VIRTUAL ELECTRODES

Where are the modelers when you have unexplained phenomena?

Virtual Electrodes Defined

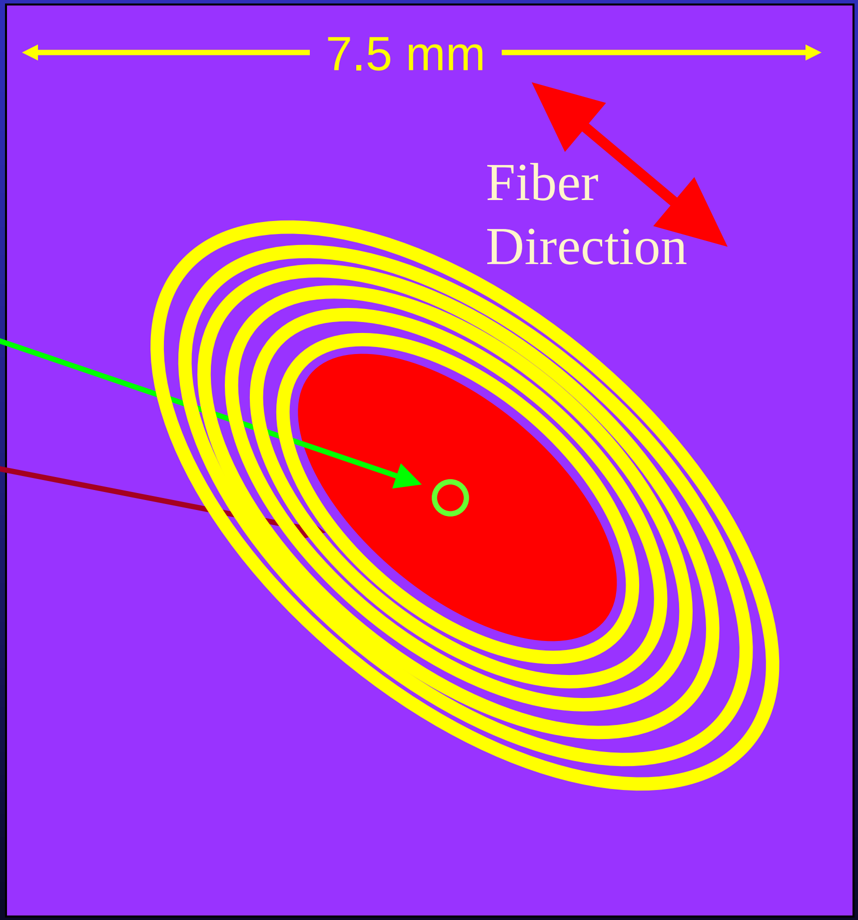
- The regions of cardiac tissue for which the membrane potential is electrotonically altered by the stimulus current
- If propagation is initiated, it will generally occur at the edge of a virtual electrode
- Activation starts at the cathode for make excitation
- Activation starts at the anode for break excitation

- **Where are the virtual cathodes and anodes during defibrillation?**
- **How do they behave at threshold and in ischemia?**

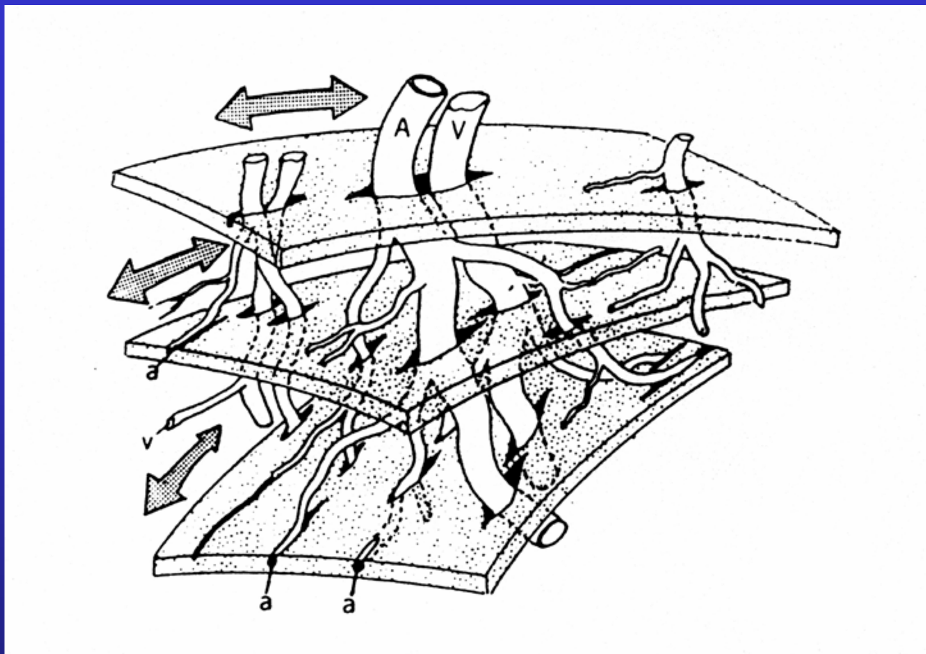
Equal-Anisotropy Model

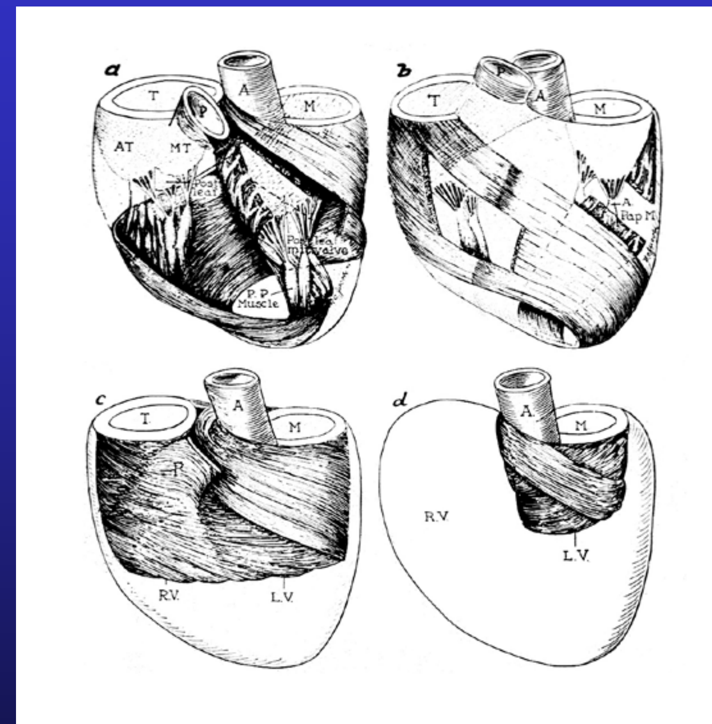
Cardiac tissue while injecting -20 mA at a point electrode

- Point cathodal stimulation
- **Elliptical virtual cathode** depolarizes (red)
- This is NOT what is seen in cardiac tissue!



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

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

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

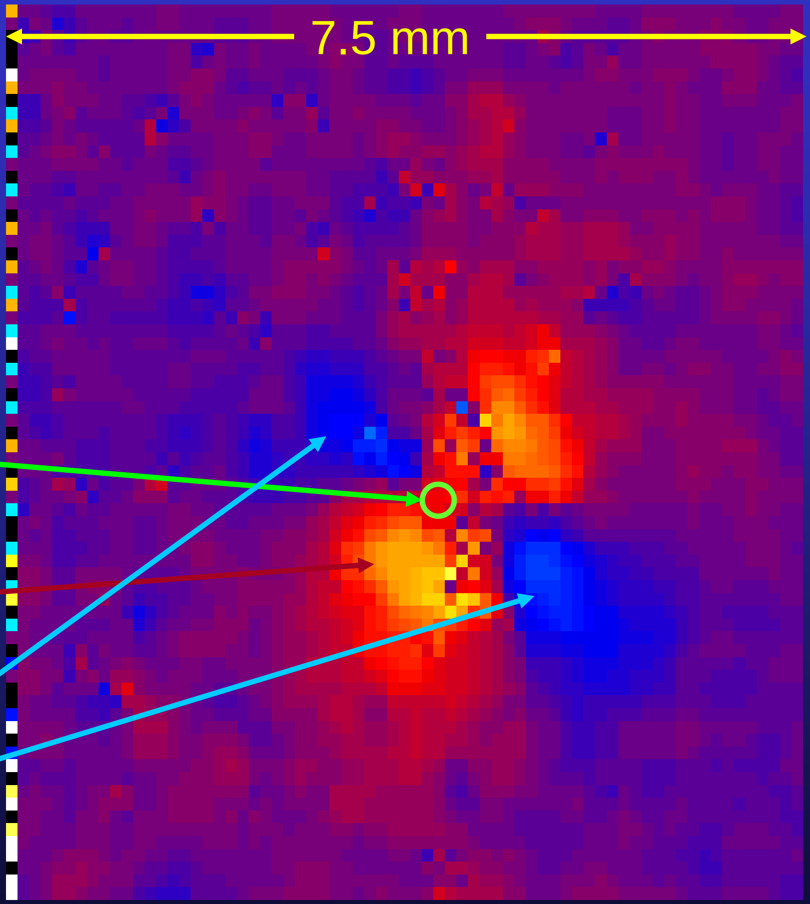
There is no single coordinate system in which the tensor conductivity is everywhere diagonal!

s0704 s1325

Virtual Electrodes in Anisotropic Cardiac Tissue

- REALITY

  Unequal electrical anisotropies in intracellular and extracellular spaces
- Point cathodal stimulation
- Dogbone virtual cathode depolarizes (red)
- Virtual anodes hyperpolarize (blue)
- ~ Consistent with theory



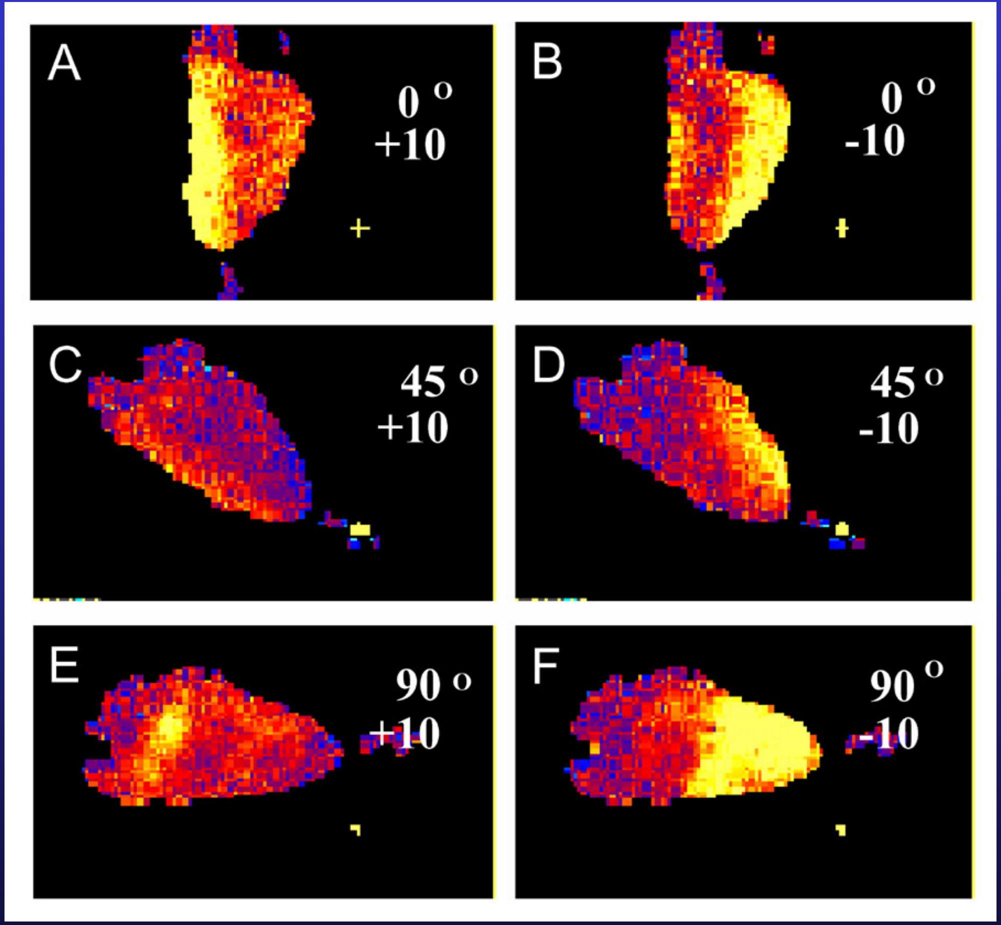
"Virtual Electrodes in Cardiac Tissue: A Common Mechanism for Anodal and Cathodal Stimulation," J.P. Wikswo, Jr., S.F. Lin, and R.A. Abbas, Biophys. J., 69: 2195-2210 (1995).

Where are the modeling problems?

- What is the response of cardiac tissue to field stimulation?
  – What are the effects of intramyocardial heterogeneities?
  – What is the spatial scale of the heterogeneities?
  – What is the temporal response of virtual electrodes in defibrillation?
  – What are the effects of nonlinearities?
  – Do we REALLY know how the external shock couples to the cellular membrane?
- What happens with threshold point stimulation?
  – How do you identify make versus break stimulation?
  – What are the effects of ischemia on activation?
  – What are the effects of nonlinearities, even in diastolic shock?

Rabbit Heart Response to a Defibrillation-Strength Field Shock

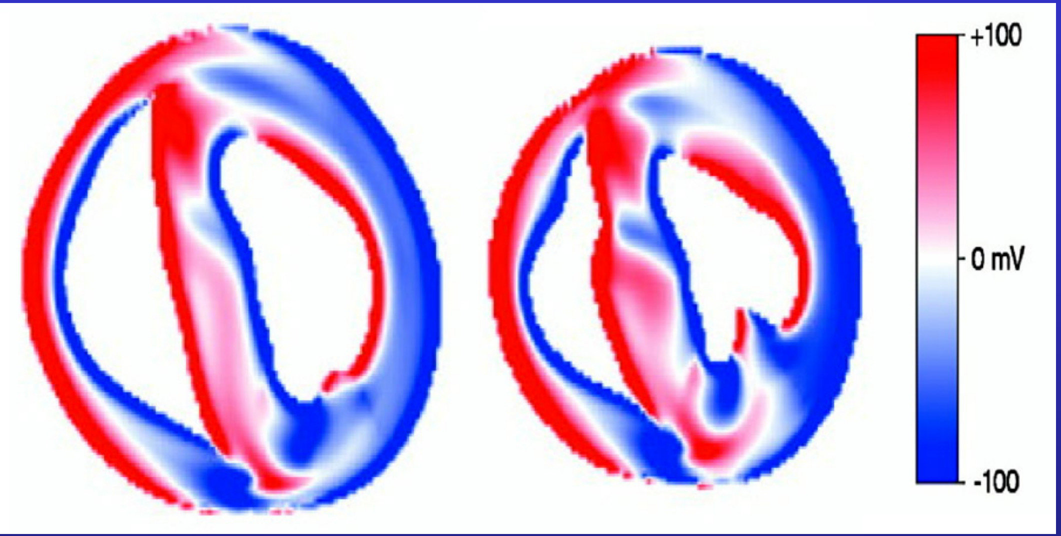
- Entire rabbit heart
- 10 V/cm field shock
- Horizontal field
- Different polarities
- Cathode to the left in **A**,**C**, **E** and to the right in **B**,**D**,**F**
- Different heart orientations – right/left stays with the field



"The Drug-Independent Roles of Cardiac Geometry and Tissue Anisotropy in Defibrillation and Reentry," J.P. Wikswo, Jr. and S.F. Lin, Cardiostim 98, 11th International Congress, Nice, France, p. 112, no. 53-3 (1998)..

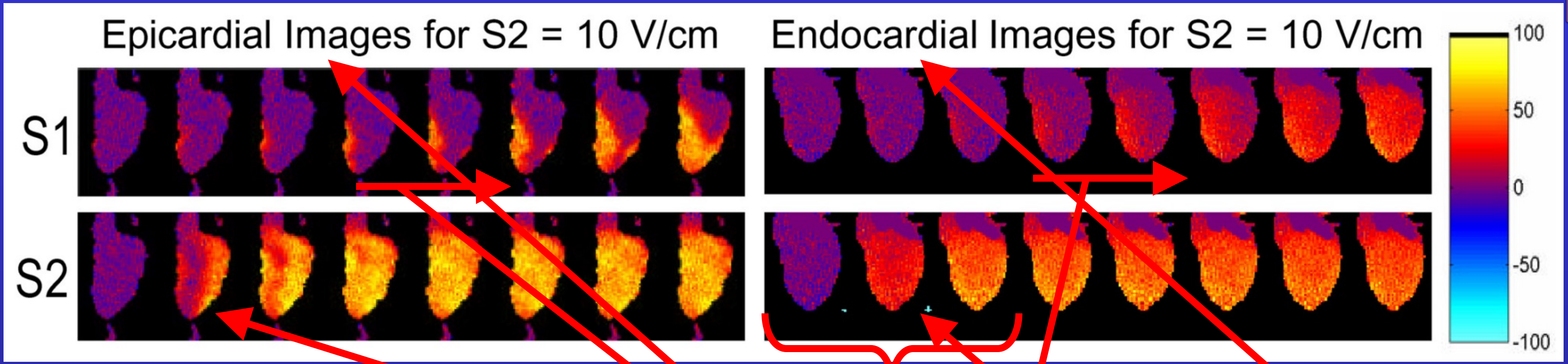
Response of a Whole-Heart Numerical Model to Field Shock

- Predicted whole-heart response to field shock, for two cross-sectional planes
- 5.8 V/cm electric field applied across the heart from right to left
- VCs and VAs are red and blue, respectively
- Endocardial polarity is predicted to be opposite to that on the endocardium



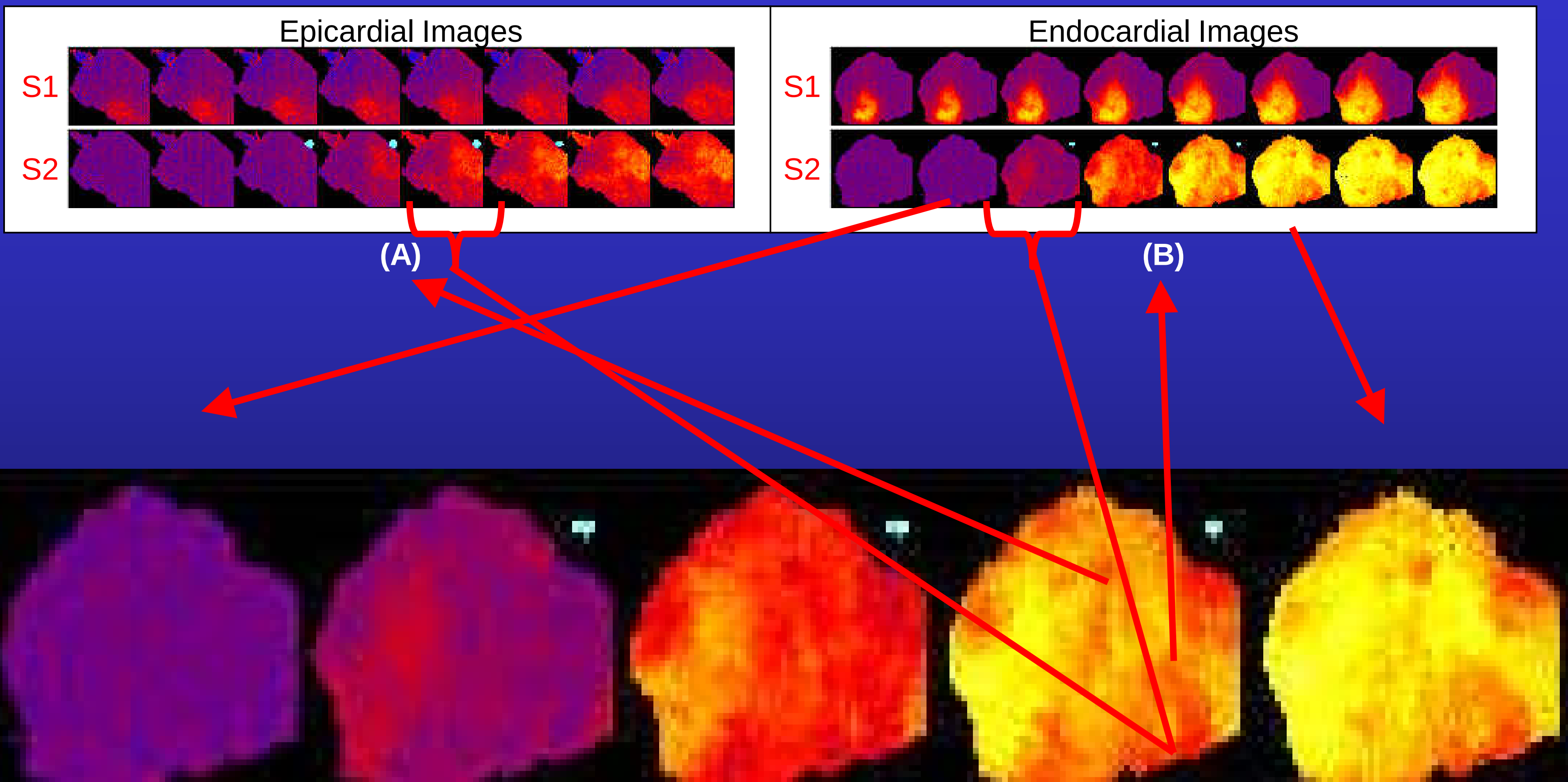
Efimov,IR, Aguel,F, Cheng,Y, Wollenzier,B, Trayanova,N.
Virtual Electrode Polarization in the Far Field: Implications for External Defibrillation.
American Journal of Physiology: Heart and Circulatory Physiology, 279, H1055-H1070, 2000

Whole Heart Field Stimulation



- Whole-heart, epicardial camera
- Illumination: epicardial (left), endocardial (right)
- S1 propagation in both movies
- S2 right-left asymmetry on epicardial illumination
- No S2 right-left effect on endocardial illumination
- Why is activation so fast? (3.6 ms/frame)

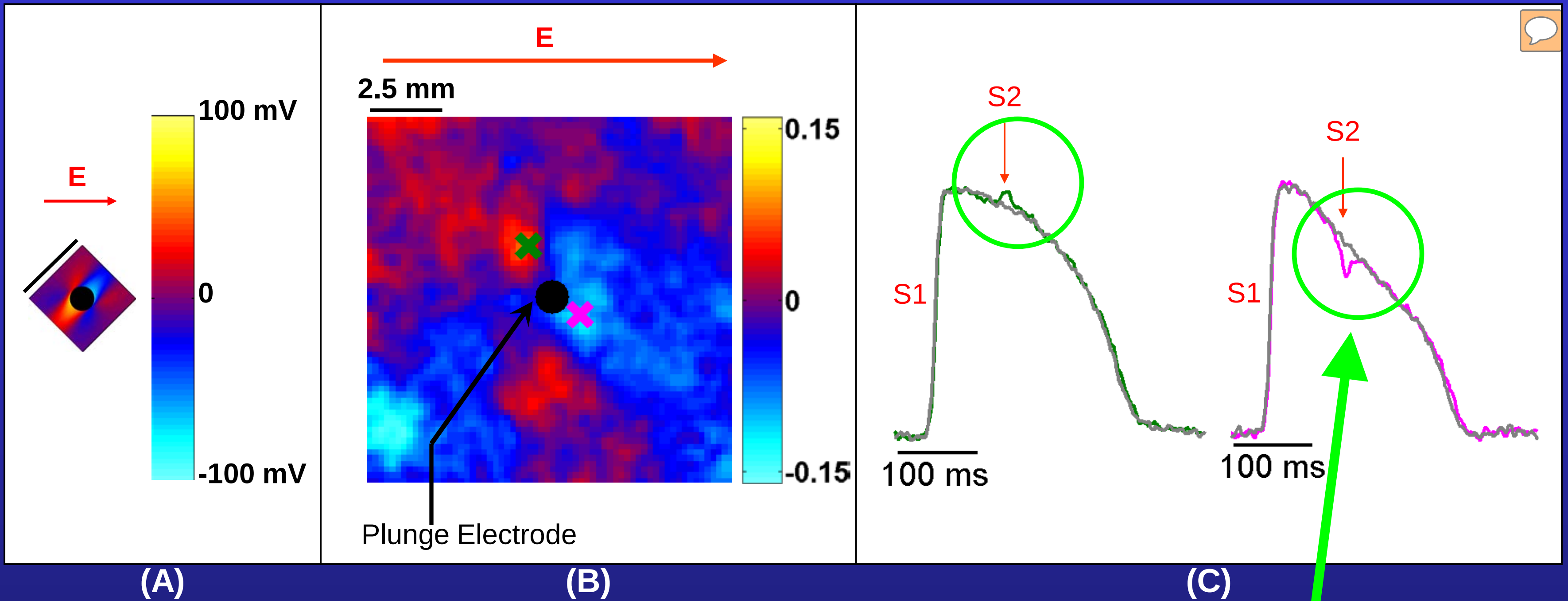
Flat RV Field Stimulation



- Why is activation so fast? (0.8 msec/frame)
- Where are the virtual **ANODES** from heterogeneities?

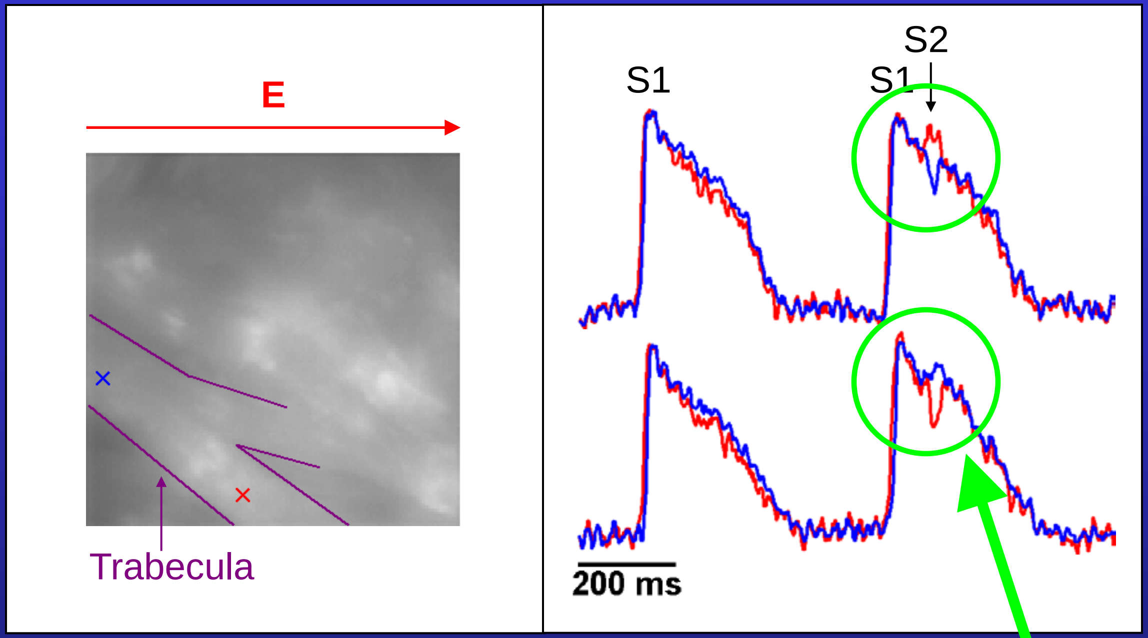
Where are the diastolic field-shock virtual anodes from the heterogeneities?

Artificial Heterogeneities



- Insulated needle in refractory field shock
- Theory and experiment are in qualitative agreement
- See both virtual anodes and cathodes

Natural Heterogeneities



(A) (B)

- Papillary muscle in refractory field shock
- Theory and experiment are in qualitative agreement
- See both S2 virtual anodes and cathodes

Where are the Diastolic Field-Shock Virtual Anodes from Heterogeneities?

- Subendocardial?
- Too small to see?
- Short-lived?
  - Faster response at shorter spatial scales?
  - Don't appear
  - Overrun by the cathodes
  - Make versus break activation
- Non-linear effect?
- Do we know what we are looking for?

Cathode/Anode Make/Break

Four modes of stimulating cardiac tissue

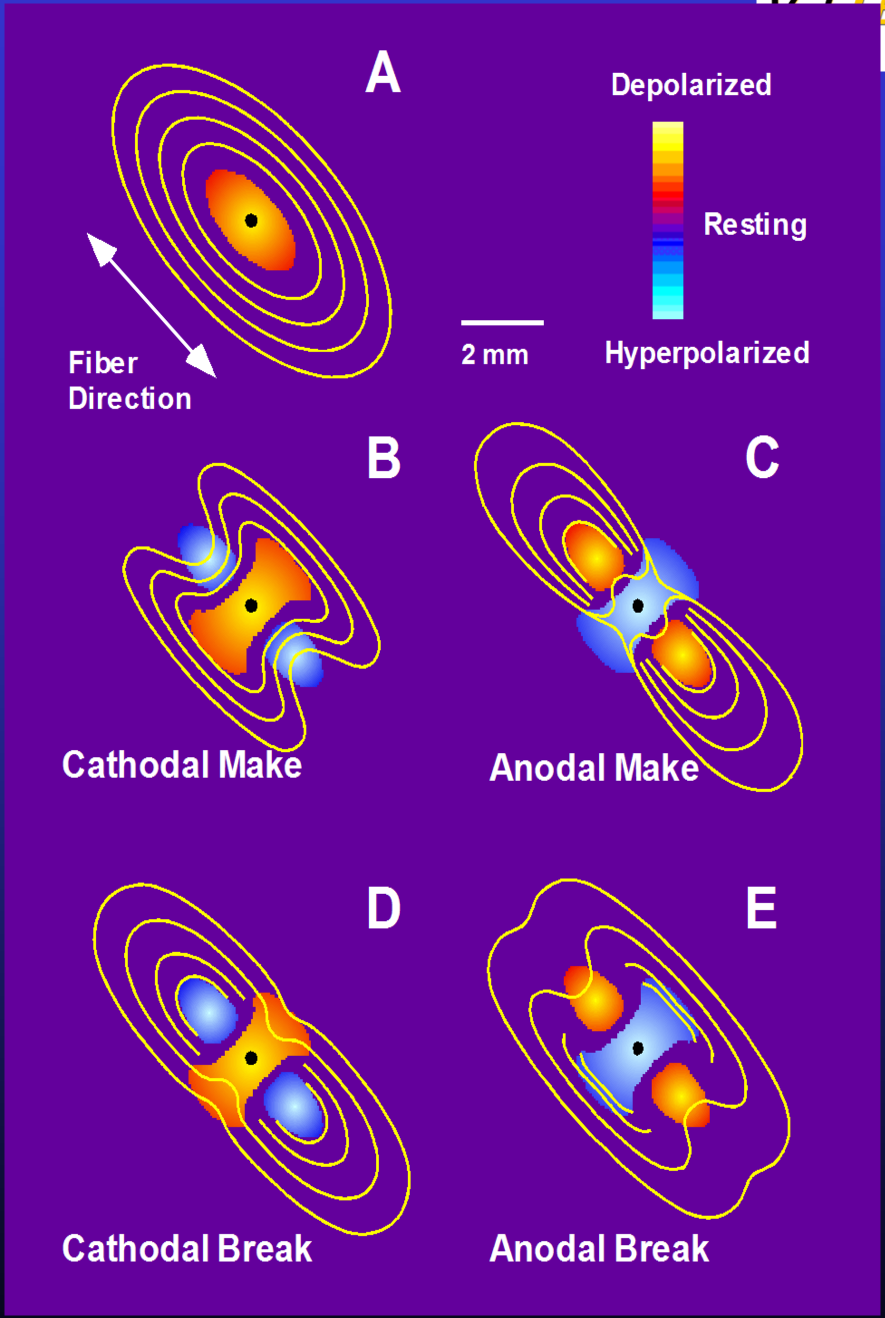
- **Cathode make** (turn on negative current)
- **Anode make** (turn on positive current)
- **Cathode break** (turn off long negative current)
- **Anode break** (turn off long positive current)

- Dekker, E. "Direct current make and break thresholds for pacemaker electrodes on the canine ventricle." Circ Res, 27:811, 1970
- Roth,B.J. A Mathematical Model of Make and Break Electrical Stimulation of Cardiac Tissue by a Unipolar Anode or Cathode. IEEE Transactions on Biomedical Engineering 42, 1174-1184 (1995)

Four Modes of Cardiac Activation

Cathode Anode

Make Break



VIRTUAL ELECTRODES

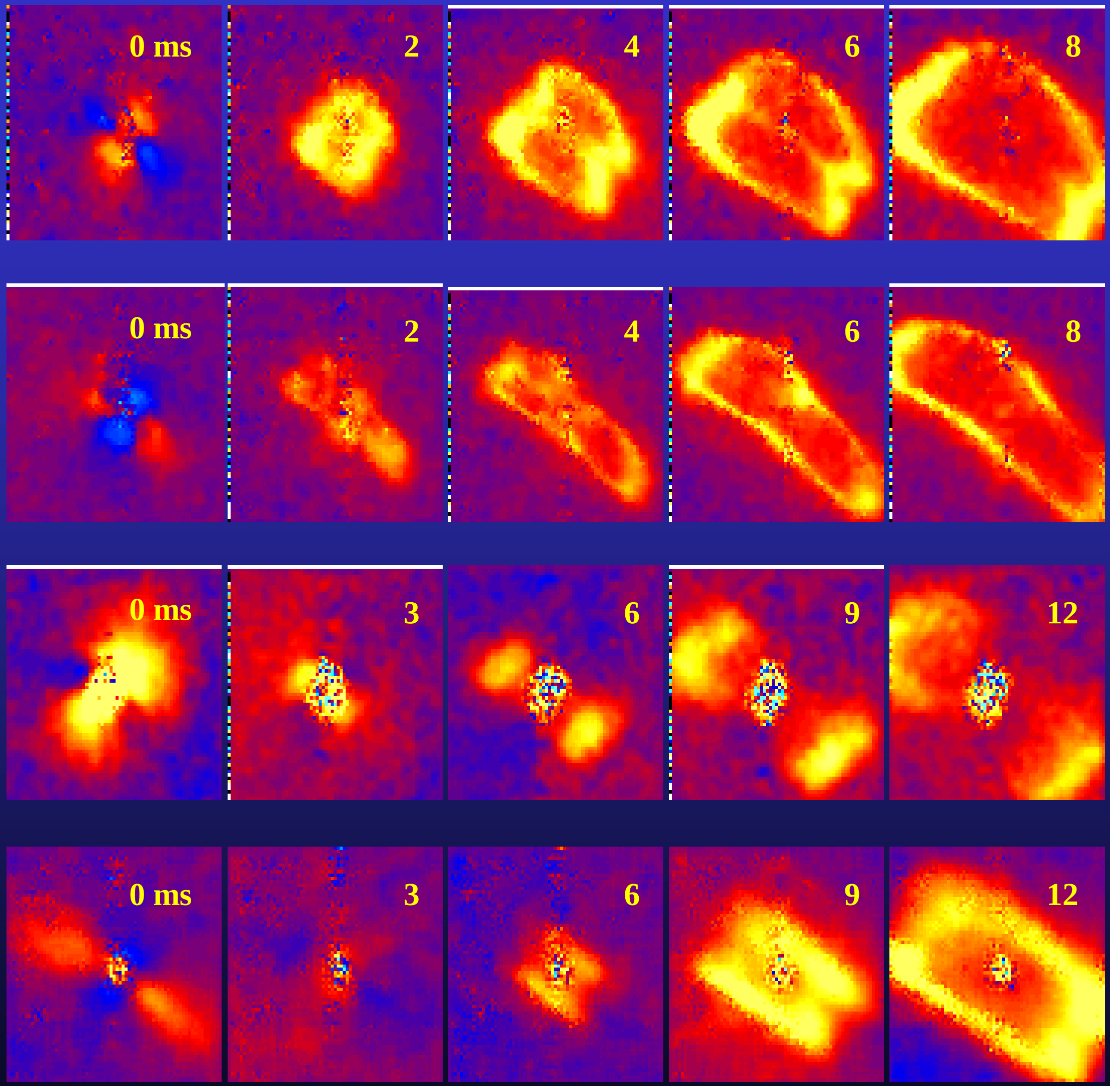
The Key to Cathode/Anode Make/Break Stimulation

Cathode Make -10 mA

Anode Make +10 mA

Cathode Break -2 mA

Anode Break +3mA



Fiber Direction

1 mm

Depolarized

<-2

-1

0

1

>2

ΔF/F (%)

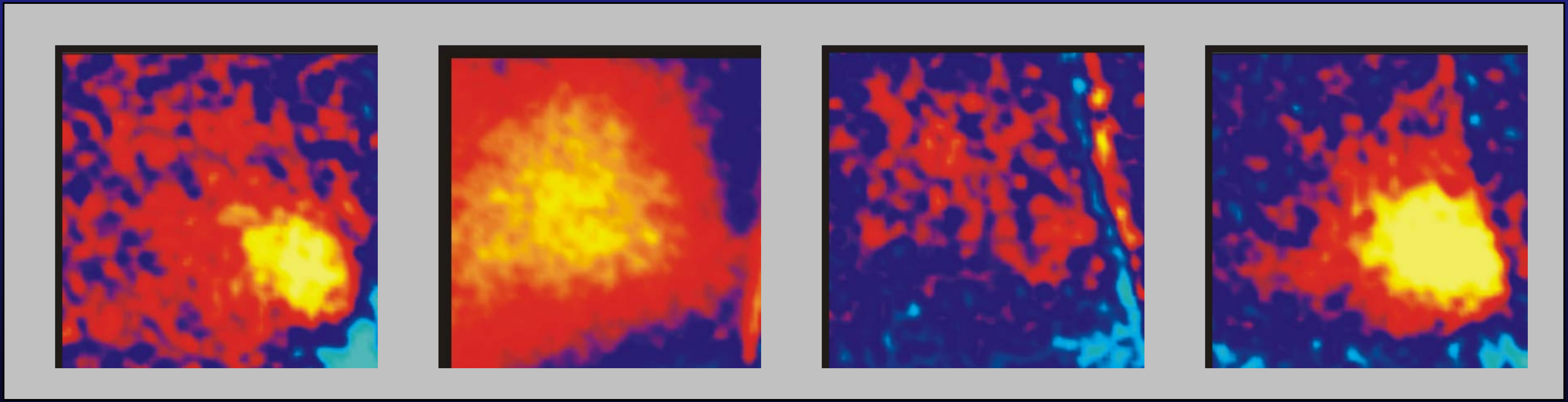
Hyperpolarized

"Virtual Electrodes in Cardiac Tissue: A Common Mechanism for Anodal and Cathodal Stimulation," J.P. Wikswo, Jr., S.F. Lin, and R.A. Abbas, <u>Biophys. J.</u>, <u>69</u>: 2195-2210 (1995).

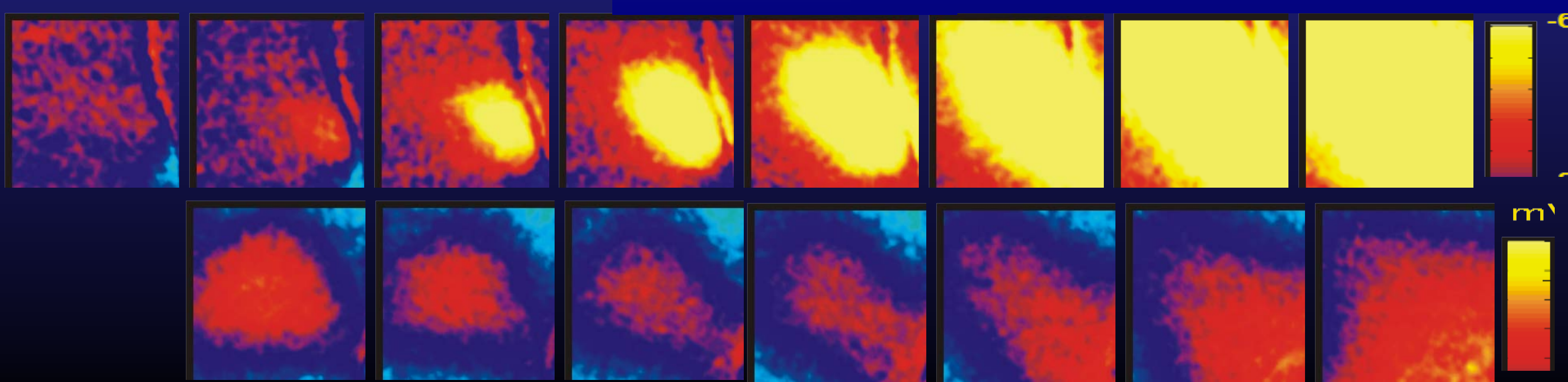
Anodal Stimulation Near Threshold

- How do you tell what is happening at threshold?
- Can you discriminate between make and break?
- What happens with high K^+ altered threshold?

Case A Case B Case C Case D

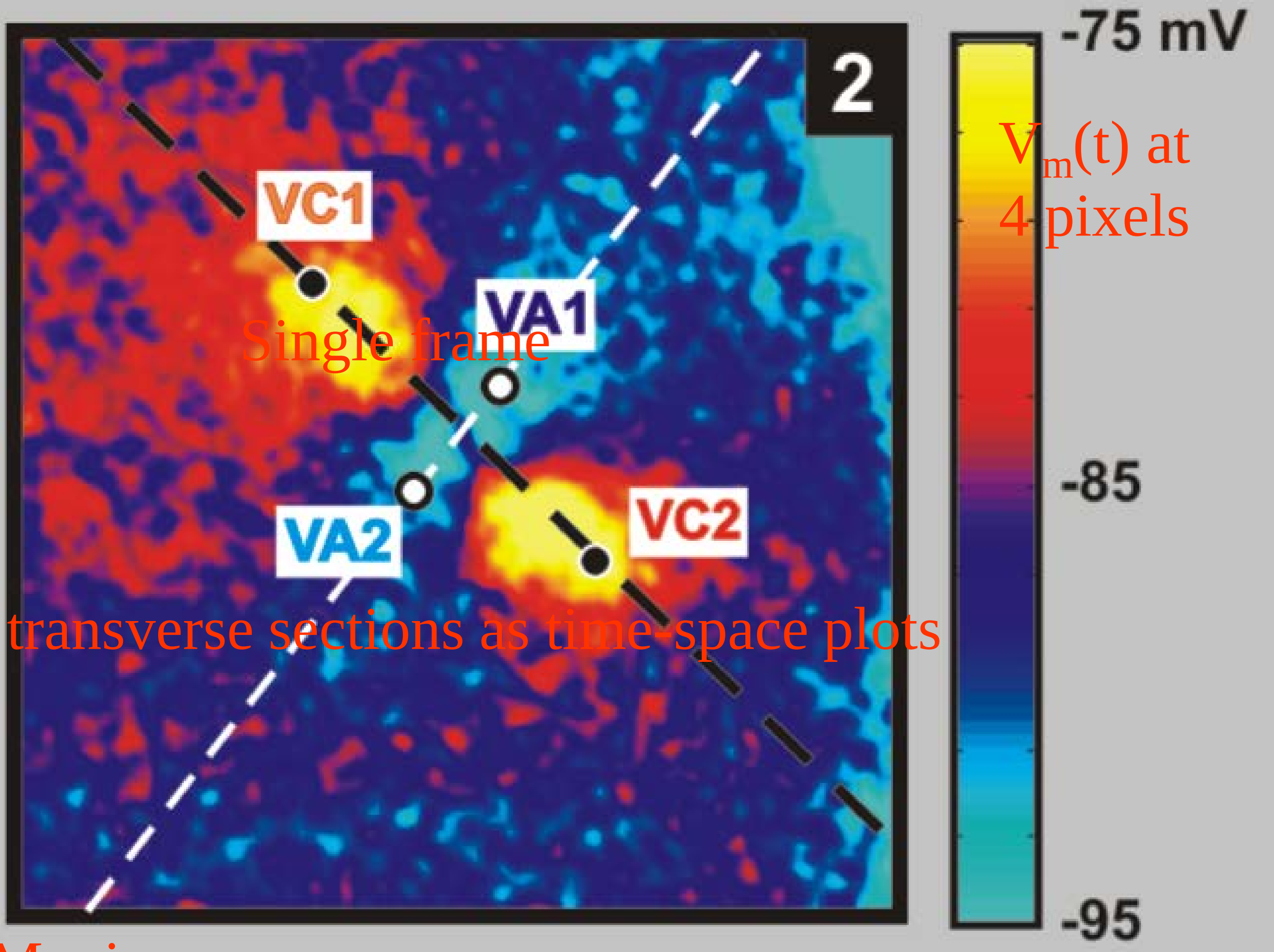


- S1: anodal make excitation of diastolic tissue from VC
- Apply S2 to refractory tissue
- S2 off: anodal break excitation of refractory tissue from VA



Case A

- Dogbone virtual anode (VA)
- Virtual cathode (VC) on either side

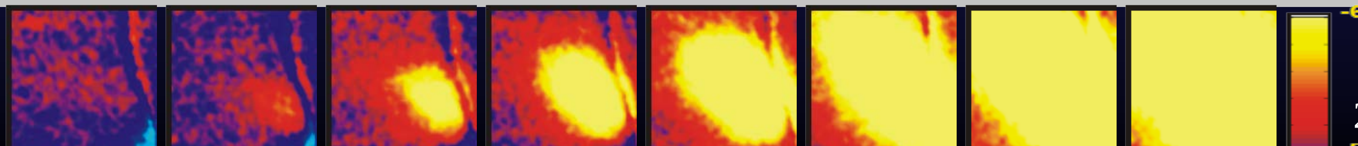


$V_m(t)$ at 4 pixels

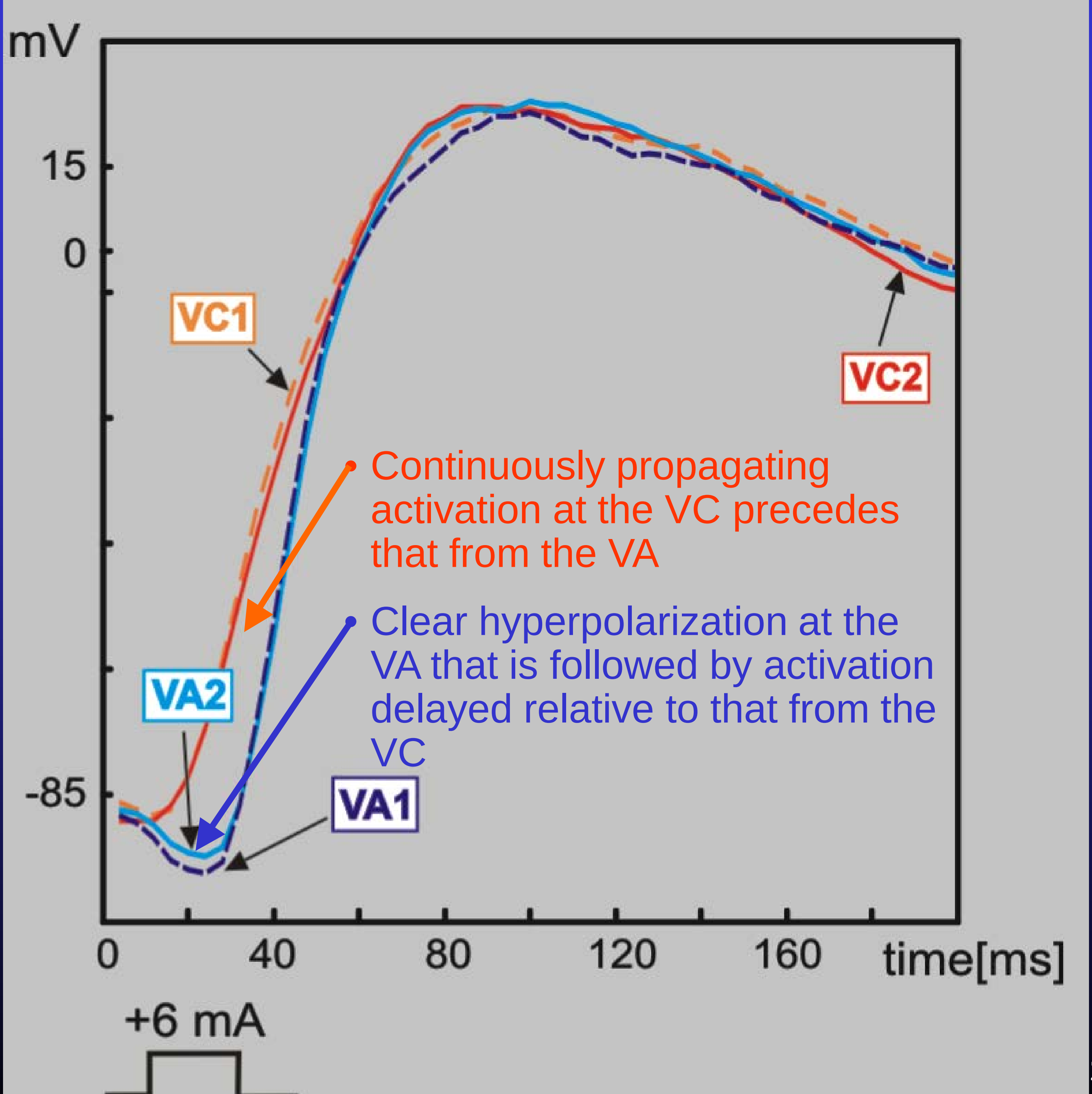
Single frame

Longitudinal and transverse sections as time-space plots

Movie



Case A


mV
15
0
-85
VC1
VC2
VA2
VA1
Continuously propagating activation at the VC precedes that from the VA
Clear hyperpolarization at the VA that is followed by activation delayed relative to that from the VC
0
40
80
120
160
time[ms]
+6 mA

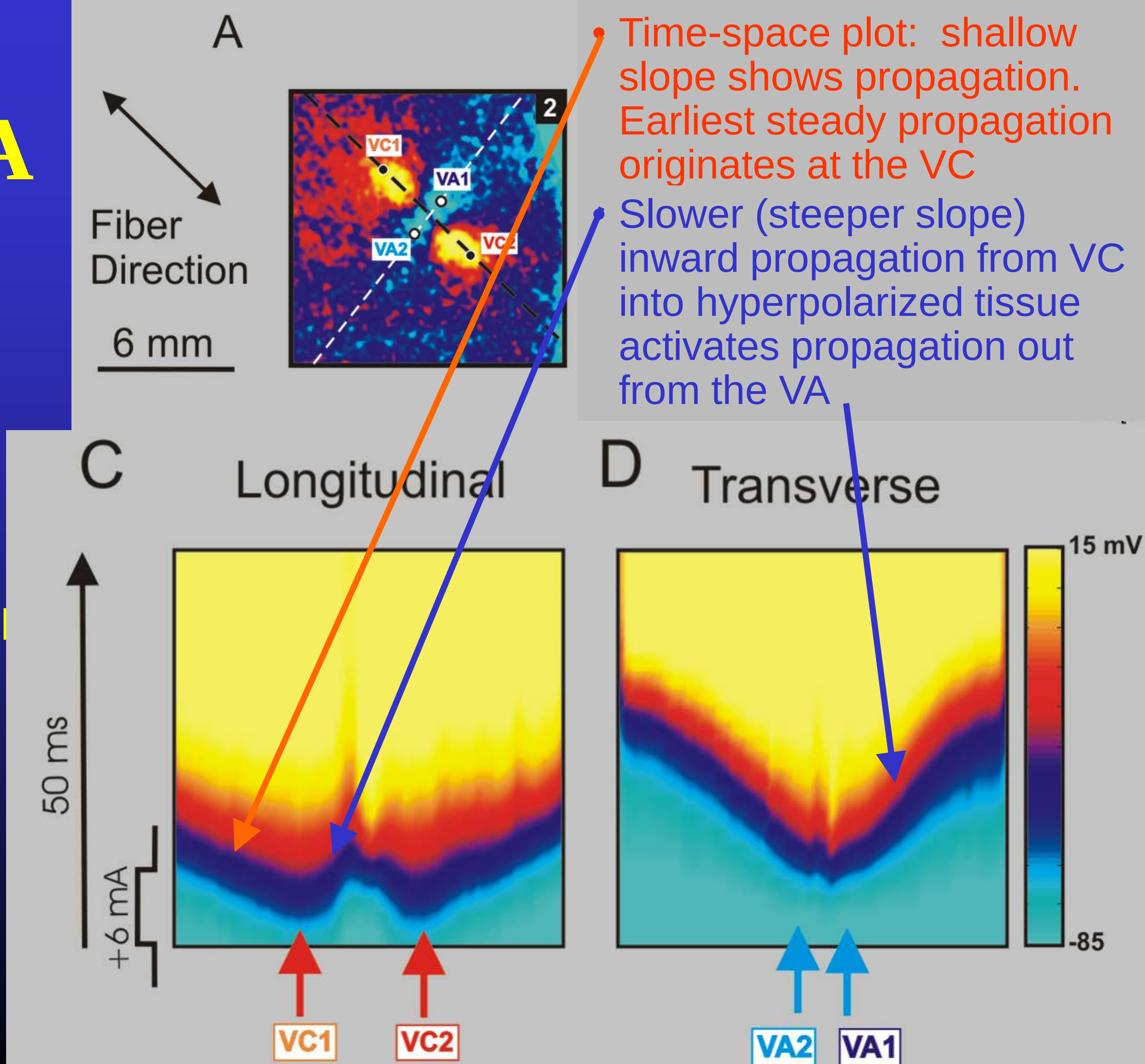
Case A

Anodal make

3x V_{thresh}

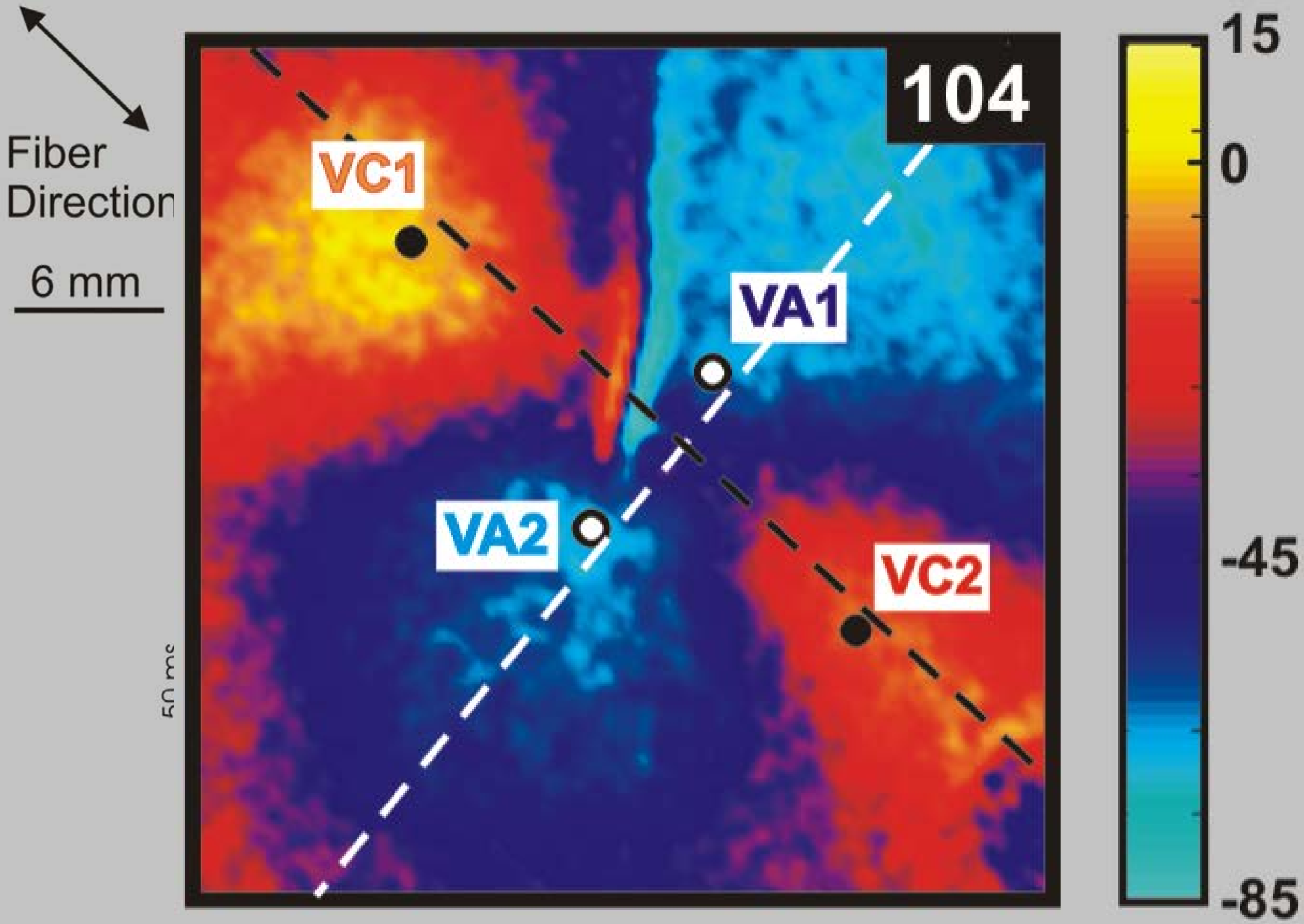
K^+ = 4 mM

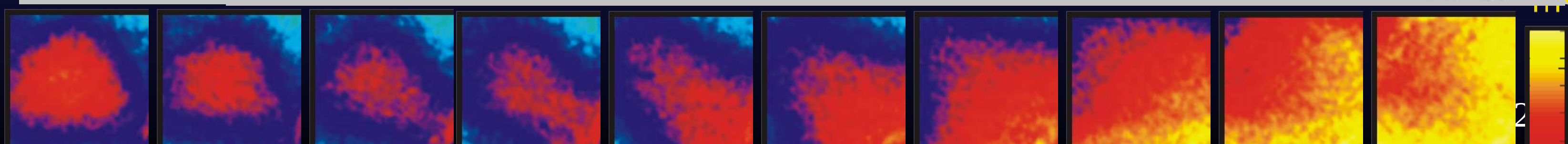
- Time-space plot: shallow slope shows propagation. Earliest steady propagation originates at the VC
- Slower (steeper slope) inward propagation from VC into hyperpolarized tissue activates propagation out from the VA



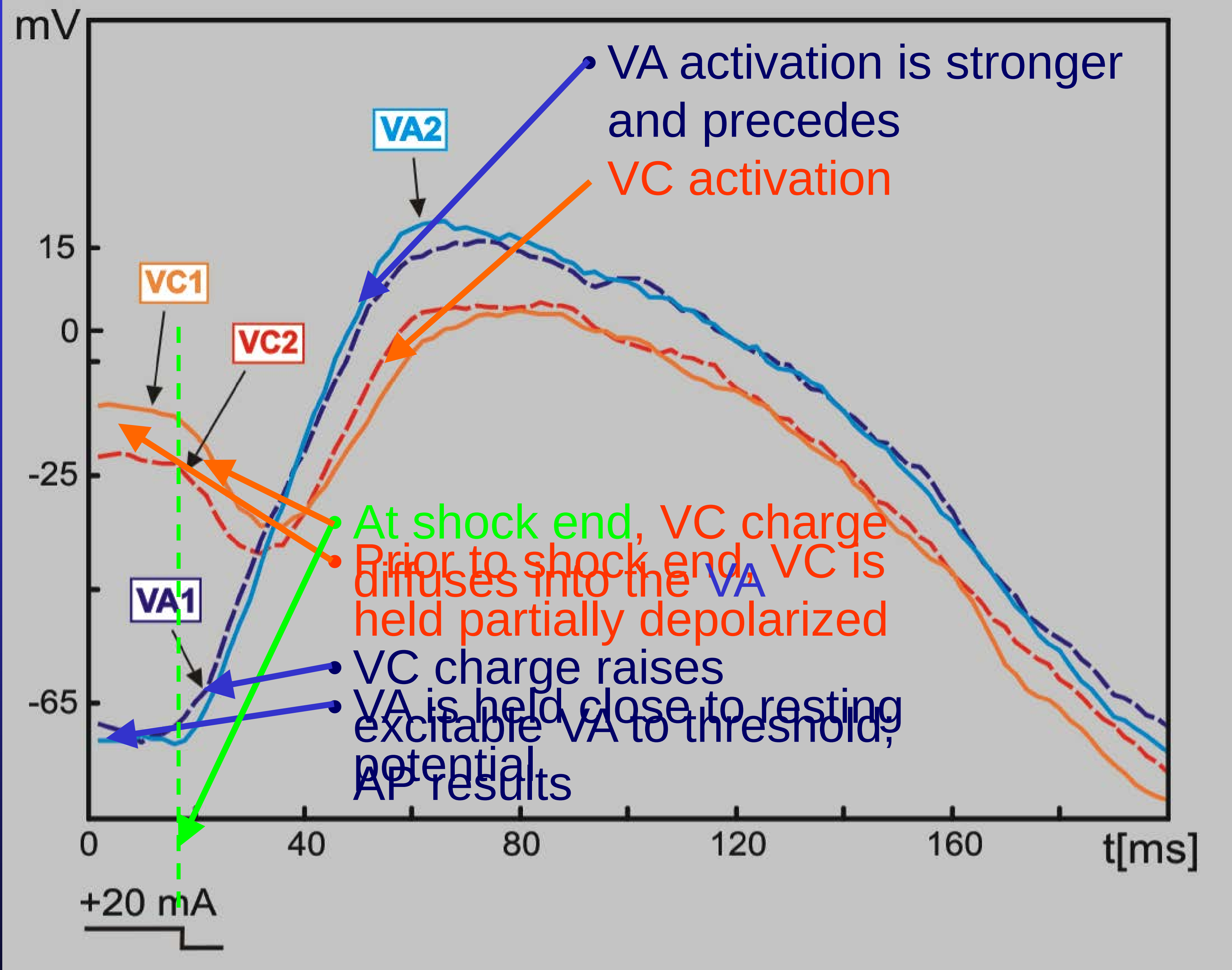
Case B

- **Strong dogbone virtual anode (VA)**
- Strong virtual cathode (VC) on either side

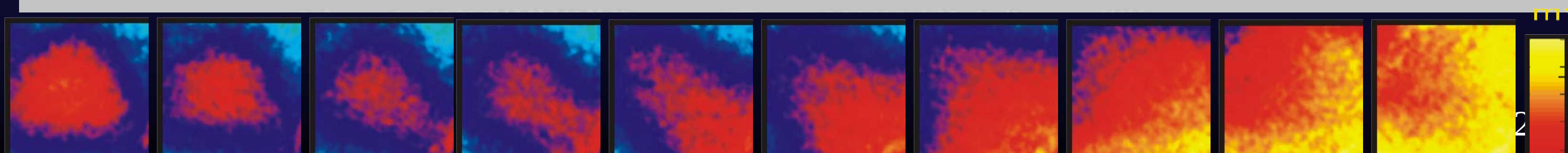




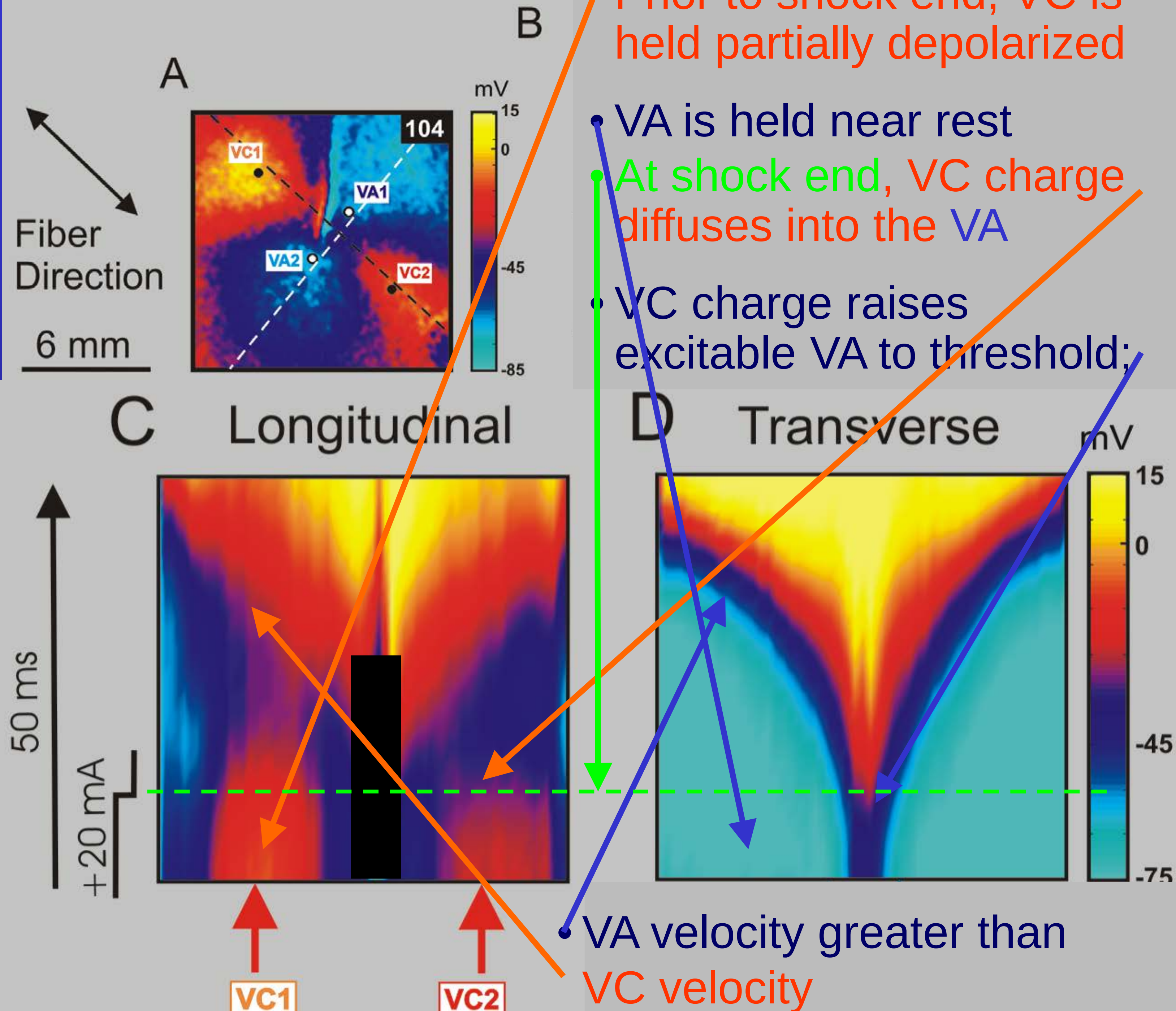
Case B



mV
15
0
-25
-65
0
40
80
120
160
t[ms]
+20 mA
VA1
VA2
VC1
VC2
VA activation is stronger and precedes
VC activation
At shock end, VC charge diffuses into the VA
Prior to shock end, VC is held partially depolarized
VC charge raises excitable VA to threshold; AP results
VA is held close to resting potential



Case B



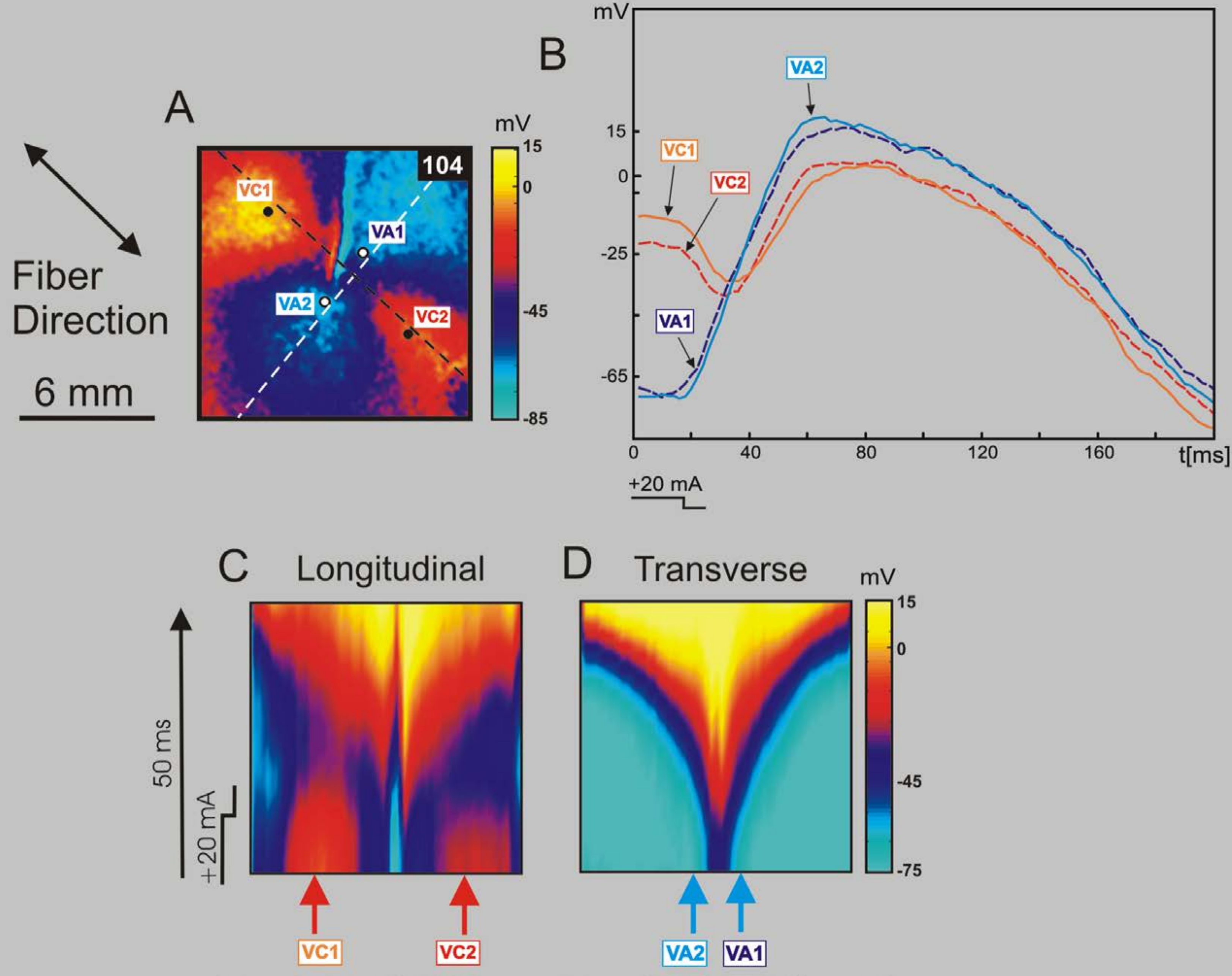
- Prior to shock end, VC is held partially depolarized
- VA is held near rest
- At shock end, VC charge diffuses into the VA
- VC charge raises excitable VA to threshold;
- VA velocity greater than VC velocity

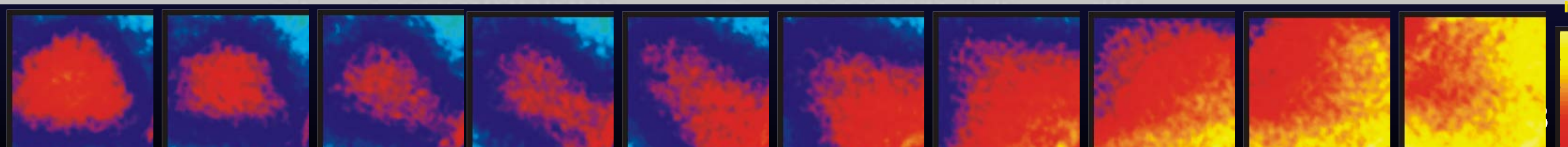
Case B

Anodal break

20 mA

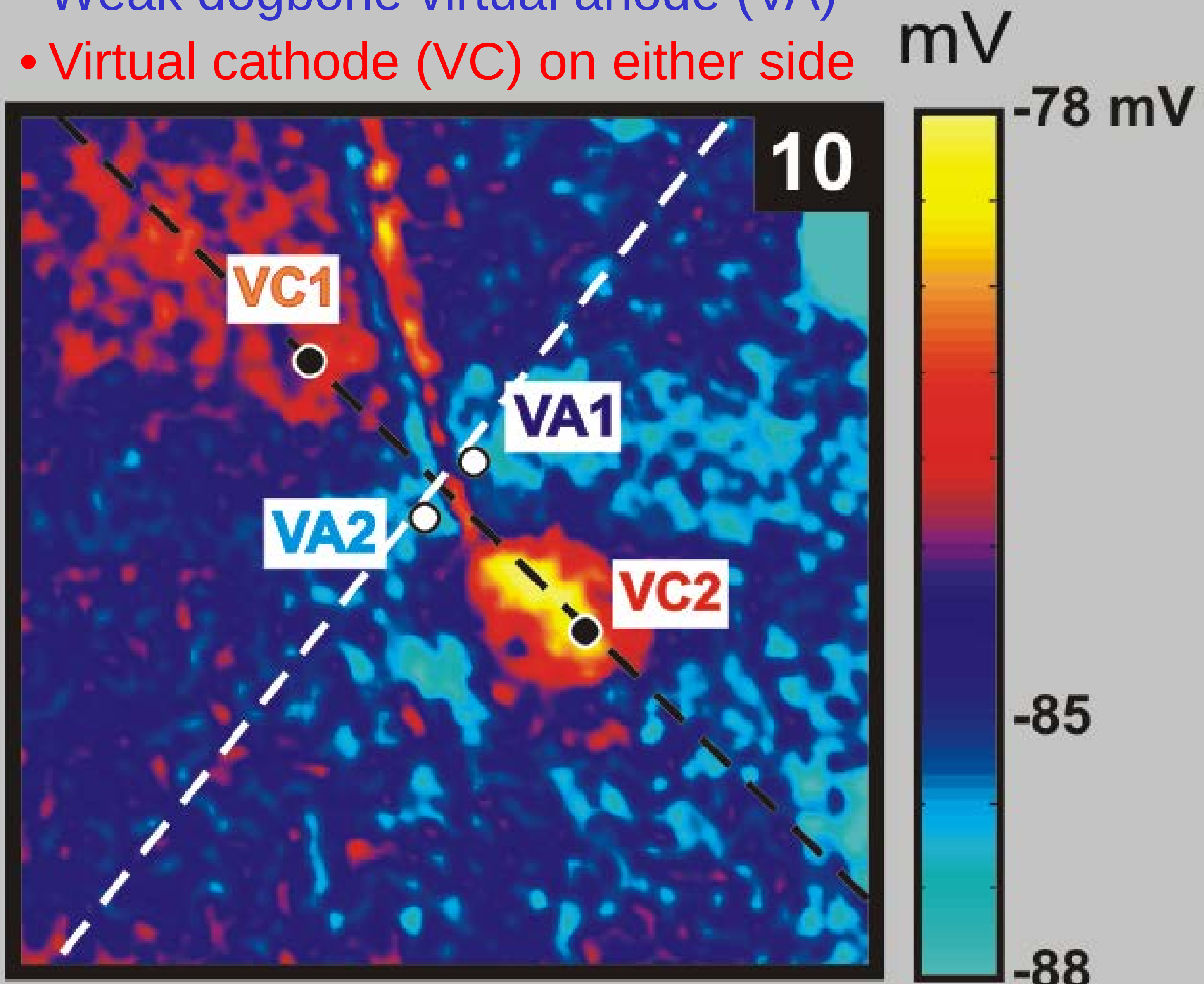
K^+ = 4 mM

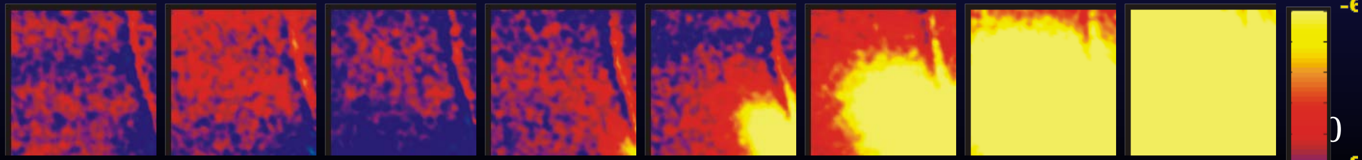




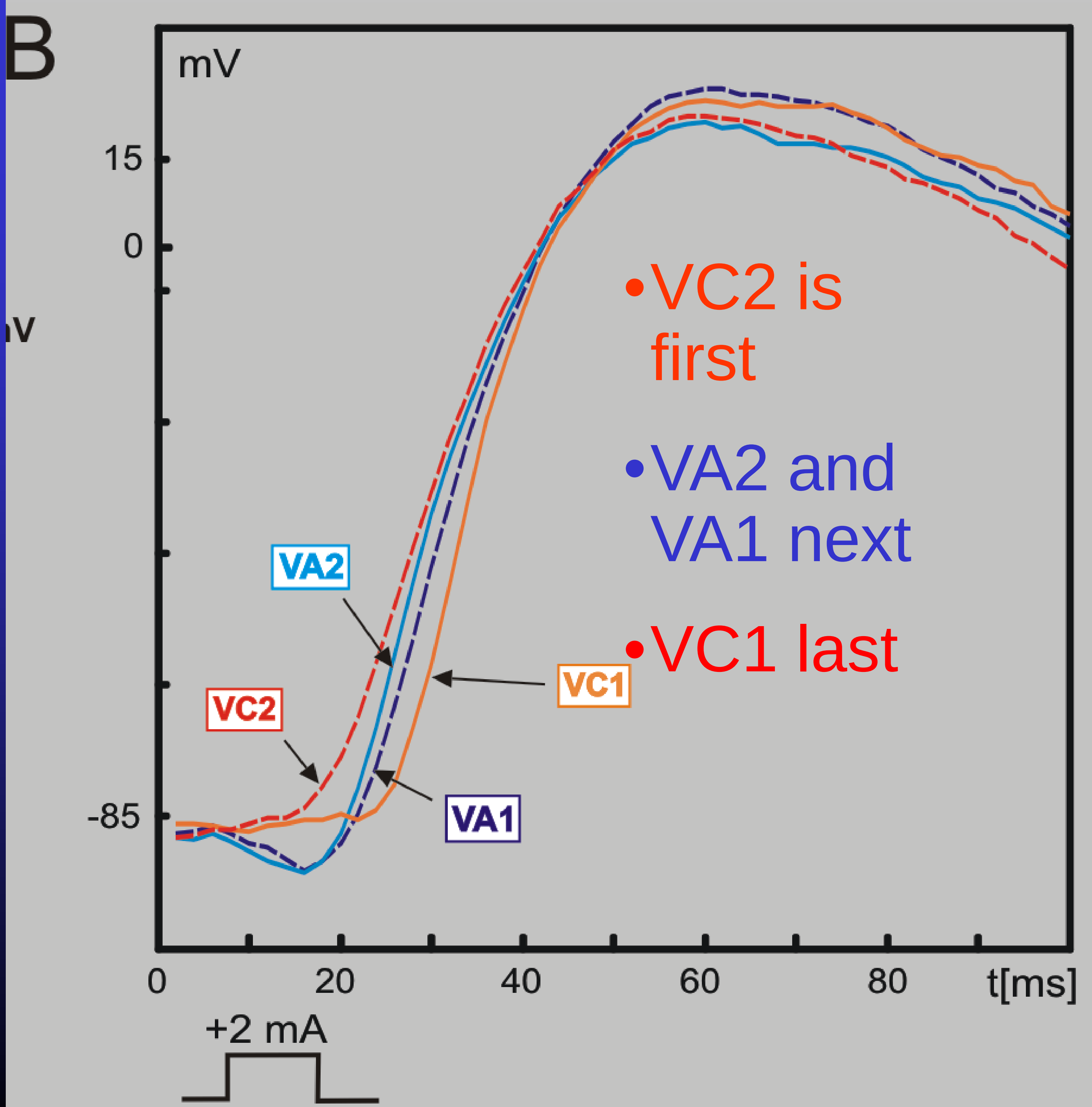
Case C

- Weak dogbone virtual anode (VA)
- Virtual cathode (VC) on either side





Case C

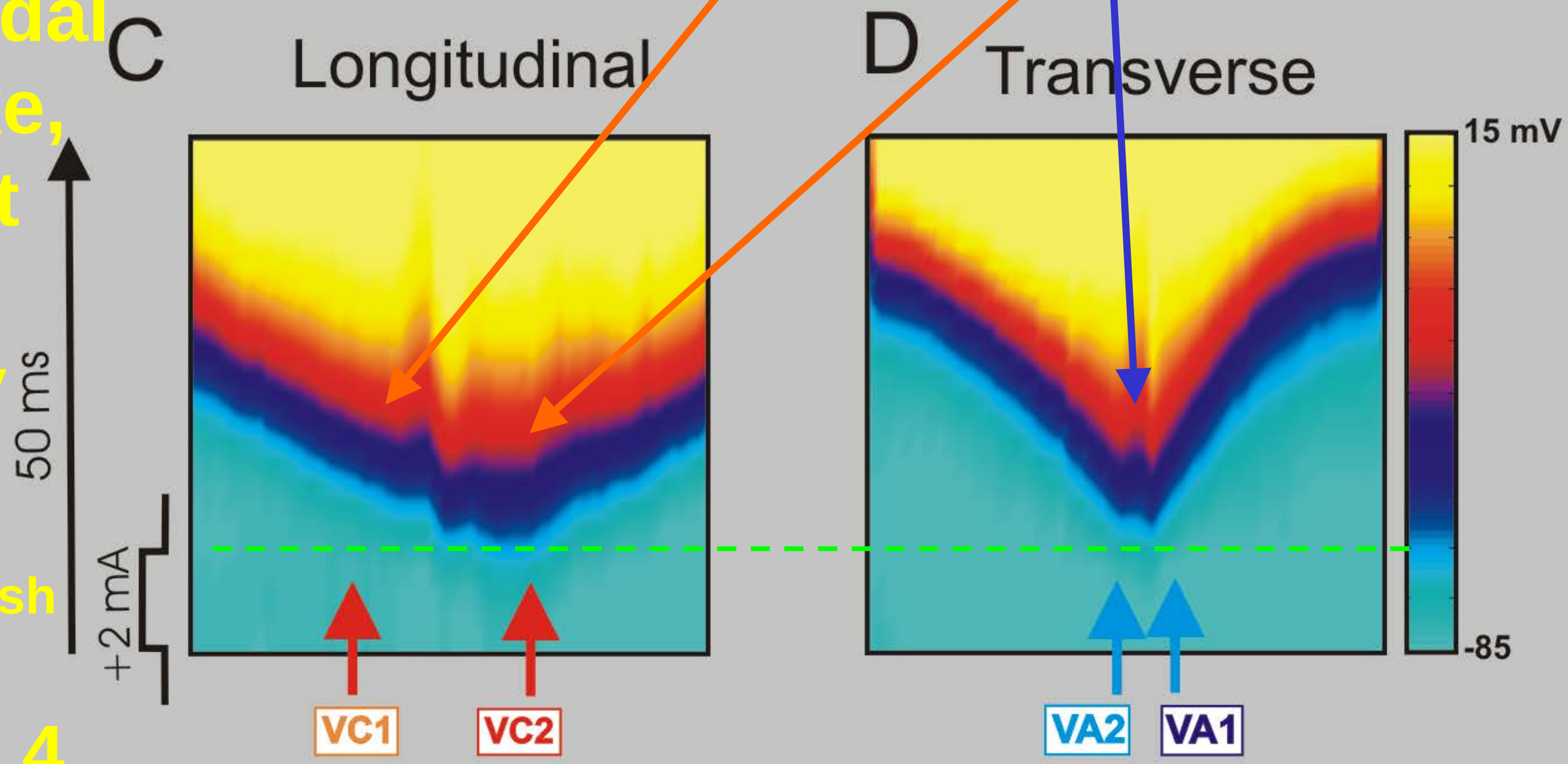


- VC2 is first
- VA2 and VA1 next
- VC1 last

Case C

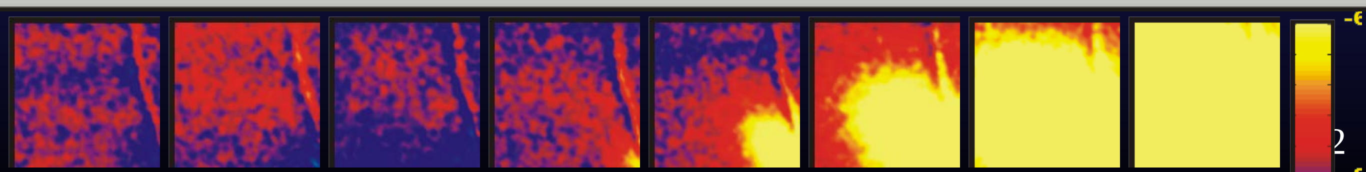
- VC2 first, but after S1 end
- VA2 and VA1 next
- VC1 last

Anodal make, right side only

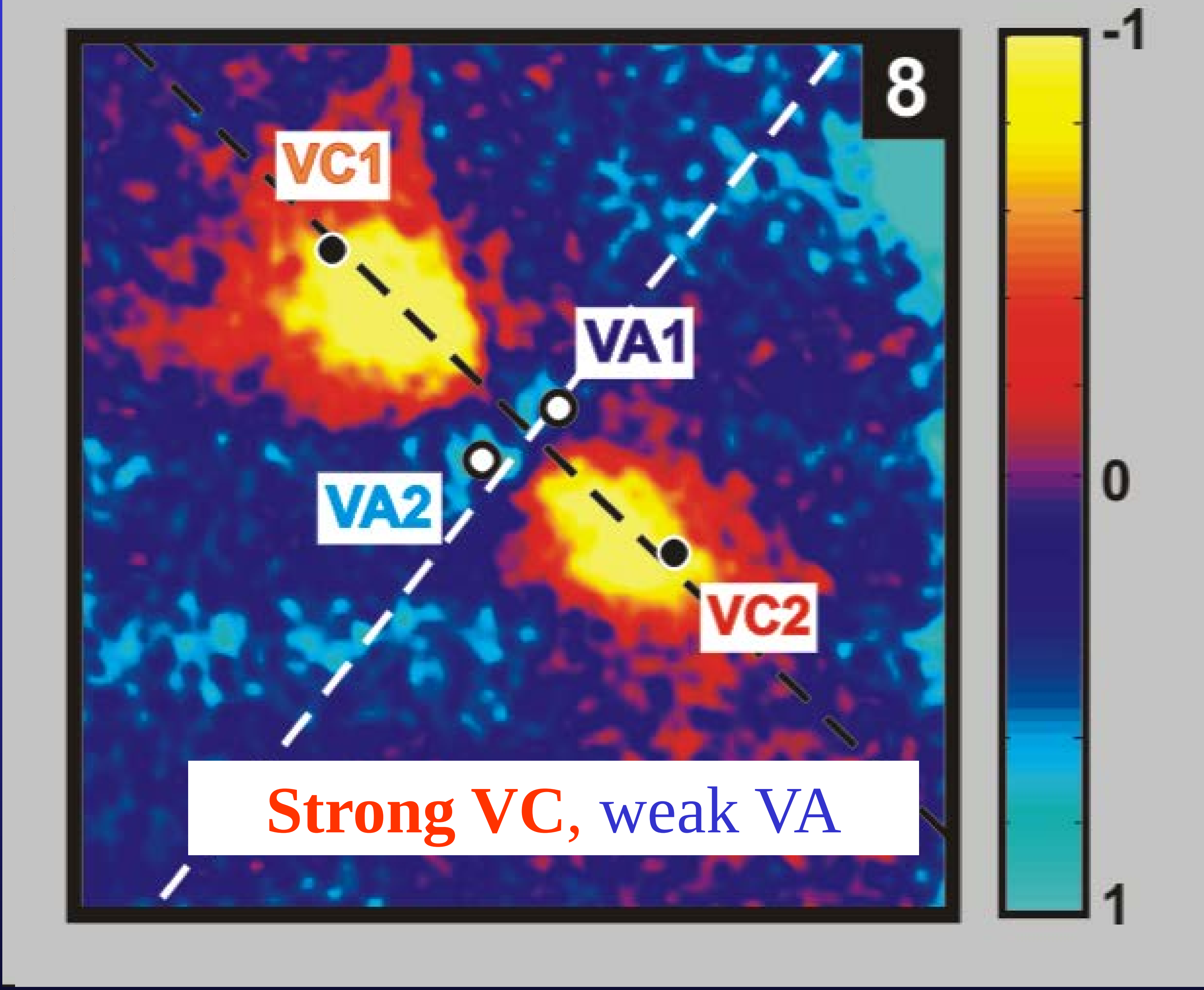


V_{thresh}

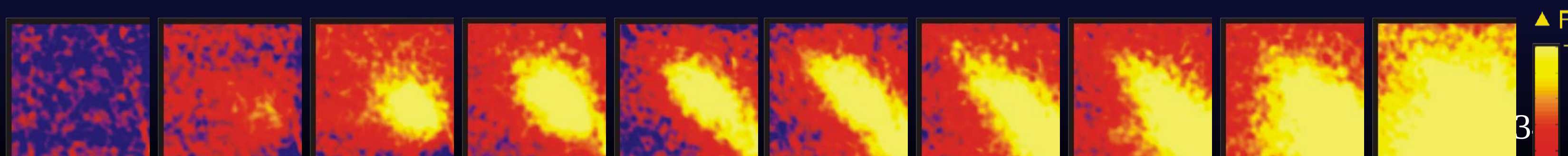
$K^+ = 4$ mM



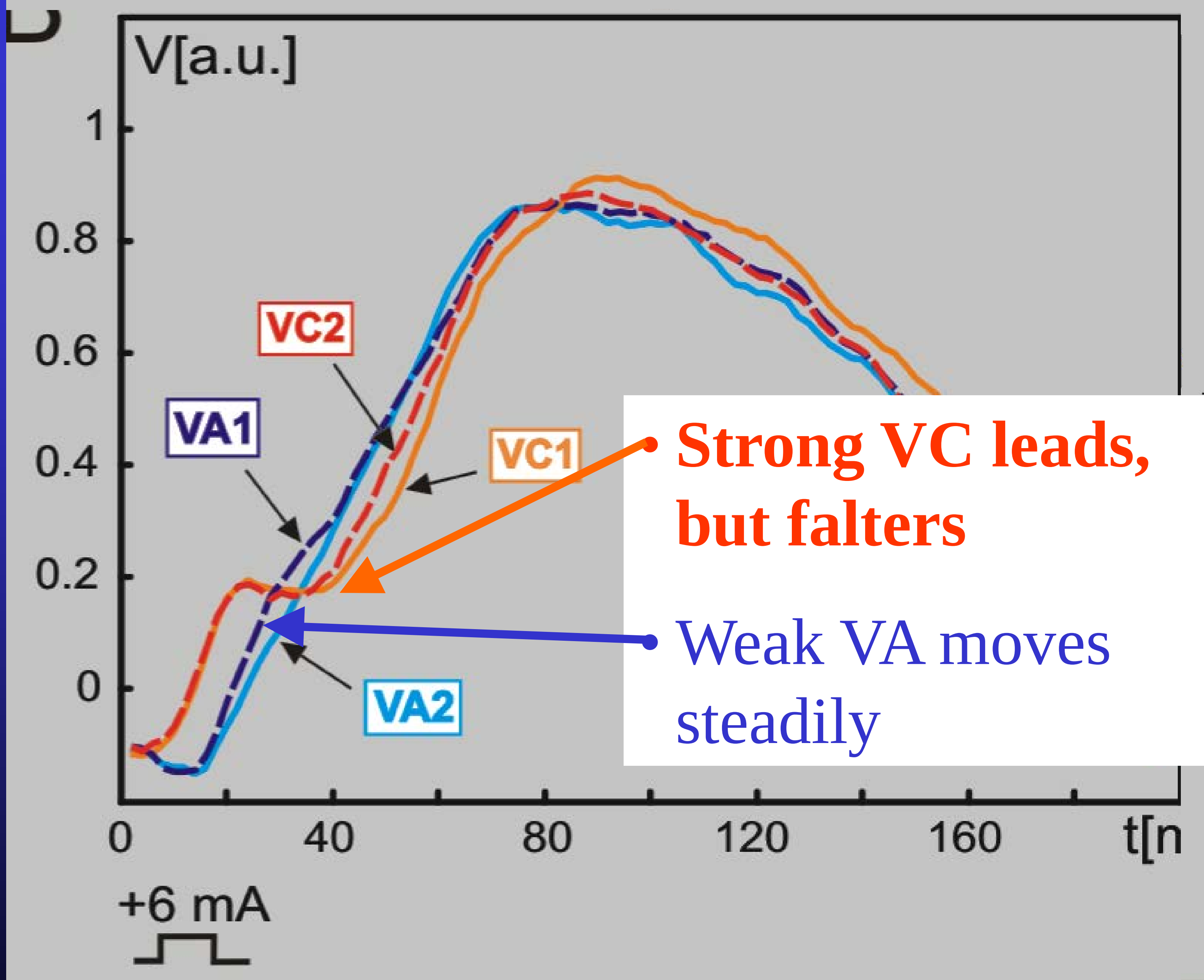
Case D

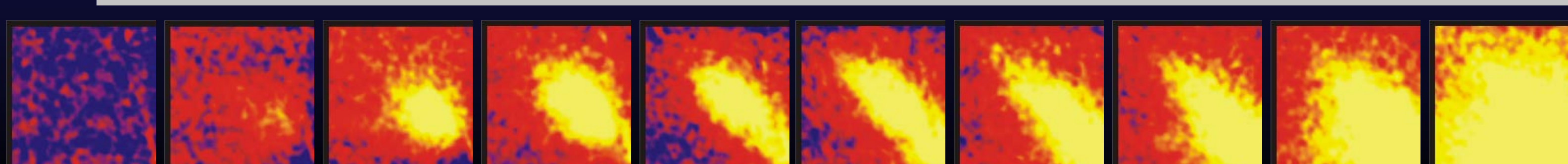


Strong VC, weak VA



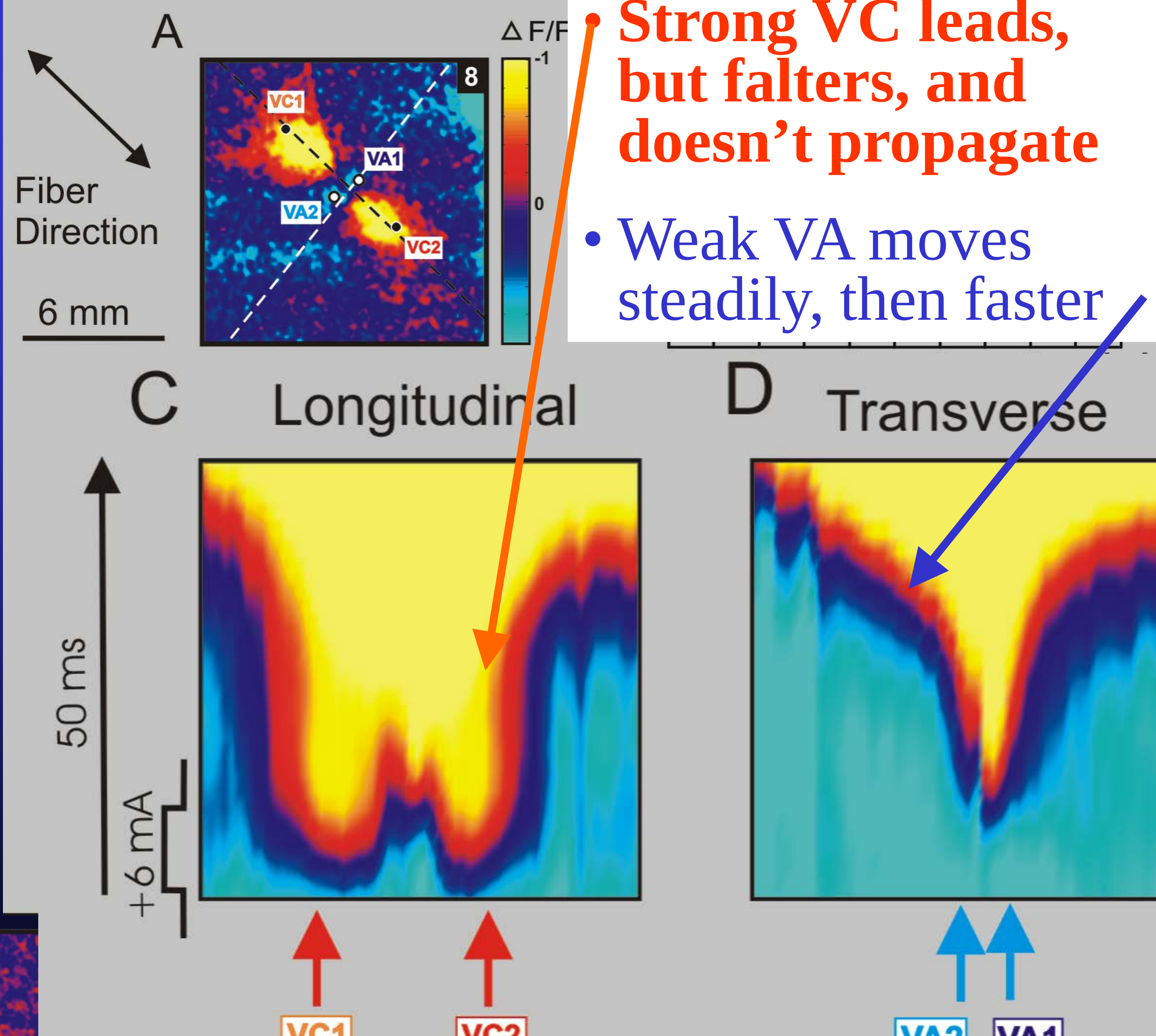
Case D


V[a.u.]
1
0.8
0.6
0.4
0.2
0
0
40
80
120
160
t[n
VC2
VA1
VC1
VA2
+6 mA
Strong VC leads, but falters
Weak VA moves steadily

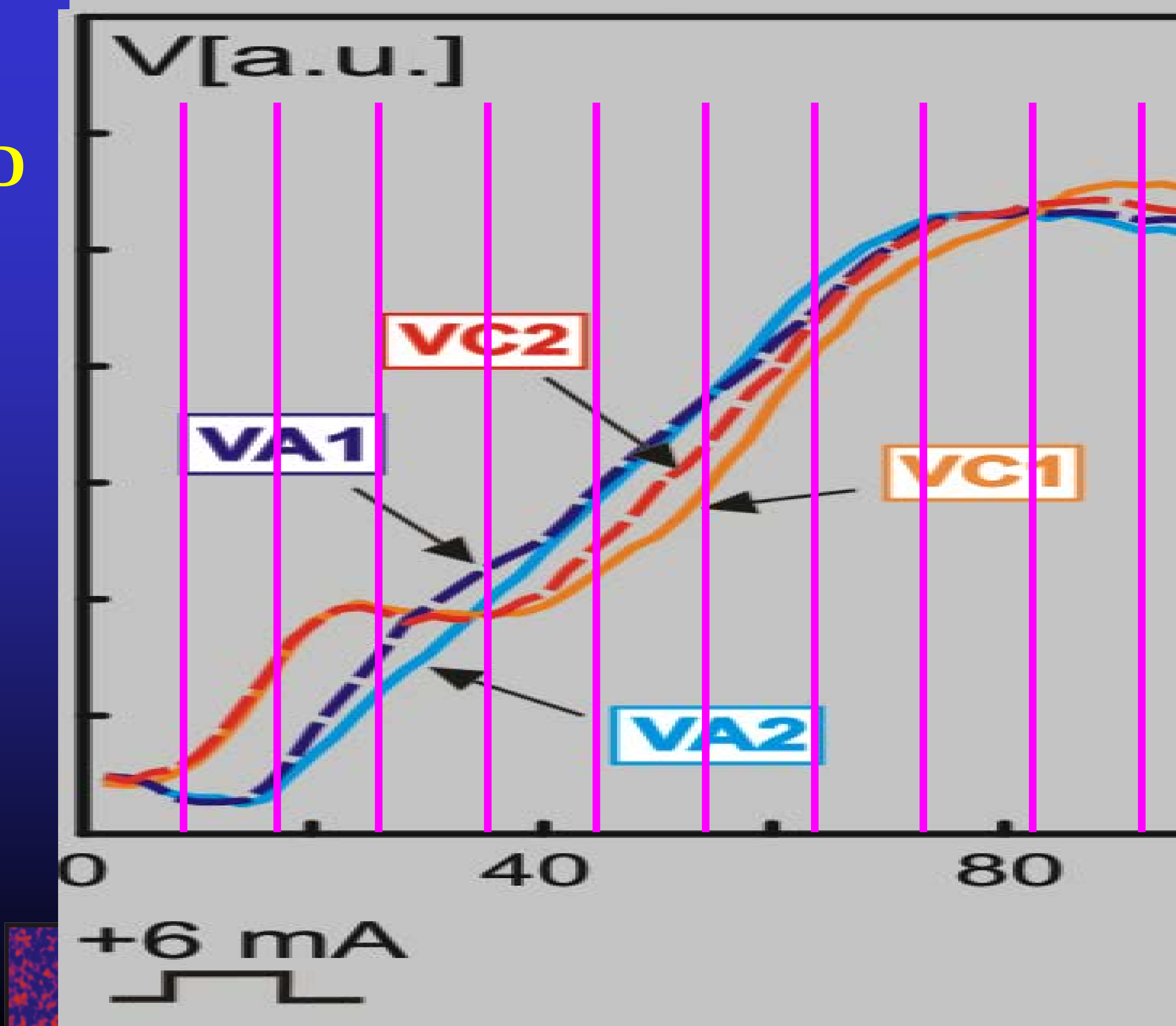


Case D

- **Strong VC leads, but falters, and doesn’t propagate**
- Weak VA moves steadily, then faster



Case D

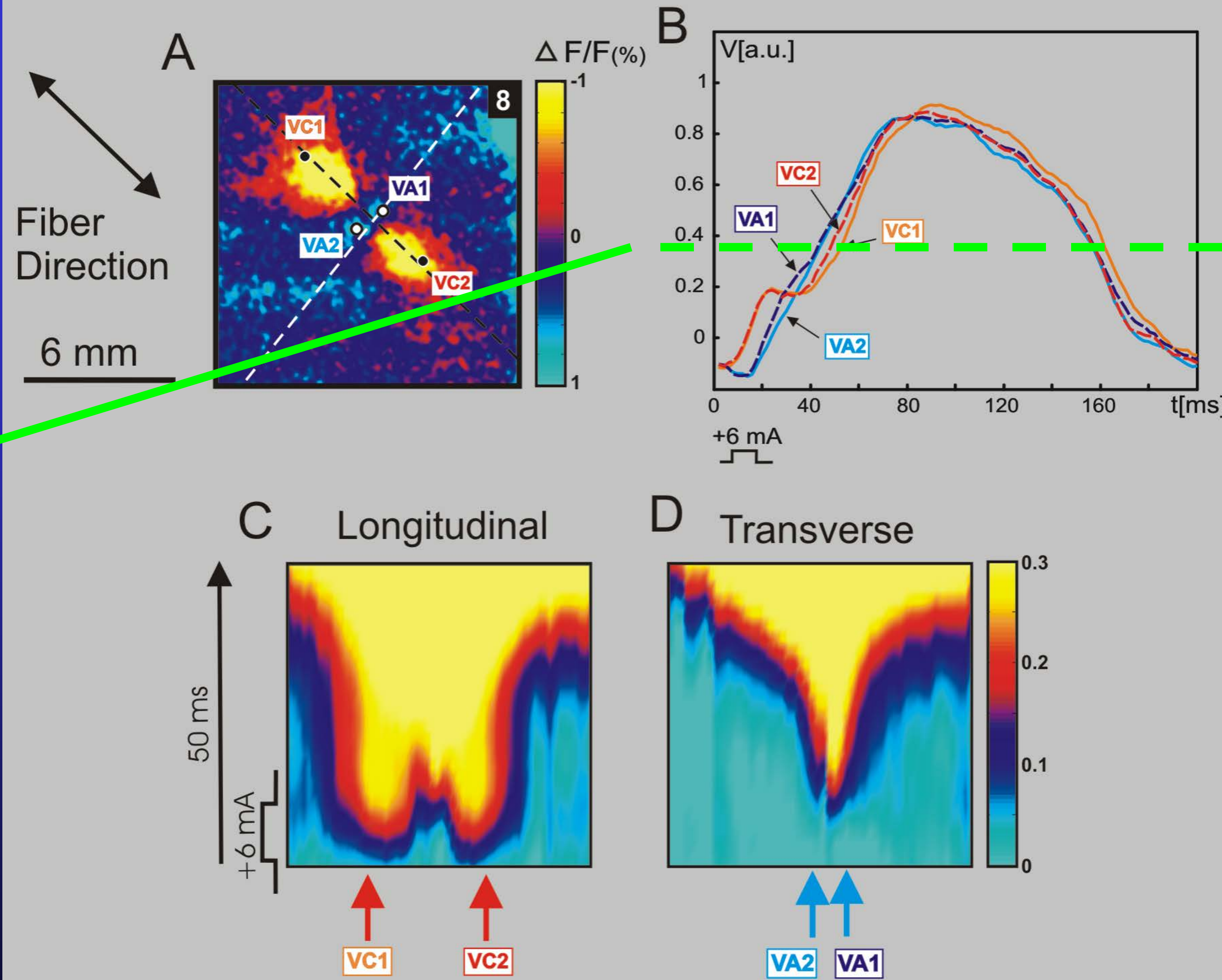


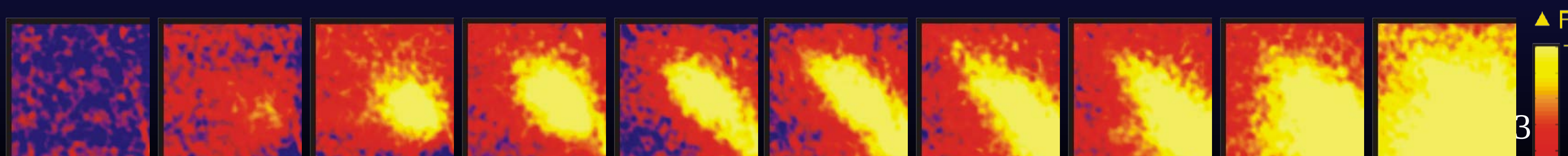
Case D

Anodal make or break?

V_{thresh}

$K^+ = 8$ mM





Conclusions, and Questions for the Modelers…

- While the epicardial whole-heart field shock data are consistent with models, the observed right-left virtual electrode effects are due largely to the curvature of the epicardium-bath interface.
- The right-left effects are less obvious for a flattened RV preparation.
- Virtual anodes are not detectable in diastolic field shocks of isolated, flattened RV.
- Virtual cathodes and anodes in refractory tissue are evident for heterogeneities from insulated needles and papillary muscles.
- Make and break activation are difficult to distinguish at threshold, particularly when there are excitability heterogeneities and at high K^+.

Acknowledgments

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- Bradley J. Roth
  Oakland University, Rochester MI, USA.

Analog vs Digital Computers

- The isolated rabbit heart is a massively parallel high-speed analog computer capable of solving a micromole of equations per second at $25/hour.
- As a computer, the rabbit heart is hard to program and harder to read out.

John Wikswo, “Cell to Bedside”, Keystone, 1993