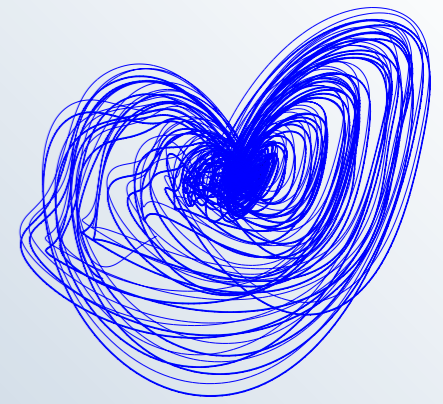


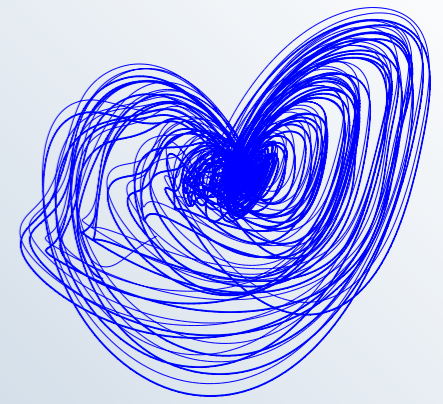
The desynchronization of cardiac cells : changing point of view on fibrillation.



Guillaume Attuel, Hussein Yahia
GEOSTAT, INRIA

- ➔ Help settle an old debate on objective ground.
- ➔ What is the data telling us for sure?
- ➔ How to extract precisely relevant information?

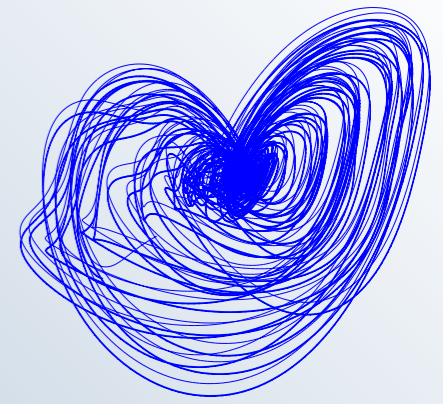
The desynchronization of cardiac cells : changing point of view on fibrillation.



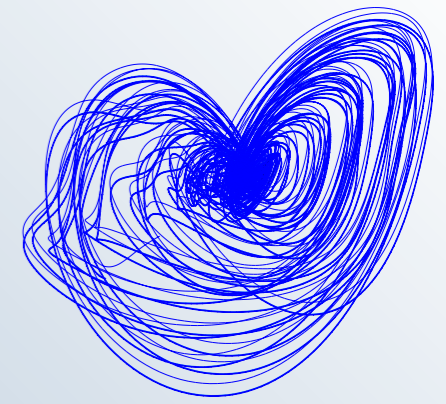
Guillaume Attuel, Hussein Yahia
GEOSTAT, INRIA

- Status of understanding, unknowns.
- Intermittency in the data?
- Models and impact on signal processing.

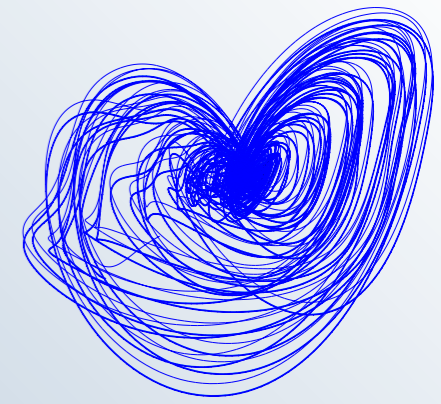
The normal heart on Wikipedia



The fibrillating atria on Wikipedia

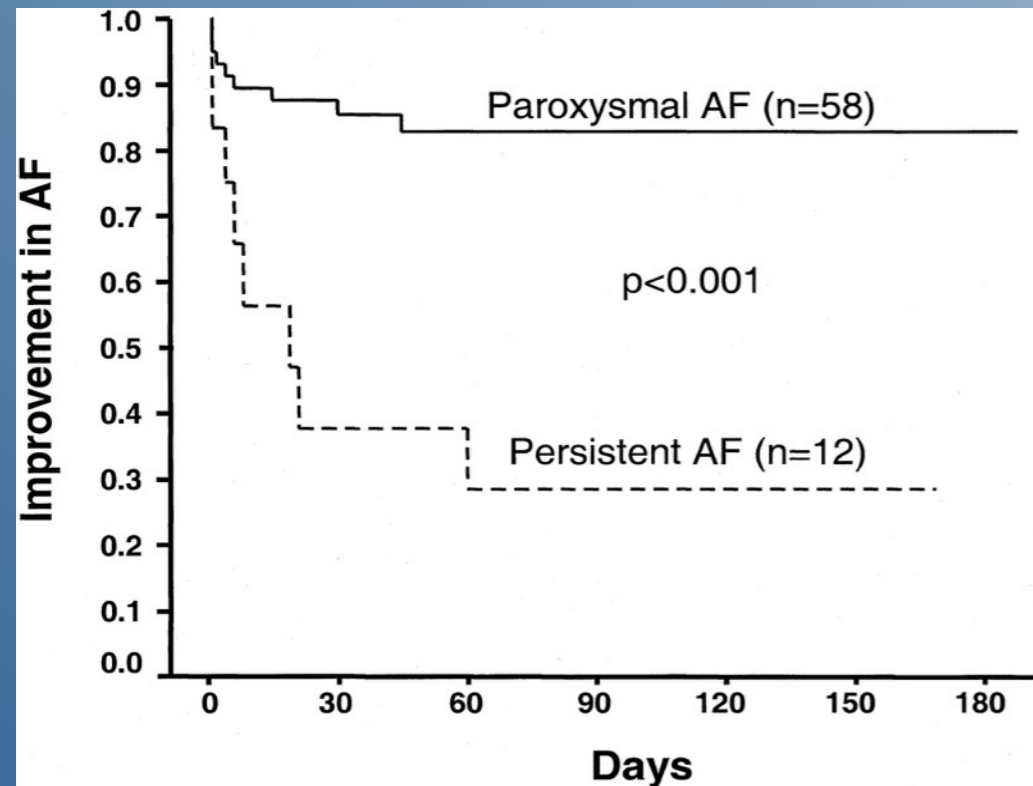


A Public Health problem

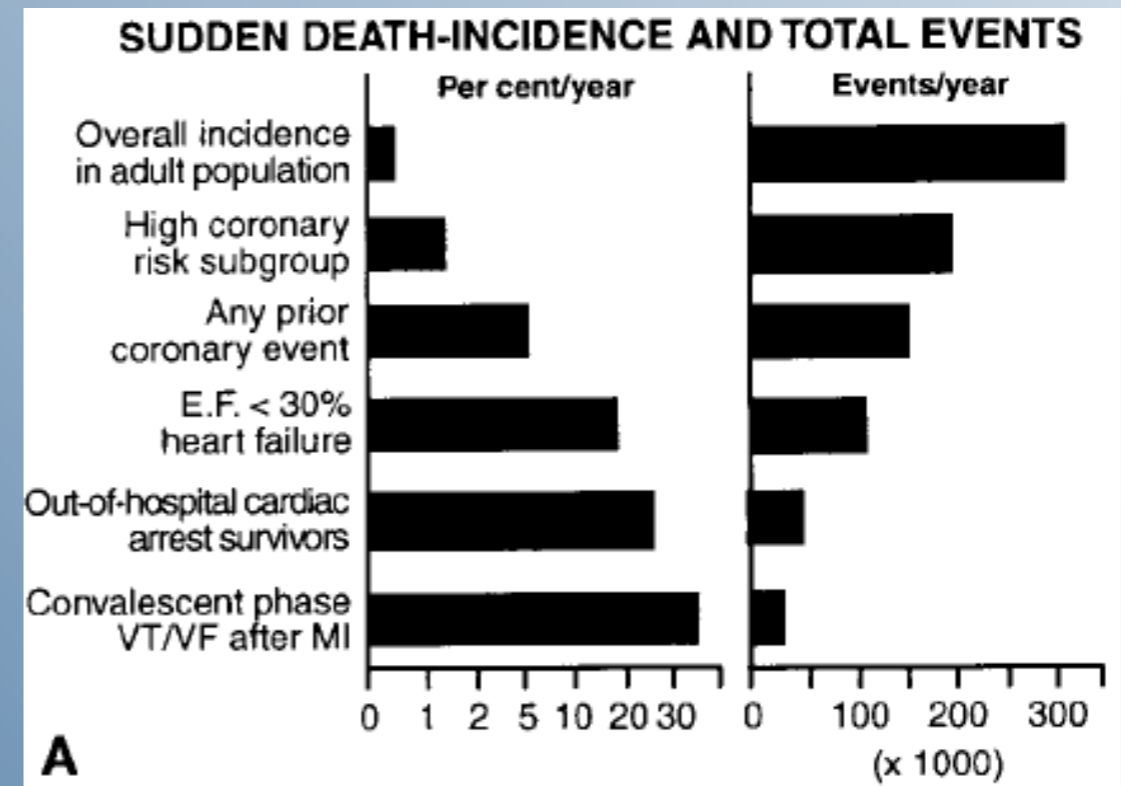


- Fibrillation in Ventricles is *sudden death*.
 - ➔ *No prediction, no treatment.*
- Fibrillation in Atria is *stroke*.
 - ➔ *No cure*

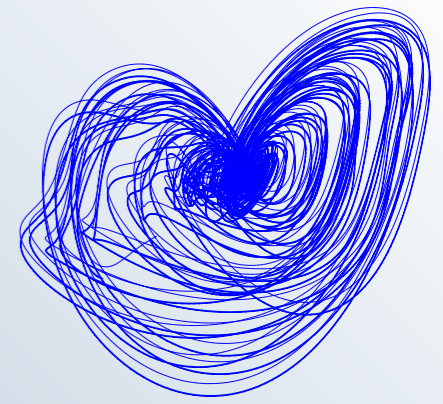
Treatment of AF



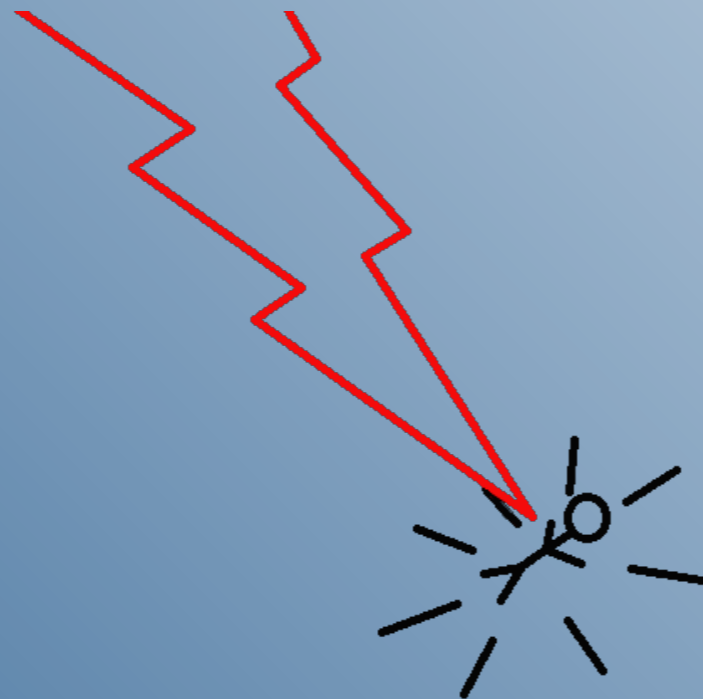
Epidemiology



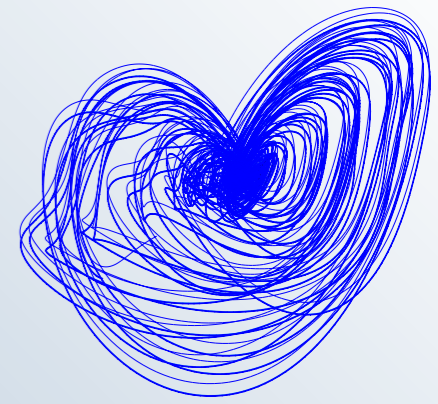
Miracles



A bad blow strikes you to death...



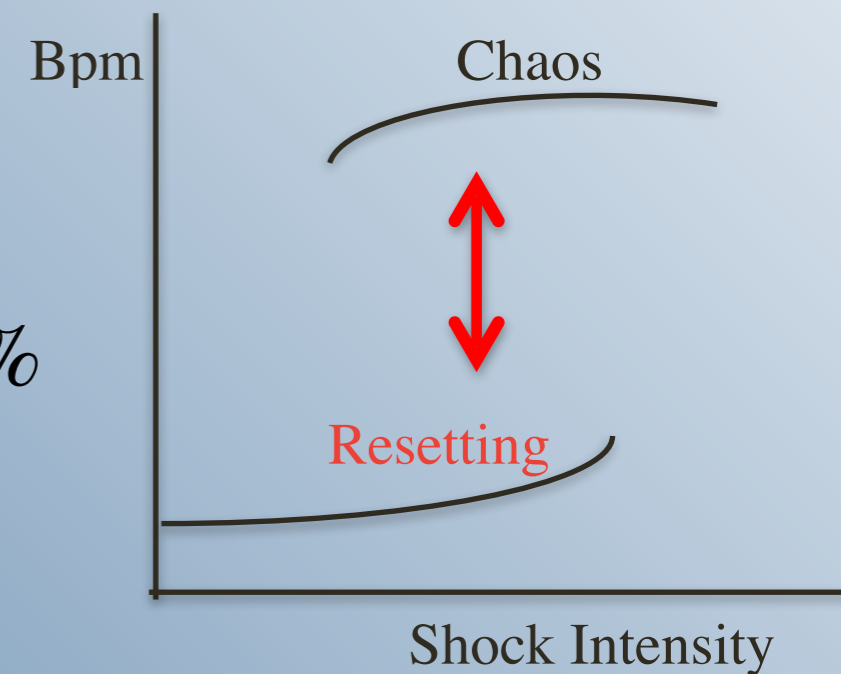
5% Miracles



Another blow resuscitates you!

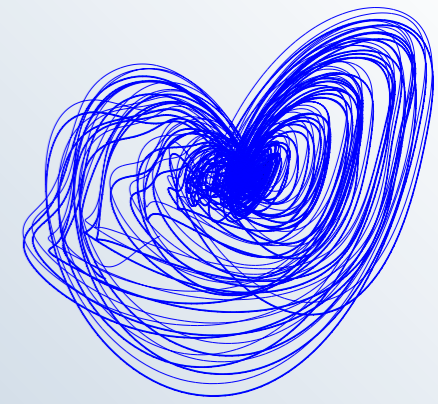


- Fatal prognosis 98%
- Defibrillators save 7%
- ➔ Can we do better?

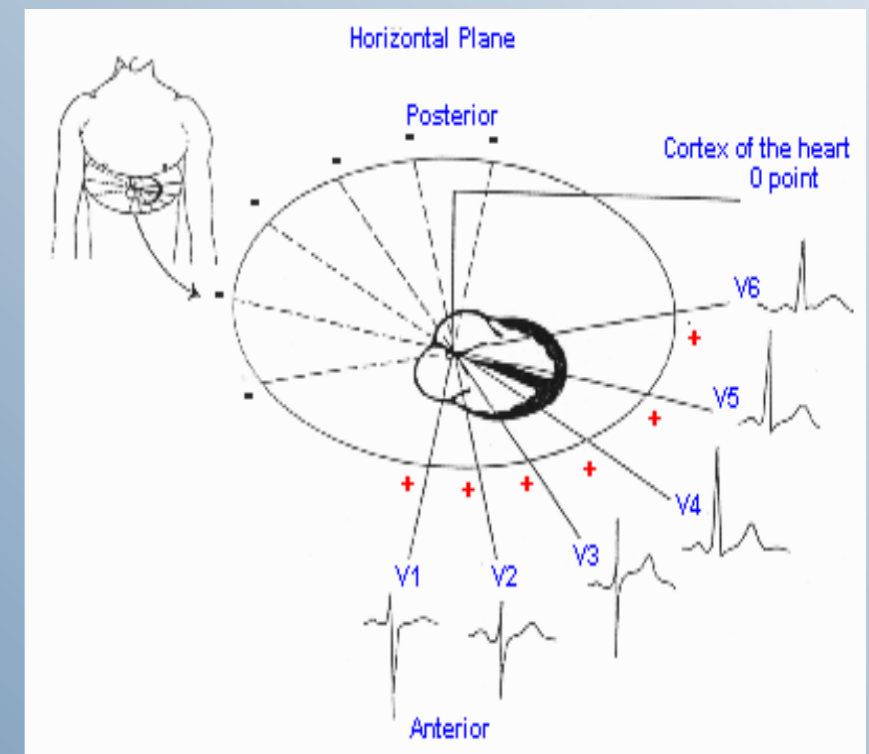
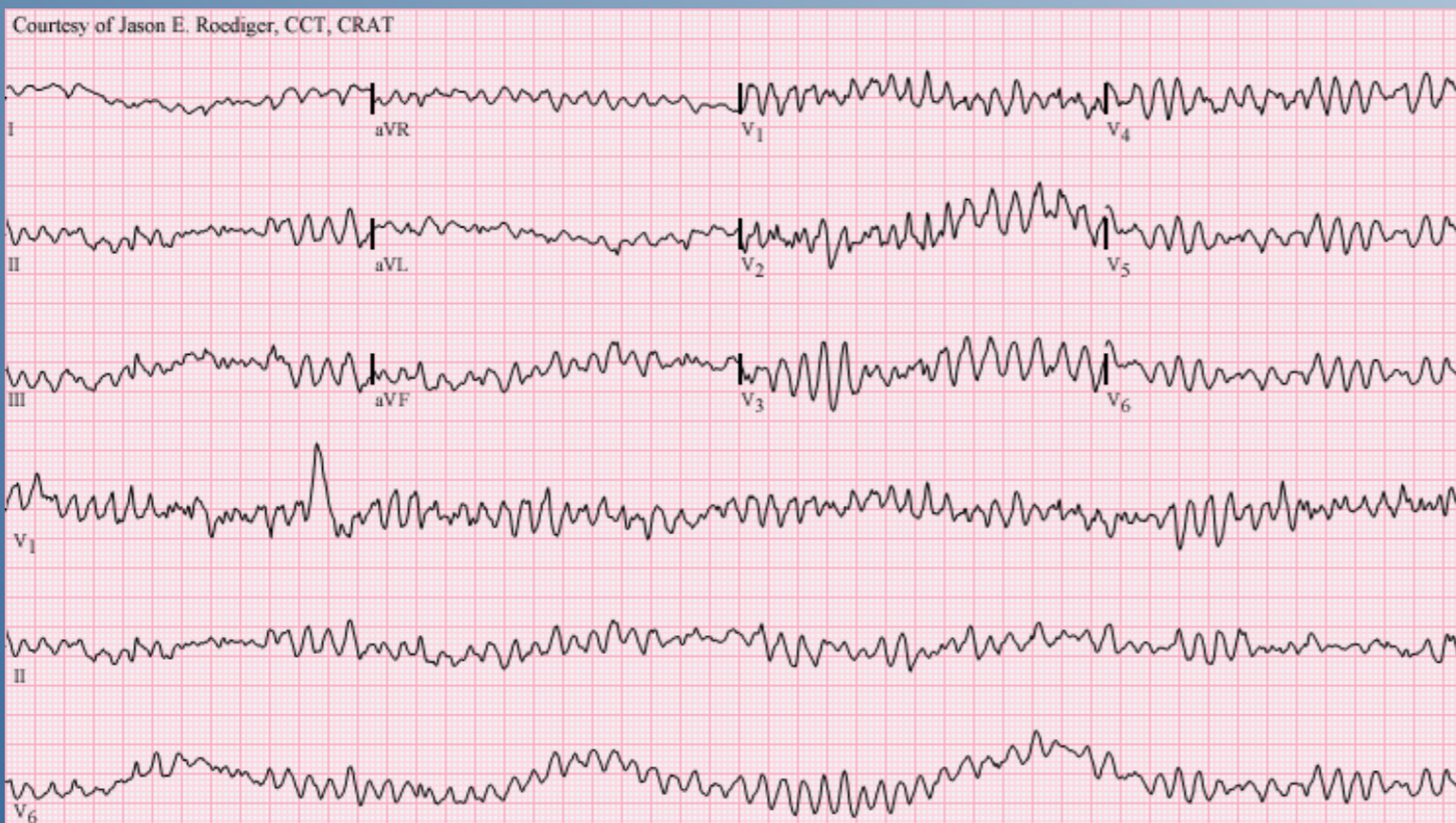


Different complexity

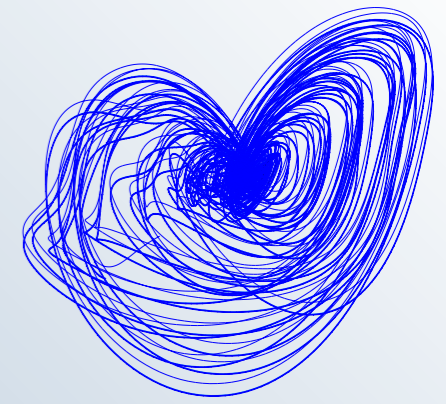
- Fibrillation in Ventricles is *smooth*
- Fibrillation in Atria is *much less*.



FV ECG

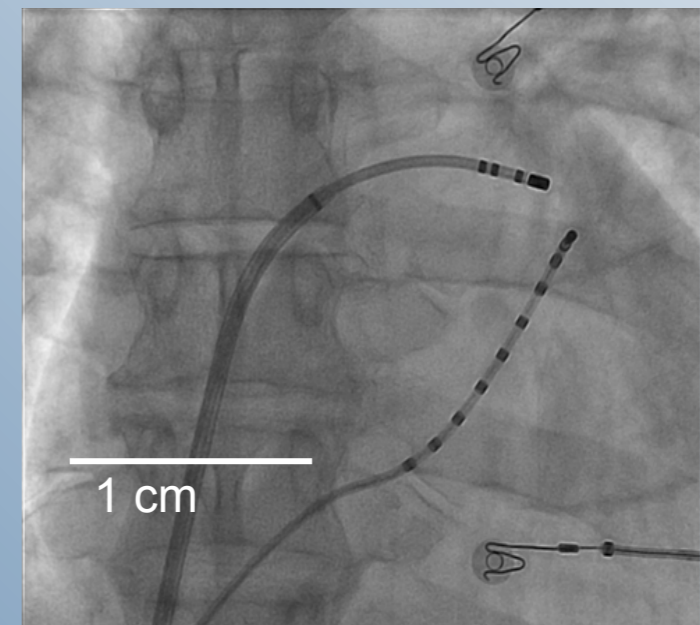
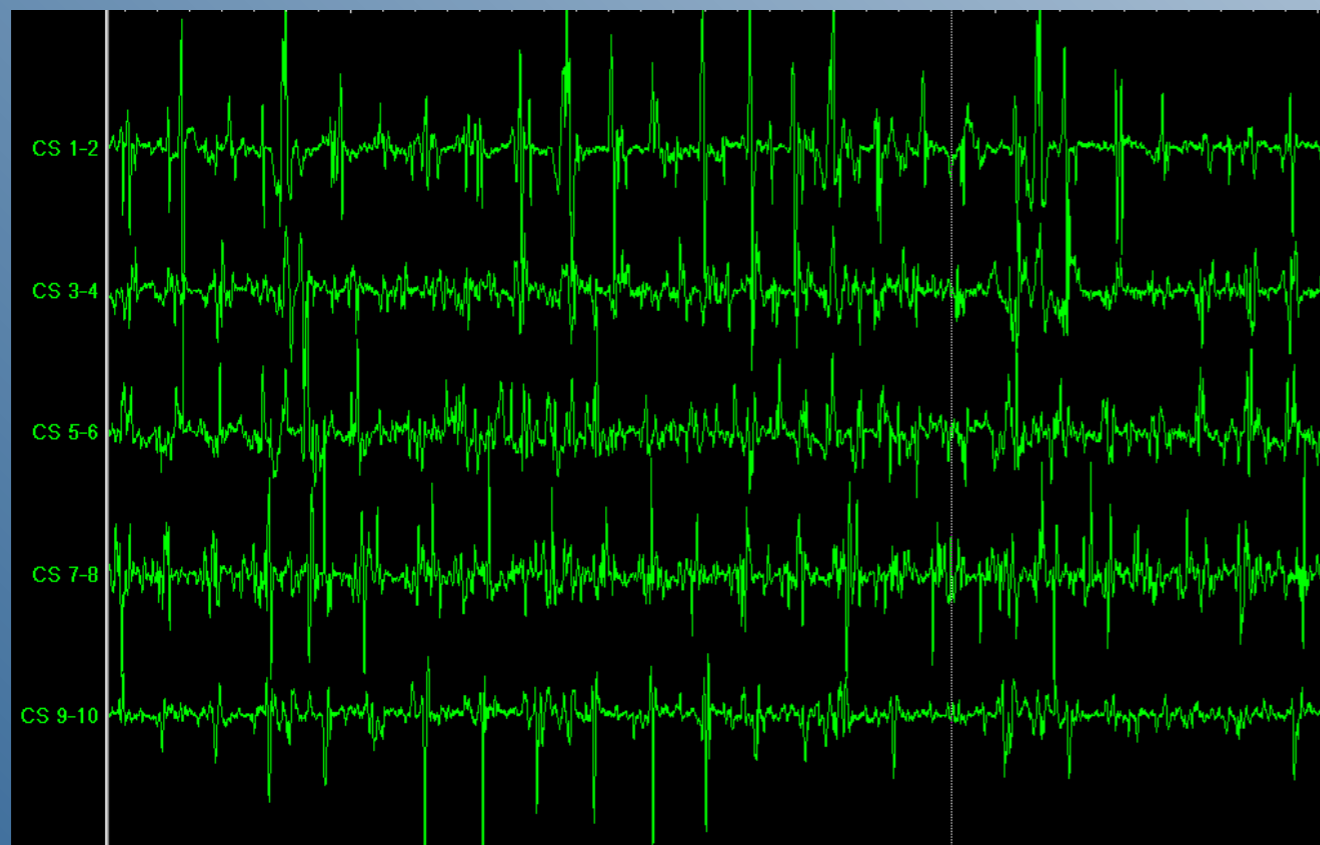


Different complexity

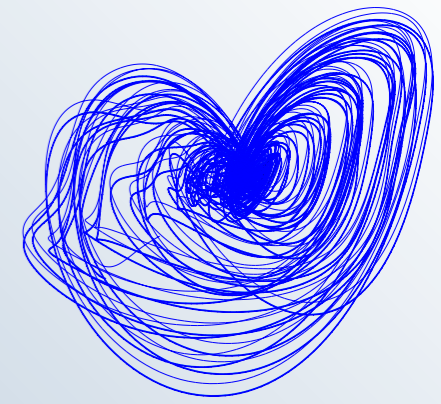


- Fibrillation in Ventricles is *smooth*
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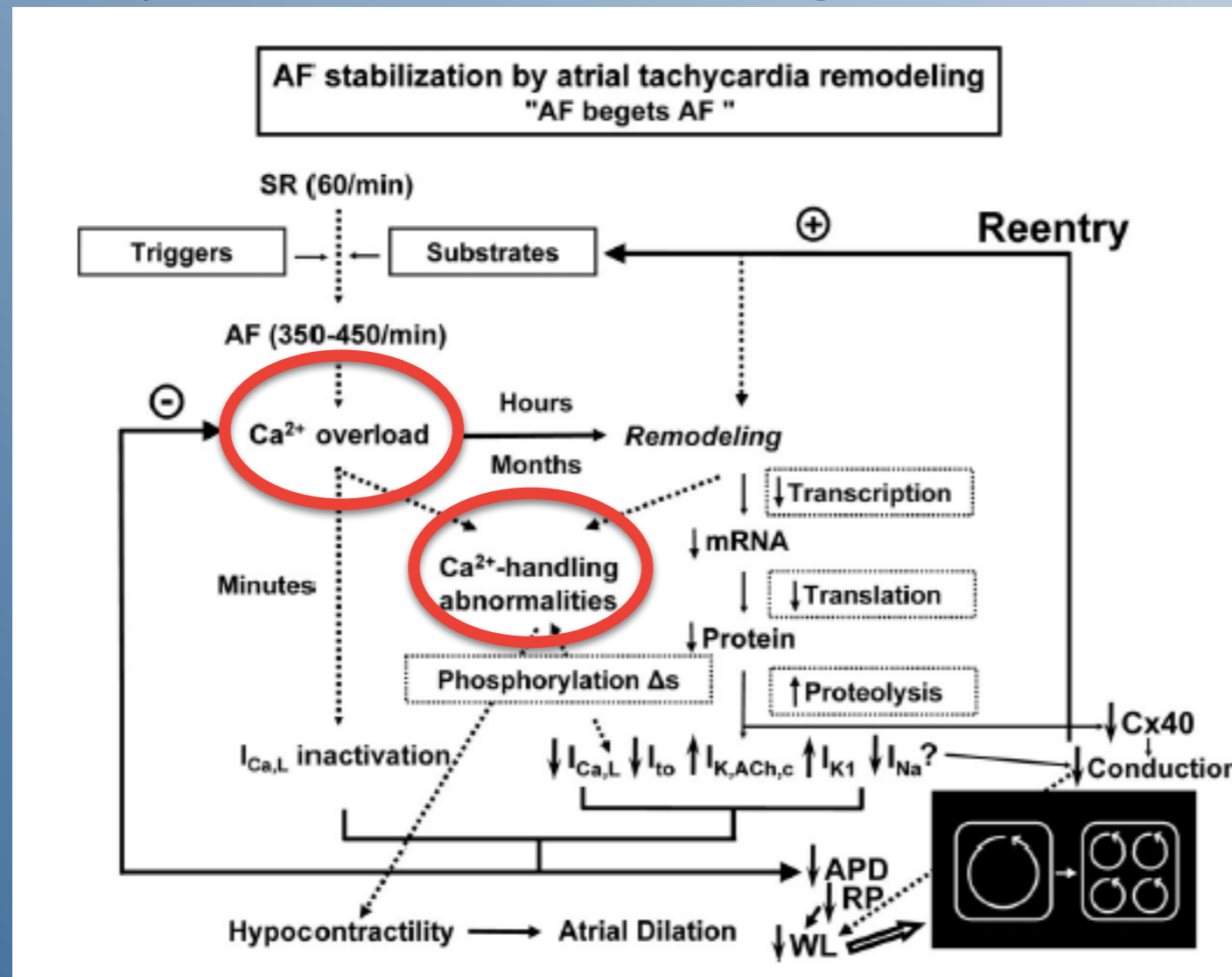
FA catheter recording



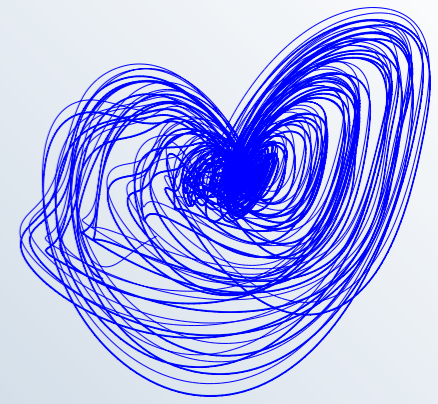
AF for EPs



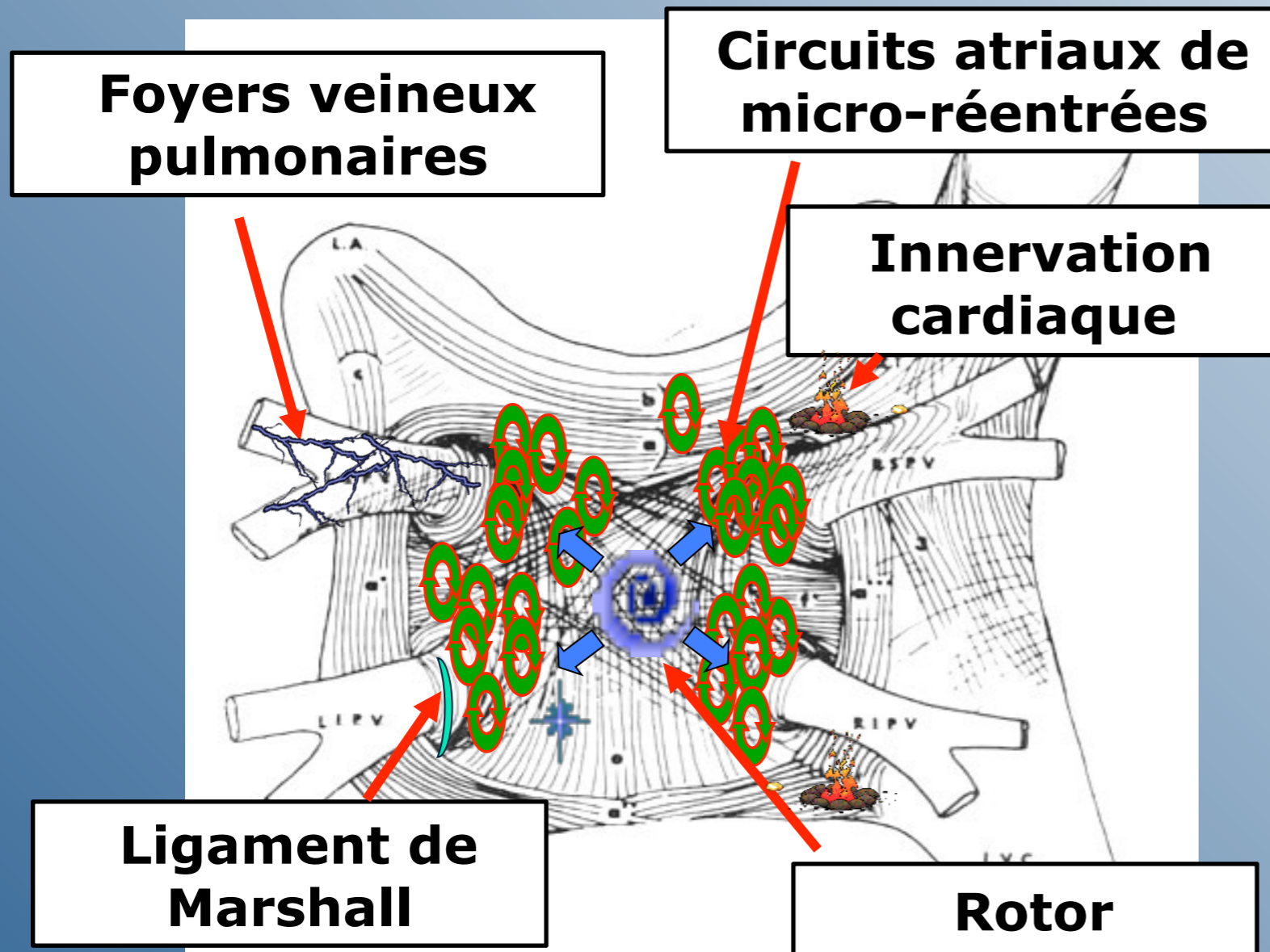
Many intricate down/up regulations



AF for MDs

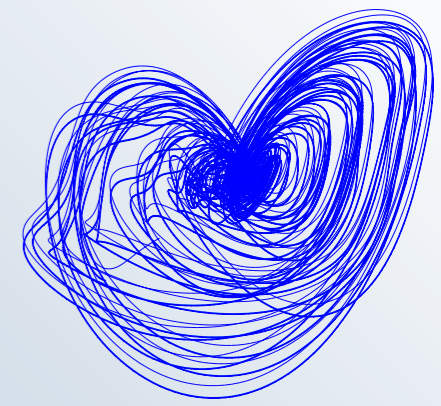


A bit messy!



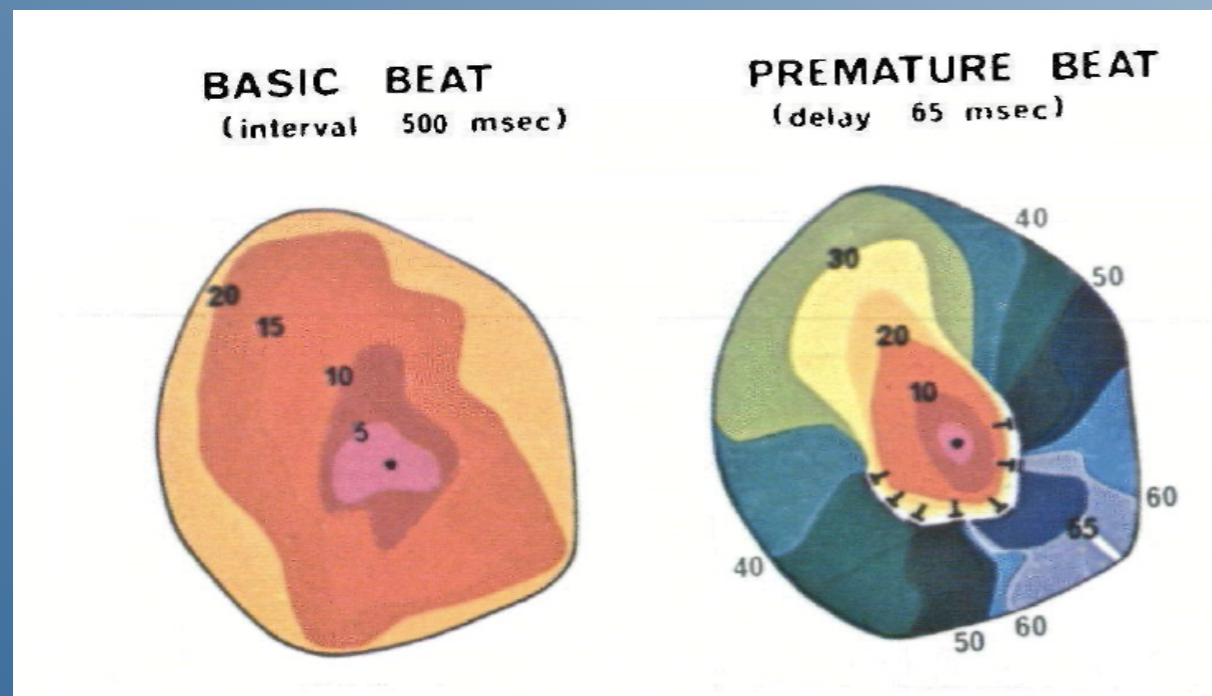
➔ Competing views, contradictory

Anatomical versus Functional



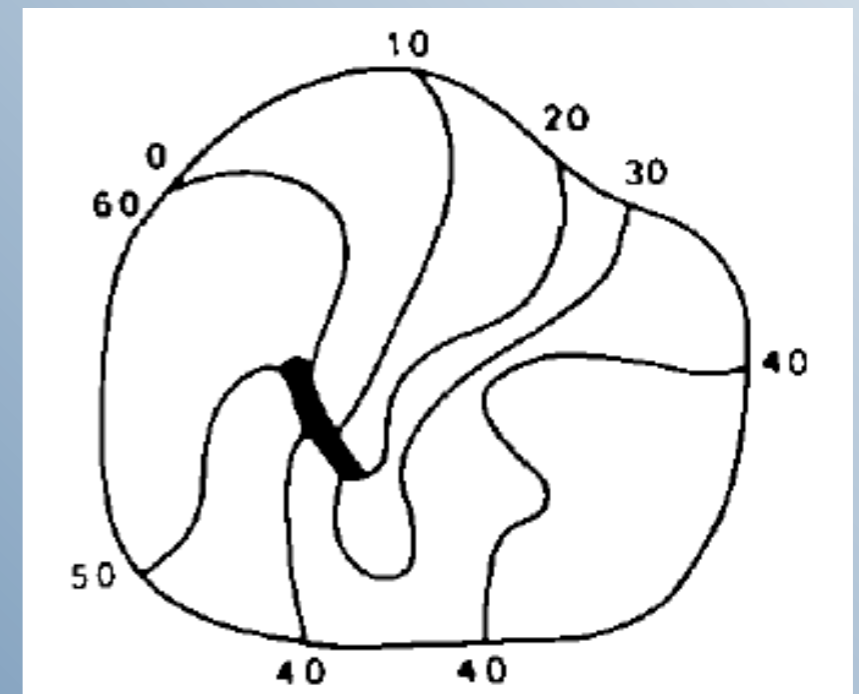
- The very old and unresolved problem is :
 - ➔ How does A/V Fib *spontaneously* start and maintain, especially *without* any *anatomical* signs of disorder?

Functional reentry



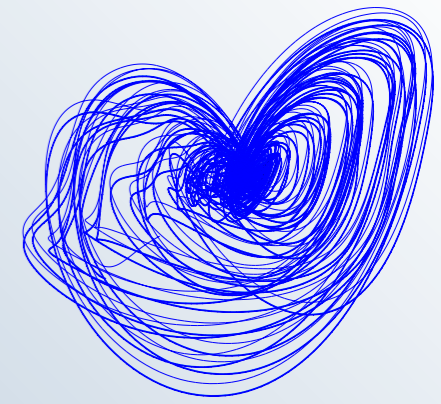
Allessie 1973/76

Wavelength criterion



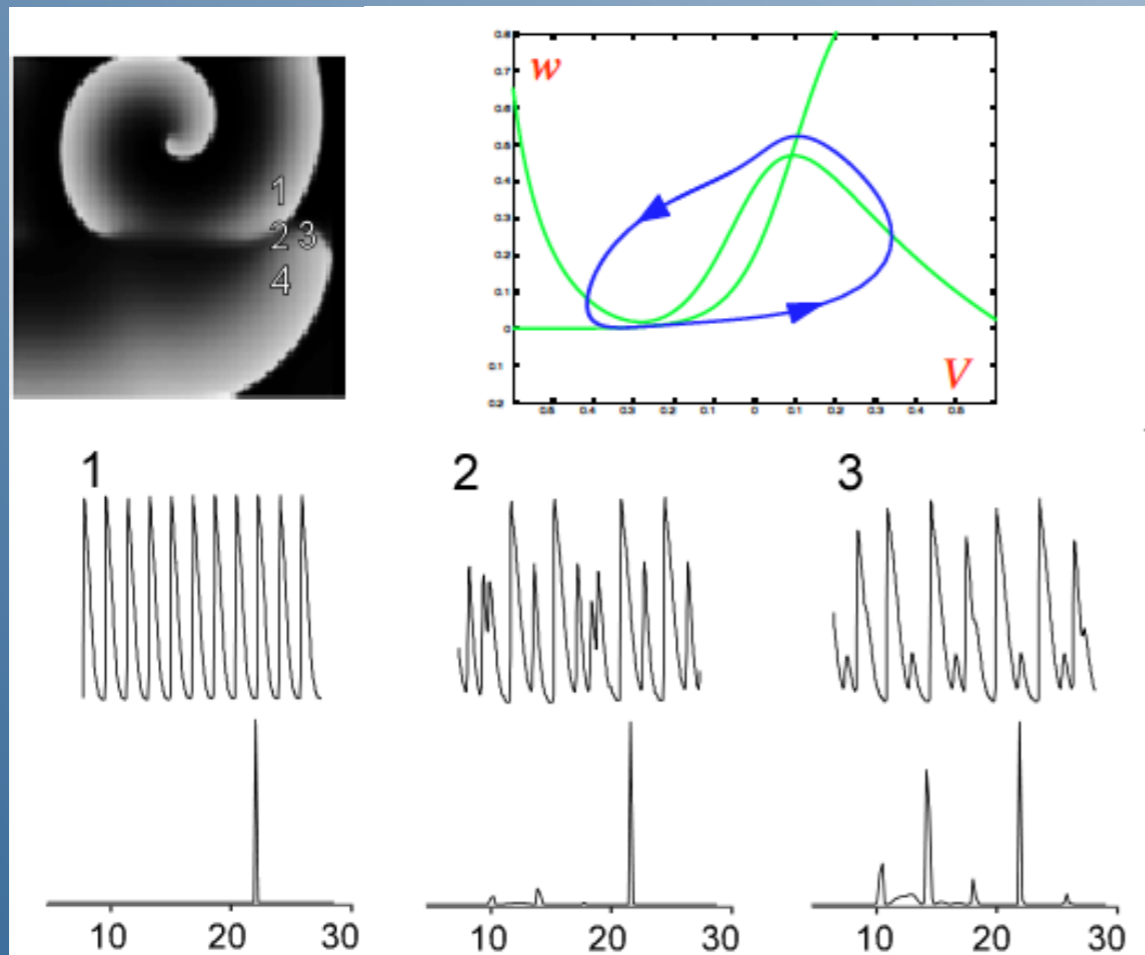
Allessie 1986

Two main contradictory views



- « Rotors » versus « fragmentation »

Reaction-Diffusion model

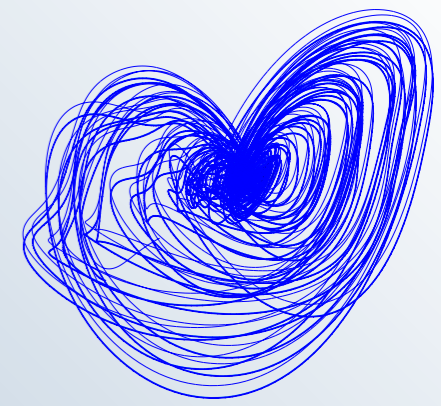


Defect mediated



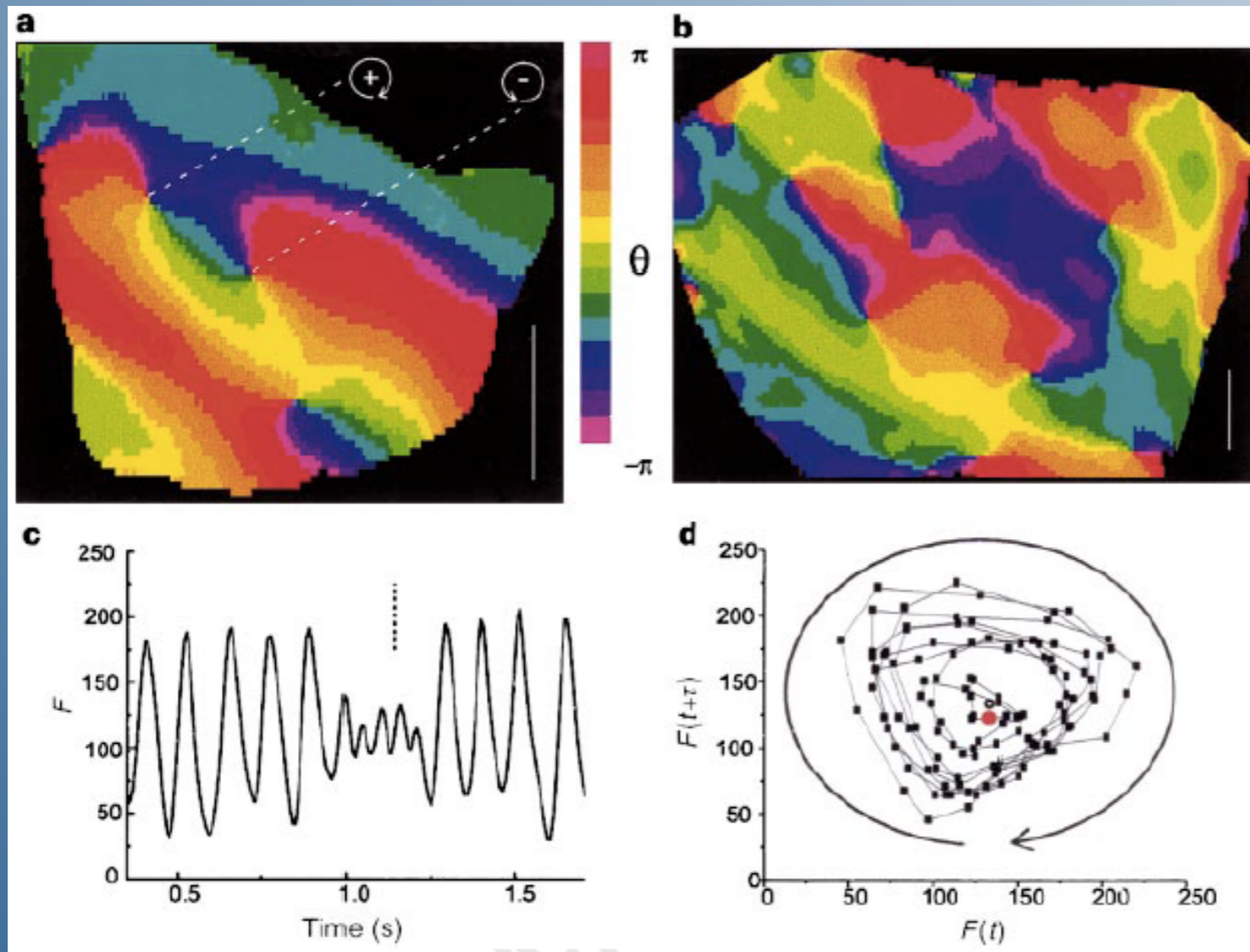
Fenton et. al 2002

Two main contradictory views



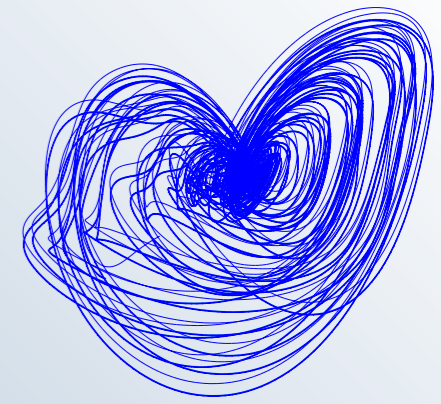
- « Rotors » versus « fragmentation »

Ventricles phase mapping



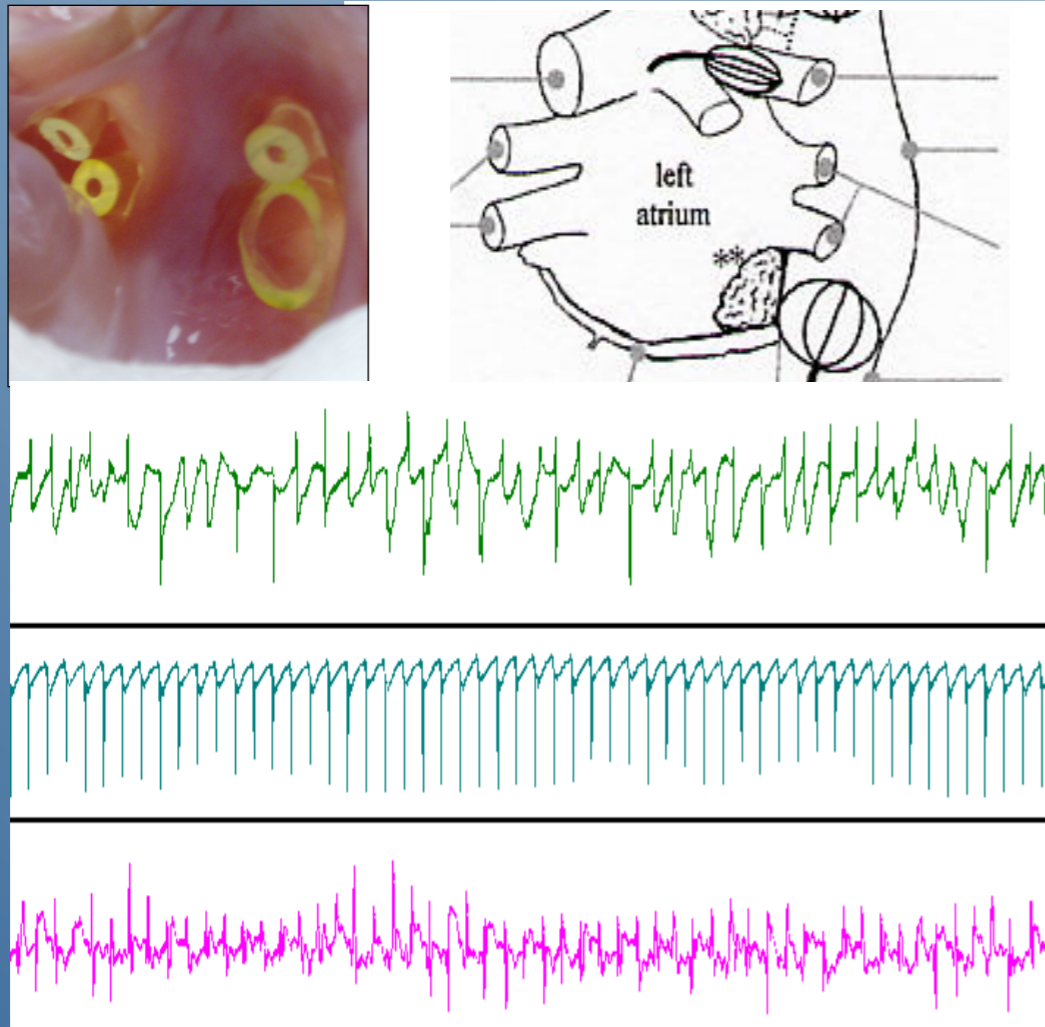
Jalife et al. 1998

Two main contradictory views

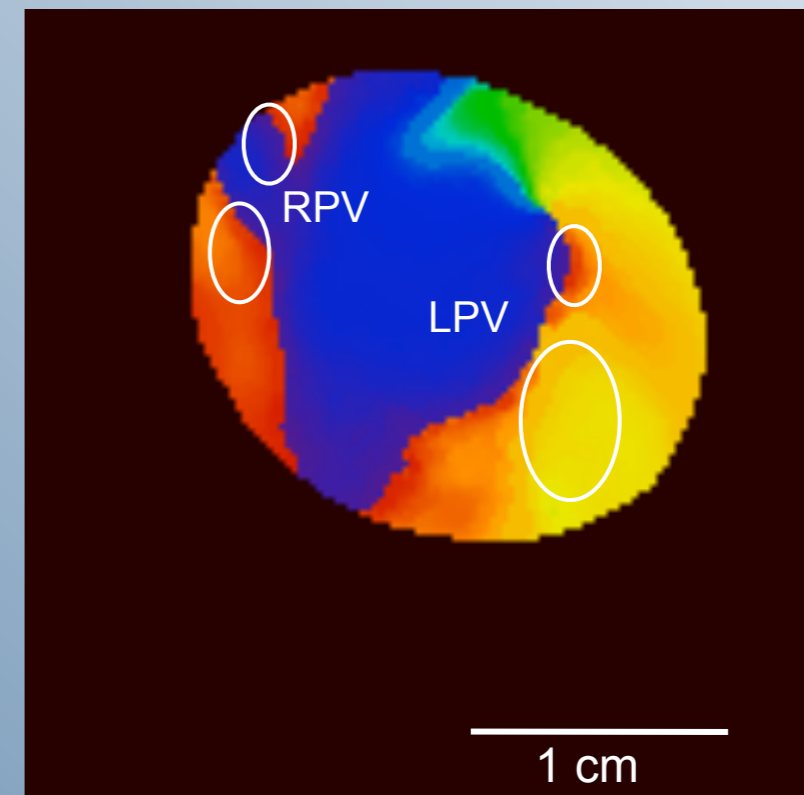


- « Rotors » versus « fragmentation »

Left Atrium

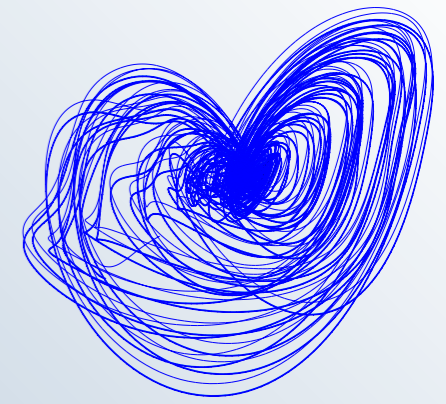


Phase mapping



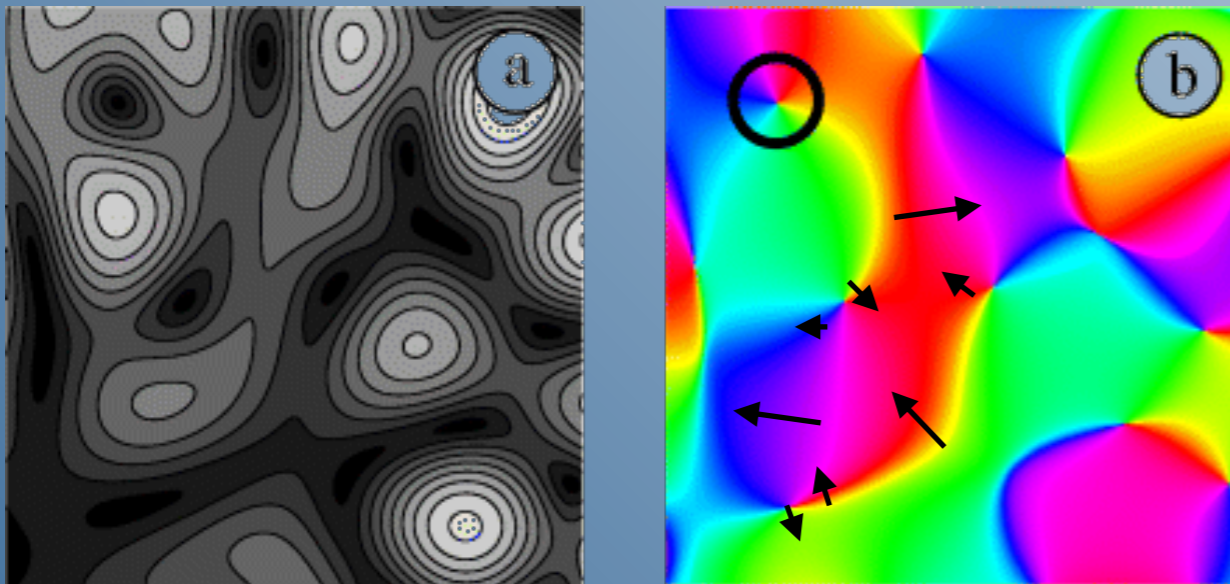
Kalifa et al. 2007

Something went wrong: Dubious mapping !



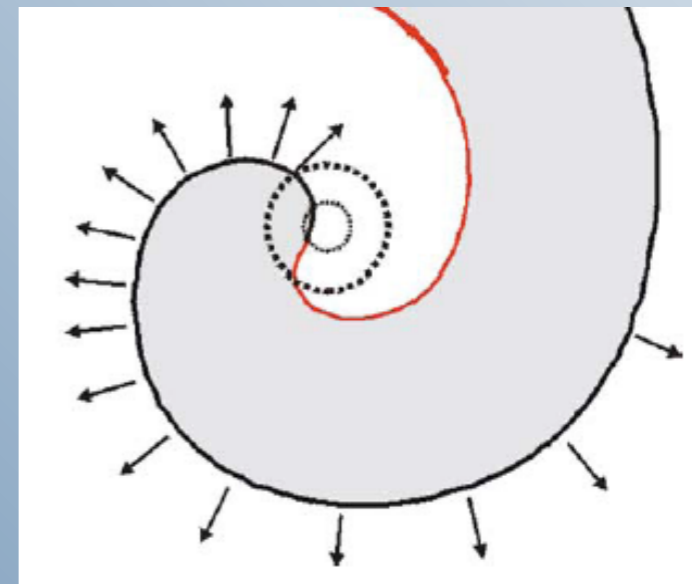
$$\rho(x, t)e^{i\varphi(x, t)}$$
$$\vec{J} = \rho^2 \vec{\nabla} \varphi$$

Speckle random phase defects



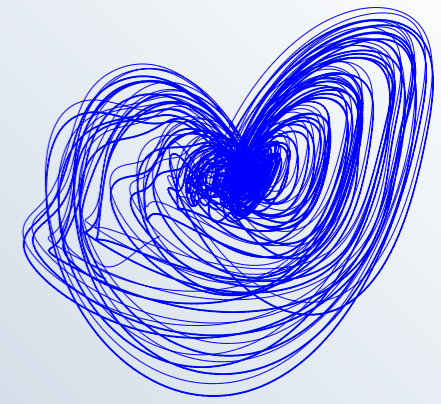
$$\vec{\nabla} \cdot \vec{J} = 0 \quad \vec{\nabla} \times \vec{J} \neq 0$$

Spirals



$$\vec{\nabla} \times \vec{J} = 0 \quad \vec{\nabla} \cdot \vec{J} \neq 0$$

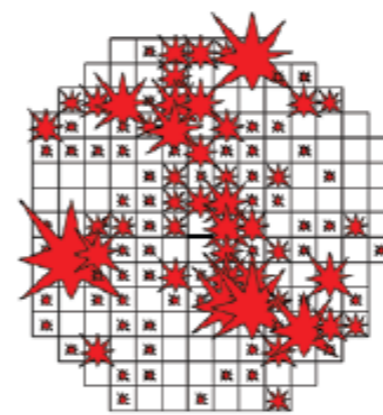
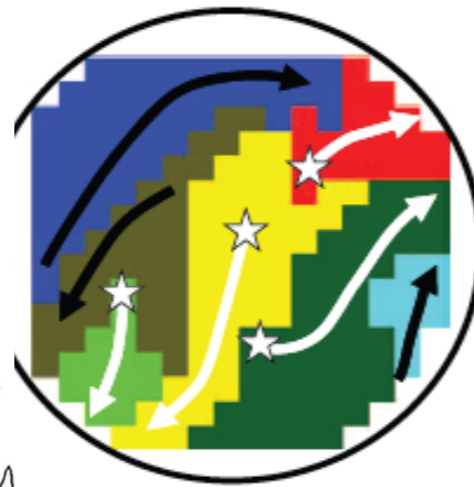
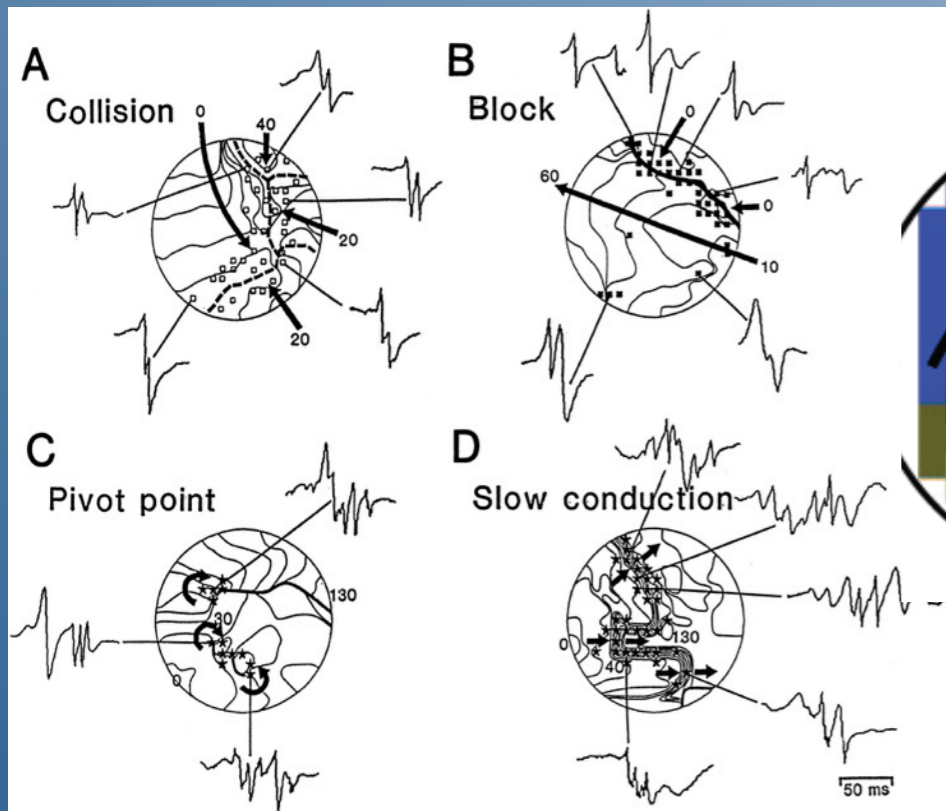
Two main contradictory views



- Complex morphologies and paths

Low voltage too $\rho \approx 0$ but no phase singularity

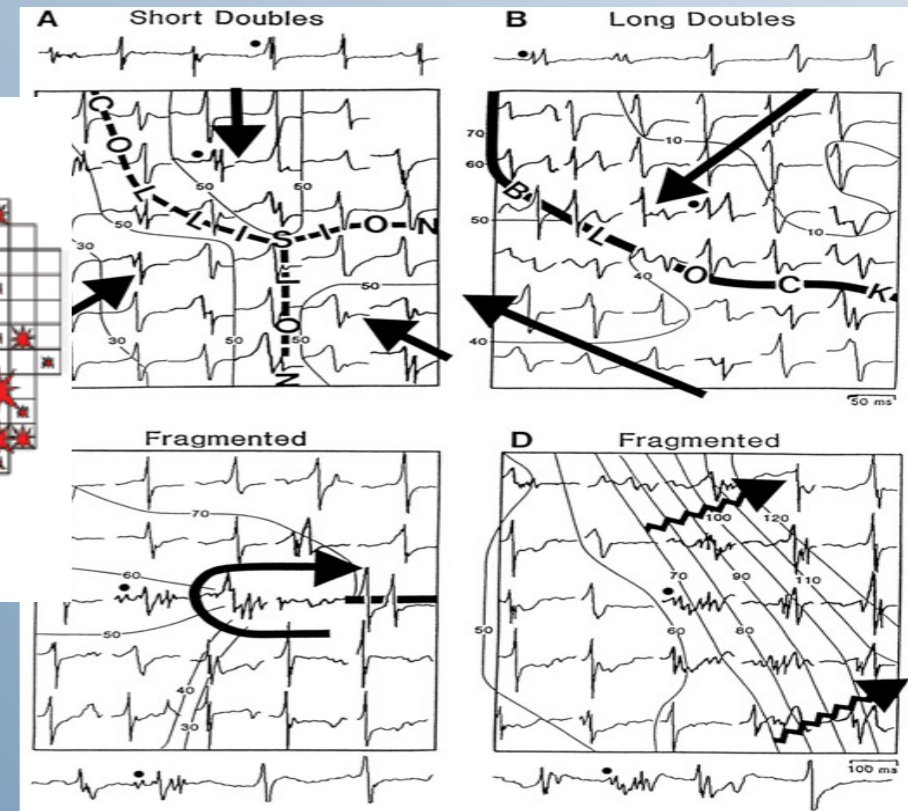
➔ The battle still rages!



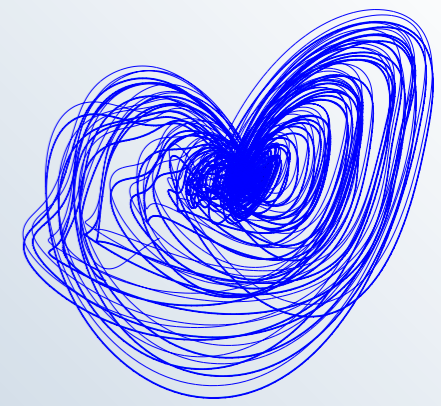
2.06 /cm² /sec

Konings et al. 1997

$$\vec{\nabla} \cdot \vec{J} \neq 0$$



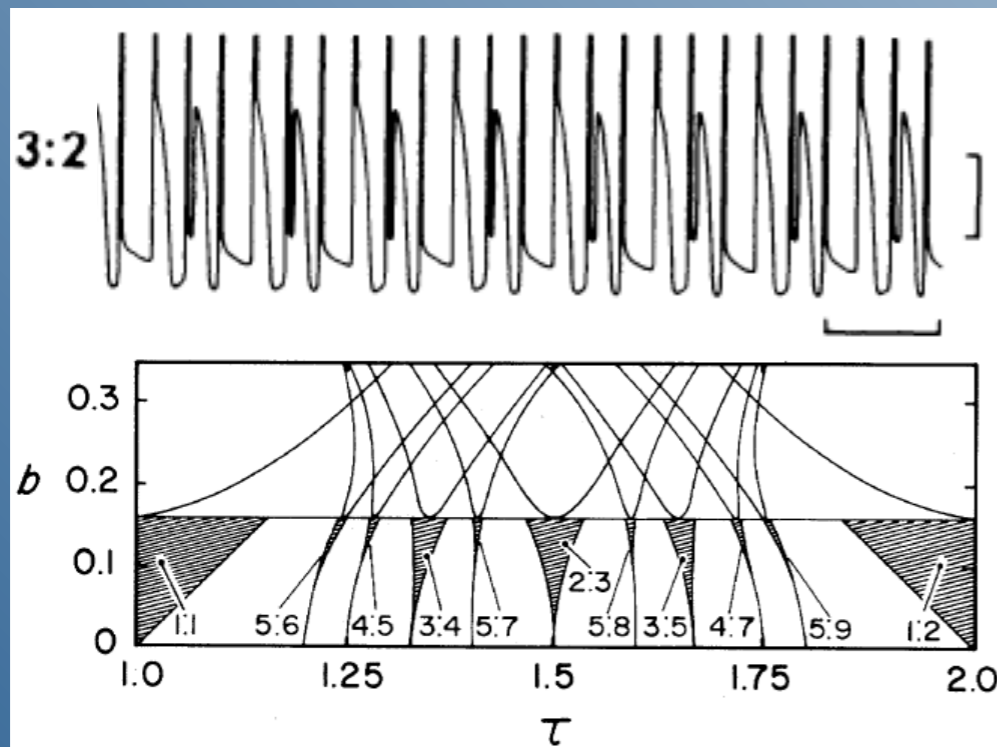
Chaos in the data?



- Chaos has been observed for *periodic stimulation* and spontaneously *before onset*

Periodic forcing of limit cycle :

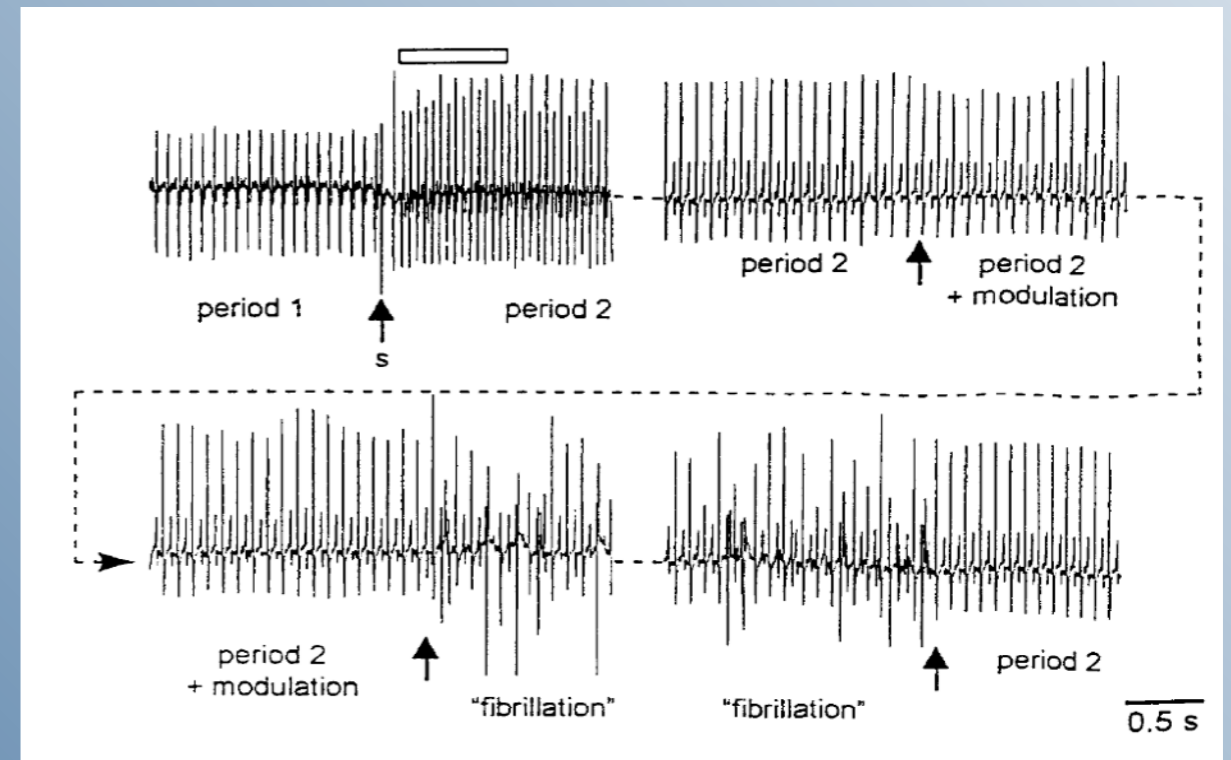
$$\theta_i = \theta_{i-1} + \Omega + G(\theta_{i-1})$$



Glass et al. 1983

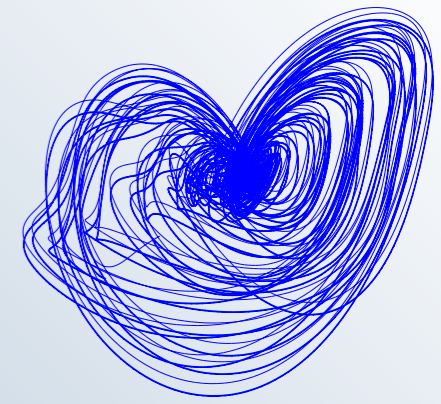
Spontaneous onset and return:

Time series



Garfinkel et al. 1999

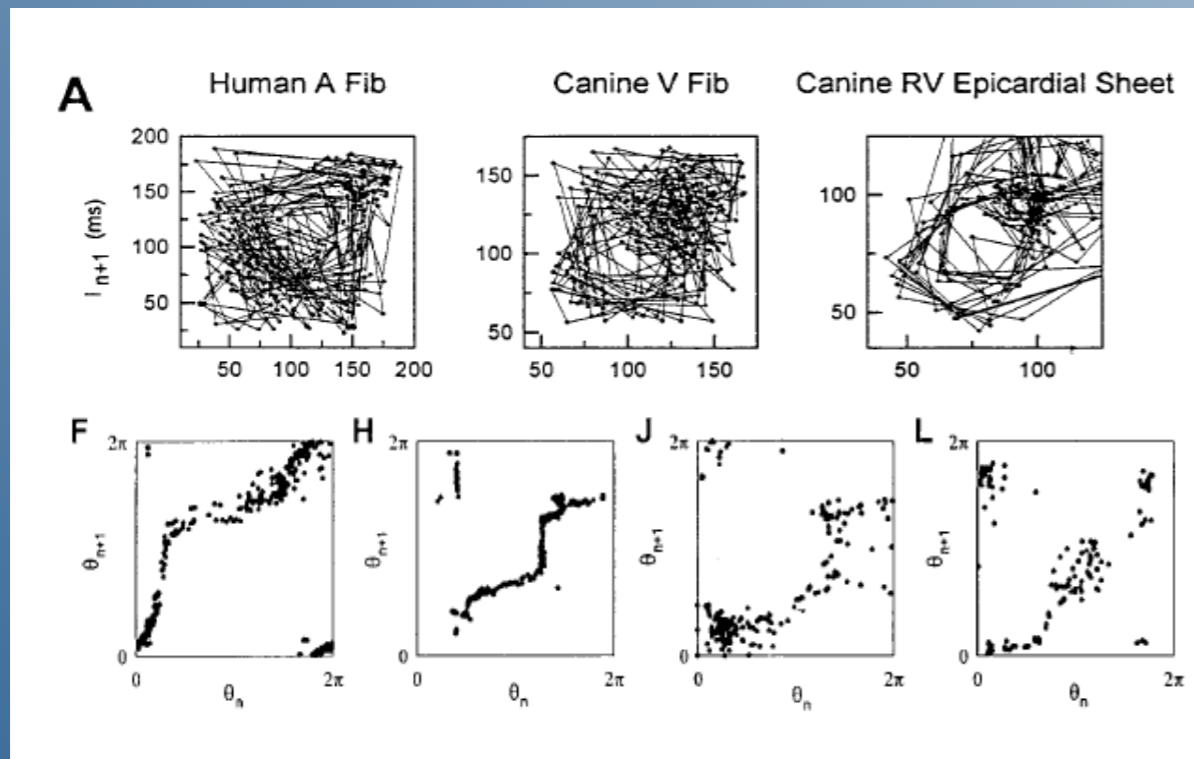
Chaos in the data?



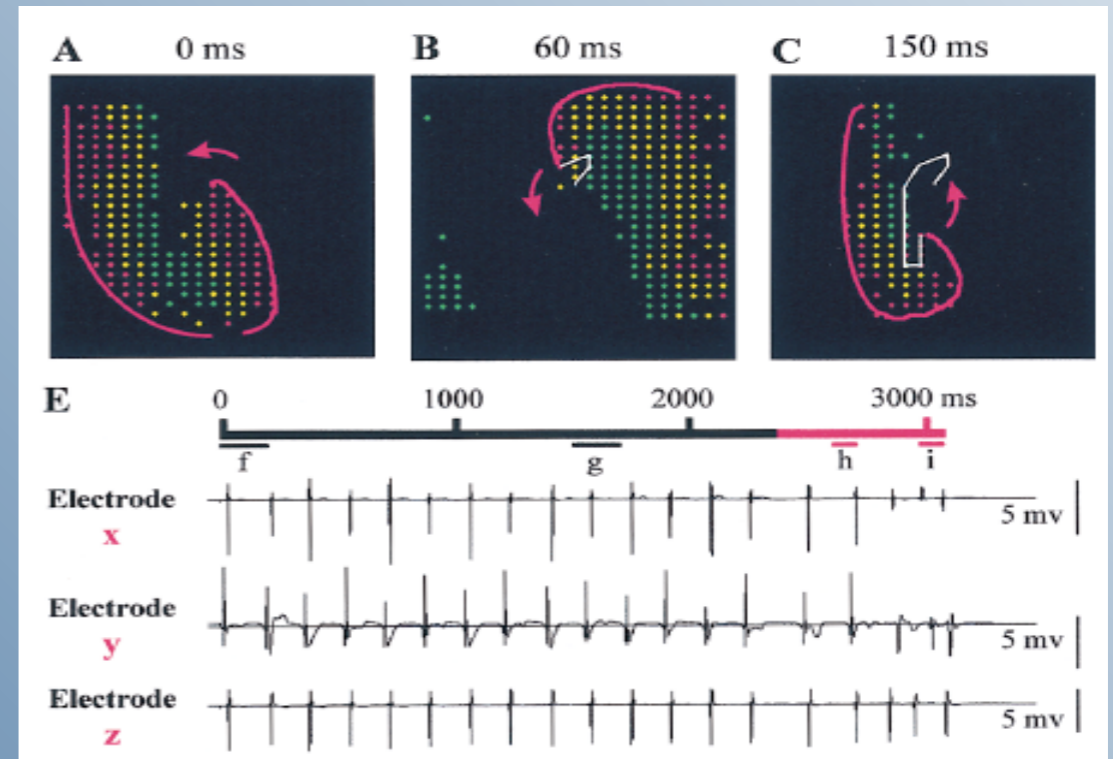
- Chaos has been observed for *periodic stimulation* and spontaneously *before onset*

Quasi Periodicity before onset :

Return maps

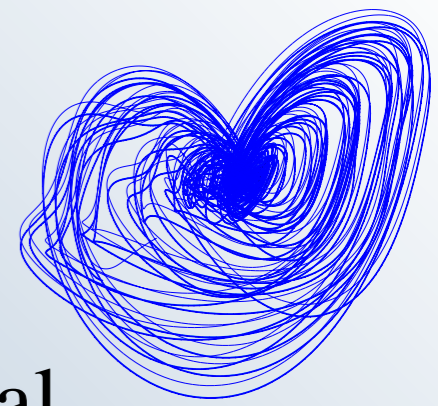


Spiral tip



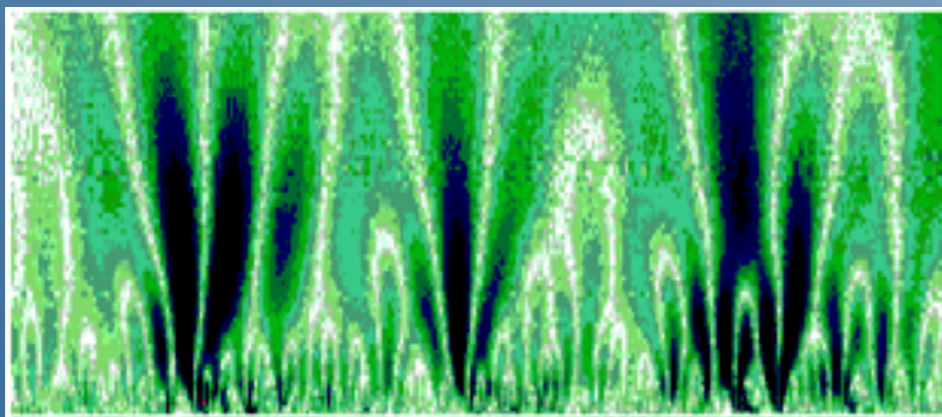
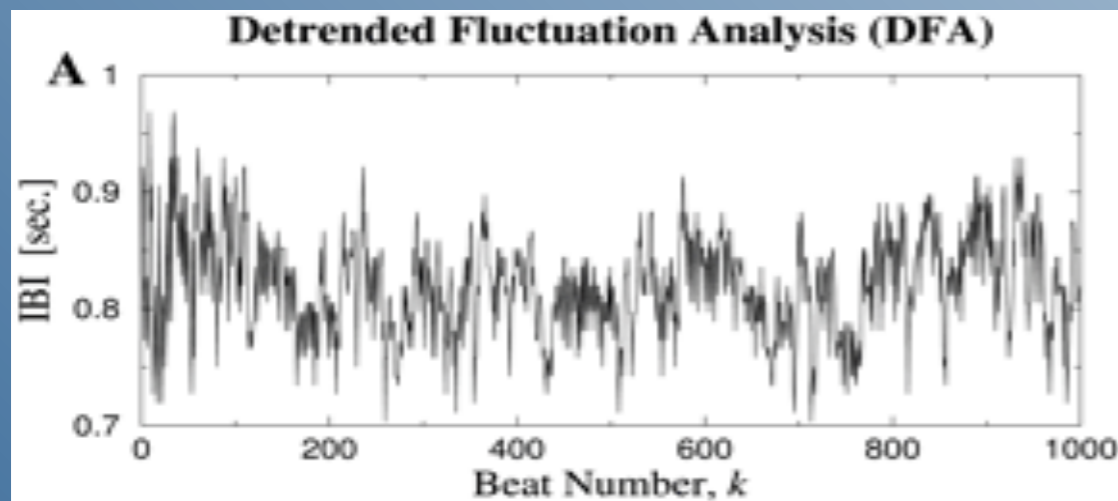
Garfinkel et al. 1999

Intermittency in healthy patients!



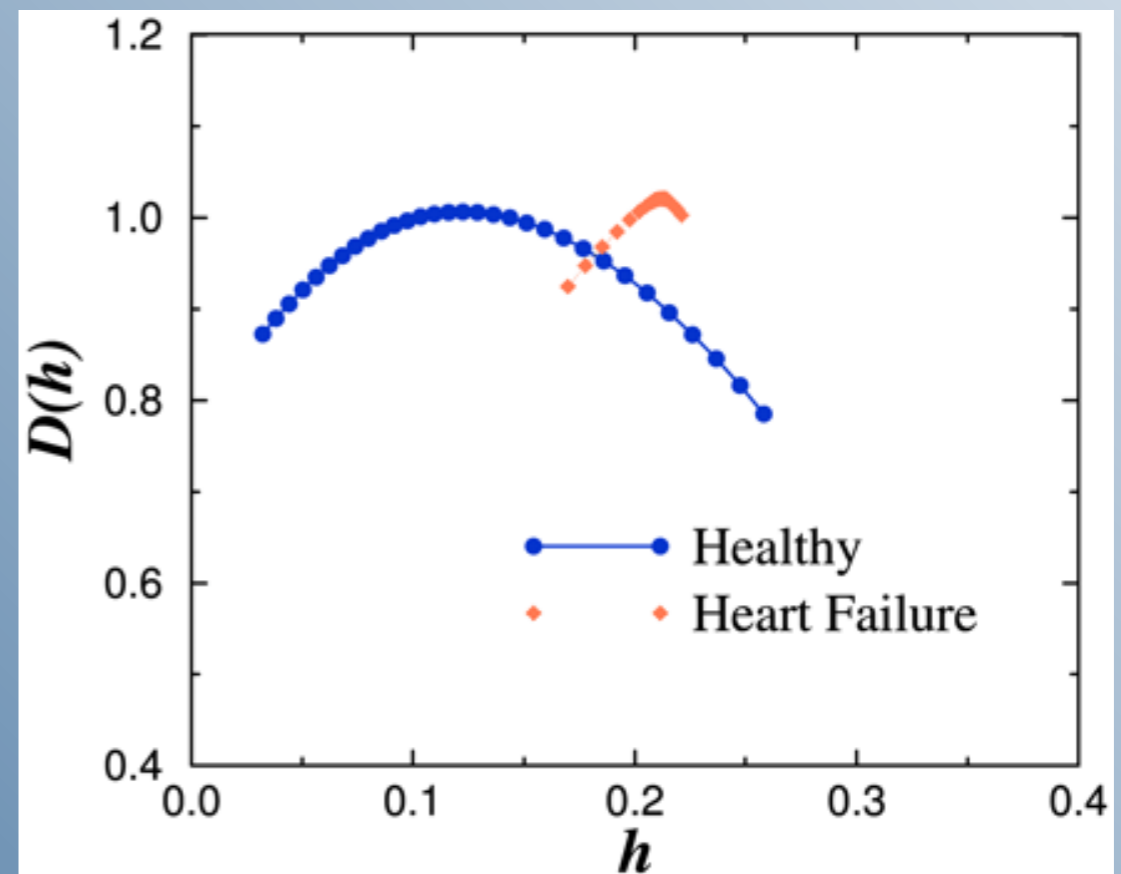
- In sinus rhythm, heart rate variability shows multifractal scaling. Heart failure exhibits monofractal scaling.

Holter tachogram WTMM analysis



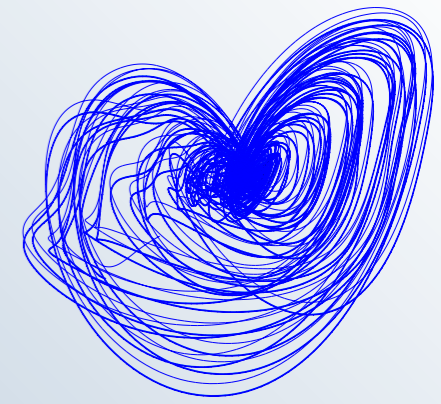
MF spectrum

$$\delta I \sim \Delta t^h \text{ with proba } p(h) \sim \Delta t^{D(h)}$$



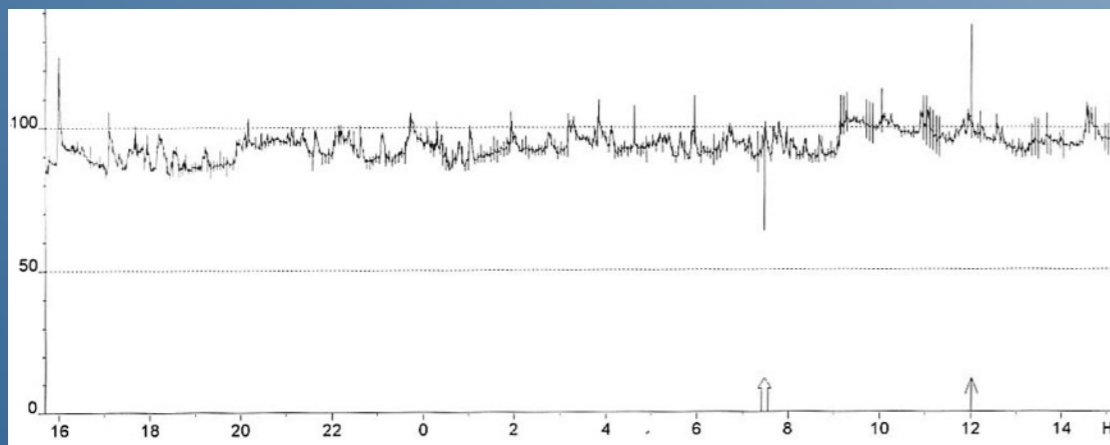
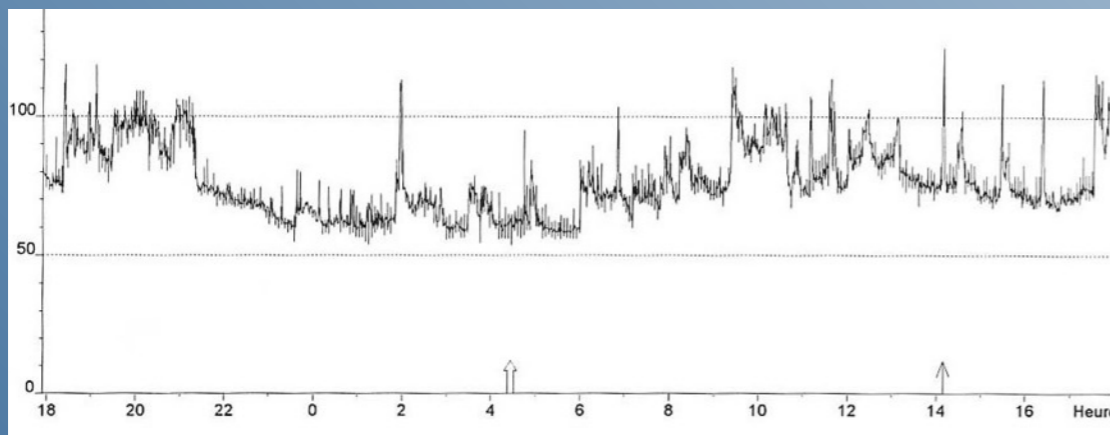
Ivanov et al. 1999

Intermittency in healthy patients!



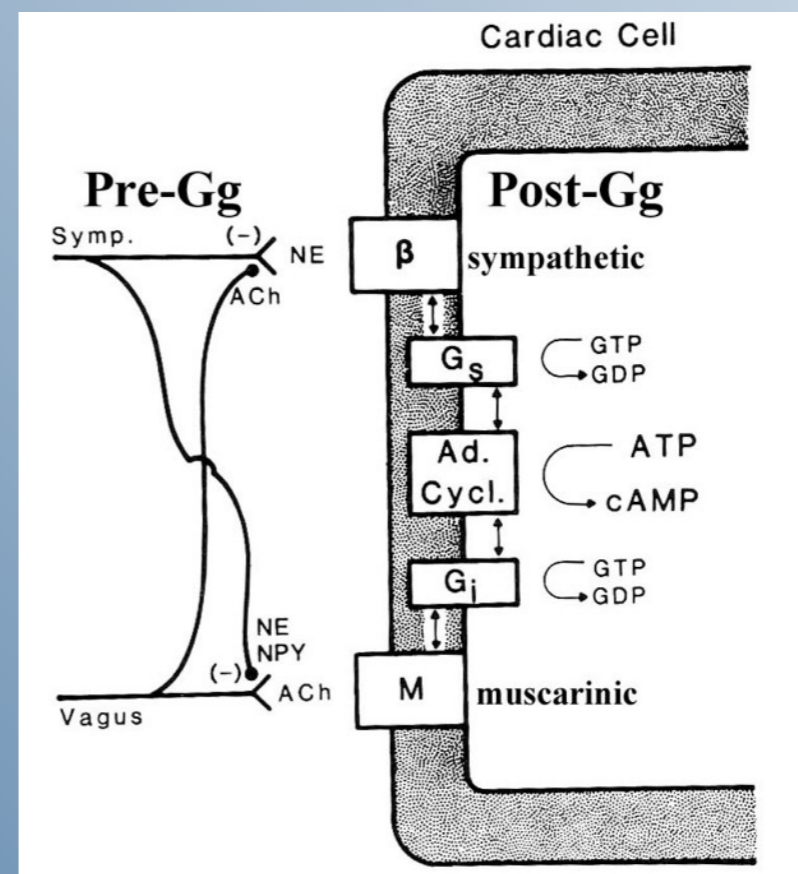
- The sinus node is sensitive to the ANS *antagonist* stimuli
- The SN comprises automatic cells *collectively* beating

Before/After denervation



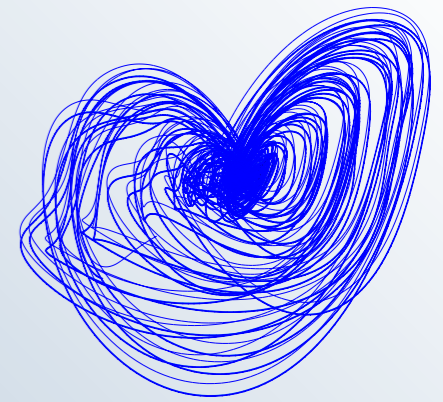
ANS feedbacks

Short time scale is $\sim 1\text{mn}$

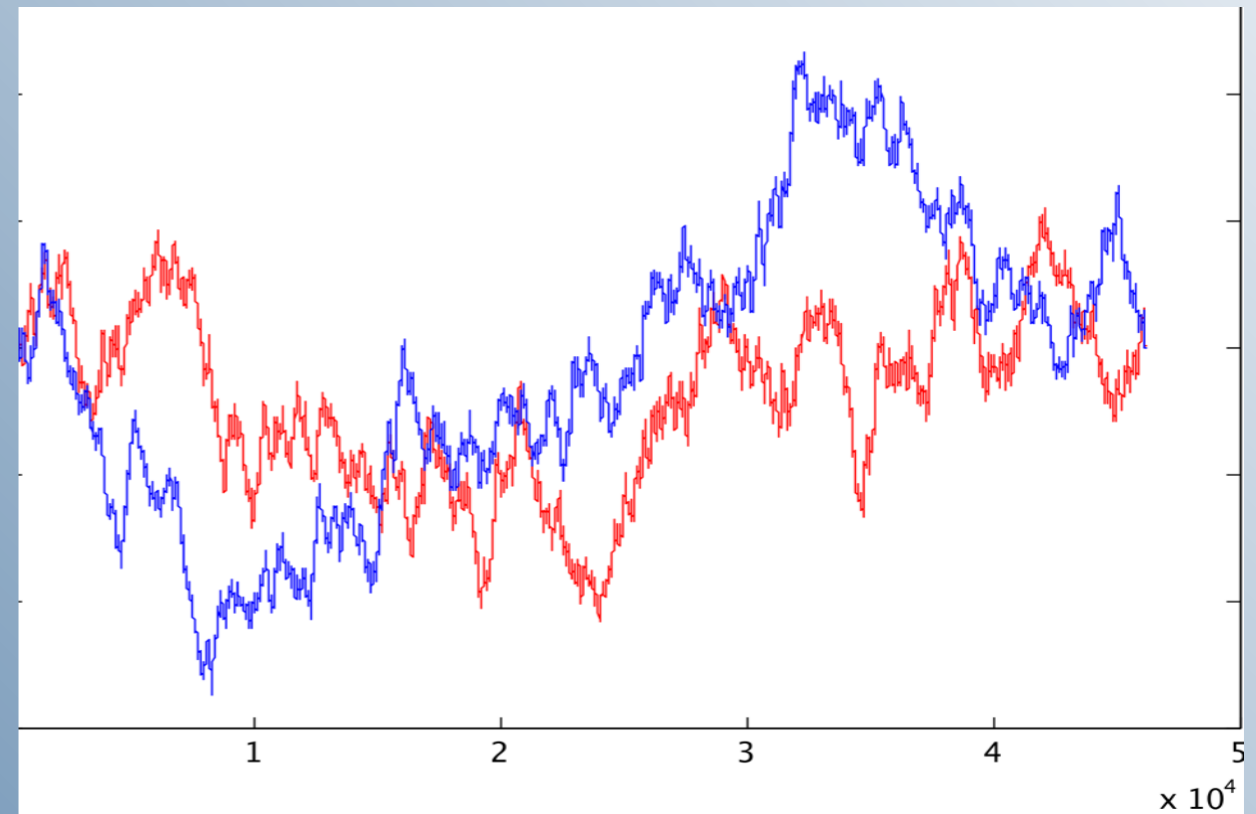
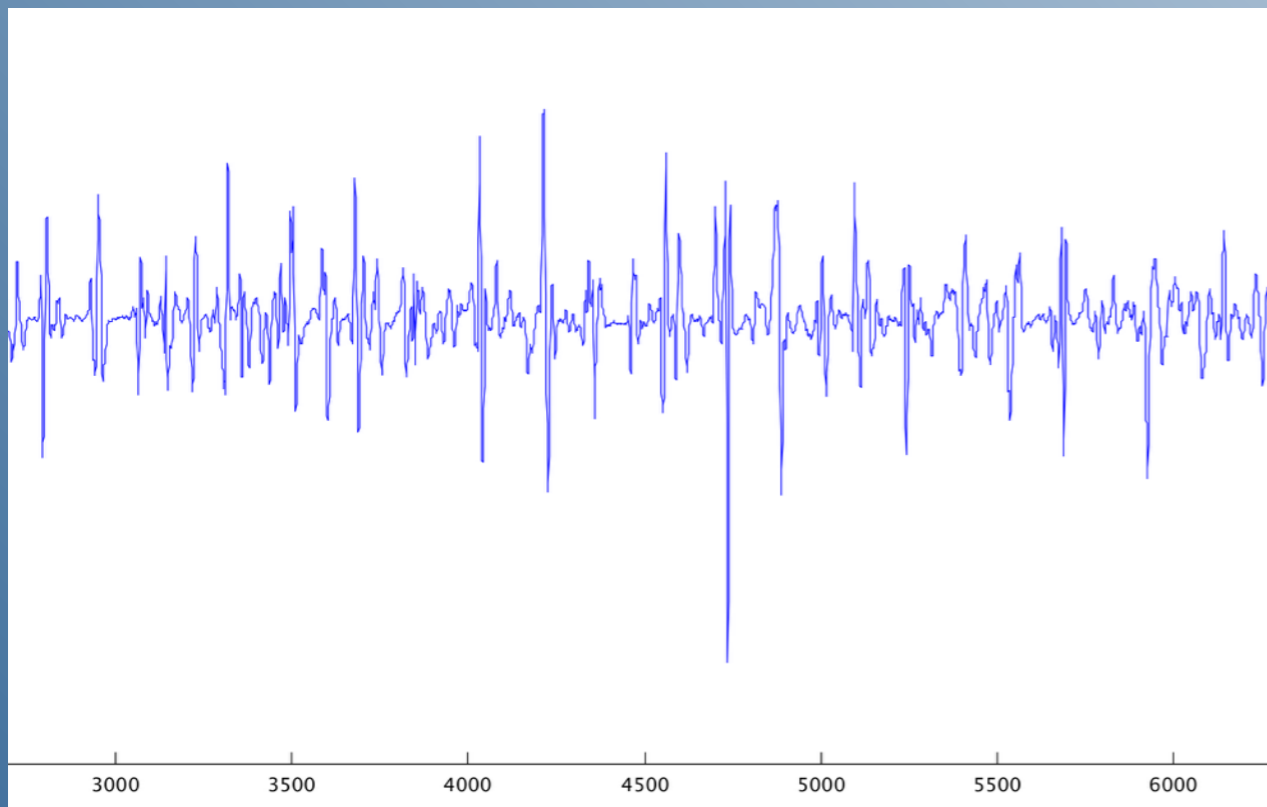


How to settle on objective ground?

The data



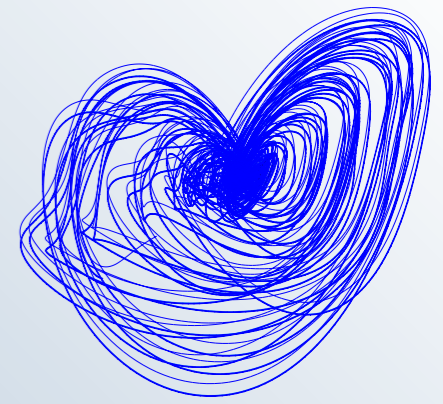
- What if we compute the phase of time series?



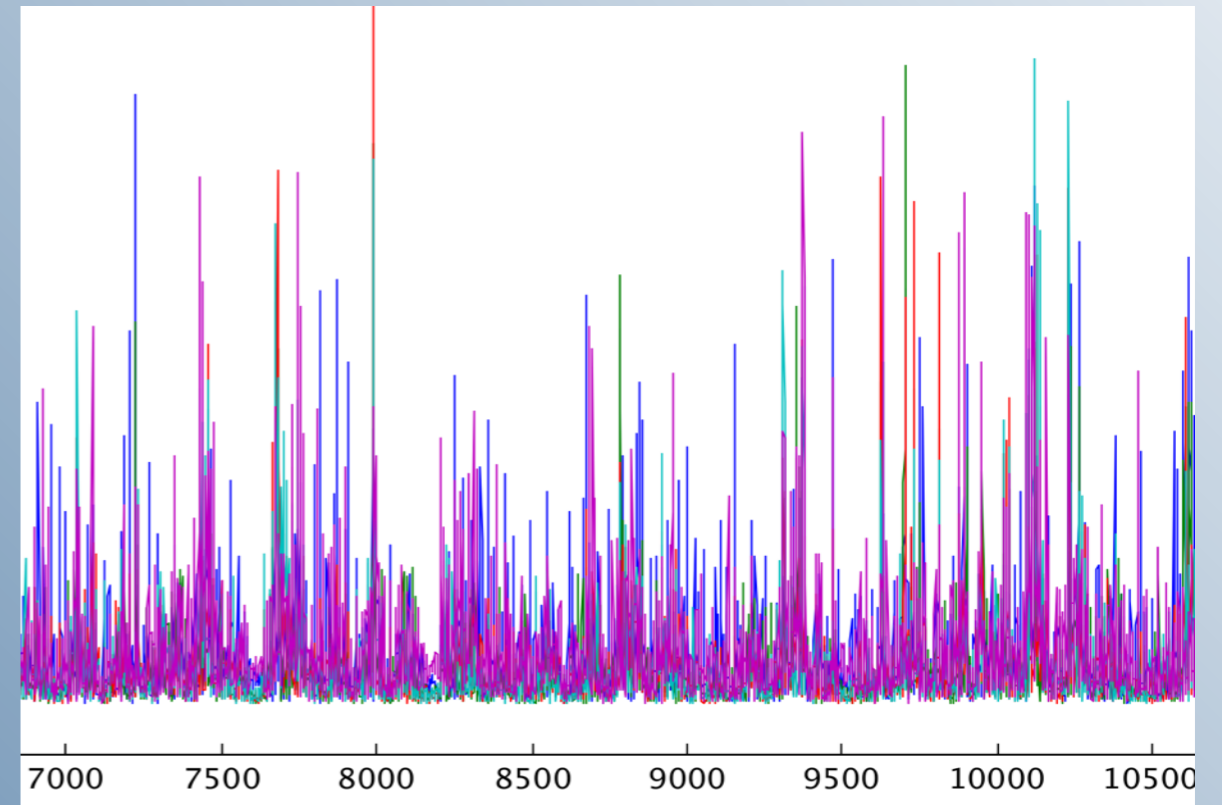
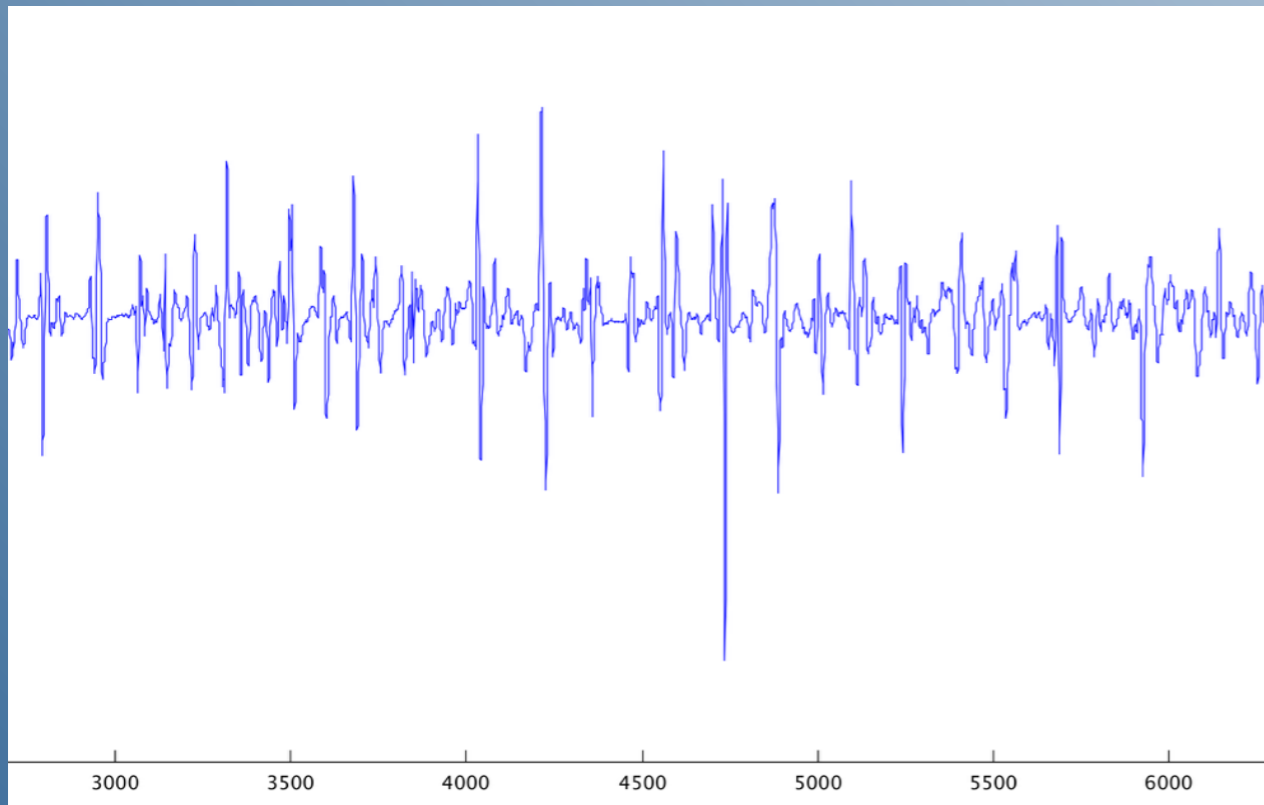
➔ Random walk with positive or negative oscillations
However Hilbert technique is weak, \mathbb{C} -wavelet is computationally heavy

How to settle on objective ground?

The data



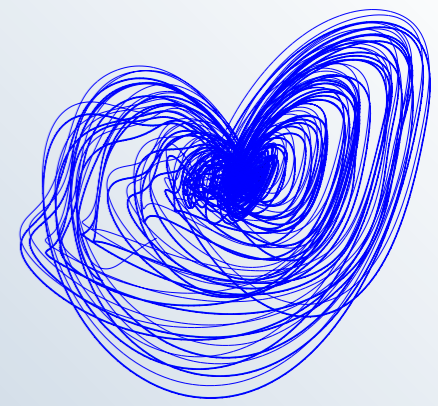
- What if we compute the phase of time series?



➔ Random walk with large deviations

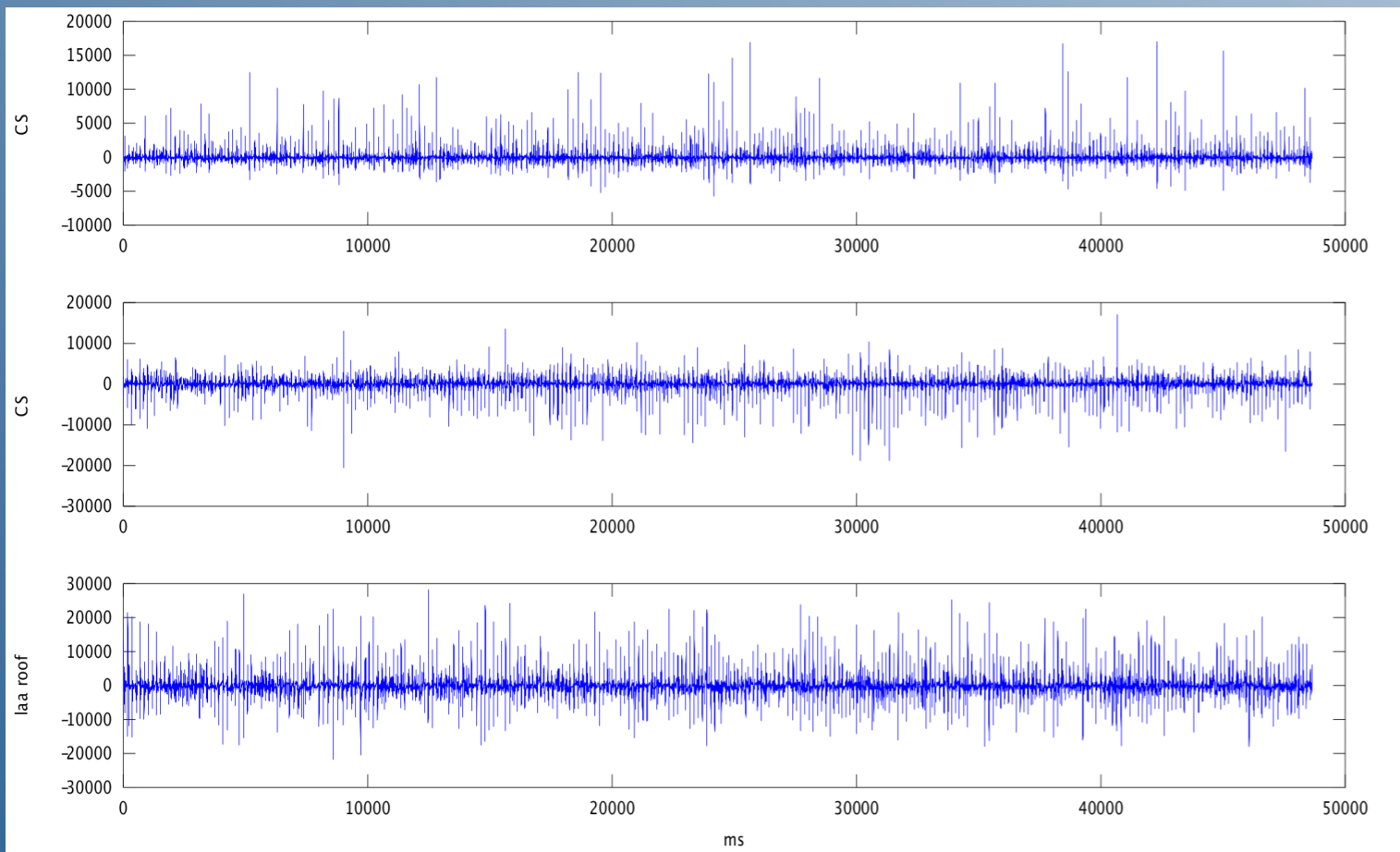
However Hilbert technique is weak, \mathbb{C} -wavelet is computationally heavy

Intermittency in the data?

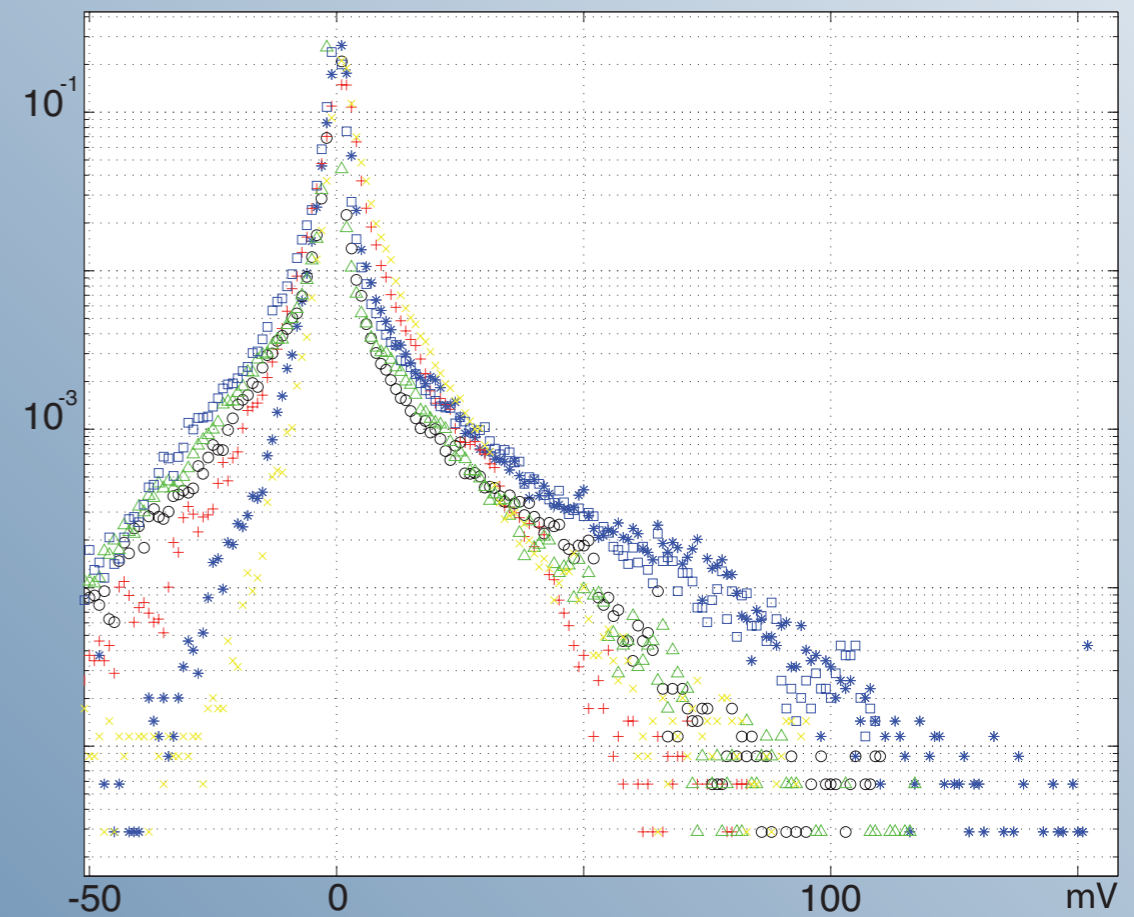


- What about amplitude fluctuations?

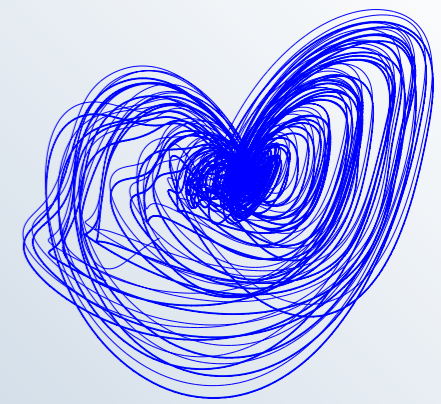
Time series



Skewed PDFs

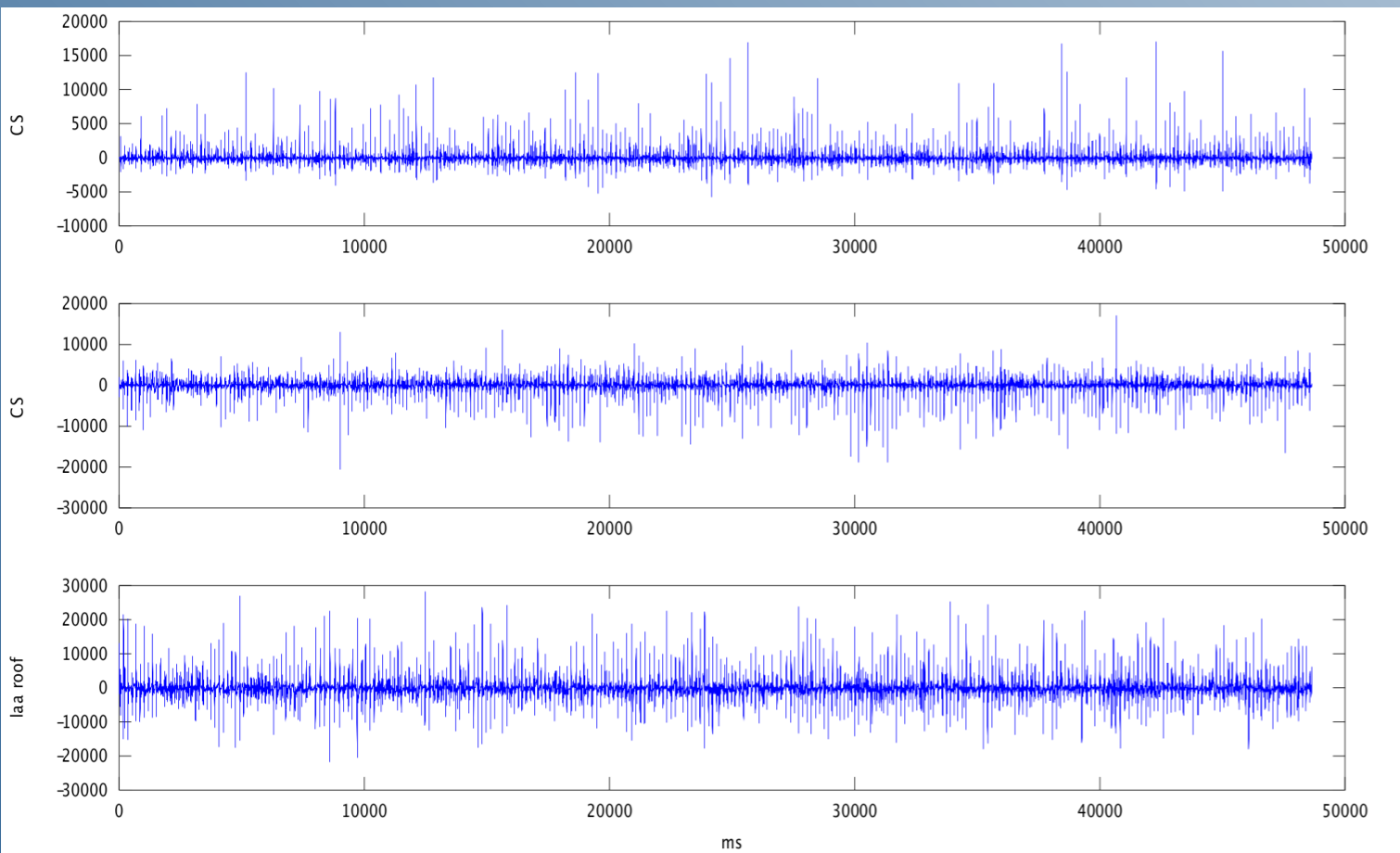


Intermittency in the data?



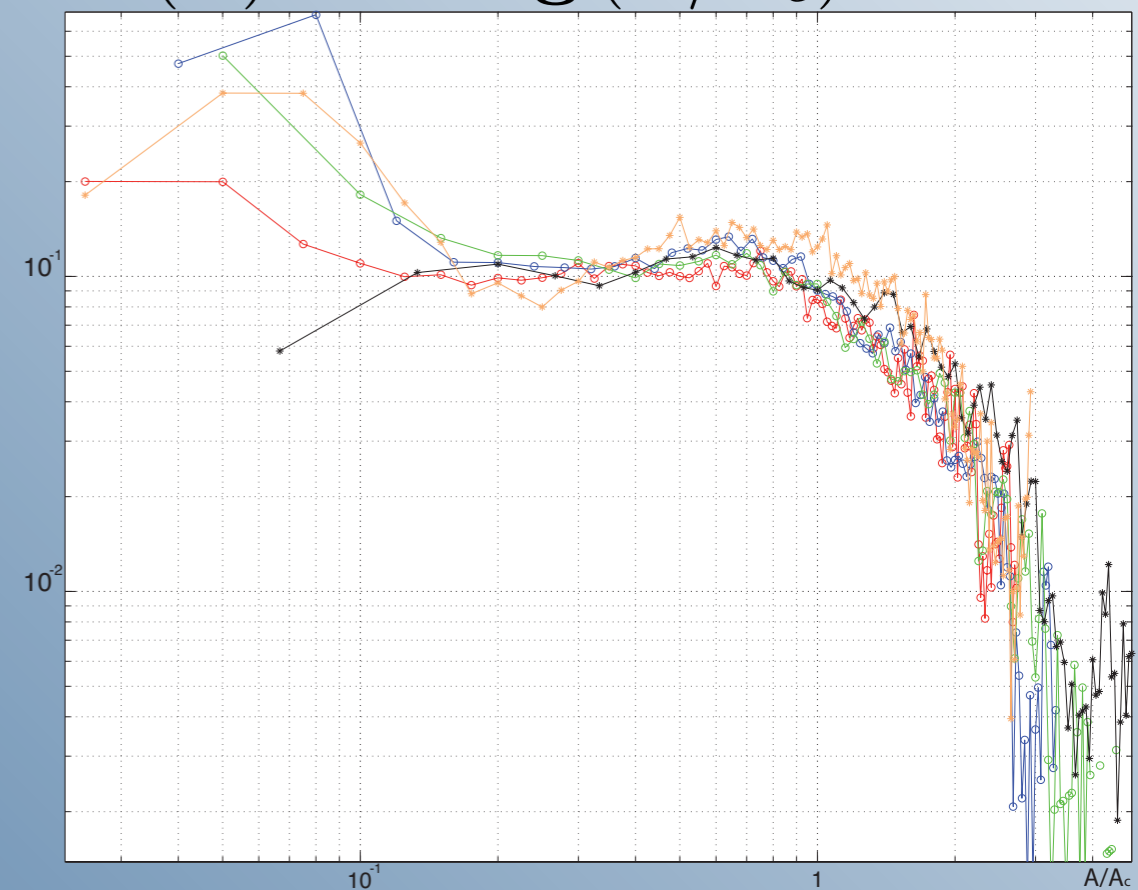
- What about amplitude fluctuations?

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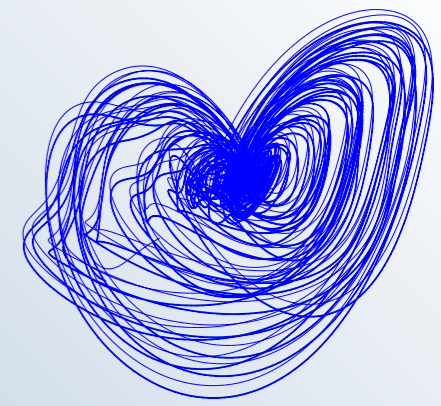
Collapse on scaling function

$$P(A) = A^{-\tau} g(A/A_c)$$



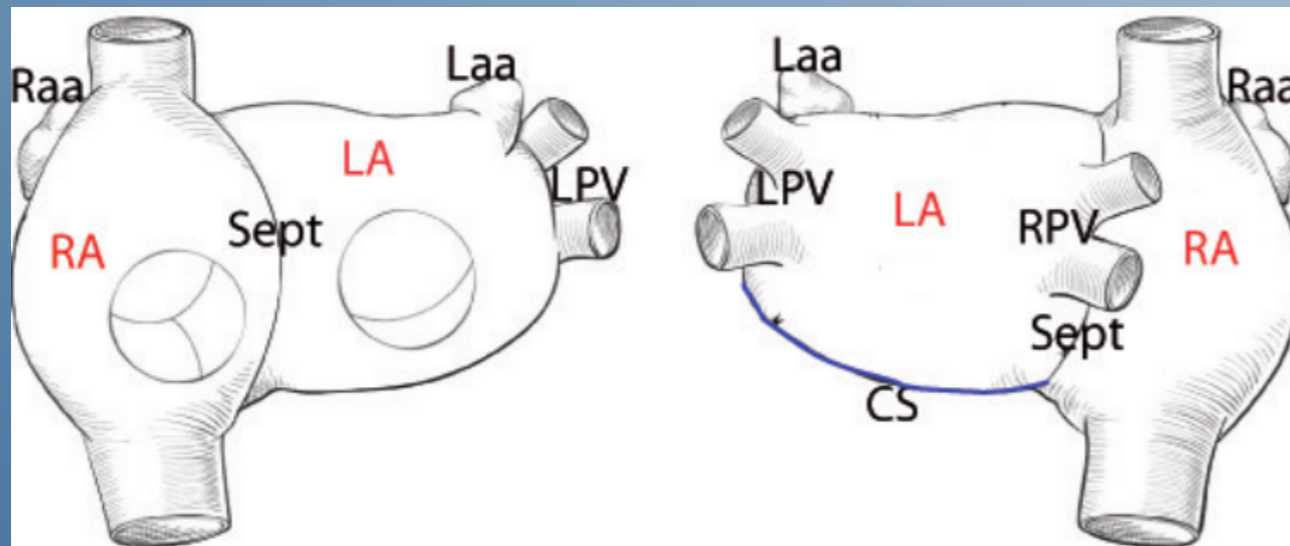
But contribution of very low amplitude must be cured...

Intermittency in the data?



- Non-universal exponents
- Are there any spatial patterns?

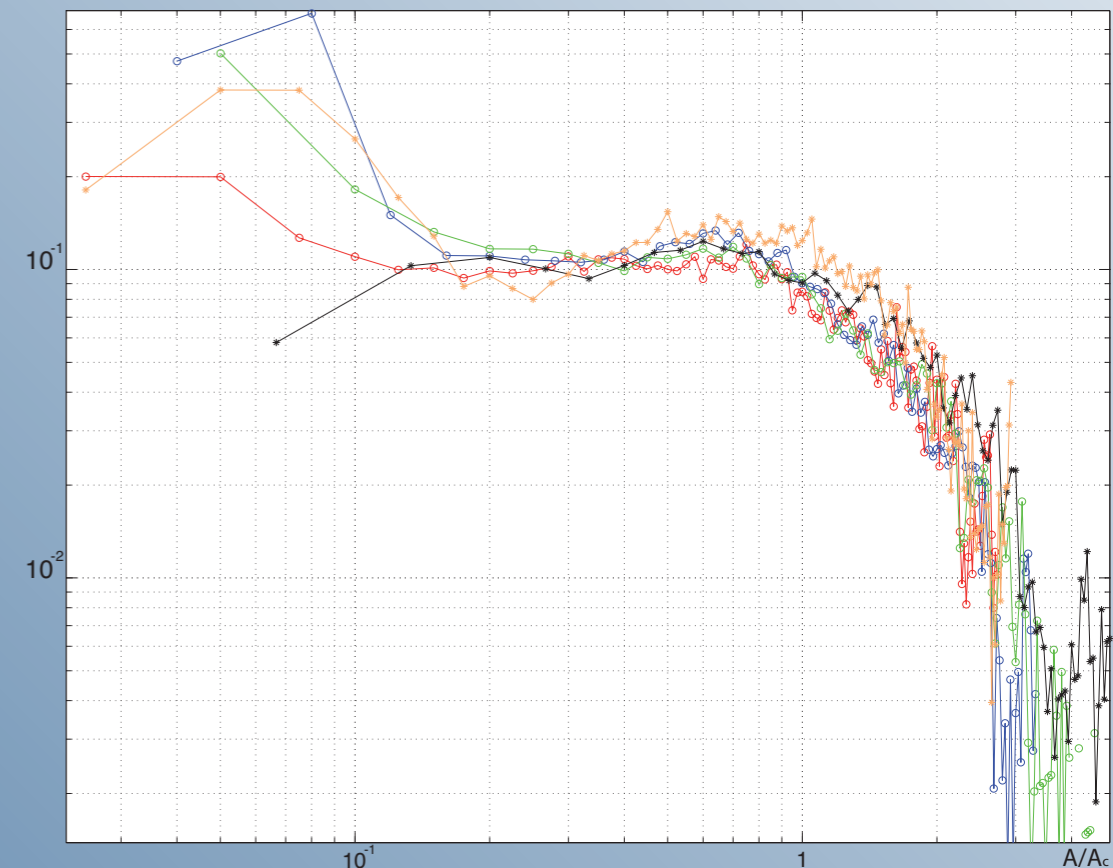
Table of Fisher exponents



#	RA	Raa	Sept	CS	RPV	LPV	Laa
1		1.4	1.5	1.8-2.4			
2	Exp		2.8	2.9	2.3	1.7	2.2
3						1.9	
4	2.3			2.2	2.2	2.2	
5			0.8	1.3	1.1	1.9	

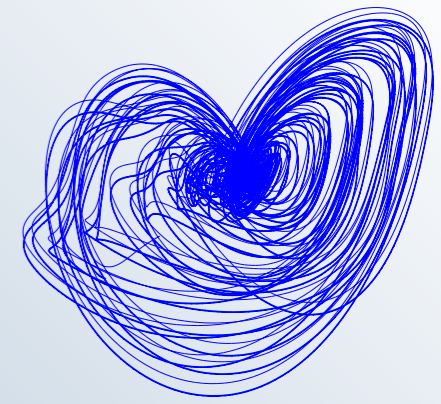
Collapse on scaling function

$$P(A) = A^{-\tau} g(A/A_c)$$



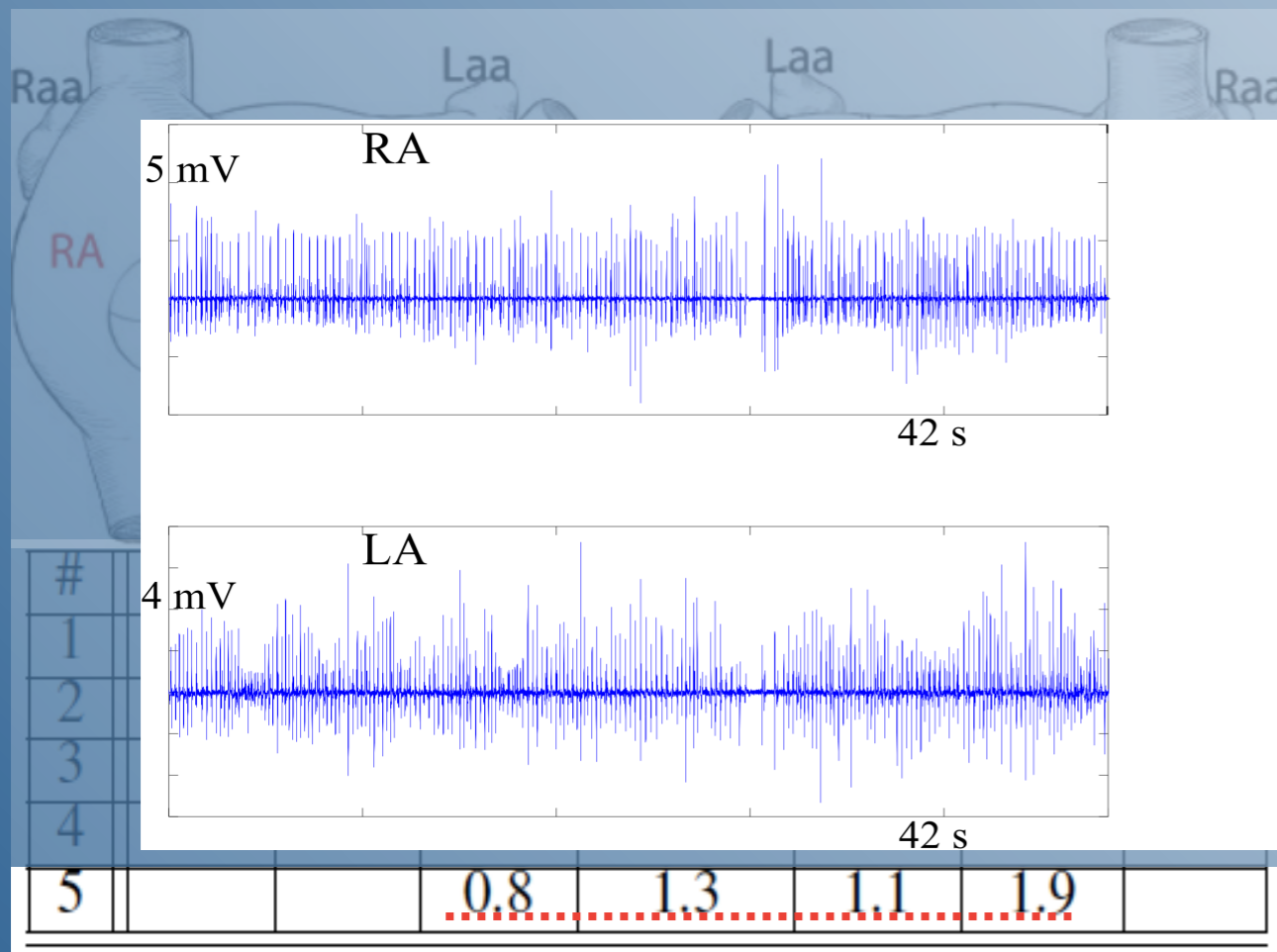
But contribution of very low amplitude must be cured...

Intermittency in the data?



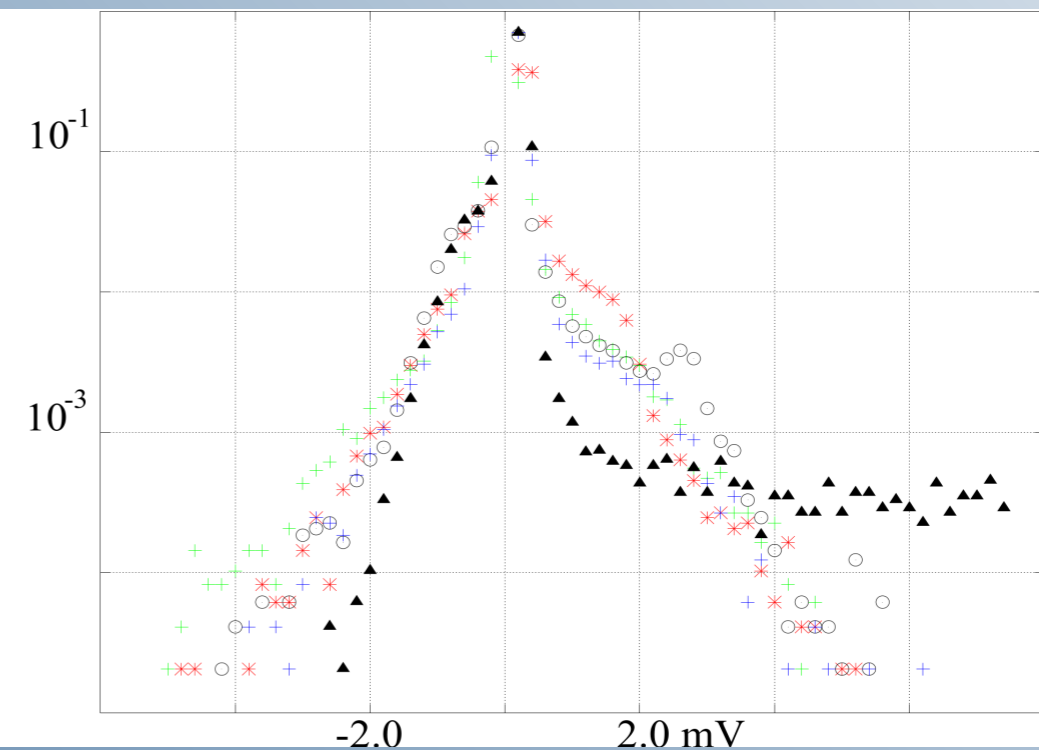
- Non-universal exponents
- Are there any *spatial patterns*?

Table of Fisher exponents

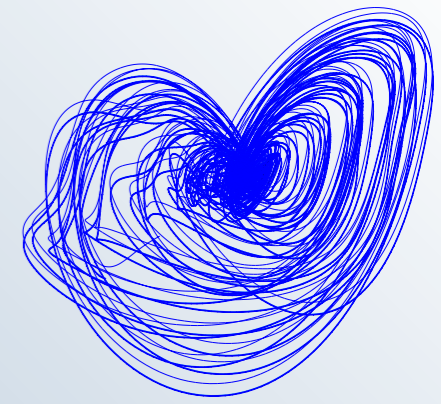


e.g. Patient #5

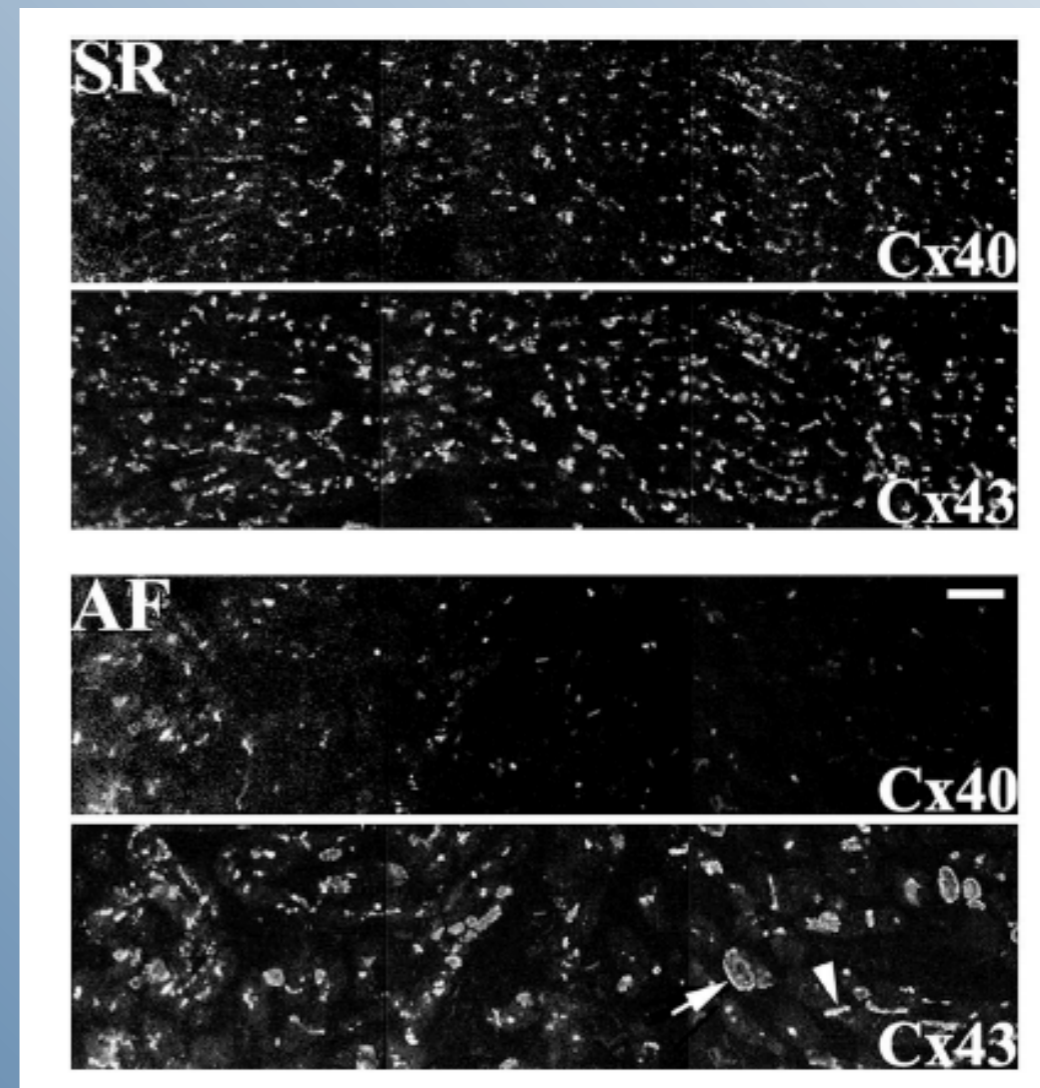
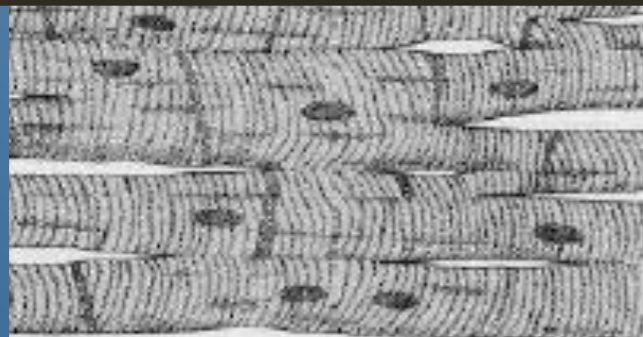
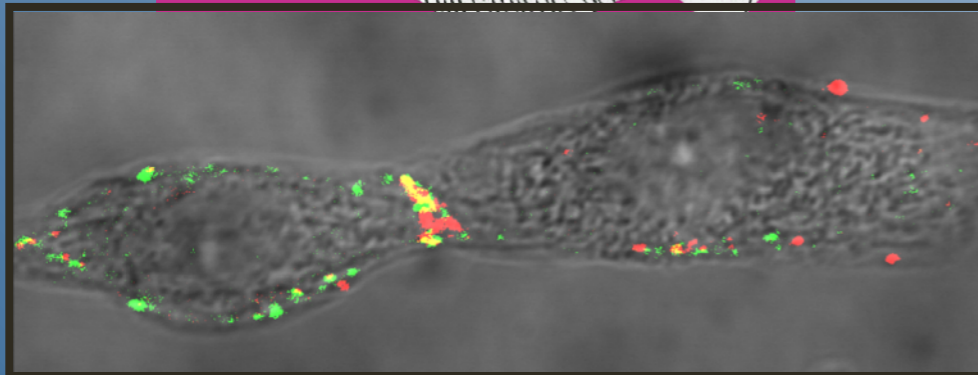
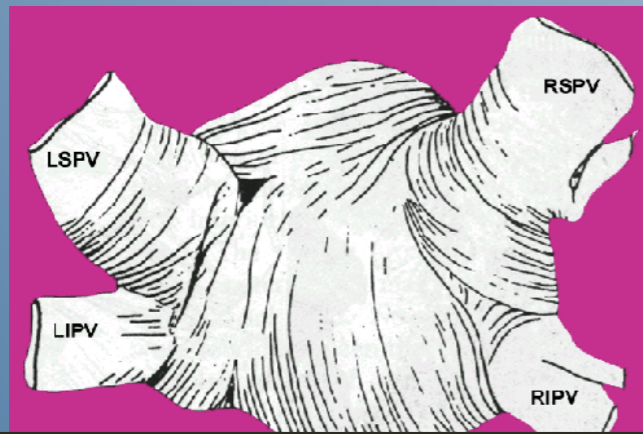
$$P(A) = A^{-\tau} g(A/A_c)$$



A myocardium of fibers



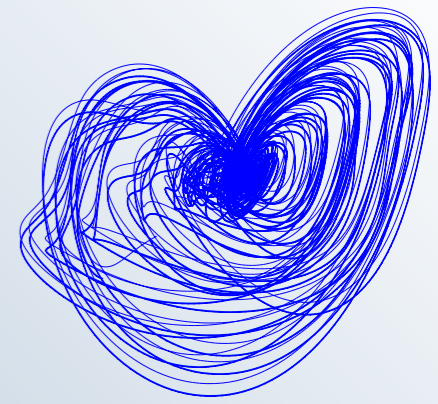
- A syncytium under normal circumstances.
- Conduction guaranteed by electrical synapses.
- Anisotropic.
- Distribution of Cx40/43 is more *dilute* after Fib.



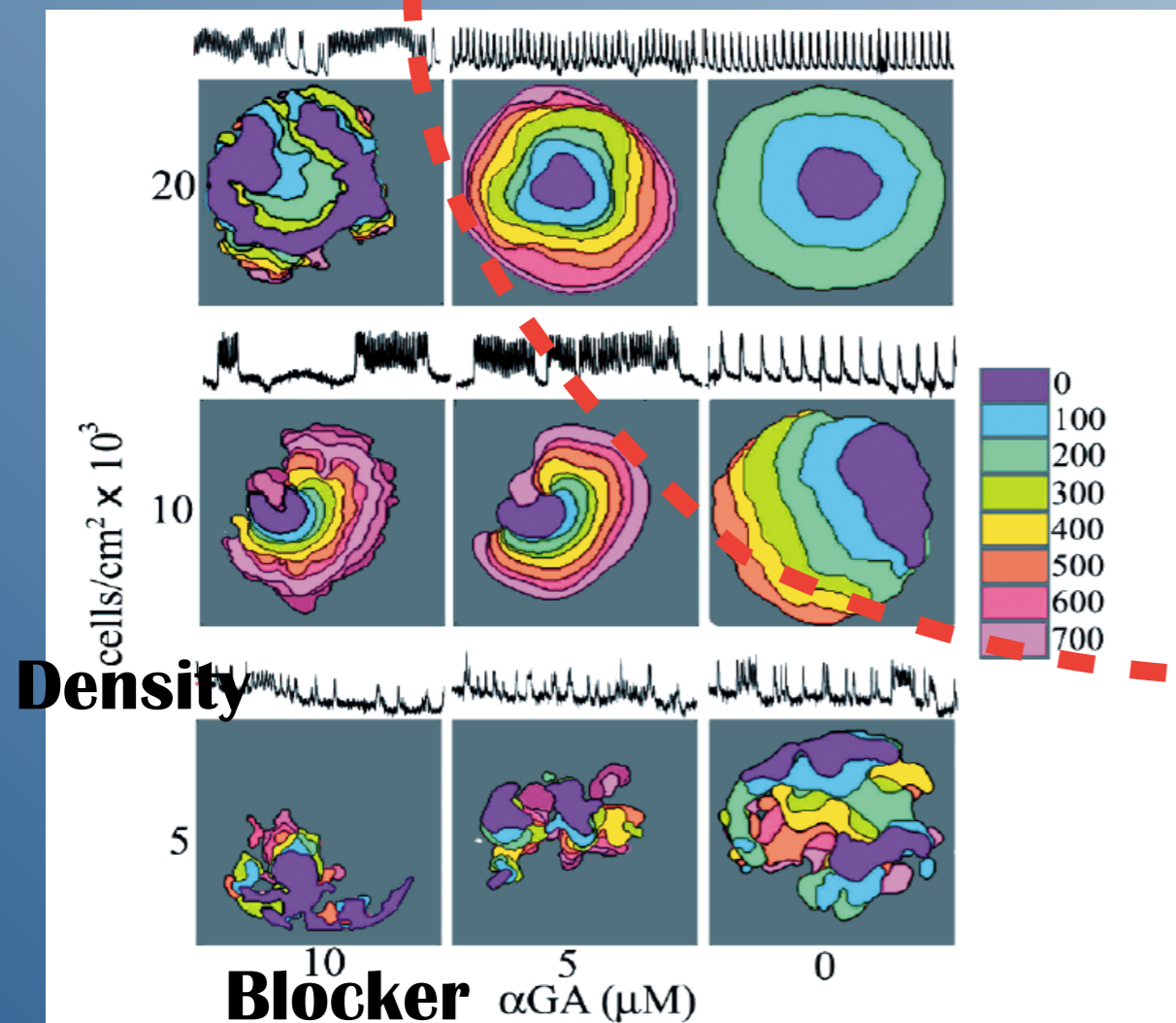
van der Velden et al. 2002

A useful analogy?

- Can we build a phase diagram?
- Find a critical point?
- What order parameter?

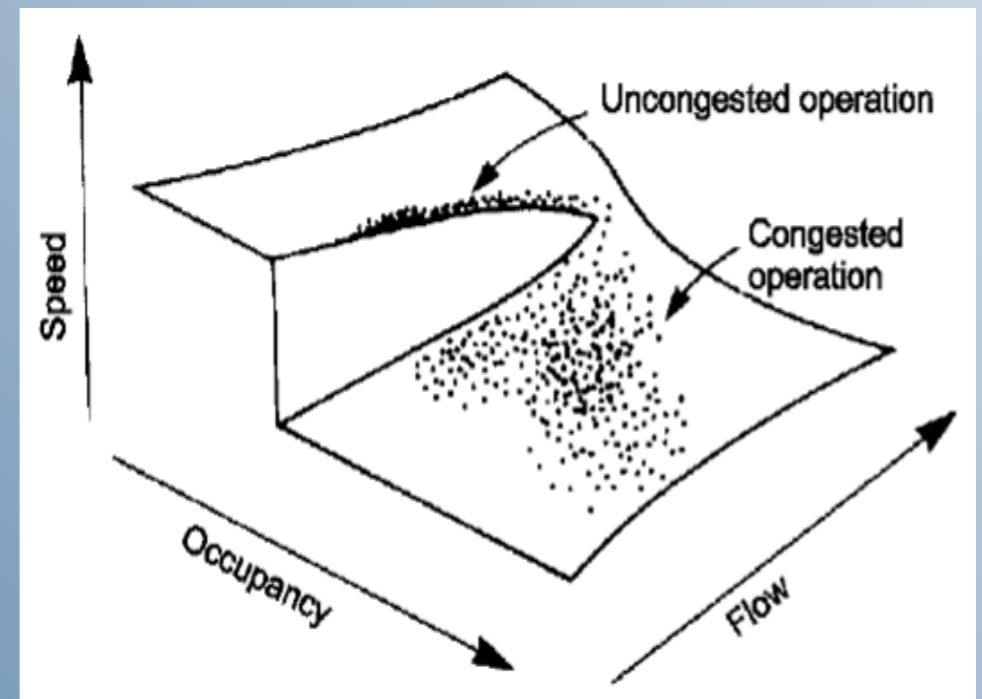
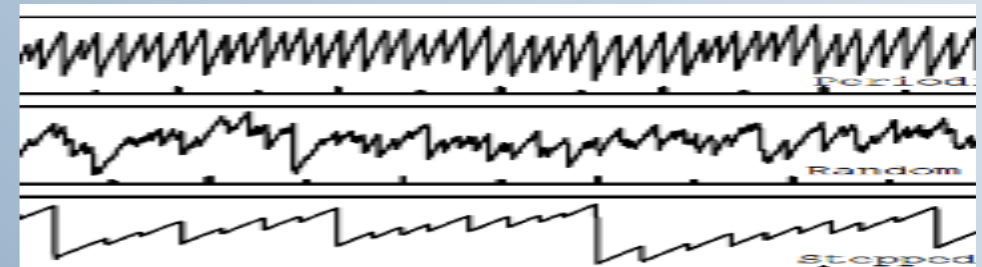


Synapse empirical phase space



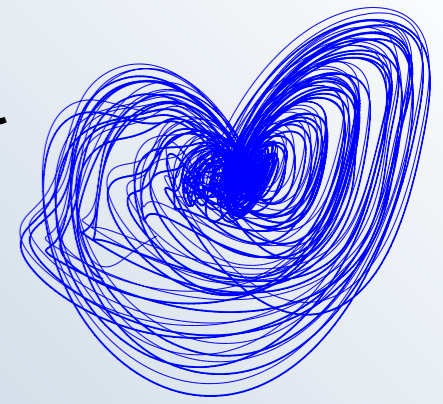
Bub et al. 2005

Traffic jams bottle necks



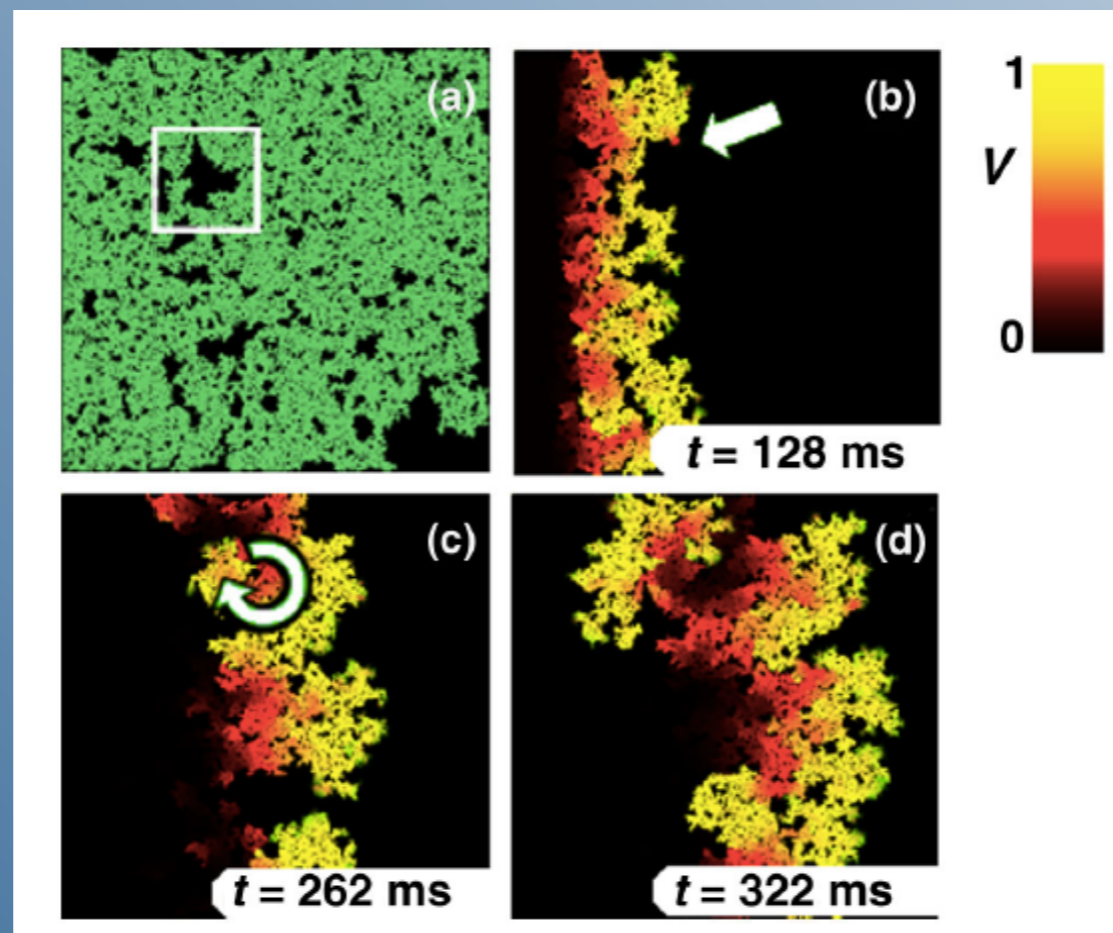
Kerner 1998

Excitable fronts on heterogeneous media



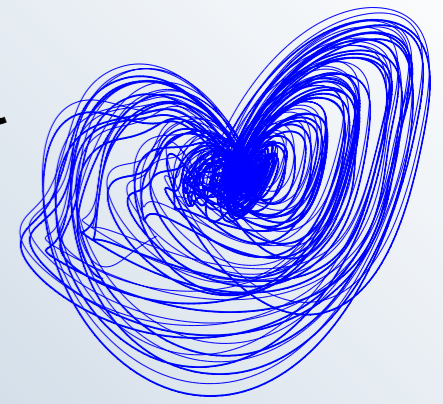
$$\begin{aligned}\partial_t U_i &= \mu \mathbf{f}(U_i) - I_i + D \sum_{\langle i,j \rangle} \eta_{i,j} (U_j - U_i) \\ p(\eta_{i,j} = 1) &= p \\ p(\eta_{i,j} = 0) &= 1 - p\end{aligned}$$

- As clusters of disconnected cells grow and allowing *lower excitability* $\mu_{cl} < \mu$ leads to reentries



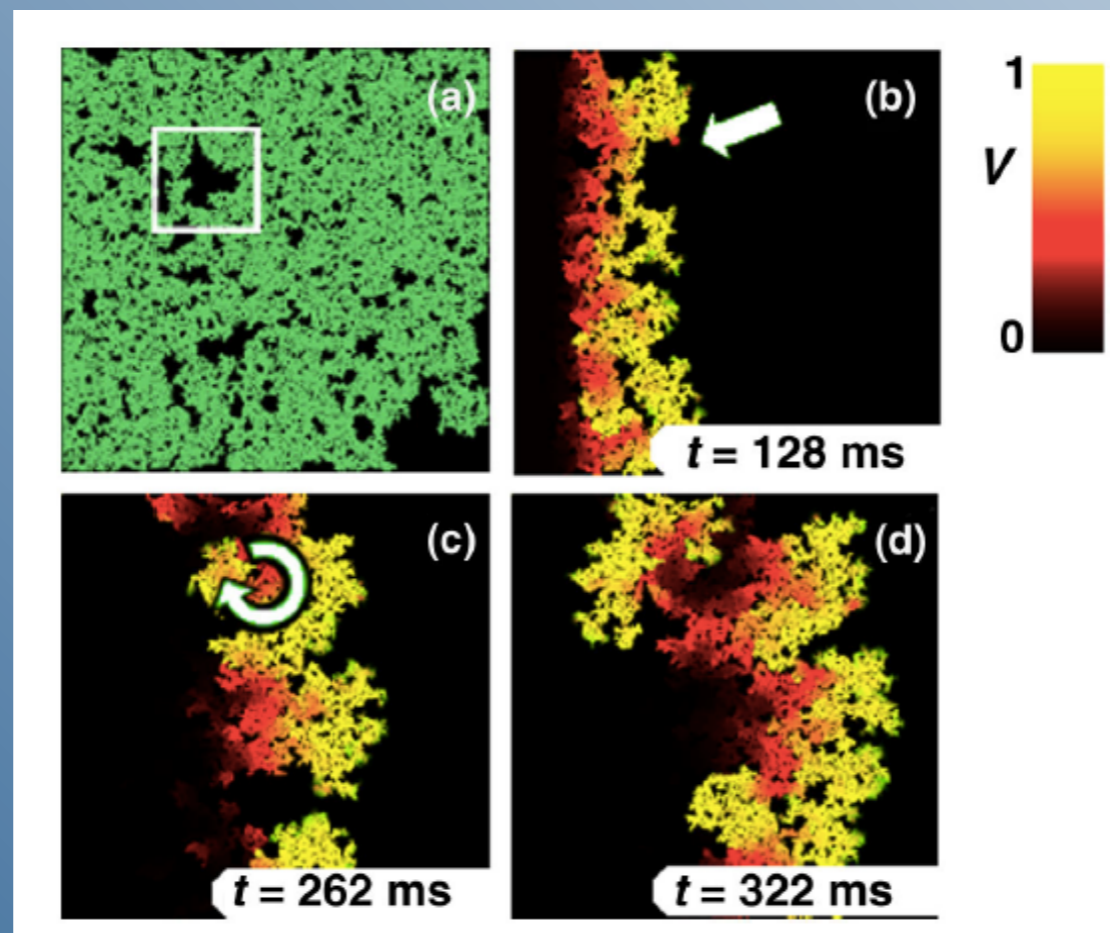
Alonso, Baer 2013

Excitable fronts on heterogeneous media



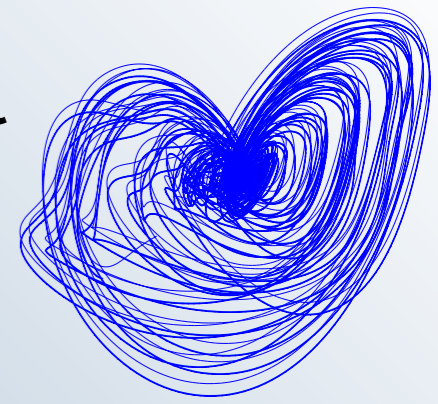
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- If $A \sim S_{cl}$, then Fisher exponent $\tau > 2$
- *Monofractal* scaling



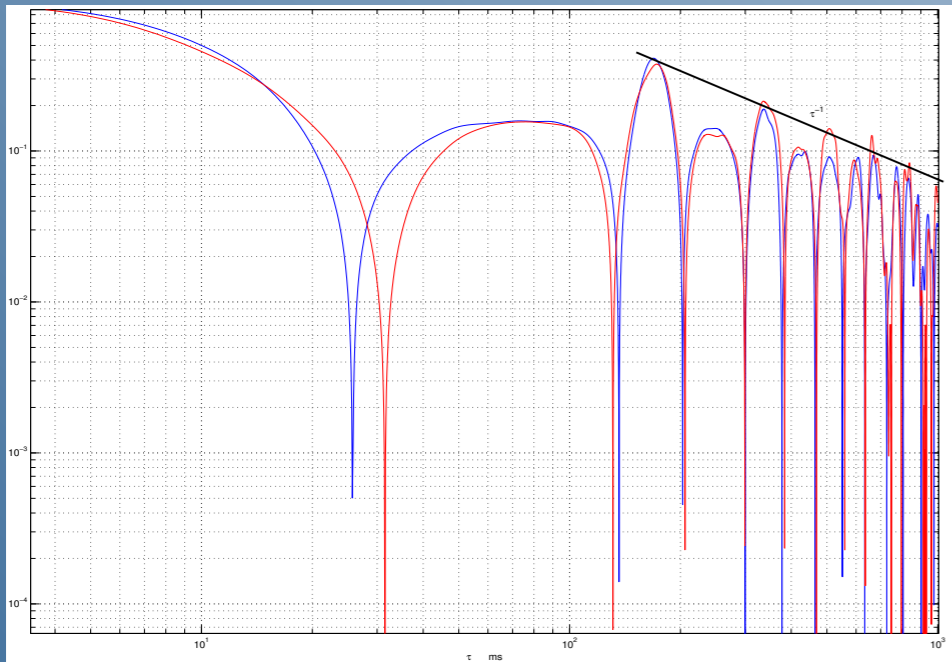
Alonso, Baer 2013

Excitable fronts on heterogeneous media

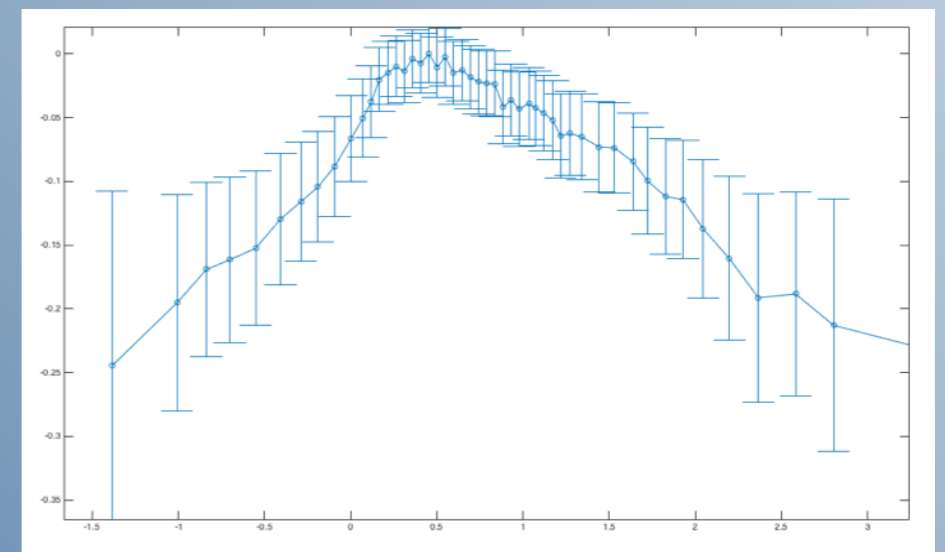
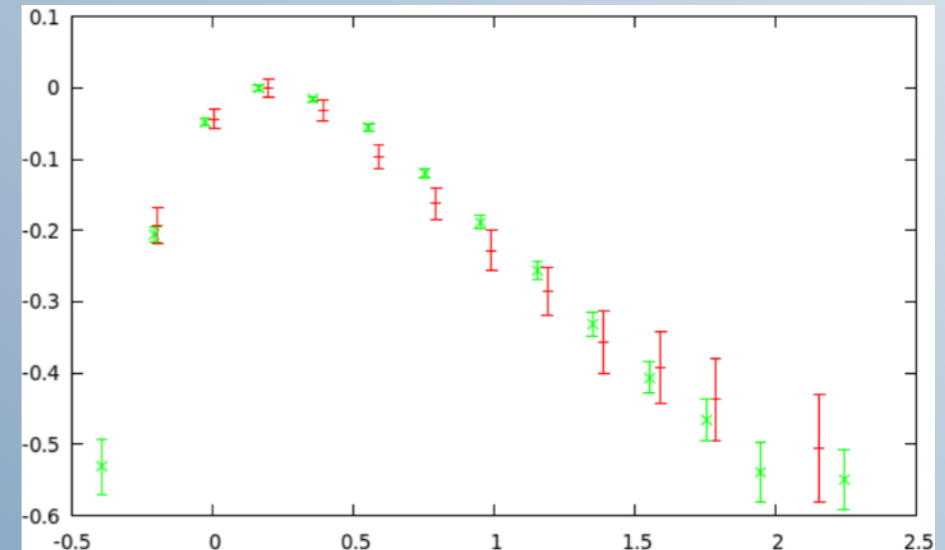


→ Where else does one find such features?

$\langle A_t A_0 \rangle \sim t^{-\theta}$ over ~ 100 beats

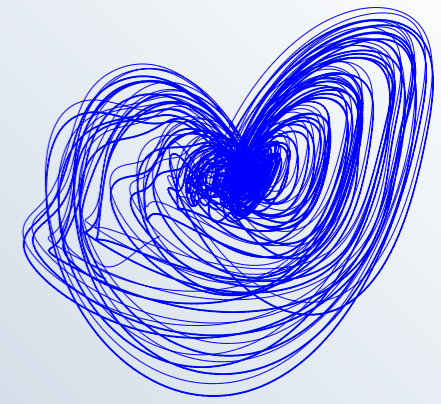


$\delta A \sim \delta t^h$ with $p(h) \propto \delta t^{D(h)}$



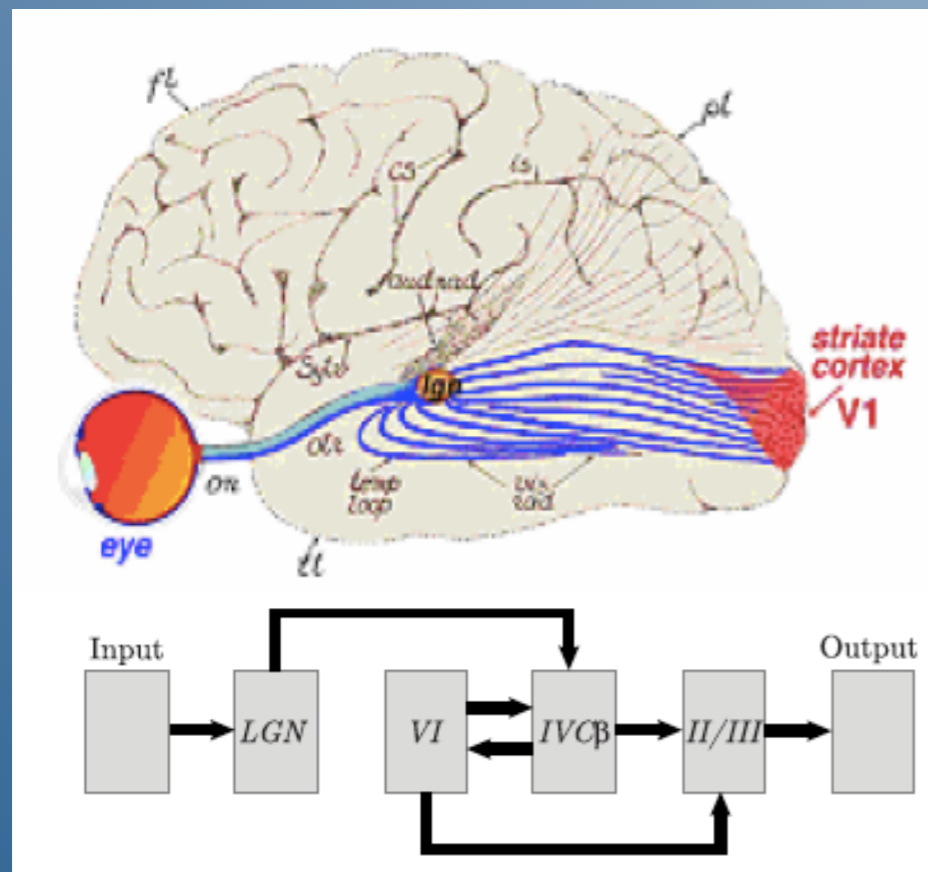
Working on error bars...!

Excitable fronts on heterogeneous networks



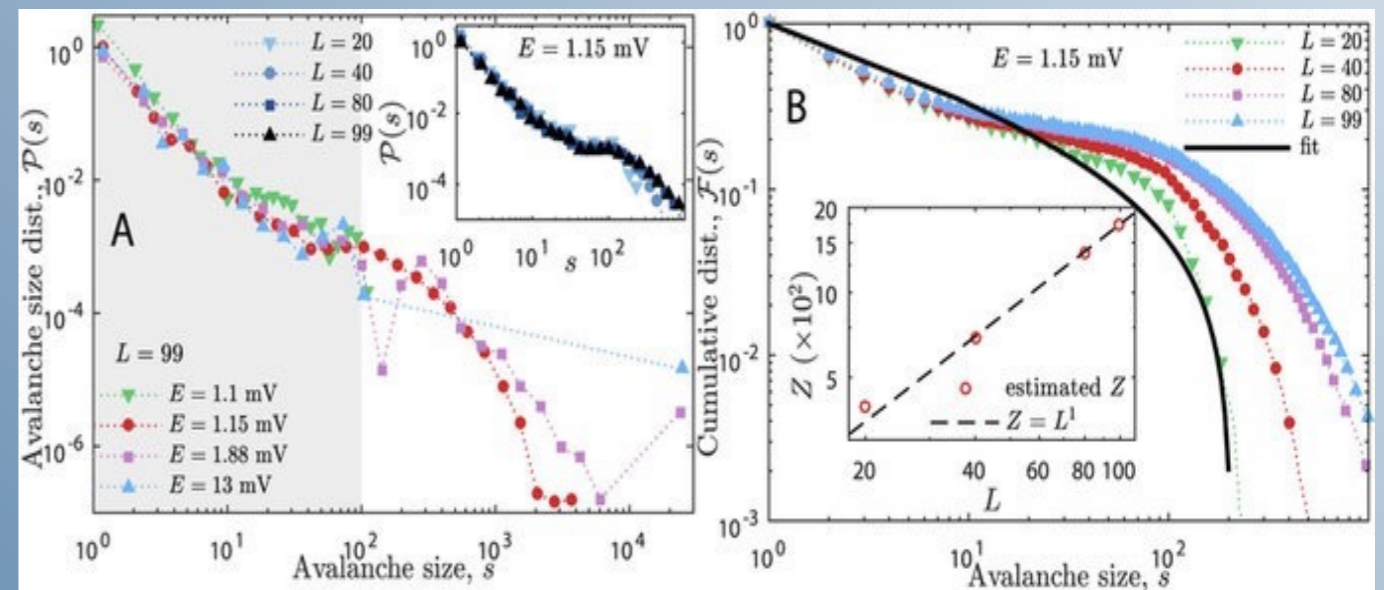
- *Extended critical* phases, e.g. in the visual cortex, brain resting state ...
- *Dynamical* processes on hierarchical, dilute, disordered network.

Visual cortex recurrent layers



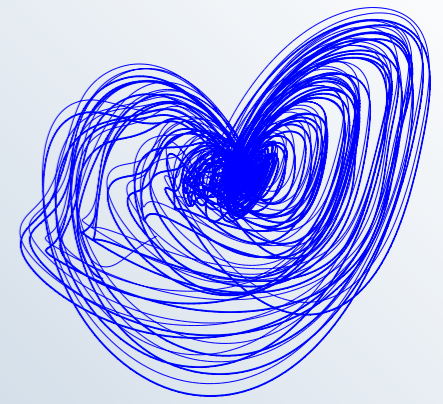
Avalanche size PDFs

Flash on the retina triggers activity, \neq EPSP



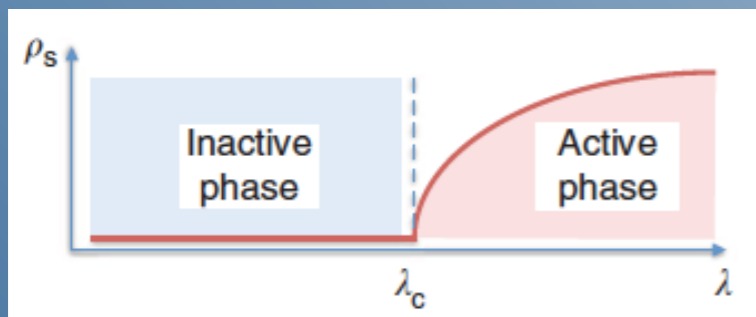
Girardi-Shappo et al. 2016

Excitable fronts on heterogeneous networks



- *Extended critical* phases, e.g. in the visual cortex, brain resting state ...
- *Dynamical* processes on hierarchical, dilute, disordered network.

Critical

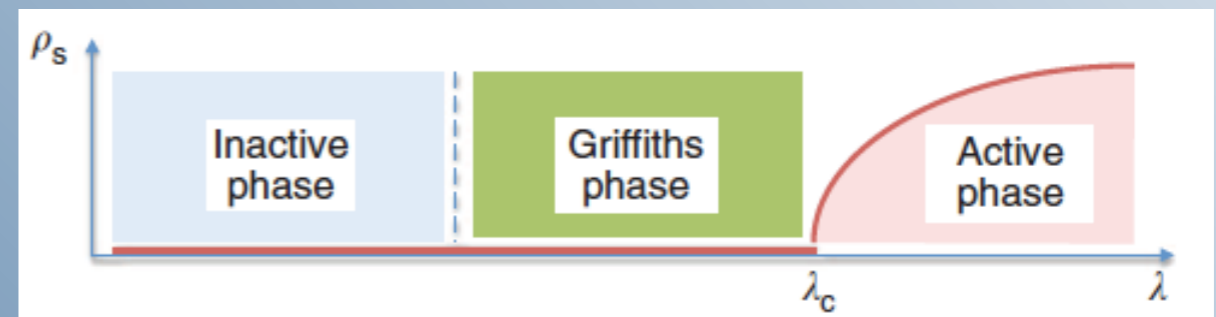


Control parameter fine tuned :
 $\lambda = \lambda_c$

Classical scaling laws :

$$C(t) \sim t^{-\theta}$$

Griffiths

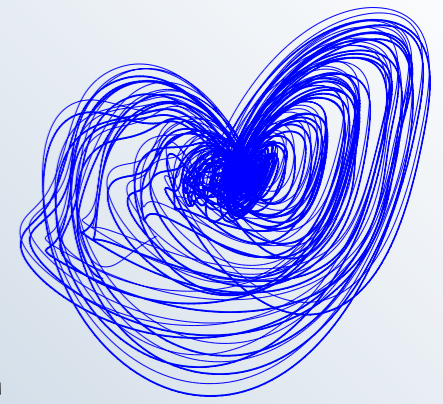


Control parameter *distributed* :
 $\lambda = \lambda_m + \delta\lambda \Rightarrow \lambda_c < \lambda_m c$

Rare regions $P(L)$ smear the transition :

$$C(t) \sim \int dL P(L) e^{-t/t_0} e^{\alpha(\lambda)L} \sim t^{-\theta(\lambda)}$$

Our model



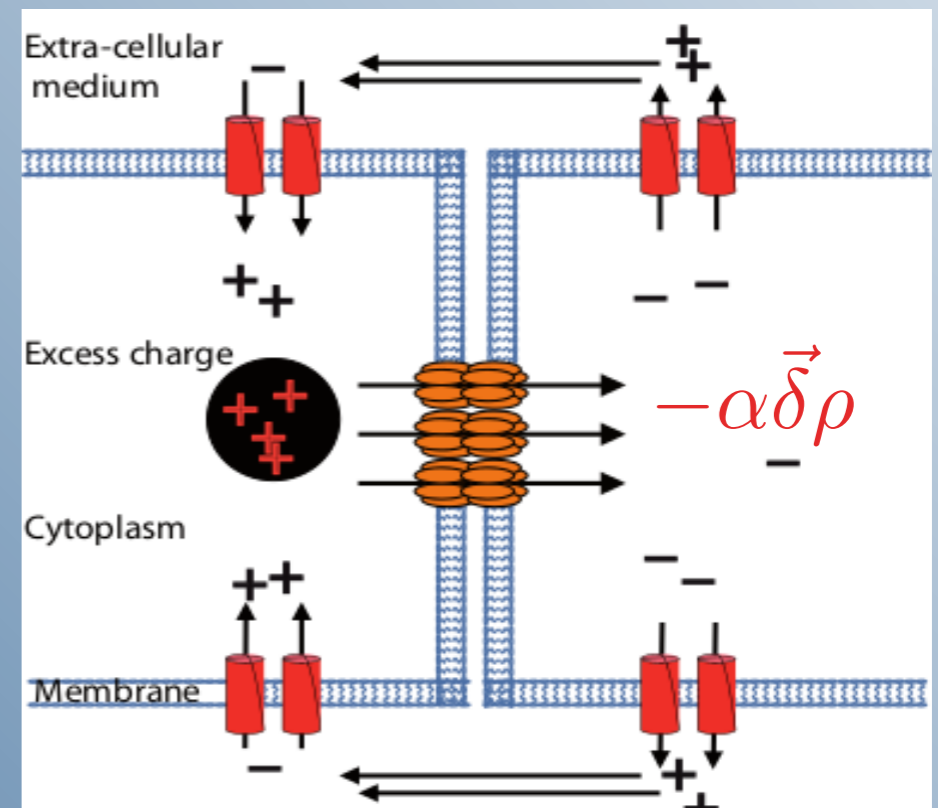
- Assume local modulations of synapse conductances
- This stems from reaction kinetics with bound charges chemical potential at gap junctions (Calcium overload)
- Time scales are resonant $\sim 100ms$

Resonant time scales

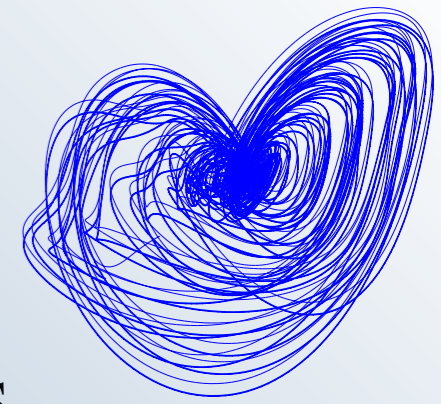
This may lead synapse cycles and cell cycle to be in *phase opposition*

There might be a *critical* value of a control parameter for a *transition* from *absorbing* to *active* state ?

Main assumption



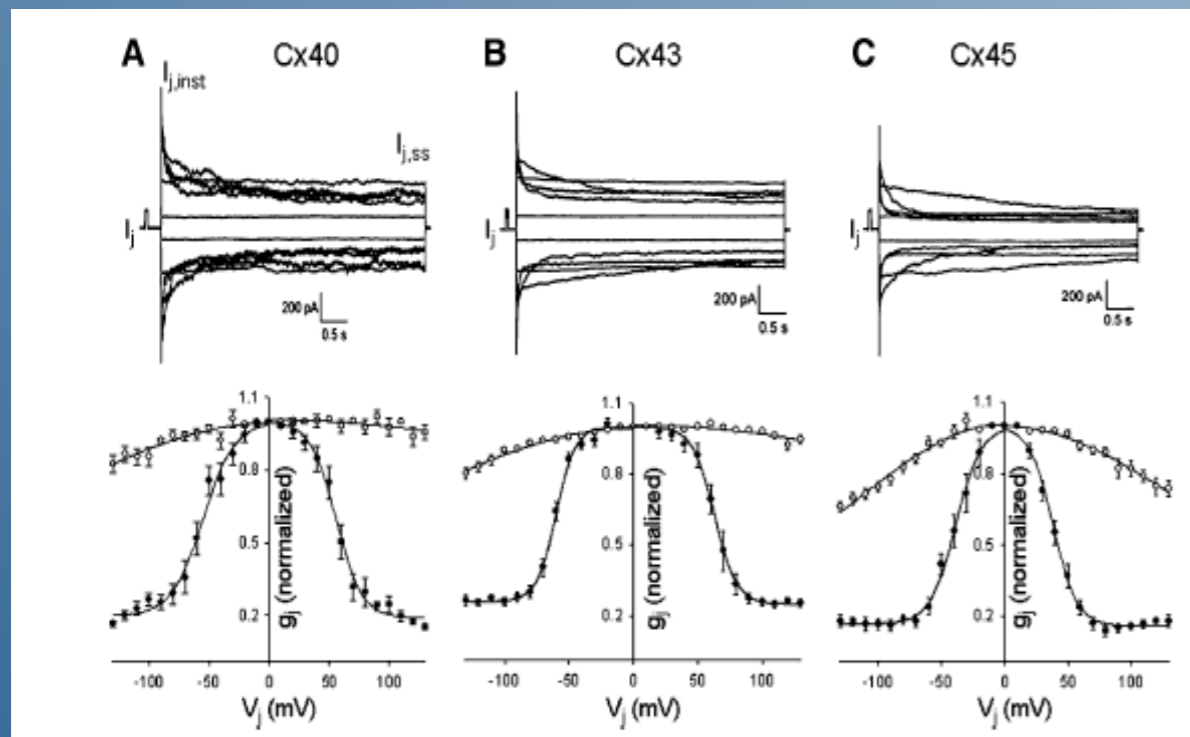
Our model



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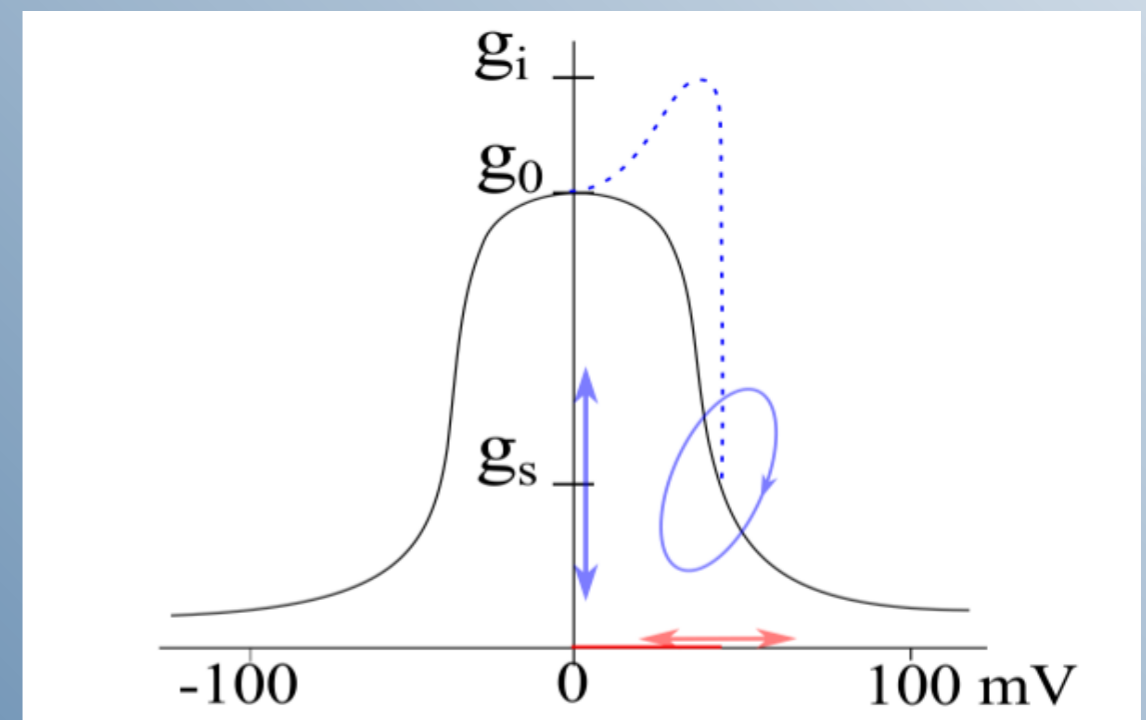
Gap junction static conductance

Bi-patch clump RLC-like measurements

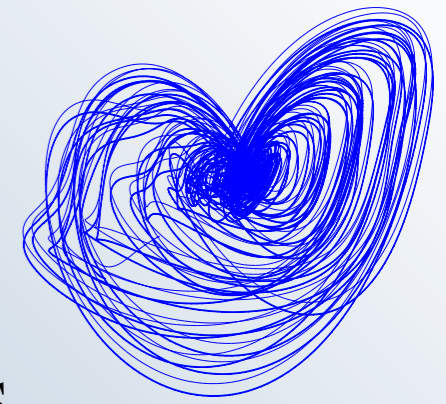


Desplantez et al 2007

Main assumption : synapse cycles



Our model



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Dynamical system

$$\begin{cases} \partial_t U &= \mathbf{f}(U) - I &+ D\Delta U - \vec{\nabla} \cdot g\rho \\ \partial_t g &= -\alpha \vec{\delta}\rho &- \nu g \\ \partial_t \rho &= -g \cdot \vec{\nabla} U &- \nu_2 \rho \end{cases}$$

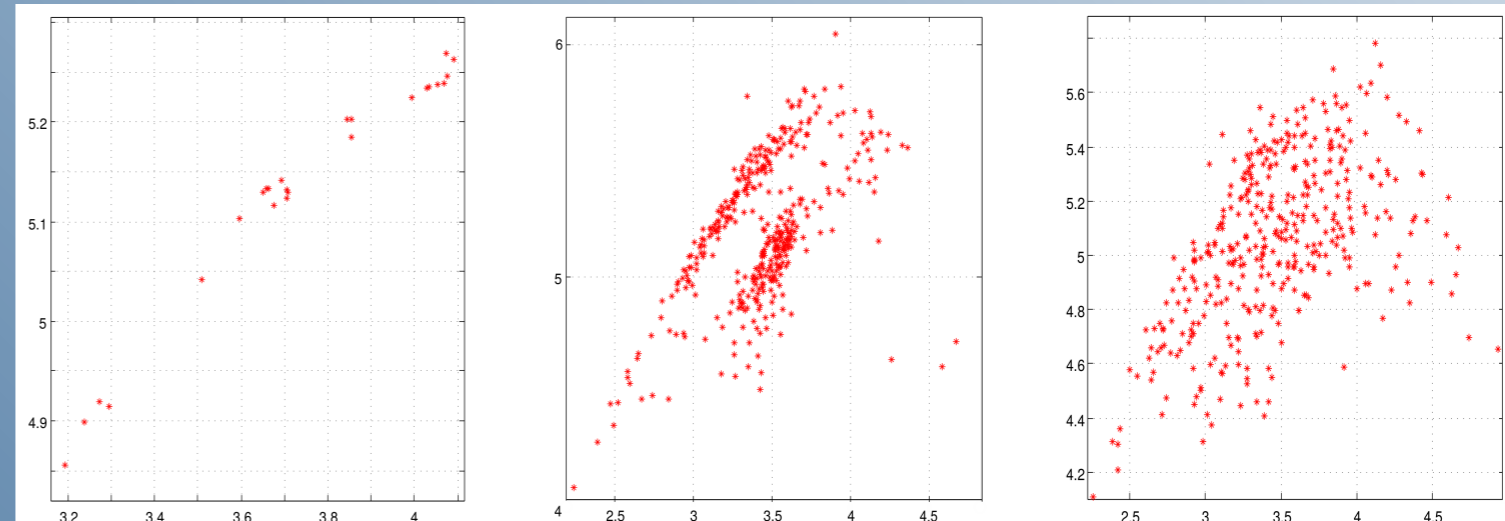
Chaotic oscillations

$$\mathbf{R}_a \approx \mathbf{R}_a c$$

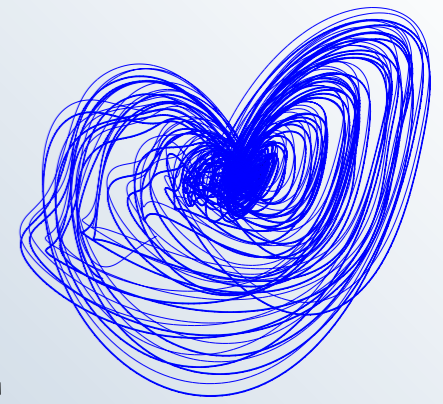
Poincaré sections for 2, 3, 4 coupled cells

Dimensionless Rayleigh number:

$$\mathbf{R}_a = \frac{\alpha I}{D\nu\nu_2}$$



Our model



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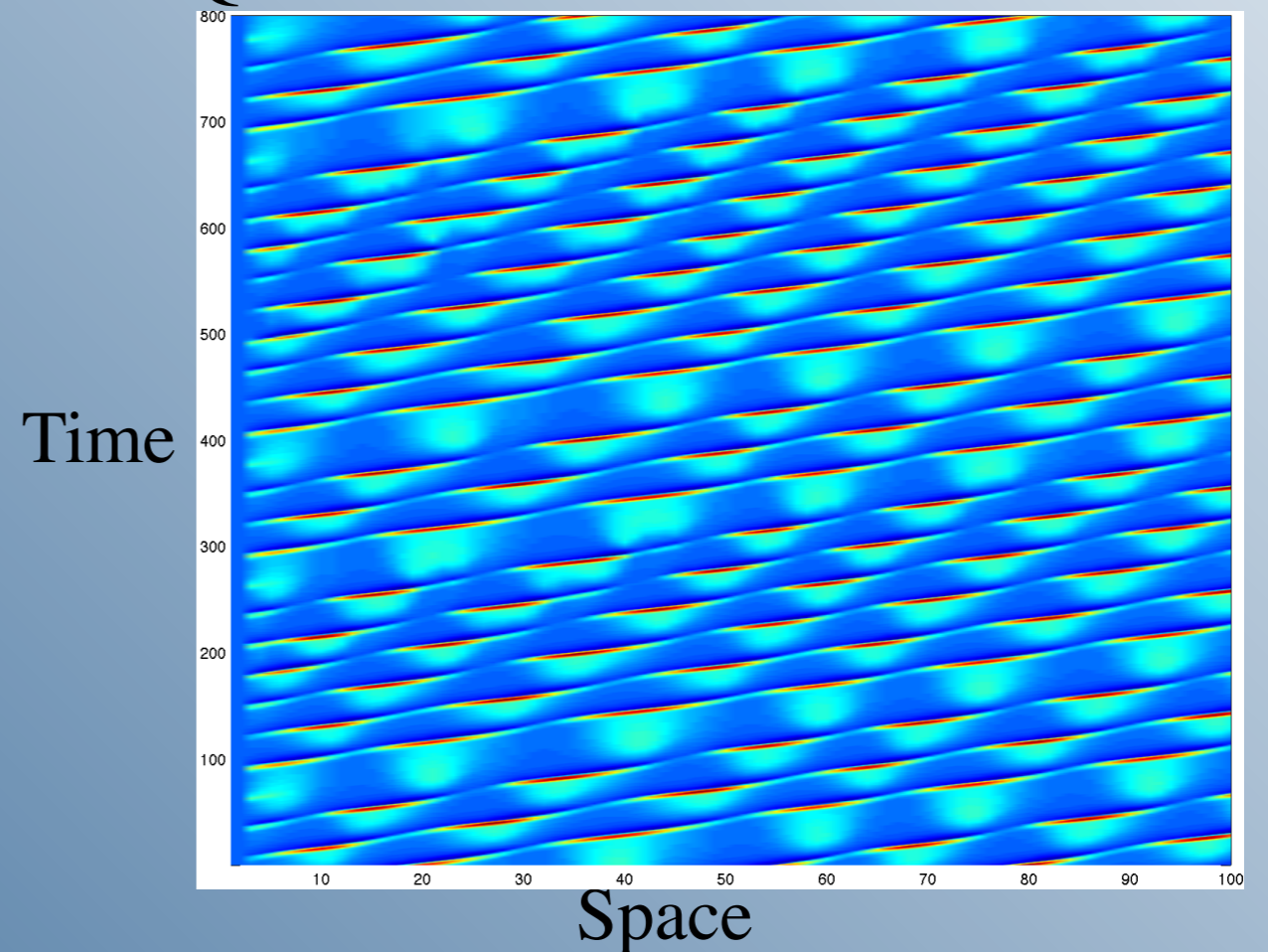
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Dimensionless Rayleigh number:

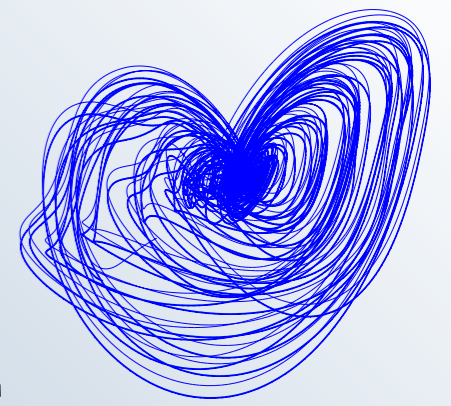
$$\mathbf{R}_a = \frac{\alpha I}{D\nu\nu_2}$$

Zoology of S-T patterns

QP $\mathbf{R}_a \approx \mathbf{R}_a c$



Our model



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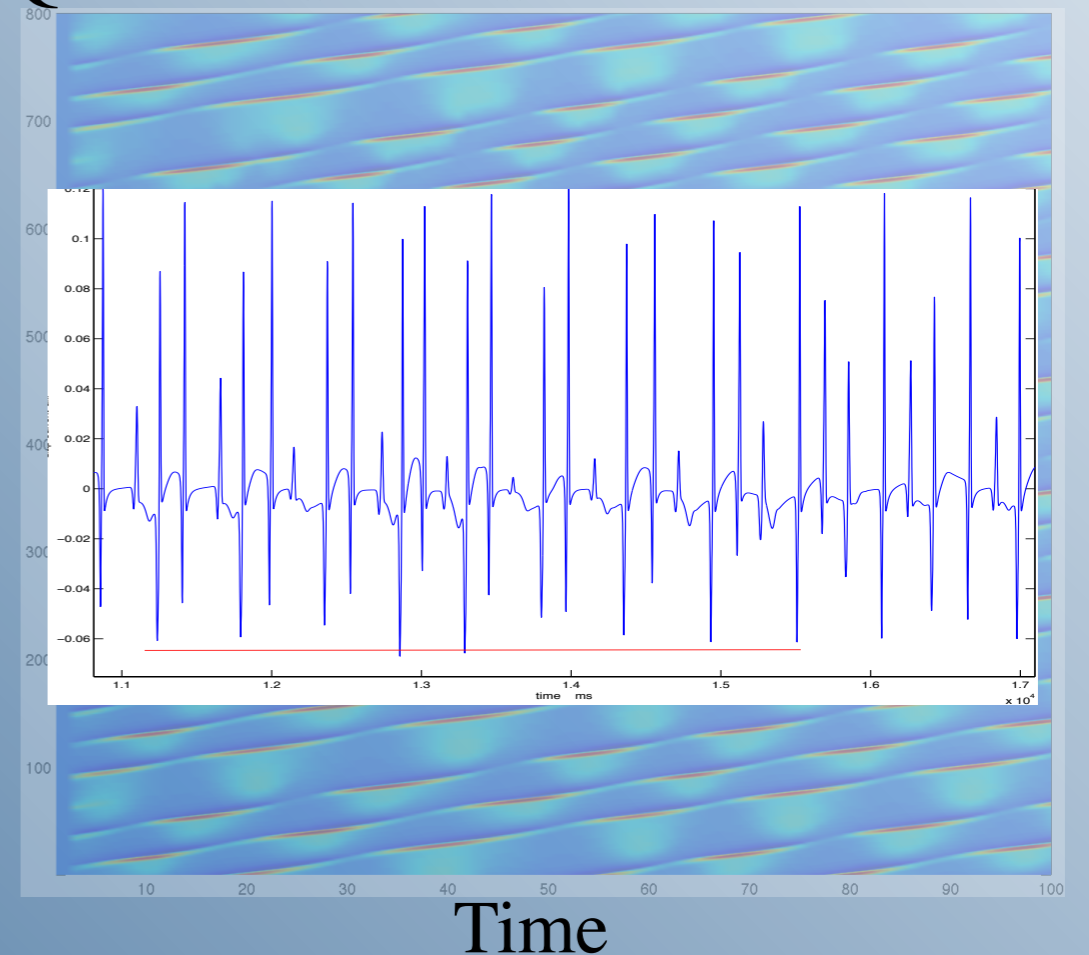
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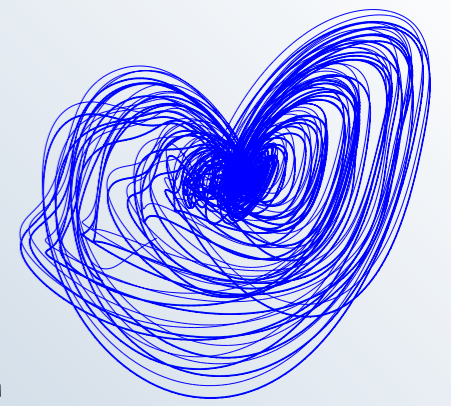
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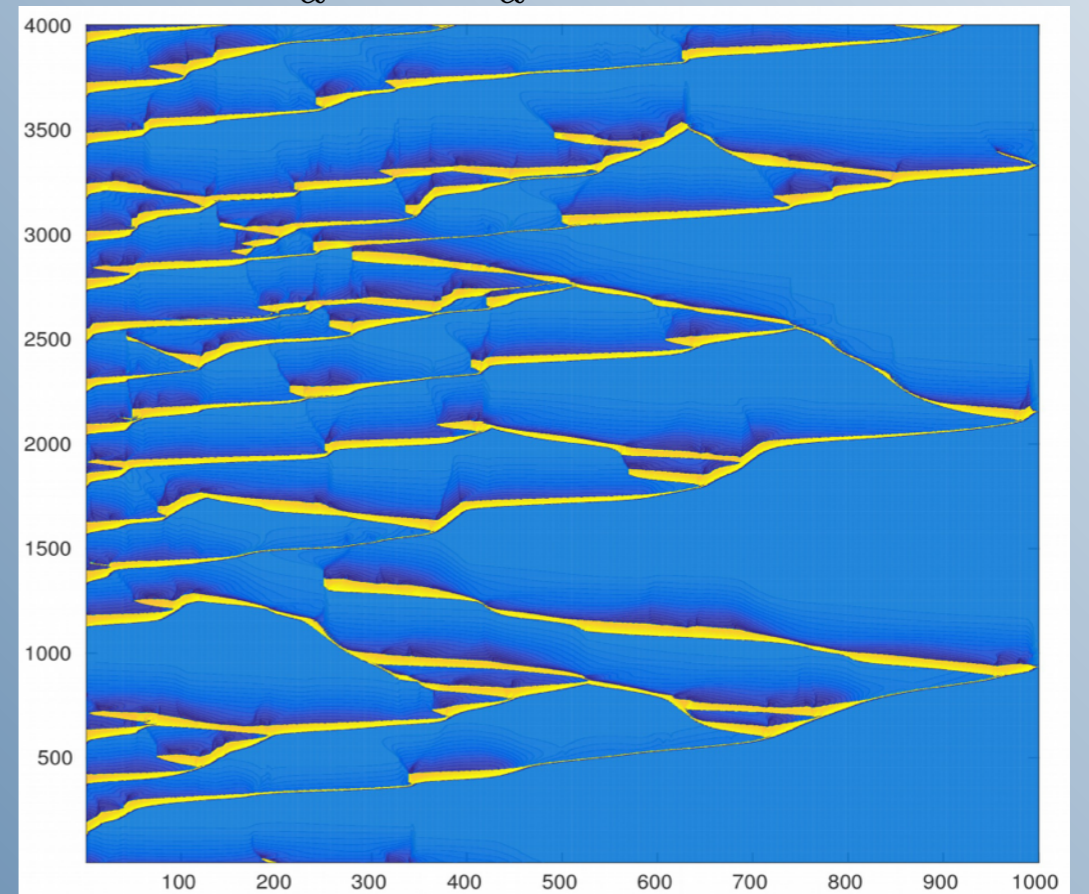
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Zoology of S-T patterns

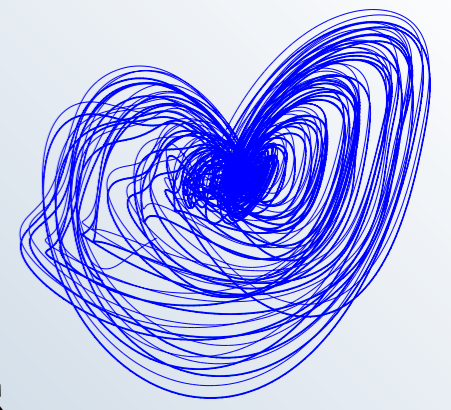
Fib $\mathbf{R}_a > \mathbf{R}_a c$

Time



Space

Our model



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Dynamical system

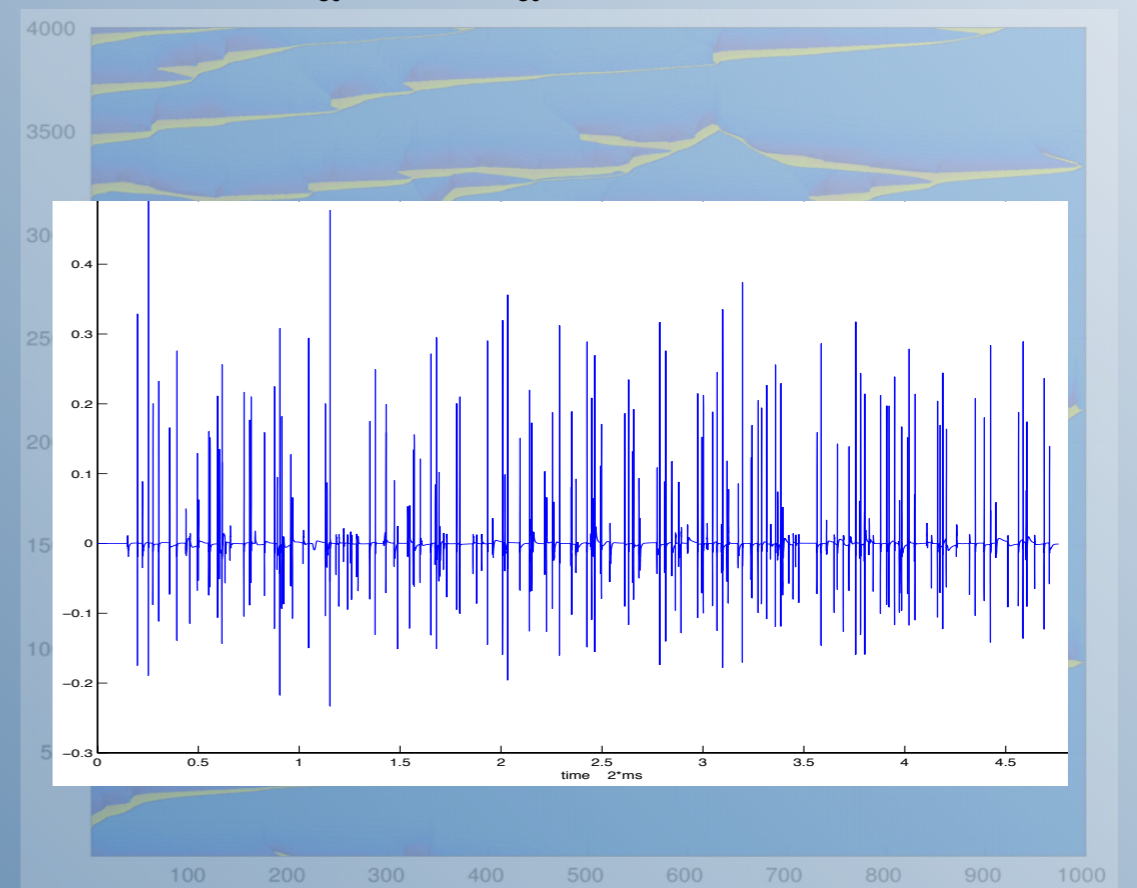
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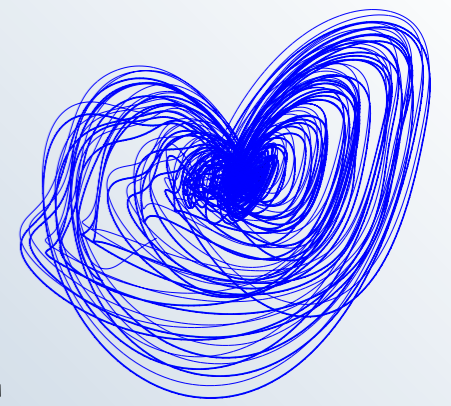
Zoology of S-T patterns

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Time

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Dynamical system

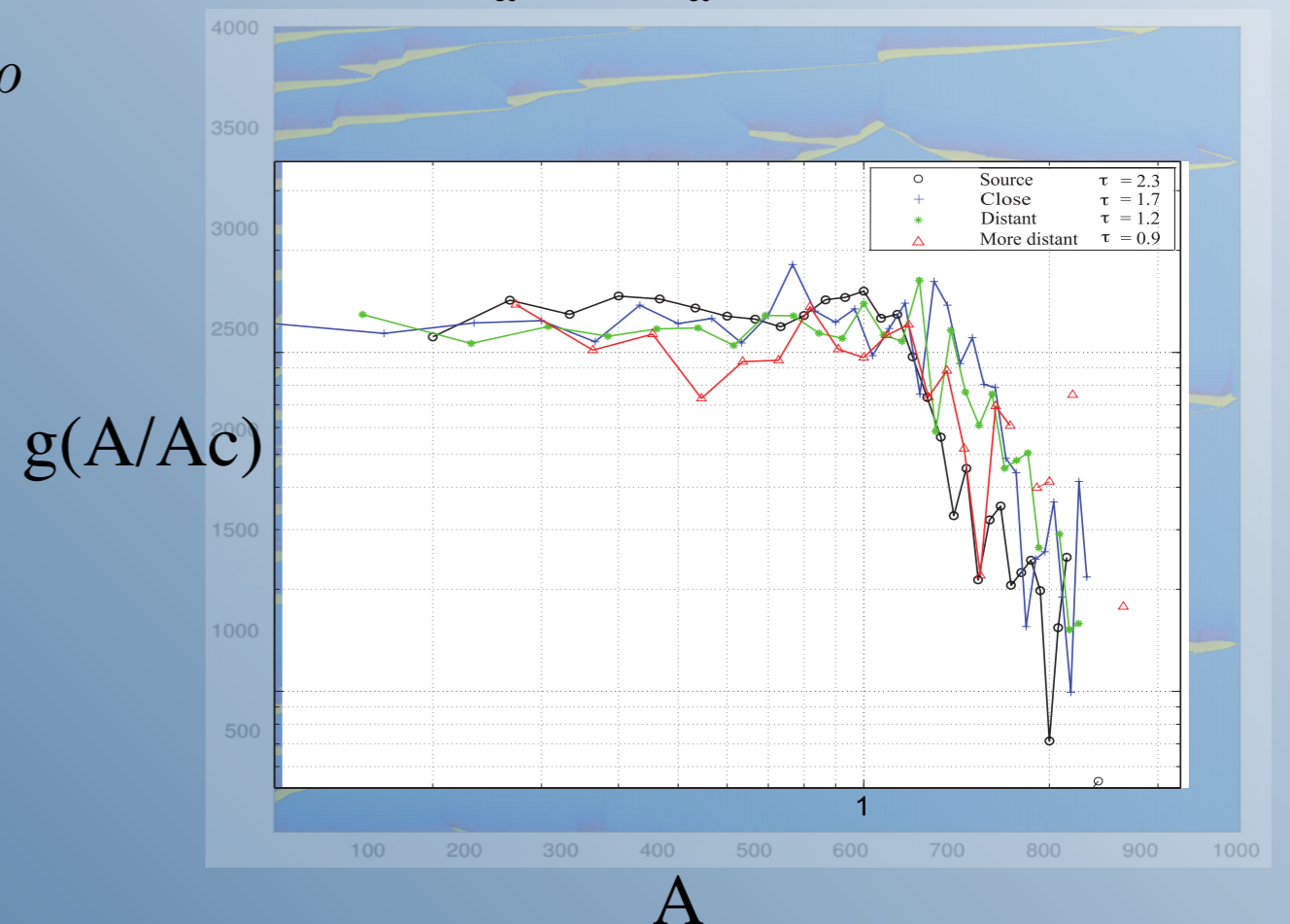
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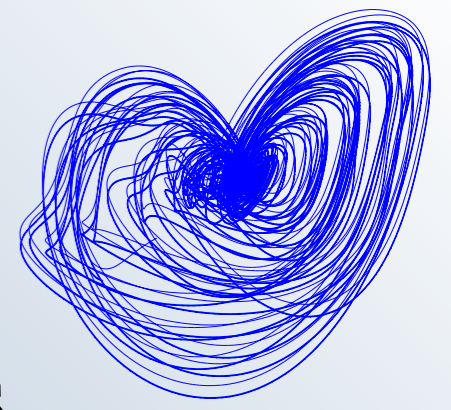
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Zoology of S-T patterns

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Our model



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Dynamical system

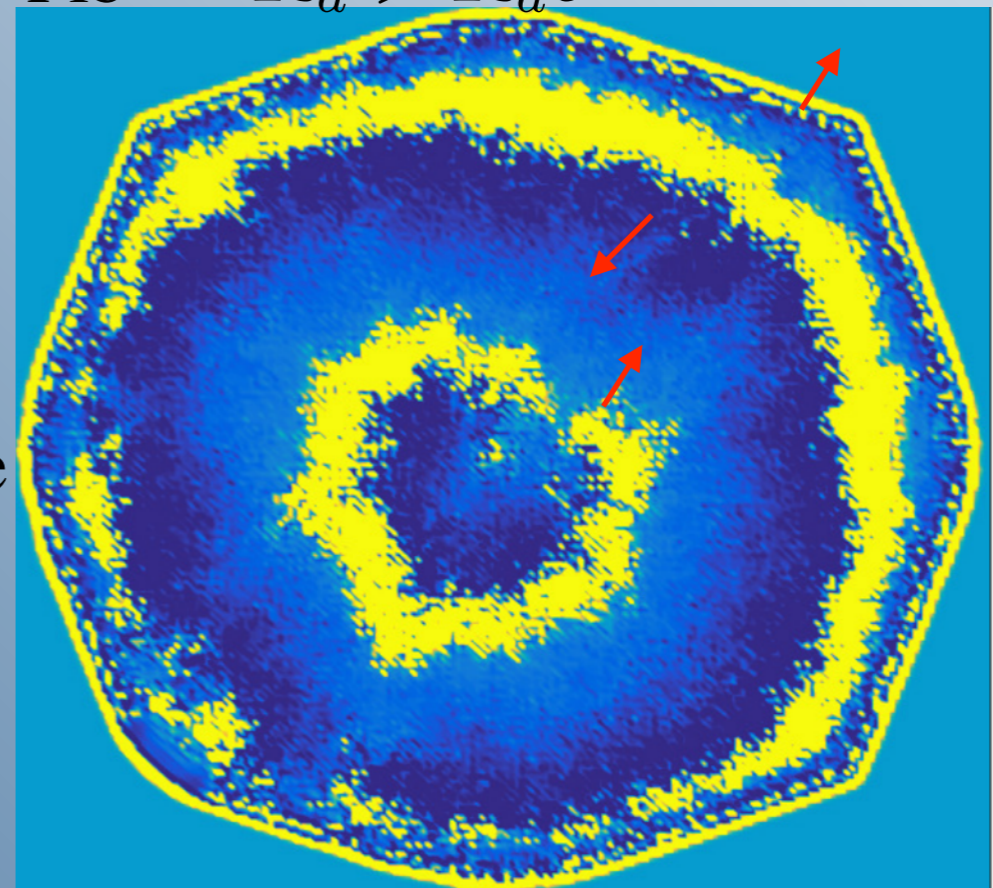
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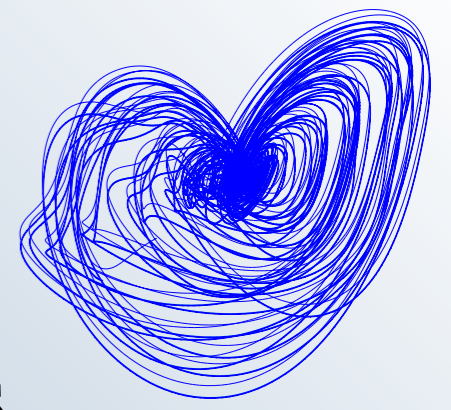
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Zoology of S-T patterns

Fib $\mathbf{R}_a > \mathbf{R}_{ac}$



Our model



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Dynamical system

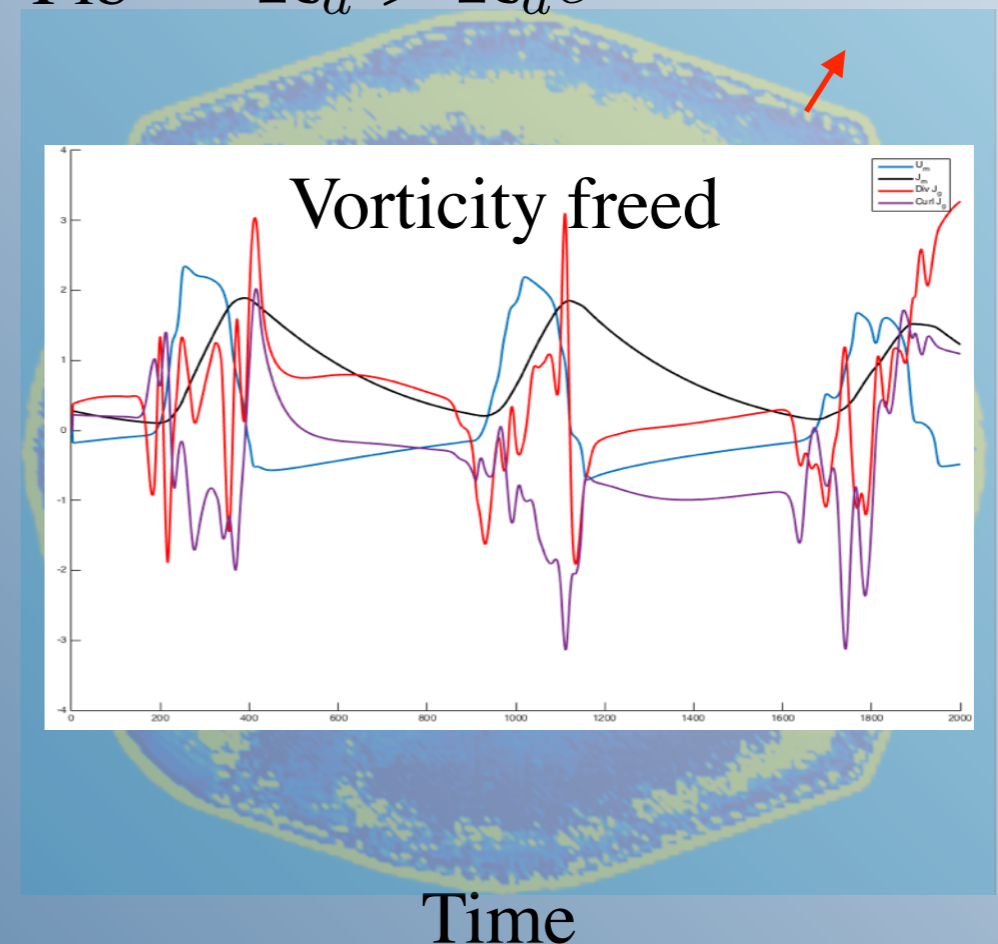
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Zoology of S-T patterns

Fib $\mathbf{R}_a > \mathbf{R}_a^c$



Random phase and back-scattering

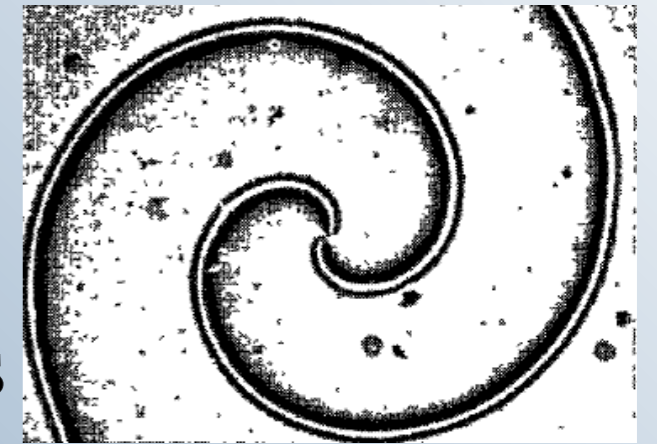


- The system is like a $\mathbb{C}GL$ eq. with *chiral* terms, below the *Ising-Bloch transition*: $\Psi \equiv U + iI$

$$\partial_t \Psi = ia\Psi + D\nabla^2 \Psi - i\nu \Delta \psi + i\gamma \Psi^*$$

- Parameters are modulated* by synapse currents

$$\gamma \rightarrow \gamma(x, t)$$



Gilli et al. 1993

Back-scattering happens when I-B transition is reached:

1 I-front gives birth to 2 counter-moving B-fronts

- Approximative* global $U(1)$ symmetry becomes « *dirty* » (local)

$\Psi \rightarrow \Psi e^{i\varphi}$ then $\gamma \rightarrow -i\gamma e^{i\varphi}$ rotates from $\mathbb{C}GL$ eq. to Fitzhugh-Nagumo

Front dynamics are pretty much similar in both: « conservative » and

« dissipative » aspects of chiral terms are irrelevant.

Any rotation in between is acceptable, at the expense of local resting angle

$$\theta_{eq} = \theta_{eq} + \delta\varphi$$

Random phase and back-scattering



- The system is like a CGL eq. with chiral terms, below the *Ising-Bloch transition* $\Psi \equiv U + iI$

$$\partial_t \Psi = ia\Psi + D\nabla^2 \Psi - i\nu \Delta \psi + i\gamma \Psi^*$$

- Parameters are modulated by synapse currents
- The new *local* « dirty » degree of freedom originates in *collective* behavior. It is *functional disorder*.

Back-scattering happens when I-B transition is reached:

1 I-front gives birth to 2 counter-moving B-fronts

- *Approximative*

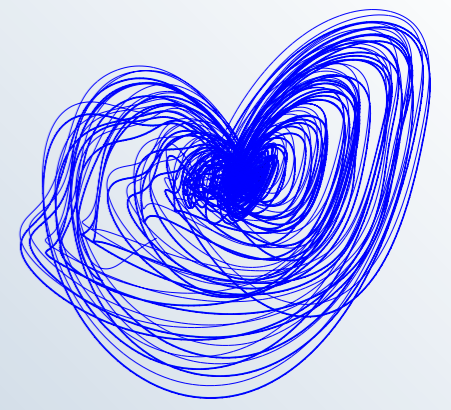
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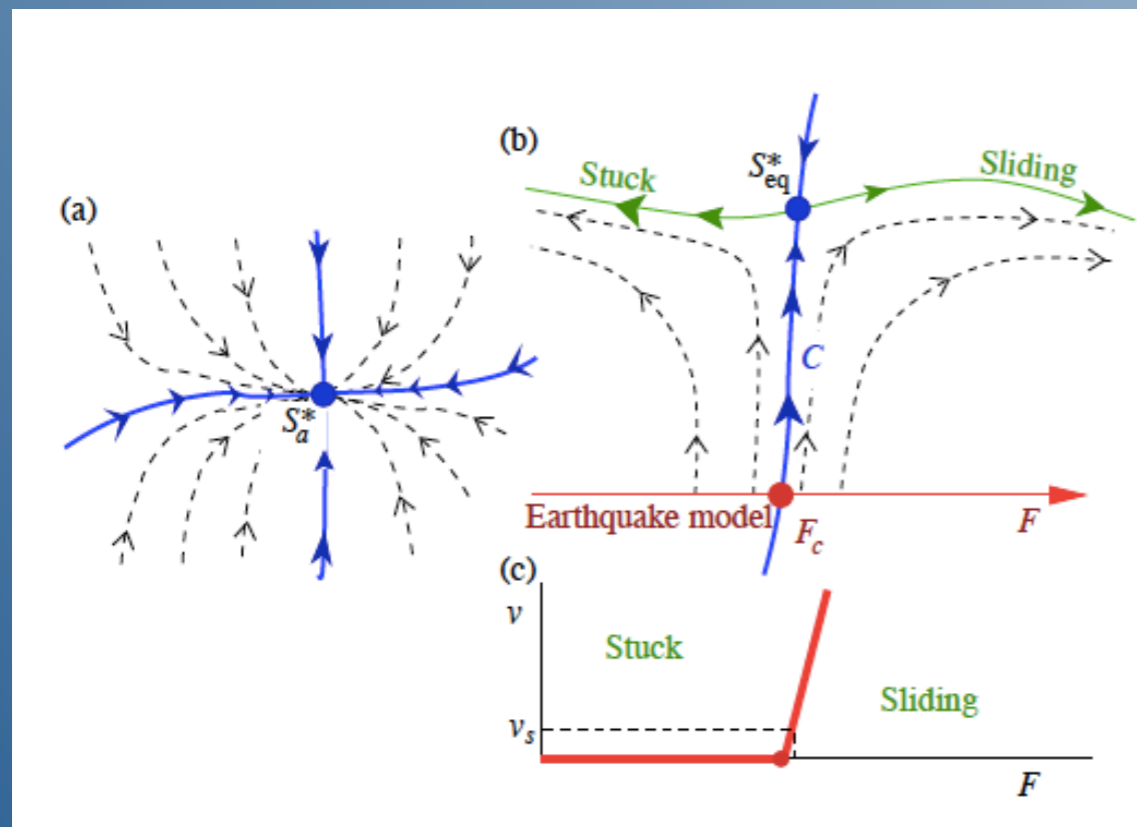
Random phase and back-scattering



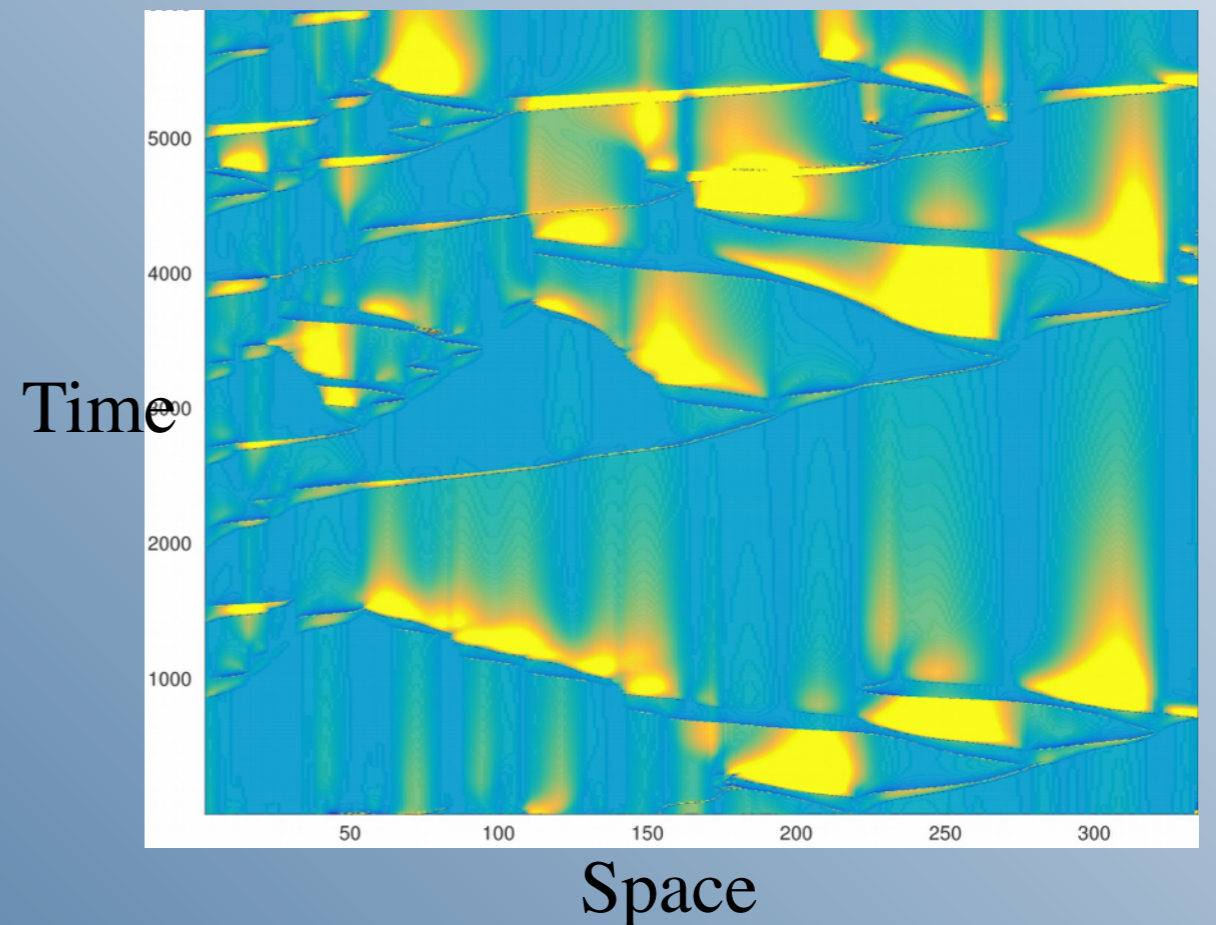
- The new local « dirty » degree of freedom triggers avalanches: $\theta_{eq} = \theta_{eq} + \delta\varphi$
- It is quenched disorder for each front, but is dynamical on longer times scales

$$\partial_t \theta = D \nabla^2 \theta - \mu \sin(\theta + \delta\varphi) + F$$

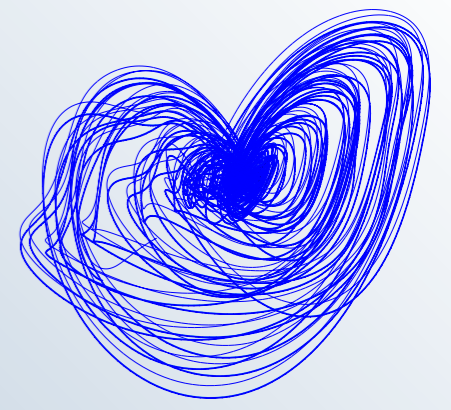
Critical Stick-Slip like



Synapse current avalanches



Random phase and back-scattering

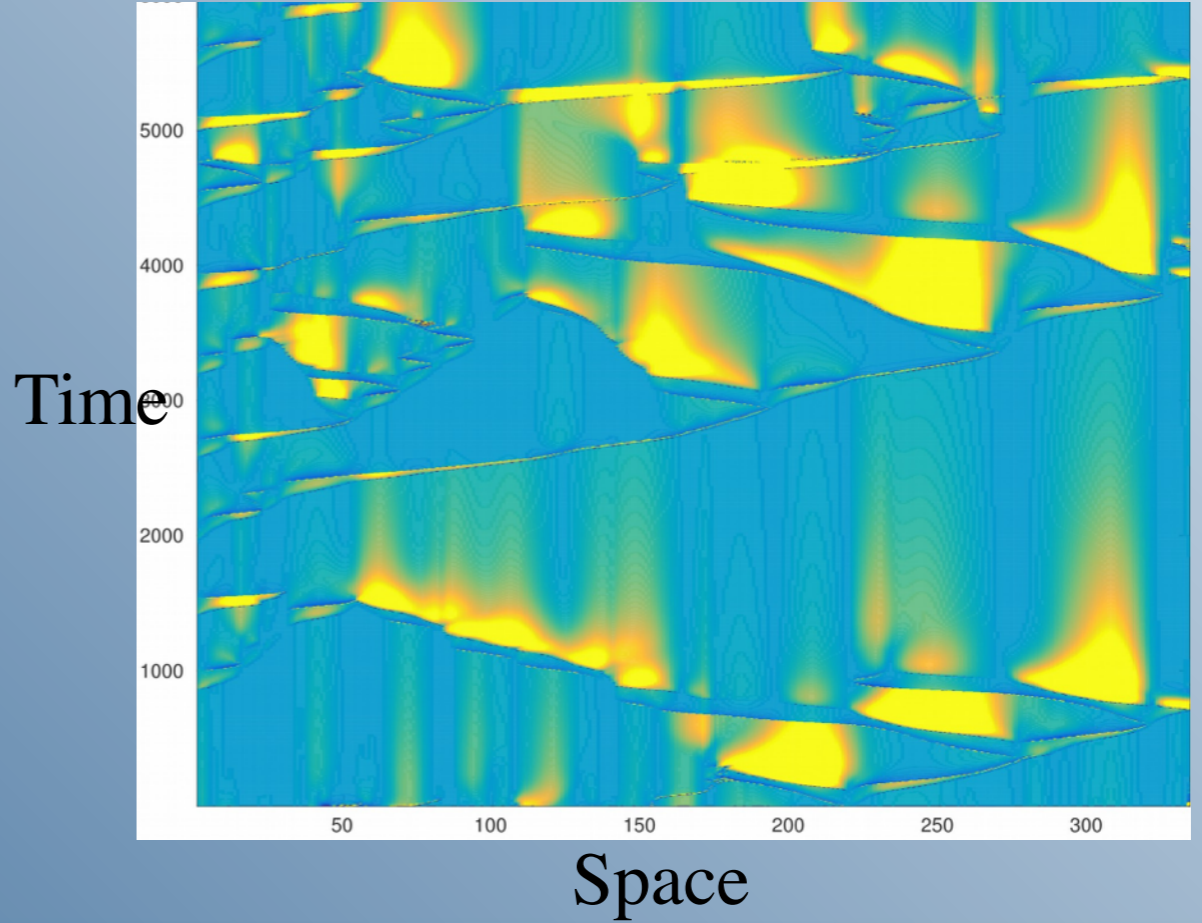
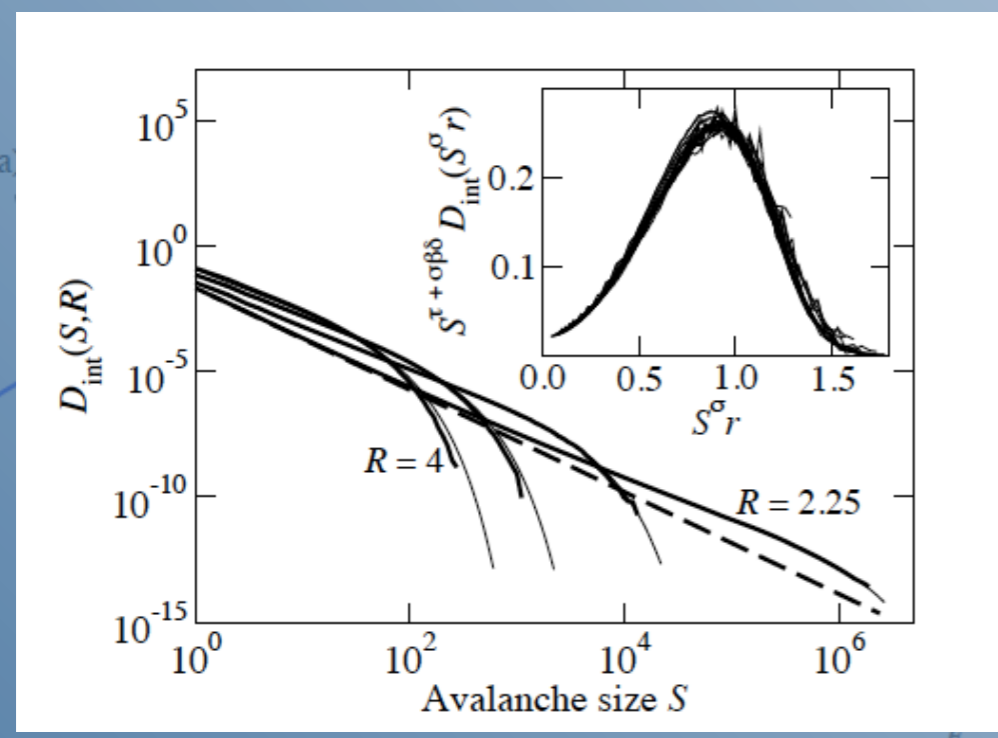


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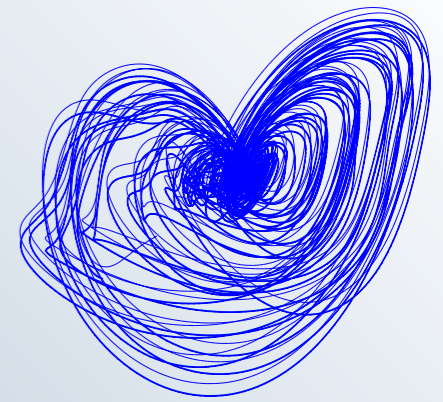
Synapse current avalanches



Sethna et al. 1996



Moving fronts on random media and signals?



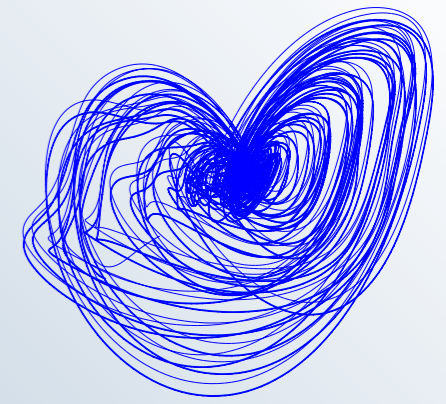
- According to this phenomenology the dynamics is of domain walls on random bonds:

$$\partial_t \mathbf{Z}(X, t) = D \nabla^2 \mathbf{Z}(X, t) + \eta(X, t) \mathbf{Z}(X, t)$$

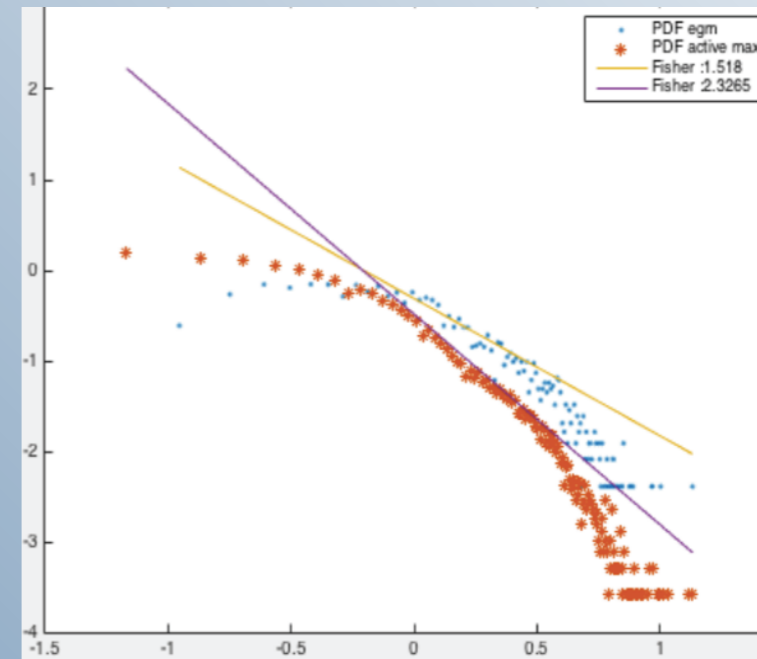
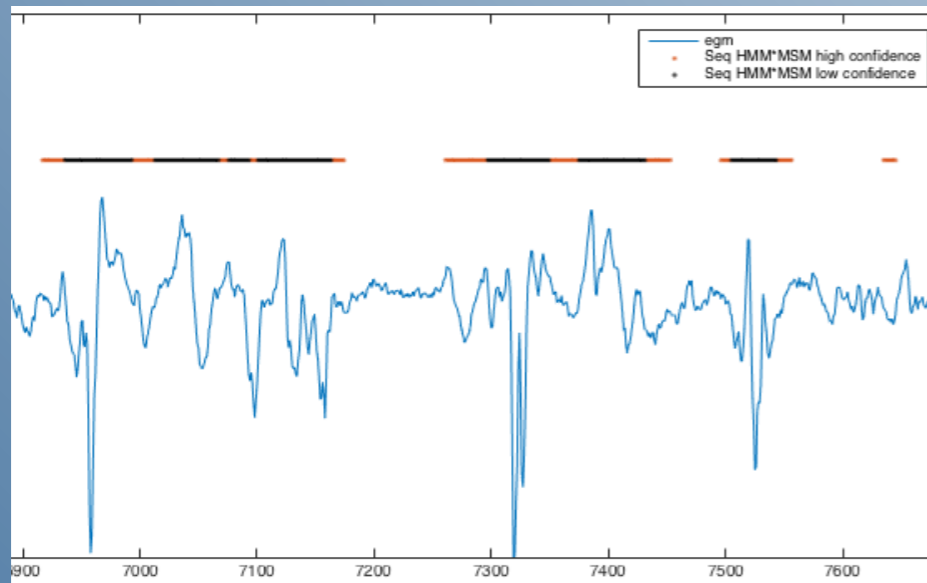
- The noise is *not white* due to dilute random connectivity.
- Can we tune the noise term from the data using MF-analysis to assess the substrate?
 - ➔ Statistical methods needed.

Thank you

Debuts



- Curing the very low potential contributions



- We are « segmenting » active windows only using HMM technique and MF-analysis (MSM). *Refines* scaling exponent measurements.
- How can we incorporate this « compressed sensing » in ConvNets of annotated data for classification of Fibs?

