

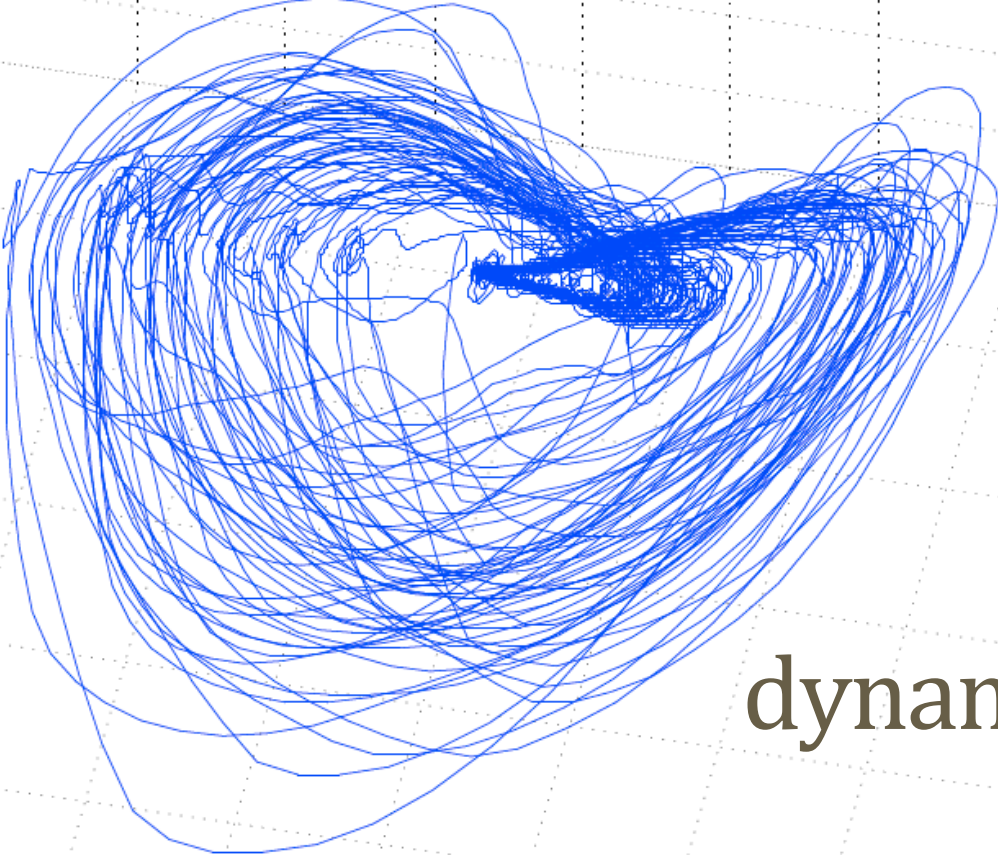


Intermittency in AF

G. Attuel; N. Derval; T. Desplantez; R. Dubois; M. Haissaguerre;
M. Hocini; P. Jaïs



guillaume.attuel@espci.fr



From chaos to dynamical disorder in AF

G. Attuel; N. Derval; T. Desplantez; R. Dubois; M. Haissaguerre;
M. Hocini; P. Jaïs



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The institution

IHU - Projet LIRYC

Electrophysiologie.....INSERM

Animalerie



Veronique Lacombe, MCU

3 techniciens :

- Préparation chirurgicale
- Handling
- Animalerie

EP cellulaire/Biologie moléculaire



Sébastien Chaigne – FP7



Serge Sicouri



Thomas Desplantez – CDD 3 ans INSERM

5 techniciens :

- Microscopie confocale
- Gestion
- 2 Bio-Mol
- Culture cellulaire

Fibrillation Atriale



Jérôme Kalifa, Pr



Masatoshi Yamazaki, MCU

- 6 techniciens :
- 2 Prep Solutions
 - 2 Optical Mapping
 - 1 Patch Clamp
 - 1 Preparation

Krishna Baudaru
Uma Aavula

Fibrillation Ventriculaire/Insuffisance

Cardiaque



Ed White



Olivier Bernus, Pr



Ruben Coronel, Pr



Philippe Diolez, CR



Véronique Arsac, MCU

Steve Gilbert – Marie Curie
David Benoit – Louis Jeantet
Richard Walton – Delalande

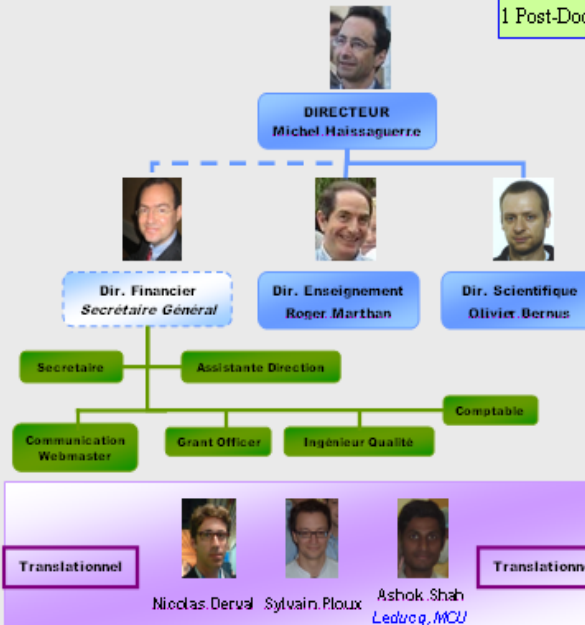
CONSEIL SCIENTIFIQUE

CONSEIL D'ADMINISTRATION

Université – CHU – INSERM – INRIA – CNRS – Collectivités



1 Post-Doc, IHU



ImagerieCNRS



Bruno Quesson



Hubert Cochet

Mathilde Merle – FP7
Delphine Elbes – FP7

- 1 Ingénieur – CNRS
- Nicolas Toussaint**
- 1 Technicien

LabEx TRAIL - BRAIN



Daniel Choquet



Vincent Dousset



Jean-Michel Franconi



Chrit Moonen

Collaboration : INRIA/Sophia Antipolis- LaBRI

Modélisation.....INRIA



Edward Vigmond, Pr – IHU/UB1
1 Post-Doc, IHU



Jacques Henry, DR2



Mark Potse – IHU/DR?
1 Post-Doc, IHU



Yves Coudière, DR
(Délégation-20 12)



Nejib Zemzemi, CR

Simon Labarthe - Région

Signal.....INRIA/IMB



Hussein Yahia, CR



Bedr Eddine Aïnseba, Pr



Mostafa Bendahmane, MCU



Rémi Dubois, EPCSP

Oriol Pont - Leducq

Alex Lopez
Guillaume Attuel – FP7

Epidemiology

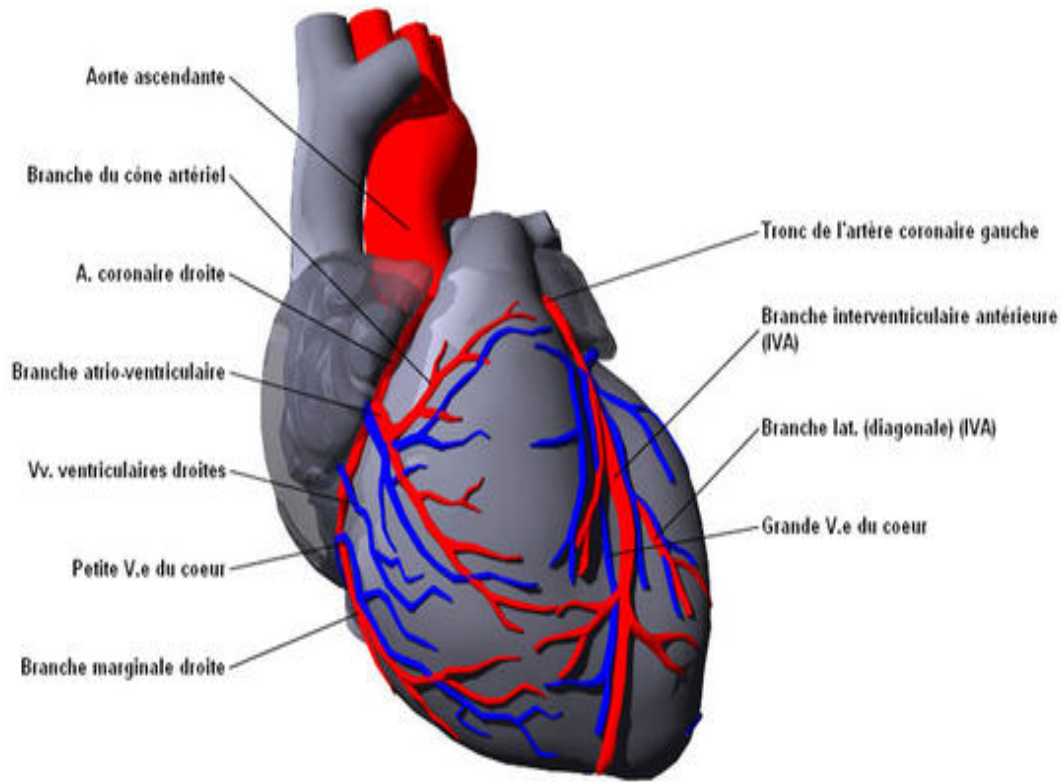
Major cause of stroke

EUROPE: 5 MILLIONS

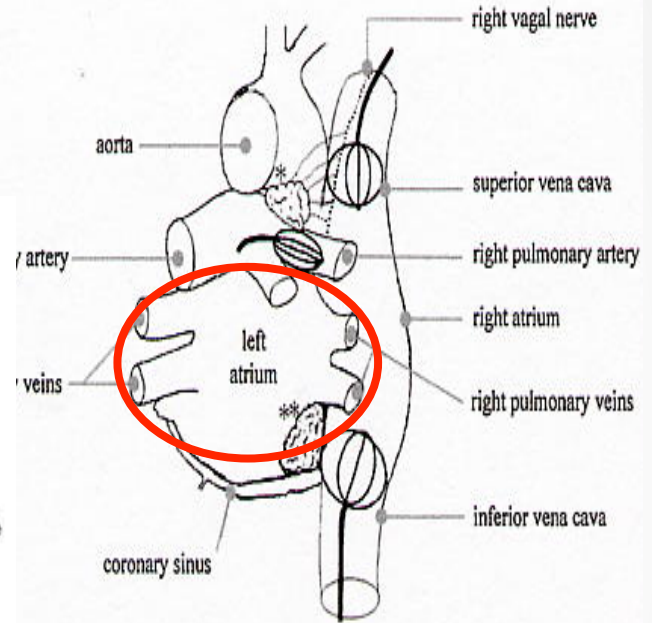
Terminologie	Caractéristiques cliniques	Récurrence
1 ^{er} évènement	Symptomatique ou symptomatique Durée inconnue	
Paroxysmal	Arrêt spontané <7 jours Le plus souvent <48h	Récurrent
Persistent	Pas d'arrêt spontané >7 jours Cardioversion nécessaire	Récurrent
Permanent	FA en place Cardioversion sans succès	Etabli
Chronique		

The heart

Complex anatomy (right anterior view)

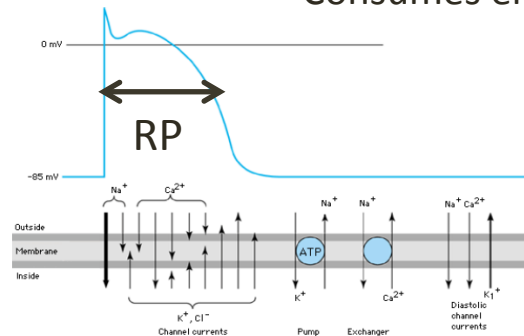


Left atrium (left posterior view)



Cardiac Action Potential

Consumes energy



Current status

Foci



Reentry

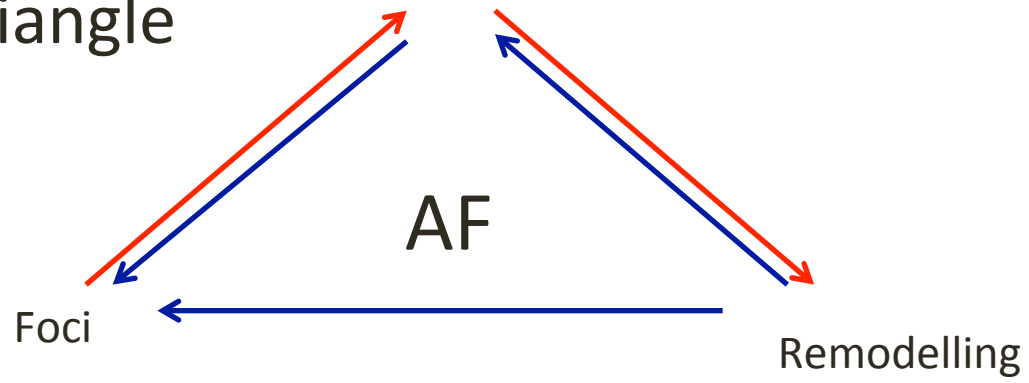


Remodelling



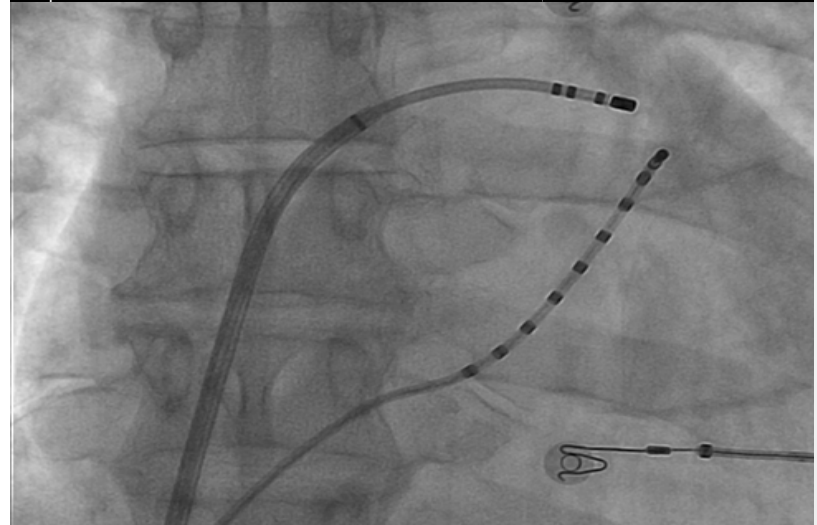
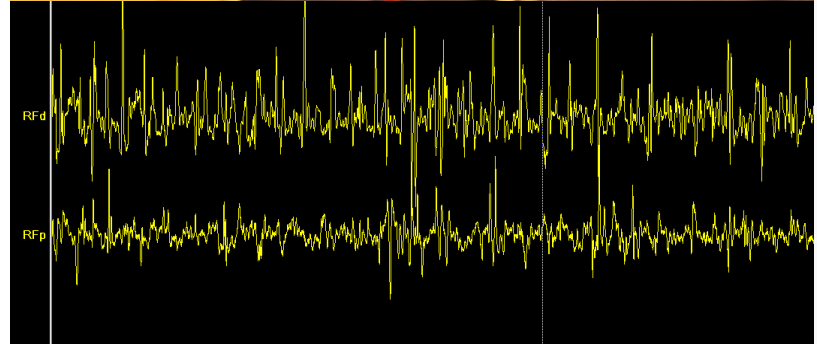
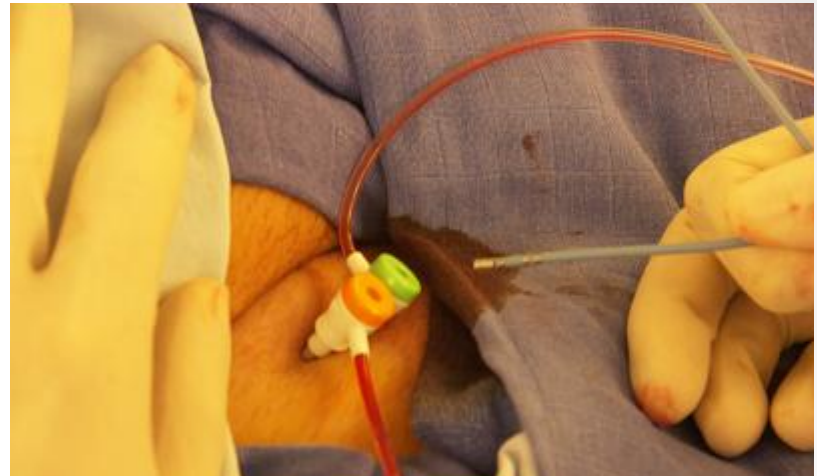
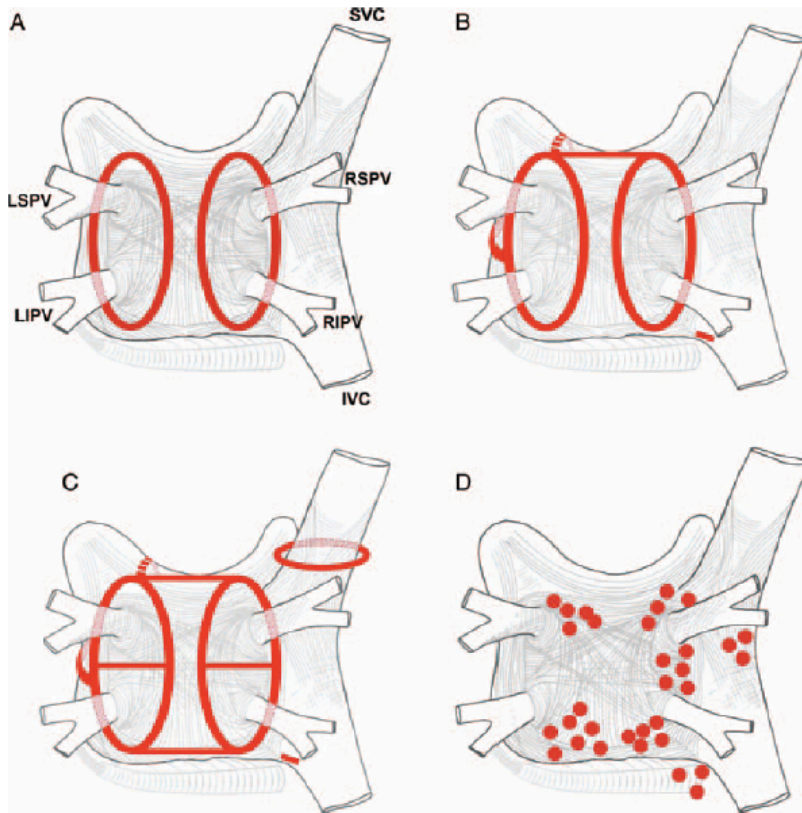
Coumel Triangle

Nervous modulation



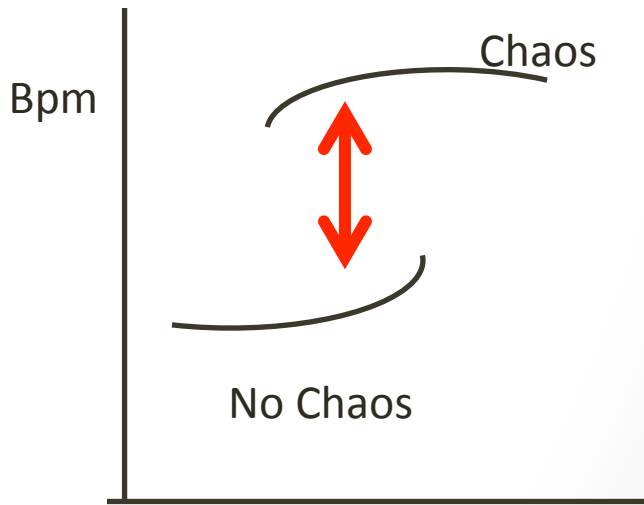
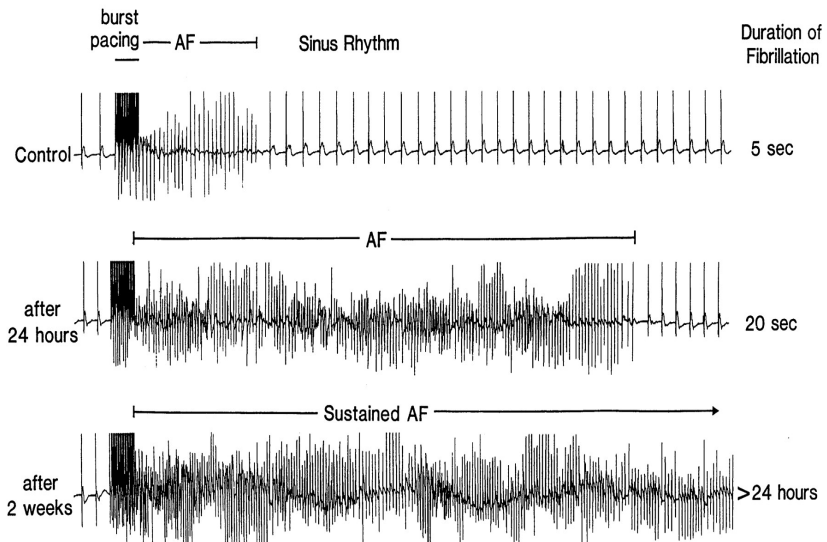
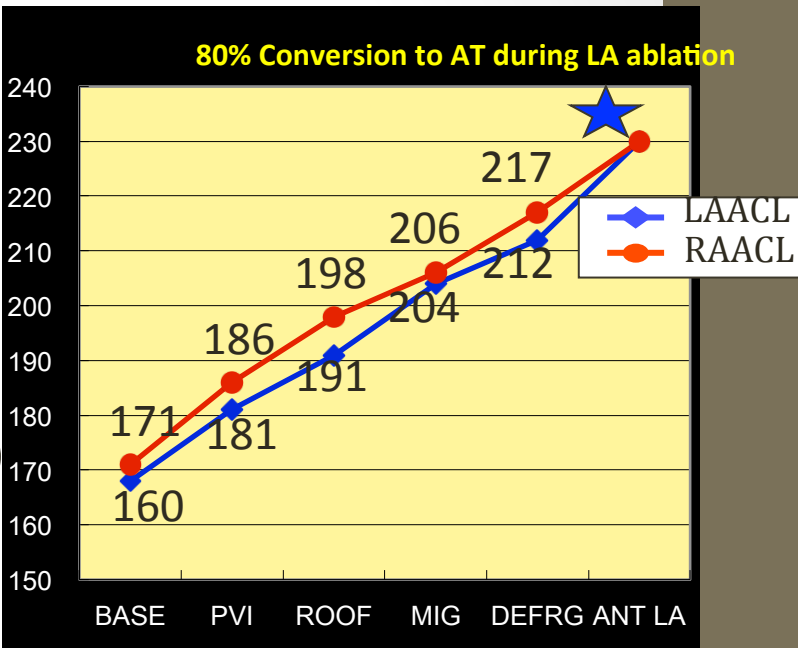
Ablation

Paroxysmal AF w post treatment: ~80%



Some phenomena

- Local onset
- Remodelling
- Inadaptation, dispersion RP
- Quasi periodicity
- Bigeminy protocol (far from cell vulnerability)
- Cardio version **hysteresis**
- Cycle length increases while ablating ...

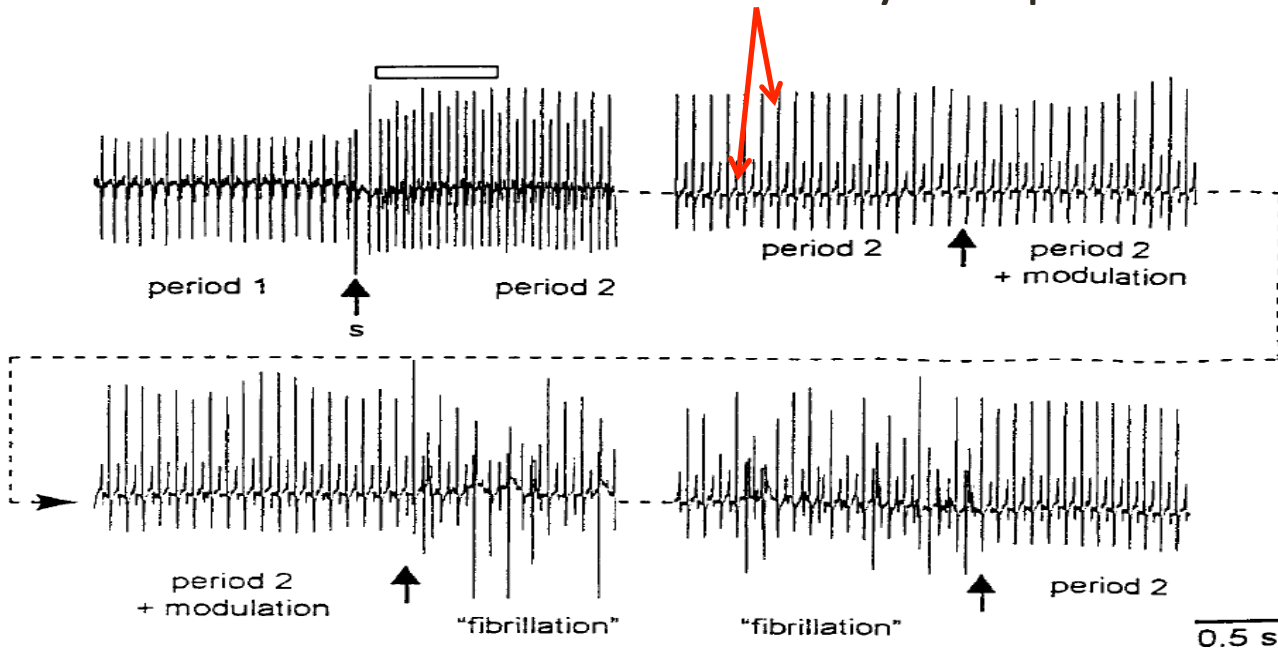


Allessie

2 sec

Evidence of modulation

Bistability and phase locking?



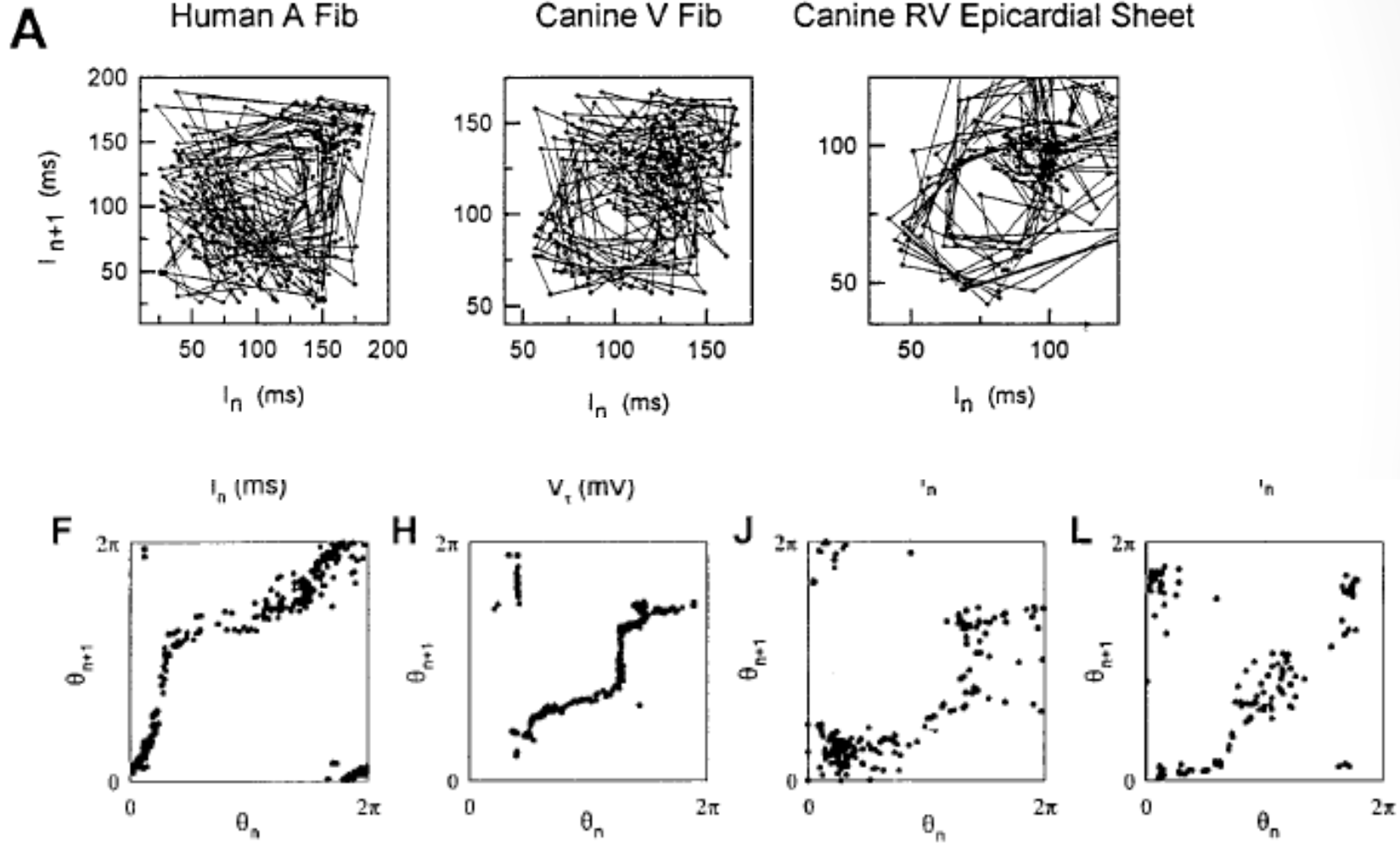
modulation, thus exemplifying the “quasiperiodic transition to chaos” first suggested by Ruelle and Takens. This suggests that fibrillation is a form of spatio-temporal chaos, a finding that implies new therapeutic approaches. (*J. Clin.*

Garfinkel

Quasi Periodicity

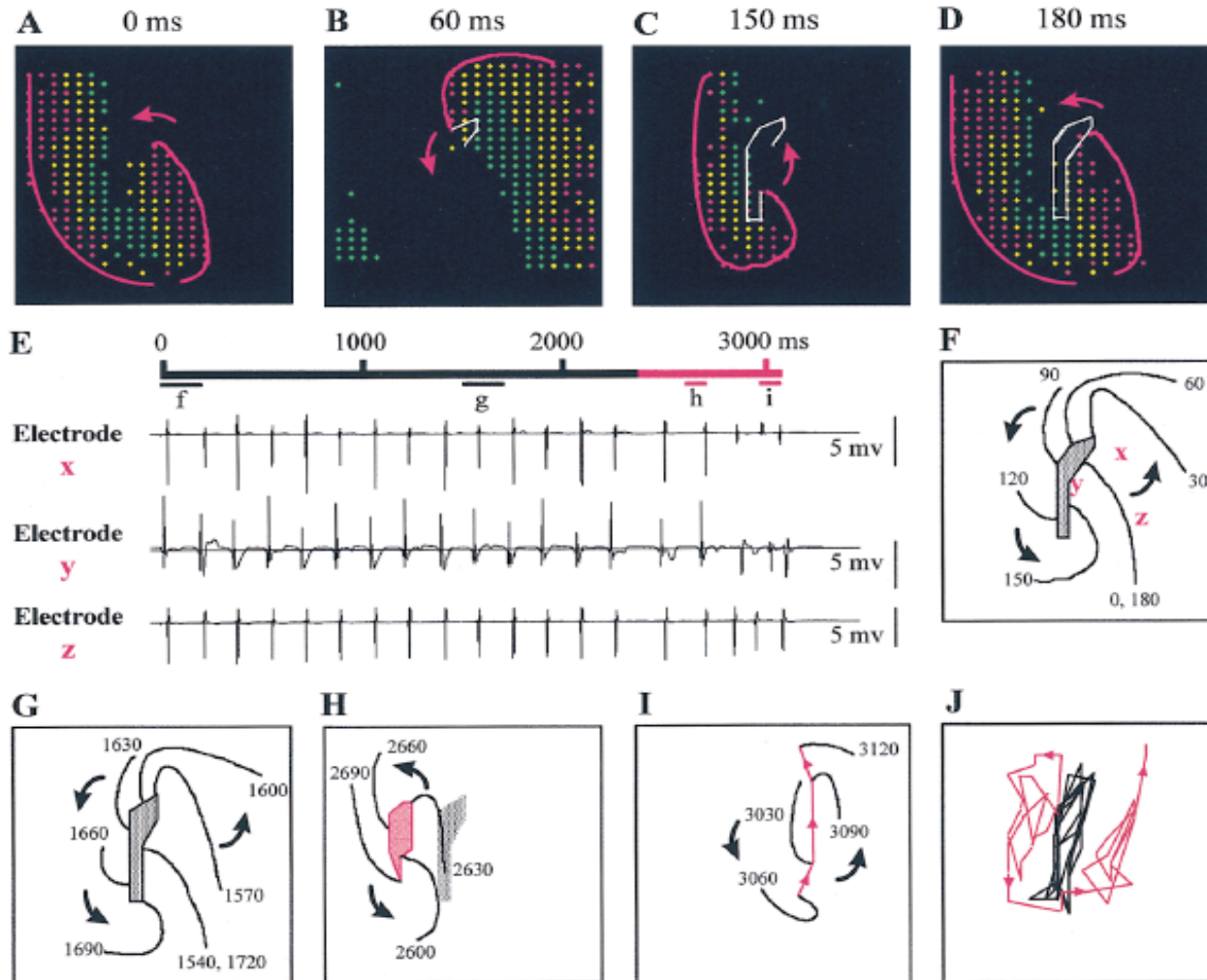
Examples before onset with 'irregular' tachycardia

Universal



Spatial structure of QP

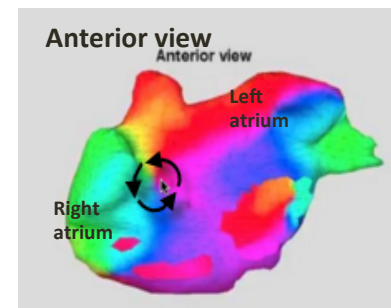
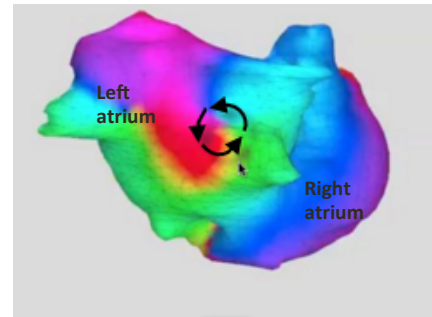
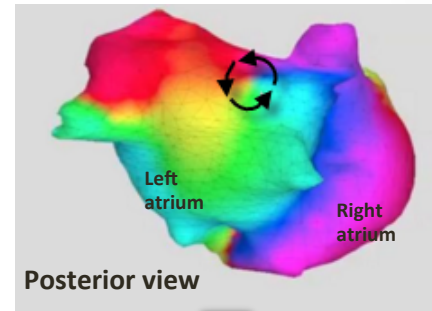
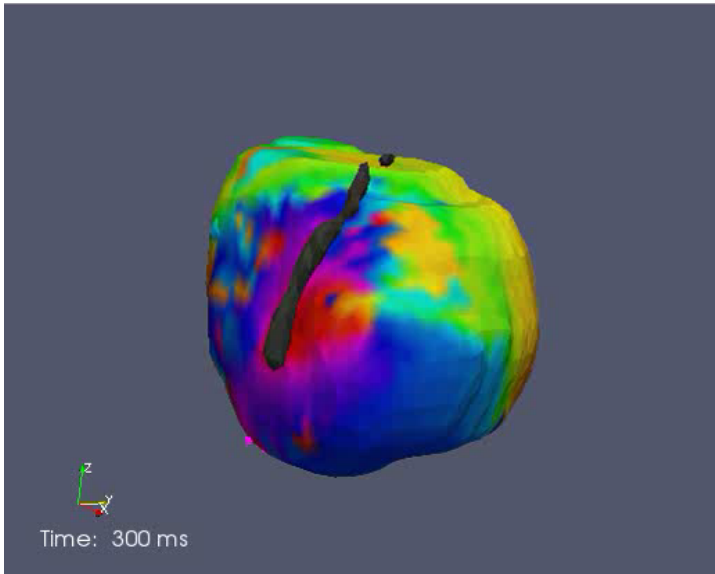
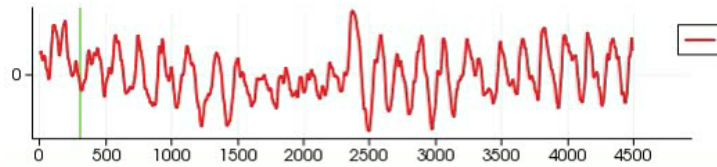
Rotors



Fibrillation: phase mapping

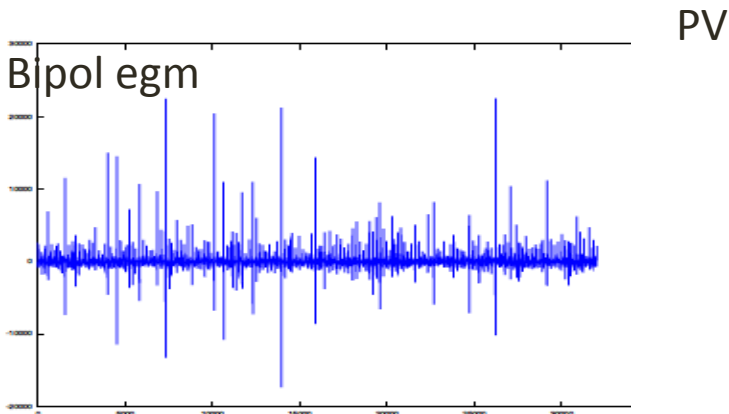
Distinguishing feature? AF

VF

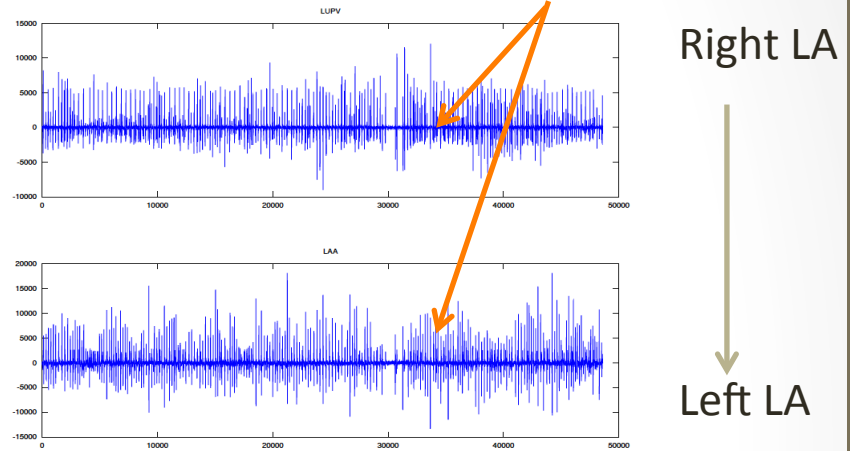


Intermittency in AF

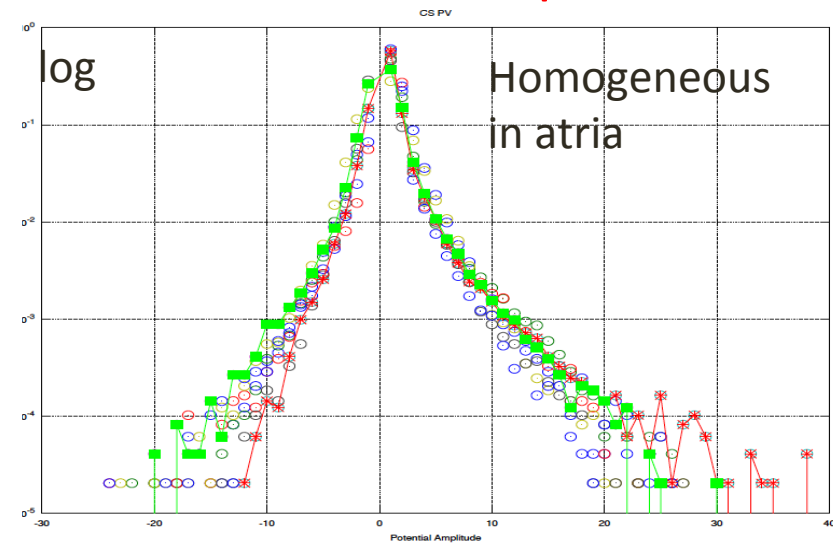
Persistent AF



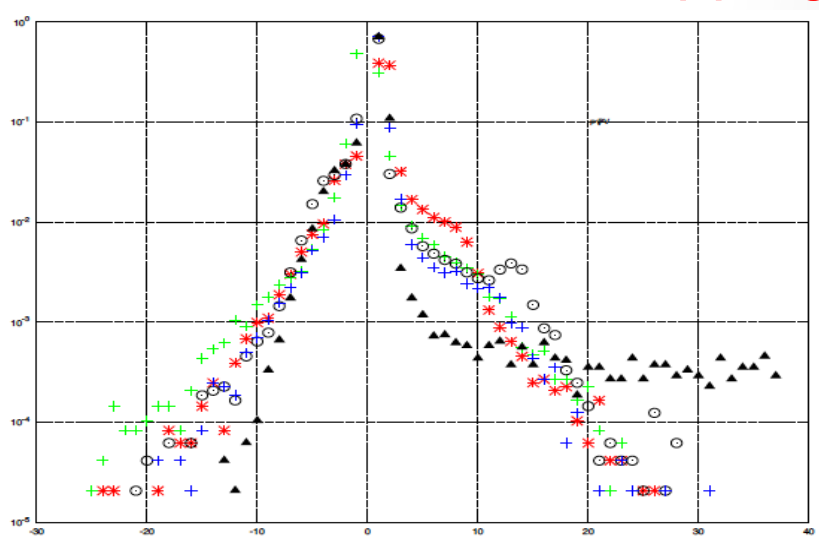
Persistent AF **sinus pause**



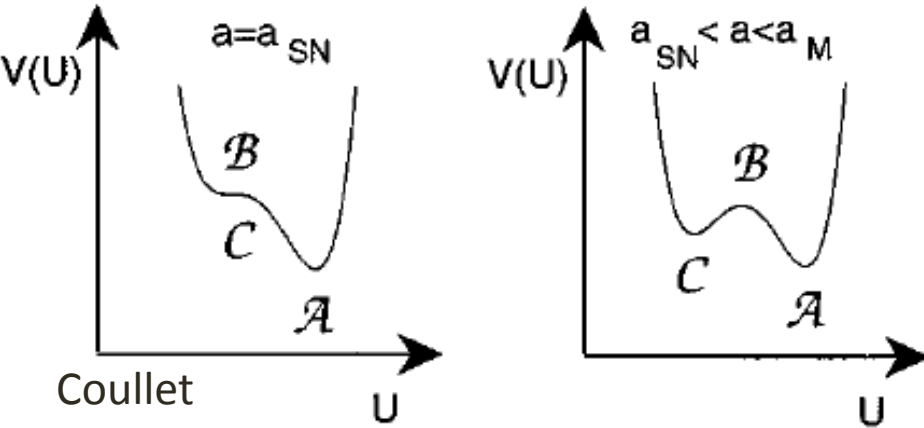
Probability density of **amplitude** egm



Smooth deformation along **mapping**



Spatio-temporal intermittency

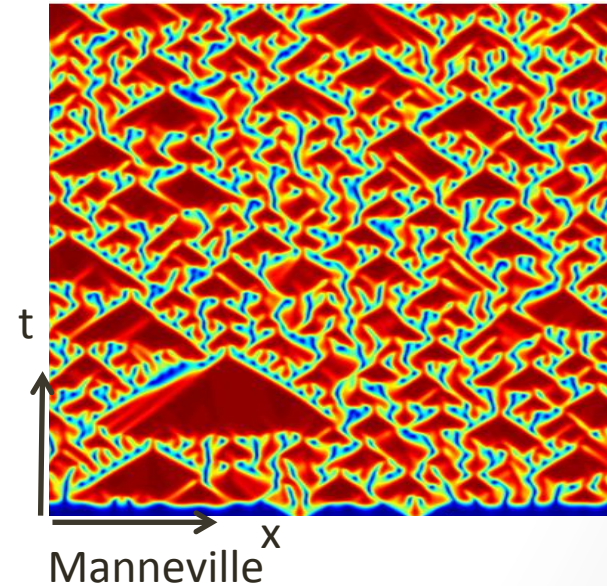
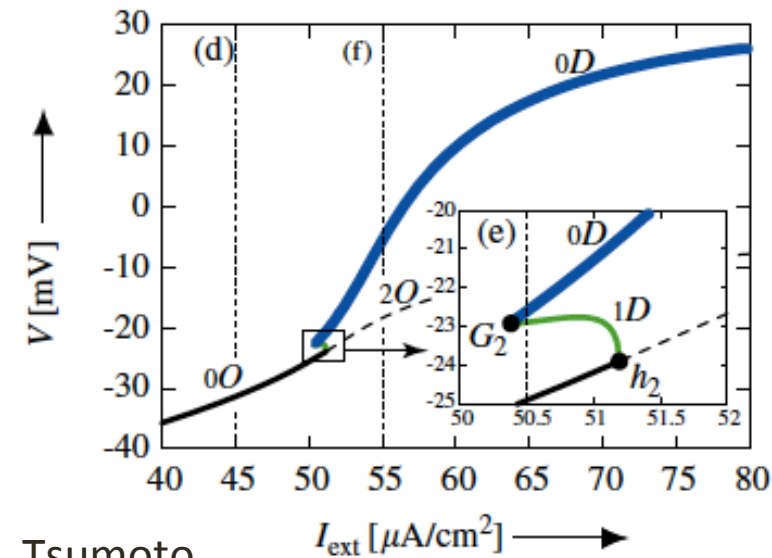


Necessary locally:

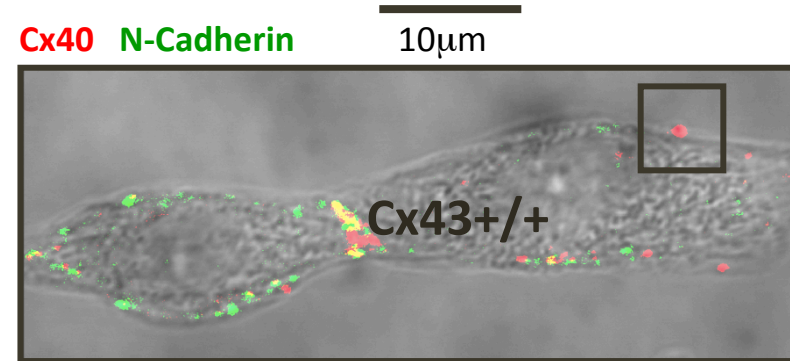
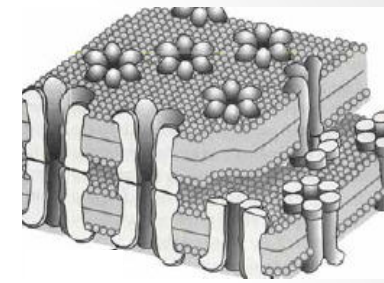
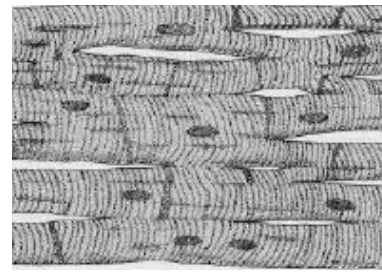
- **Bistability**
- Local structures
- Excitable ok

Example: Morris-Lecar with **external current**

CGL intermittency



Gap junctions

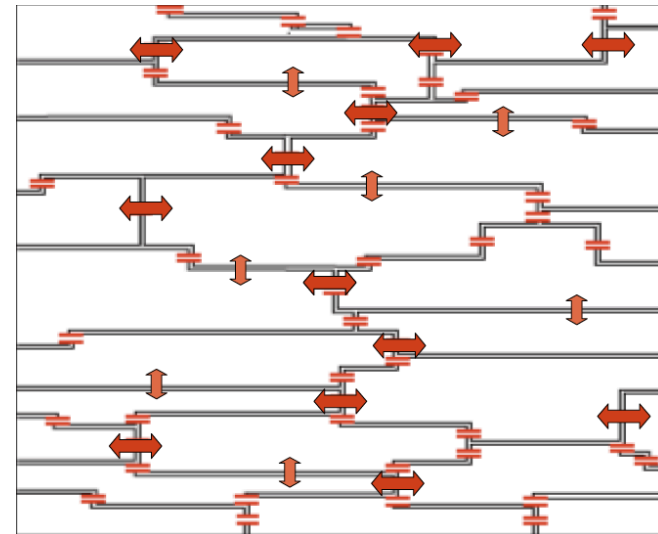


Desplantez

Gap currents:

- **Non** diffusive
- Anisotropic **network**

Ionic direct **exchanges**



→ Sync & **anti** Sync coupling :

- Dynamical **frustration** might occur

Cell-Cell coupling models

~~$$\partial_t U + f(U, w, \epsilon) + \mathbf{D}\Delta U = 0$$~~

$$\partial_t U + f\left(U, \vec{\nabla}U, w, \epsilon\right) + \mathbf{D}\Delta U = 0$$

Modulation, QP, phase locking, chaos, **AND disorder**... are possible

The model should include

- Micro scale \approx mean field
- Meso scale \approx XY or worse symmetry



+

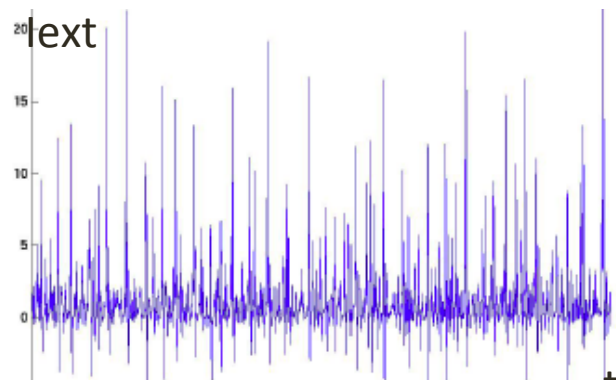
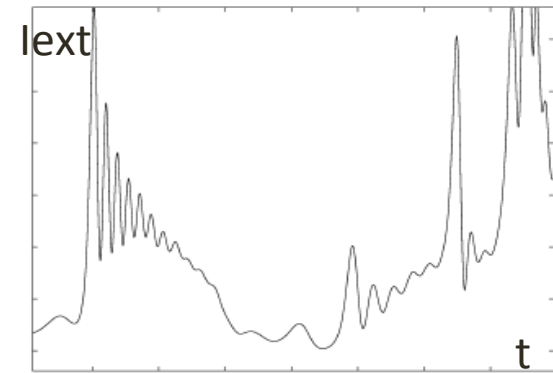
Feedback

Dynamical example: 1D Lorenz

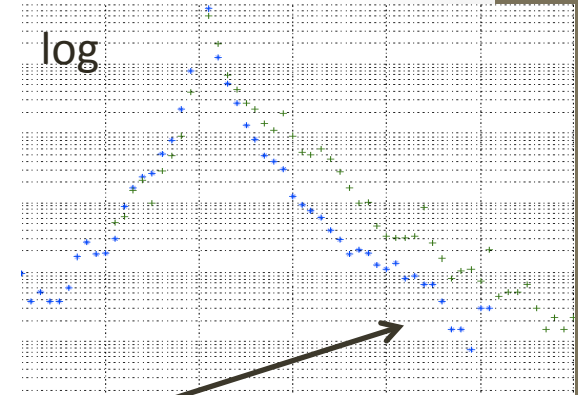
$$\begin{aligned} \partial_t w &= gu - \nu w \\ \partial_t u &= -w \vec{\nabla}U - \sigma u \\ \partial_t U &= -\vec{\nabla}(uw) + \mathbf{D}\Delta U \end{aligned}$$

Spatially extended Lorenz

Lorenz model extended 1D (all Couillet's requirements + non diffusive)

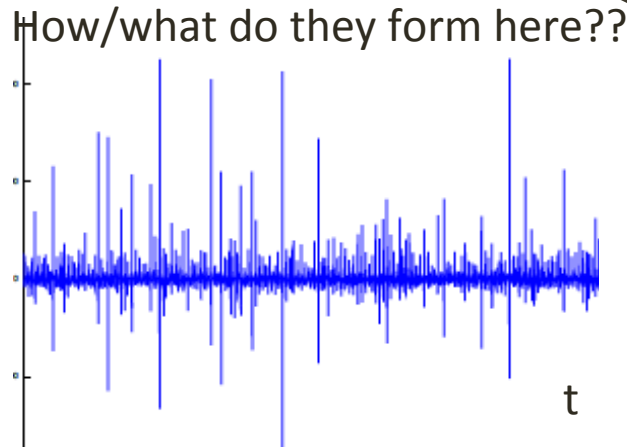
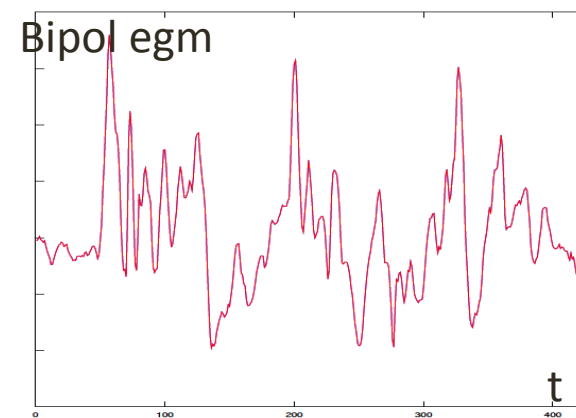


Frustration. Density wave trapping OK t

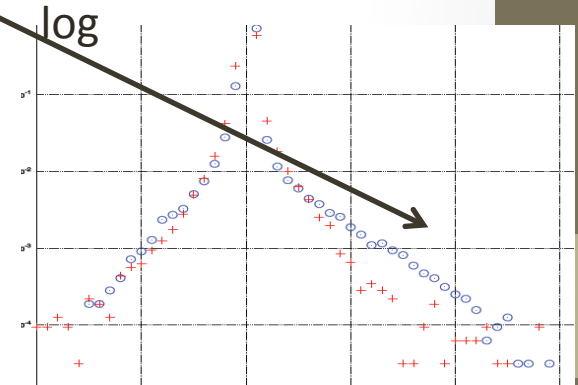


Clusters

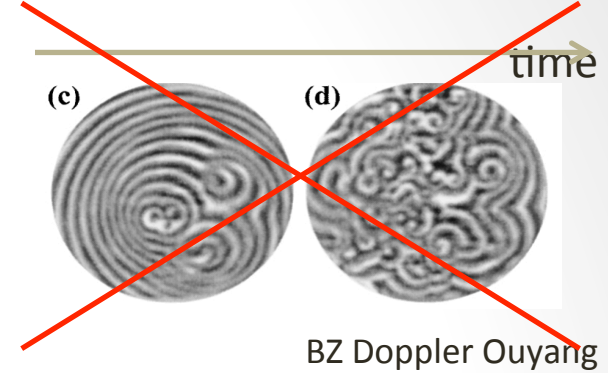
Clinical case Persistent AF, PV



How/what do they form here??



Addressing naturally:



- Allesie wavelength revisited
 - Analogy Type I - Type II **transition** (~Hertz model, CDW)
 - Find a **disorder penetration length**
 - Different stages of AF through **phase transitions** ?
- Remodelling
 - Non stationary, memory (~aging)
- Chaos is still included as
 - **Dynamical frustration**

Prospects: Chaotic disorder model

$$\mathcal{H}_{eff} = \frac{1}{2} \int d^d \mathbf{x} \tilde{r} |\Psi|^2 + \frac{1}{4} u_0 |\Psi|^4 + |(\vec{\nabla} - i\mathbf{Q})\psi|^2 + |\vec{\nabla} \wedge \mathbf{Q}|^2$$
$$\langle \mathbf{Q} | \Psi \rangle = g(|\Psi|)$$

Thank you !

Cell-Cell coupling model

Lorenz 1D

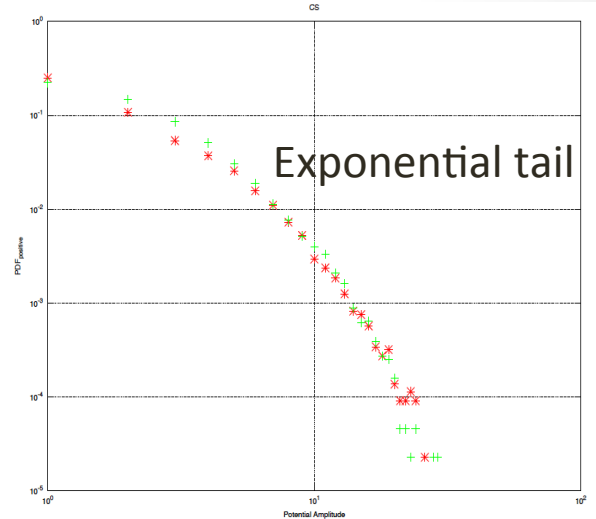
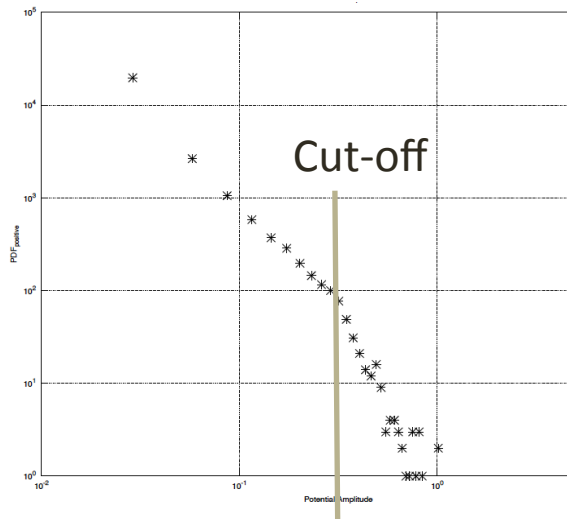
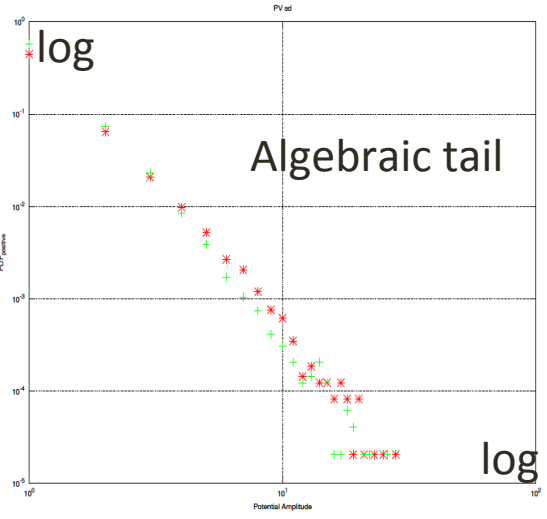
$$\begin{aligned}\partial_t w &= gu - \nu w \\ \partial_t u &= -w \vec{\nabla} U - \sigma u \\ \partial_t U &= -\vec{\nabla}(uw) + \mathbf{D}\Delta U\end{aligned}$$

Slightly more physiological?

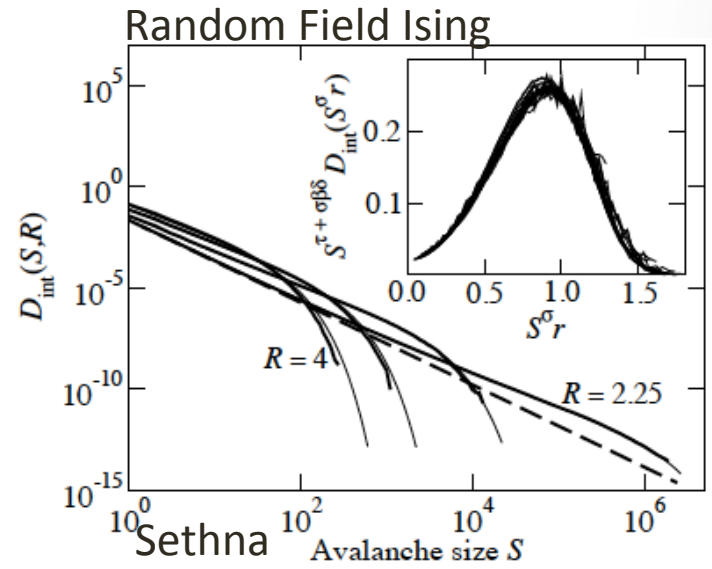
$$\begin{aligned}\partial_t U &= f(U, w, \epsilon) - \sigma_{RC} U \\ \partial_t v &= -g \vec{\nabla} U - \nu v \\ \partial_t w &= -v \vec{\nabla} W + \mathbf{D}\Delta w \\ \partial_t W &= -\vec{\nabla}(vw) + \mathbf{D}\Delta W\end{aligned}$$

New markers ?

Transition from Paroxysmic to Persistent to Chronic or else ?



- Local nonlinear mechanisms
 - Read scaling, cut-off ... systematic classification
 - Abnormal morphology distance to source?
- Global **disorder** ?



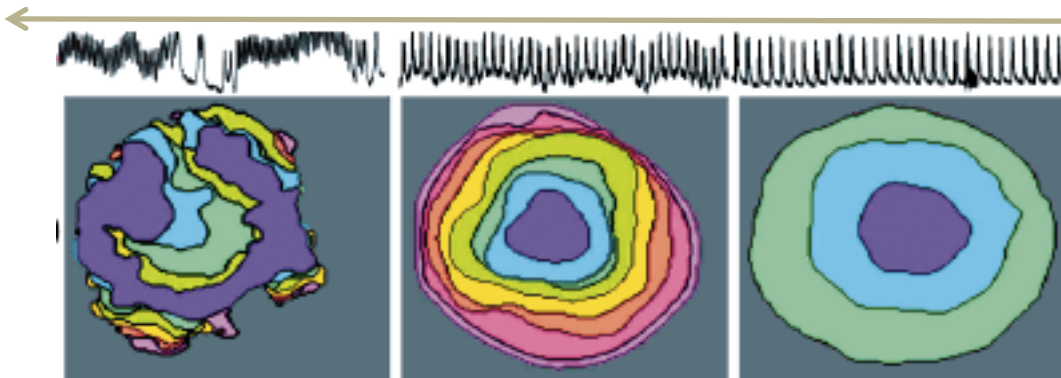
Courants de jonction

Ca blocker



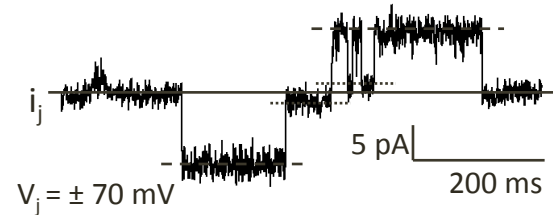
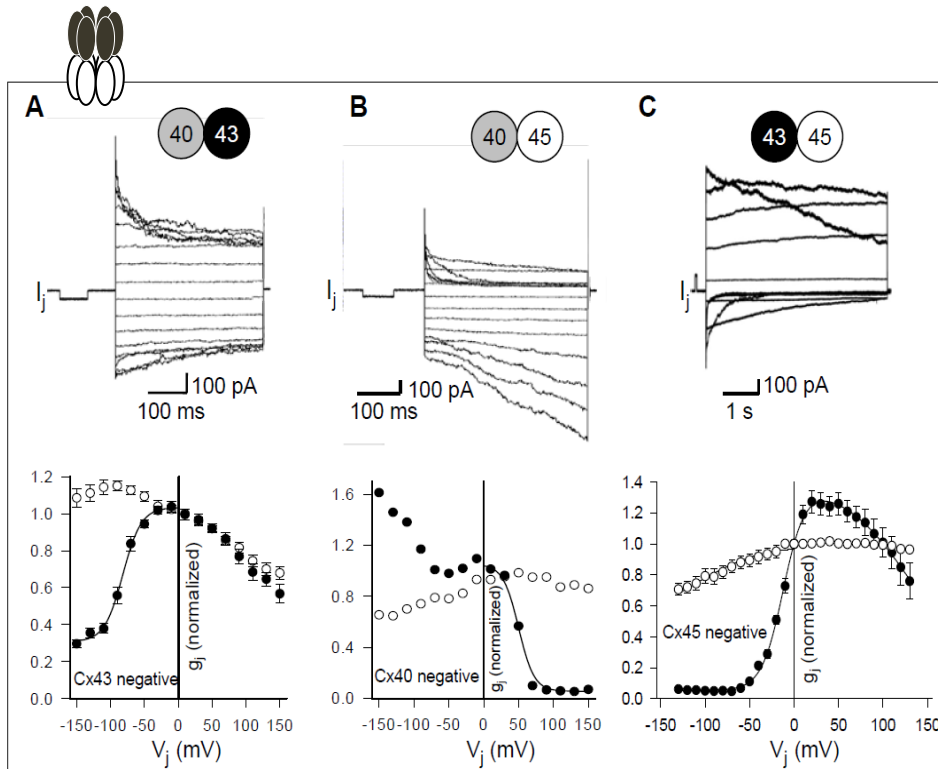
Canine experiments

Glycyrrhethinic acid / gap junctions



Though not very specific

Conductance non-linéaire



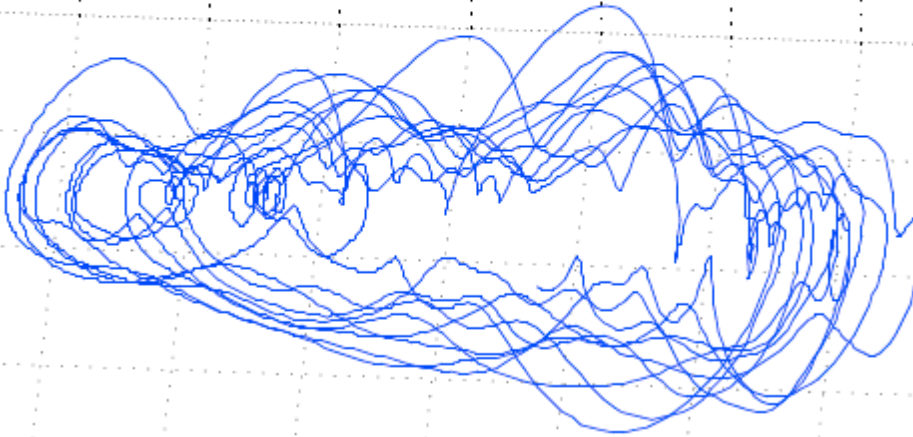
Desplantez

→ Induce **synchronization / anti-synchronization coupling?**

Ex: Kuramoto + désordre Daido

Chaos

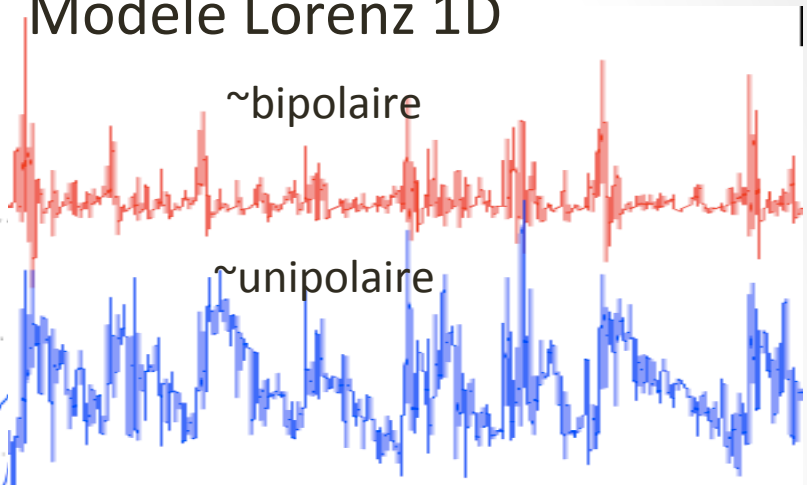
30 cellules



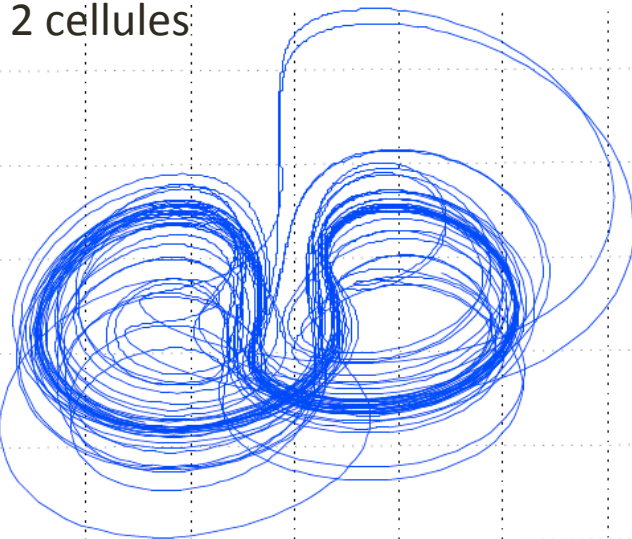
Modèle Lorenz 1D

~bipolaire

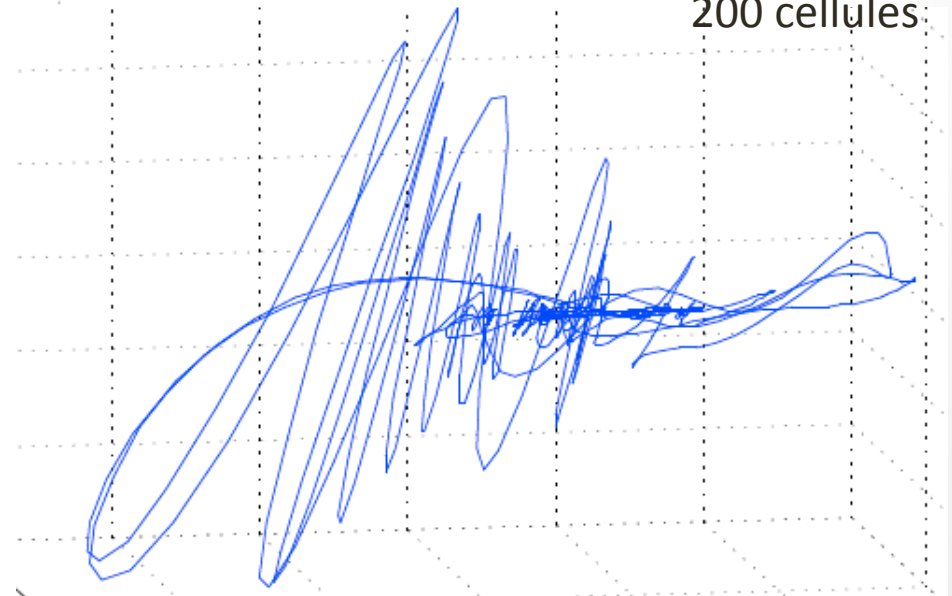
~unipolaire



2 cellules

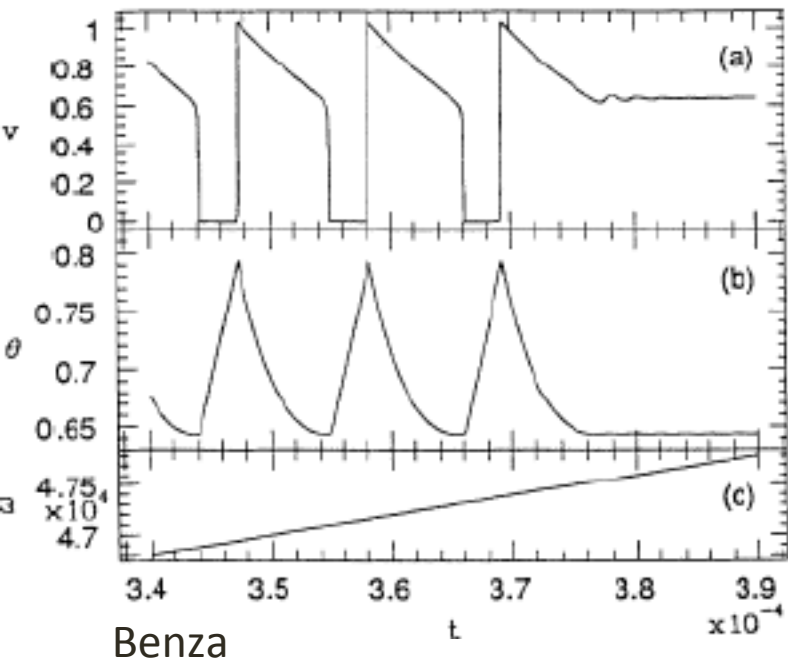


200 cellules

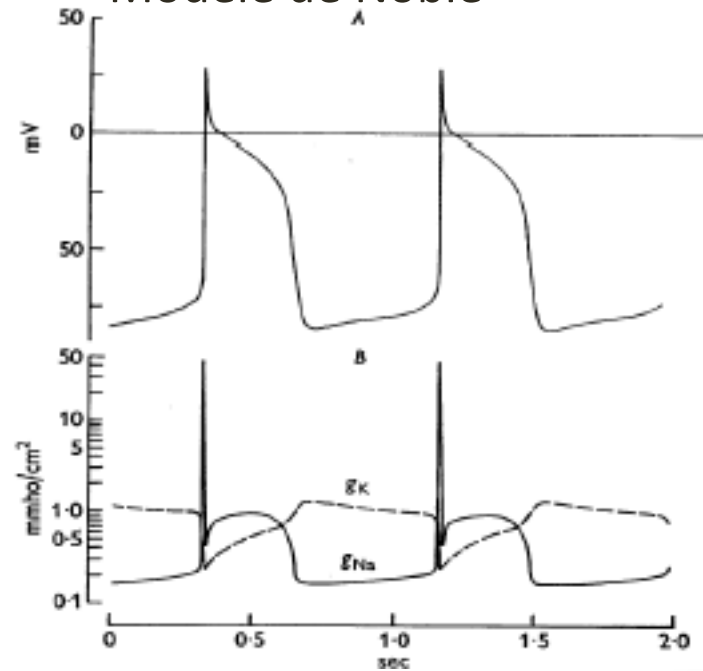


Autre milieu excitable

Tas de sable tambour rotatif

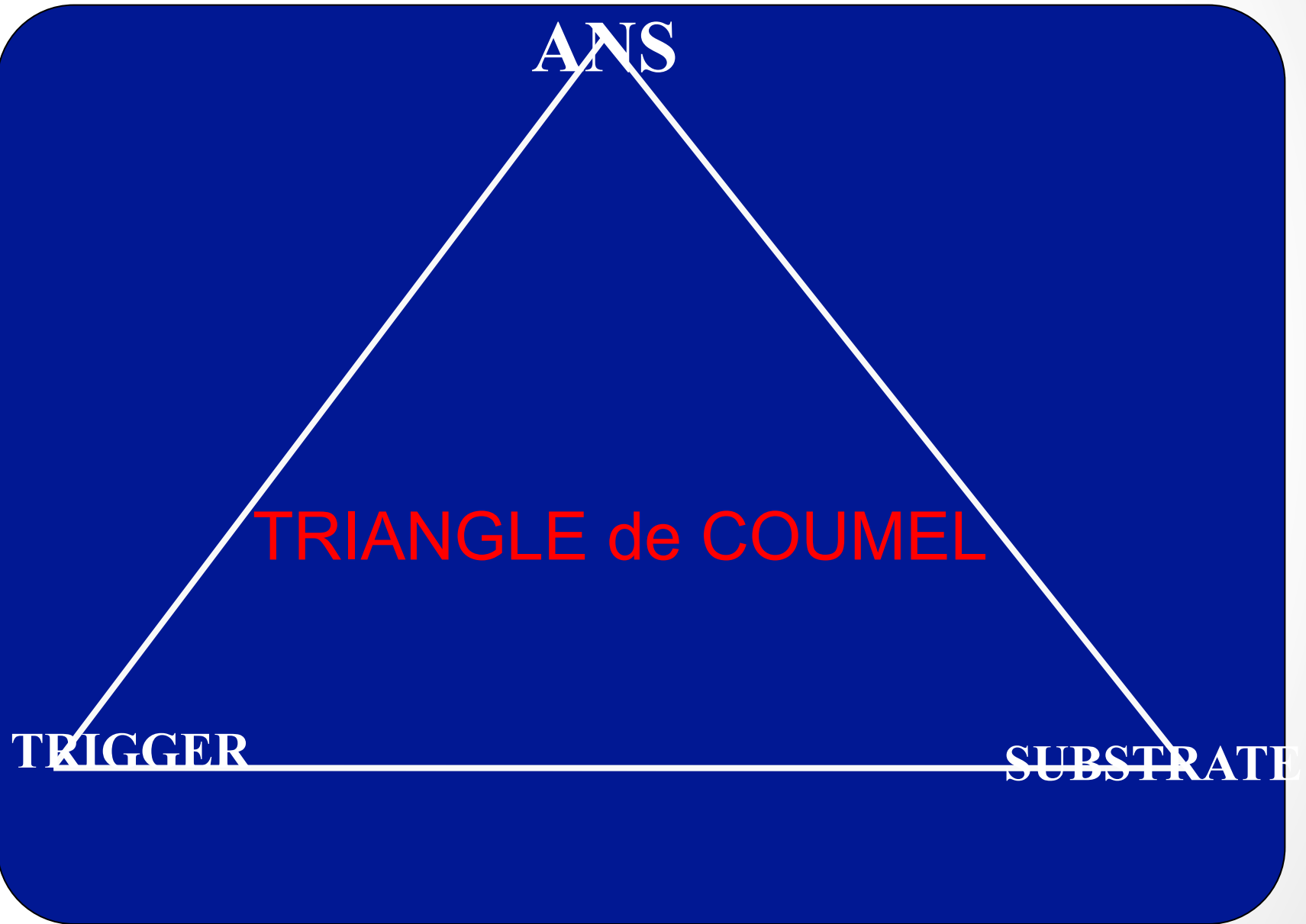


Modèle de Noble



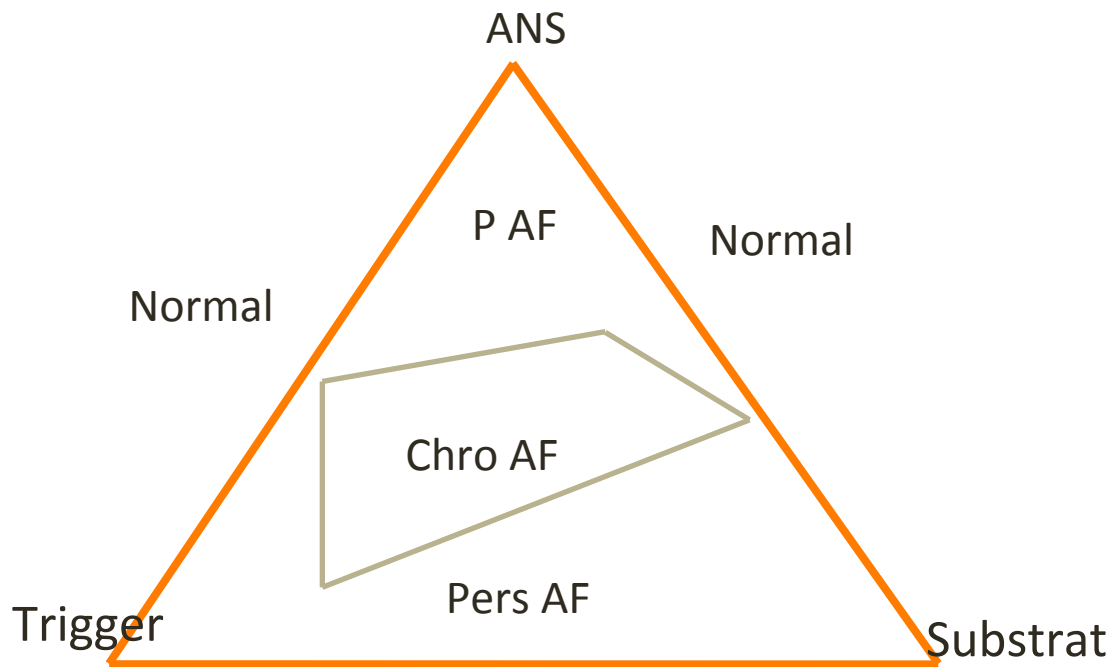
Seuil d'excitabilité imprécis

Evaluating mechanisms



Phase transition

??



Reaction-diffusion avec brisure de symétrie

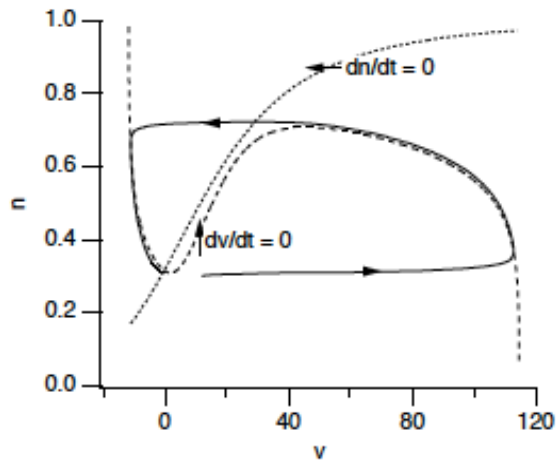
Modified FitzHugh Nagumo

$$\partial_t u = -\frac{1}{\varepsilon} u(u - 1) \left(u - \frac{v + b}{a} \right) + \Delta u$$

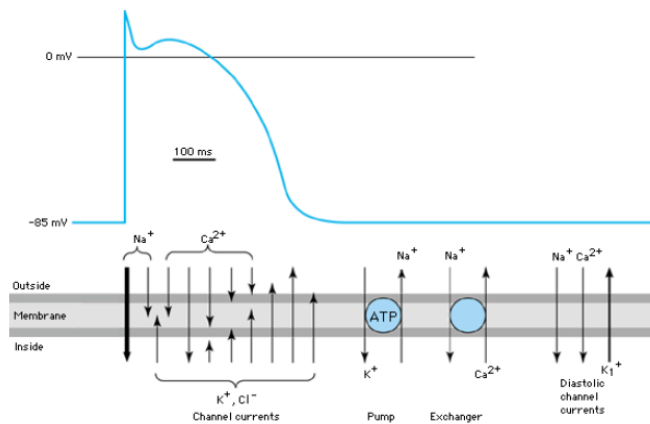
$$\partial_t v = f(u) - v.$$

Function f such as spirals can be unstable

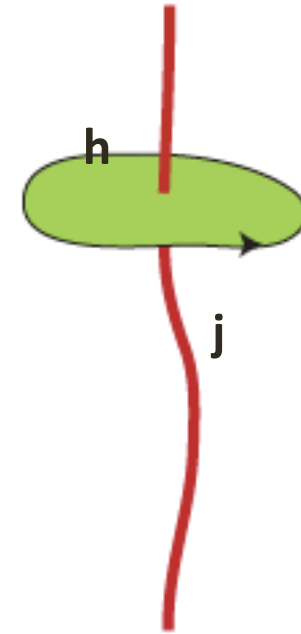
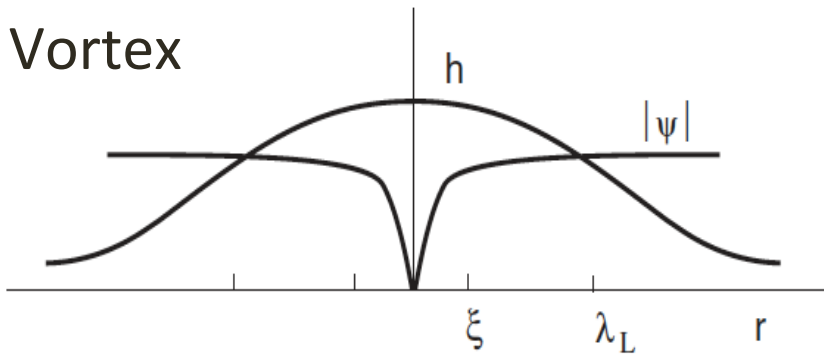
Rappel:



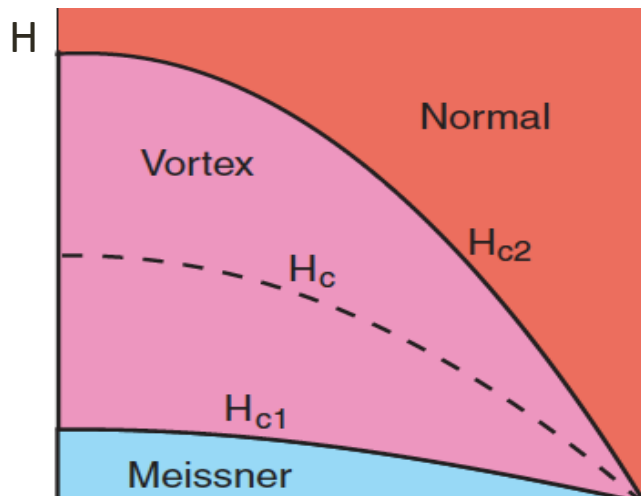
Cardiac Action Potential



Superconductor type II



Phases



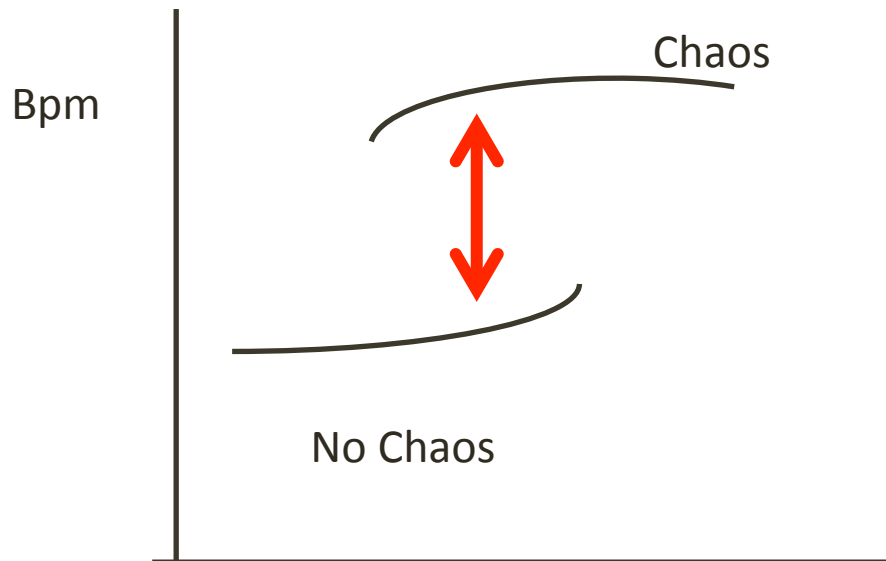
Two characteristic lengths

$$\xi = \frac{\hbar}{\sqrt{2m_e |\alpha|}}$$

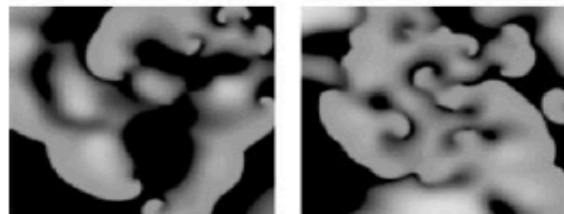
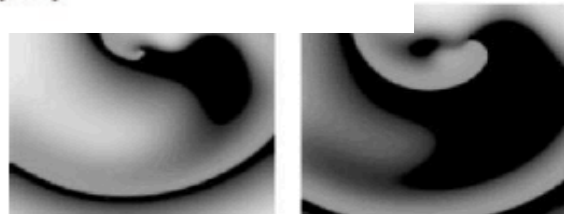
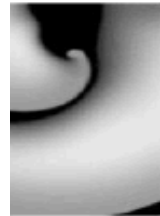
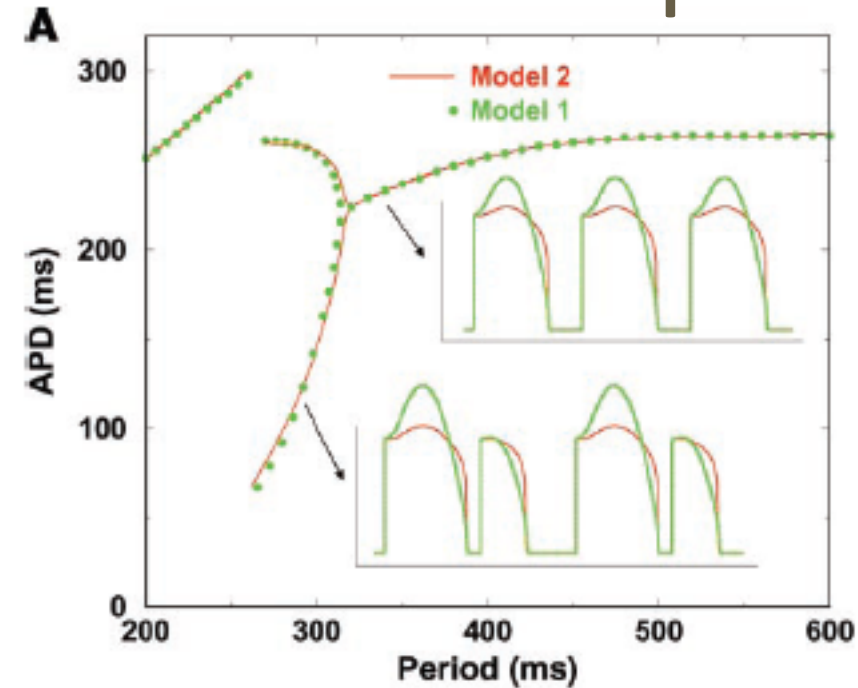
$$\lambda = \sqrt{\frac{m_e \beta}{4e^2 \mu_0 |\alpha|}}$$

Experiments?

- Tenter la cardio version préalable à l'intervention pour toute FA chronique: **Y a-t-il une corrélation statistique entre succès et CV ?**
- Protocole de brûlure aléatoire (ou similaire): **idem ?**

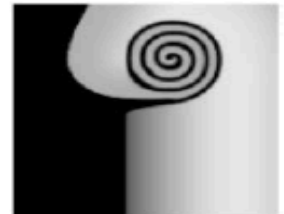


Importance des courants électrotoniques



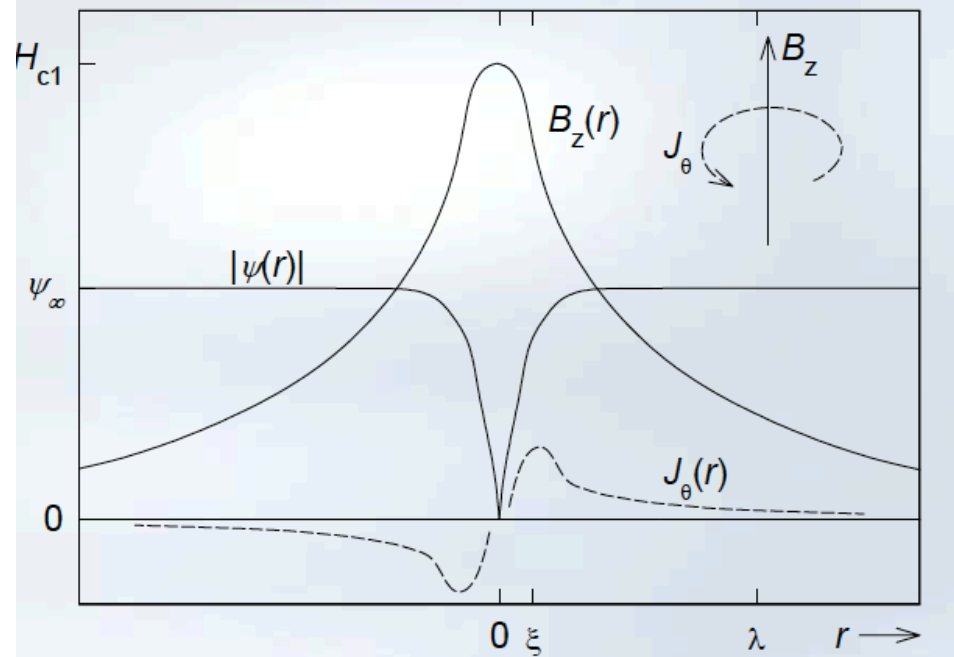
Fenton

B



$$\xi = \frac{\hbar}{\sqrt{2m_e |\alpha|}}$$

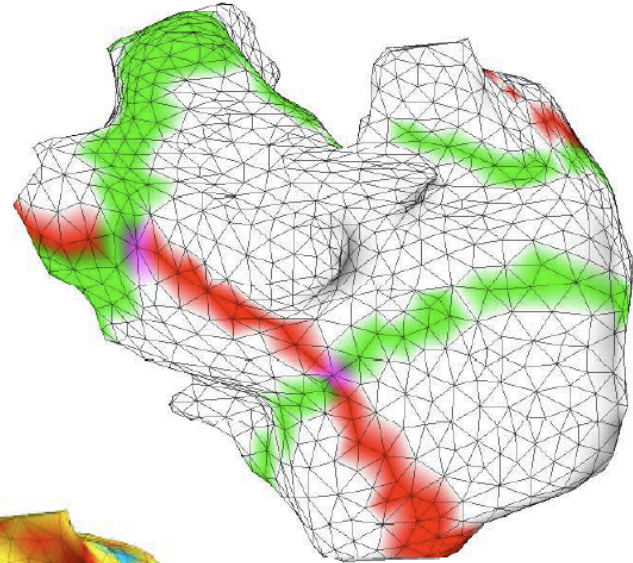
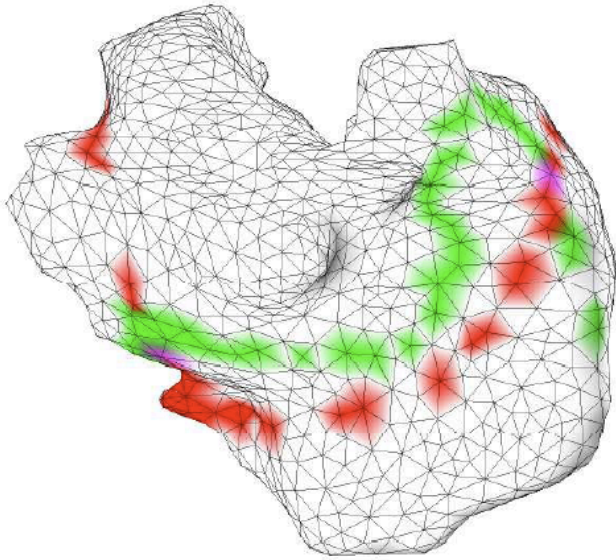
$$\lambda = \sqrt{\frac{m_e \beta}{4e^2 \mu_0 |\alpha|}}$$



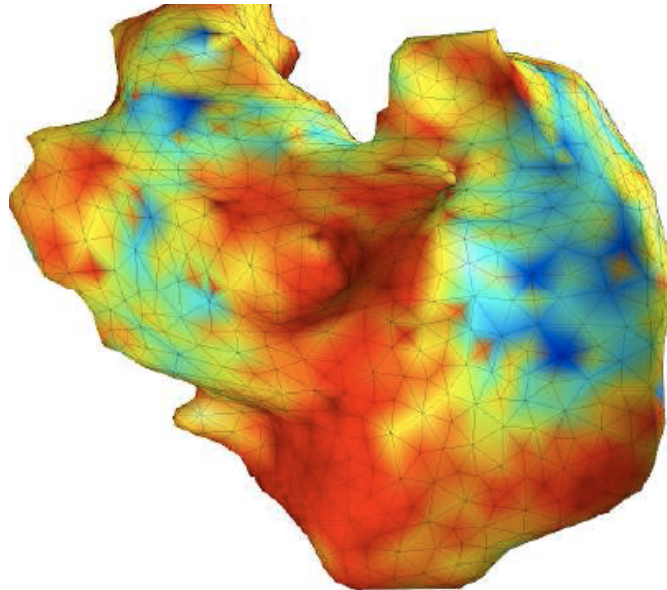
$$f_s - f_n = \alpha |\psi|^2 + \frac{\beta}{2} |\psi|^4 + \frac{1}{2m} |(-i\hbar\nabla - 2eA)\psi|^2 + \frac{|B|^2}{2\mu_0}$$

Vortex & intermittency ?

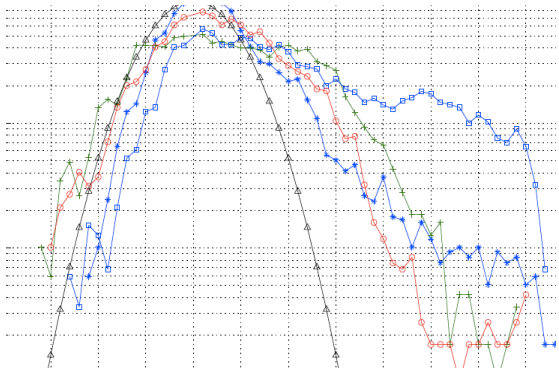
Phase defects



Skewness



Courants ?



Distinguish which type of intermittency

- EGM aux temps **longs**
 - Reaction-diffusion \sim haute T
 - Lorenz 1D ou supra \sim basse T
- Mesures 'simultanées' **egm-C.I.**
 - Courants vs cœurs de vortex

→ Vortex comme **épiphénomène** ?

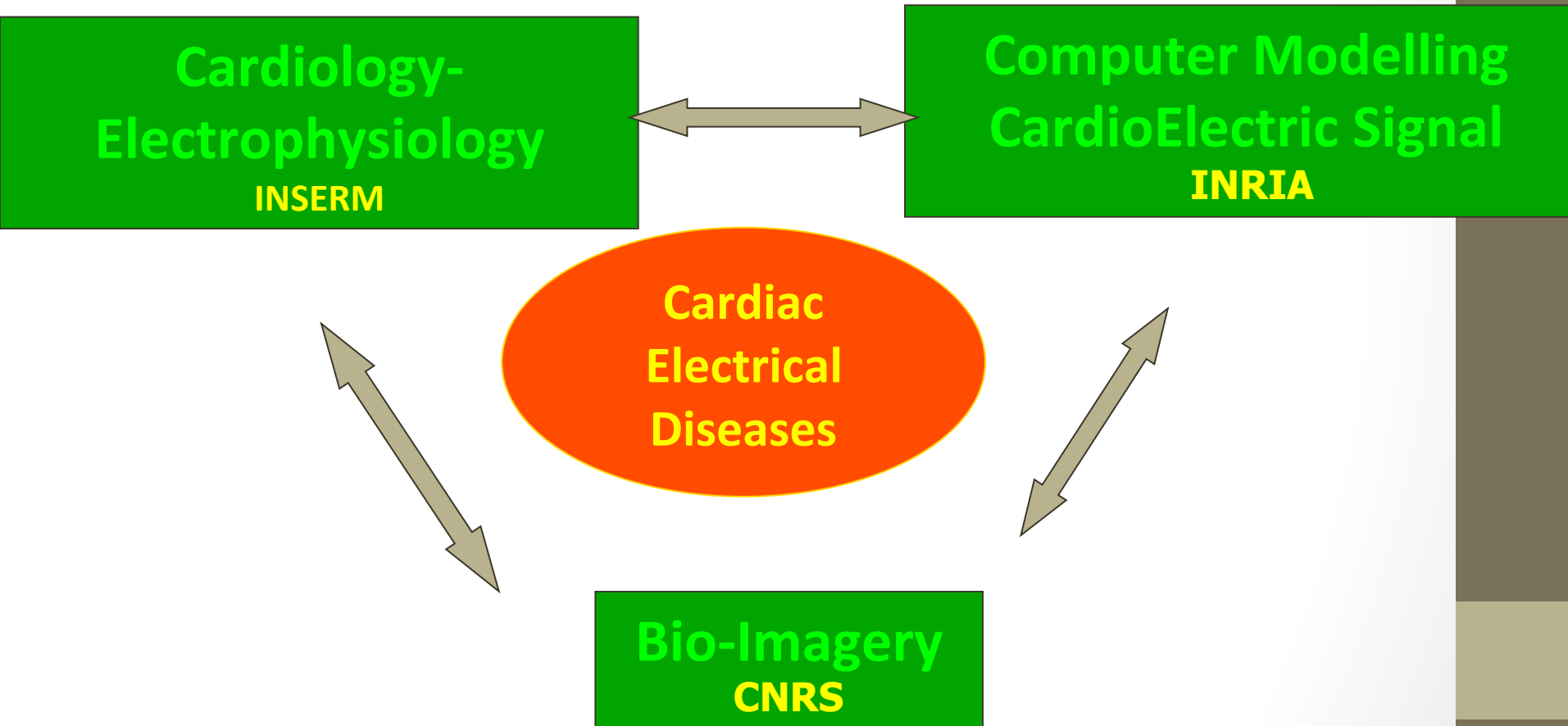
Cardiac Arrhythmia

Major cause of stroke

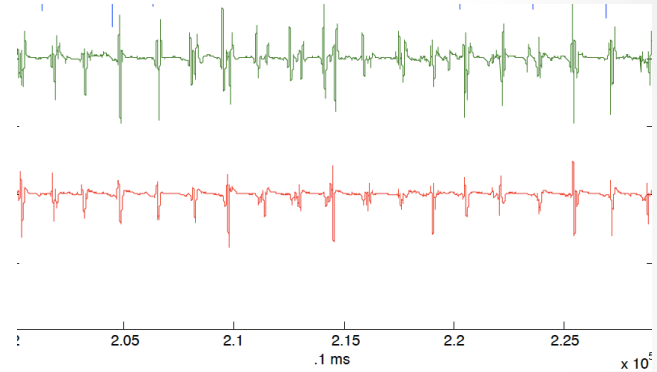
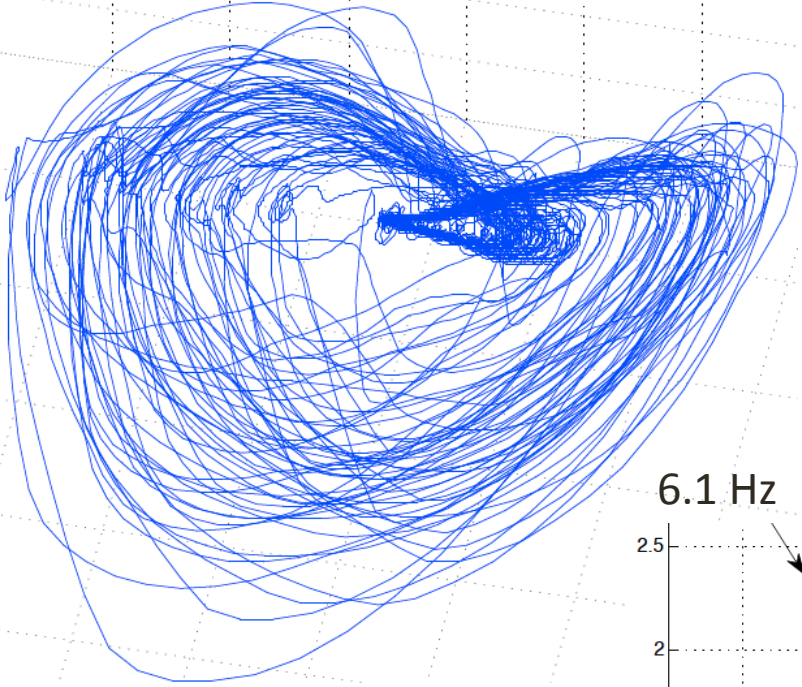
EUROPE: 5 MILLIONS

L' Institut de RYthmologie et modelisation Cardiaque

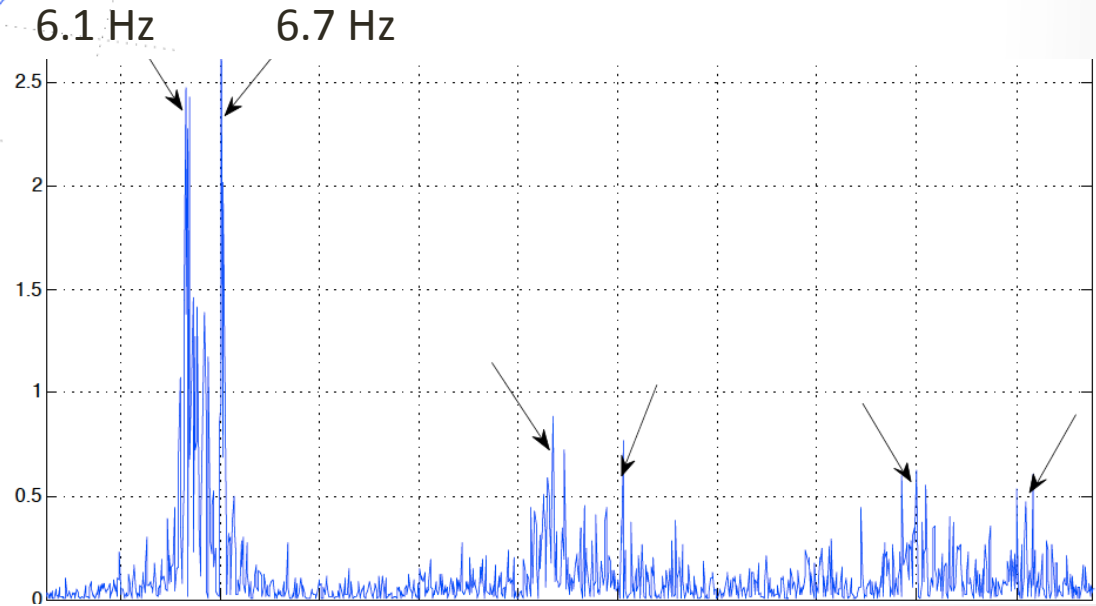
research, pt care , teaching, Transfer



Quasi periodicity



(Pseudo) TA



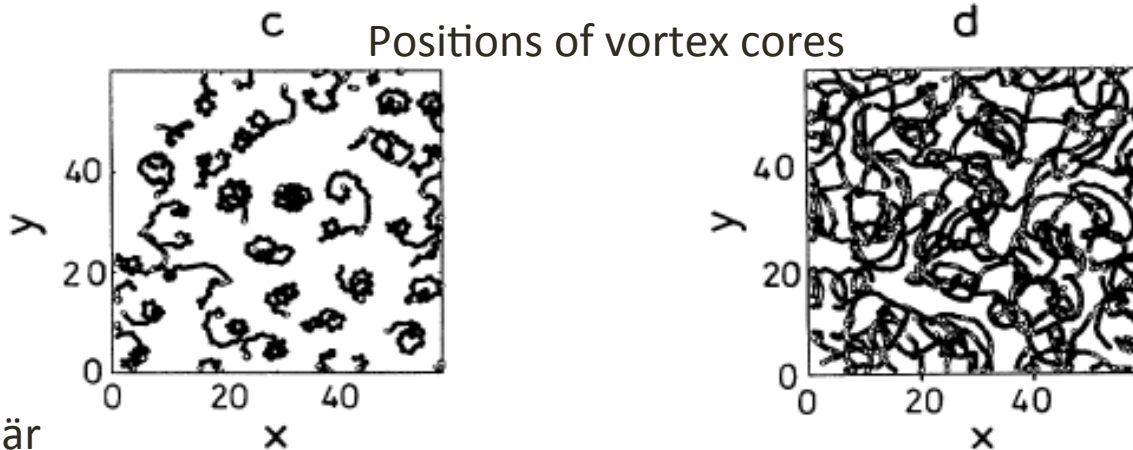
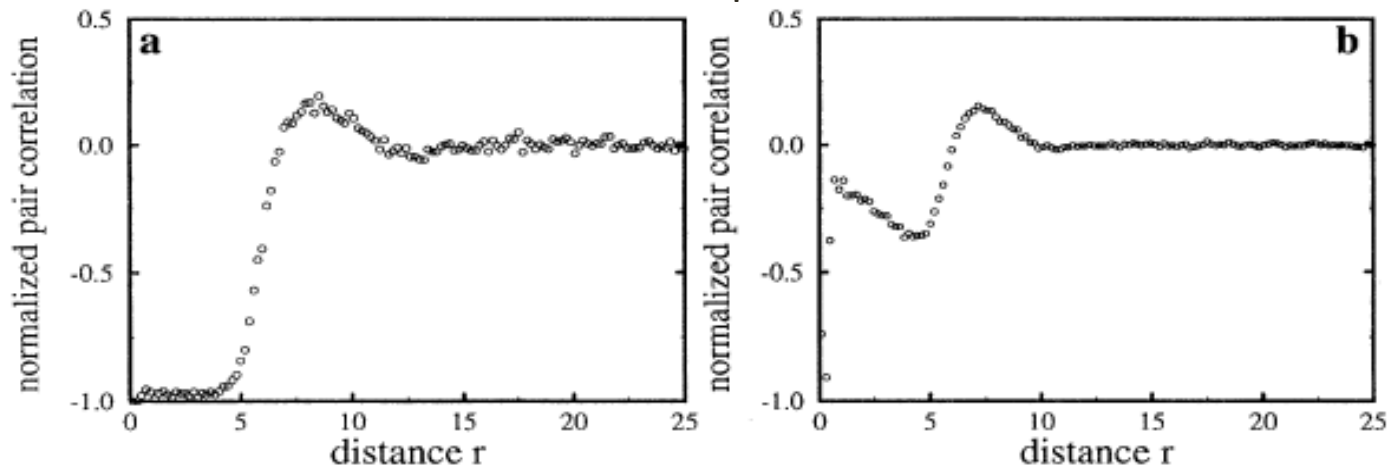
Vortices in reaction diffusion epiphenomena?

Spiral break up

Limit cycle



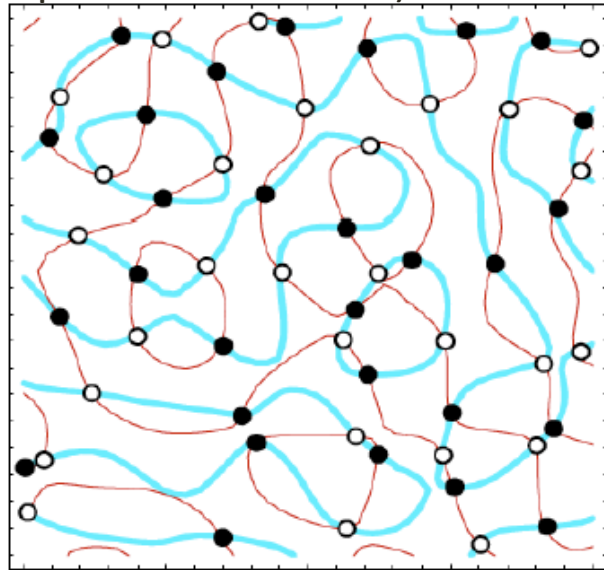
Vortex-vortex spatial correlations



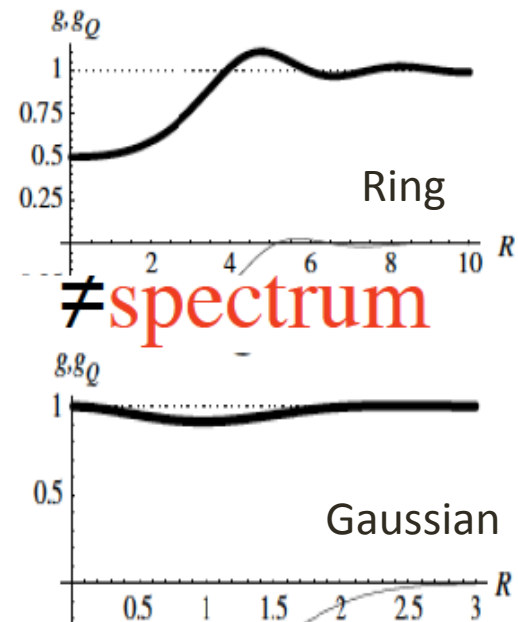
Random optical vortex field

Similar transition depending upon **spectrum only**

Phase defects
(=optical vortex cores)



Pair correlations

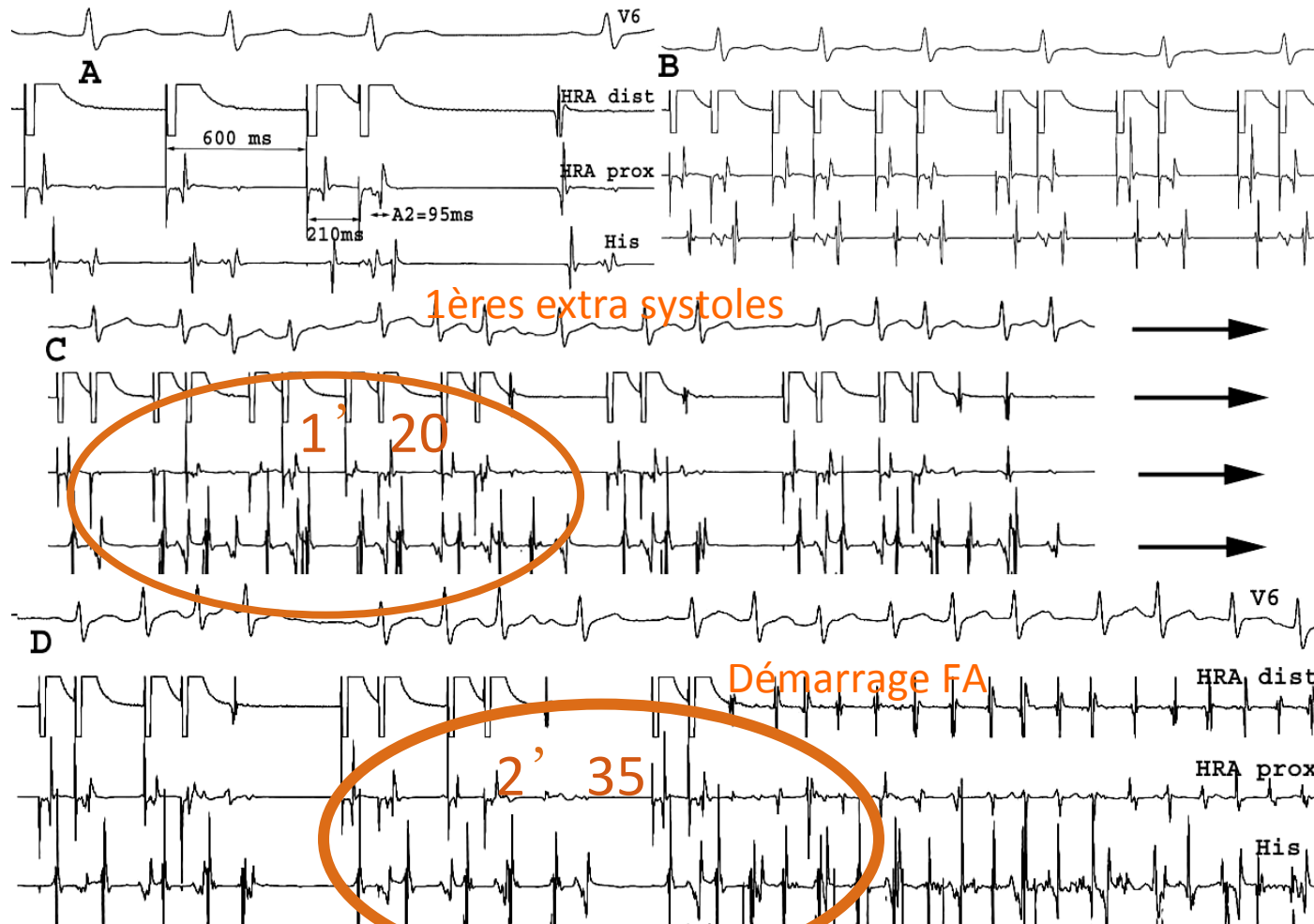


Berry

Atrial Bigeminy as a test of Vulnerability

Modulation ? Autre ?

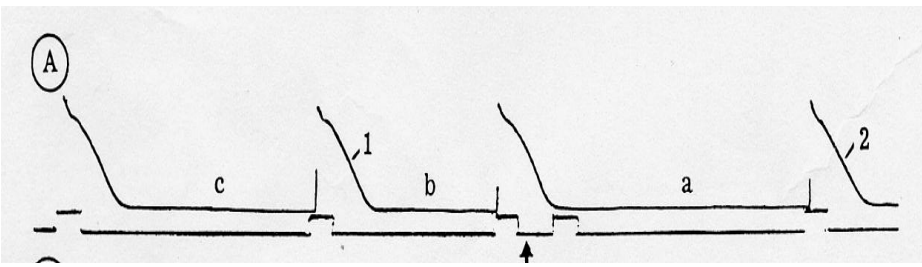
Période de stimulation > ERP + 30ms



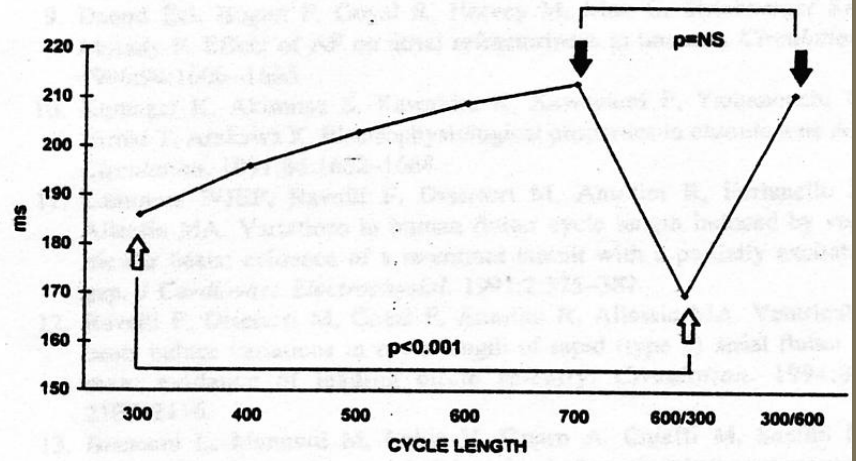
Effects of LONG-SHORT cycle-Length sequences

Pandozi *RP overshortening*

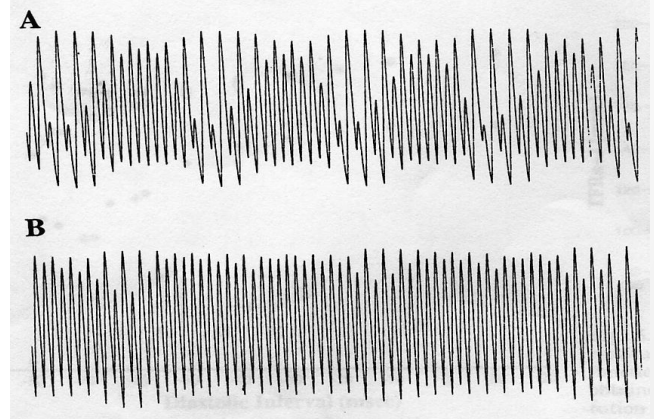
Alteration on Cardiac Action Potentials
Greenspan et al.



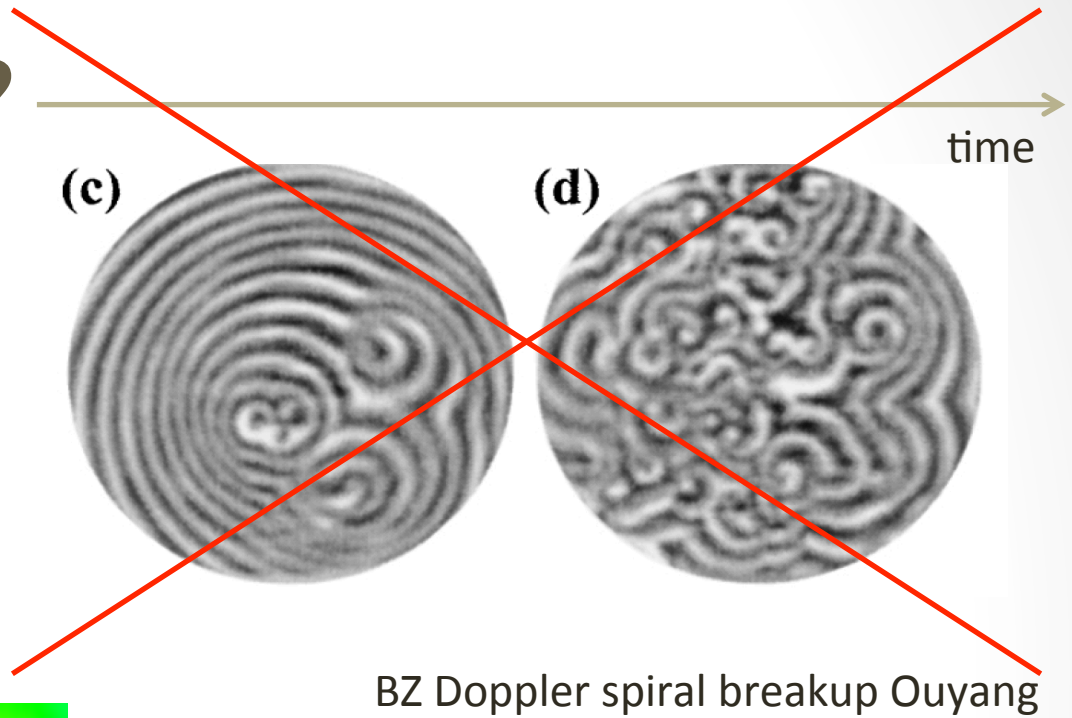
Stretch phenomenon



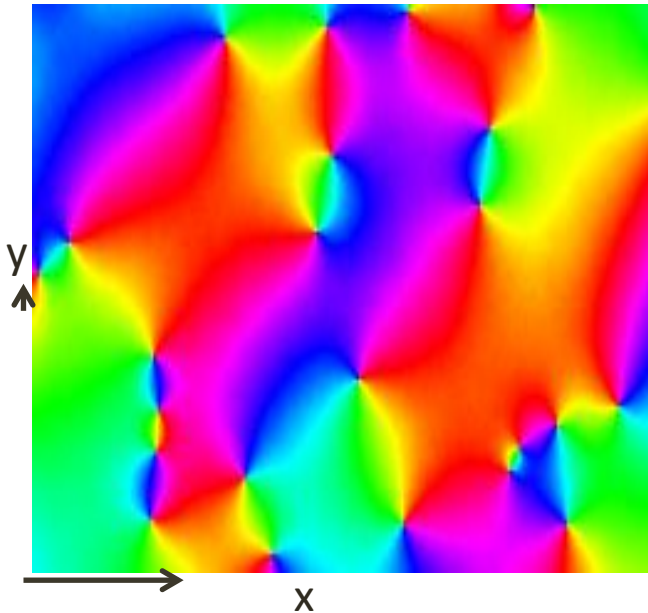
Nonlinear electrical behavior
Higher-order periodic and aperiodic activity during constant pacing



Paradigme?



XY paired vortices



Argument: observation d'**intermittence**