Continuous Models Fail to Capture Details of Reentry in Fibrotic Myocardium

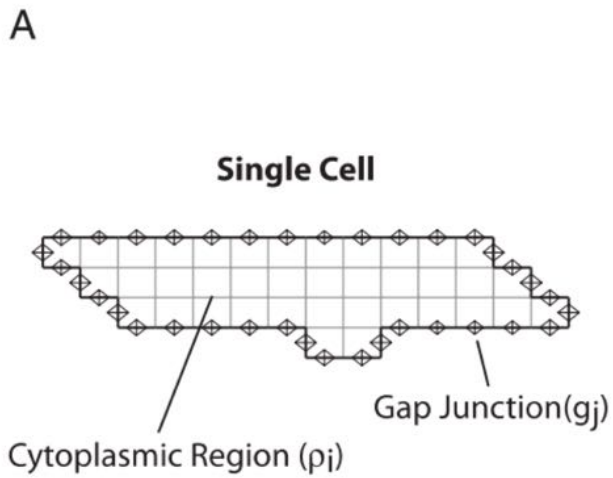
Tanmay Gokhale, Eli Medvescek and Craig Henriquez
Duke University

Duke
PRATT SCHOOL OF
Engineering

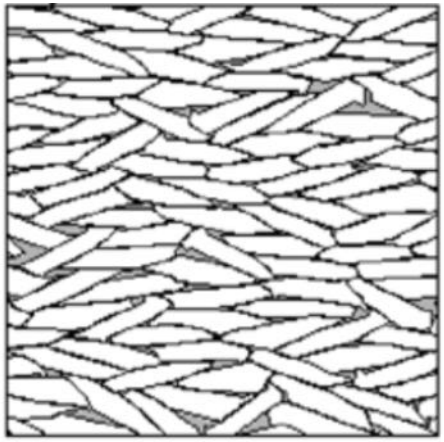
Outline

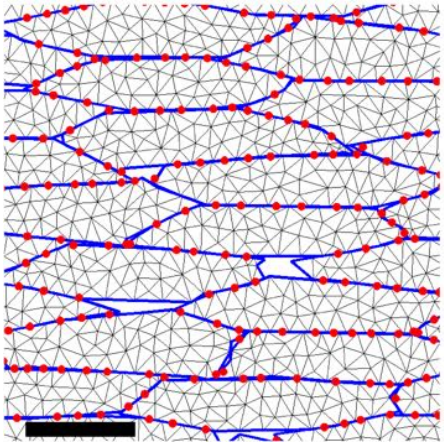
- Discrete vs Continuous Models
  - and how they're used to model fibrosis
- Comparing re-entry in discrete model of fibrosis versus homogenized continuous model of fibrosis
- Examining re-entry in "hybrid" continuous model with discrete discontinuities

Microstructural Discrete Models



Hubbard and Henriquez. *Europace* 2012





Kim and Henriquez. *Biophysical Journal*. 2010

Duke
PRATT SCHOOL of ENGINEERING

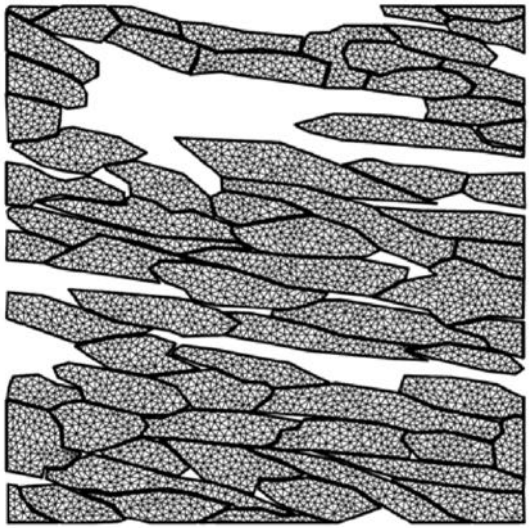
Continuous Models

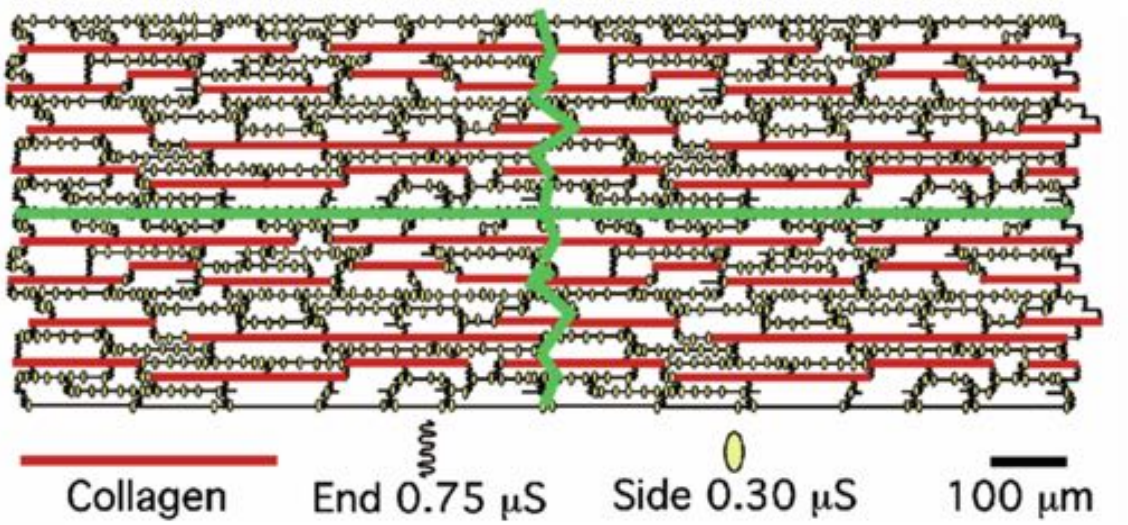
- Substantially increase computational efficiency
  - Decrease spatial discretization from 5-20μm to 100-200 μm in each dimension
- Electrical properties selected to match experimental macroscopic conduction velocities and anisotropy
  - Able to reproduce conduction with high fidelity

Modeling Tissue Fibrosis

- Disease state with collage deposition, fibroblast proliferation and gap junctional modification
- Enhanced collagen density associated with conduction slowing, conduction heterogeneity and arrhythmogenesis

Modeling Fibrosis - Discrete





Histologically accurate

Electrical decoupling only

Kim, JM A Discrete Monolayer Cardiac Tissue Model for Tissue Preparation Specific Modeling. Thesis. Duke University

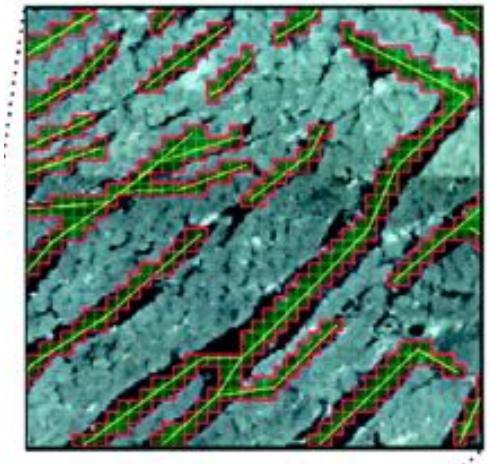
Spach et al. *Heart Rhythm*. 2007

Duke
PRATT SCHOOL of ENGINEERING

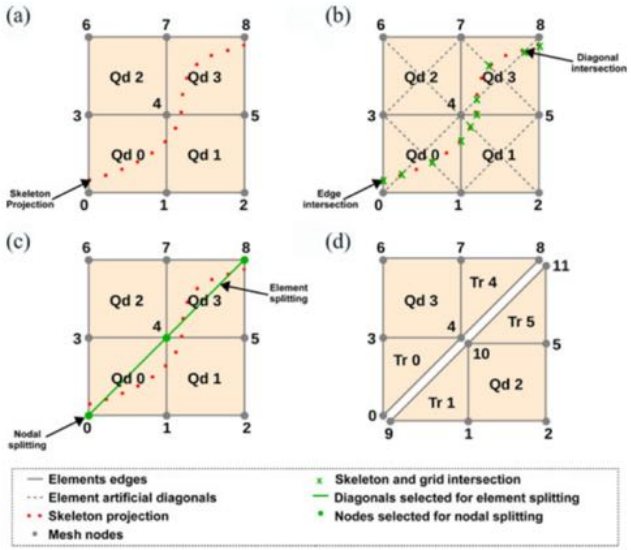
Modeling Fibrosis - Continuous

$\downarrow \sigma$
$\uparrow$ AR

Reduced conductivities



Accurate spatial representation



Node decoupling

Hooks et al. *Circulation Research*. 2002

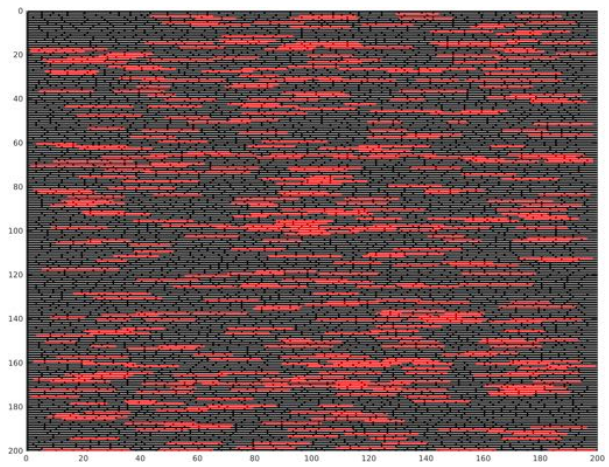
Costa et al. *IEEE Trans Bio Med Eng.* 2014

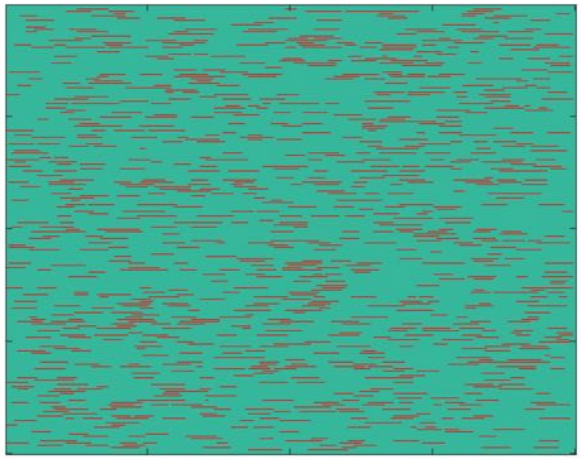
Duke PRATT SCHOOL of ENGINEERING

Motivation

- How well can continuous models recreate complex conduction behaviors like reentry that are critical in arrhythmogenesis?

Three Models of Fibrosis





Discrete

dx: 20 μm

Up to 30% fibrosis

(700 μm mean length)

Continuous

dx: 100 μm

Reduced conductivities

Hybrid

dx: 100 μm

Up to 30% fibrosis

(700 μm mean length)

+ partially reduced conductivities

All models are 2 cm x 2 cm

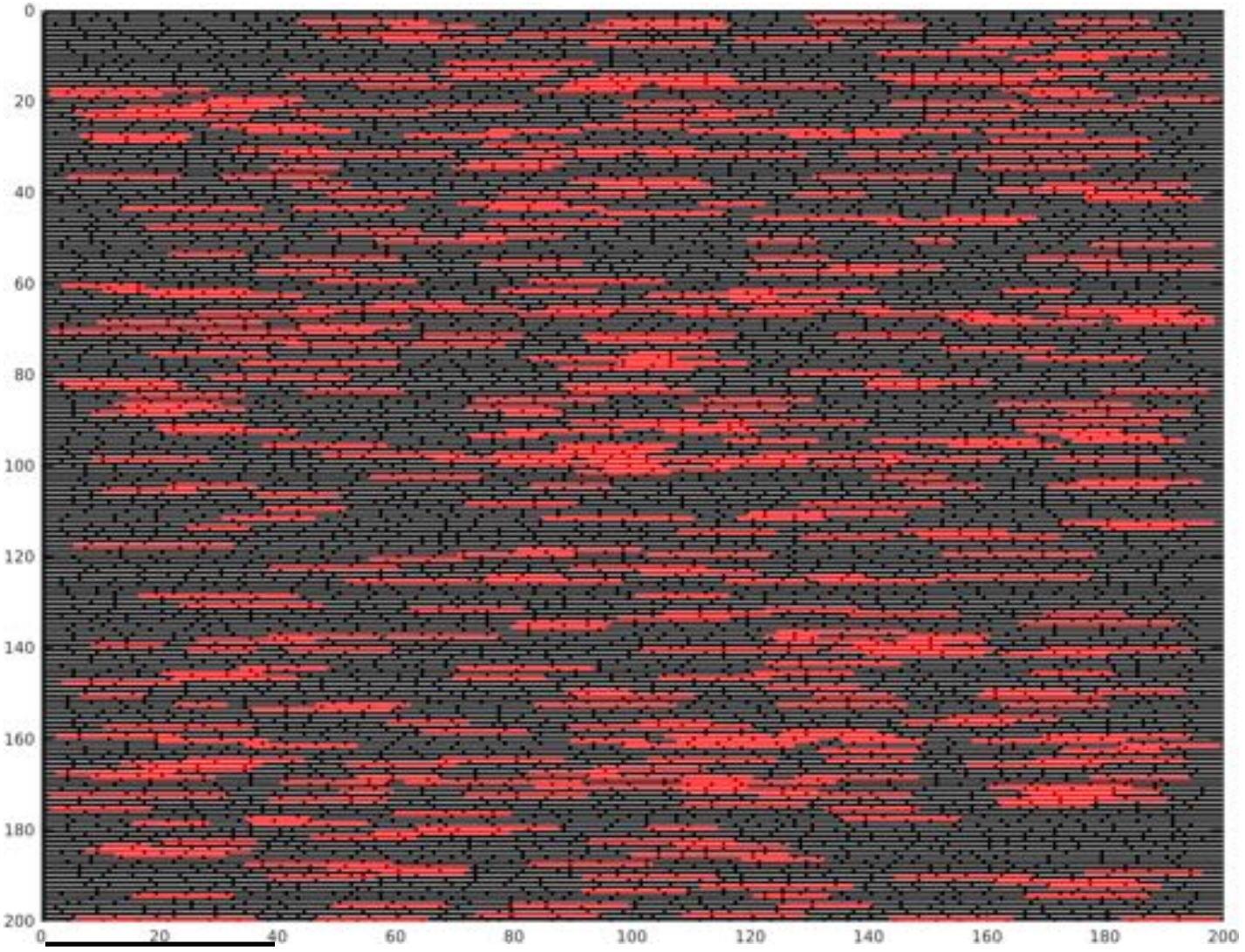
Duke
PRATT SCHOOL of ENGINEERING

Motivation

- How well can continuous models recreate complex conduction behaviors like reentry that are critical in arrhythmogenesis?

  – Part 1: Compare discrete model with “equivalent” continuous model w/ modified conductivities

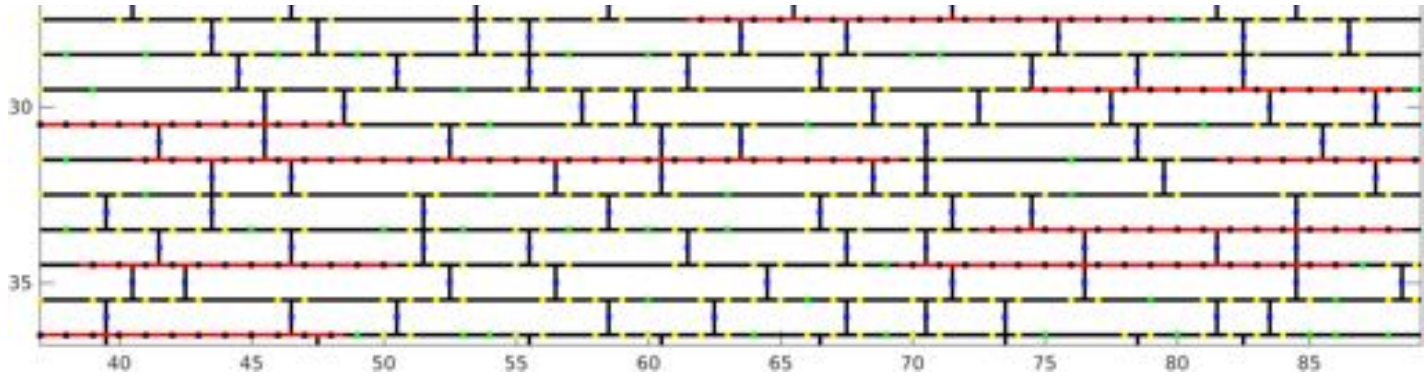
Discrete Fibrotic Model



Duke
PRATT SCHOOL of ENGINEERING

Discrete Fibrotic Model

- dx = dy = 20 μm
- Average cell size: 100 μm x 20 μm
- Transverse decoupling for adult phenotype
- + Collagenous septa that cover between 0% and 30% of the total lateral cell surface
  - Mean length: 700 um; Poisson distribution



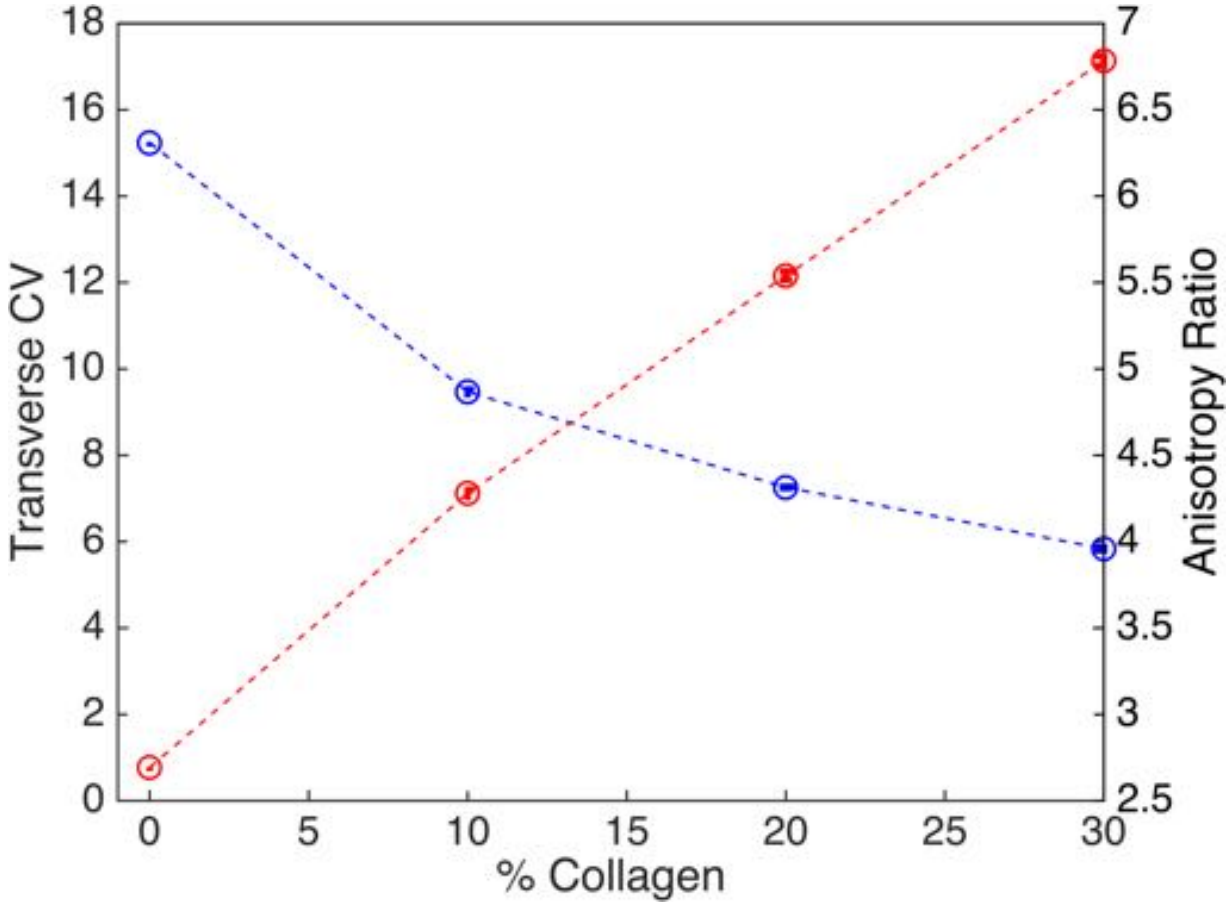
Duke
PRATT SCHOOL of ENGINEERING

Numerical Methods

- Bondarenko mouse membrane model
- Simulations performed using Cardiowave (http://cardiowave.duke.edu)

Duke
PRATT SCHOOL of ENGINEERING

Discrete Fibrotic Model



Using these conduction velocities, equivalent continuous models were developed

Duke
PRATT SCHOOL of ENGINEERING

Reentry in Fibrotic Model

Discrete

30% fibrosis

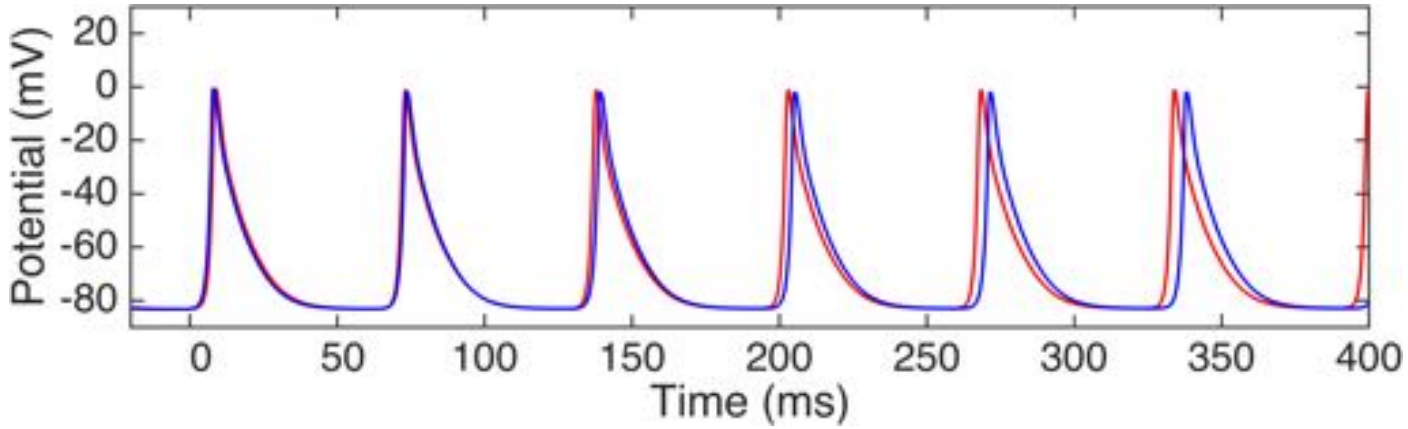
Continuous

Reduced conductivities

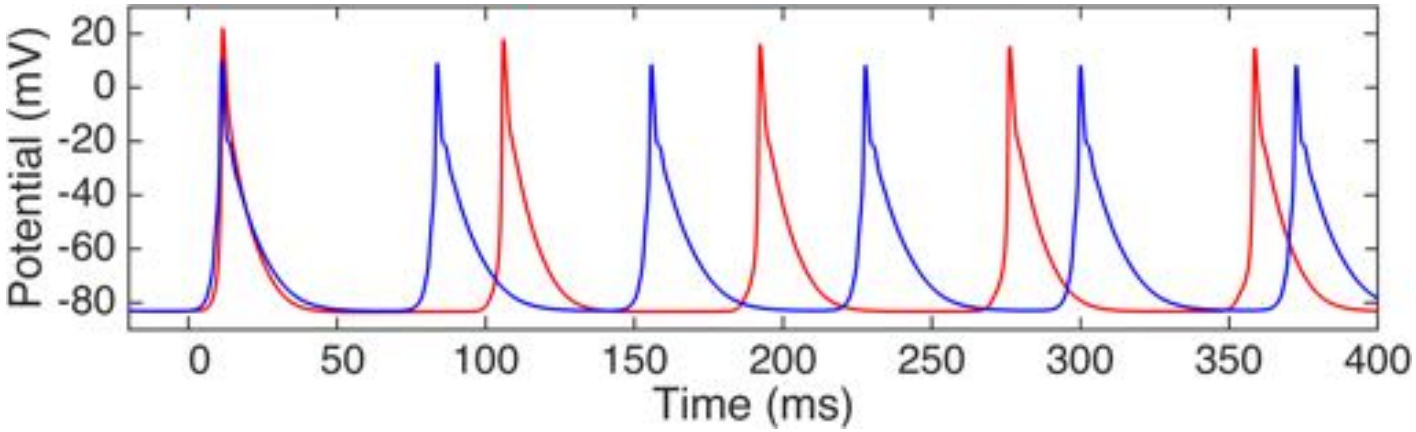
Duke
PRATT SCHOOL of ENGINEERING

Comparison of Discrete and Continuous Model Reentry

0% fibrosis



30% fibrosis

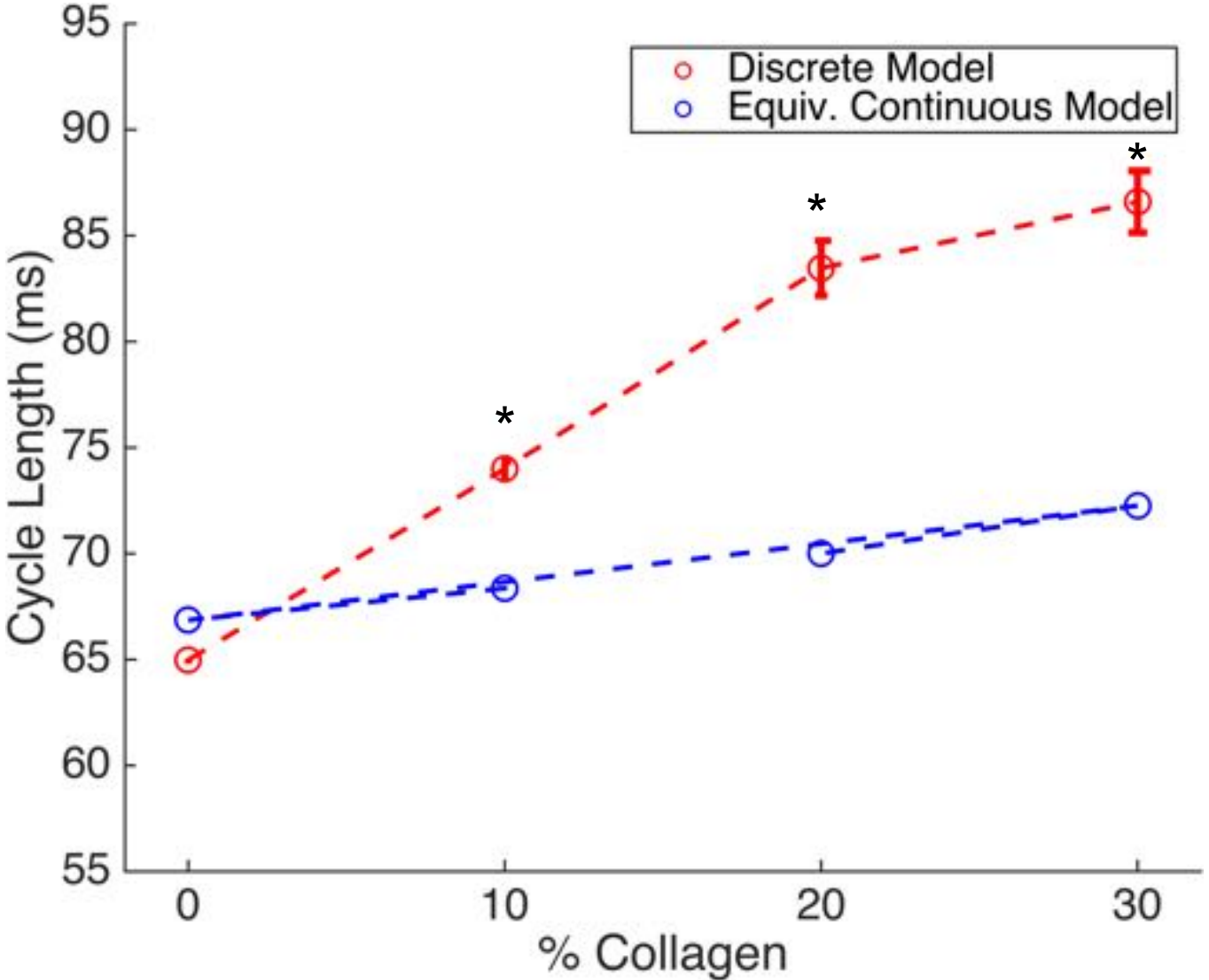


Discrete Tissue Model

Equivalent Continuous Model

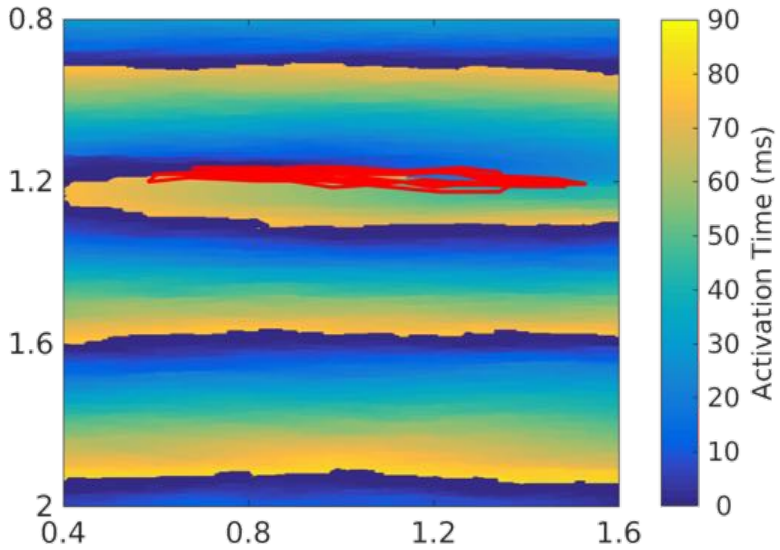
Duke
PRATT SCHOOL of ENGINEERING

Comparison of Discrete and Continuous Model Reentry



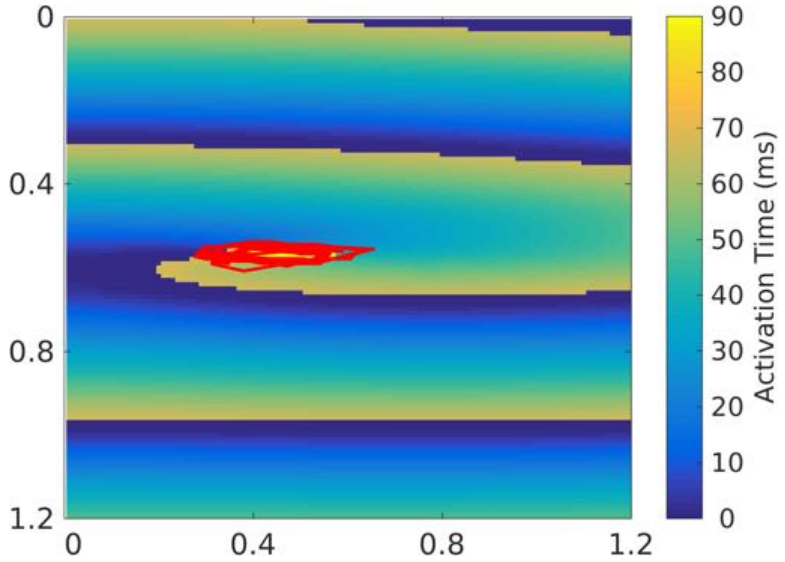
Duke
PRATT SCHOOL of ENGINEERING

Comparing Tip Trajectory



Discrete

Longer and thinner tip trajectory; no unexcitable core

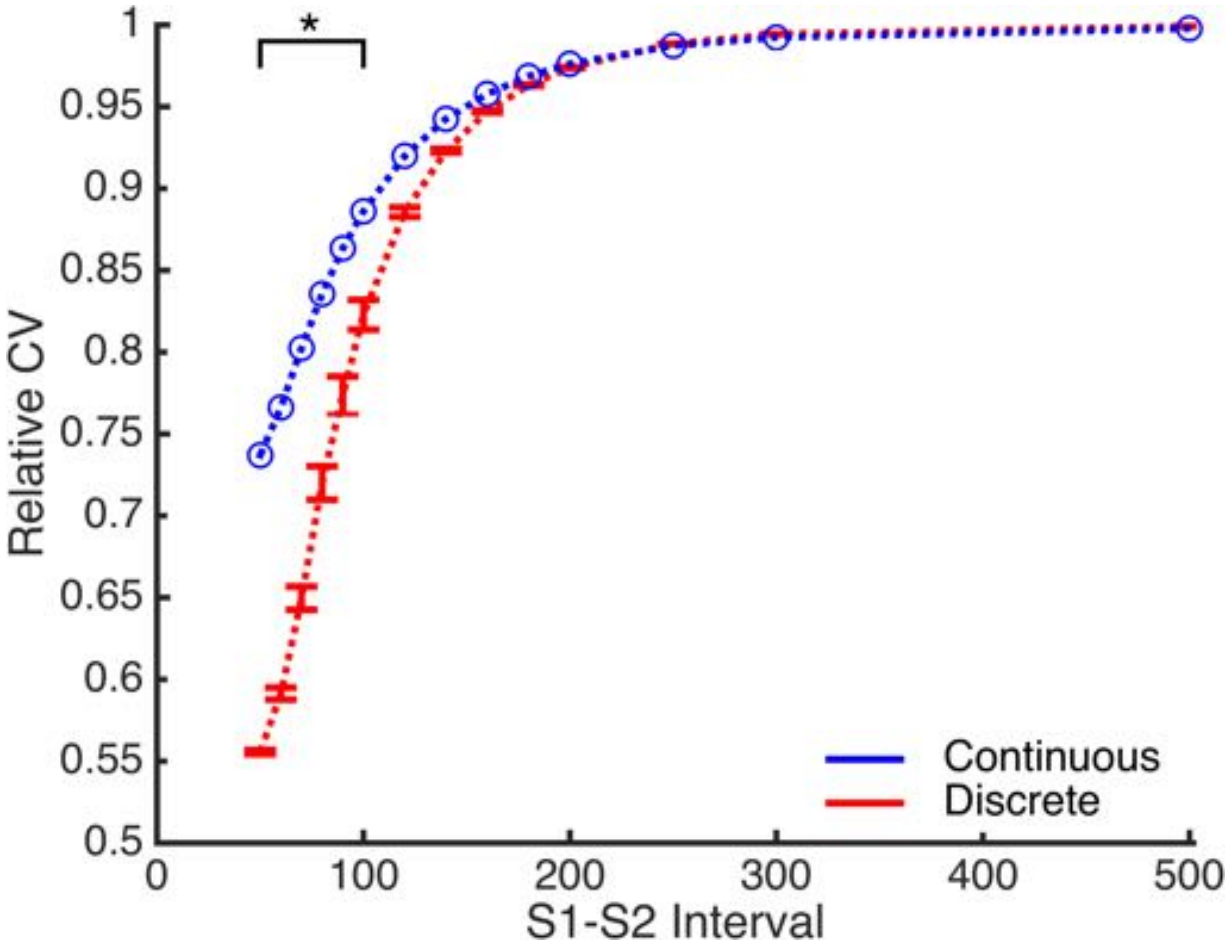


Continuous

Shorter, elliptical tip trajectory with unexcitable core

Duke
PRATT SCHOOL of ENGINEERING

Effect of Fibrosis on Restitution

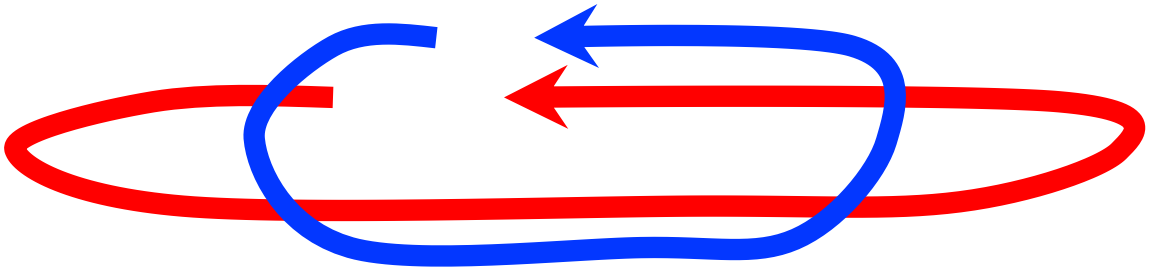


* $p < 0.05$ for discrete vs continuous at this S1-S2
(Two-way ANOVA + post-hoc pairwise Tukey HSD)

Duke
PRATT SCHOOL of ENGINEERING

Summary: Factors Affecting Cycle Length

Tip Path Length – model with discrete heterogeneities able to capture anatomical reentry around sub-mm scale discontinuities



Local CV – dependent not only on macroscopic CV at pacing rate but also CV at shorter diastolic intervals (i.e. restitution)

Duke
PRATT SCHOOL of ENGINEERING

Motivation

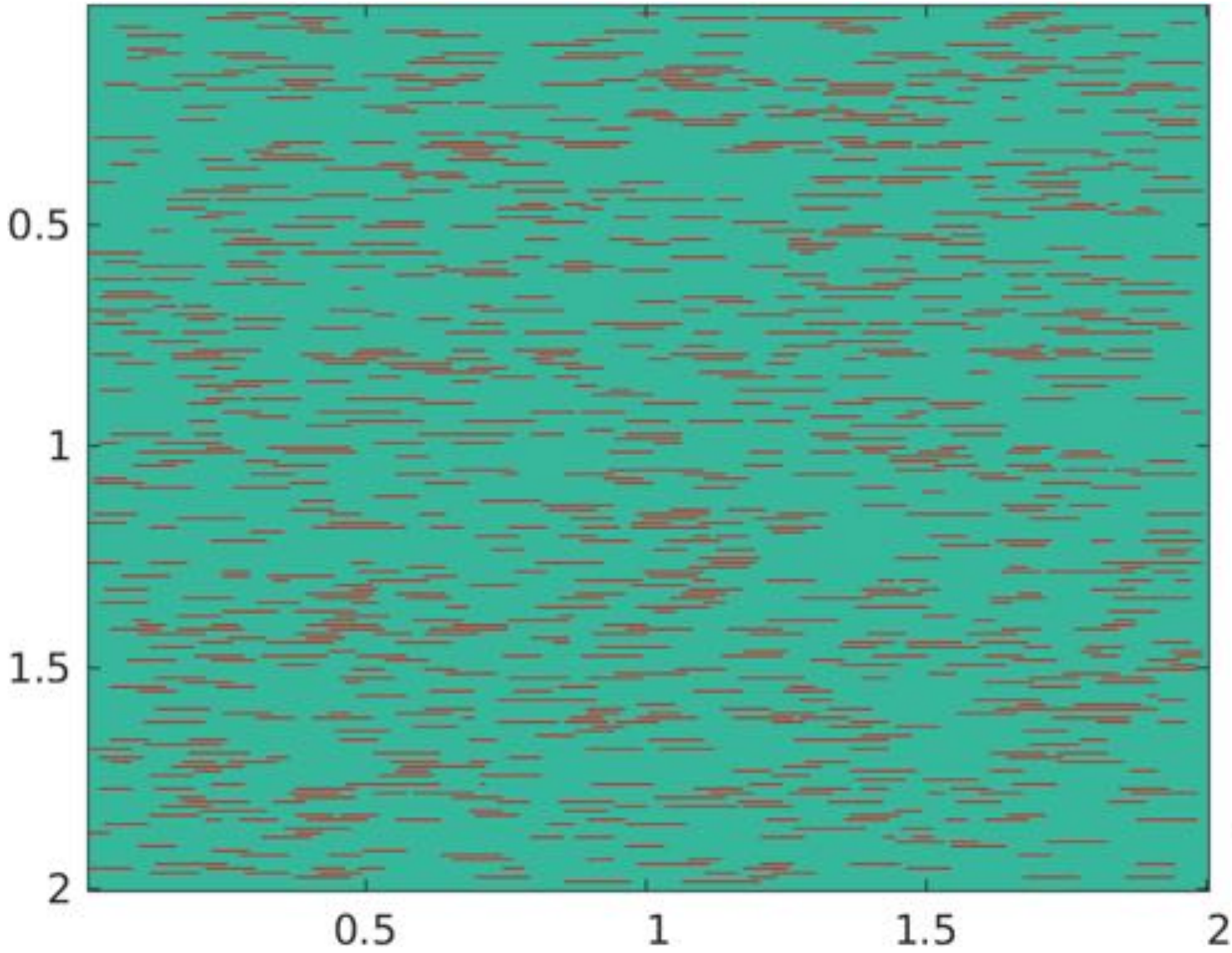
- How well can continuous models recreate complex conduction behaviors like reentry that are critical in arrhythmogenesis?
  - Part 1: Homogenized continuous model of fibrosis doesn't do a great job capturing dynamic of reentry
  - Part 2: Compare discrete model with "hybrid" continuous model w/ modified conductivities

Duke
PRATT SCHOOL of ENGINEERING

“Hybrid Models”

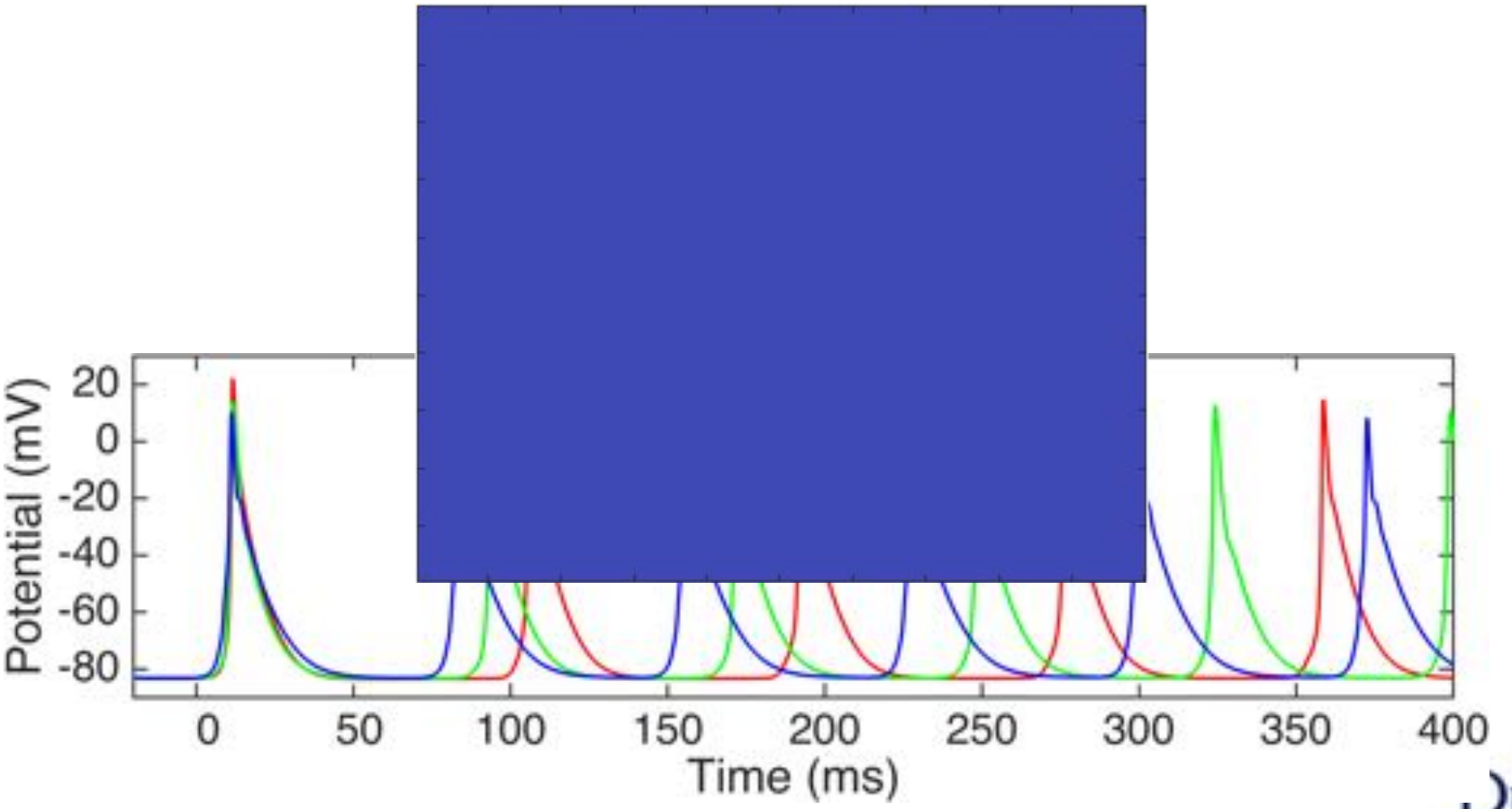
- Continuous models with discrete discontinuities
  - Include some collagenous septa
    - Reduced total collagen length because of larger discretization
  - Tissue conductivities adjusted so that combination of septa and tissue give same macroscopic CV as discrete model
- “Discontinuous” or “continuous with discontinuities”

Hybrid models



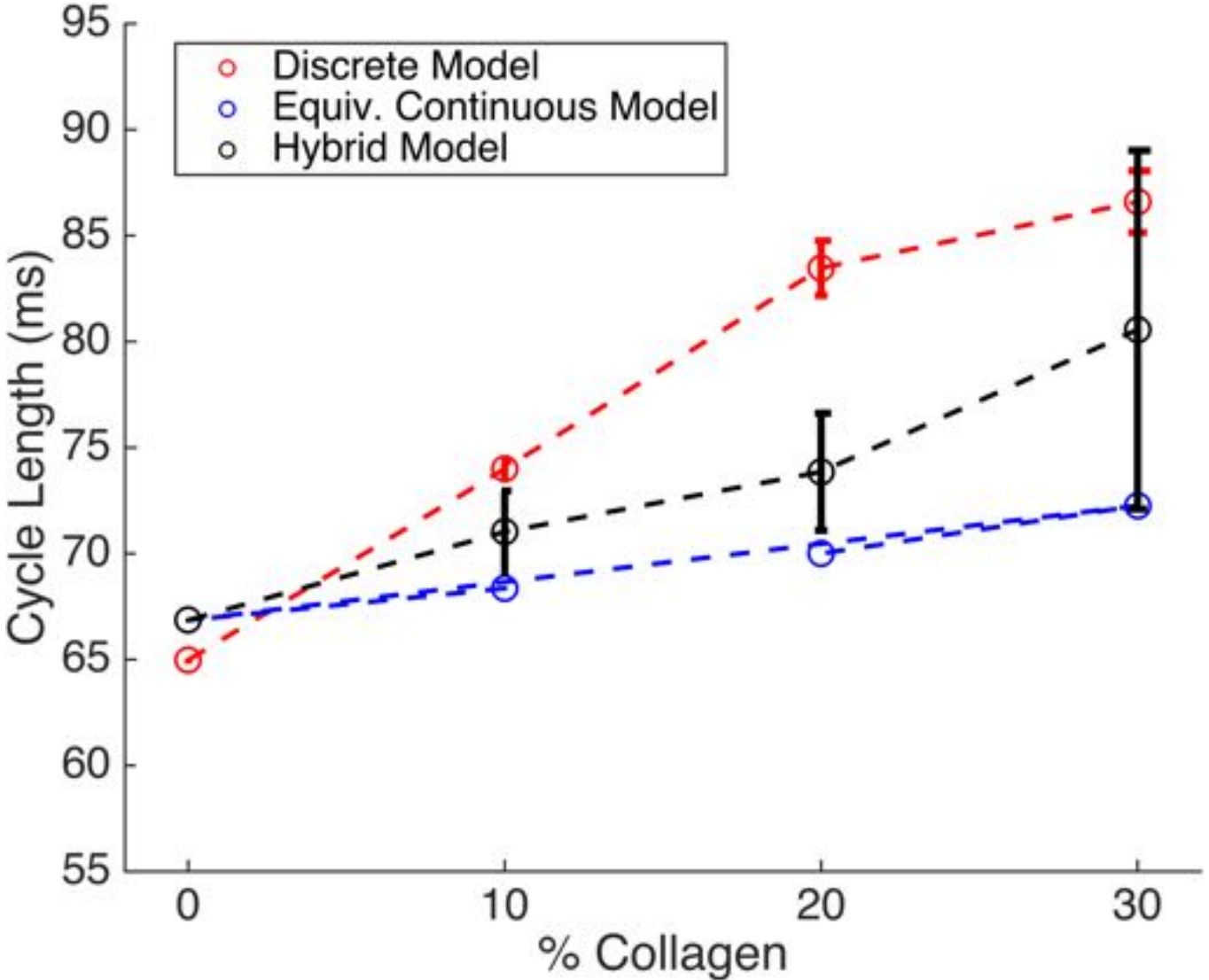
Duke
PRATT SCHOOL of ENGINEERING

Reentry in hybrid model



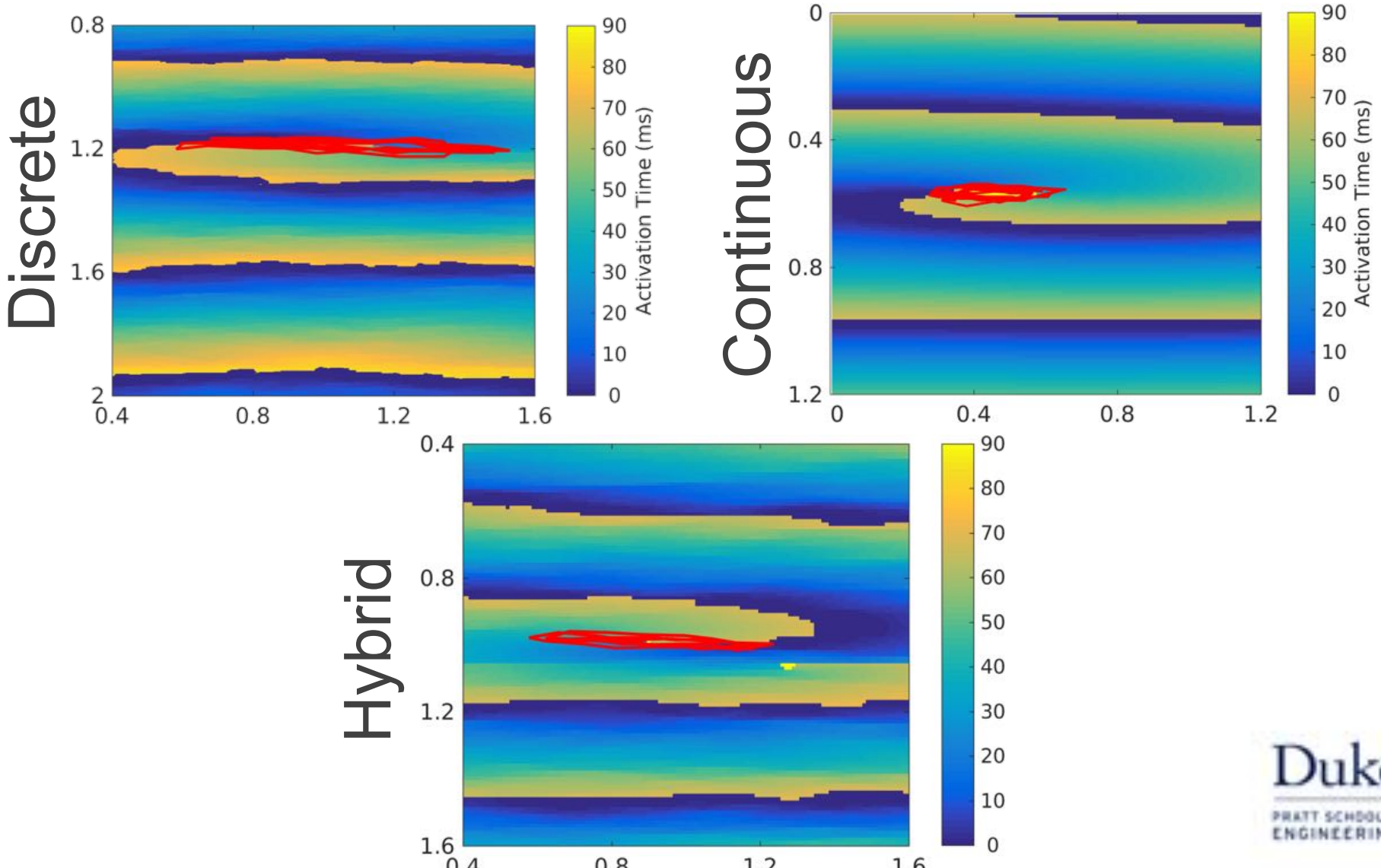
Duke
PRATT SCHOOL of ENGINEERING

Conduction slowing in hybrid



Duke
PRATT SCHOOL of ENGINEERING

Comparing Tip Trajectory

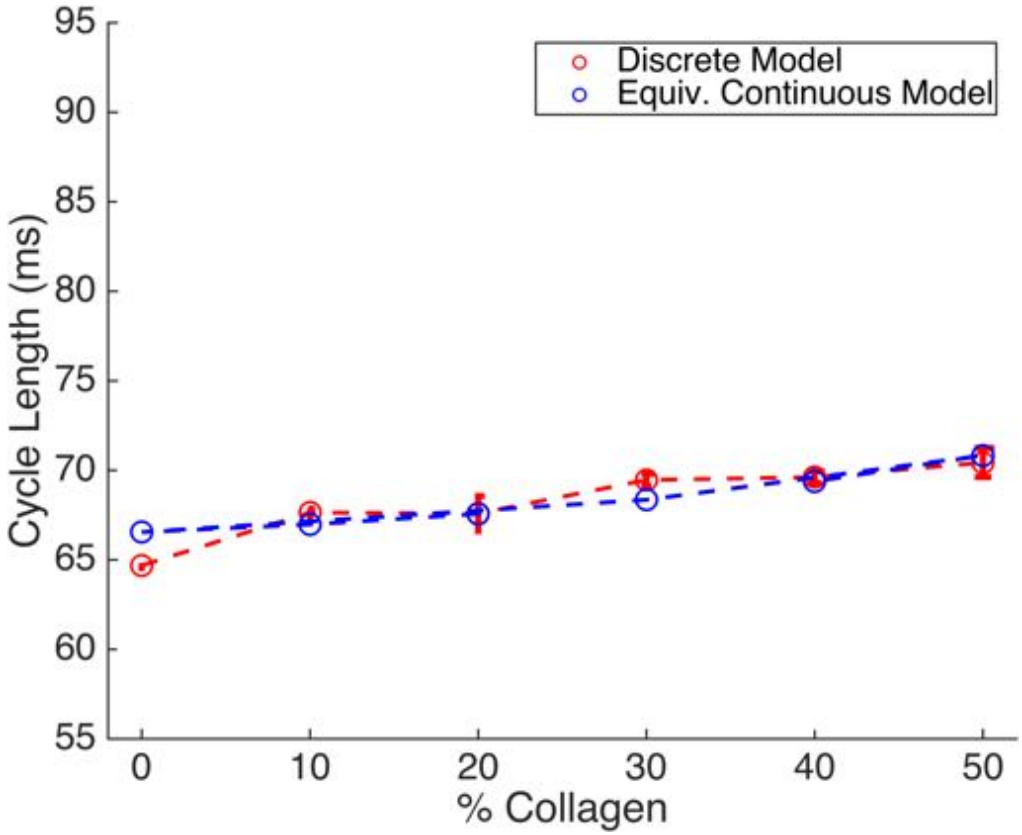


Duke
PRATT SCHOOL of ENGINEERING

Impact of septa size

At what size scale do the discontinuities created by septa become important?

Mean septa size reduced from 700 μm to 200 μm



Duke
PRATT SCHOOL of ENGINEERING

Conclusions

- Local discontinuities due to fibrosis appear to have a significant impact on complex conduction behavior
- Neither the homogenous continuous model nor the “hybrid” model are able to fully capture this effect for larger (but still sub-millimeter) discontinuities
- Limitations:
  - 2D model, perfectly regular cells
  - Mouse membrane model

Duke
PRATT SCHOOL of ENGINEERING

Conclusions

- Hybrid model is promising in capturing discrete behavior – other approaches to selecting hybrid model parameters may improve accuracy
- Take Away: Important to consider and validate methodology of modeling fibrosis prior to implementation in clinically relevant models

Duke
PRATT SCHOOL of ENGINEERING

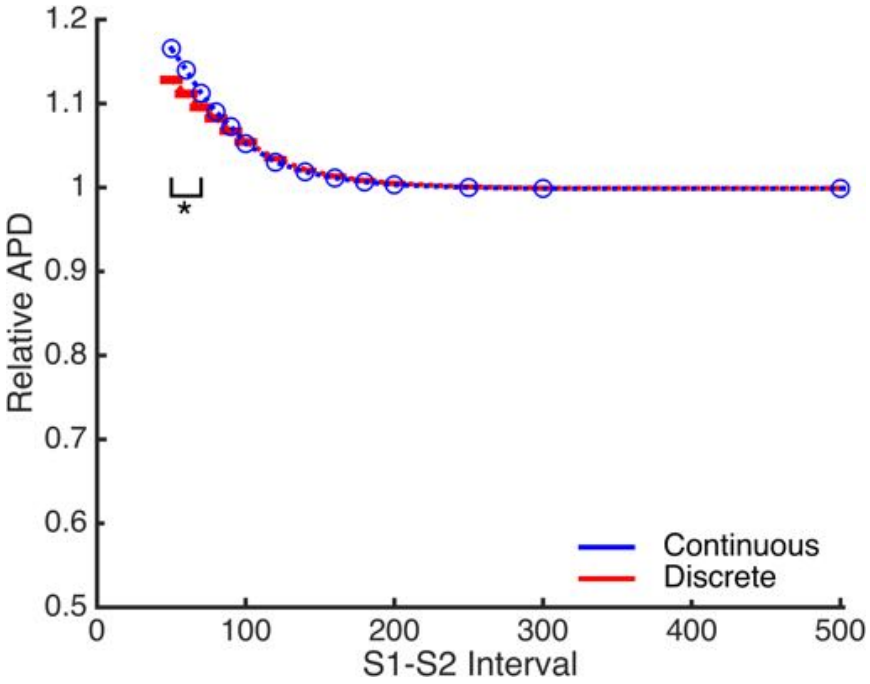
Thank you

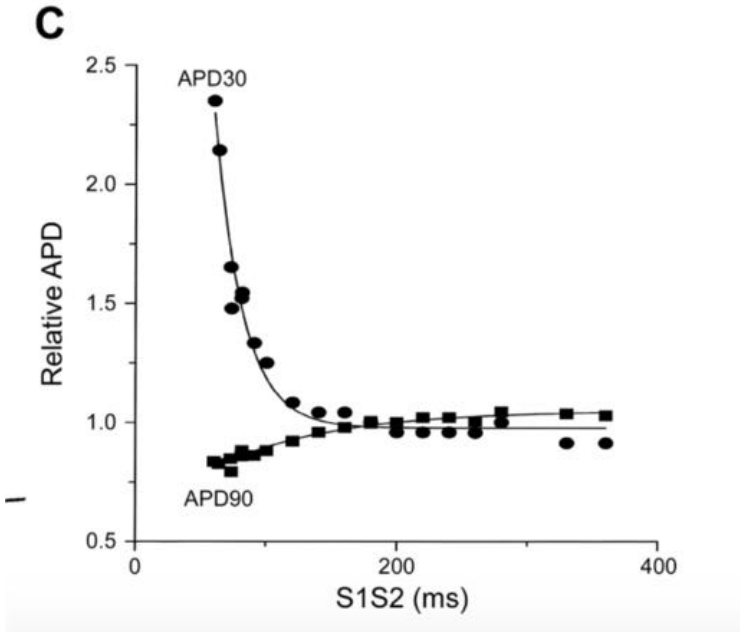
- Duke Department of Biomedical Engineering
  - Craig Henriquez, PhD
  - Eli Medvescek
  - Nenad Bursac, PhD
- Duke Medical Scientist Training Program

Funding sources: National Institutes of Health Grant R01-HL093711 to C.H. and the MSTP Training Grant T32-GM007171

Duke
PRATT SCHOOL OF
Engineering

APD Restitution





Knollmann et al. *AJP-HCP*. 2007

Duke
PRATT SCHOOL of ENGINEERING