From the cell to the organ: examples of Signal Processing tools for the analysis of the cardiac electrical activity

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Domain of "Expertise" - Research driven by the physio/clinical needs

Applications :

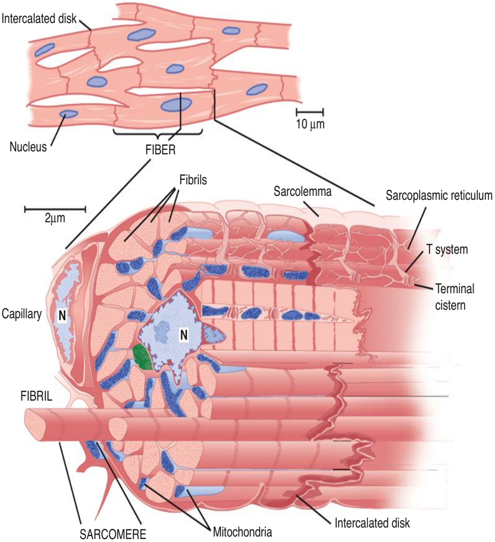
- EMG (exercise, fatigue, WBV, ...)
- Brain (EEG, ERP, Cilia)
- ECG (Cardio-respiratory coupling, Intervals analysis, HRV, Arrhythmias, ...)

Methods :

- Modeling
- Time-Frequency Analysis
- Time delay estimation
- Functional data analysis

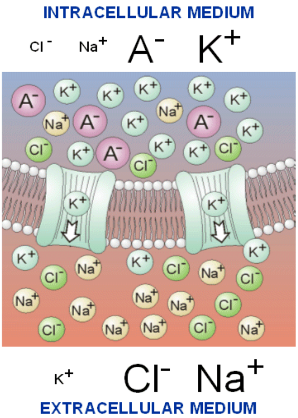
Publications : IEEE TBME, IEEE TSP, MBEC, NATURE Neuro, JEK, AJP, ...

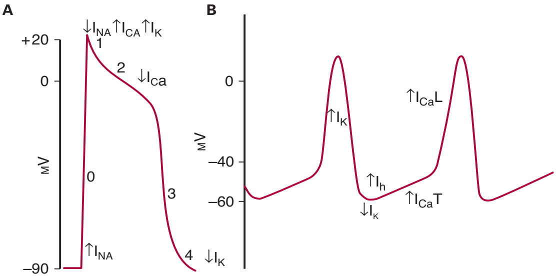
Cardiac cells : cardiomyocytes and nodal tissues



- The cell type depends on the location in the heart
- Cardiac muscle and nodal tissue
- The cells are interconnected to a large extent (myocytes)
- The cells contract (myocytes) and spread electrical wavefront from one cell to another in any direction
- Different than skeletal myocytes (spindle)

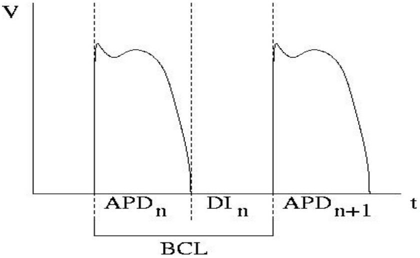
Focus on the electrical behavior of the cardiac cells

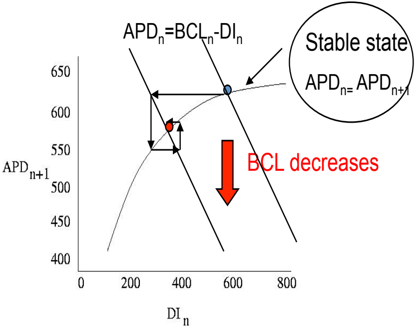




- The transmembrane voltage (Vi - Vo) changes with time : inflow (sodium) and ouflow (potassium) of ions
- Depolarize and repolarize : Action Potential (AP)
- Contract and propagate information to adjacent cells
- Different AP profiles for cardiomyocytes (left) and nodal tissue (right)
- Possible automaticity (nodal) $\rightarrow$ depolarizes interconnected cells
- "Blind" (refractory) during the repolarization

Dynamic of the AP & Restitution Curve



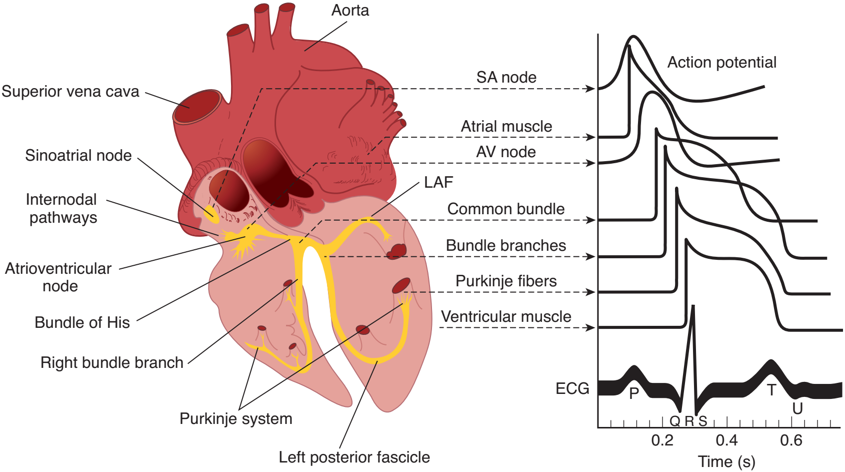


- The APD mostly represents the repolarization phase
- DI=diastole
- The BCL=APD+DI=ECG RR interval
- APD(n+1) is function of previous DI(n) : **restitution curve for fast adaptation**
- APD dynamically adapts

The restitution curve (fast adaptation)

- RR changes : straight line moves
- **Instability may occur !**
- Could explain the T-wave alternans phenomenon [MBEC16]

ECG and depolarization/repolarization sequence



- ECG is recorded on the surface of the Body **(Easy)**
- ECG is not at all simply explained by the Action Potentials
- ECG reflects the sequence of Depolarization/Repolarization (**R-R, P-R, Q-T**), the Electrical pathway geometry, the volume conductor (Forward problem). **(Difficult)**

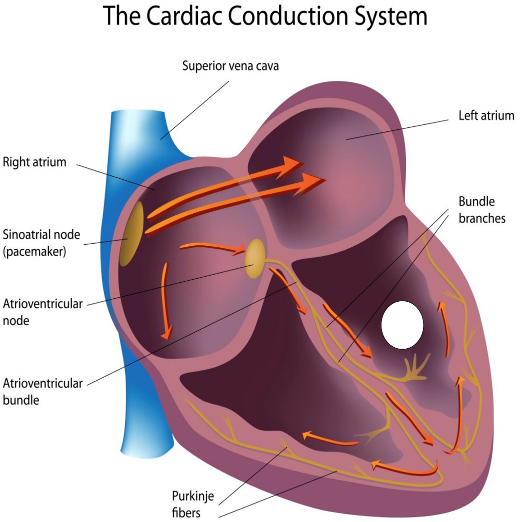
From cell to the organ

Aim of this talk : Illustrate how the electrophysiological knowledge improves the modeling and the processing of the ECG signals :

- Cellular level : control vs diabetic mice Action Potential & ECG analysis
- Influence of ANS over the nodal cells (HRV)

- Cellular level $\rightarrow$ Organ level : QT (ventricular repolarization) and RR (ventricular depolarization) relationship ... next time

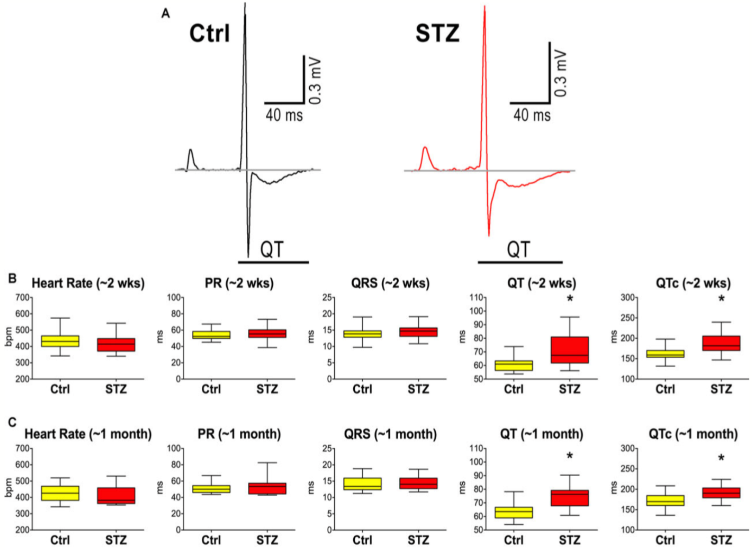
I-Focus on the Ventricular Cardiomyocytes (Mice)-Harvard Med. Sch.



Compare the control (40) and diabetic (40) cells **(part of a more global study [JAHA])** :

- Explain what is observed at the organ level by cellular behavior
- Only repolarization periods
- Sequentially stimulated (2Hz)
- Automatic analysis
- Analyse the dynamics throughout the stimulations
  $\Rightarrow$ Based on specific model of Repol. Phase
  $\Rightarrow$ Needs the computation of inverse functions
  (**relevant information is in the time variable**)

What is observed at the organ level (surface ECG) ?



What is observed at the cellular level (AP) : Models and methods

It is observed **APmagnitude(t)** but we would like **t(APmagnitude)** $\rightarrow$ compute the inverse function

For the **following computations**, each stimulated repolarization phase i from one cell is considered strictly monotonic decreasing, if not use the model :

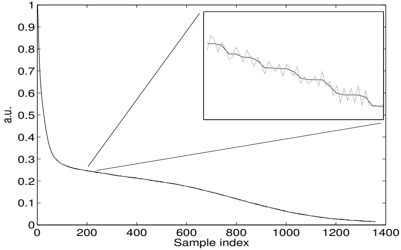
$$x_i(n) = f(n;\theta_i) + e_i(n) \quad n = 1,\dots,N \tag{1}$$

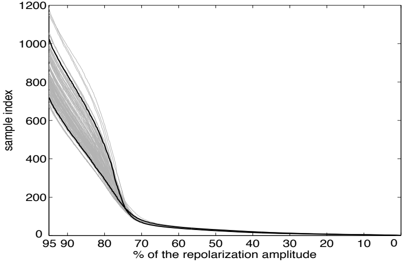
$f(n;\theta_i)$ is a piecewise linear parametric function ($v_l(n)$ are triangle shape functions) :

$$f(n;\theta_i) = \sum_{l=1}^{L} \theta_{i,l} v_l(n) \tag{2}$$

It is demonstrated [IEEE-TBME] that imposing $f(n;\theta_i)$ to be monotonic $\Leftrightarrow \forall l \in [1:L-1], \theta_{i,l} > \theta_{i,l+1} > 0$

Example





- A single AP (repolarization) and the transformed version (also smoothed)
- Monotonicity allows the computation of the inverse functions (70 APs)
  x axis → magnitude ; y axis → time

Mean and Std Repolarization duration :
Diab. > Cont. (80%-0%)

What about the dynamic throughout the stimulation ?

Model and methods

Simple dynamic- One global parameter [CinC15]
Each individual repolarization phase is modeled as (α shortens or prolongates the AP) :

$$x_i(t) = rep(\frac{t-d_i}{\alpha_i}) \quad (3)$$

Imposing monotonicity allows the derivation of the corresponding inverse function :

$$t_i = \alpha_i rep^{-1}(x_i(t_i)) + d_i = \alpha_i rep^{-1}(y) + d_i \quad (4)$$

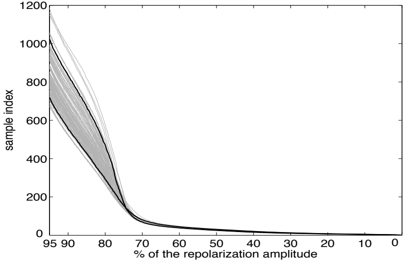
Combining all the possible values of t_i we get a vector formulation of relation (4) :

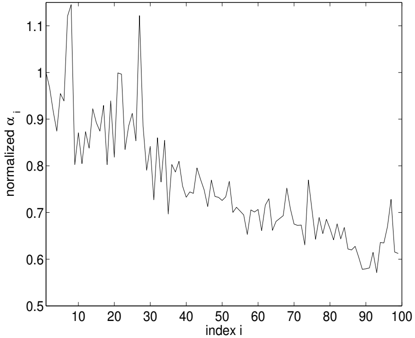
$$\mathbf{t}_i = \alpha_i \mathbf{t} + d_i \mathbb{1} \quad (5)$$

Estimation of the α_is, d_is and $\mathbf{t} \rightarrow$ SVD of matrix $\mathbf{T} = [\mathbf{t}_1 \cdots \mathbf{t}_I]$ combining all the repolarizations.

Linear regression is computed over the α_is $\Rightarrow$ slope value (global dynamic shortening or prolongation)

Example and Results





Upper line : first stimulation
Lower line : last stimulation
&
The normalized $\tilde{\alpha}_i = \alpha_i/\alpha_1$ (used for regression)

Diabetic group significantly shortens
only the late (95% - 60%) repolarization phase

No significant differences between Cont. and Diab.

The variability is very large (Cont. and Diab.) :
random behavior

Single parameter describes each cell $\Rightarrow$ more ?

Model and methods

Complex dynamic- Characterize the dynamic for each repolarization % (not yet published !)

M1 : A linear regression is computed for each repolarization % $\Rightarrow$ local behavior, % independent

M2 : Use SVD-like approach : % $\Rightarrow$ local behavior, % are not independent, latent variables

Let's define the order 1 model for $i = 1, \ldots, I$ stimulations and n the % index :

$$x_n(i) = p_n(i)v(i) + e_n(i) \tag{6}$$

The functions $p_n(i)$ are assumed to be decomposed over a set of K basis function $b_k(i)$ (e.g. polynomial) such that :

$$p_n(i) = \sum_{k=0}^{K-1} b_k(i)\theta_{n,k} \tag{7}$$

In vector form, the expressions are :

$$\mathbf{x}_n = \mathbf{p}_n \circ \mathbf{v} + \mathbf{e}_n = \mathbf{B} \circ (\mathbf{v}\mathbf{1}^T)\theta_n + \mathbf{e}_n = \mathbf{M}_v\theta_n + \mathbf{e}_n \neq \alpha_{1,n}\mathbf{eigvec}_1 + \mathbf{e}_n \tag{8}$$

Model and methods

Considering a LMS criterion (similar to SVD), the stationary conditions give :

$$\hat{\boldsymbol{\theta}}_i = (\mathbf{M}_v^T \mathbf{M}_v)^{-1} \mathbf{M}_v^T \mathbf{x}_i \tag{9}$$

$$\hat{\mathbf{v}} = (\sum_{i=1}^{I} diag(\mathbf{p}_i)^2)^{-1} (\sum_{i=1}^{I} (\mathbf{x}_i \circ \mathbf{p}_i)) \tag{10}$$

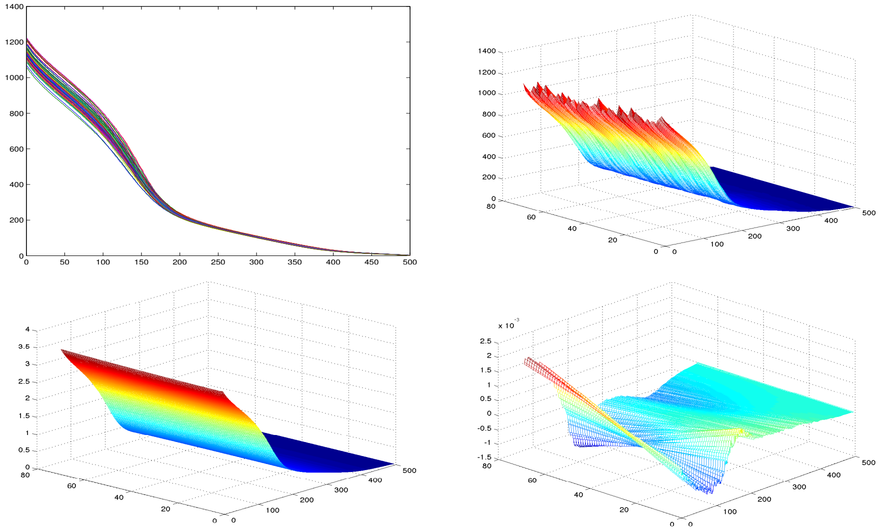
Minimization is solved by using an alternated least square.

If the property $\sum_{n=1}^{N} \mathbf{x}_n = \tilde{\mathbf{v}}$ (similar to SVD), then apply :

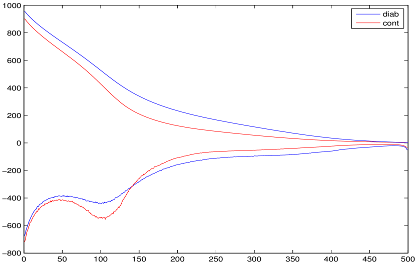
$$\tilde{p}_n(i) = p_n(i)/(\sum_{n=1}^{N} p_n(i)); \tilde{v}(i) = (\sum_{n=1}^{N} p_n(i)).v(i) \Rightarrow \mathbf{x}_n = \tilde{\mathbf{p}}_n \circ \tilde{\mathbf{v}} \tag{11}$$

Each $\tilde{\mathbf{p}}_n$ brings the dynamic evolution of the shape changes $\Rightarrow$ the derivative of $\tilde{\mathbf{p}}_n$ function of i (the stimulation index) is computed for each n (AP magnitude).

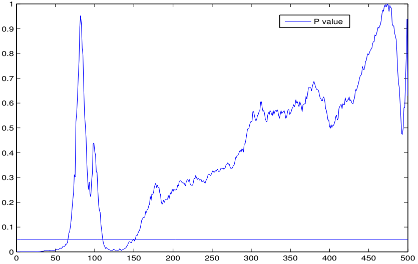
Example


1400
1200
1000
800
600
400
200
0
0 50 100 150 200 250 300 350 400 450 500
80 60 40 20 0
0 100 200 300 400 500
4
3.5
3
2.5
2
1.5
1
0.5
0
x 10^-3
2.5
2
1.5
1
0.5
0
-0.5
-1
-1.5

Results



- Mean of all the repolarization phases
- Derivatives of the mean of all the repolarization phases
- The median test (ranksum) for M2



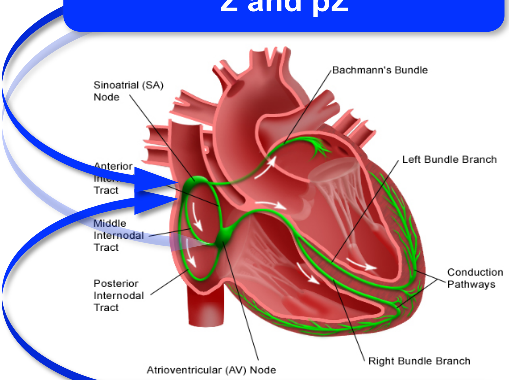
M1 fails to distinguish the two populations

M2 distinguishes the two populations at specific % repolarization

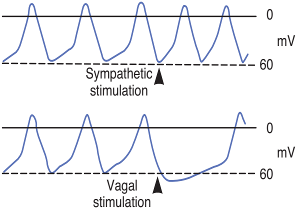
What is the relationship with
a complex ionic current remodeling
(Hyperglycemia reduces Kv currents) ?

Heart electrical pathway and depolarization sequence

NEURAL influences
Σ and pΣ

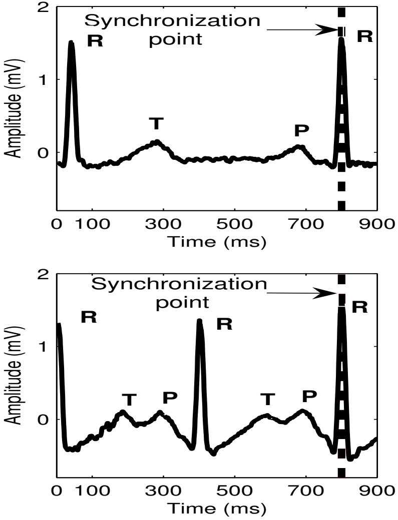


NON NEURAL influences
Hormones / Mechan. stretch



- Beating ignitiates at the SA node.
- Nodes are subject to ANS influence
- SA node affected by streching
- ANS (Σ and *P*Σ) has a key role
- Depolarizations follow a sequence
- Use pathways and myocytes binding geometry to propagate

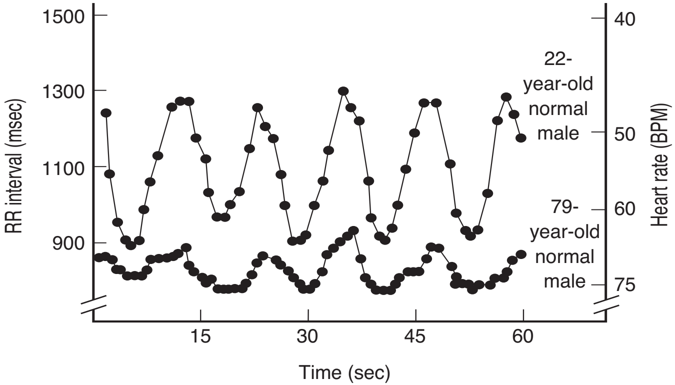
Stress test example



During exercise :

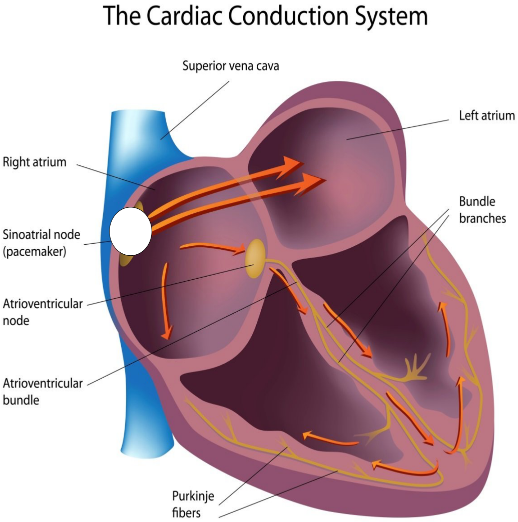
- Body demand changes
- ANS adapts to the demand
- (Symp.) $\Sigma \nearrow$ and (Vagal) $P\Sigma \searrow$
- RR, PR, RT (QT) $\searrow$ (Adaptation)
- But also subtle **variability** of the intervals : RSA, MSA, ...

Respiratory Sinus Arrhythmia (RSA)



- Primarily due to the stretch receptors in the lungs connected to ANS
- The ANS Vagal-(PΣ) slightly modulates the Heart rate to benefit from the full lungs (oxygen)
- If the PΣ withdraws then the RSA is canceled

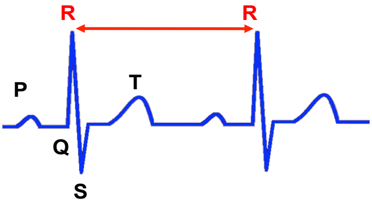
II-Focus on the Modulation of the Heart Rhythm/Period- Zaragoza

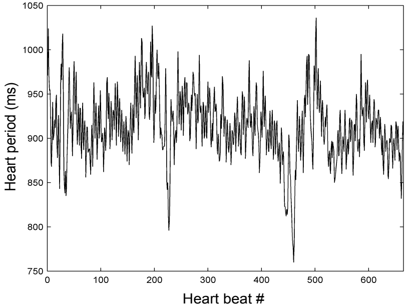


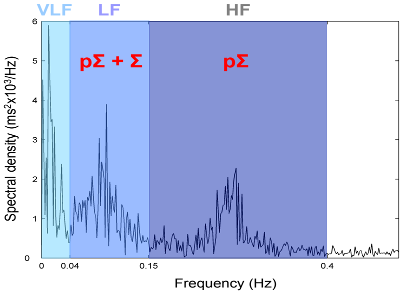
Heart is a not blind pump :

- Neural and Non neural affect the SA node
- ↘ or ↗ the PP (RR) and PR intervals
- Adaptation to body demands

HRV frequency analysis (steady)

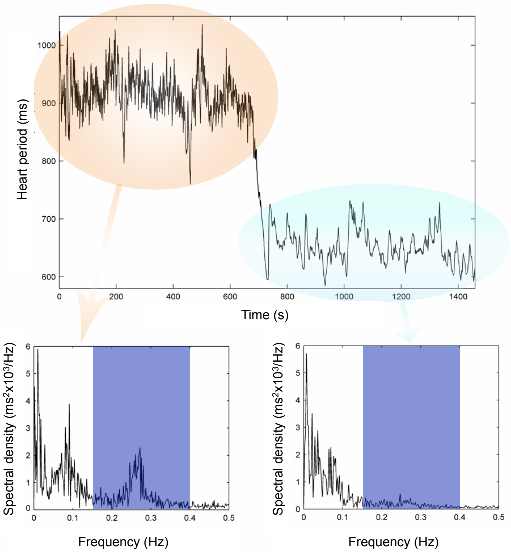






- RR instead of PP
- Σ (slow) and pΣ (fast)
- HF mostly respiration (RSA)
- baroreflex mechanism evidence

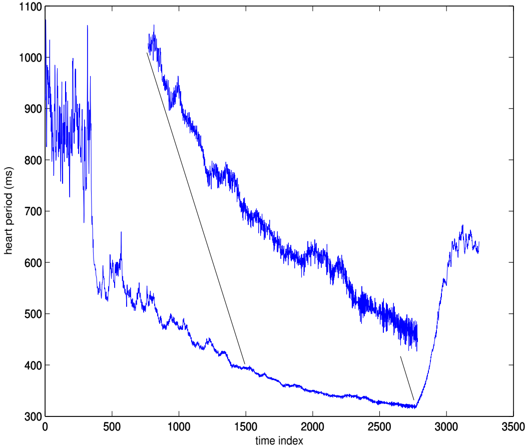
HRV frequency analysis (two steady states : tilt table test)



During tilt test table :

- Supine ⇒ Upright position
- Blood pressure regulation
- ↗ heart rate or ↘ heart period
- pΣ (vagal) ↘
- quantification

A more complex example

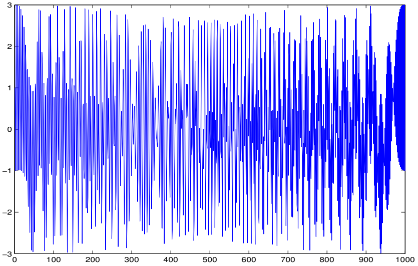


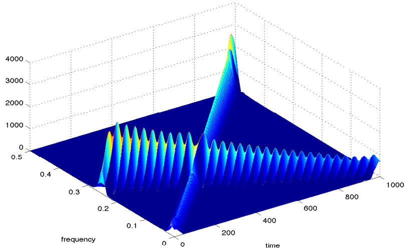
During stress test protocol (cycling) :

- The mean heart rate $\nearrow$
- The variability (Low-High) $\searrow$
- The RSA $\searrow$ (? ?)
- Mechanical influences ?

- Observation model ?
  (self sampled signal !)
- Non-stationnary ?
  (frequencies & amplitudes)
- Qualitative/Quantitative analysis ?
  (local or global analysis)

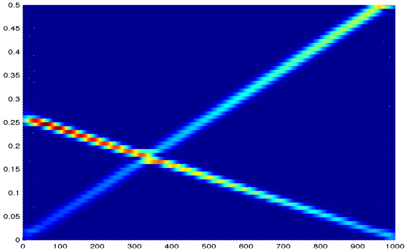
Spectrogram for the non-stationarity





Defined by

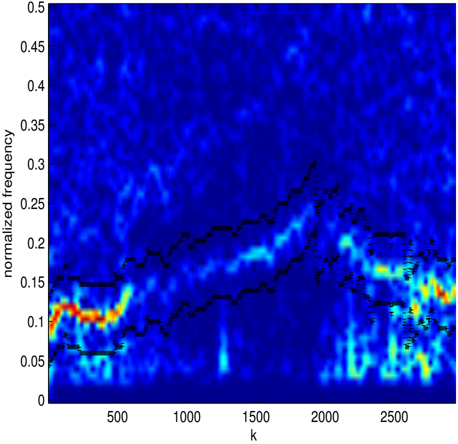
$$S(t,f) = |\int m(s)h^*(s-t)e^{-i2\pi fs}ds|^2$$

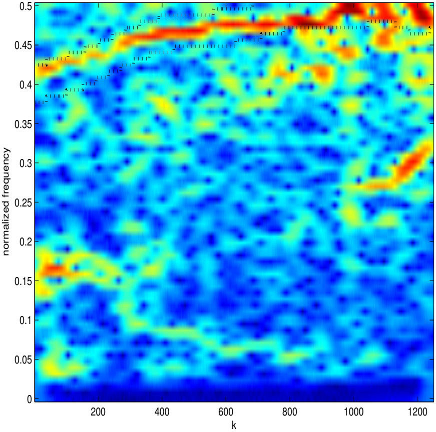


- Quadratic TFR (Cohen's class)
- Bad TF resolution
- But well located cross-terms !
- Closely related to the STFT (linear)

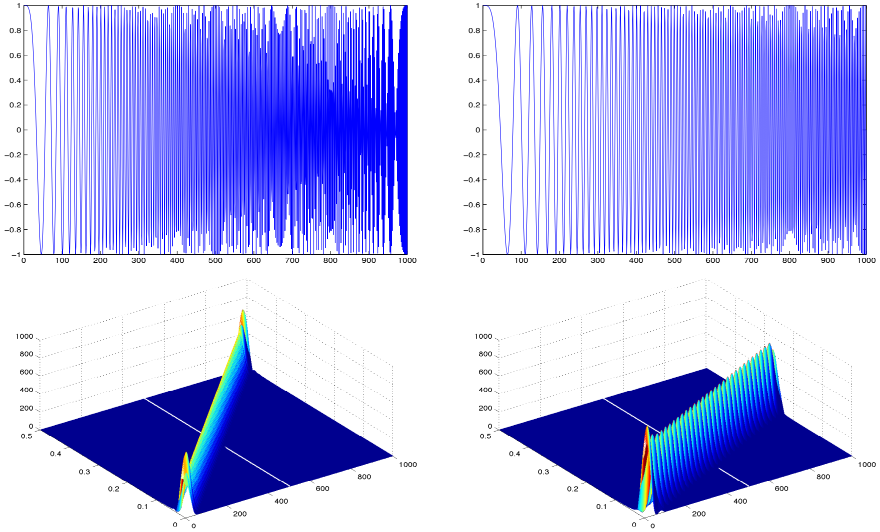
Spectrogram for the non-stationarity

Needs quantitative assessment : not so easy with real data (noisy, multicomponent, ...) !

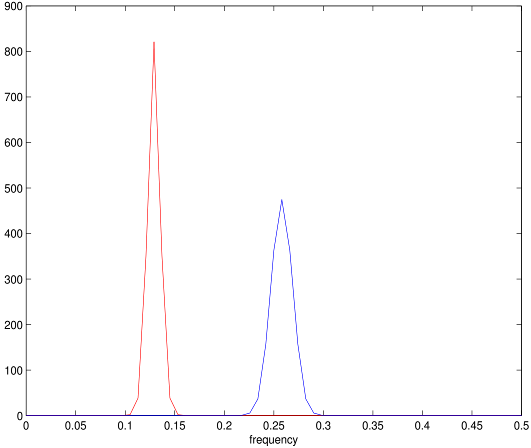




Chirp signals : different modulation rates, same amplitudes



Magnitude extracted from the TF plane ?



For a given t_0 (white line) :

- Different widths
- Different amplitudes
- Integrals are equal

$\Rightarrow$ OK for visual inspection but not for quantification !

TF processing (not developed here)

I) Magnitude of the modulation directly computed from the TF plane

$$R(k) = \sqrt{\frac{1}{K} \sum_{f=f_{obs}(k)-\delta}^{f_{obs}(k)+\delta} |M(k,f)|^2}$$

with $f_{obs}(k)$ the time-varying frequency of interest. $M(k,f)$ is the STFT of the R-R intervals variability.

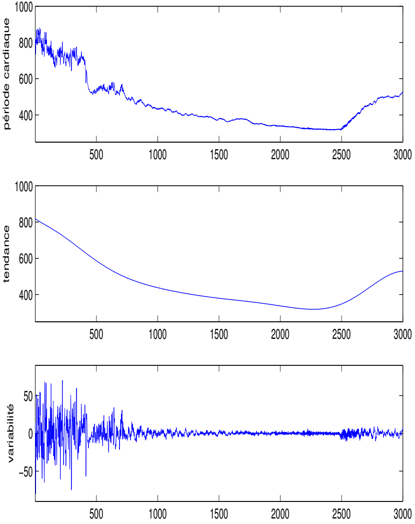
$$M(k,f) = \sum_u m(u)h(u-k)e^{-j2\pi\frac{\ell}{K}u}$$

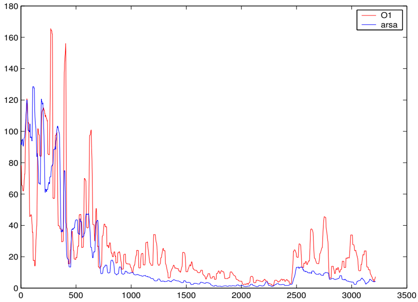
with $-K/2 \leq \ell \leq K/2-1$ integer and $f = \ell/K$

The analysis window $h(u)$ is energy normalized.

$\Rightarrow$ Integrate over the given frequency range (the two black lines) !

Simple example-ANS modulation of the SA node

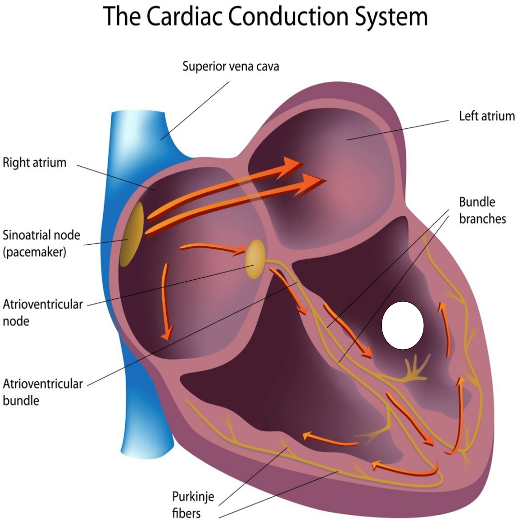




- From the Heart periods series :
  - the trend $T(t)$
  - the variability (TF processed)
- Clear vagal withdrawal
- Strong vagal return
- Tool for the cardiorespiratory coupling assessment [AJP]

III-Focus on T waves duration-EPFL

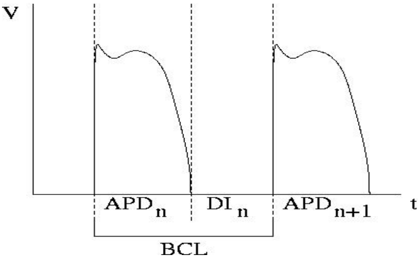
→ Impact of the Restitution Curve properties (oscillation) over the Ventricular Repolarization

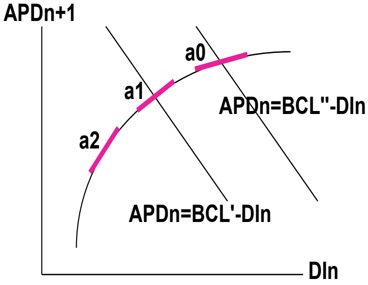


Explain the QT/RR adaptation based on the AP restitution curve :

- The macro level (organ) should reflect the micro level (cell)
- Assessment of repolarization disturbances (Ischemia)

Approximation and modeling





- The sum of all the Ventricular Cells AP almost explains the QT duration.
- The APD is mostly composed by the repolarization
- The BCL is similar to the Heart period (R-R)
- For a given BCL, the curve can be approximated by an affine function (a = slope)

We get for the fast adaptation :

$$APD(n+1) = -aAPD(n) + aBCL(n) + b \quad (12)$$

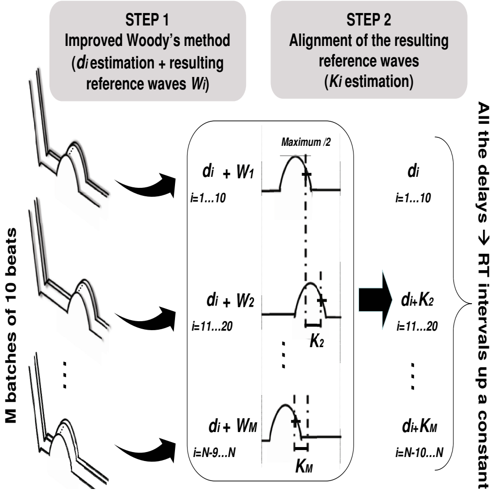
or

$$QT_F(n+1) = -aQT_F(n) + aRR(n) + b \quad (13)$$

and for the slow (not explained by the Restitution Curve)

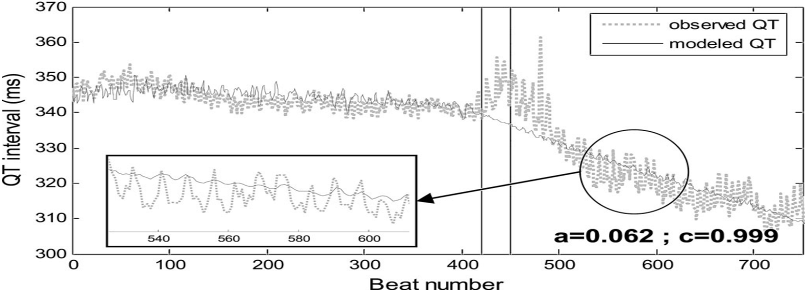
$$QT_S(n+1) = cQT_S(n) + RR(n) \quad (14)$$

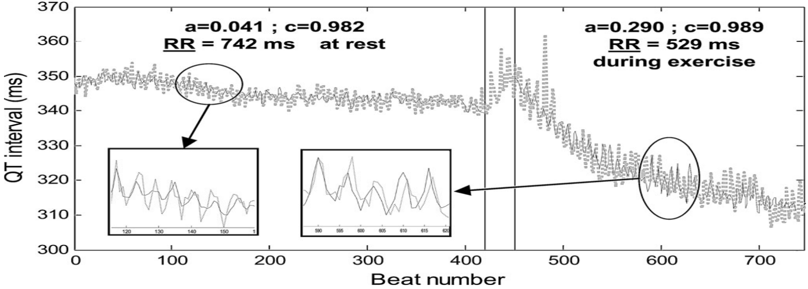
QT(n) and (a,b,c) parameters Estimation



- We consider blocks of 10 waves for shape adaptation
- The $QT(n)$ are estimated by using an original and optimal method [IEEE-SPL]
- The observed $QT(n)$ and $RR(n)$ feed the estimation process
- The (a,b,c) are estimated by using alternated Least Square algo. [IEEE-TBME]
- The modeled $\hat{QT}(n)$ only uses $(\hat{a},\hat{b},\hat{c})$ and $RR(n)$
- Outperforms standard models with only few parameters

Example : exercise test (variable R-R)



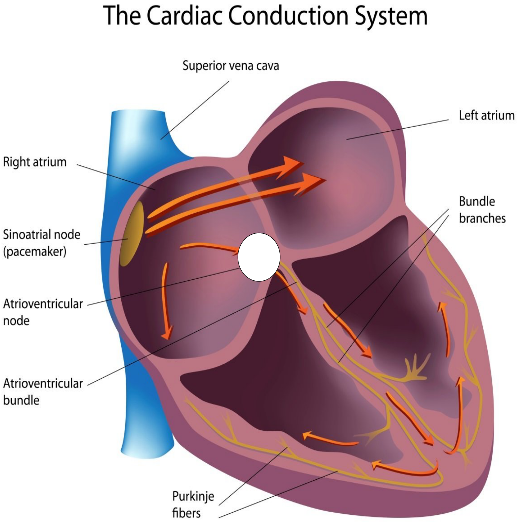


Still many things to present

This type of topic :

- Needs strong collaborations with clinicians
- Needs large background knowledge
- Provides research topics for Computer Science (IBM very active in the simulation field), Biology (Pharmacological Companies), Engineering (Pacemakers, Defibrillators) etc ...
- Questions ?

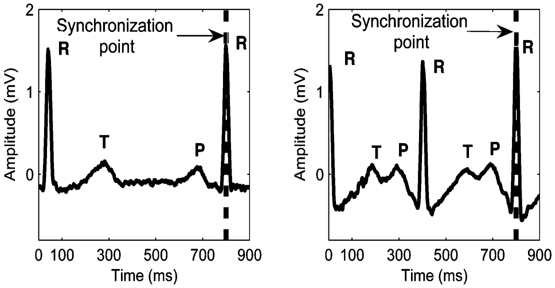
V-Focus on the Effect of the ANS on the AV Velocity Conduction



Strong vagal return visible in the Heart Rate Variability (SA node)

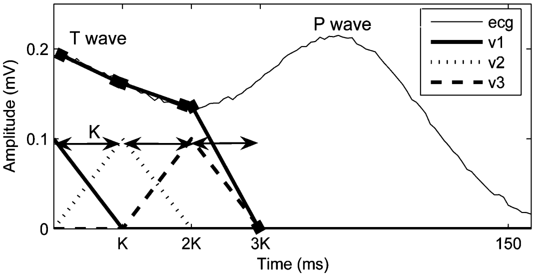
- Visible in the PR (includes AV node conduction) ?
- Adapted to subject status (elite/sedentary) ?

PR intervals analysis-Observations modeling



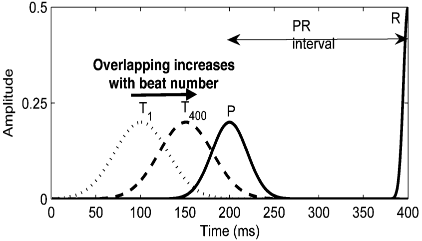
- ECG recorded during maximal exercise tests (cycling)
- Segmentation of RR windows
- P waves, delays, factors are unknown & T waves overlaps P waves
- The model is $x_i(n) = \alpha_i s_{d_i}(n) + f(n;\theta_i) + e_i(n)$ but $i = 1 \dots I$

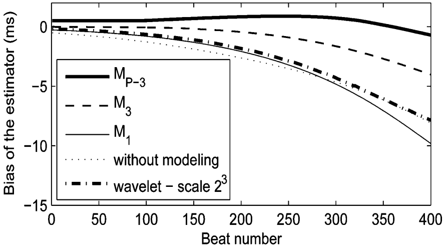
PR intervals analysis-T wave modeling



- T waves are modeled with sum of piecewise affine functions
- Monotonicity is imposed
- MLE : iterative LS problem with linear inequality constraint (LSI problem)

PR intervals analysis- Simulations

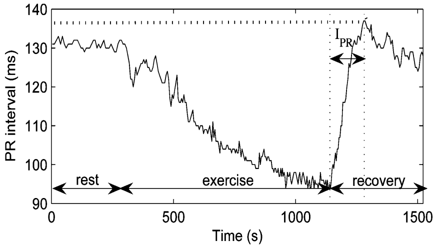




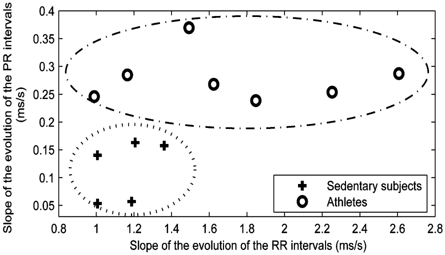
- Constant PR
- 400 overlapping T waves

- Small bias
- Bias almost removed
- Justified by weak PR variations (real)

PR intervals analysis- Results slopes

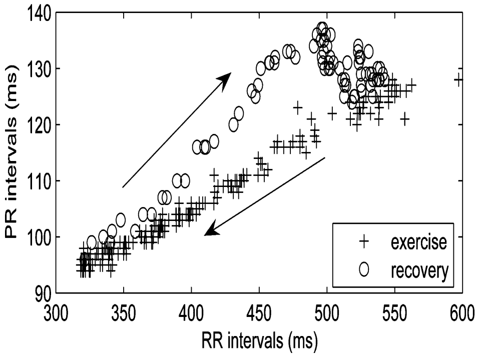


- Clear variation
- Overshoot during recovery
- focus on the slopes



- Athletes (professionals) & sedentaries
- Better clustering with PR slope

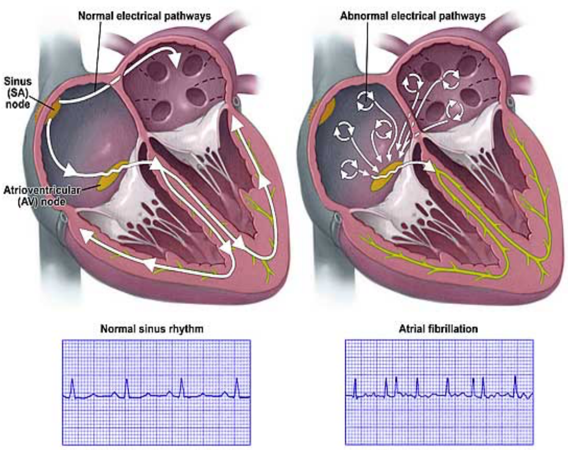
PR intervals analysis- Results hysteresis



- Similar to overshoot
- Computed Hysteresis Area
- Original results
- Strong return of the vagal

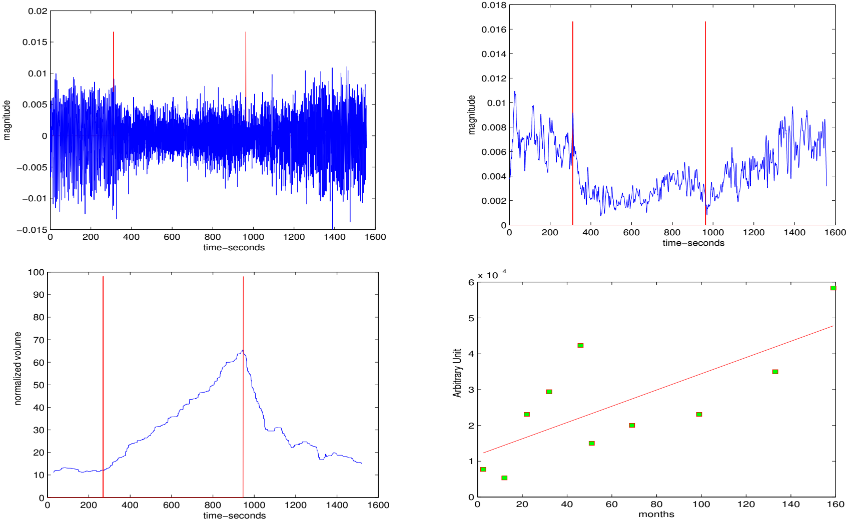
T-wave model	SED	ATH
M_{P-3}	7.84 ± 2.52	13.49 ± 3.64
M_3	6.33 ± 4.32	13.35 ± 2.58
M_1	7.05 ± 3.12	9.70 ± 8.74

Assess the complexity of the AF

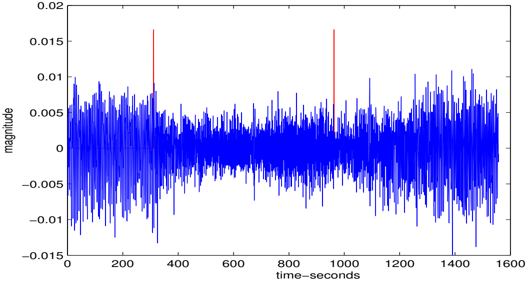


- Similar to overshoot
- Computed Hysteresis Area
- Original results
- Strong return of the vagal

Transplanted heart subjects



Transplanted hearts



	(rest)	**(max)**	**(rest)-(max)**
$stand$	R=0.25, p=0.48	R=0.27 , p=0.45	R=0.11 , p=0.76
mag	R=0.43, p=0.22	R=-0.21, p=0.56	R=0.29 , p=0.40
mag_{tv}	R=0.61, p=0.06	R=-0.14, p=0.69	R=0.67 , p=0.03
$mag_{tv,resp}$	R=0.74, p=0.01	R=0.09 , p=0.80	R=0.82, p=0.003