Nonlinear Dynamics of the Heart (II)

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Signal Analysis and Classification

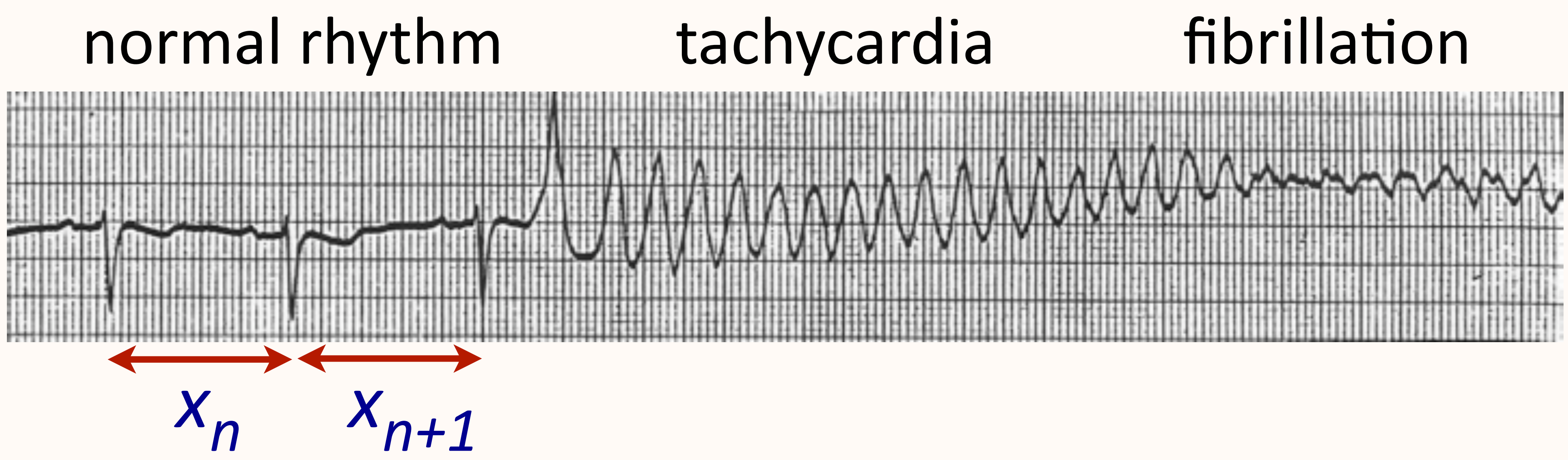
goals:

- optimization of low-energy anti-fibrillation pacing (LEAP)
- detecting patients with high risk for suffering from arrhythmias (ICD candidates)

In the following:
novel features (parameters, biomarkers) for signal analysis and classification employing Ordinal Patterns

Classifying Beat-to-Beat Time Series Using Ordinal Patterns

Electrocardiogram

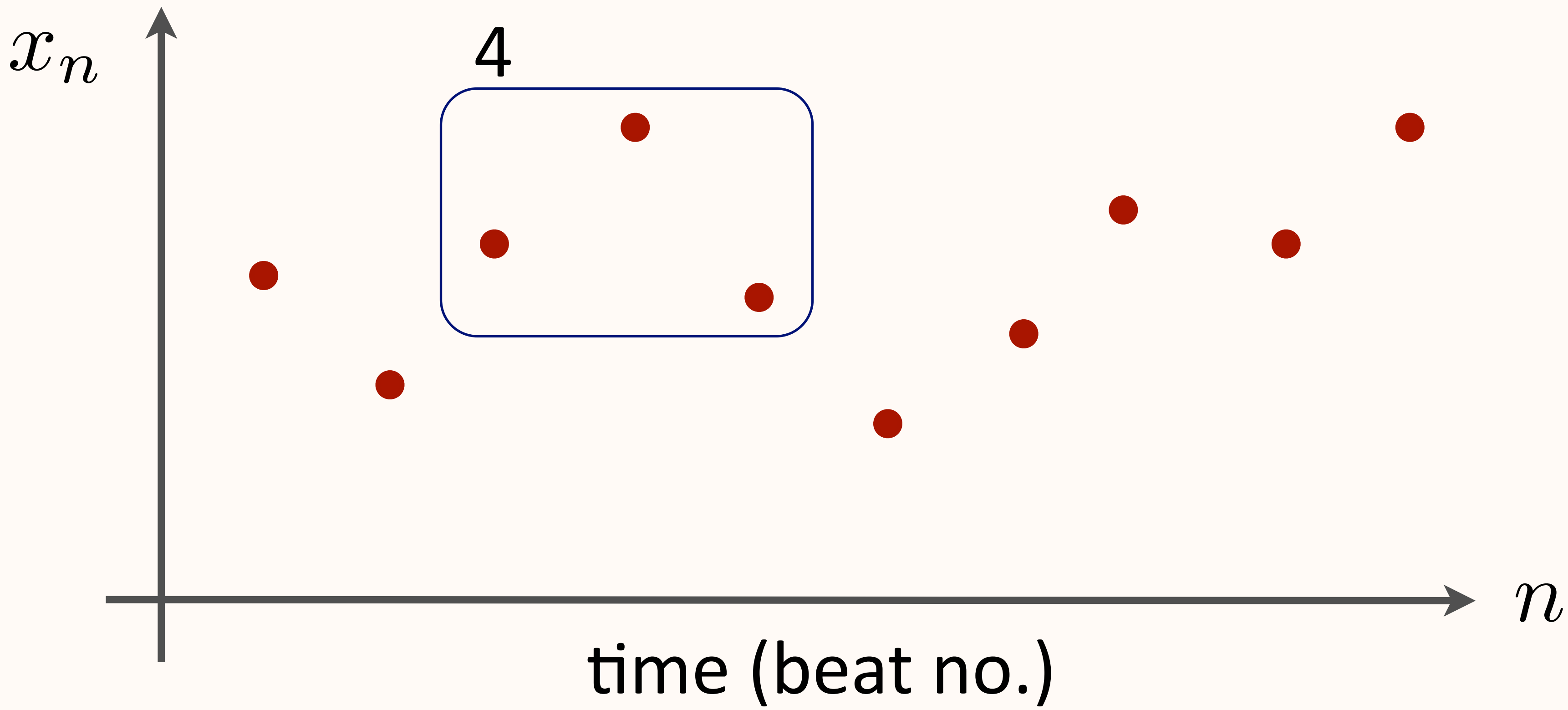


beat-to-beat intervals (RR intervals) $\longrightarrow$ time series $\{x_n\}$

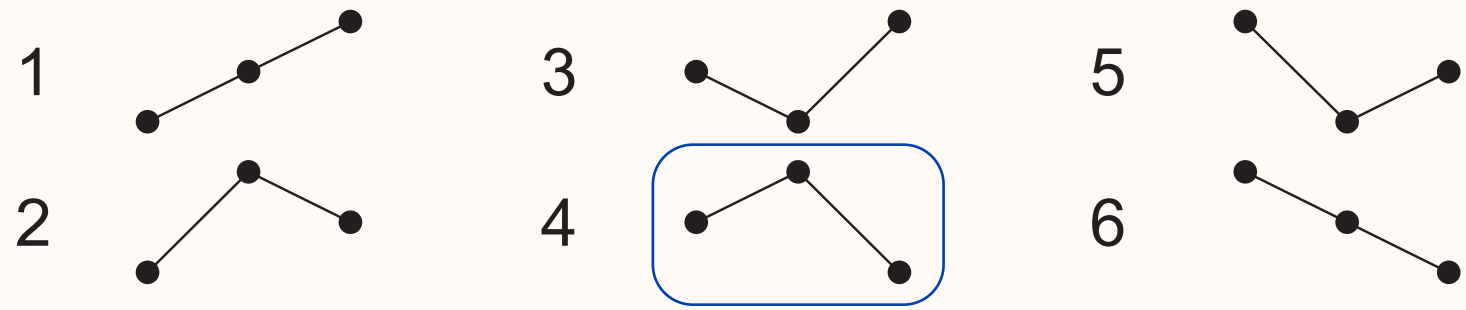
Characterization of RRI-time series using ordinal patterns describing amplitude relations within segments of time series.

Ordinal Patterns

time series (e.g., beat-to-beat intervals)

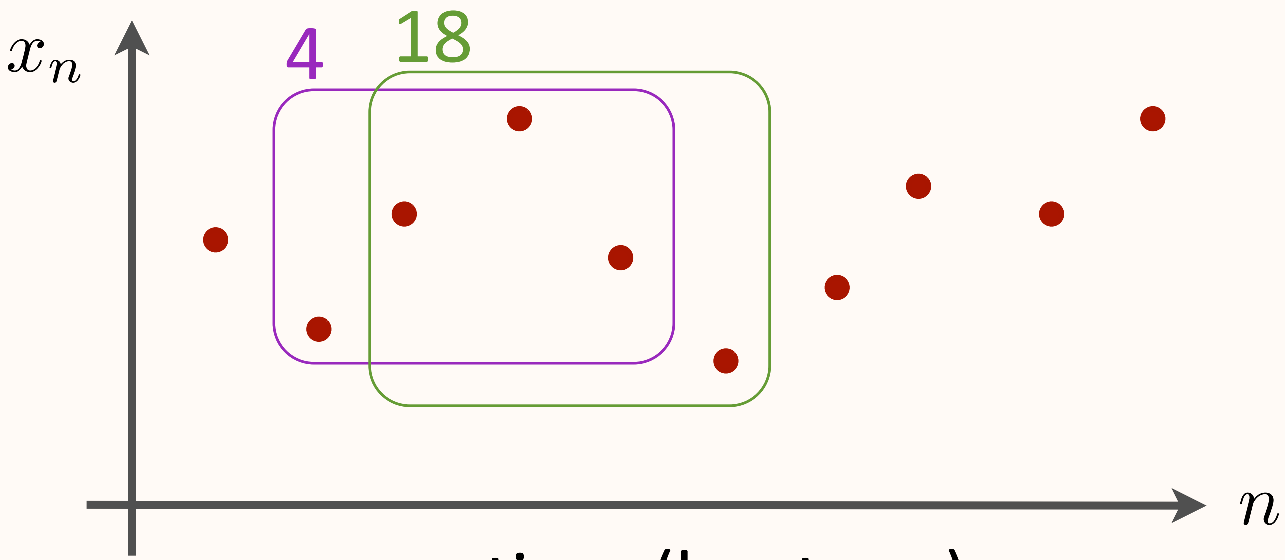


all ordinal patterns
of lenght $W = 3$



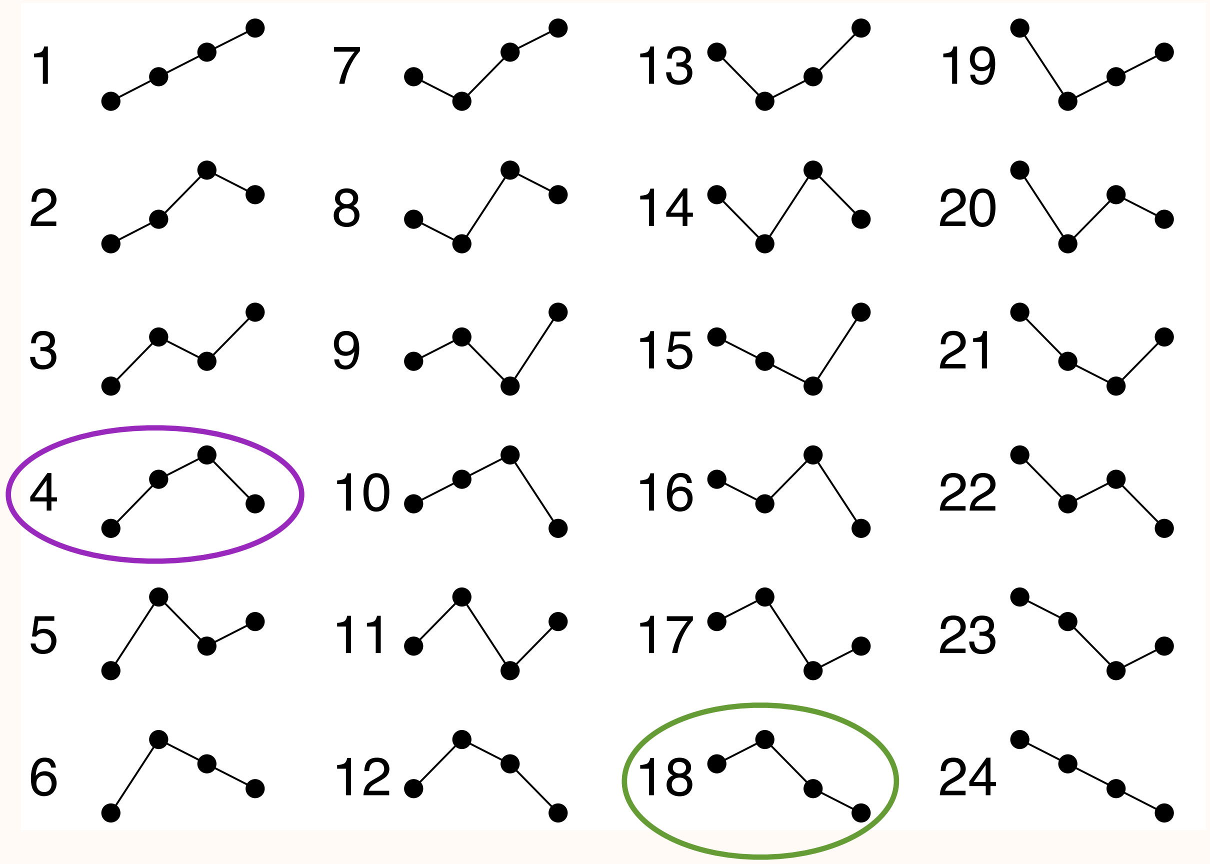
Ordinal Patterns

time series



time (beat no.)

Ordinal patterns of length *W=4* and corresponding permutation indices



time series $\{x_n\}$

↓

sequence of integers ranging from 1,...,$W!$
(symbols of a finite alphabet)

Determine how often a specific ordinal pattern occurs in the given times series ➞ ordinal pattern distribution

Ordinal Patterns (Order Patterns)

early work

- C. Bandt, B. Pompe, Phys. Rev. Lett. 88, 174102 (2002)

used for:

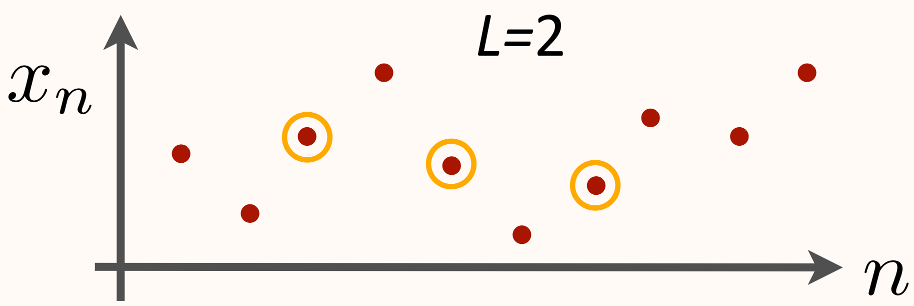
- detection of determinism in noisy time series
  - J.M. Amigo et al. Europhys. Lett. 79, 50001 (2007)
  - J.M. Amigo et al. Europhys. Lett. 83, 60005 (2008)
- estimation of transfer entropy in epilepsy
  - M. Staniek, K. Lehnertz, Phys. Rev. Lett. 100, 158101 (2008)
- detecting changes in time series
  - Y. Cao et al., Phys. Rev. E 70, 046217 (2004)

book

- J. M. Amigo, *Permutation Complexity in Dynamical Systems*, Springer-Verlag (2010)

Ordinal Pattern Distributions Characterizing Heart Rate Variability

Consider subsequences of beat-to-beat intervals sampled with lag *L*:



$$x_n, x_{n+L}, x_{n+2L}, \ldots, x_{n+(W-1)L}$$

Features (Heart Rate Variabilty (HRV) parameters, biomarkers) based on ordinal pattern statistics:

perm(L, W, I) = probability of occurrence of patterns with permutation index *I* for a given lag *L* and length *W*

perm entropy(L, W) = Shannon entropy based on all probabilities for a given lag *L* and a given word length *W*

are compared with other heart rate variability parameters

U. Parlitz et al., Computers in Biology and Medicine 42, 319-327 (2012)

Other HRV parameters

- conventional heart rate variability parameters, like
  - meanNN = mean RRI (inversely related to mean heart rate)
  - sdNN = standard deviation of RRI values
  - (V)LF = (very) low frequency band (0.0033–0.04 Hz) 0.04-0.15 Hz
  - HF = high frequency band 0.15–0.4 Hz
  - LFn = normalized low frequency band (LF/(LF-HF))
  - shannon = Shannon entropy (using amplitude binning)

- features based on symbolic dynamics, like
  - POLVARΔ = probability of occurrence of the subsequence ''000000'' in a symbolic string defined by:

$$s_n(x_n) = \begin{cases} 0: & |x_n - x_{n-1}| < \Delta\mathrm{ms} \\ 1: & |x_n - x_{n-1}| \geq \Delta\mathrm{ms} \end{cases}$$

  - FWSHANNON and FORBWORD = Shannon entropy and probability of forbidden words of length three (based on 4 symbols from non-uniform quantization levels)

Evaluation of Classification Performance

Two data sets (24h beat-to-beat intervals, @256hz):

- 15 patients (11 male, 4 female, ages 56 ± 11 yr) suffering from congestive heart failure (CHF) (from physionet)
- 15 healthy subjects (11 male, 4 female, ages 56 ± 5 yr)

Task: Distinguish (classify) both groups using
probabilities of ordinal patterns
(ordinal pattern distributions) as features

Leave-one-out cross validation for a simple classification scheme minimizing the number of misclassifications on the training set.

Evaluation of classification using *p*-values and cross-validation

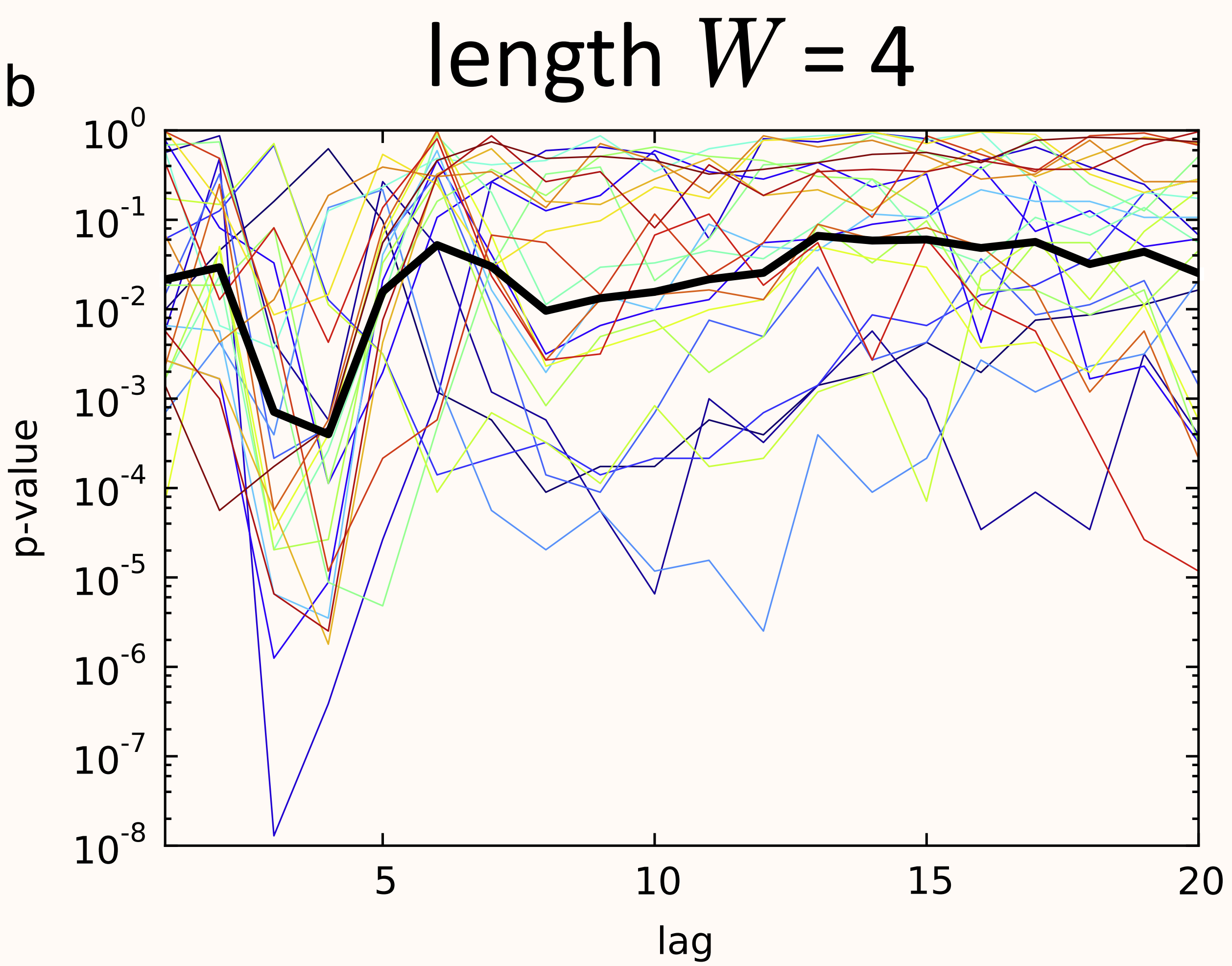
Typical results : *perm(L, W, I)*

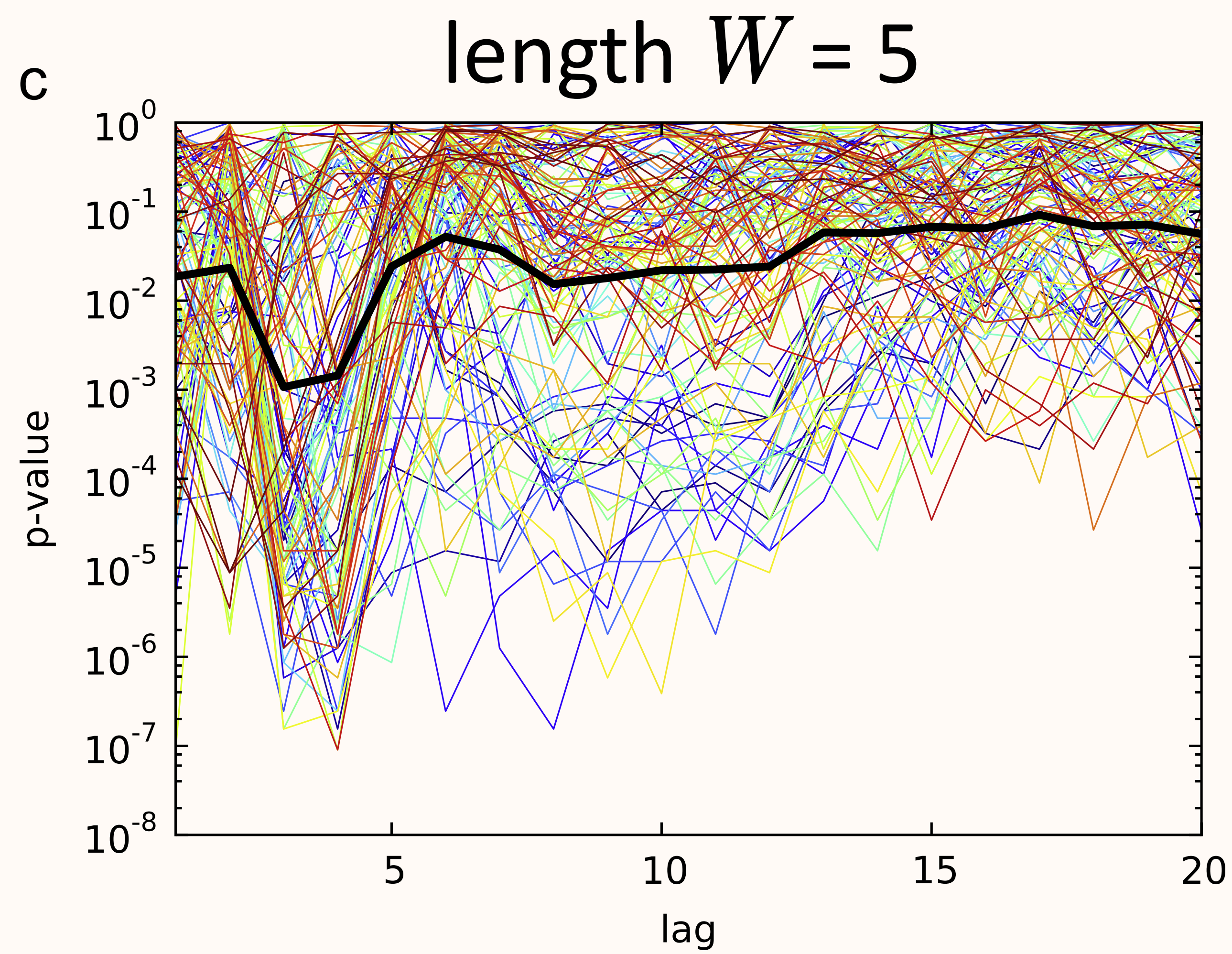
Feature	mean value ± standard deviation		p-value	% of correct classifications		
	Control	CHF		Both	Control	CHF
perm(3,3,5)	13.8 ± 0.7	15.3 ± 0.6	$1.6 \cdot 10^{-05}$	87	80	93
perm(3,4,3)	2.89 ± 0.64	4.49 ± 0.52	$1.3 \cdot 10^{-08}$	**100**	**100**	**100**
perm(4,4,3)	2.76 ± 0.40	4.53 ± 0.80	$3.9 \cdot 10^{-07}$	97	100	93
perm(3,4,5)	2.87 ± 0.64	4.50 ± 0.66	$1.3 \cdot 10^{-06}$	87	93	80
perm(4,5,109)	1.34 ± 0.11	0.83 ± 0.20	$9.0 \cdot 10^{-08}$	97	100	93
VLF	7.8 ± 4.9	2.5 ± 4.1	$2.7 \cdot 10^{-05}$	80	80	80
LF	3.24 ± 2.34	0.55 ± 0.62	$1.6 \cdot 10^{-05}$	70	73	67
HF	0.90 ± 0.84	0.41 ± 0.50	$4.3 \cdot 10^{-03}$	73	80	67
LFn	0.79 ± 0.07	0.55 ± 0.12	$1.3 \cdot 10^{-06}$	83	87	80
meanNN	786 ± 60	668 ± 119	$3.7 \cdot 10^{-03}$	77	93	60
sdNN	121 ± 31.1	62 ± 24	$3.5 \cdot 10^{-06}$	90	93	87
shannon	3.10 ± 0.24	2.33 ± 0.40	$2.4 \cdot 10^{-07}$	87	87	87
FORBWORD	4.07 ± 4.27	0.87 ± 1.75	$1.6 \cdot 10^{-03}$	80	87	73
FWSHANNON	3.60 ± 0.15	3.83 ± 0.13	$1.7 \cdot 10^{-04}$	80	73	87
POLVAR5	$6.9 \cdot 10^{-04} \pm 1.0 \cdot 10^{-03}$	0.036 ± 0.033	$5.2 \cdot 10^{-08}$	93	93	93
POLVAR20	0.286 ± 0.194	0.683 ± 0.216	$1.1 \cdot 10^{-04}$	80	80	80

Features based on ordinal patterns provide competitive classification results!

Dependence of Ordinal Pattern Distributions on Sampling Lag

p-values of ordinal pattern distributions vs. sampling lag L





colored curves: different ordinal patterns

black curve: mean value of $\log(p)$-values

lag L=3 ➛ pattern of length W = 4 spans 12 heart beats which corresponds to a period of roughly ten seconds or 0.1Hz (LF range).

Evaluation of the classifier's performance

$\oplus, \ominus$ classification result

$+, -$ true value

N the number of observations

$$N(\bullet,\bullet) = \begin{pmatrix} N(\oplus,+) & N(\ominus,+) \\ N(\oplus,-) & N(\ominus,-) \end{pmatrix} = \begin{pmatrix} \text{True positive} & \text{False negative} \\ \text{False positive} & \text{True negative} \end{pmatrix}$$

sensitivity: $$p(\oplus|+) = \frac{N(\oplus,+)}{N(\oplus,+)+N(\ominus,+)}$$

specificity: $$p(\ominus|-) = \frac{N(\ominus,-)}{N(\oplus,-)+N(\ominus,-)}$$

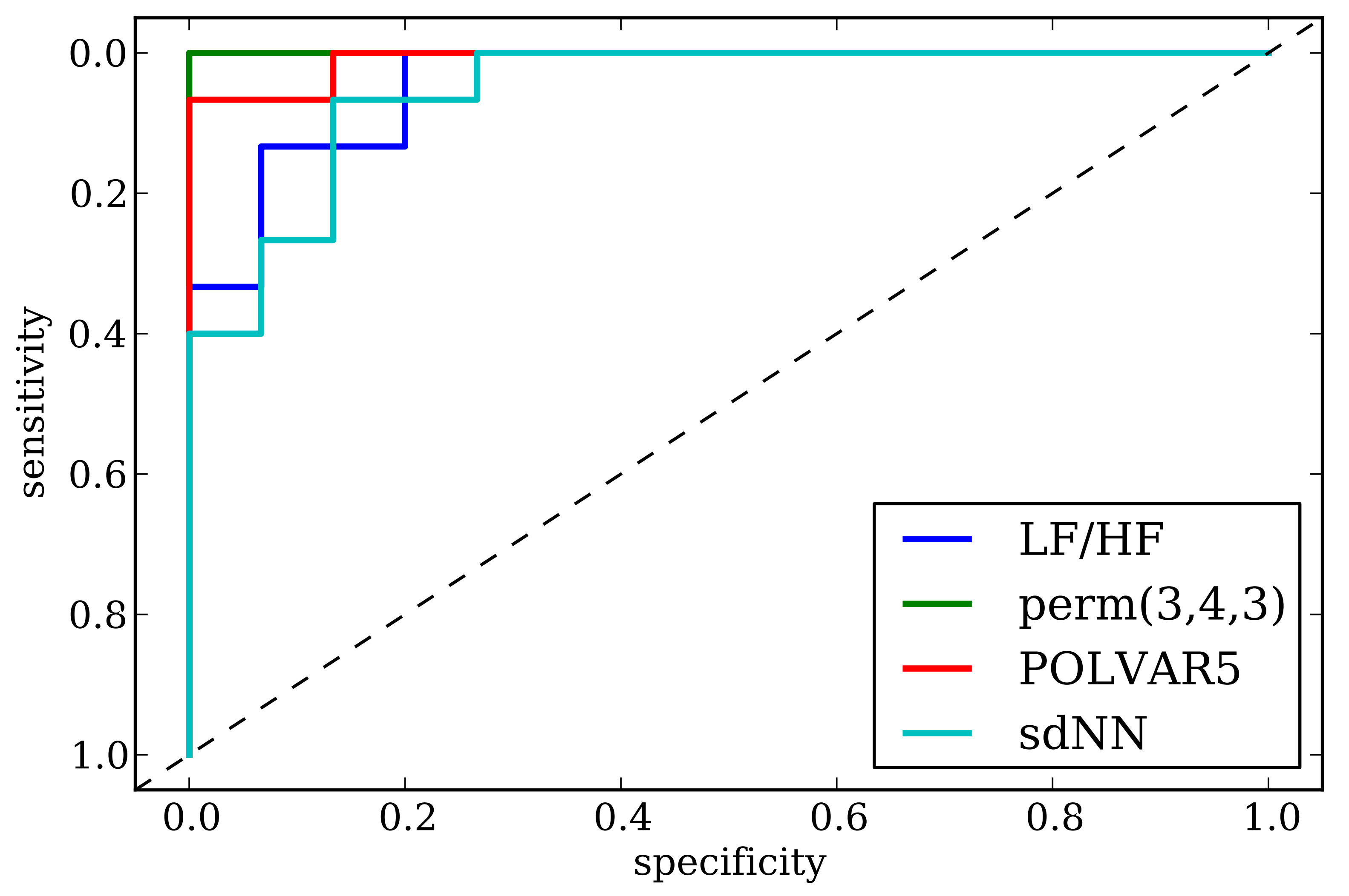
positive predictive value: $$p(+|\oplus) = \frac{N(\oplus,+)}{N(\oplus,+)+N(\oplus,-)}$$

negative predictive value: $$p(-|\ominus) = \frac{N(\ominus,-)}{N(\ominus,+)+N(\ominus,-)}$$

Evaluation of the classifier's performance

Receiver operating characteristic curves

sensitivity vs. specificity as a function of a bias parameter



- diagonal represents a random guess
- the larger the area under the ROC-curve, the better the classifier

Robustness

with pre-filtering

Feature	p-value	% of correct class. Both	Con.	CHF	sensitivity	specificity	predicitive value positive	negative
sdNN	$3.5 \cdot 10^{-6}$	90	93	87	87	93	93	88
VLF	$2.7 \cdot 10^{-5}$	80	80	80	80	80	80	80
LF	$1.6 \cdot 10^{-5}$	70	73	67	67	73	71	69
HF	$4.3 \cdot 10^{-3}$	73	80	67	67	80	77	71
perm(3,4,3)	$1.3 \cdot 10^{-8}$	100	100	100	100	100	100	100
perm(4,4,3)	$3.9 \cdot 10^{-7}$	97	100	93	93	100	100	94
perm(3,4,5)	$1.3 \cdot 10^{-6}$	87	93	80	80	93	92	82
perm(4,4,18)	$1.8 \cdot 10^{-6}$	93	100	87	87	100	100	88
perm(4,5,109)	$9.0 \cdot 10^{-8}$	97	100	93	93	100	100	94

without pre-filtering

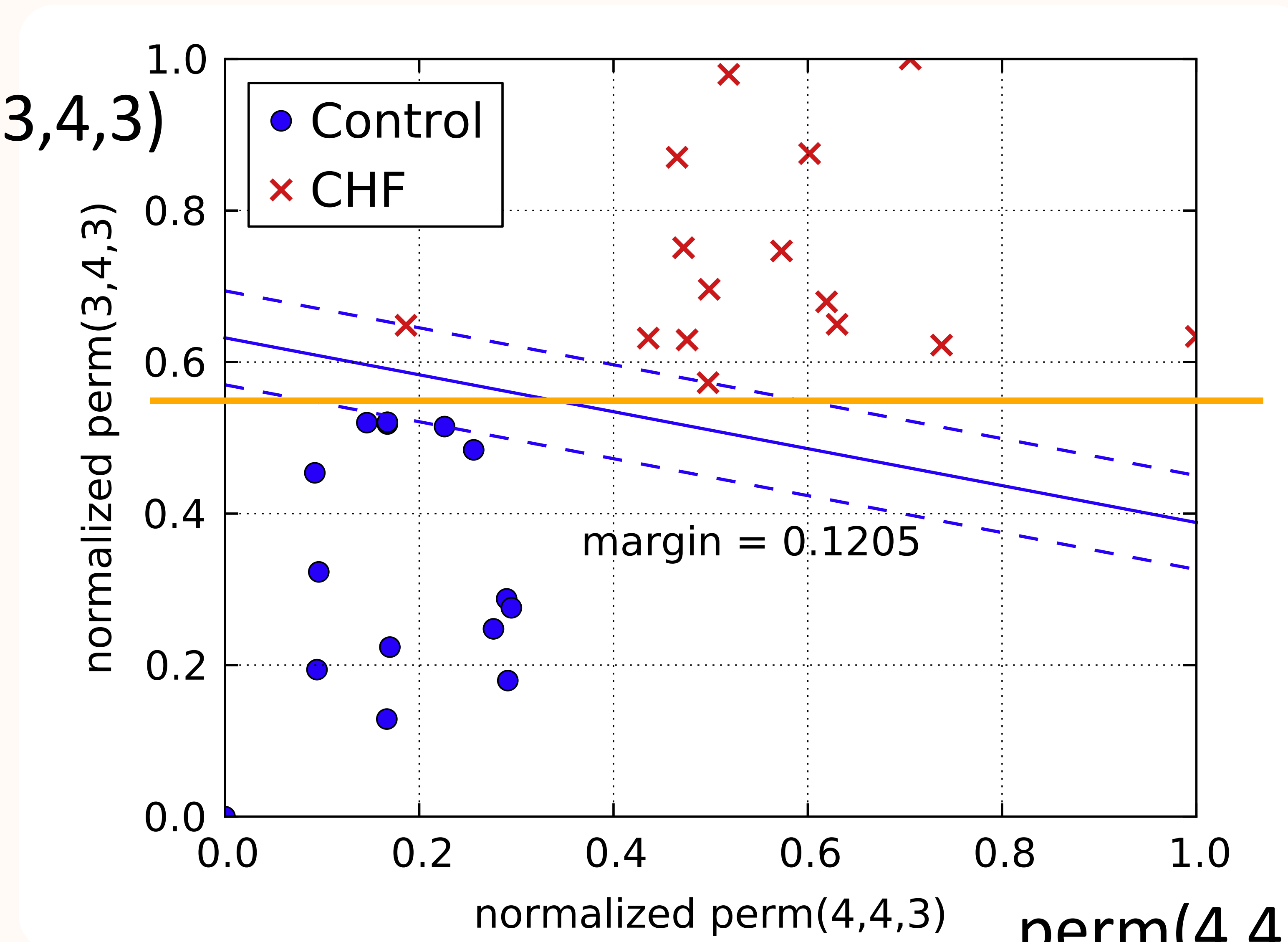
features based on ordinal pattern are not sensitive to noise

Feature	p-value	Both	Con.	CHF	sensitivity	specificity	positive	negative
sdNN	$2.7 \cdot 10^{-1}$	67	87	47	47	87	78	62
VLF	$2.9 \cdot 10^{-2}$	67	80	53	53	80	73	63
LF	$2.2 \cdot 10^{-1}$	60	73	47	47	73	64	58
HF	$2.7 \cdot 10^{-1}$	70	100	40	40	100	100	63
perm(3,4,3)	$1.3 \cdot 10^{-8}$	100	100	100	100	100	100	100
perm(4,4,3)	$5.8 \cdot 10^{-7}$	97	100	93	93	100	100	94
perm(3,4,5)	$3.9 \cdot 10^{-7}$	90	93	87	87	93	93	88
perm(4,4,18)	$2.5 \cdot 10^{-6}$	97	100	93	93	100	100	94
perm(4,5,109)	$9.0 \cdot 10^{-8}$	97	100	93	93	100	100	94

Bivariate classification using pairs of (successful) features

Distribution of CHF cases (red crosses) and healthy subjects (blue filled circles) in two-dimensional feature space. The separating (solid) lines are computed using a linear support vector machine maximizing the margins (indicated by dashed lines).

perm(3,4,3)



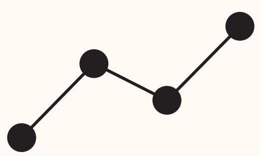
perm(4,4,3)

lag $L = 3$

word length $W = 4$

pattern no. $I = 3$

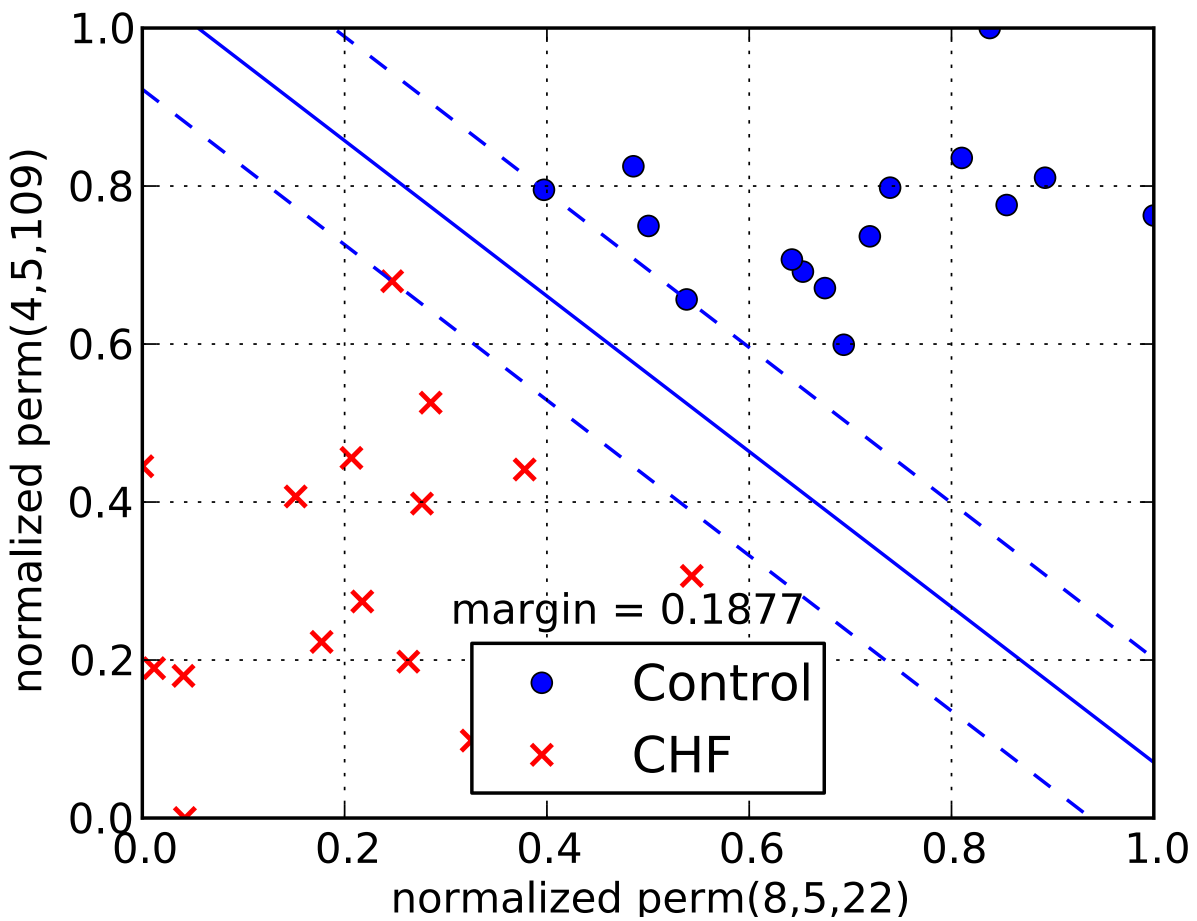
3



Bivariate classification using pairs of (successful) features

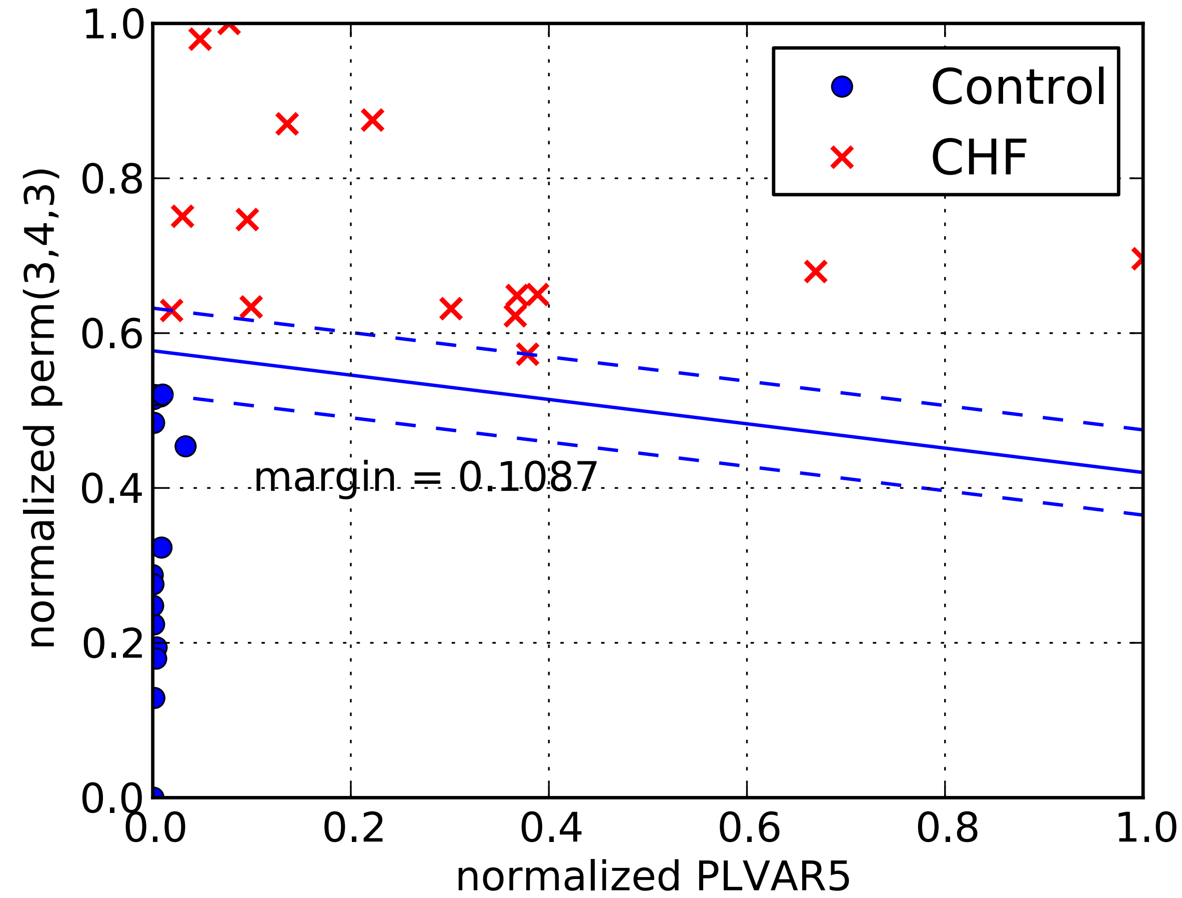
W = 5

perm(4,5,109) vs. perm(8,5,22)



W = 4

perm(3,4,3) vs. PLVAR5



Controlling Cardiac Arrhythmias

- Cardiovascular Diseases (CVDs) are the leading causes of death and disability in the world.
- An estimated 17.3 million people died from CVDs in 2008 (30% of all global deaths)
- By 2030, almost 23.6 million people will die from CVDs

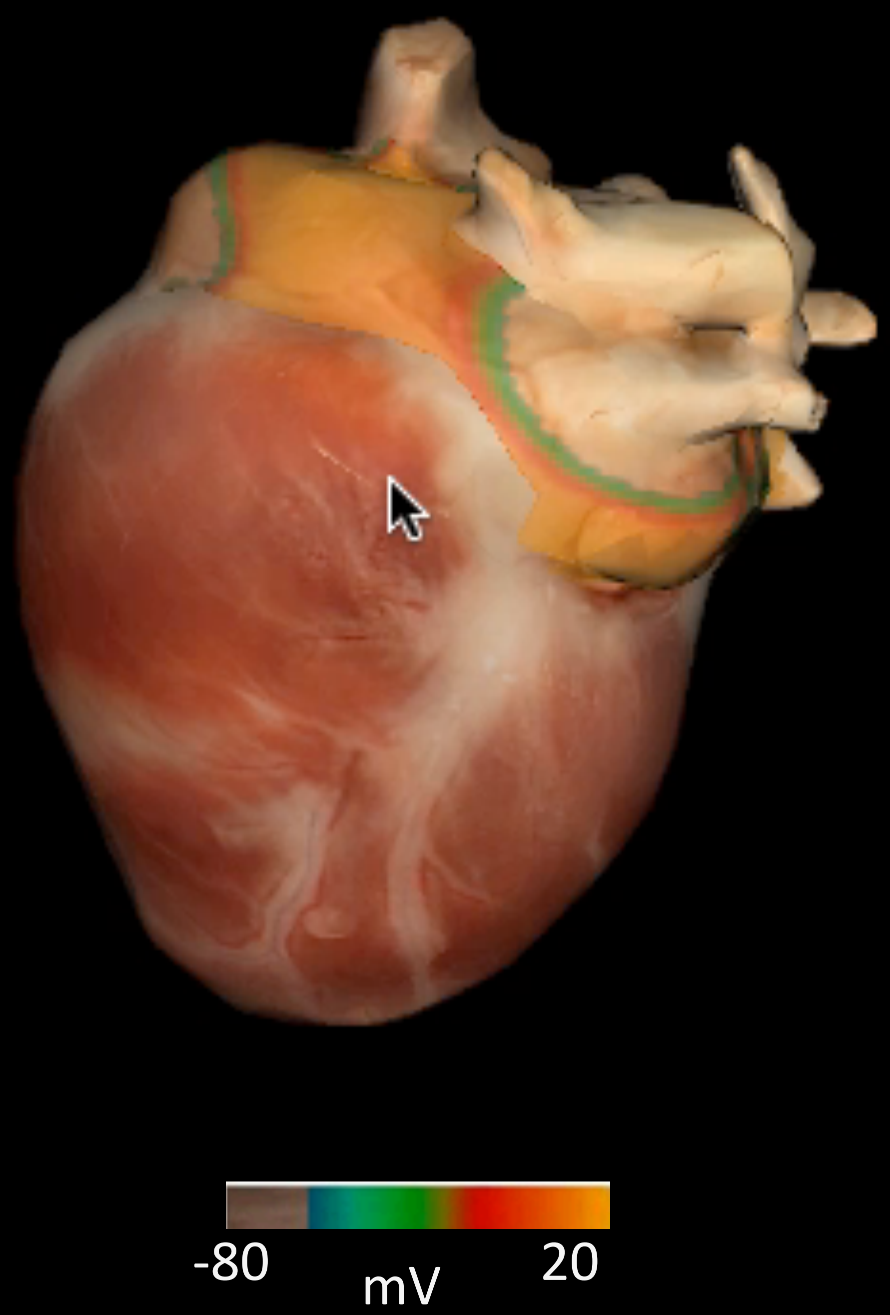
World Health Organization

Ventricular Fibrillation (VF)

http://thevirtualheart.org/

- Most common deadly manifestation of cardiac disease
- 100.000 – 200.000 sudden cardiac deaths (SCD) in Germany per year
- Requires immediate defibrillation using high-energy shock

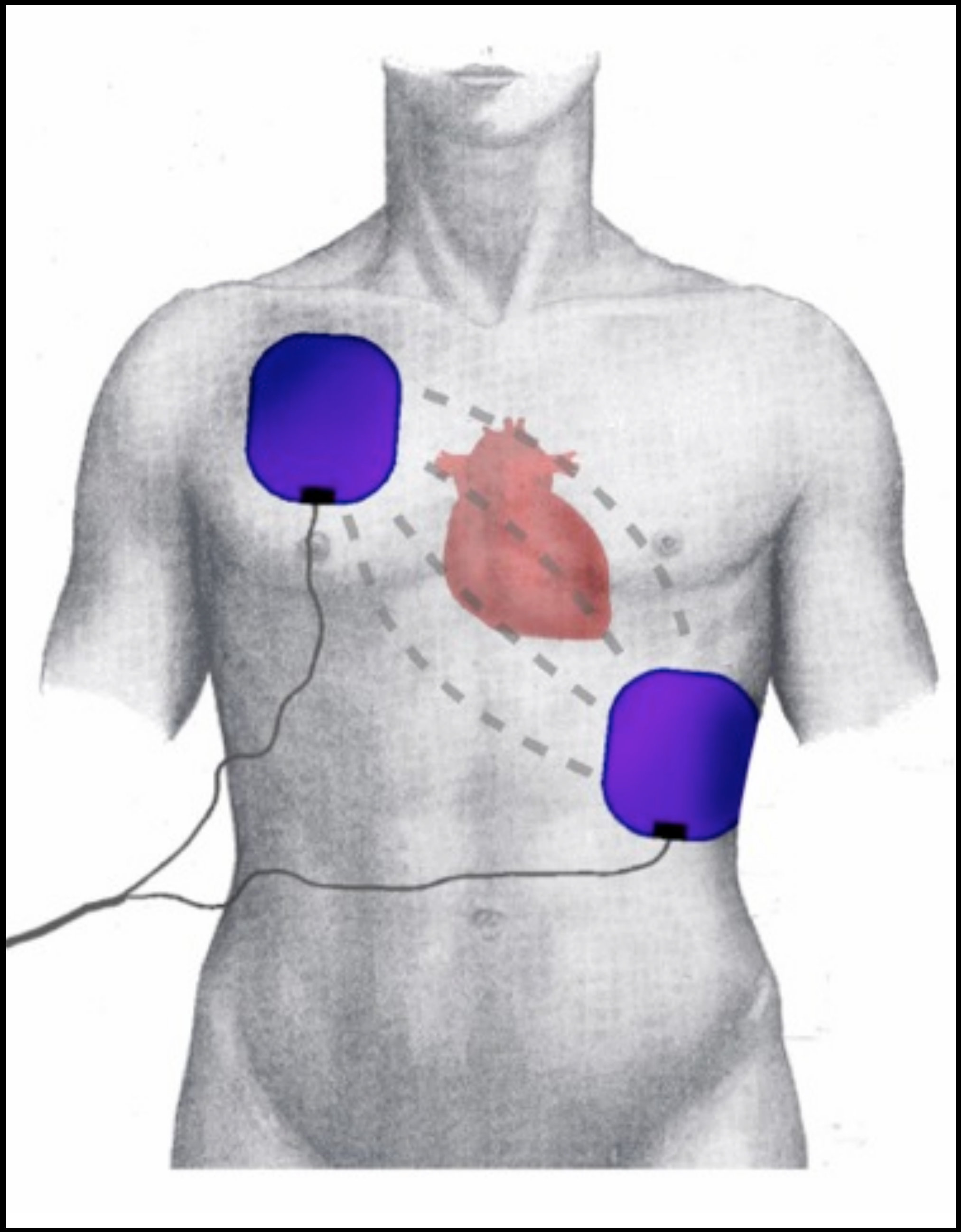
Atrial Fibrillation (AF)



http://thevirtualheart.org/

- Most common form of arrhythmia
- 1 million patients in Germany
- Not immediately life-threatening
- Chronic AF increases risk of thrombo-embolism and stroke

Defibrillation



Principle:
Reset electrical activity

Electric shocks, energy 360J

- 1000 V
- 30 A
- 12 ms

Severe side effects

- tissue damage
- traumatic pain

G.P. Walcott et al Resuscitation 59 59-70 (2003)

Scientific Challenges

- **How is cardiac fibrillation induced?**
  Understand genetic/molecular and dynamic arrhythmia trigger mechanisms.

- **How to control cardiac fibrillation?**
  - Advance fundamental understanding of control of spatially extended biological dynamical systems.
  - Develop quantitative electro-mechanical model of the (diseased) heart, including fluid dynamics, based on parameter estimation and model evaluation.

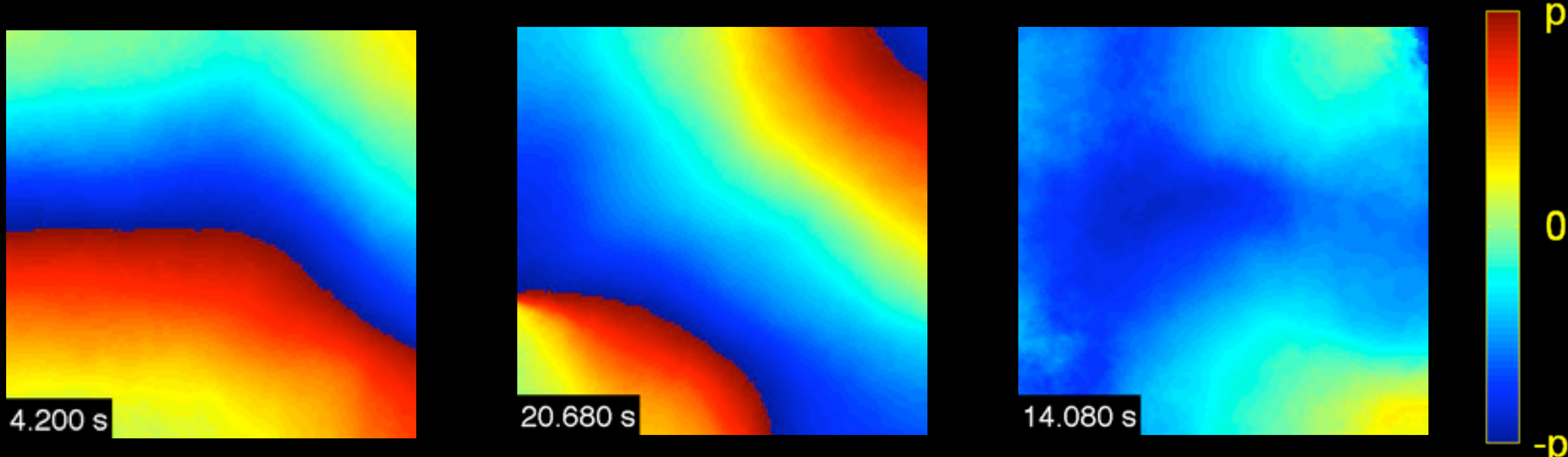
Long-term perspective: Open the path for painless and non-damaging defibrillation.

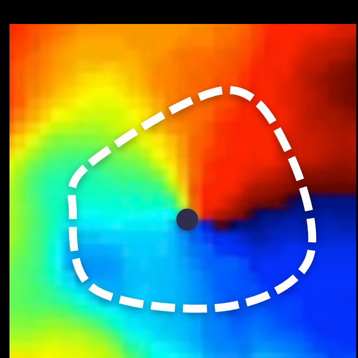
WHY ARE ARRHYTHMIAS DIFFICULT TO TERMINATE?

Phase Singularities

Phase Dynamics of Electrical Excitation in a Cardiac Monolayer

Plane Wave $\longrightarrow$ Instability $\longrightarrow$ Fibrillation





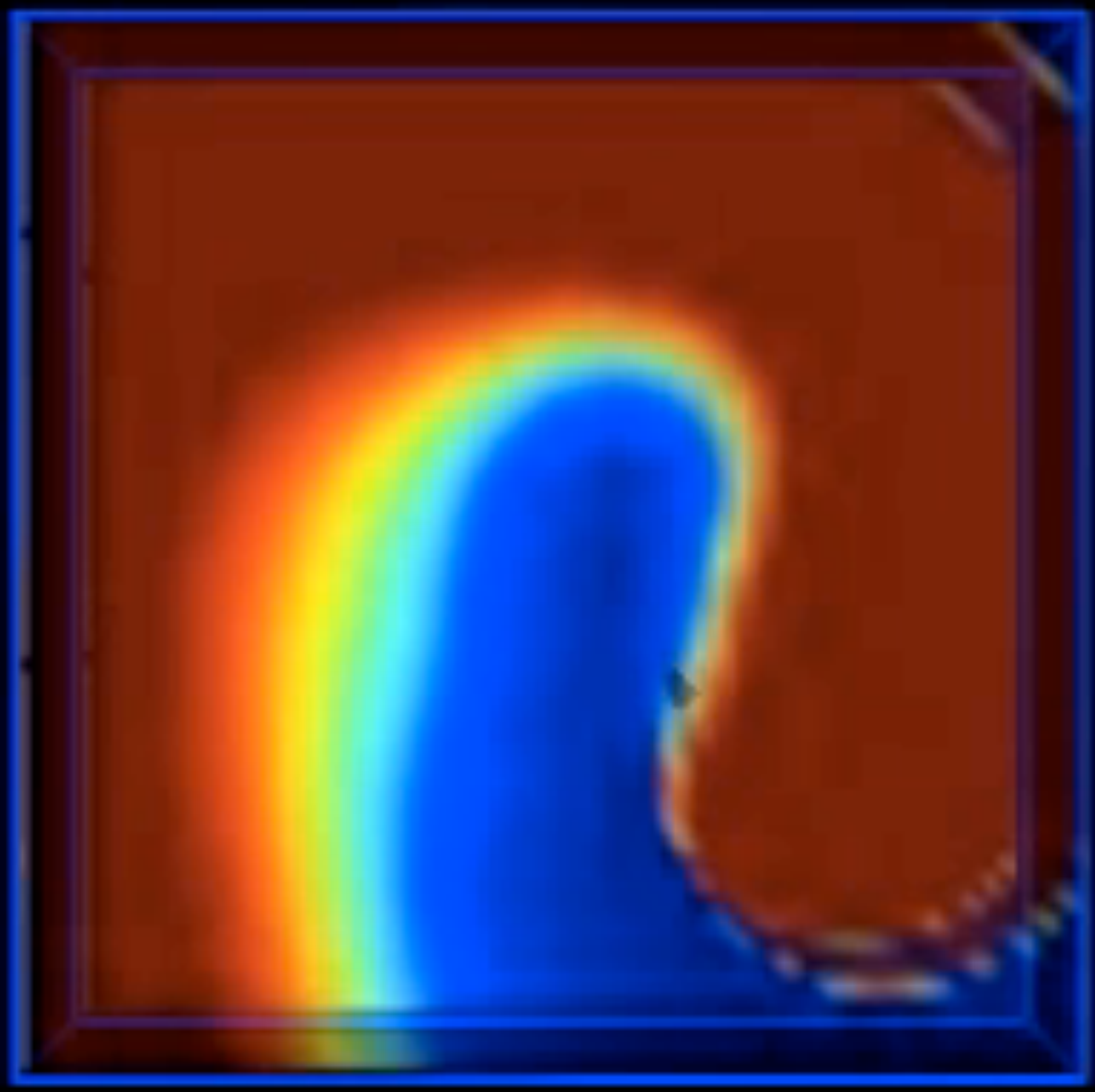
$$\oint \vec{\nabla}\phi \cdot d\vec{l} = 2\pi(n-m)$$

n # clockwise

m # counter

Three dimensional spiral waves

2D		3D
Spiral waves	→	Scroll waves
Spiral tip	→	Vortex filament



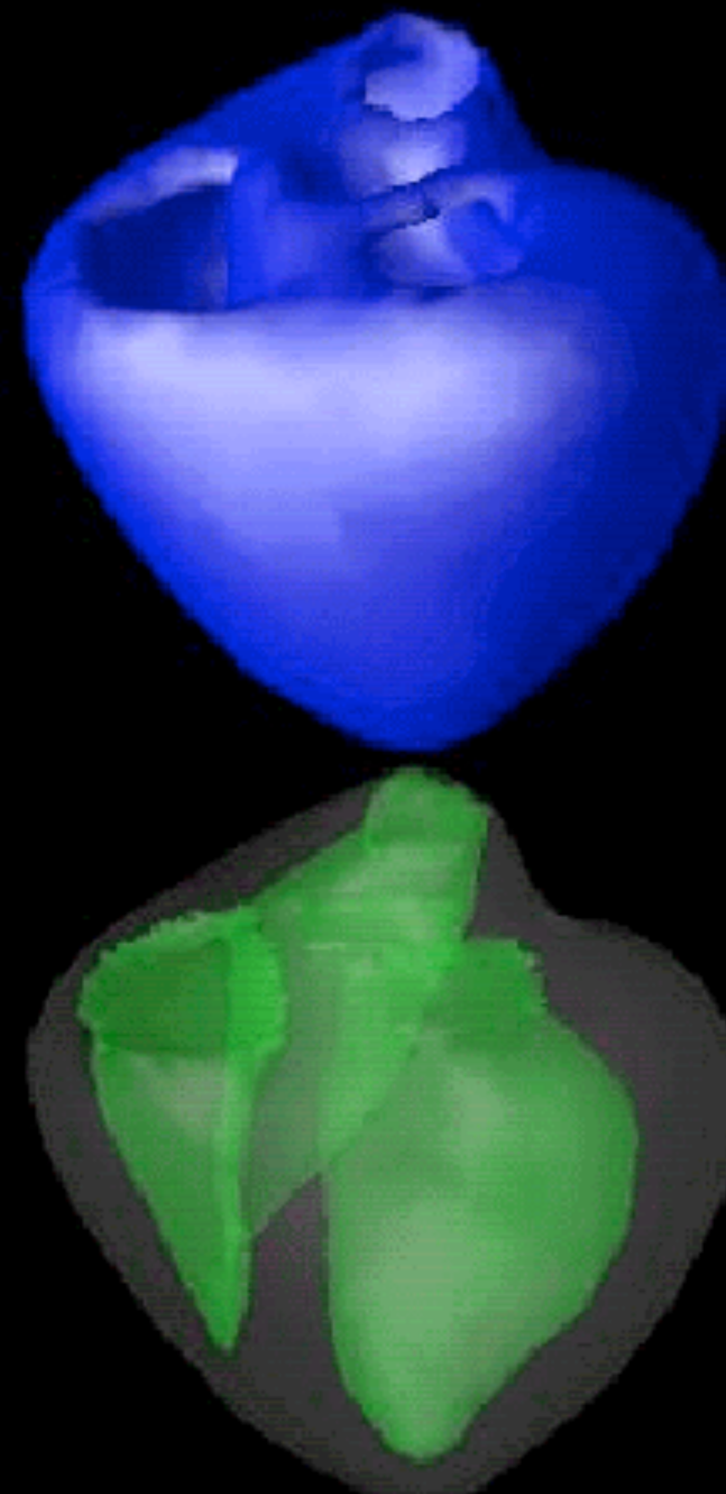
Ventricular Fibrillation (VF)

3D Simulation

Membrane potential

Phase singularities

(Filaments)



F. Fenton, E. Cherry

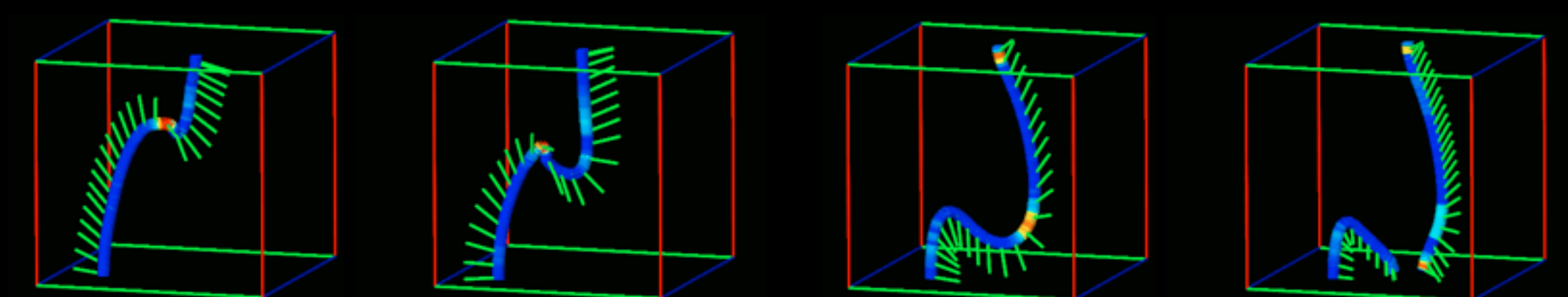
Phase Singularities

… are the organizing centers of fibrillation.

… obey conservation law for topological charge.

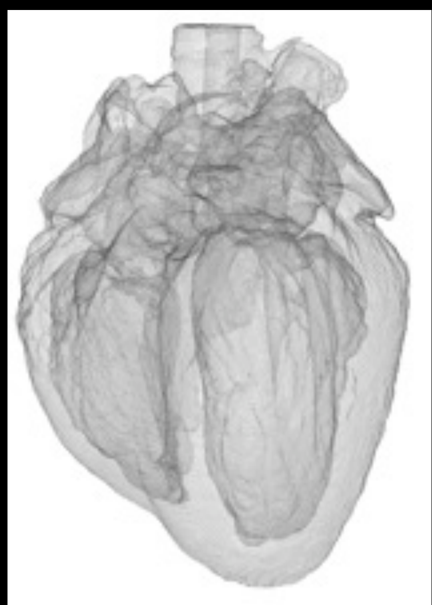
… interact with inhomogenous anatomical substrate.

… indicate where the system is most susceptible
to pertubations.

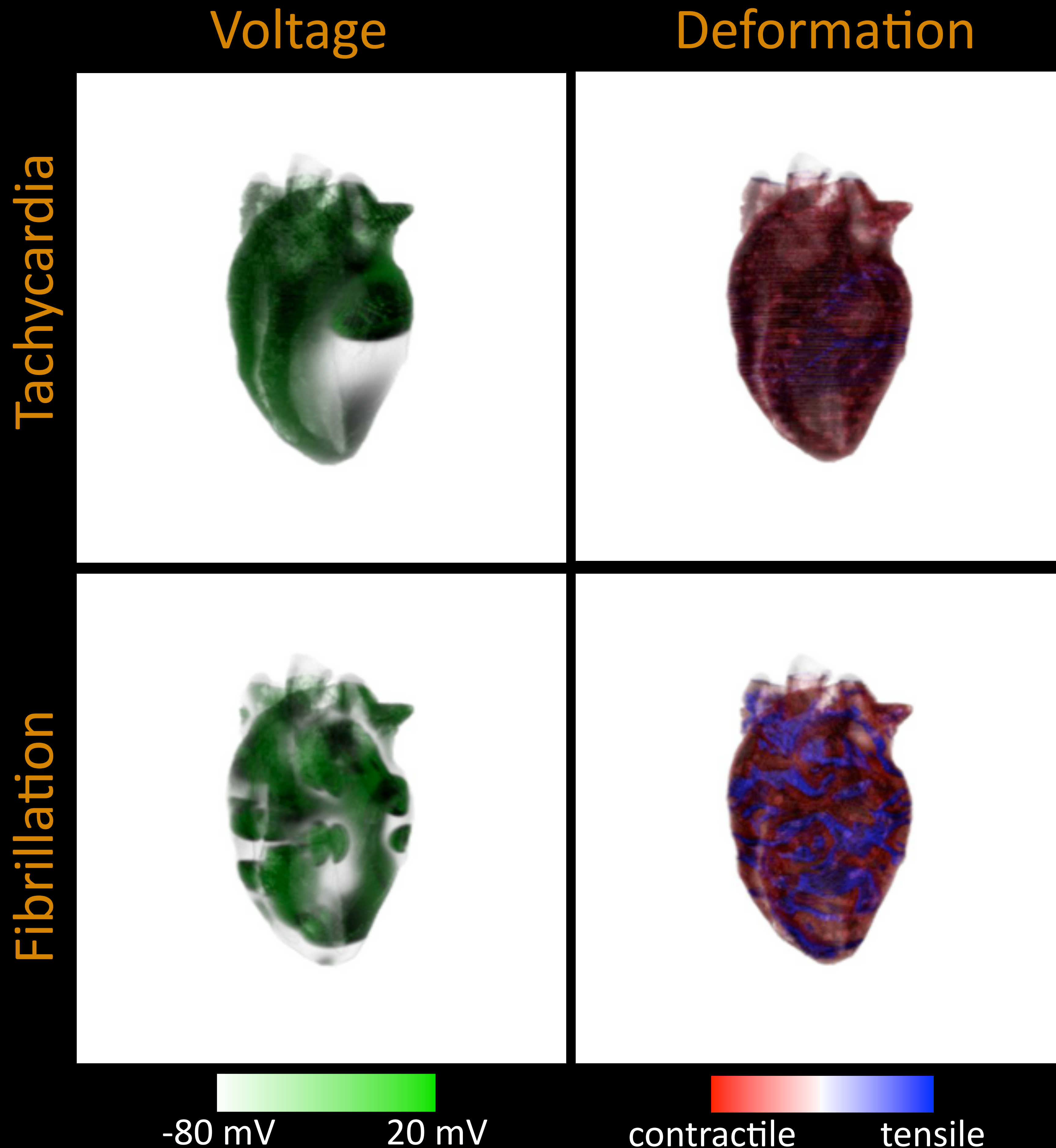


Fiber-Rotation-Induced Vortex Turbulence
Fenton, Karma, PRL 81, 481 (1998)

Contracting Heart

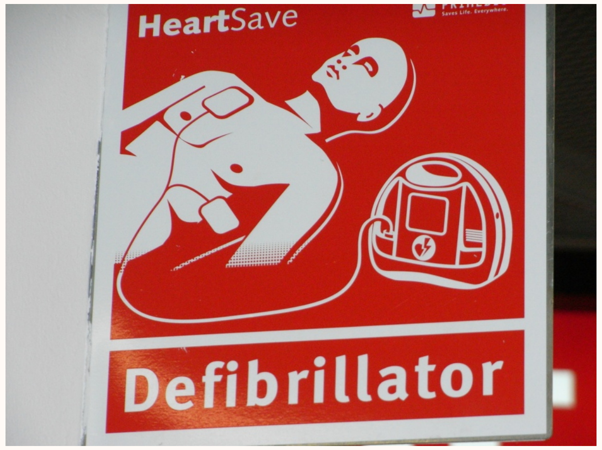


Rabbit Heart



Terminating Arrhythmias by Defibrillation

defibrillator



- by a large electric current, all cells in the heart are excited putting them into the refractory period (i.e. all activity ceases)
- the result is a quiescent medium, which can now resume normal activity (triggered by the sine node .... hopefully)
- problem: huge amounts of energy are delivered to the cardiac muscle that they can cause injuries that are very painful and increase the risk of future fibrillation
- a more gentle way of terminating arrhythmia is needed

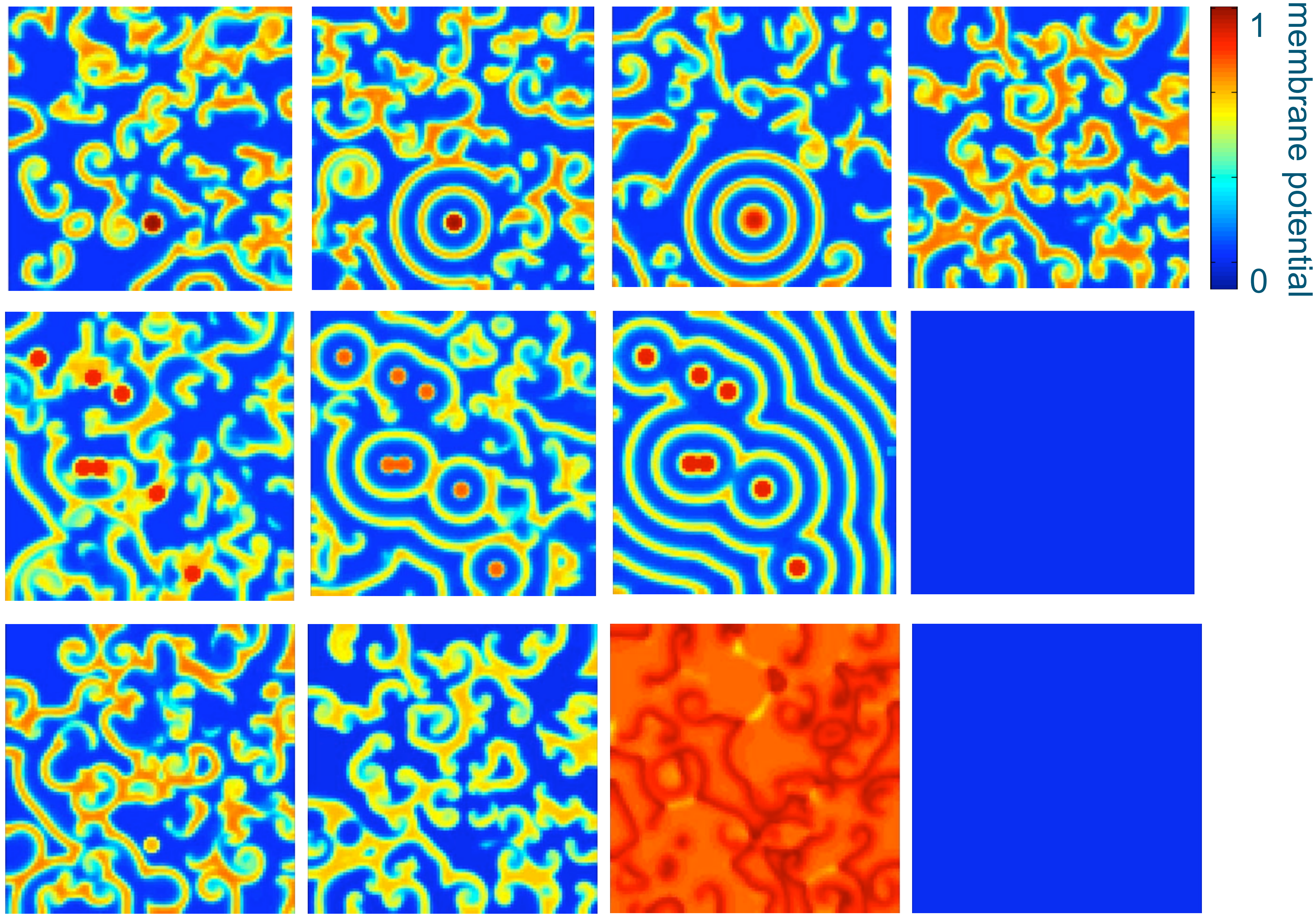
Local Excitation using Sequences of Pulses

fails!

8 pulses at
1 location

8 pulses at
7 locations

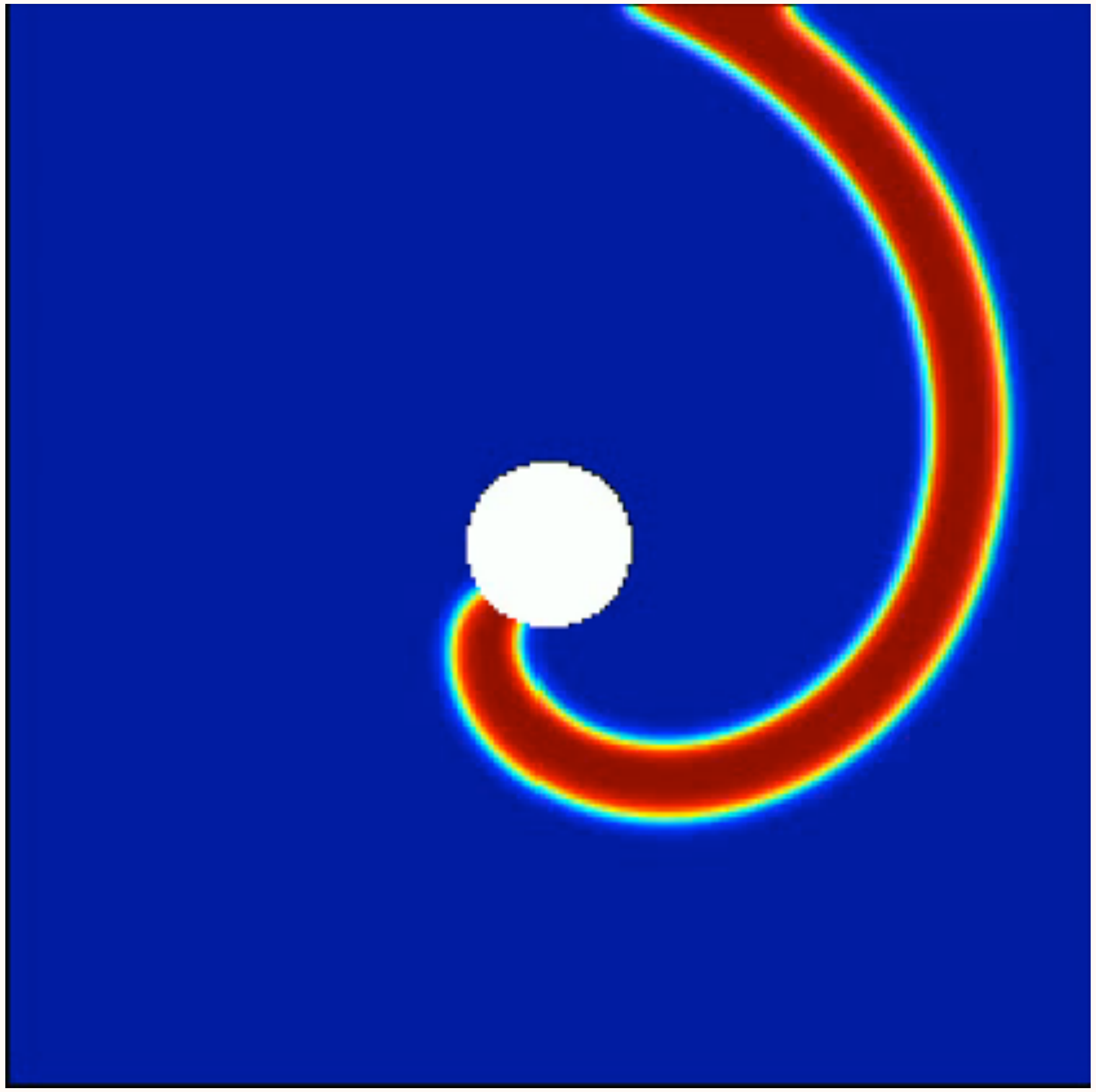
conventional
defibrillation



simulation: P. Bittihn

Another Problem: Pinned Spiral Waves

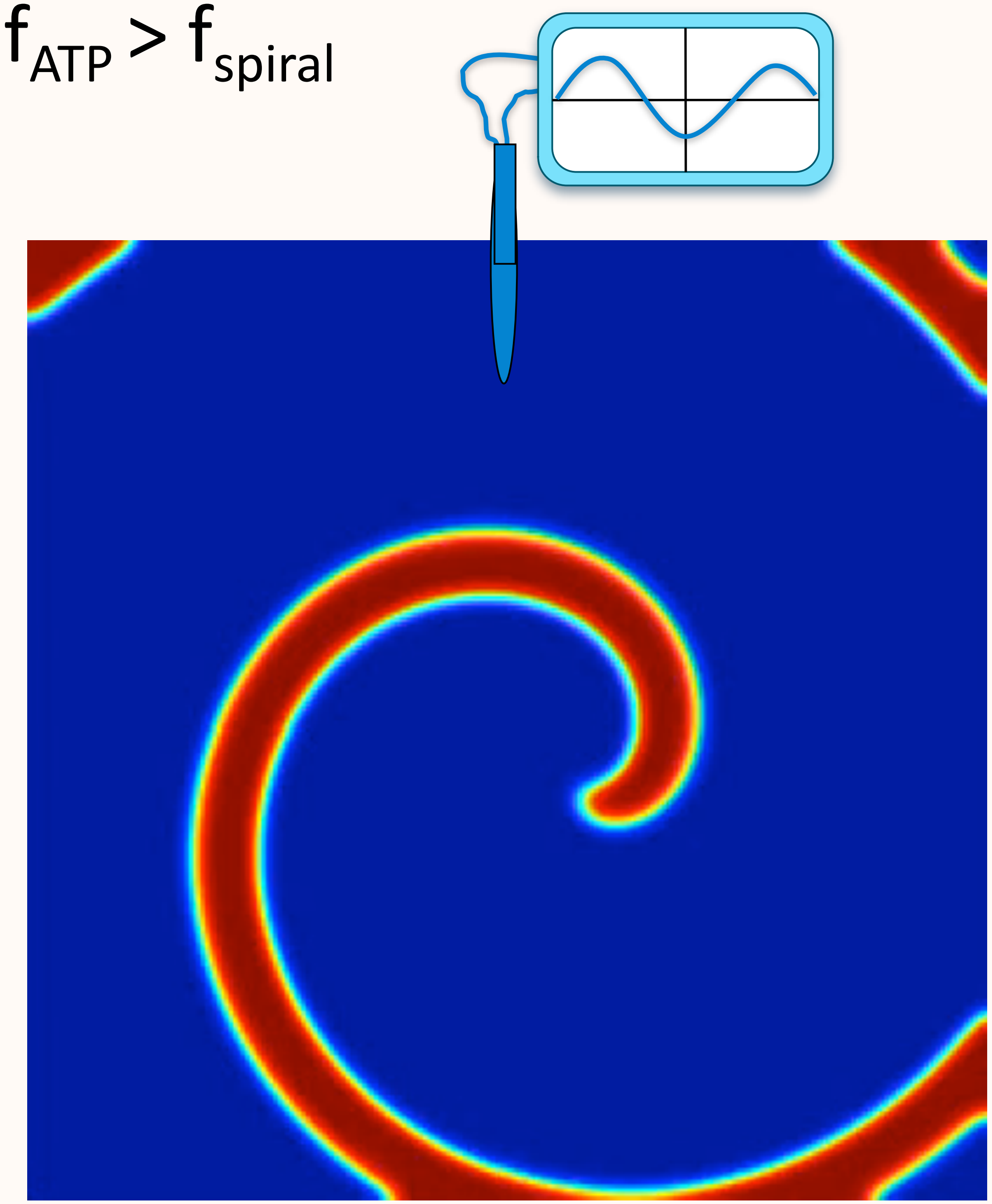
Spiral waves can pin to electrical obstacles, like blood vessels, scars, fatty tissue.



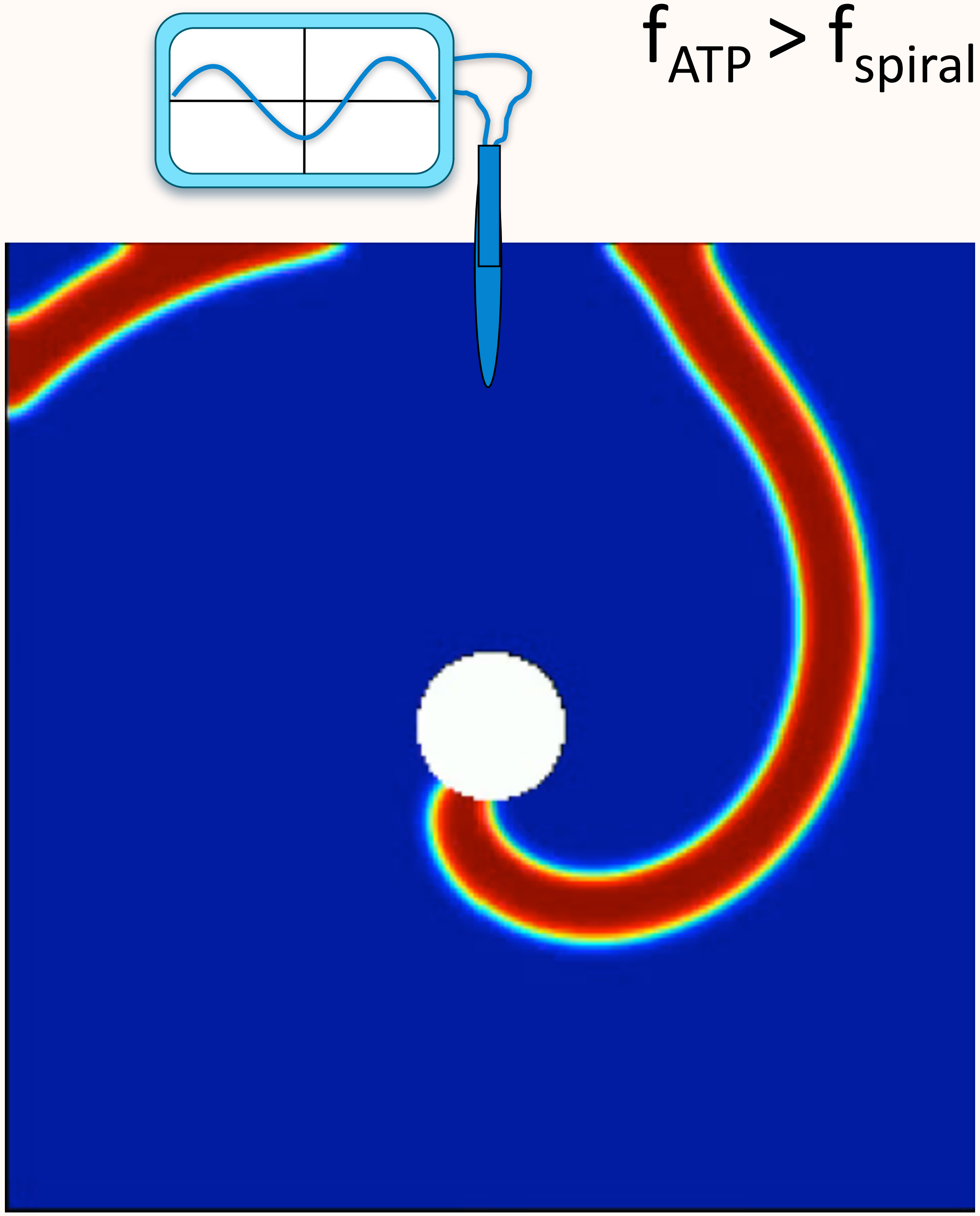
Pinned Spiral Waves

Pinned spirals are more "resistant" to termination efforts using sequences of low energy pulses.

$f_{ATP} > f_{spiral}$



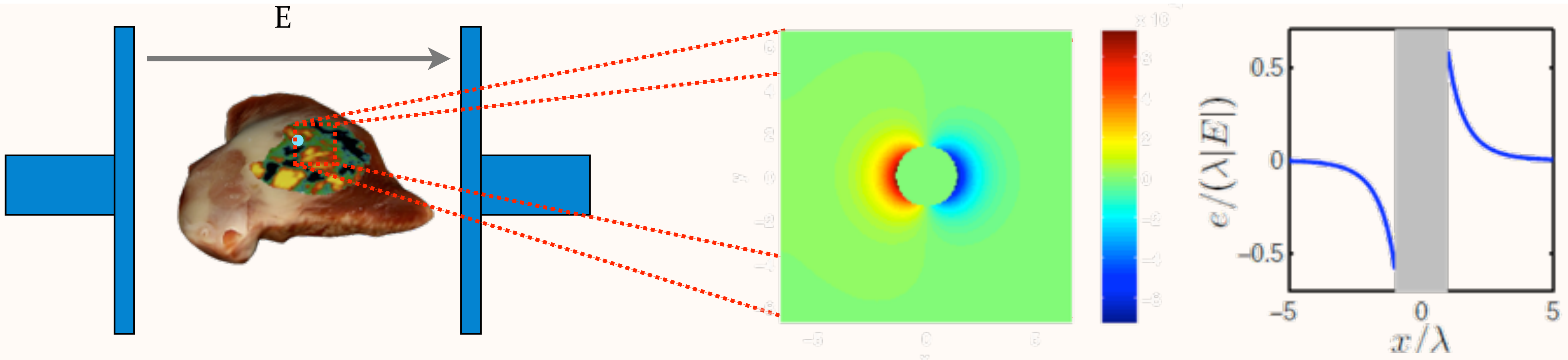
$f_{ATP} > f_{spiral}$



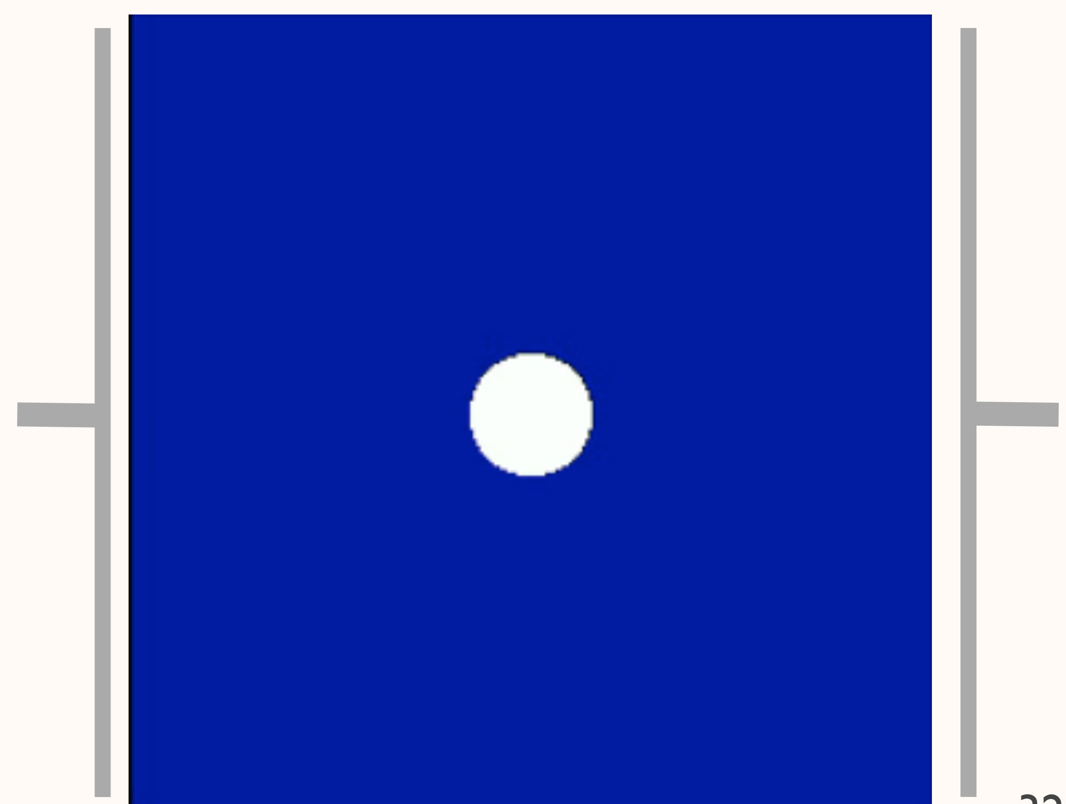
Virtual Electrodes

Blood vessels, scars, fatty tissue

- are obstacles to electrical conduction
- may act as virtual electrodes
  (Pumir&Krinsky, J. Theor. Biol. 199, 311 (1999))



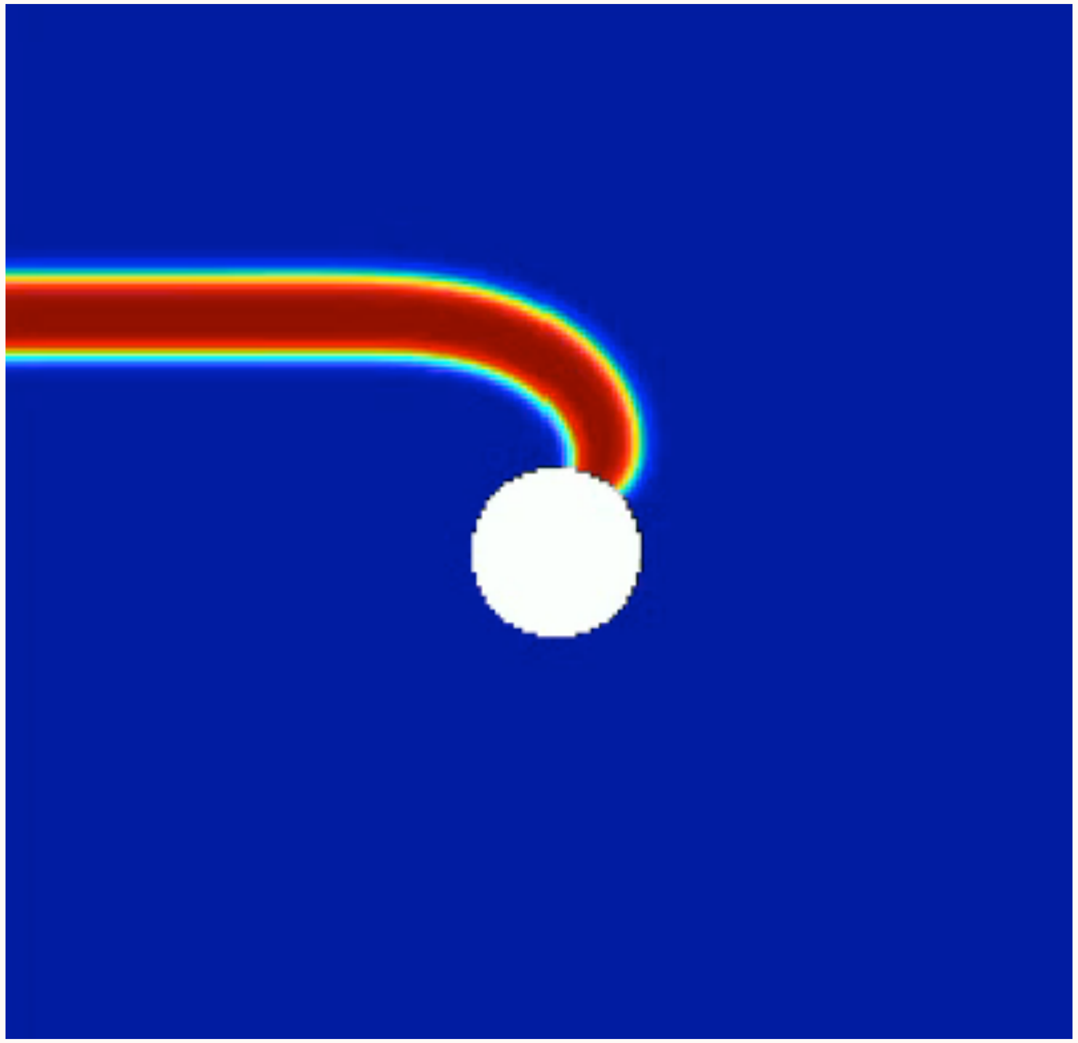
Super-threshold depolarization leads to wave emission if a short rectangular electric field pulse is applied.



Unpinning of spiral waves using virtual electrodes

Global electric field pulse generates local excitation wave that detaches the spiral away from the obstacle.

Once unpinned the spiral wave can be pushed away by subsequent pulses.



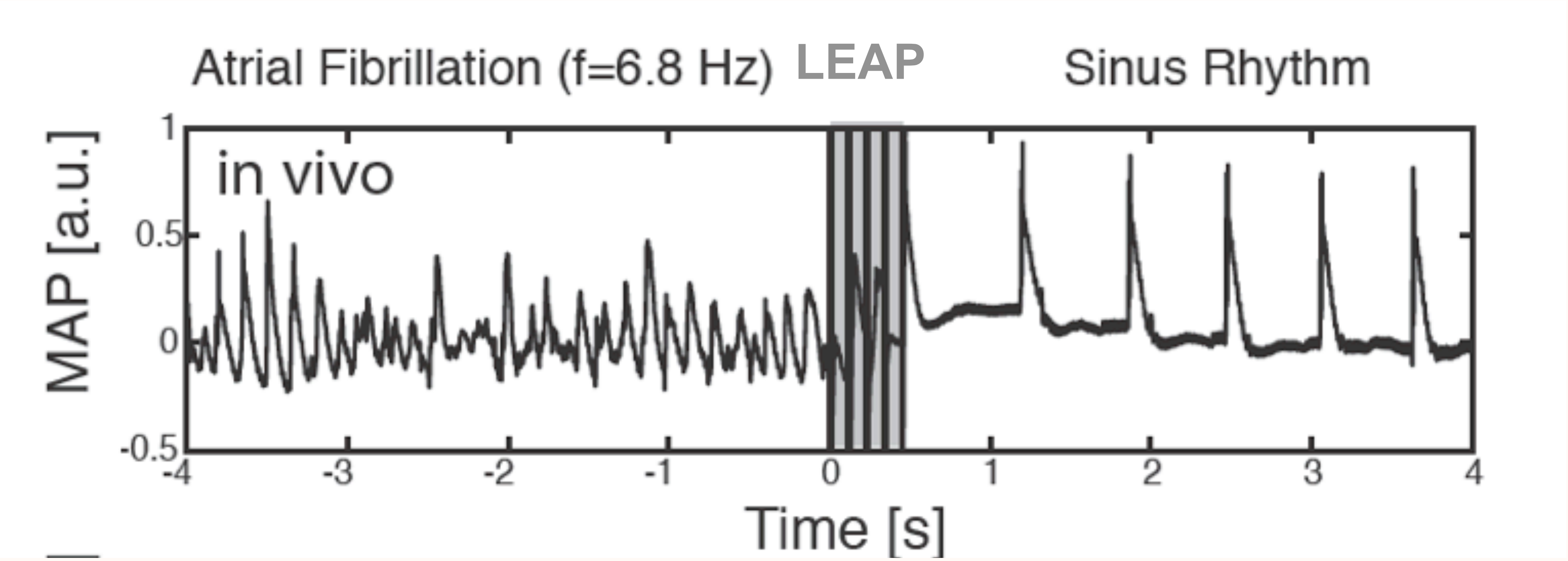
simulation: P. Bittihn

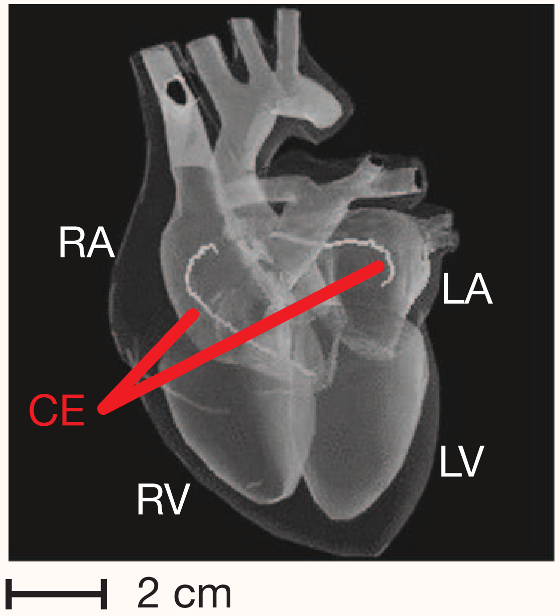
P. Bittihn et al., New Journal of Physics 10, 103012 (2008);
Phil. Trans. R. Soc. A 368, 2221-2236 (2010)

Termination of Atrial Fibrillation using LEAP

LEAP = low-energy antifibrillation pacing

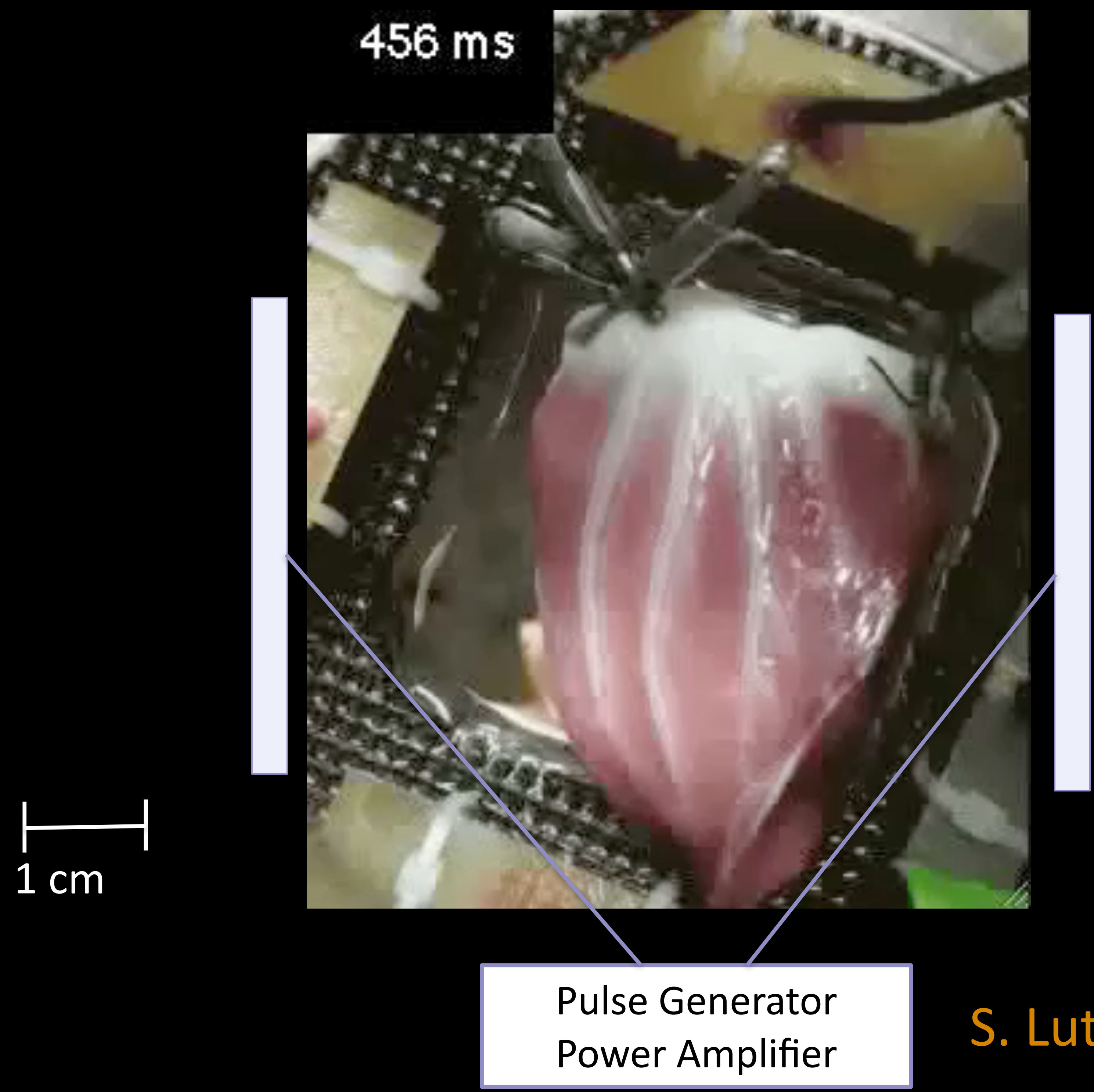
Low-energy control of electrical turbulence in the heart
S. Luther et al., Nature 475, 235 (2011)





- pulsed electric field applied with standard electrodes (CE) inserted into the left and right atria by catheters
- strengthening the electric field increases the density of wave sources (activated virtual electrodes)

Low-Energy Anti-Fibrillation Pacing (LEAP)

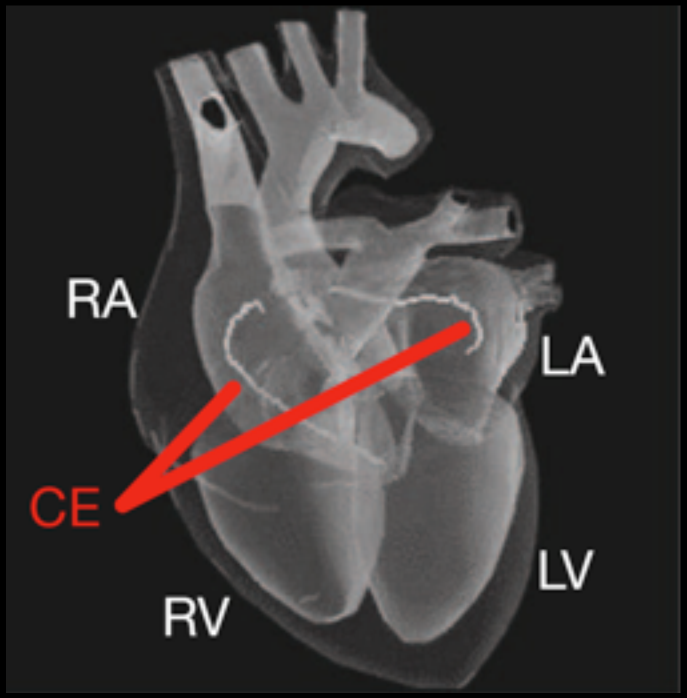


N = 5 low energy pulses
E = 1.4 V/cm
dt = 90 ms

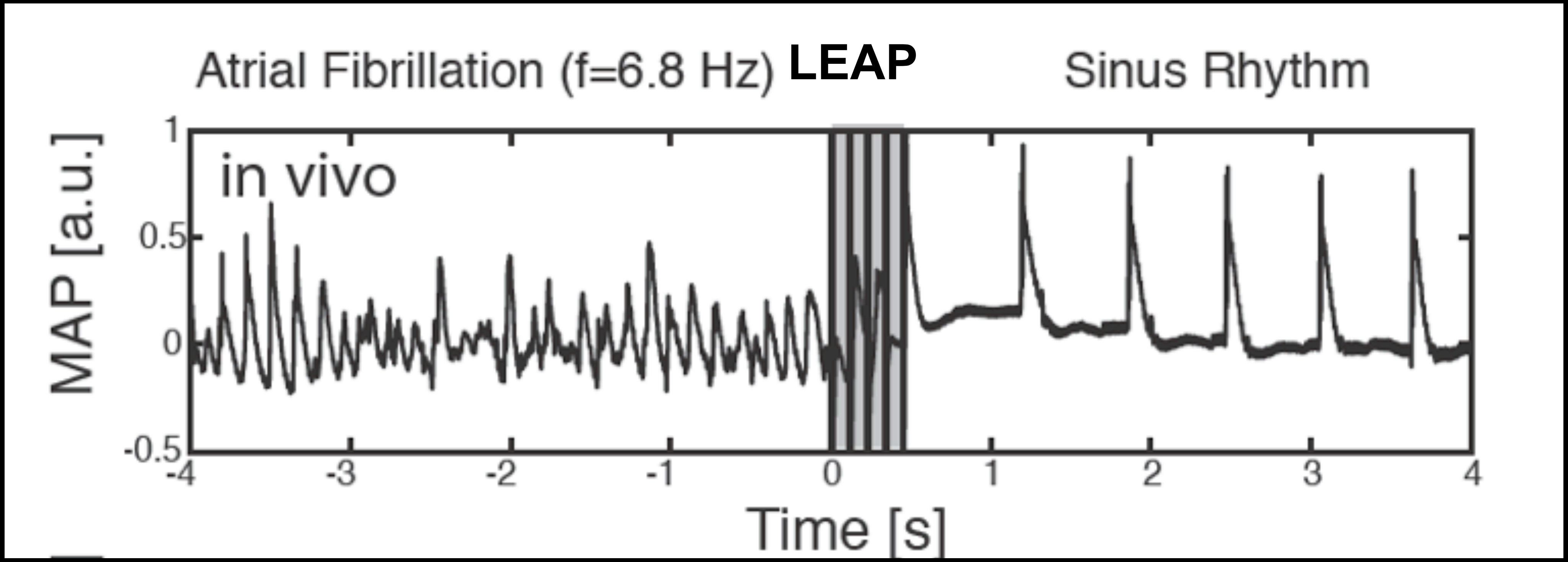
Energy reduction: 82 %

S. Luther et al., Nature 475, 235 (2011)

LEAP: In vivo Proof-of-concept



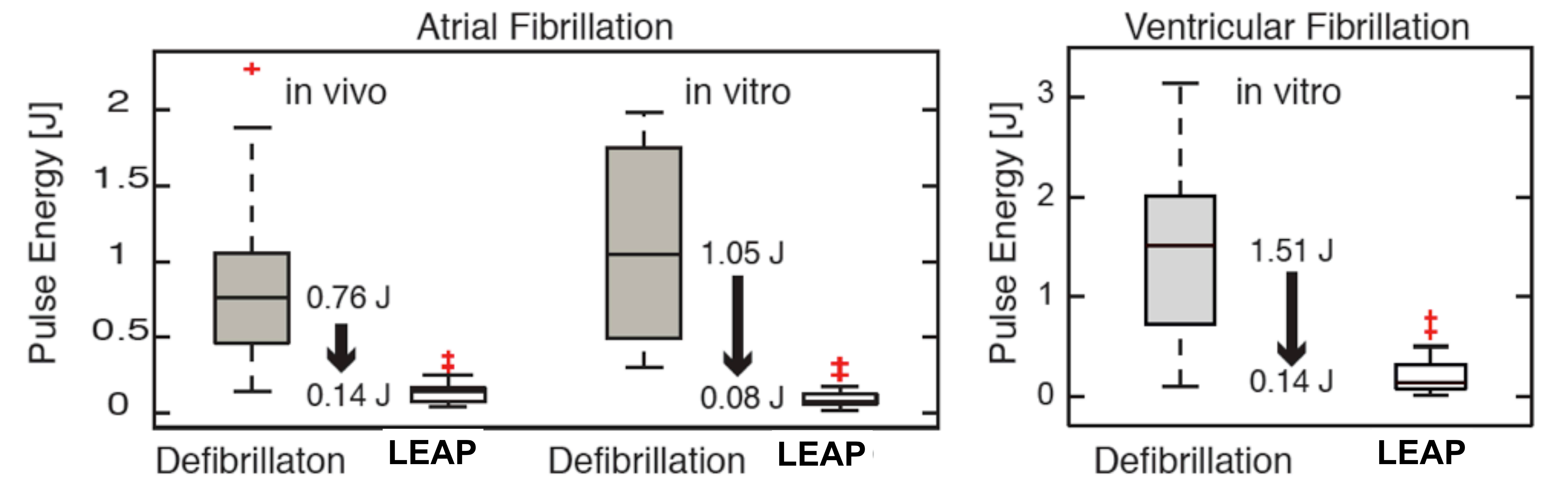
- First low-energy termination of atrial fibrillation *in vivo* (canine)
- Catheter in left and right atria (LA,RA)



Luther et al. *Nature* **475**, 235-239 (2011)

Energy Reduction

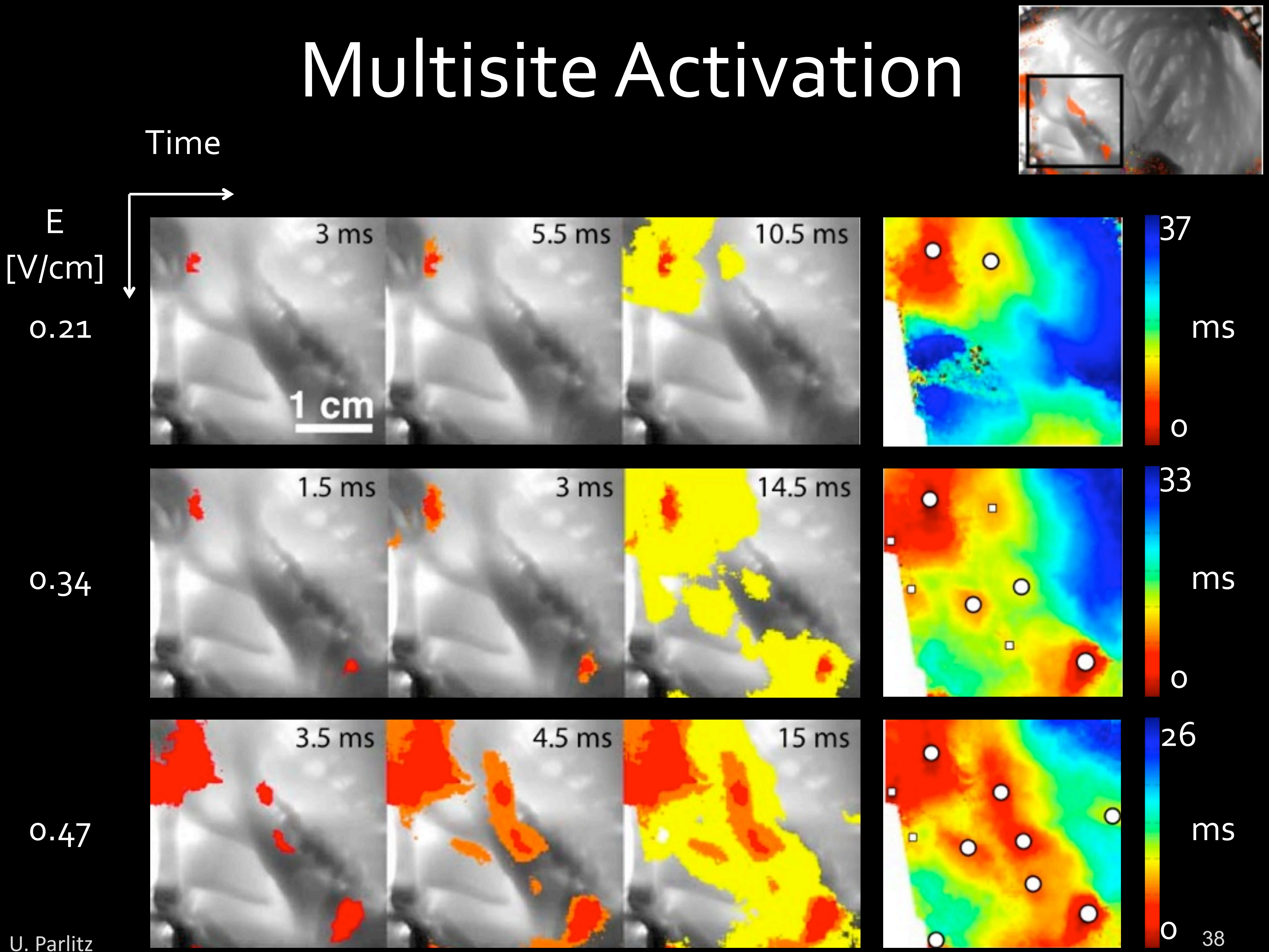
LEAP vs. standard defibrillation



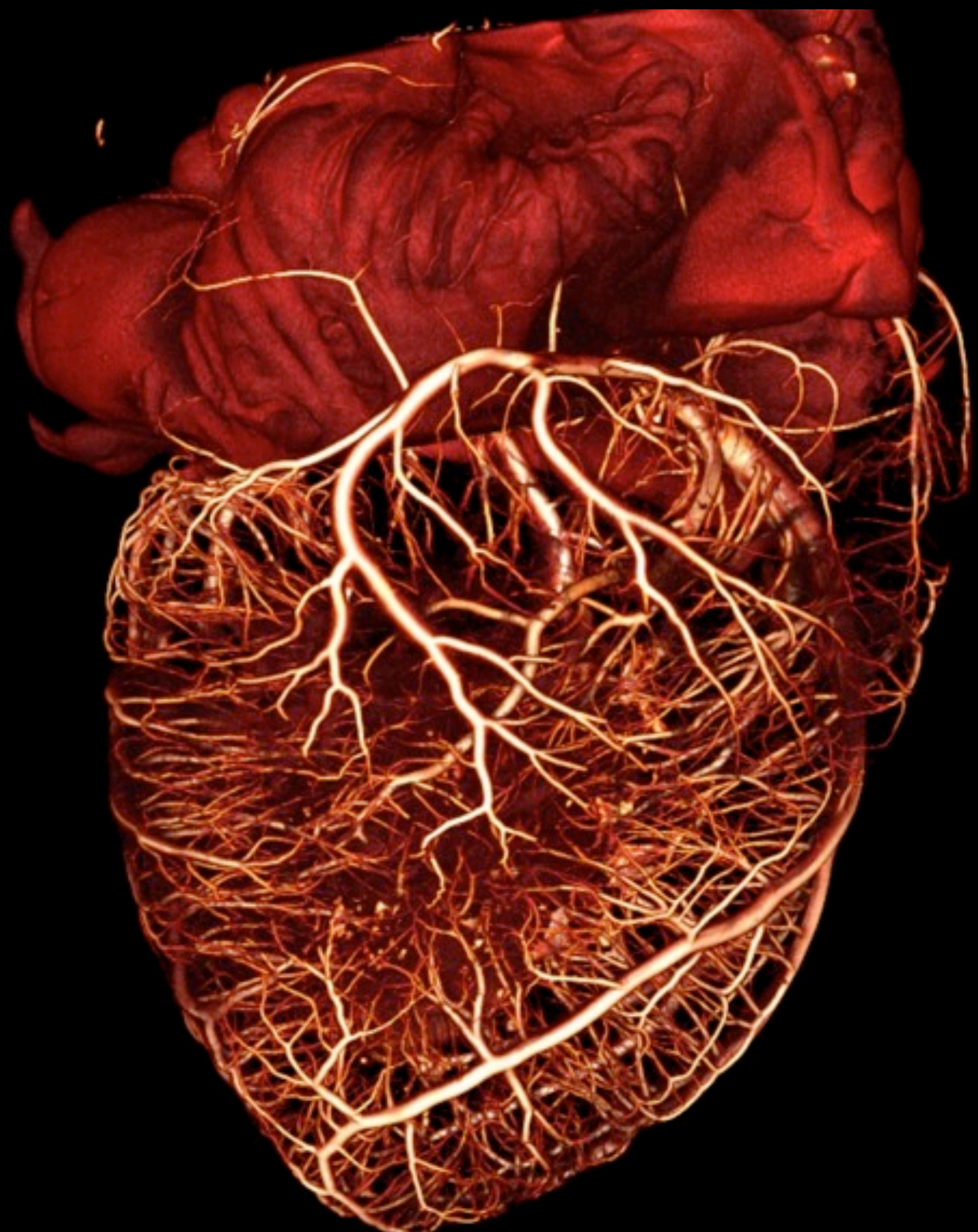
- Pulse energy at or below pain threshold.
- Opens path to painless and non-damaging defibrillation.

Luther et al. *Nature* **475**, 235 (2011)

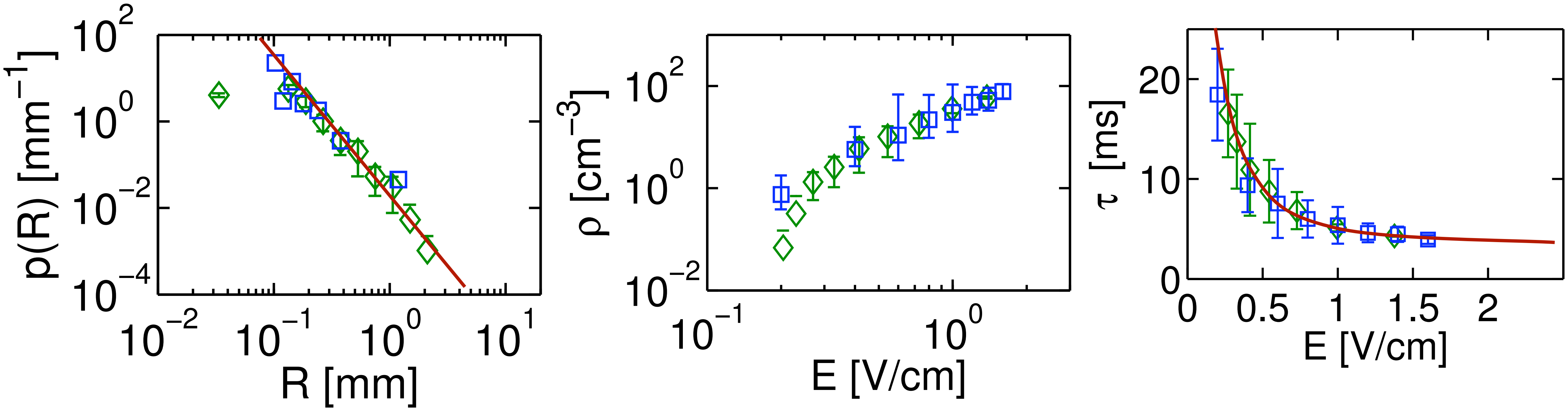
Multisite Activation



Cardiac Vasculature



Structure-Function-Relation



Size distribution $p(R) \propto R^{\alpha}$

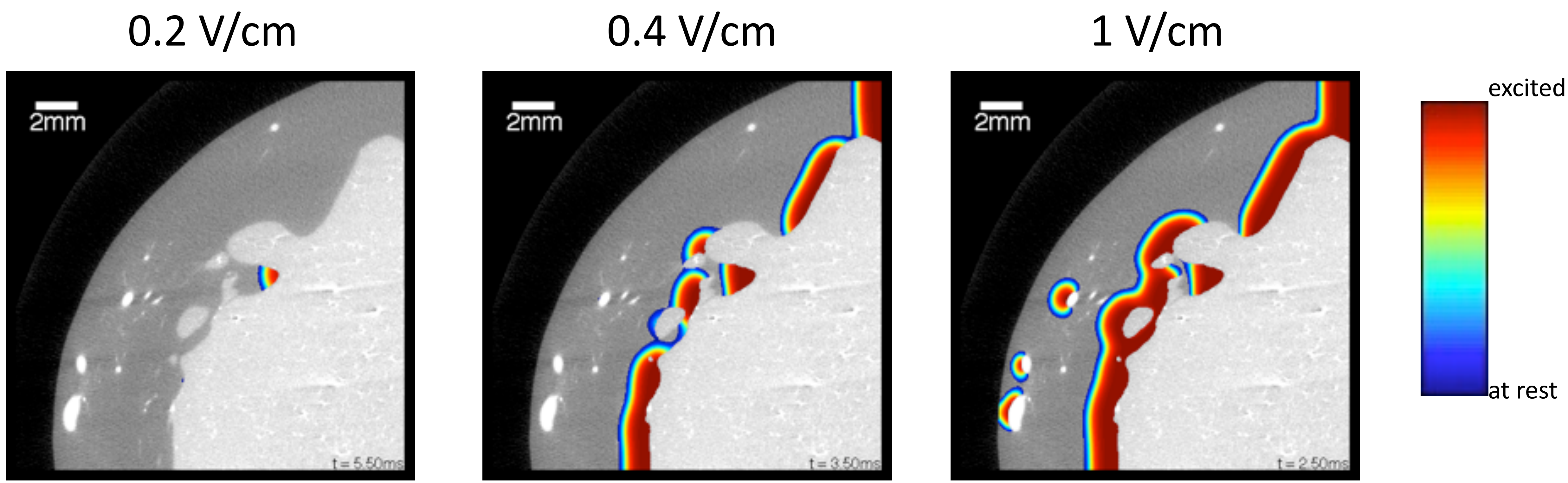
Activation time $\tau \propto \bar{E}^{\beta}$

$$\beta = (1+\alpha)/d$$

Table 1 | Observed and predicted scaling exponents for the size distribution

Tissue	d	α_o	β_o	β_p†	β_p*
Atrium	2	-2.74 ± 0.05	-0.81 ± 0.23	-0.88 ± 0.20	-0.87 ± 0.03
Ventricle	3	-2.75 ± 0.30	-0.75 ± 0.18	-0.74 ± 0.25	-0.58 ± 0.10

The effect of curved boundaries



E

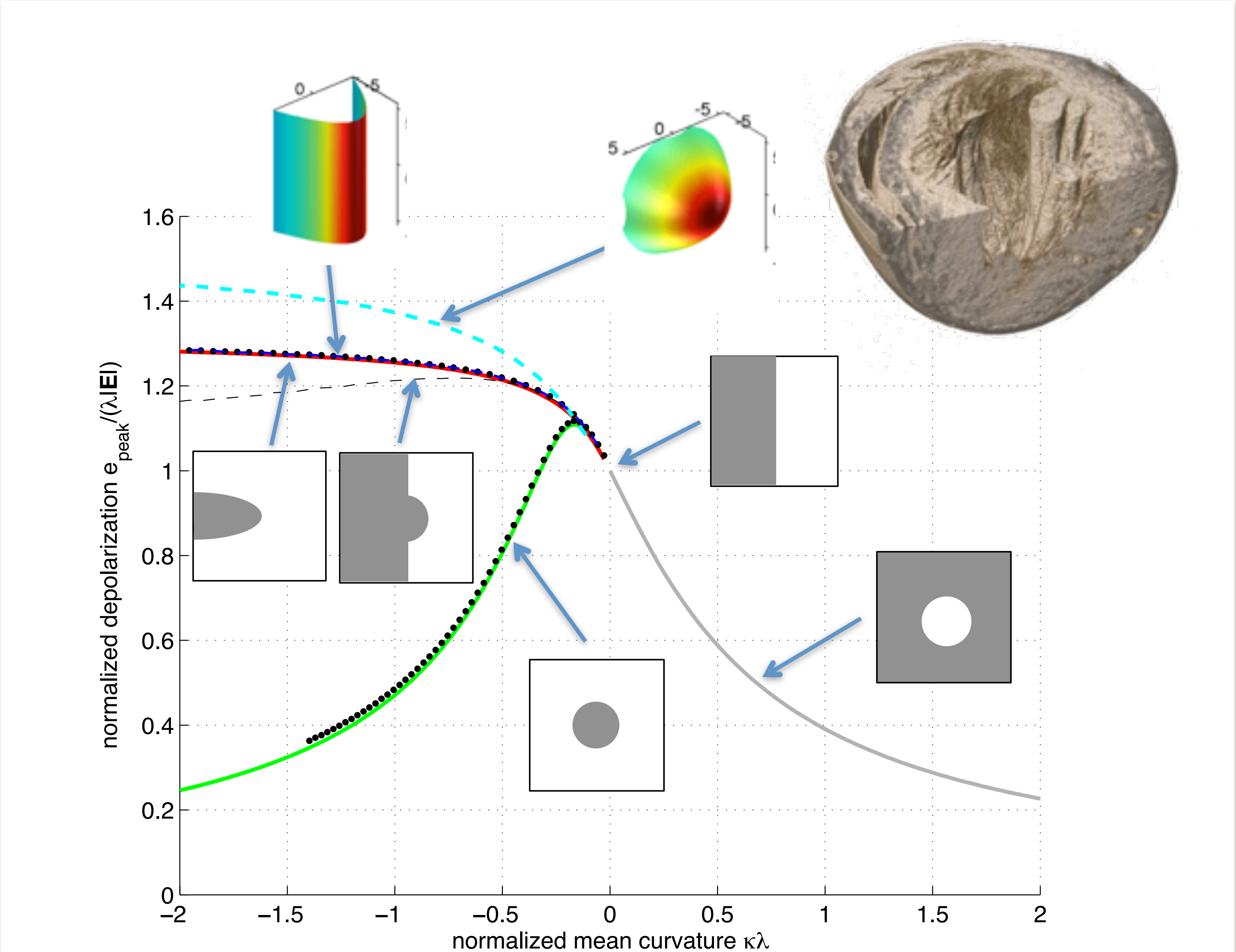
Short rectangular electric field pulse

Simulation with the phase-field method: Fenton et al., Chaos 15 (2005)

- Method modified to implement modified boundary condition
- On a 2d geometry from a µCT scan of a left ventricular rabbit wall
- Model: Fenton & Karma (Chaos 8, 1998)

P. Bittihn, M. Hörning, S. Luther, Phys. Rev. Lett. 109, 118106 (2012).

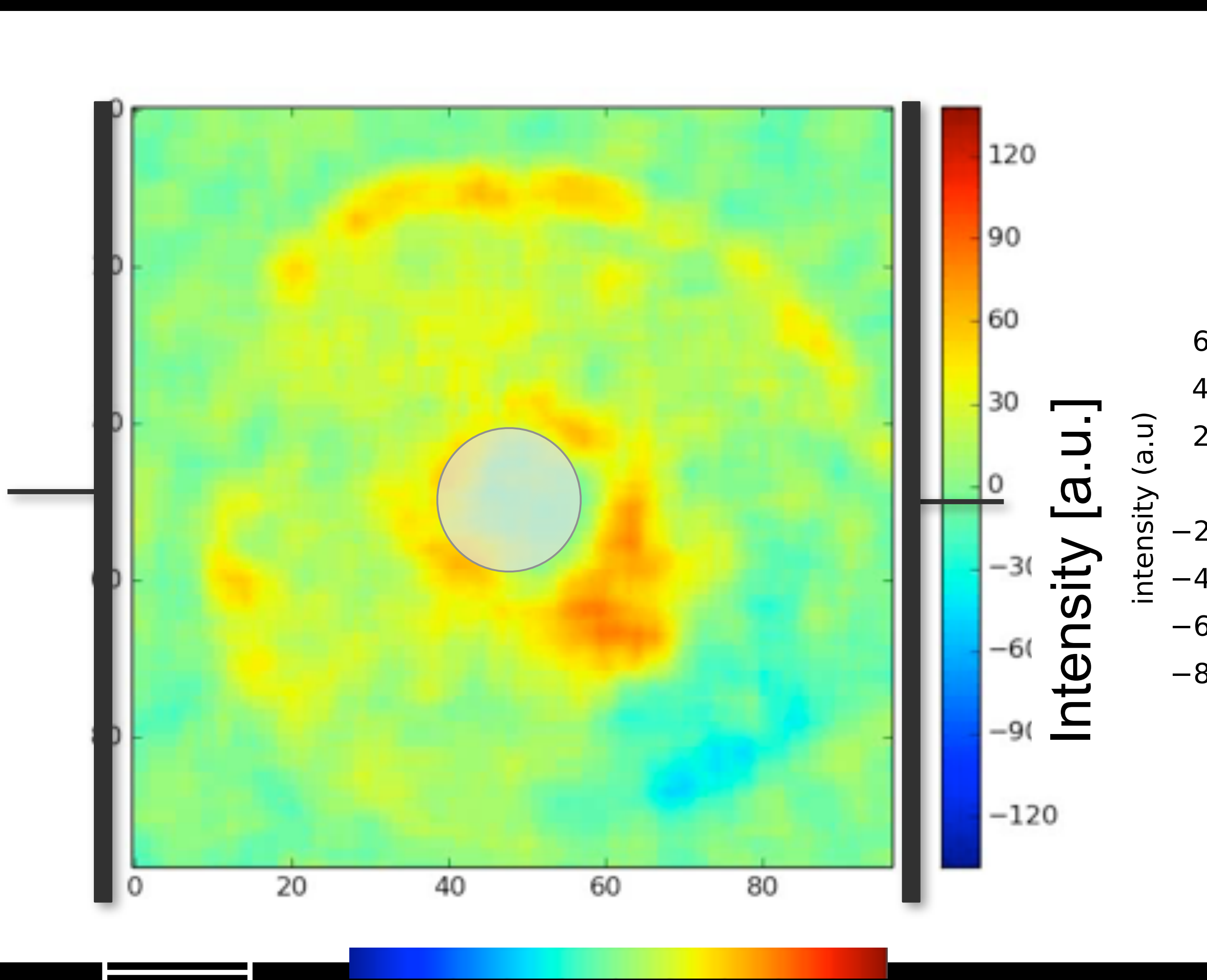
The effect of curved boundaries

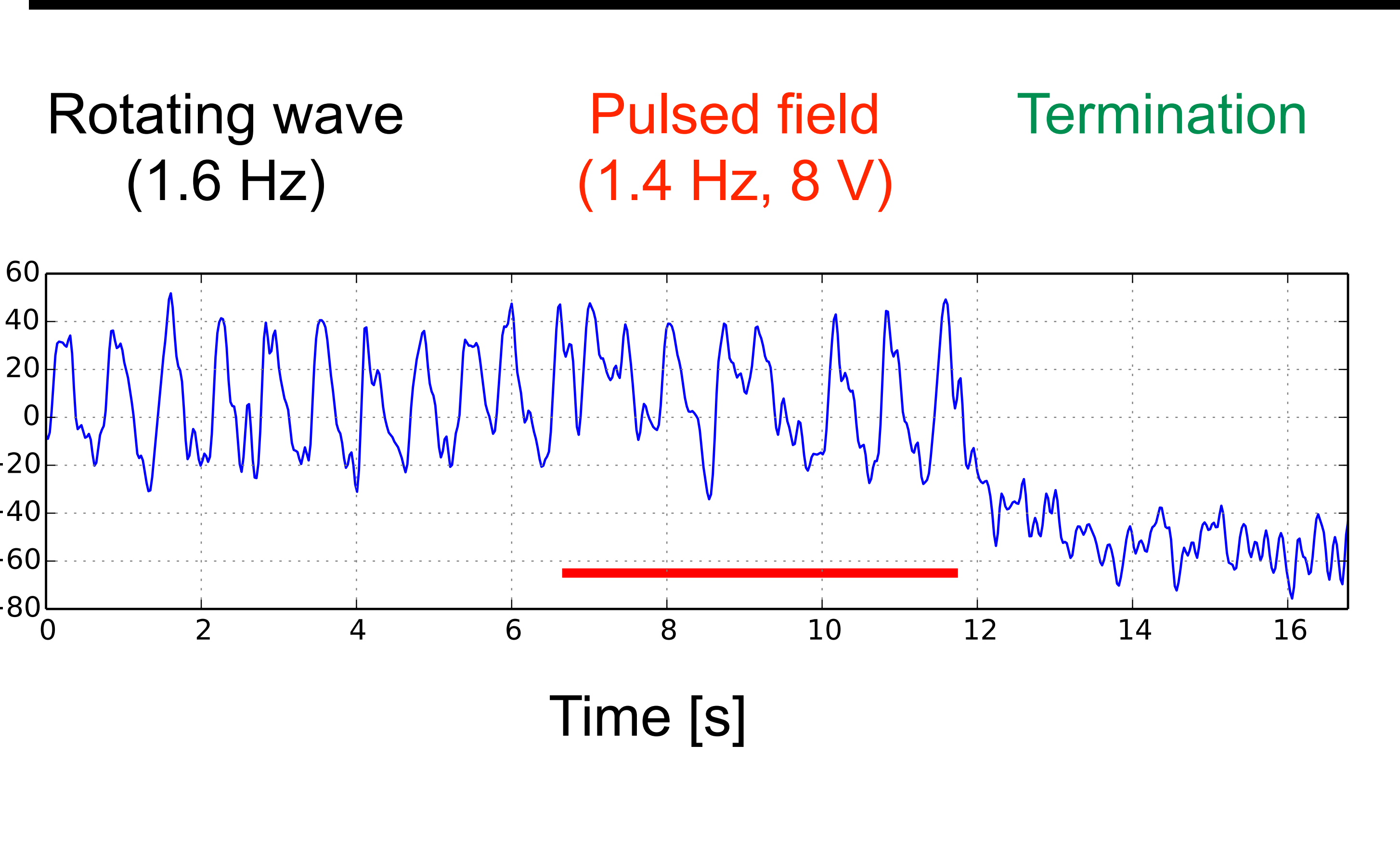


Bittihn et al.　　Pumir & Krinsky

P. Bittihn, Horning, S. Luther, Phys. Rev. Lett. 109, 118106 (2012).

Terminating pinned spiral wave in a cardiac monolayer using field stimulation





- Dye: Ca green
- Resolution: 40 fps, 100 x 100 pixels
- Ventricular myocytes (embryonic chick, 8d)

Aim: Study vortex-structure interaction and control in 2D experiment.

Courtesy of T.K. Shajahan

Conclusion

Using Ordinal Patterns Statistics

for classifying beat-to-beat time series

LEAP - Low-Energy Anti-Fibrillation Pacing

- recruit virtual electrodes
- unpin spiral waves
- terminate arrhythmias

Thanks: Stefan Luther, Philip Bittihn, ... Flavio Fenton & Elizabeth Cherry

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