THE DRUG-INDEPENDENT ROLES OF CARDIAC GEOMETRY AND TISSUE ANISOTROPY IN DEFIBRILLATION AND REENTRY

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There is more to reentry and defibrillation than just channel effects ….

- Antiarrhythmic drugs primarily alter tissue excitability
- Defibrillation and reentry are also affected by tissue tissue anisotropy and cardiac geometry, which are not altered directly by drugs

Antiarrhythmic drugs are not the entire story….

- A high percentage of patients with an implantable ICD/defibrillator also take antiarrhythmic drugs.
- Agonistic/antagonistic effects of drugs on arrhythmias, fibrillation, and defibrillatory efficacy are the subject of intense study at the microscopic level of the ion channel.
- The primary effect of antiarrhythmic drugs is to alter tissue excitability, through changes in threshold, rate of rise, and refractoriness; **antiarrhythmic drugs do not strongly affect cell-to-cell coupling**.

The rest of the story….

- To first order, the shock-tissue interaction is determined by tissue anisotropy and cardiac geometry, and **is not altered directly by drugs**.

- The shock-tissue interaction is poorly understood: there is not yet an answer to the question "*How does defibrillation work?*"

Possible explanations for the ability of strong stimuli to defibrillate the heart

Discrete Mechanisms

- Intracellular junctions
- Uncoupled fiber bundles
- Patches of fat or collagen
- Bidomain heterogeneities

Continuous Mechanisms

- Cardiac surfaces
- Fiber ends
- Tissue anisotropy
- Fiber curvature
- Fiber branching
- Strand taper
- Fiber rotation

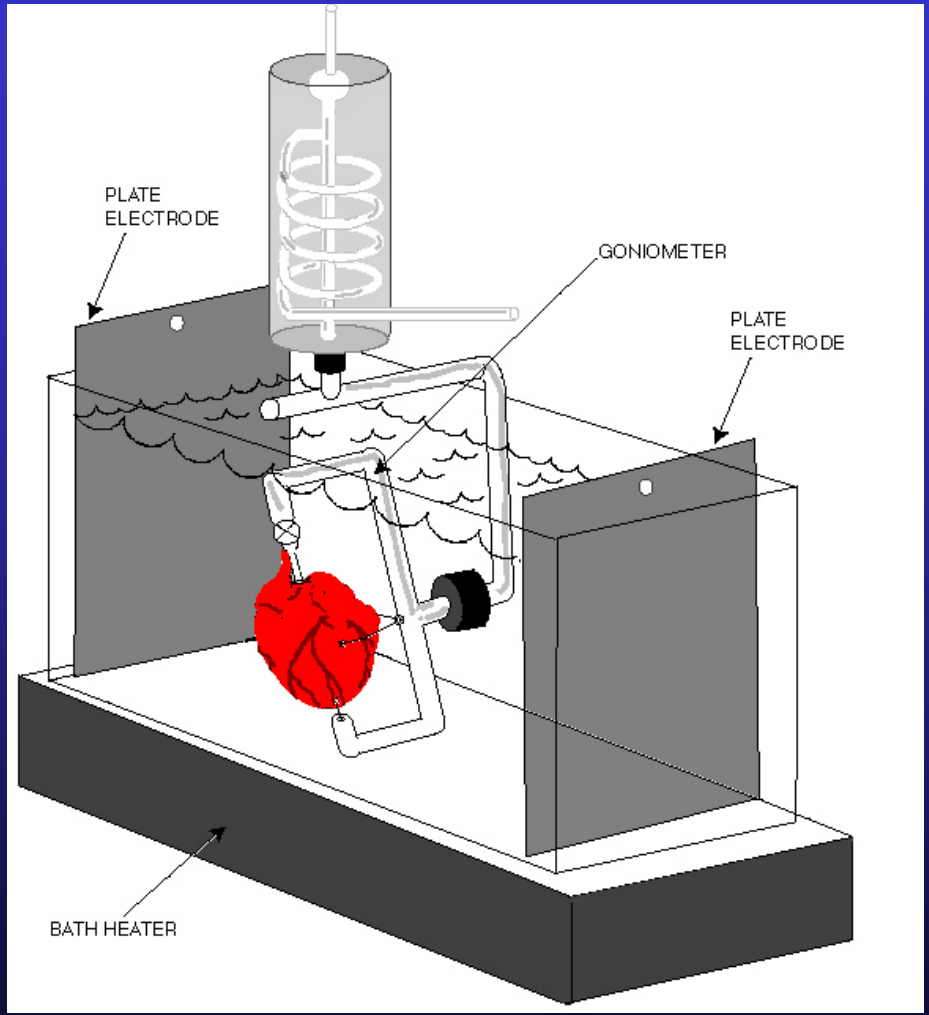
Approach

- Optical imaging of the transmembrane potential, and the bidomain model allow us to study the shock-tissue interaction and reentry.

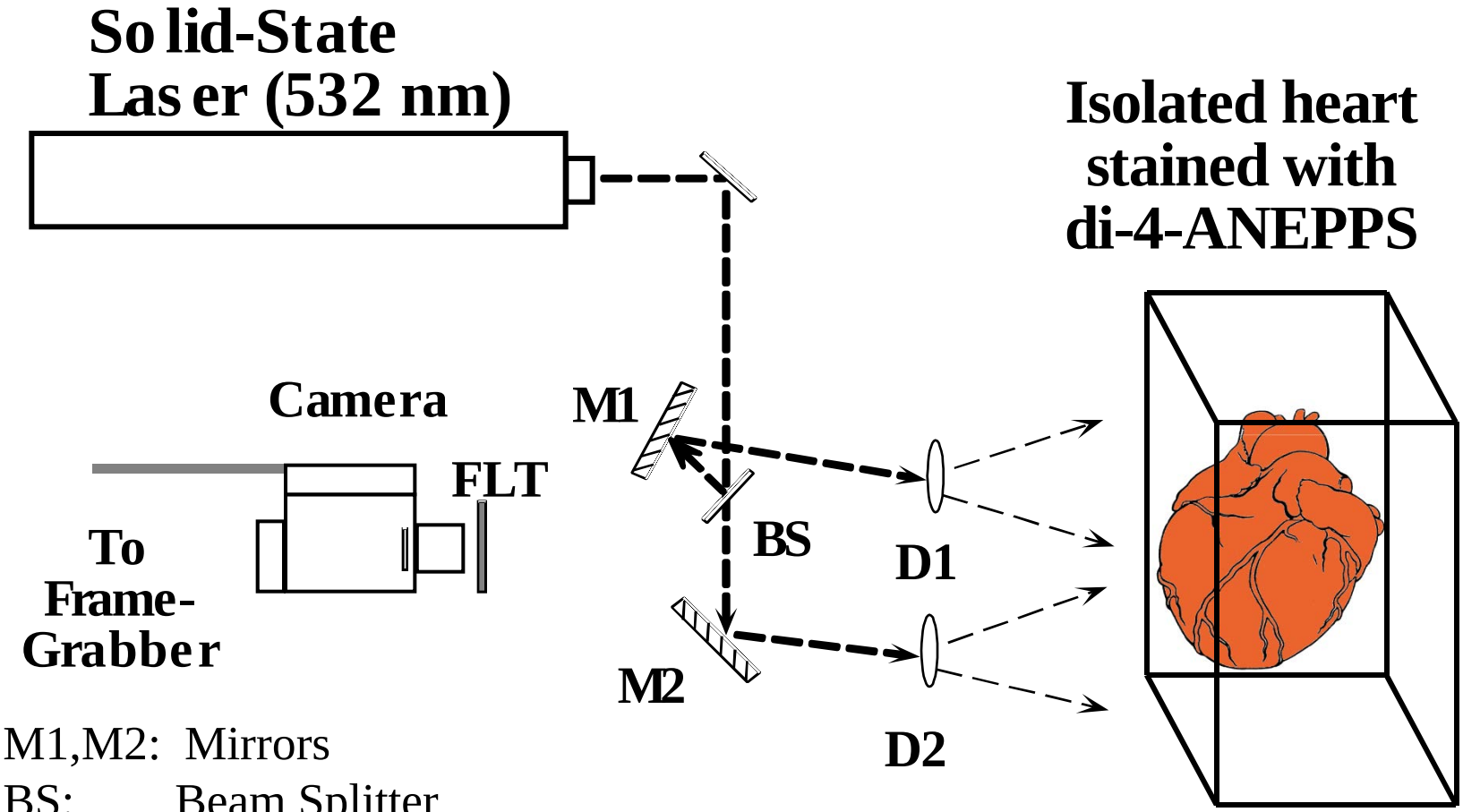
- We examined the rate of activation of the endocardium and epicardium during normal activation and field stimulation.

Methods: Perfusion

- Langendorff-perfused, di-4-ANNEPPS stained, isolated rabbit hearts with atria excised (N=5)
- 10 x 10 x 15 cm^3 bath of Tyrode's solution at 37 ^oC.
- Goniometer allows 360^o rotation of the axis of the heart in the imaging plane.



Optical Imaging Setup



M1,M2: Mirrors
BS: Beam Splitter
D1, D2: Diffusers
FLT: Long-Pass Filter (590 nm)

Methods: Imaging

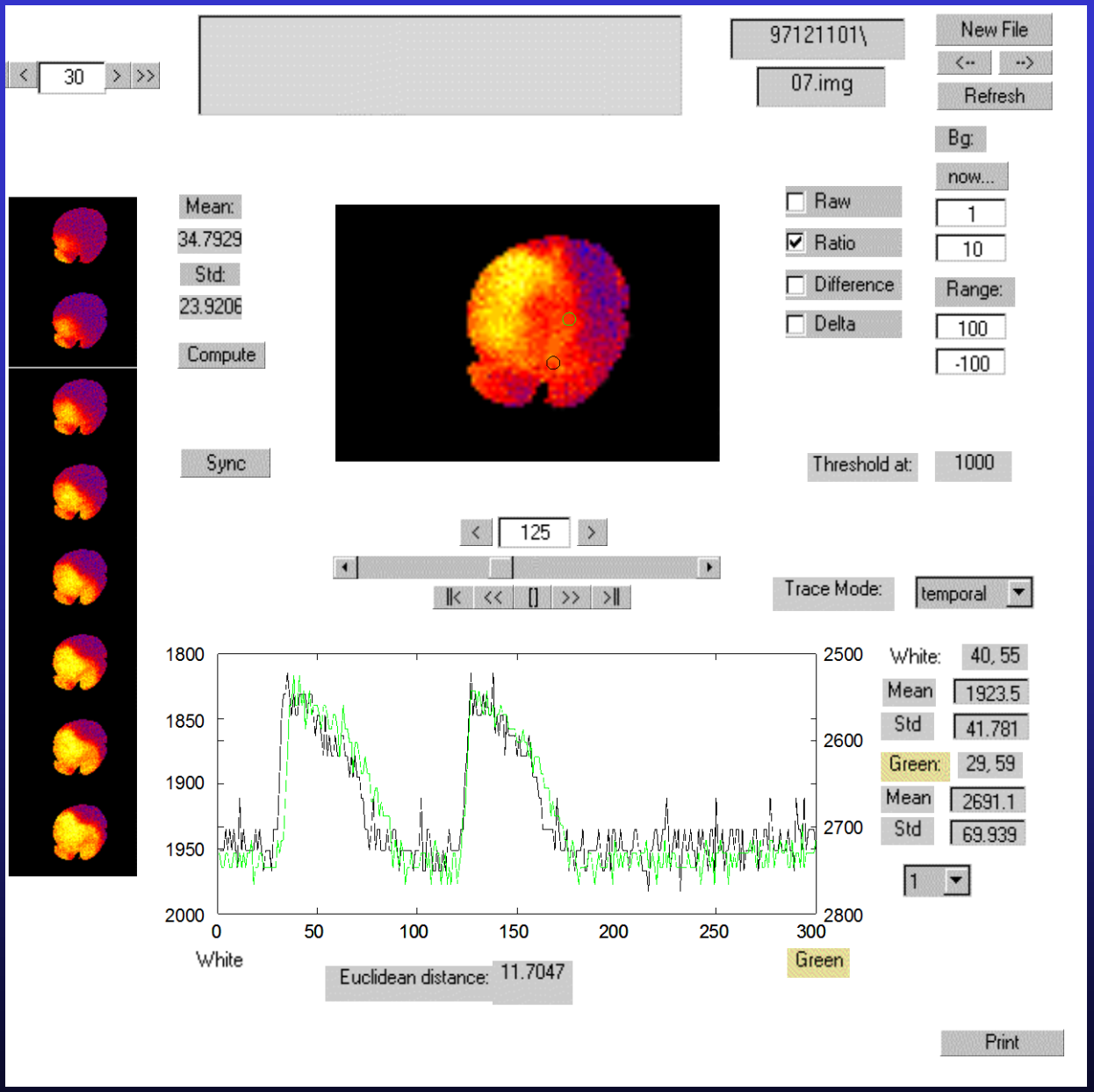
- Optical imaging of V_m changes following S1 as well as during and after S2.
- High-speed (322 or 1000 frames/second) 12-bit Dalsa CCD camera.
- Heart illuminated by a diode-pumped laser with multiple, 1 mm plastic optical fibers.

Methods: Pacing

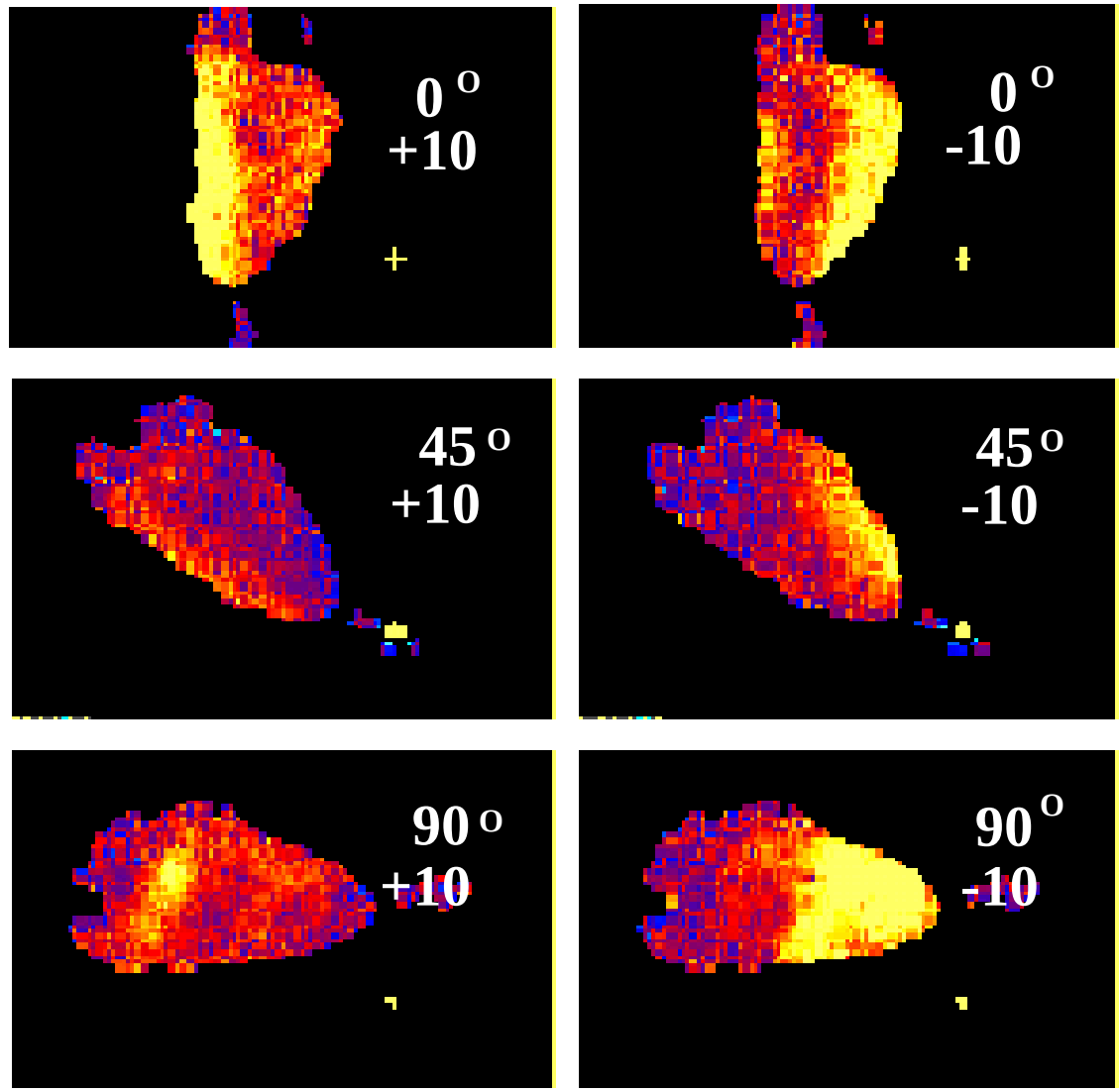
- 20 S1 pacing pulses to the right-ventricle 500 ms cycle length
- Custom Ventritex computer-controlled stimulator delivered a 1 ms S2 to plate electrodes at the ends of the bath to produce horizontal shock fields of up to +/- 33 V/cm

Gus2 MatLab Data Viewing Program

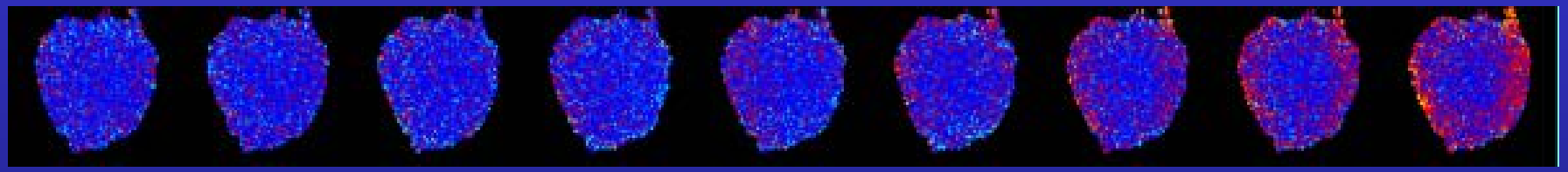
Gustavo Rohde



Tissue Response to Field Shock



Faster Response with Increasing Shock Strength



98021001\10 20 Volts/cm, 3 ms shock, 1 ms per frame

Methods: Image Processing

- $Q(t)$ -- measure of total activation in the image

  $Q(t) = \Sigma_{ij} \{\Delta F(t)/F(0)\}_{ij}$, *i.e.*, sum of all pixels

- $p_x(t)$ -- dipole moment along the x axis

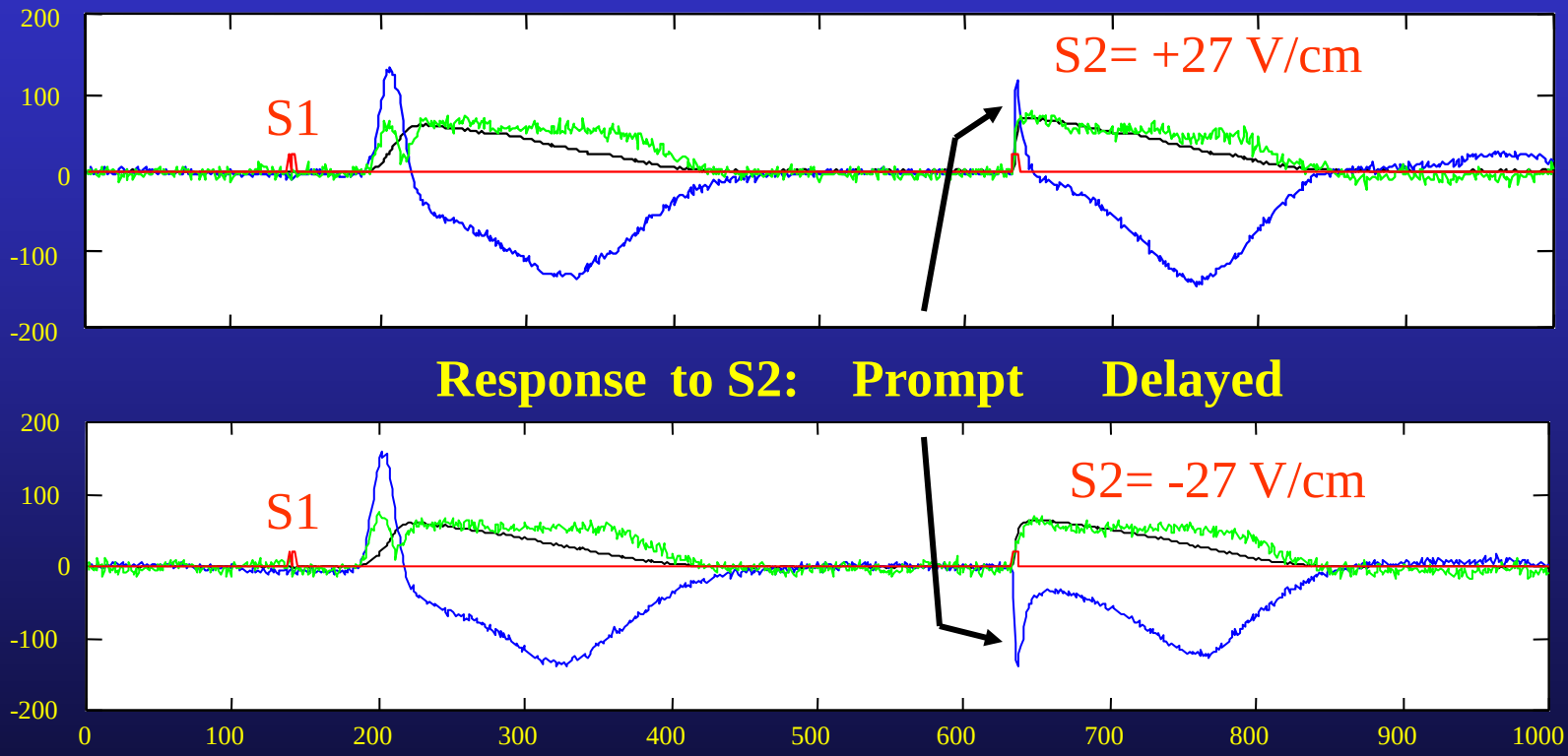
  $p_x(t) = \Sigma_{ij} x_i \{\Delta F(t)/F(0)\}_{ij}$, *i.e.*, intensity times x

- $p_y(t)$ -- dipole moment along the y axis

  $p_y(t) = \Sigma_{ij} y_i \{\Delta F(t)/F(0)\}_{ij}$, *i.e.*, intensity times y

$Q(t)$, $p_x(t)$, $p_y(t)$ for S1 and +/- 27 V/cm S2

- Q(t) rises faster for S2 than S1
- p_x prompt S2 response reverses sign
- p_y prompt S2 response unchanged



Red: Shock Black: $Q(t)$ Blue: $P_x(t)$ Green: $P_y(t)$

How fast is the heart being activated by S1 and S2?

- Measure maximum rate of rise

  $[dQ(t)/dt]_{max}$

- Measure maximum value of $Q(t)$

  $Q(t)_{max}$

- Define activation time

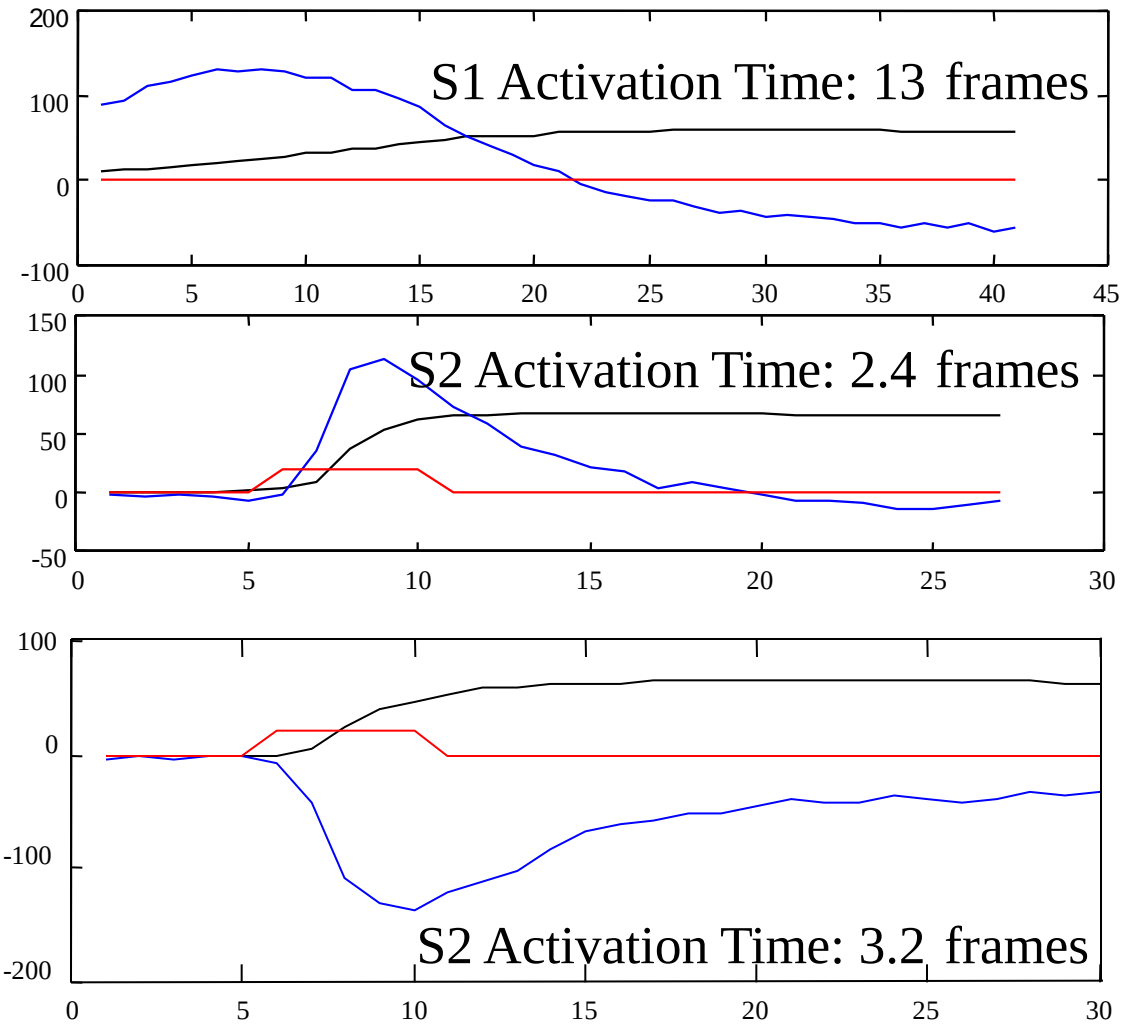
  $T_{activ} = Q(t)_{max}/[dQ(t)/dt]_{max}$

Activation Times

S2: +27 V/m

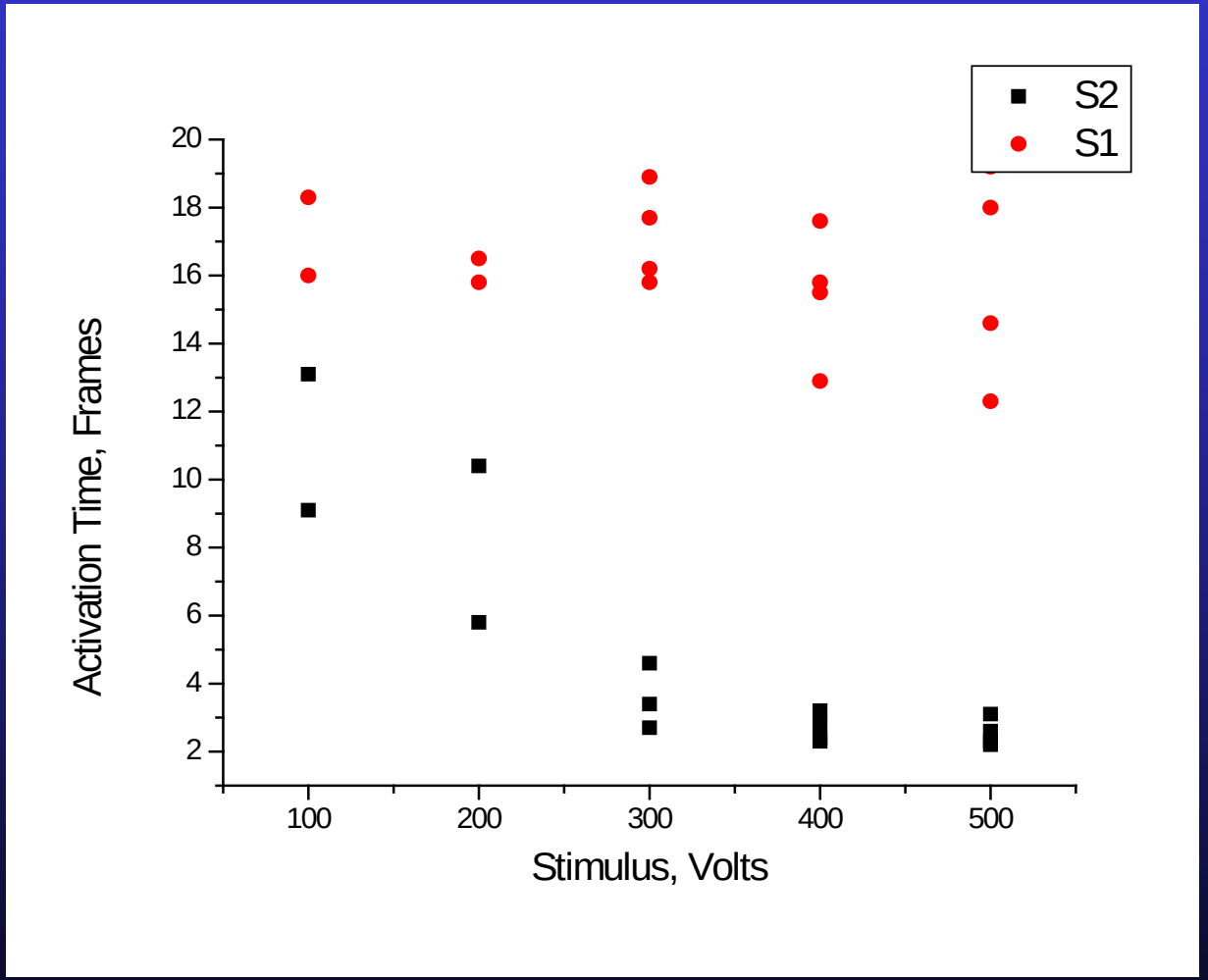
S2: -27 V/m

Red: Shock
Black: $Q(t)$
Blue: $P_x(t)$



Activation Time versus S2 Field Strength

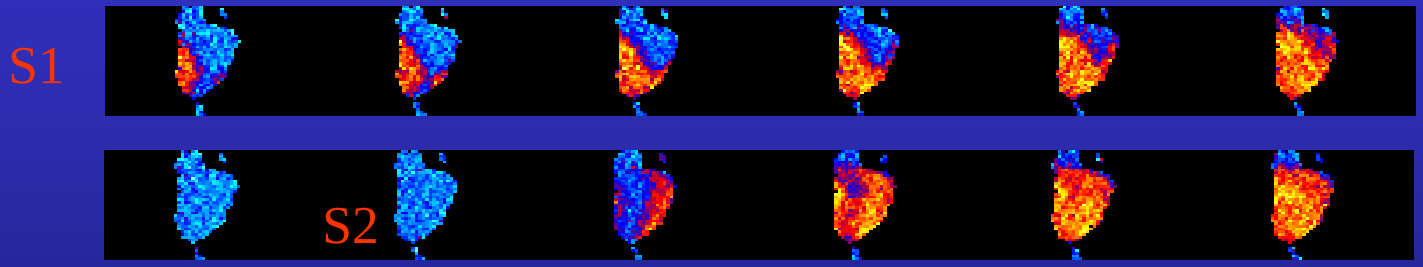
- S1 activation time independent of S2 field strength
- S2 activation time decreases with increasing S2 field strength



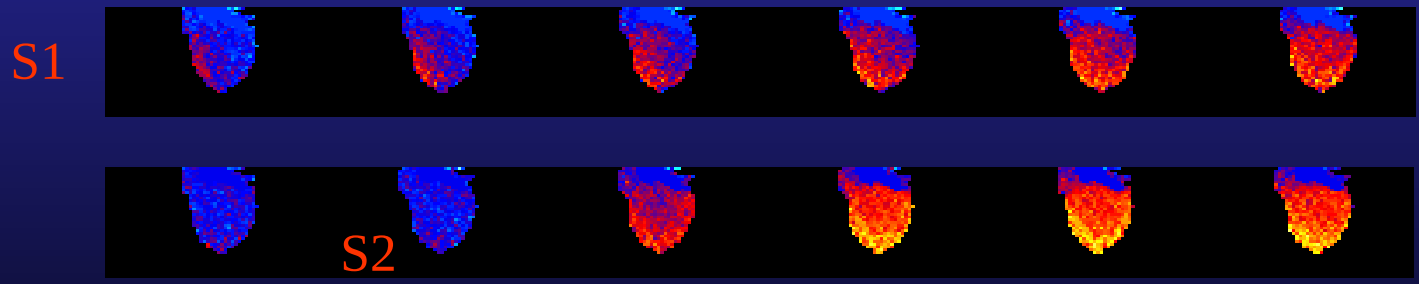
Transmural Imaging of Endocardial Activation

- Optical fibers with tapered diffusers illuminate the endocardium
- CCD camera views activity transmurally
- No endocardial p_x dipole moment
- Rapid endocardial activation

Epicardial Images for S2 = +10 V/cm

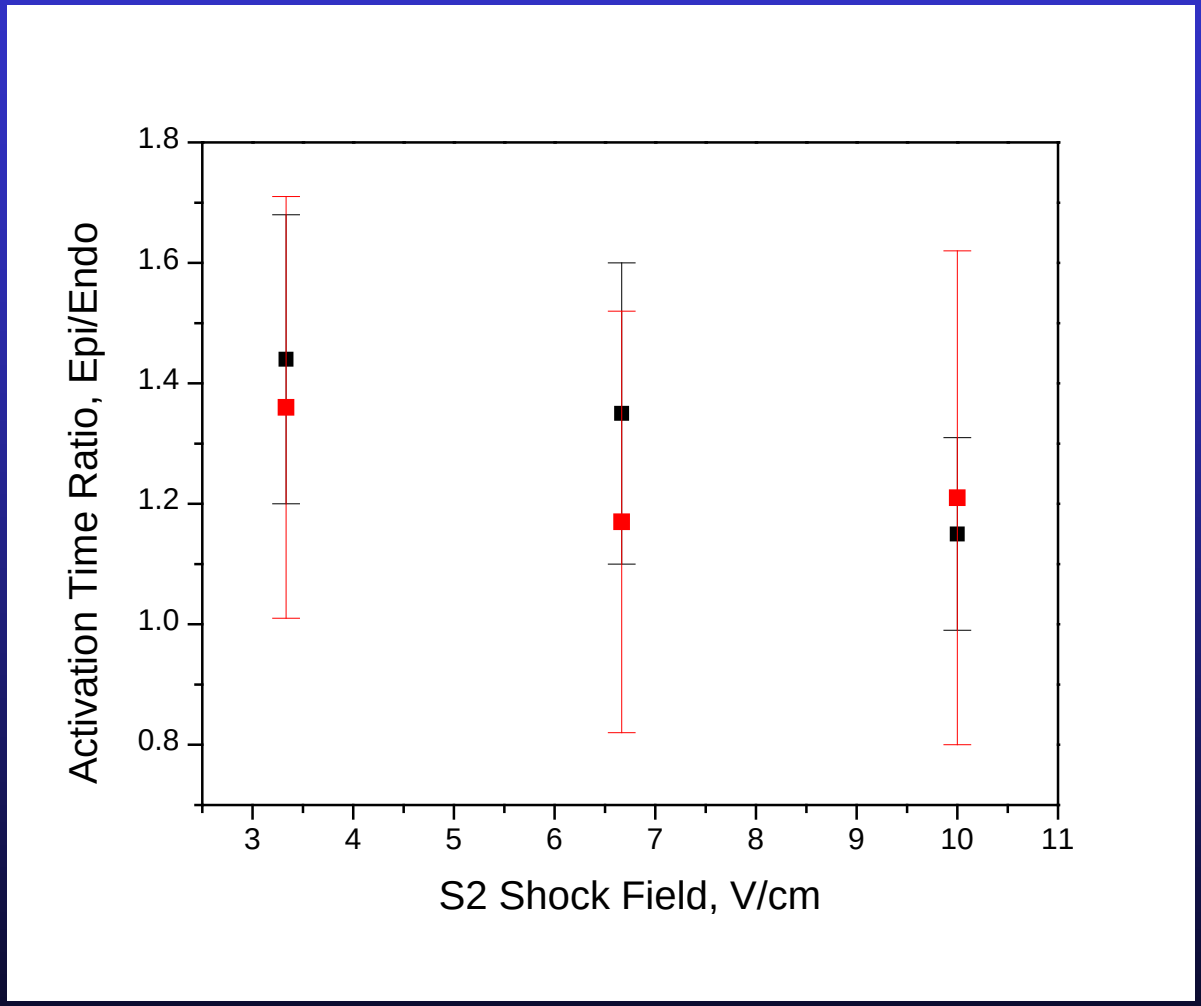


Endocardial Images for S2 = +10 V/cm



Endocardial versus Epicardial Activation Times

- Activation time decreases with increasing shock field
- Endocardial response 20%-40% faster than endocardial
- Trend: S1 response (Black) slower than S2 (Red)



Summary

Endocardial and endocardial responses to field stimulation differ:

- Dipolar response of epicardium consistent with bidomain predictions
- Endocardium does not show dipolar response. Why?
- Endocardium activates faster than epicardial. Why?
- Not due solely to Purkinje fibers -- trabeculae and papillary muscles?

Hypothesis:

The complex geometrical structure of the endocardial surface plays an as-yet-unappreciated role in the rapid and uniform activation of the endocardium during defibrillation.