Computational Modeling of the Cardiovascular System

Modeling of Electrical Conduction in Cardiac Tissue

CVRTI

Frank B. Sachse, University of Utah

Overview

- Experimental Studies
- Reaction Diffusion Systems
  - Cable Model
  - Monodomain Model
  - Bidomain Model
- Cellular Automata

Group work & pause

Group work

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Experimental Studies of Cardiac Electrical Conduction

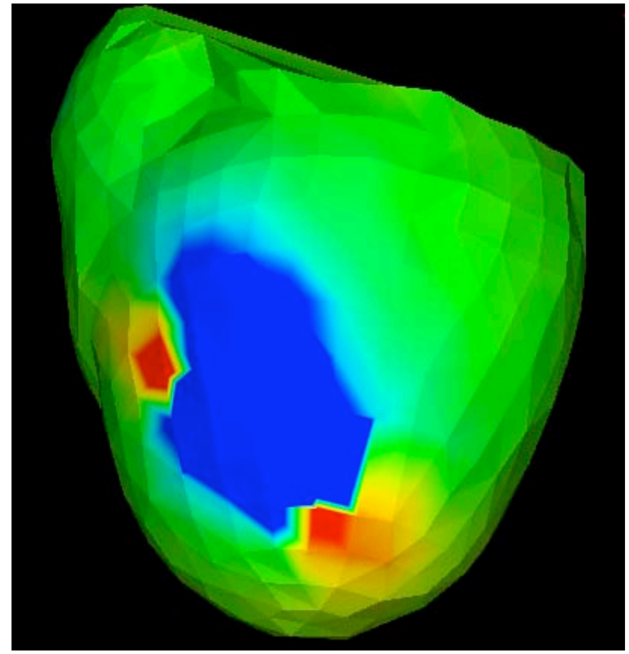
Measurement methods

- Electrode arrays: Extracellular voltages
  (similar ECG measurements on body surface)
  Sampling rate up to several kHz
  Channels up to 2000
- Optical: Transmembrane voltages
  CCD-camera
  Photodiode array

Preparations

- Cell strands - Purkinje fibers
- Small muscles - papillary muscle, trabeculae
- Sections - wedge preparations from ventricles
- Atria/ventricle
- Whole heart

in vivo/in vitro



Color-coded visualization of extracellular voltages measured on surface of canine ventricles

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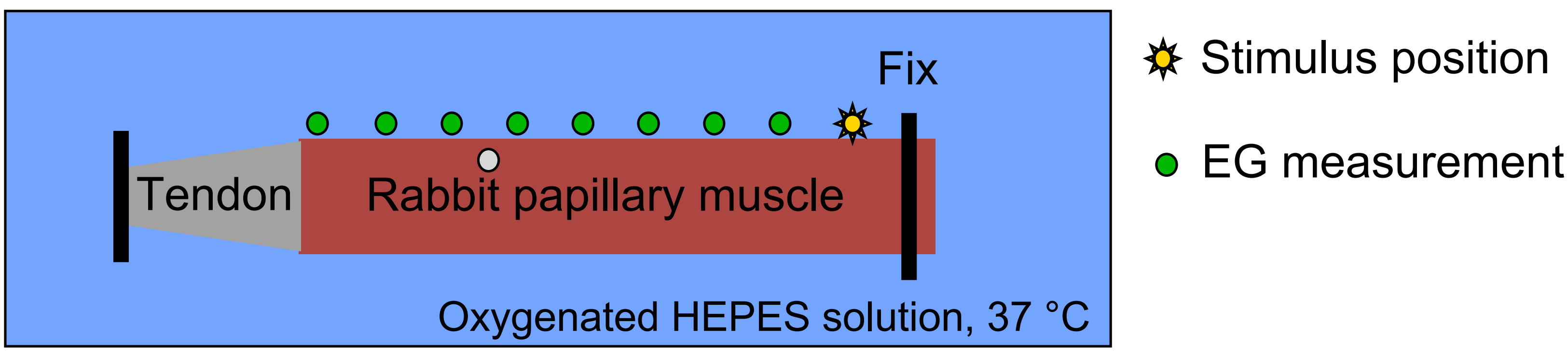
Experimental Studies in Papillary Muscle

Species: Adult New Zealand White rabbits (1.5-3.0 kg)

1. Anti-coagulated with heparin and anesthetized with pentobarbital
2. Hearts are rapidly excised and moved to dissection tray
3. Retrograde perfusion via aorta with modified Tyrode solution
4. Opening of right ventricle
5. Selection and excision of papillary muscle including onset of chordae tendinae
   Criteria: Small diameter, large length, unramified
6. Transfer to horizontal flow-through chamber
7. Fixation of muscle
8. Measurement



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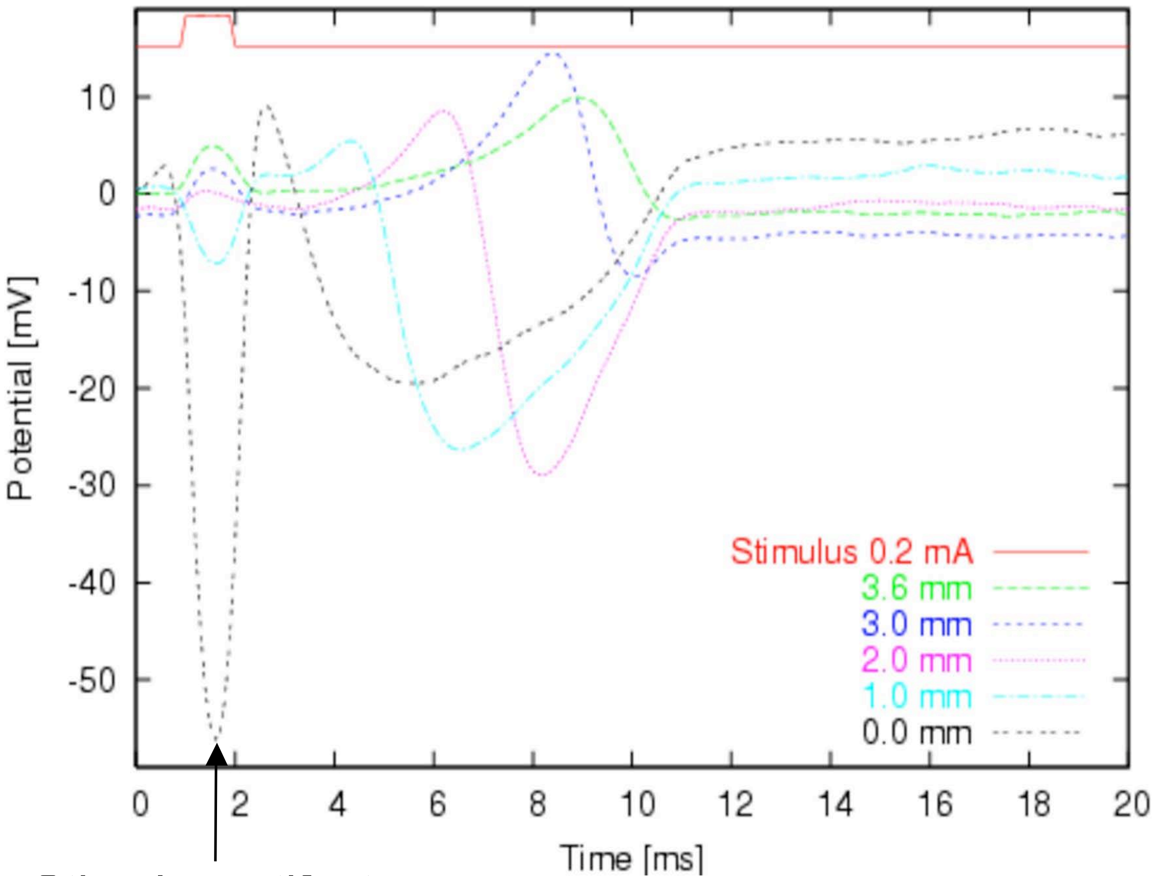
Measurement Results: Electrograms



Distance to stimulus site

Stimulus artifact

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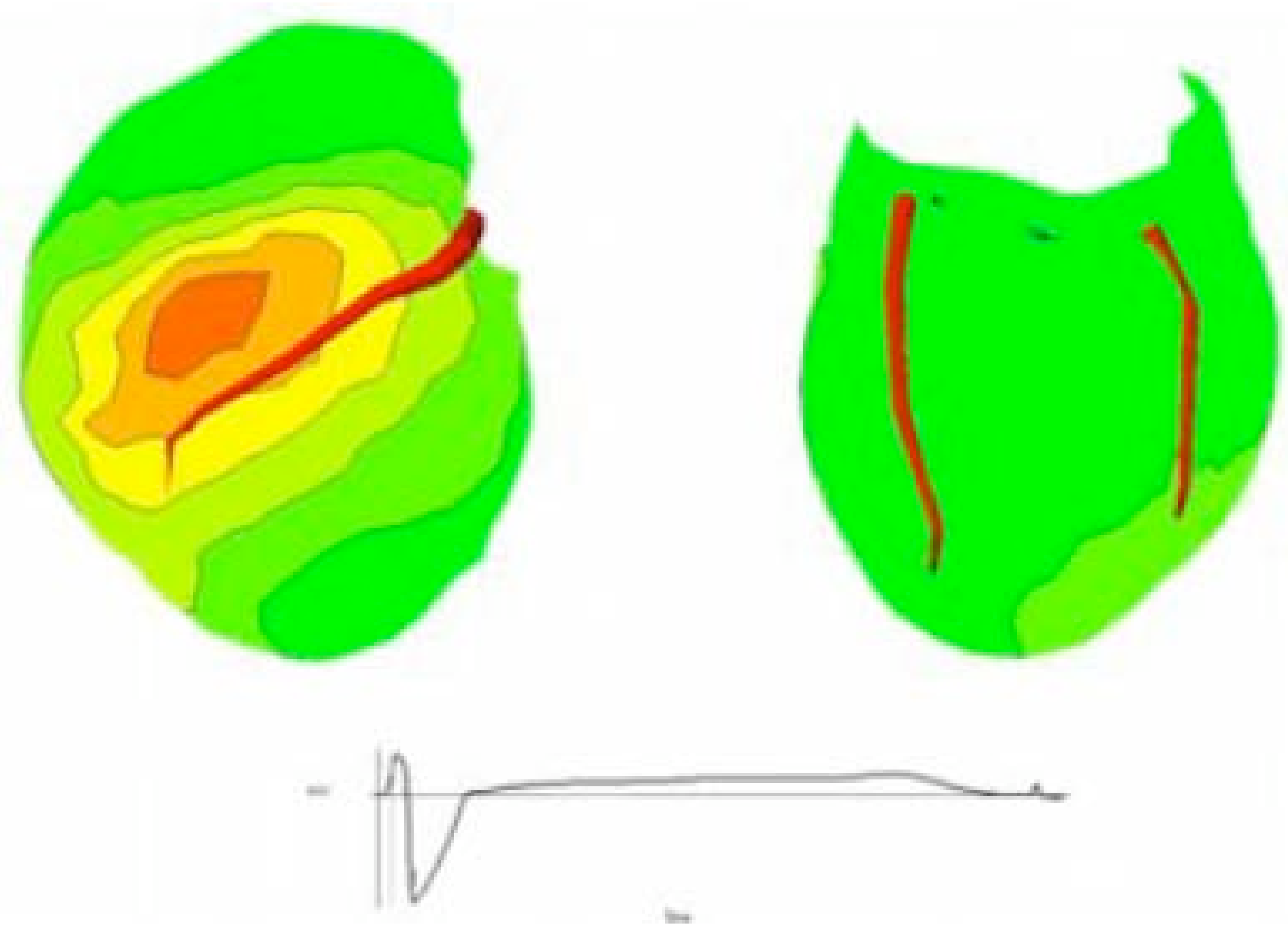
Electrical Mapping of Canine Ventricles



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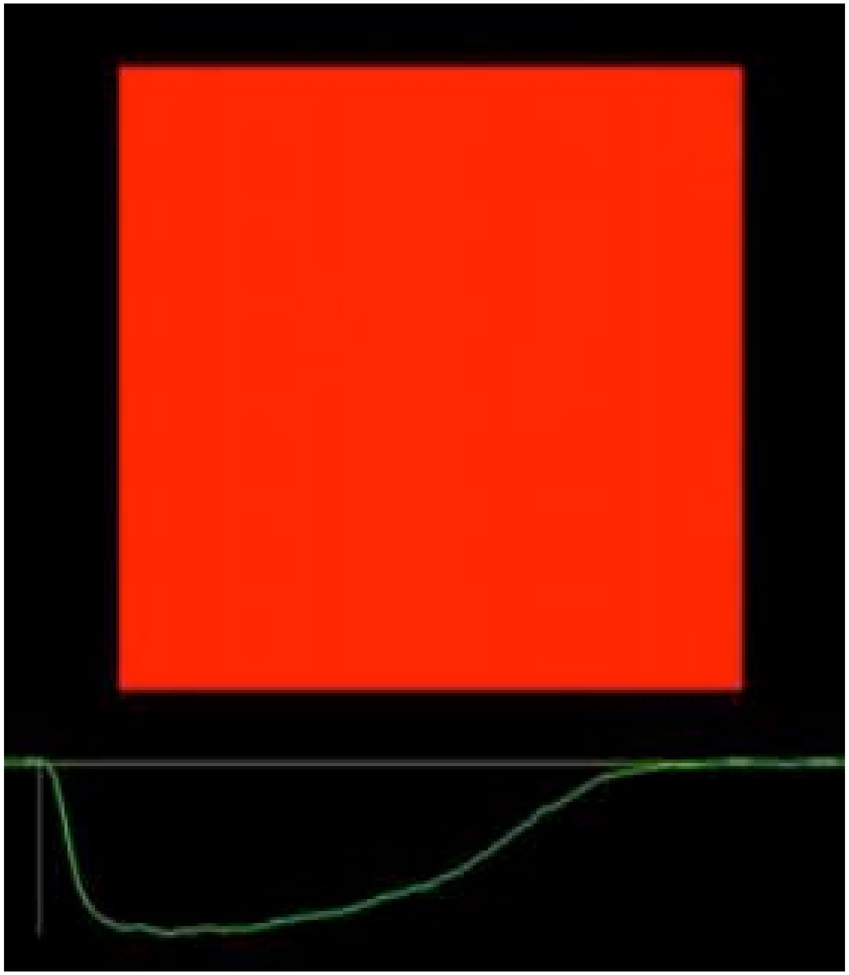
Optical Mapping of Canine Ventricular Area



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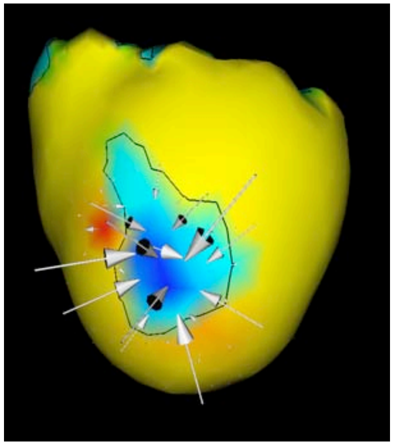
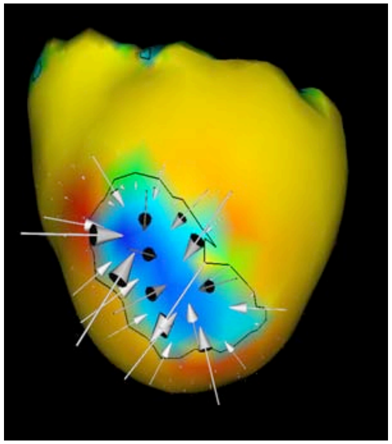
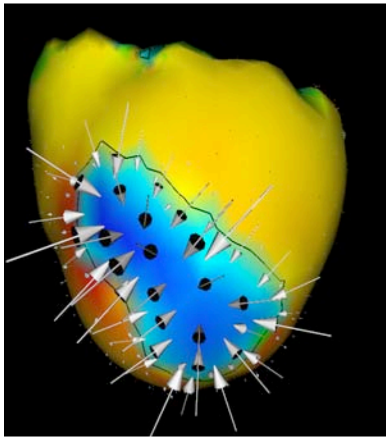
In-/Outflow of Currents during Excitation



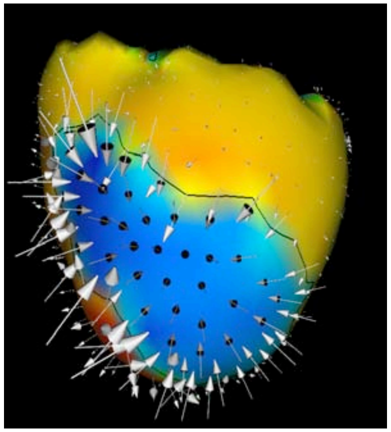
10 ms



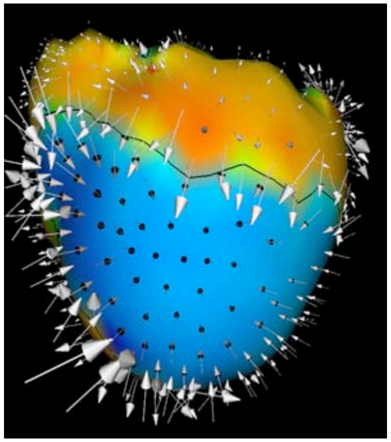
20 ms



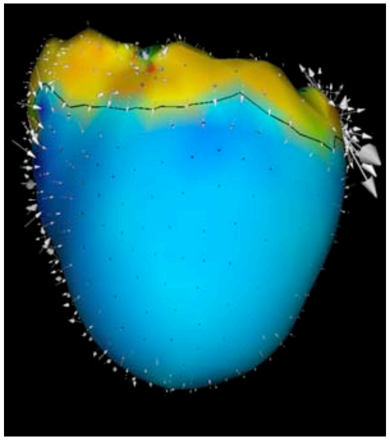
30 ms



40 ms



50 ms



60 ms

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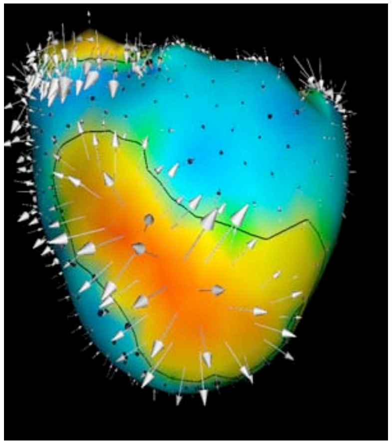
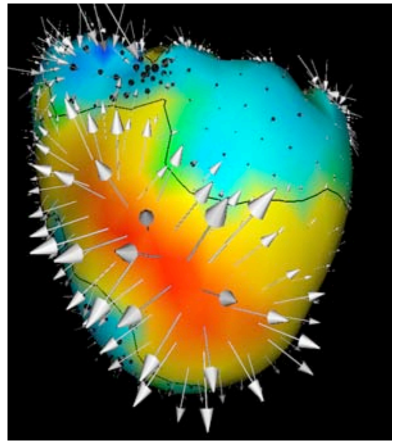
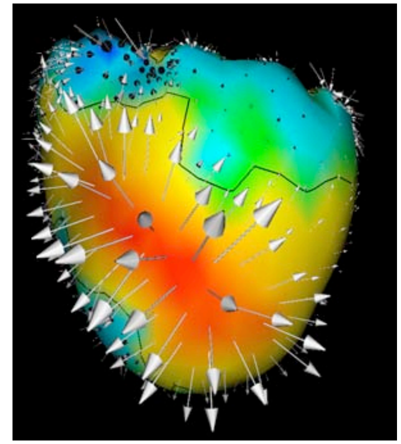
In-/Outflow of Currents during Repolarization



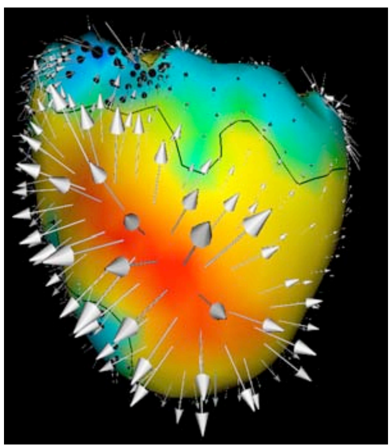
110 ms



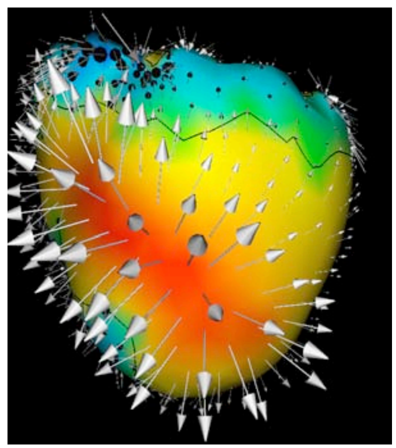
130 ms



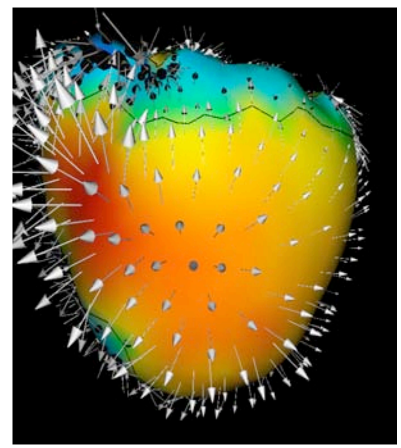
150 ms



170 ms



190 ms



210 ms

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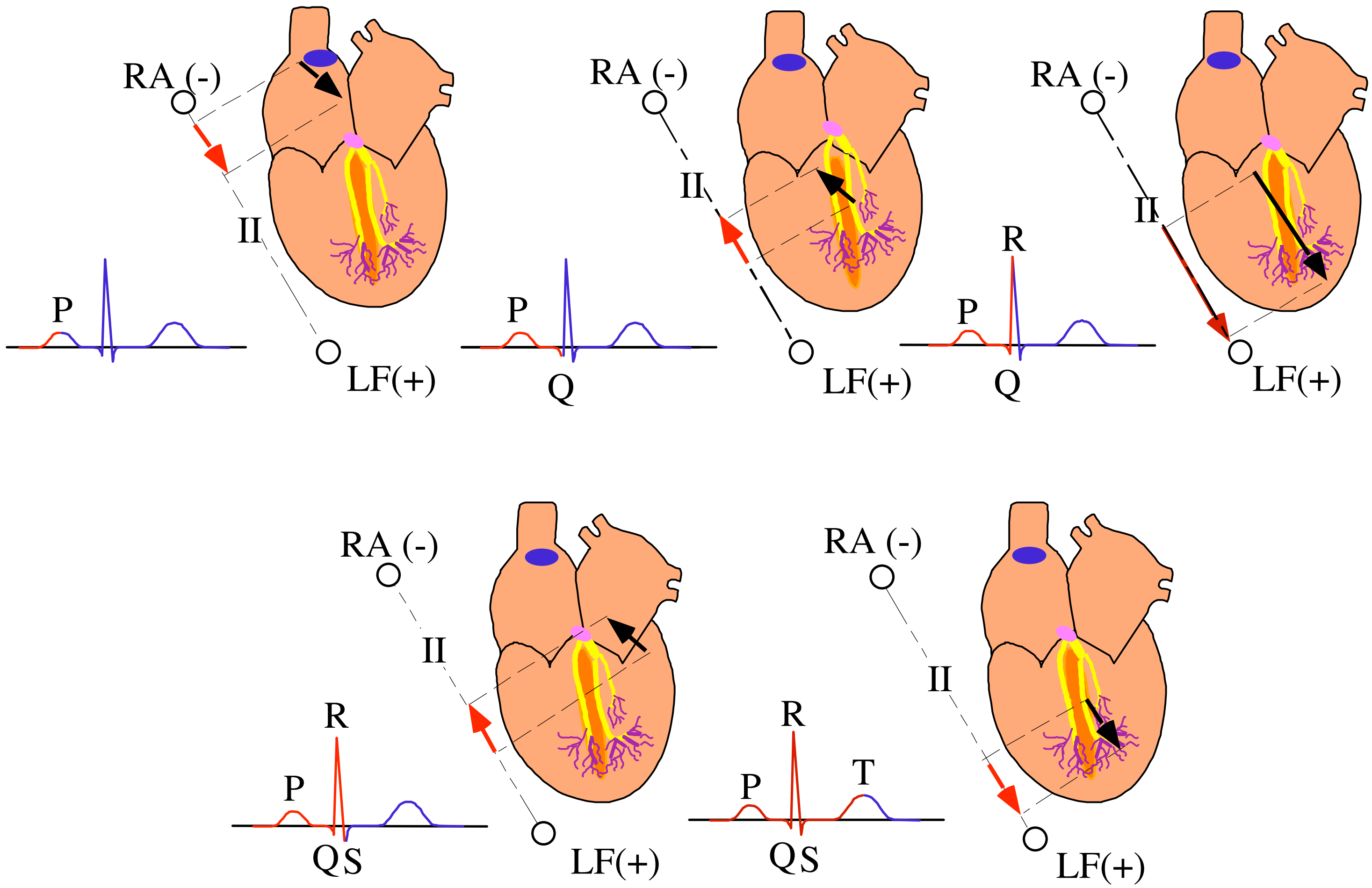
Dipole Approximation and Surface ECG



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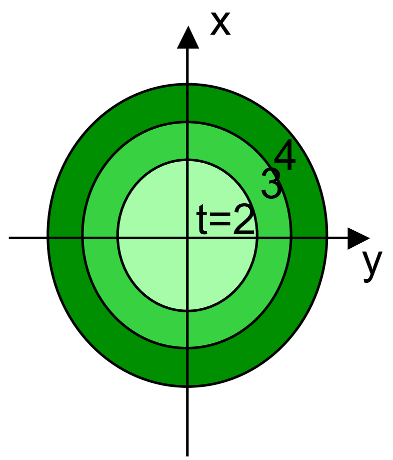
Isotropic/Anisotropic Excitation Propagation (2D)

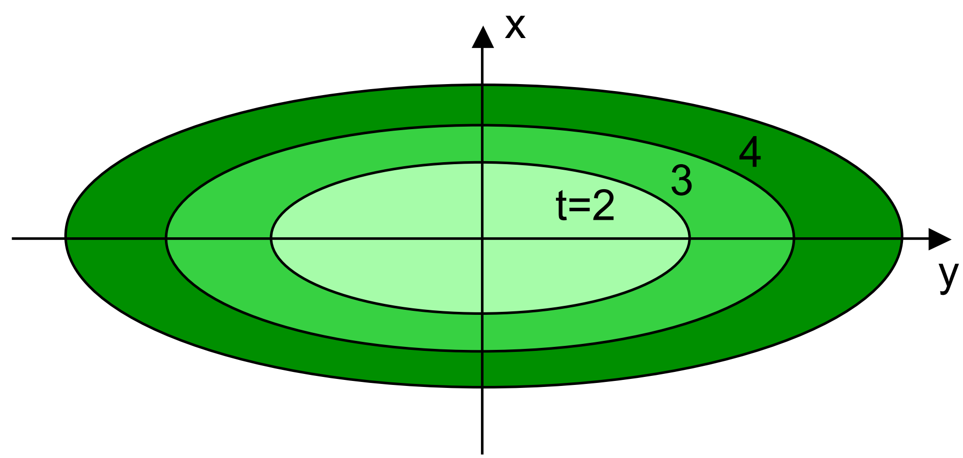
Simplifications

- Homogeneous tissue
- Long axis of myocytes parallel to y-axis
- Stimulus at point (0,0)

Isotropic x/y - 1/1
Velocity v: 1 / s



Anisotropic x/y - 1/3
Velocity v_x: 1 / s, v_y: 3 / s



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Models of Electrical Conduction

- **Macroscopic**
  - **Rule based / cellular automata**
    (Moe 62, Eifler-Plonsey 75, Killmann-Wach 91, Wei-Okazaki 95, Werner-Sachse-Dössel 97, Siregar 98, Simelius 00 etc.)
  - **Reaction diffusion systems**
    - **Simplified**
      (FitzHugh-Nagumo 61, Rogers-McCulloch 94 etc.)
    - **Combined with models of cellular electrophysiology**
      - **monodomain**
        (Rudy 89, Virag-Vesin-Kappenberger 98 etc.)
      - **bidomain**
        (Henriquez-Plonsey 89, Sepulveda-Wiksow 93, Sachse-Seemann-Riedel-Werner-Dössel 00 etc.)
- **Microscopic**
  (Spach 81)

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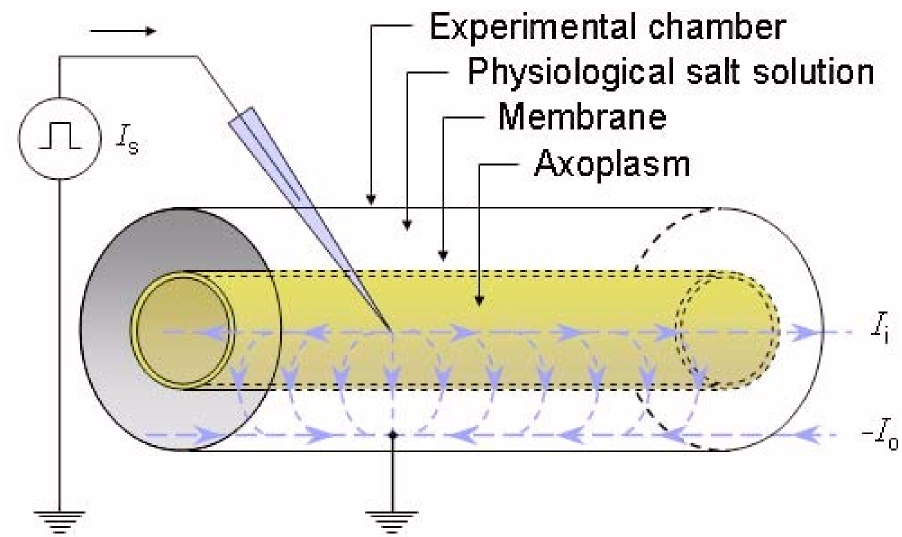
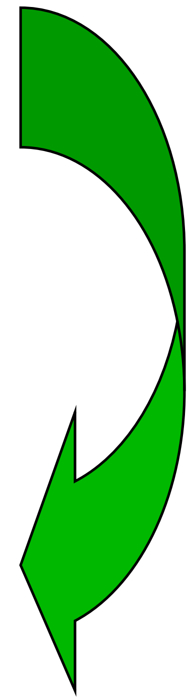
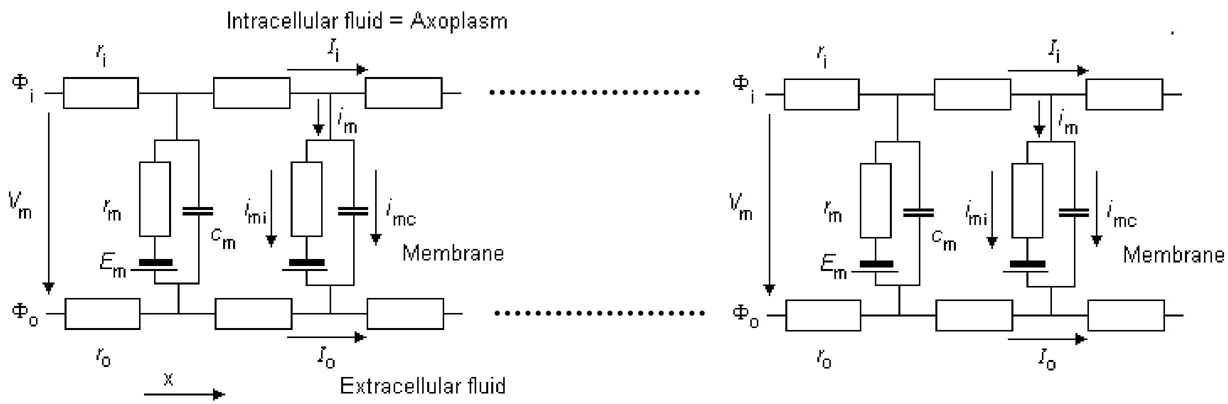
Reaction Diffusion System: Cable Model



Reduction to 1D Discretization





1D Bidomain

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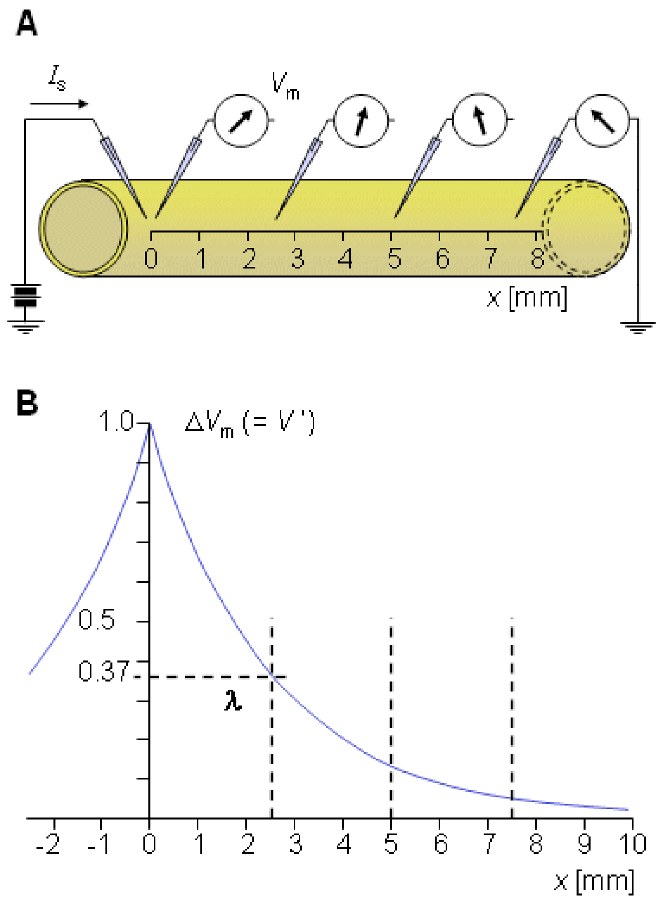
Cable Model: Steady State Response to Non-Excitatory Current

Length constant λ describes spatial distance between two points:

1. Location of electrode for injection of current leading to ΔV_m.
2. Location at which the voltage $\Delta V_m/e$ is interpolated from measurements.

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

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



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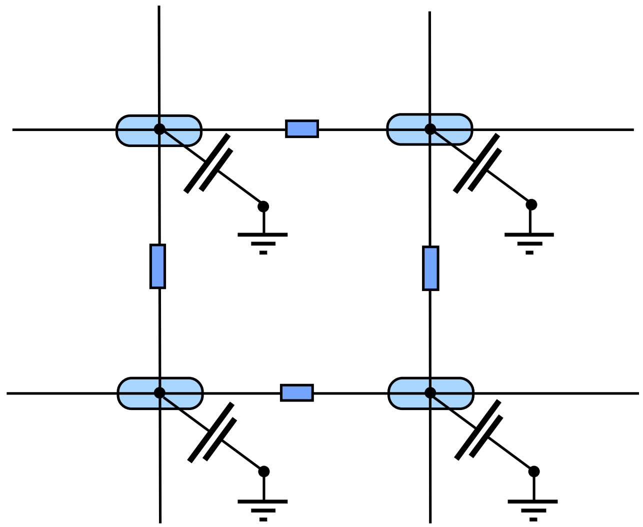
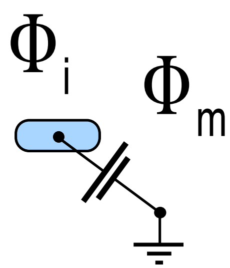
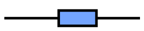
Monodomain Modeling of Electrical Conduction in 2D

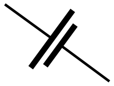






Resistor of gap junctions
(average conductance between cell pairs 250-1000 nS)

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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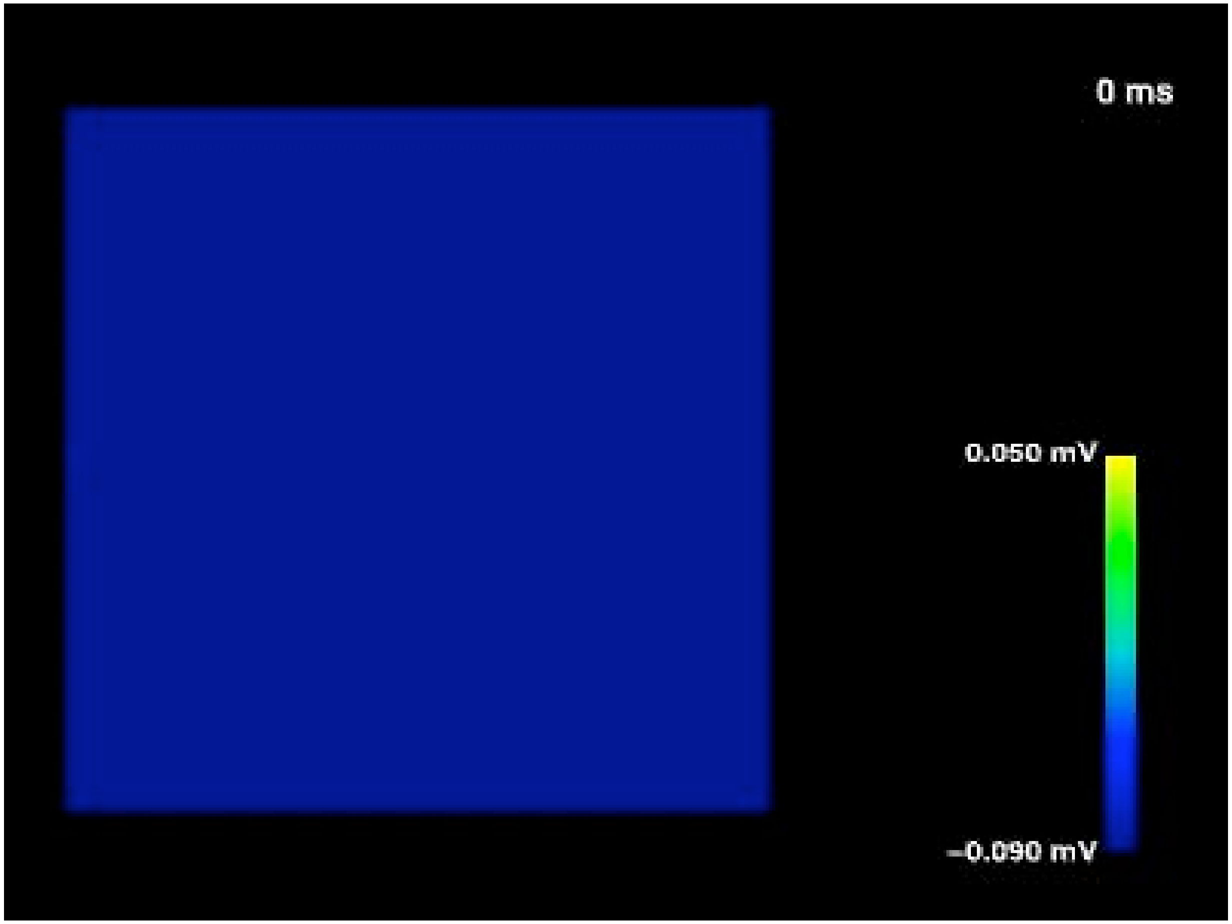
2D-Simulation



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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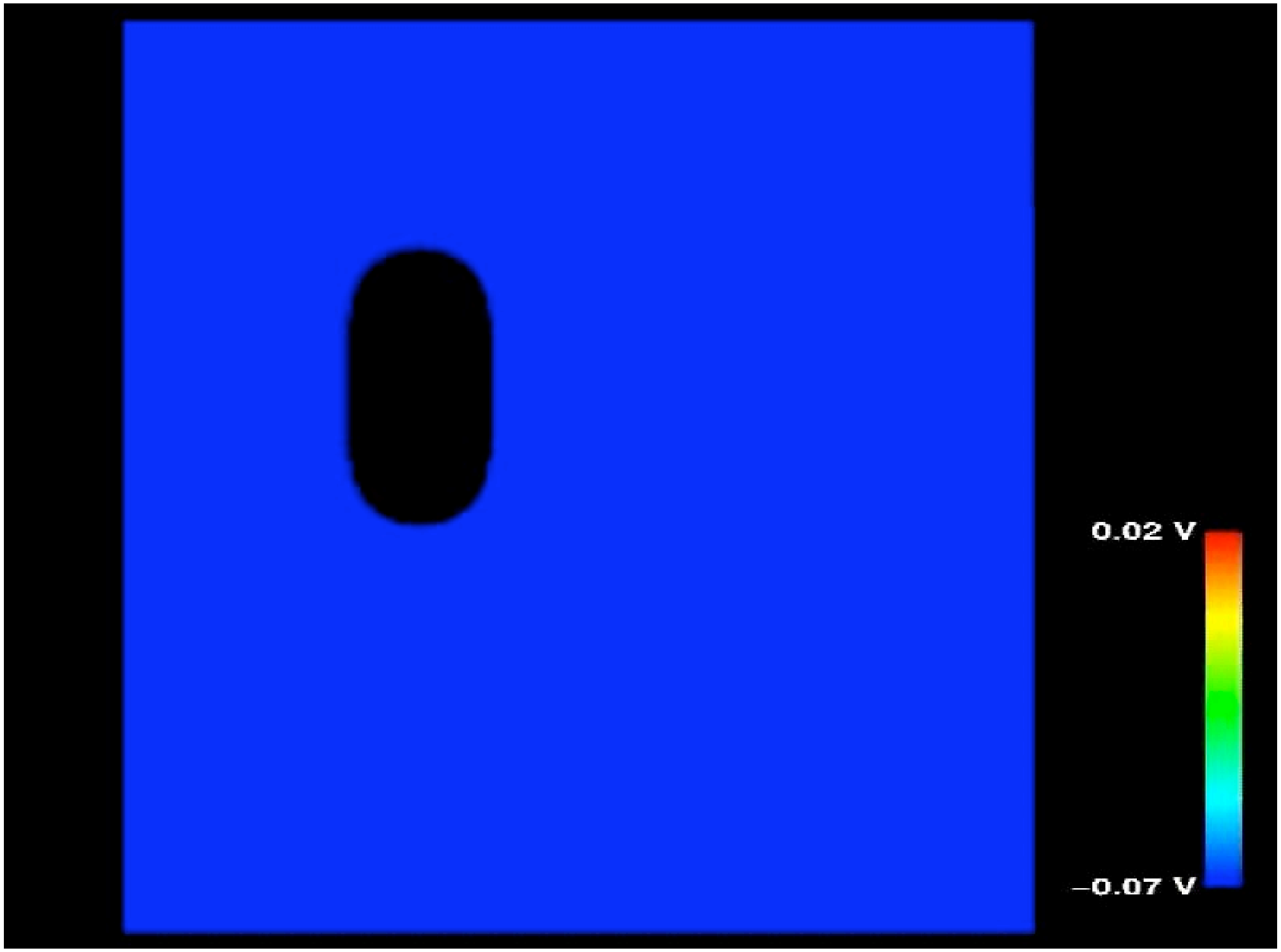
2D-Simulation of Arrhythmia



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Current Flow in 3D-Model of Electrical Conduction

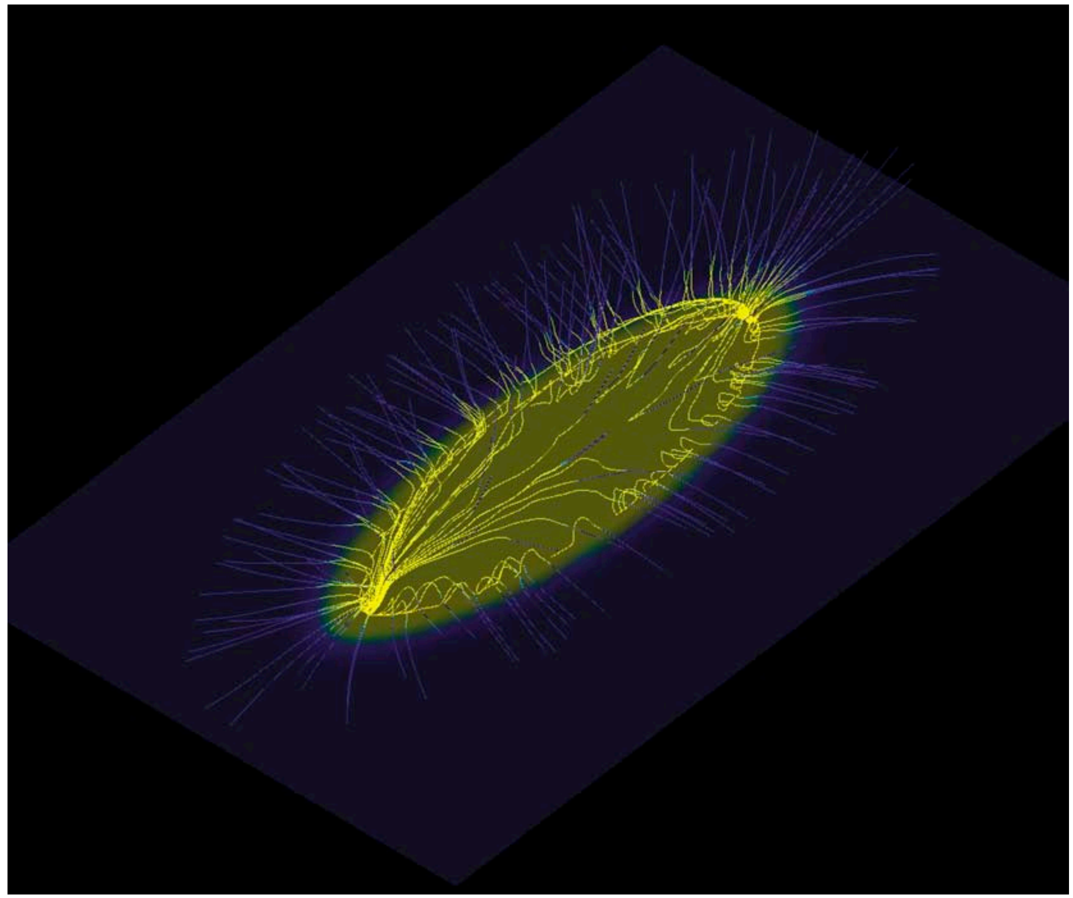
Anisotropic Monodomain Model

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.

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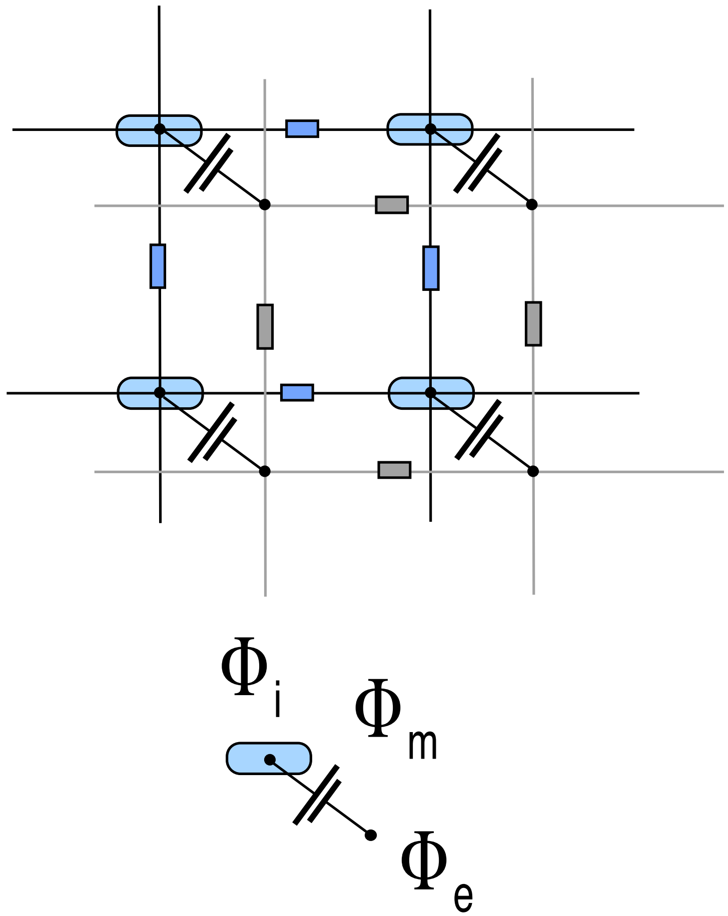
Bidomain Modeling of Electrical Conduction in 2D



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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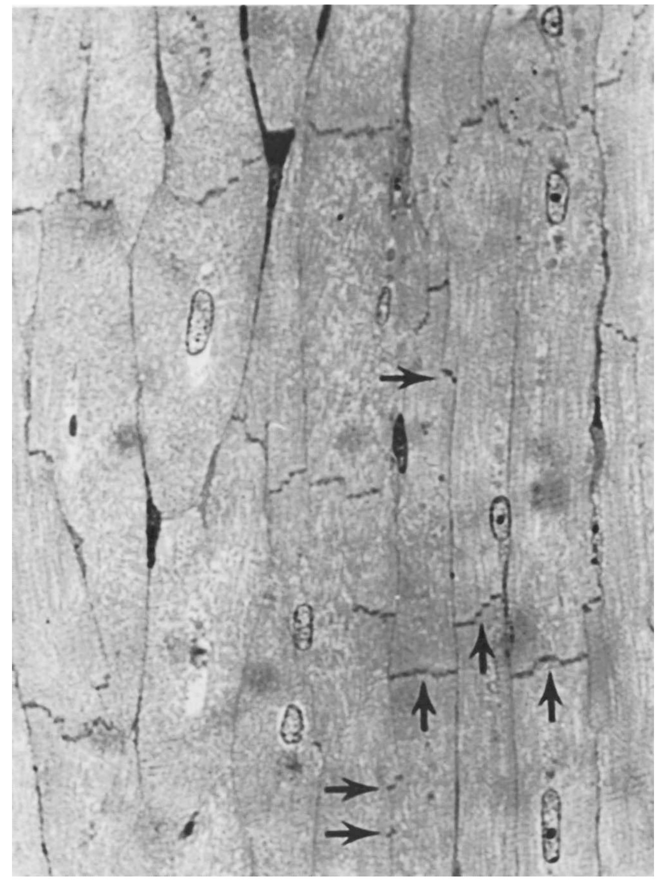
Bidomain Model: Motivation

Intra- and extracellular voltage distribution relevant for:
- cardiac excitation propagation
- body surface potential maps (BSPM)
- electrocardiogram (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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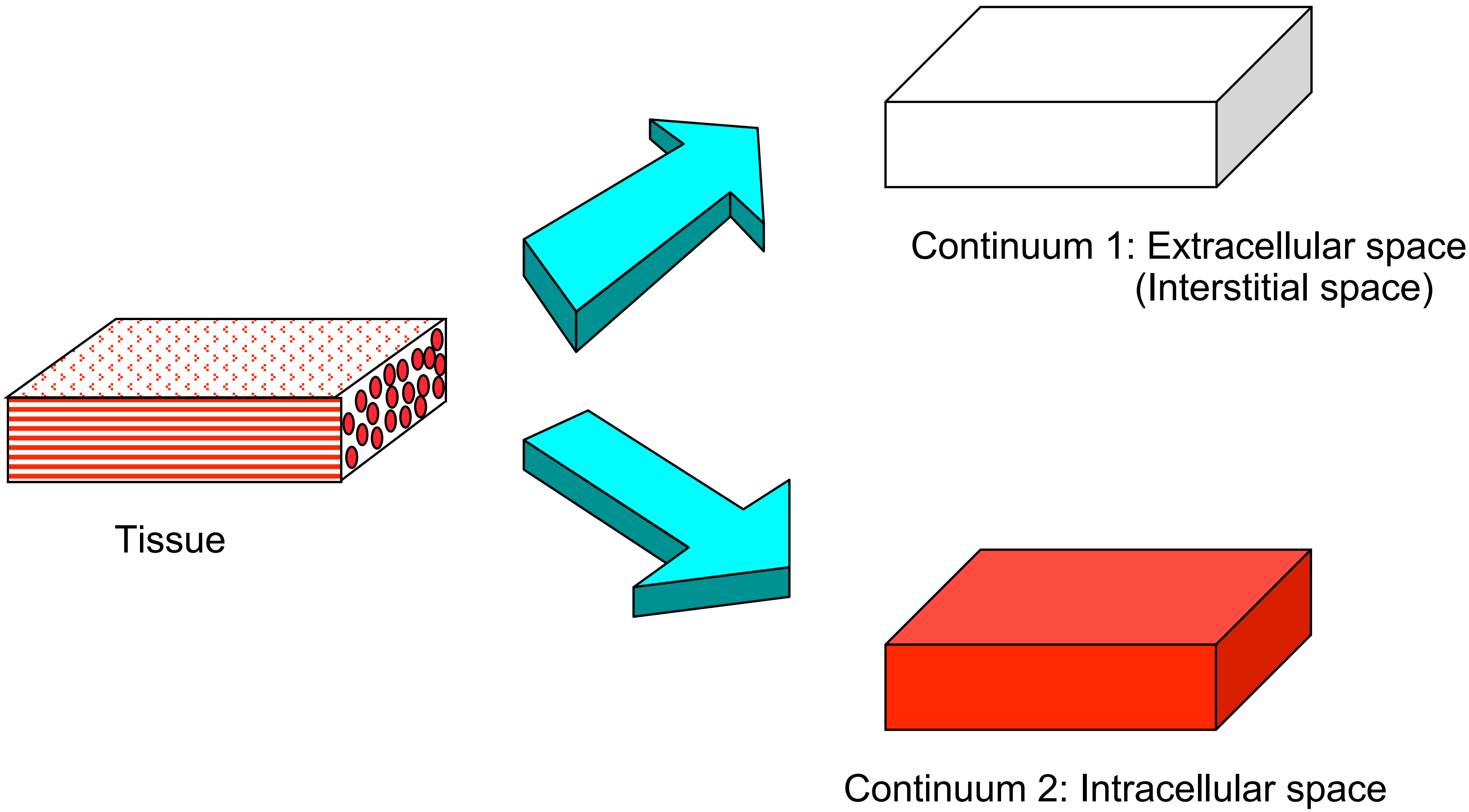
Bidomain Model: Basics



Group Work

Find and describe other applications for (non-electrical) multidomain models in

- physics
- biology
- …

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

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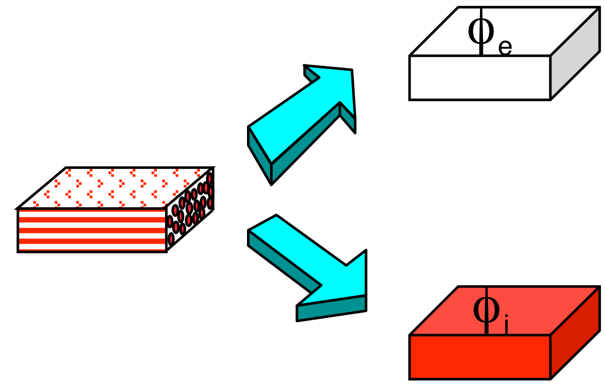
Bidomain Model: Basics

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

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

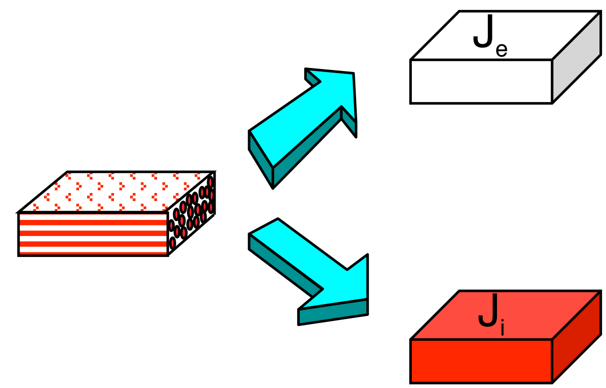
$\Phi_{i/e}$: Intra - /extracellular potential $\left[\mathrm{V}\right]$



$$J = J_i + J_e$$

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

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



Bidomain Model: Intracellular Space

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

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

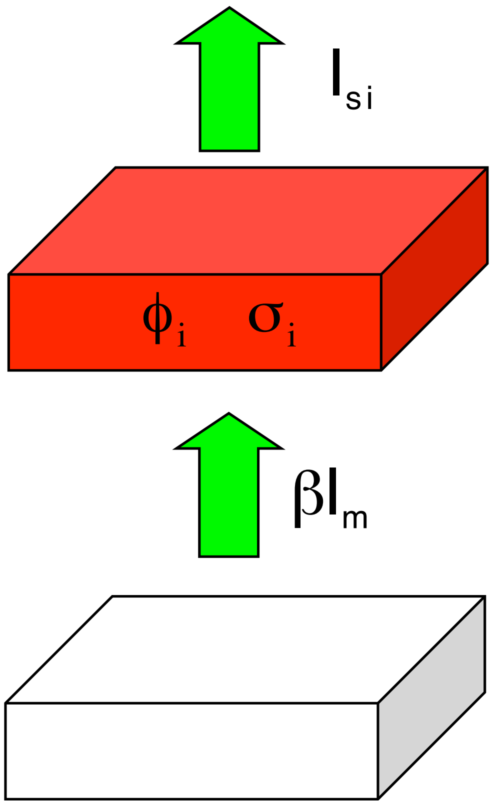
J_i : Intracellular current density $\left[\frac{A}{m^2}\right]$

Φ_i : Intracellular potential $\left[V\right]$

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 $\left[m^{-1}\right]$



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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 $\left[\frac{S}{m}\right]$

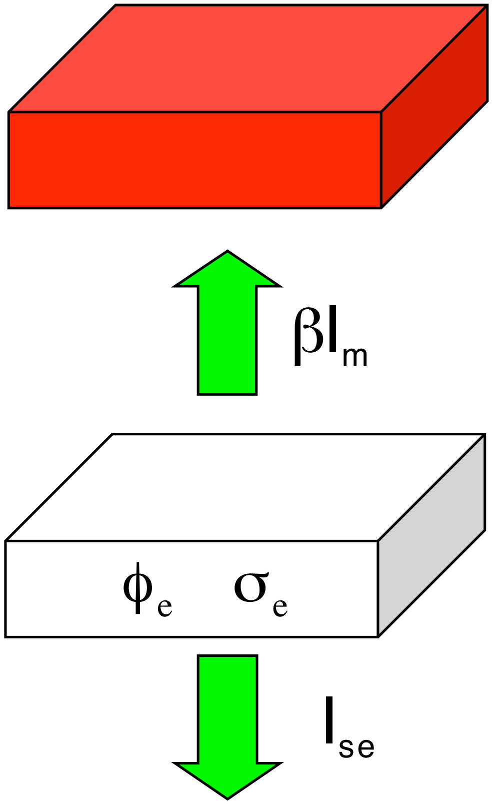
J_e : Intracellular current density $\left[\frac{A}{m^2}\right]$

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

$$J = J_i + J_e = -\sigma_i \nabla\phi_i - \sigma_e \nabla\phi_e$$

with $\phi_m = \phi_i - \phi_e$:

$$J = -\sigma_i \nabla\phi_m - \sigma_i \nabla\phi_e - \sigma_e \nabla\phi_e$$

with $\sigma_H = \sigma_i + \sigma_e$:

$$J = -\sigma_i \nabla\phi_m - \sigma_H \nabla\phi_e$$

with $\nabla J = 0$:

$$\sigma_i \nabla\phi_m = -\sigma_H \nabla\phi_e$$

Generalized Poisson's Equation

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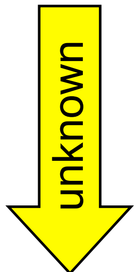
Bidomain Model: Numerical Solution

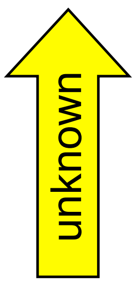
$\Phi_m(\mathbf{x},t)$ and $\Phi_e(\mathbf{x},t)$ are unknown

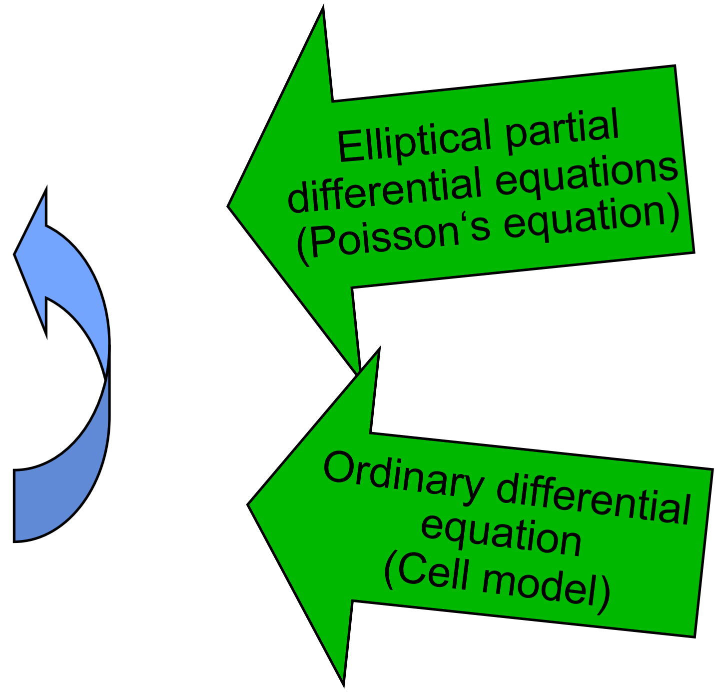


$$\nabla(\sigma_i \nabla \Phi_m) = -\nabla(\sigma_H \nabla \Phi_e)$$

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

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





Problem: Spatio-temporal discretization!

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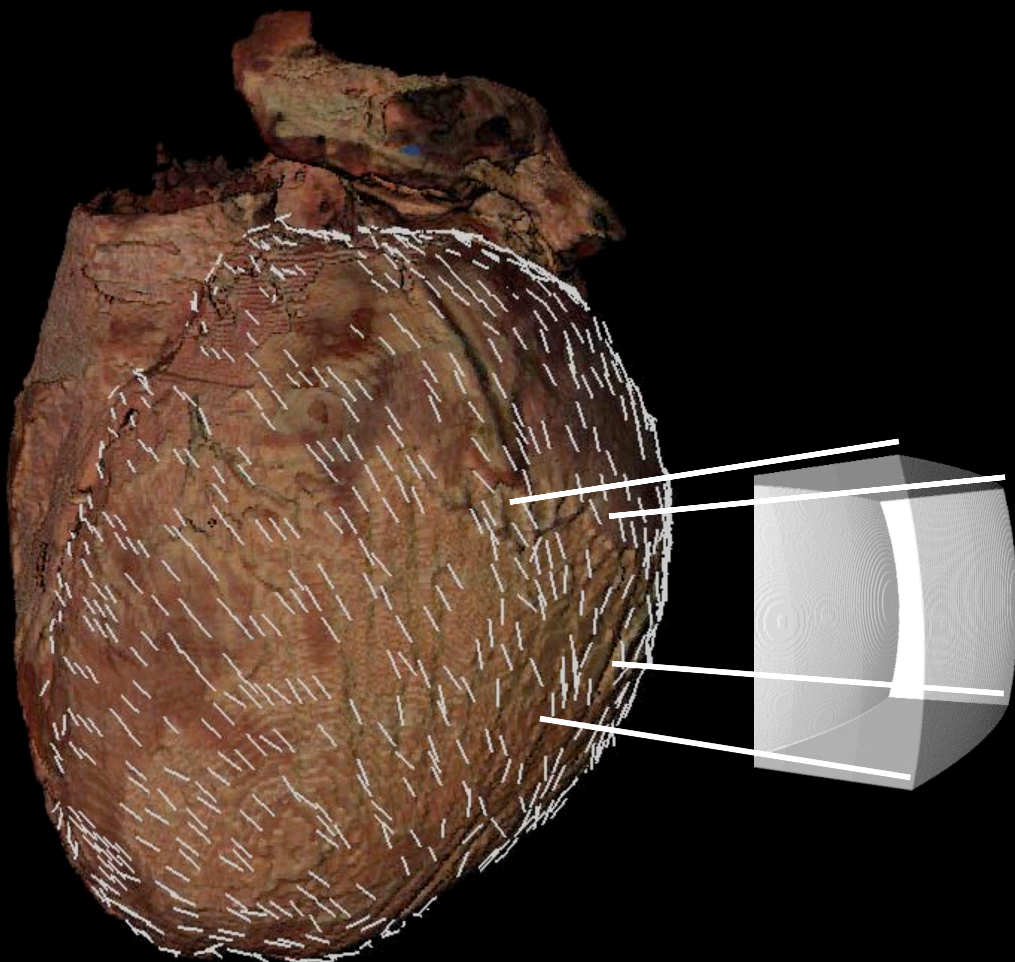
Simulation of Electrophysiology in Myocardial Area



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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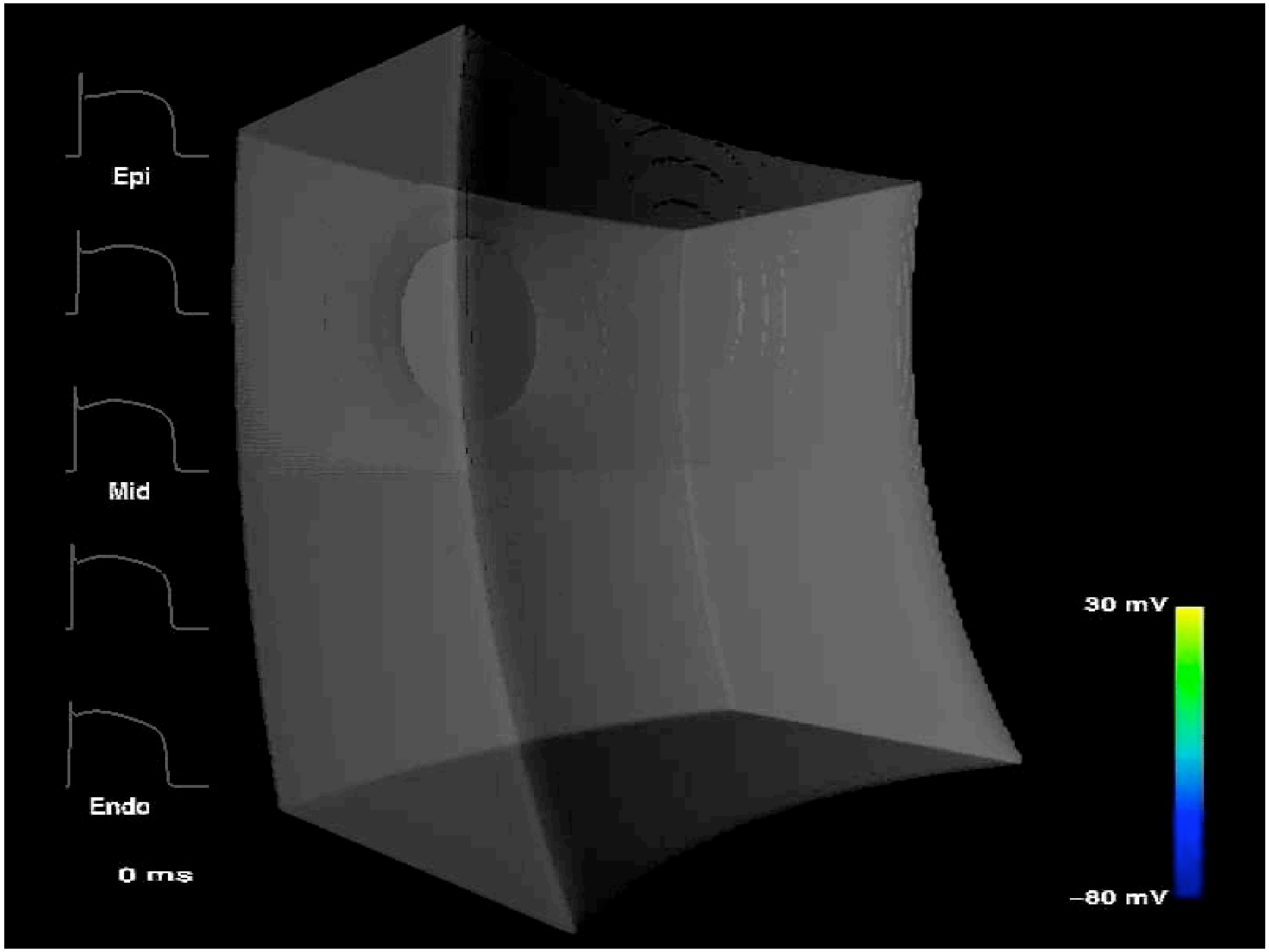
Transmembrane Voltage in Static Myocardial Area



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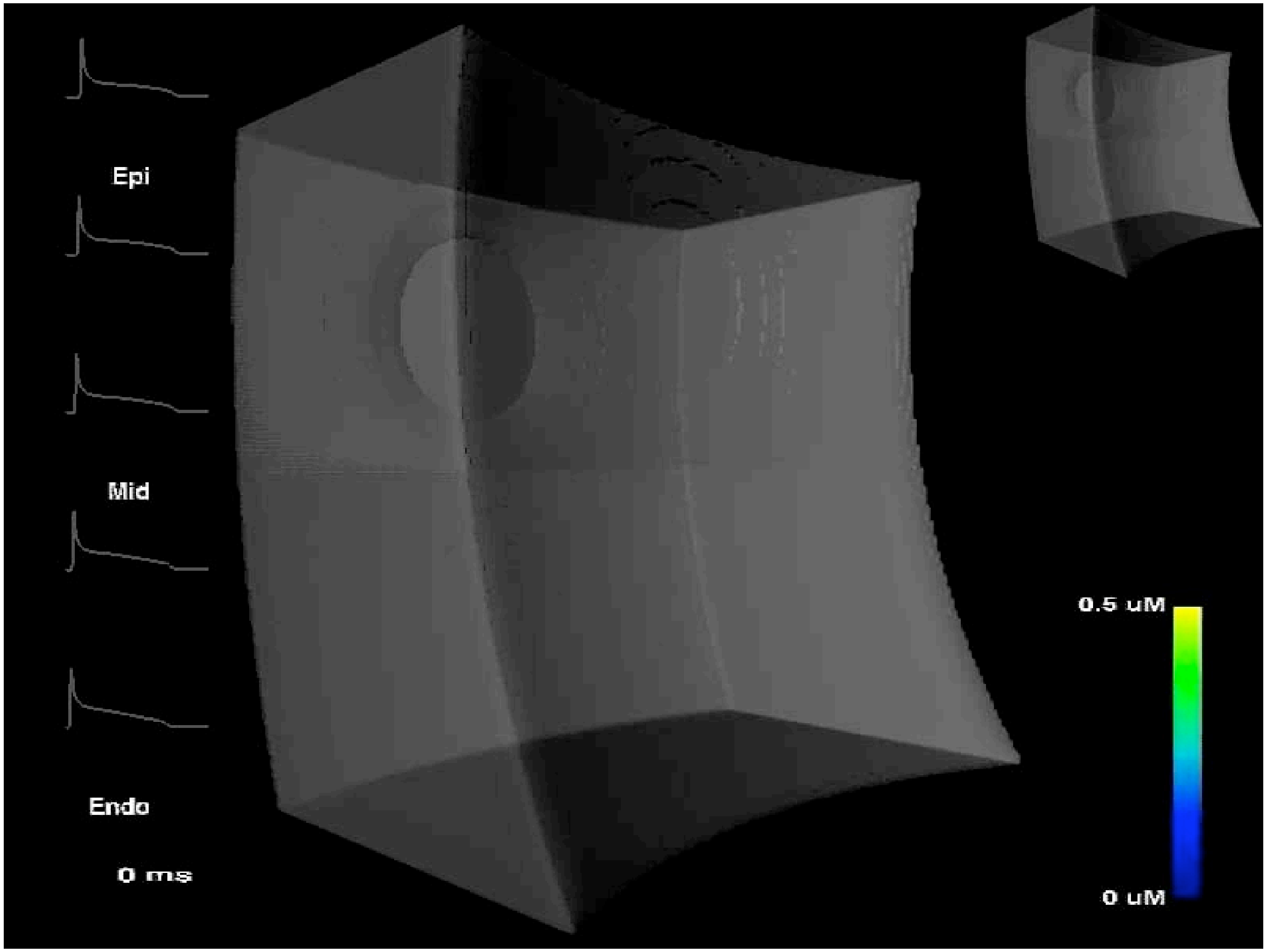
Calcium Concentration in Static Myocardial Area



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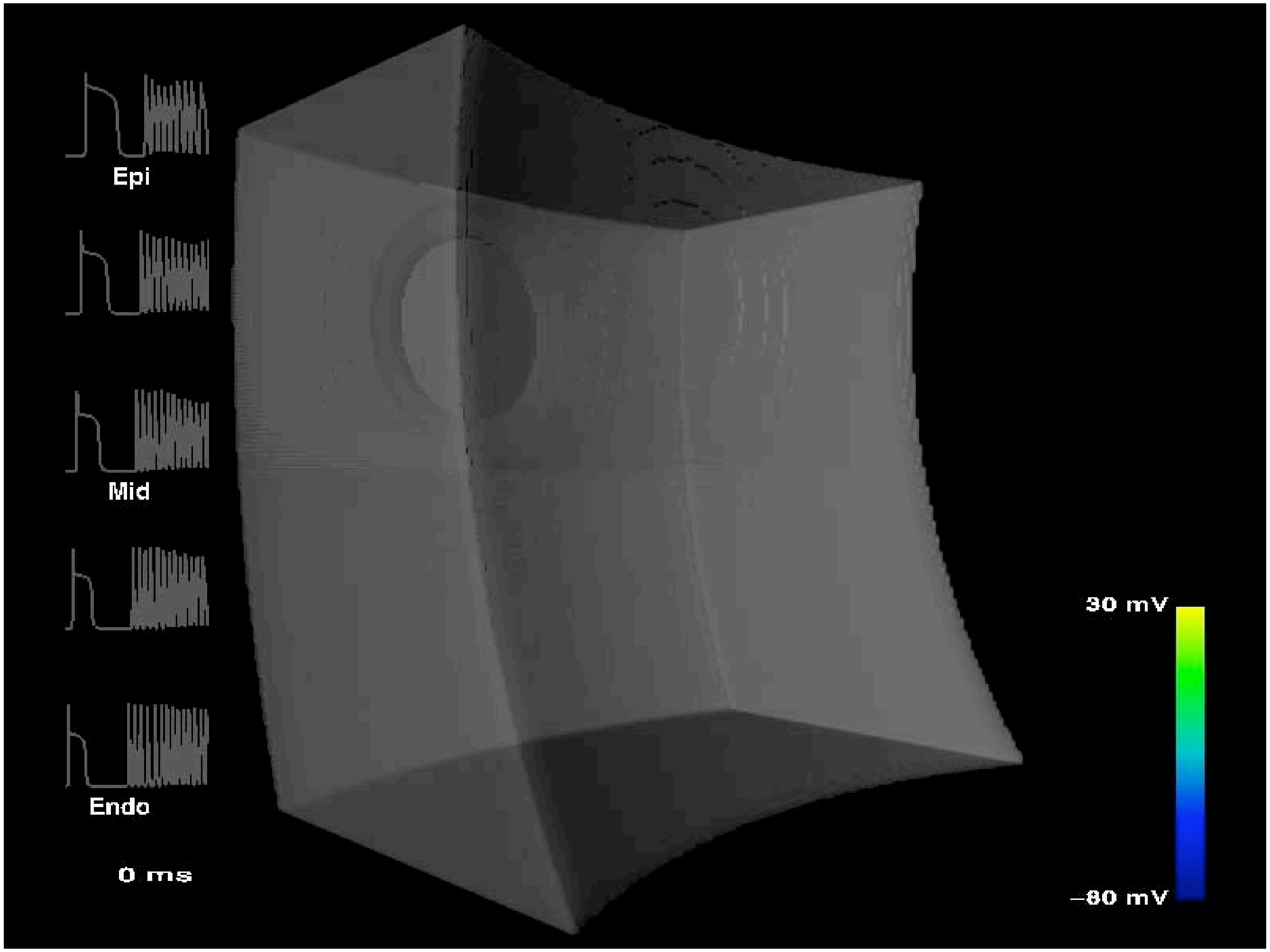
Rotor in Static Myocardial Area



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Cellular Automatons of Cardiac Excitation Propagation

1946

• Wiener, Rosenblueth	2D sheets
• Moe, Rheinboldt, Abildskov	Atria (2D sheet)
• Eiffler, Plonsey	Ventricular myocardium (2D sheet)
• Adam	Human ventricles (ellipsoids)
• Killmann, Wach, Dienstl	Human heart (from drawings)
• Saxberg, Cohen	Myocardium
• Wei, Okoazaki, Harumi, Harasawa, Hosaka	Human ventricles (Anisotropic)
• Siregar, Sinteff, Chadine, Le Beux	Human heart (2D)
• Werner, Sachse, Dössel	Human heart (Anisotropic)
• Siregar, Sinteff, Julen, Le Beux	Human heart (CAD)

…

today

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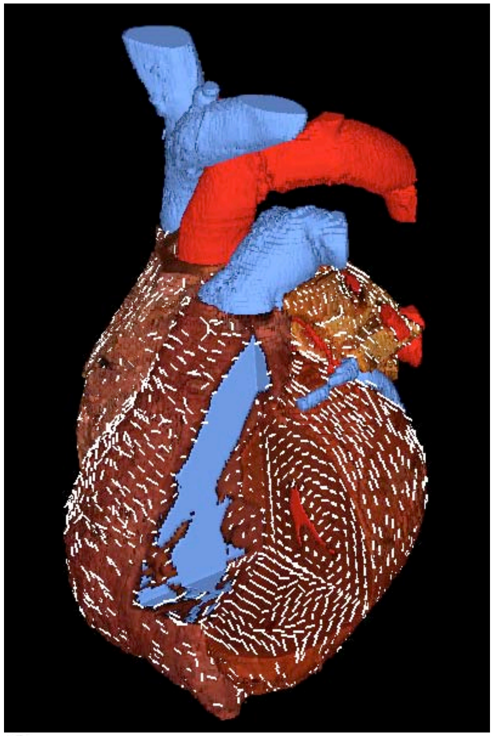
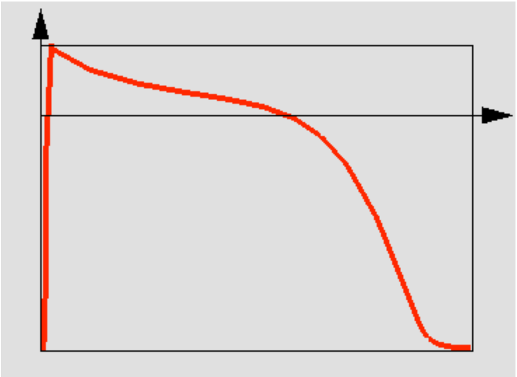
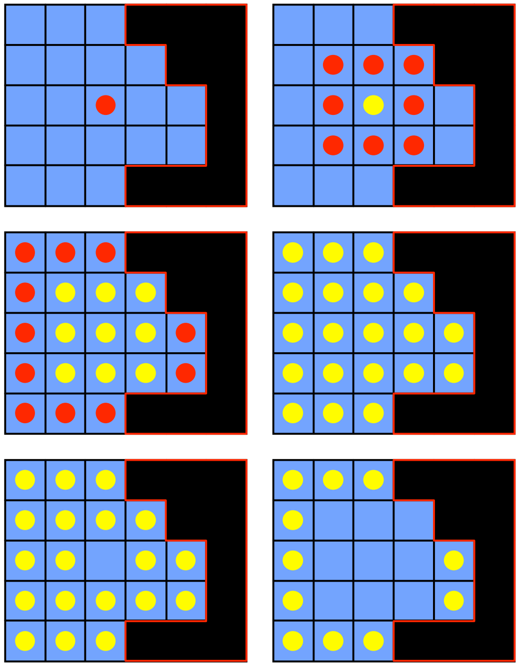
Cellular Automaton: Basics

Anatomical Model	Physiological Parameters	Cellular Automaton



- Autorhythmicity
- Transmembrane voltage
- Conduction velocity
- Refractory period





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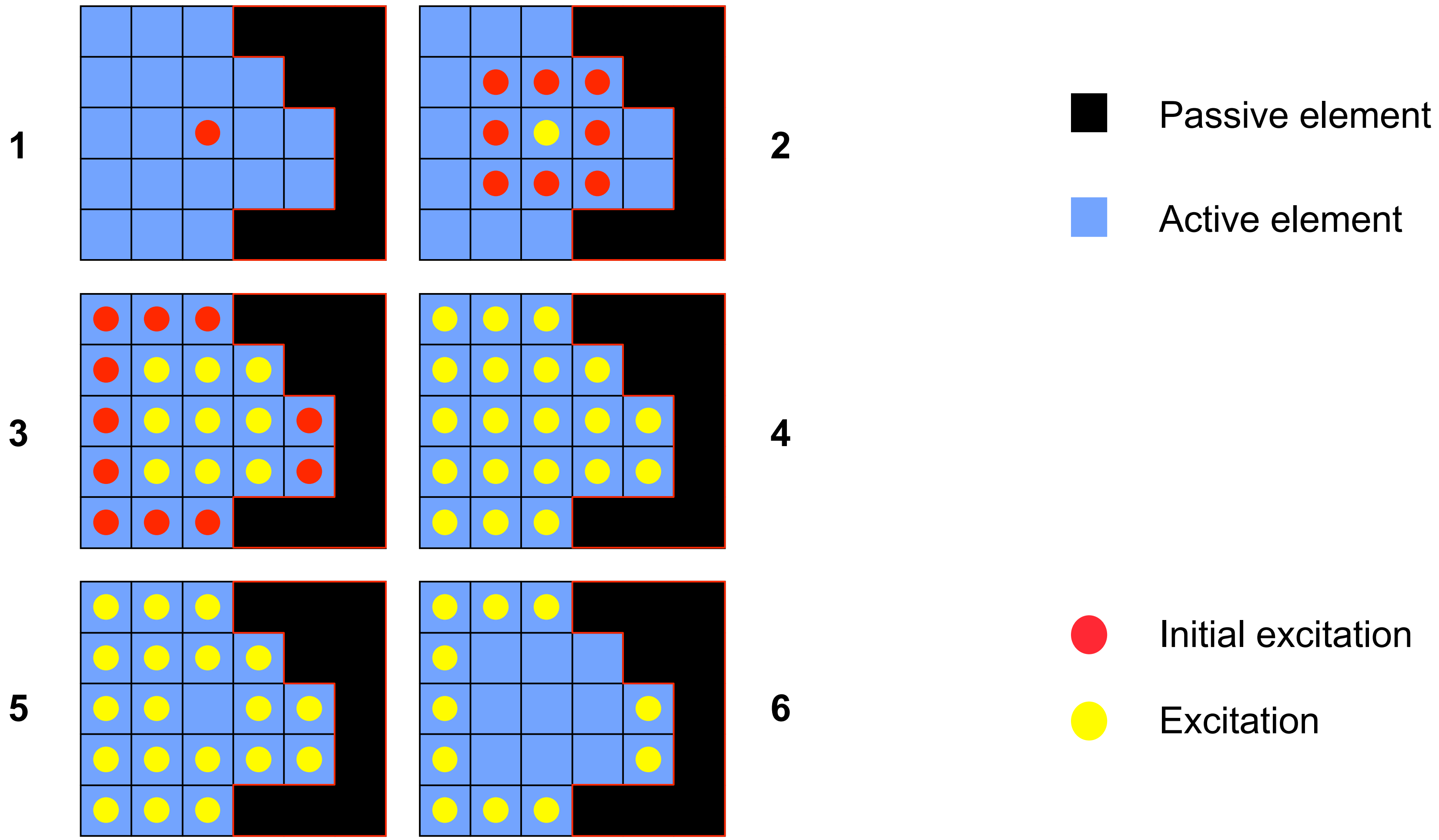
Cellular Automaton: Modeling of Propagation



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Anatomical Model of Heart: Requirements

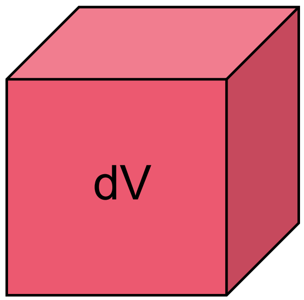
Necessary: Anatomical model of all excitation triggering and conductive components

Example: Components in model of Werner et al.:

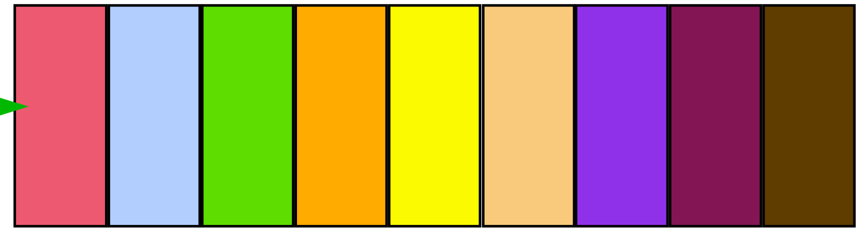
Image segmentation	Manual/rule-based definition
• left atrial myocardium • right atrial myocardium • left ventricular myocardium • right ventricular myocardium	• Sinus node • AV node • His bundle • Tawara bundle branches • Purkinje fibers • Fiber orientation

Parameters for Simulation: Lookup Tables

Known per
volume element dV
and for time t



- Stimulus
- Time since activation t_S
- Stimulus frequency f
- Tissue type



- Transmembrane voltage (t_S)
- Refractory period (t_S)
- Autorhythmicity (t_S)
- Conduction velocity (f)
- Excitable neighborhood (constant)

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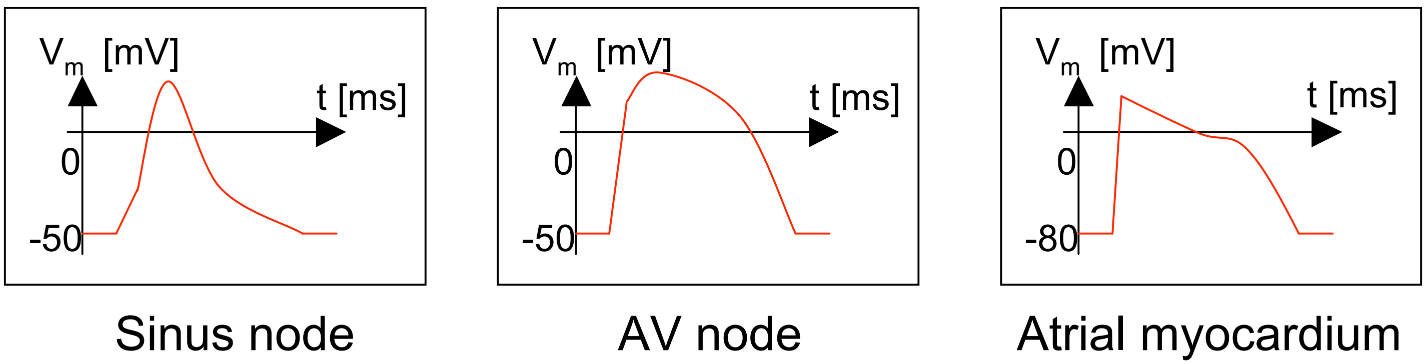
Cellular Automaton: Parameter - Transmembrane Voltage

Course of transmembrane voltage is dependent on tissue type and stimulus frequency.
Activation is only possible outside of absolute refractory time.



Most cellular electrophysiological properties, e.g. ion and transmitter concentrations, nervous influences, extracellular potentials etc. are neglected!

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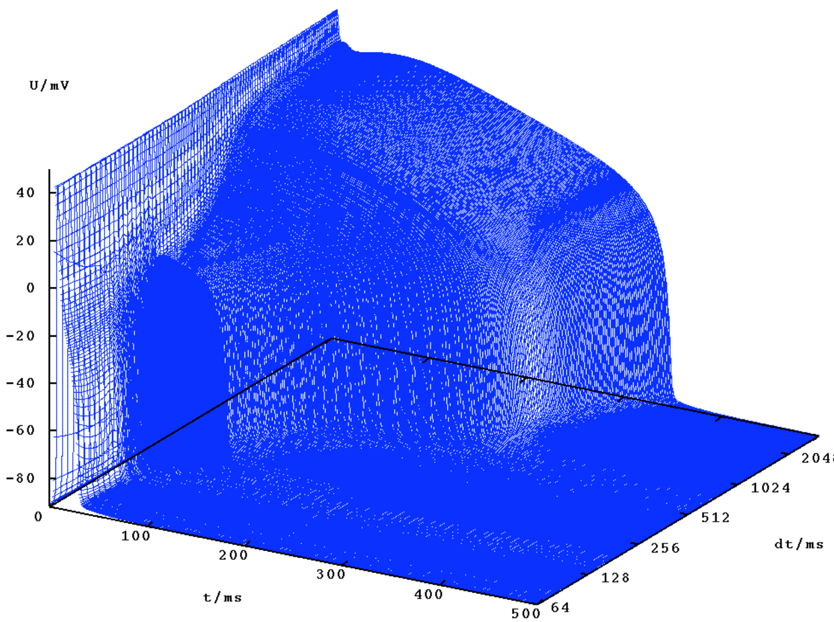
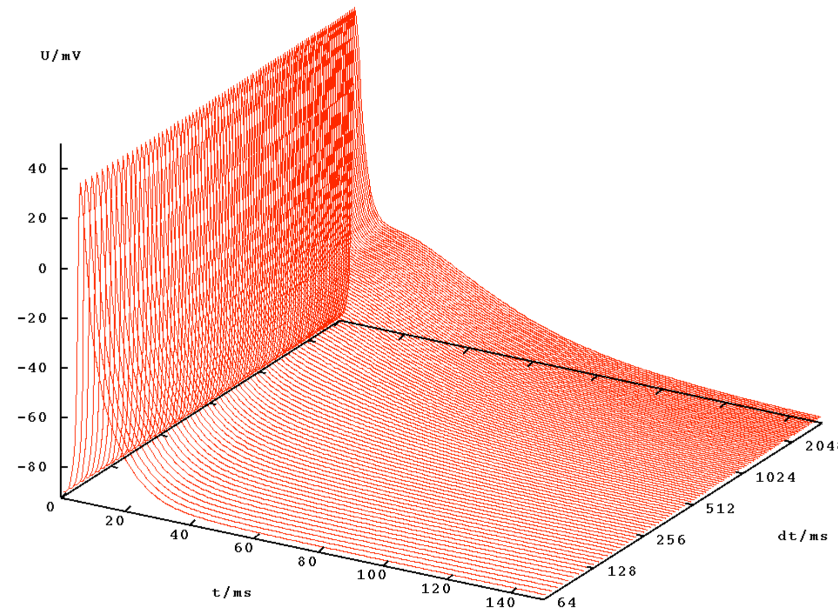
Cellular Automaton: Parameterization

Course of transmembrane voltage
Longitudinal/transversal propagation velocity

} {

Measurements
Numerical experiments





Ventricle: Noble-Varghese-Kohl-Noble 98

Atrium: Earm-Hilgemann-Noble 90

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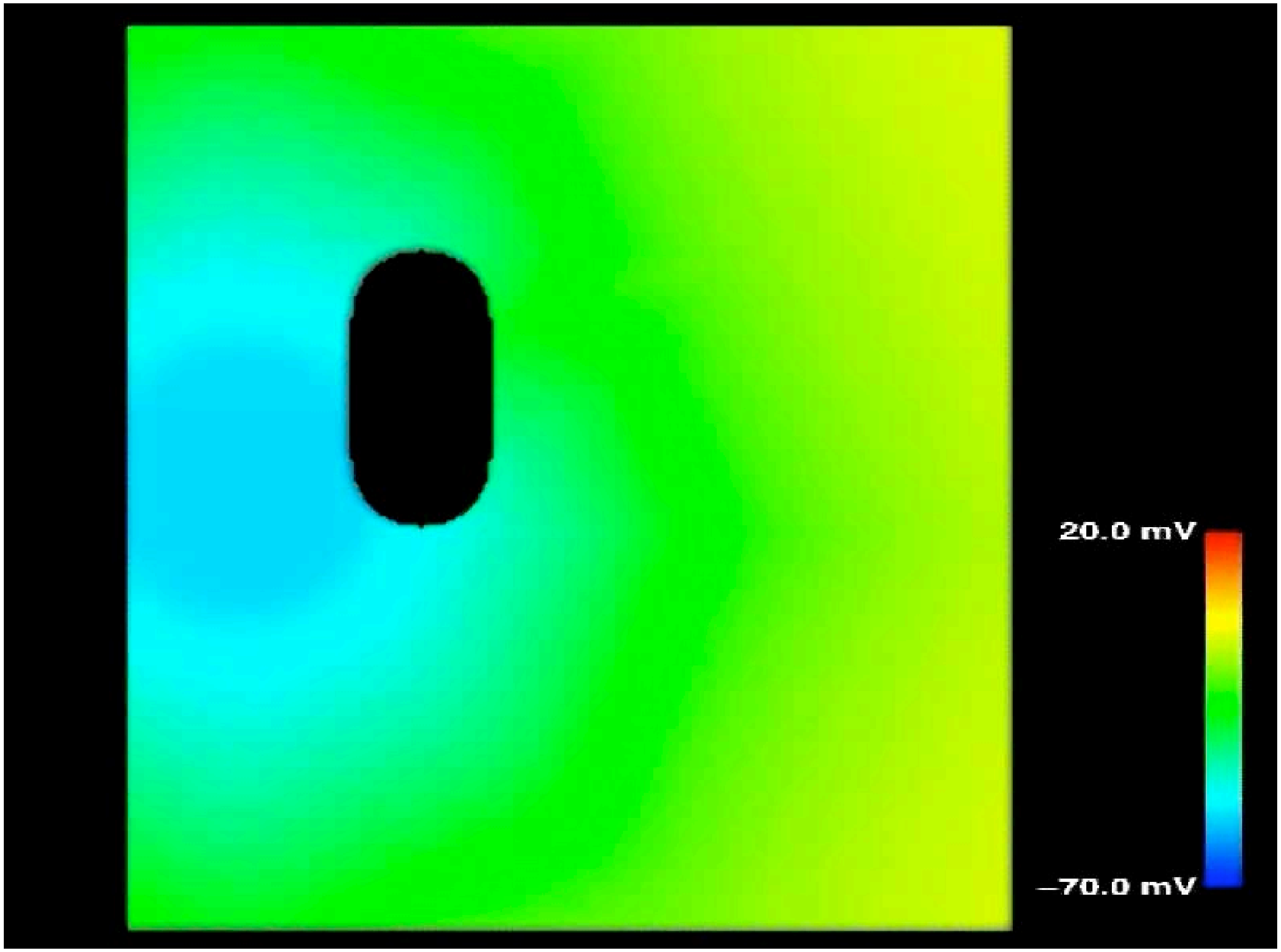
Unidirectional Block/Rotation Around Obstacles (2D)



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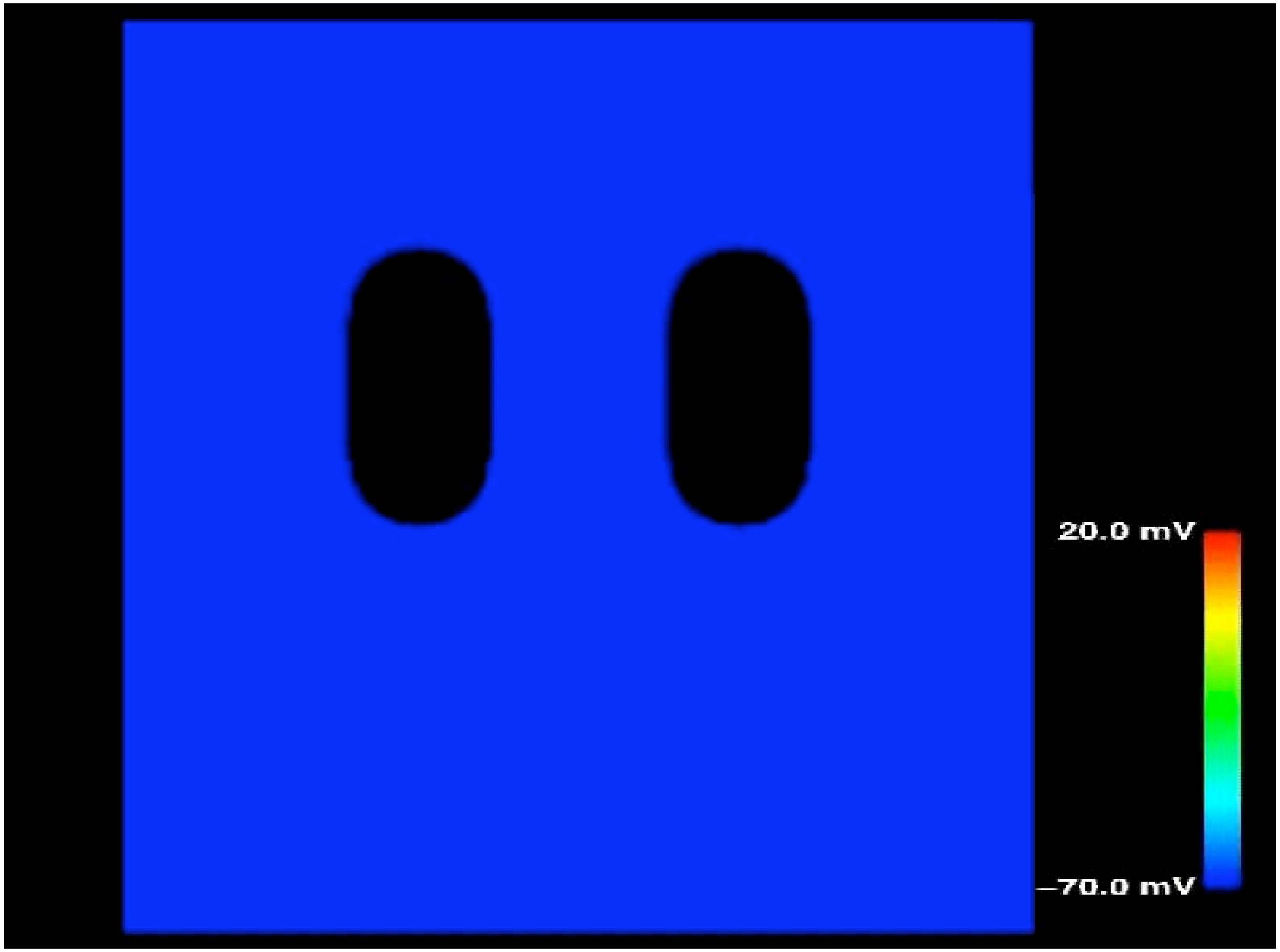
Unidirectional Block/Rotation Around Obstacles (2D)



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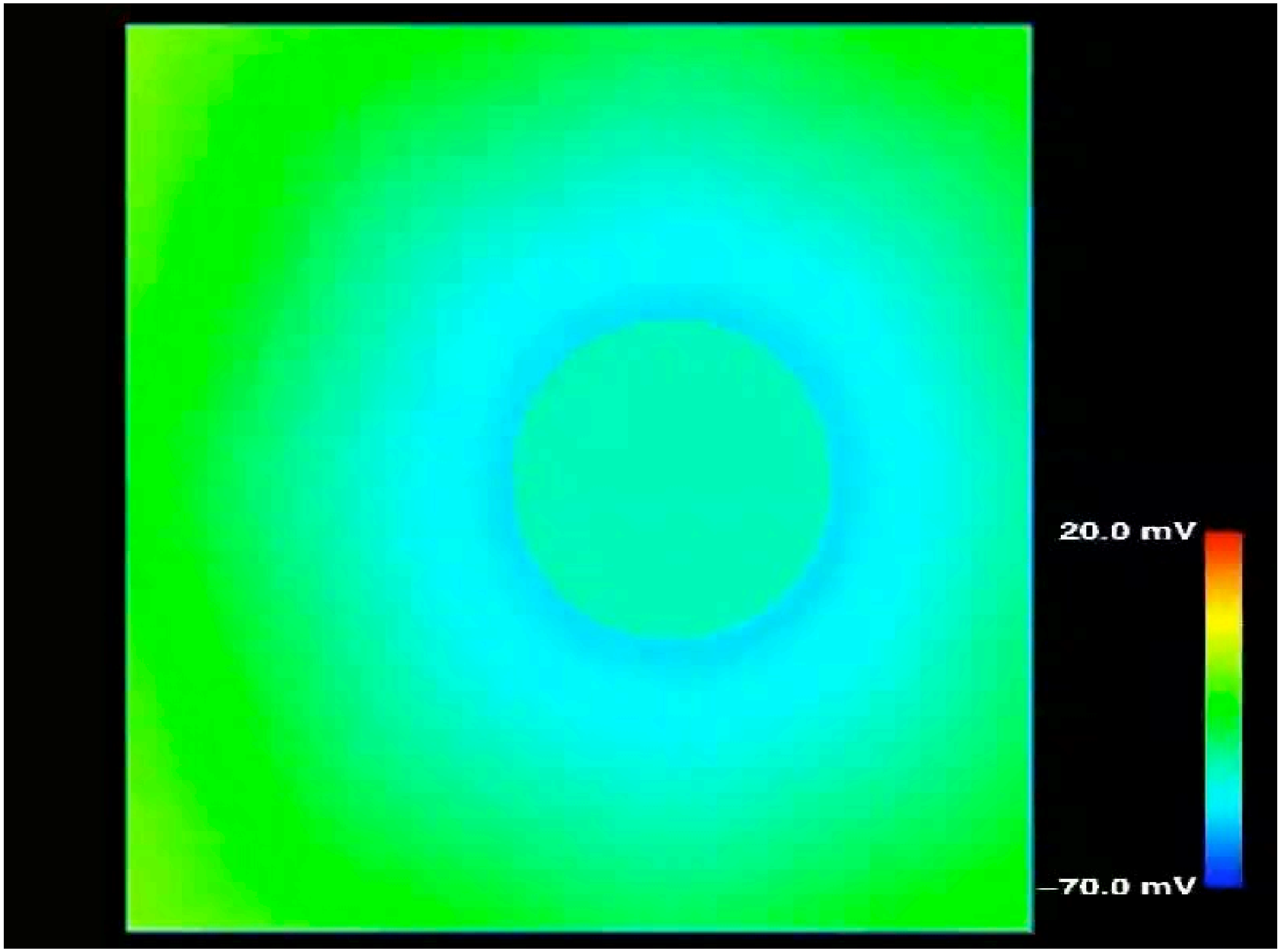
Unidirectional Block in Homogeneous Slice (2D)



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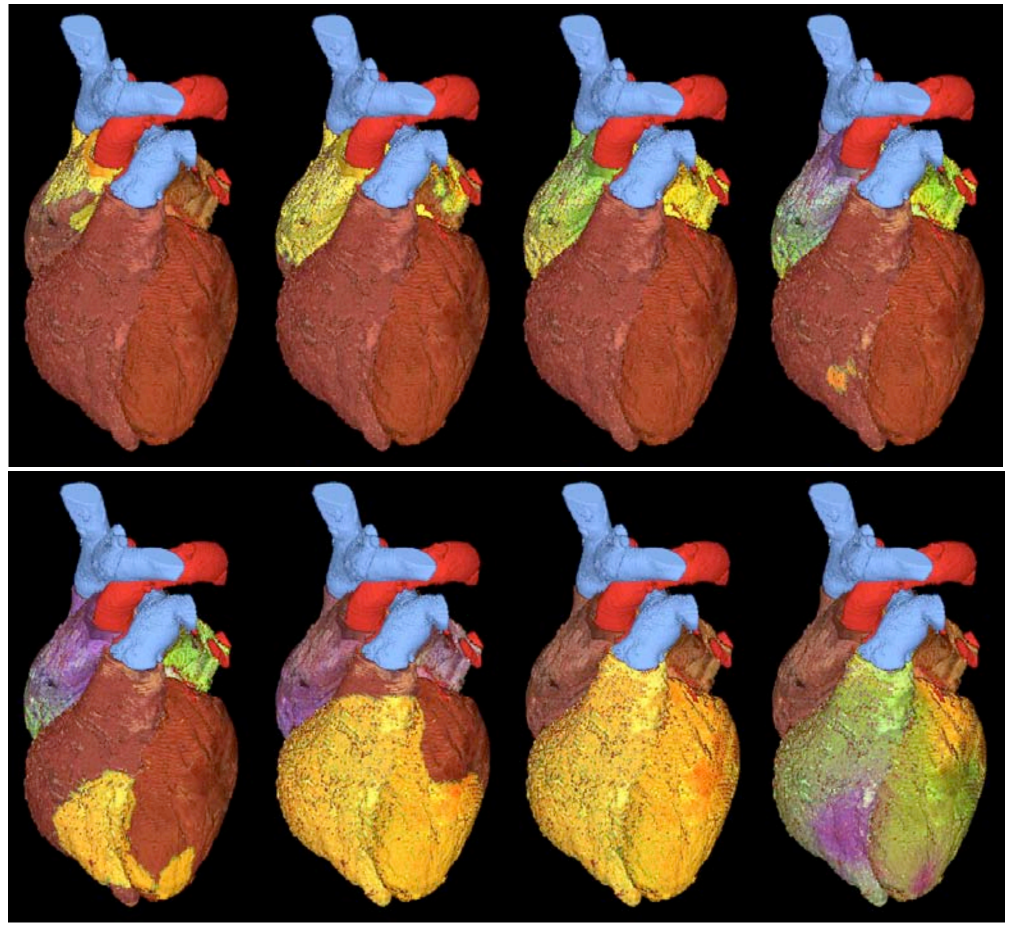
Results of Whole Heart Simulations

Transmembrane voltage color-coded at heart surface for physiological excitation propagation

8 time steps

- atrial activation starting at sinus node
- ...
- atrial repolarisation
- ventricular activation starting at subendocardium
- ...
- ventricular repolarisation



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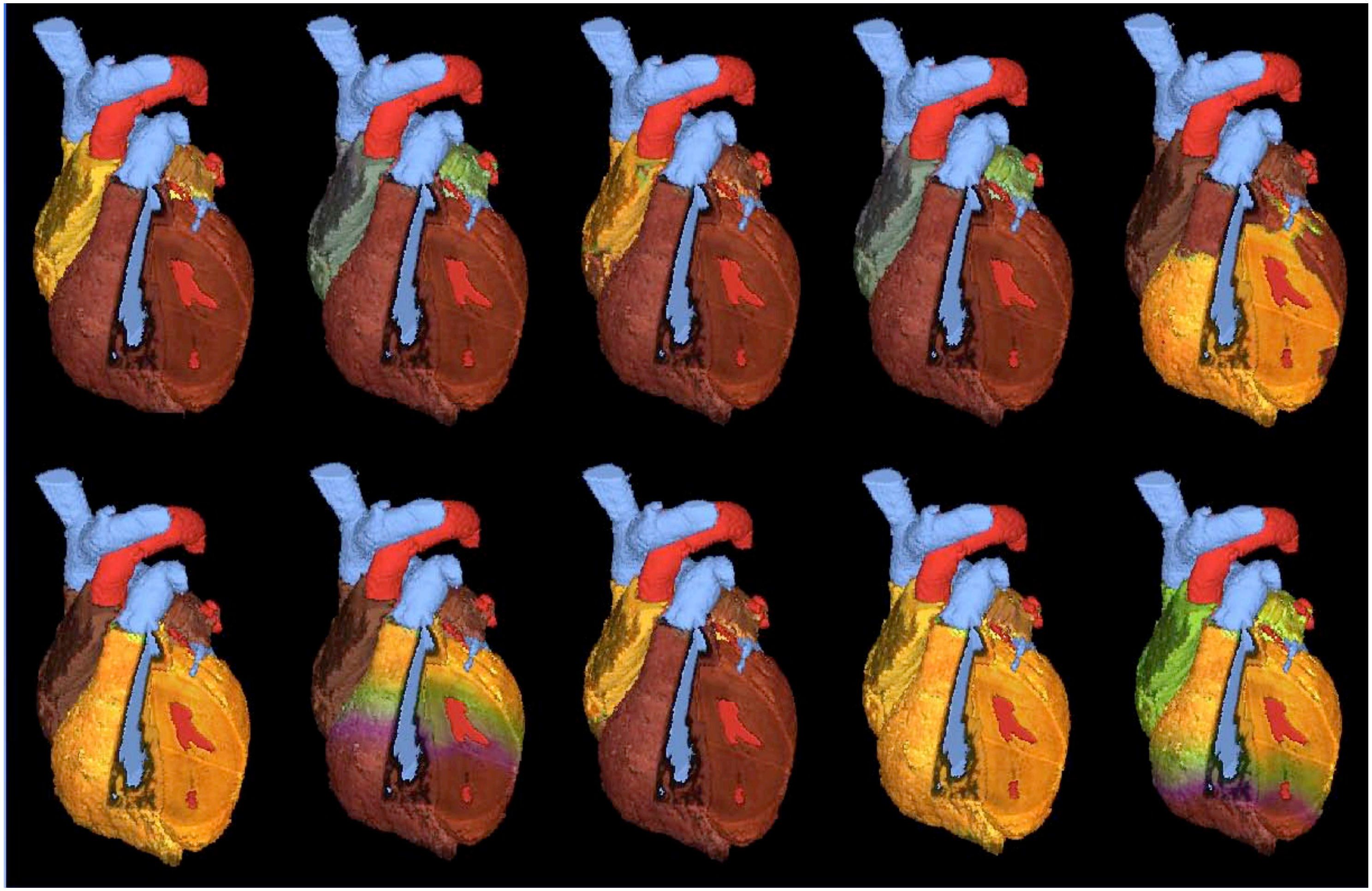
Simulation of 3rd Degree AV Block



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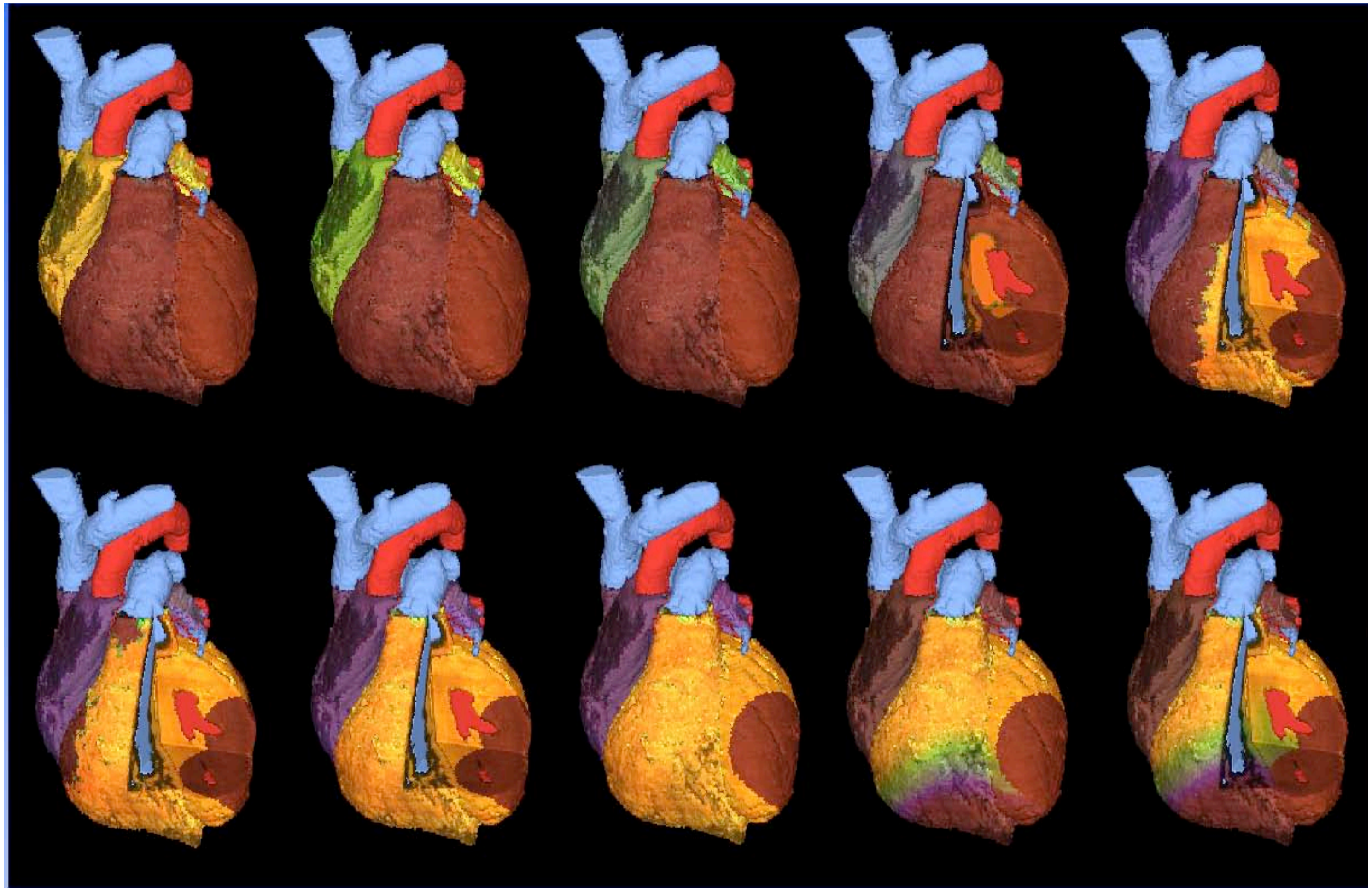
Simulation of Infarction



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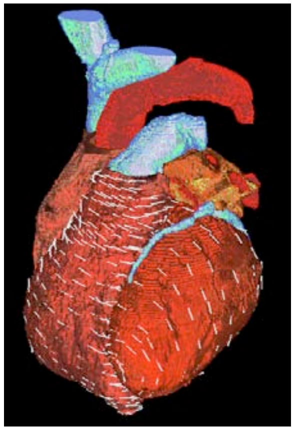
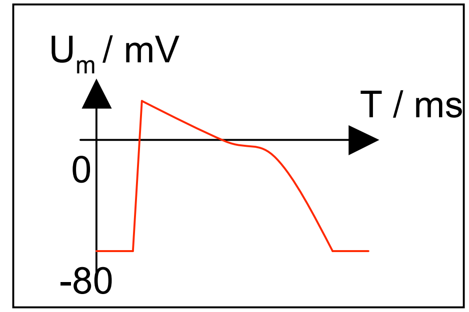
Cellular Automaton: Application in ECG/BSPM Simulation



Anatomie

Cellular Automaton

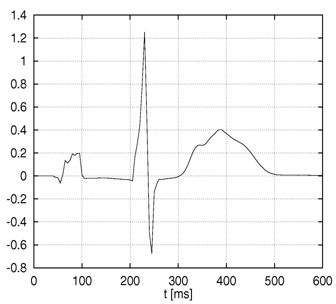
- Transmembrane voltages
- Membrane current densities



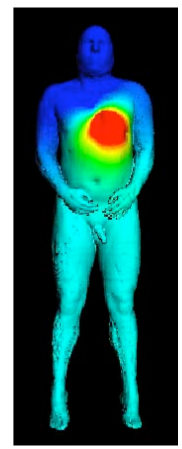
Electrophysiology

Numerical Field Calculation

- Volume and surface voltages
- Current densities



EKG



BSPM

Body
Surface
Potential
Map

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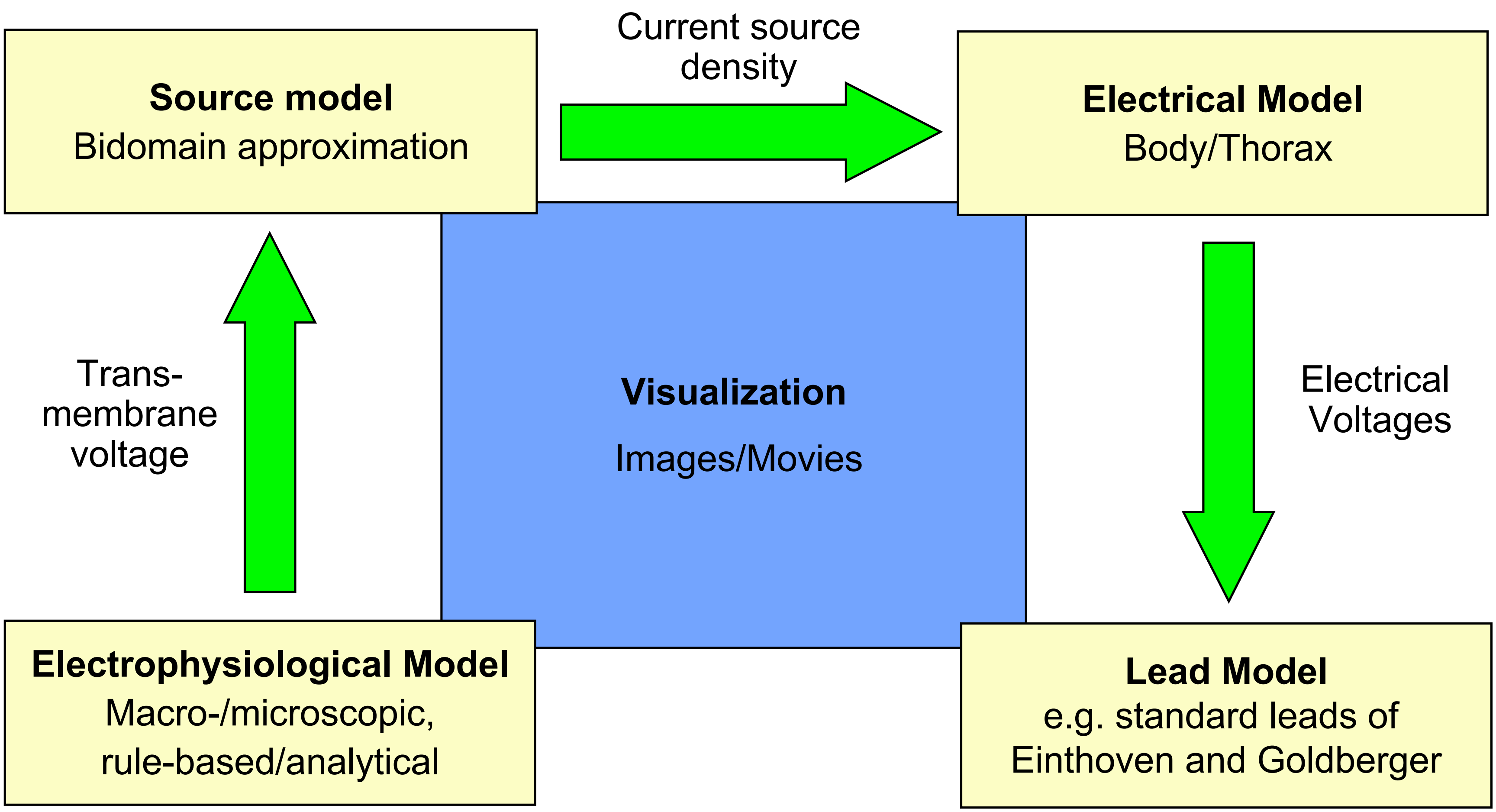
Simulation System: Overview



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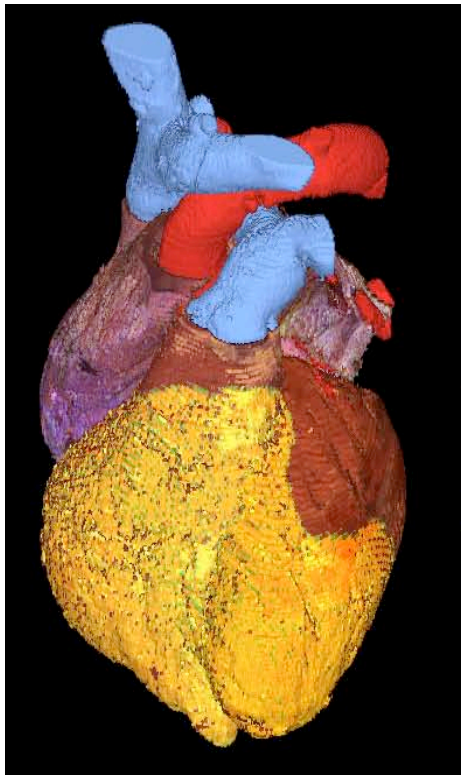
Example: ECG Simulation

V_m

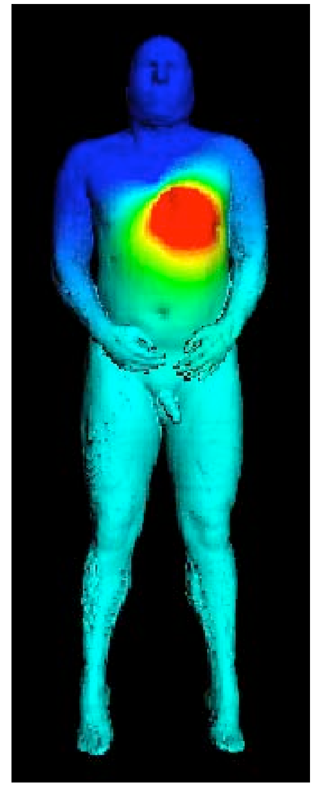
Trans-
membrane
voltage



Cellular automaton
of excitation propagation

f_e

Current
source
densities



Bidomain
model

ECG

BSPM

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[redacted]

Group Work

Compare cellular automata with mono-/bidomain models of cardiac conduction! Apply ~5 criteria for comparison.