Termination of fibrillation using low-energy far-field stimulation: A computational and optical mapping study

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Outline

• Why far-field (FF) low-energy defibrillation?

• What are virtual electrodes?

• How can they be recruited?

• Examples of synchronization and termination of arrhythmias (in canine preparations).
Introduction

• Termination of Atrial arrhythmias
• Antiarrhythmic drug therapy
• Ablation
• Electrical therapies
  – ATP (effective only for slow tachycardias)
  – Electrical cardioversion (requires >5V/cm)\(^1\)
    External \(\sim 100\)J - 280J up to 360J (1000V, 30-45 A)\(^3\)
    Internal \(\sim 7\)J (350V, 4 A)\(^2\)

Objective

- Demonstrate that cardioversion can be achieved by a series of far-field low-energy pulses (~1.4V/cm) delivered at a frequency close to the dominant frequency of the arrhythmia.
- Internal ~7J (350V, 4 A) (requires >5V/cm)
- This method is based on the idea of recruitment of virtual electrodes in cardiac tissue and global synchronization.
Virtual electrodes and intrinsic tissue heterogeneities

Fibers (regions where divergence is not zero)

Discontinuities in conductivity can result in virtual electrodes

Heart stripped of all cardiac cells, extracellular matrix
University of Minnesota

Extracellular matrix
University of Auckland

Vessels

• Virtual electrodes and intrinsic tissue heterogeneities


Discontinuities in conductivity can result in virtual electrodes

When an electric field is applied current flows in the extracellular and intracellular media
• Virtual electrodes and intrinsic tissue heterogeneities


Discontinuities in conductivity can result in virtual electrodes that can produce secondary sources


When an electric field is applied current flows in the extracellular and intracellular media
Virtual electrodes and intrinsic tissue heterogeneities

The larger the inexcitable (change in conductivity) area, the smaller the electric field strength necessary to initiate a “secondary source” or “secondary activation.”

Proof of concept
Virtual electrodes and intrinsic tissue heterogeneities

The larger the inexcitable (change in conductivity) area, the smaller the electric field strength necessary to initiate a “secondary source” or “secondary activation.”

Field Strength Threshold

Bidomain (GMRES)
dx=.01 cm, dt=.01 ms
Zero-flux B.C.s, phase field
$I_{ion}$: Fox et al. model
Virtual electrodes and intrinsic tissue heterogeneities

The larger the inexcitable (change in conductivity) area, the smaller the electric field strength necessary to initiate a "secondary source" or "secondary activation."

Bidomain (GMRES)

\[ dx = 0.01 \text{ cm}, \ dt = 0.01 \text{ ms} \]

Zero flux B.C. Phase field

\( I_{\text{ion}} \)

Fox et al. model

Proof of concept

Field Strength Low

Bidomain (GMRES)

\[ dx = 0.01 \text{ cm}, \ dt = 0.01 \text{ ms} \]

Zero flux B.C. Phase field

\( I_{\text{ion}} \) Fox et al. model
Virtual electrodes and intrinsic tissue heterogeneities

The larger the inexcitable (change in conductivity) area, the smaller the electric field strength necessary to initiate a “secondary source” or “secondary activation.” (more than size, ~solid angle)

![Diagram of simulation system](image)

**Field Strength Medium**

Bidomain (GMRES)
\[ dx = 0.01 \text{ cm}, \ dt = 0.01 \text{ ms} \]
Zero flux B.C. Phase field
\[ I_{ion}, \text{Fox et al. model} \]

![Diagram of tissue conductivity](image)
Virtual electrodes and intrinsic tissue heterogeneities

The larger the inexcitable (change in conductivity) area, the smaller the electric field strength necessary to initiate a “secondary source.”
Virtual electrodes and intrinsic tissue heterogeneities

The larger the inexcitable (change in conductivity) area, the smaller the electric field strength necessary to initiate a “secondary source.”

Proof of concept (experimental) Cryoablation and optical mapping
Virtual electrodes and secondary sources

The larger the inexcitable (change in conductivity) area, the smaller the electric field strength necessary to initiate a “secondary source.”

Field Strength
$E = 0.18 \text{ V/cm}$
Virtual electrodes and secondary sources

The larger the inexcitable (change in conductivity) area, the smaller the electric field strength necessary to initiate a “secondary source.”

Field Strength
E = 0.56 V/cm
Virtual electrodes and secondary sources

The larger the inexcitable (change in conductivity) area, the smaller the electric field strength necessary to initiate a “secondary source.”
Virtual electrodes and secondary sources
Virtual electrodes and secondary sources

Bidomain (GMRES)
\(dx = 0.01 \text{ cm}, \ dt = 0.01 \text{ms}\)
Zero-flux B.C.s, phase field
\(I_{\text{ion}}\): Fox et al. model
Virtual electrodes and secondary sources

Example with large holes was a proof of concept

Not only large holes but also smaller conductivity discontinuities can act as “virtual electrodes.”
Virtual electrodes and secondary sources

Example with large holes was a proof of concept

Not only large holes but also smaller conductivity discontinuities can act as “virtual electrodes.”

Field Strength
\[ E = 0.6 \, \text{V/cm} \]

Field Strength
\[ E = 1.2 \, \text{V/cm} \]

Bidomain (GMRES)
\[ dx = 0.01 \, \text{cm}, \ dt = 0.01 \, \text{ms} \]
Zero flux B.C.s, finite volume
\[ I_{\text{ion}}: \text{Fox et al. model} \]
Collagen \( \sim 0.065\text{cm} \)
Virtual electrodes and secondary sources

Example with large holes was a proof of concept

Not only large holes but also smaller conductivity discontinuities can act as “virtual electrodes.”

The more “virtual electrodes” recruited, the faster the whole tissue is excited.
Defibrillation via Virtual Electrodes by synchronization

Termination of spiral waves in simulated cardiac tissue by 4 low-energy shocks.

As the tissue synchronizes to the pacing period, more tissue gets activated simultaneously, and the reentries are terminated.

Bidomain (GMRES)
dx=.01cm, dt=.01ms
Zero flux B.C.s, finite volume
$I_{ion}$: Nygren et al. atrial cell model
Collagen ~ .065cm
• Virtual Electrodes: Summary

• Larger heterogeneities are involved at lower field strengths.
• As more virtual electrodes are recruited, the time required to activate the entire tissue decreases (as more tissue is recruited).
Virtual Electrode Formation: Experimental Confirmation

**Point stimulus:**
32 ms to activate

Fenton et al., Circulation, in press
Virtual Electrode Formation: Experimental Confirmation

**Point stimulus:**
32 ms to activate

Electric field, **0.32 V/cm**:
20 ms to activate

Fenton et al., Circulation, in press
Virtual Electrode Formation: Experimental Confirmation

**Point stimulus:**
32 ms to activate

Electric field, **0.32 V/cm**:
20 ms to activate

**0.46 V/cm**:
16 ms to activate

Fenton et al., Circulation, in press
Virtual Electrode Formation: Experimental Confirmation

**Point stimulus:**
32 ms to activate

Electric field, **0.32 V/cm**:
20 ms to activate

0.46 V/cm:
16 ms to activate

1.4 V/cm:
12 ms to activate

Average from 5 different experiments
Virtual Electrode Formation: Experimental Confirmation

The change in membrane potential \( e = V - V_{\text{rest}} \) around an obstacle by a small electric field is given by

\[
\nabla^2 e - \frac{e}{\lambda^2} = 0
\]

With boundary conditions \( \nabla (e + E \cdot \mathbf{r}) \cdot \mathbf{n} = 0 \) at \( r = R \).

The minimum electric field \( E \) necessary to bring the voltage above threshold in 3D is given by where \( \alpha = \frac{\lambda}{R} \)

\[
E = \frac{V_t - V_{\text{rest}}}{1 + 2\alpha + 2\alpha^2} \frac{1}{\lambda} \frac{1 + \alpha}{1 + \alpha}
\]

For low electric fields \( E \sim 1/R \)

An activation from a SS propagating radially with constant velocity \( v \) will excite a volume \( V = 4/3 \pi (v \tau)^3 \) at time \( t \)

For \( N \) obstacles uniformly distributed in tissue with the entire tissue will be excited in \( \tau \approx (3/(4 \pi \rho))^{1/3}/v \)

The density of recruited obstacles is given by

\[
\rho(E) \propto \frac{1}{E^{1.52}} = E^{1.52 \pm 0.07}
\]

\( \tau \propto E^{-0.5} \)

Virtual Electrode Formation: Experimental Confirmation

**Point stimulus:**
32 ms to activate

**Electric field, 0.32 V/cm:**
20 ms to activate

**0.46 V/cm:**
16 ms to activate

**1.4 V/cm:**
12 ms to activate

Average from 5 different experiments
Examples of low-energy far-field stimulation

• Cardioversion success
  \[E = 1.4 \text{ V/cm}\]
  Fenton et al., Circulation, in press

• Cardioversion failure
  \[E = 0.93 \text{ V/cm}\]
Examples of low-energy far-field stimulation and single high-energy pulse cardioversion

FF Failure $E=0.9$ V/cm

FF Success $E=1.4$ V/cm

Cardioversion Failure $E=4.0$ V/cm

Cardioversion Success $E=4.67$ V/cm
Examples of low-energy far-field stimulation in different preparations
Dominant periods 30 - 60 ms

Fenton et al., Circulation, in press
Conclusions

• We show that a series of pulses at low field strength (0.9-1.4 V/cm) recruits a sufficient number of activation sites to entrain, synchronize and extinguish AF.

• Success rate of 93 percent (69/74 trials in 8 canine atrial preparations).

• The energy needed for successful defibrillation using FF-AFP ranged between 0.074 and 0.81 J, with an average of 0.24 J, which is below the energy where sedation is necessary (0.5 to 1 J).

• Cardioversion by single shock in same preparations required > 4 J.

• FF-AFP reduces energy up to 90% in some examples.

Fenton et al., Circulation, in press
Future directions

Ventricular fibrillation
Future directions

Ventricular fibrillation

FF Failure $E=1.2$ V/cm

FF Success $E=1.4$ V/cm
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http://TheVirtualHeart.org

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Future directions

- Use protocol for VT/VF (7 in vitro experiments already)
- Use protocol in vivo
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• Use protocol in vivo (2 canine trials already)

• Use newly digitized high-resolution 3d canine hearts to study numerically
  - Electrode shape and position
  - Wave forms (biphasic, truncated etc…)

250 micron resolution with fiber orientation

http://thevirtualheart.org
\[ C_m \frac{\partial V}{\partial t} = \nabla \cdot D \nabla V - I_{ion} \]

\[ \nabla^2 e - \frac{e}{\lambda^2} = 0 \quad e = V - V_{rest} \]

\[ E_{3\text{dim}} = \frac{V_i - V_{rest}}{\lambda} \frac{1 + 2\alpha + 2\alpha^2}{1 + \alpha} \]

\[ \alpha = \frac{\lambda}{R} \]

\[ V = \frac{4}{3} \pi (\nu \tau)^3 \quad \rho = \frac{N}{V} \]

\[ \tau \approx \frac{3}{(4\pi\rho)}^{1/3} / \nu \]

\[ \rho(E) = \int_{R_{\text{min}}(E)}^{R_{\text{max}}} p(R) \, dR \]

\[ p \propto 1/R^{2.52 \pm 0.07} \]

\[ \tau \propto E^{-0.51 \pm 0.02} \]

\[ \rho \propto E^{1.52 \pm 0.07} \]
Future directions

• Use protocol in vivo (2 canine trials already)

• Use protocol for VT/VF (3 in vitro experiments already)

• Use newly high resolution digitized 3d canine hearts to study numerically
  - Electrodes shape and position
  - Wave forms (biphasic, truncated etc…)

http://thevirtualheart.org
No VT/VF initiation
FF-AFP success in vivo
• Reconstruction of whole hearts (from DTMRI)

With (DTMRI @ 250 microns resolution)
3D Heart Reconstruction

Canine heart (MRI @ 120 microns resolution)

With (DTMRI @ 250 microns resolution)
Use of Blebbistatin

Canine tissue (microelectrode recordings)
Use of Blebbistatin

Equine tissue (microelectrode recordings)
• **Virtual Electrodes: Theory**

- Electric field induces tissue depolarization/hyperpolarization at tissue edges.
- Intrinsic heterogeneities provide additional edges, allowing “virtual electrodes” to form deep within tissue.

Field Strength

0.5 V/cm

1.0 V/cm

1.4 V/cm

_Fenton FH et al., submitted_