CS5540: Computational Techniques for Analyzing Clinical Data Lecture 7:

Statistical Estimation: Least Squares, Maximum Likelihood and Maximum A Posteriori Estimators

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Outline

- Part I: Recap of Wavelet Transforms
- Part II: Least Squares Estimation
- Part III: Maximum Likelihood Estimation
- Part IV: Maximum A Posteriori Estimation : Next week

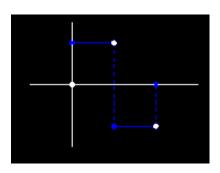
Note: you will not be tested on specific examples shown here, only on general principles

Basis functions in WT

- Basis functions are called "wavelets"
- Important wavelet property:
- All basis functions are scaled, shifted copies of the same mother wavelet
- By clever construction of mother wavelet, these scaled, shifted copies can be made either orthonormal, or at least linearly independent
- Wavelets form a complete basis, and wavelet transforms are designed to be easily invertible
- Online wavelet tutorial:

http://cnx.org/content/m10764/latest/

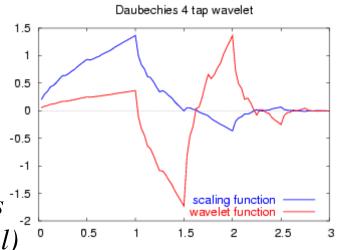
Daubechies [1.] (orthonormal)



Haar



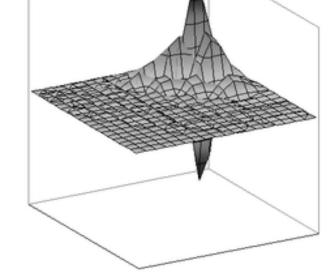
Mexican Hat



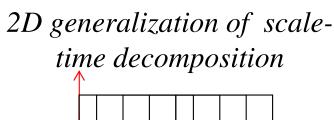
WT in images

- Images are piecewise smooth or piecewise constant
- Stationarity is even rarer than in 1D signals
- FT even less useful (nnd WT more attractive)
- 2D wavelet transforms are simple extensions of 1D WT, generally performing 1D WT along rows, then columns etc

 Sometimes we use 2D wavelets directly, e.g. orthonormal Daubechies 2D wavelet

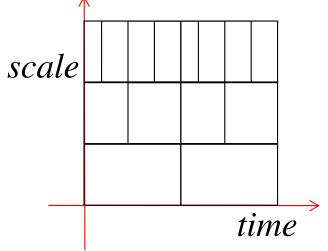


WT on images









Scale 1



H-V

Scale 2

Successive application of dot product with wavelet of increasing width. Forms a natural pyramid structure. At each scale:

H = dot product of image rows with wavelet

V = dot product of image columns with wavelet

H-V = dot product of image rows then columns with wavelet

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Wavelet Applications

- Many, many applications!
- Audio, image and video compression
- New JPEG standard includes wavelet compression
- FBI's fingerprints database saved as waveletcompressed
- Signal denoising, interpolation, image zooming, texture analysis, time-scale feature extraction
- In our context, WT will be used primarily as a feature extraction tool
- Remember, WT is just a change of basis, in order to extract useful information which might otherwise not be easily seen

WT in MATLAB

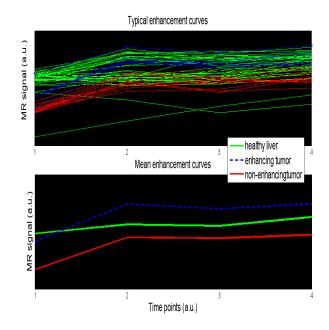
- MATLAB has an extensive wavelet toolbox
- Type help wavelet in MATLAB command window
- Look at their wavelet demo
- Play with Haar, Mexican hat and Daubechies wavelets

Project Ideas

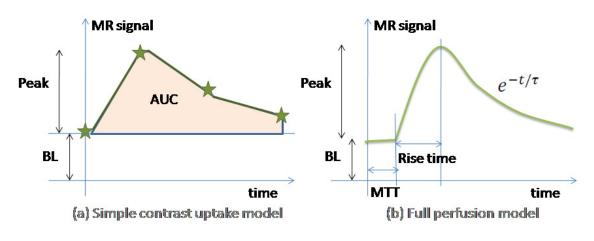
- Idea 1: use WT to extract features from ECG data
 - use these features for classification
- Idea 2: use 2D WT to extract spatio-temporal features from 3D+time MRI data
 - to detect tumors / classify benign vs malignant tumors
- Idea 3: use 2D WT to denoise a given image

Idea 3: Voxel labeling from contrast-enhanced MRI

 Can segment according to time profile of 3D+time contrast enhanced MR data of liver / mammography



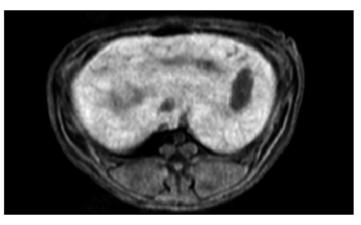
Typical plot of time-resolved MR signal of various tissue classes



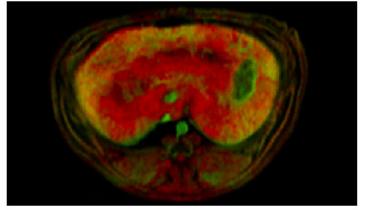
Temporal models used to extract features

Instead of such a simple temporal model, wavelet decomposition could provide spatio-temporal features that you can use for clustering

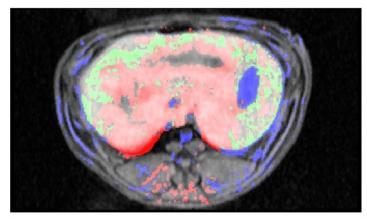
Liver tumour quantification from DCE-MRI



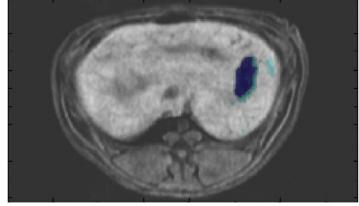
baseline MR image



dynamic parameter map



initial 5-way clustering



final tumor segmentation

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Further Reading on Wavelets

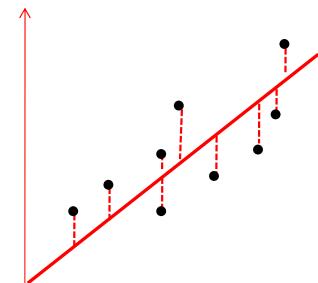
- A Linear Algebra view of wavelet transform <u>http://www.bearcave.com/misl/misl_tech/wavelets/matrix/index.html</u>
- Wavelet tutorial
- http://users.rowan.edu/~polikar/WAVELETS/WTpart1.html
- http://users.rowan.edu/~polikar/WAVELETS/WTpart2.html
- http://users.rowan.edu/~polikar/WAVELETS/WTpart3.html
- Wavelets application to EKG R wave detection: http://www.ma.utexas.edu/users/davis/reu/ch3/wavelets/wavelets.pdf

Part II: Least Squares Estimation and Examples



A simple Least Squares problem – Line fitting

- Goal: To find the "best-fit" line representing a bunch of points
- Here: y_i are observations at location x_i,
- Intercept and slope of line are the unknown model parameters to be estimated
- Which model parameters best fit the observed points?



$$E(y_{\text{int}}, m) = \sum_{i} (y_i - h(x_i))^2$$
, where $h(x) = y_{\text{int}} + mx_i$

Best
$$(y_{int}, m)$$
 = arg min $E(y_{int}, m)$

This can be written in matrix notation, as

$$\theta_{LS} = arg min ||\mathbf{y} - \mathbf{H}\boldsymbol{\theta}||^2$$

What are \boldsymbol{H} and $\boldsymbol{\theta}$?

Least Squares Estimator

Given linear process

$$y = H \theta + n$$

Least Squares estimator:

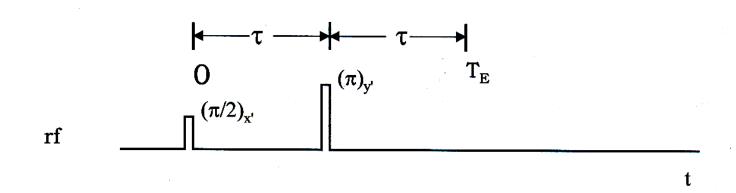
$$\theta_{LS} = \operatorname{argmin} ||\mathbf{y} - \mathbf{H}\theta||^2$$

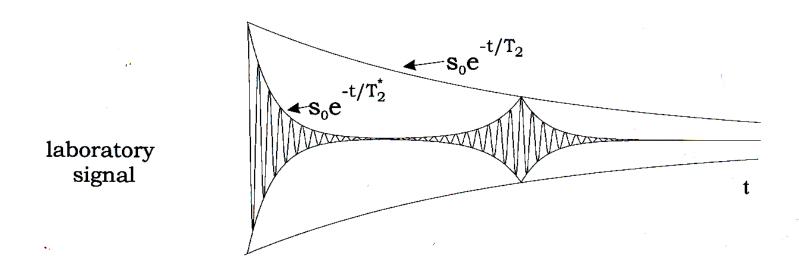
- Natural estimator want solution to match observation
- Does not use any information about n
- There is a simple solution (a.k.a. pseudo-inverse):

$$\theta_{LS} = (\mathbf{H}^{\mathsf{T}}\mathbf{H})^{-1} \mathbf{H}^{\mathsf{T}}\mathbf{y}$$

In MATLAB, type pinv(y)

Example - estimating T₂ decay constant in repeated spin echo MR data





Example – estimating T₂ in repeated spin echo data

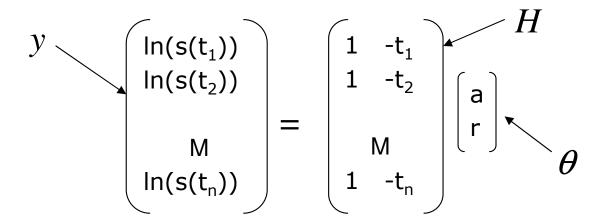
$$s(t) = s_0 e^{-t/T_2}$$

• Need only 2 data points to estimate T₂:

$$T_{2est} = [T_{E2} - T_{E1}] / ln[s(T_{E1})/s(T_{E2})]$$

- However, not good due to noise, timing issues
- In practice we have many data samples from various echoes

Example – estimating T₂



Least Squares estimate:

$$\theta_{LS} = (H^T H)^{-1} H^T y$$
$$T_2 = 1/r_{LS}$$

Estimation example - Denoising

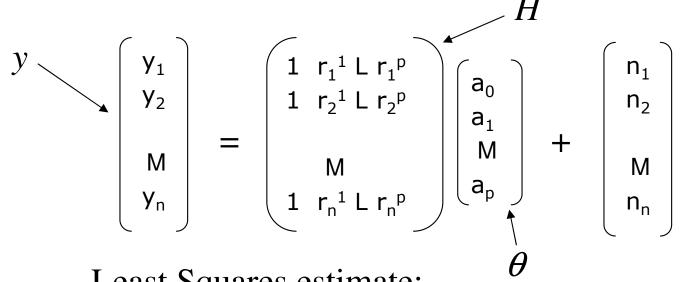
 Suppose we have a noisy MR image y, and wish to obtain the noiseless image x, where

$$y = x + n$$

- Can we use LSE to find x?
- Try: H = I, $\theta = x$ in the linear model
- LS estimator simply gives x = y!
 - we need a more powerful model
- Suppose the image x can be approximated by a polynomial, i.e. a mixture of 1st p powers of r:

$$x = \sum_{i=0}^{p} a_i r^i$$

Example - denoising



Least Squares estimate:

$$\theta_{LS} = (H^T H)^{-1} H^T y$$
$$x = \sum_{i=0}^{p} a_i r^i$$

Part III: Maximum Likelihood Estimation and Examples



Estimation Theory

Consider a linear process

$$y = H \theta + n$$

y = observed data

 θ = set of model parameters

n = additive noise

- Then Estimation is the problem of finding the statistically optimal θ, given y, H and knowledge of noise properties
- Medicine is full of estimation problems

Different approaches to estimation

- Minimum variance unbiased estimators
- Least Squares
- Maximum-likelihood
- Maximum entropy
- Maximum a posteriori

has no statistical basis

uses knowledge of noise PDF

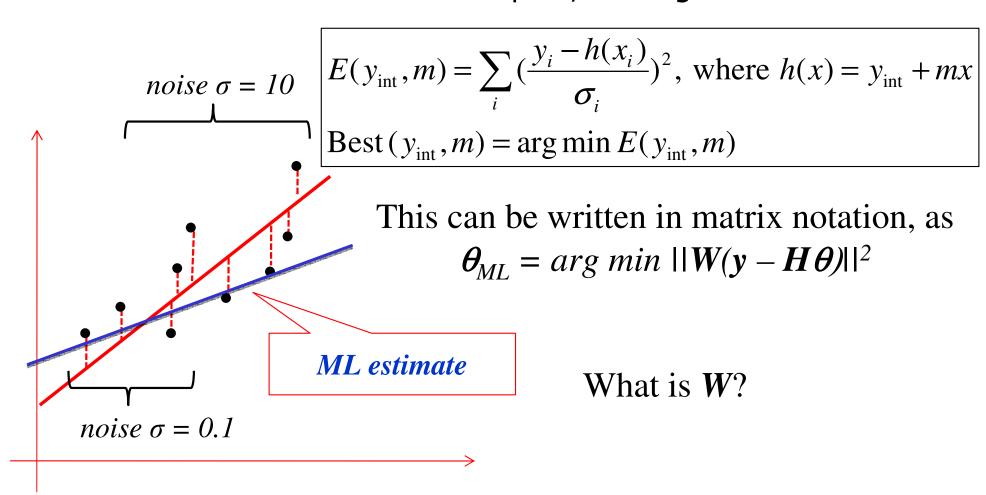
uses prior information about θ

Probability vs. Statistics

- Probability: Mathematical models of uncertainty predict outcomes
 - This is the heart of probability
 - Models, and their consequences
 - What is the probability of a model generating some particular data as an outcome?
- Statistics: Given an outcome, analyze different models
 - Did this model generate the data?
 - From among different models (or parameters),
 which one generated the data?

Maximul Likelihood Estimator for Line Fitting Problem

- What if we know something about the noise? i.e. Pr(n)...
- If noise not uniform across samples, LS might be incorrect



Definition of likelihood

- Likelihood is a probability model of the uncertainty in output given a known input
- The likelihood of a hypothesis is the probability that it would have resulted in the data you saw
 - Think of the data as fixed, and try to chose among the possible PDF's
 - Often, a parameterized family of PDF's
 - ML parameter estimation

Gaussian Noise Models

- In linear model we discussed, likelihood comes from noise statistics
- Simple idea: want to incorporate knowledge of noise statistics
- If uniform white Gaussian noise:

$$\Pr(\mathbf{n}) = \frac{1}{Z} \prod_{i} \exp\left(-\frac{|n_{i}|^{2}}{2\sigma^{2}}\right) = \frac{1}{Z} \exp\left(-\frac{\sum_{i} |n_{i}|^{2}}{2\sigma^{2}}\right)$$

If non-uniform white Gaussian noise:

$$\Pr(\mathbf{n}) = \frac{1}{Z} \exp\left(-\frac{\sum_{i} |n_{i}|^{2}}{2\sigma_{i}^{2}}\right)$$

Maximum Likelihood Estimator - Theory

- $n = y-H\theta$, $Pr(n) = exp(-||n||^2/2\sigma^2)$
- Therefore $Pr(y \text{ for known } \theta) = Pr(n)$
- Simple idea: want to maximize Pr(y|θ) called the likelihood function
- Example 1: show that for uniform independent Gaussian noise $\theta_{ML} = arg min ||y-H\theta||^2$
- Example 2: For non-uniform Gaussian noise $\theta_{ML} = arg min ||W(y-H\theta)||^2$

Maximum Likelihood Estimator

- But if noise is jointly Gaussian with cov. matrix C
- Recall C, E(nn^T). Then

$$Pr(n) = e^{-\frac{1}{2} n^{T} C^{-1} n}$$

 $L(y|\theta) = \frac{1}{2} (y-H\theta)^{T} C^{-1} (y-H\theta)$
 $\theta_{ML} = argmin \frac{1}{2} (y-H\theta)^{T} C^{-1} (y-H\theta)$

This also has a closed form solution

$$\theta_{MI} = (H^{T}C^{-1}H)^{-1} H^{T}C^{-1}y$$

- If n is not Gaussian at all, ML estimators become complicated and non-linear
- Fortunately, in MR noise is usually Gaussian

MLE

- Bottomline:
- Use noise properties to write $Pr(y|\theta)$
- Whichever θ maximize above, is the MLE

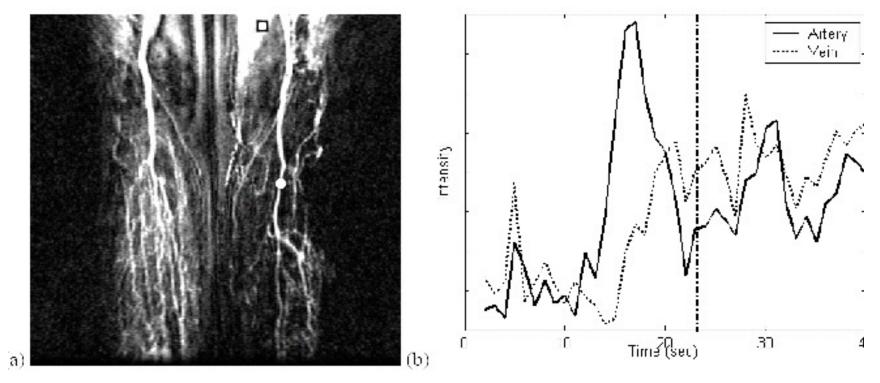
Example – Estimating main frequency of ECG signal

- Model: $y(t_i) = a \sin(f t_i) + n_i$
- What is the MLE of a, f?
- $Pr(y \mid \theta) = exp(-\Sigma_i (y(t_i) a sin(f t_i))^2 / 2 \sigma^2)$

Maximum Likelihood Detection

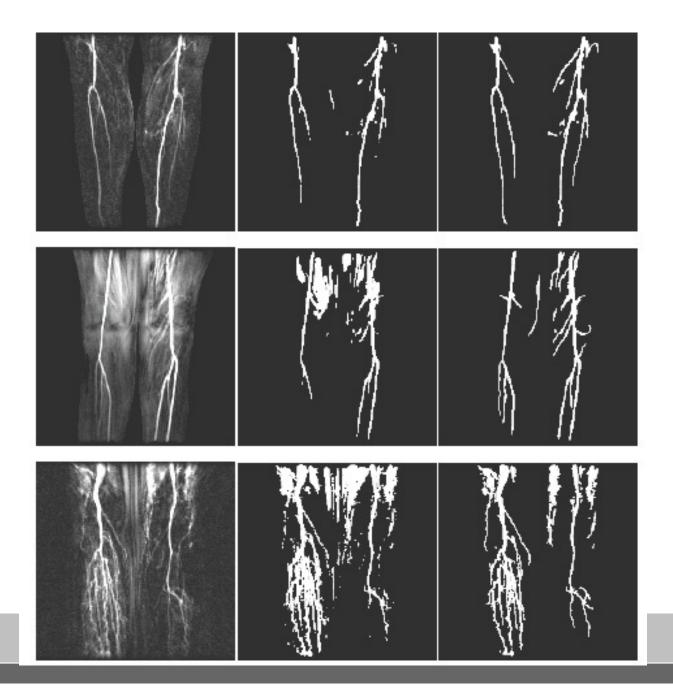
- ML is quite a general, powerful idea
- Same ideas can be used for classification and detection of features hidden in data
- Example 1: Deciding whether a voxel is artery or vein
- There are 3 hypotheses at each voxel:
 - Voxel is artery, or voxel is vein, or voxel is parenchyma

Example: MRA segmentation



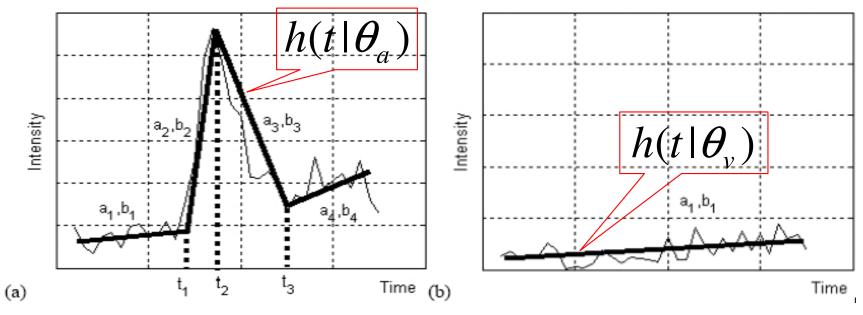
- artery/vein may have similar intensity at given time point
- but different time profiles
- wish to segment according to time profile, not single intensity

Expected Result



Example: MRA segmentation

First: need a time model of all segments



- Lets use ML principles to see which voxel belongs to which model
- Artery: $y_i = h(t_i \mid \theta_a) + n_i$
- Vein: $y_i = h(t_i \mid \theta_v) + n_i$
- Parench: $y_i = h(t_i | \theta_p) + n_i$

Maximum Likelihood Classification

Artery:
$$y_i = h(t_i \mid \theta_a) + n_i$$
 Pr $(y_i \mid \theta_a) = \exp\left(-\frac{(y_i - h(t_i \mid \theta_a))^2}{2\sigma^2}\right)$

Vein: $y_i = h(t_i \mid \theta_v) + n_i$ Pr $(y_i \mid \theta_v) = \exp\left(-\frac{(y_i - h(t_i \mid \theta_v))^2}{2\sigma^2}\right)$

Paren: $y_i = h(t_i \mid \theta_p) + n_i$ Pr $(y_i \mid \theta_p) = \exp\left(-\frac{(y_i - h(t_i \mid \theta_v))^2}{2\sigma^2}\right)$

So at each voxel, the best model is one that maximizes:

So at each voxel, the best model is one that max
$$\Pr(y_i|\theta) = \prod_i \Pr(y_i|\theta) = \exp\left(-\frac{\sum_i (y_i - h(t_i|\theta))^2}{2\sigma^2}\right)$$
 Or equivalently, minimizes:

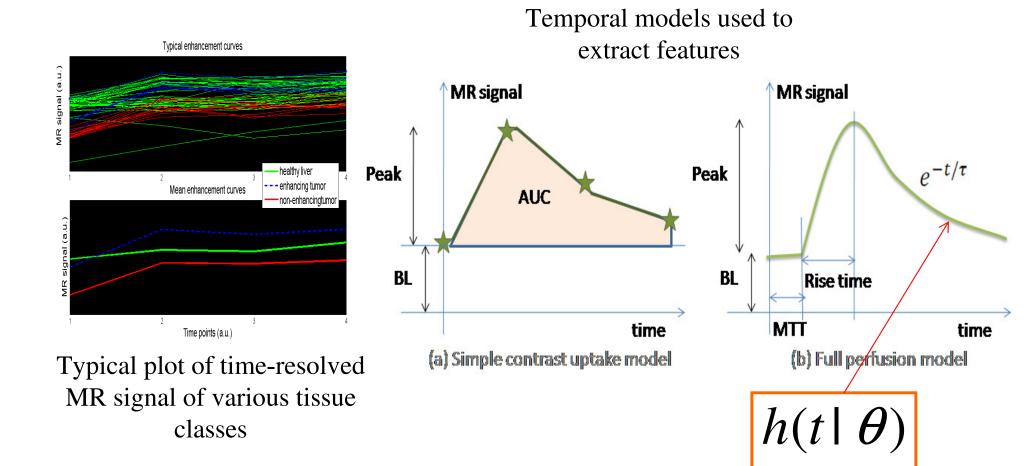
$$\sum_{i} (y_i - h(t_i \mid \boldsymbol{\theta}))^2$$

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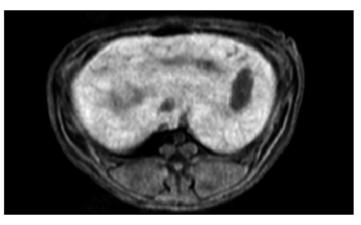
Liver tumour quantification from Dynamic Contrast Enhanced MRI

- Data: Tumor model Rabbit DCE-MR data
- Paramegnetic contrast agent , pathology gold standard
- Extract temporal features from DCE-MRI
- Use these features for accurate detection and quantification of tumour

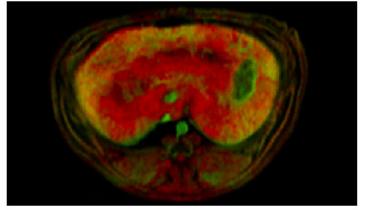
Liver Tumour Temporal models



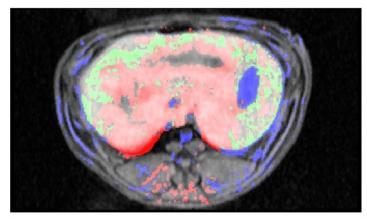
Liver tumour quantification from DCE-MRI



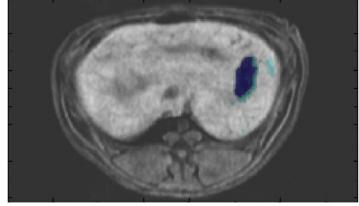
baseline MR image



dynamic parameter map



initial 5-way clustering



final tumor segmentation

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ML Tutorials

Slides by Andrew Moore (CMU): available on course webpage
Paper by Jae Myung, "Tutorial on Maximum Likelihood": available on course webpage

Max Entropy Tutorial

http://www.cs.cmu.edu/~aberger/maxent.html

Part IV: Maximum A Posteriori (Bayesian) Estimation and Examples



Failure modes of ML

- Likelihood isn't the only criterion for selecting a model or parameter
 - Though it's obviously an important one
- ML can be overly sensitive to noise
- Bizarre models may have high likelihood
 - Consider a speedometer reading 55 MPH
 - Likelihood of "true speed = 55": 10%
 - Likelihood of "speedometer stuck": 100%
- ML likes "fairy tales"
 - In practice, exclude such hypotheses
- There must be a principled solution...
 - We need additional information to unwedge ML from bad solutions, Radiology, Cornell

If PDF of θ (or x) is also known...

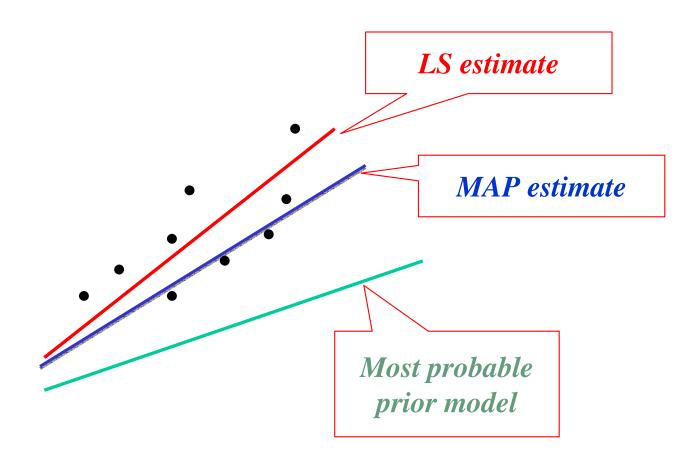
$$y = H x + n$$
, $n ext{ is } Gaussian$ (1)

- If we know both Likelihood AND some prior knowledge about the unknown x
- Then can exploit this knowledge
- How? Suppose PDF of x is known

$$y = Hx + n$$
, n, x are Gaussian (2)

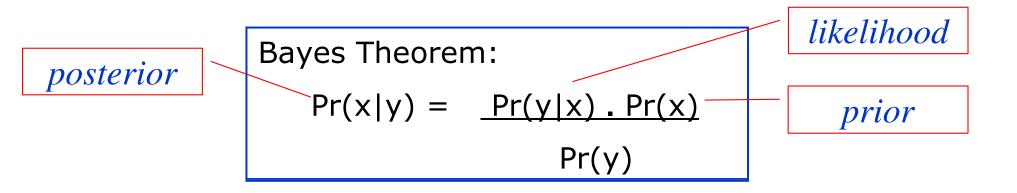
MAP for Line fitting problem

- If model estimated by ML and Prior info do not agree...
- MAP is a compromise between the two



Maximum a Posteriori Estimate

- Prior knowledge about random variables is generally expressed in the form of a PDF Pr(x)
- Once the likelihood L(x) and prior are known, we have complete statistical knowledge
- MAP (aka Bayesian) estimates are optimal



Maximum a Posteriori (Bayesian) Estimate

- Consider the class of linear systems y = Hx + n
- Bayesian methods maximize the posterior probability:

$$Pr(x|y) \square Pr(y|x) . Pr(x)$$

- Pr(y|x) (likelihood function) = $\exp(-\frac{||y-Hx||^2}{2})$
- Pr(x) (prior PDF) = exp(-G(x))
- Non-Bayesian: maximize only likelihood

$$x_{est} = arg min ||y-Hx||^2$$

Bayesian:

$$X_{est} = arg min ||y-Hx||^2 + G(x)$$
,

where G(x) is obtained from the prior distribution of x

Example Bayesian Estimation

Example: Gaussian prior centered at zero:

$$Pr(x) = exp{- \frac{1}{2} x^T R_x^{-1} x}$$

Bayesian methods maximize the posterior probability:

$$Pr(x|y) \square Pr(y|x) \cdot Pr(x)$$

- Pr(y|x) (likelihood function) = $\exp(-\frac{||y-Hx||^2}{2})$
- ML estimate: maximize only likelihood

$$x_{est} = arg min ||y-Hx||^2$$

MAP estimate:

$$x_{est} = arg min ||y-Hx||^2 + \lambda x^T R_x^{-1} x$$

Makes Hx close to y

Tries to make x a sample from a Gaussian centered at 0

MAP Example: Multi-variate FLASH

- Acquire 6-10 accelerated FLASH data sets at different flip angles or TR's
- Generate T₁ maps by fitting to:

$$S = \exp\left(-TE/T_2^*\right) \sin \alpha \frac{1 - \exp\left(-TR/T_1\right)}{1 - \cos \alpha \exp\left(-TR/T_1\right)}$$

- Not enough info in a single voxel
- Noise causes incorrect estimates
- Error in flip angle varies spatially!

Spatially Coherent T₁, p estimation

- First, stack parameters from all voxels in one big vector x
- Stack all observed flip angle images in y
- Then we can write y = M(x) + n
- Recall M is the (nonlinear) functional obtained from

$$S = \exp\left(-TE/T_2^*\right) \sin \alpha \frac{1 - \exp\left(-TR/T_1\right)}{1 - \cos \alpha \exp\left(-TR/T_1\right)}$$

Solve for x by non-linear least square fitting, PLUS spatial prior:

$$\mathbf{x}_{\text{est}} = \text{arg min}_{\mathbf{x}} || \mathbf{y} - \mathbf{M} (\mathbf{x}) ||^2 + \mu^2 || \mathbf{D} \mathbf{x} ||^2$$

Makes M(x) close to y

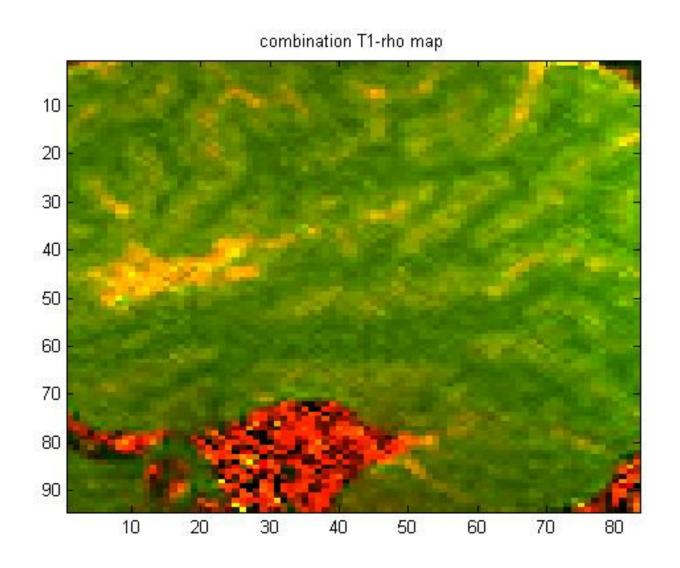
Makes x smooth

• Minimize via MATLAB's lsqnonlin function

Multi-Flip Results – combined ρ, T₁ in pseudocolour

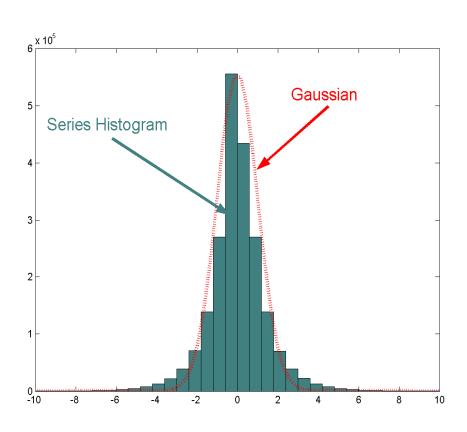


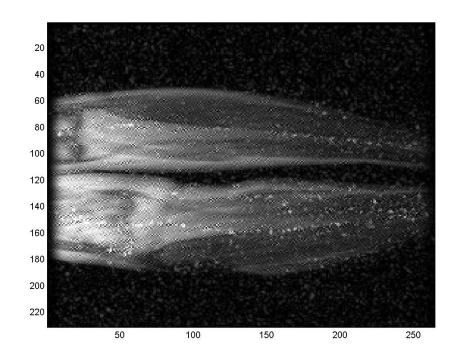
Multi-Flip Results – combined ρ, T₁ in pseudocolour



MAP example 2: Spatial Priors For Dynamic Imaging

Frames are tightly distributed around mean
After subtracting mean, images are close to Gaussian





envelope a(i,j)

Prior: -mean is μ_x

-local std.dev. varies as *a(i,j)*

Spatial Priors for MR images

stationary process

Stochastic MR image model:

$$x(i,j) = \mu_{x}(i,j) + a(i,j) (h^{**}p)(i,j)$$
 (1)

** denotes 2D convolution

$$r(\tau_1, \tau_2) = (h^{**}h)(\tau_1, \tau_2)$$

 $\mu_{x}(i,j)$ is mean image for class p(i,j) is a unit variance i.i.d. stochastic process a(i,j) is an envelope function h(i,j) simulates correlation properties of image x

$$x = ACp + \boldsymbol{\mu} \tag{2}$$

where A = diag(a), and C is the Toeplitz matrix generated by h

Can model many important stationary and non-stationary cases

MAP estimate for Imaging Model (3)

The Wiener estimate

$$X_{MAP} - \mu_{X} = HR_{X} (HR_{X}H^{H} + R_{D})^{-1} (y - \mu_{Y})$$
 (3)

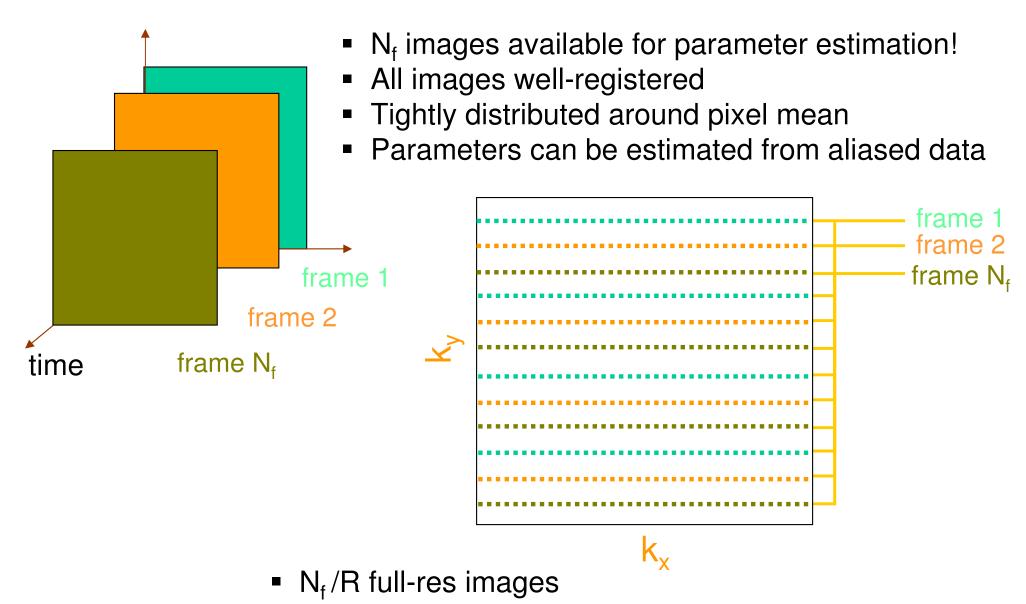
 R_x , R_n = covariance matrices of x and nStationarity $\Rightarrow R_x$ has Toeplitz structure \Rightarrow fast processing $X_{MAP} - \mu_x = HACC^HA^H (HACC^HA^HH^H + \sigma_n^2 I)^{-1} (y - \mu_y) (4)$

- Direct inversion prohibitive; so use CG iterative method
- (4) better than (3) since A and C are O(N log N) operations, enabling much faster processing

How to obtain estimates of A, C?

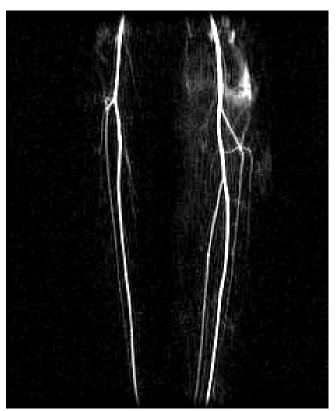
- Need a training set of full-resolution images x_k , k = 1,...,K
- Parallel imaging doesnt provide un-aliased full-res images
- Approaches:
 - 1. Use previous full-res scans
 - time consuming, need frequent updating
 - 2. Use SENSE-reconstructed images for training set
 - very bad noise amplification issues for high speedu ps
 - 3. Directly estimate parameters from available parallel data
 - Aliasing may cause inaccuracies

MAP for Dynamic Parallel Imaging

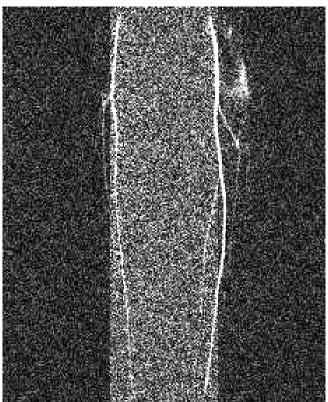


MAP-SENSE Preliminary Results

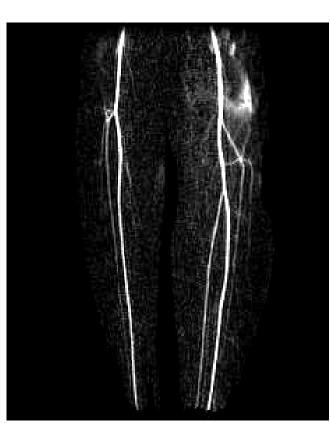
- Scans acceleraty 5x
- The angiogram was computed by: avg(post-contrast) – avg(pre-contrast)







5x faster: SENSE



5x faster: MAP-SENSE

Part V: Time Series Analysis

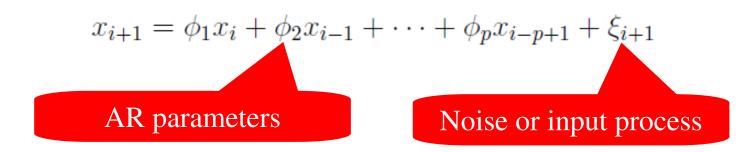
Finding statistically optimal models for time series data

Time Series Analysis

- Lots of clinical data are time series
 - ECG, MR contrast enhanced tumor data,
 - ER caseload, cancer patient survival curves,...
- How to extract temporal features from these data?
 - Use Fourier, Wavelet Transforms, fit piecewise linear models
 - Good, but... features are arbitrary, no optimality properties
- Now: better models for time series with memory
 - Autoregressive (AR) model
 - Moving Average (MA) model
 - Both AR + MA

Autoregressive models

- When current signal depends on past signal
 - Data has "memory"
- Quite natural for biological and physiological data
 - Because real systems cannot change arbitrarily
 - Current state depends on previous state
- Model:



How to estimate phil?

Estimating AR parameters

• Example: For p = 1 $x_{i+1} = \phi_1 x_i + \xi_{i+1}$

$$\underbrace{\begin{pmatrix} x_2 \\ x_3 \\ \vdots \\ x_N \end{pmatrix}}_{\mathbf{b}} = \underbrace{\begin{pmatrix} x_1 \\ x_2 \\ \vdots \\ x_{N-1} \end{pmatrix}}_{\mathbf{A}} \phi_1$$

 If noise is independent Gaussian, then show that ML estimate is

$$\hat{\phi}_1 = \left(\mathbf{A}^T \mathbf{A}\right)^{-1} \mathbf{A}^T \mathbf{b}$$

Estimating AR parameters

$$p = 2 x_{i+1} = \phi_1 x_i + \phi_2 x_{i-1} + \xi_{i+1}$$

$$\underbrace{\begin{pmatrix} x_3 \\ x_4 \\ \vdots \\ x_N \end{pmatrix}}_{\mathbf{b}} = \underbrace{\begin{pmatrix} x_2 & x_1 \\ x_3 & x_2 \\ \vdots & \vdots \\ x_{N-1} & x_{N-2} \end{pmatrix}}_{\mathbf{A}} \underbrace{\begin{pmatrix} \phi_1 \\ \phi_2 \end{pmatrix}}_{\mathbf{\Phi}}$$

Can you do this for any p?

More on this at:

http://www-

stat.wharton.upenn.edu/~steele/Courses/956/Resource/YWS ourceFiles/YW-Eshel.pdf

Moving Average Process

MA process model:

Model order

$$X_t = \mu + \varepsilon_t + \sum_{i=1}^{r} \theta_i \varepsilon_{t-i}$$

Noise or input process

MA parameters

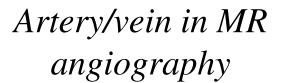
- Autoregressive moving average (ARMA) model:
- Combines both AR and MA processes

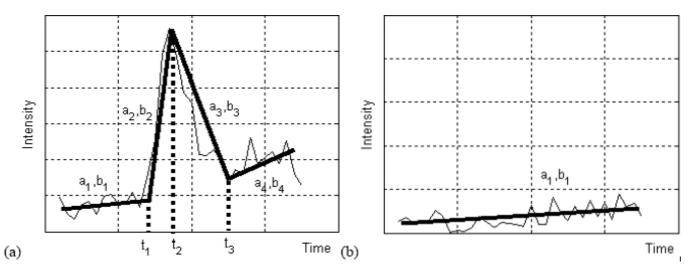
$$X_{t} = c + \varepsilon_{t} + \sum_{i=1}^{p} \varphi_{i} X_{t-i} + \sum_{i=1}^{q} \theta_{i} \varepsilon_{t-i}.$$

Estimating MA and ARMA parameters

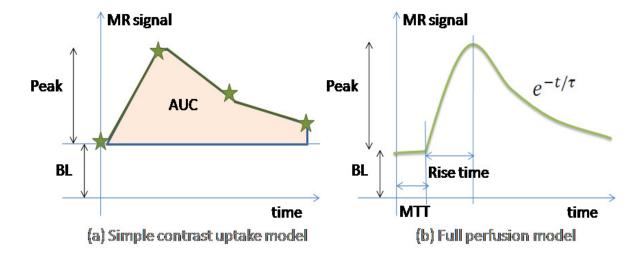
- MA parameters = from Fourier Transforms
- ARMA: more complicated, but most languages have library routines that do this
- E.g. in MATLAB: ar(), arma(), etc
- What is the benefit of estimating AR and ARMA parameters?
 - Might provide better temporal features than FT, WT or arbitrary temporal features
- Example: could apply this to mammography or liver tumor data

Examples





Liver Tumour time profiles



Maybe these are better modeled as ARMA???

References

- Simon Kay. Statistical Signal Processing. Part I: Estimation Theory. Prentice Hall 2002
- Simon Kay. Statistical Signal Processing. Part II: Detection Theory. Prentice Hall 2002
- Haacke et al. Fundamentals of MRI.
- Zhi-Pei Liang and Paul Lauterbur. Principles of MRI A Signal Processing Perspective.

Info on part IV:

- Ashish Raj. Improvements in MRI Using Information Redundancy. PhD thesis, Cornell University, May 2005.
- Website: http://www.cs.cornell.edu/~rdz/SENSE.htm

Next lecture (Friday)

- Non-parametric density estimation
 - Histograms + various fitting methods
 - Nearest neighbor
 - Parzen estimation

Next lecture (Wednesday)

- Maximum A Posteriori Estimators
 - Several examples

CS5540: Computational Techniques for Analyzing Clinical Data Lecture 7:

Statistical Estimation: Least Squares, Maximum Likelihood and Maximum A Posteriori Estimators

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