (\Phi^T\Phi)^{-1}\Phi^T\mathbf{y},$$

so that  $\mathbf{y}$  is approximated by

$$\hat{\mathbf{y}} = \Phi\hat{\beta} = \Phi(\Phi^T\Phi)^{-1}\Phi^T\mathbf{y} = \mathbf{H}\mathbf{y},$$

where  $\mathbf{H} = \Phi(\Phi^T\Phi)^{-1}\Phi^T$  is a  $N \times N$  matrix that transforms  $\mathbf{y}$  into  $\hat{\mathbf{y}}$ .

### Task 1

Consider the case

$$\mathbf{y} = \begin{pmatrix} 2 \\ 1 \\ 3 \end{pmatrix} \quad \text{and} \quad \Phi = \begin{pmatrix} 1 \\ 1 \\ 1 \end{pmatrix}.$$

What is  $\hat{\beta}$ ?

### Task 2

In the same case

$$\mathbf{y} = \begin{pmatrix} 2 \\ 1 \\ 3 \end{pmatrix} \quad \text{and} \quad \Phi = \begin{pmatrix} 1 \\ 1 \\ 1 \end{pmatrix},$$

what is  $\mathbf{H}$ , what is the number of degrees of freedom  $\text{tracce}(\mathbf{H})$ , and what is  $\hat{\mathbf{y}}$ ? Can you explain (e.g., draw) what is happening?

### Task 3

Now consider the slightly harder problem

$$\mathbf{y} = \begin{pmatrix} 2 \\ 1 \\ 3 \end{pmatrix} \quad \text{and} \quad \Phi = \begin{pmatrix} 1 & 1 & 1 \\ 1 & 2 & 4 \\ 1 & 3 & 9 \end{pmatrix}.$$

Again: what is  $\mathbf{H}$ , what is the number of degrees of freedom  $\text{tracce}(\mathbf{H})$ , and what is  $\hat{\mathbf{y}}$ ? Can you explain (e.g., draw) what is happening?

## Solution to task 1

Consider the case

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## Solution to task 1

Consider the case

$$\mathbf{y} = \begin{pmatrix} 2 \\ 1 \\ 3 \end{pmatrix} \quad \text{and} \quad \Phi = \begin{pmatrix} 1 \\ 1 \\ 1 \end{pmatrix}.$$

What is  $\hat{\beta}$ ?

Solution:

$$\Phi^T \mathbf{y} = 1 + 2 + 3 = 6,$$

and

$$\Phi^T \Phi = 1^2 + 1^2 + 1^2 = 3,$$

so

$$\hat{\beta} = (\Phi^T \Phi)^{-1} \Phi^T \mathbf{y} = 3^{-1} 6 = 2.$$

## Solution to task 2

In the same case

$$\mathbf{y} = \begin{pmatrix} 2 \\ 1 \\ 3 \end{pmatrix} \quad \text{and} \quad \Phi = \begin{pmatrix} 1 \\ 1 \\ 1 \end{pmatrix},$$

what is  $\mathbf{H}$ , what is the number of degrees of freedom  $\text{tracc}(\mathbf{H})$ , and what is  $\hat{\mathbf{y}}$ ? Can you explain (e.g., draw) what is happening?

## Solution to task 2

In the same case

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what is  $\mathbf{H}$ , what is the number of degrees of freedom  $\text{tracc}(\mathbf{H})$ , and what is  $\hat{\mathbf{y}}$ ? Can you explain (e.g., draw) what is happening?

Solution:

$$\begin{aligned} \mathbf{H} &= \Phi (\Phi^T \Phi)^{-1} \Phi^T \\ &= \begin{pmatrix} 1 \\ 1 \\ 1 \end{pmatrix} \cdot 3^{-1} \cdot (1 \ 1 \ 1) \\ &= 3^{-1} \cdot \begin{pmatrix} 1 \\ 1 \\ 1 \end{pmatrix} (1 \ 1 \ 1) \\ &= 3^{-1} \cdot \begin{pmatrix} 1 & 1 & 1 \\ 1 & 1 & 1 \\ 1 & 1 & 1 \end{pmatrix} \\ &= \begin{pmatrix} 1/3 & 1/3 & 1/3 \\ 1/3 & 1/3 & 1/3 \\ 1/3 & 1/3 & 1/3 \end{pmatrix}, \end{aligned}$$

so

$$\text{trace}(\mathbf{H}) = 1/3 + 1/3 + 1/3 = 1,$$

and

$$\hat{\mathbf{y}} = \begin{pmatrix} 1/3 & 1/3 & 1/3 \\ 1/3 & 1/3 & 1/3 \\ 1/3 & 1/3 & 1/3 \end{pmatrix} \begin{pmatrix} 2 \\ 1 \\ 3 \end{pmatrix} = \begin{pmatrix} 2 \\ 2 \\ 2 \end{pmatrix}.$$

Interpretation: We are fitting a horizontal line to three points. Offset is the only parameter we get to play with (one degree of freedom). Figure 1 illustrates the situation.

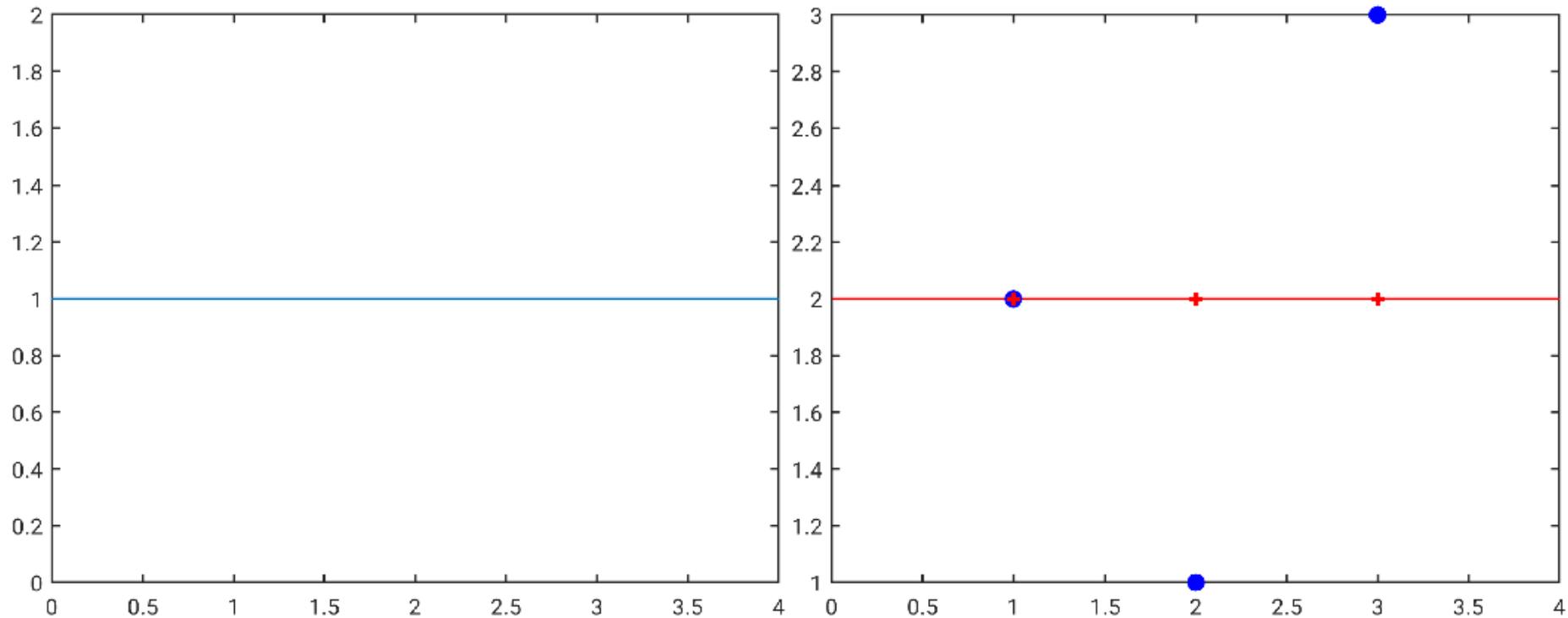


Figure 1: Left: the one column in  $\Phi$  represents a horizontal line. Right: the horizontal line is fitted to the input measurements  $y$  (blue dots), resulting in  $\hat{y}$  (red crosses).

### Solution to task 3

Now consider the slightly harder problem

$$\mathbf{y} = \begin{pmatrix} 2 \\ 1 \\ 3 \end{pmatrix} \quad \text{and} \quad \Phi = \begin{pmatrix} 1 & 1 & 1 \\ 1 & 2 & 4 \\ 1 & 3 & 9 \end{pmatrix}.$$

Again: what is  $\mathbf{H}$ , what is the number of degrees of freedom  $\text{trace}(\mathbf{H})$ , and what is  $\hat{\mathbf{y}}$ ? Can you explain (e.g., draw) what is happening?

### Solution to task 3

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Again: what is  $\mathbf{H}$ , what is the number of degrees of freedom  $\text{trace}(\mathbf{H})$ , and what is  $\hat{\mathbf{y}}$ ? Can you explain (e.g., draw) what is happening?

Solution: since  $\Phi$  is square and invertible, we have that

$$(\Phi^T \Phi)^{-1} = \Phi^{-1} (\Phi^T)^{-1},$$

so that

$$\begin{aligned} \mathbf{H} &= \Phi (\Phi^T \Phi)^{-1} \Phi^T \\ &= \overbrace{\Phi \Phi^{-1}}^{\mathbf{I}} \underbrace{(\Phi^T)^{-1} \Phi^T}_{\mathbf{I}} \\ &= \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix}. \end{aligned}$$

Therefore

$$\text{trace}(\mathbf{H}) = 1 + 1 + 1 = 3,$$

and  $\hat{\mathbf{y}}$  is simply  $\mathbf{y}$ :

$$\hat{\mathbf{y}} = \mathbf{H}\mathbf{y} = \mathbf{y} = \begin{pmatrix} 2 \\ 1 \\ 3 \end{pmatrix}.$$

Interpretation: we're fitting three basis functions (quadratic function) to three measurement points. We have three coefficients to play with, so three degrees of freedom for three measurement points, and as a result we can fit the curve perfectly through the measurement points (no smoothing). Figure 2 illustrates the situation.

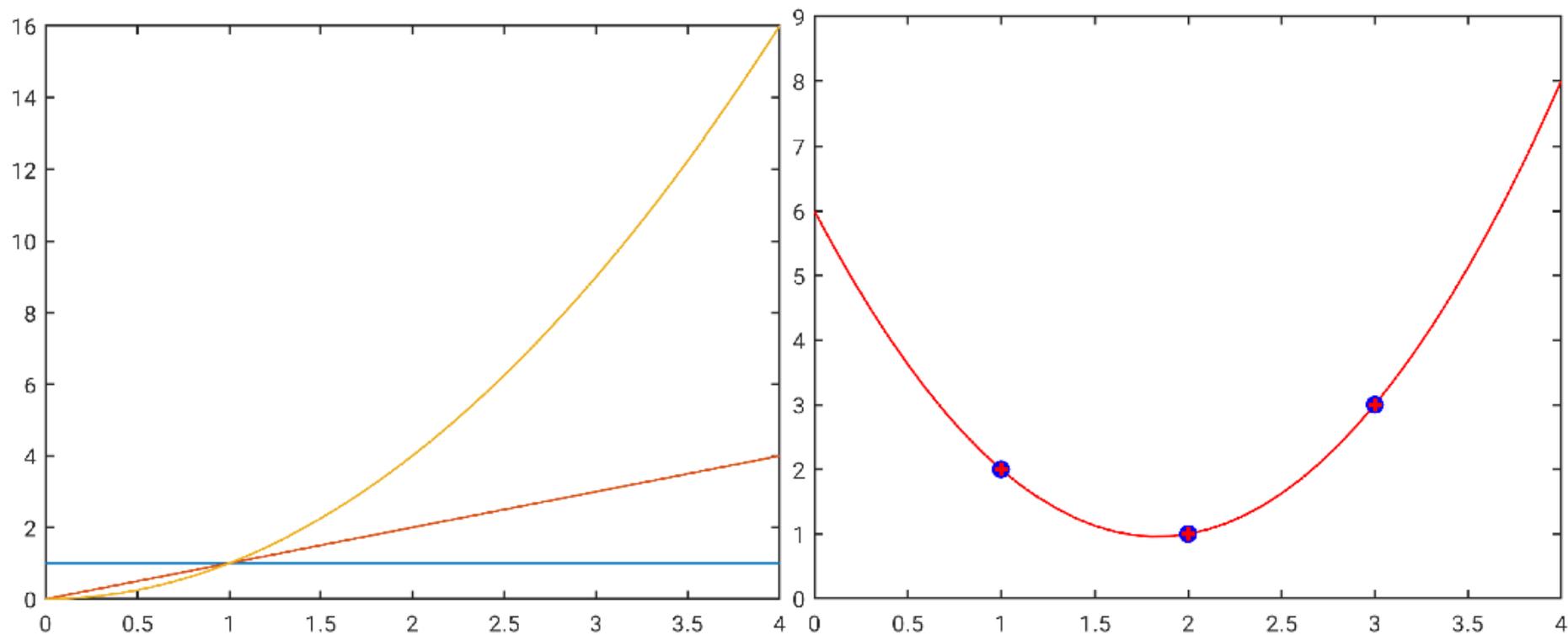


Figure 2: Left: the three columns in  $\Phi$  represents polynomials of degrees 0, 1 and 2. Right: a quadratic curve is fitted to the input measurements  $y$  (blue dots), resulting in  $\hat{y}$  (red crosses).

# Cubic smoothing spline

So far, *imposed* smoothness by limiting models to be linear combinations of smooth basis functions

What happens if we don't impose such structure, but simply look for the function  $f(x)$  that minimizes

$$\sum_{i=1}^N (y_i - f(x_i))^2 + \lambda \int (f''(t))^2 dt \quad ? \quad (1D)$$

# Cubic smoothing spline

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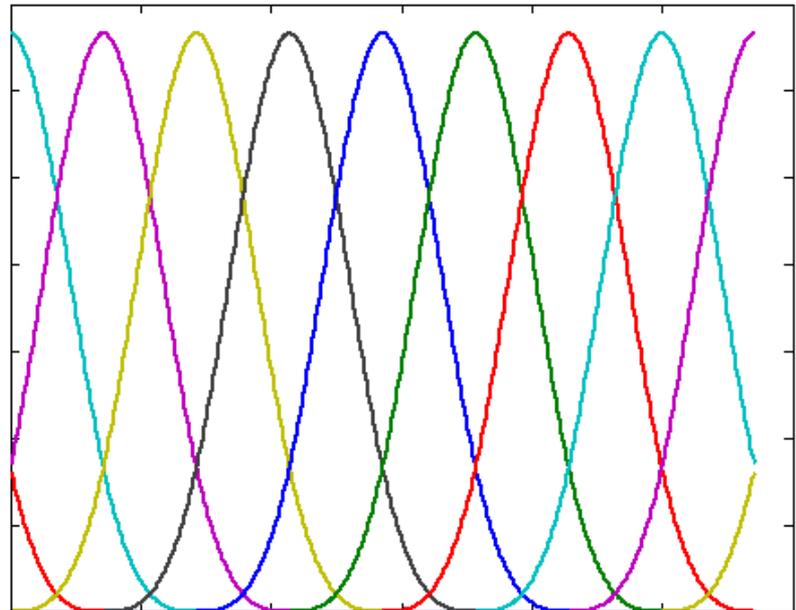
It can be shown to have the structure

$$f(x) = \sum_{m=1}^M \beta_m \phi_m(x) \quad !$$

# Cubic smoothing spline

$\phi_m(x)$  can be shown to be so-called cubic B-spline basis functions  $B_m(x; \xi)$

for equidistantly placed input points  $x_i$ , these are the uniform cubic B-spline basis functions encountered before



# Cubic smoothing spline

Plugging  $f(x) = \sum_{m=1}^M \beta_m \phi_m(x)$

into  $\sum_{i=1}^N (y_i - f(x_i))^2 + \lambda \int (f''(t))^2 dt,$

we have to minimize  $(\mathbf{y} - \mathbf{B}\boldsymbol{\beta})^T (\mathbf{y} - \mathbf{B}\boldsymbol{\beta}) + \lambda \boldsymbol{\beta}^T \boldsymbol{\Omega}_{\mathbf{B}} \boldsymbol{\beta}$

$\mathbf{B}$  contains the basis functions

$$\{\boldsymbol{\Omega}_{\mathbf{B}}\}_{jk} = \int B_j''(t; \xi) B_k''(t; \xi) dt$$

# Cubic smoothing spline

We've seen this before!

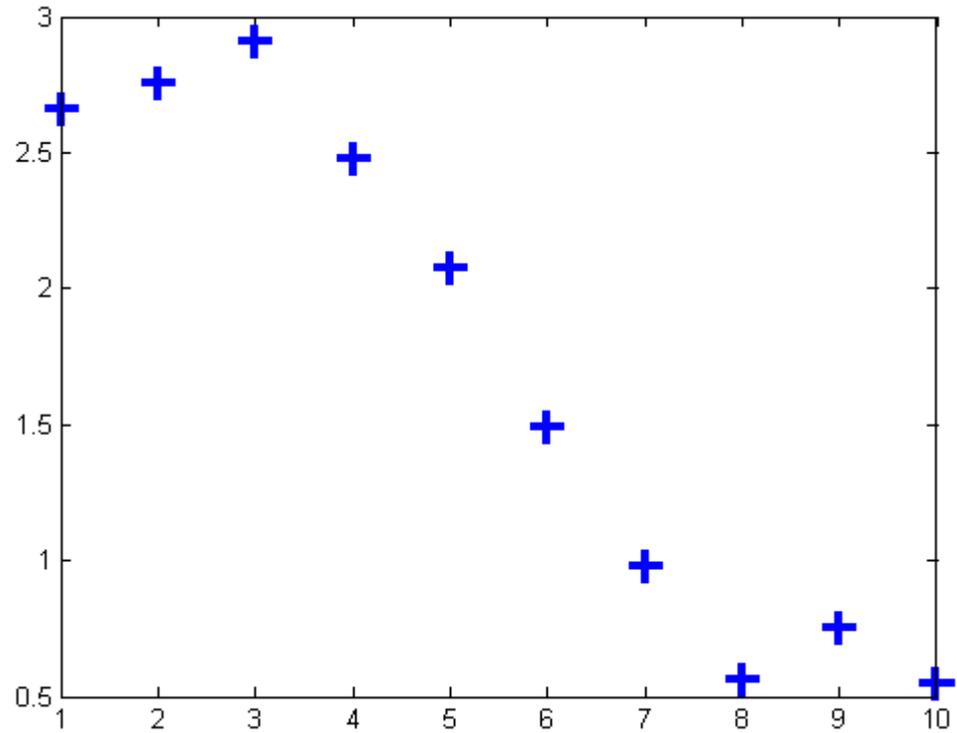

$$\hat{\beta} = (\mathbf{B}^T \mathbf{B} + \lambda \Omega_{\mathbf{B}})^{-1} \mathbf{B}^T \mathbf{y}$$

Predicted values at training points:

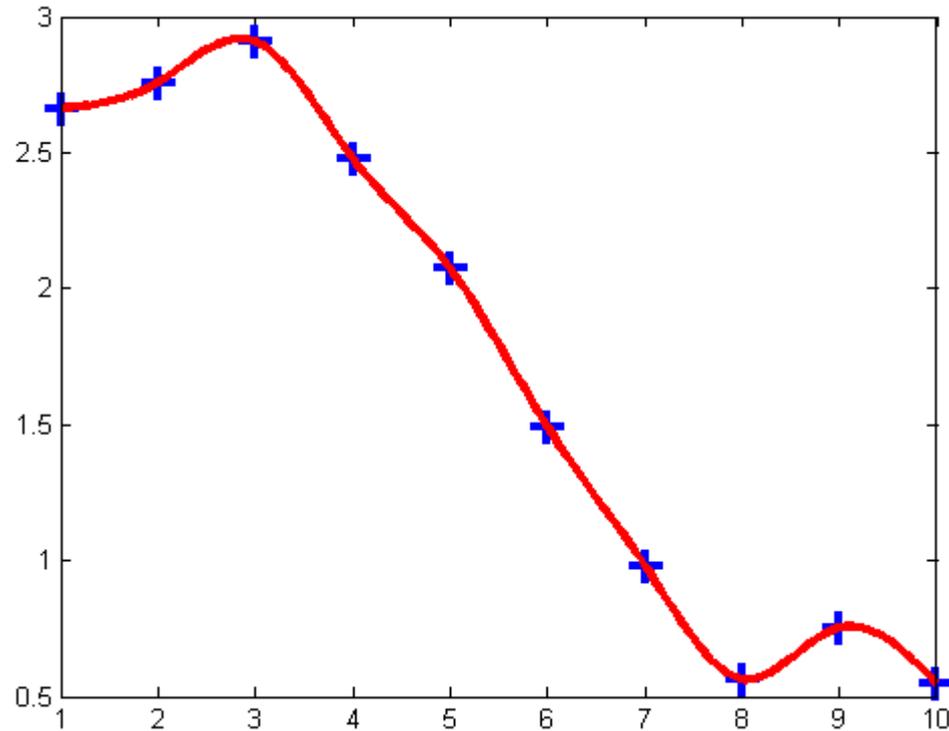
$$\begin{aligned} \hat{\mathbf{y}} &= \mathbf{B}(\mathbf{B}^T \mathbf{B} + \lambda \Omega_{\mathbf{B}})^{-1} \mathbf{B}^T \mathbf{y} \\ &= \mathbf{S}_{\lambda} \mathbf{y}. \end{aligned}$$

Effective degrees of freedom,  $\text{tr}(\mathbf{S}_{\lambda})$ , depends on  $\lambda$

# Cubic smoothing spline

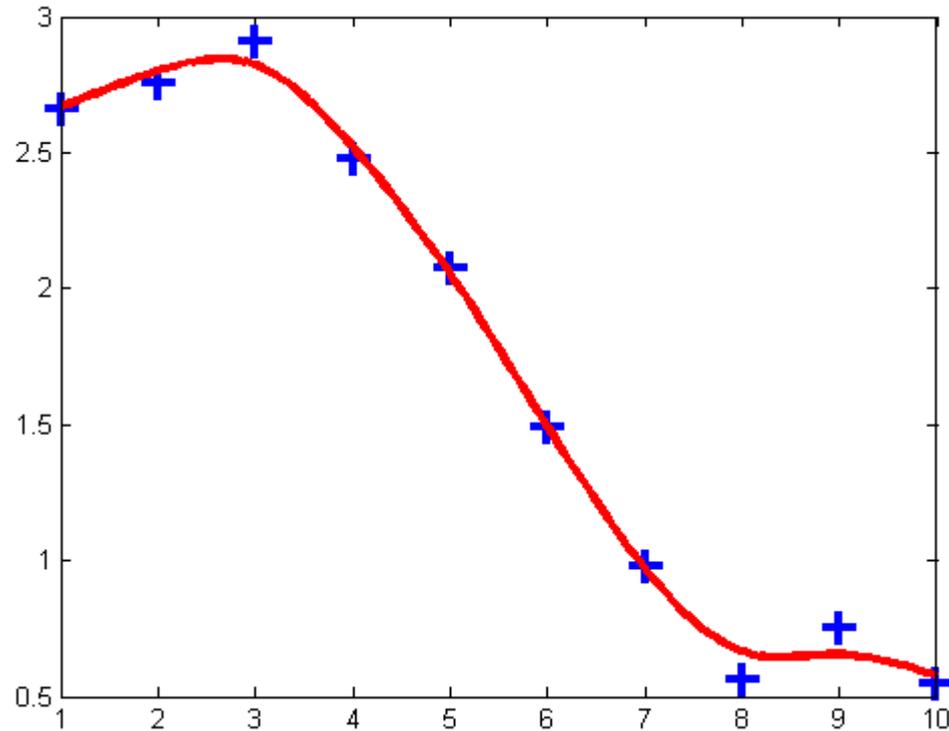


# Cubic smoothing spline



$\lambda = 0$ : spline passes exactly through measurements

# Cubic smoothing spline



$\lambda > 0$ : spline smooths measurements

# Thin plate spline

Generalization of cubic smoothing spline to 2D and 3D

Find function  $f(\mathbf{x})$  that minimizes  $\sum_{i=1}^N (y_i - f(\mathbf{x}_i))^2 + \lambda J_p(f)$

with 
$$J_p(f) = \int_{\mathbb{R}^p} \sum_{i=1}^p \sum_{j=1}^p \left[ \frac{\partial^2 f}{\partial u_i \partial u_j} \right]^2 d\mathbf{u}$$

e.g., in 2D: 
$$J_2(f) = \int_{\mathbb{R}^2} \left[ \frac{\partial^2 f}{\partial u_1^2} \right]^2 + 2 \left[ \frac{\partial^2 f}{\partial u_1 \partial u_2} \right]^2 + \left[ \frac{\partial^2 f}{\partial u_2^2} \right]^2 d\mathbf{u}$$

# Thin plate spline

Can be shown to be of the form

$$f(\mathbf{x}) = \beta_0 + \boldsymbol{\beta}_1^T \mathbf{x} + \sum_{i=1}^N \alpha_i \eta_p(\|\mathbf{x} - \mathbf{x}_i\|),$$

with

$$\eta_2(r) = \begin{cases} r^2 \log r & \text{if } r > 0 \\ 0 & \text{if } r = 0 \end{cases} \quad (2D)$$

$$\eta_3(r) = \|r\|^3. \quad (3D)$$

# Thin plate spline

Plugging  $f(\mathbf{x}) = \beta_0 + \boldsymbol{\beta}_1^T \mathbf{x} + \sum_{i=1}^N \alpha_i \eta_p(\|\mathbf{x} - \mathbf{x}_i\|),$

into  $\sum_{i=1}^N (y_i - f(\mathbf{x}_i))^2 + \lambda J_p(f)$

yields minimization problem of the form (see course notes):

$$\begin{aligned} & \|\mathbf{y} - \mathbf{P}^T \boldsymbol{\beta} - \mathbf{K} \boldsymbol{\alpha}\|^2 + \lambda \boldsymbol{\alpha}^T \mathbf{K} \boldsymbol{\alpha} \\ & \text{s.t. } \mathbf{P} \boldsymbol{\alpha} = \mathbf{0} \end{aligned}$$

Solution (see course notes):

$$\begin{pmatrix} \mathbf{K} + \lambda \mathbf{I} & \mathbf{P}^T \\ \mathbf{P} & \mathbf{0} \end{pmatrix} \begin{pmatrix} \boldsymbol{\alpha} \\ \boldsymbol{\beta} \end{pmatrix} = \begin{pmatrix} \mathbf{y} \\ \mathbf{0} \end{pmatrix}$$

# Thin plate spline

Predicted values at training points:

$$\hat{\mathbf{y}} = \begin{pmatrix} \mathbf{K} & \mathbf{P}^T \end{pmatrix} \begin{pmatrix} \hat{\boldsymbol{\alpha}} \\ \hat{\boldsymbol{\beta}} \end{pmatrix} = \begin{pmatrix} \mathbf{K} & \mathbf{P}^T \end{pmatrix} \begin{pmatrix} \mathbf{K} + \lambda \mathbf{I} & \mathbf{P}^T \\ \mathbf{P} & \mathbf{0} \end{pmatrix}^{-1} \begin{pmatrix} \mathbf{y} \\ \mathbf{0} \end{pmatrix} = \mathbf{S}_\lambda^* \begin{pmatrix} \mathbf{y} \\ \mathbf{0} \end{pmatrix}$$

$N \times N$  “smoother matrix”  $\mathbf{S}_\lambda$  is the first  $N$  columns of  $\mathbf{S}_\lambda^*$

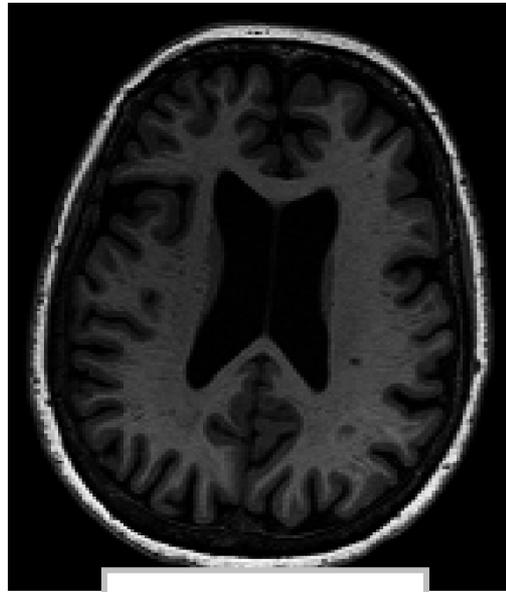
Effective degrees of freedom is again  $\text{trace}(\mathbf{S}_\lambda)$

$\lambda = 0$ : spline passes exactly through measurements  
 (“thin plate spline”)

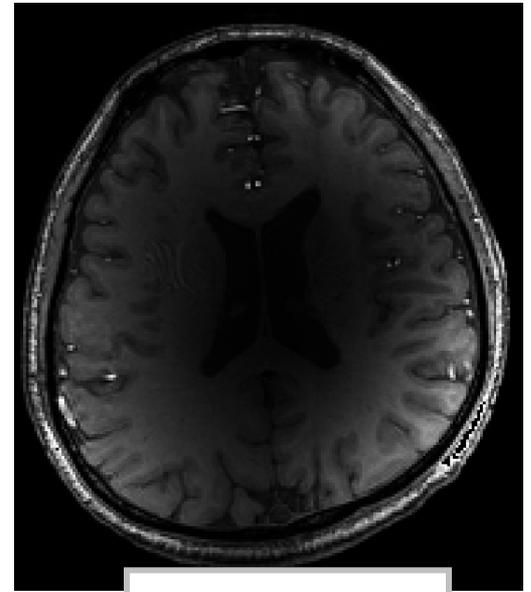
# Application: MR bias field



1.5 Tesla  
scanner

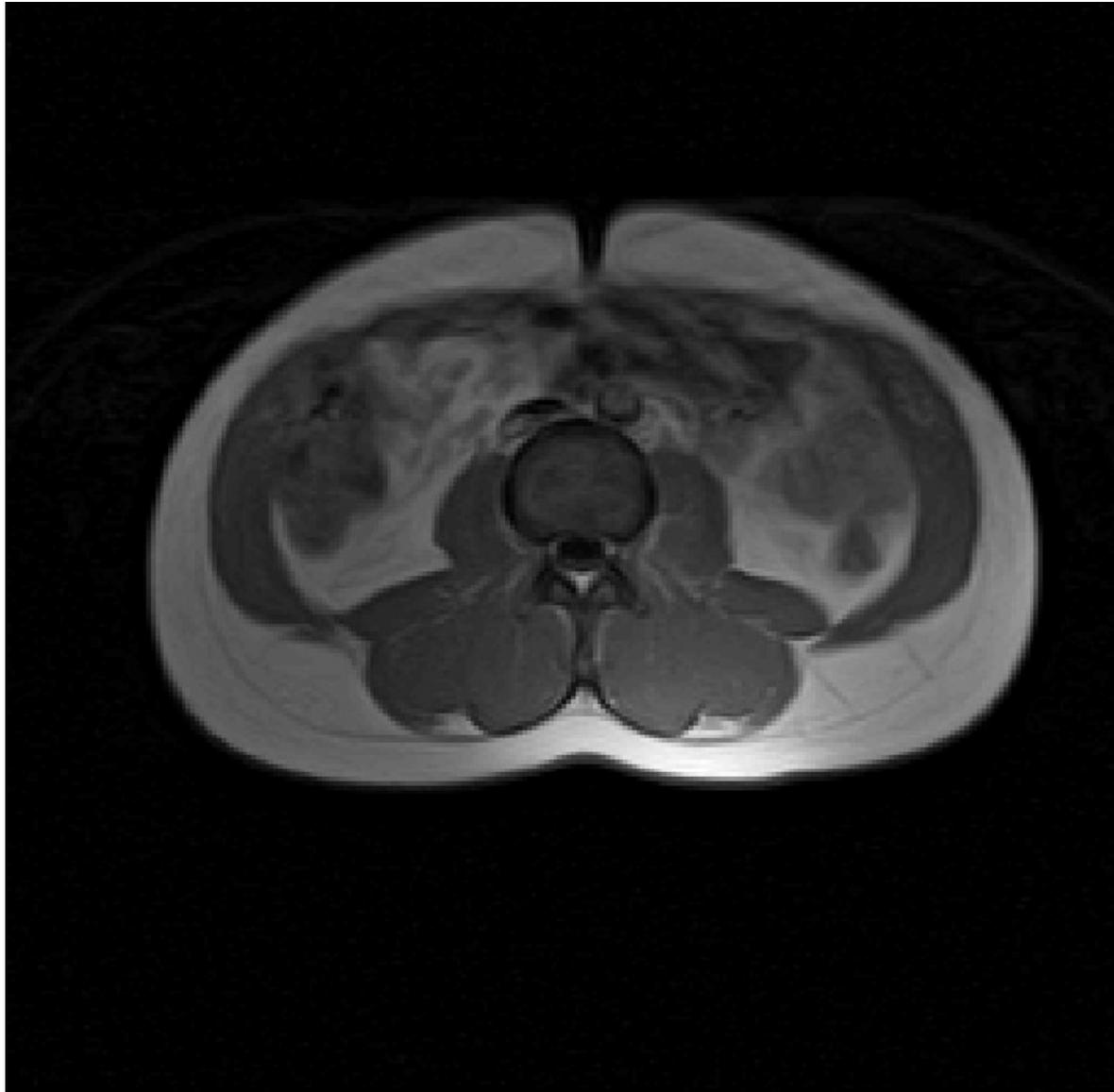


3 Tesla  
scanner

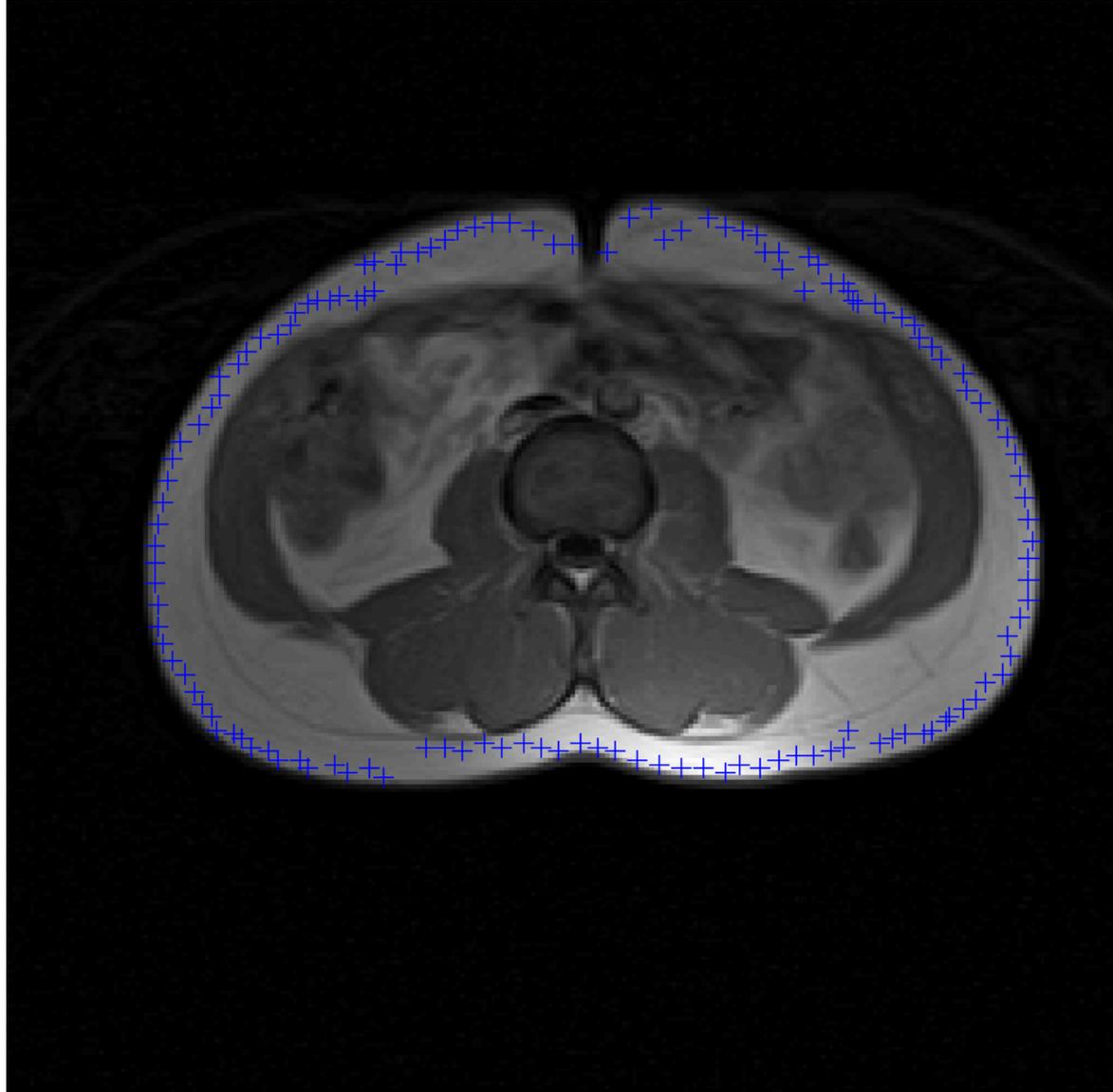


7 Tesla  
scanner

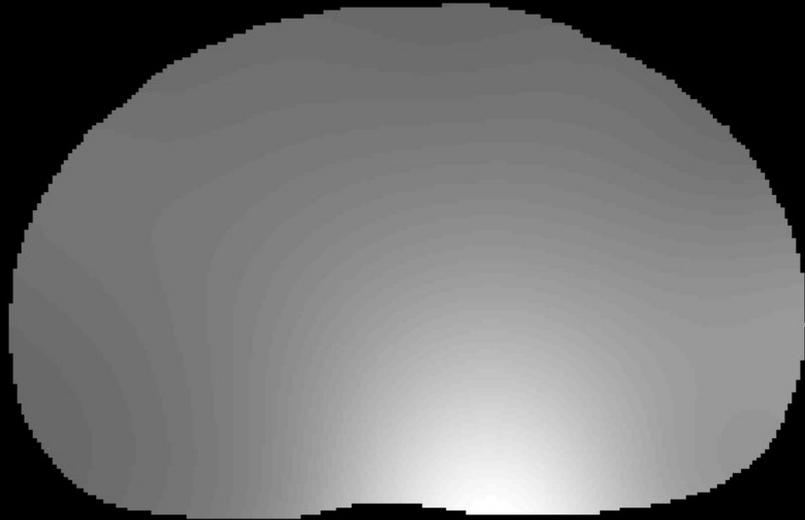
# Abdominal MR slice



# Same tissue (fat) pixels



# Bias and corrected image



Thin plate  
spline

