Experimental Studies of Wave Propagation during Tachyarrhythmias

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CRML "Heart of Dixie"

Electrical Mapping

- Simultaneous recording from "many" channels
- Requires banks of filters, amplifiers, and A to D converters and a recording system with sufficient bandwidth to keep up with the data stream.
- Mapping systems at UAB
  - 528 channels.
  - 14 bit resolution
  - Up to 2000 Hz sampling rate (more if fewer channels are used)
  - Two or three systems can be slaved to a common clock for up to 1584 simultaneous channels

Extracellular Signals

- Practical to record in large numbers
- Ag/AgCl electrodes are usually used (to reduce electrode polarization — this is especially important when shocks are recorded)
- Unipolar
  - potential of recording site relative to distant reference
  - Contains information on "distant" activity
- Bipolar
  - Potential between adjacent electrodes
  - Rejects distant activity
  - Sensitive to wavefront orientation relative to electrode axis.

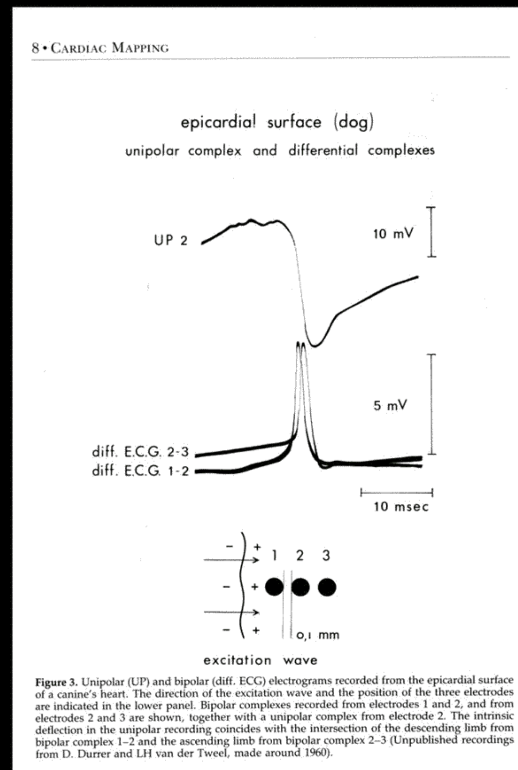


Figure 3. Unipolar (UP) and bipolar (diff. ECG) electrograms recorded from the epicardial surface of a canine's heart. The direction of the excitation wave and the position of the three electrodes are indicated in the lower panel. Bipolar complexes recorded from electrodes 1 and 2, and from electrodes 2 and 3 are shown, together with a unipolar complex from electrode 2. The intrinsic deflection in the unipolar recording coincides with the intersection of the descending limb from bipolar complex 1–2 and the ascending limb from bipolar complex 2–3 (Unpublished recordings from D. Durrer and LH van der Tweel, made around 1960).

Electrode Plaques

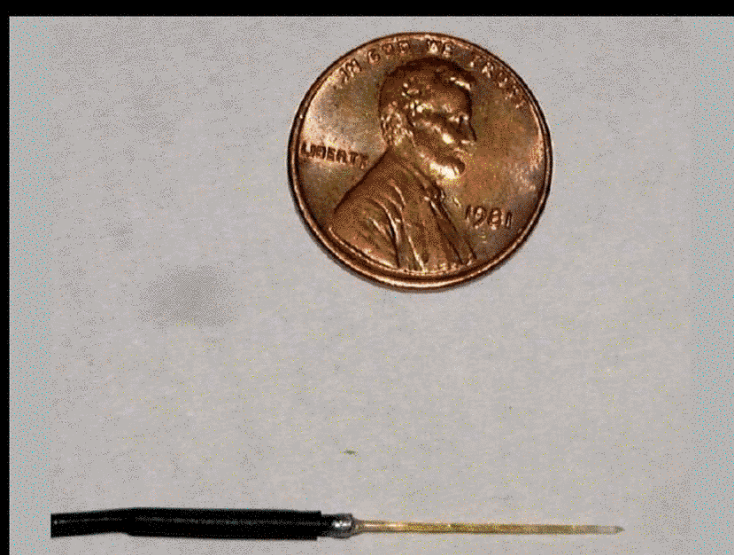
- Uniform, high density electrode spacing over a limited region
- 1-2 mm spatial resolution is appropriate for VF (Bayly et al. 1993)
- Sometimes fabricated on a flexible substrate to conform to the shape of the heart

Electrode Socks

- Slipped over the heart
- Coarse mapping of most of most of the epicardium (~4 mm spacing)
- Irregular electrode spacing

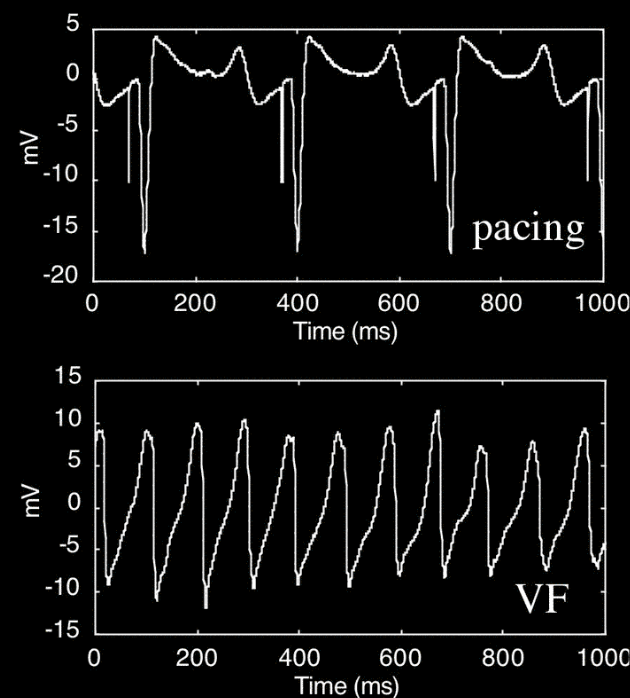
Plunge Needles

- Intramural recordings
- Traditionally fabricated from steel hypodermic needles
- Dimensions (and tissue damage) can be reduced by fabricating needles from reinforced epoxy
- Fabrication using microelectronic techniques is possible, but such needles have not yet been successful in practice.



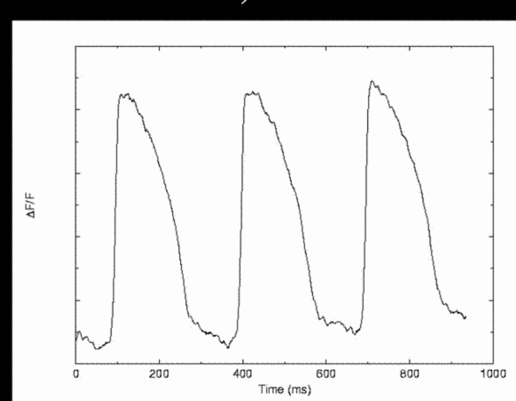
Problems

- Electrical mapping is poorly suited for measuring repolarization during tachyarrhythmias
  - Information on recovery is contained in the T-wave (Activation Recovery Intervals, ARIs)
  - However, T-waves are obscured by the following activation when the activation rate is high
- Electrical recordings are "blinded" following shocks (~25 ms with our systems)



Optical Mapping

- Cardiac tissue is stained with a voltage-sensitive dye (e.g., di-4-ANEPPS, RH-237).
- When stained tissue is illuminated by light within the absorption band of the dye (~480 nm for di-4-ANEPPS) it emits light with a different wavelength (>610 nm for di-4-ANEPPS).
- The resulting signal consists of background fluorescence upon which is superimposed a signal proportional to the transmembrane potential. This action potential signal is roughly 5-15% of the background fluorescence.



Optical Mapping Systems

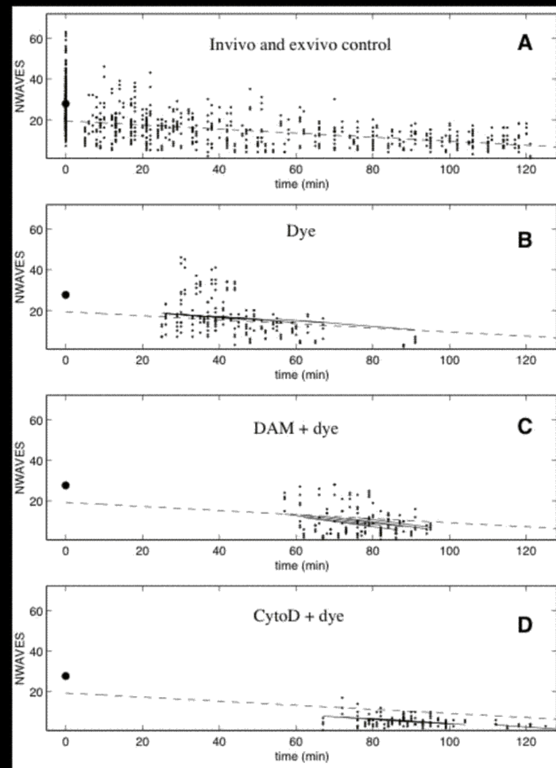
- Light Source
  - Tungsten halogen lamps
  - Xe or Hg Arc lamps
  - Laser
  - Light Emitting Diodes (Luxeon Star)
- Optics/filters for light delivery and collection
- Photodetector
  - Photodiode Array (16x16)
  - Single photodiode (for laser scanning systems)
  - Video Camera—more pixels, more noise
    - CCD
    - CMOS
- Data acquisition hardware and software

Advantages of Optical Mapping

- Allows action potentials to be recorded from hundreds to thousands of sites simultaneously
  - -> Huge benefit for tachyarrhythmia research in which data on recovery is crucial
- Recordings are insensitive to electrical stimuli, allowing the effects of shocks on transmembrane potential to be directly measured
  - -> Huge benefit for defibrillation research

Disadvantages of Optical Mapping

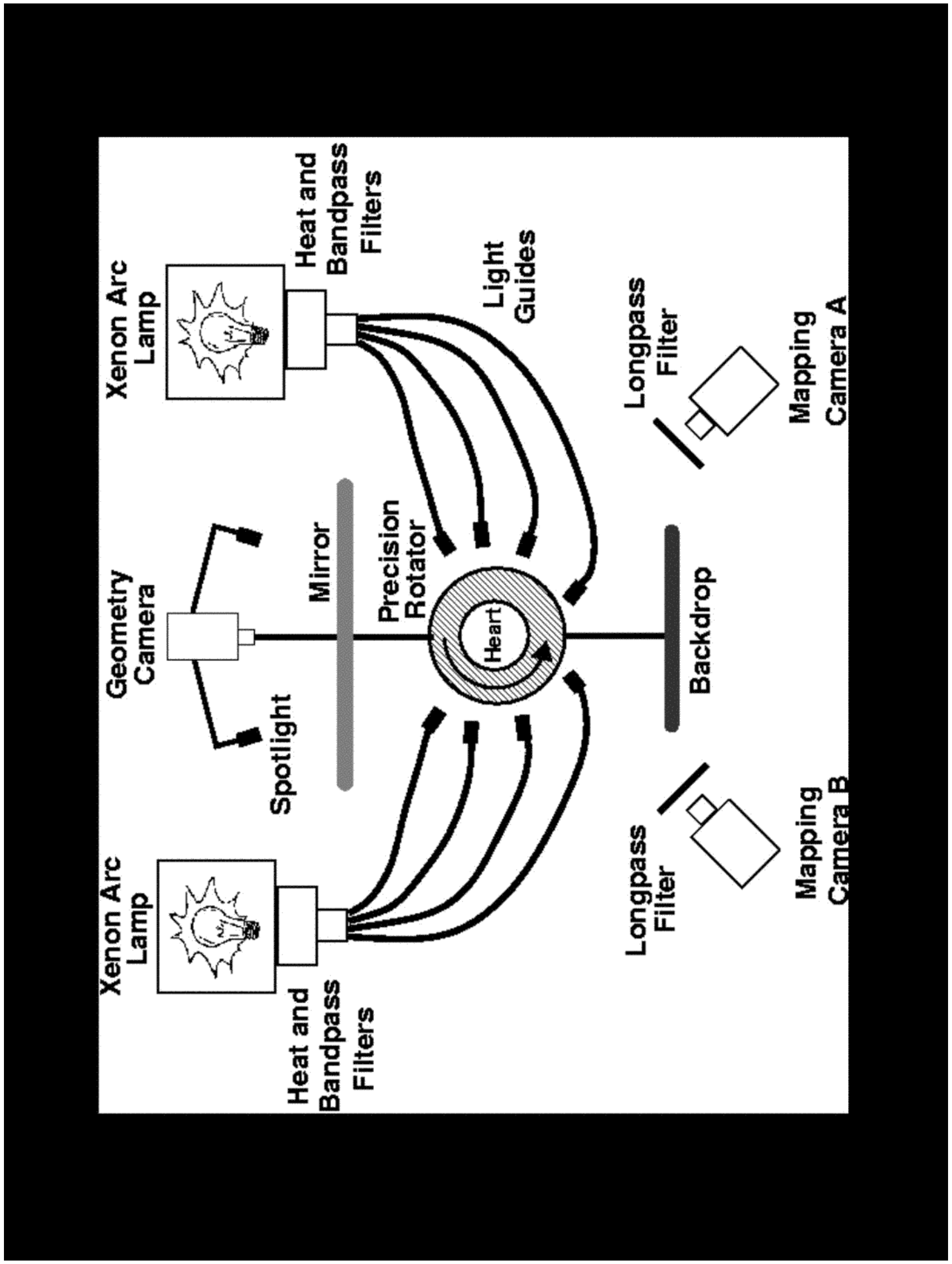
- Usually requires isolated tissue preparation (e.g., whole heart, slab, cultured monolayer)
- Because sensors are usually not attached to the preparation, motion must be arrested pharmacologically (e.g., DAM, cytoD) or mechanically
- Technology for intramural recording immature (transillumination, optrodes)

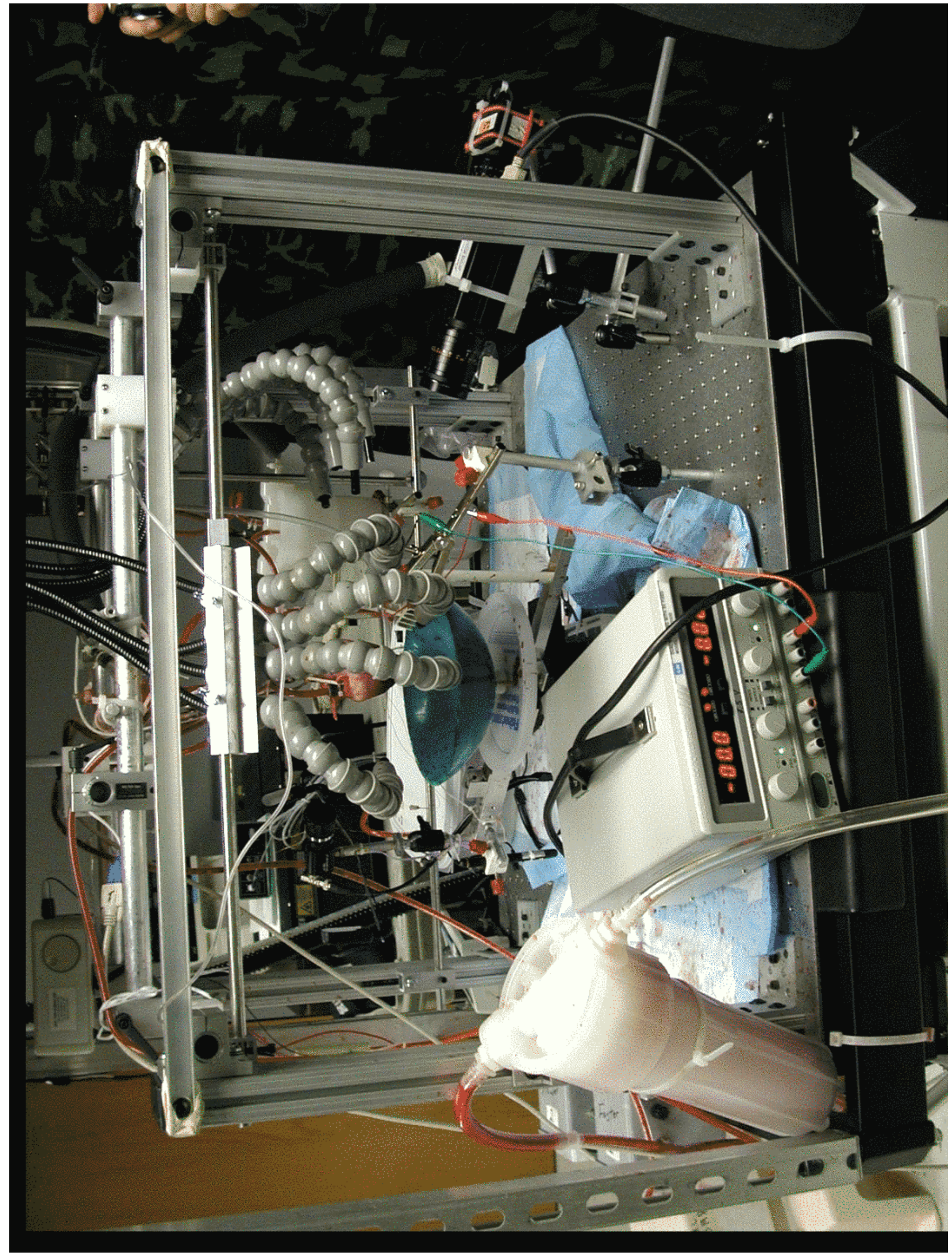


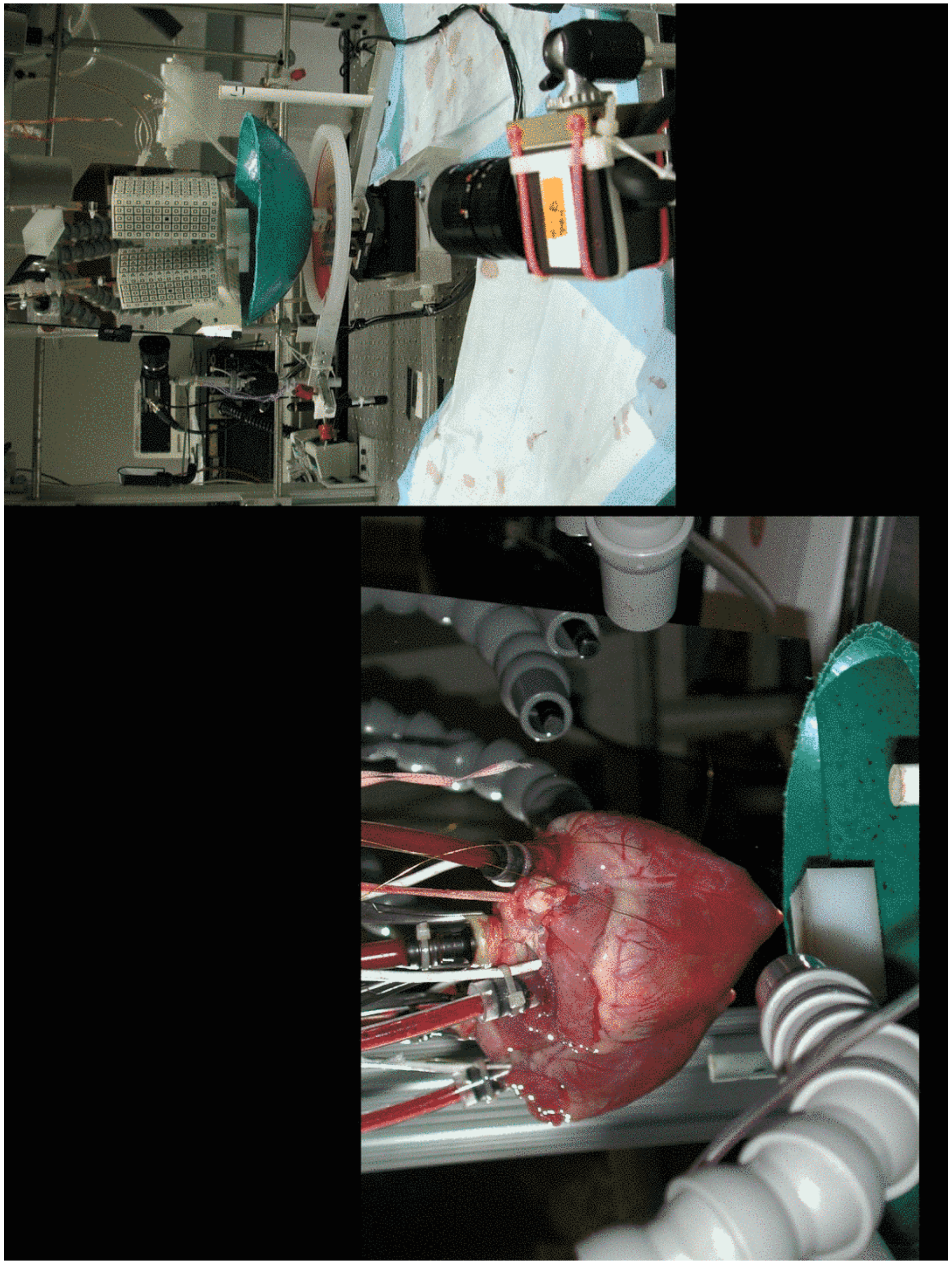
Qin, et al. , 2003

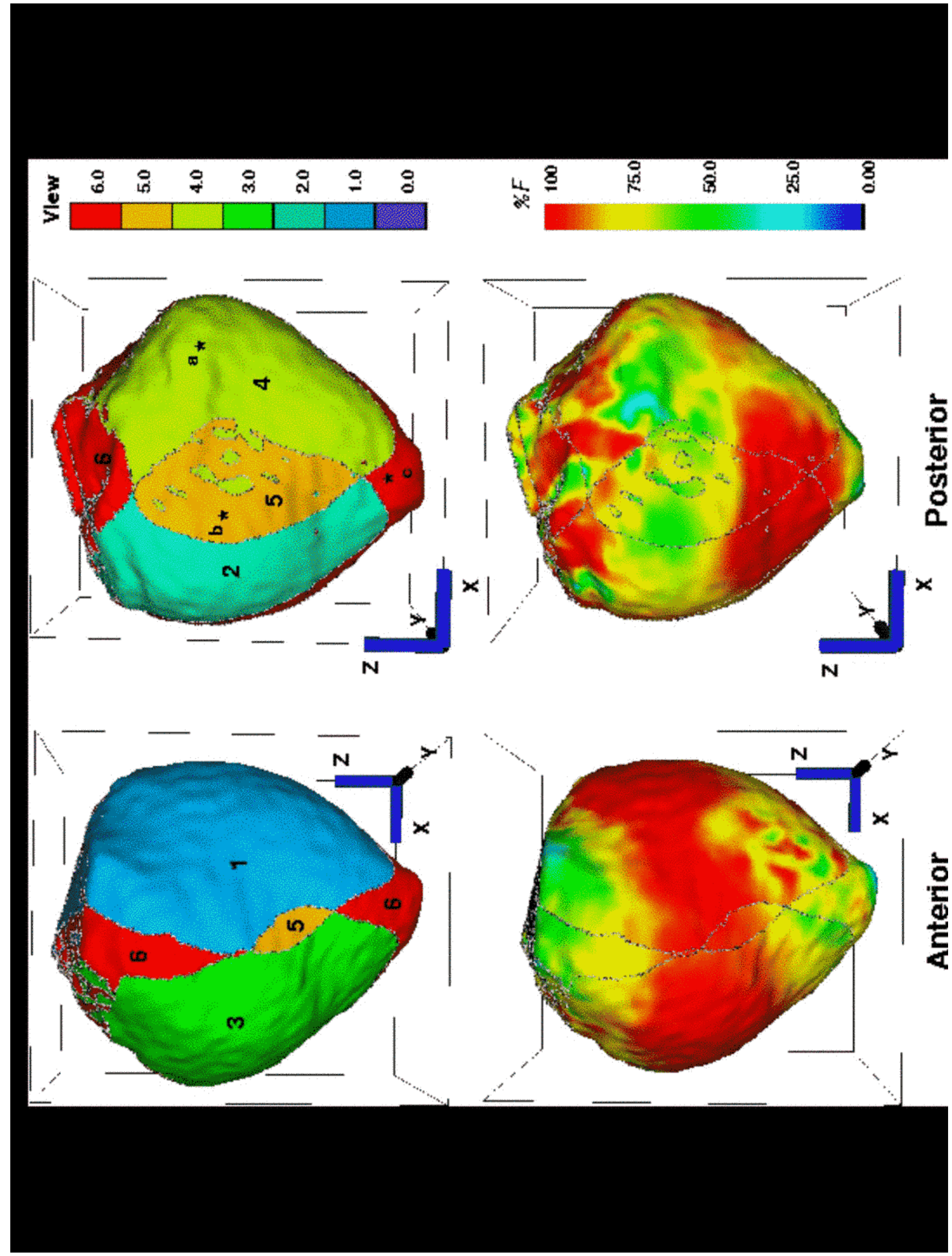
Panoramic Optical Mapping

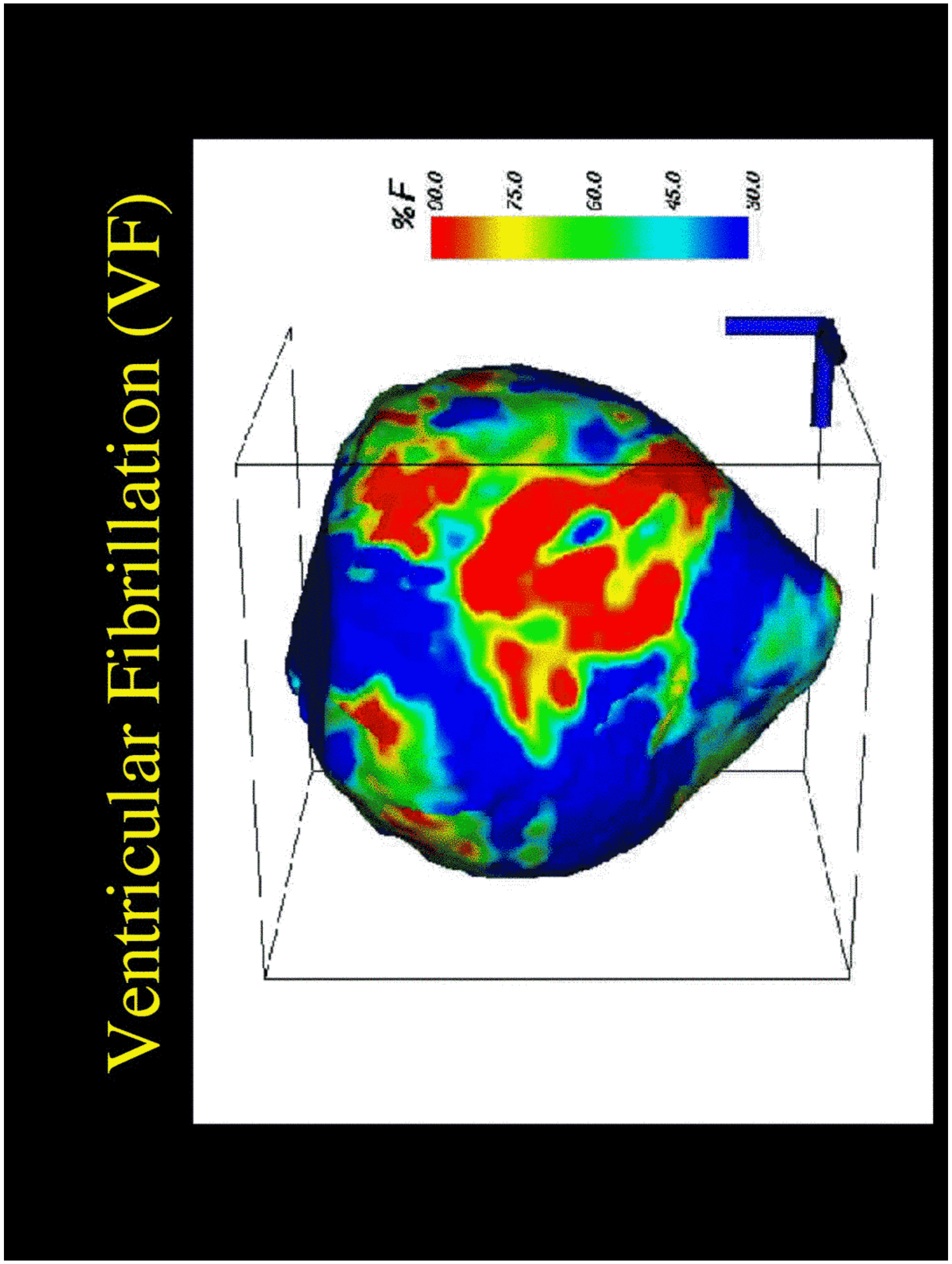
- Designed to map electrical activity from the entire epicardium
- Originally developed by Bray et al. for rabbit hearts
- Our system is engineered for large hearts (e.g., pig, dog)
  - Isolate heart
  - Reconstruct epicardial geometry
  - Record fluorescence from multiple views
  - Texture map fluorescence data onto reconstructed geometry

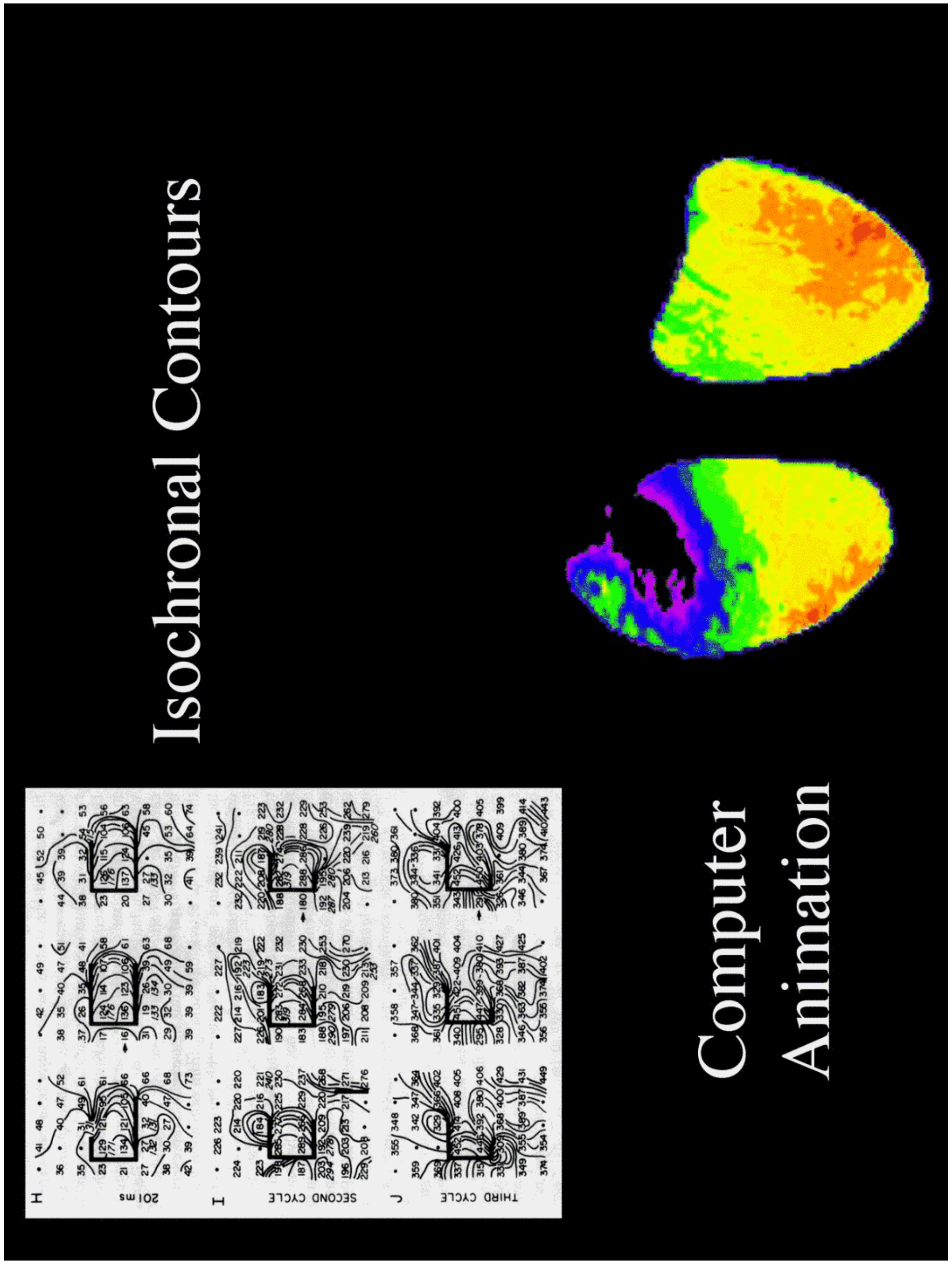

Xenon Arc Lamp
Heat and Bandpass Filters
Light Guides
Longpass Filter
Mapping Camera A
Geometry Camera
Mirror
Precision Rotator
Heart
Backdrop
Spotlight
Xenon Arc Lamp
Heat and Bandpass Filters
Longpass Filter
Mapping Camera B





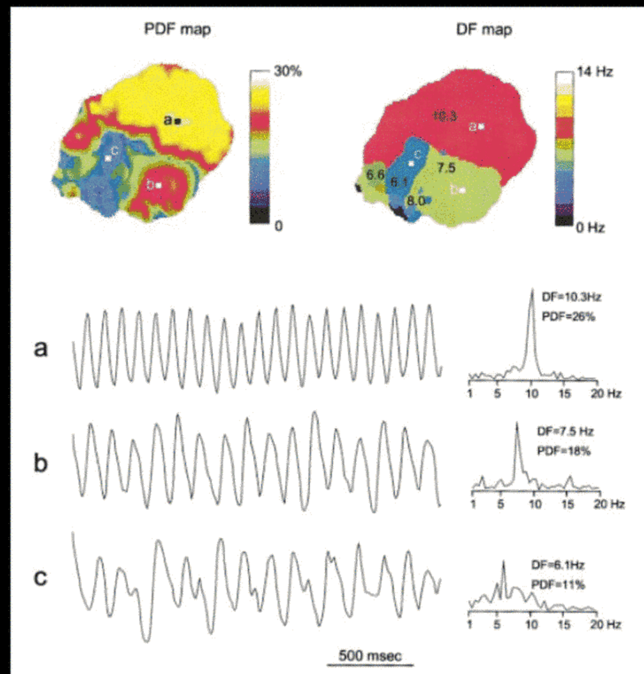

View
6.0
5.0
4.0
3.0
2.0
1.0
0.0
%F
100
75.0
50.0
25.0
0.00
Posterior
Anterior
X
Y
Z


Ventricular Fibrillation (VF)
%F
90.0
75.0
60.0
45.0
30.0


Isochronal Contours
Computer Animation

Dominant Frequency Maps

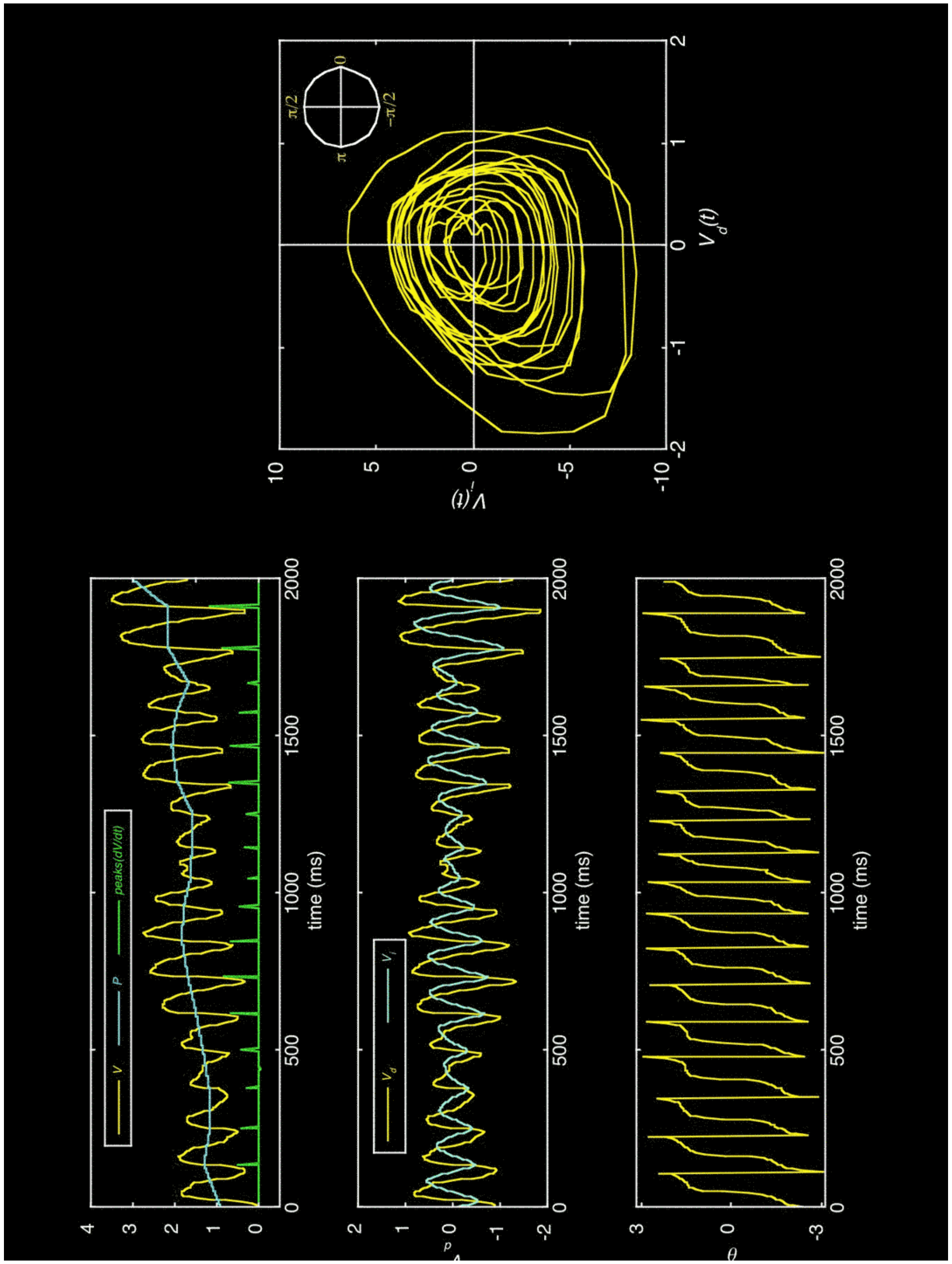
- Estimate the power spectrum of the signal at each site
- Find the frequency with peak power—the dominant frequency
- Plot a spatial map of dominant frequency



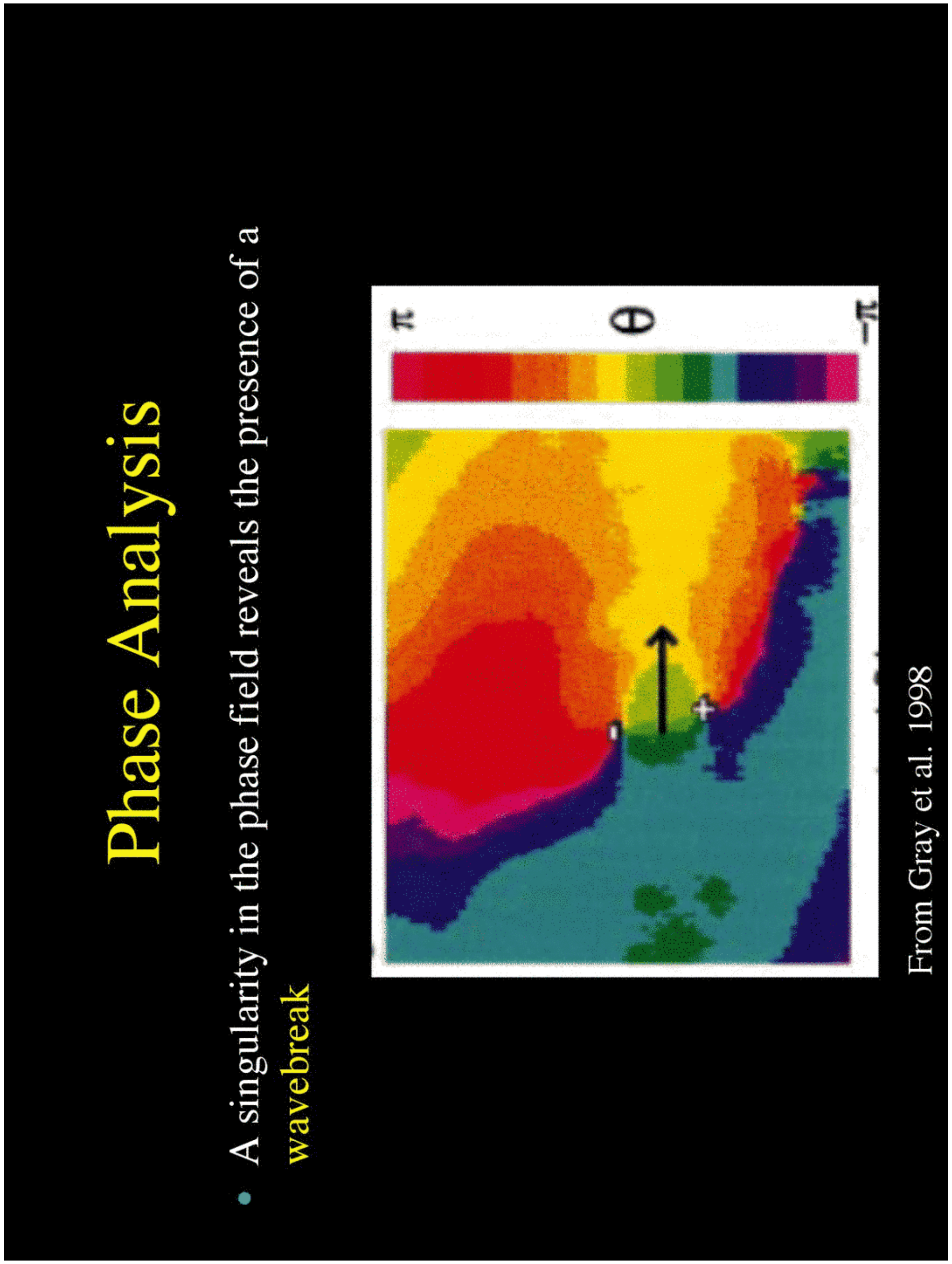
From Zaitsev, et al. 2000

Phase Analysis

- If we assume that the cardiac action potential (AP) is governed by two state variables (not true, but a useful approximation), then the AP can be represented by a closed-loop trajectory through a 2D phase plane.
- If we place the origin of a polar coordinate system at the center of the loop, then each instant of the AP can be tagged with its angular coordinate through the trajectory, i.e., its phase.
- In experimental data, we generally record only one variable, V. Thus, the phase plane trajectory must be reconstructed from a single time series
  - Plot $V(t)$ vs. $V(t+\tau)$
  - Plot $V(t)$ vs. dV/dt
  - Plot $V(t)$ vs. $\int V dt$



V
P
peaks(dV/dt)
time (ms)
time (ms)
time (ms)
V_d(t)
V_i(t)
θ



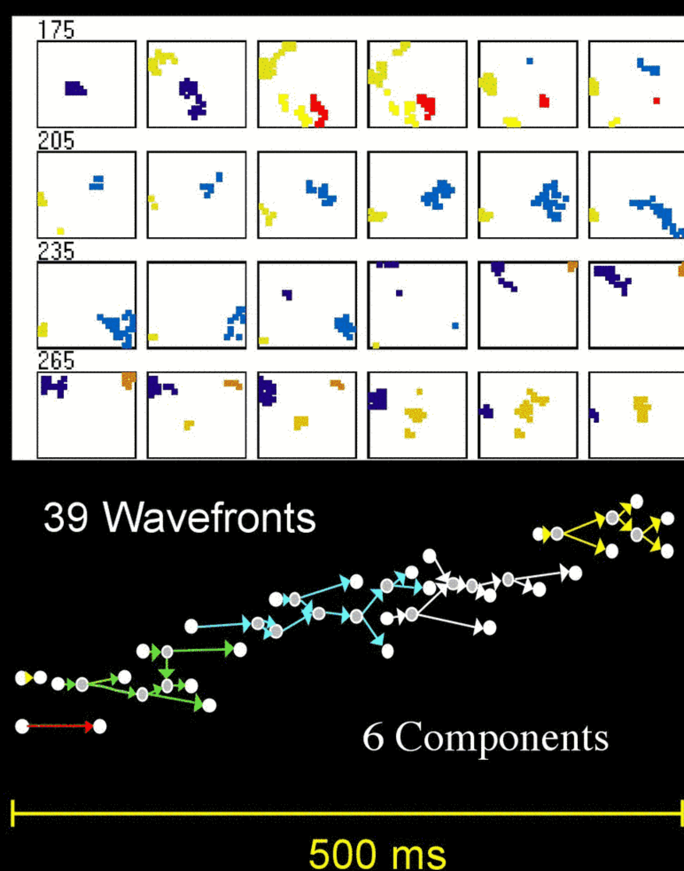
Phase Analysis
A singularity in the phase field reveals the presence of a wavebreak
From Gray et al. 1998

Wavefront Decomposition

- Developed for electrical mapping data
- Compute the first temporal derivative of all signals
- Identify the active samples—those electrode site/times at which dv/dt is more negative than a threshold, typically -0.5 V/sec
- Group active samples that are adjacent in space and time into wavefronts
- Keep track of the relationships between wavefronts using a directed graph data struture

Snapshots of isolated wavefronts (5 ms separation)

A wave graph for a 0.5 sec recording of VF

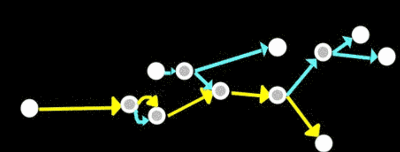


Wavefront Analysis

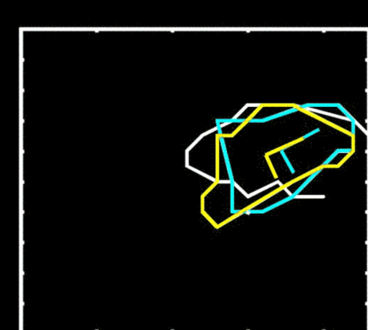
- With this decomposition of the overall VF pattern, VF can be quantified…
  - in terms of graph properties: number of wavefronts, components, fragmentations, collisions, etc.
  - in terms of wavefront properties: size, velocity, origin, fate, duration, etc.
- Multiplicity/Repeatability
  - Estimates of pattern organization
  - Multiplicity counts the number of distinct activation pathways
  - Repeatability counts the number of wavefronts that follow each pathway..

Automatic Reentry Detection

- Identify parent-child chains of wavefronts that activate the same tissue more than once



- Use a network optimization algorithm to find the path traced by the wavetip



Wavefront Analysis

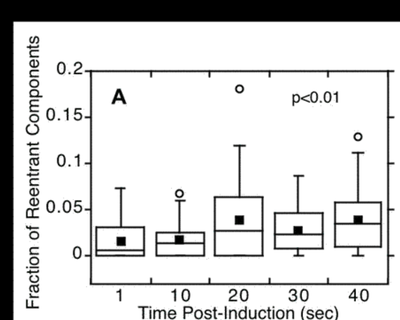
Measure Effects on VF patterns of…

- Time
- Chemical agents
- Position
- Heart failure
- Cardioplegia
- Ablation lesions
- Heart isolation

Moter Rotor Hypothesis

Is VF maintained by a distributed mechanism or driven by a small number of sources (e.g., rotors)?

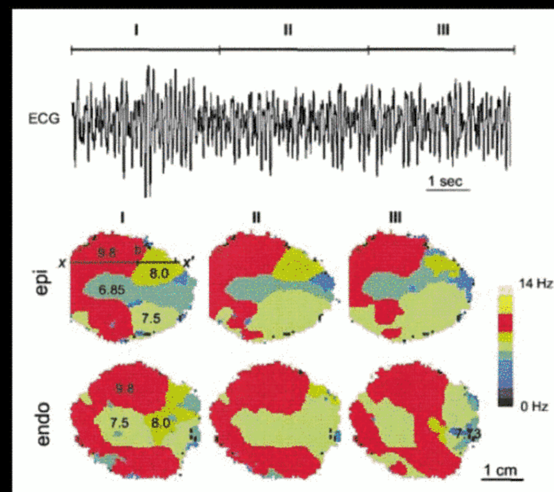
- VF on swine RV (electrically mapped, in situ, open chest prep):
  - Only 2.3% of activation pathways (wavefront graph components) were reentrant
  - Reentry persisted for 1.5 cycles



Rogers, et al. 1999

Mother Rotor Hypothesis

- Zaitsev, et al. 2000
- Isolated, perfused sheep ventricular slabs
- Dominant frequency maps organized into domains of common frequency that were stable with time
- High-frequency domains spawned wavefronts that propagated into neighboring domains with Wenckenbach-like block at neighboring regions
- Sustained reentry was rare
- VF driven by sustained intramural rotor interacting with heterogeneity



Mother Rotor Hypothesis

- Samie, et al. 2001
- Isolated perfused guinea pig hearts
- Fastest domain on LV, due to rotor
- LV-RV difference due to inter-chamber differences in I_{k1}

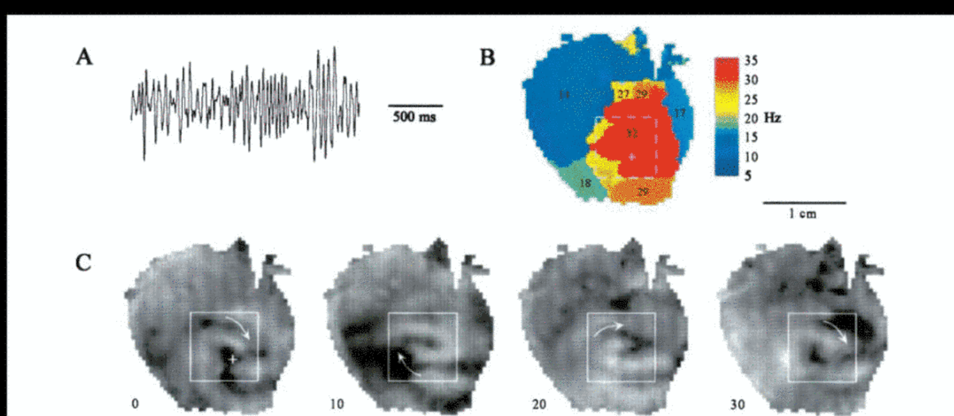
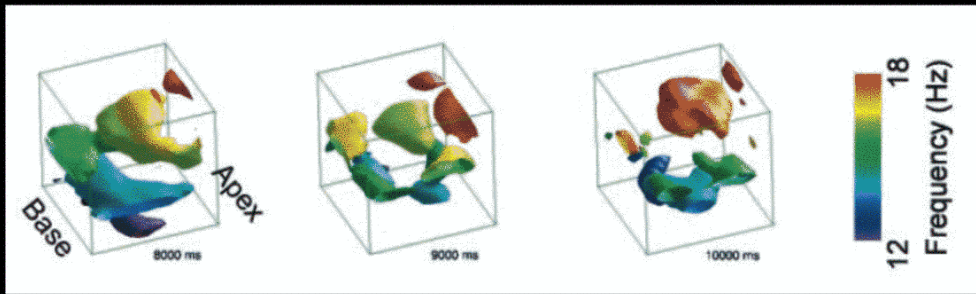
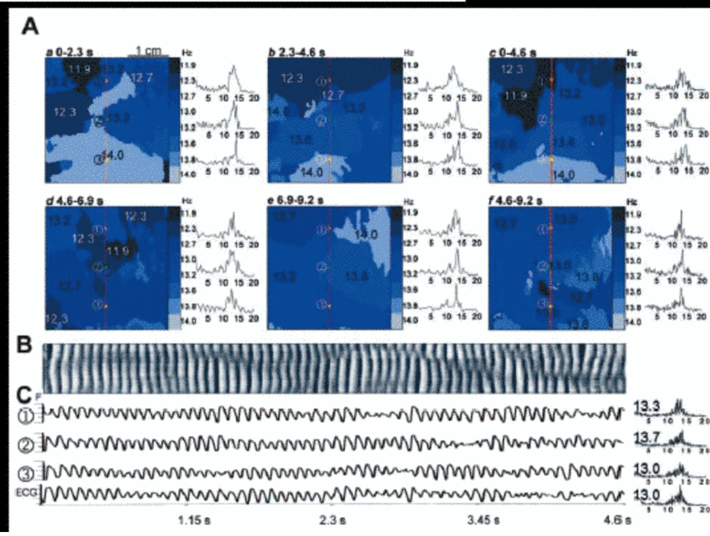


Figure 3. High-frequency rotor. A, ECG trace of VF. B, DF map showing the LV-RV gradient in frequencies. C, Snapshots of a long-lasting rotor on the anterior LV wall at 4 different times during one rotation. Numbers in panel B are in Hz; numbers in panel C are in ms.

Mother Rotor Hypothesis?



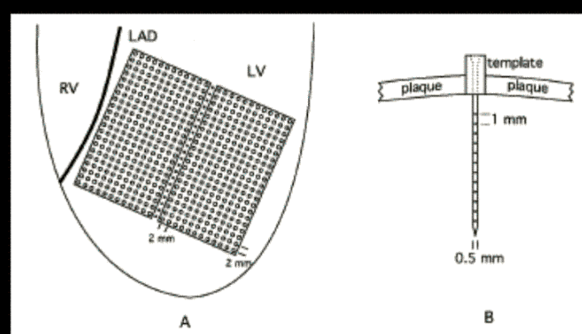
Choi, et al. 2002

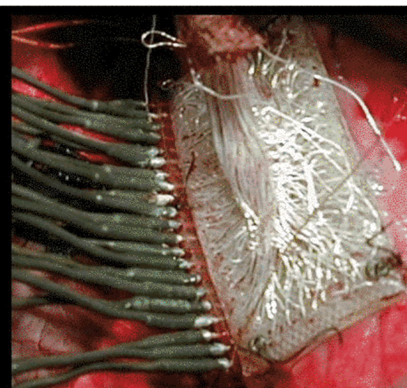


Valderrabano, et al. 2002

Simultaneous Epicardial and Intramural Mapping of VF in the Swine LV

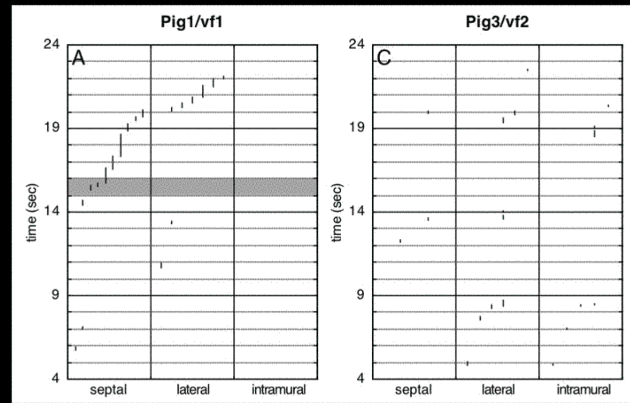
- In situ swine hearts (6 animals)
- Recorded VF patterns from 2 adjacent epicardial electrode arrays and an orthogonal intramural array (88 5 sec epochs)
- Used automated algorithms to identify reentry

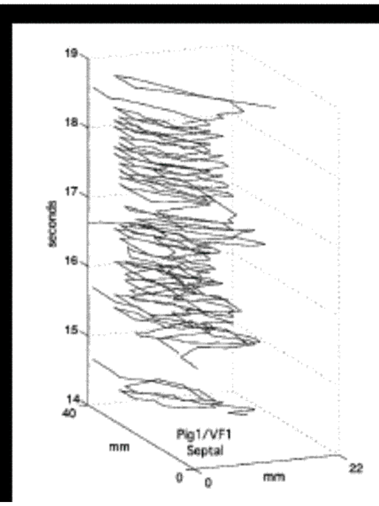




Rogers, et al., 2003

- Intramural reentry was present sporadically (29 total occurrences) and was short lived 127±57 ms
- In 3 of 6 animals sustained epicardial reentry was consistently present, often lasting for several seconds
- But were they mother rotors…?





- When sustained reentry was present on one epicardial array, it was not present on the other
- Thus, according to the mother rotor hypothesis, the rotor-containing array should
  - be faster than the non-rotor-containing array
  - send more wavefronts into the non-rotor-containing array than it receives in return

$$R_{SL}=\sum_{S=1}^{N}R_S-\sum_{L=1}^{M}R_L$$

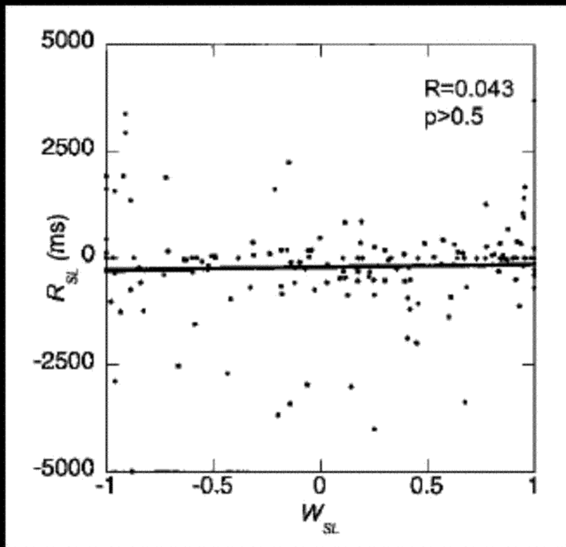
Quantifies relative duration of reentry on the epicardial arrays. R_{SL}>>0 when sustained reentry is present on septal array, but not lateral array

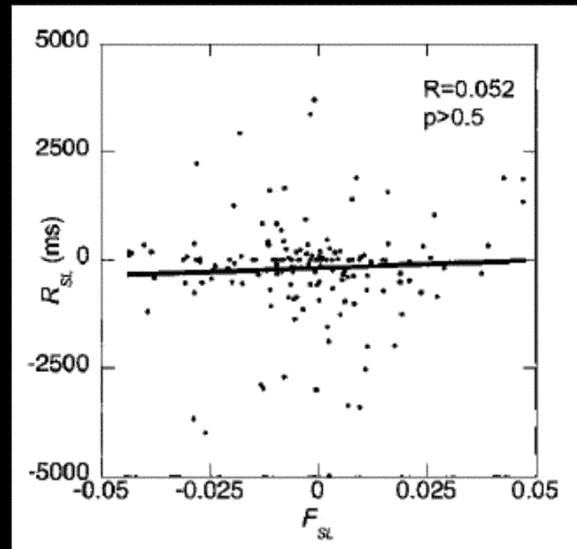
$$W_{SL}=\frac{(In_L-In_S)}{(In_L+In_S)}$$

Quantifies wavefront flow. In_L= sum of areas-swept-out by wavefronts entering lateral array from septal array. W_{SL} =1 when wavefronts from lateral array have no influence on septal array

$$F_{SL}=\frac{F_S-F_L}{F_S+F_L}$$

Quantifies relative activation rates. F_S = global activation rate of septal array





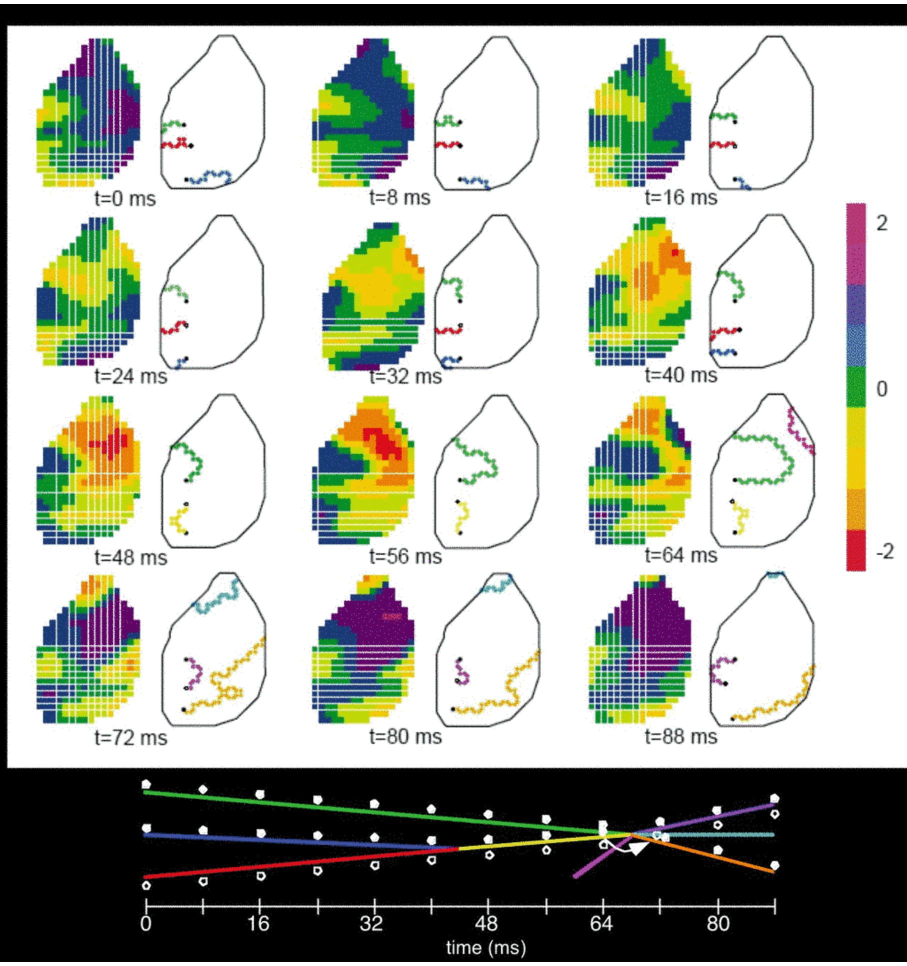
Although rotors were present in this study, they did not appear to sustain VF as outlined by the mother rotor hypothesis

Back to Phase…
Topological Rules (in 2D)

- Wavefronts (which are isolines of phase) must form rings, terminate at boundaries, or terminate at singularities.
- If a wavefront has singularities on either end, they must be of opposite chirality.
- A phase singularity can only be terminated by colliding with a singularity of opposite chirality or with a boundary.
- In the absence of boundary effects, phase singularities are only created in pairs of opposite chirality.

Combined Wavefront/Phase Analysis of VF

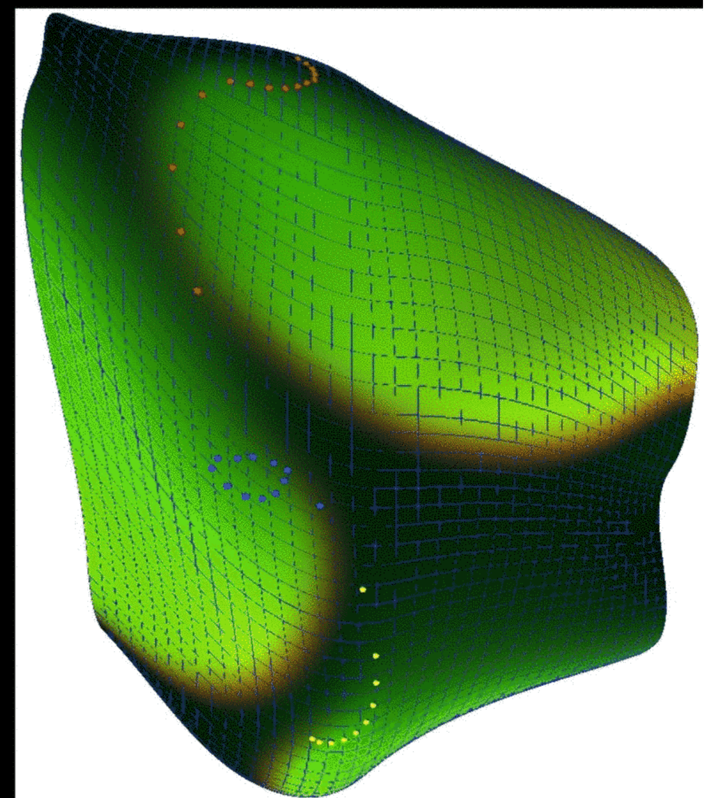
- Extension of wavefront analysis to optical data -- takes advantage of recovery information
- Identify phase singularities in each frame of the phase map.
- Trace wavefronts in each frame in accordance with topological rules.
- Associate singularities with the wavefronts they are attached to.
- Track wavefronts from frame-to-frame, keeping track of wavefront collisions and fragmentations.
- Identify paired births and deaths of phase singularities.



Propagation Block Detection

- Propagation block is an important hallmark of VF
- It is characterized by the fragmentation of one wavefront into two, with the concomitant birth of two singularities of opposite chirality attached to the two daughter wavefronts.
- Such events are contained within our parameterization, and their occurrence can be correlated with the history of activation at the site, tissue properties, etc.

Wavefront Destabilization due to Geometry



Rogers, 2002

- Zhou, et al. 1998
- Isolated guinea pig papillary muscle
- Shocks delivered during plateau (10 ms square wave >5 V/cm)
- Double barrel microelectrode rotated perpendicular to shock field so that no shock artifact was recorded
- 8 kHz temporal sample rate
- 20 μm and 200 μm spatial step