Models and Measurements of the Anisotropic Cardiac Bidomain

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Vanderbilt Institute for Integrative Biosystems Research and Education
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
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

10 centimeters

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

- \( m = \frac{1}{2} \mathbf{r} \times \mathbf{p} \) explains relation of electric and magnetic vectors
- Double-layer rim determines both \( m \) and \( p \)
- Little significant new information in the MCG…?
Add the effects of tissue anisotropy…

10 centimeters
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

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

A cardiac cell: an 80 variable automaton

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

\[
\begin{align*}
\sigma_{ix} &= 2 \times 10^{-4} \\
\sigma_{iy} &= 2 \times 10^{-5} \\
\sigma_{ex} &= 8 \times 10^{-4} \\
\sigma_{ey} &= 2 \times 10^{-4}
\end{align*}
\]

\[
\frac{\sigma_{ix}}{\sigma_{iy}} = 10 \\
\frac{\sigma_{ex}}{\sigma_{ey}} = 4
\]

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

\[
C_m \frac{\partial V_m}{\partial t} = - J_{ion} - \frac{1}{\beta} \nabla \cdot \tilde{g}_e \nabla V_e ,
\]

\[
\nabla \cdot (\tilde{g}_i + \tilde{g}_e) \nabla V_e = - \nabla \cdot \tilde{g}_i \nabla V_m ,
\]

where $\tilde{g}_i$ and $\tilde{g}_e$ are the intracellular and extracellular conductivity tensors; $\beta$ 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 (≤250)

• Intracellular potential
  – Intracellular microelectrodes (≤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 cm³ bath

37 ºC Tyrode’s solution
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)
There is no single coordinate system in which the tensor conductivity is everywhere diagonal!
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)

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)

Synchronous Imaging of Point Activation Patterns

--- Virtual Electrodes ---

Cathode Make
-10 mA

Anode Make
+10 mA

Cathode Break
-2 mA

Anode Break
+3 mA

Depolarized

Hyperpolarized

Fiber Direction

10,000 pixel/frame

1 mm

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

![Graph showing field sensitivity](image)

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

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

1 ms after stimulus

b-fmpr1.mpg

1 millimeter

Courtesy of Franz Baudenbacher
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
Experimental Setup - Optical Imaging

Laser Light 532nm

CCD-Camera

Heart

fl4.mpg

Courtesy of Jenny Holzer and Franz Baudenbacher
fiber direction

SQUID scan area

fluorescent image area

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*

![NO SINGULARITIES](image1)

![FOUR SINGULARITIES](image2)
Quatrefoil Reentry

Numerical

Experimental

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°, ...

From Voltage to Phase Space

Theory

Experiment

Frame Difference

Numerical

Experimental

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

\[ n_t = \frac{1}{2\pi} \int_c \nabla \phi \cdot d\vec{l} \]

where \( \phi \) 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 $k$.
- $\text{Curl } k$ is equivalent to the topological charge, which is zero everywhere except at singularities.

\[
(\nabla \times \vec{k}) \cdot \hat{z} = \lim_{a \to 0} \frac{1}{\pi a^2} \int_c \frac{k^2}{d\ell}
\]
Calculation of topological charge

- We can use image processing operations that evaluate $\text{curl } k$ to track phase singularities in reentry movies

- $\text{Curl } k$ may be approximated with the following:

\[
(\nabla \times \vec{k}) \cdot \hat{z} \propto \nabla_x \otimes k_y + \nabla_y \otimes k_x
\]

\[
\nabla_x = \begin{bmatrix} -1/2 & 0 & +1/2 \\ -1 & 0 & +1 \\ -1/2 & 0 & +1/2 \end{bmatrix} \quad \nabla_y = \begin{bmatrix} +1/2 & +1 & +1/2 \\ 0 & 0 & 0 \\ -1/2 & -1 & -1/2 \end{bmatrix}
\]
Simulated Fibrillation

$V_m$ Phase

Variance Curl

Vm_Var_Phase_Curl.mp4

Courtesy of Mark Bray and Rubin Aliev
3-D Filaments

The convolution operation can be extended to 3 dimensions

Courtesy of Mark Bray
What Does a Defibrillation Shock Do?

- 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)

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
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