Modeling approaches to characterizing irregular conduction in micro-heterogeneous tissues

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Motivating Question

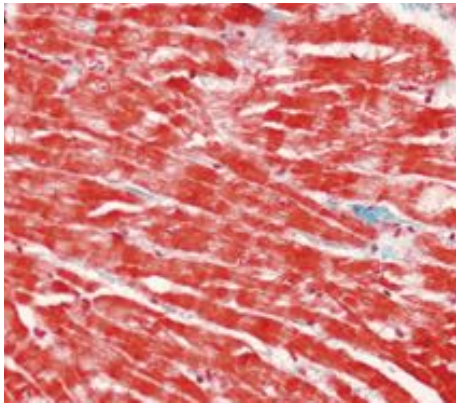
How do microscopic changes in the structure of the heart tissue, such as those caused by aging and diseases, affect the electrical conduction of the heart?

Outline

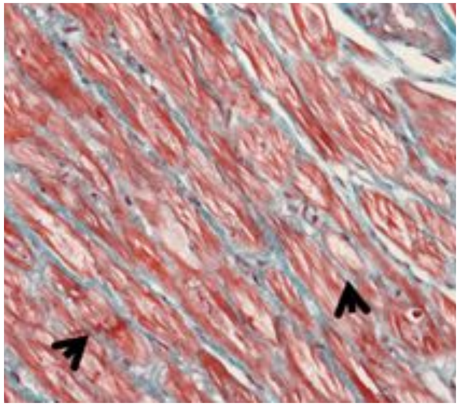
- Background
- Methodology of Paired Computational and Experimental Studies
- Effects of Microheterogeneities on Conduction

Fibrosis Distorts Conduction

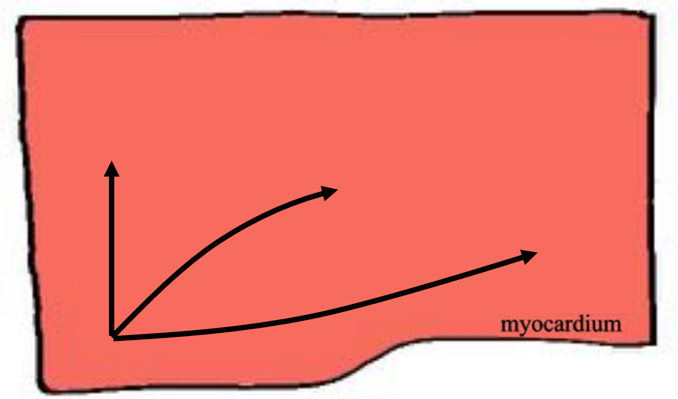
Healthy Control

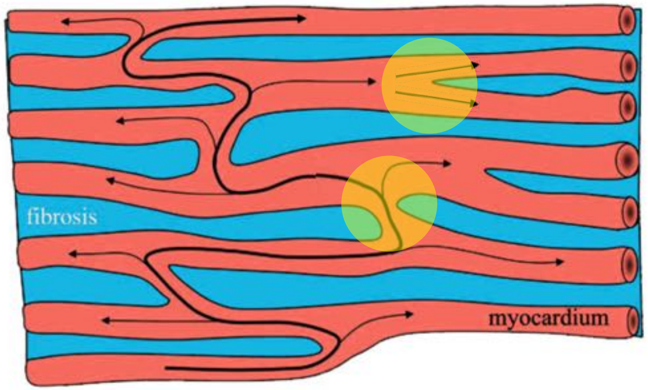


Atrial Fibrillation



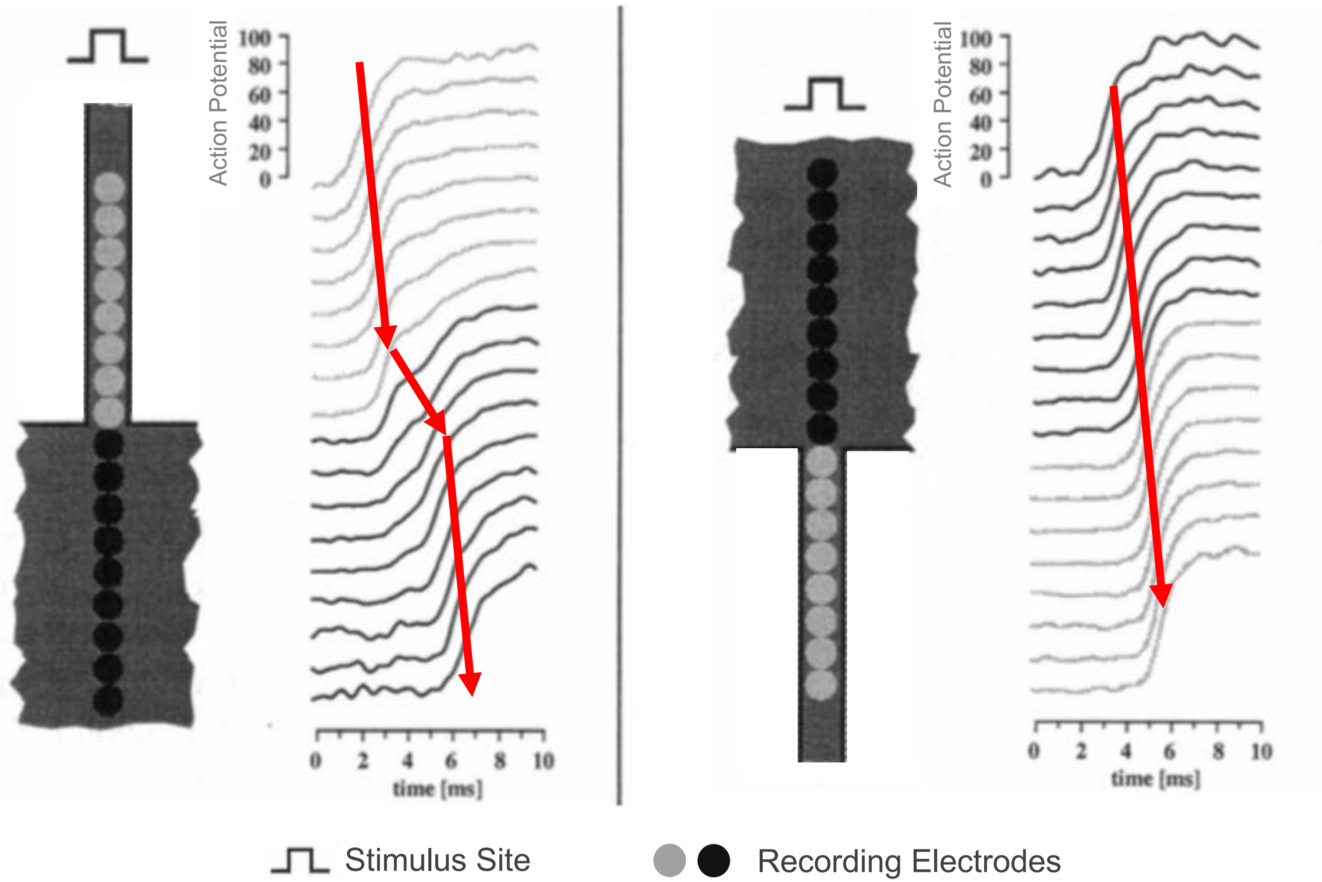
Red: Normal cardiac muscle
Blue: Collagen
Arrow: Muscle breakdown





Zhang et al. 2013;
Adapted from de Jong et al. 2011

Tissue Geometry Alters Conduction

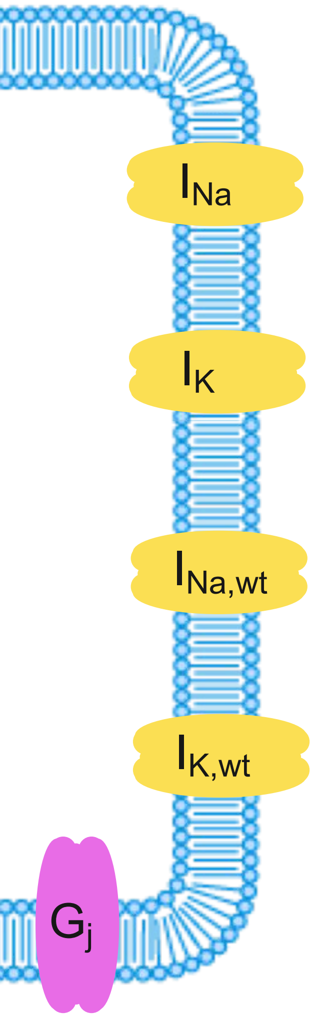


Adapted from Rohr and Kucera 1997

What about more complex fibrosis?

- Individual heterogeneities change geometry and modulate local conduction
- → What is the effect of numerous heterogeneities in aggregate (i.e. complex fibrosis)?

Engineered Excitable Cells for Paired Studies



- HEK-293 cell + $Na_v1.5$ + $K_{ir}2.1$ + Cx43
  - Excitable ”Ex293 cells”
  - Kirkton et al. 2011
- Mathematical model of Ex293 cells
  - Inter-cell variability in current densities
  - Gokhale et al. 2017

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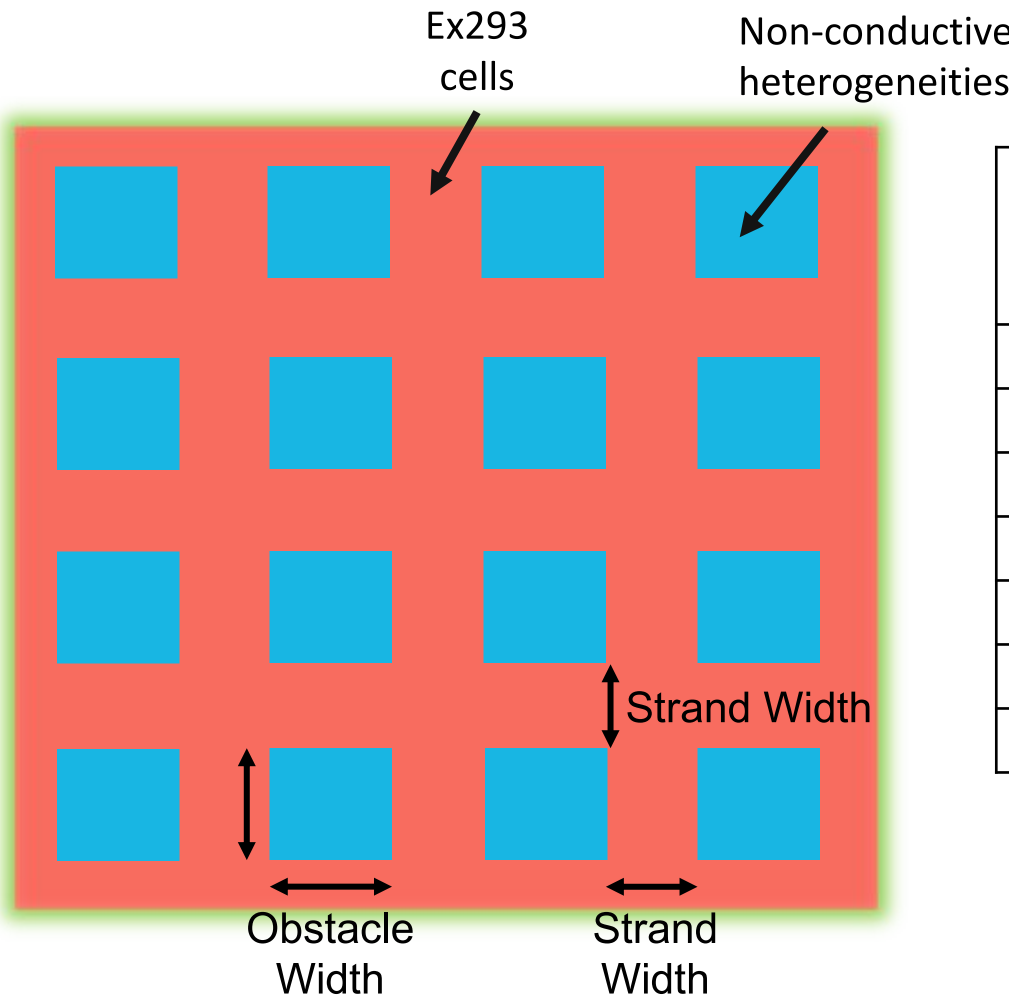
Regular patterns of heterogeneity

Idealized geometry of fibrotic tissue with regularly spaced and equally sized non-conductive heterogeneities



Obstacle to Strand Ratio	Obstacle Width	Strand Width	Obstacle Density
0	—	—	0 %
0.3	150 μm	520 μm	5 %
0.6	150 μm	240 μm	15 %
1.5	150 μm	100 μm	35 %
3.0	300 μm	100 μm	56 %
5.0	500 μm	100 μm	69 %
7.0	700 μm	100 μm	77 %

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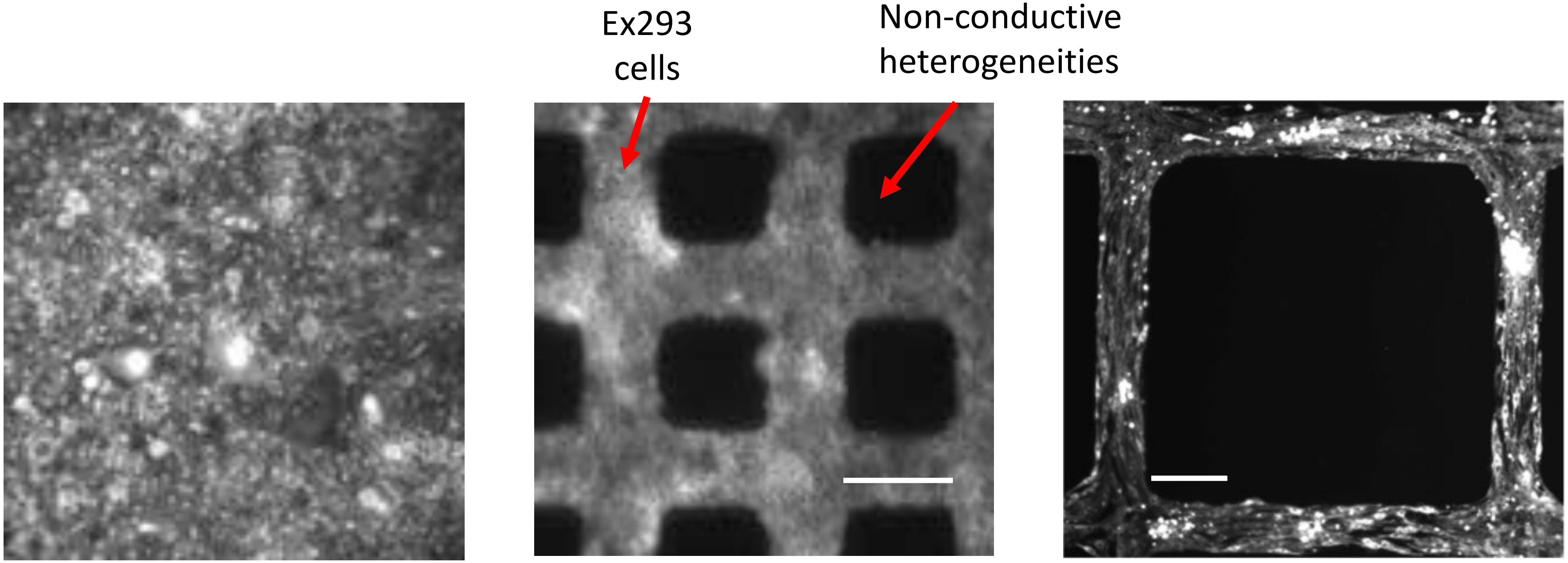
Regular patterns of heterogeneity



Control | Obstacle to Strand: 1.5 | Obstacle to Strand: 7.0

Obstacles patterned as 150 µm in width were 151.7 µm to 162.6 µm after 4 days of culture

Scale bar: 150 µm

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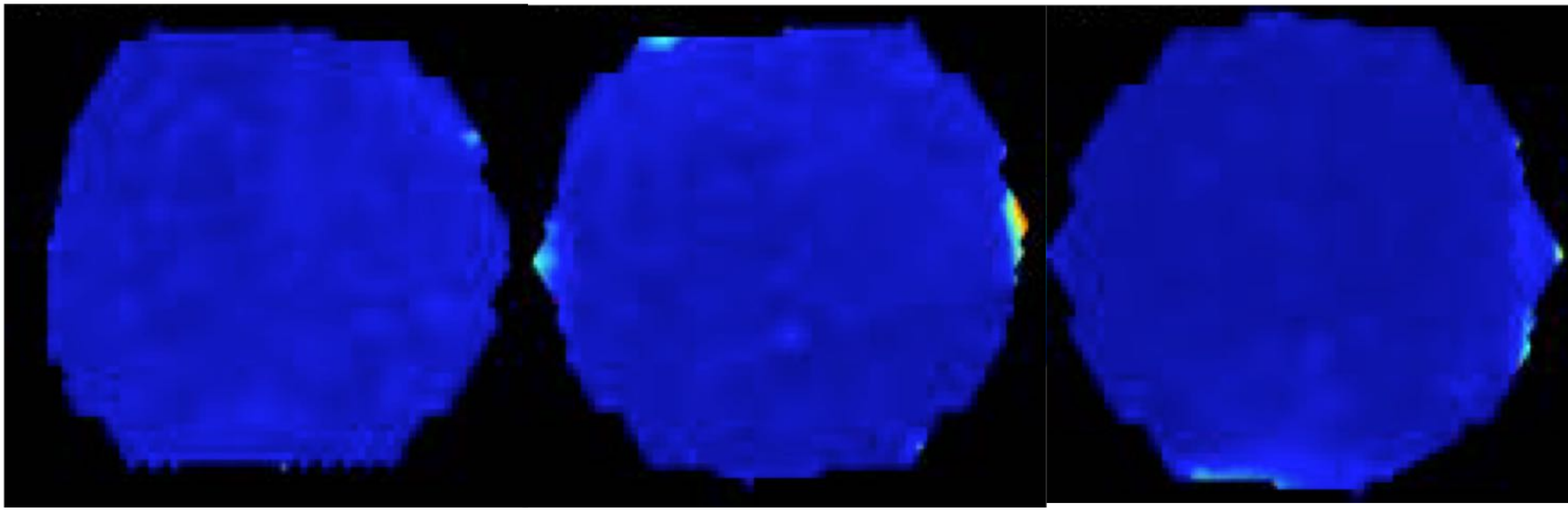
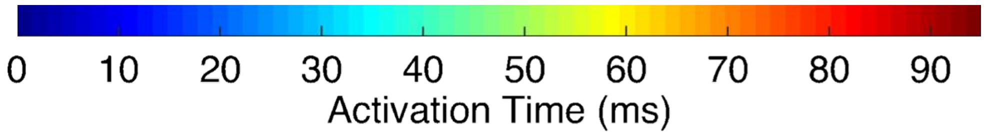
Effects of Heterogeneity



Obstacle-to-Strand Ratio: 0
Relative CV: 1.0

Obstacle-to-Strand Ratio: 1.5
Relative CV: 0.862

Obstacle-to-Strand Ratio: 7.0
Relative CV: 0.794



0.5 cm

CV: Conduction velocity

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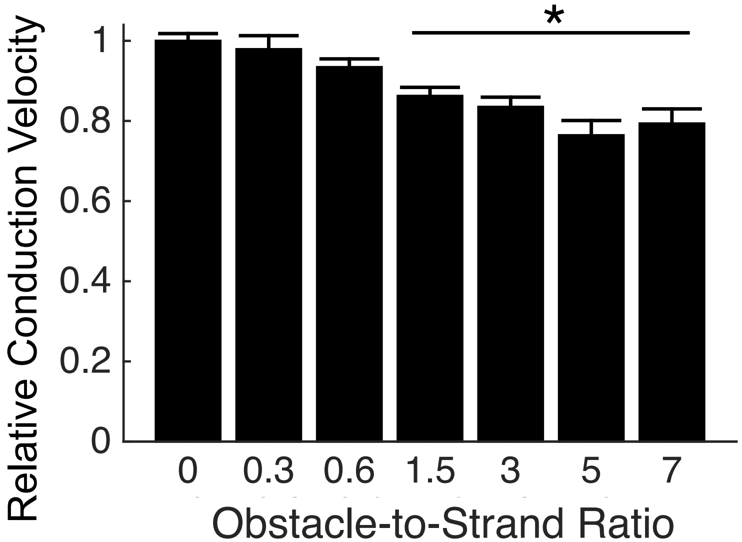
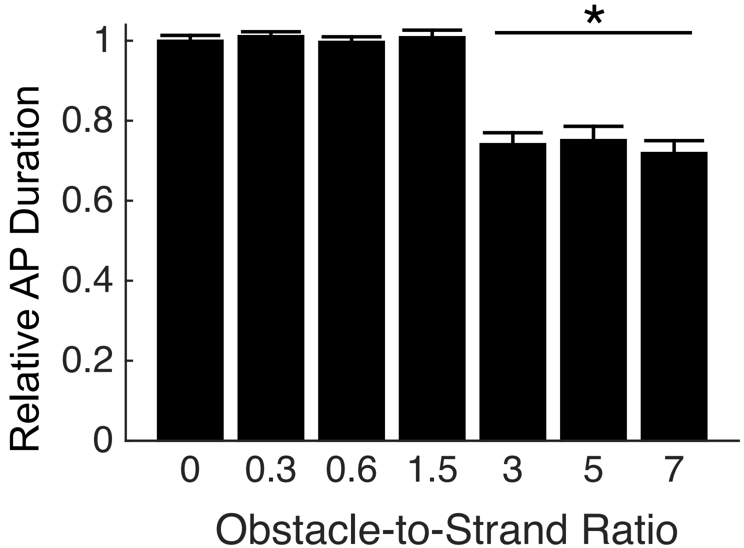
Effects of Heterogeneity



Mean ± se; n = 13-68 monolayers
Asterisk indicates difference from 0 case



Mean ± self; Asterisk indicates difference from 0 case

AP: Action potential

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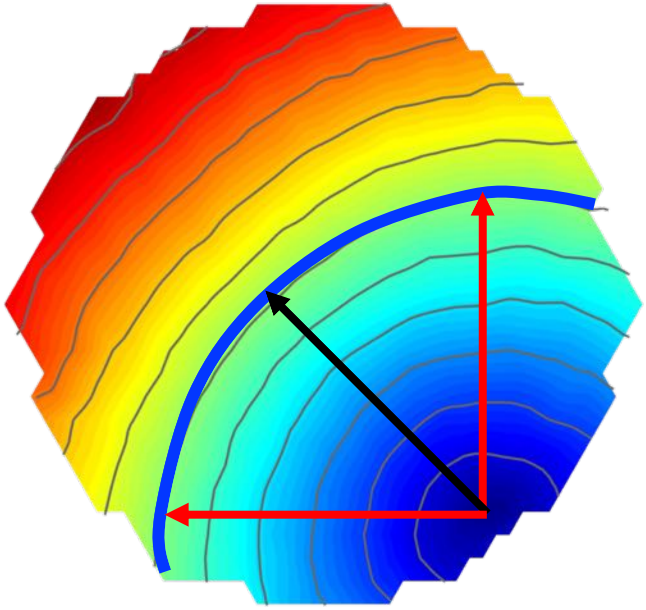
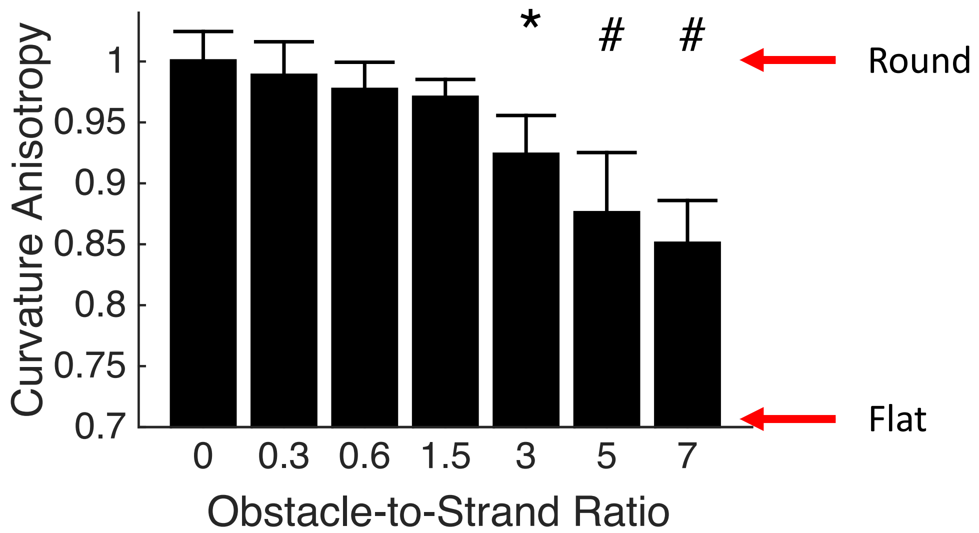
Effects of Heterogeneity





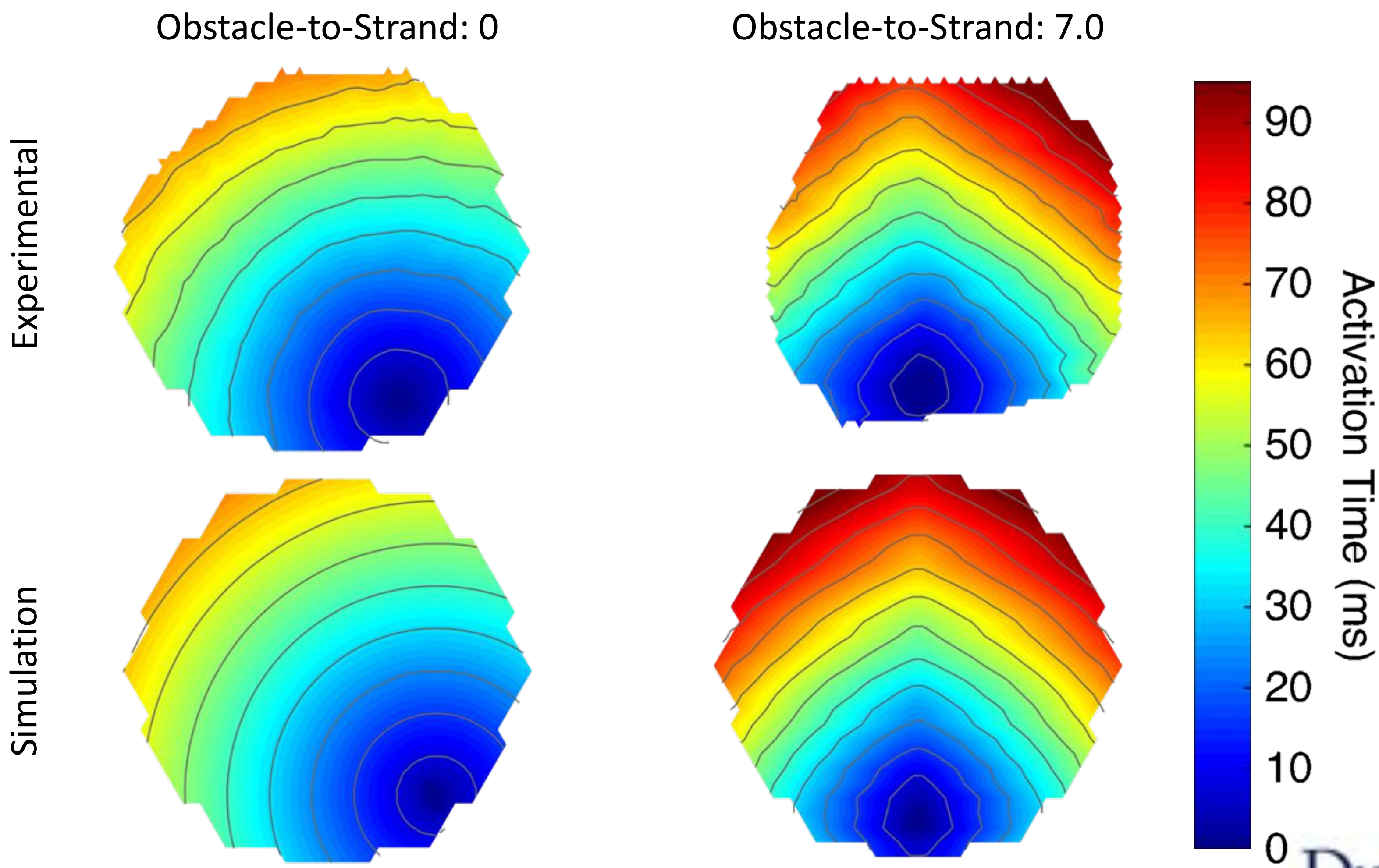
Mean ± sd; n = 10-15 monolayers
* and # indicate difference from all lower

Curvature anisotropy: ratio of distance along diagonal (black) to distance along principal axes (red)

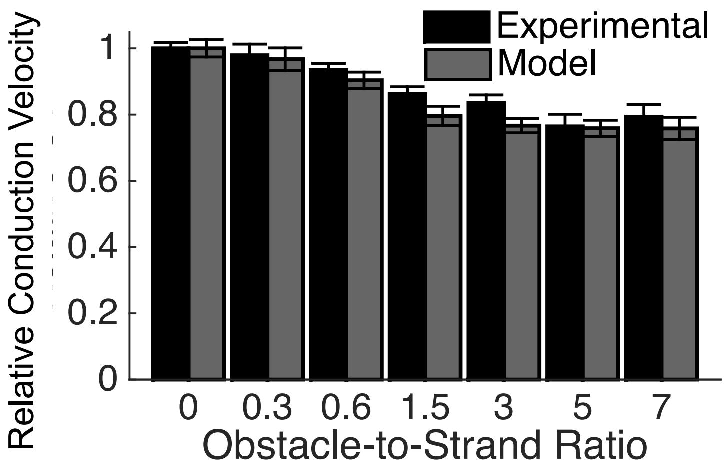
Model Specifications

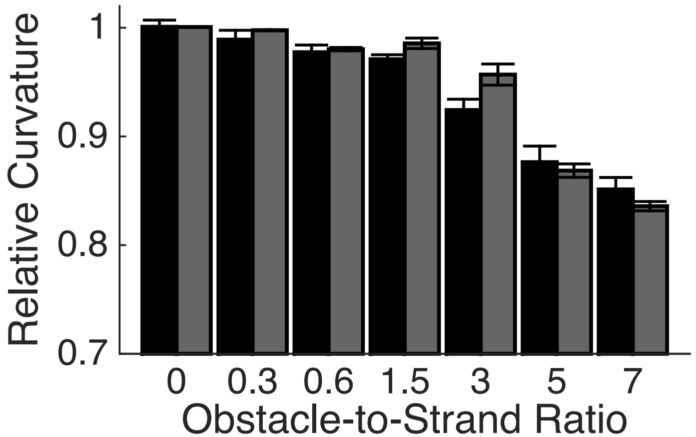
- Monodomain formulation
- Finite differences discretization of spatial operator with $dx = dy = 10\ \mu m$
- Obstacles with no-flux boundaries
- Simulated potentials processed to make comparable to experimental optical mapping data

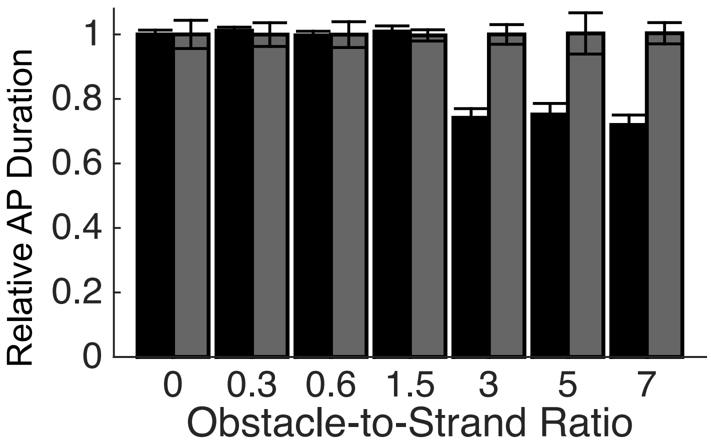
Comparing Model and Experiments



Comparing Model and Experiments







Limitation: model does not replicate reduction in AP duration

AP: Action potential

Factors Affecting Macroscale Conduction

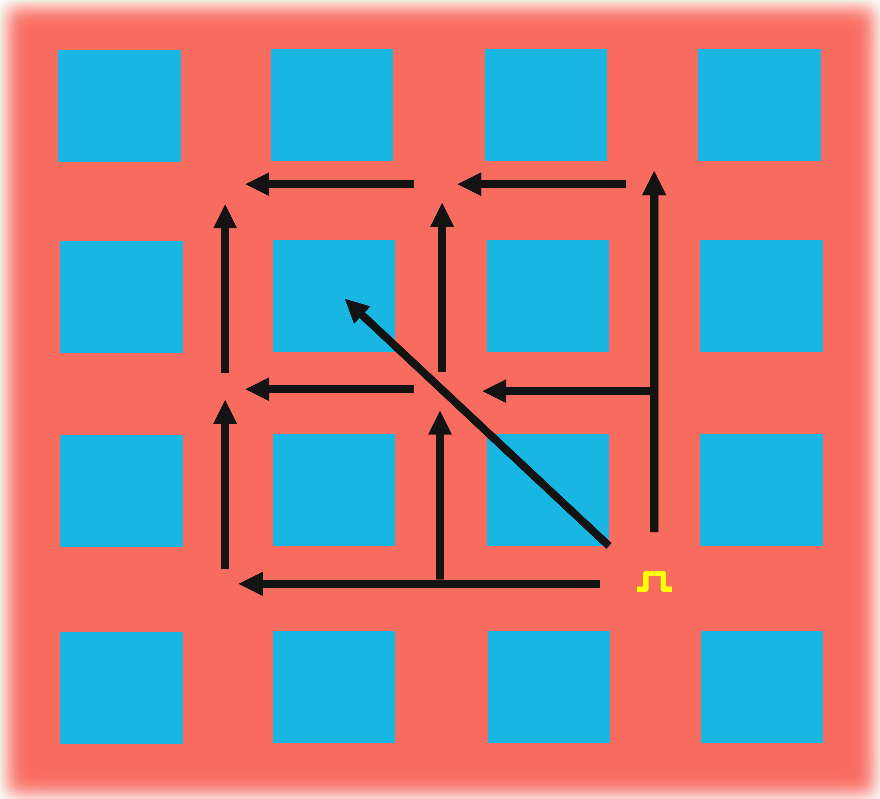
$$Conduction\ Velocity = \frac{Distance\ \ Of\ Conduction\ Path}{Time\ to\ Travel}$$

Depends on total path length

Depends on microscale conduction velocity

Conduction with Heterogeneities

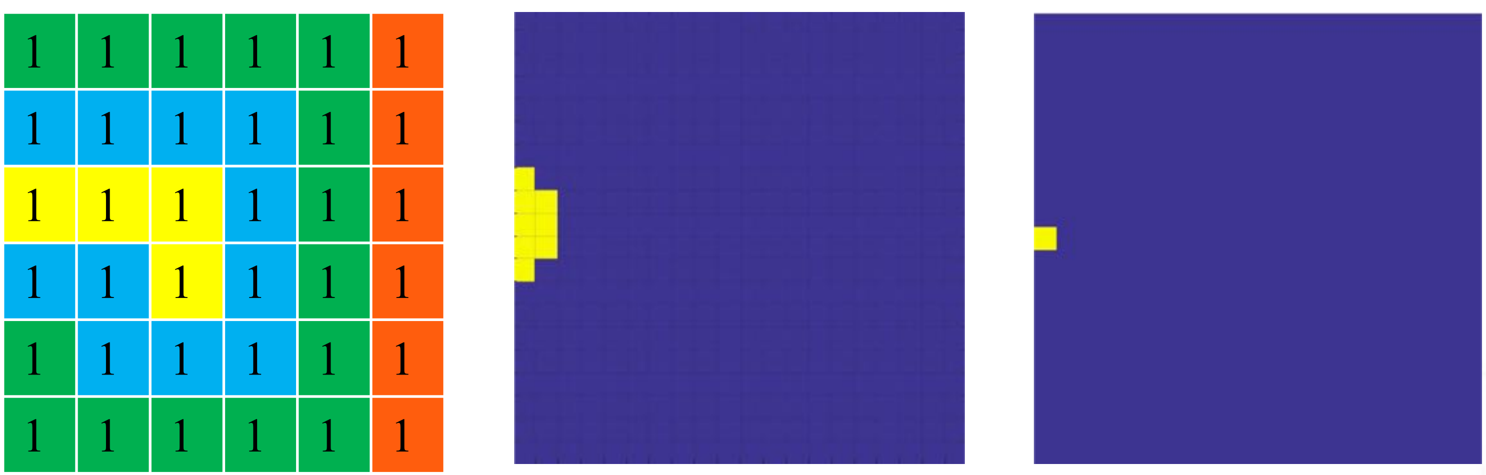
Presence of heterogeneities causes path tortuosity



⎍: Stimulus

Evaluating Effect of Path Tortuosity with Automata Models

- Rules-based approach
- Each node exists in one of fixed # of states
- Limitation: ignores effects of electrical load
  - → Allows us to isolate impact of path tortuosity by removing effects of source-load mismatches on local conduction velocity



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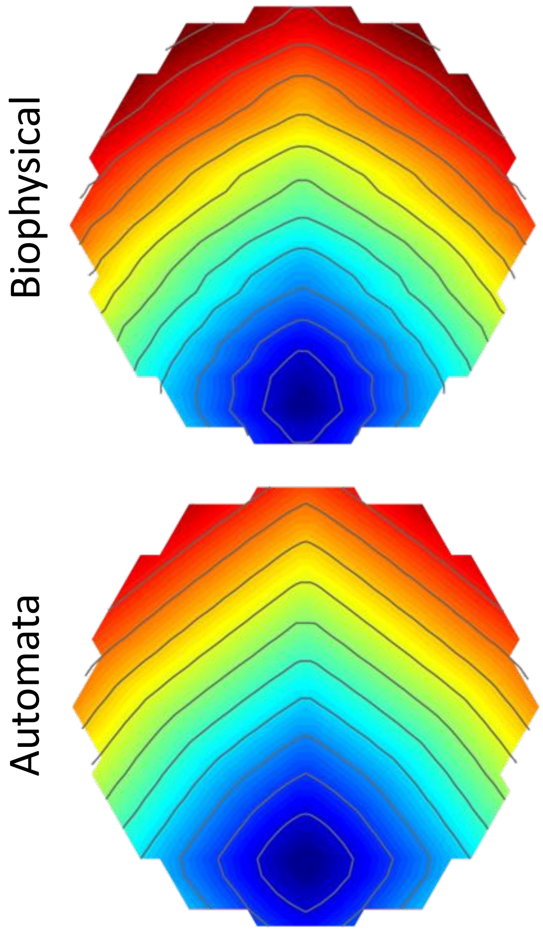
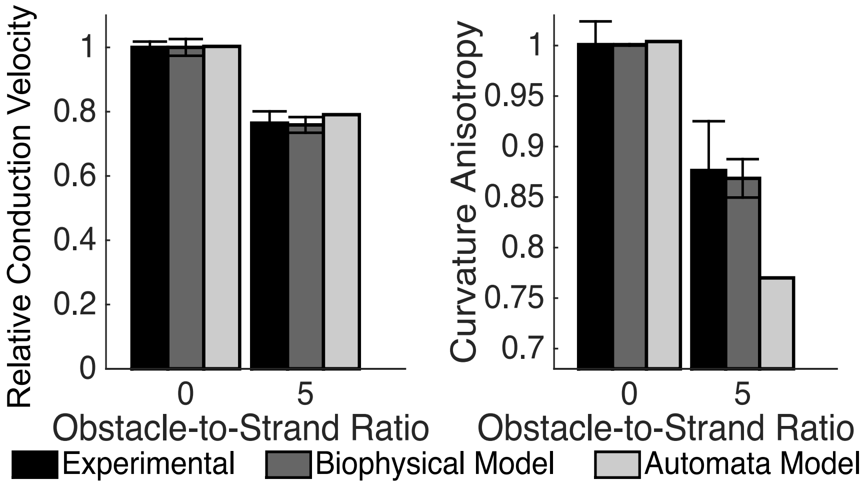
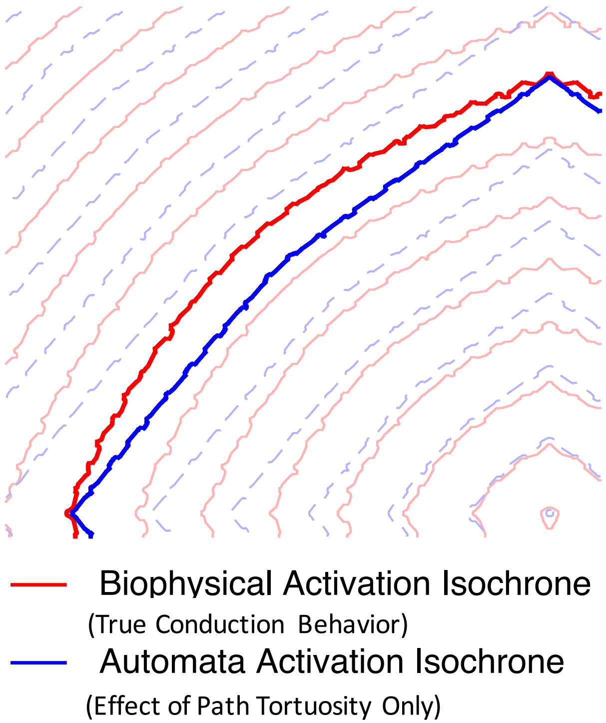
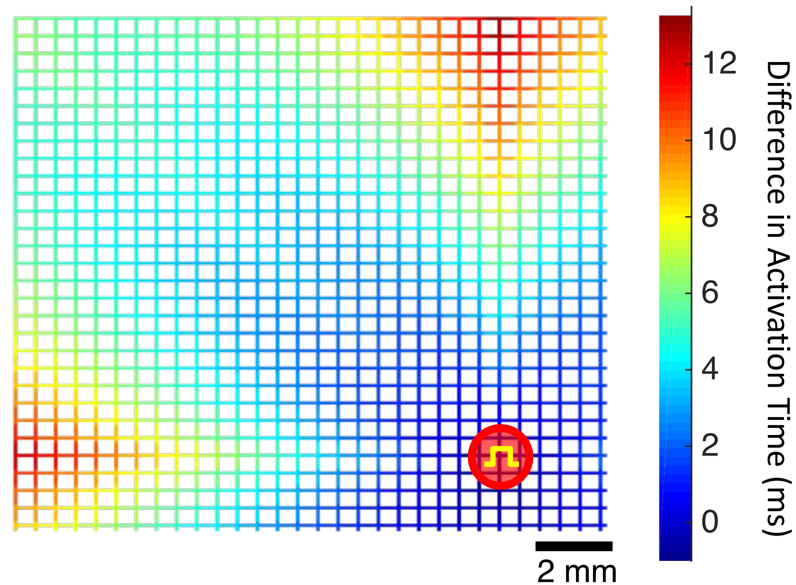
Effect of Path Tortuosity





Effect of Path Tortuosity

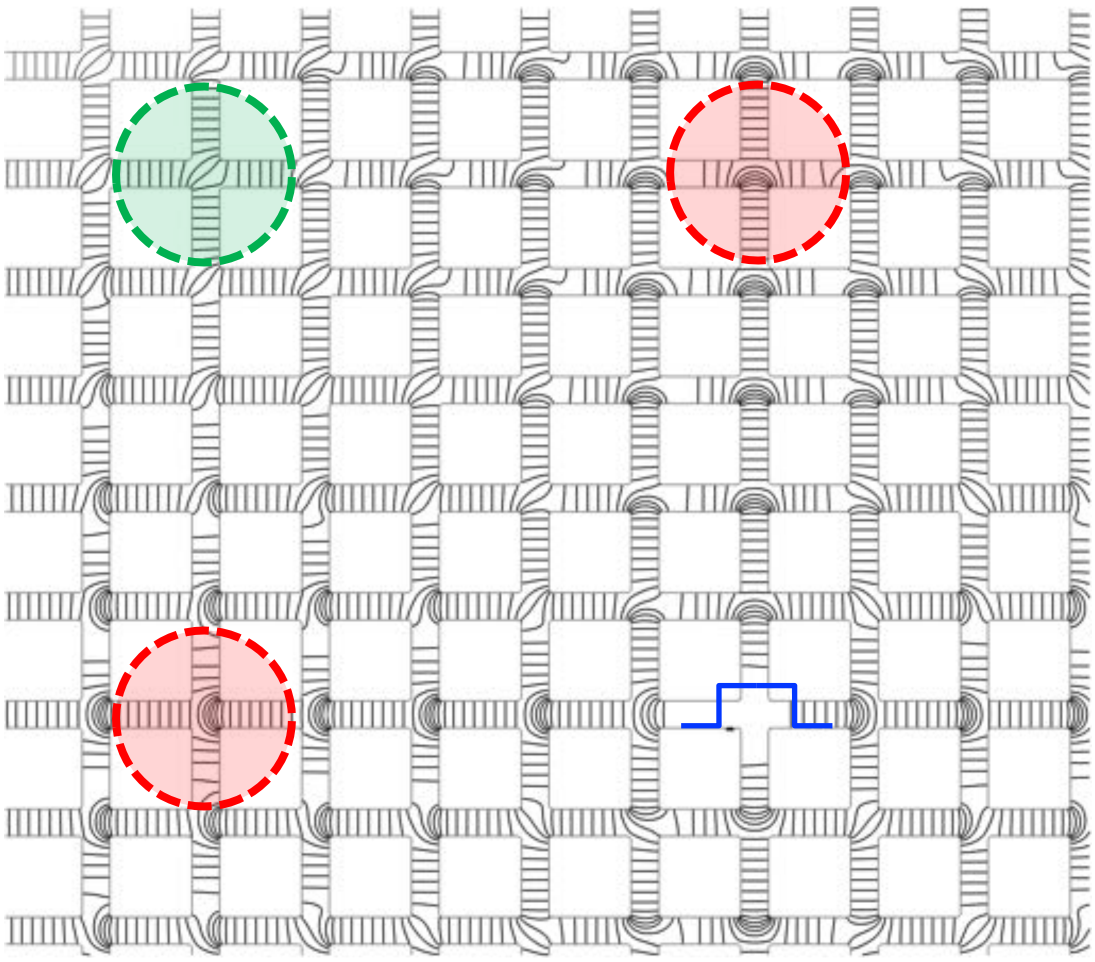




∴ Path tortuosity alone does not explain the observed macroscopic changes. There must be local variation in microscopic conduction velocity that directly affects macroscale behavior

Regions of Focus for Studying Microscale Behavior

Intersection Sites:
Two wavefronts arriving simultaneously



Branching Sites:
Arriving wavefront branches in three directions

⎍: Stimulus

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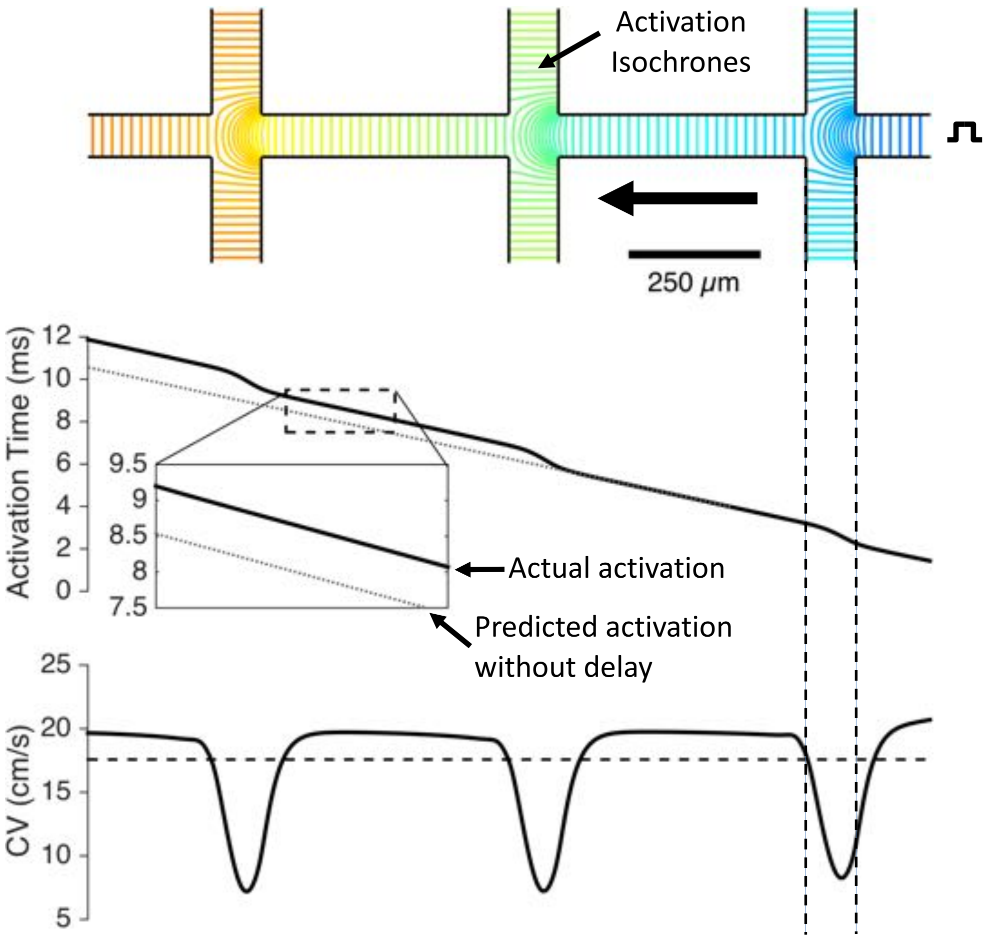
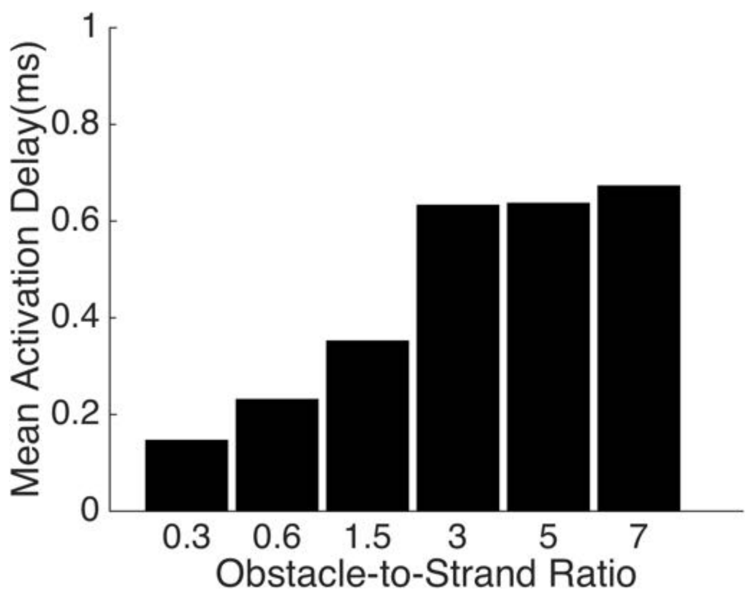
Behavior Along Principal Axes





→ Branching along principal axes leads to conduction slowing

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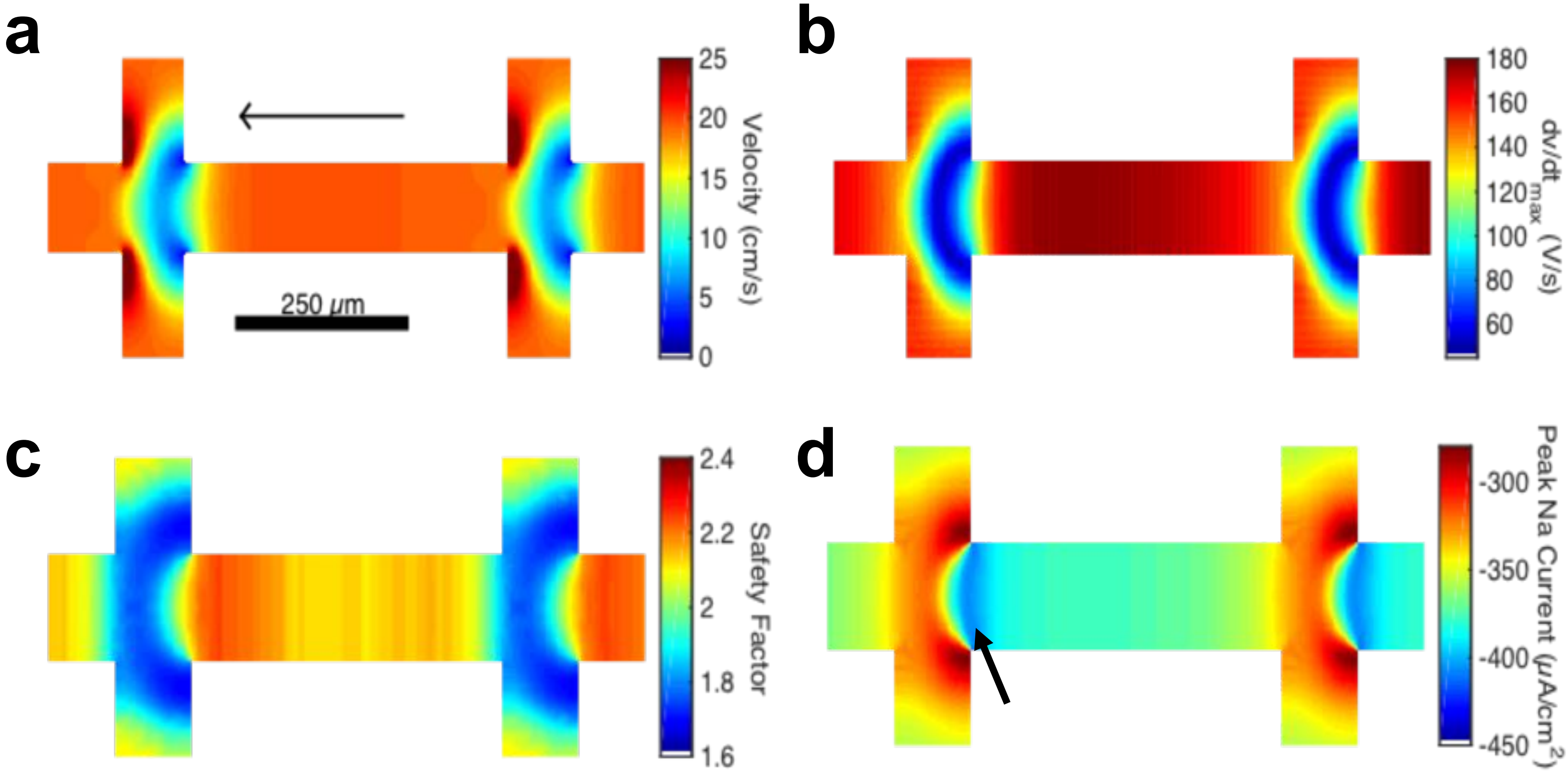
Behavior Along Principal Axes



$(dV_m/dt)_{max}$: Maximal upstroke velocity

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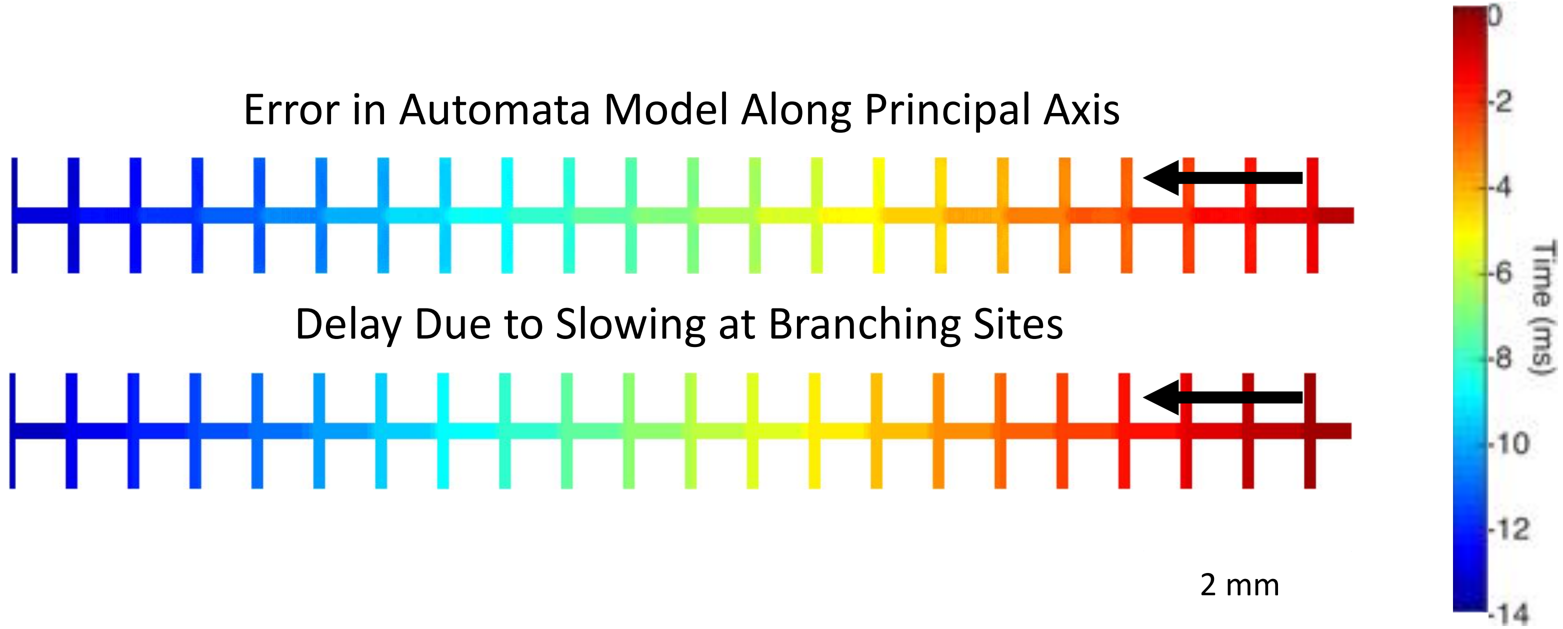
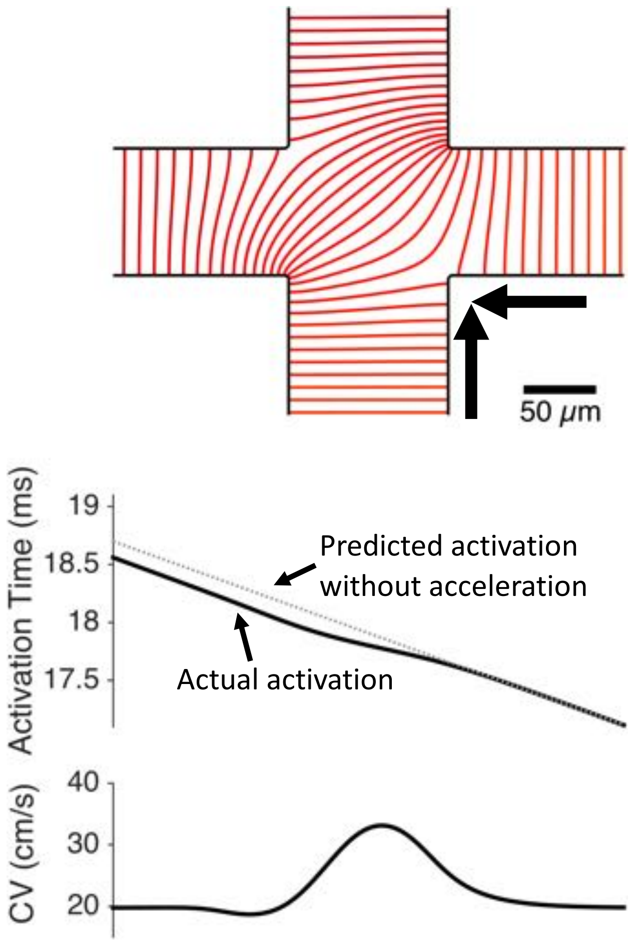
Net Effect of Branching Delays

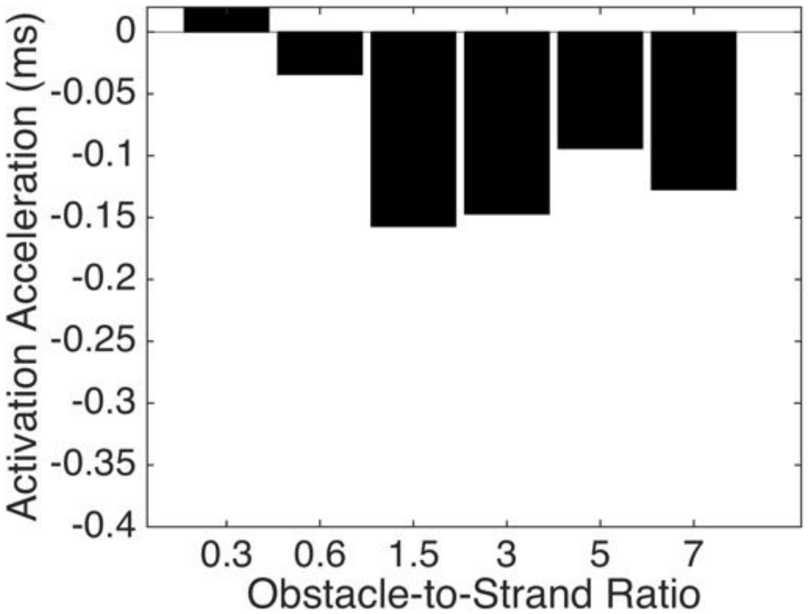


→ Branching related slowing is the **<u>primary mechanism of microscale conduction variation</u>** along the principal axes

⎍: Stimulus

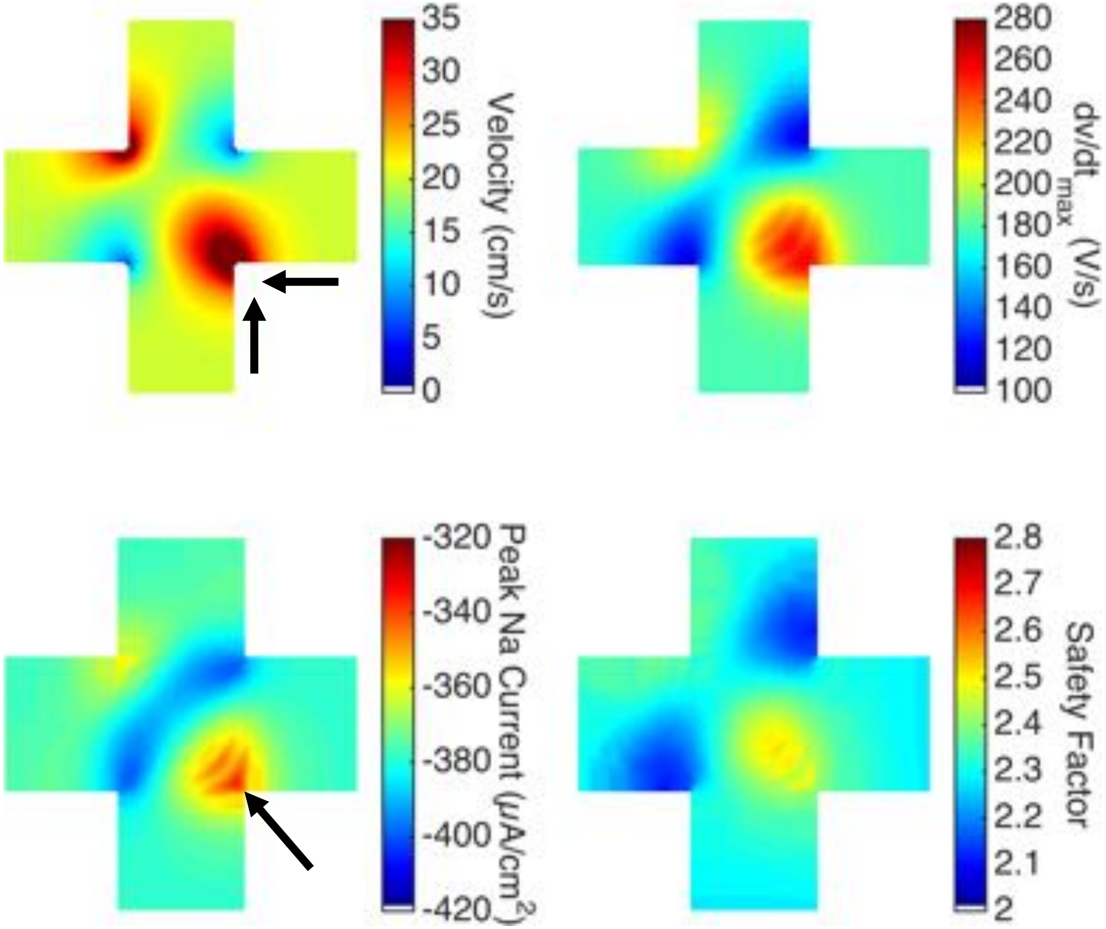
Behavior At Intersection Sites





Wavefront collisions at intersections accelerate propagation

Behavior At Intersection Sites



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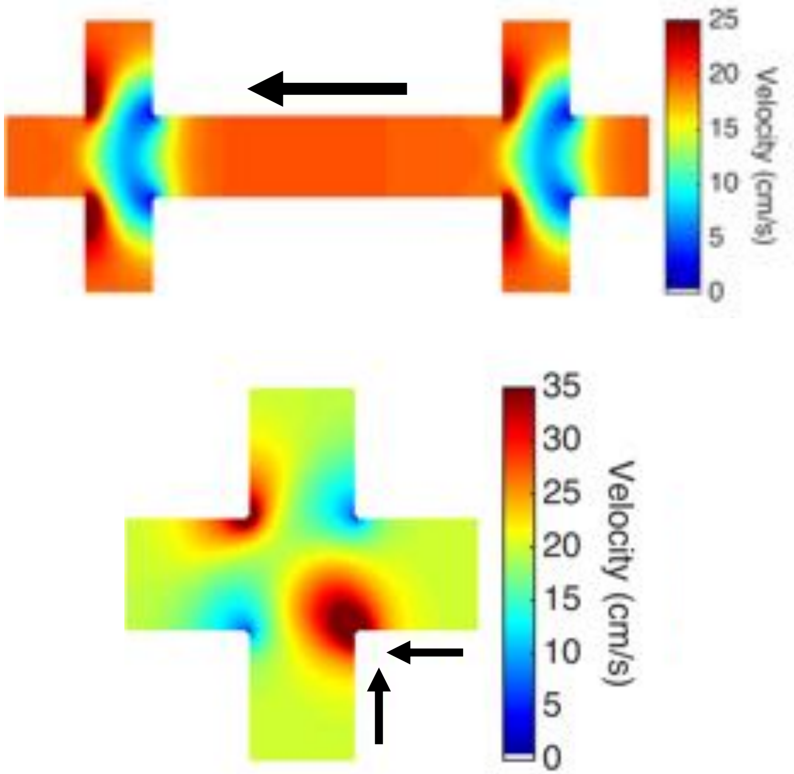
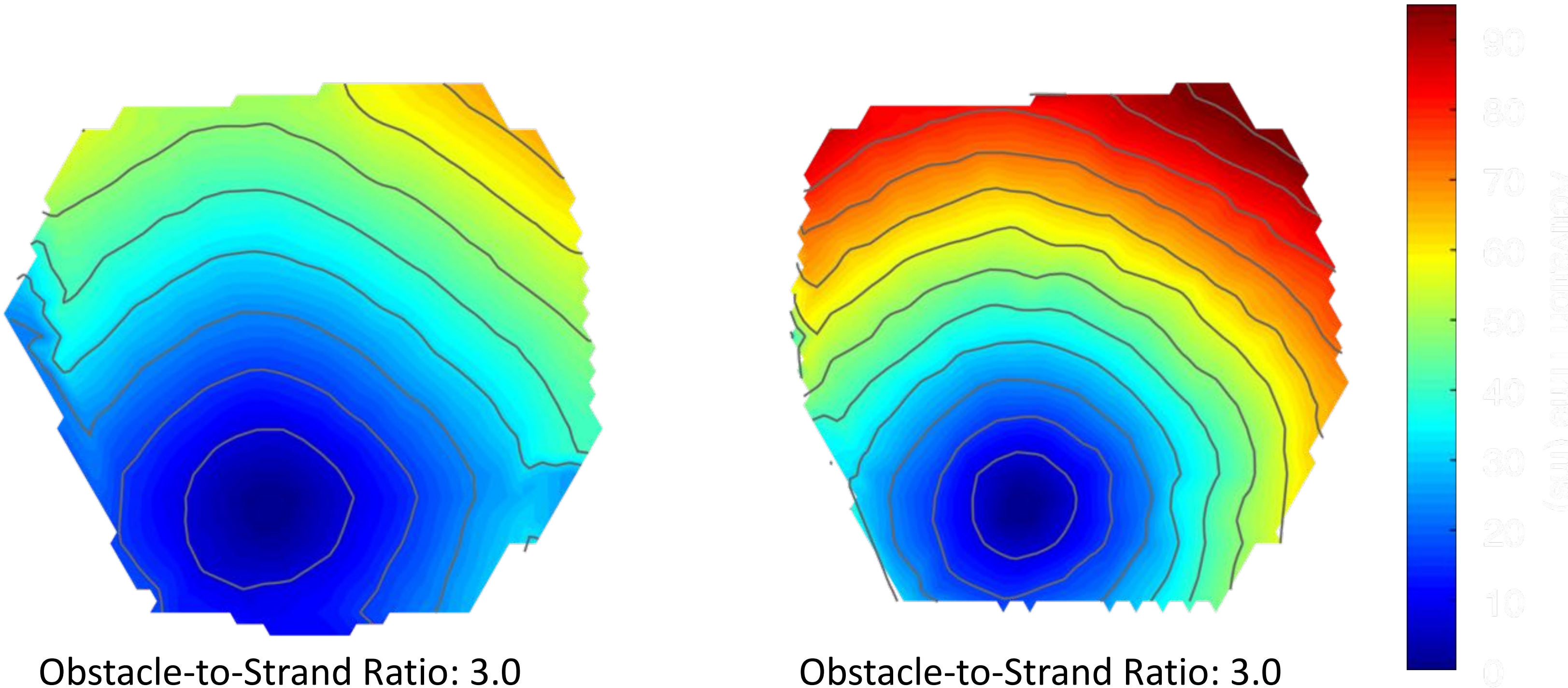
Recap



- Source-load imbalances → Changes in microscale conduction
  - Conduction slowing at branching sites
  - Conduction speeding at intersections
- Path tortuosity + source-load imbalances → macroscopic slowing and wavefront curvature changes
- How does reduced excitability affect these macro- and micro-scale behaviors?

Macroscopic Behavior Under Reduced Excitability



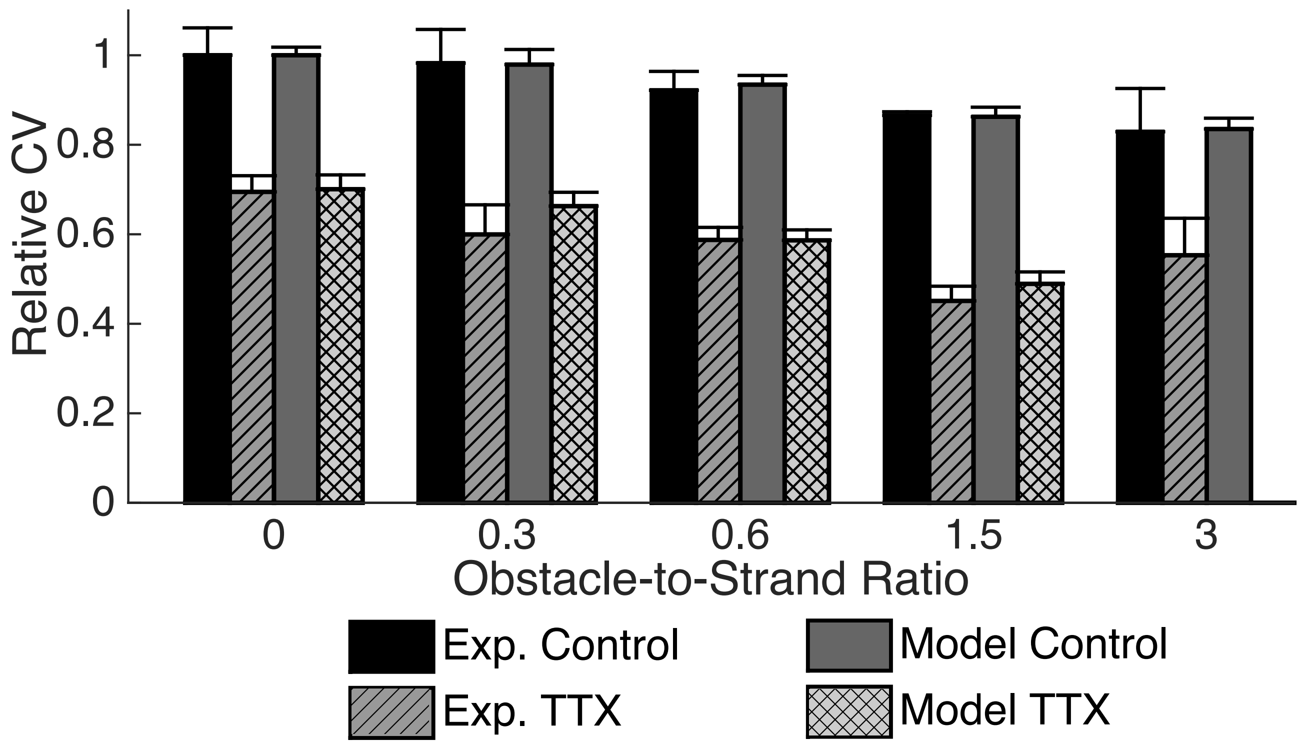
Obstacle-to-Strand Ratio: 3.0

Obstacle-to-Strand Ratio: 3.0
With 100 μm TTX

Reduced sodium excitability results in slowing and a change in wavefront curvature

TTX: tetrodotoxin, Na^+ channel blocker

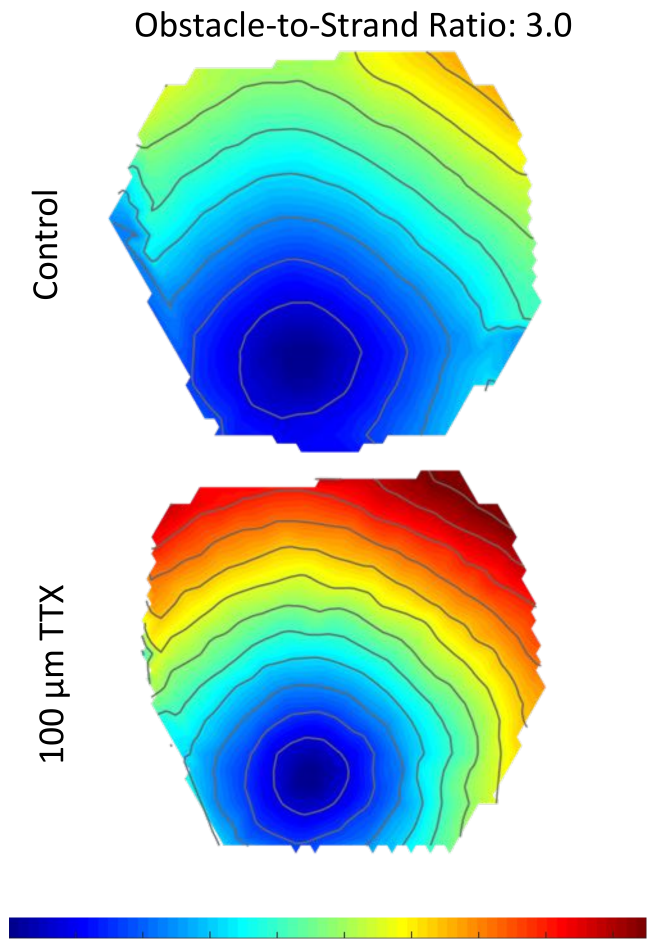
Conduction Slowing due to Reduced Excitability

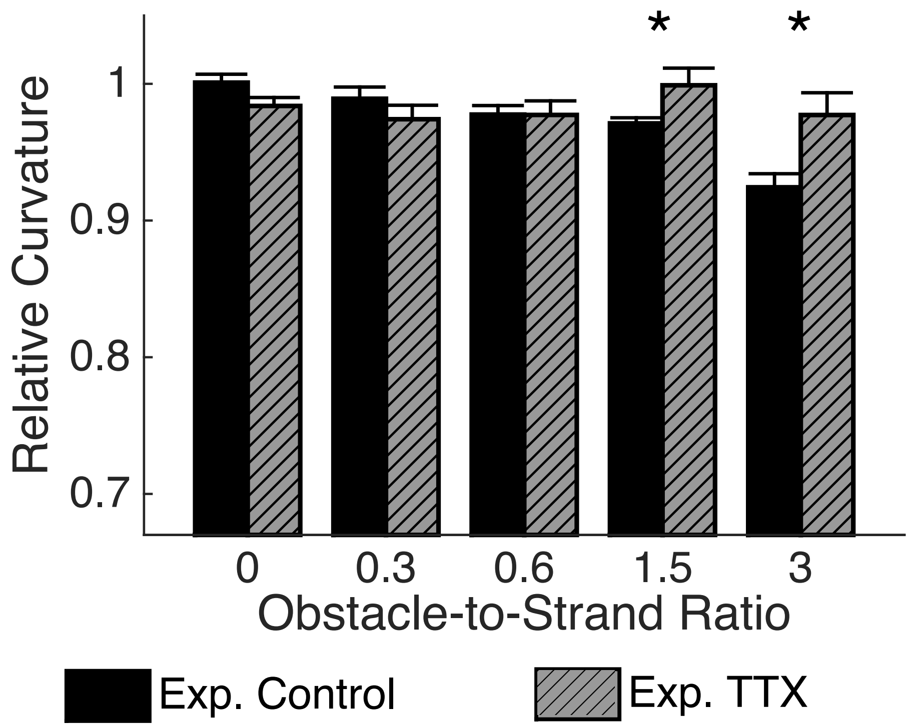


Model exhibits block at OSR of 3.0
Experiments show wavebreak and meandering at OSR 5.0 and not sustained at 7.0

TTX: tetrodotoxin, Na^{+} channel blocker

Reduced Excitability Attenuates Heterogeneity-Related Curvature Anisotropy

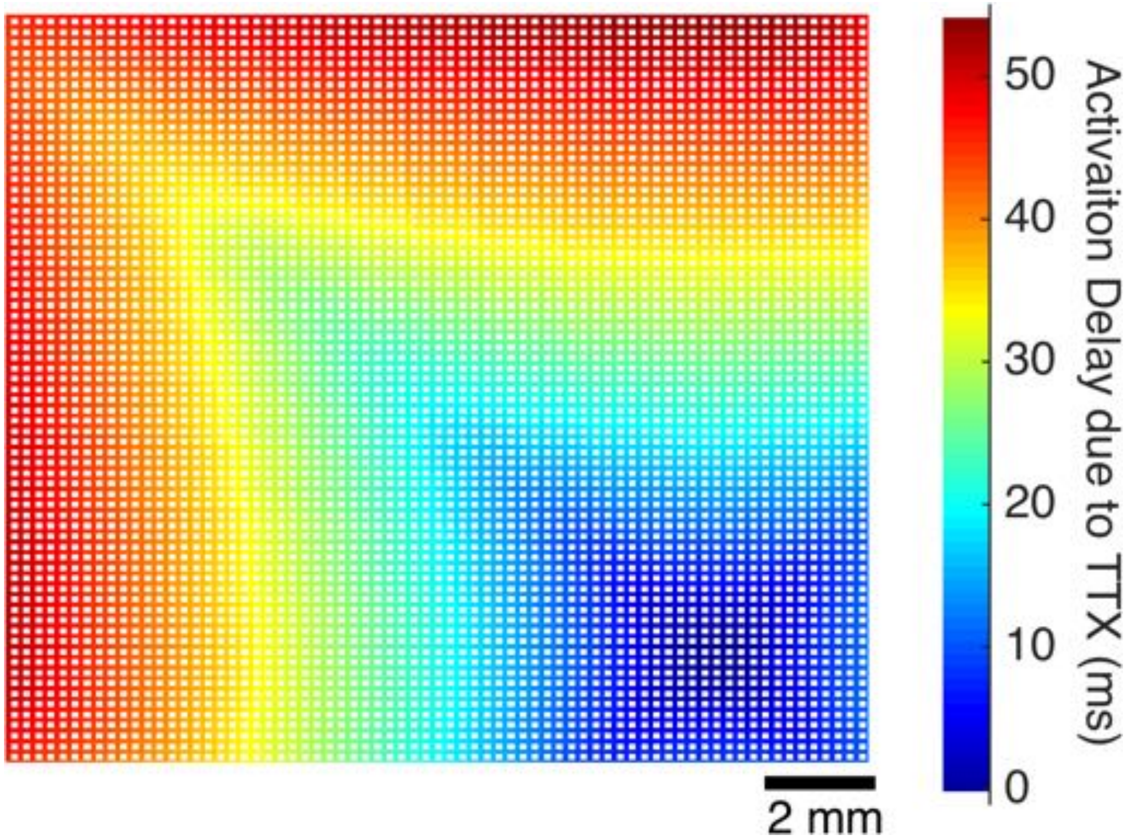




TTX: tetrodotoxin, Na^{+} channel blocker

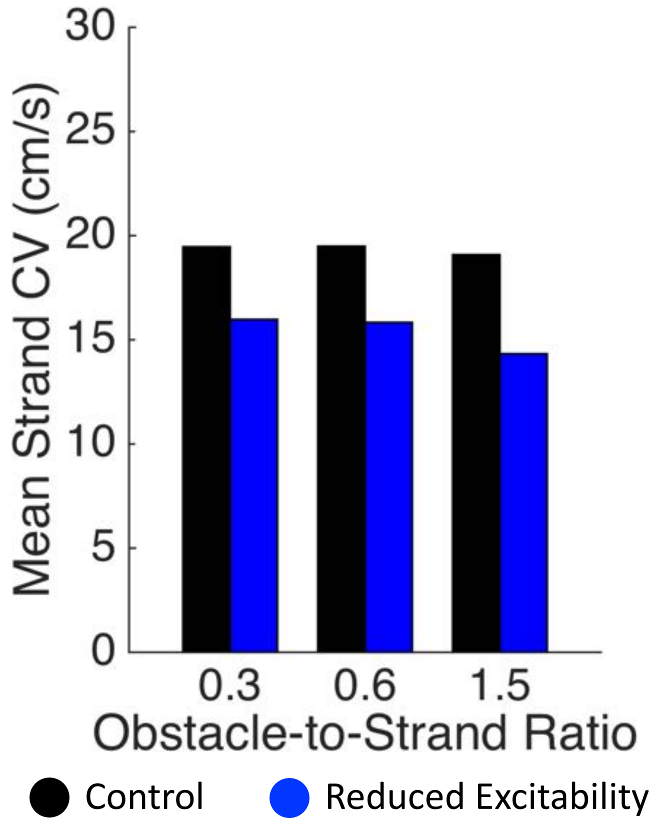
* $p < 0.05$ by post-hoc Tukey

Conduction Slowing due to Reduced Excitability is Anisotropic



TTX: tetrodotoxin, Na^+ channel blocker

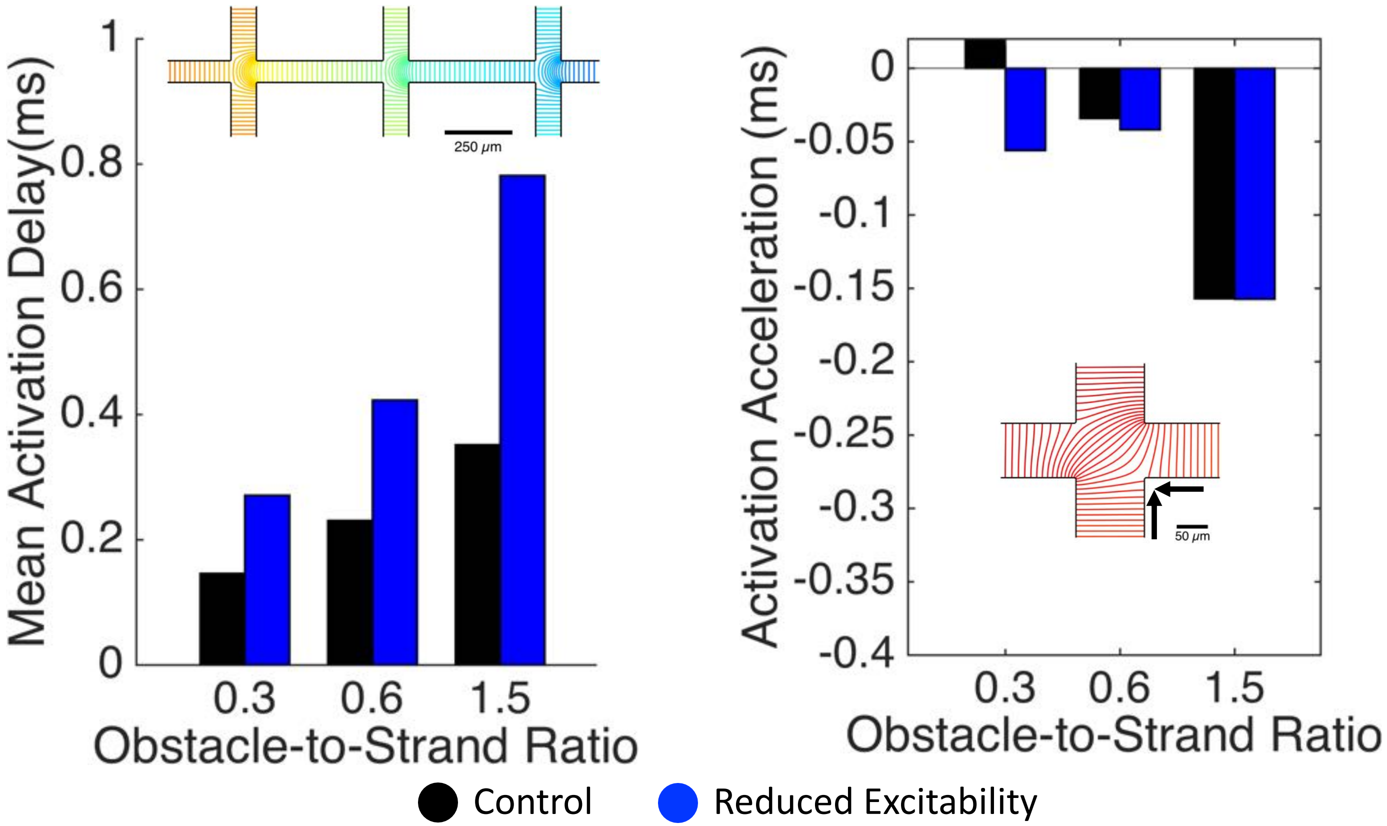
Effects of Reduced Excitability



Global slowing of conduction within strands

 CV: Conduction velocity

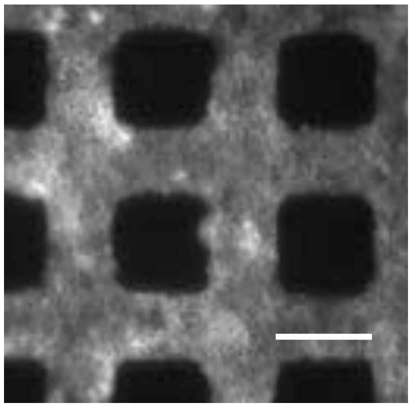
Effects of Reduced Excitability



Increased delay at branches and no change in acceleration at collisions drives change in wavefront curvature

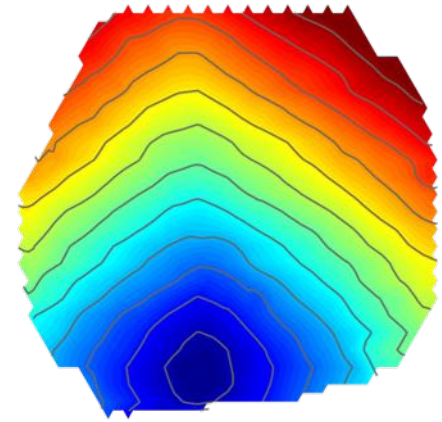
Conclusions

Regular heterogeneities



Path tortuosity

Conduction slowing &
Wavefront curvature anisotropy



Effects of source-load mismatch:

Branching → Slowing

Collisions → Speeding

Previously described by Fast, Kleber, Rohr, Kucera and others

Novel mechanism of microscale conduction modulation

- Reduced excitability → greater slowing at branches → exaggerated effect of collisions → rounder wavefronts and slowed conduction

Limitations

- Highly idealized geometry of fibrosis
- Complexity of real myocardium (3D structure, fibroblasts etc)
- Question of APD reduction at high obstacle-to-strand ratios

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Future Directions

- Incorporation of local anisotropy to try to understand changes in APD
- Effect of heterogeneities on dynamic properties (i.e. restitution, rate dependence, reentry)
- Transition to realistic, histologically-inspired tissue structure (fibrosis distribution, fibroblasts, anisotropy etc)

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Thank you!

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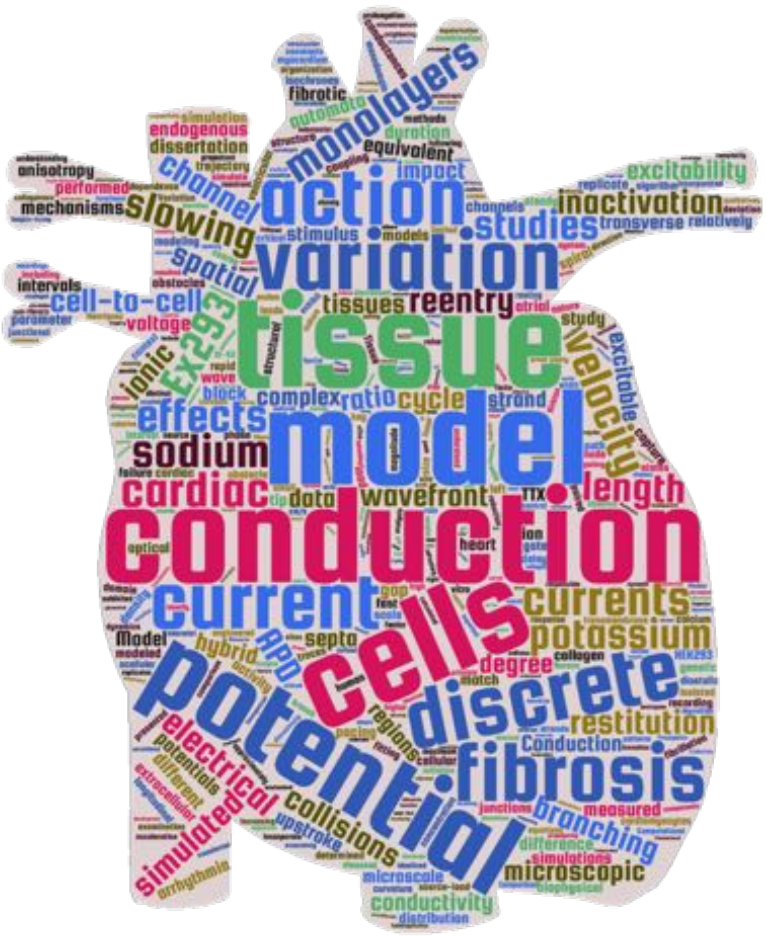
Thank you!



Word cloud of dissertation

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