Bioeng 6460
Electrophysiology and Bioelectricity

Modeling of Electrical Conduction in Cardiac Tissue I

Frank B. Sachse
fs@cvrti.utah.edu

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Overview

- Modeling of Cellular Electrophysiology
- Approaches for Modeling of Tissue
- Reaction Diffusion Systems
  - Overview
  - Cable Model
  - Monodomain Model
  - Bidomain Model
- Summary

Group work

Group work

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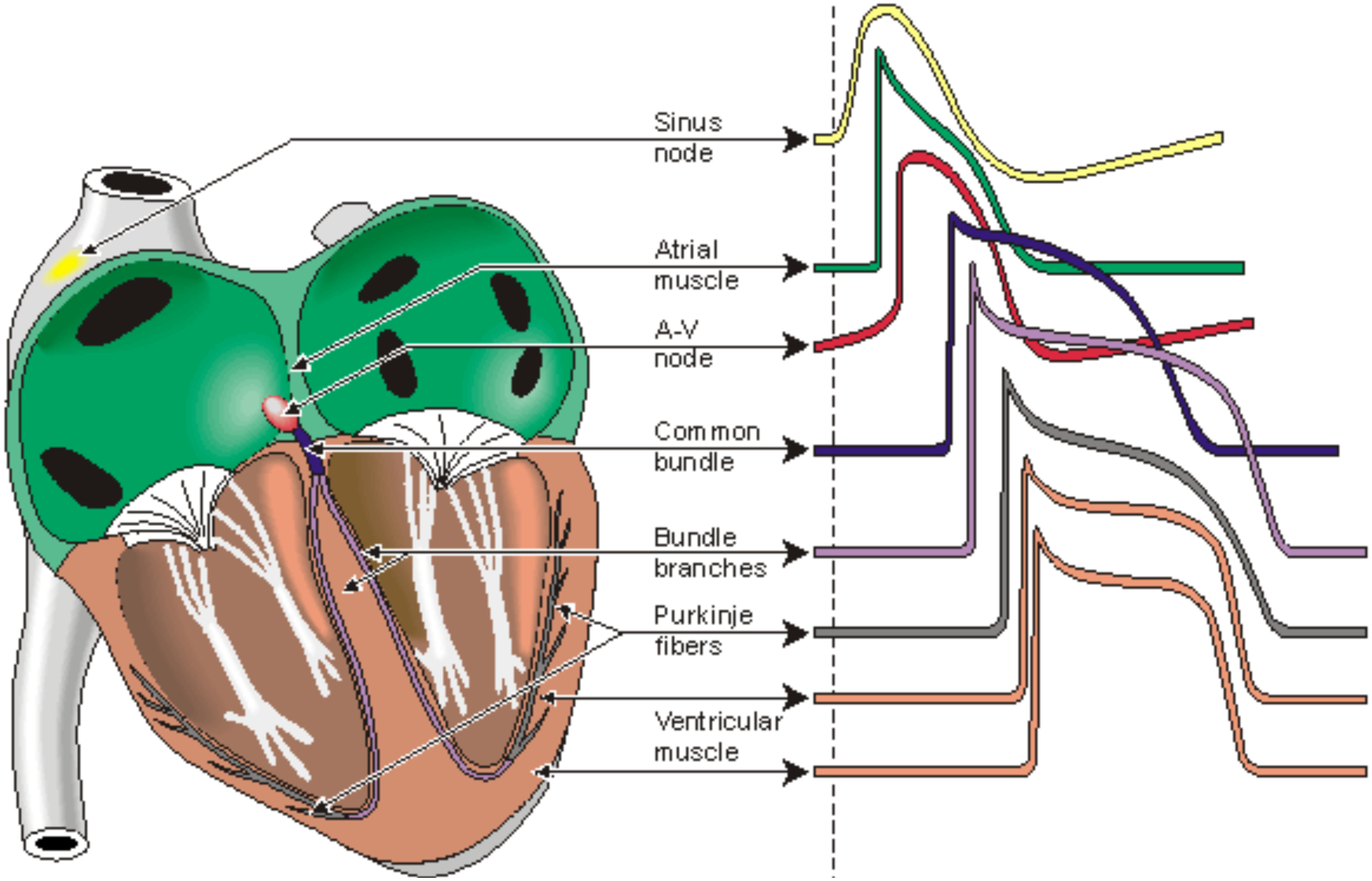
Transmembrane Voltages Measured at Different Positions



(Malmivuo and Plonsey, Bioelectromagnetism)

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Models of Cellular Electrophysiology

1952 → today

• Hodgkin-Huxley	axon membrane	giant squid
• Noble	Purkinje fiber	-
• Beeler-Reuter	ventricular myocyte	mammal
• DiFrancesco-Noble	Purkinje fiber	mammal
• Earm-Hilgemann-Noble	atrial myocyte	rabbit
• Luo-Rudy	ventricular myocyte	guinea pig
• Demir, Clark, Murphey, Giles	sinus node cell	mammal
• Noble, Varghese, Kohl, Noble	ventricular myocyte	guinea pig
• Winslow, Rice, Jafri, Marban, O'Rourke	ventricular myocyte	canine
• Ten Tusscher, Noble, Noble, Panfilov	ventricular myocyte	human
• Sachse, Moreno, Abildskov	fibroblast	rat
• Weiss, Ifland, Sachse, Seemann, Dössel	ischemic myocyte	human
• …		

Models describe cellular electrophysiology by set of ordinary differential equations. Equations are assigned to the cell membrane and some of its compartments.

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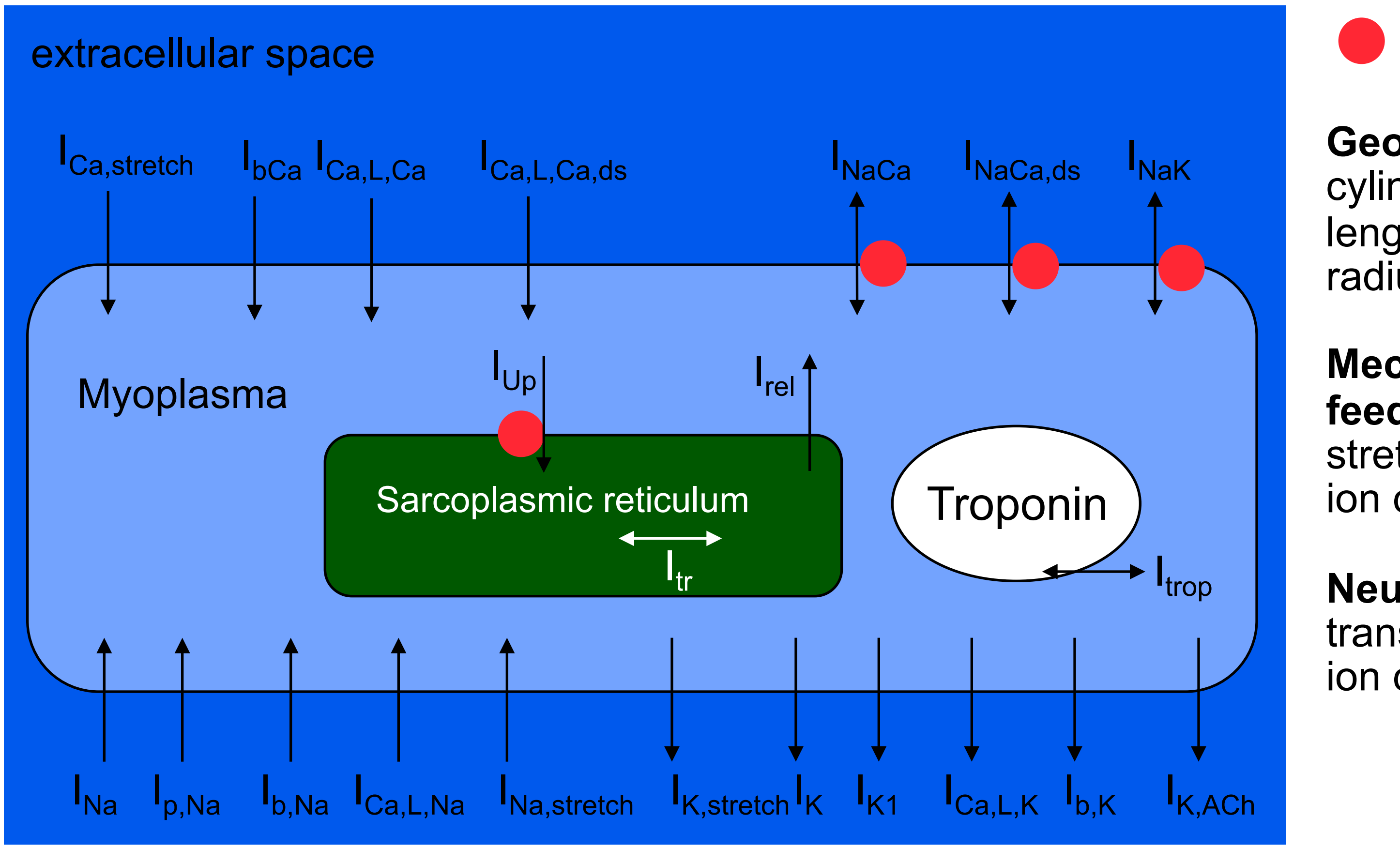
Noble-Kohl-Varghese-Noble Model 1998

Mathematical description of ionic currents and concentrations, transmembrane voltage, and conductivities of guinea-pig ventricular myocytes



Geometry
cylinder-shaped
length: 74 μm
radius: 12 μm

Mechano-electrical feedback by stretch activated ion channels

Neural influence by transmitter activated ion channels etc.

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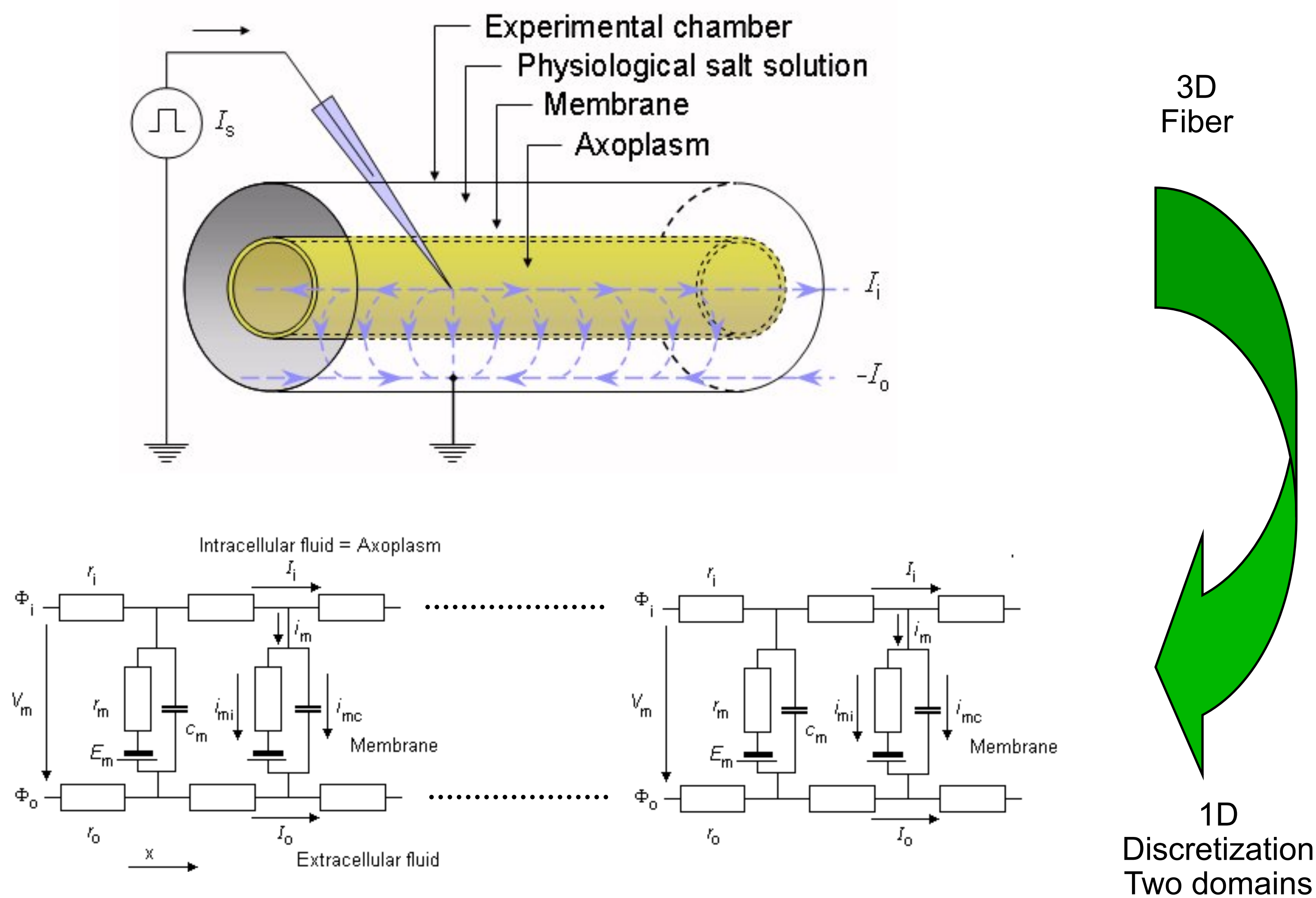
Models of Electrical Conduction

- **Macroscopic**
  - **Reaction diffusion systems**
    - **Simplified**
      (FitzHugh-Nagumo 61, Rogers-McCulloch 1994, …)
    - **Biophysically Detailed**
      - **monodomain**
        (Rudy 1989, Virag-Vesin-Kappenberger 1998, …
      - **bidomain**
        (Henriquez-Plonsey 1989, Sepulveda-Wikswo 1994, …)
      - **multidomain**
        (Sachse-Seemann-Moreno-Abildskov 2009)
  - **Rule based / cellular automata**
    (Moe 1962, Eifler-Plonsey 1975, …)
- **Microscopic**
  (Spach 1981, Roberts-Stinstra-Henriquez 2008)

Reaction Diffusion System: Cable Model



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Cable Model: Steady State Response to Non-Excitatory Current

Length constant λ describes spatial distance between two points:

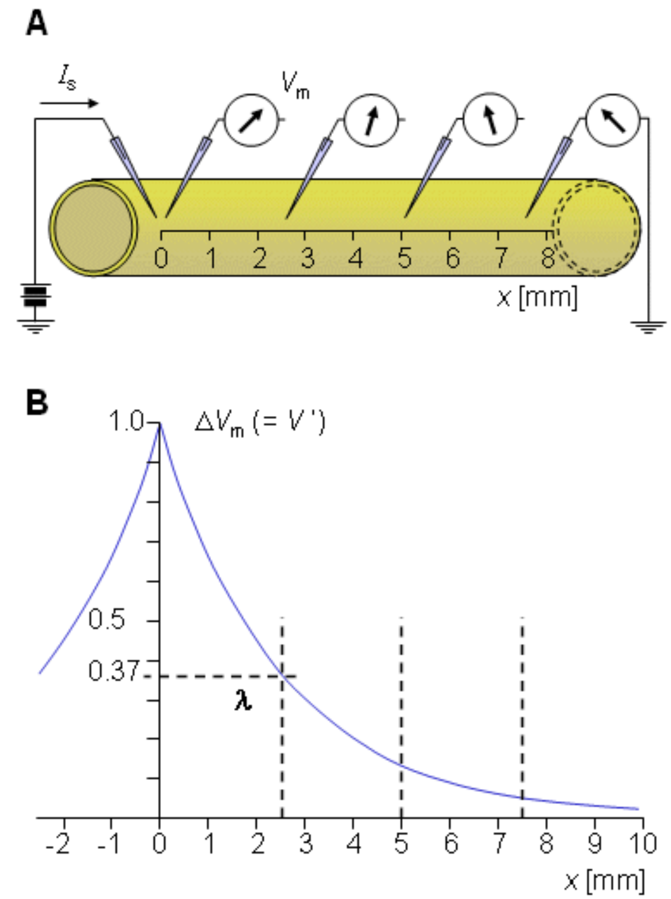
1. Position of electrode for injection of current causing voltage step ΔV_m.
2. Position at which the voltage $\Delta V_m/e$ is interpolated from measurements.

$\Delta V_m(\lambda) = 0.368\ \Delta V_m(0)$

Length constant λ is determined by intra-, extracellular and membrane resistances, r_i, r_o, and r_m:

$$\lambda = \sqrt{\frac{r_m}{r_i + r_o}} \approx \sqrt{\frac{r_m}{r_i}}$$

Assumption: r_m is constant



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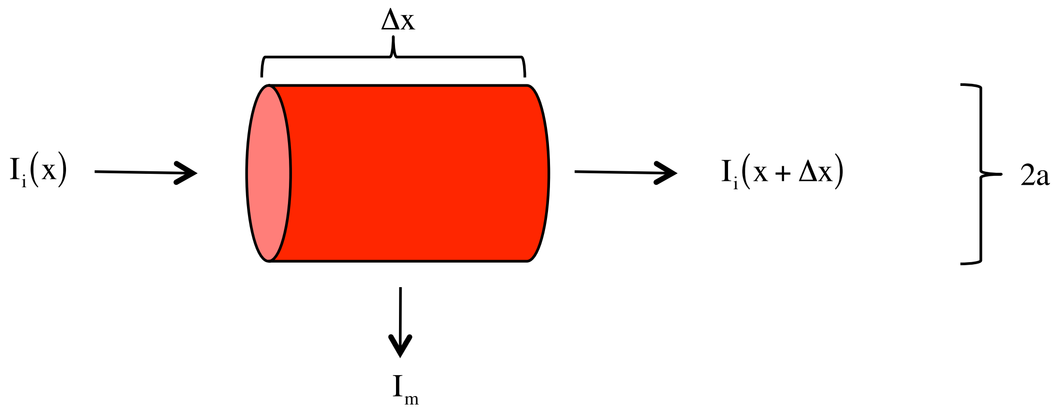
Monodomain Cable (1D) Model of Electrical Conduction



Kirchhoff's first rule $\quad I_i(x) - I_i(x+\Delta x) - I_m = 0$

$\Delta x \rightarrow 0$

$$\frac{a}{2}\frac{\partial}{\partial x}\left(\frac{1}{\rho(x)}\frac{\partial V_m(x,y)}{\partial x}\right) = I_m$$

a : Radius of cable

ρ : Resitivity

I_m : Membrane current

V_m : Membrane voltage

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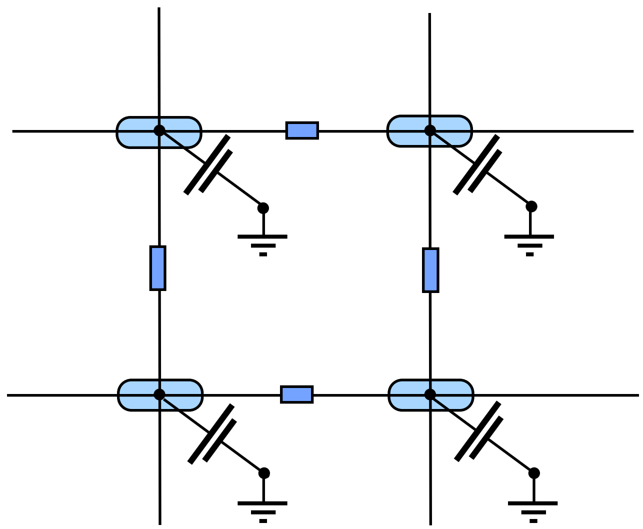
Monodomain Modeling of Electrical Conduction in 2D

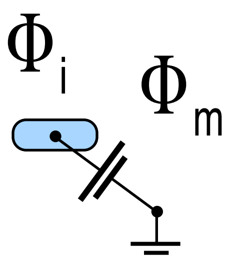


Resistor of gap junctions
(average conductance between cell pairs 250-1000 nS)

Myocyte
intracellular space surrounded by sarcolemma

Membrane Voltage Source

Ground



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Monodomain Model for Electrical Conduction in 2/3D

$$\nabla(\sigma_i \nabla \Phi_m) = \beta I_m - I_{si}$$

Coupling with cell model
Numerical Procedure

$\Phi_m(\mathbf{x},t)$ is unknown

$$I_i = \nabla(\sigma_i \nabla \Phi_m) + I_{si}$$

$$\frac{\partial \Phi_m}{\partial t} = \frac{1}{C_m}\left(\frac{I_i}{\beta} - I_{ion}\right)$$

Φ_m Transmembrane voltage

I_m Transmembrane current

I_{si} External intracellular current

σ_i Intracellular conductivity tensor (includes conductivity of gap junctions)

β Surface-volume ratio of cell

I_{ion} Current through ion channels

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Group Work

Assume an electrical field $\Phi(x,y,z)=x\ 4$ V/m in a cube 1 m x 1 m x 1 m

Determine the gradient ∇ of the electrical field.

How would create this field?

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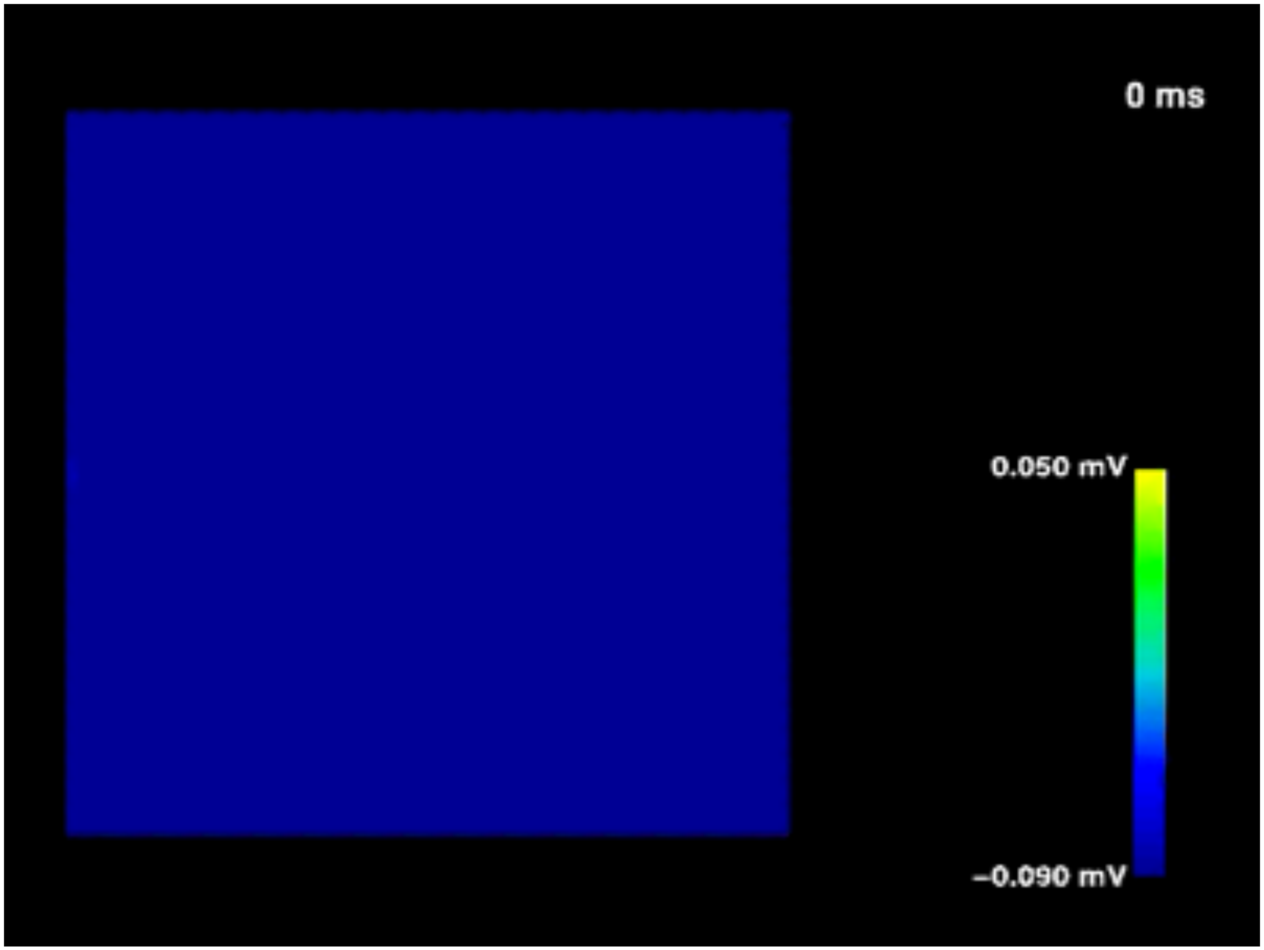
2D-Simulation



Array of myocytes

Area: 6.4^2 mm^2
Elements
• number: 64^2
• size: 0.1^2 mm^2
with fiber orientation

Electrophysiology

Noble et al. 98
Monodomain model

Stimulus

1. left, middle

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Bidomain Model: Motivation

Inclusion of extracellular conduction relevant for modeling of:

- anisotropic propagation of excitation
- stimulation with extracellular current sources
- body surface potential maps (BSPM) and electrocardiograms (ECG)

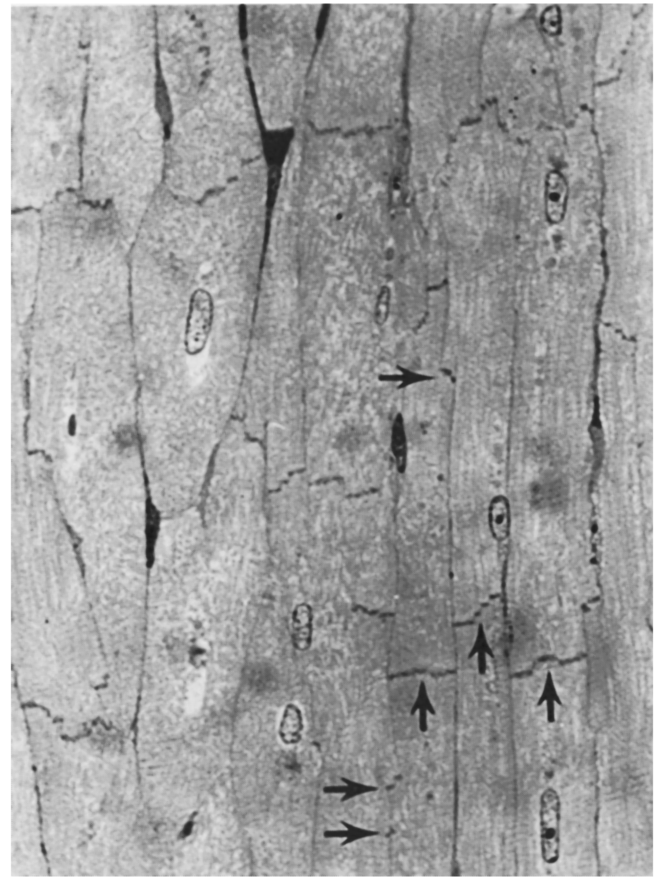
Problem

Realistic cell-based modeling of tissue

- complex geometry of cells
- large number of cells

Idea „Bidomain Model"

- division of space in two domains
- separated calculation



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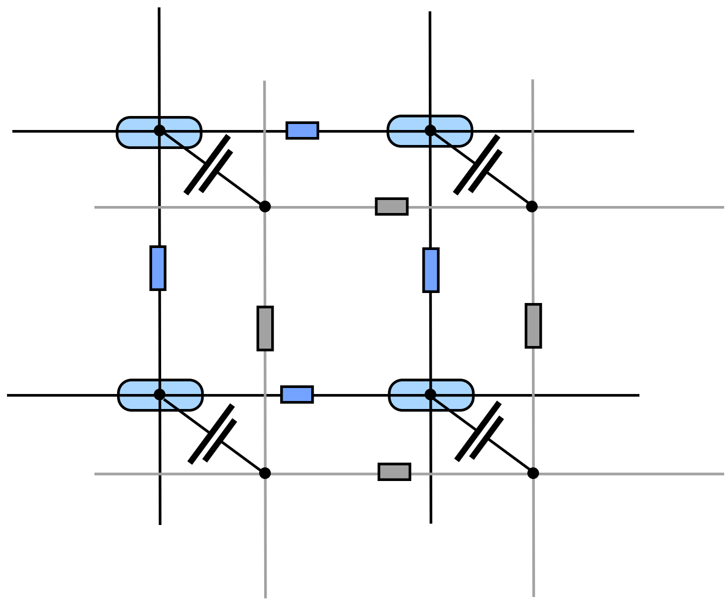
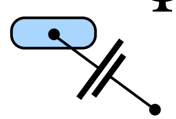
Bidomain Modeling of Electrical Conduction in 2D





Resistor of gap junctions
(average conductance between cell pairs 250-1000 nS)

Resistor of extracellular space

Myocyte
intracellular space surrounded by sarcolemma

Membrane Voltage Source

Φ_m Transmembrane Voltage

Φ_i Intracellular potential

Φ_e Extracellular potential

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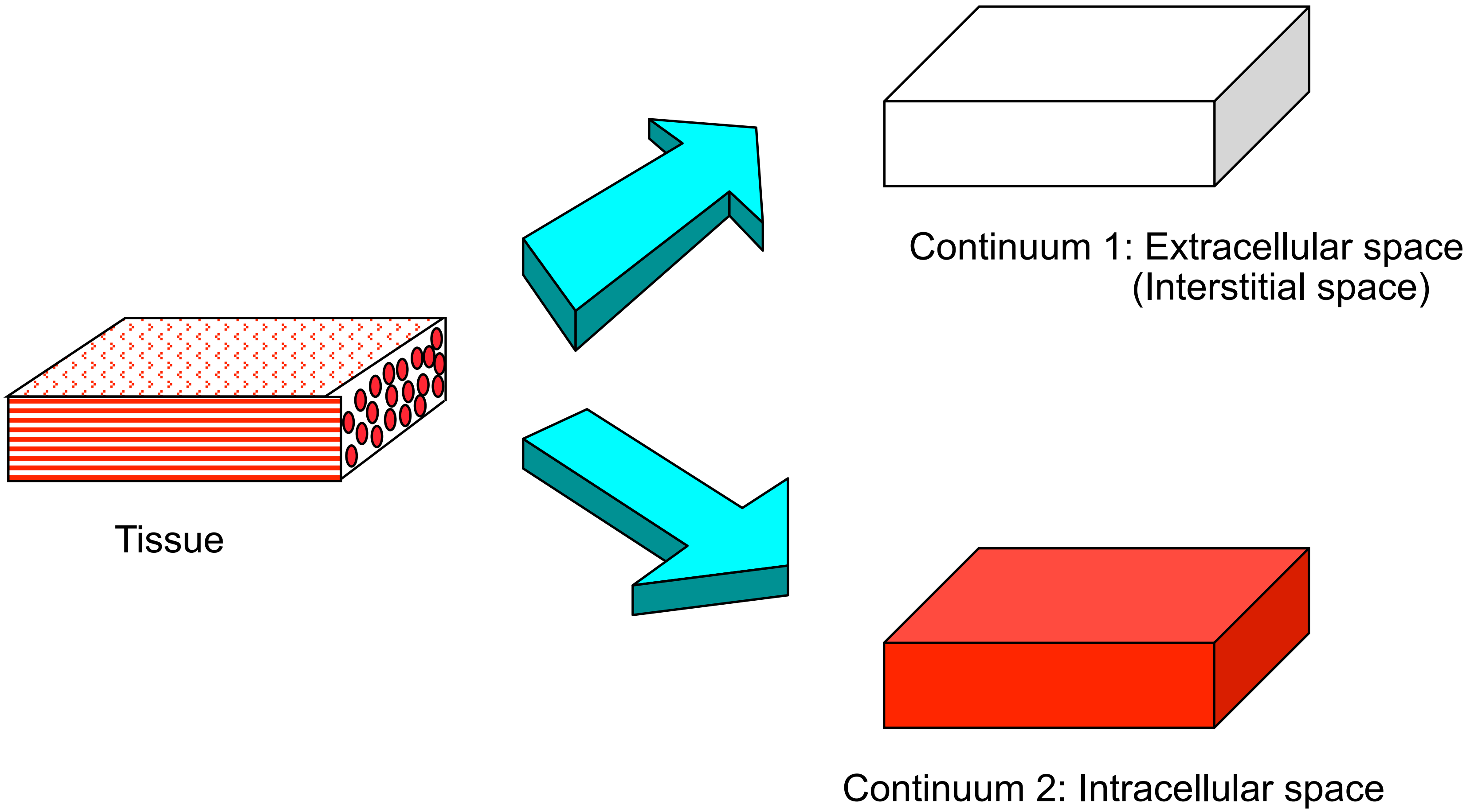
Bidomain Model: Basics

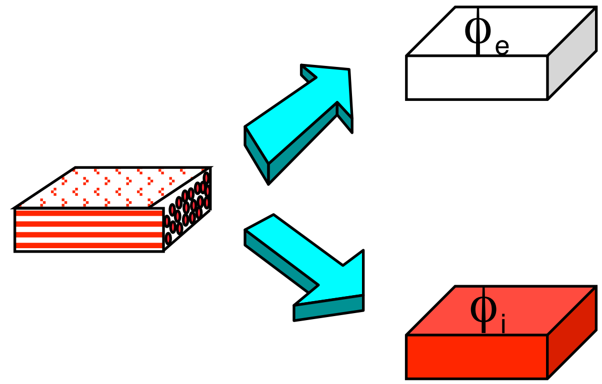


Bidomain Model: Basics

$$\Phi_m = \Phi_i - \Phi_e$$

Φ_m : Transmembrane voltage $[\mathrm{V}]$

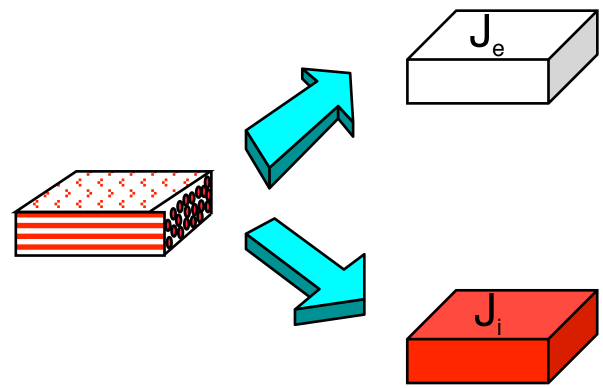
$\Phi_{i/e}$: Intra-/extracellular potential $[\mathrm{V}]$



$$J = J_i + J_e$$

J : Summary current density $[\mathrm{A/m^2}]$

$J_{i/e}$: Intra-/extracellular current density $[\mathrm{A/m^2}]$



Bidomain Model: Intracellular Space

$$-\nabla(\sigma_i J_i) = \nabla(\sigma_i \nabla \Phi_i) = \beta I_m - I_{si}$$

σ_i : Intracellular conductivity $\left[\frac{S}{m}\right]$

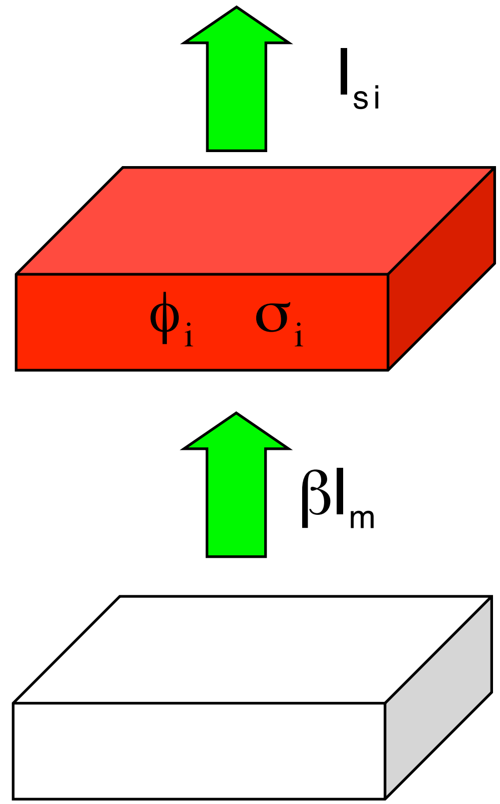
J_i : Intracellular current density $\left[\frac{A}{m^2}\right]$

Φ_i : Intracellular potential $[V]$

I_{si} : Intracellular current source density $\left[\frac{A}{m^3}\right]$

I_m : Membrane source density $\left[\frac{A}{m^2}\right]$

β : Ratio of membrane surface to volume $[m^{-1}]$



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Bidomain Model: Extracellular Space

$$-\nabla(\sigma_e J_e) = \nabla(\sigma_e \nabla \Phi_e) = -\beta I_m - I_{se}$$

σ_e : Intracellular conductivity $\left[\frac{S}{m}\right]$

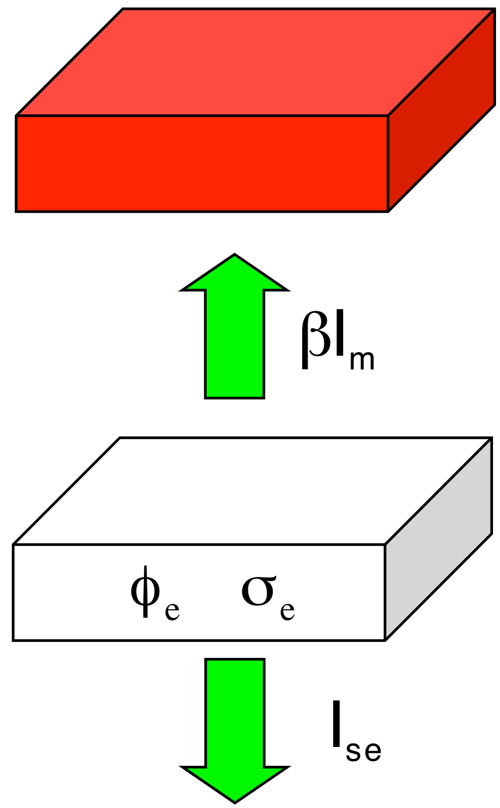
J_e : Intracellular current density $\left[\frac{A}{m^2}\right]$

Φ_e : Intracellular potential $[V]$

I_{se} : Intracellular current source density $\left[\frac{A}{m^3}\right]$

I_m : Membrane source density $\left[\frac{A}{m^2}\right]$

β : Ratio of membrane surface to volume $[m^{-1}]$



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Bidomain Model: Relationships

$$\mathrm{J} = \mathrm{J}_\mathrm{i} + \mathrm{J}_\mathrm{e} = -\sigma_\mathrm{i}\nabla\phi_\mathrm{i} - \sigma_\mathrm{e}\nabla\phi_\mathrm{e}$$

with $\phi_\mathrm{m} = \phi_\mathrm{i} - \phi_\mathrm{e}$:

$$\mathrm{J} = -\sigma_\mathrm{i}\nabla\phi_\mathrm{m} - \sigma_\mathrm{i}\nabla\phi_\mathrm{e} - \sigma_\mathrm{e}\nabla\phi_\mathrm{e}$$

with $\sigma_\mathrm{H} = \sigma_\mathrm{i} + \sigma_\mathrm{e}$:

$$\mathrm{J} = -\sigma_\mathrm{i}\nabla\phi_\mathrm{m} - \sigma_\mathrm{H}\nabla\phi_\mathrm{e}$$

with $\nabla\cdot \mathrm{J} = 0$:

$$\nabla\cdot\left(\sigma_\mathrm{H}\nabla\phi_\mathrm{e}\right) = -\nabla\cdot\left(\sigma_\mathrm{i}\nabla\phi_\mathrm{m}\right)$$

Generalized Poisson‘s Equation

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Bidomain Model: Numerical Solution

$\Phi_m(\mathbf{x},t)$ and $\Phi_e(\mathbf{x},t)$ are unknown

unknown

$$\nabla(\sigma_i \nabla \Phi_m) = -\nabla(\sigma_H \nabla \Phi_e)$$

$$I_{stim} = \nabla(\sigma_i \nabla \Phi_m) + \nabla(\sigma_i \nabla \Phi_e)$$

$$\frac{\partial \Phi_m}{\partial t} = \frac{1}{C_m}\left(\frac{I_{stim}}{\beta} - I_{ion}\right)$$

unknown

Elliptical partial differential equations (Poisson's equation)

Ordinary differential equation (Cell model)

Problem: Spatio-temporal discretization!

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Current Flow in 3D-Model of Electrical Conduction

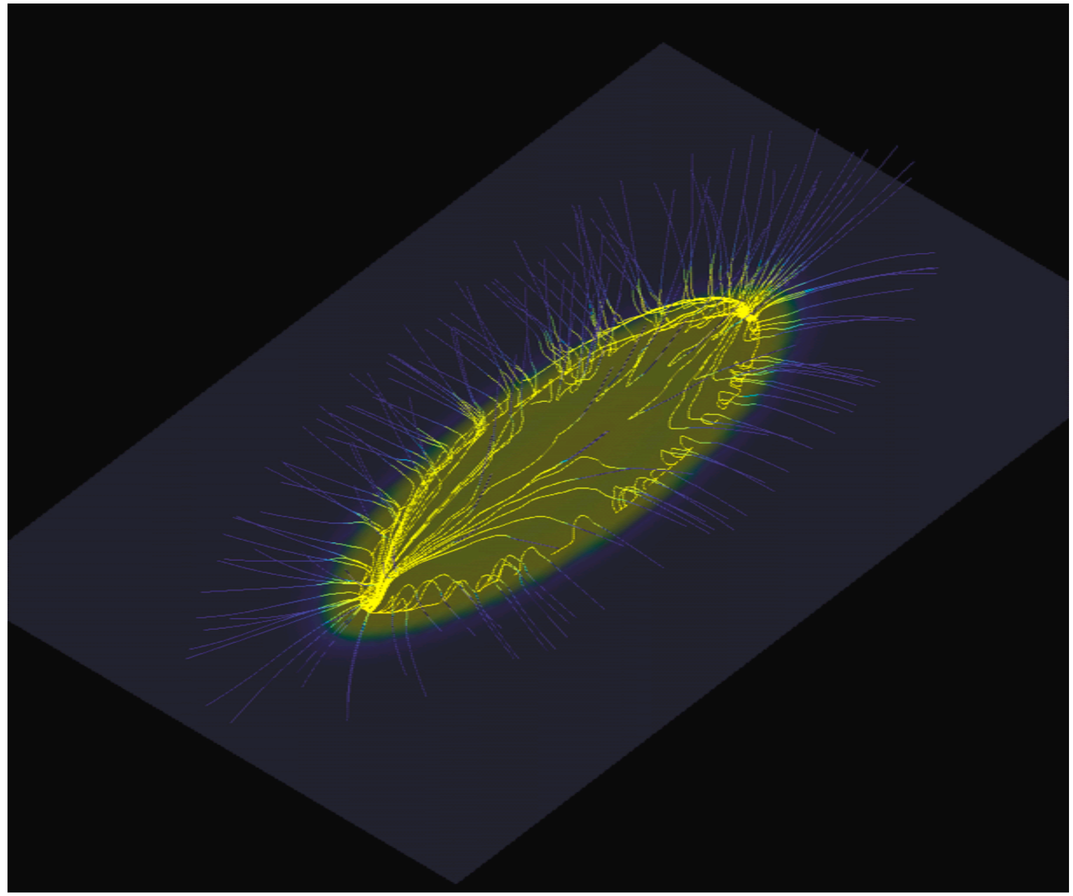
Anisotropic Monodomain Model

64 x 64 x 128 elements
with electrophysiology of
ventricular myocytes
(Noble-Varghese-Kohl-Noble)

Stimulus at center of
plane (Z=0) at time t=0 ms

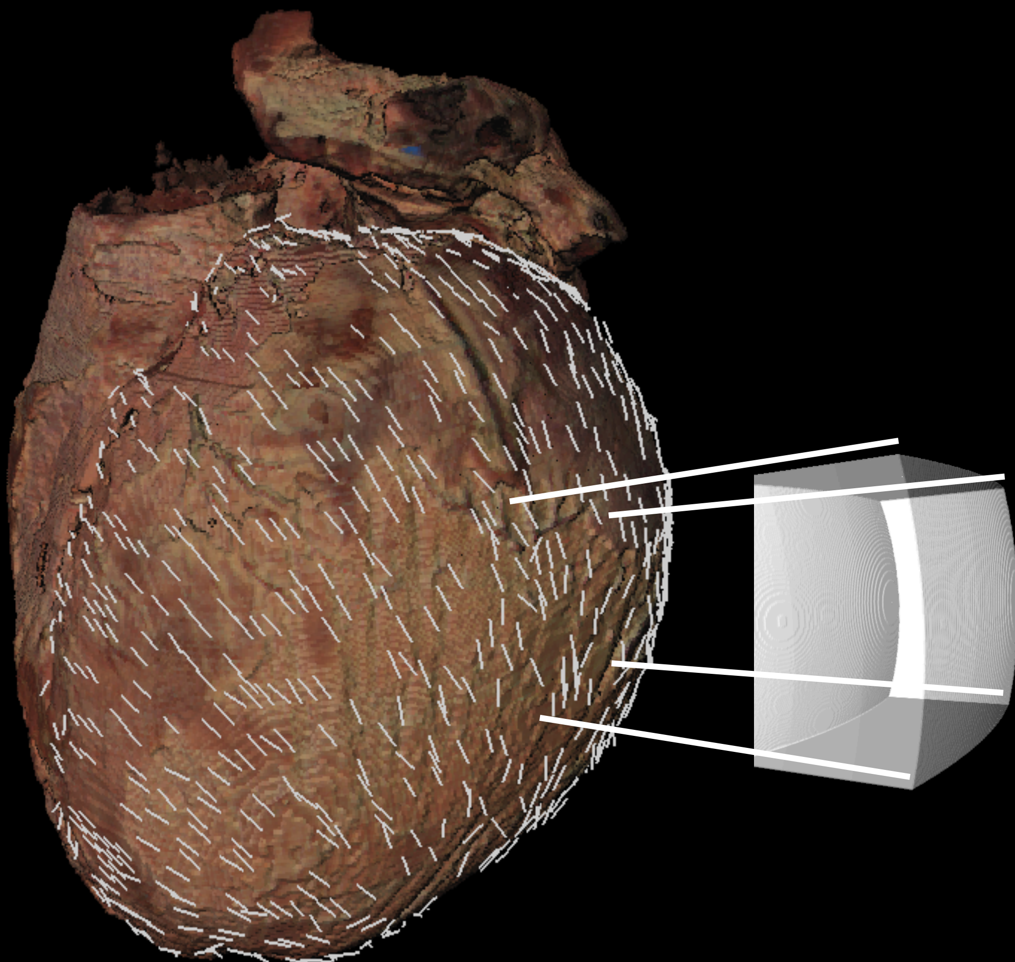
Fiber orientation parallel to Z-axis

Duration of simulation: 500ms



Colour-coded voltages and streamlines at time t=10 ms in plane (Z=0). Colour indicates transmembrane voltage.

Simulation of Electrophysiology in Myocardial Area



Myocyte cluster in left ventricular free wall

128 x 128 x 128 elements with electrophysiology of ventricular myocytes (Noble-Varghese-Kohl-Noble)

Inclusion of wall depth dependent
- myocyte orientation
- current I_{to}

Element coupling via bidomain model

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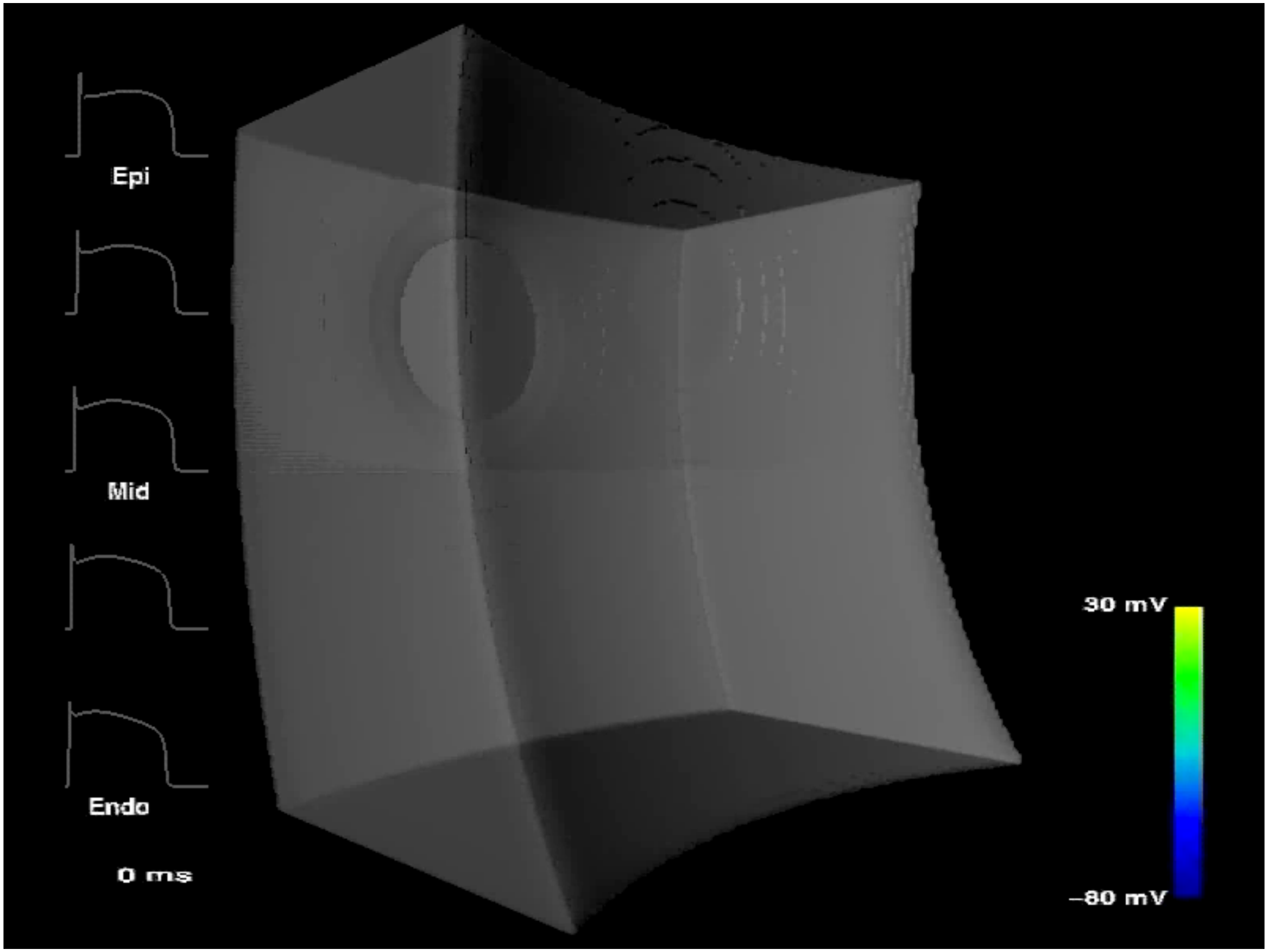
Transmembrane Voltage in Static Myocardial Area



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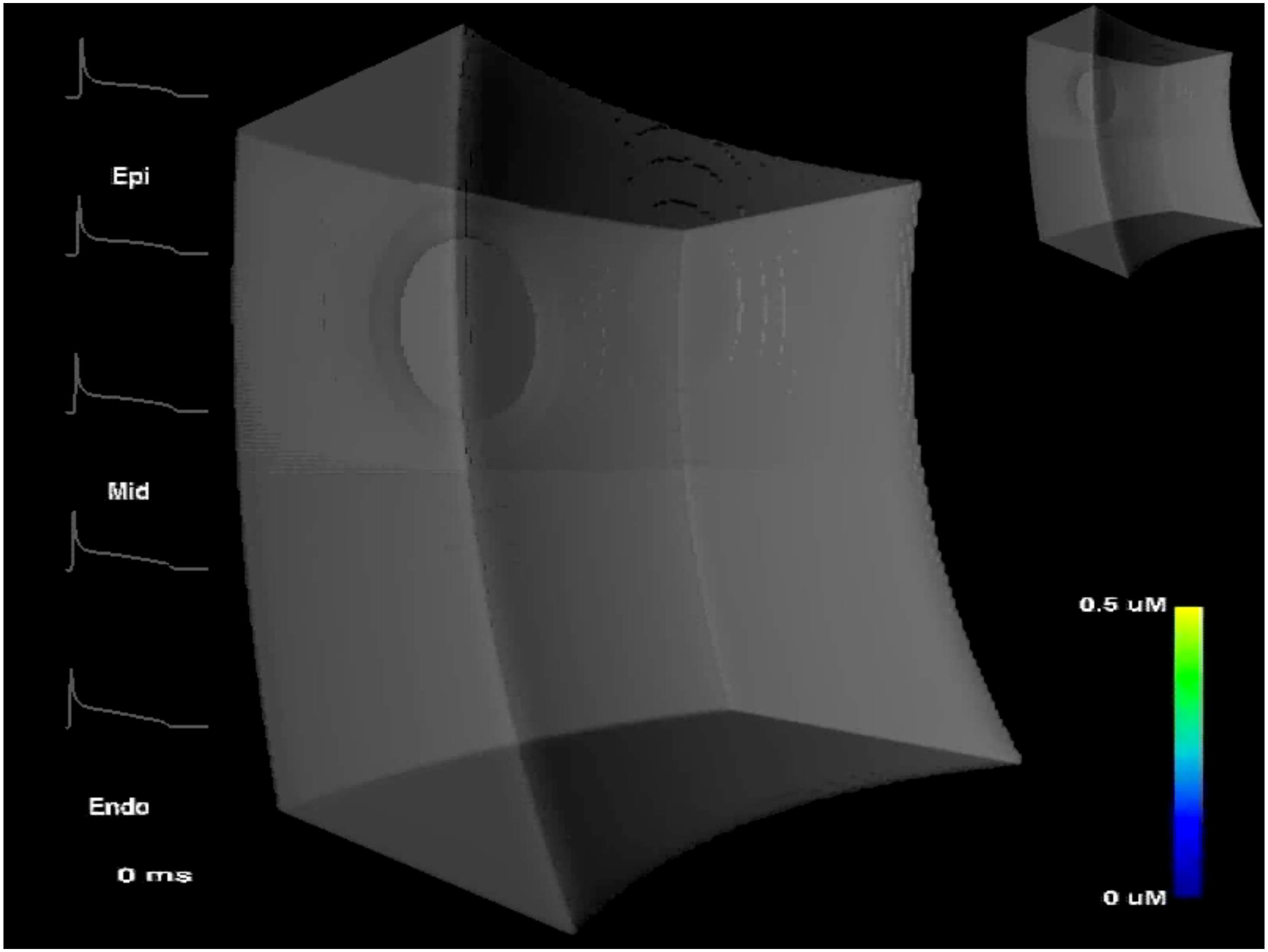
Calcium Concentration in Static Myocardial Area



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Group Work

What are the limitations of bidomain modeling? List 5 limitations.

Identify and describe other applications for (non-electrical) multidomain models in
- physics
- biology
- …

What might be the domains of a tridomain model of cardiac electrophysiology?

Summary

- Modeling of Cellular Electrophysiology
- Approaches for Modeling of Tissue
- Reaction Diffusion Systems
  - Overview
  - Cable Model
  - Monodomain Model
  - Bidomain Model

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