Models and Measurements of the Anisotropic Cardiac Bidomain

John P. Wikswo

Instituto de Matemática Pura e Aplicada
Rio De Janeiro, Brazil

6 May 2002

Living State Physics Group, Department of Physics & Astronomy
Vanderbilt Institute for Integrative Biosystems Research and Education (VIIBRE)
Instrumenting and Controlling the Single Cell (ICSC) Project

Vanderbilt University

Department of Physics and Astronomy
http://www.vanderbilt.edu/lsp
http://www.physics.vanderbilt.edu

Department of Biomedical Engineering
http://www.bme.vanderbilt.edu/

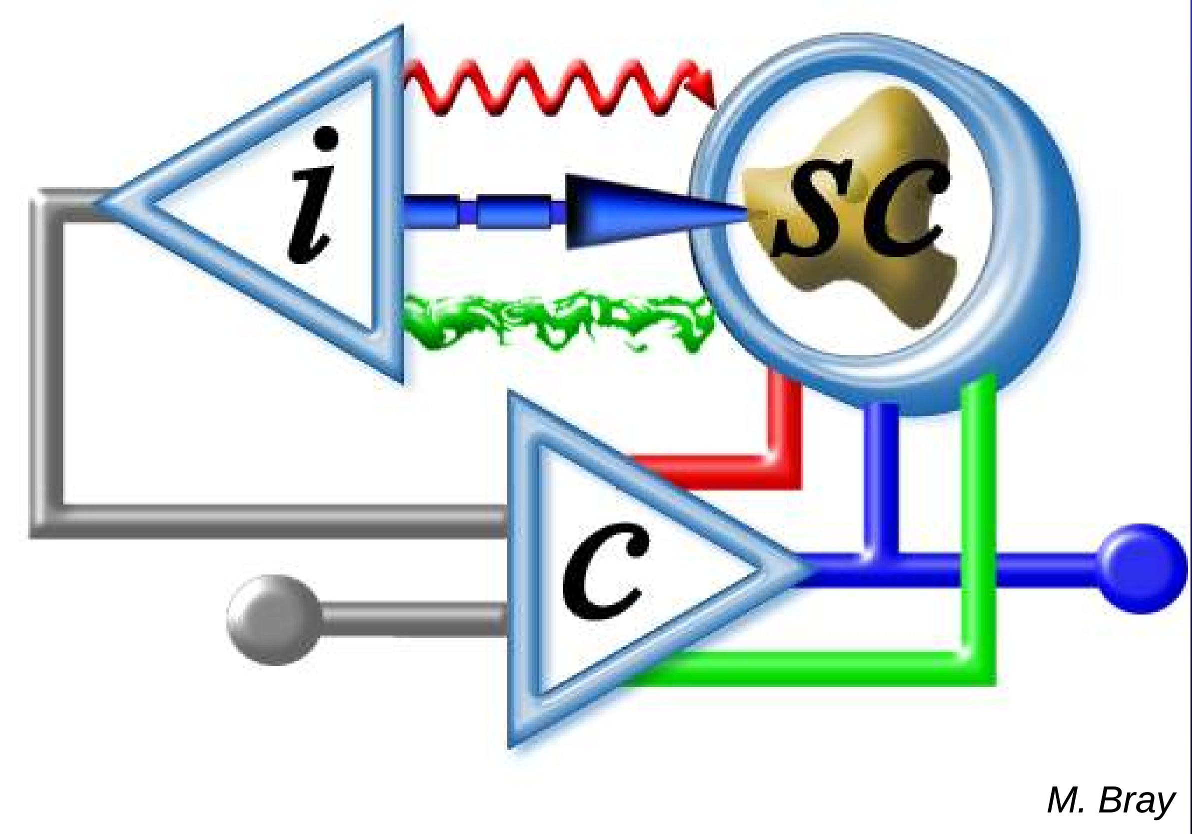
Department of Molecular Physiology and Biophysics
http://medschool.mc.vanderbilt.edu/mpb/

Vanderbilt Institute for Integrative Biosystems Research and Education (VIIBRE)
http://www.vanderbilt.edu/viibre (coming soon)

Vanderbilt Institute for Integrative Biosystems Research and Education

VI∫BRE

Instrumenting and Controlling



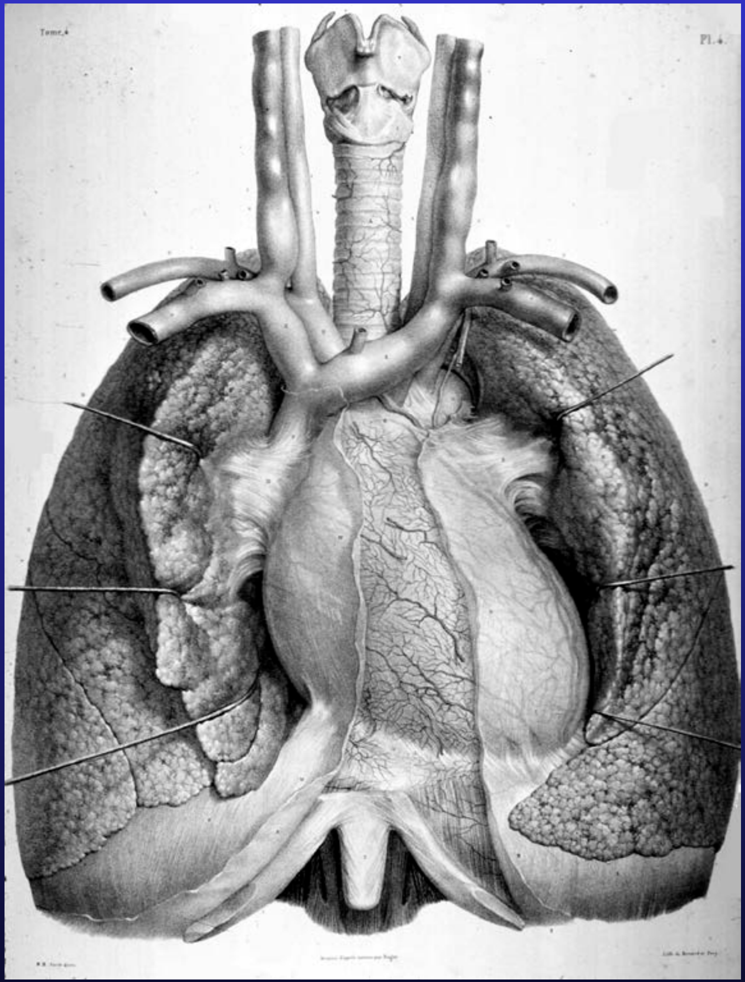
The Single Cell

Abstract

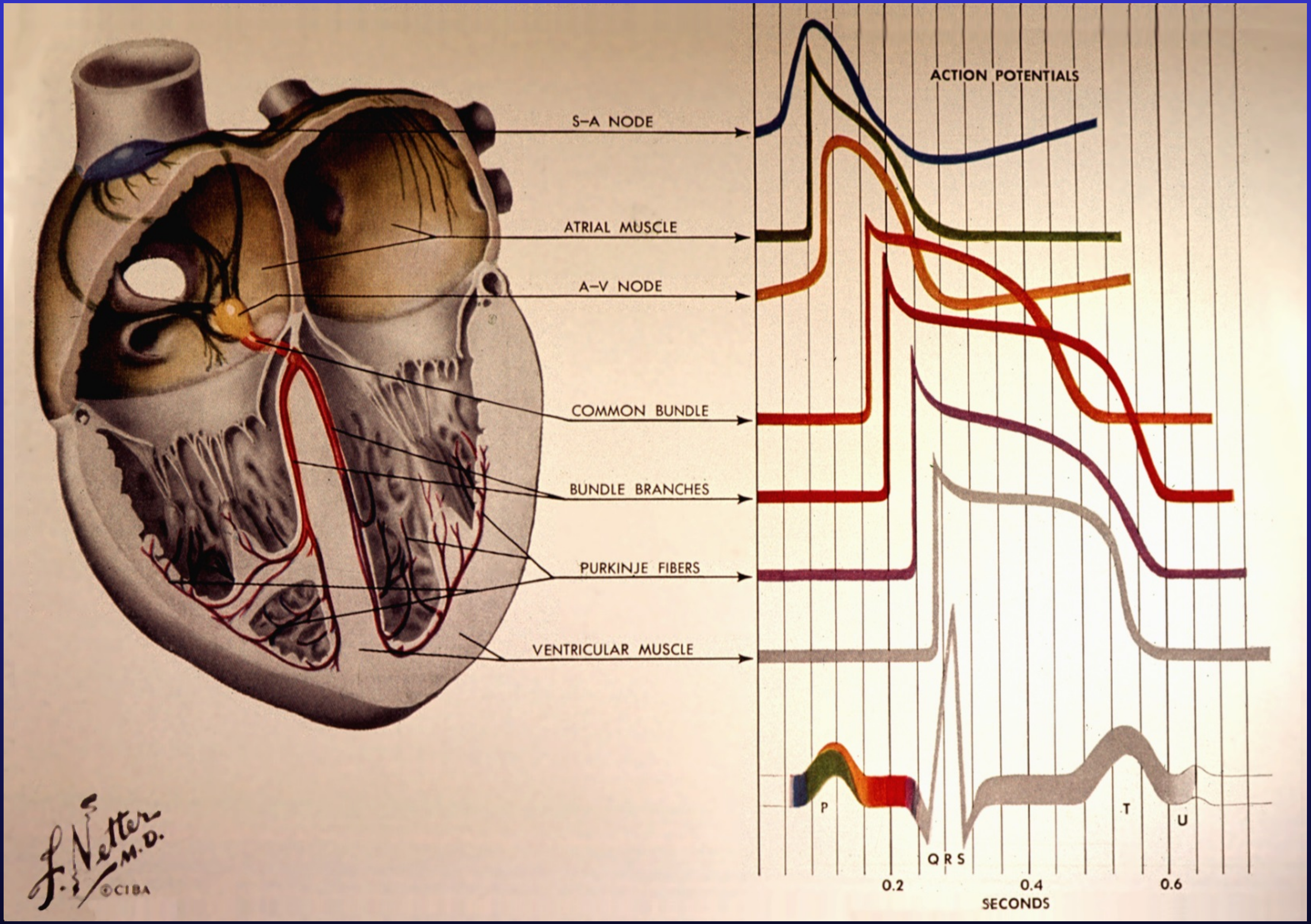
The electrical anisotropy of the heart, most obviously manifested by the two-fold difference in conduction velocity between directions parallel and perpendicular to the cardiac fiber axis, is the result of larger but more difficult-to-detect anisotropies of the electrical conductivities of the intracellular and extracellular spaces. While it is straightforward to approximate the conduction-velocity anisotropy with a monodomain model of the heart, the more complicated bidomain model is required to account for differences in the anisotropies between the two spaces. During point stimulation of cardiac tissue, the differences in the anisotropy ratios result in a number of important effects which were predicted numerically and confirmed experimentally with measurements of extracellular and transmembrane potentials and the magnetic field resulting. Of these, one of the most intriguing is quatrefoil reentry, a pattern of reentry that produces four synchronized phase singularities. New analytical techniques are proving useful to understand the dynamics of these singularities. Based upon numerical and experimental studies, it is clear that bidomain anisotropy differences can play an important role in both the stimulation of the heart and in certain reentrant arrhythmias.

The Heart is an …

- Electrically activated,
- Biochemically powered,
- Electrically non-linear,
- Pressure- and volume-regulated,
- Tandem,
- Two-stage,
- Mechanical pump
- With a mean time-to-failure of approximately two billion cycles.



The Heart is … an electrically activated, mechanical pump



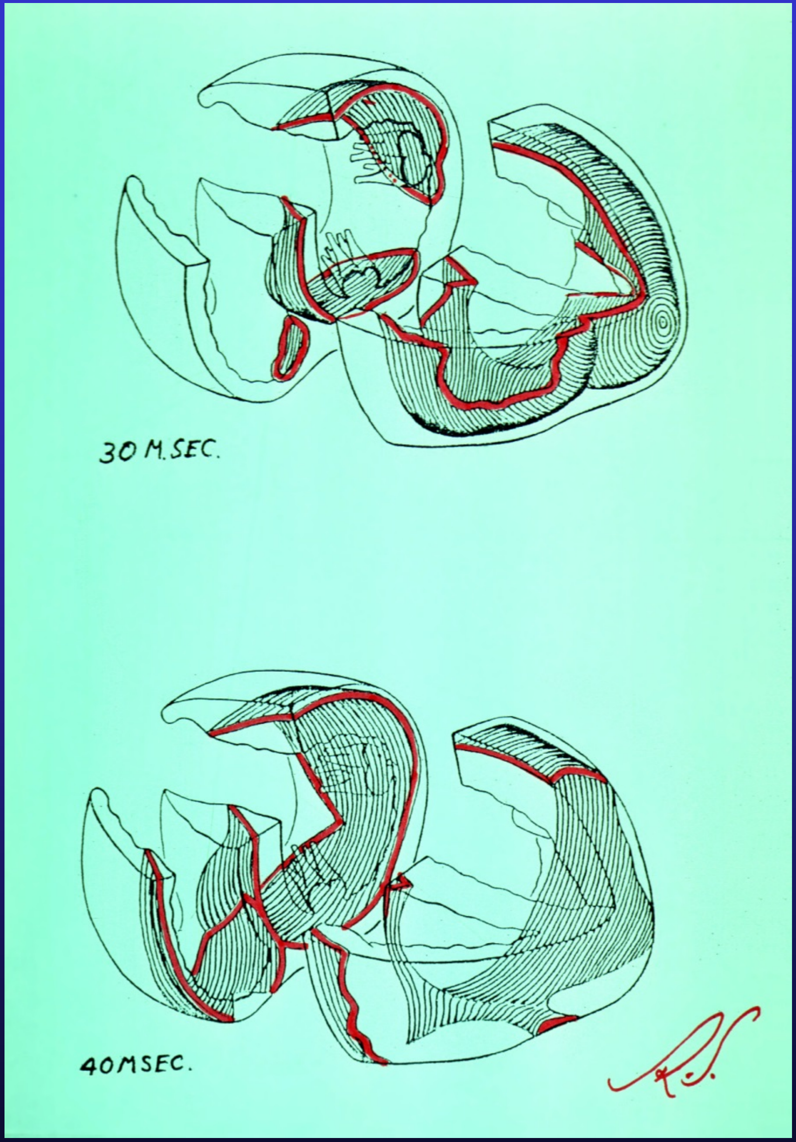
10 centimeters

The cardiac depolarization wave front

- Activated cells collectively form a sheet that is a moving 3-dimensional battery
- 1 mm thick
- Moving at ~1 m/sec

Courtesy of Rubin Aliev

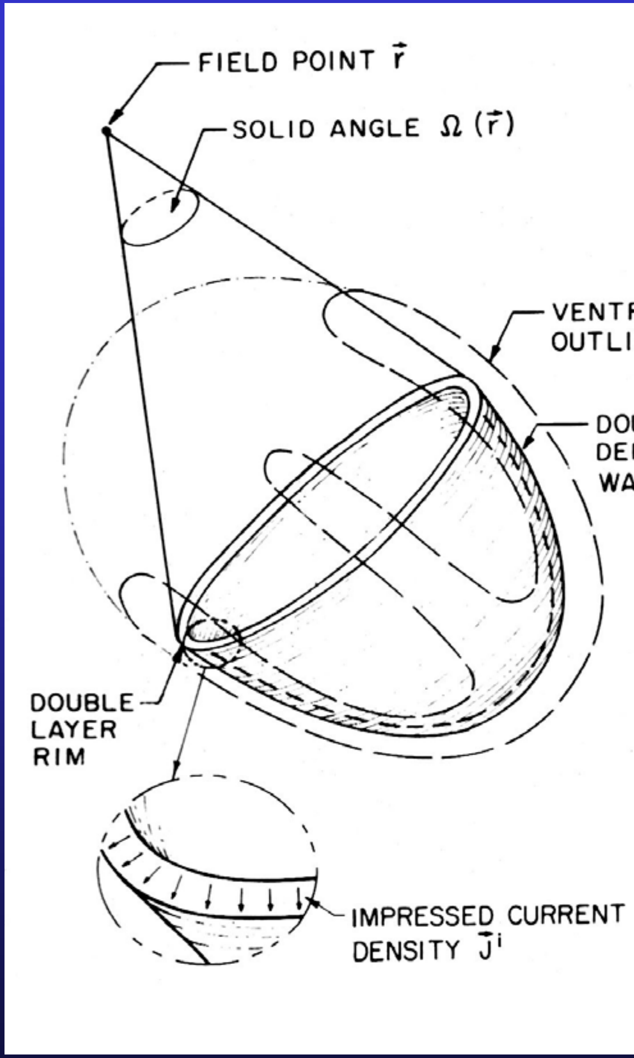
HLR2.mpg

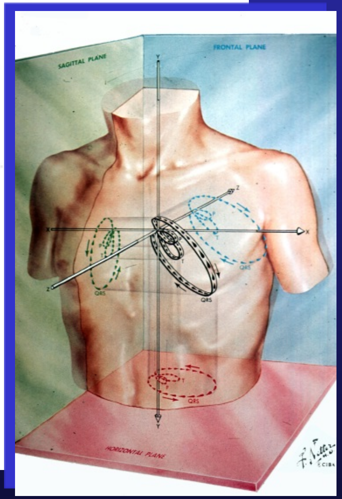


Courtesy of Ron Selvester

The uniform double-layer model

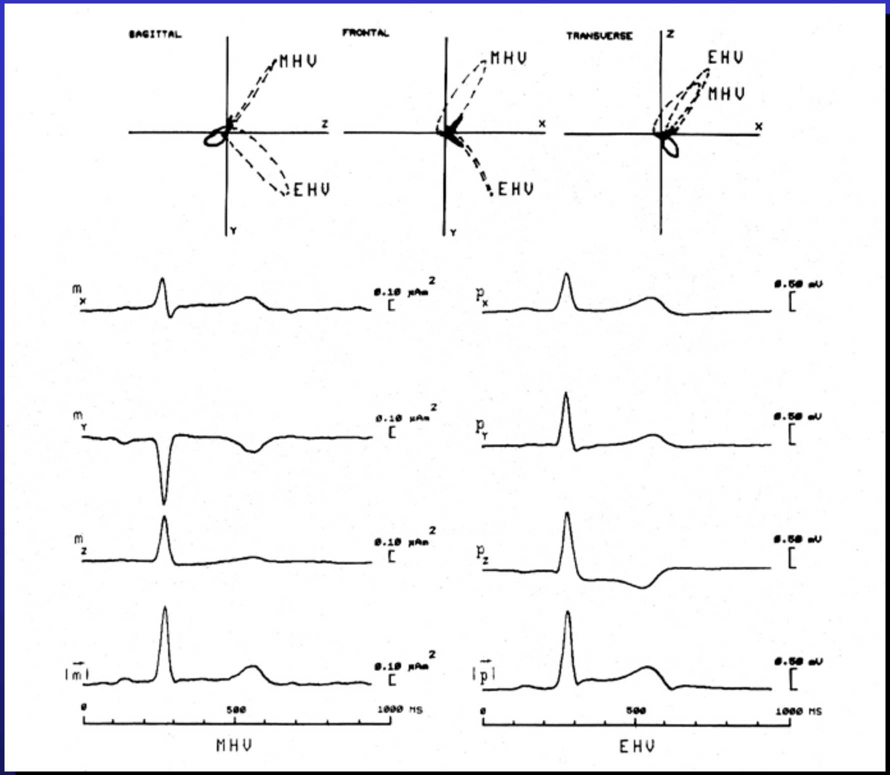
- Assumes
  - Uniform thickness
  - Uniform strength
  - Current perpendicular to the wave front
- Dipole moment and potential V(r) are determined by the solid angle subtended by the double-layer rim ; (

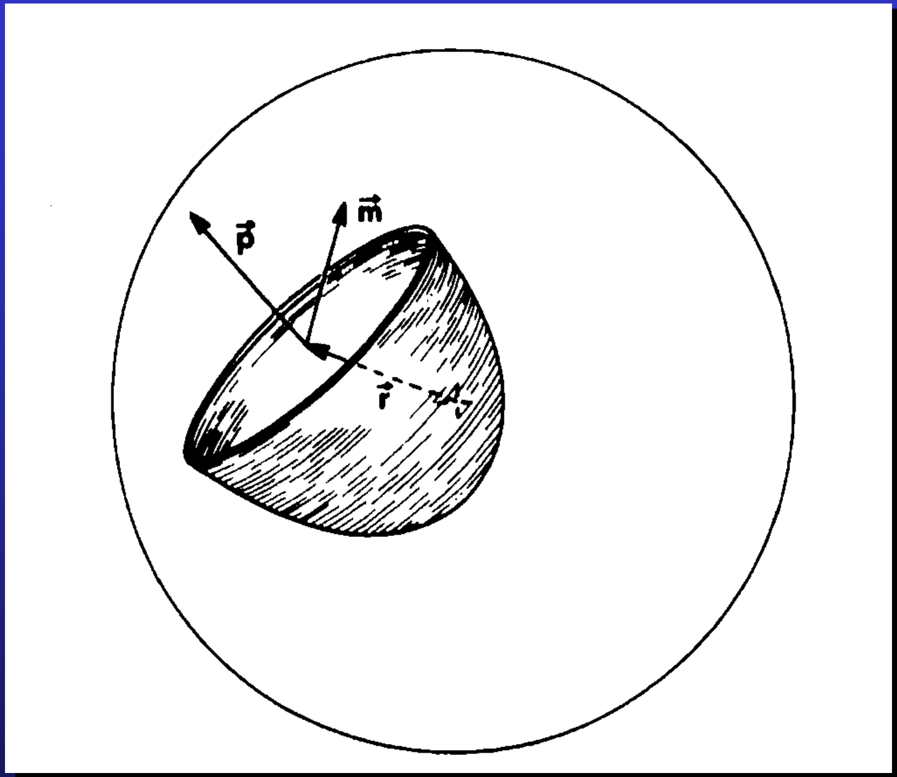




Heart vector or dipole moment versus time

The electric and magnetic heart vectors





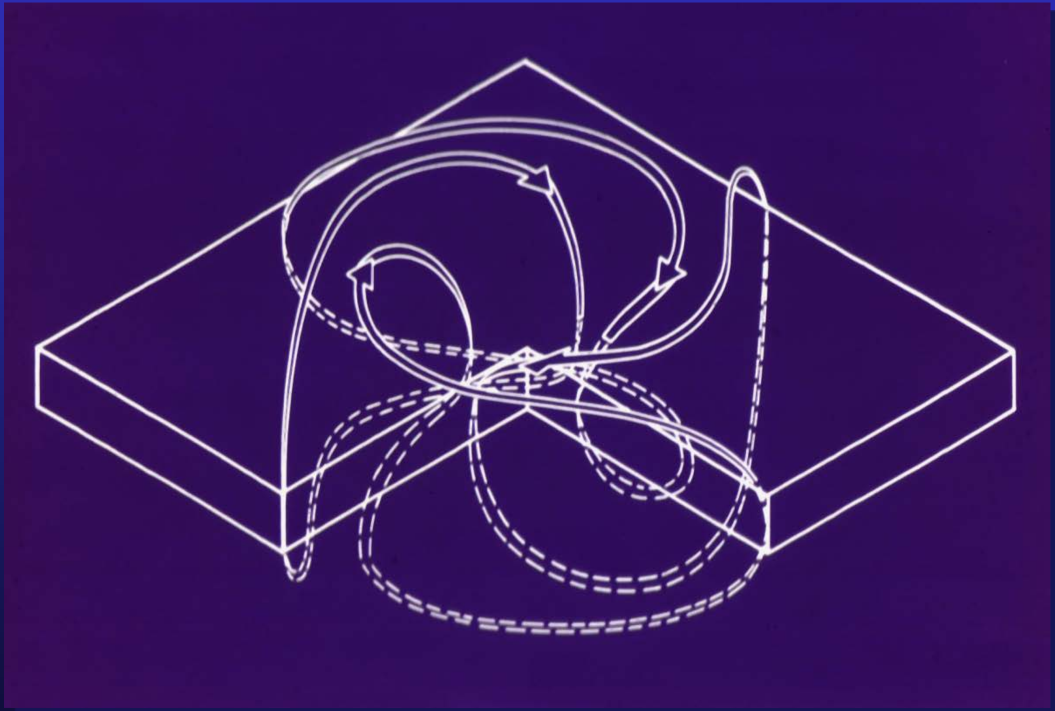
- $m = \frac{1}{2}\, r \times p$ explains relation of electric and magnetic vectors
- Double-layer rim determines both *m* and *p*
- Little significant new information in the MCG…?

s0338

s0159

10 centimeters

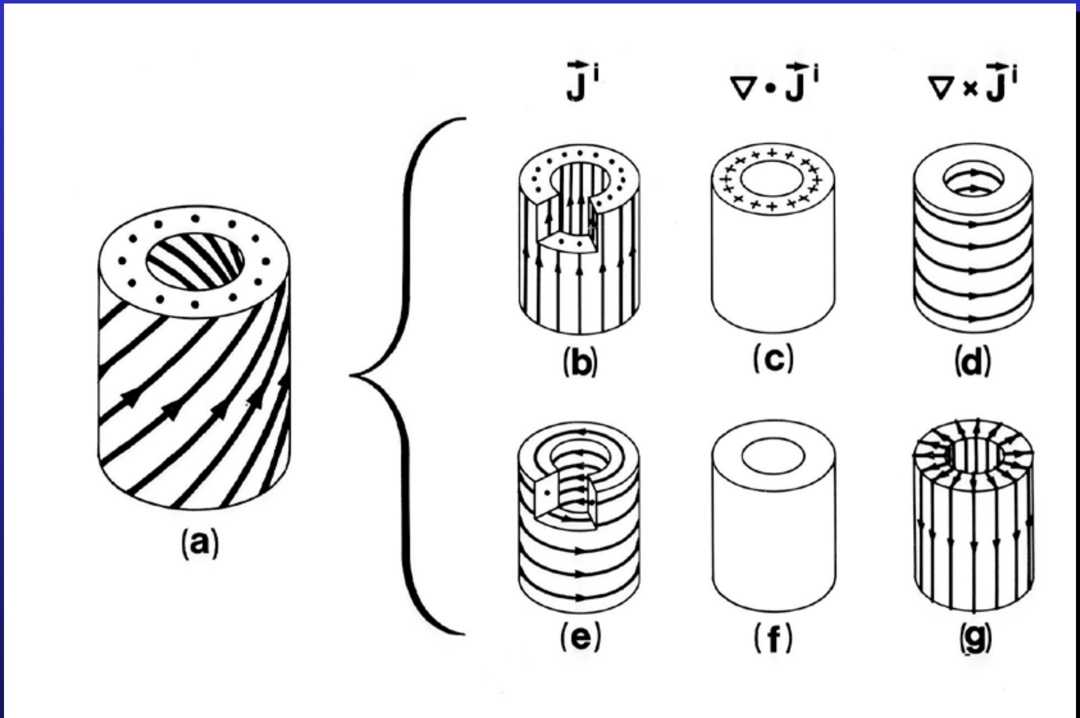
Add the effects of tissue anisotropy…

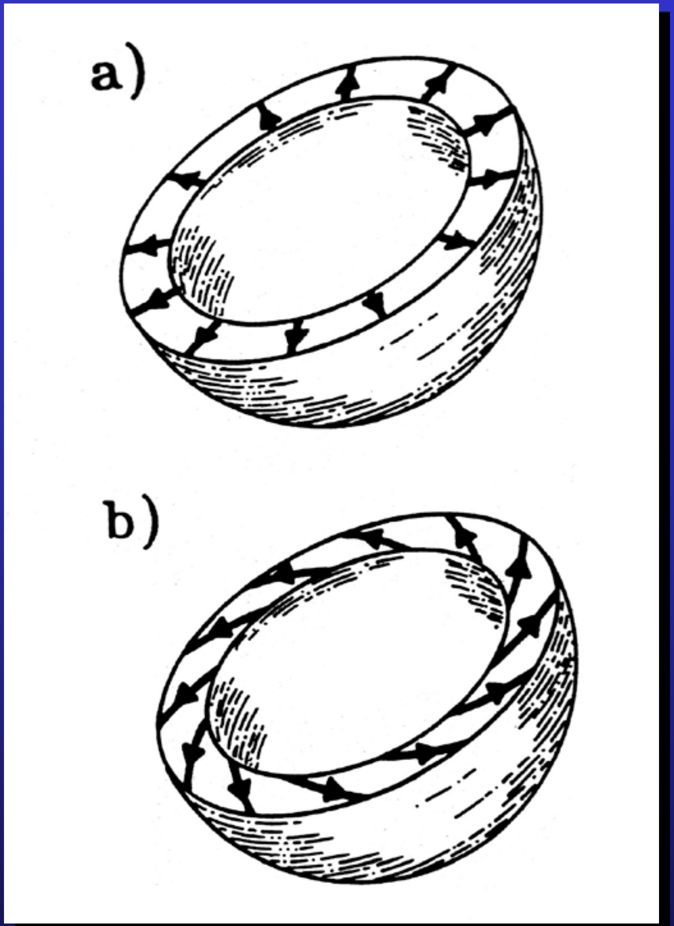


s1157

s1151

Cardiac fiber orientation is the source of the new information

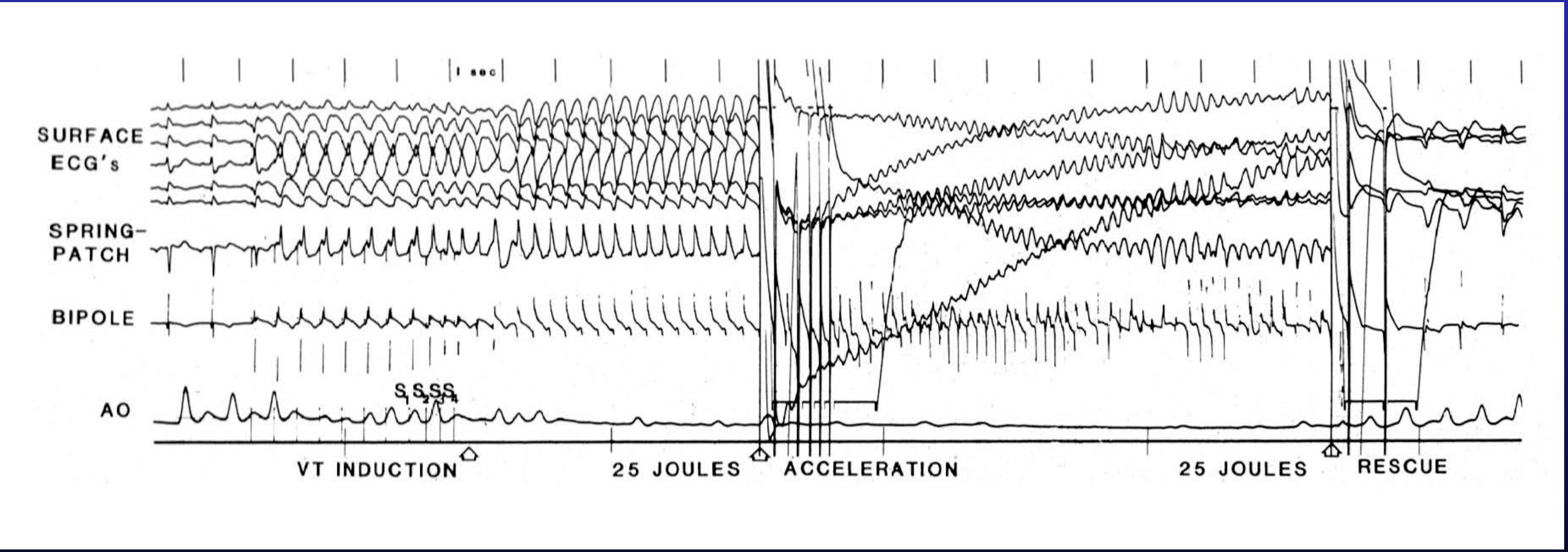




- Circulating current components are electrically silent
- Only magnetic fields can distinguish between two possible models

Fibrillation and Defibrillation

- …with a mean time-to-failure of approximately two billion cycles….



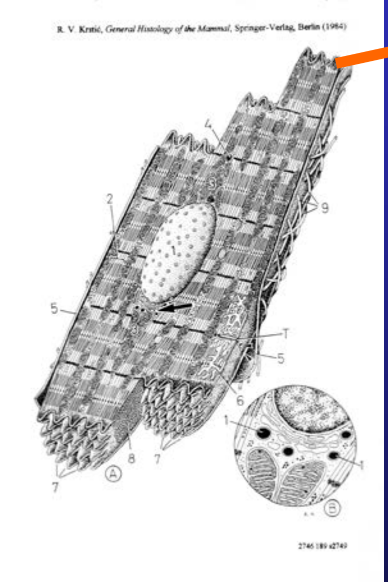
Courtesy of Debra Echt

Simple Questions

- Why is less than 1 joule of electrical energy required to **fibrillate** the heart while much as 100 joules of electrical energy are required to **defibrillate** the heart?
- Will a particular antiarrhythmic drug alter either the fibrillation or defibrillation thresholds?

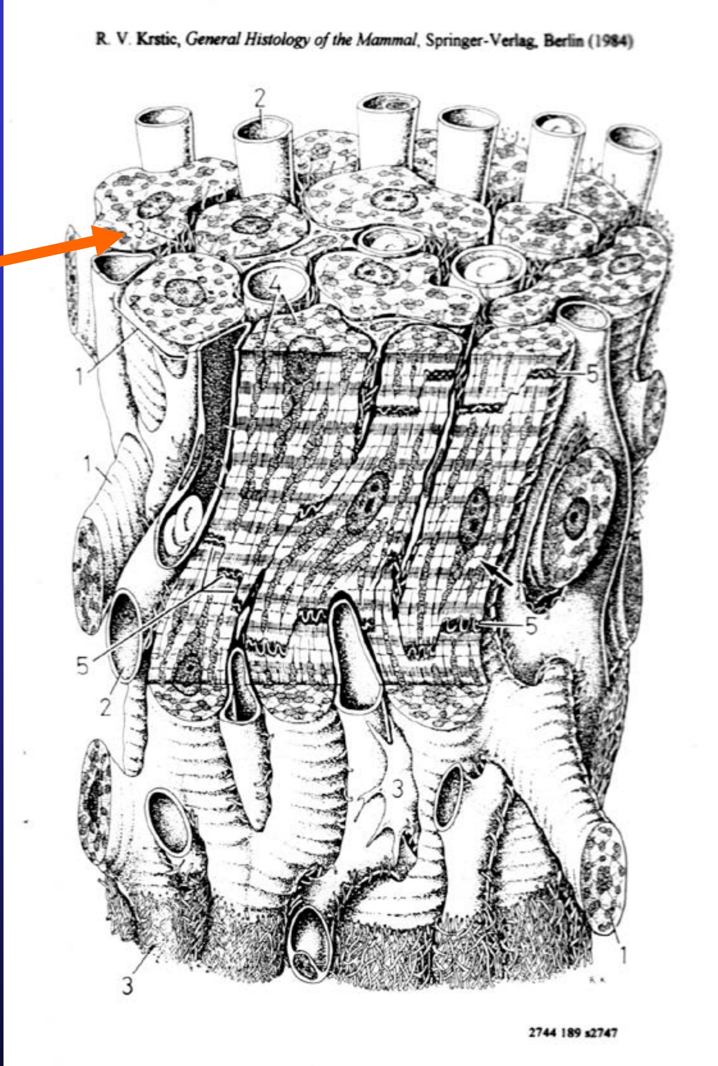
Non-linear dynamics should (?) provide the answers.

The Cardiac Syncytium: A Three-dimensional Anisotropic Bidomain



A cardiac cell: an 80 variable automaton

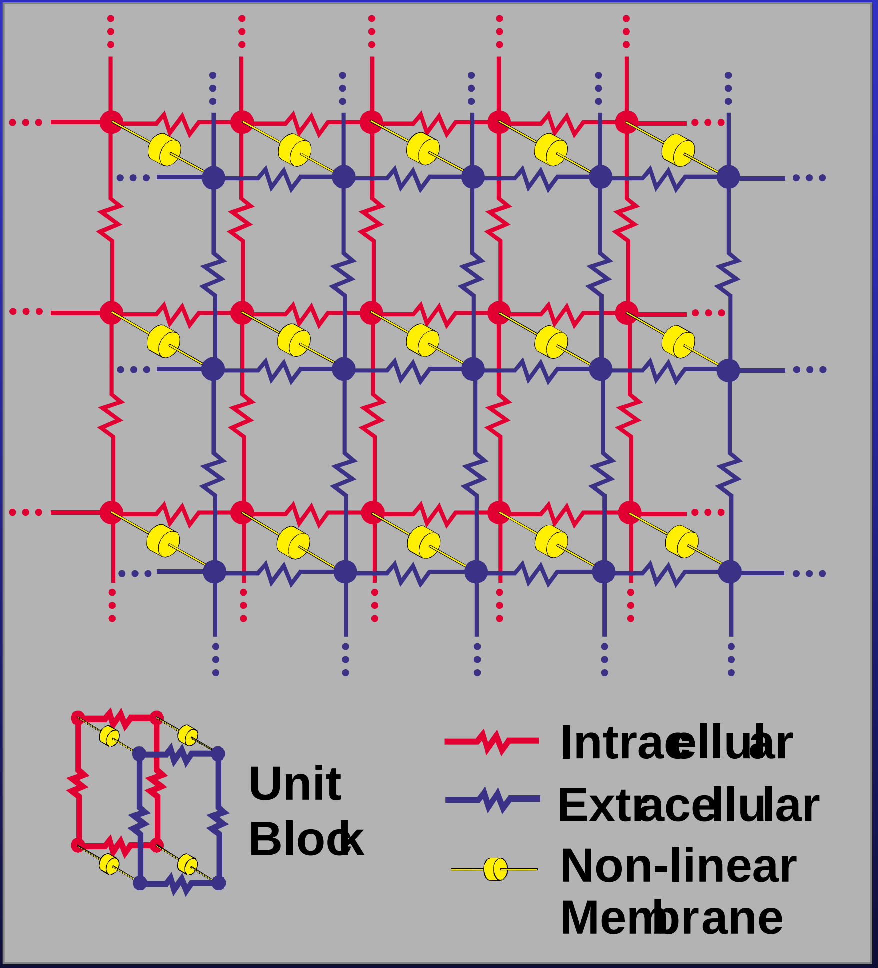
- Multicellular
- Non-linear
- Three-dimensional
- Anisotropic
- Bidomain or Bisyncytial



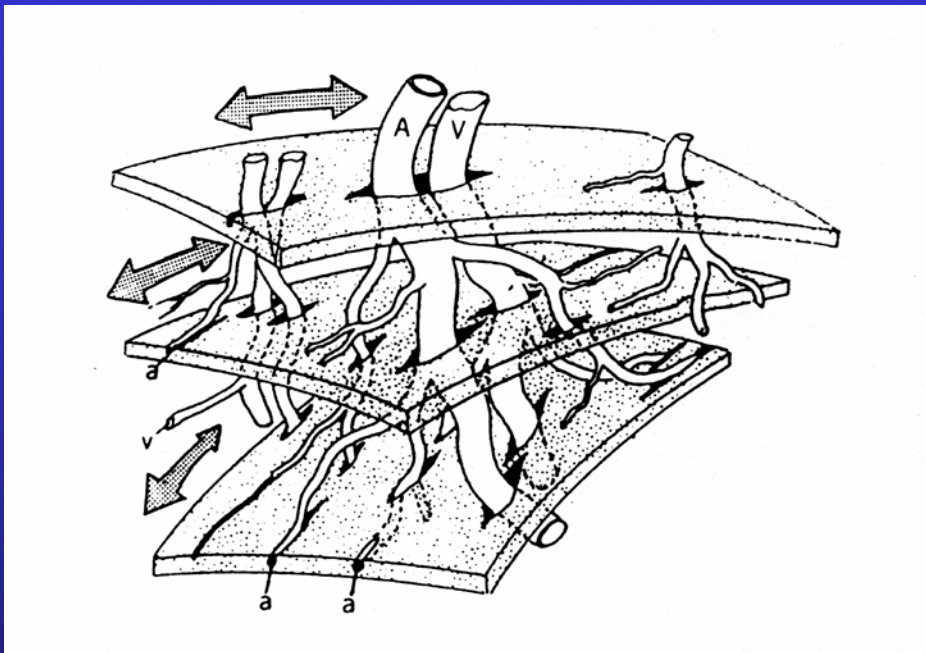
Cardiac tissue: a three-dimensional coaxial cable

The Cardiac Bidomain

- A nerve is a one-dimensional non-linear coaxial cable
- Cardiac tissue is a three-dimensional, nonlinear coaxial cable
- Intra- and extracellular spaces have unequal anisotropies in their electrical conductivities
  - Magnetic fields
  - Virtual electrodes
  - Quatrefoil reentry



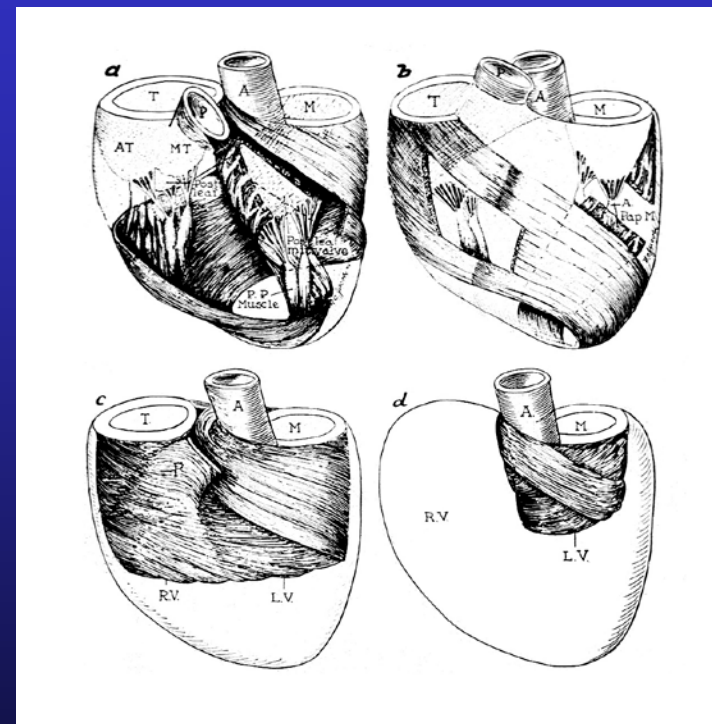
Bidomain Anisotropy



σ_{ix}	2×10^{-4}
σ_{iy}	2×10^{-5}
σ_{ex}	8×10^{-4}
σ_{ey}	2×10^{-4}

$$\sigma_{ix} / \sigma_{iy} = 10$$

$$\sigma_{ex} / \sigma_{ey} = 4$$



There is no single coordinate system in which the tensor conductivity is everywhere diagonal!

2-D Bidomain Equations

- Homogenized
- Coupled V_m & V_e
- Nonlinear reaction-diffusion equation
- Boundary value equation

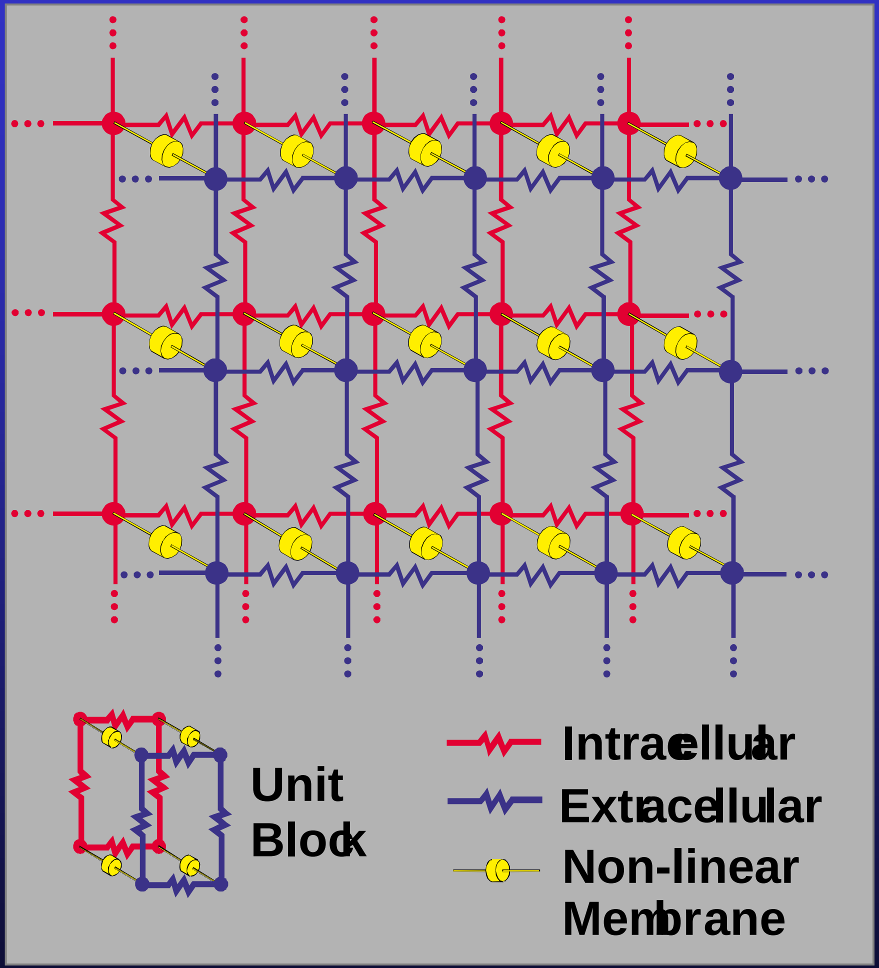
$$C_m \frac{\partial V_m}{\partial t} = -J_{ion} - \frac{1}{\beta} \nabla \bullet \tilde{g}_e \nabla V_e \quad ,$$

$$\nabla \bullet (\tilde{g}_i + \tilde{g}_e) \nabla V_e = -\nabla \bullet \tilde{g}_i \nabla V_m \, ,$$

where $\tilde{g}_i$ and $\tilde{g}_e$ are the intracellular and extracellular conductivity tensors; β is the ratio of membrane surface area to tissue volume (0.3 μm^{-1}); C_m is the membrane capacitance per unit area (0.01 F/m^2); and J_{ion} is the membrane current per unit area, determined by the Beeler-Reuter model[9].

The Cardiac Bidomain

- A nerve is a one-dimensional non-linear coaxial cable
- Cardiac tissue is a three-dimensional, nonlinear coaxial cable
- Intra- and extracellular spaces have unequal anisotropies in their electrical conductivities
  - Magnetic fields
  - Virtual electrodes
  - Quatrefoil reentry
  - Defibrillation?

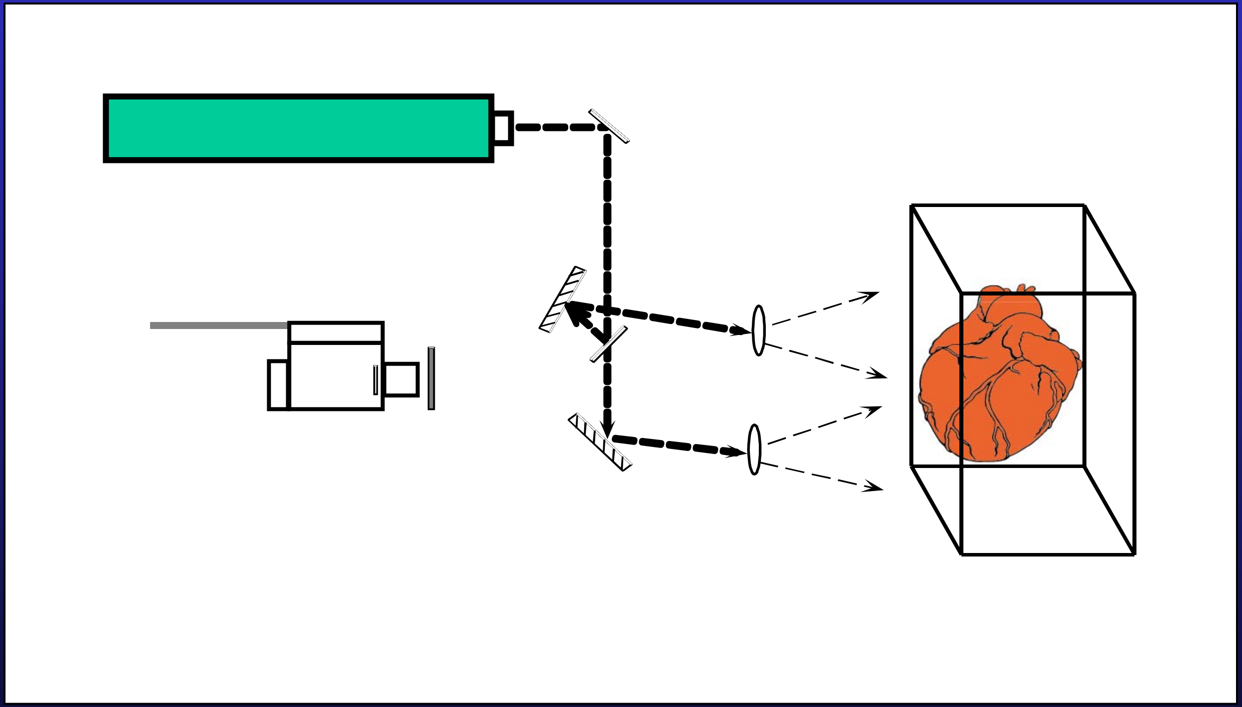


Recording from the Bidomain

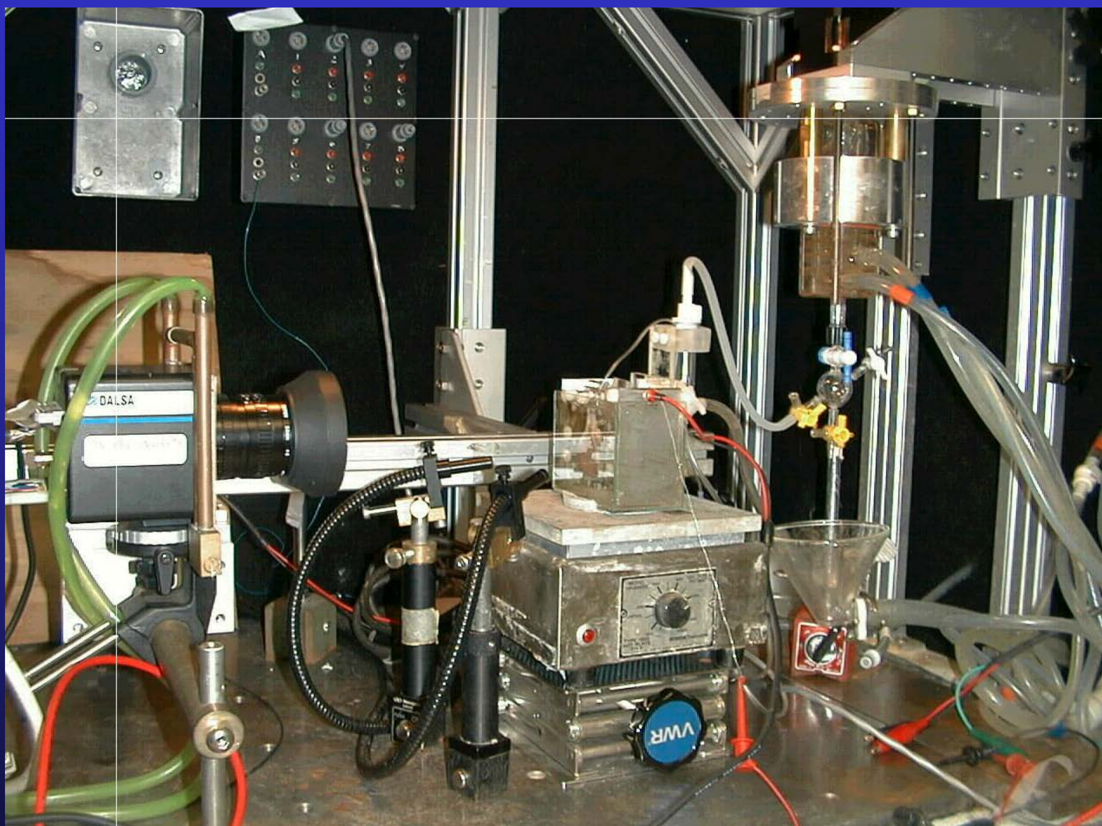
- Extracellular potential
  - Extracellular electrode arrays ($\leq$ 250)
- Intracellular potential
  - Intracellular microelectrodes ($\leq$ 2)
- Membrane potential
  - **Voltage-sensitive fluorescent dyes (256 – 10,000)**
- Net action currents
  - Scanning SQUID microscope (1)

Optical Imaging of the Transmembrane Action Potential During Stimulation, Reentry, Fibrillation, and Defibrillation

- Langendorff-perfused rabbit heart
- Voltage-sensitive dye in membrane measures V_m
- Laser illumination
- High-speed charge-coupled-device (CCD) camera



Vanderbilt cardiac imaging system



Verdi diode-pumped solid-state laser

Di-4-ANEPPS voltage dye

Light delivered by bundles of optical fibers

Dalsa CCD camera:
- 12 bit
- 64x64 pixels
- **1200 frames/sec**

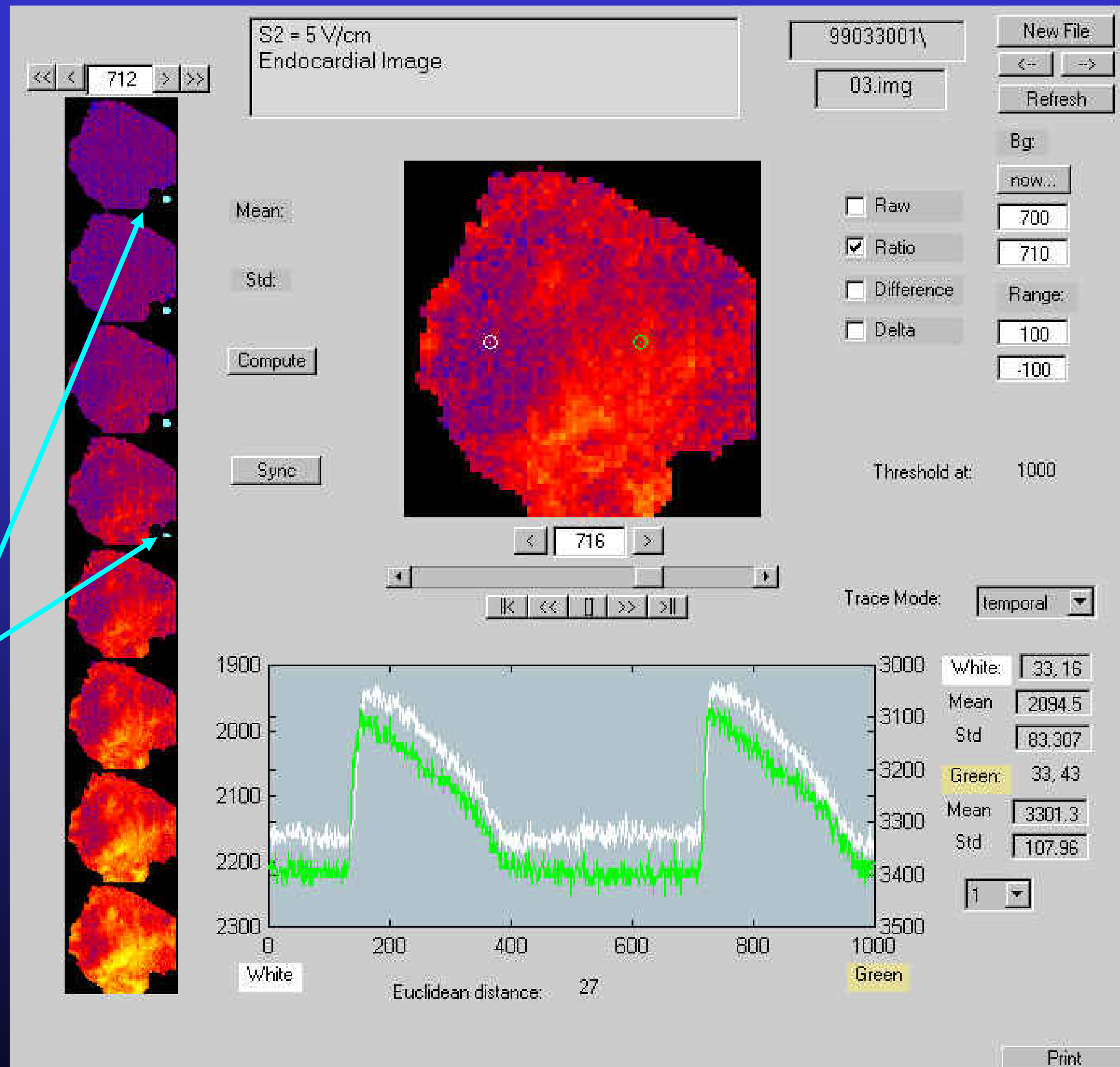
10 x 5 x 7.5 cm^3 bath

37 ^oC Tyrode's solution

TL129 S4609

Gus2: MATLAB Data Viewing Program

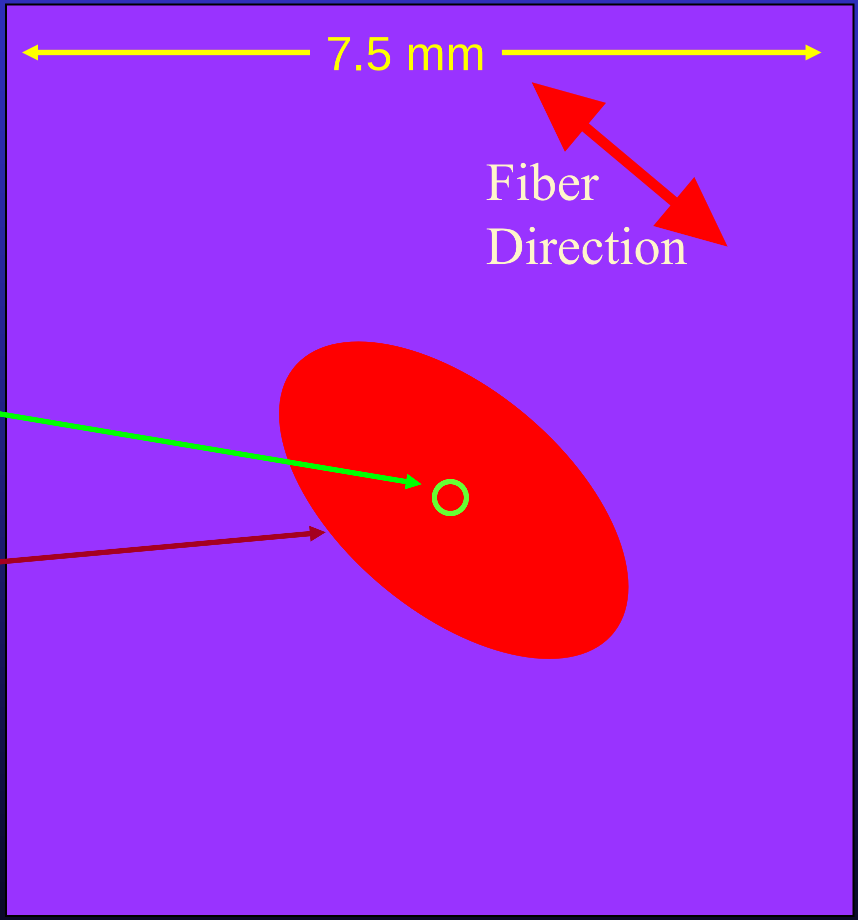
Four S2 frames indicated by LED



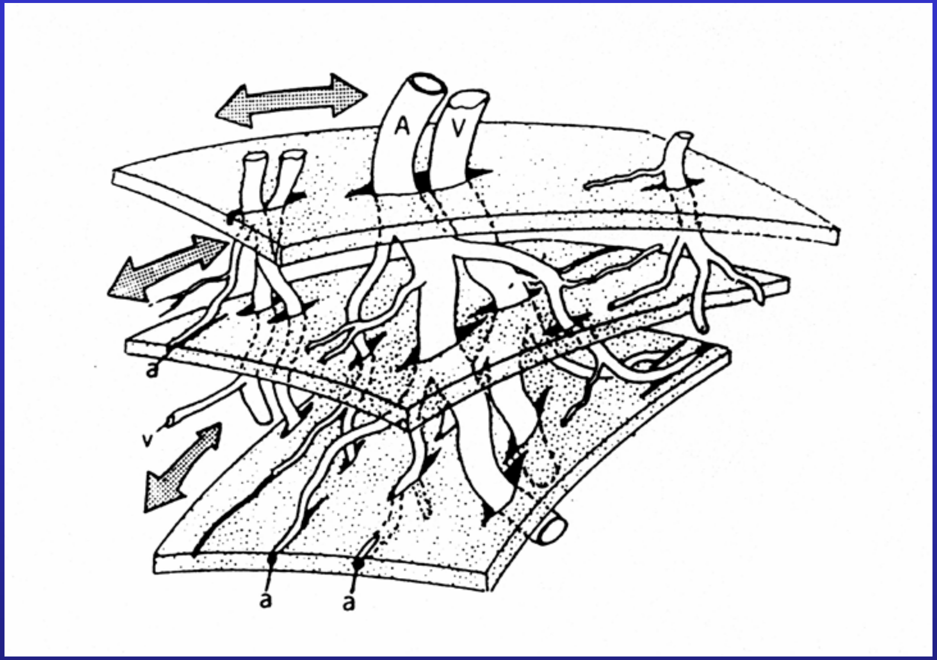
Written by Gustavo Rohde

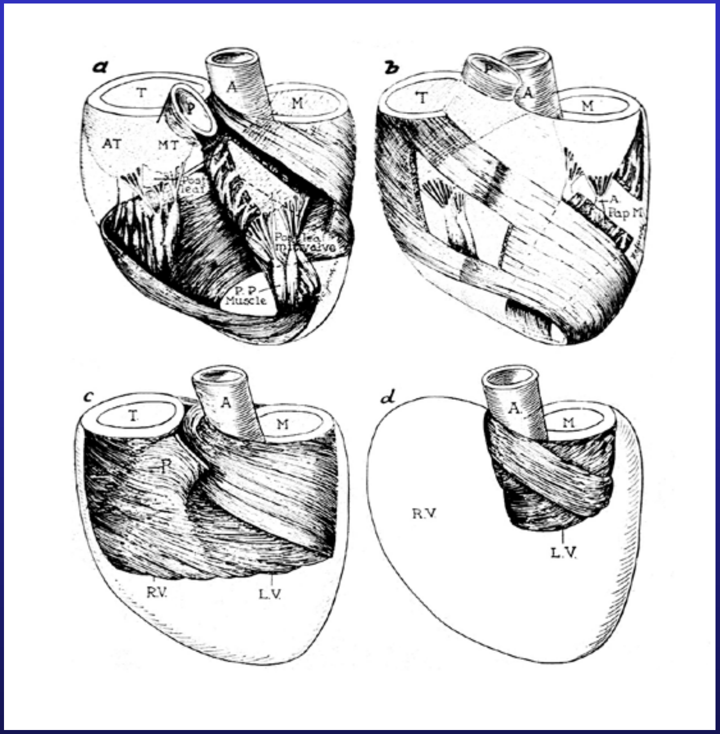
Injecting -20 mA into Equal-Anisotropy Cardiac Tissue

- Point cathodal stimulation
- Virtual cathode depolarizes (red)



Bidomain Anisotropy





σ_{ix}	0.2 S/m
σ_{iy}	0.02 S/m
σ_{ex}	0.8 S/m
σ_{ey}	0.2 S/m

$$\sigma_{ix} / \sigma_{iy} = 10$$

$$\sigma_{ex} / \sigma_{ey} = 4$$

There is no single coordinate system in which the tensor conductivity is everywhere diagonal!

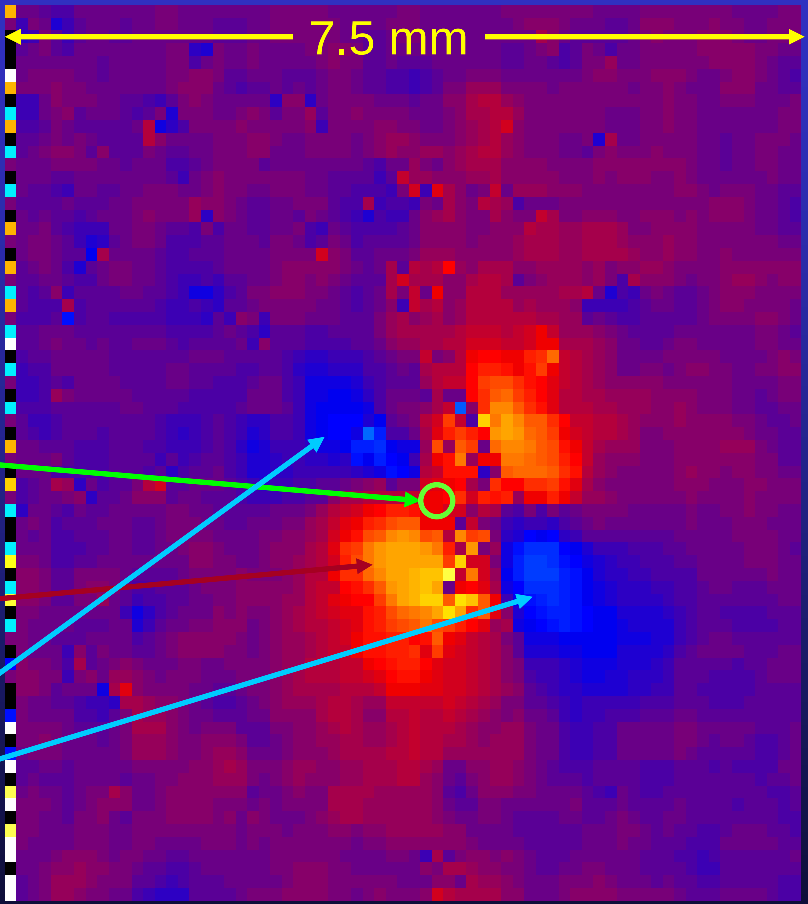
s0704

s1325

1 millimeter

Virtual electrodes in cardiac tissue

- As a result of unequal electrical anisotropies in intracellular and extracellular spaces:
- Point cathodal stimulation
- Virtual cathode depolarizes (red)
- Virtual anodes hyperpolarize (blue)



(Wikswo, Lin and Abbas. *Biophys. J.* 69 :2195-2210, 1995)

Puzzle

Four modes of stimulating cardiac tissue

- **Cathode make** (turn on negative current)
- **Anode make** (turn on positive current)
- **Cathode break** (turn off long negative current)
- **Anode break** (turn off long positive current)

Dekker, E. "Direct current make and break thresholds for pacemaker electrodes on the canine ventricle." Circ Res, 27:811, 1970

1 millimeter

VI∫BRE

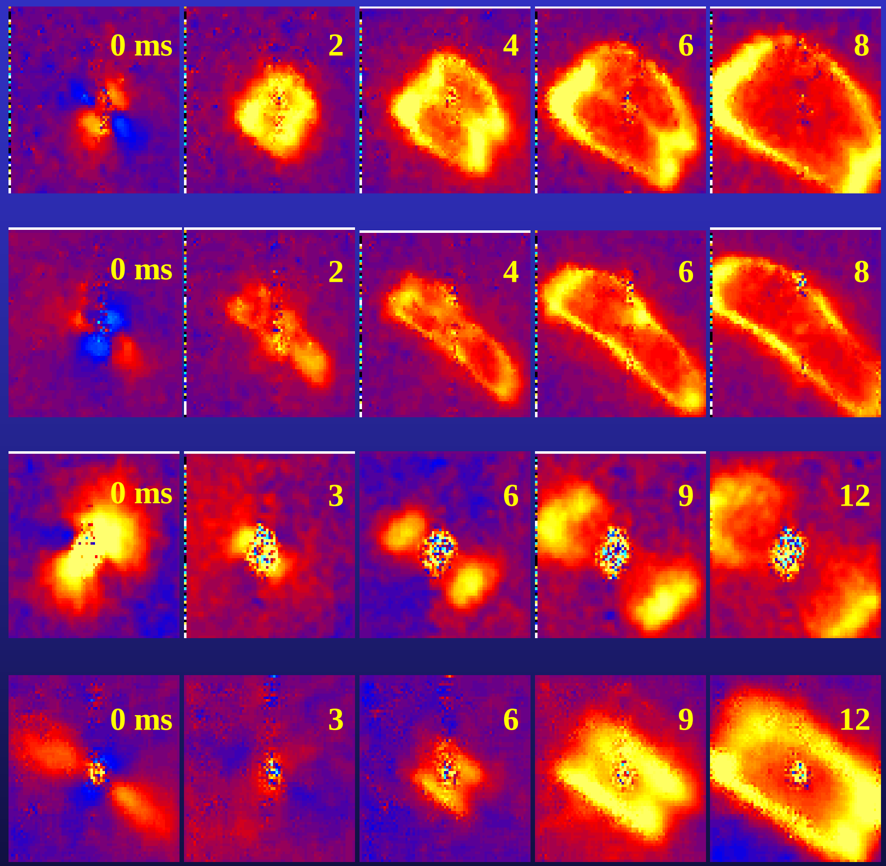
Synchronous Imaging of Point Activation Patterns
--- Virtual Electrodes ---

Cathode Make -10 mA

Anode Make +10 mA

Cathode Break -2 mA

Anode Break +3mA



▬ 1 mm

10,000 pixel/frame

Fiber Direction

Depolarized

ΔF/F (%)

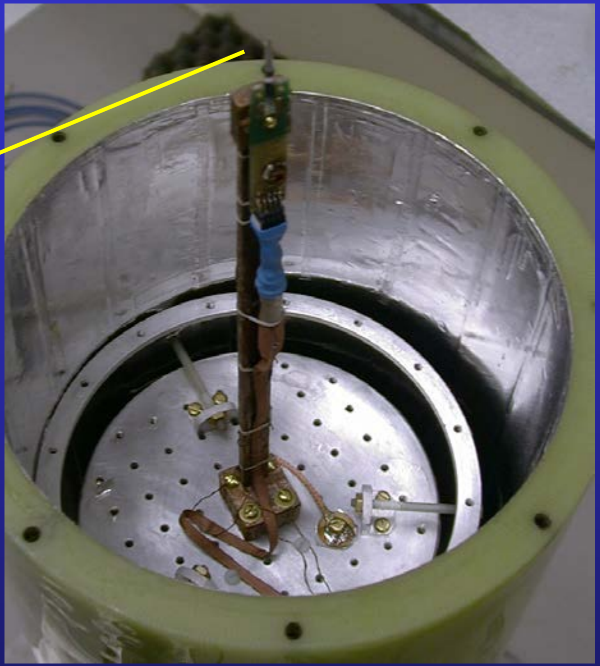
Hyperpolarized

(Wikswo, Lin and Abbas. *Biophys. J.* 69 :2195-2210, 1995)

TL129 S4614

1 millimeter

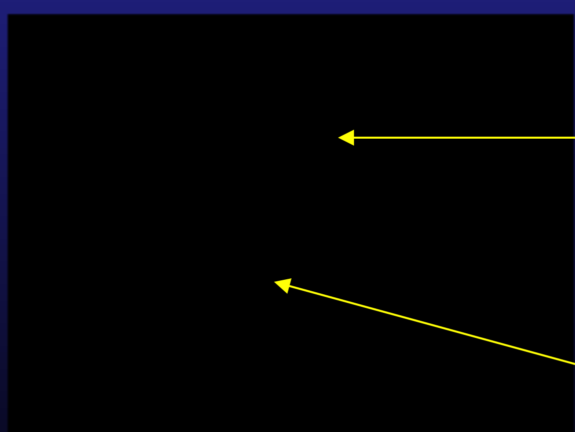
LTS-SQUID microscope

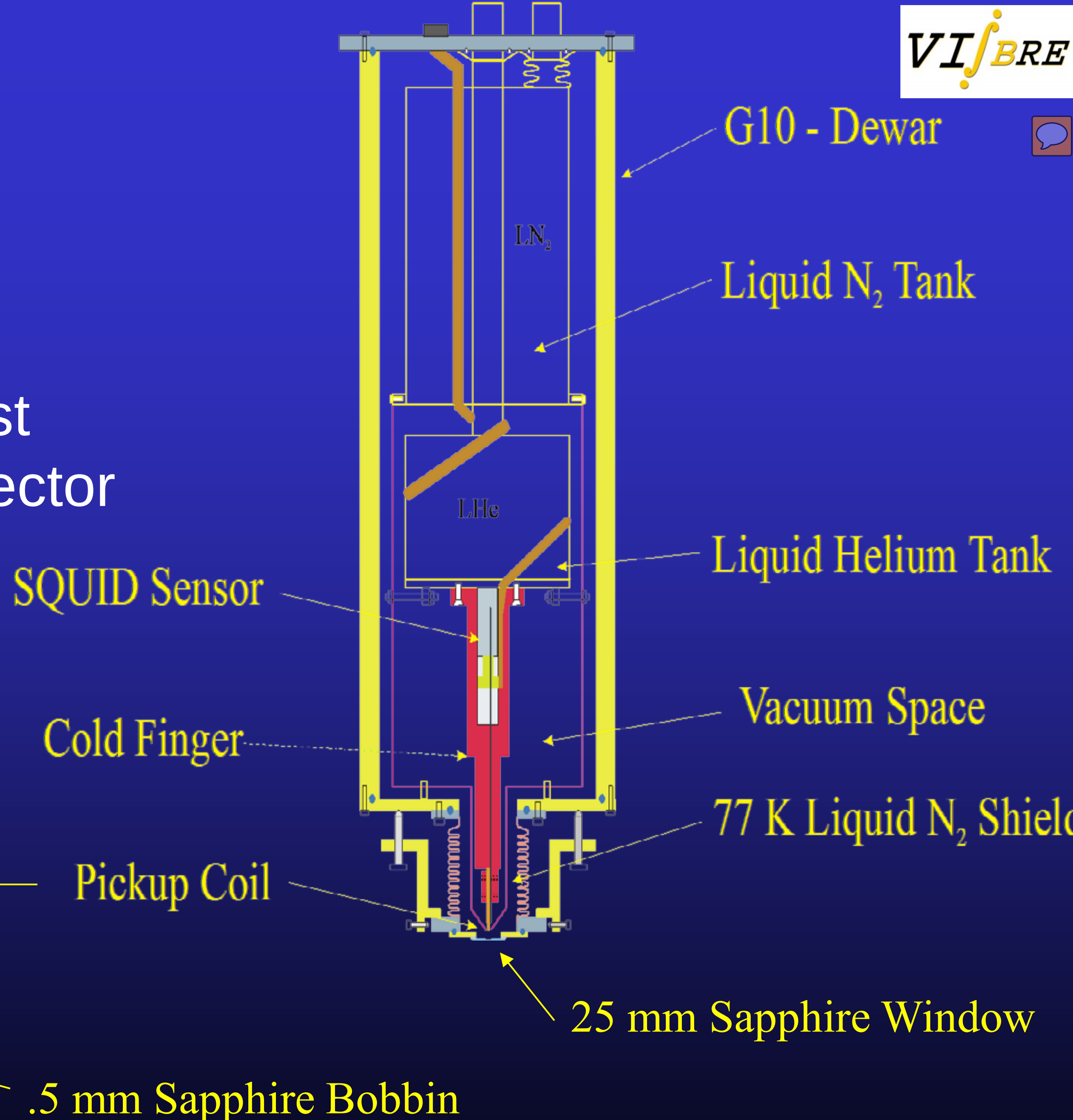


- 30 μm   300 K – 4 K
  Grad(T) = 10^7 K/m
- 250 μm coil diameter
- 1 pT/$Hz^{1/2}$ sensitivity

Cryostat Design

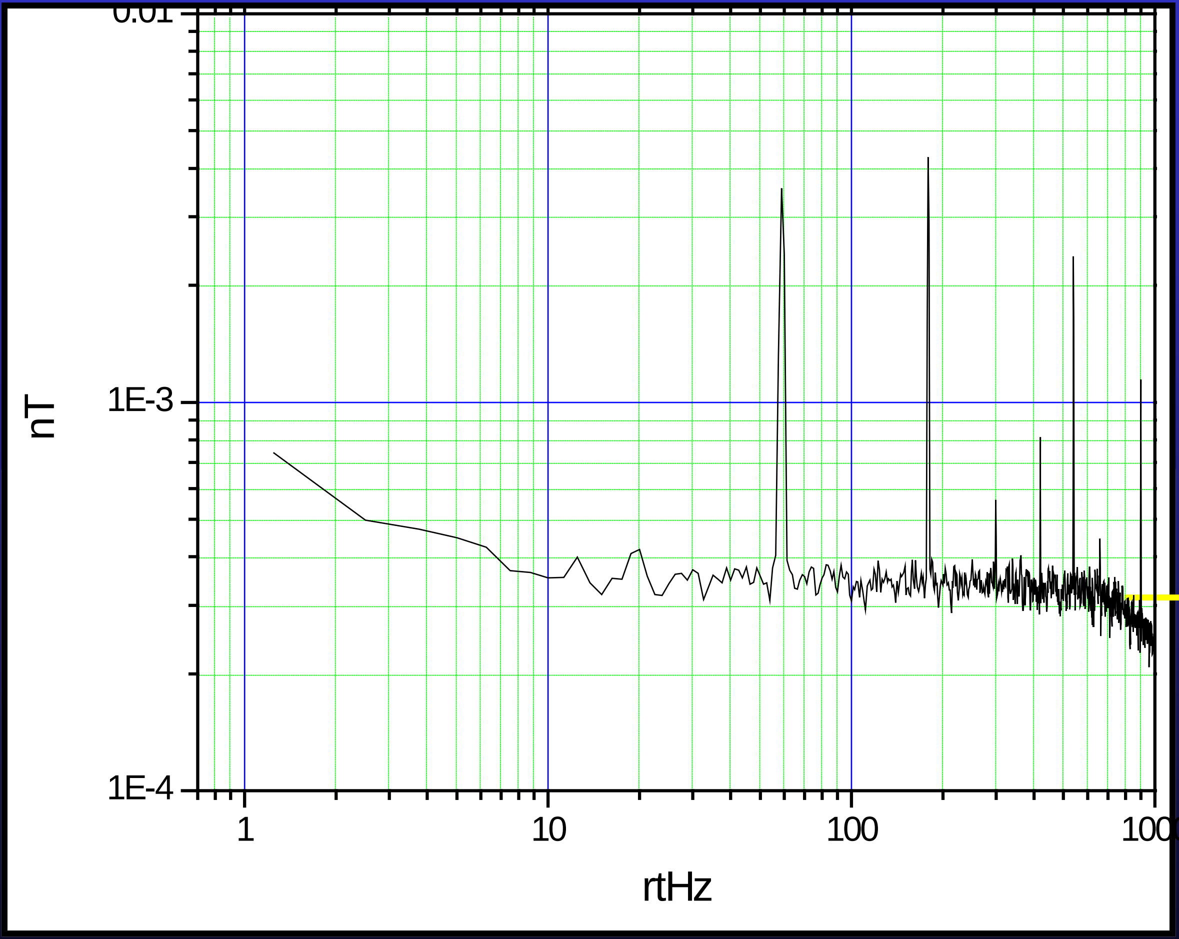
SQUIDs are the most sensitive known detector of magnetic fields





Field Sensitivity

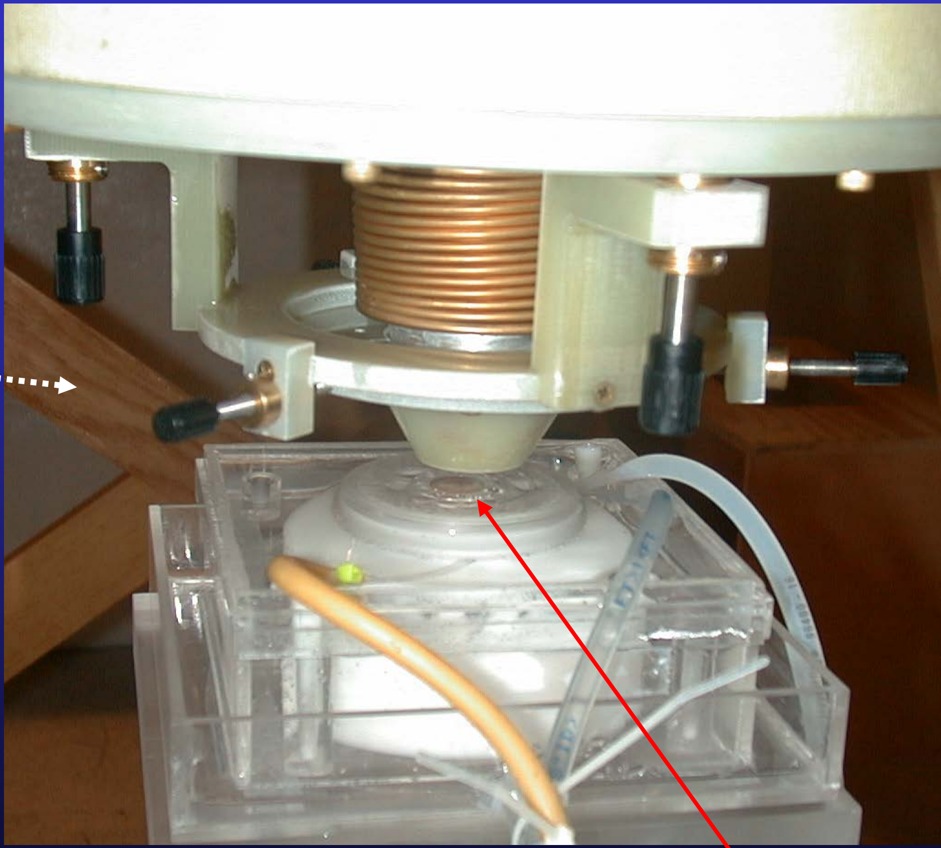
20 turn Nb-wire pickup coil on 500 µm sapphire bobbin



$$330 \frac{fT}{\sqrt{Hz}}$$

Courtesy of Jenny Holzer and Franz Baudenbacher

Experimental Setup – Magnetic Imaging



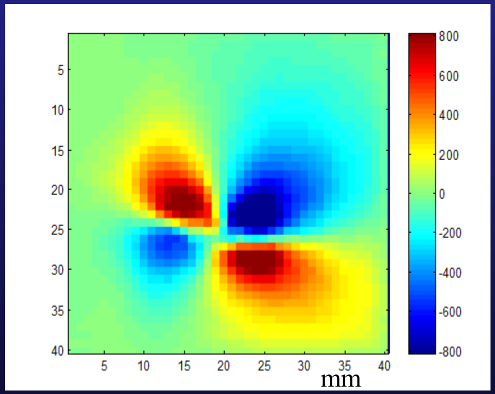
Isolated rabbit heart

Courtesy of Jenny Holzer and Franz Baudenbacher

1 millimeter

The magnetic field from action currents in isolated cardiac tissue – left ventricle

- Scanning SQUID microscope
- Isolated rabbit heart
- Point stimulation
- Anisotropy produces quatrefoil pattern

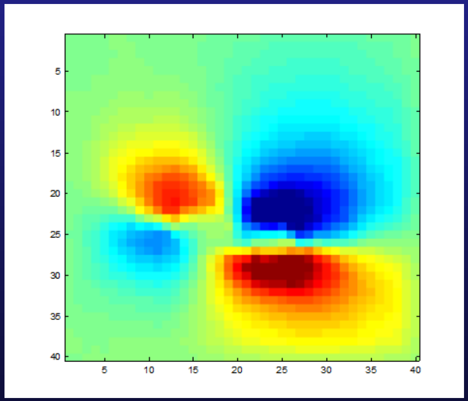


800

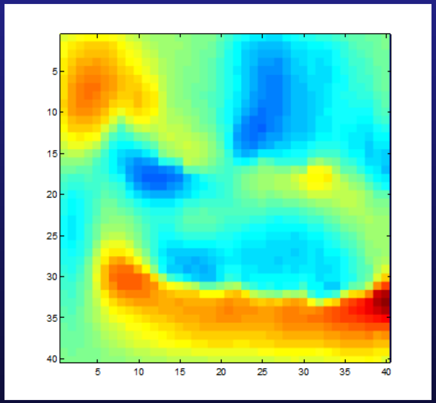
pT

-800

1 ms after stimulus



4 ms



10 ms

Courtesy of Franz Baudenbacher

b-fmpr1.mpg

Plane Wavefront Propagation

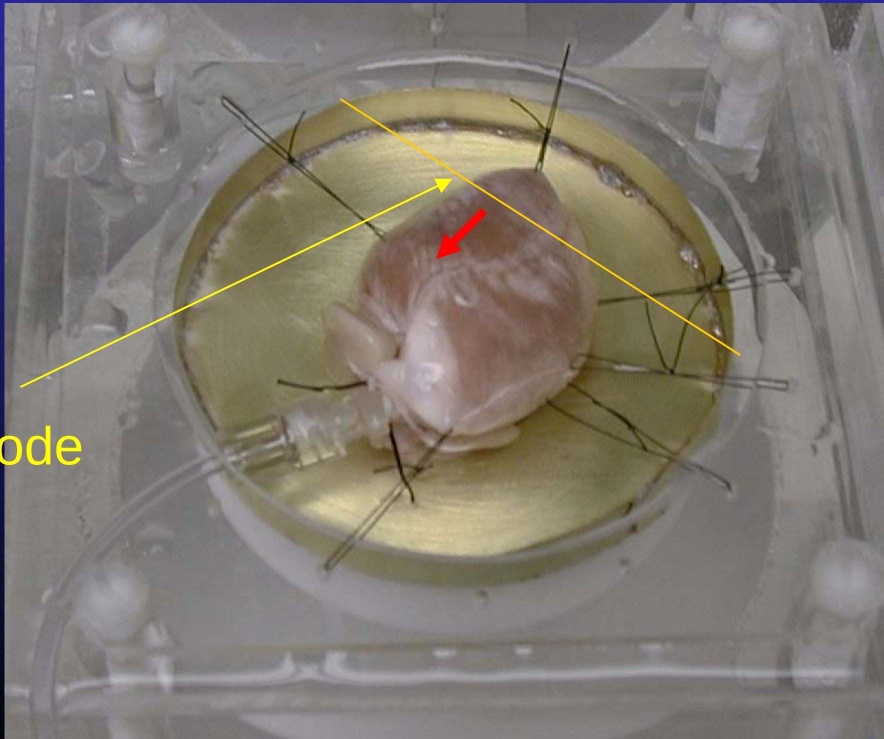
Langendorff perfused isolated rabbit heart

- **High-Resolution LTS-SQUID Microscopy**

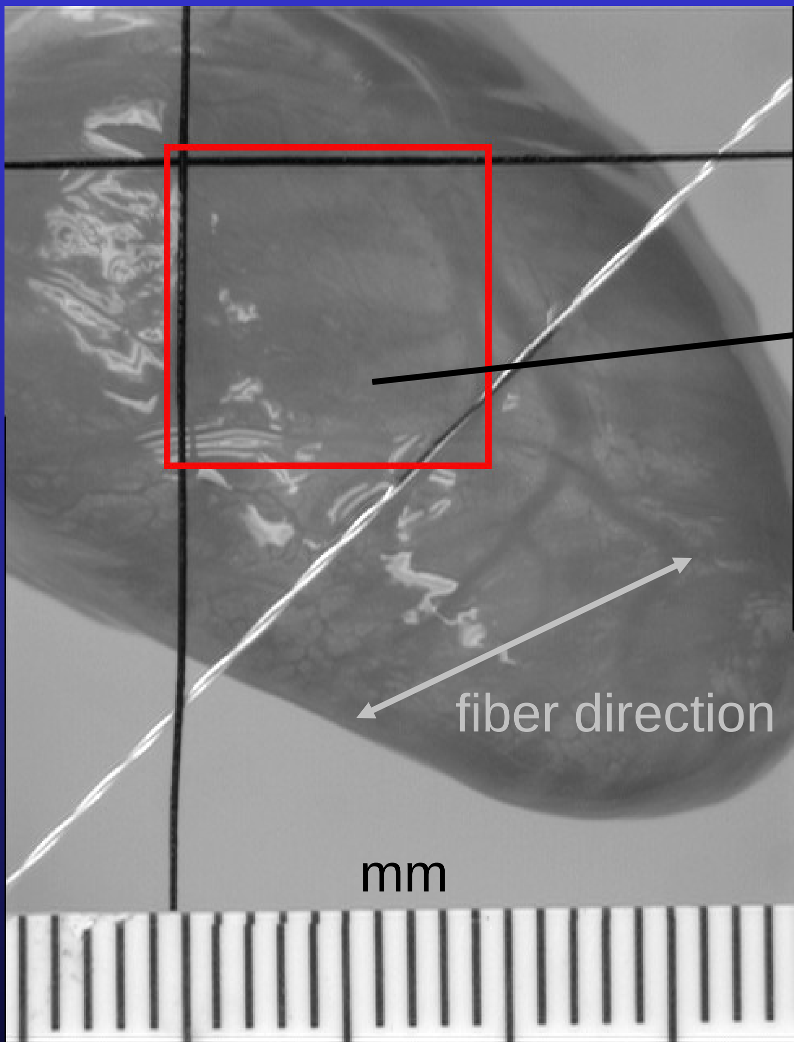
  Measure B, calculate net current distribution

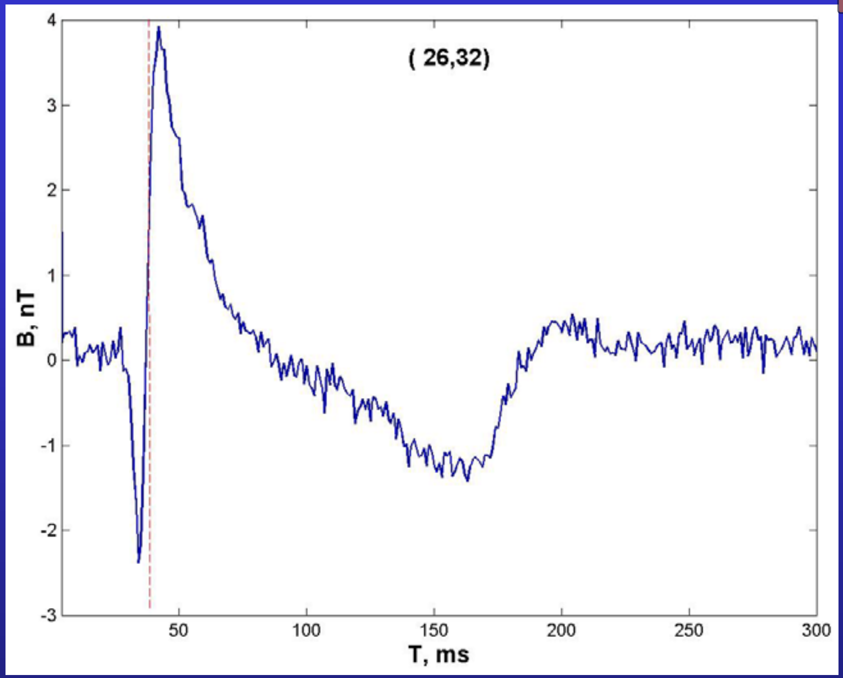
- **Epifluorescent Imaging**

  Measure transmembrane potential, V_m



Courtesy of Jenny Holzer and Franz Baudenbacher



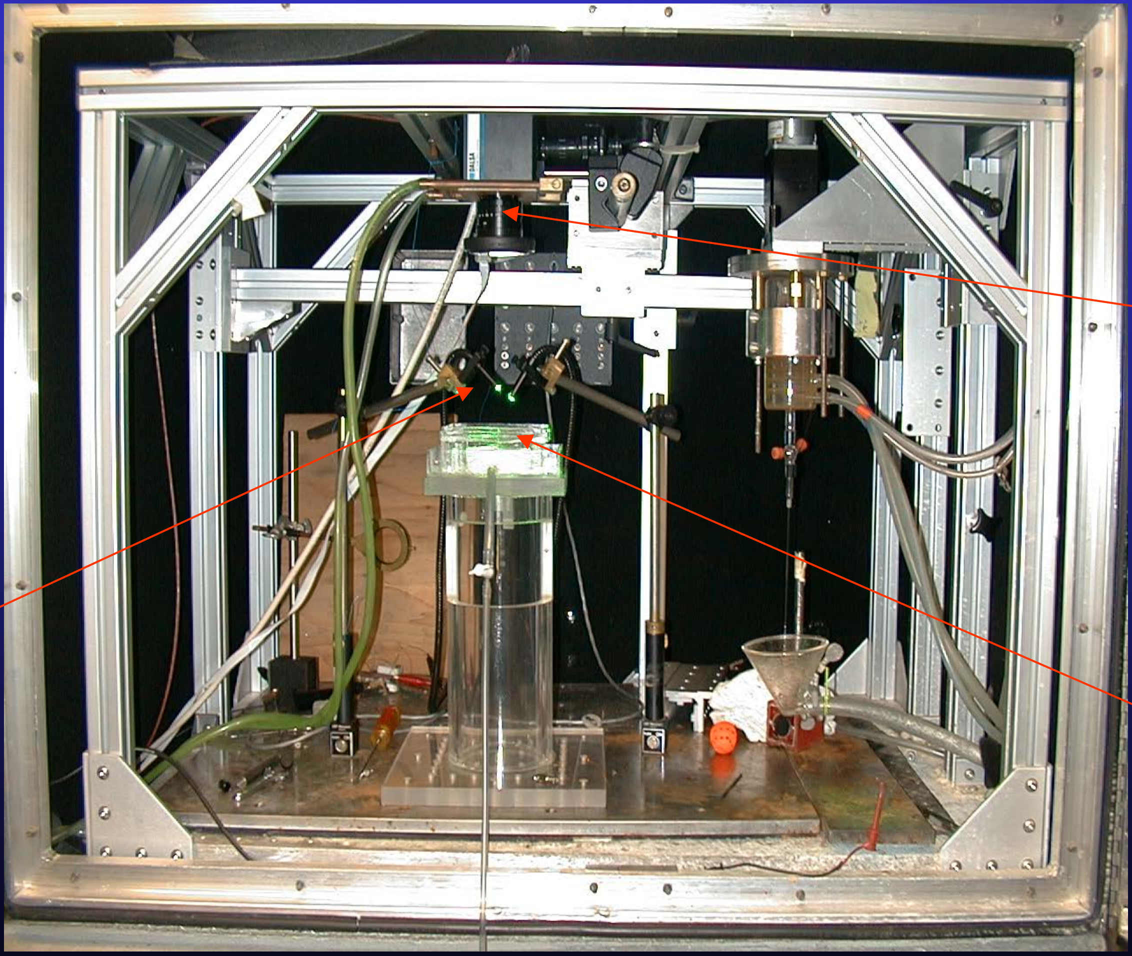


Measure MCG as a function of position

Courtesy of Jenny Holzer and Franz Baudenbacher

Scan2.mpg

Experimental Setup - Optical Imaging



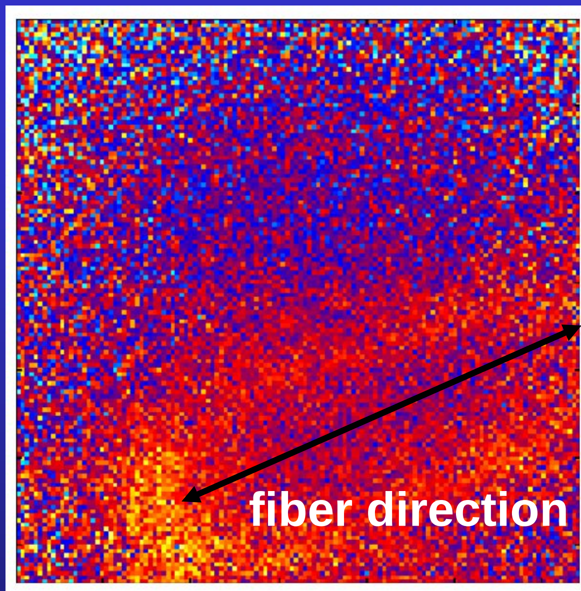
fl4.mpg

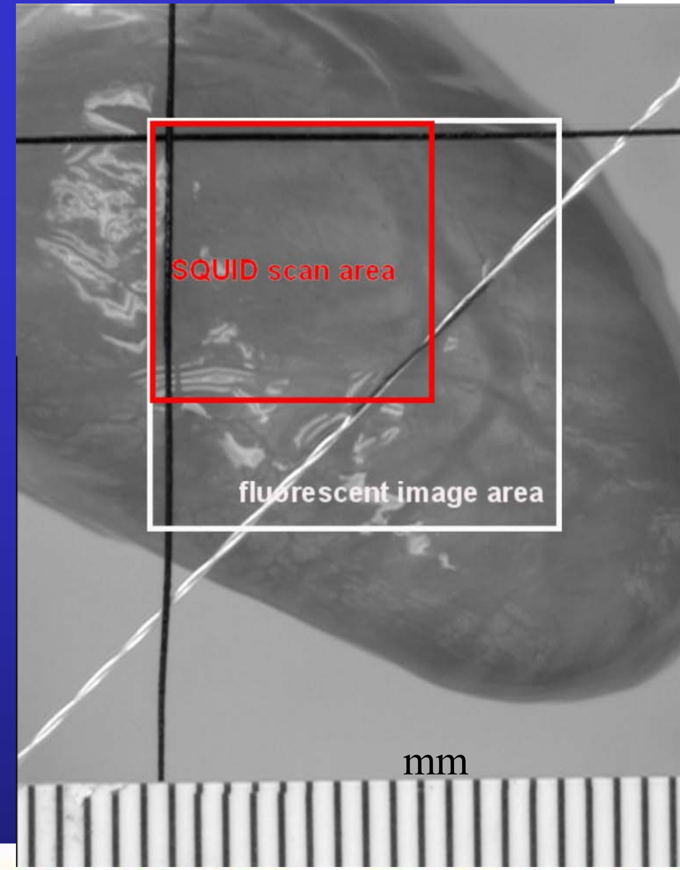
CCD-Camera

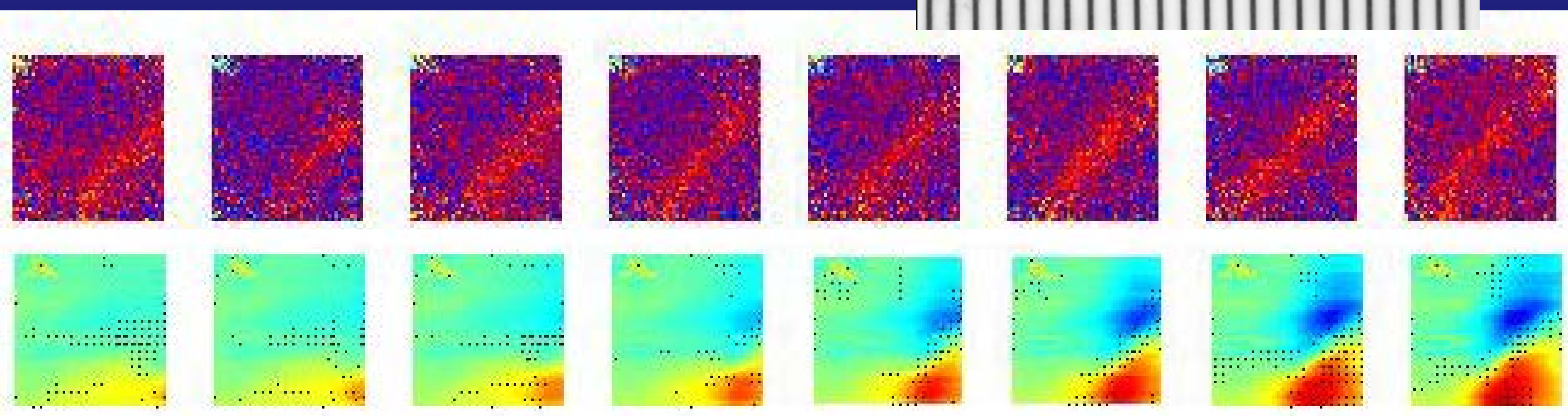
Laser Light
532nm

Heart

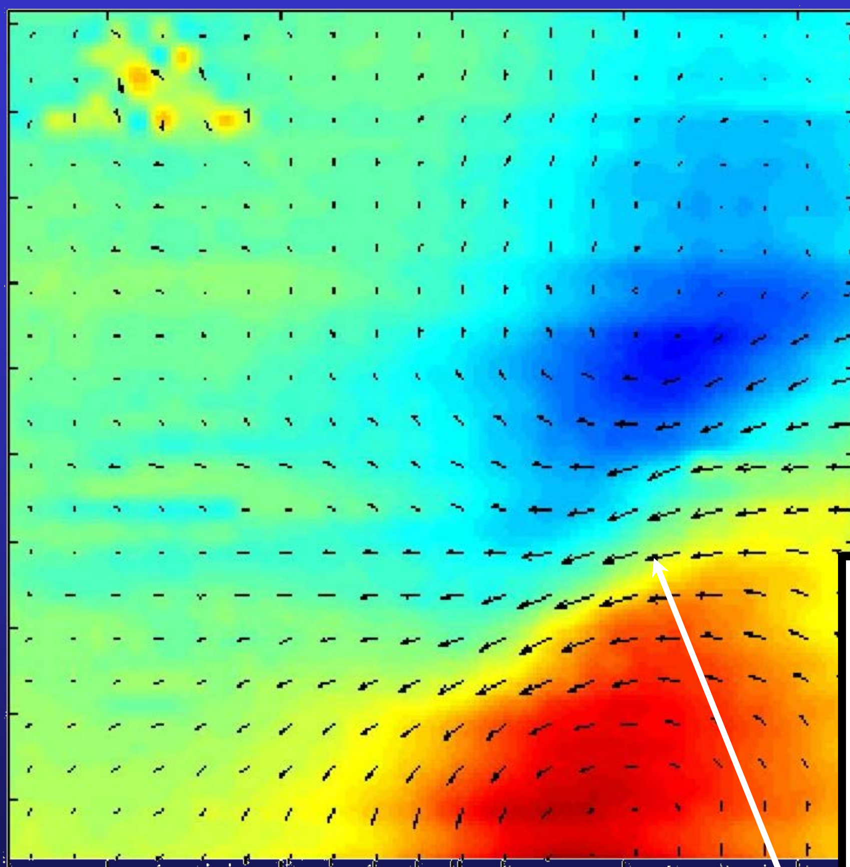
Courtesy of Jenny Holzer and Franz Baudenbacher

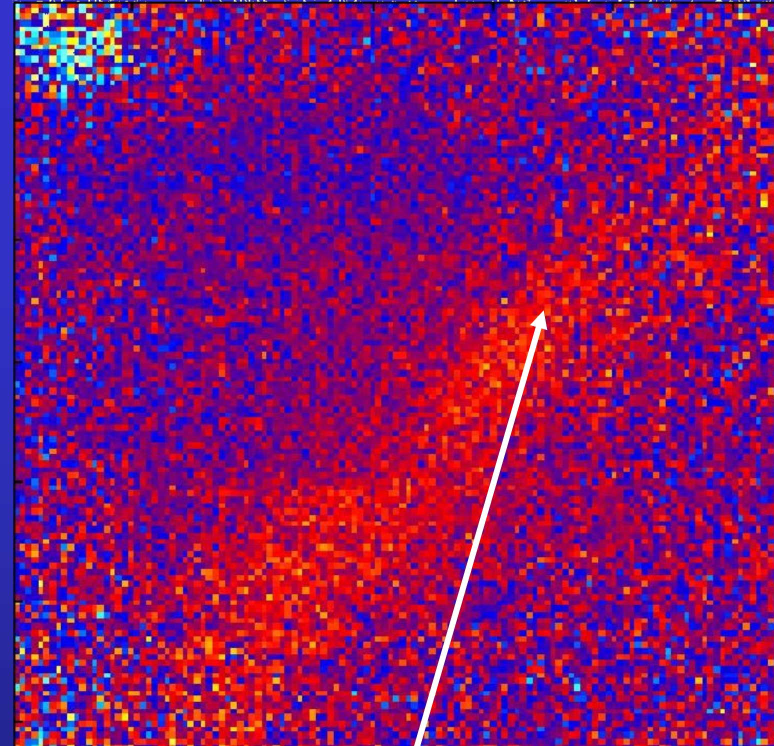


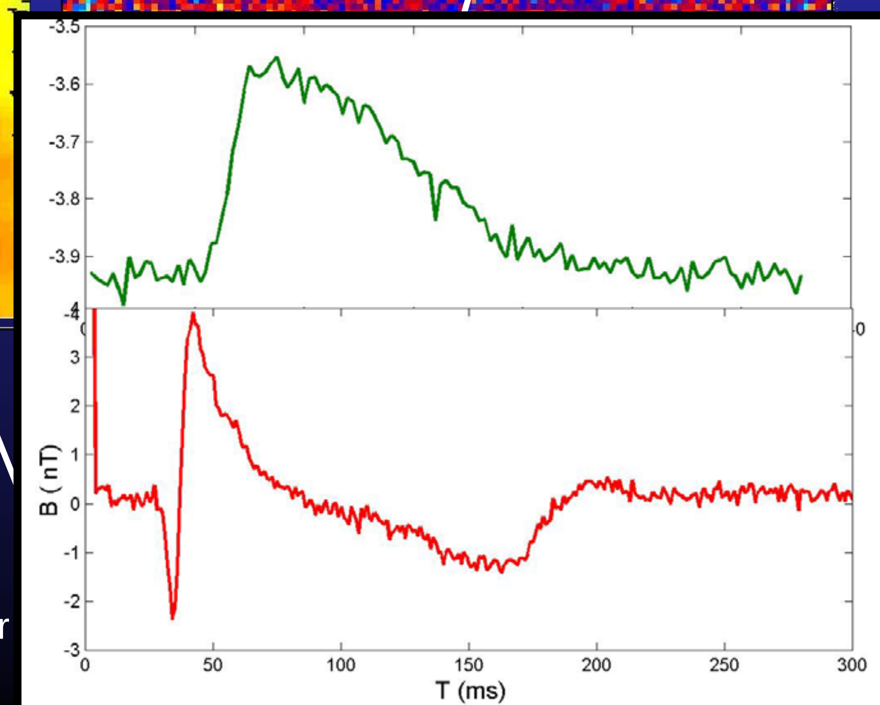




Courtesy of Jenny Holzer and Franz Baudenbacher



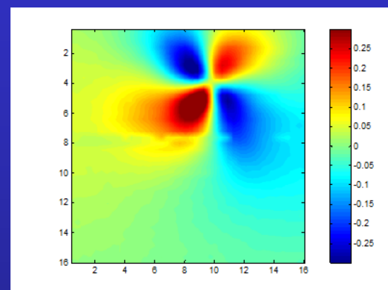




Currents are parallel to wavefront

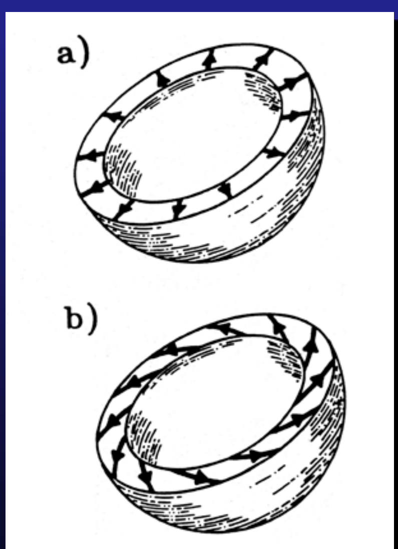
Courtesy of Jenny Holzer and Franz Baudenbacher

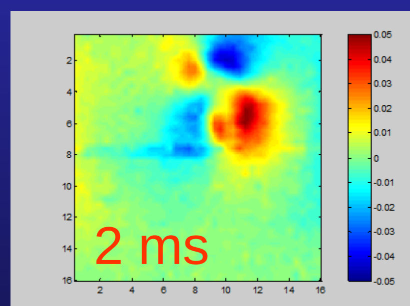
The magnetic field from action currents in isolated cardiac tissue – the apex

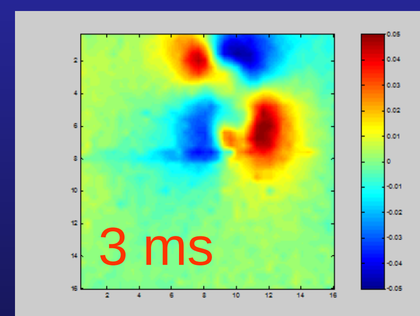


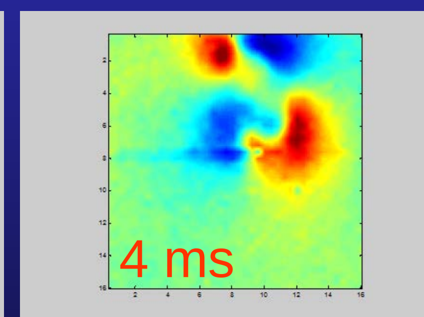
Stimulus
0.6 mA 5 ms

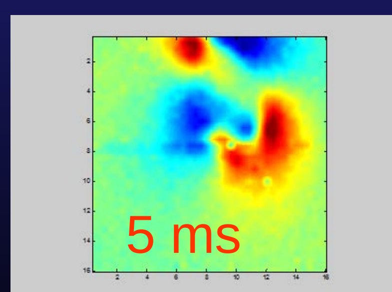
near_apex.mpg

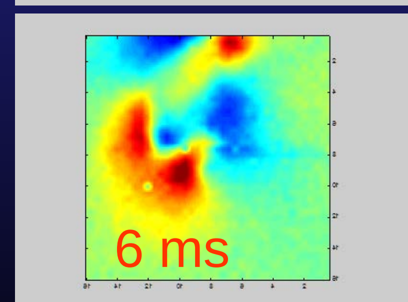


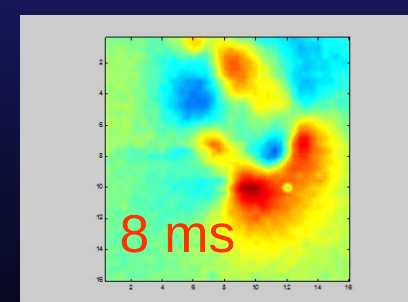






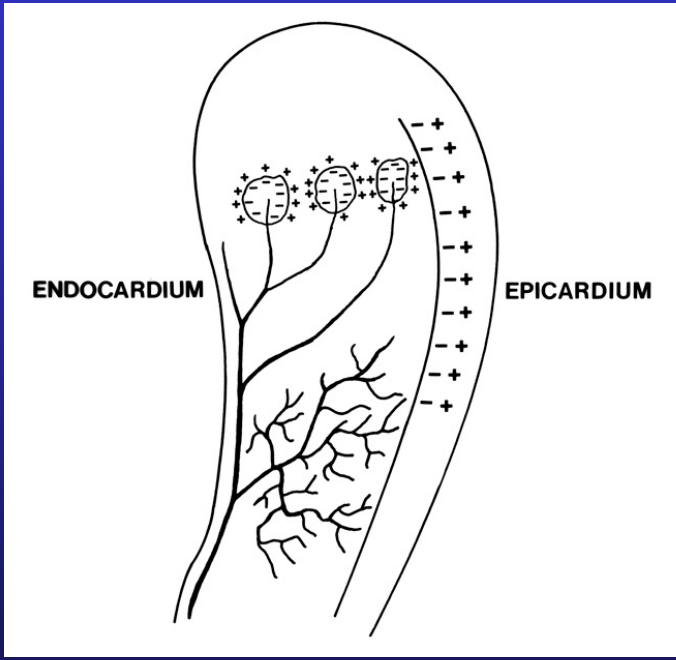


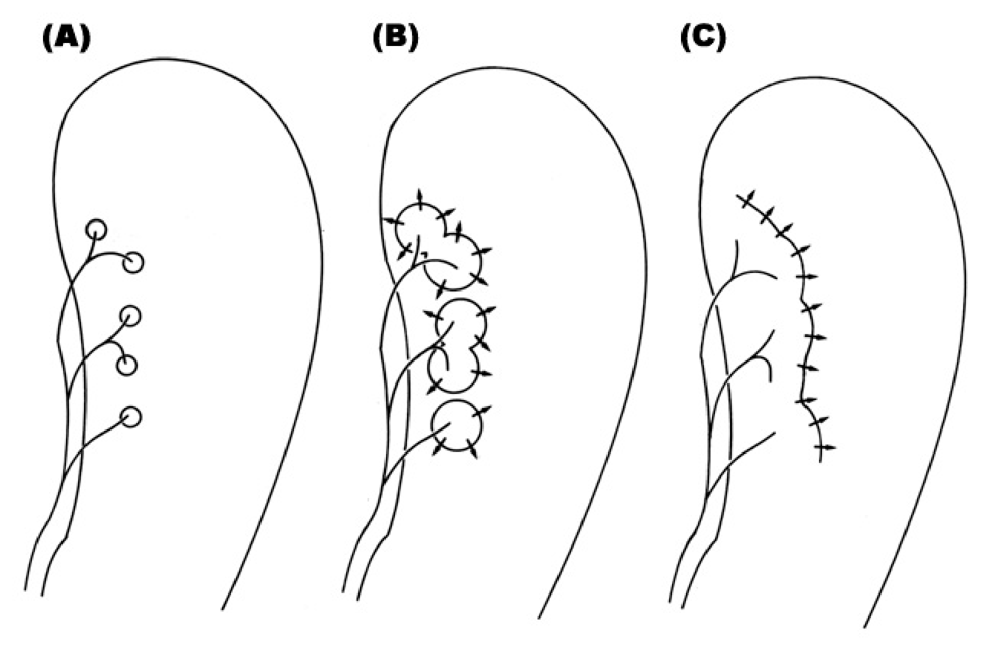




Courtesy of Franz Baudenbacher

Are there other strange source distributions?



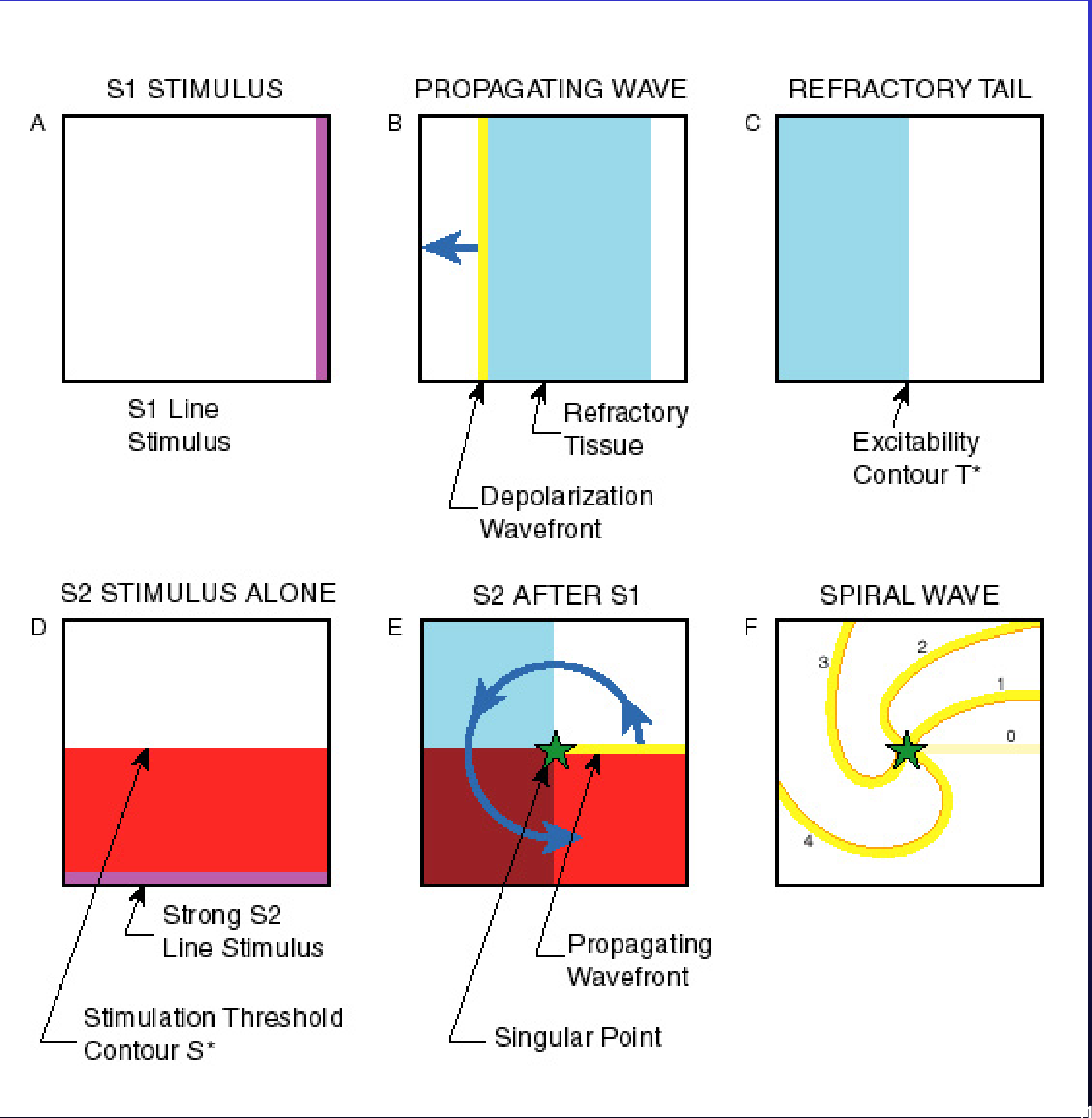


Non-linear dynamics of reentry, fibrillation, and defibrillation

- Reentry -- Self-sustained excitation due to propagating activation wave fronts in the heart that continue to re-excite different regions of tissue rather than terminating after a single excitation
- Anatomical reentry -- activation wave fronts that travel in one direction around an anatomical obstacle
- **Functional reentry -- activation circulate around a dynamical phase singularity**

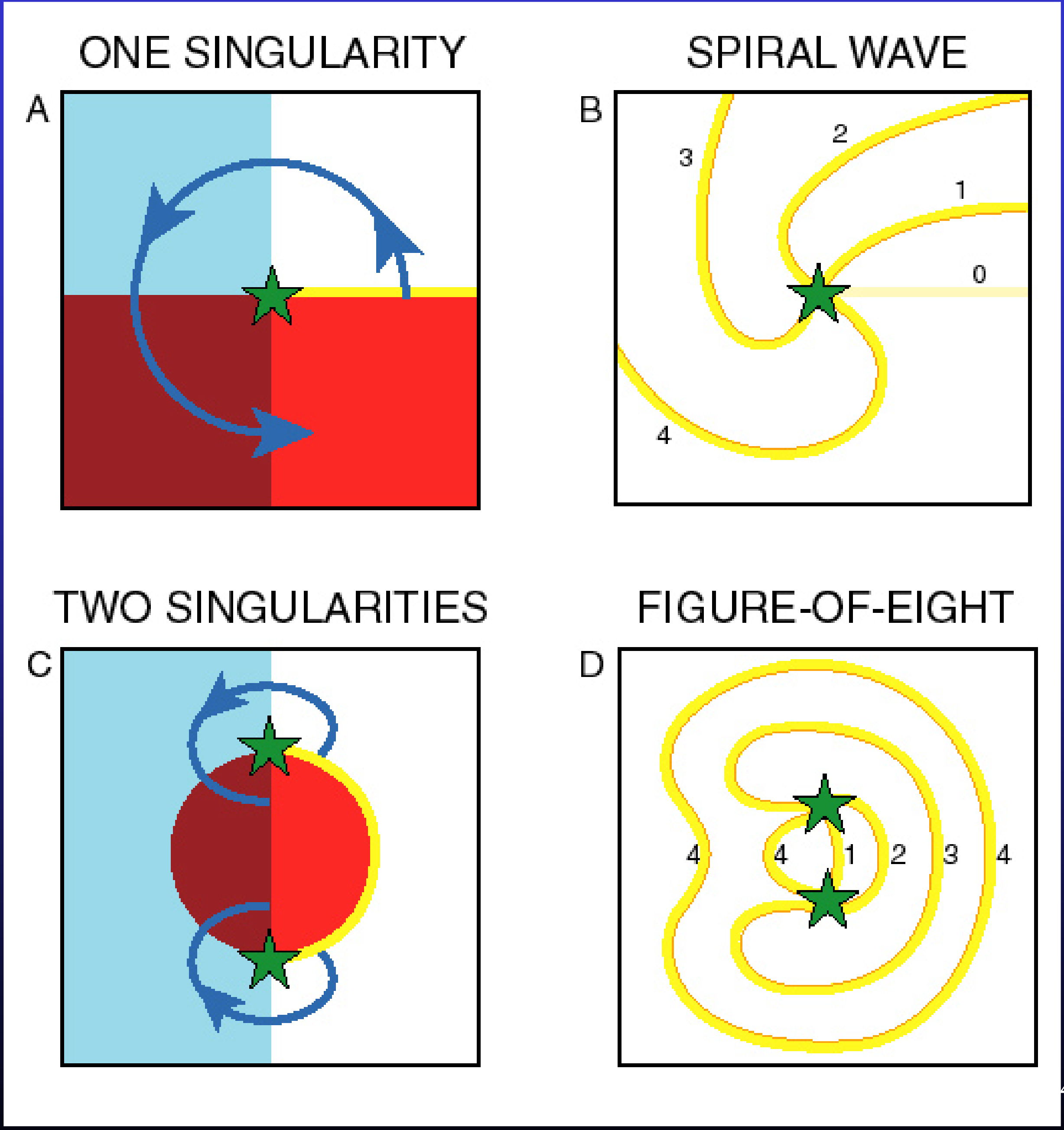
Initiation of Spiral Wave Reentry

S1-S2 crossed-field stimulation



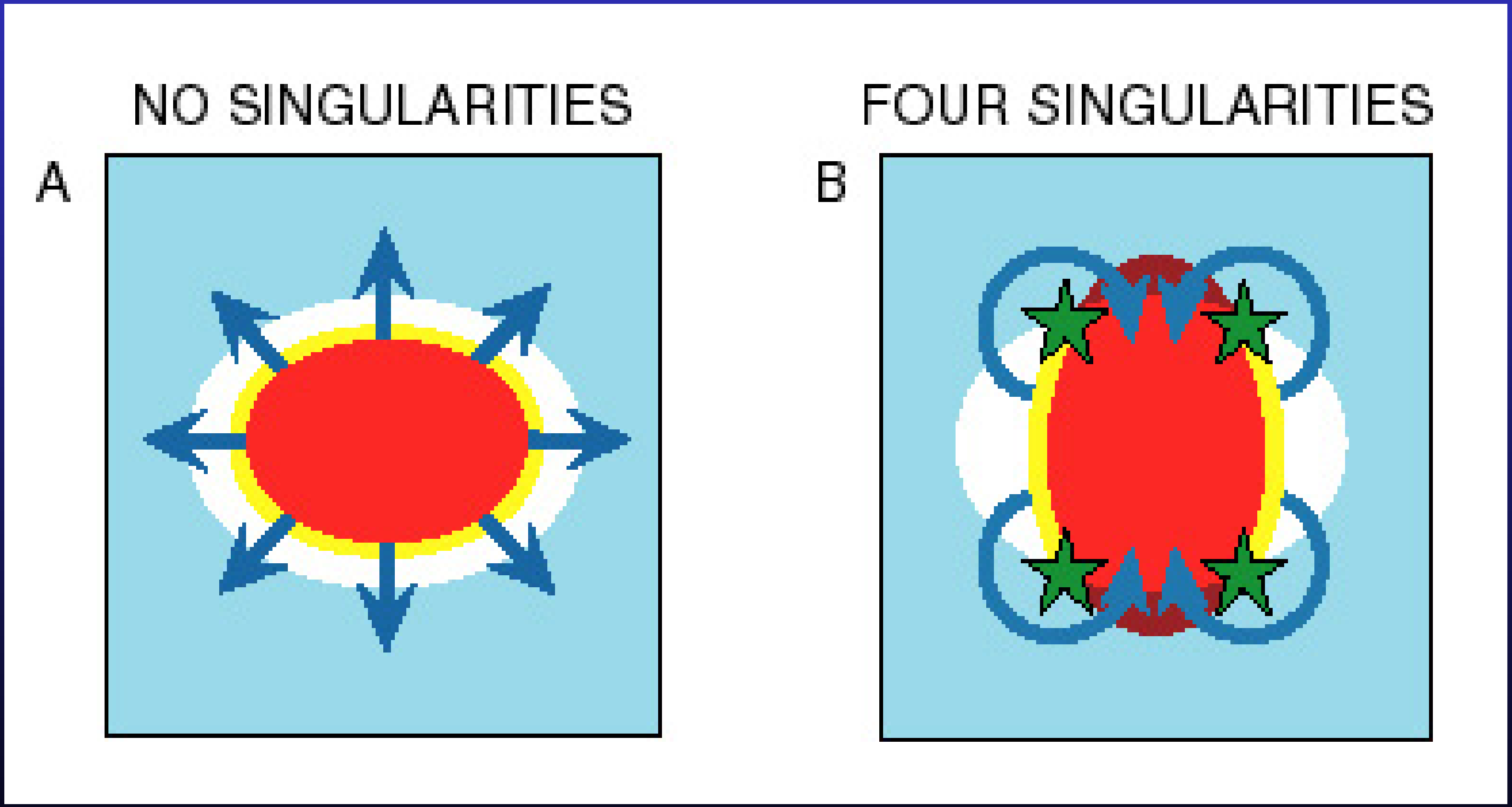
Spiral Wave and Figure-of-Eight Reentry

- Spiral Wave:
  - S1 vert line
  - S2 horiz line
- Figure-of-Eight
  - S1 vert line
  - S2 point

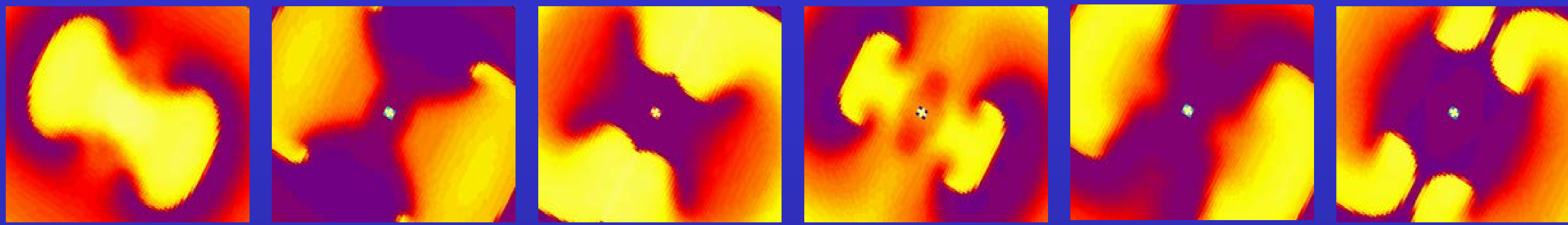


Bidomain Anisotropies and the Critical Point Hypothesis

Equal Anisotropy Ratios *Unequal Anisotropy Ratios*

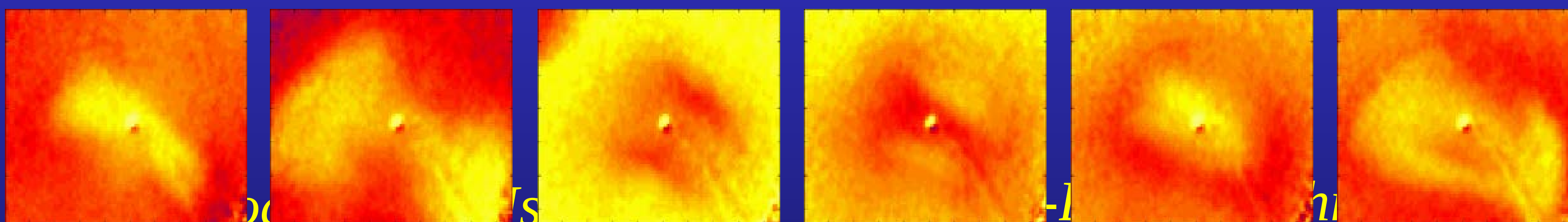


Quatrefoil Reentry



30 37 43 51 58 65

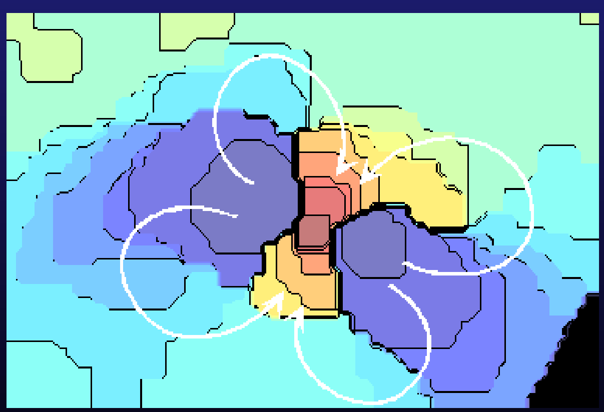
Numerical

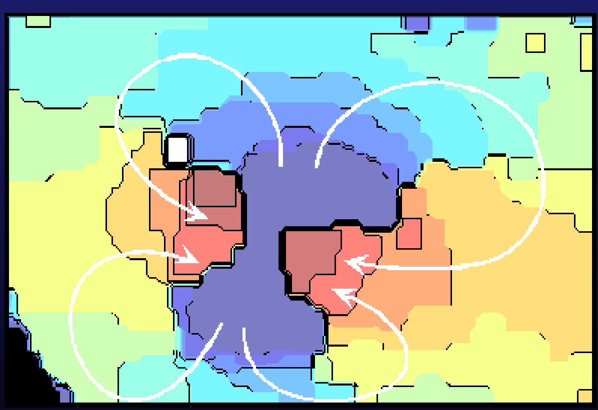


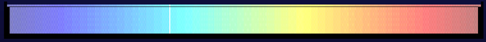
67 74 81 89 95 102

Experimental

Vm_expt.mpg





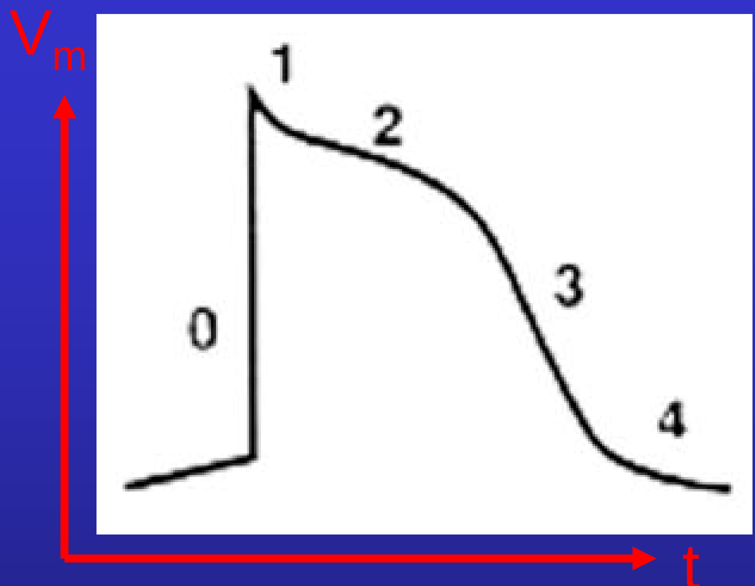


Time →

Courtesy of Marc Lin

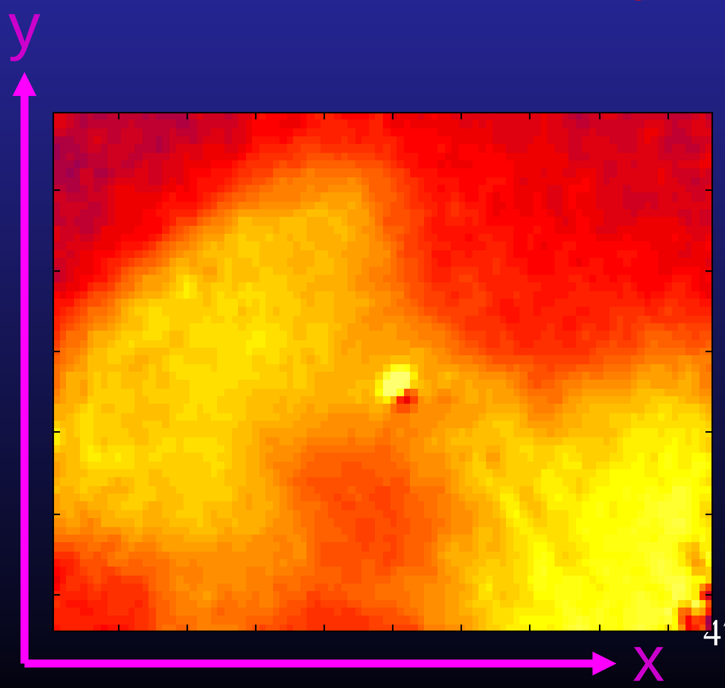
Voltage versus Phase

- The problem: a given voltage can either be rising or falling



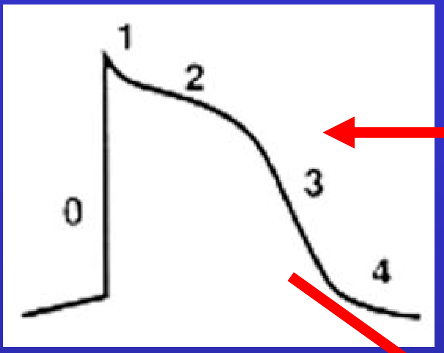
One frame of the transmembrane potential during quatrefoil reentry

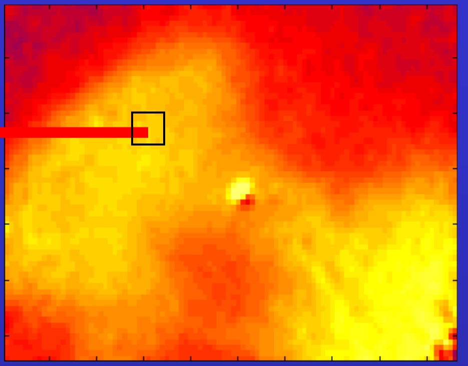
Depolarizing (0) vs *repolarizing* (3) ?



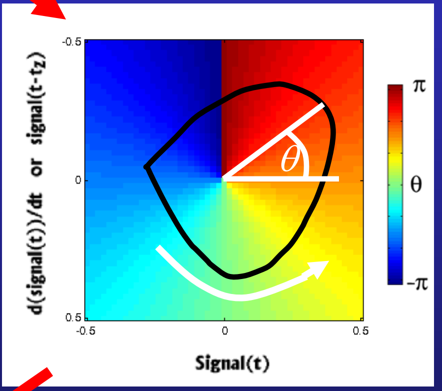
Voltage(t)
or
Phase(t) ?

- The problem: a given voltage can either be rising or falling
- The solution: represent the cardiac action potential in terms of "phase" in the cardiac cycle
  - 0, 1, 2, 3 …
  - 1%, 2%, 3%, 3%, 5%, …
  - 0°, 5°, 10°, 15°, 20°, 25°, …



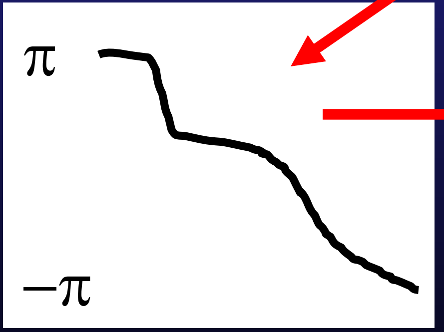


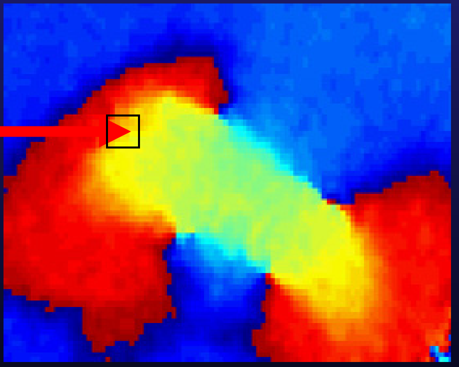
Transmembrane Potential



Pixel-by-Pixel

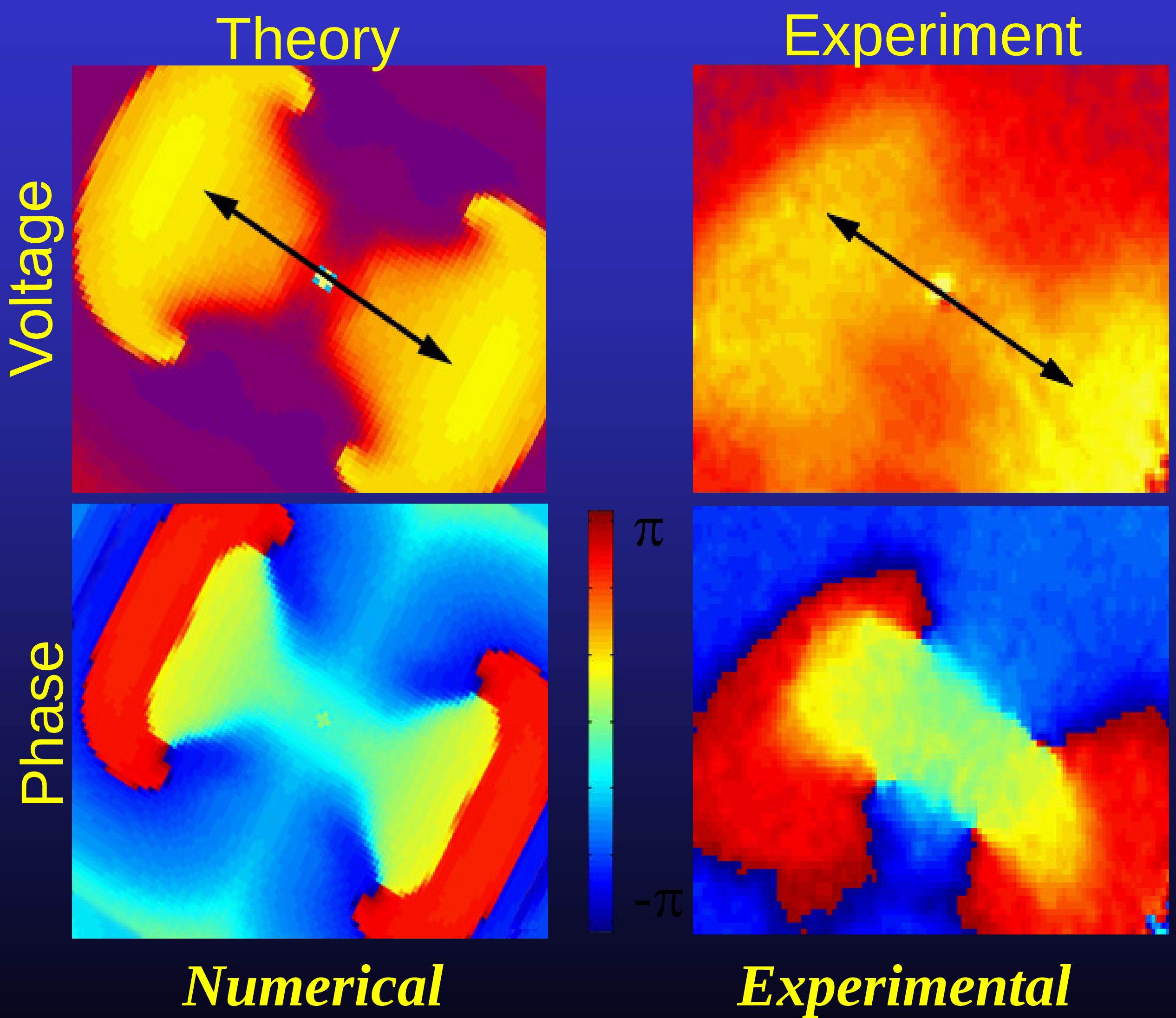
Phase

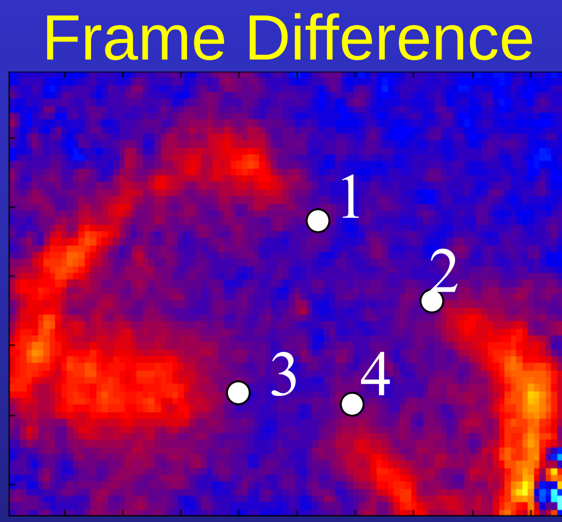




Method by R.A. Gray, A.M. Pertsov, and J. Jalife, Nature **392:** 75 (1998).

From Voltage to Phase Space





Note four singularities of indeterminate phase – points surrounded by all colors

Courtesy of Mark Bray and Marc Lin

Phase Singularities

- How best do we find them?
- What do they mean?
- How do they behave?

Topological Charge

- The phase singularity is a defect in the topology of activation patterns within the excitable media
- The topological charge may be defined as

$$n_t \equiv \frac{1}{2\pi} \oint_C \nabla\phi \cdot \vec{d\ell}$$

where ϕ is the local phase and the line integral is taken on a closed curve

Calculation of topological charge

- We define the spatial gradient of the phase ($\nabla \phi$) as the wave vector *k*
- *Curl k* is equivalent to the topological charge, which is zero everywhere except at singularities

$$(\nabla \times \vec{k}) \cdot \hat{z} = \lim_{a \to 0} \frac{1}{\pi a^2} \oint_C \vec{k} \cdot d\vec{\ell}$$

Calculation of topological charge

- We can use image processing operations that evaluate *curl k* to track phase singularities in reentry movies
- *Curl k* may be approximated with the following:

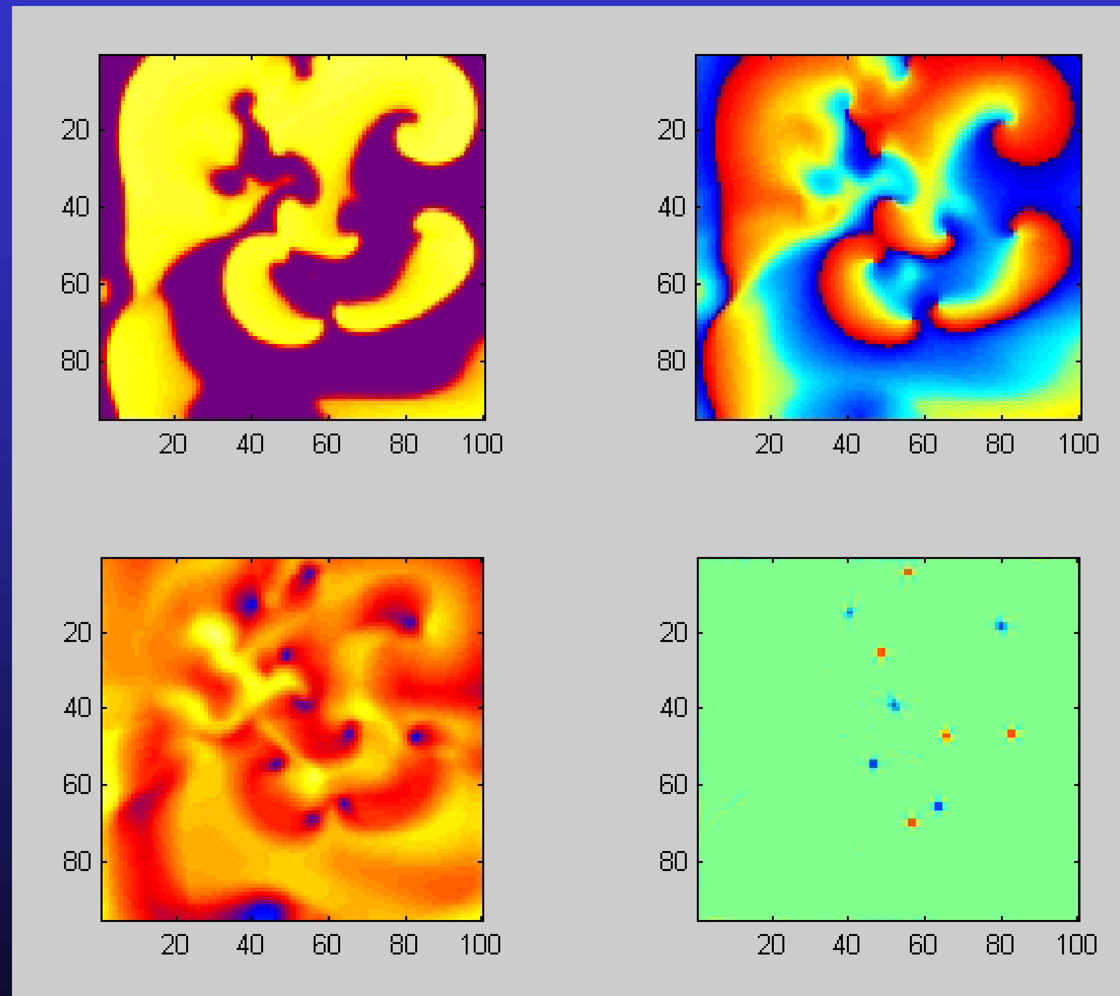
$$\left(\nabla \times \vec{k}\right) \cdot \hat{z} \propto \nabla_x \otimes k_y + \nabla_y \otimes k_x$$

$$\nabla_x = \begin{bmatrix} -1/2 & 0 & +1/2 \\ -1 & 0 & +1 \\ -1/2 & 0 & +1/2 \end{bmatrix} \qquad \nabla_y = \begin{bmatrix} +1/2 & +1 & +1/2 \\ 0 & 0 & 0 \\ -1/2 & -1 & -1/2 \end{bmatrix}$$

Simulated Fibrillation

V_m Phase

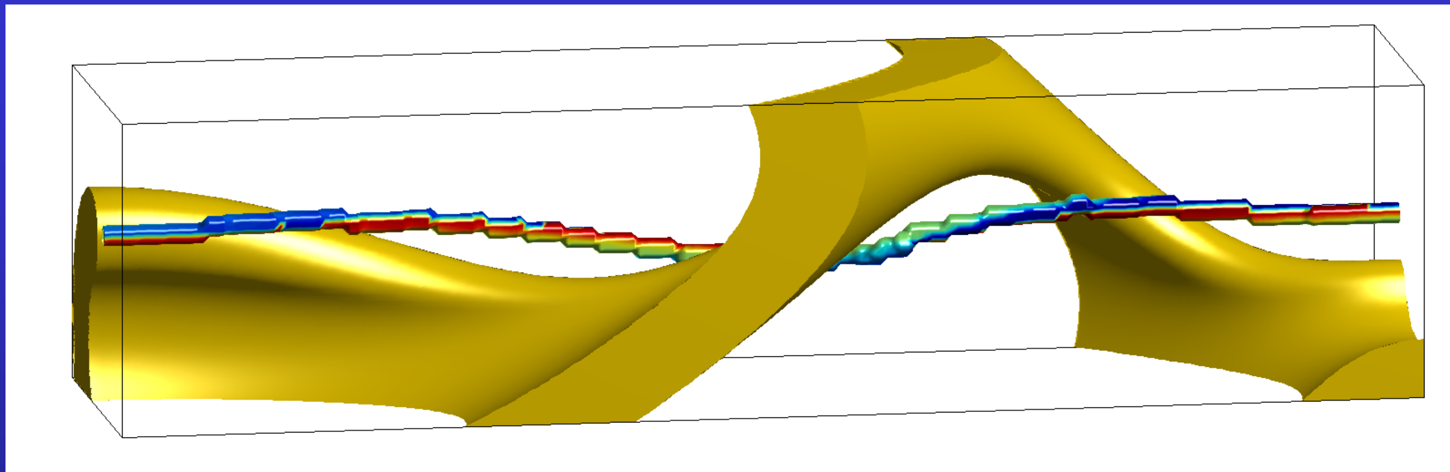
Variance Curl

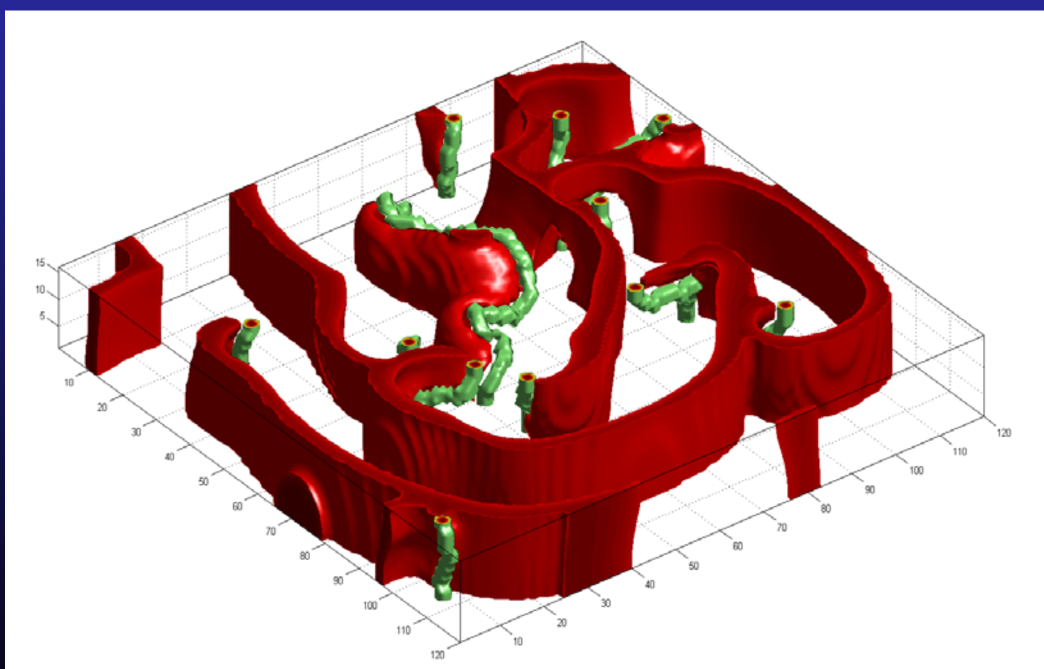


Vm_Var_Phase_Curl.mp4

Courtesy of Mark Bray and Rubin Aliev

3-D Filaments



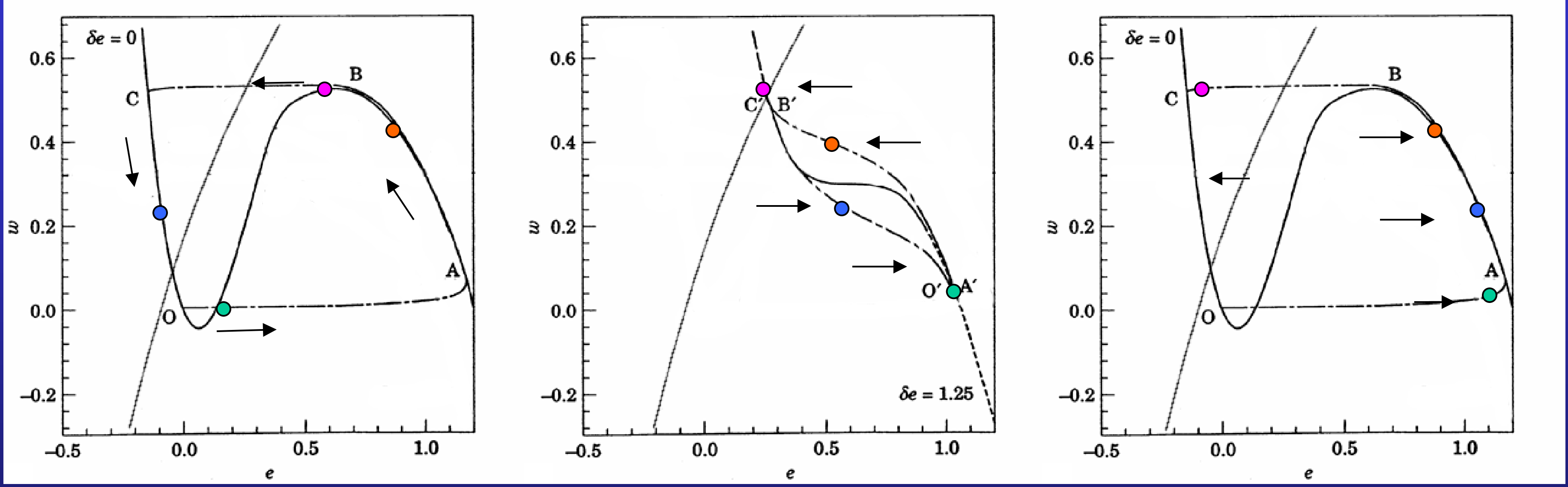


Courtesy of Mark Bray

The convolution operation can be extended to 3 dimensions

scroll_wave_breakup.mov

What Does a Defibrillation Shock Do?

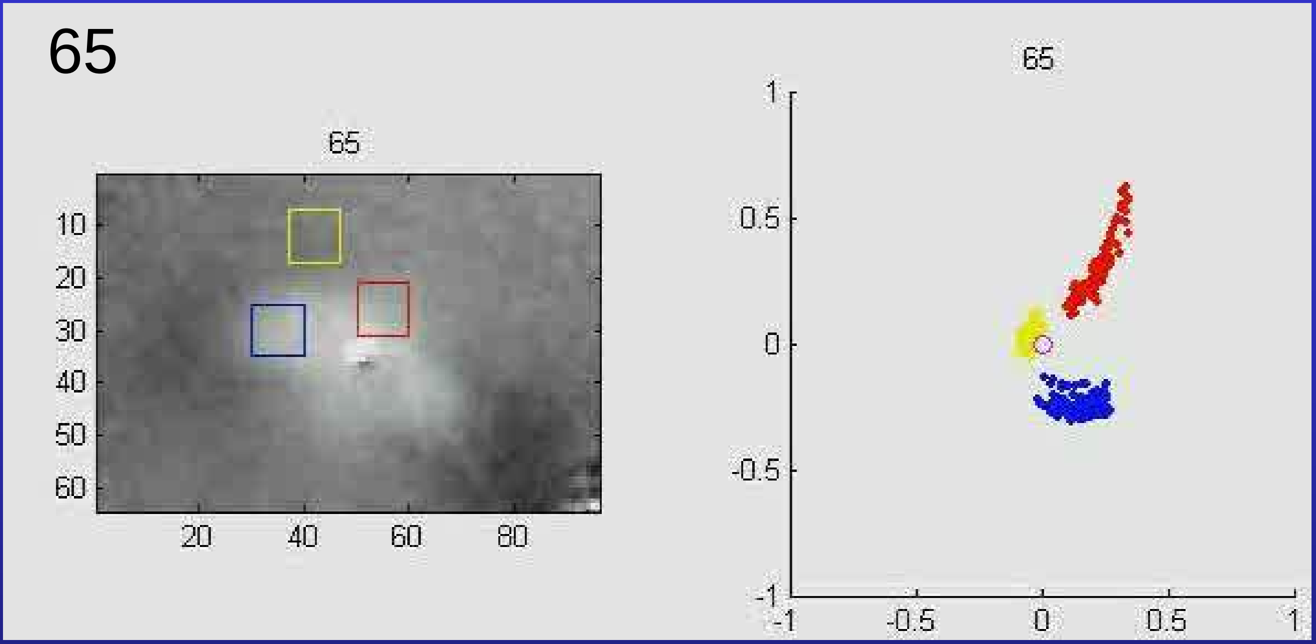


Before S2 During S2 After S2

- Krinsky & Pumir
- Strong electrical stimulus shifts the fast nullcline
- Possible explanation for the mechanism of defibrillation

Cathode Break Stimulation:

Virtual Cathodes versus Virtual Anodes



- Hyperpolarized under anode (phase advanced – CCW reset)
- No change near zero-potential line
- Depolarized under cathode (phase retarded -- CW reset)

phase_reset_color_v3.mpg

Courtesy of Mark Bray

The Future

- Shock resetting
  - Theory – bidomain to the phase plane
  - Experiment – S1 S2 S3 …
  - Correlation of spatial and phase planes
- Whole-heart phase analysis
- ….
- Cellular metabolic networks

Acknowledgements

- Rubin Aliev – Cardiac modeling and non-linear dynamics
- Franz Baudenbacher – SQUID microscope
- Mark Bray – Singularity dynamics and phase resetting
- Rick Gray – Phase encoding & singularity detection
- Jenny Holzer – SQUID microscope
- Brad Roth – Prediction of four modes of make & break stimulation; quatrefoil reentry

Department of Physics and Astronomy
http://www.vanderbilt.edu/lsp
http://www.physics.vanderbilt.edu

Department of Biomedical Engineering
http://www.bme.vanderbilt.edu/

Department of Molecular Physiology and Biophysics
http://medschool.mc.vanderbilt.edu/mpb/

Vanderbilt Institute for Integrative Biosystems Research and Education (VIIBRE)
http://www.vanderbilt.edu/viibre (coming soon)