Wavelets, Wavebreaks
and
Ventricular Fibrillation

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Mechanisms Underlying VF

Mother Rotor Hypothesis (Lewis, 1920)

- High resolution fluorescence imaging of perfused hearts show that VF is organized in discrete regions with dominant frequencies (Zaitsef et al., 1999, Chen et al., 2000, Samie et al., 2001).

Multiple Wavelet Hypothesis (Garrey, 1914; Moe et al, 1964)

- Dynamics of inter-activation interval are not compatible with mother rotor hypothesis (Evans et al. 1998, Garfinkel et al., 1997).
- Theoretical and experimental studies suggested that wave breaks may occur due to cardiac restitution (Karma, 1994; Weiss et al., 1999; Riccio et al., 1999; Qu et al., 2000).
- FFT analysis of VF showed complex multi-component peaks (Choi et al., 2001, Valderrábano et al., 2002).

VF is a Dynamic Process
A Tale of Many Fibrillations?

- *In situ*, VF exhibits in distinct stages in the first 10 min, as ischemia sets in (Wiggers et al., Am Heart J, 1930; Huang et al., Am J Physiol., 2004)
- Initial phase of VF: multiple high frequency wavelets (type I VF) progresses to low frequency organized VF or dominant mother rotor (type II VF) in ischemic hearts (Chen et al., Circ. 2004)
- Experimental studies perfuse hearts under constant flow and induced VF by burst pacing. A quasi-static state of VF lasts up to 30 min. Multiple waves (12-18 Hz, type I) (Choi et al., Circ Res. 2001; 2002) and organized focal VF (up 32 Hz, type II) (Chen et al., Circ. Res. 2000) have been reported with VF frequencies higher on left than right ventricle.
- Global ischemia decreases the dominant frequency of VF (Mandapadi et al., Circ 1998); in severe ischemia, hearts rarely fibrillate.

Cellular Determinants of VF
Evidence for the Wavelet Hypothesis

- **VF Frequencies**

  - Spatial distribution-correlated with APDs and Refractoriness (Choi et al., Circ Res. 2001)

  -Time-Frequency Distribution analysis revealed that numerous VF events co-exist, appear and disappear dynamically with brief lifespan (0.39 ± 0.13 s) (Choi et al., Circ Res. 2002)

- **Time-Lag Cross correlation (CC_{max}) and Mutual Information (MI_{max})**

  - Cell-cell coupling influences VF dynamics

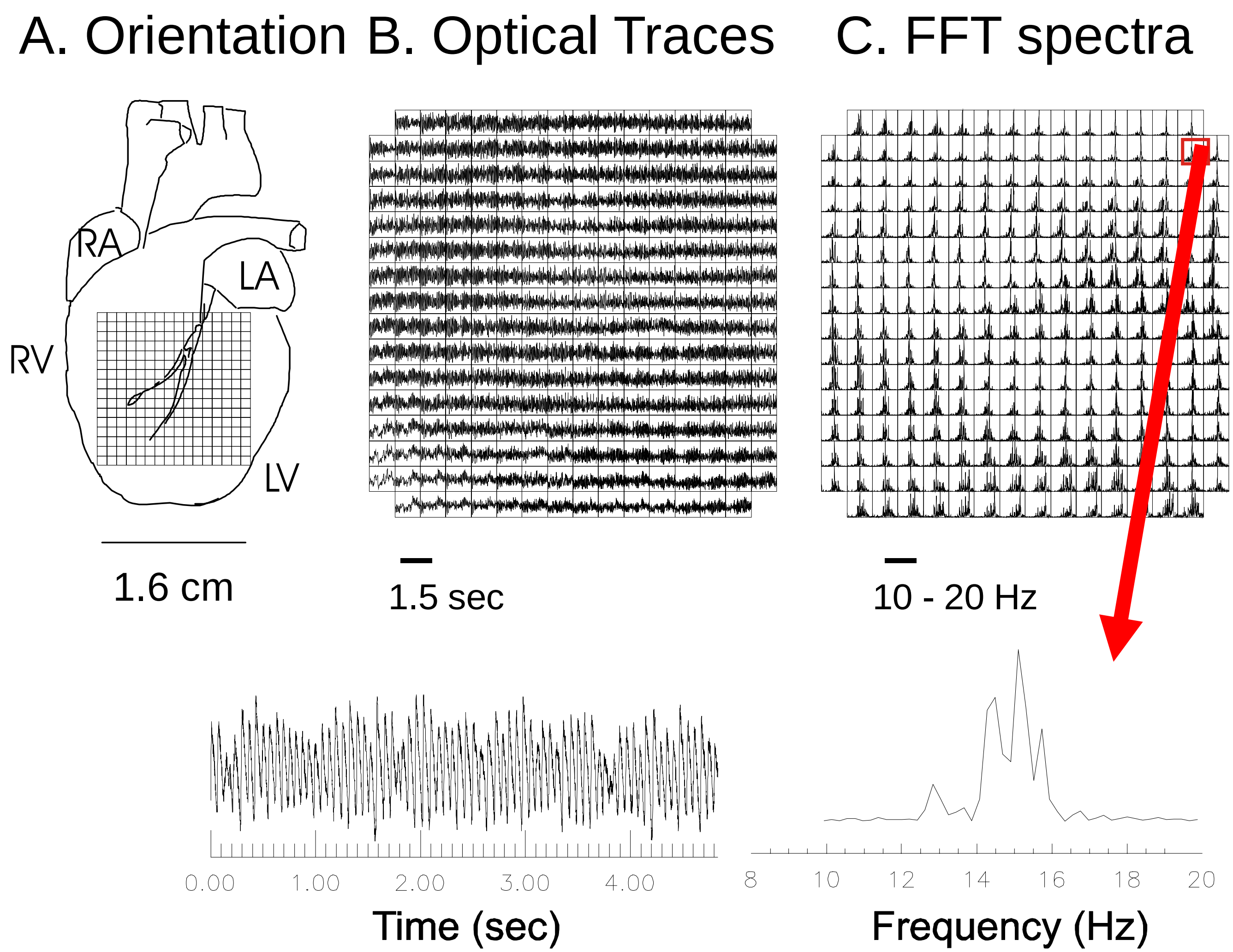
  - CC_{max} and MI_{max} did not detect clusters of high similarity, indicative of dominant rotors (Choi et al., JCE, 2003)

- **Swelling Activated Cl^- currents in hypo-osmotic solutions alters VF dynamics. (Choi et al., Heart Rhythm 2006, in press)**

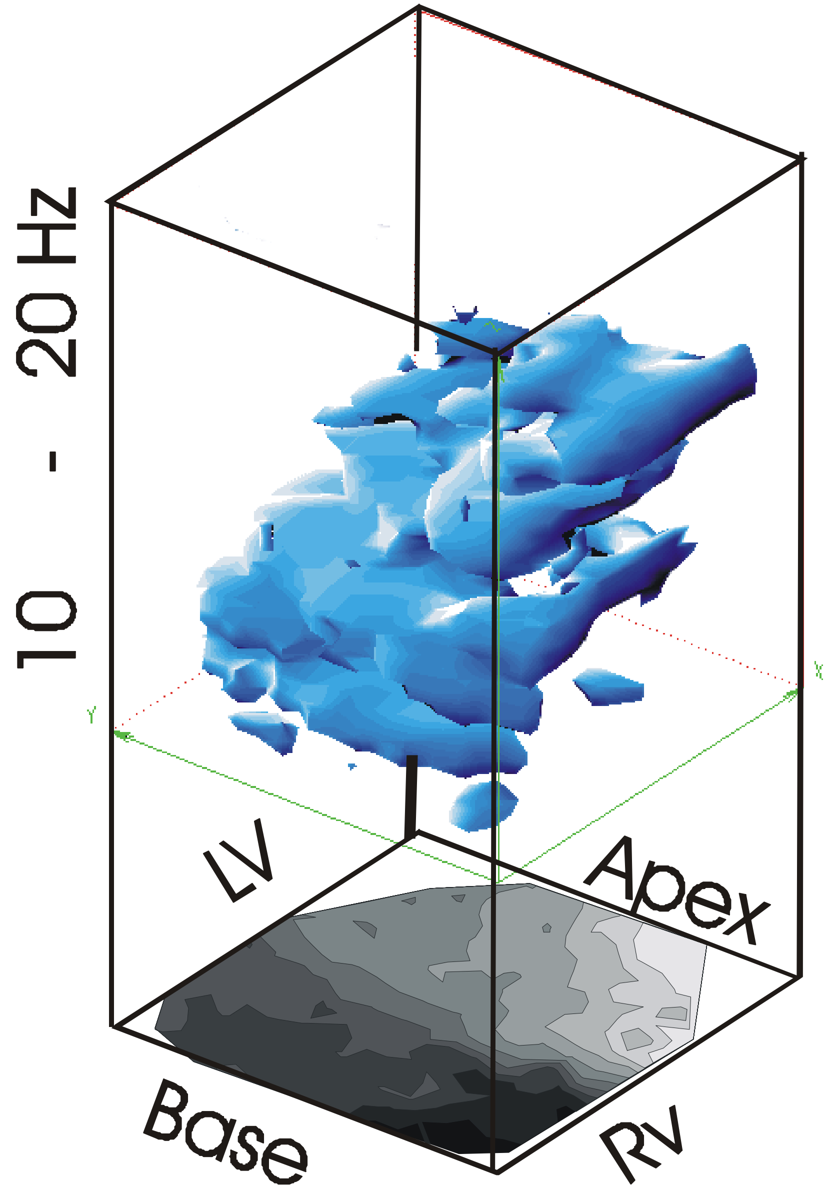
- **Potential Limitation: Poor Spatial Resolution of diode arrays-** New data with CMOS camera: 100x100 pixels, up to 10k frames/s

- **Analysis of Wave breaks Locations (Choi et al., submitted)**

FFT Spectra of Optical Traces in VF



Spatial Distribution of VF Frequencies



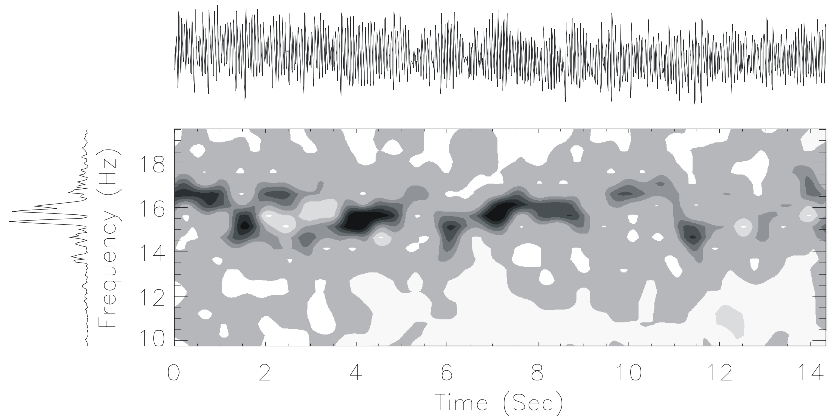
R ~ 0.7
Guinea Pig Heart

Mean APDs:
Apex: 154 ± 9.1 ms
Base: 189 ± 9.3 ms
Lines 5 ms apart

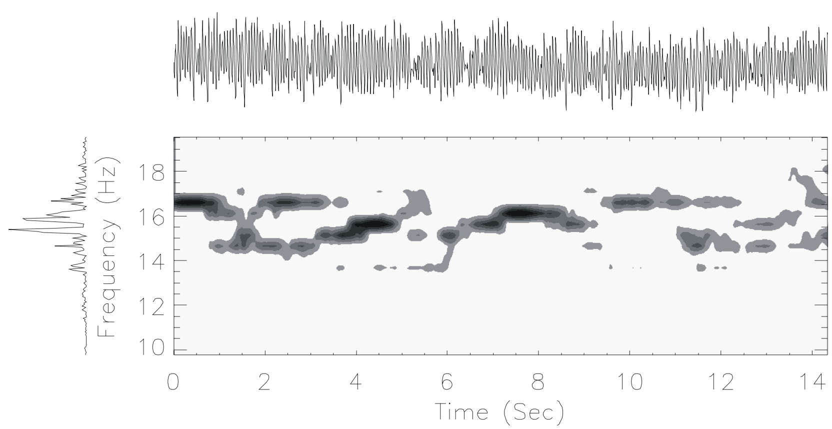
Choi et al., *Circ Res*, 2002

Time-Frequency Distribution

A. Spectrogram

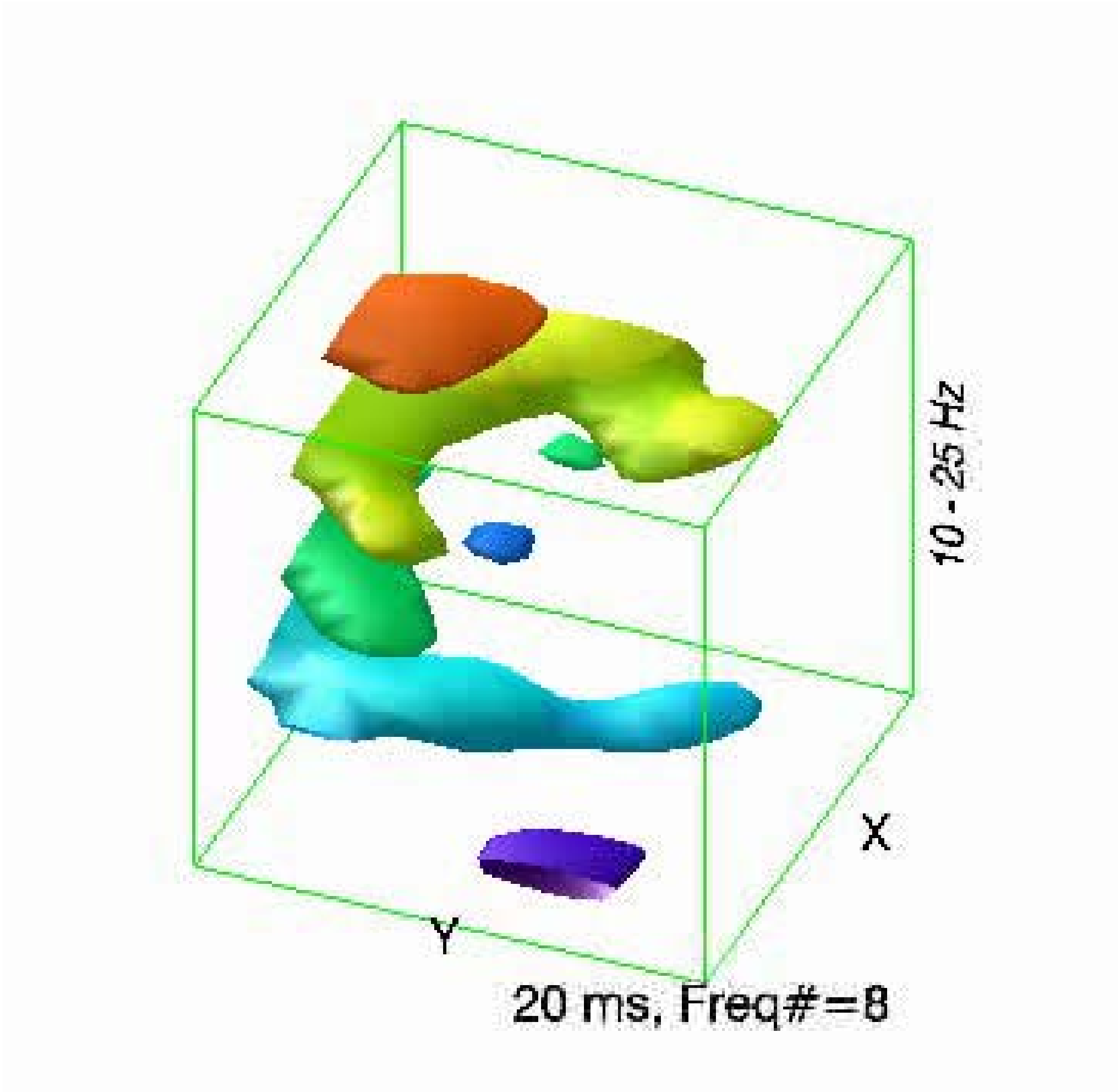


B. Cone shape kernel



Choi et al., *Cir Res*, 2002

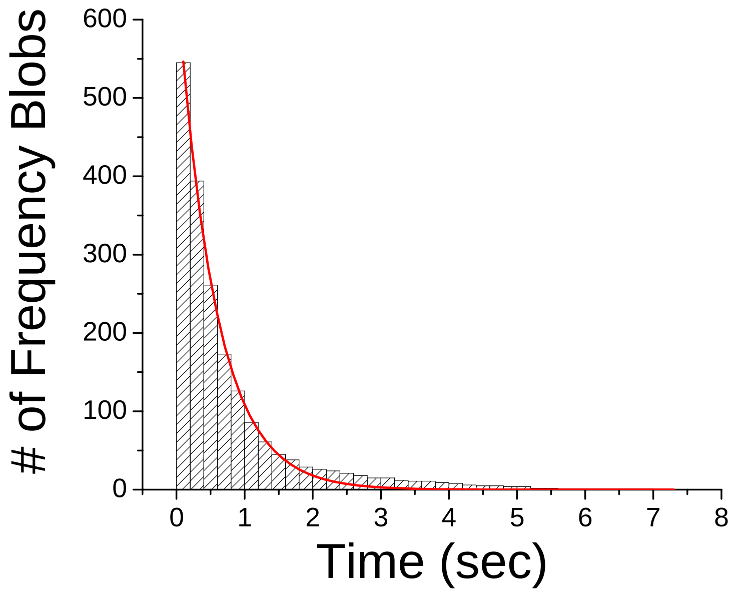
VF → VT with Nifedipine (2 μM)



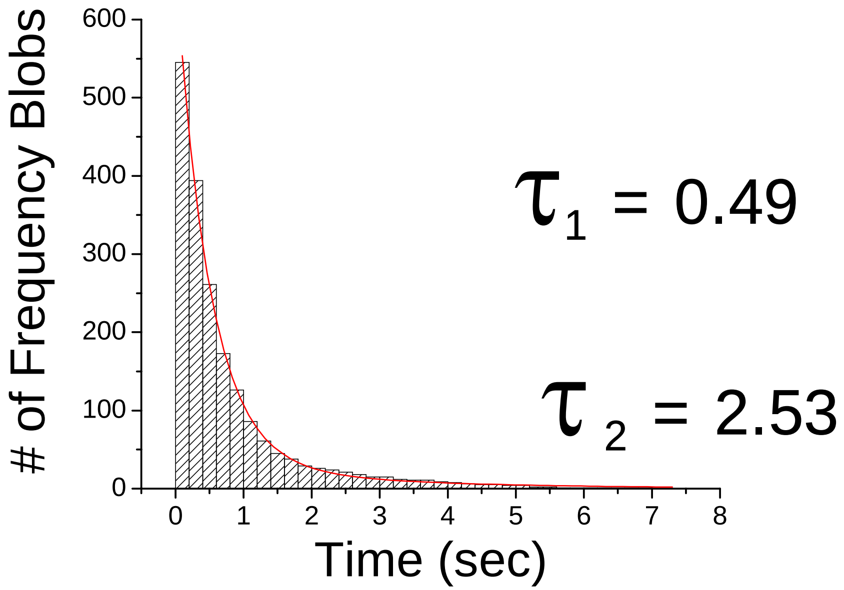
Choi et al., *Cir Res*, 2002

Life Span of VF Frequency Blobs

First Order Decay



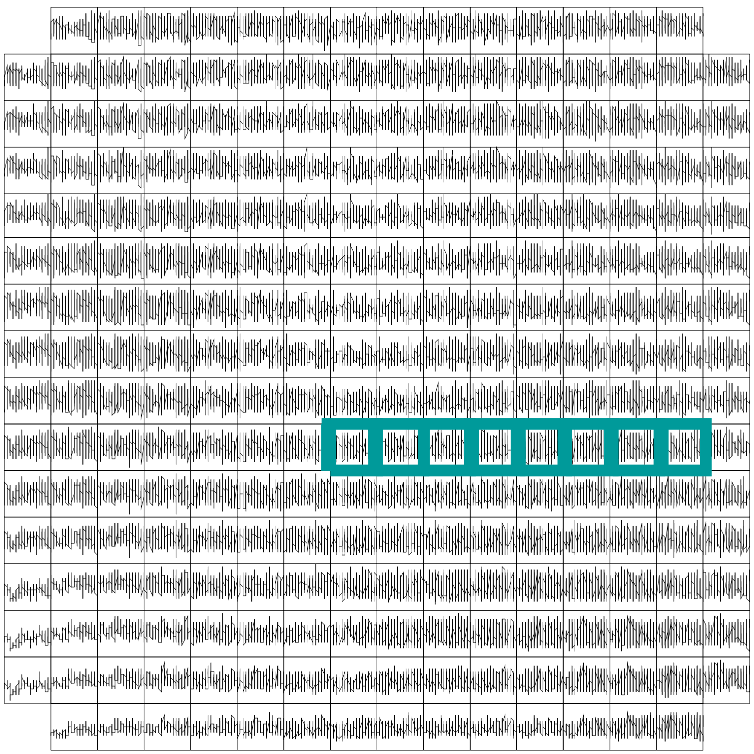
Second Order Decay



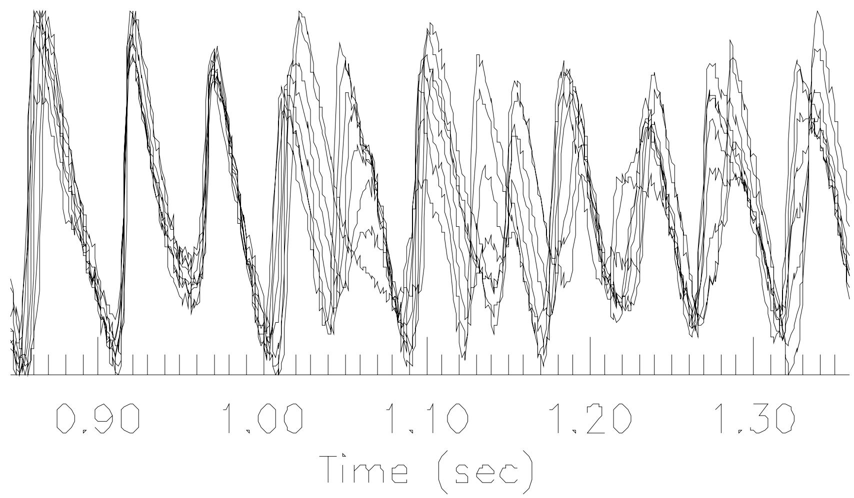
Choi et al., *Cir Res*, 2002

Similarity of V_m Oscillations between sites in VF

A. VF Traces



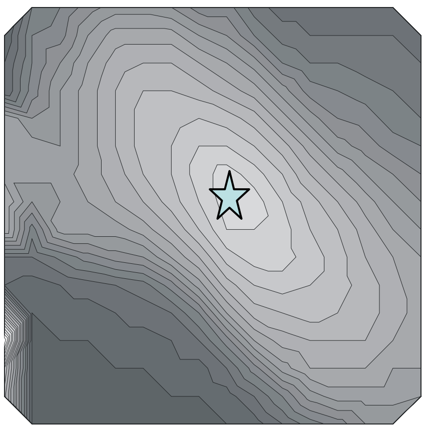
B. Detail Traces



Rabbit Heart

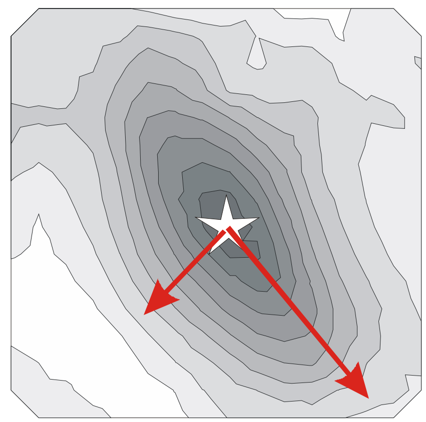
Fiber Orientation and Correlation Map from LV

Activation Map



Lines 1 ms apart

Correlation Map

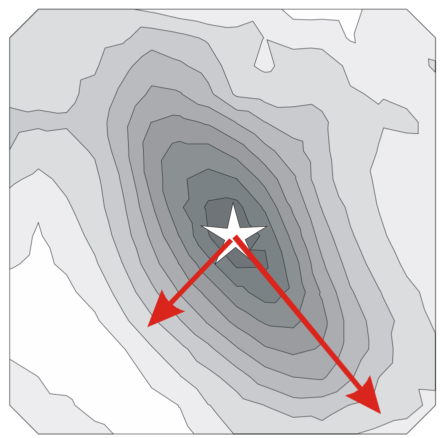


0.1 isolevel

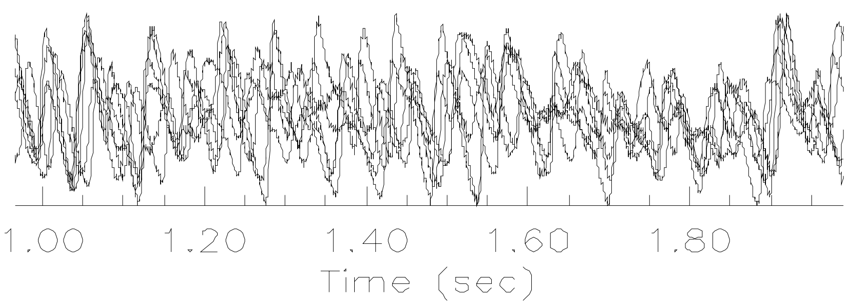
Ratios ~ 2/1

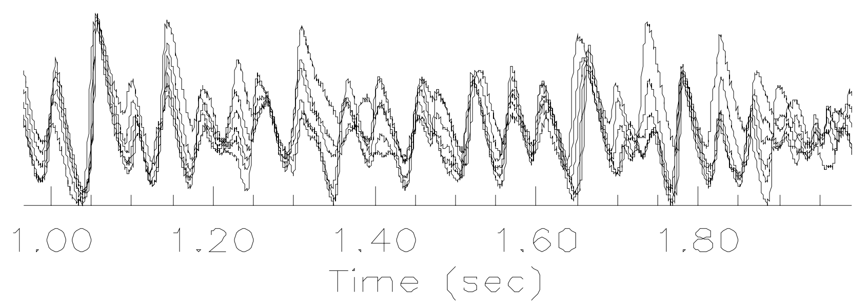
Similar results with MI_{max}, Choi et al, *JCE*, 2003.

Similarity Along the Fiber Orientation



Major angle
126.7 ± 7.8^{o} (n=6)





Correlation length = 2.2 ± 0.2 mm

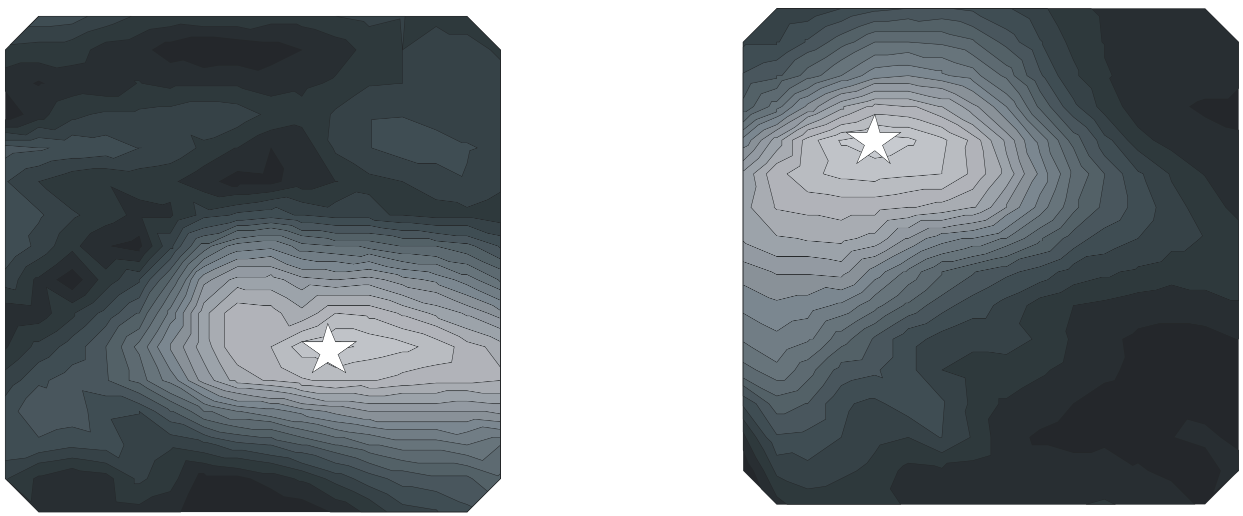
3.6 ± 0.3 mm

Choi et al, JCE, 2003.

Anterior Region of Heart

A. Ref at LV

B. Ref at RV

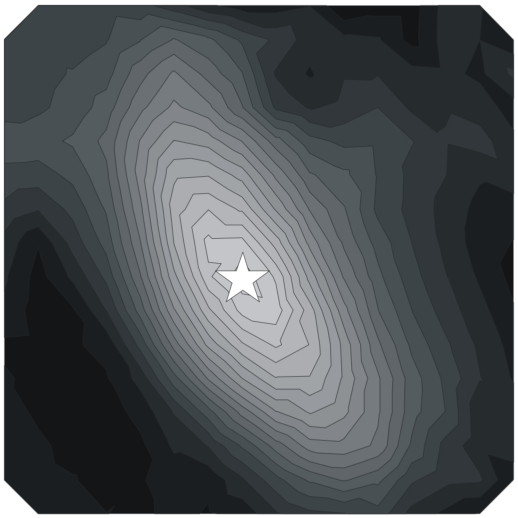


0.1 level

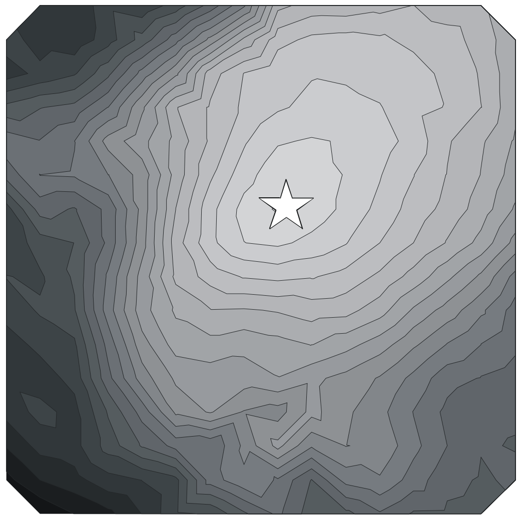
Choi et al, *JCE*, 2003.

Maps of Maximum Cross Correlation

A. Left Ventricle



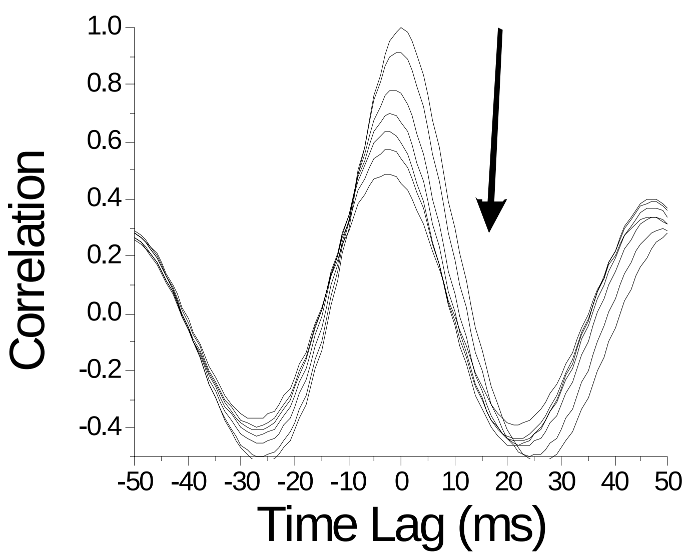
B. Right Ventricle

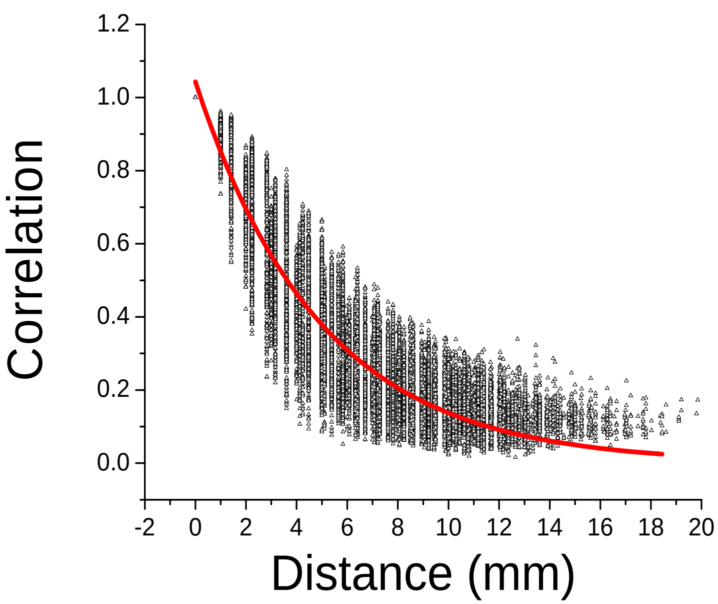


0.1 level

Choi et al, *JCE*, 2003.

Decay of Correlation with Distance

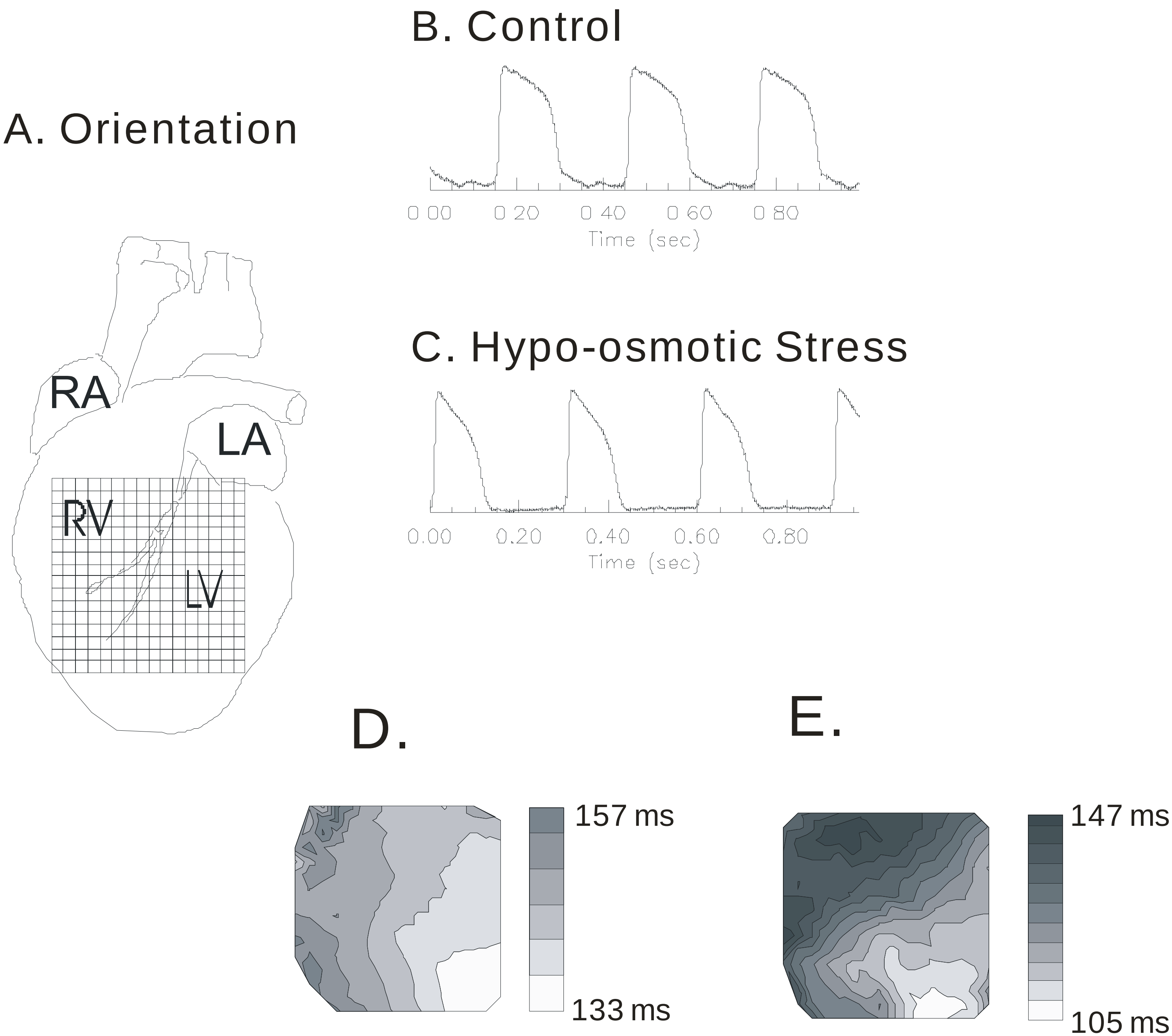




Choi et al, JCE, 2003

Clues To Different VF Dynamics

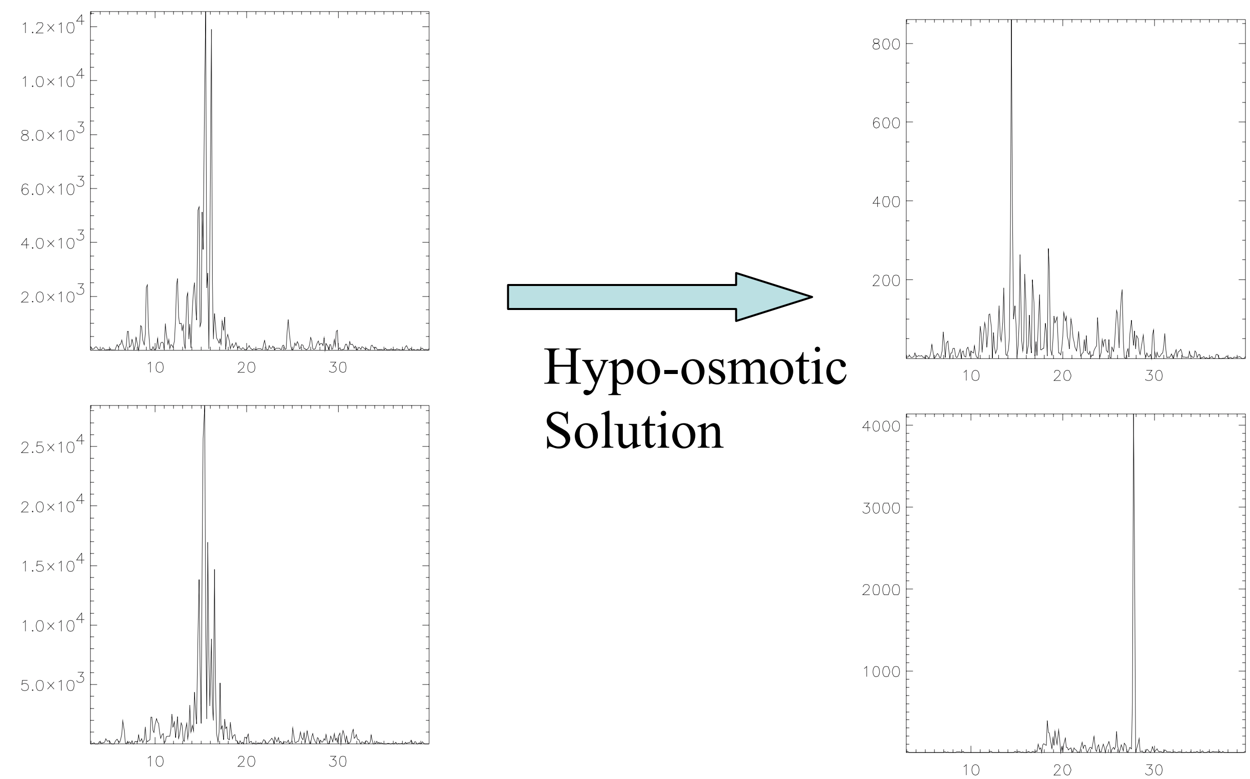
- Does ischemia explain multiple wavelets vs. dominant frequency? In these studies oxygenation and flow rates were normal.
- Swelling of myocardium under perfusion in constant flow rate and hypo-osmotic solution.
- Cell volume is well regulated by maintaining osmotic pressure.
- Ischemic condition: Break down of metabolic molecules such as glycogen $\rightarrow$ Increase of osmotic pressure $\rightarrow$ cell swelling.
- Cell swelling $\rightarrow$ Opening of Chloride swelling channel, $I_{Cl,swell}$ blocked by: DIDS, IAA-94 (indanyloxyacetic acid-94)

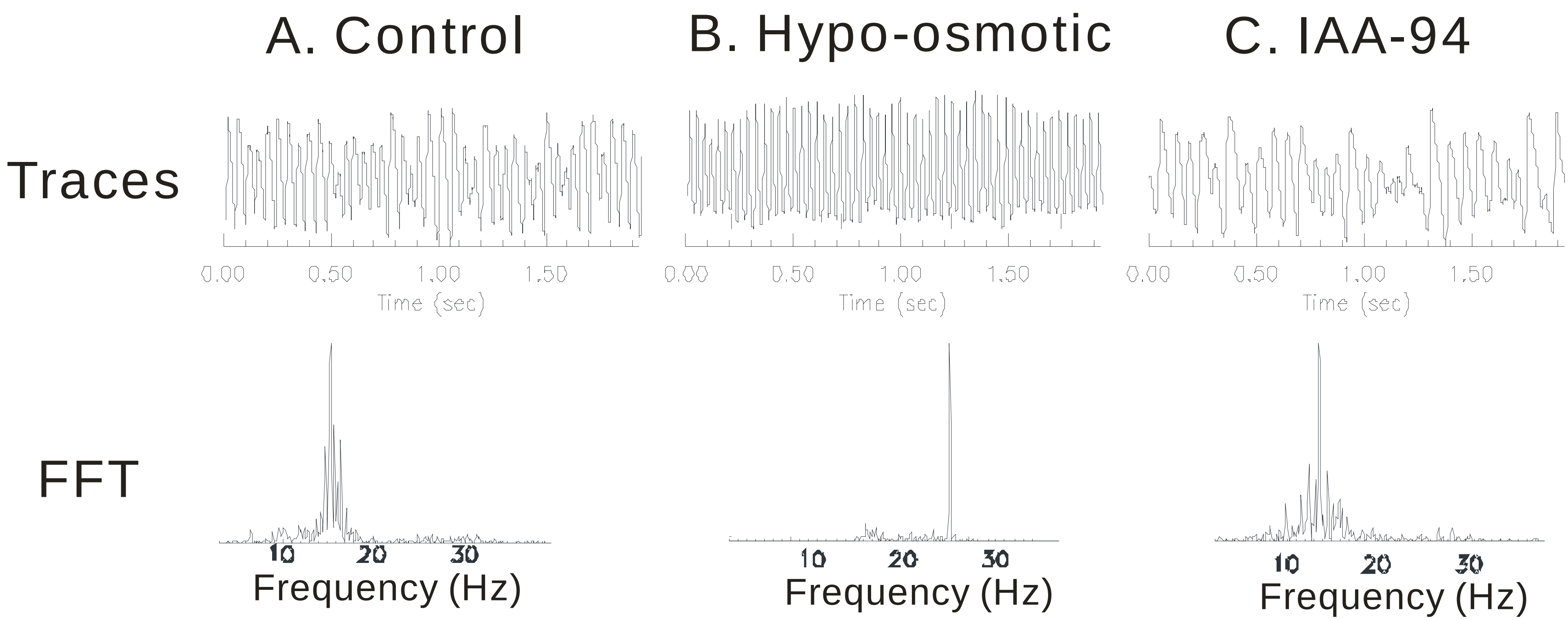

A. Orientation
RA
LA
RV
LV
B. Control
0.00
0.20
0.40
0.60
0.80
Time (sec)
C. Hypo-osmotic Stress
0.00
0.20
0.40
0.60
0.80
Time (sec)
D.
157 ms
133 ms
E.
147 ms
105 ms

VF Frequency in Hypo-osmotic Solution
(± 45 mM Mannitol)

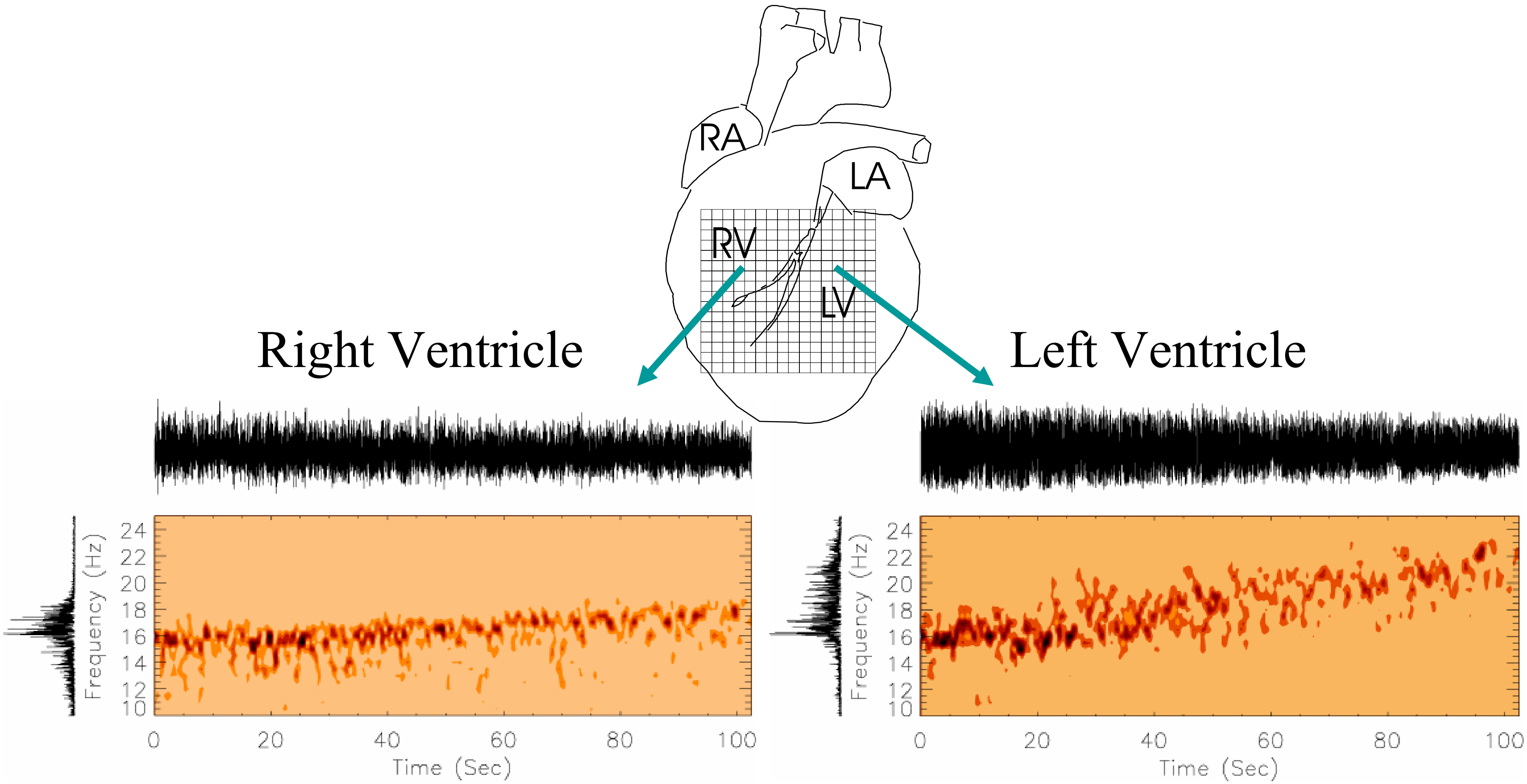
Right
Ventricle

Left
Ventricle

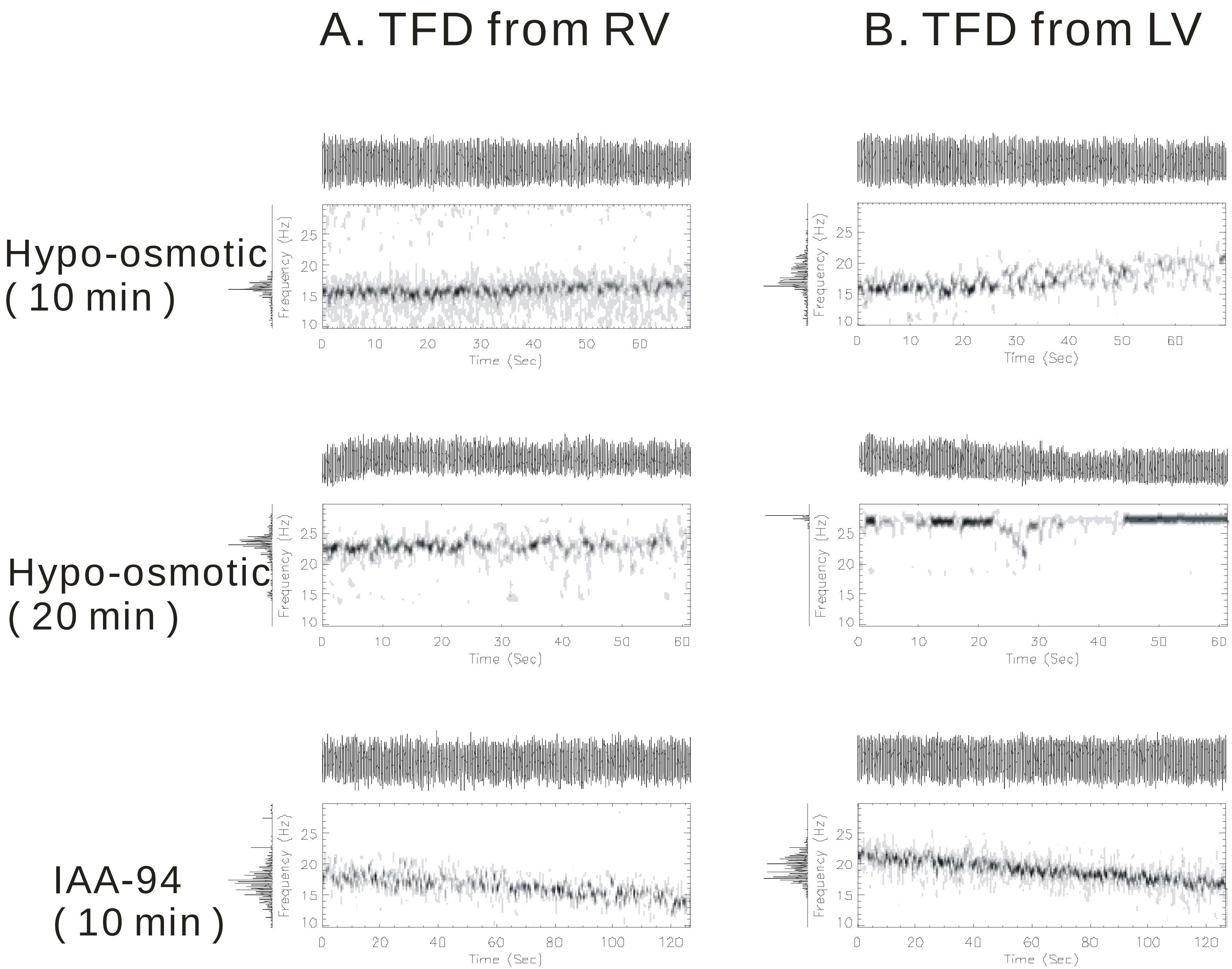


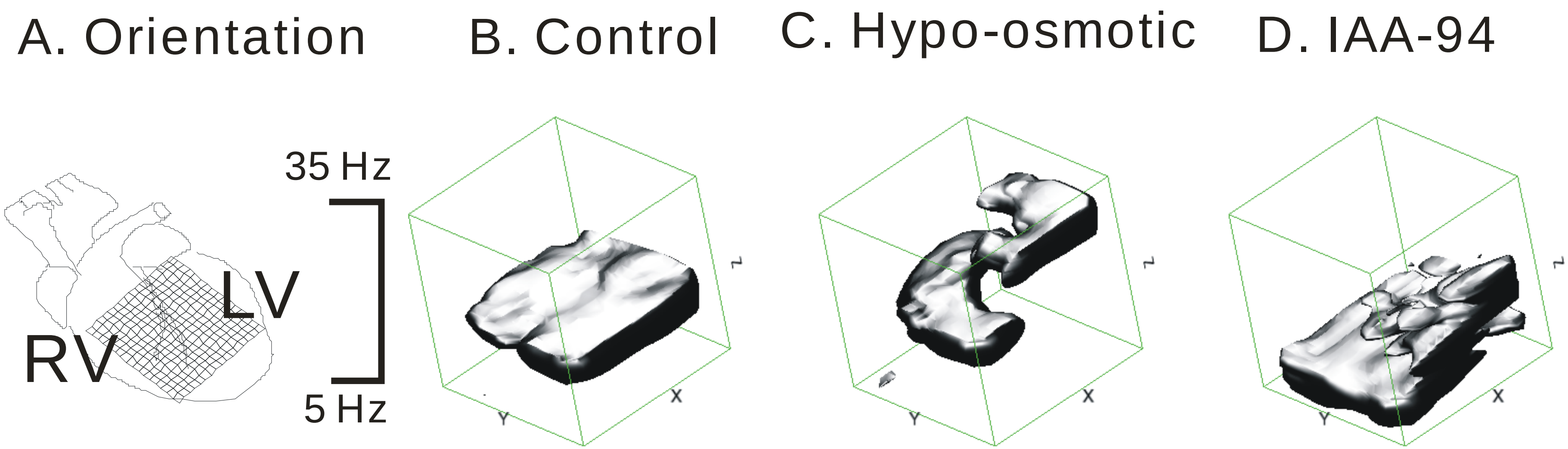

A. Control
B. Hypo-osmotic
C. IAA-94
Traces
FFT
0.00
0.50
1.00
1.50
Time (sec)
10
20
30
Frequency (Hz)

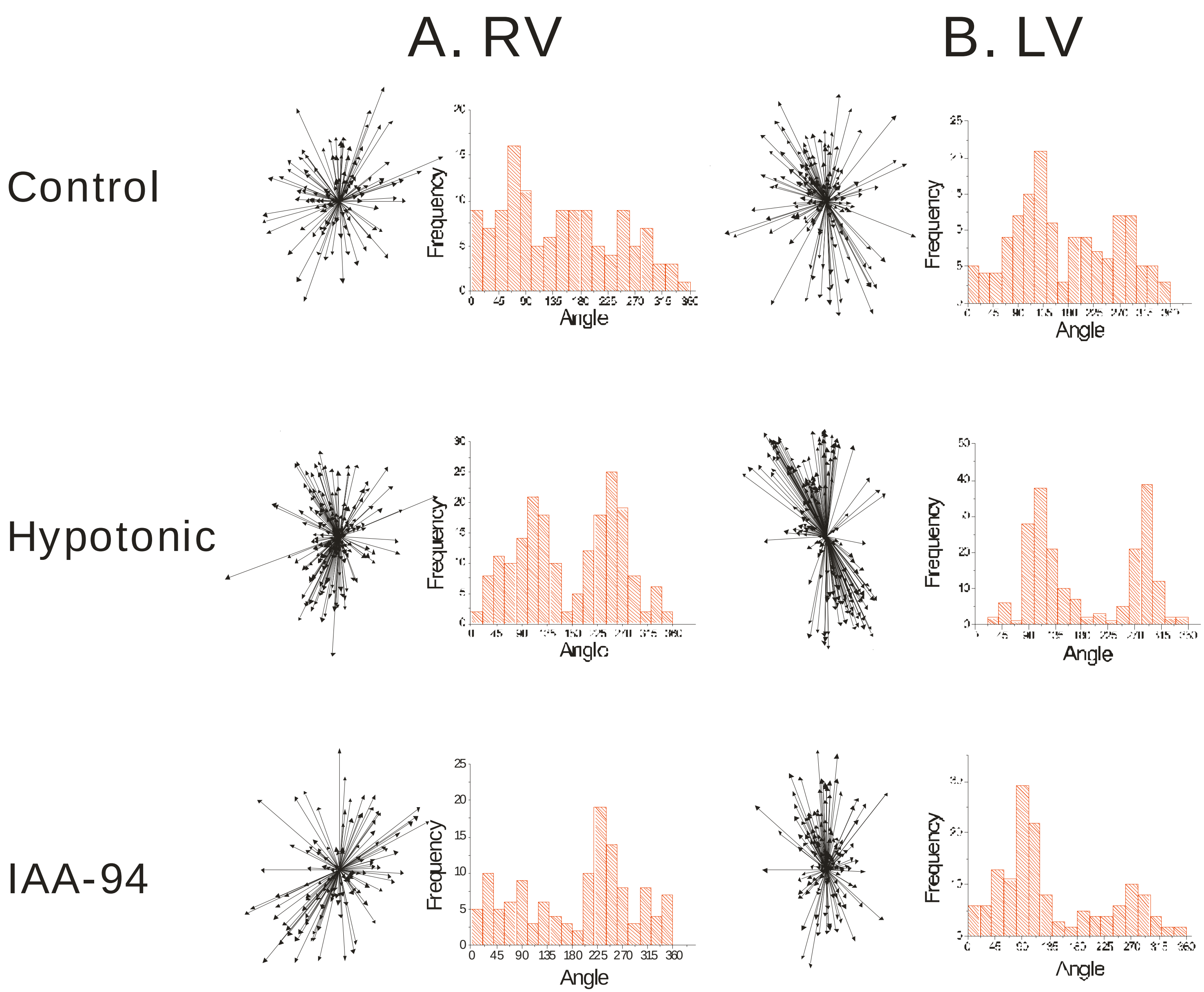
Time Frequency Distribution in Hypo-osmotic Solution



Spectrogram using 1.5 s Gaussian Kernel

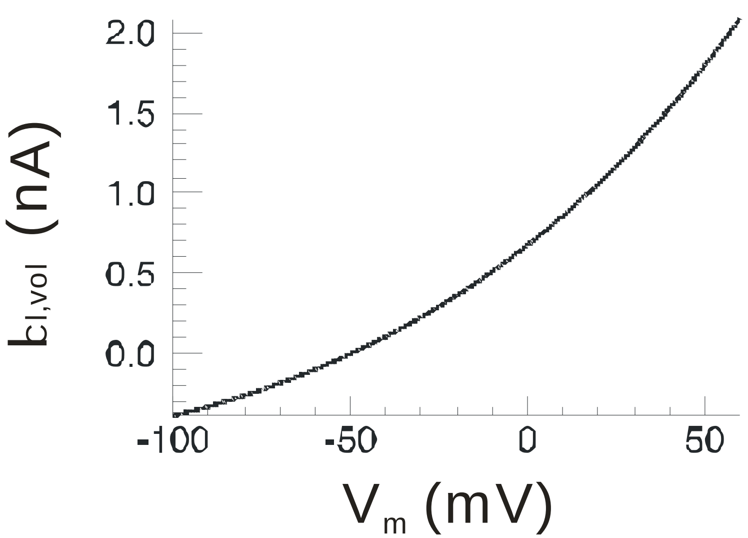

A. TFD from RV
B. TFD from LV
Hypo-osmotic
(10 min)
Hypo-osmotic
(20 min)
IAA-94
(10 min)
Frequency (Hz)
Time (Sec)


A. Orientation
B. Control
C. Hypo-osmotic
D. IAA-94
35 Hz
5 Hz
LV
RV
X
Y
Z

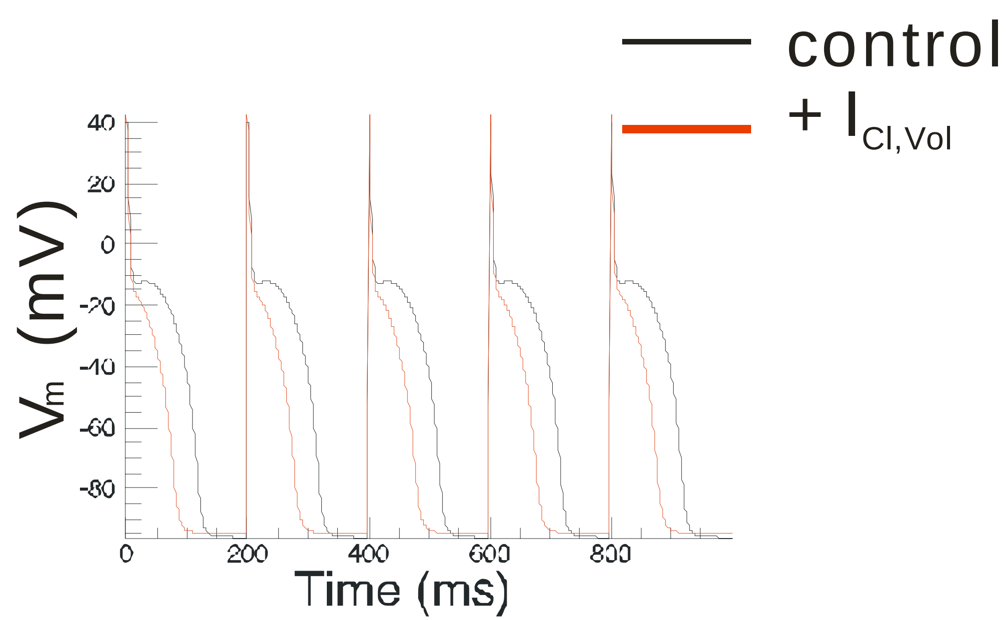


A. RV
B. LV
Control
Hypotonic
IAA-94
Frequency
Angle
0 45 90 135 180 225 270 315 360

A. $I_{Cl,Vol}$ vs. V_m



B. Traces



Modeling $I_{Cl,vol}$ on VF

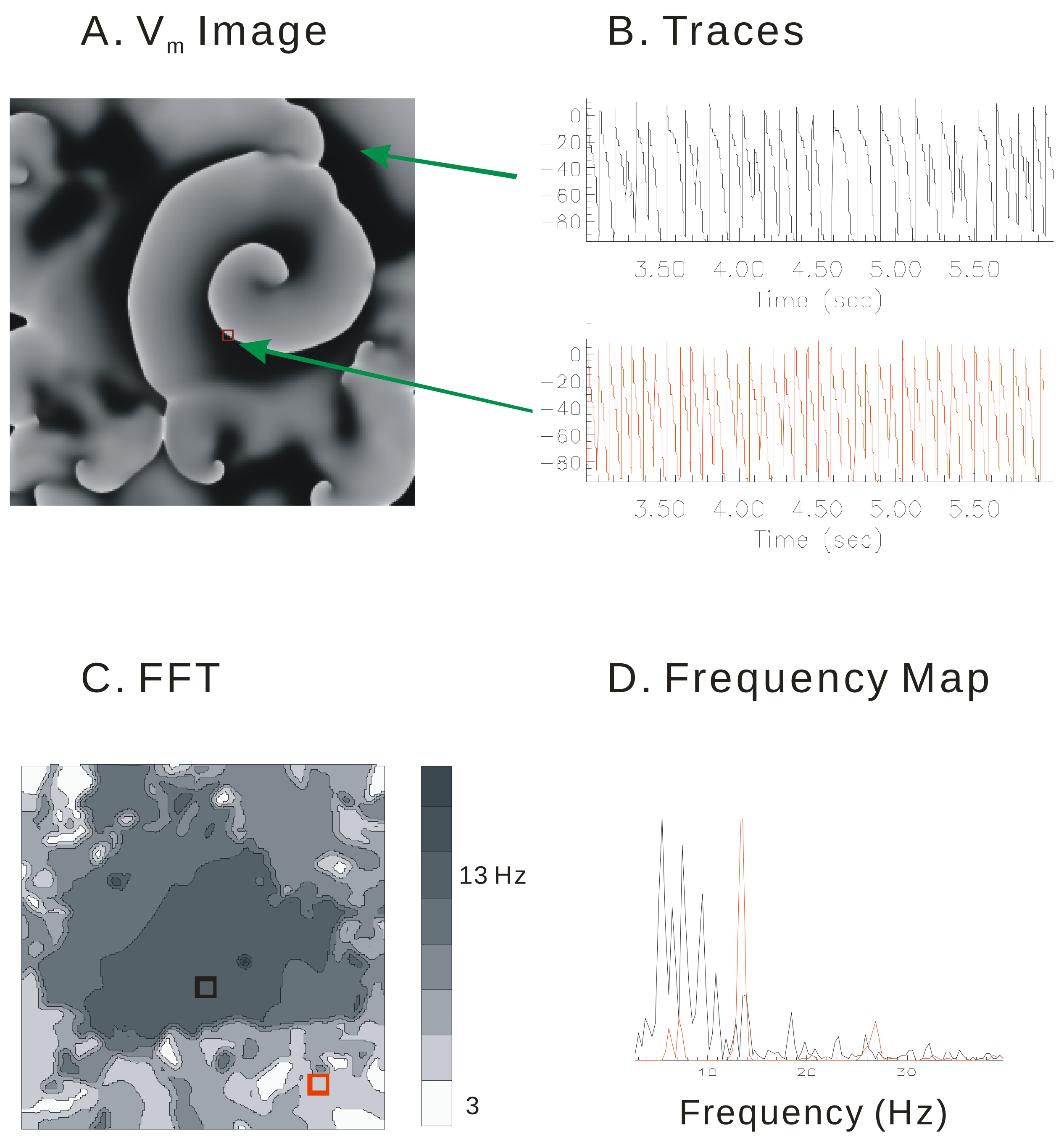
- CMV model of Fox et al., 2002
- Conductance of $I_{Cl,vol}$ from the model by Vandenberg et. al. 1997

$$I_{Cl,vol} = \gamma_{Cl,vol}(E_m - E_{Cl}) \cdot \exp\left[\frac{steep_{Cl,vol}(E_m - E_{Cl} + shift_{Cl,swell})F}{RT}\right]$$

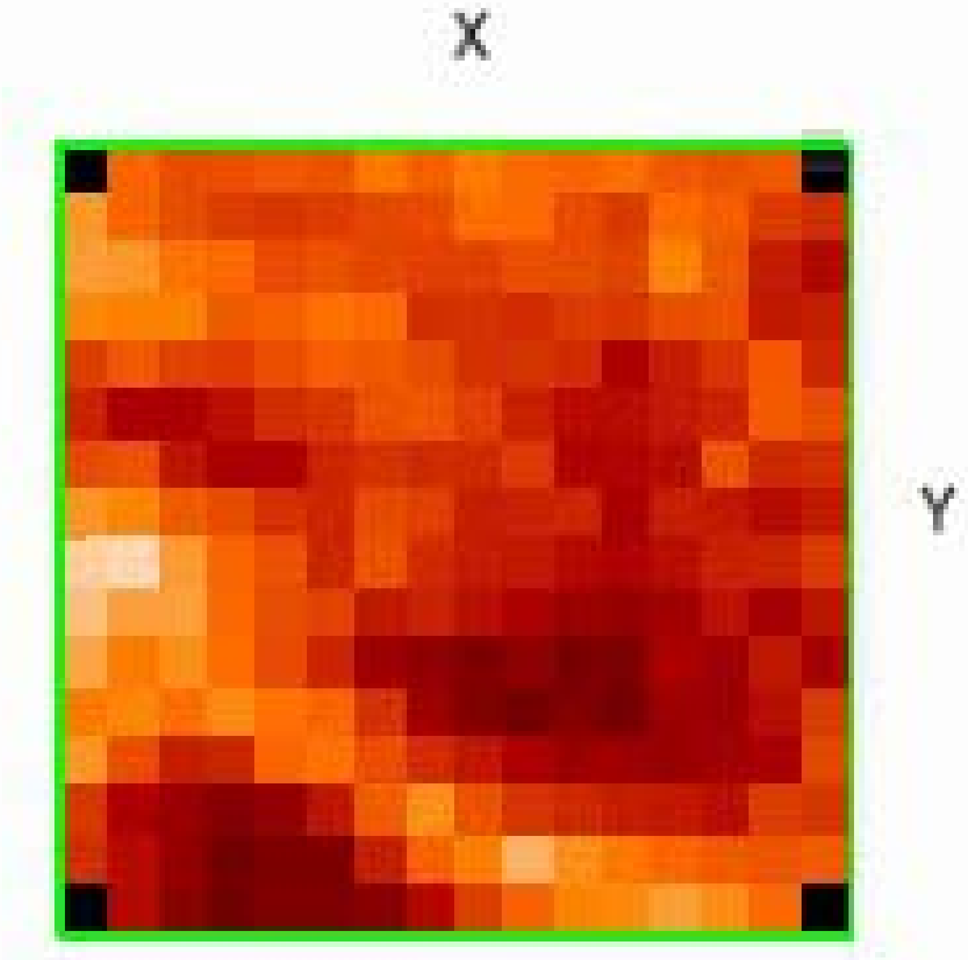
2-D sheet of 500×500 nodes, APDs short at the apex. ICl,vol high (25%) in the center of the sheet, decreasing gradually according to:

$$\gamma_{Cl,Vol}(x,y,t) = \overline{\gamma}_{Cl,Vol} \bullet \left(1 + 0.25 \bullet e^{-\frac{(x-Nx/2)^2+(y-Ny/2)^2}{\sigma^2}}\right) \bullet (t/2)$$

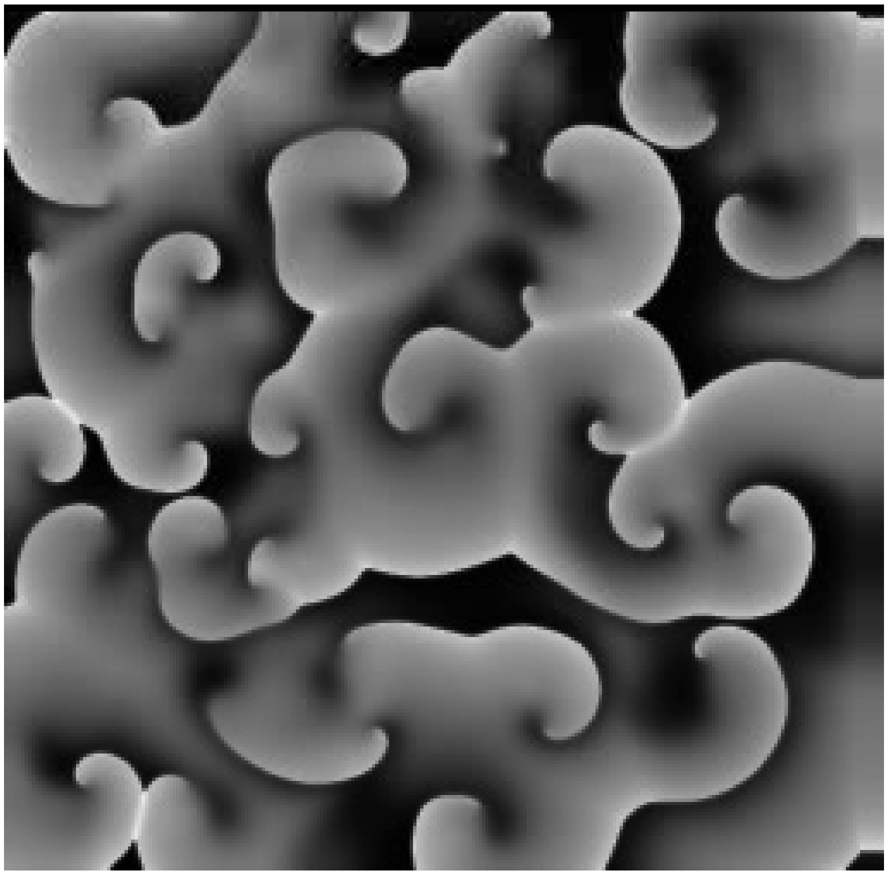
Nx and Ny is the number of nodes in x and y (500), σ was set to Nx/3, *t* is in seconds


A. V_m Image
B. Traces
0
−20
−40
−60
−80
3.50
4.00
4.50
5.00
5.50
Time (sec)
0
−20
−40
−60
−80
3.50
4.00
4.50
5.00
5.50
Time (sec)
C. FFT
13 Hz
3
D. Frequency Map
10
20
30
Frequency (Hz)

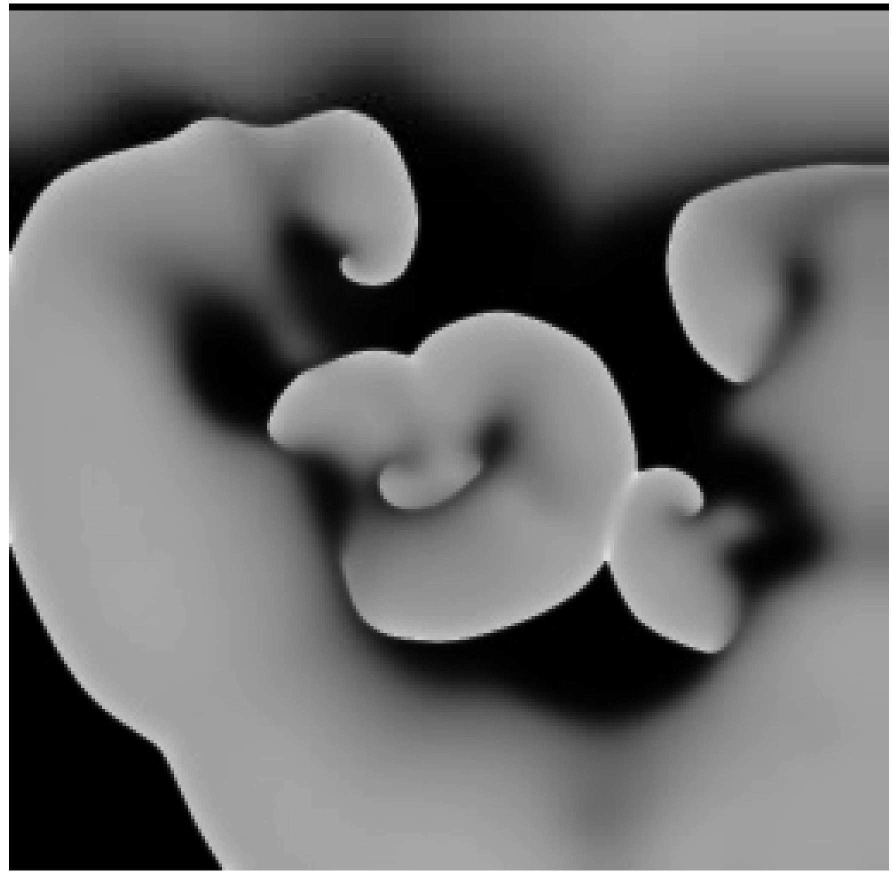
Experimental Confirmation of Mother Rotor in Hypo-Osmotic and Hypotonic Solutions



CMV model of VF



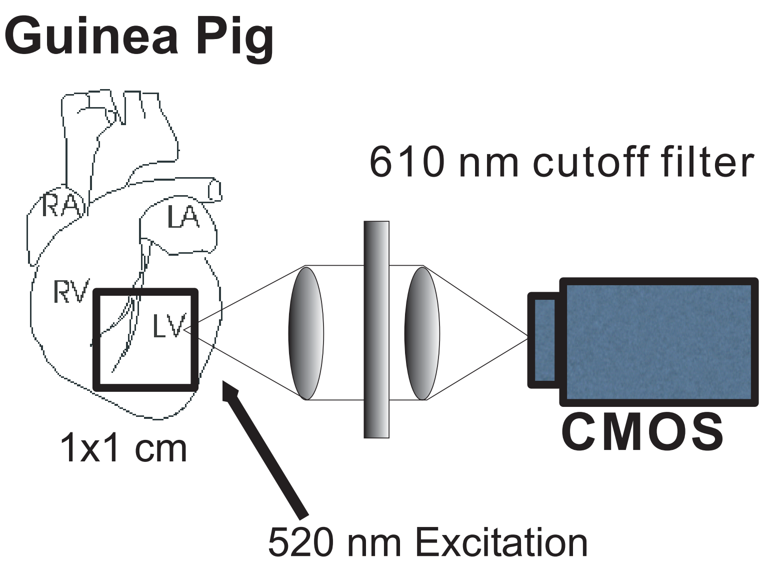
Control



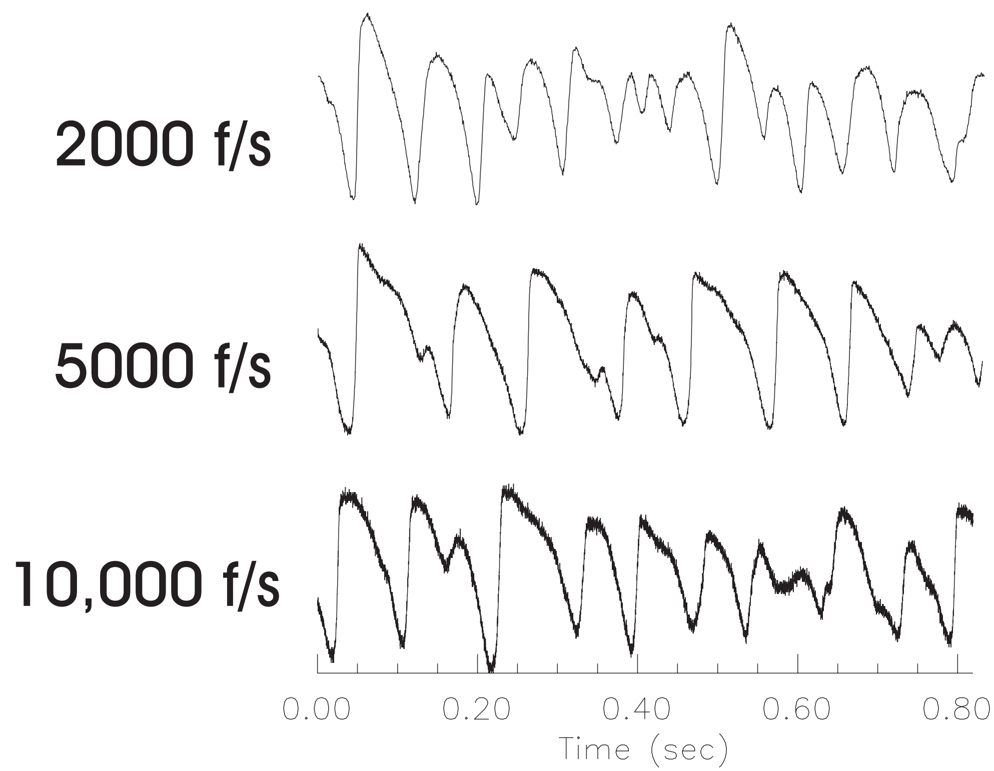
+ $I_{Cl,vol}$

Mechanism underlying Wavebreaks

A. Optical Apparatus

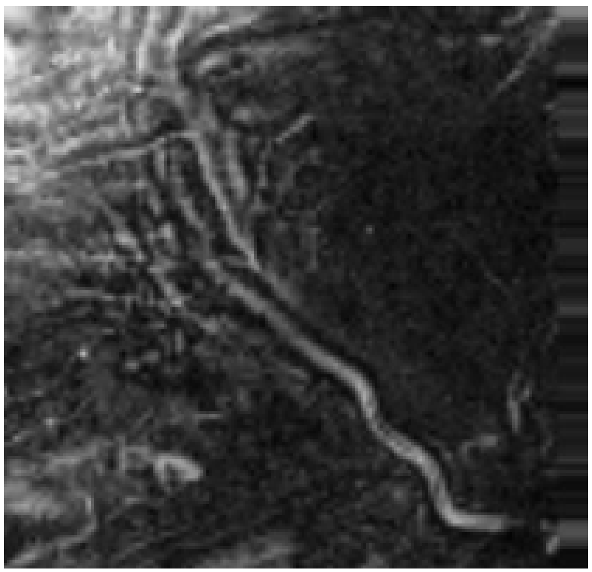


B. Optical Trace in VF

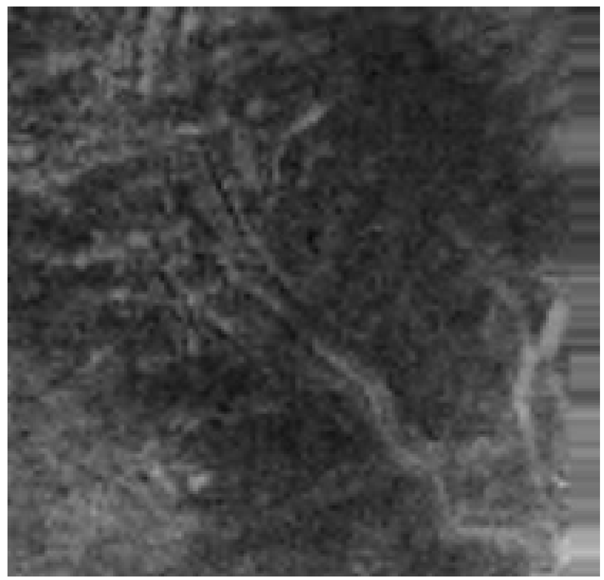


AP Propagation (10,000 f/s)

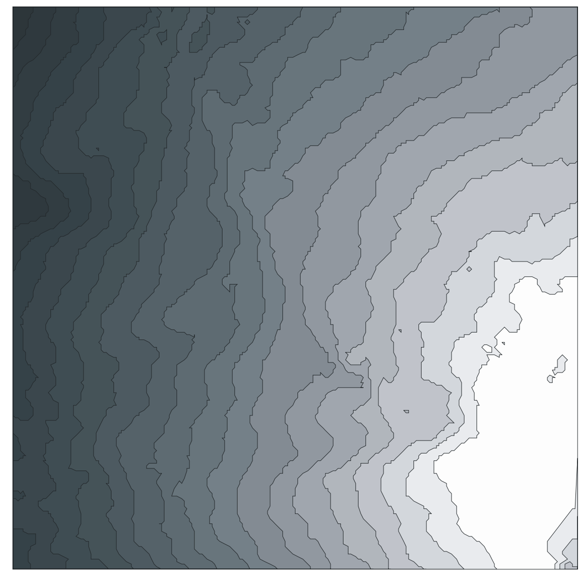
ΔF Movie



dF/dt



Map (1ms)



Spatial resolution : 100x100 μm^2

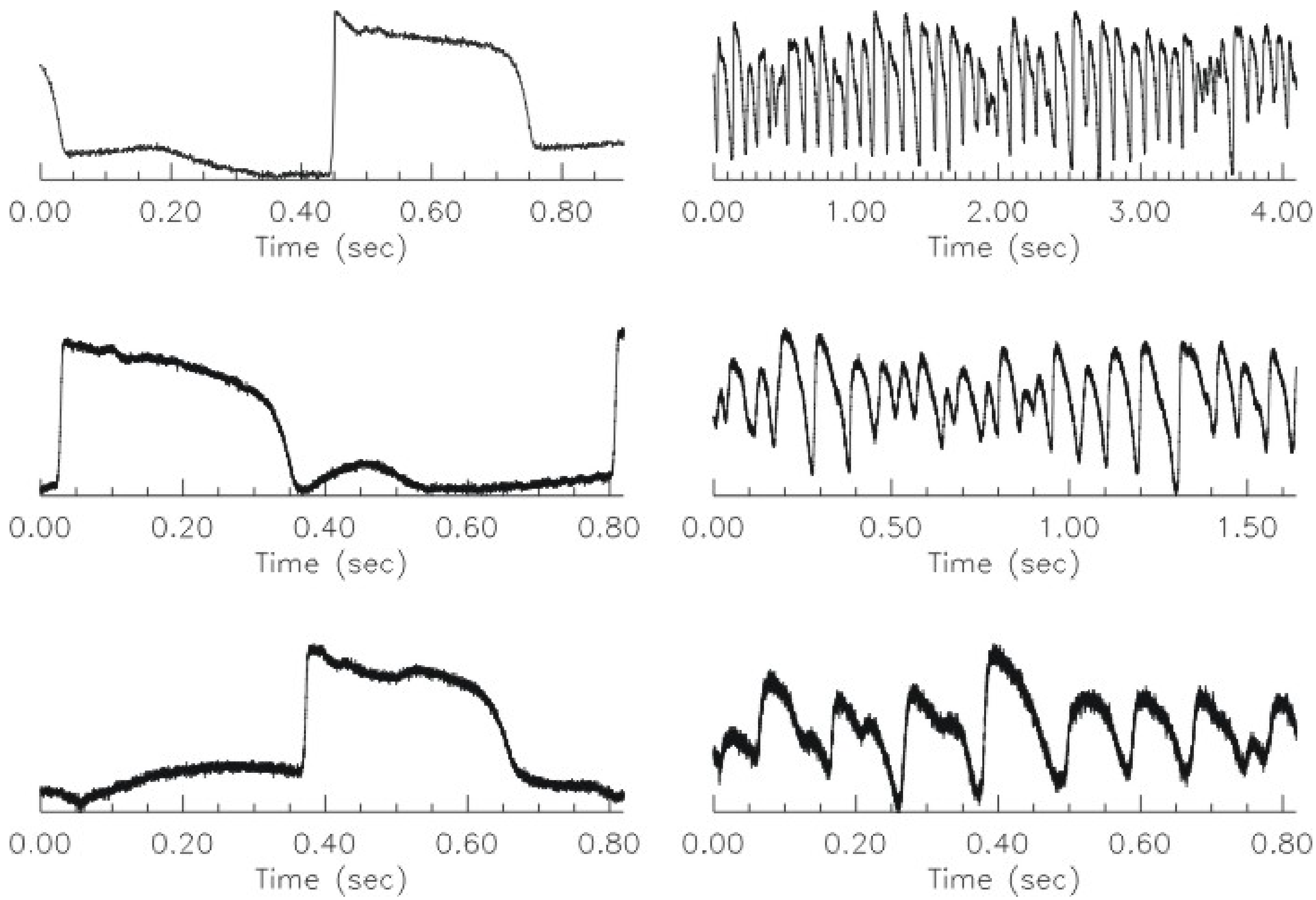
Temporal resolution: 0.1 ms

® Can detect velocities of propagation as high as 0.5 m/s between pixels at this magnification.

Raw Traces from Ultima CMOS

Spontaneous AP

VF



2000 f/s

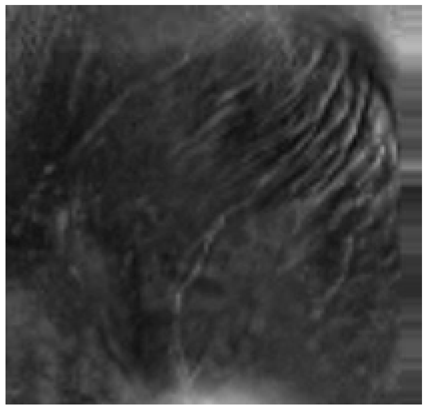
5000 f/s

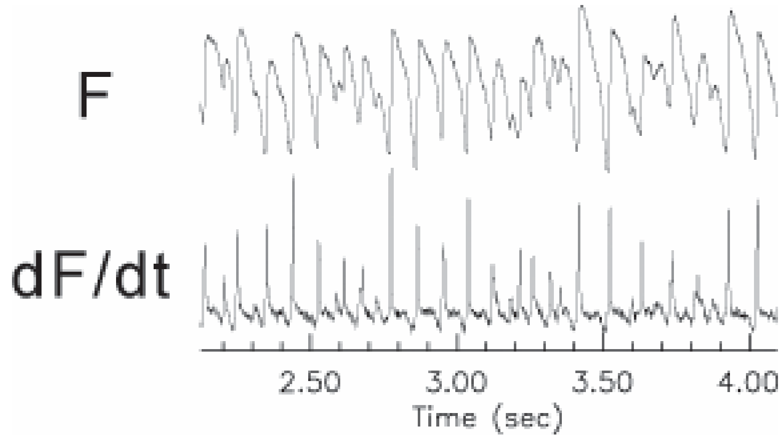
10000 f/s

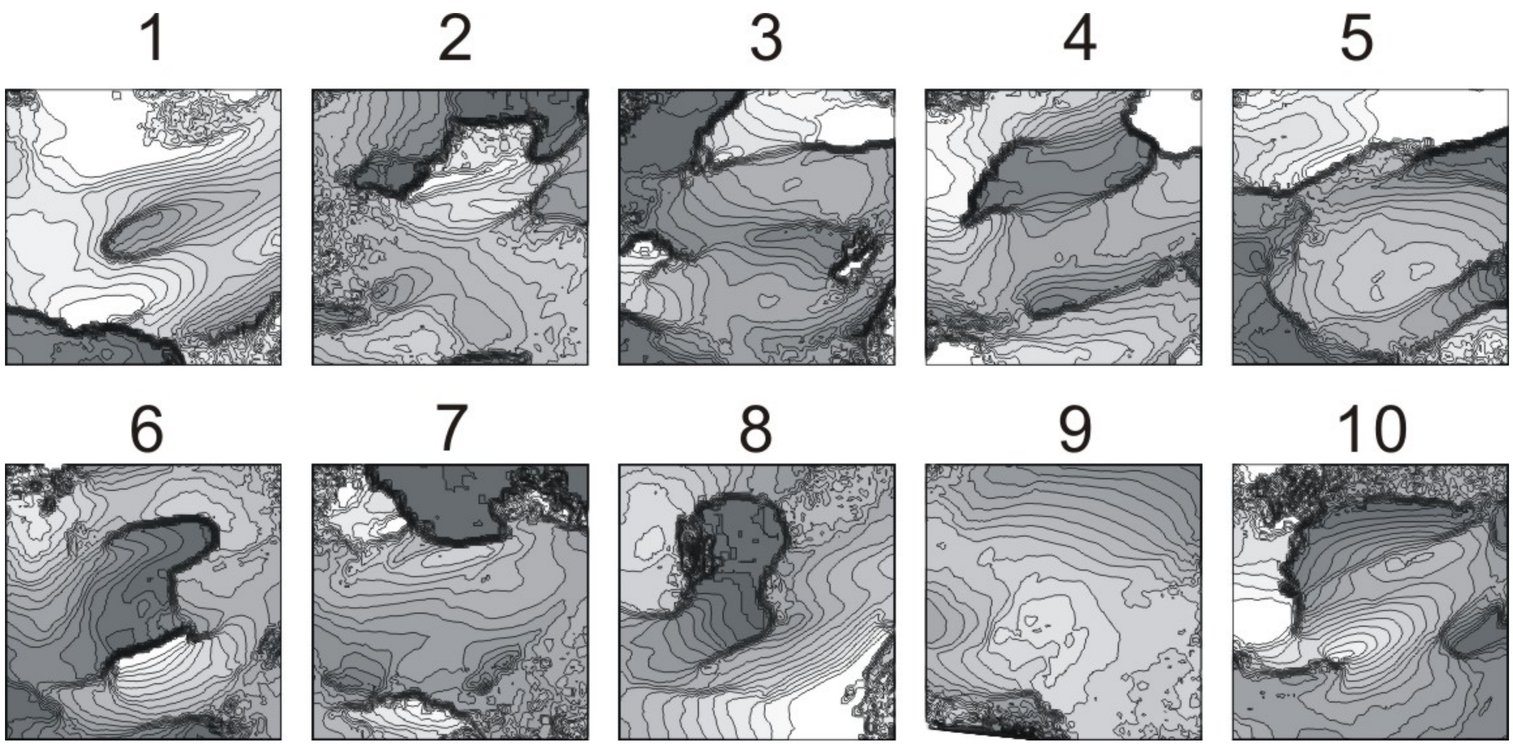
S/N = 30/1

AP Propagation in VF

dF/dt

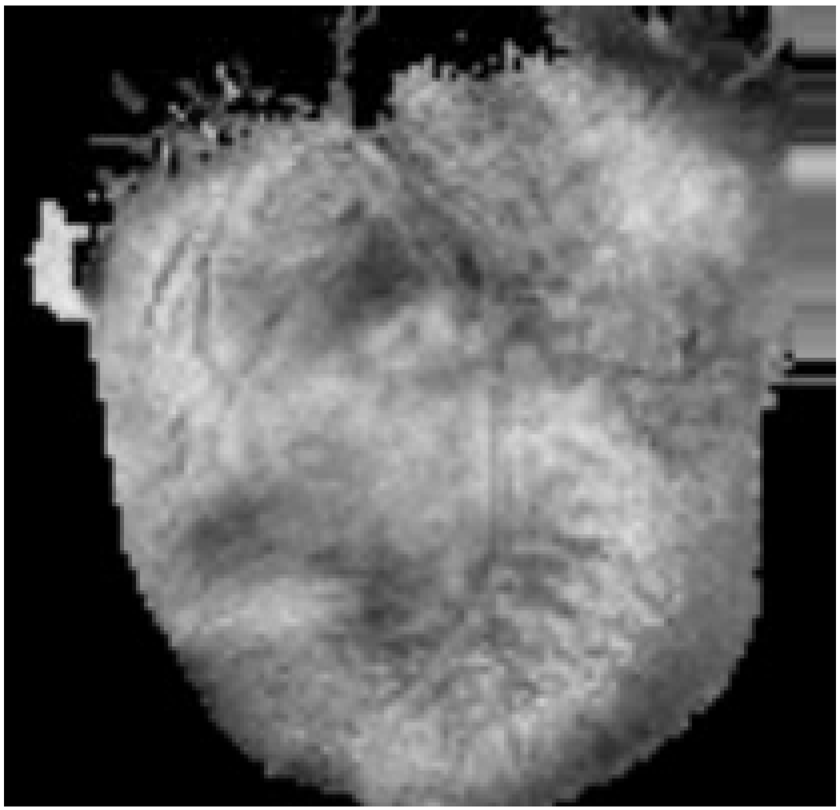




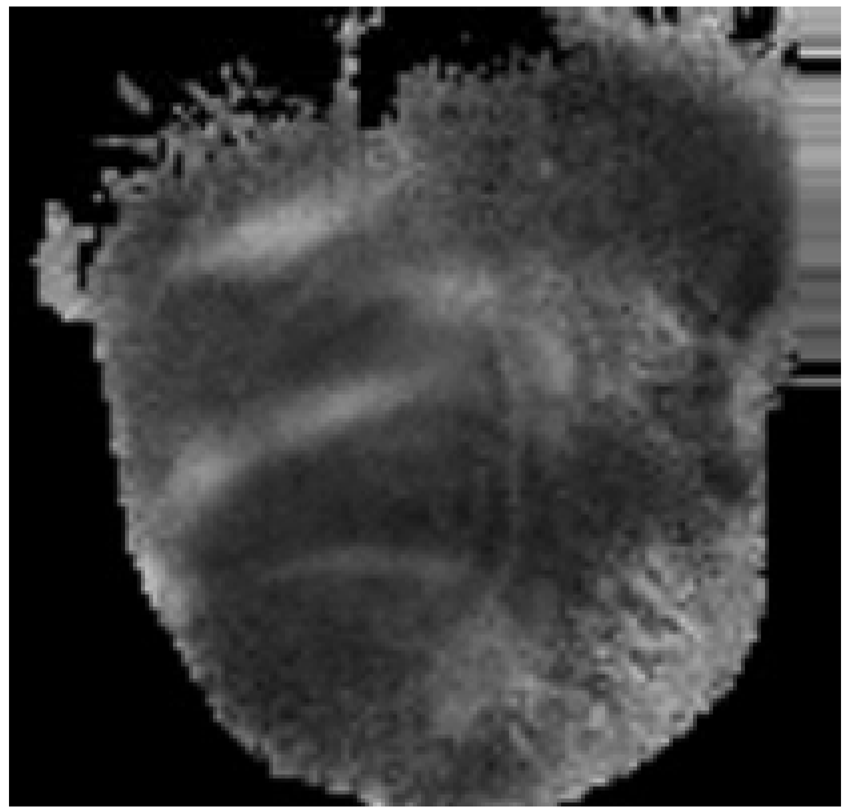


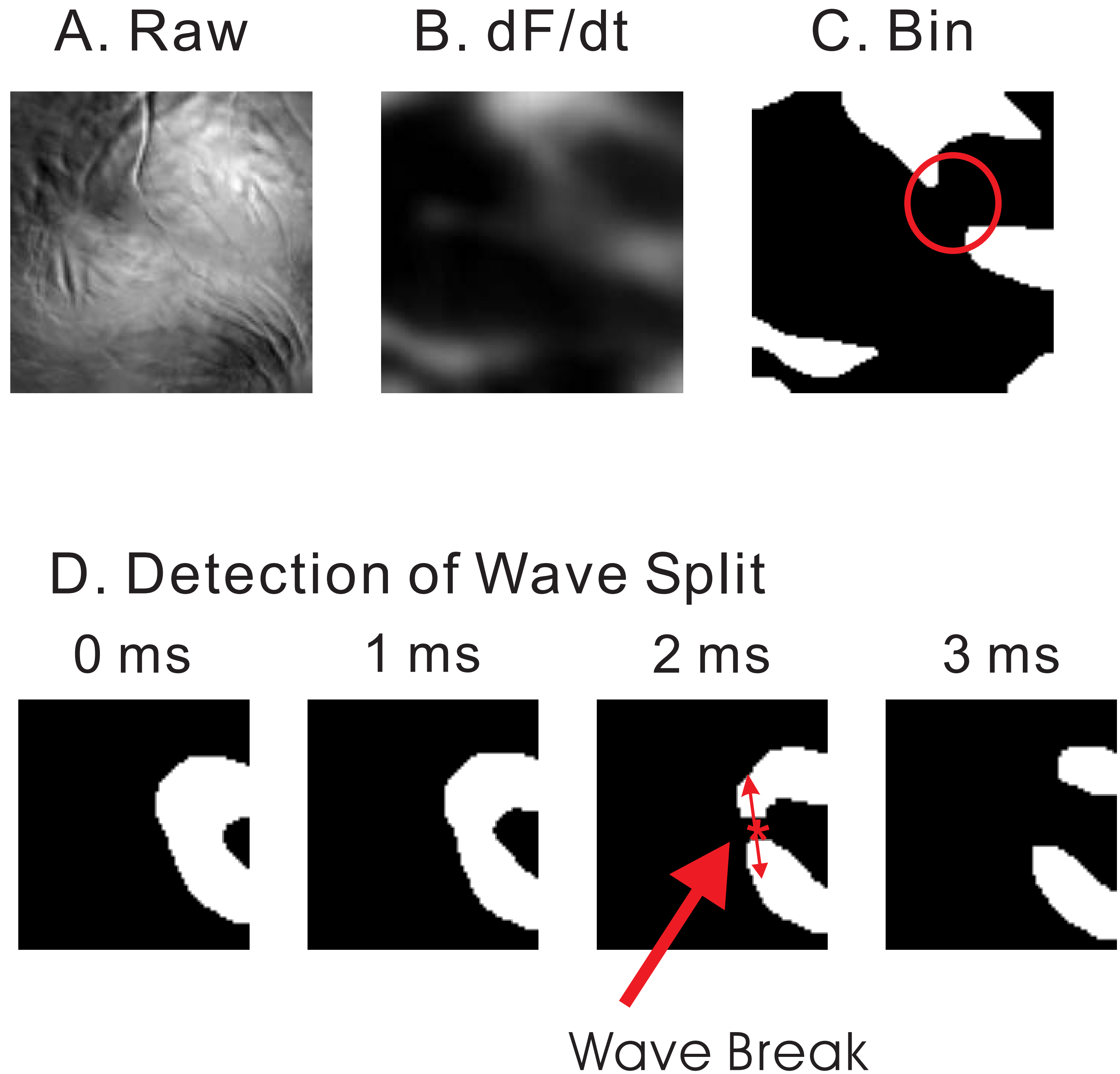
VF in guinea pig hearts

$F \propto Vm$

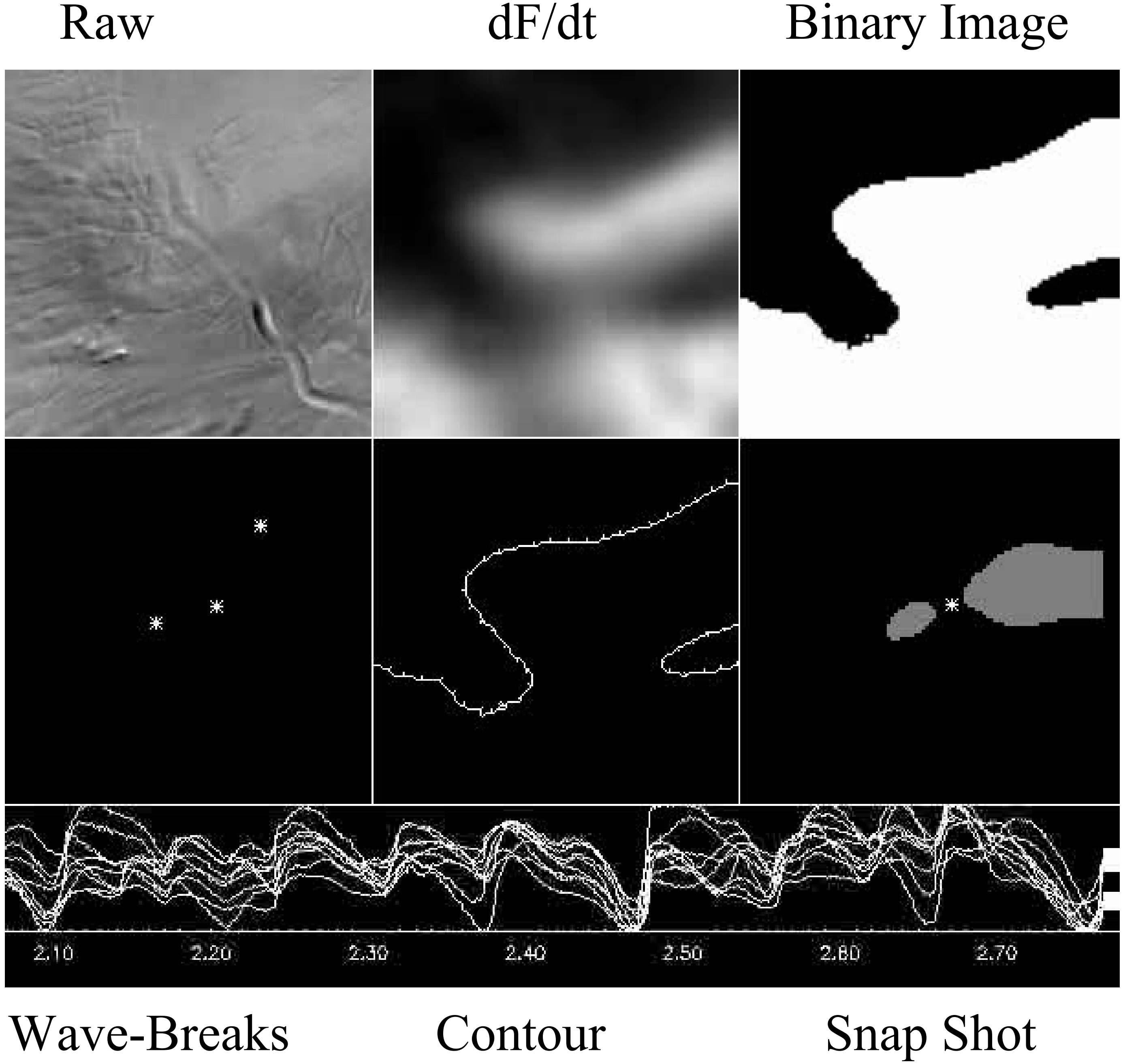


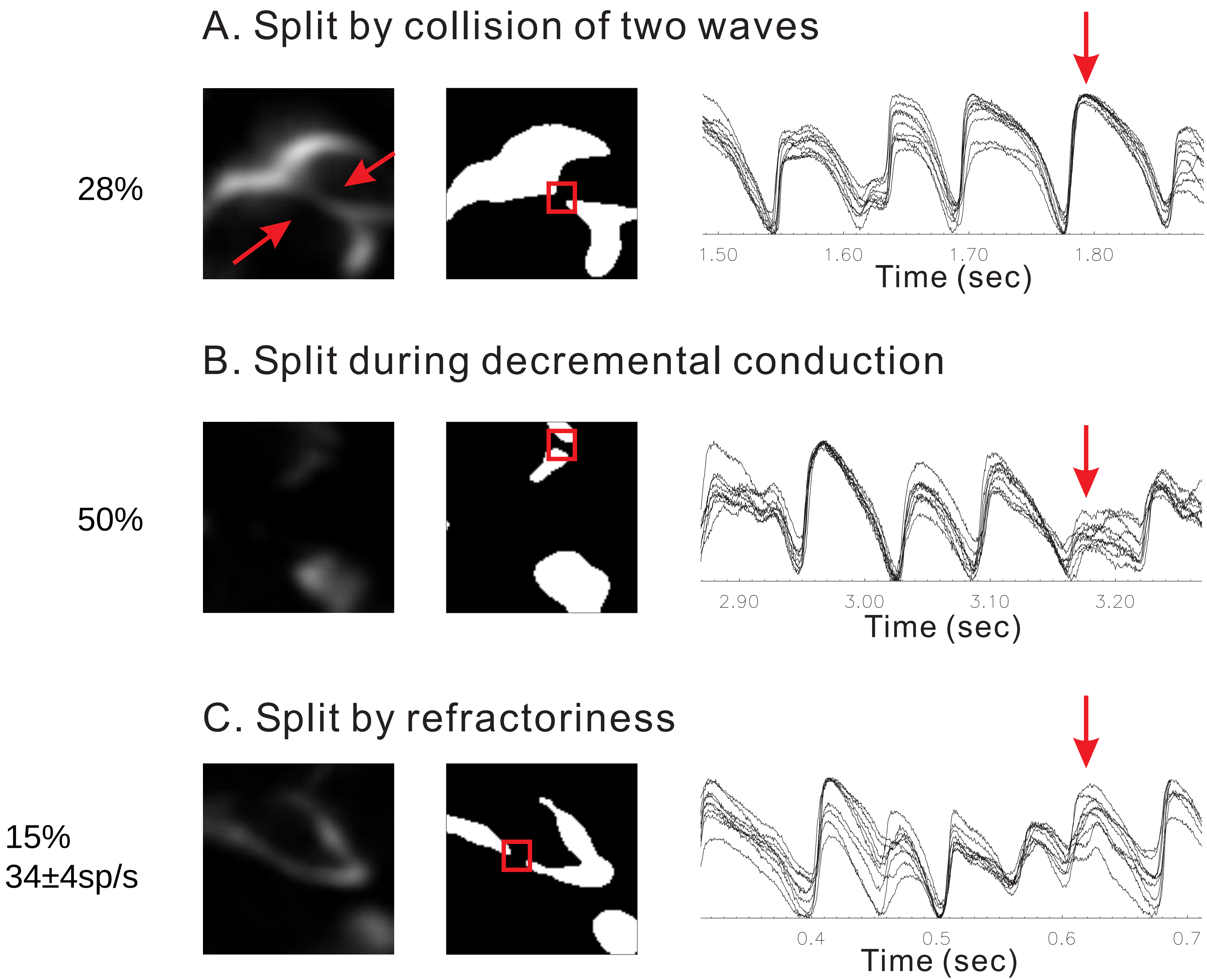
dF/dt



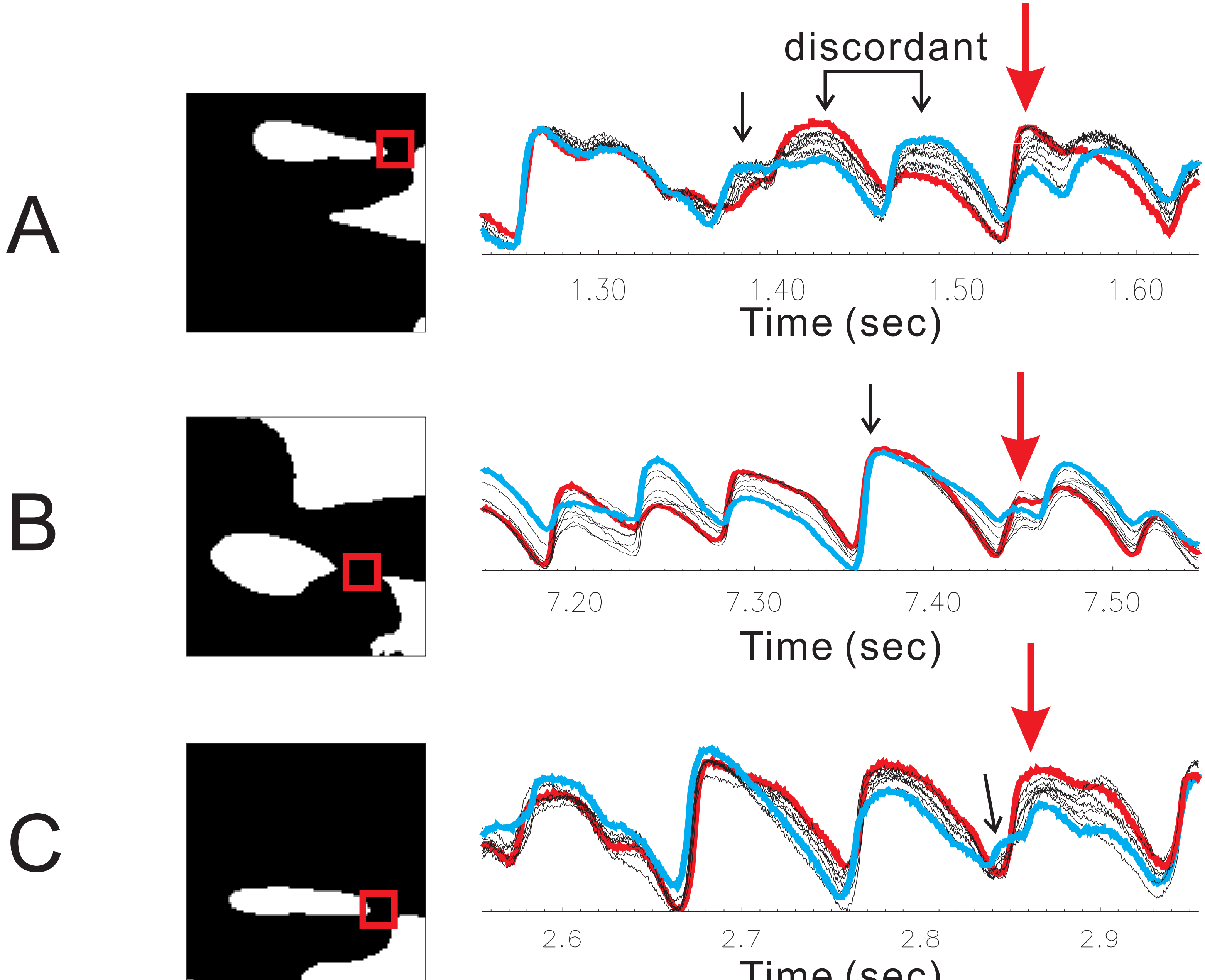

A. Raw
B. dF/dt
C. Bin
D. Detection of Wave Split
0 ms
1 ms
2 ms
3 ms
Wave Break

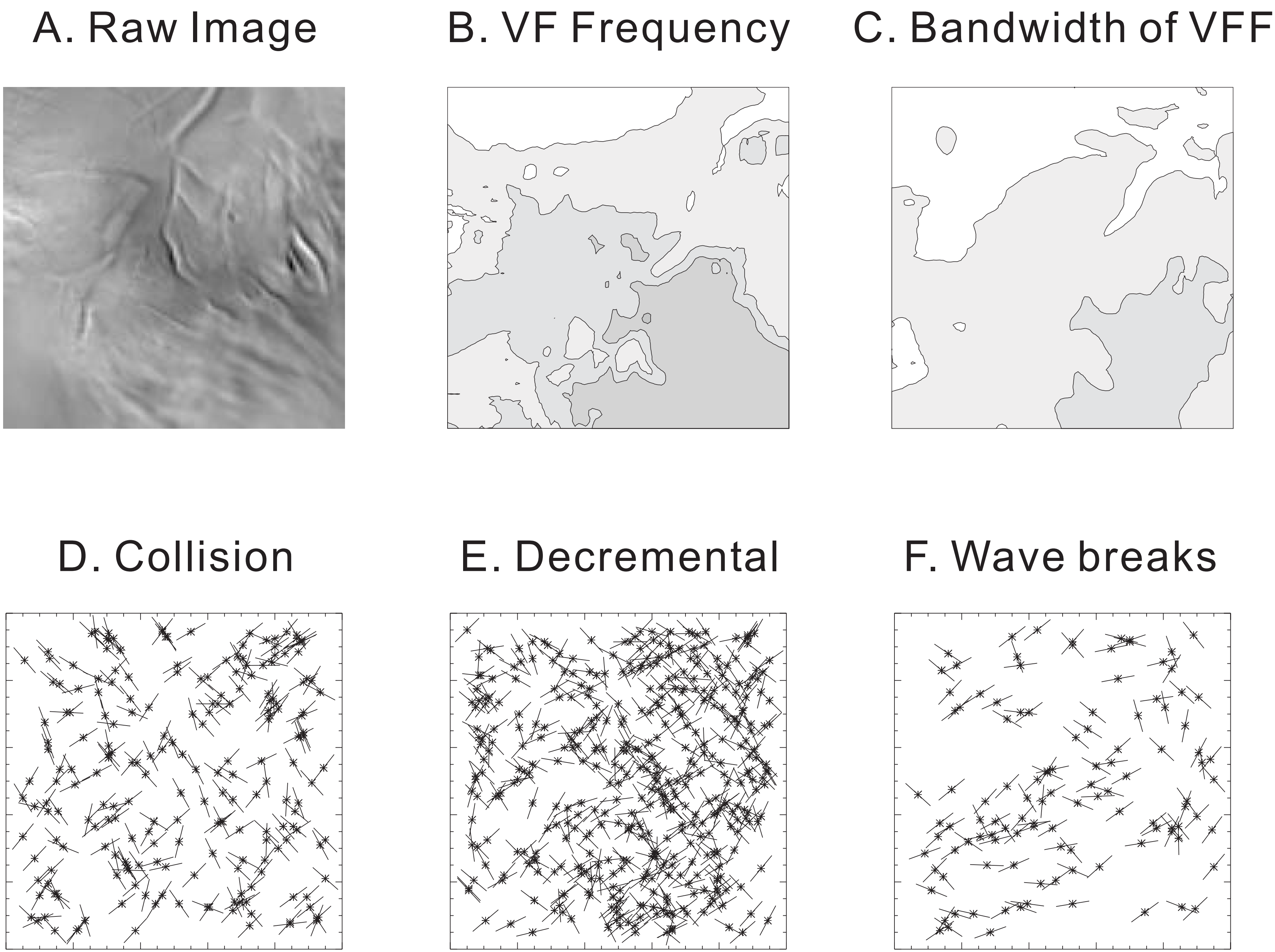
Cumulative Plot of Wave Breaks




A. Split by collision of two waves
28%
1.50
1.60
1.70
1.80
Time (sec)
B. Split during decremental conduction
50%
2.90
3.00
3.10
3.20
Time (sec)
C. Split by refractoriness
15%
34±4sp/s
0.4
0.5
0.6
0.7
Time (sec)

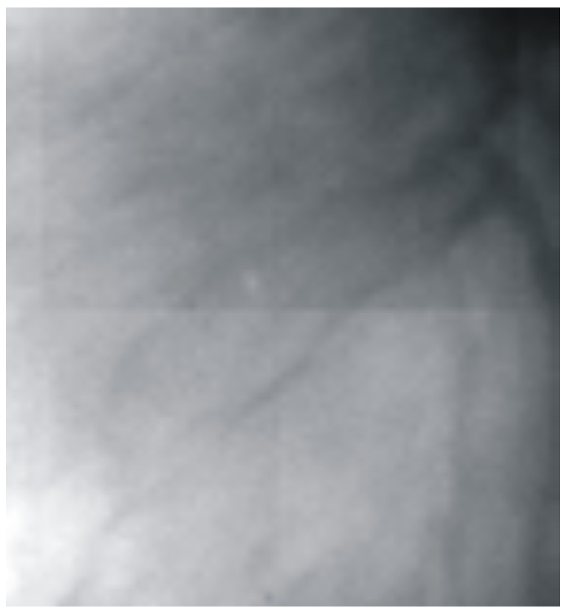
Examples of Wavebreaks and Vm in Neighboring sites




A. Raw Image
B. VF Frequency
C. Bandwidth of VFF
D. Collision
E. Decremental
F. Wave breaks

Vessel and Wave Breaks

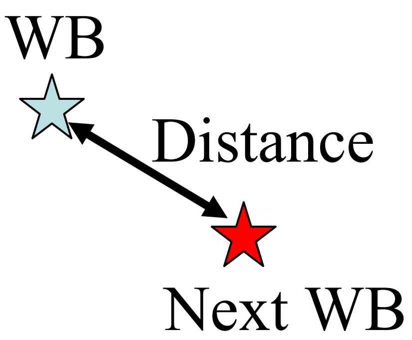
A. Raw Image

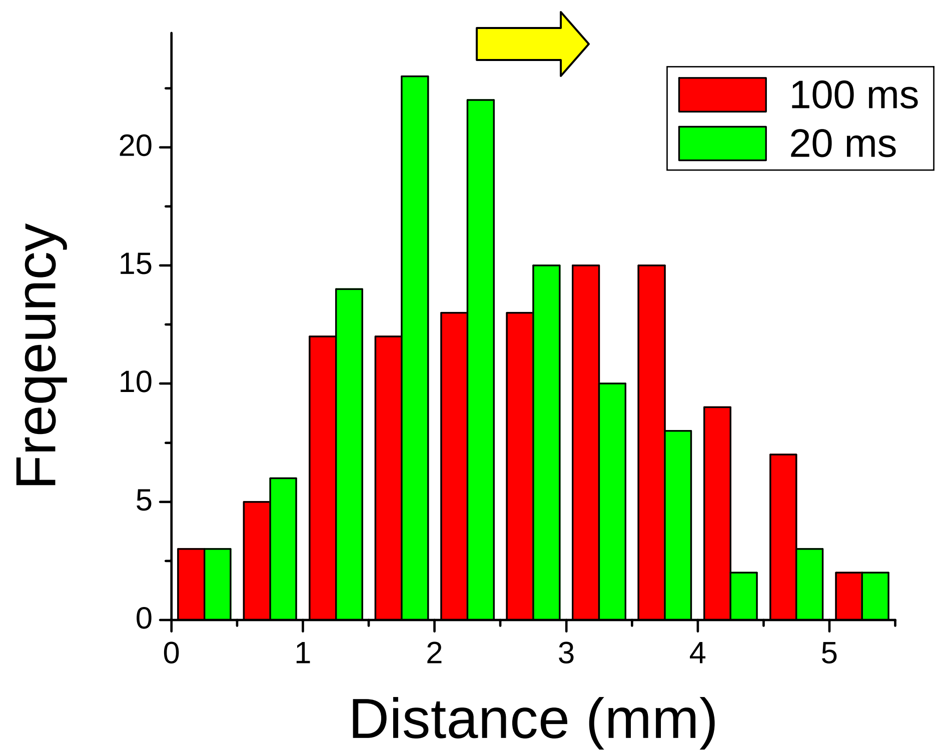


B. Vessel and WBs

< 25 % overlap

Distance between Wavebreaks





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Carnegie Mellon University

Statistics
Wonchul Jang

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