LIVING STATE PHYSICS
DEPARTMENT OF PHYSICS & ASTRONOMY, VANDERBILT UNIVERSITY

CARDIOLOGY GRAND ROUNDS

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“Tissue Anisotropy and Re-entry in the Heart”

Learning Objectives:

1) The heart as an electrical generator - how to describe the electrical activity of the heart.
2) The electrical anisotropy of cardiac tissue - the heart as a three-dimensional cable.
3) The role of anisotropy in reentry and defibrillation - the effects of strong currents cardiac tissue.

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Outline

- Simple unanswered questions
- The problem of scale
- The uniform double layer model
- The failure of uniform double-layer models
- Cardiac cables
- Cellular discontinuities
- Tissue anisotropy and the cardiac bidomain
- Partial answers

Two Simple Questions

- Why does it require less than 1 joule of electrical energy to fibrillate the heart?
- Why does it require as much as 100 joules of electrical energy to defibrillate the heart?

Simple Unanswered Questions

- How do you relate the kinetics of single ion channels to the electrocardiogram?
- Are there any macroscopic electrical manifestations, *e.g.* in the ECG, of stochastic channel behavior?
- How do you describe the propagation of electrical activity through the entire heart?
- What are the effects of the electrical anisotropy of cardiac tissue?

Simple Unanswered Questions, con't

- What factors affect the initiation of propagated cardiac activation?
- What are the effects of intercellular discontinuities?
- What are the cellular mechanisms for cardiac defibrillation?
- What cellular factors govern spiral wave re-entry?

Models of Cardiac Activity

- Einthoven triangle and the heart vector
- Uniform double-layer model of action potential wavefronts
  - Discontinuous cardiac cells become a continuum
  - The heart is a continuous, homogeneous conductor
- Bidomain models
- Hodgkin-Huxley (BR, EJ, MNT, ND, etc.) membrane models
  - Ion channels melded into a smooth, non-linear membrane
  - Gating described by analytical functions
- Patch clamp and single channel kinetics

How do you relate the kinetics of single ion channels to the electrocardiogram?

The Problem of Scale: Numerical Models

- Divide each cardiac cell into 10 segments
  4×10^{10} segments per heart
- 50 currents and other variables per segment
  2×10^{12} variables per heart
- 5 μs per time step
  2×10^{6} timesteps per 10 sec of fibrillation
- 4×10^{18} equations to solve

- 46,000 years on a 25 MFLOP workstation
- 10 years on 1200 100 MFLOP workstations
- 1 year on a 1 TFLOP workstation
- At 100 bytes per segment, 4 Tbytes of memory or disk to store the model

How do you describe the propagation of electrical activity through the entire heart?

The Uniform Double-Layer Model

- The heart homogeneous, isotropic conductor
- Electrical activity impressed on conductor
- Wavefront 1 mm thick
- Wavefront moves at 1 mm/msec
- Resting cells in front
- Depolarized cells behind
- Current appears on leading surface
- Current disappears on trailing surface
- Uniform wavefront thickness
- Current strength uniform
- Wavefront current perpendicular to surface
- Wavefront described by multiple vectors
- External potential given by solid angle of rim
- No signal outside closed activation wavefront

What are the effects of electrical anisotropy of cardiac tissue?

Cardiac Anisotropy

- Mechanical strength
- Mechanical contraction
- Propagation velocity
- Time constant of the action potential foot
- Rate of rise of the action potential
- Electrical conductivity

Current not parallel to voltage gradient

Cardiac Fibers as One-Dimensional Cables

- Intracellular space
  - Gap functions
  - Functional syncytium
- Extracellular space
- Membrane capacitance and resistance
- Membrane time constant
- Length constant

- Non-linear membrane (BR, EJ, MNT, etc.)
- Extracellular potentials those of a moving dipole

Bidomain Models

- Homogeneous
- Extracellular space
- Intracellular space
- Membrane between
- Current leaving one space must enter the other space
- Ohm’s law applies in each space
- Potential in each space obeys Poisson’s equation
- A three-dimensional cable
- Differing electrical anisotropy for the two spaces

Phenomena unique to the cardiac bidomain with unequal intracellular and extracellular anisotropies

- Extended, quatrefoil current loops exist outside an expanding, activation wave front.
- Measurable, quatrefoil magnetic fields are produced by the extended current loops.
- The virtual cathode from strong, point stimulation has a dog bone shape.
- The virtual cathode exists in three dimensions, and rotates with depth due to the differing fiber orientations.
- The shape of the virtual cathode is altered pharmacological agents that block ion channels.
- Fiber rotation can alter the shape of the virtual cathode recorded on the epicardium.

Phenomena unique to the cardiac bidomain with unequal intracellular and extracellular anisotropies, con’t

- Point stimulation produces longitudinal hyperpolarization.
- Point anodal stimulation can produce adjacent depolarization.
- Simultaneous virtual cathodes and anodes explain make and break stimulation.
- Bipolar stimulation produces complex areas of depolarization and hyperpolarization.
- Directionally-dependent time constant of the action potential foot.
- Uniform field defibrillation of hearts with curved fibers can polarize membranes deep within the myocardium.
- Strong point stimulation can produce quatrefoil spiral-wave reentry.

Prediction

Unequal anisotropy ratios cause action currents to form extended, clover-leaf loops outside of an expanding, circular wavefront.

"Current flow patterns in two-dimensional anisotropic bisynctia with normal and extreme conductivities," R. Plonsey and R.C. Barr, *Biophysical* J., **45**: 1191-1202 (1984).

What factors affect the initiation of propagated cardiac activation?

Definition

In nerves, the **virtual cathode** is the region adjacent to a stimulating cathode that is depolarized rapidly by electrotonic spread; propagation begins at the virtual cathode edge, not at the electrode.

Prediction

The virtual cathode has a dog-bone shape at high stimulus strengths.

“Current Injection into a Two-Dimensional Anisotropic Bidomain,” N.G. Sepulveda, B.J. Roth, and J.P. Wikswo, Jr., *Biophysical* J., **55**: 987-999 (1989).

Prediction

A region of hyperpolarization exists along the fiber direction outside of the dog-bone shaped virtual cathode.

"Current Injection into a Two-Dimensional Anisotropic Bidomain," N.G. Sepulveda, B.J. Roth, and J.P. Wikswo, Jr., *Biophysical J*., **55:** 987-999 (1989)

Long-Standing Puzzle

Why can the heart be stimulated electrically in four different ways?

- Turning-on of negative current (cathodal make)
- Turning-on of positive current (anodal make)
- Turning-off of negative current (cathodal break)
- Turning-off of positive current (anodal break)

Prediction

The region of hyperpolarization distant from a cathodal electrode becomes a region of depolarization for an anodal electrode, providing one explanation for anodal stimulation.

"Electrical stimulation of cardiac tissue: A bidomain model with active membrane properties," B.J. Roth and J.P. Wikswo, Jr., IEEE *Trans. on Biomed. Eng.*, **41:** 232-240 (1994).

What cellular factors govern spiral wave re-entry?

Prediction

In tissue with differing intracellular and extracellular anisotropies, a second, strong stimulus, delivered at the same location and during the vulnerable phase of the first wave front, results in a reentrant wave with four phase singularities.

- Thick line - depolarization phase
- Thin line - repolarization

“ The formation of a re-entrant action potential wave front in tissue with unequal anisotropy ratios,” B.J. Roth and J.M. Saypol, *International J. of Bifurcation and Chaos*, **1:** 927-928 (1991)

The Problem of Defibrillation

If the heart is a cable with a length constant of 1 mm to 3 mm, the transmembrane potential will fall below threshold within several length constants of the electrodes.

Possible Answers

- Discrete mechanisms
  - Intracellular junctions
  - Uncoupled bundles
  - Patches of fat or collagen
- Continuous mechanisms
  - Cardiac surfaces
  - Fiber ends
  - Tissue anisotropy
  - Fiber curvature
  - Fiber branching
  - Strand taper
  - Fiber rotation

“Cardiac tissue in an electrical field: A study in electrical stimulation,” N.A. Trayanova and B.J.Roth, *Computers in Cardiology 1992*, (IEEE Computer Society Press, 1992) pp. 695-698.

Prediction

When a spherical heart with curved or branched fibers is placed in a uniform electric field, equal anisotropies will produce depolarization or hyperpolarization only near the surfaces, whereas nominal anisotropy or no transverse coupling will produce bulk depolarization.

“The response of a spherical heart to a uniform electric field: A bidomain analysis of cardiac stimulation,” N.A. Trayanova, B.J. Roth, and L.J. Malden, *IEEE Trans Biomedical Engineering*, **40**: 899-908 (1993).

The Challenges

- Continue to develop realistic models that provide a physiologically-interpretable connection between channel-level pharmacology and the whole heart.
- Use clever instrumentation and experimental interventions to test the models quantitatively.