

# Computational Medical Research

N. Laskaris

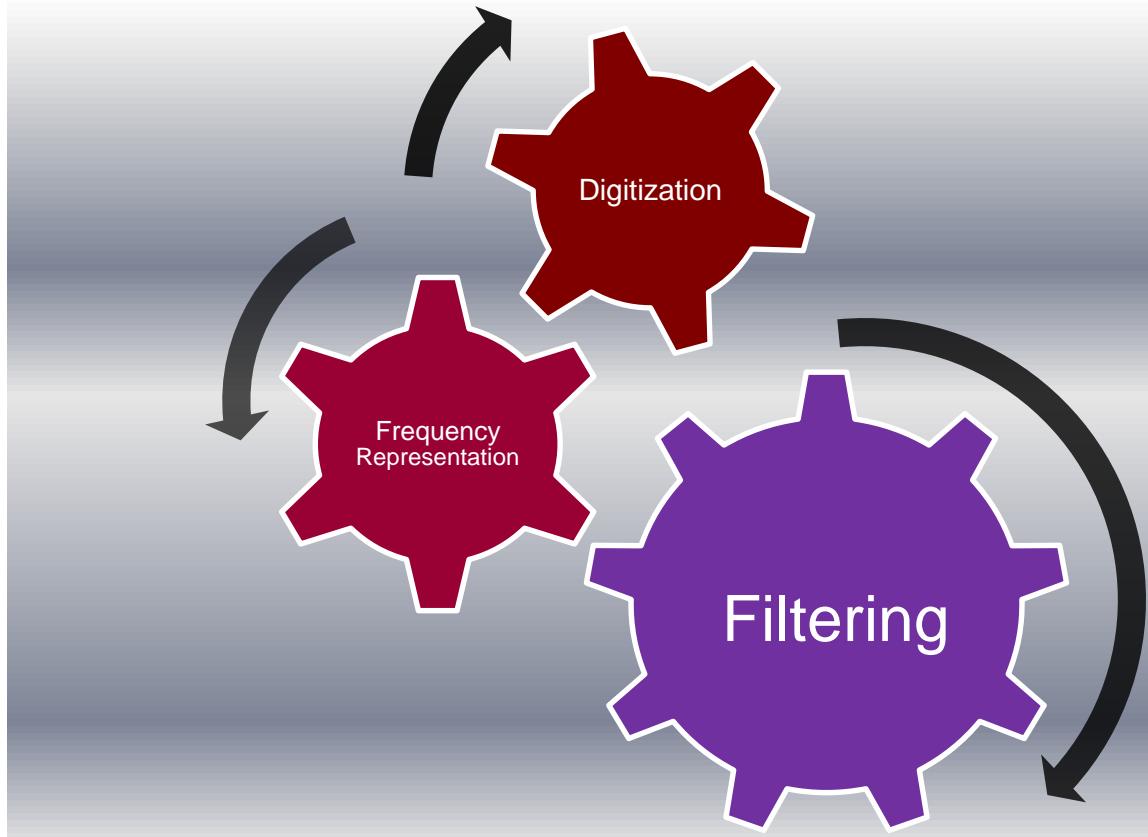
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*Computational  
Medical Research*

# Biosignal Processing



**Enhancing-Extracting-Presenting  
and Handling Information from  
signals abundant  
in digital medical reality**

**Signal** is any **variable** that carries information about (the behavior or attributes of) a system (**some phenomenon**).

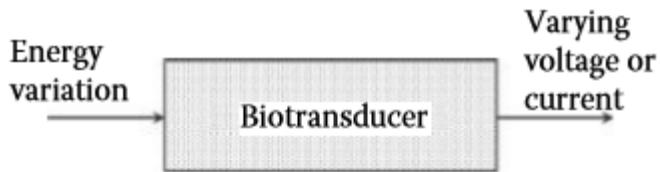
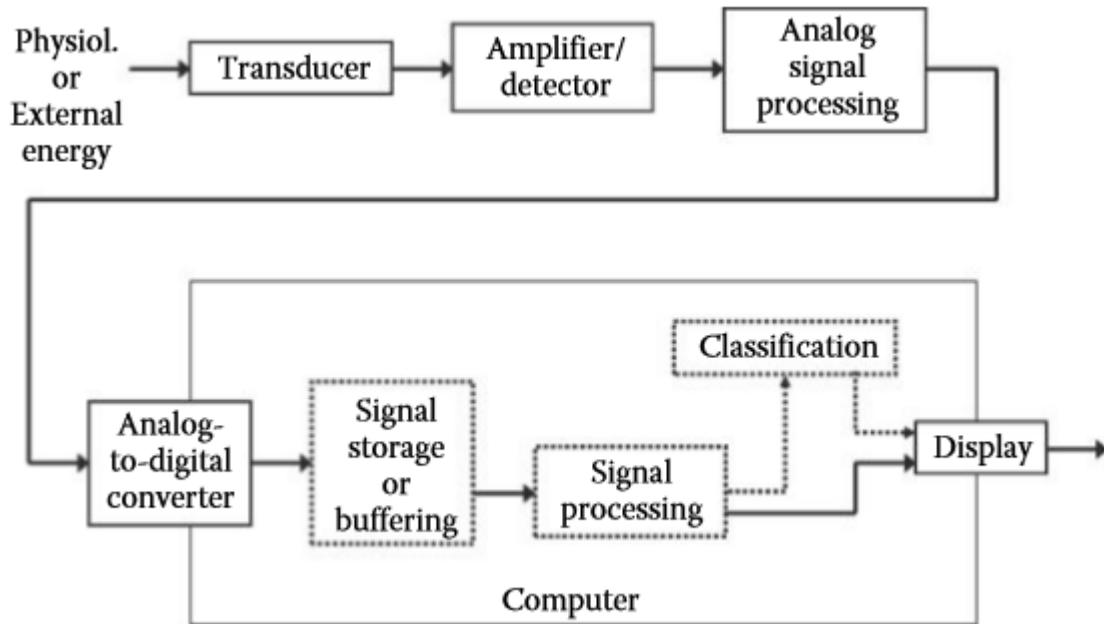
**Digital Signal** is sequence of numbers that results from the digitization of an observable quantity.

**Biosignals** are inherent in life and constitute invaluable tools to gain insights...

Information about internal states of the body can be obtained through the acquisition and interpretation of **biosignals**. Expanding such information is an ongoing endeavor of medicine and medical research.

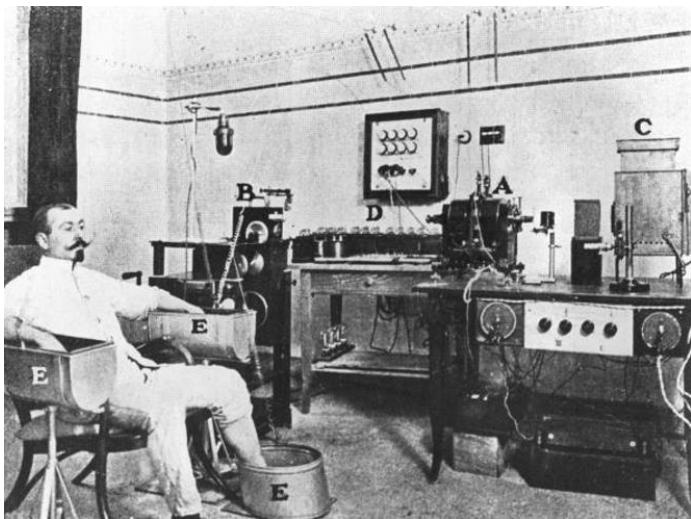


# a typical biomedical measurement system



Energy	Measurement
Mechanical Length, position, and velocity Force and pressure	Muscle movement, cardiovascular pressures, muscle contractility valve, and other cardiac sounds
Heat	Body temperature and thermography
Electrical	EEG, ECG, EMG, EOG, ERG, EGG, and GSR
Chemical	Ion concentrations

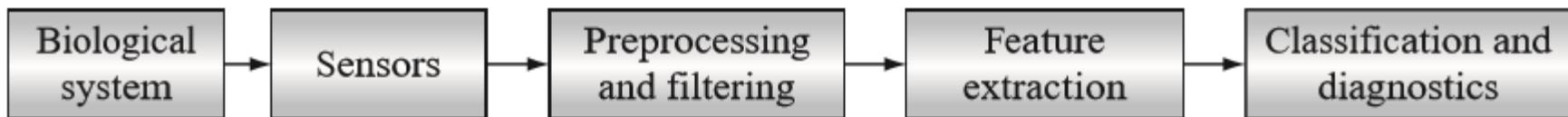
# Bio-measurements advances at the same pace with current technology



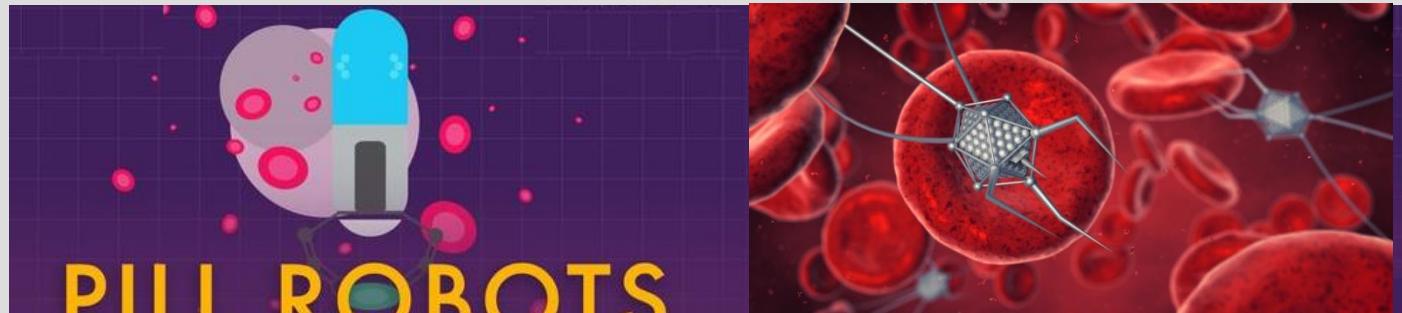
Proteus Digital Health Feedback System  
ingestible sensors embedded in tablets,  
a skin-worn receiver patch and a mobile

Signal Processing/Analysis techniques constantly evolve to catch up.  
Some core-principles however remain unaltered.

The most common theme :



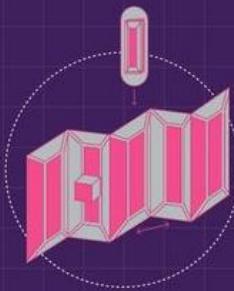
# ... Nanomedicine



## PILL ROBOTS

The Future of Non-Invasive Surgery

There are 3,500 cases of children swallowing button batteries reported yearly in the U.S. alone—a potentially debilitating and life-threatening hazard. Pill robots are seen as a viable, non-invasive option in severe cases, while opening up many other potential medical applications.

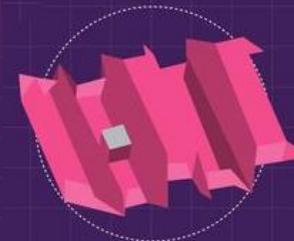


### FORM

Packed into a pill-shaped container, the pill robot unfolds “origami fashion” after it is swallowed.

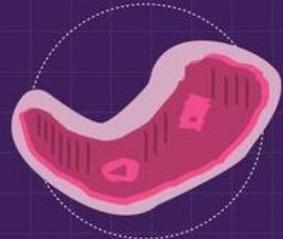
### INSERTION

The origami robot is compressed inside an inch-long, 0.09-ounce pill, which dissolves in the stomach within a minute, and then expands to its full size.



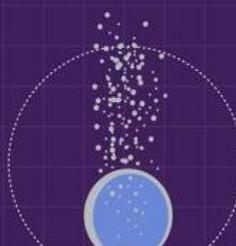
### NAVIGATION

The pill robot is untethered, and propels itself with a “stick-slip” motion, or is steered with magnetic fields near the patient to guide the robot inside the digestive system.



### FUNCTION

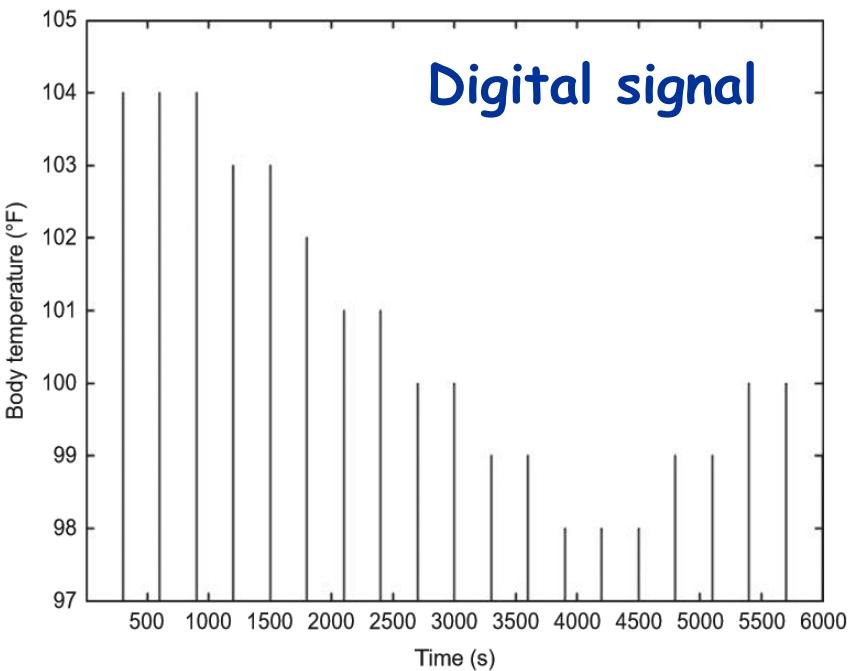
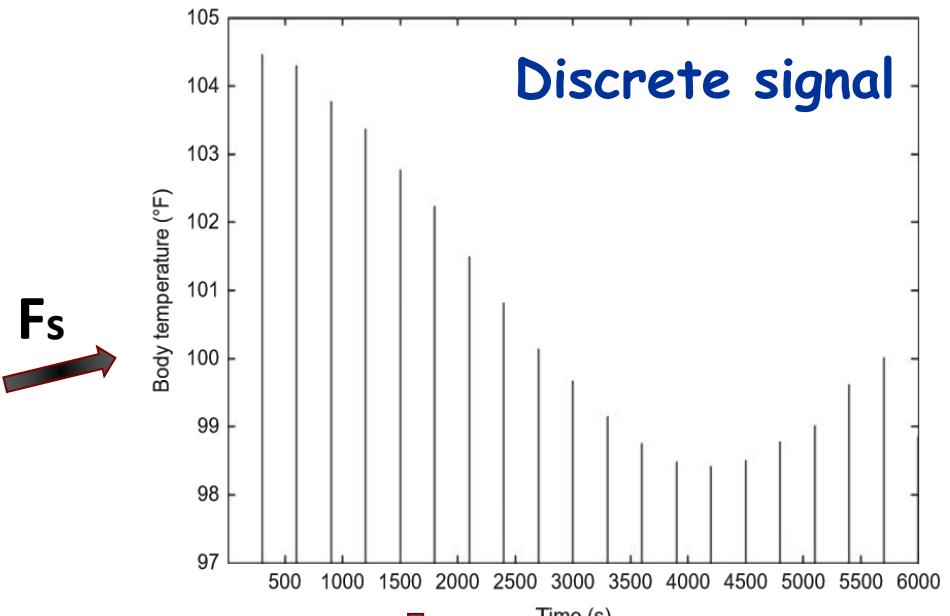
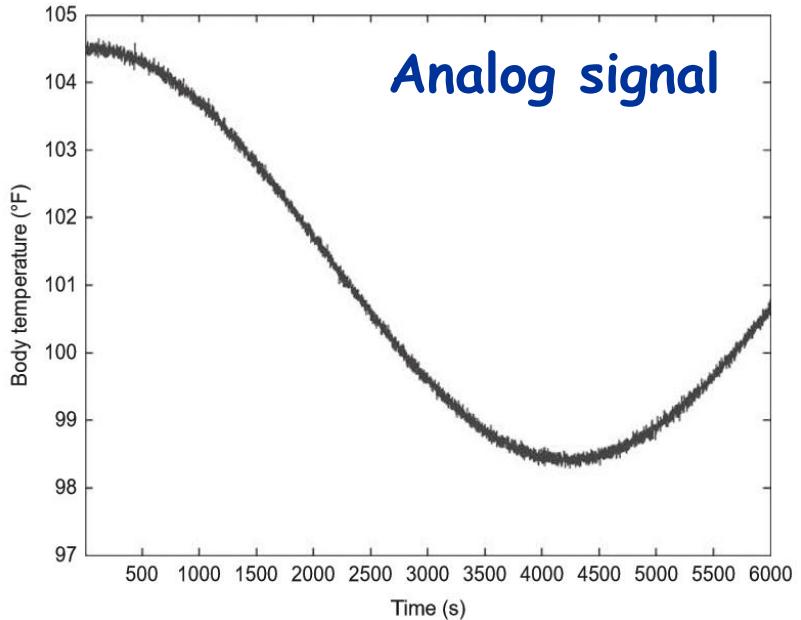
The robot is guided by a tiny magnet to remove foreign objects from the stomach or intestine, or administer medication to treat internal wounds.



### BIODEGRADABLE

With material parts made from pig intestine—which is also used in sausage casings—the pill robot breaks down in the stomach like food.

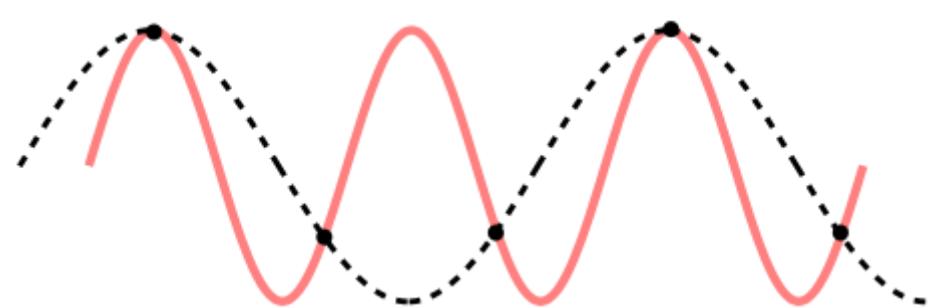
# Digitization



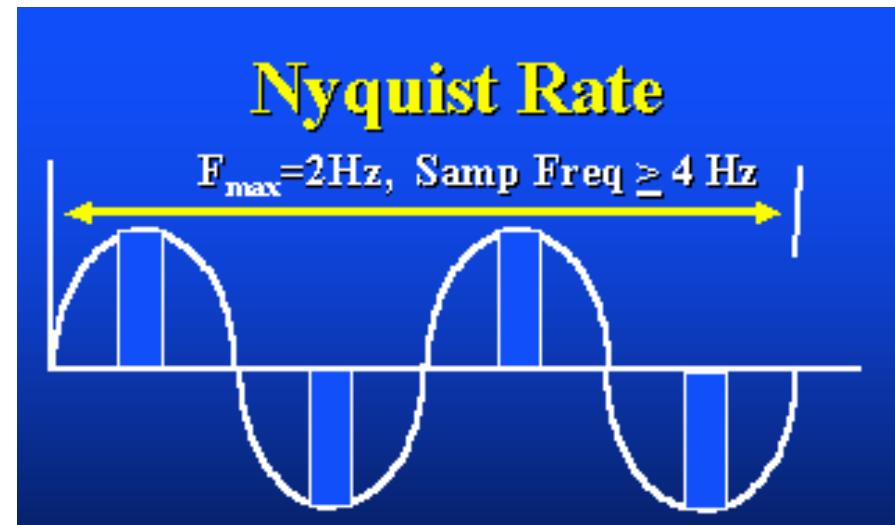
Sampling Frequency:  $F_s = 1/T_s$

Quantization.

## Sampling Theorem - Nyquist Rate



"A signal  $x(t)$  with maximum frequency  $f_{MAX}$  can be recovered if sampled at frequency  $f_s > 2 f_{MAX}$ "

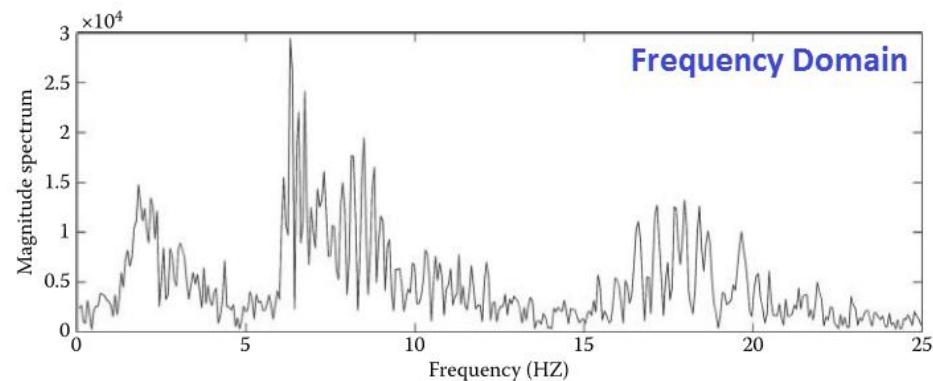
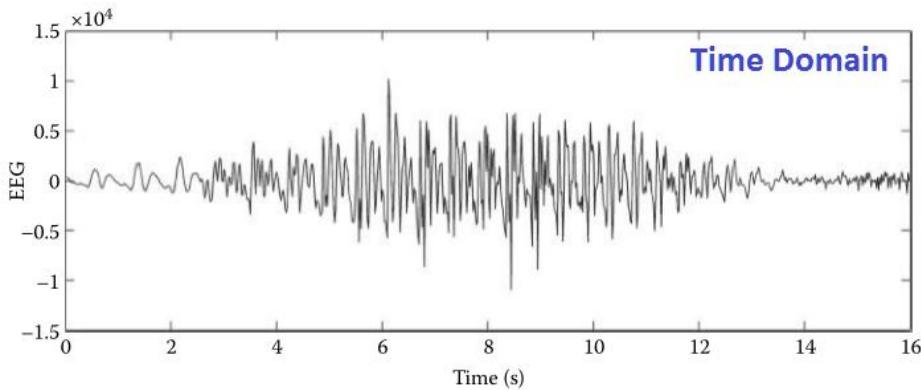


-Aliasing effect

-Anti-aliasing filter

**-Nyquist Frequency:**  $F_N = F_s/2$

# Frequency Representation



Fourier Transform (FT)

DFT (discrete FT) - FFT (fast-FT)

Spectral representation techniques (Welch's method etc.)

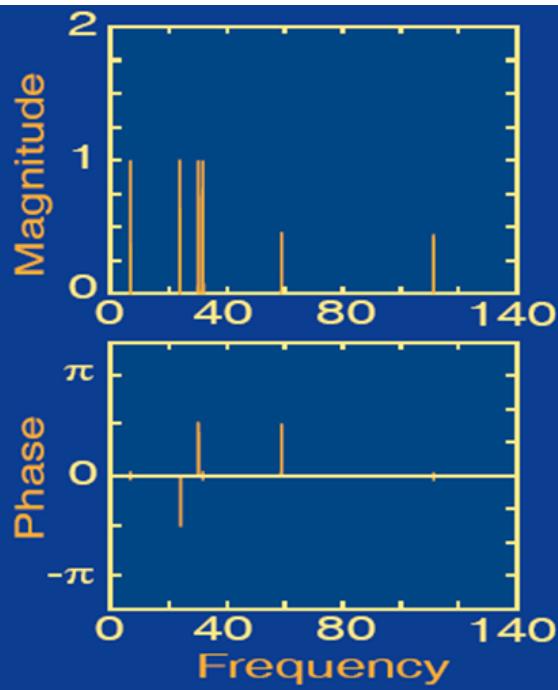
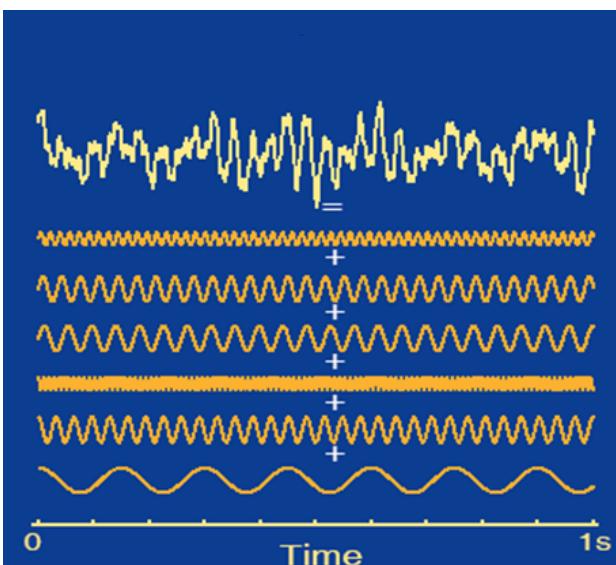
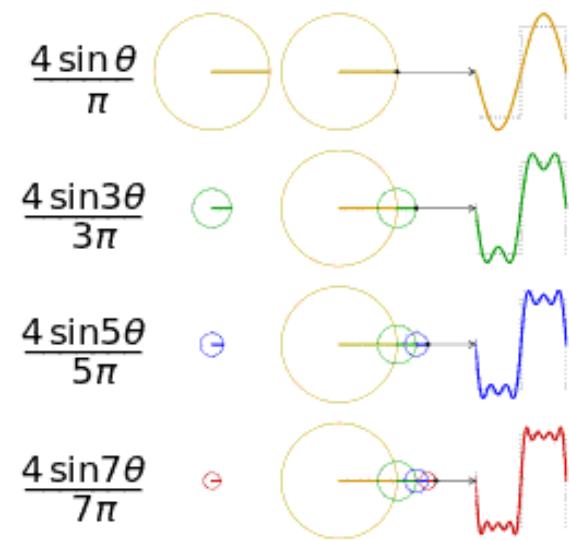


Fourier Transform

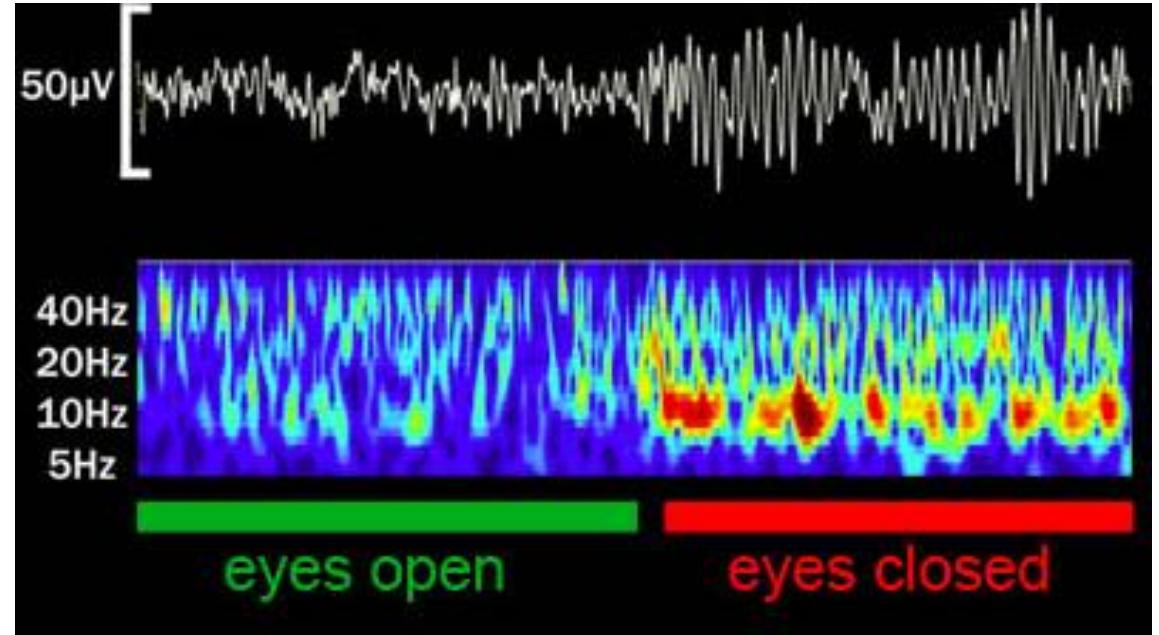


Jean-Baptiste-Joseph Fourier  
(1768–1830)

Fourier: “any signal or waveform could be made up just by adding together a series of pure tones (sine waves) with appropriate **amplitude** and **phase**”

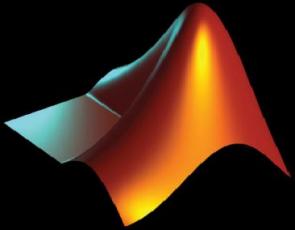


**Frequency spectrum**



# Brain Signal Spectral Content

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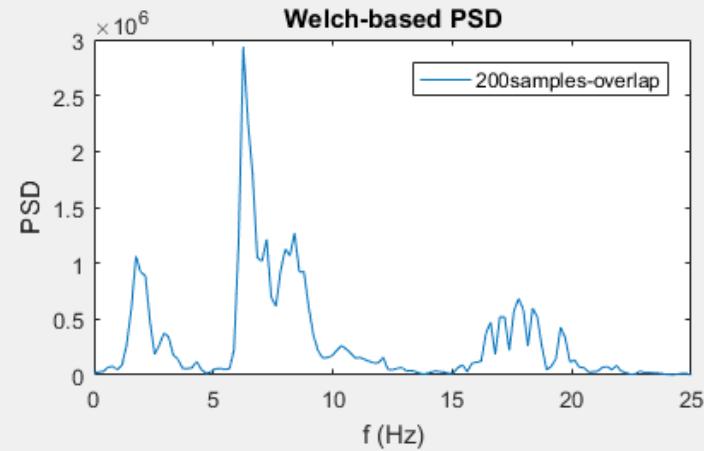
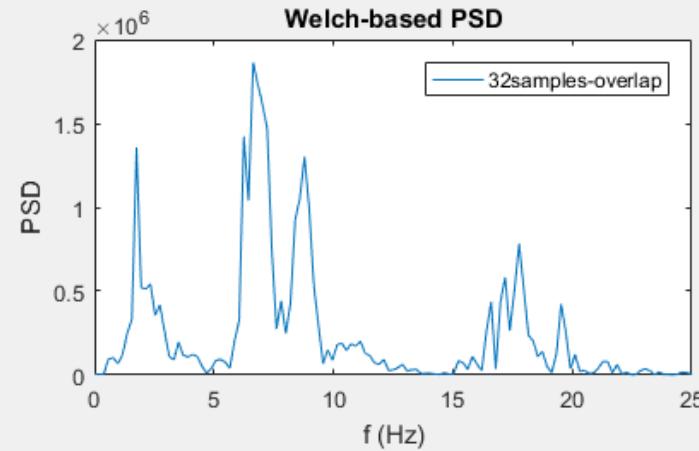
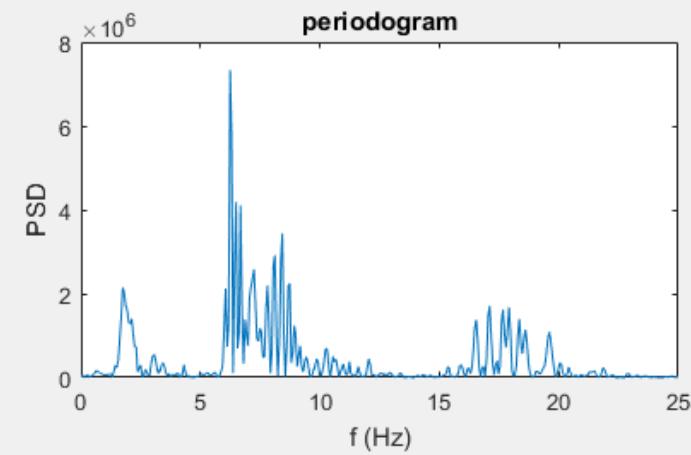
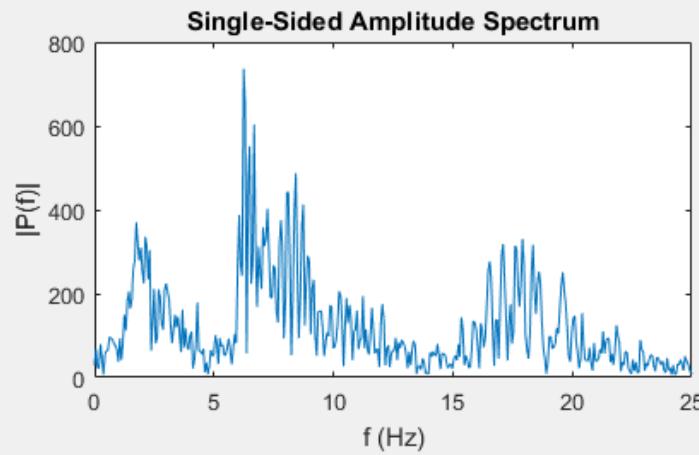
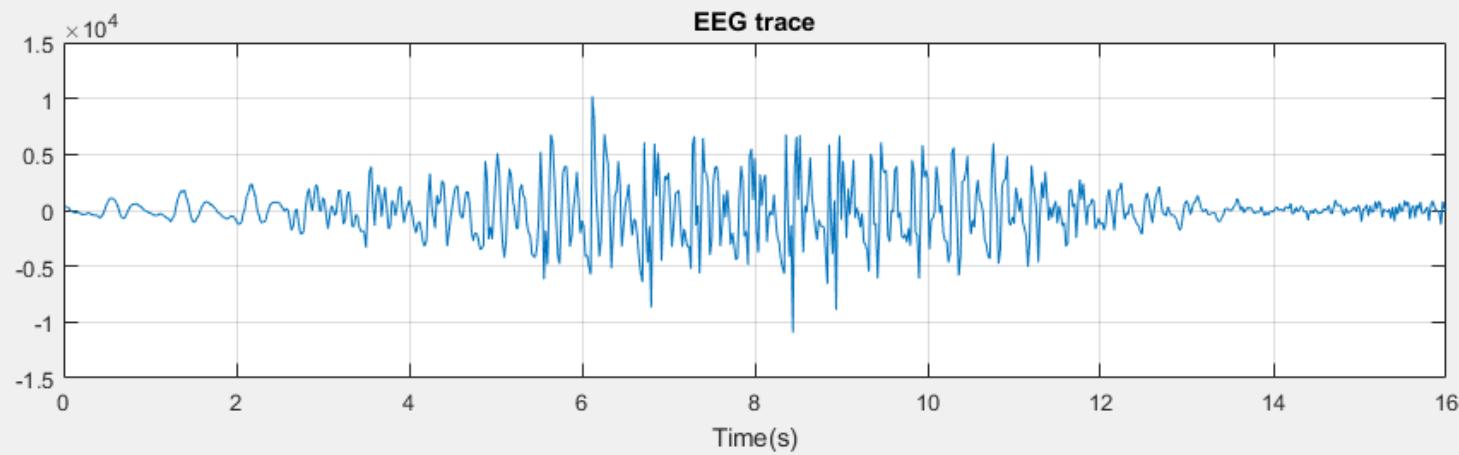
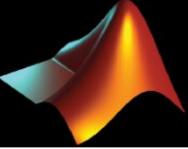
**fft****periodogram****pwelch****+ sptool**

NL\_script\_spectral\_analysis\_EEGtrace.m

```
load eeg_data, Fs=50;; time=[1:numel(eeg)]*(1/Fs);
% frequency-domain representation via FFT
L=numel(eeg);
Y = fft(eeg); %Compute the Discrete Fourier Transform
P2 = abs(Y/L); P1 = P2(1:round(L/2+1));P1(2:end-1) = 2*P1(2:end-1);
%Define the frequency domain f and plot the single-sided amplitude spectrum P1.
f = Fs*(0:round(L/2))/L;
..., plot(f,P1),title('Single-Sided Amplitude Spectrum'), xlabel('f (Hz)'), ylabel('|P(f)|'), xlim([0 25])

% frequency-domain representation via periodogram
[pxx,faxis] = periodogram(eeg,hamming(L),L,Fs,'psd') ;
subplot(3,2,4),plot(faxis,pxx),title('periodogram'), xlabel('f (Hz)'), ylabel('PSD'), xlim([0 25])

% WELCH-technique for estimating PSD
WINDOW=256;NOVERLAP=32;NFFT=256;
[pxx,faxis] = pwelch(eeg,WINDOW,NOVERLAP,NFFT,Fs,'onesided') ;
subplot(3,2,5),plot(faxis,pxx), xlabel('f (Hz)'), ylabel('PSD'), xlim([0 25]), title('Welch-based PSD'), legend('32samples-overlap ')
```



Biosignals are certainly **nonstationary**, with frequency content changing over time.

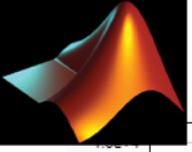
Such reflections of dynamics constitute the most interesting part of the signal.

*Spectro-temporal analysis* is the way to deal with them.

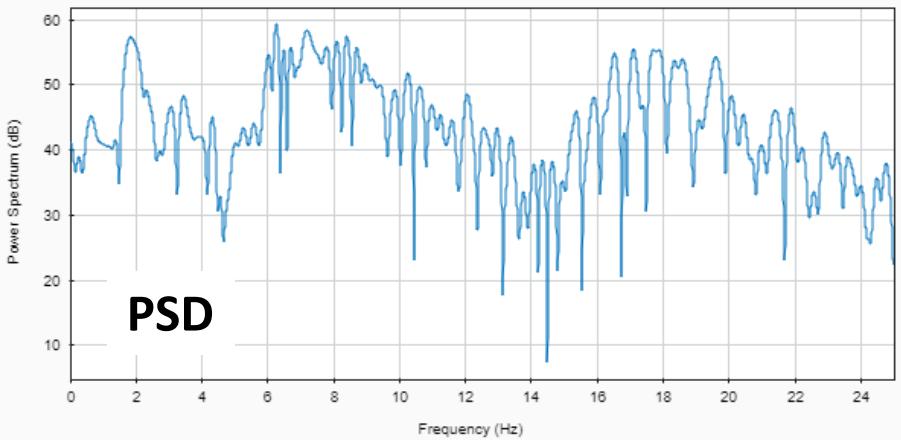
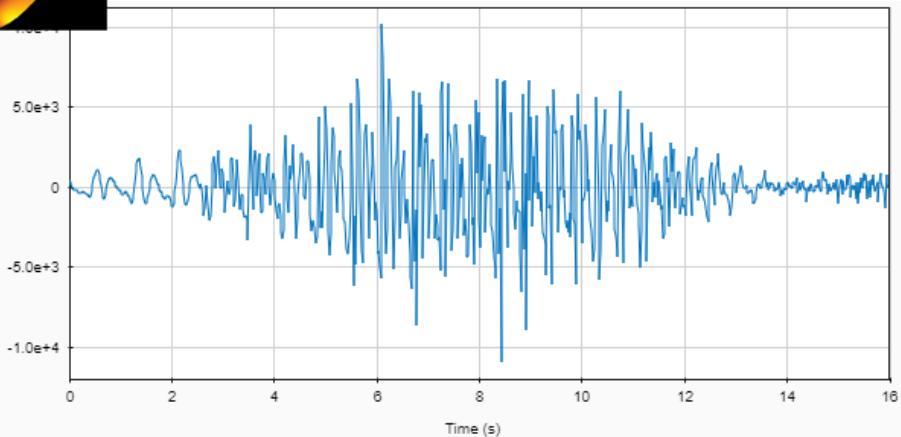
Two main ways to achieve it :

**Short-Time-Fourier Transform (STFT)** and **Wavelet-Transform (WT)**

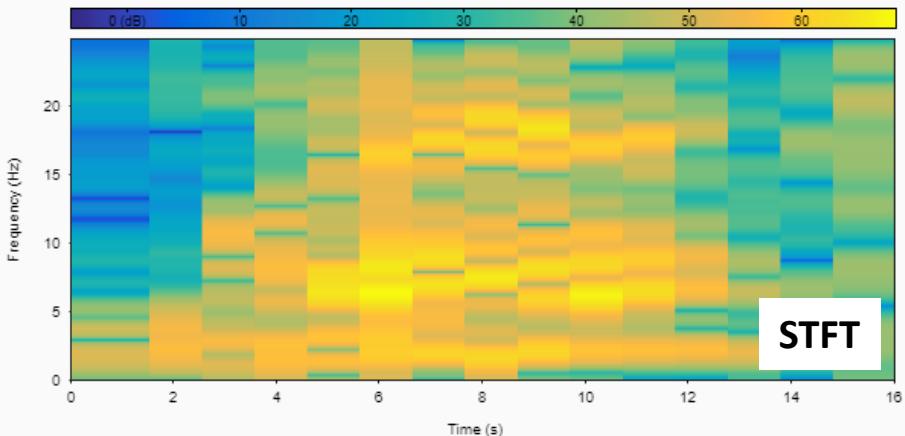
signalAnalyzer App



## EEG trace

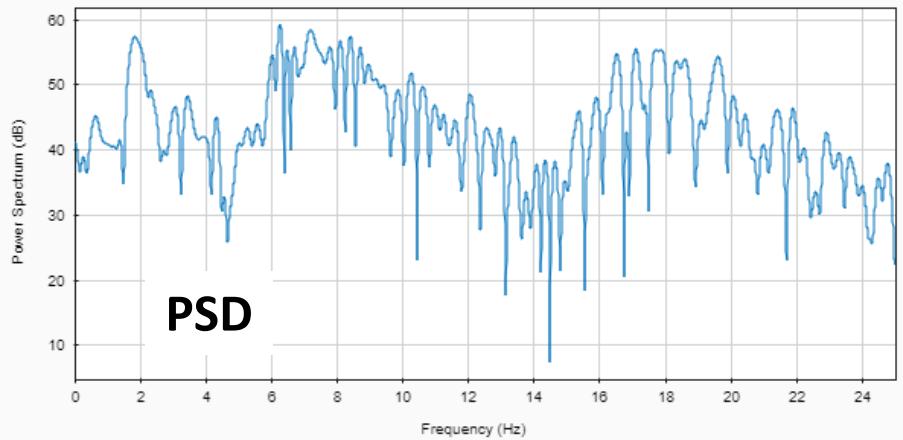
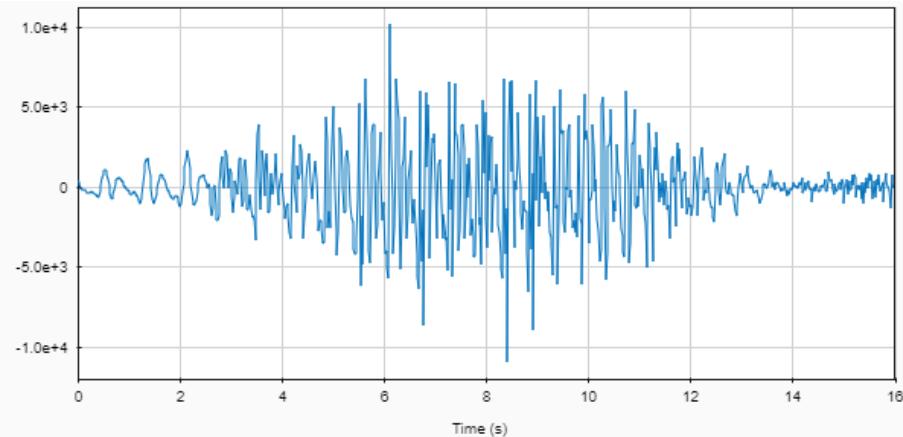


**PSD**

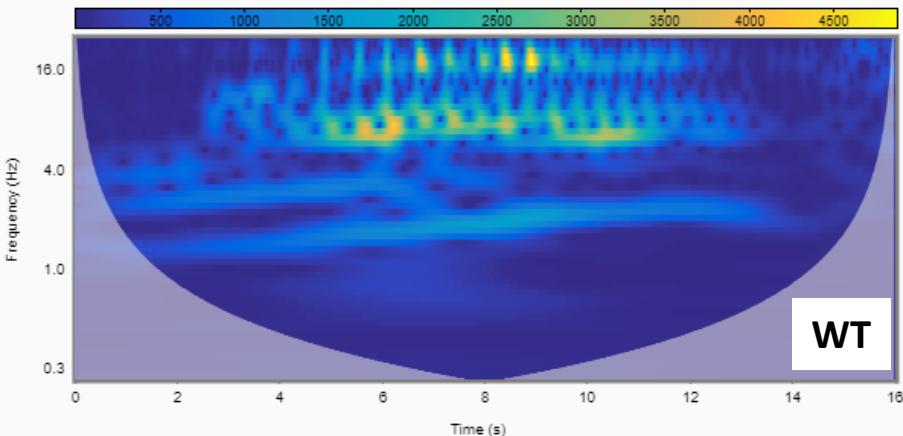


**STFT**

## EEG trace



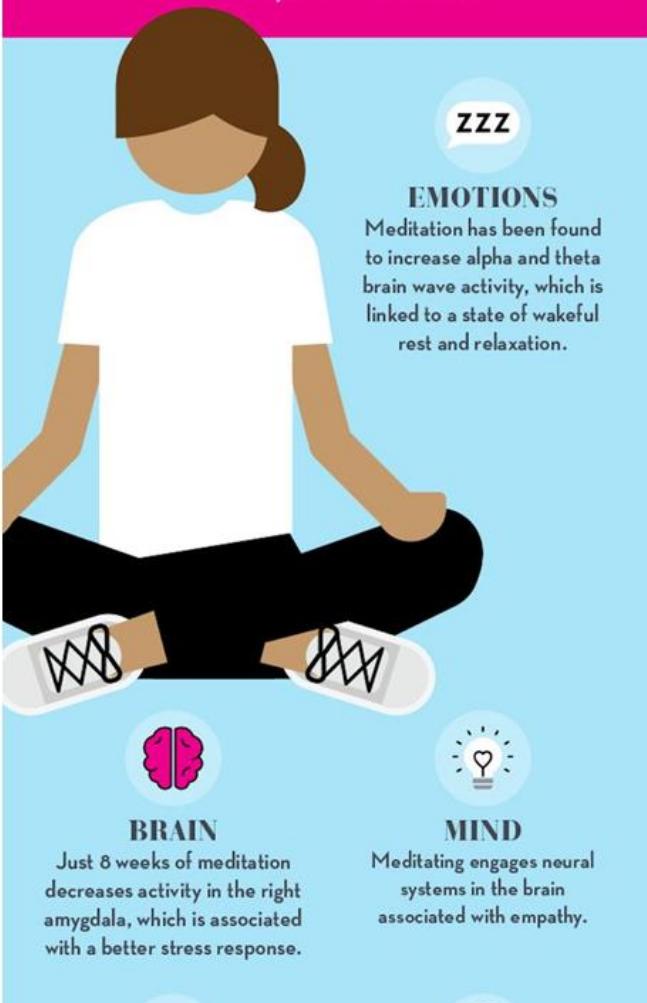
**PSD**



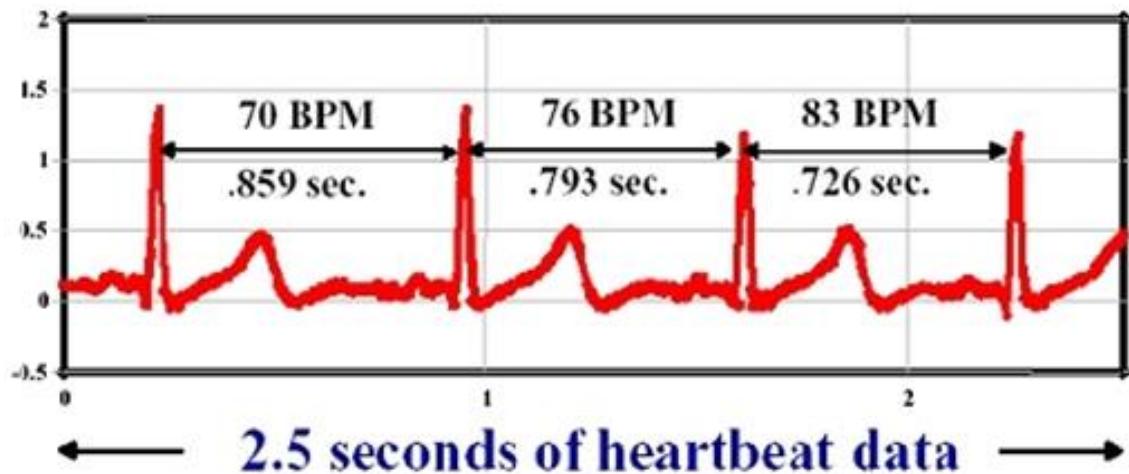
**WT**

# YOUR BODY ON MEDITATION

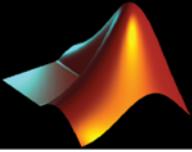
A regular practice can calm your brain, help your heart, and even make you a better person. Take a belly breath and read on.



# Heart Rate Variability



## Meditation and HRV



# Spectral analysis for *non-uniformly* sampled signals



NL\_script\_spectral\_analysis\_HeartRate\_signals.m

```
load Hr_pre, fs=1; ts=1/fs;

% form a regular time-axis (equally spaced time intervals)
timeaxis=[ceil(t_pre(1)):ts:floor(t_pre(end))];

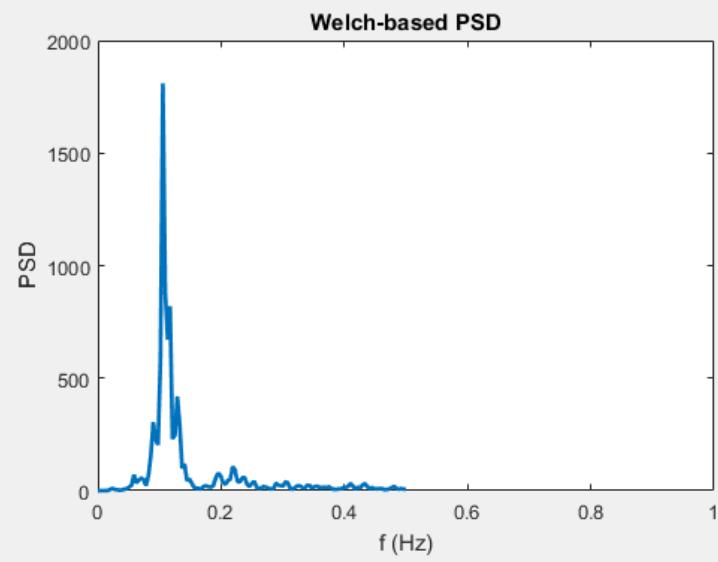
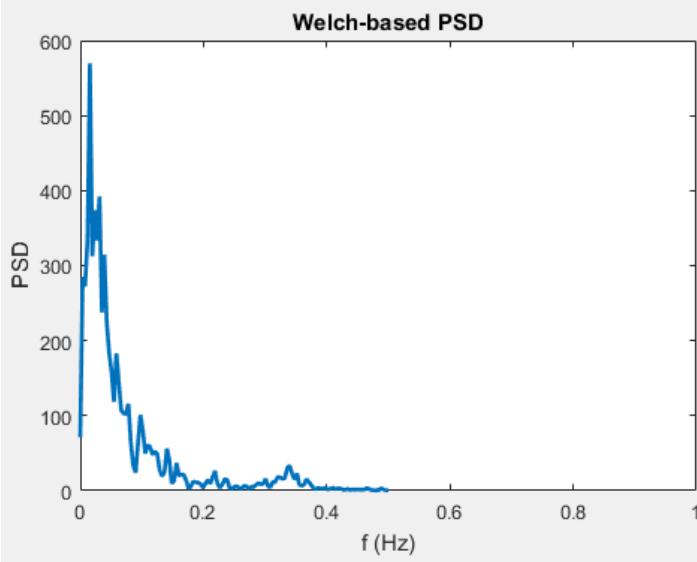
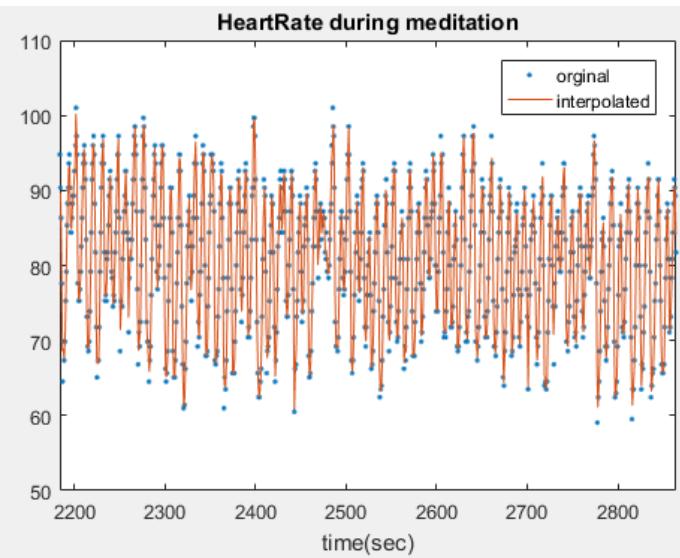
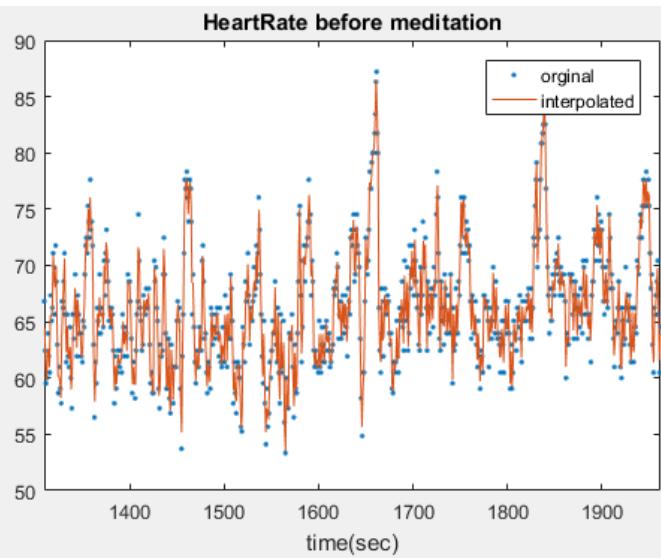
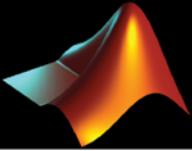
% using the given time-signal pairs ''predict'' the signal at timeaxis
hr_pre_interpolated=interp1(t_pre,hr_pre,timeaxis);

WINDOW=256;NOVERLAP=200;NFFT=256;
[pxx,faxis] = pwelch(detrend(hr_pre_interpolated),WINDOW,NOVERLAP,NFFT,fs,'onesided');
% Note: detrend is necessary

load Hr_med,

timeaxis_med=[ceil(t_med(1)):ts:floor(t_med(end))];
hr_med_interpolated=interp1(t_med,hr_med,timeaxis_med);

WINDOW=256;NOVERLAP=200;NFFT=256;
[pxx,faxis] = pwelch(diff(hr_med_interpolated),WINDOW,NOVERLAP,NFFT,fs,'onesided');
subplot(2,2,4),plot(faxis,pxx), xlabel('f (Hz)'), ylabel('PSD'), xlim([0 1]), title('Welch-based PSD')
```



State-specific spectral characteristics can easily be defined

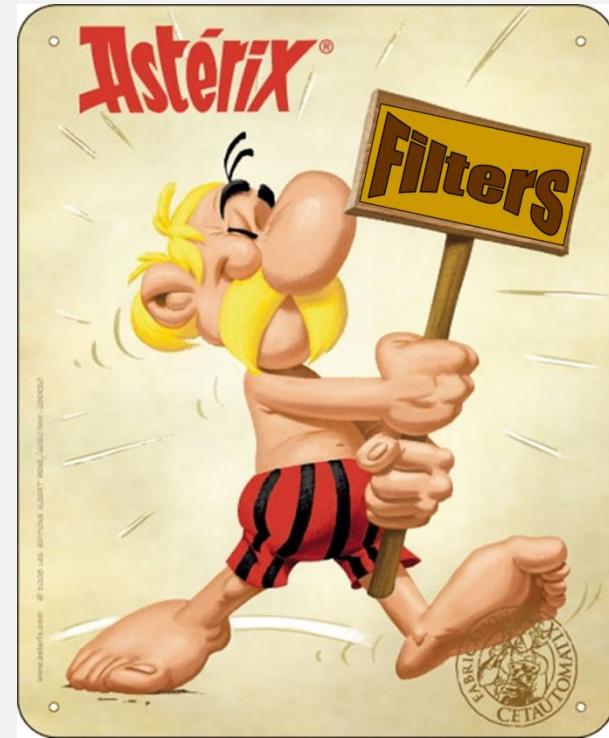


# Filtering

Signal Averaging

Time-Domain operations

FT-based Filter Design

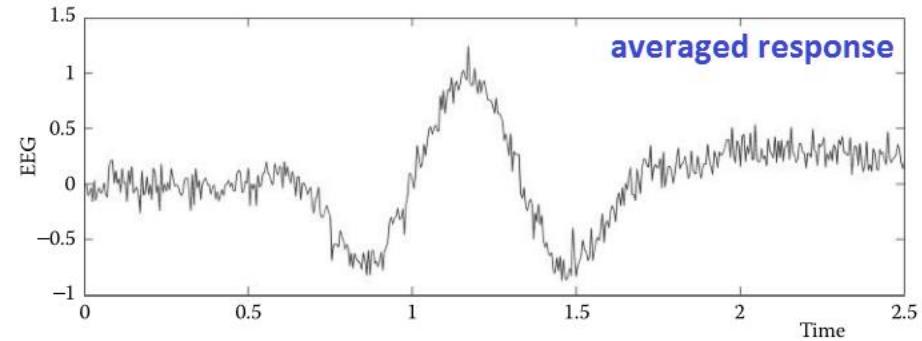
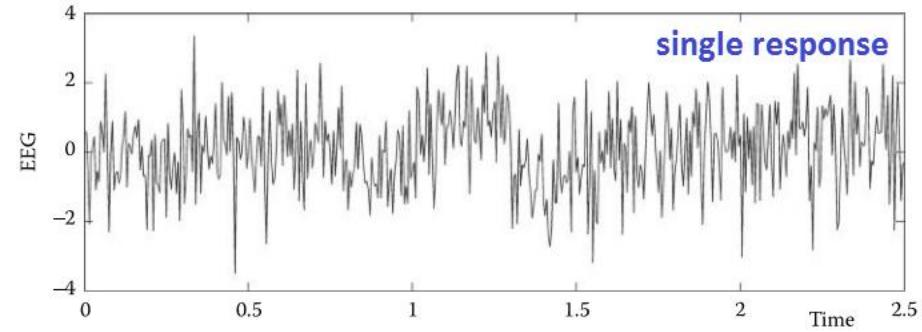


# Signal Averaging : denoising repetitive signal waveforms

e.g. heart-beat in high resolution ECG  
and single-trial Evoked Responses

Under the  
**'constant signal' + 'noise'** model,  
the underlying signals recovers better  
with more repetitions

$$x_i(n) = s(n) + noise_i(n), \quad i = 1 : N_{\text{trials}}$$



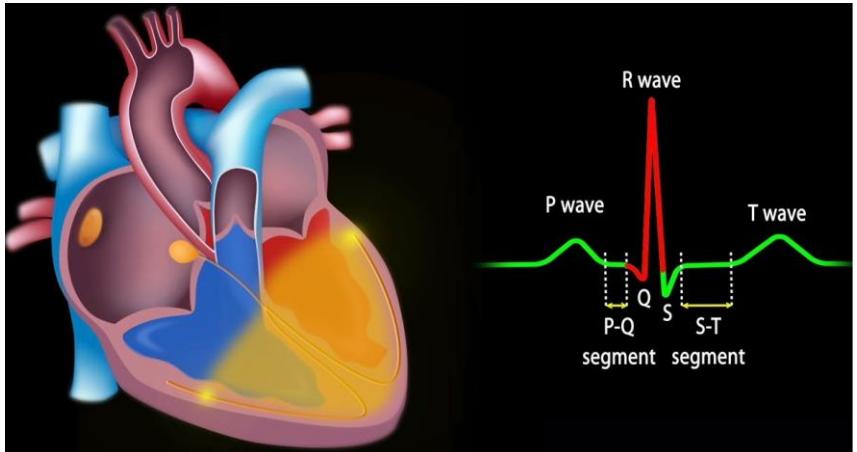
$$\frac{1}{N_{\text{trials}}} \sum_1^{N_{\text{trials}}} x_i(n) = \frac{1}{N_{\text{trials}}} \sum_1^{N_{\text{trials}}} [s(n) + noise_i(n)] \Rightarrow$$

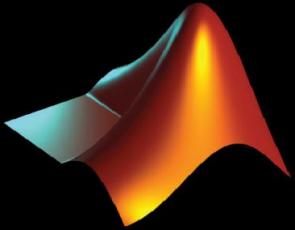
$$x_{\text{ave}}(n) = s(n) + \text{res\_noise}(n),$$

$$\text{var(res\_noise)} = 1/N_{\text{trials}} \text{ var(noise}_i\text{)}$$

# High- resolution ECG- example

23





smooth

findpeaks

mean



### NL\_script\_denoising\_signalAveraging\_highresolution\_ECG.m

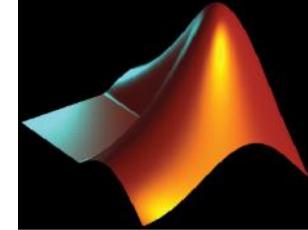
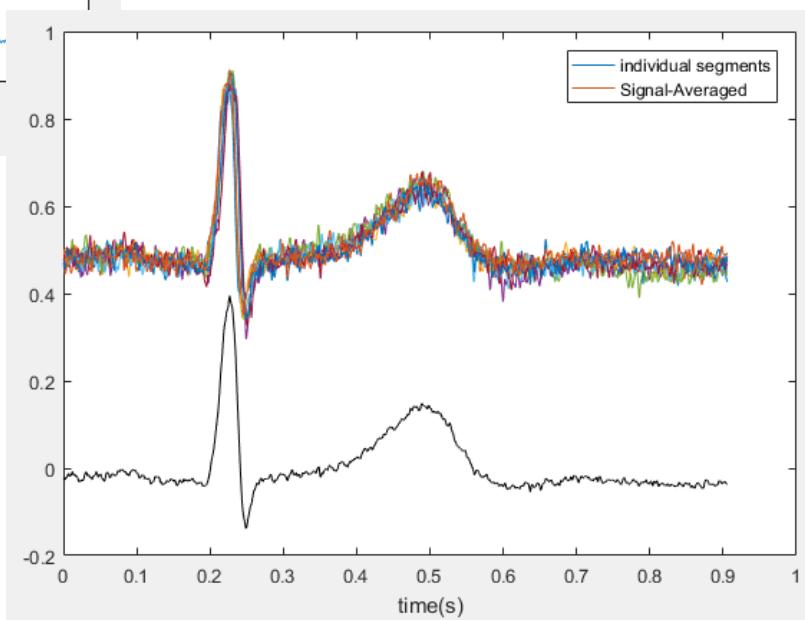
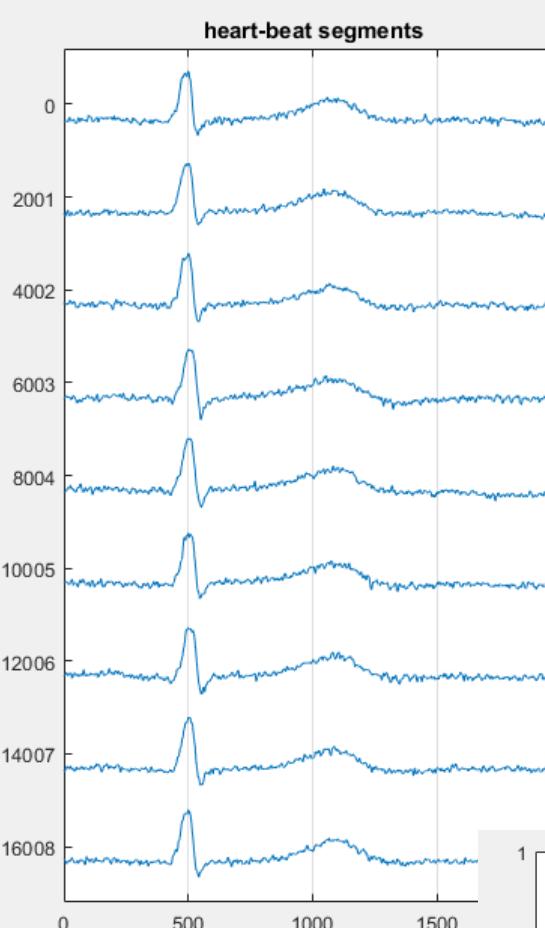
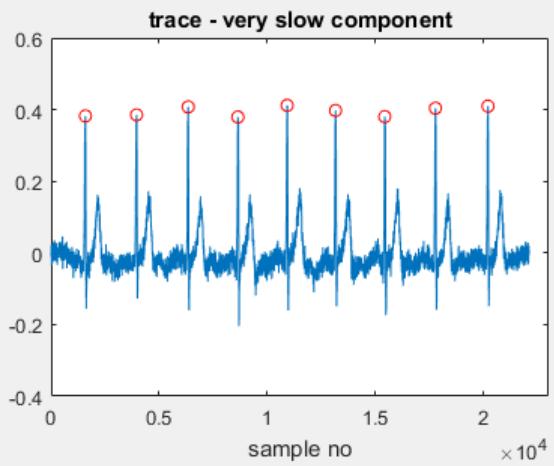
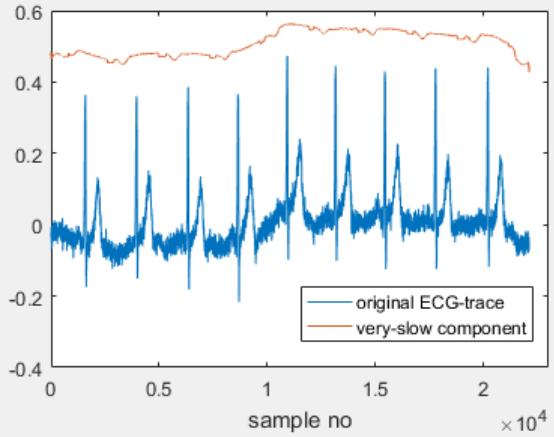
```
x=load('ECGtest.csv'); % Load the test signal
fs = 2210; % Sampling Frequency

t=[1:numel(x)]; %dcrete_time #samples
%time=[1:numel(x)]*(1/fs); % time in sec
figure(1),clf,subplot(2,2,1),plot(t,x,t,smooth(x,2051)+0.5),legend('original ECG-trace','very-slow component'),xlabel('sample no'),xlim([0,23000])
subplot(2,2,3),plot(t,x-smooth(x,2051)),hold on,title('trace - very slow component'),xlabel('sample no'),xlim([0,23000])

% detecting the R-peak based on the denoised -trace
x2= x-smooth(x,2051);
[PKS,LOCS]=findpeaks(x2,t,'minpeakheight',0.3,'MinPeakDistance',100);
plot(LOCS,PKS,'ro'),hold

% segmenting around the QRS complex
ECG_traces=[];for i=1:numel(LOCS)
    segment=x2(LOCS(i)-500:LOCS(i)+1500)';
    ECG_traces(i,:)=segment;end

plot(time,ECG_traces+0.5,time,mean(ECG_traces),'k'),
xlabel('time(s)'),legend('individual segments','Signal-Averaged')
```



# Frequency selective filters



Filters are systems (of programs) that alter the signal with the scope of enhancing/extracting the useful information.

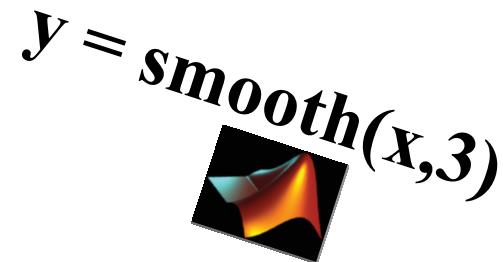
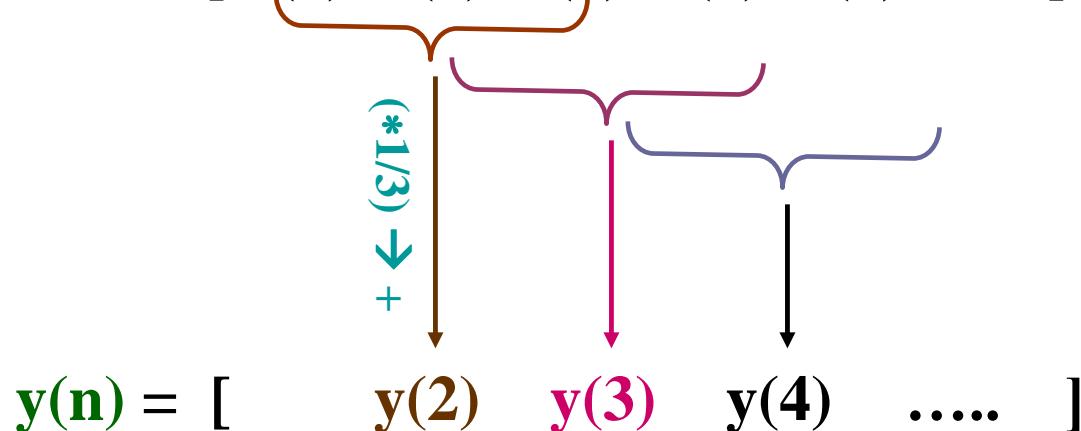


$$a_0 y(n) + a_1 y(n-1) + \dots + a_N y(n-N) = b_0 x(n) + b_1 x(n-1) + \dots + b_M x(n-M)$$

‘Designing a Filter’ means defining the coefficients  $\{a_i\}$  and  $\{b_i\}$  in the above ***Difference equation***

e.g. moving average filter  $\vec{b} = \left[ \frac{1}{3} \frac{1}{3} \frac{1}{3} \right] =: h(n)$

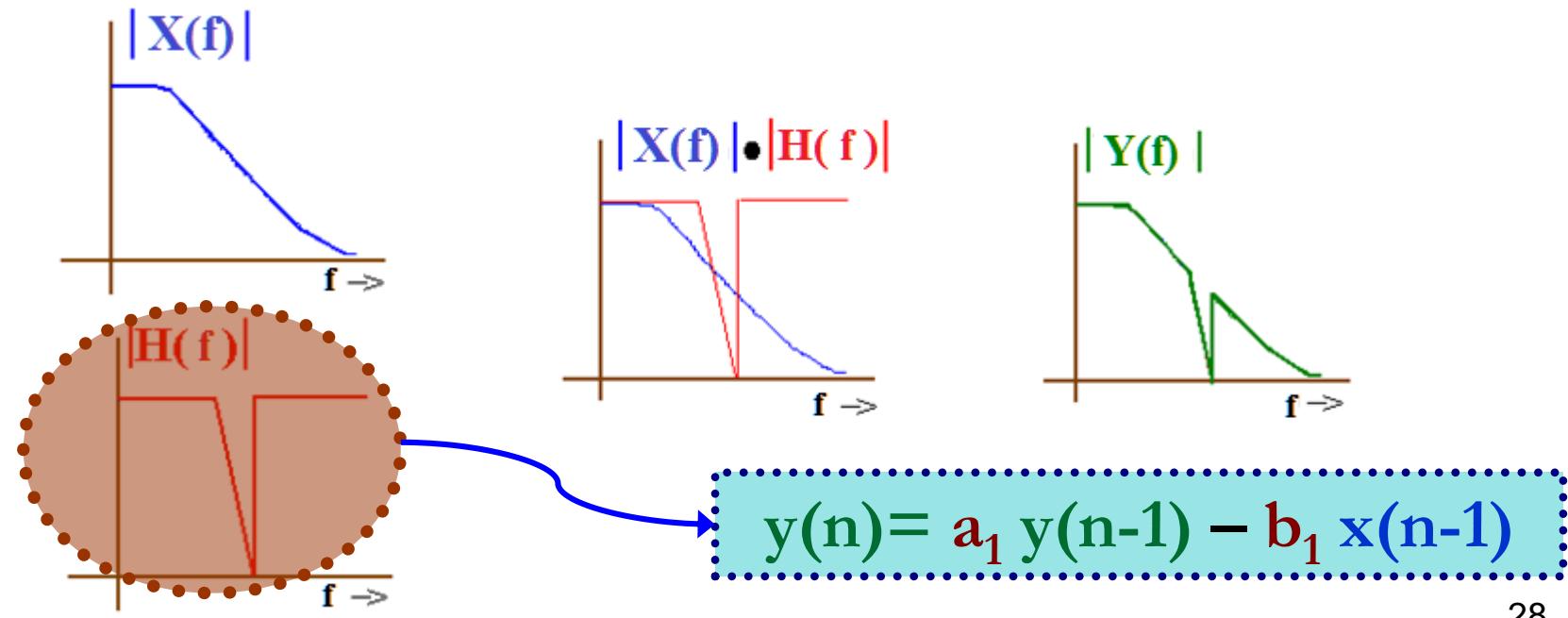
$$x(n) = [ x(1) \ x(2) \ x(3) \ x(4) \ x(5) \dots ]$$



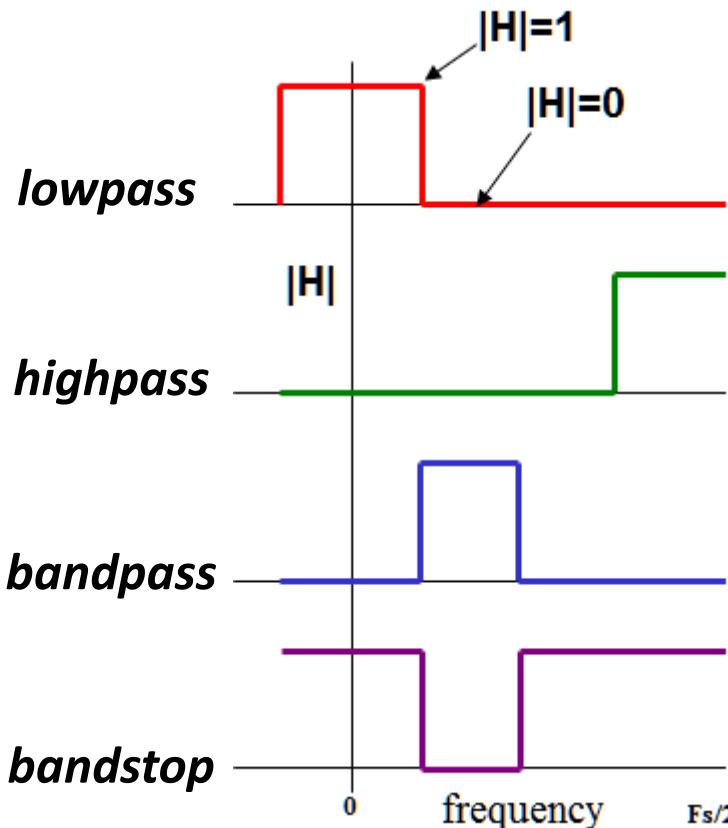
Frequency selective filters are filters that are designed in Frequency Domain thanks to *convolution theorem*

$$Y(f) \xrightarrow{H(f)} Y(f) \quad Y(f) = H(f) \cdot X(f)$$

“we define the **frequency response  $H(f)$**   
& translate it into **Difference Equation** ”

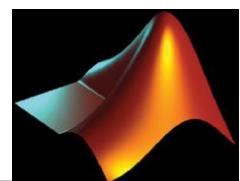


## Basic types of filters



Based on the form of *difference equation* there are two main kinds of linear filters: the **FIR filters** (with no recursive terms)  
and the **IIR filters** (using both  $b_i$  and  $a_i$  coeff's )  
which –in MATLAB- are designed with distinct commands, e.g.

**B = fir1(N, Fc)**      **[B,A] = butter(N,Fc)**



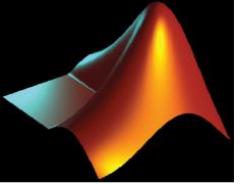
but applied with the same command **filter** or **filtfilt**

**Y = filter(B,A,X)**

# Denoising ECG



Image Credit: techcrunch.com

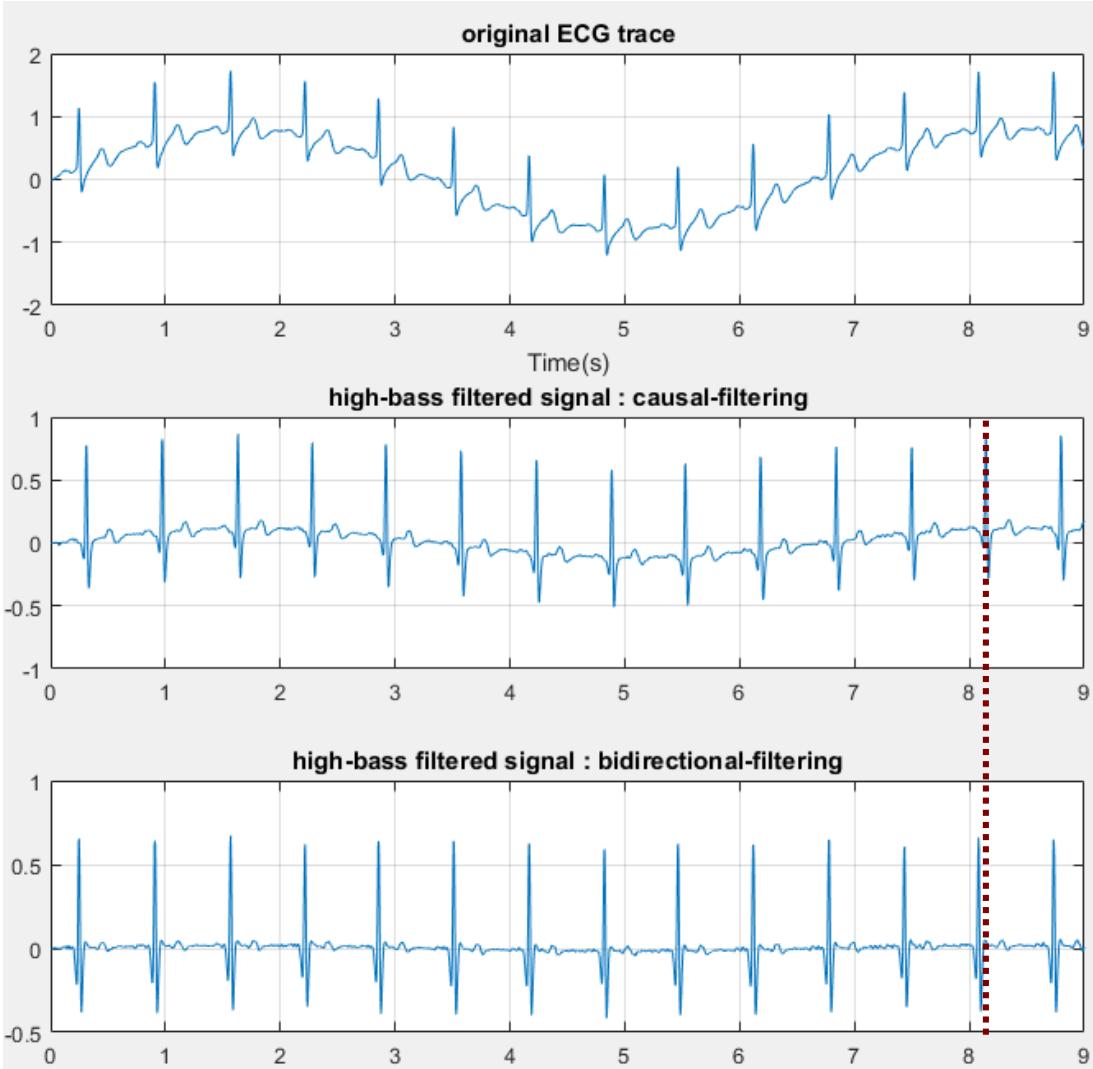


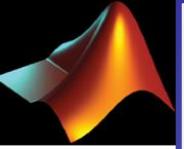
```
load ECG_9, Fs=250
% design an a high-pass FIR 32-order filter with cutoff at 8 Hz
b=fir1(32,8/(Fs/2), 'high');
filtered_x1= filter(b,1,x); % apply the filter in causal mode

filtered_x2=filtfilt(b,1,x); % apply the filter in zero-phase mode.
```



NL\_script\_Filtering\_ECG\_Signal\_to\_Cancel\_Respiratory\_artifact.m

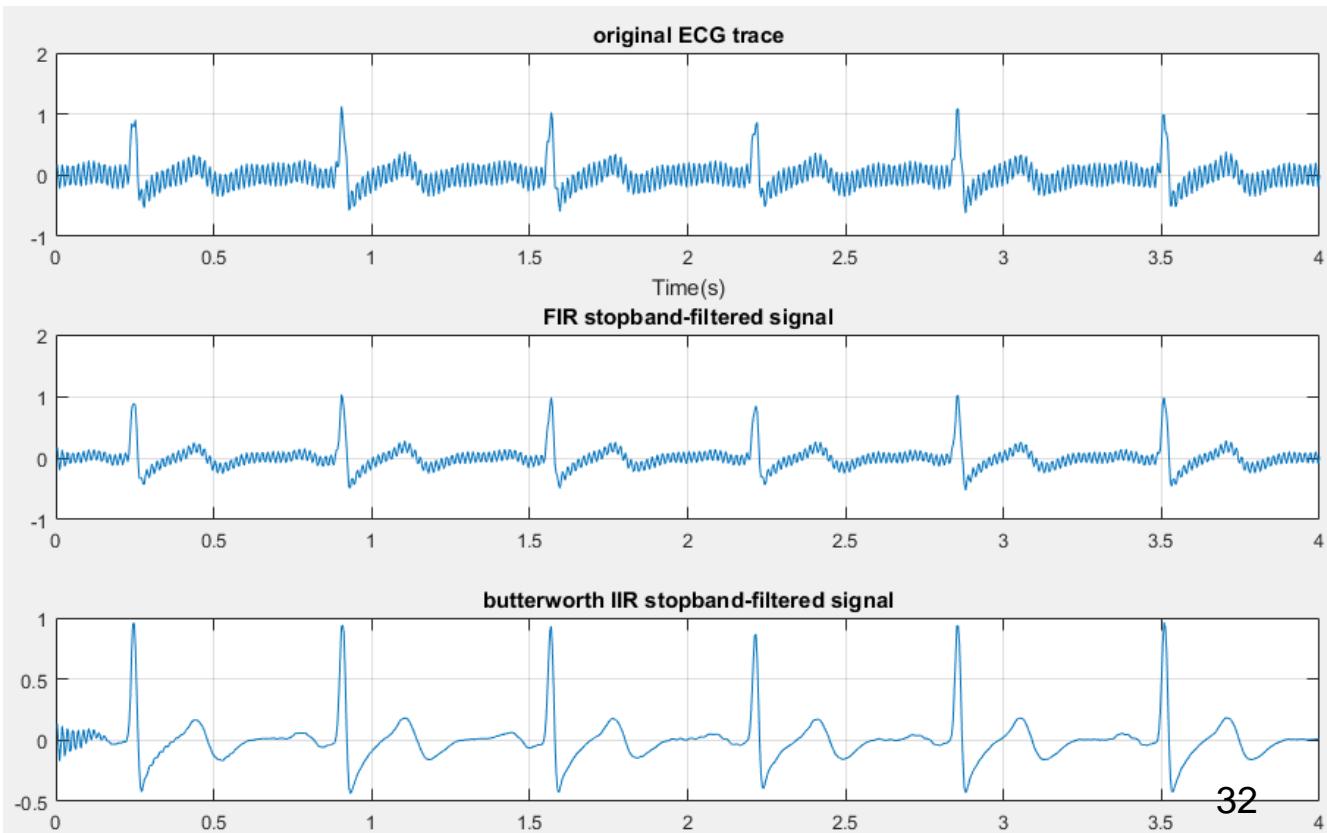




```
load ECG_60Hz_data, Fs=250
% design a stop-band FIR 36-order filter
% for removing powerline noise @ 60 Hz

b=fir1(36,[58 62]/(Fs/2),'stop');
filtered_x=filtfilt(b,1,x); % apply the filter in zero-phase mode

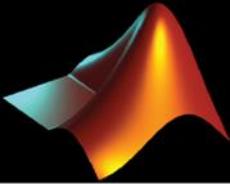
% design a stop-band IIR 3-order filter
[b,a]=butter(3,[58 62]/(Fs/2),'stop');
filtered_x=filtfilt(b,a,x); % apply the filter in zero-phase (bidirectional) mode
```



# Denoising respiratory signal

---





6



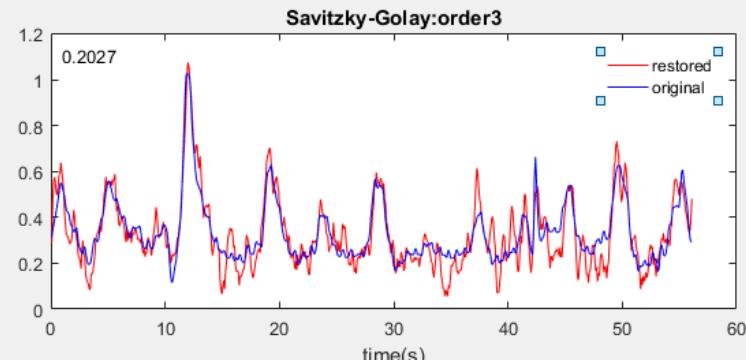
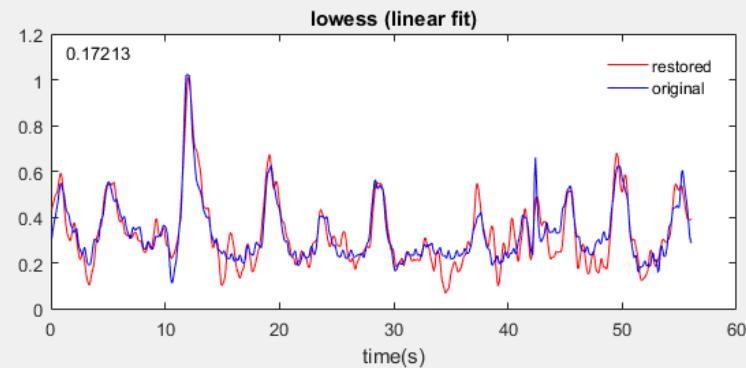
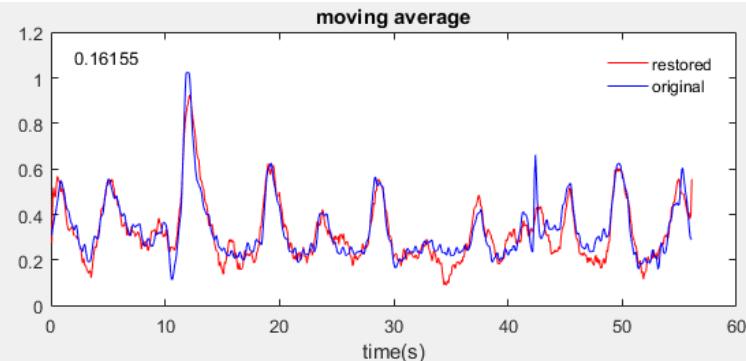
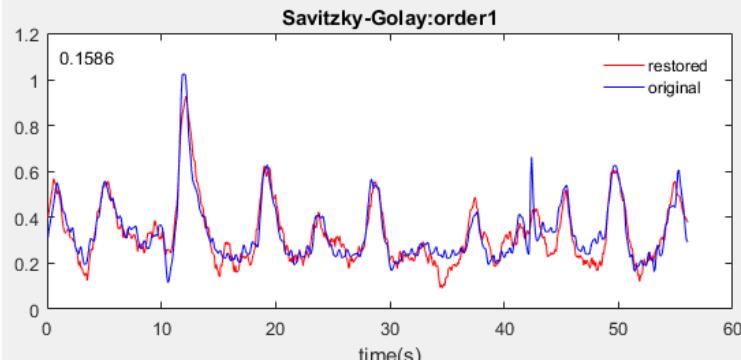
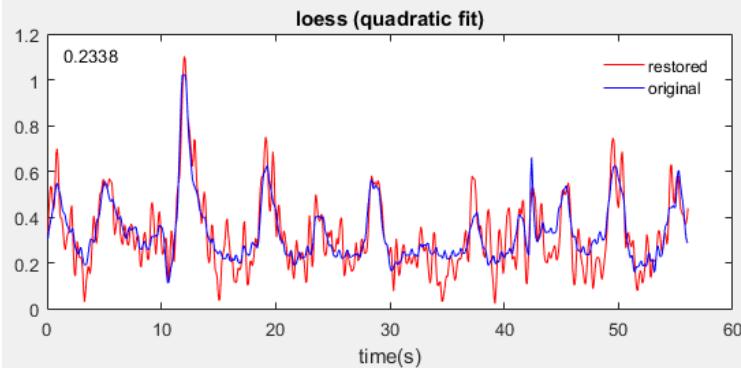
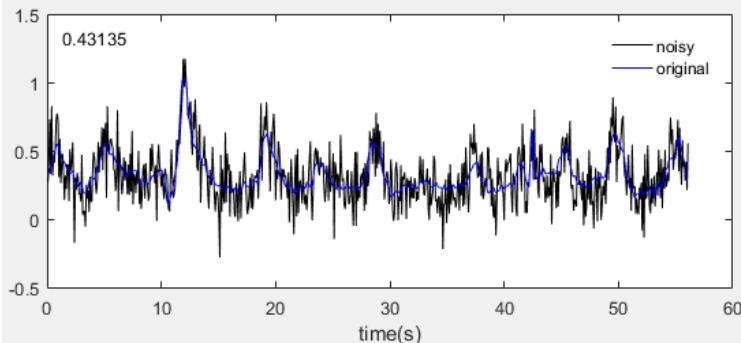
smooth

linear fit

quadratic

sgolay

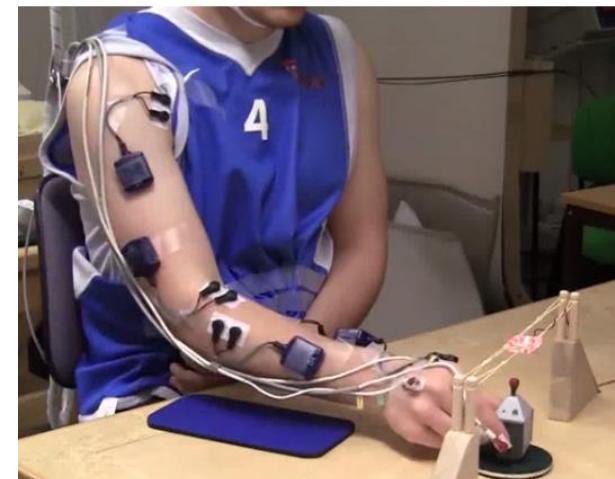
NL\_script\_filtering\_respiratory\_noisy\_Signal.m





Multivariate SP

Multichannel signals (e.g. high density EEG, ECG) are harder to analyze due to their increased data-volume.



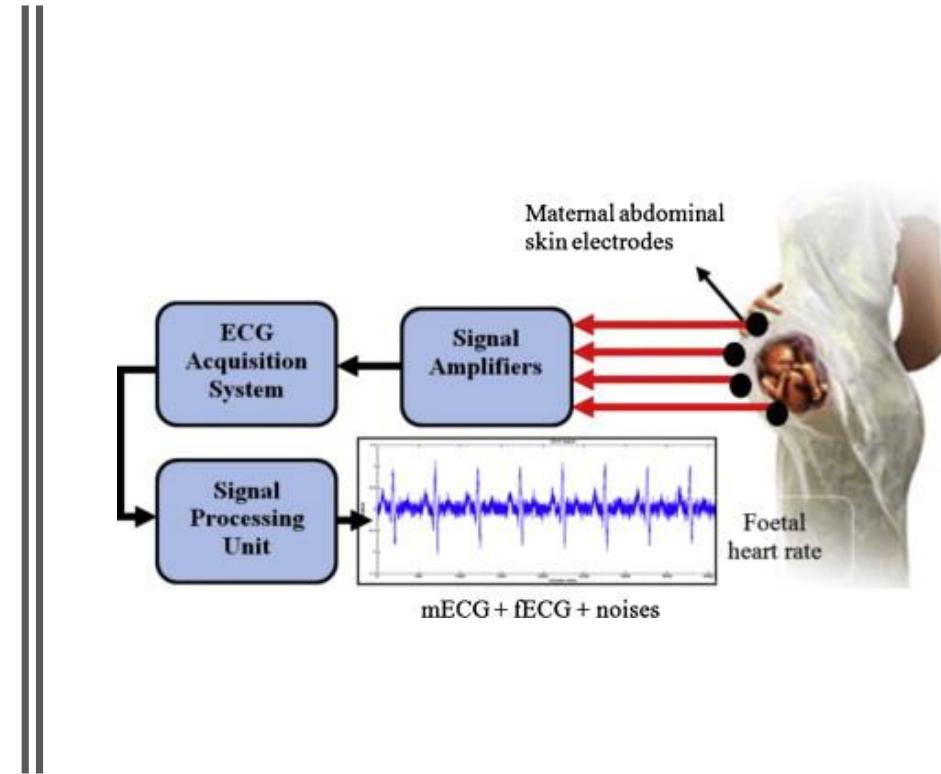
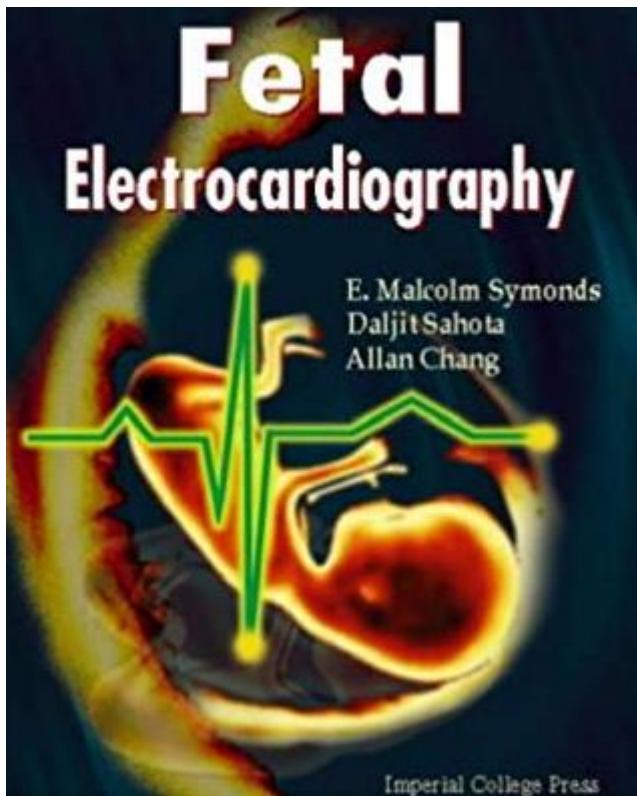
Considering the inherent redundancies, ***multivariate techniques*** are often exploited to provide convenient summaries, suppress background noise, and identify ‘unique’ signal sources

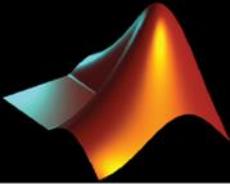
In a simplified set up, the multiple sensor traces are described as a ‘linear’ combination of ***source-signals***, each of different origin and carrying its own biological meaning.

$$\begin{bmatrix} x_{sensor1}(t) \\ x_{sensor2}(t) \\ \dots \\ x_{sensorN}(t) \end{bmatrix} \simeq [A_{N \times 2}] \begin{bmatrix} x_{source1}(t) \\ x_{source2}(t) \end{bmatrix}$$

***Principal Component Analysis*** (PCA)  
and ***Independent component analysis*** (ICA)  
are common practice tools

# Isolating Fetal ECG





ICA



NL\_script\_unmixing\_foetal\_from\_maternalECG.m

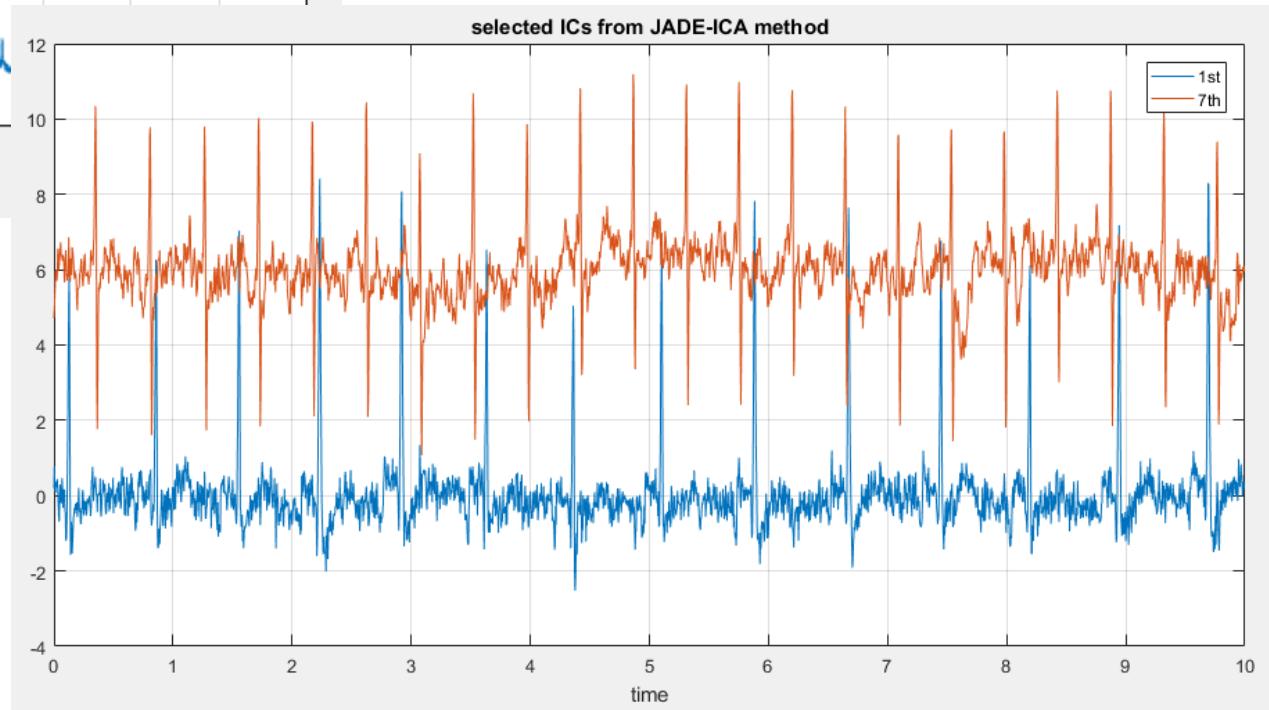
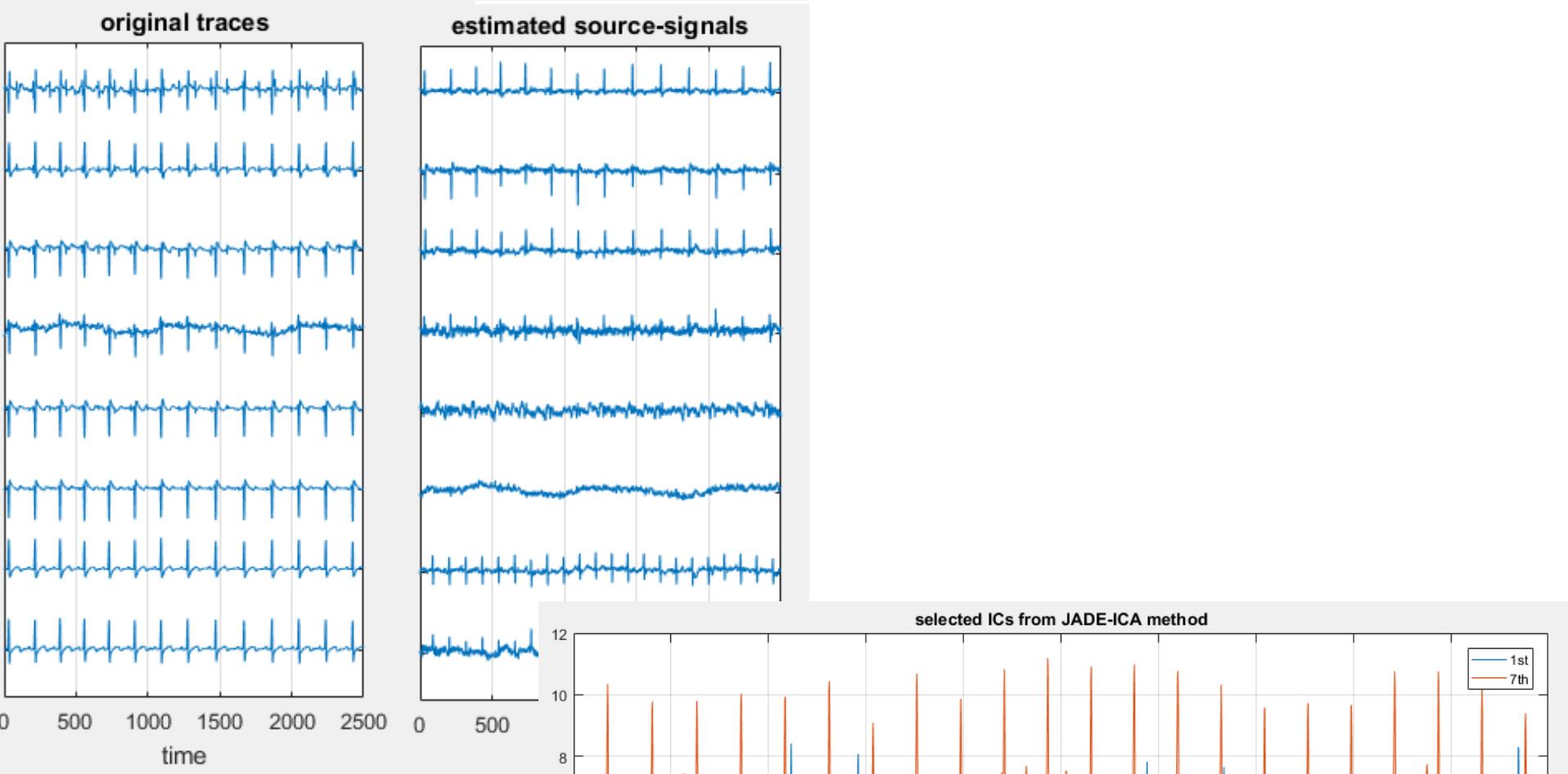
$$\mathbf{B} = \mathbf{A}^{-1}$$

```
x=load('FOETAL_ECG.dat'); time=X(:,1)'; ECGdata=X(:,2:9)';

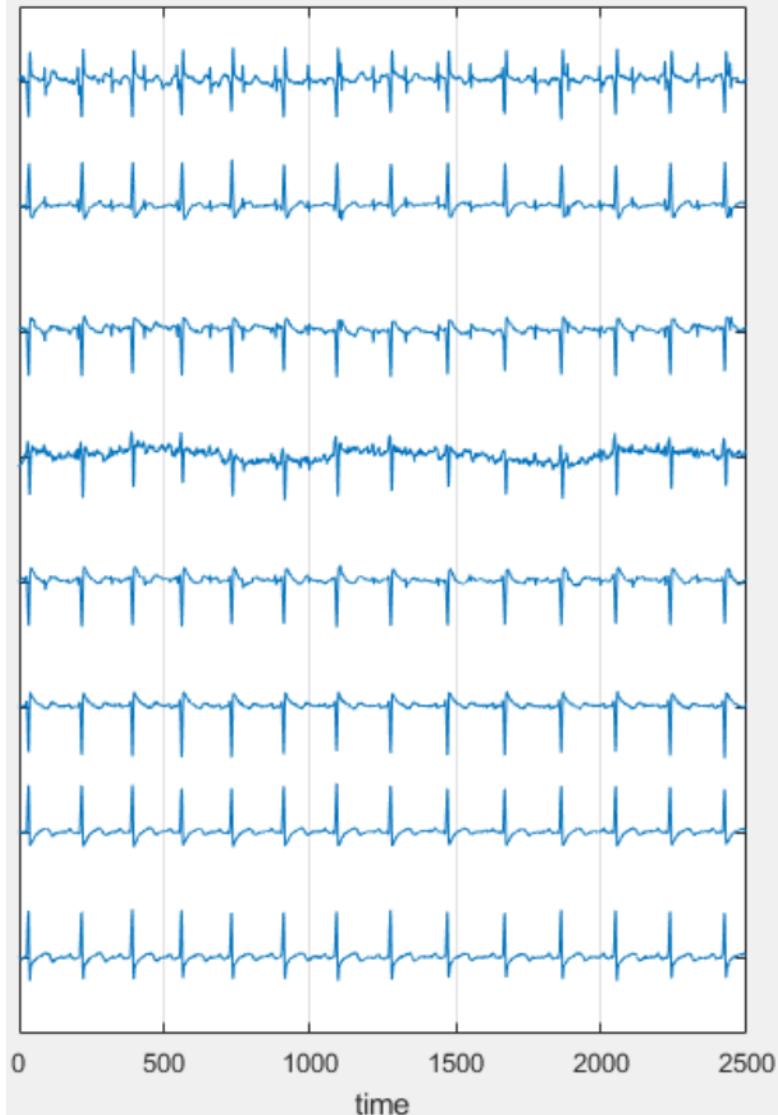
B=jadeR(ECGdata); % deriving the unmixing-matrix
Sources=B*ECGdata; % estimating the ICs (source-signal)

display('selecting the 1st and 7th ICs from the JADE-ICA method')

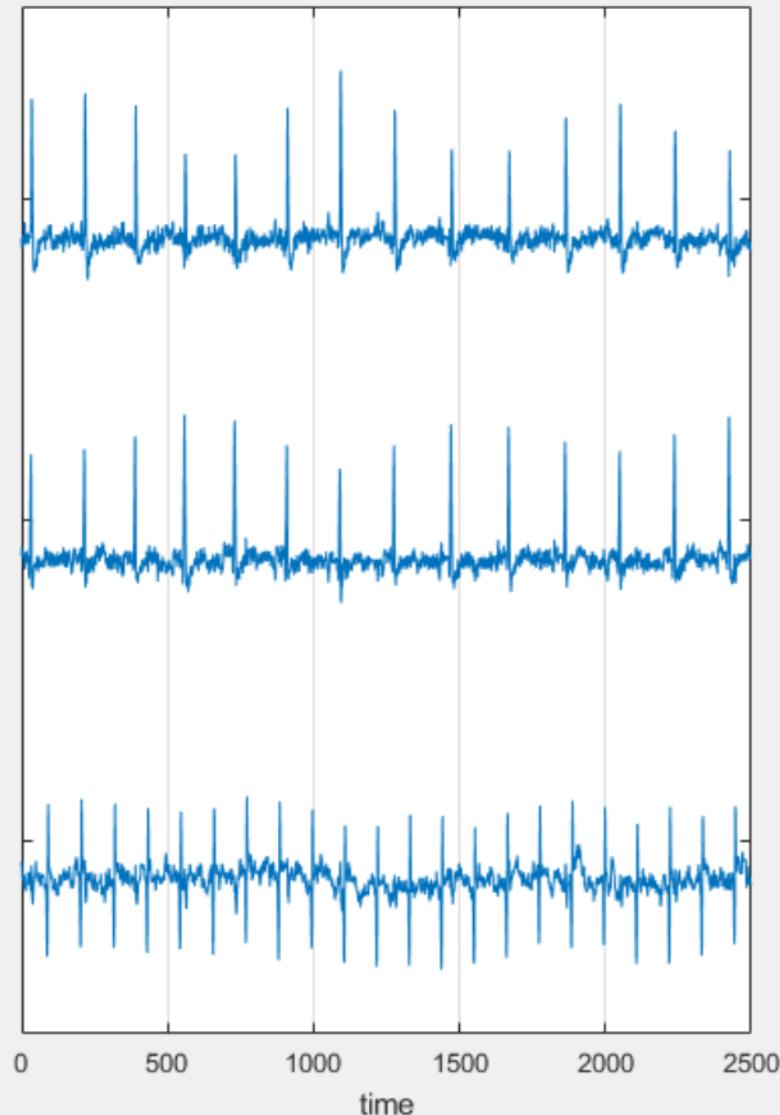
% PART-II using FAST-ICA toolbox
% you need to set FASTICA_toolbox in the path
[sources] = fastica (ECGdata, 'numOfIC', 3);
% [icasig] = fastica (ECGdata, 'lastEig', 5, 'numOfIC', 3);
```

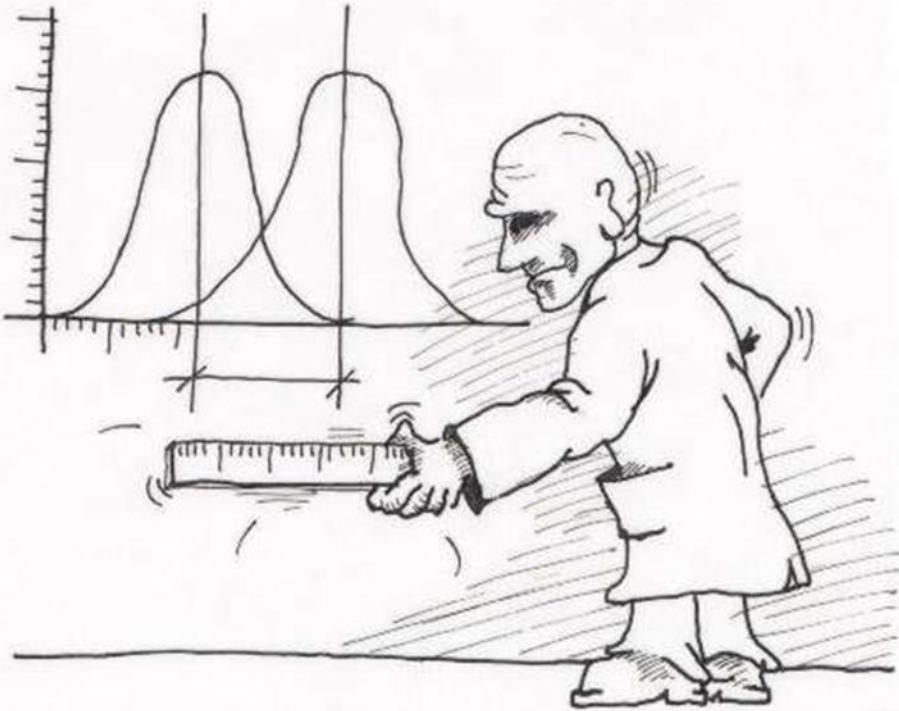


**original traces**



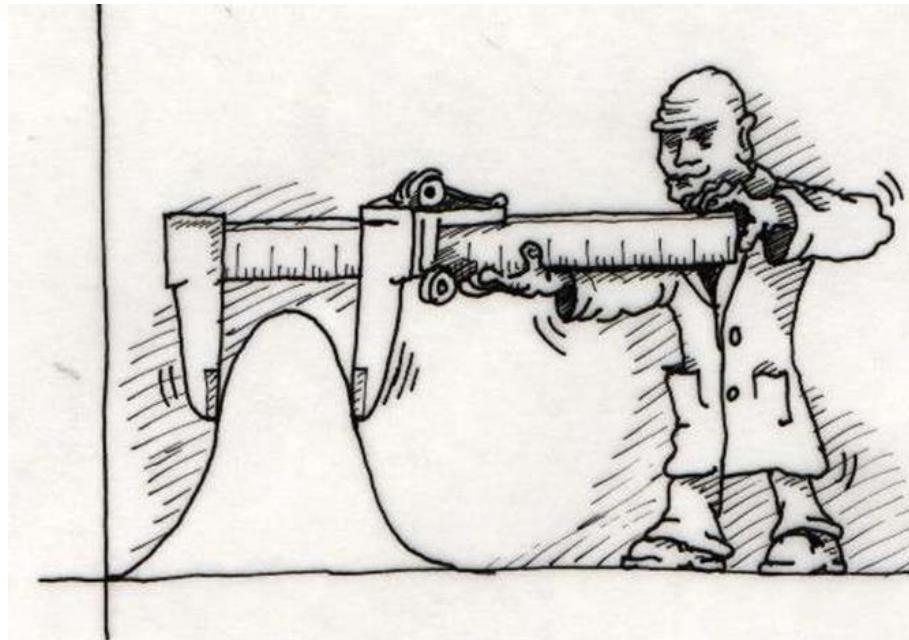
**FASTICA based estimated source-signals**

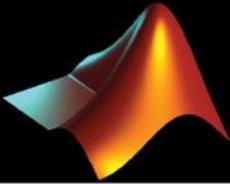




## Deriving Signal Attributes

Apart from the **Spectral content**,  
**time-domain characteristics**  
and **statistical descriptors**  
can be utilized to form  
**'biological signatures  
of a disease  
or state'**





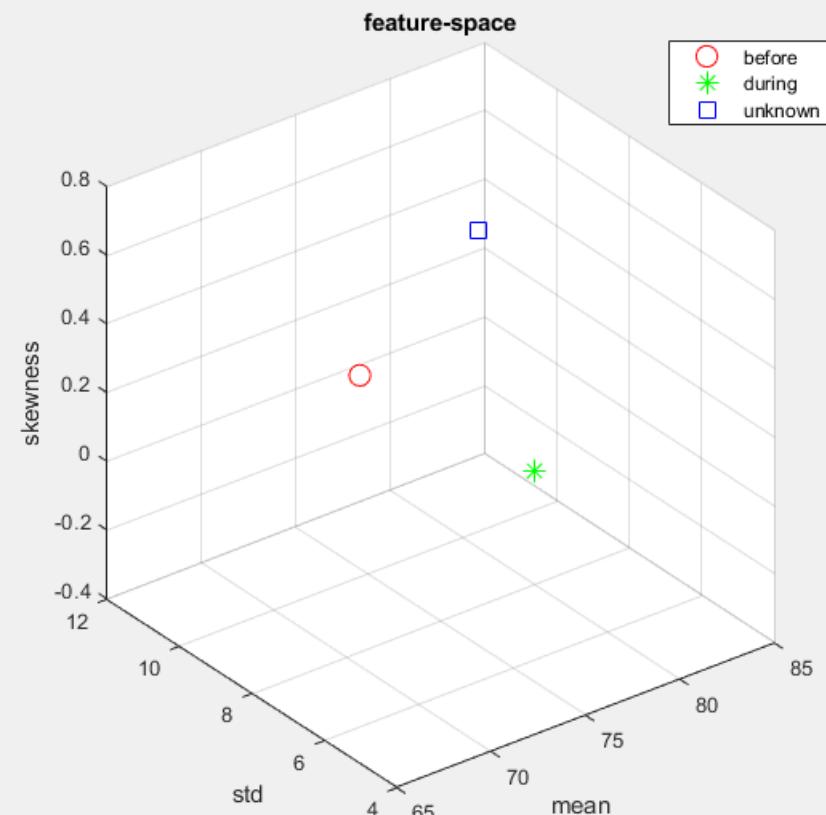
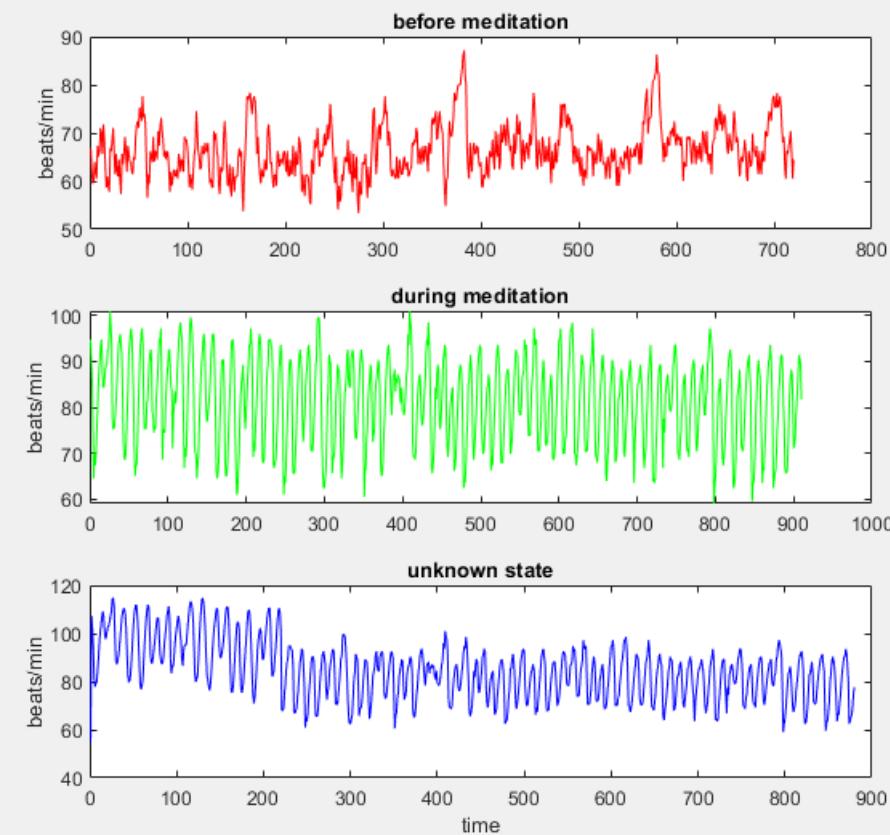
mean

std

skewness



NL\_script\_stat\_features\_from\_HR\_signal.m



# Gait Signal Analysis

## Amyotrophic lateral sclerosis (ALS)

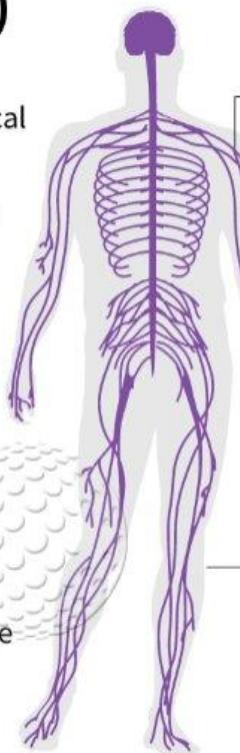
A type of motor neurone disease



Stephen Hawking was diagnosed in his early 20s

He defied predictions he would only live a few years but was wheelchair-bound and spoke through a computerised voice system

- ▶ ALS is a rare neurological condition
- ▶ Progressive -- worsens with time -- with no cure
- ▶ Gradually muscles under voluntary control are affected, individuals lose strength, ability to speak, eat, move, breath
- ▶ Most people with ALS die of respiratory failure within 3 to 5 years of first symptoms

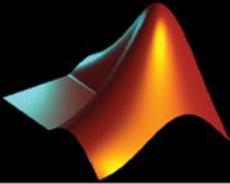


Affects nerve cells responsible for controlling voluntary muscle movement

Motor neurons link between brain and voluntary muscles

In ALS, the upper motor neurons and lower motor neurons degenerate and die

Unable to function, the muscles degenerate



midcross

diff

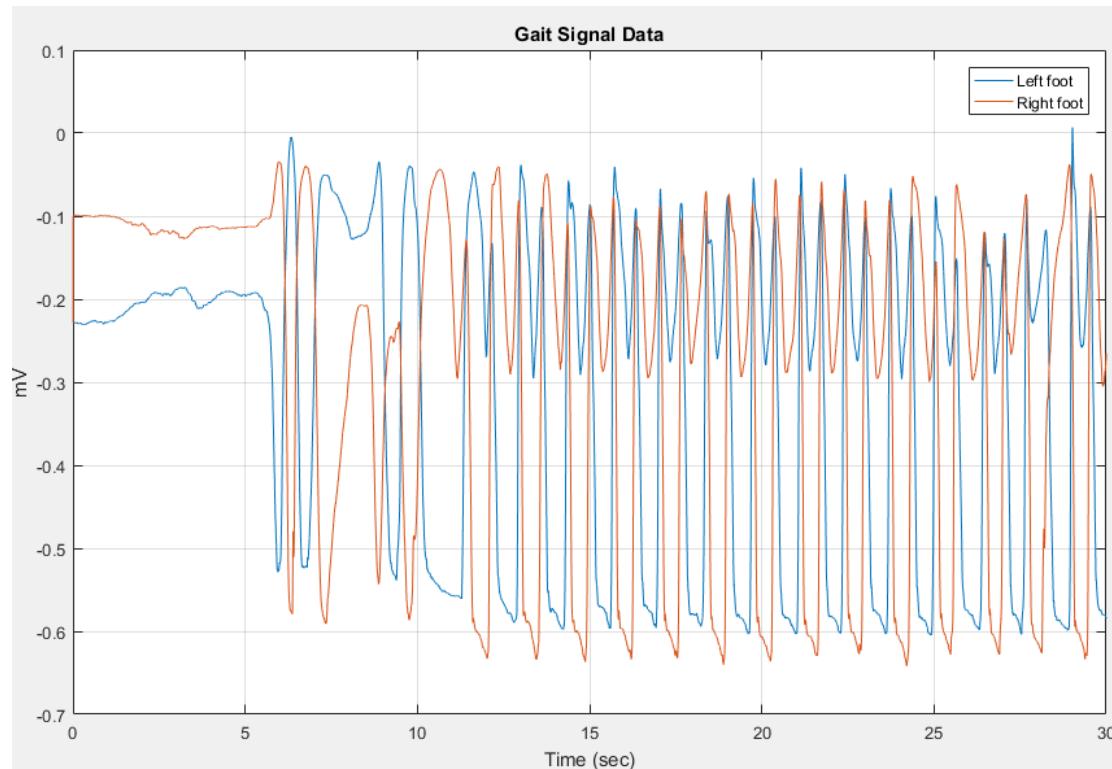
dtw

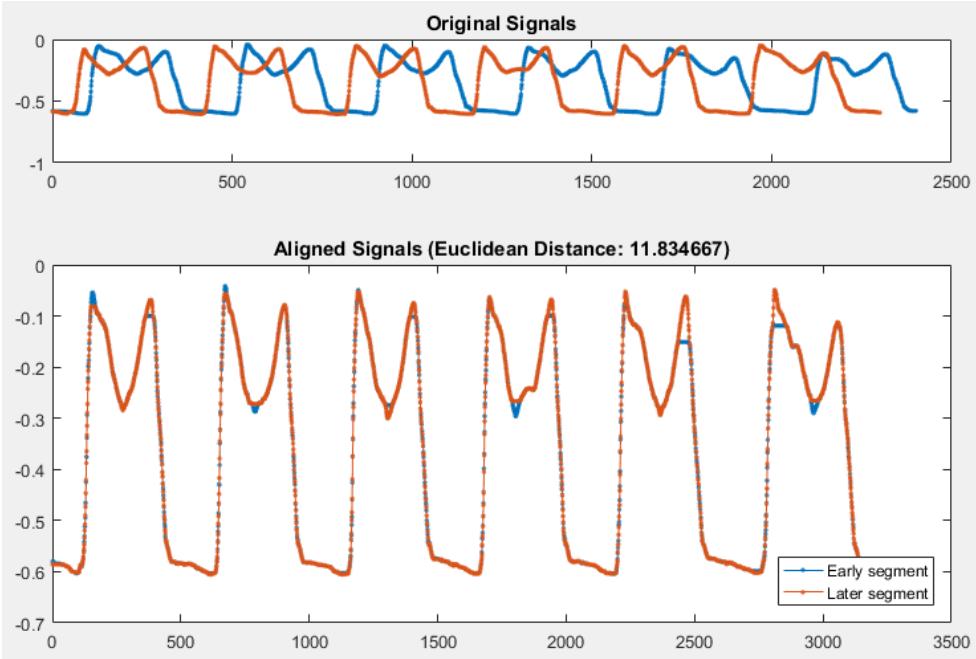
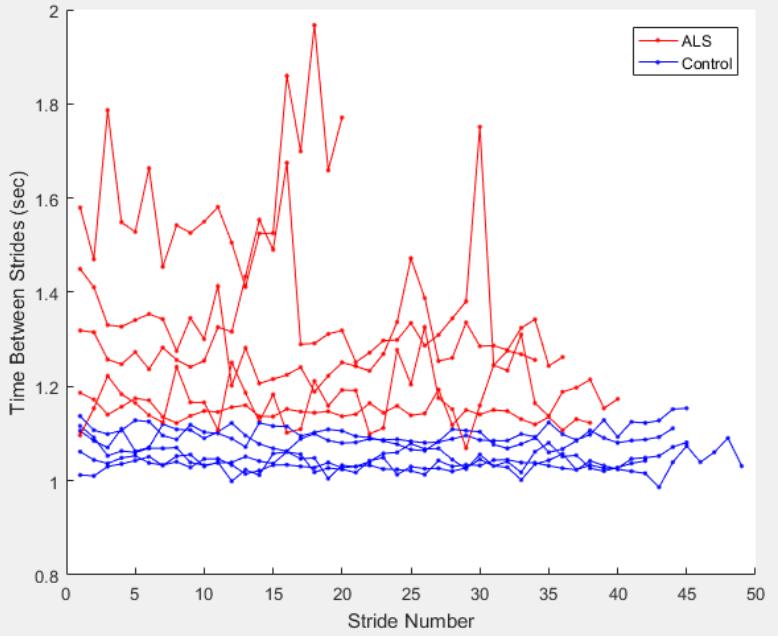
Matlab  
Live Editor

## Extracting Classification Features from Gait Signals

>> GaitAnalysisExample

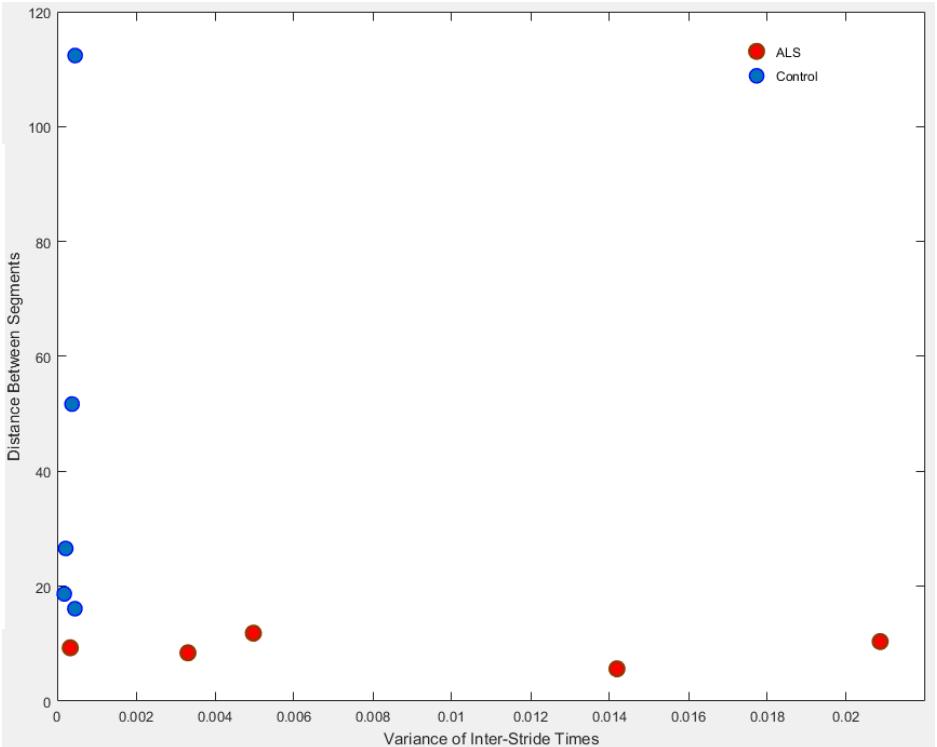
Data from a study of the walking patterns of patients with neurodegenerative disease  
5 patients with *Amyotrophic Lateral Sclerosis (ALS)* and 5 controls





ALS patients seem to have  
a **larger variance**  
in inter-stride times,

but a **smaller distance**  
via ***dtw*** between segments

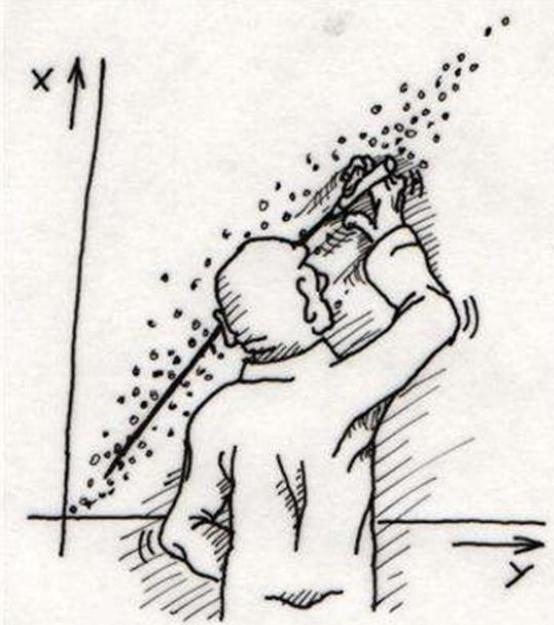




# What can be done with all these Signal Attributes ?



Machine Learning      Biomarkers



# ML & Rehabilitation



COX-media radio reporter **Jamie Dupree**

# AI in Medicine



## The polypill concept

