Diastolic Activation Dynamics in the Phase Plane

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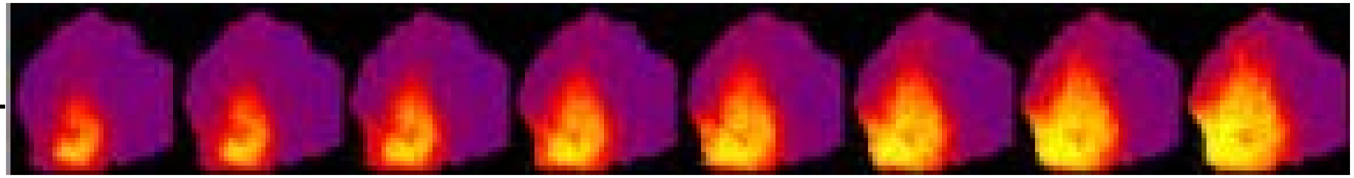
Temporal Response of Cardiac Tissue to Point S1 and Field S2

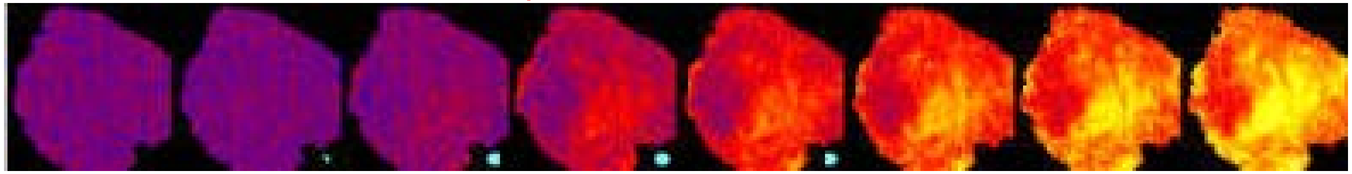
Normal, propagated activation

Point S1



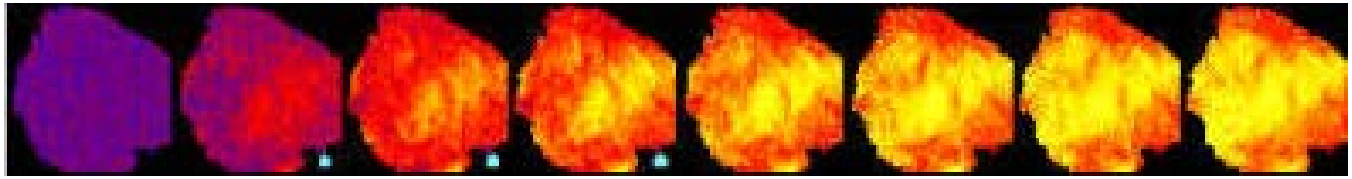
Prompt, distributed activation

10V/cm S2



Faster, distributed activation

40V/cm S2



Question: How best to quantify the differences in the three responses?

Statement of the Problem

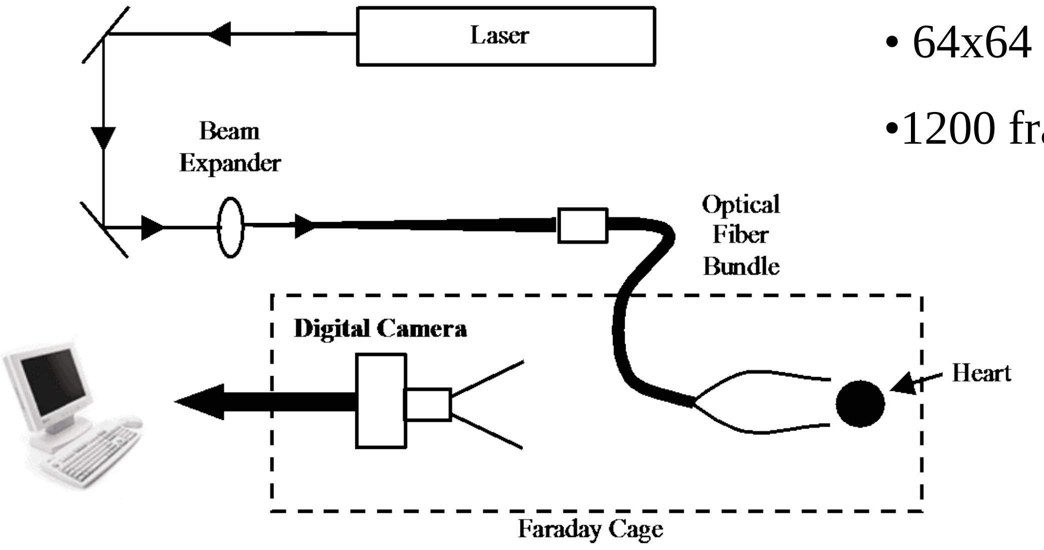
- The response of cardiac tissue to strong electrical stimulation is critical to understanding the defibrillation process.
- Theory predicts that tissue heterogeneities will produce localized regions of depolarization and hyperpolarization (virtual cathodes and virtual anodes).
- In studying the response of resting cardiac tissue to field stimulation, we observed multiple VCs but neither VAs nor the expected VC-VA pairs, and we saw distributed heterogeneous activation that was faster for stronger shocks.

Statement of the Problem

- Optical fluorescence data are typically viewed in the spatio-temporal plane.
- Phase-plane techniques are useful in studies of the dynamics of cardiac reentry and fibrillation.
  - Gray, R. A., Pertsov, A. M., and Jalife, J., "Spatial and temporal organization during cardiac fibrillation," *Nature*, **392:** 75-78, 1998.
  - Bray, M.-A., Lin, S.-F., Aliev, R. R., Roth, B. J., and Wikswo, J. P., Jr., "Experimental and theoretical analysis of phase singularity dynamics in cardiac tissue," *Journal of Cardiovascular Electrophysiology*, **12**: 716-722, 2001.
- In this presentation, we describe phase-space imaging techniques that highlight key differences between VC and VA response during strong stimuli.

Methods

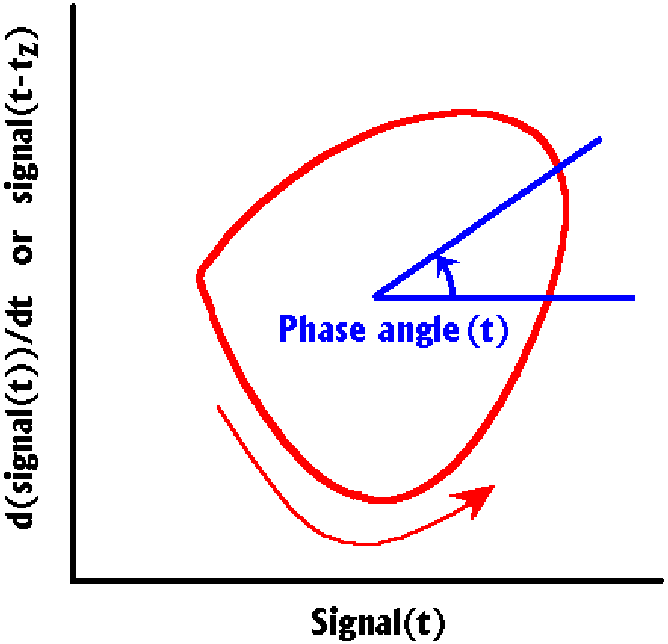
- Dye fluorescence imaging of transmembrane potential allows characterization of shock-tissue interaction.
- Isolated rabbit hearts are Langendorff-perfused and stained with the fluorescent dye, di-4-ANEPPS.
- Illumination is achieved by a diode-pumped solid state laser.
- Images are acquired with a 12-bit Dalsa CCD camera.



- 64x64 pixels
- 1200 frames/sec

Data Pre-Processing for Phase Space

- The data are spatially filtered using a 3x3 Gaussian filter with a standard deviation of one.
- No temporal filtering is utilized.
- The data are then normalized pixel-by-pixel by dividing by the pixel maximum response to S1.
- Phase space plots are developed by plotting the data against a time delayed version of itself. Unless otherwise noted, a time delay of 8 frames (6.66 ms) is used.

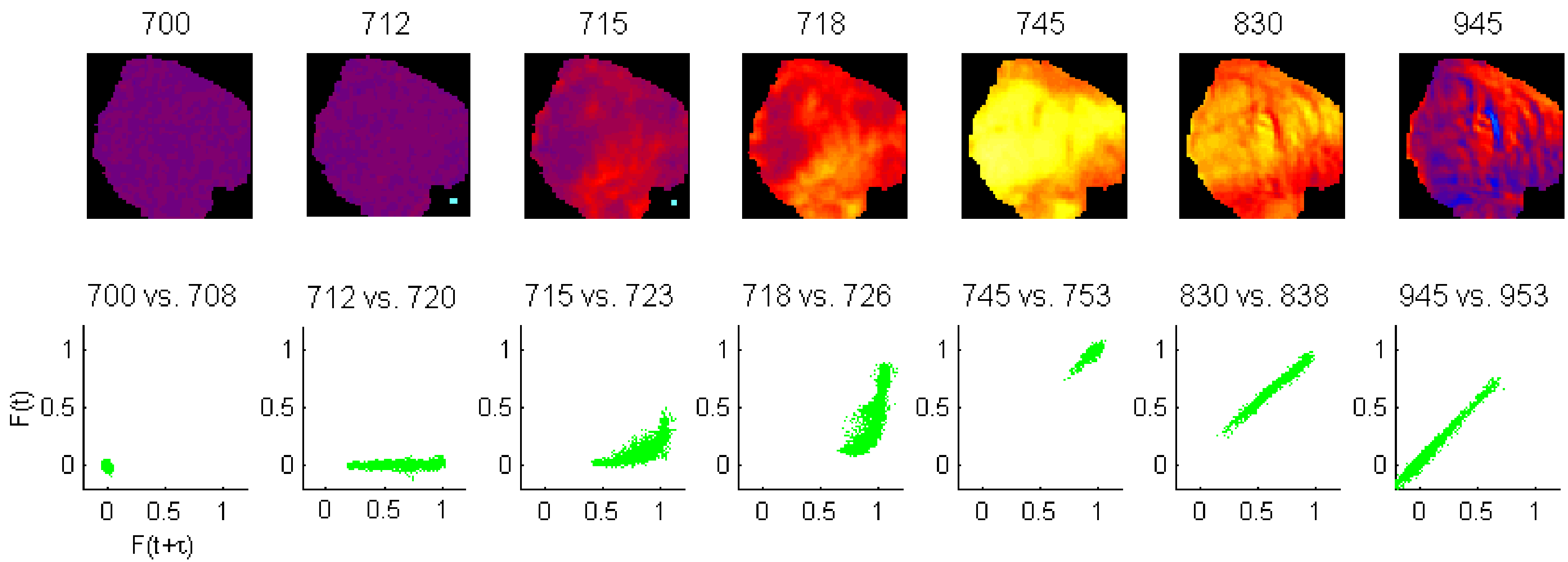


Voltage and Phase Plane Movies

Endocardial isolated right ventricle data

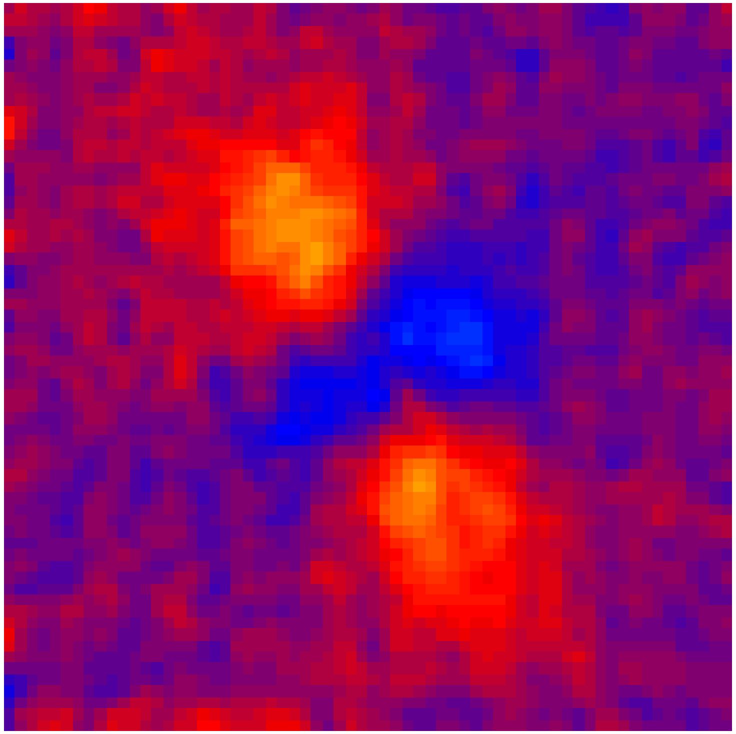
S2 = 5 V/cm field shock

0.83 ms/frame



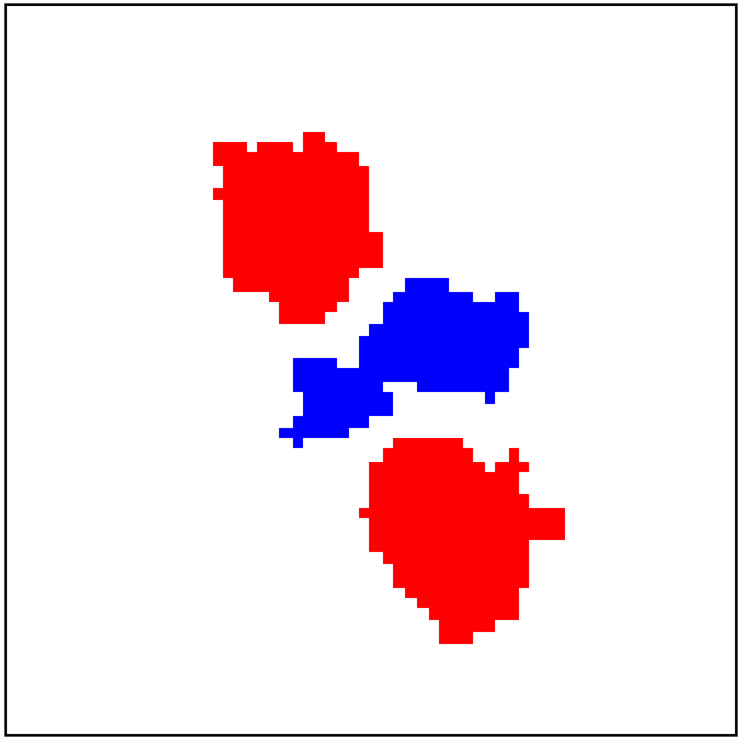
rv_5Vcm_swarm.mov

Virtual Electrode: Proof of Concept



Anodal Diastolic Point Stimulation

- 4 ms duration
- 20 mA
- S1-S2 coupling interval 330 ms



Threshold normalized voltage to demarcate Virtual Cathodes and Virtual Anodes

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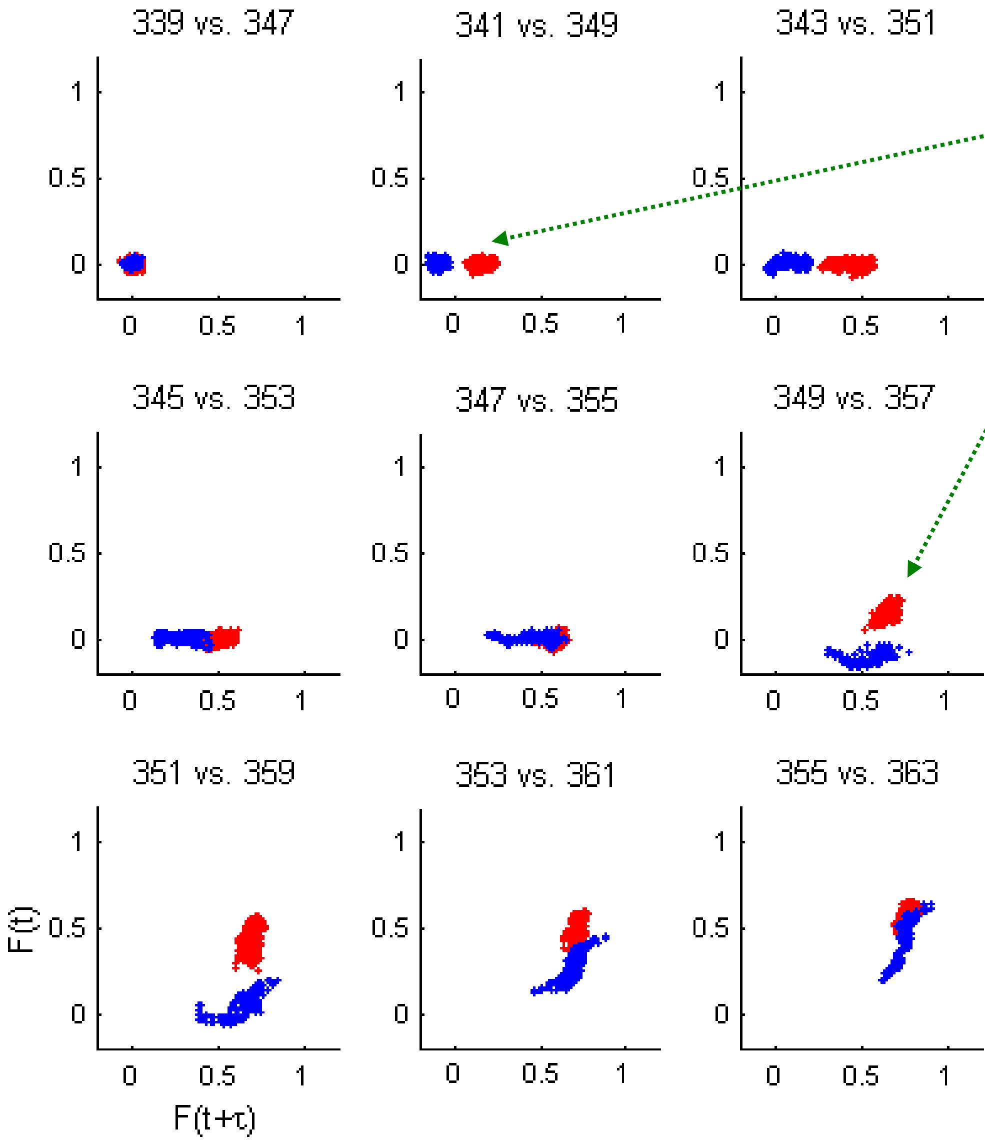
Virtual Electrode Phase Plane Movie



Hyperpolarization denoted by blue movement to the left and downward

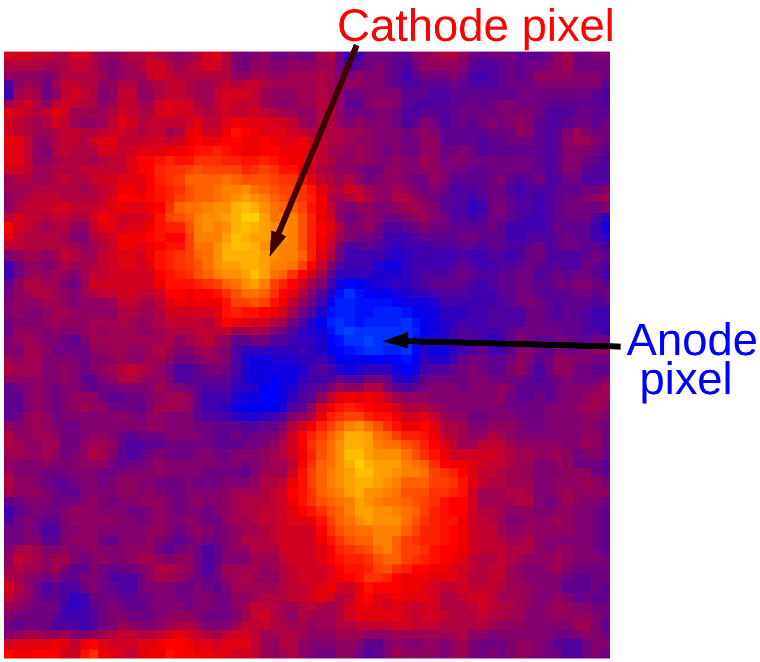
Red – cathode pixels

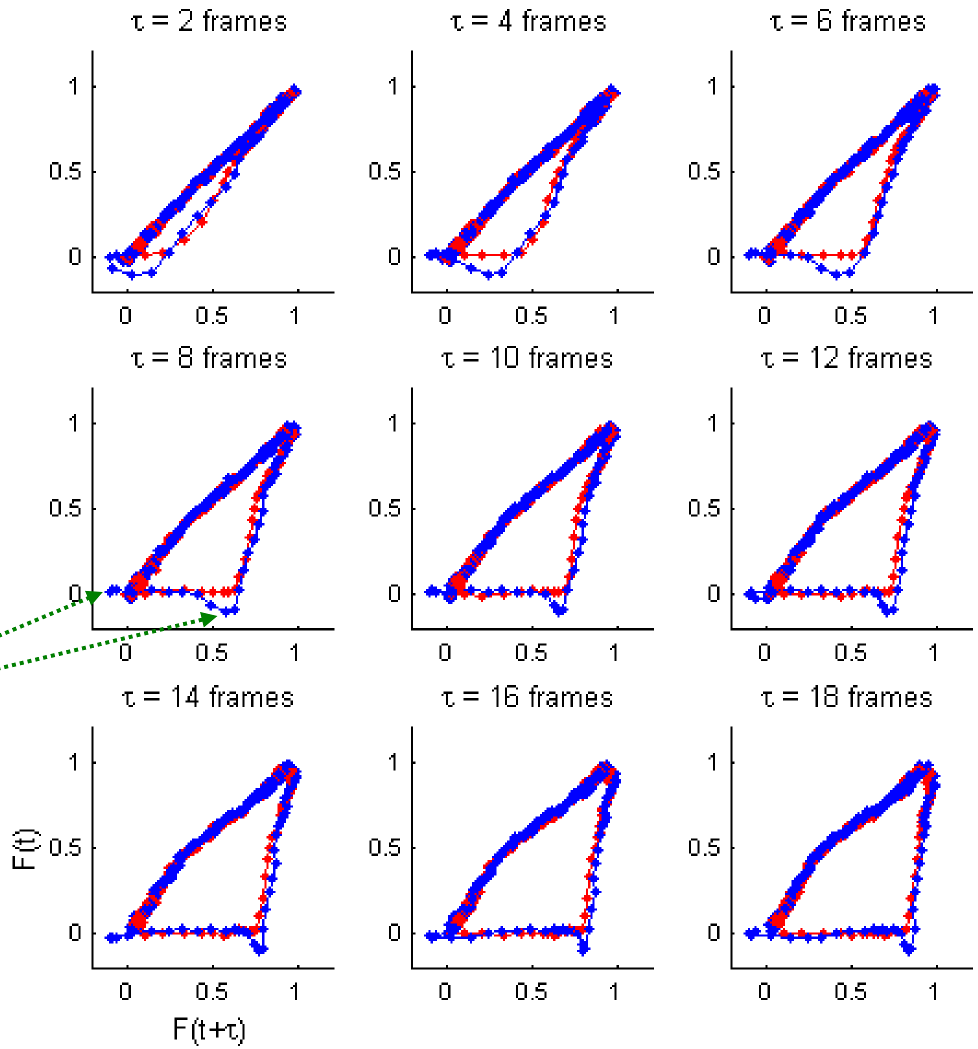
Blue – anode pixels

anode_cathode_multiplepixels_lag8.mov

Visualization in phase space clearly delineates VC and VA responses

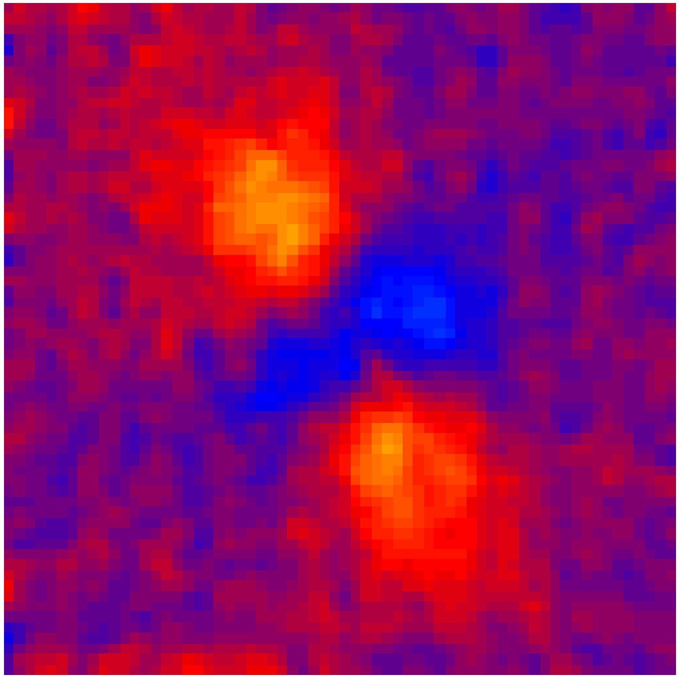
Dependence upon Lag





- Blue movement left and downward reveals hyperpolarization
- Within limits, trajectory topology is not sensitive to lag choice

Virtual Electrode and Border Region



Anodal Diastolic Point Stimulation

- 4ms duration
- 20mA
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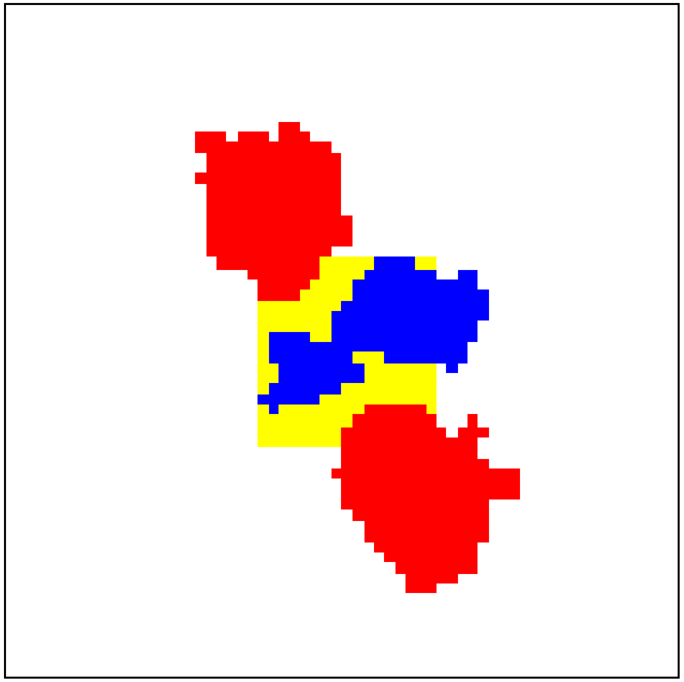

Threshold normalized voltage to demarcate Virtual Cathodes and Virtual Anodes and identify Border Regions

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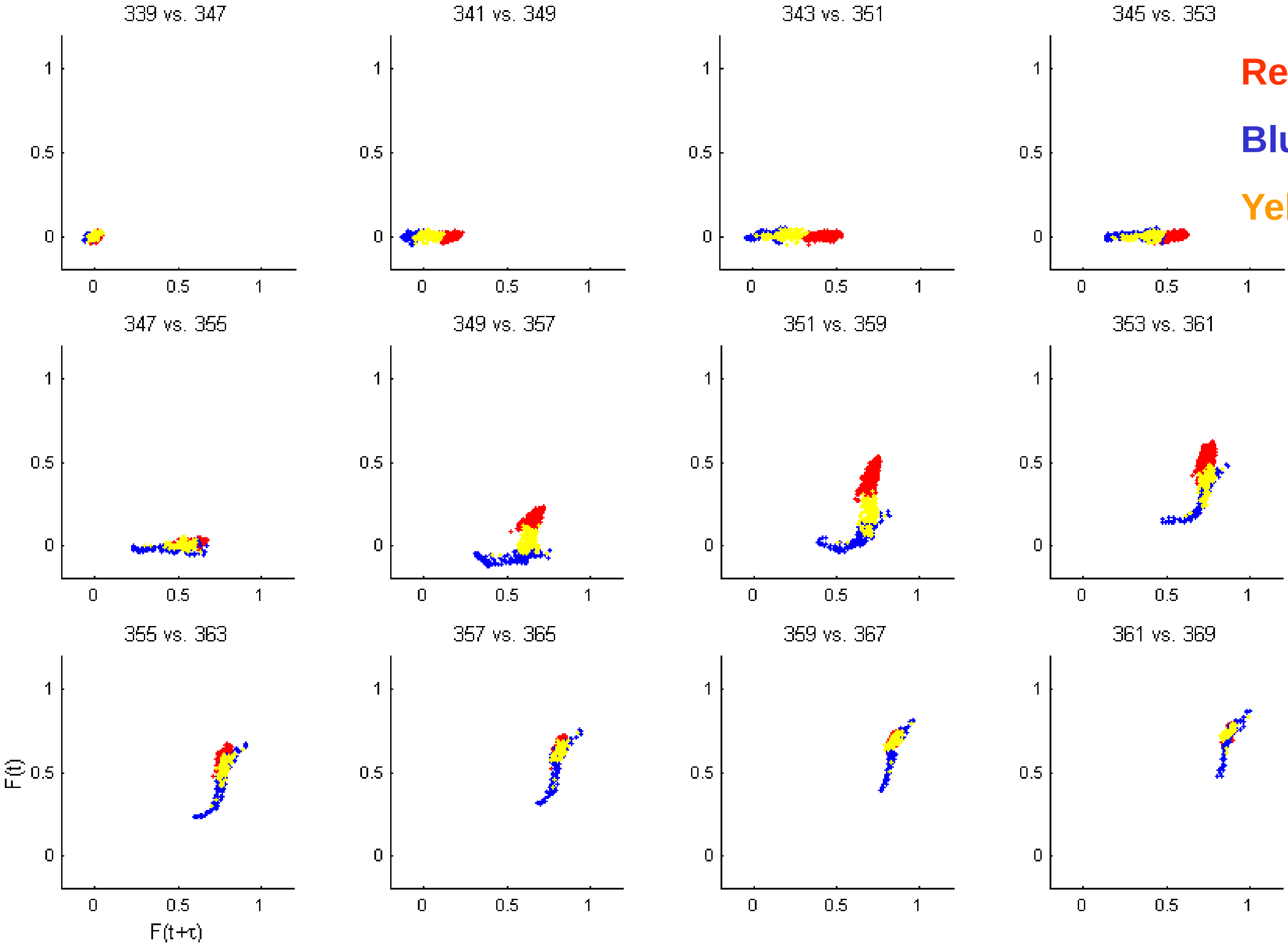
Virtual Electrode Phase Plane Movie



Red – cathode pixels

Blue – anode pixels

Yellow – border pixels

Phase plane characteristics of border regions are intermediate between those of VC and VA.

Point S1-Field S2
Voltage and Phase Plane Movies

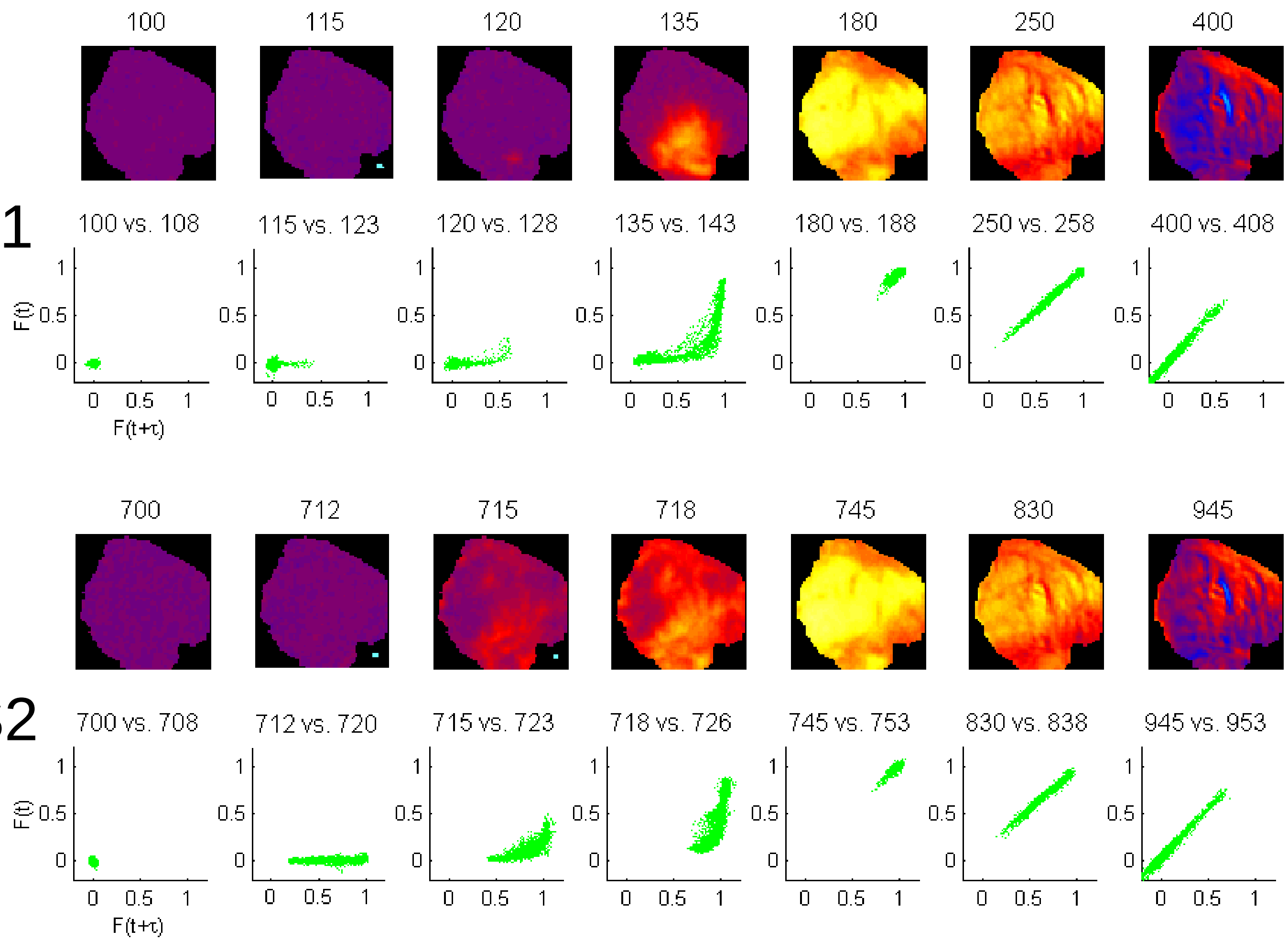
Point S1

Endocardial isolated right ventricle data

0.83 ms/frame

5 V/cm S2

rv_5Vcm_swarm.mov



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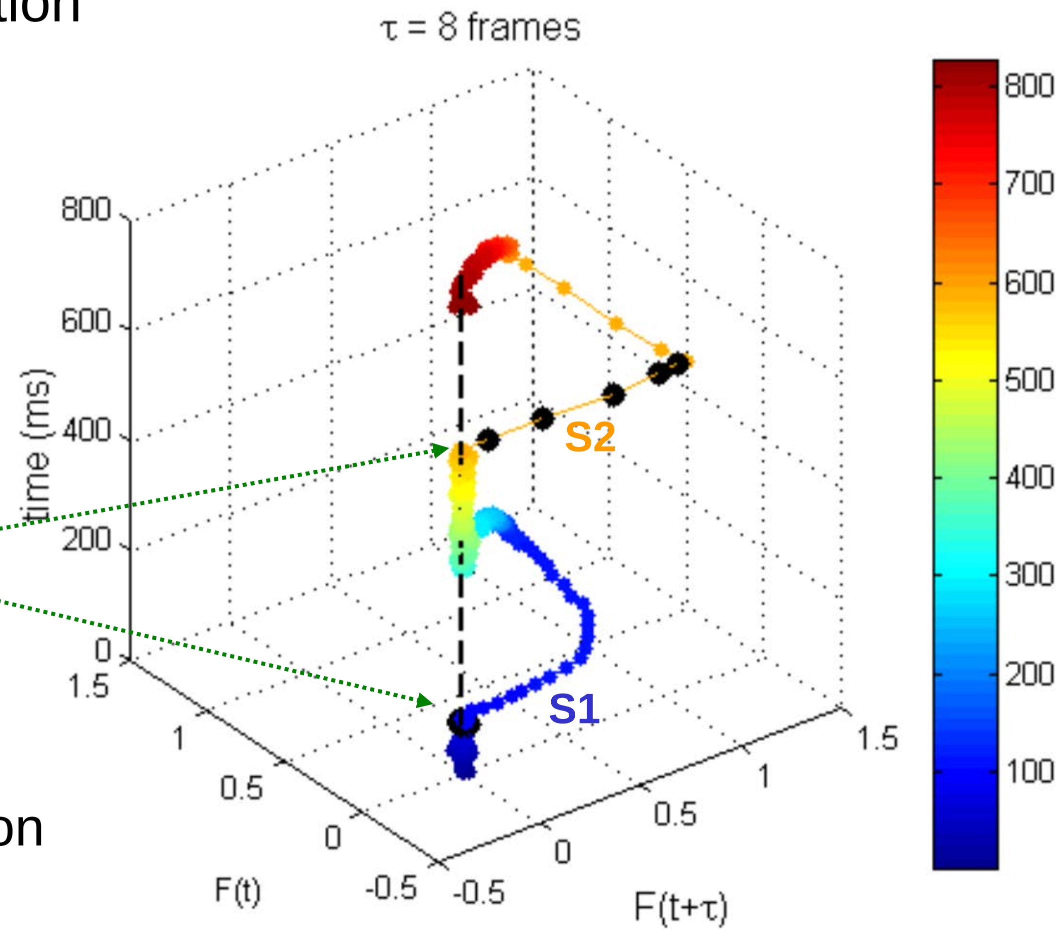
Point S1-Field S2
Activation Dynamics in Phase Space

- Isolated right ventricle preparation
  - 2 ms S1 point stimulation
  - 2 ms S2 field stimulation
  - S1-S2 coupling interval 500 ms

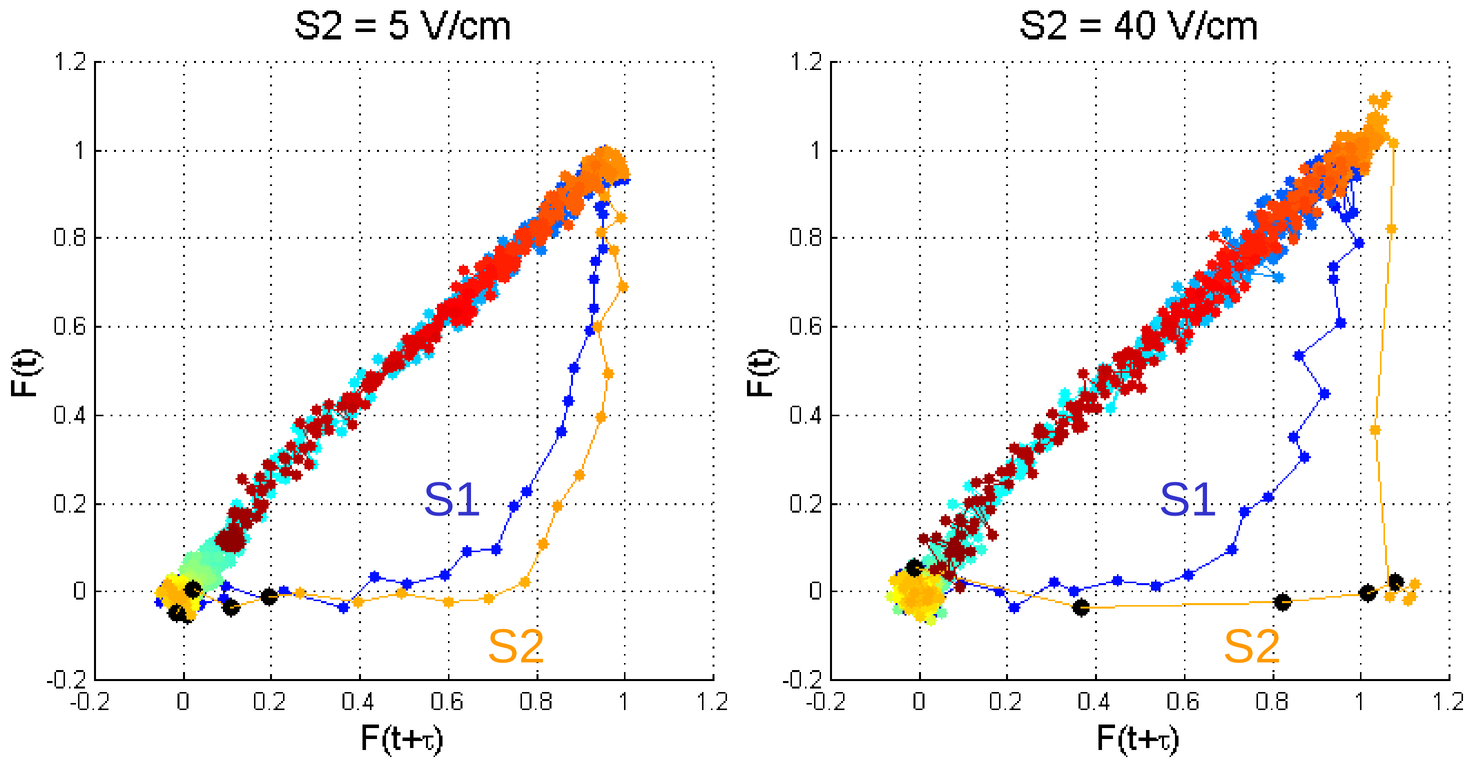
Single Endocardial Pixel Dynamics
S2 = 40 V/cm



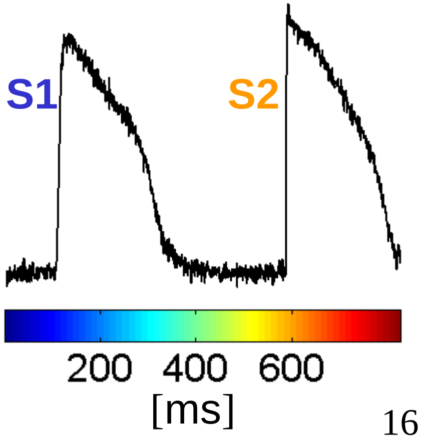
Larger black pixels ● indicate stimuli timing.

Strong field S2 reveals much more rapid change in comparison with point S1.

Endocardial Activation Dynamics



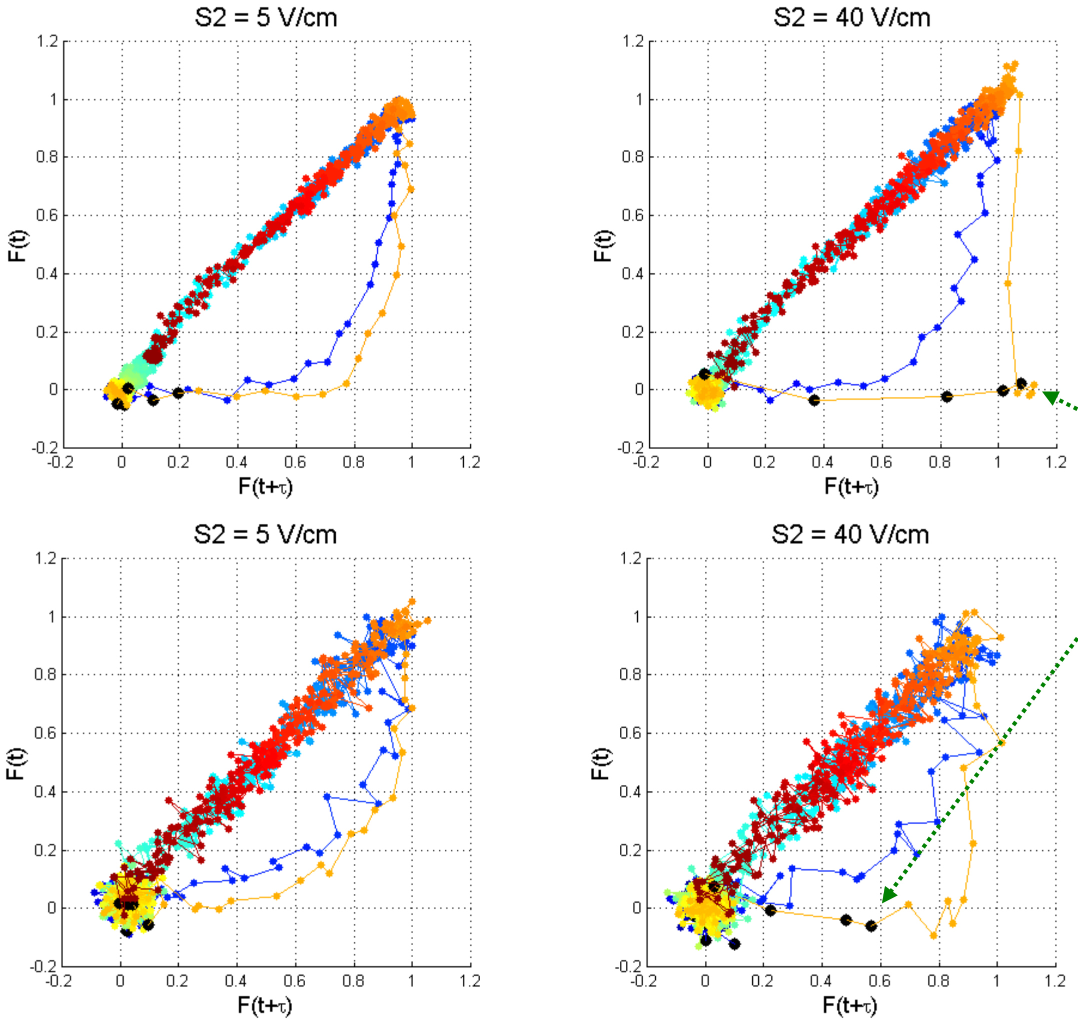
- Faster activation with stronger S2 shock strength
- S1 trajectory lies within S2 trajectory
- S1 and S2 repolarization trajectories are the same



Endocardial and Epicardial Activation Dynamics

Endocardium

Epicardium



Endocardium activates faster than epicardium.

Observations

- Activation and repolarization stages are clearly delineated in phase space.
- Virtual cathodes, virtual anodes, and border regions are uniquely characterized in phase space.
- Faster response due to stronger field shock is obvious in phase space plots.
- Repolarization after point and field stimulation follows the same path in phase space.
- Point stimulation trajectories lie within field stimulation trajectories in phase space plots.

Conclusions

- We originally developed this approach to search through large amounts of point-S1/field-S2 right ventricle data to identify any small, localized regions of hyperpolarization that we did not detect with conventional spatio-temporal imaging.
- We have not yet observed any hyperpolarization in phase space from diastolic field shocks.
- We recognize that this approach is useful for comparing cardiac response to different shocks.
  - Krinsky, VI and Pumir, A. “Models of Defibrillation of Cardiac Tissue,” *Chaos*, **8:** 188-203, 1998.

Future Work

- We have shown *qualitatively* that the details of diastolic activation dynamics are highlighted in phase space. However there is also great potential to extend this approach to *quantitative* phase space measurement:
  - Rise time calculation as the slope of the upstroke in phase space
  - Measurement of phase space trajectory area as a function of shock strength
  - Maximum dV_m/dt can be determined by computing the maximum Euclidean distance traveled in one time step in phase space
- In the virtual electrode phase space movies, we showed that the virtual anode, virtual cathode, and border regions have different phase space characteristics. Thus the dynamics in phase space can be used to back-project into physical space to delineate between regions of different activation dynamics.
- We will explore the use of the phase plane to predict shock response.

Acknowledgments

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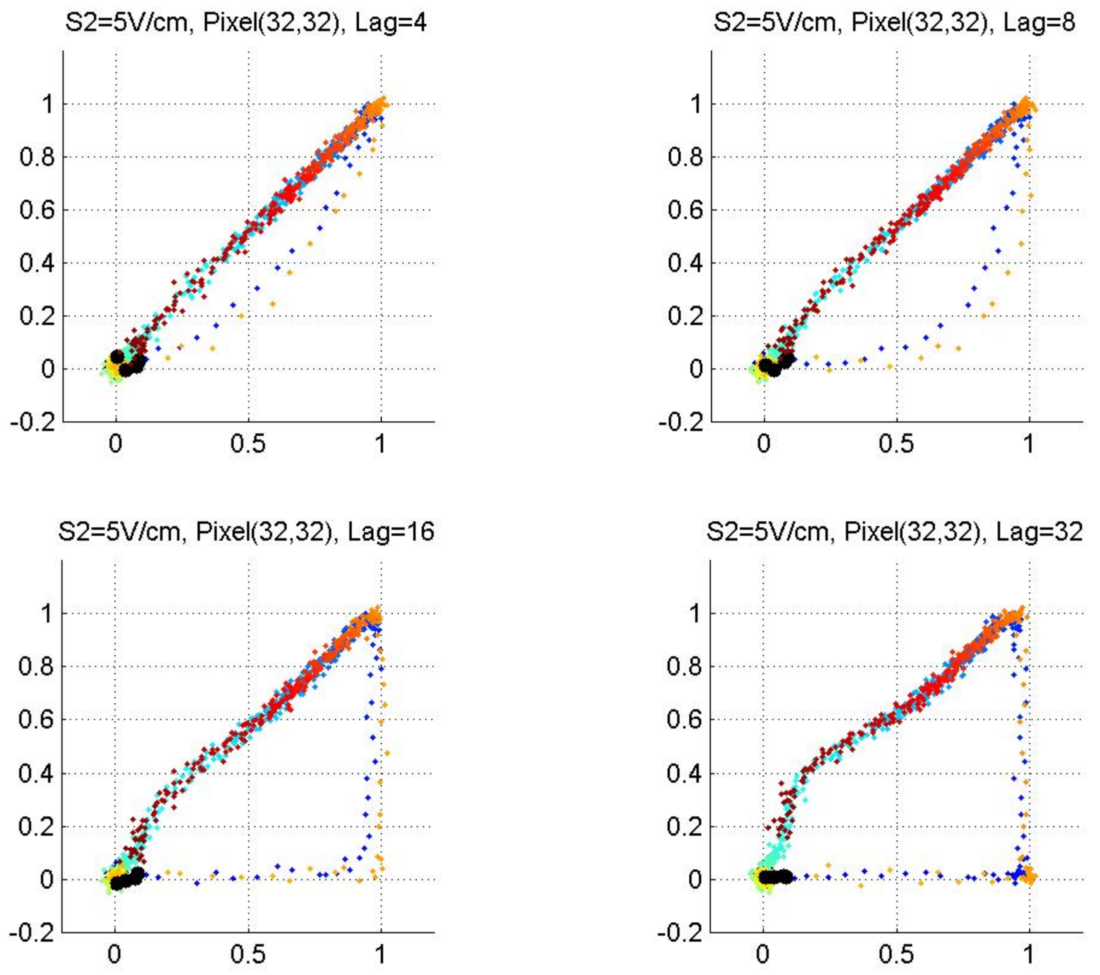
  - NIH grant R01-HL68241
  - NIH 5 T32 HL07411

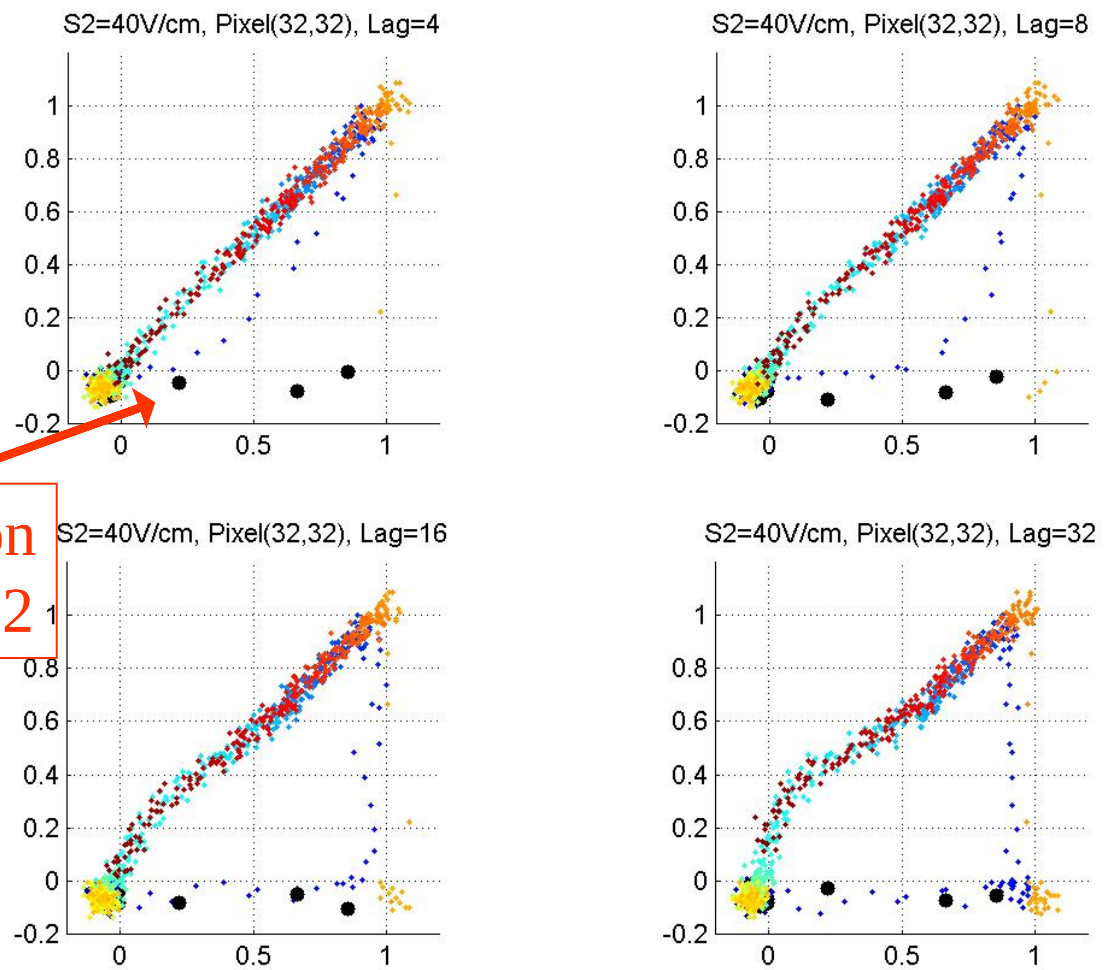
    Cardiovascular Mechanisms Training Grant

Endocardium: Dependence of Lag



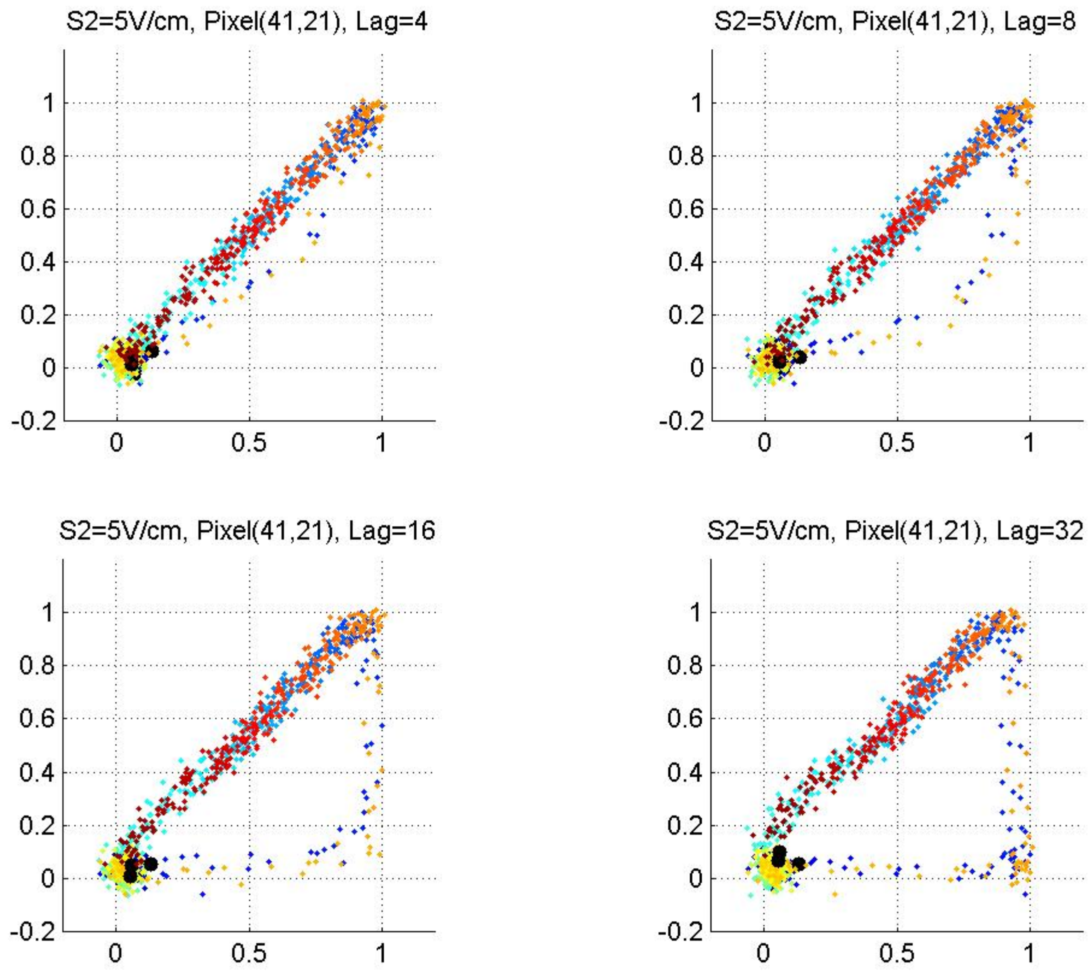
If lag is too long, the difference between S1 and S2 is lost.

Endocardium: Dependence of Lag

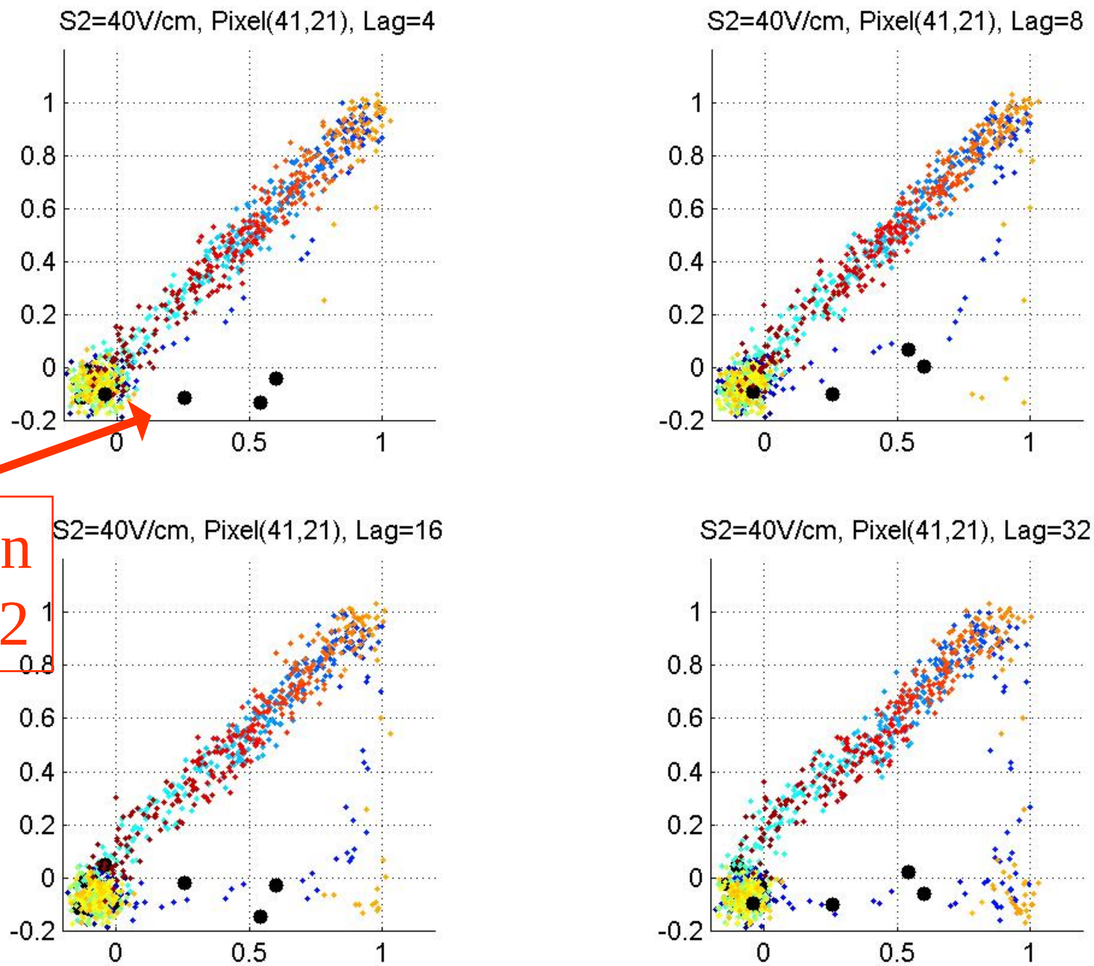


Faster activation with stronger S2

Epicardium: Dependence of Lag



Epicardium: Dependence of Lag



Faster activation with stronger S2