Multi-Scale Electrophysiological Modeling

Collaboration with

- Duke University: Biomedical Engineering Department
- Craig Henriquez’ laboratory
Background

Research:
Simulations of spread of electrical activity in the cardiac tissue

<= Spread of activity in atria

Goal:
Understanding how activation spreads in 3D and what possible mechanisms are behind Arrhythmia

CS Henriquez et al.
Research questions

➡ Is the bidomain approximation valid?
➡ What are the underlying mechanisms in the spread of activation?
➡ How do we incorporate different pathologies into the model?
At a cellular level the major factors in propagation are:
(1) Behavior of the membrane
(2) Coupling of cells through gap junctions
(3) Pathways of currents in intracellular and extracellular space
(4) Capacitance of the membrane
Bidomain approach to cardiac modeling

Continuous bidomain approach:

- Intracellular space
- Extracellular space
- Space with conductivity adjusted for the volume fraction of modeled space

Each domain is characterized by a specific one conductivity tensor

Membrane model connecting each point in space to the other domain (total domain = 4D)
Our approach:

**Discrete bidomain**

- Realistically shaped intra and extracellular spaces that do not overlap in space.
- Realistically shaped membrane model (2D) connecting to volumetric spaces (3D).

- More realistic model
- Discrete bidomain
- Realistically shaped interstitial space and myocytes.
- Discrete coupling of gap junctions.
- Membrane is located between both physical spaces.
- 3D layout of tissue
- Small piece of tissue only (400 cells)
SCI-Duke collaboration

➡️ Creation of software capable of simulating this new modeling strategy
➡️ Creation of meshing techniques to do microscopic models (unstructured grids)
➡️ Creating solvers that are capable of solving problem on unstructured grids
➡️ Visualization of results
Discrete Bidomain Model

Strand of 3 by 3 by 25 myocytes

Cells are stimulated at this end using a 0.3 ms block pulse

Reference electrode

Intercalated discs containing gap junctions

Membrane surrounding myocytes
Simple geometric models

- Proof of concept
- Validation of methods
- Finding proper settings for mesh and time scales
- Explore dependency on Extracellular matrix
**Distribution of extracellular space**

Different cross sections representing different distributions of extracellular space:

- Same ECS thickness between myocytes
- No myocyte in the center
- Same ECS thickness between myocytes

25 vol% = ECS
33 vol% = ECS
34 vol% = ECS
15 vol% = ECS
25 vol% = ECS

**TISSUE MODELING**

- Membrane model: Luo-Rudy 1
- Extracellular conductivity 20 mS/cm
- Intracellular conductivity 3 mS/cm
- Gap junction resistivity 0.0015 kΩcm²
- Timestep 50 ns

**Membrane model:** Luo-Rudy 1

- Extracellular conductivity 20 mS/cm
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Result Extracellular distribution

- Action potential conduction speed: 0.556 m/s
  - Time 1: 1.749 ms
  - Time 2: 2.868 ms
- Action potential conduction speed: 0.580 m/s
  - Time 1: 1.682 ms
  - Time 2: 2.754 ms
- Action potential conduction speed: 0.570 m/s
  - Time 1: 1.708 ms
  - Time 2: 2.800 ms
- Action potential conduction speed: 0.504 m/s
  - Time 1: 1.911 ms
  - Time 2: 3.145 ms
- Action potential conduction speed: 0.556 m/s
  - Time 1: 1.747 ms
  - Time 2: 2.866 ms
Conclusions from simple geometric models

- The amount of ECS in a bundle matters for the propagation of the action potential.
- The actual distribution has a smaller influence on the action potential propagation speed.
- The distribution of gap junctions matters.
- The bidomain and multi-domain render the same type of solutions for symmetric models.
Realistically shaped bundle: anisotropy

- Experiments suggest that shrinking EC space makes tissue more isotropic in cardiac conduction.
- Transverse conduction not well understood
- Literature suggests various theories: capacitive coupling, conduction through gap-junctions
More realistic shapes (1)

Building block: hexagon

Cluster of 27 myocytes

Capillaries
More realistic shapes (2)

Gap-junction distribution:

[Diagram showing gap-junctions and myocytes]
More realistic shapes (3)

Model of a piece of cardiac tissue:

Gap junctions

One myocyte
Simulating a slab of tissue

We replicate tissue indefinitely in the two directions perpendicular to the wave front.
Simulating propagation across fiber
Preliminary results

- Conduction across fiber seems to speed up when ECS is shrunk
- Conduction along fiber seems to slow down when ECS is shrunk
- Model seems to behave differently than classical bidomain models
Future work

- Translate findings back into bidomain modeling.
- Finding effective conductivity tensors, and membrane parameters to reflect pathologies in bidomain modeling.
TISSUE MODELING