Computational Modeling of the Cardiovascular System

Electrophysiological Modeling of Cells

CVRTI

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Overview

- Modeling of Cardiac Myocytes
- Impact of Ion Channel Mutations on Cellular Electrophysiology
- Homework I

Group work & pause

Group work

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Electrophysiological Models of Cells: Motivation

Description of
Insights in
Prediction of

} electrophysiological phenomena

Applications

- Diagnostics
  - Electro- and magneto-cardiography
  - Electro- and magneto-myography
  - Electro- and magneto-neurography

  ...
- Therapy
  - Parameterization and optimization of electrical nerve stimulators, defibrillators, and pace maker
    - electrode material, shape and position
    - signal
  - Development, evaluation and approval of pharmaceuticals
  - Education and teaching in cardiology, bioengineering, and pharmacology

  ...

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Microscopic Cellular Anatomy

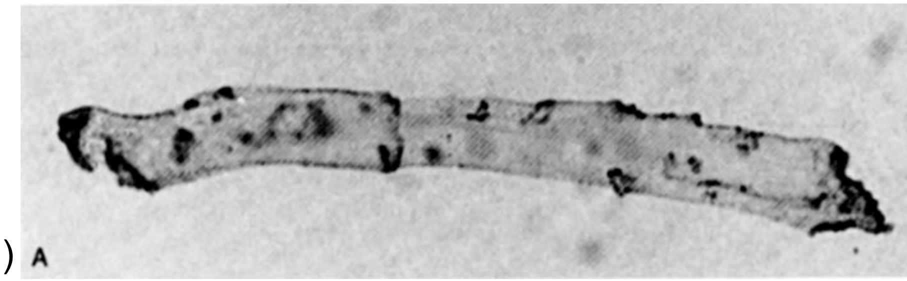
Myocyte of ventricular myocardium

cylinder-shaped

length: 60-120 µm

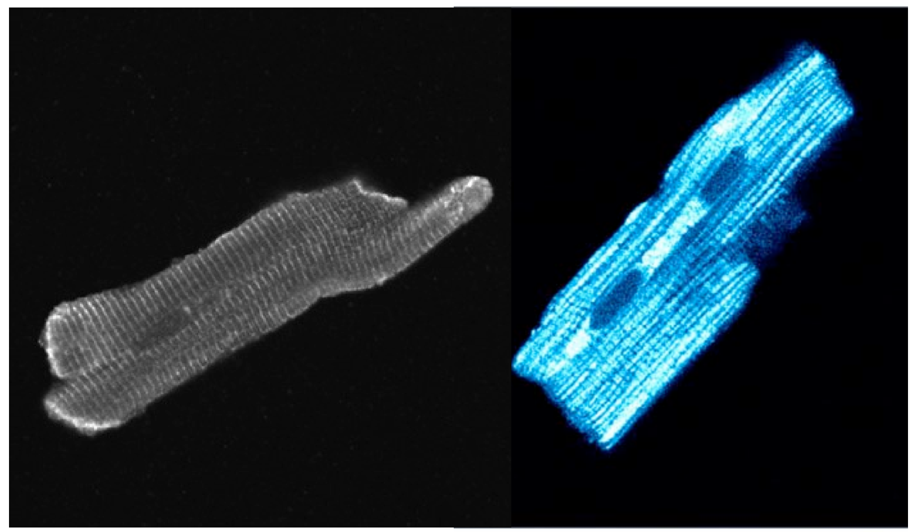
diameter: ca. 8-15 µm

(Hoyt et al. 89)



The basic shape of myocytes varies significantly for different locations, e.g.:

- cylinder-
- spindle-
- brick and
- rod-shaped



http://www.physiology.wisc.edu/walker/photo_gallery.htm

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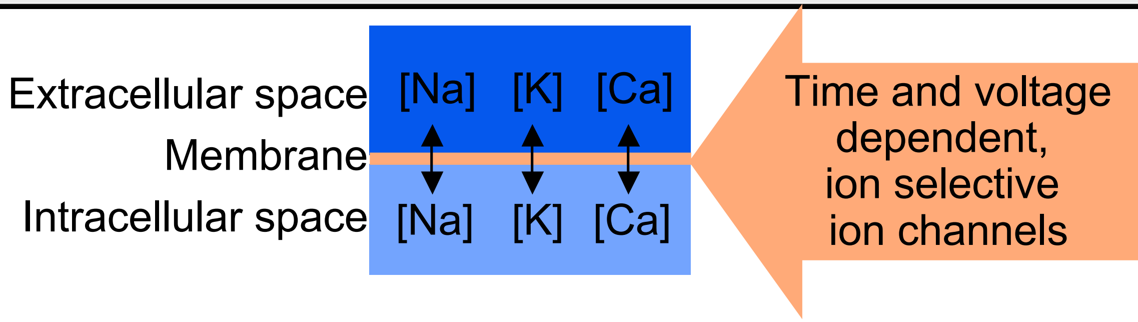
Electrophysiology of Cardiac Myocytes: Basics



Depolarization:

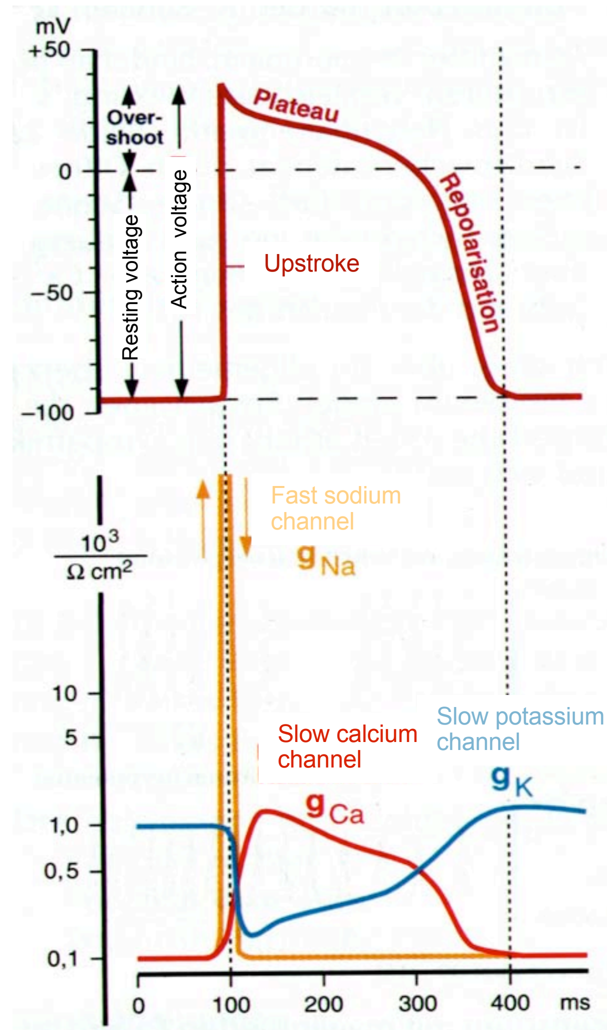
After reaching of threshold voltage:
short term increase of g_{Na^+}

Plateau phase:

Fast increase followed by slow decrease of $g_{Ca^{2+}}$
Fast decrease followed by slow increase of g_{K^+}

Repolarization:

Return of g_{Na^+}, g_{K^+} and $g_{Ca^{2+}}$ to resting values
Partly, g_{K^+} increase leads to hyperpolarization



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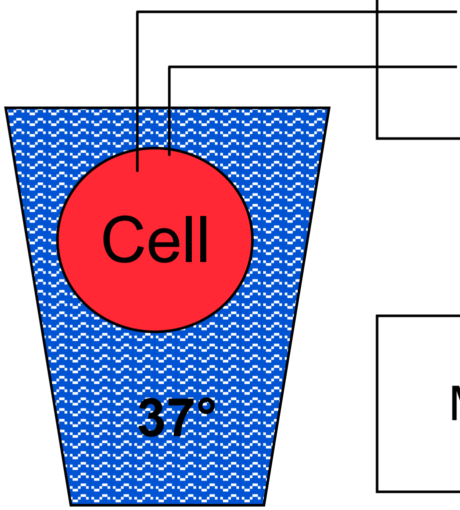
Development of Electrophysiological Cell Models



Measuring system

Space-, voltage- and patch-clamp
Voltage sensitive dyes
Channel blockers,
e.g. TTX for Na channels
…

↓

Measurement results

Action voltage, membrane currents,
conductivities, ion concentration,
membrane capacitance
length, volumes
…

↓

Mathematical model

Commonly, system of ODEs
e.g. of Hodgkin-Huxley and
Markov type

Models of Cellular Electrophysiology

1952

• 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
• Priebe, Beuckelmann	ventricular myocyte	human
• Winslow, Rice, Jafri, Marban, O’Rourke	ventricular myocyte	canine
• Seemann, Sachse, Weiss, Dössel	ventricular myocyte	human
…		

today

Models describe cells by set of ordinary differential equations
Equations are assigned to a whole cell and/or a small number of its compartments

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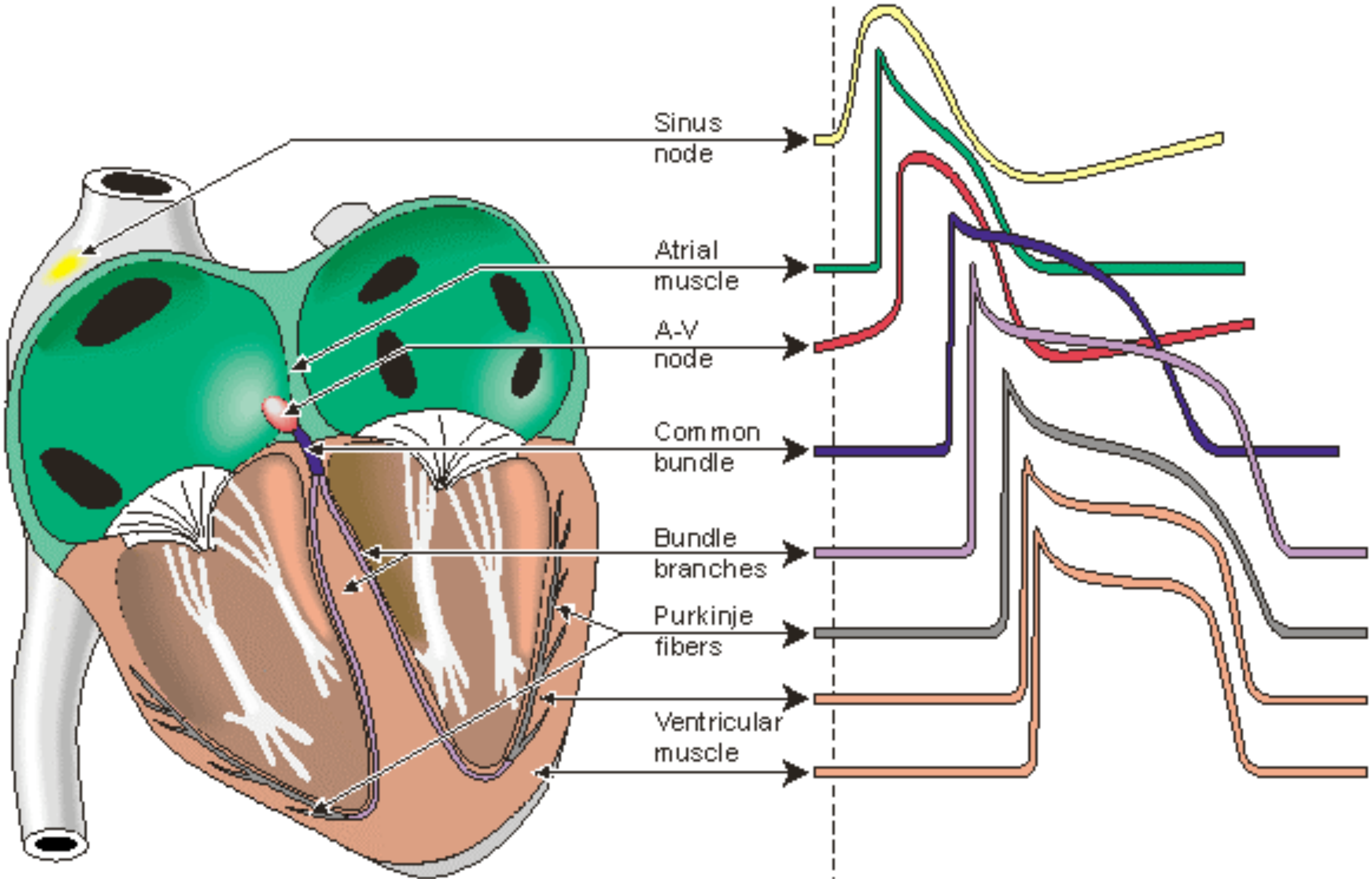
Transmembrane Voltages Measured at Different Positions

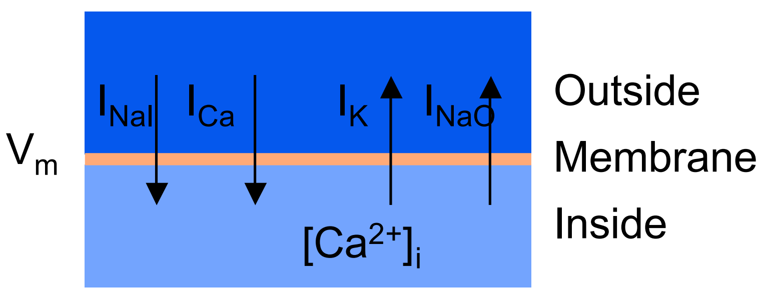


(Malmivuo and Plonsey, Bioelectromagnetism)

Beeler-Reuter Model 1977

Electrophysiological model of mammalian ventricular myocyte membrane

Parameterization by measurement with clamp techniques



I_{Na}: Inward current of sodium
I_S: Inward current (primarily calcium)
} Time and voltage dependent

I_{K1}: Outward current of potassium
} Time independent

I_{X1}: Outward current (primarily potassium)
} Time and voltage dependent

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Beeler-Reuter: Equations for Currents

$$i_{X1} = X1\ 0.8 \left(\frac{e^{0.04(V_m+77)} - 1}{e^{0.04(V_m+35)}} \right) \qquad i_{Na} = \left(g_{Na}\, m^3\, h\, j + g_{NaC} \right)\left(V_m - E_{Na}\right)$$

$$i_{K1} = 0.35\left(\frac{4e^{0.04(V_m+85)} - 1}{e^{0.08(V_m+53)} + e^{0.04(V_m+53)}} + \frac{0.2\left(V_m + 23\right)}{1 - e^{-0.04(V_m+23)}} \right) \qquad i_s = g_s\, d\, f\left(V_m - E_s\right)$$

$$E_s = -82.3 - 13.0287\ln\left[Ca^{2+}\right]_i \qquad E_{Na} = 50 \text{ mV}$$

$i_{X1}, i_{Na}, i_{K1}, i_s$: Current densities [μA/cm²]

V_m: Transmembrane voltage [mV]

E_s, E_{Na}: i_s and sodium Nernst voltages [mV]

g_s: Conductivity [mS/cm²]

g_{Na}: Conductivity of open Na channels [mS/cm²]

g_{NaC}: Conductivity of closed Na channels [mS/cm²]

$d, m, X1$: Activation state (described by ODE)

f, h, j: Inactivation state (described by ODE)

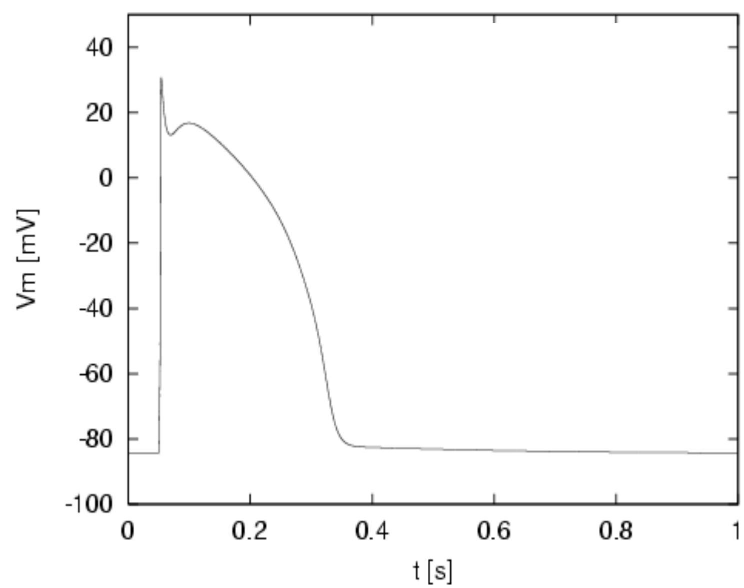
$\left[Ca^{2+}\right]_i$: Concentration of intracellular calcium [mmol/cm³]

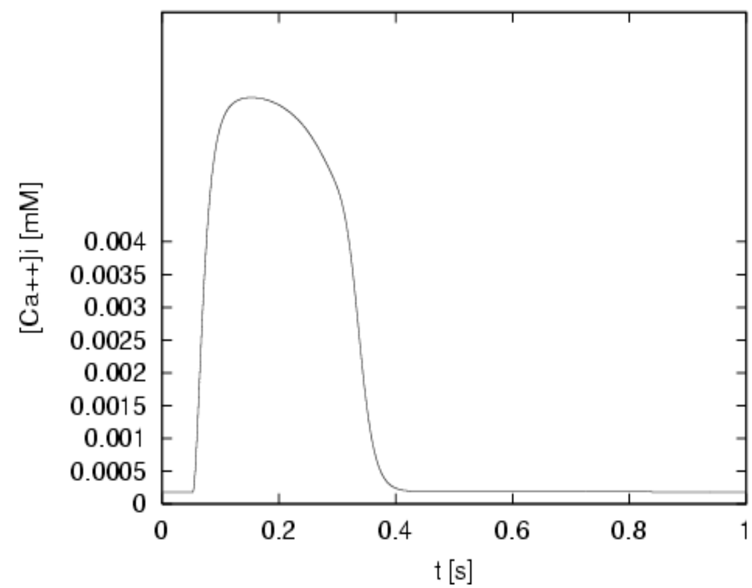
Beeler-Reuter: Equations for Currents and Concentrations

$$\frac{dV_m}{dt} = -\frac{1}{C_m}\left(i_{K1} + i_{X1} + i_{Na} + i_{Ca} + i_{external}\right)$$

$$\frac{d\left[Ca^{2+}\right]_i}{dt} = -10^{-7} i_s + 0.07\left(10^{-7} - \left[Ca^{2+}\right]_i\right)$$

$C_m = 1\,\frac{\mu\mathrm{F}}{cm^2}$: Membrane capacitance per area





Results of simulations for stimulus frequency of 1 Hz

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Luo-Rudy Model

Electrophysiological model of ventricular myocyte membrane from guinea pig

Parameterization by measurement with clamp techniques

- Phase I: 1991
- Phase II: 1994

Motivation

- Improved measurement techniques (e.g. single ion channel measurements)
- Deficits of Beeler-Reuter, e.g.
  Fixed extracellular ion concentrations
  Neglect of calcium transport and buffering in sarcoplasmic reticulum
  Neglect of cell geometry
  …

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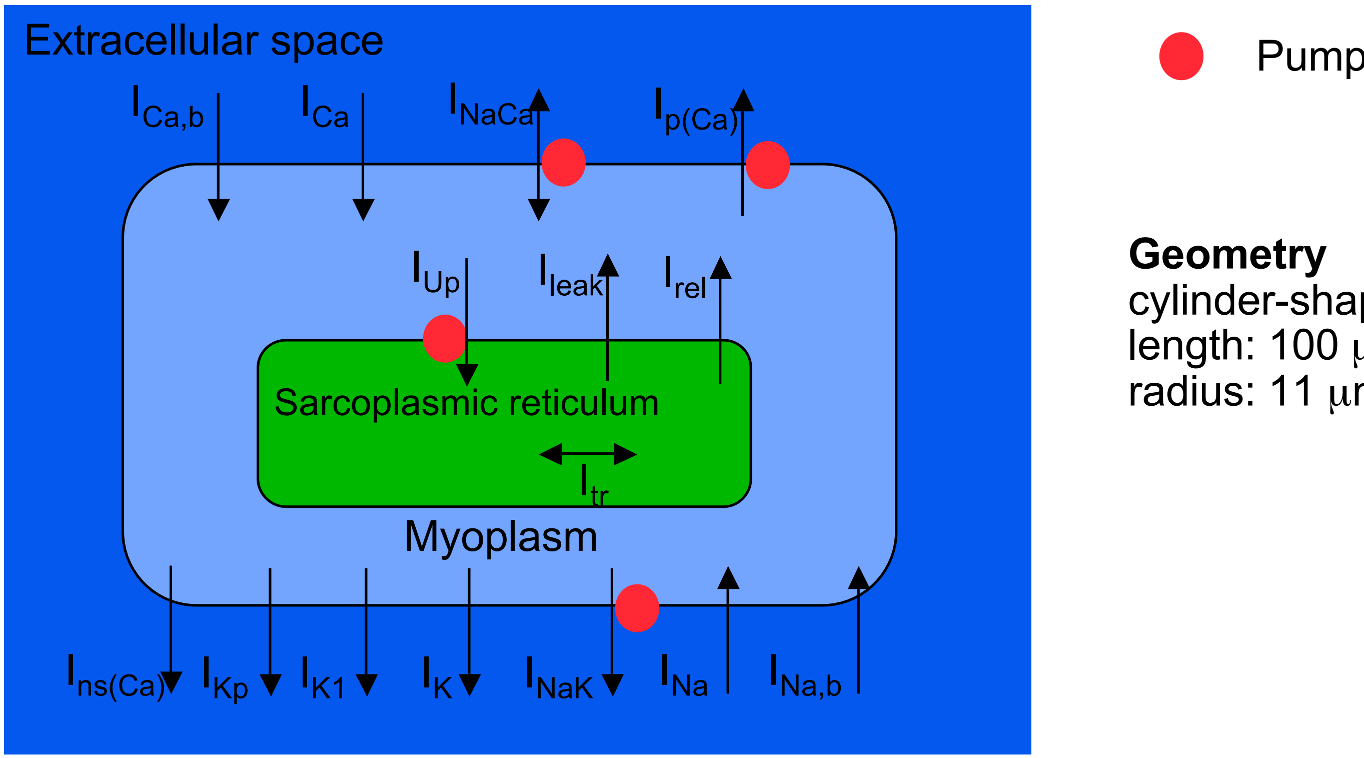
Luo-Rudy Model



Geometry
cylinder-shaped
length: 100 μm
radius: 11 μm

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Cellular Electrophysiology: Normal and Failing

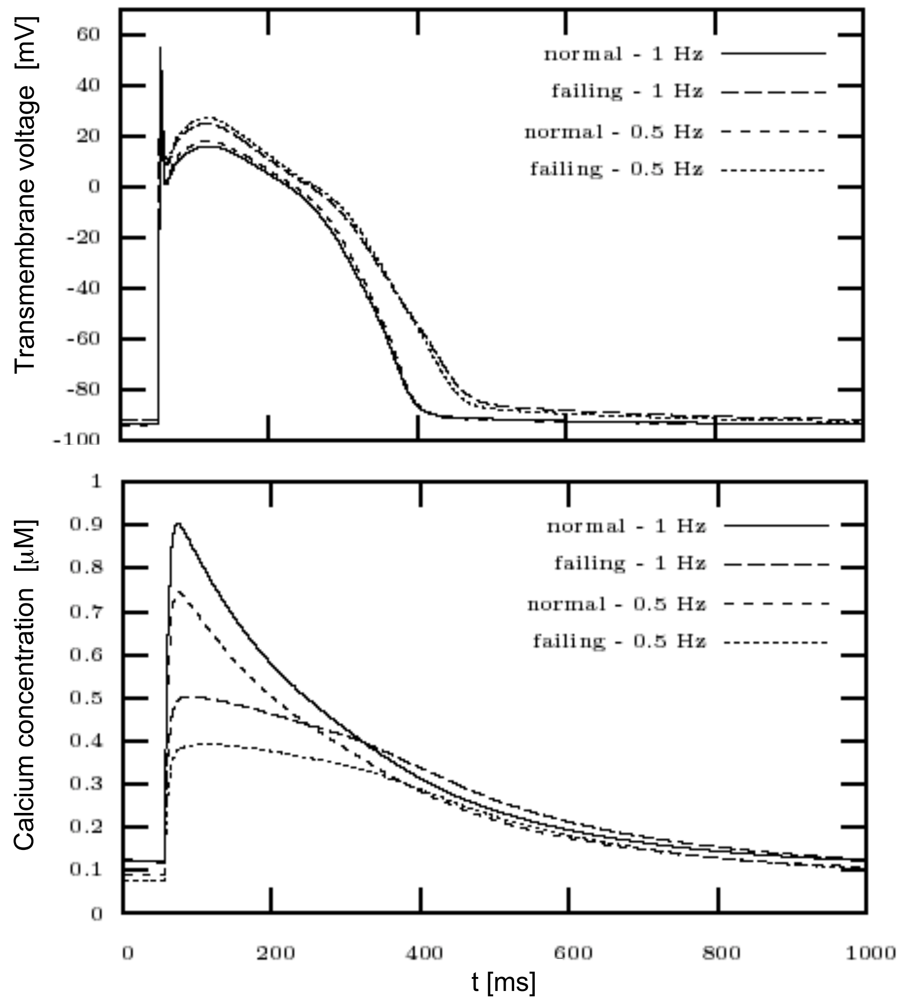
Simulation of normal and failing human ventricular myocytes with modified Priebe-Beuckelmann model

Pathology: Hypertrophy

Significant changes of density of proteins relevant for calcium transport:

- sarcolemmal NaCa-exchanger ↑
- sarcoplasmic Ca-pump ↓

(Sachse et al, JCE, 2003)



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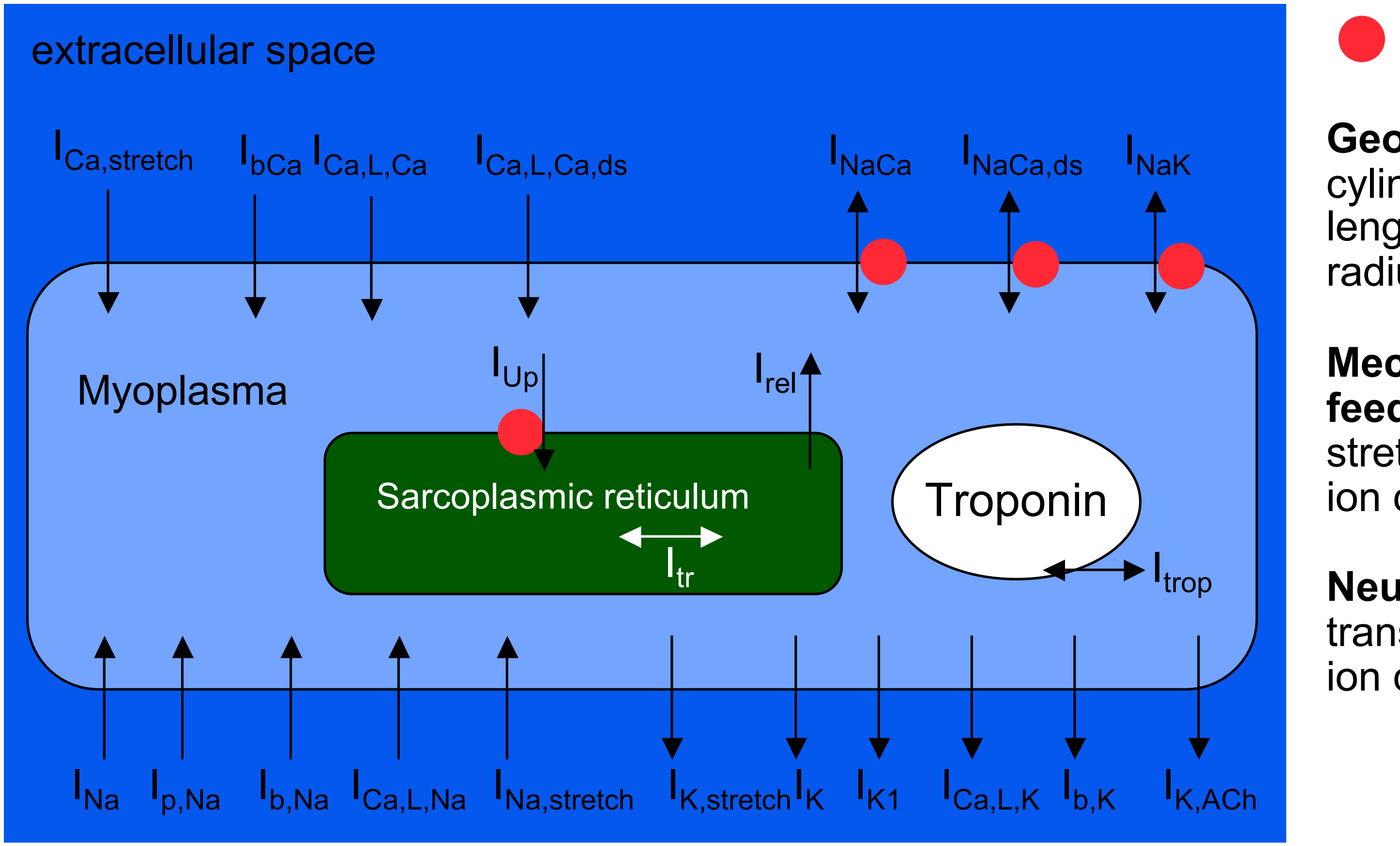
Noble-Kohl-Varghese-Noble Model 1998

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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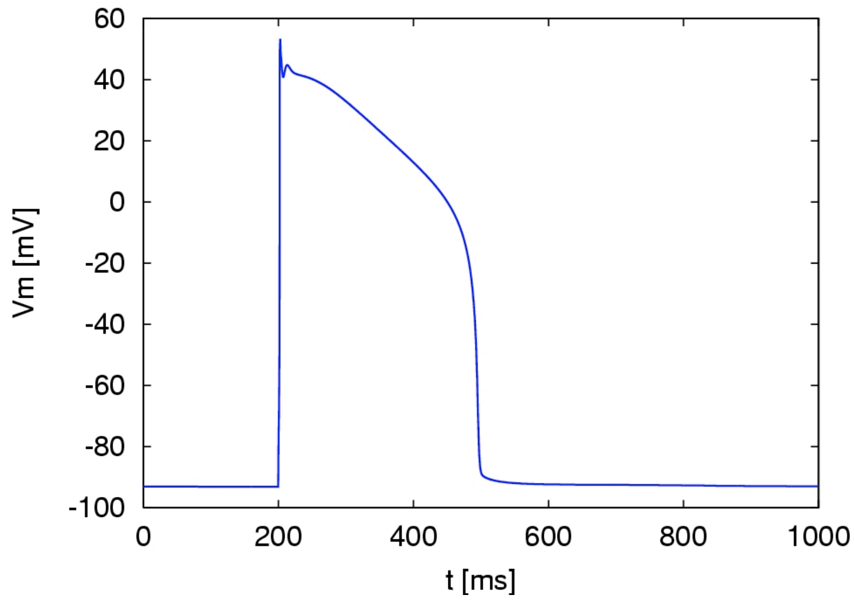
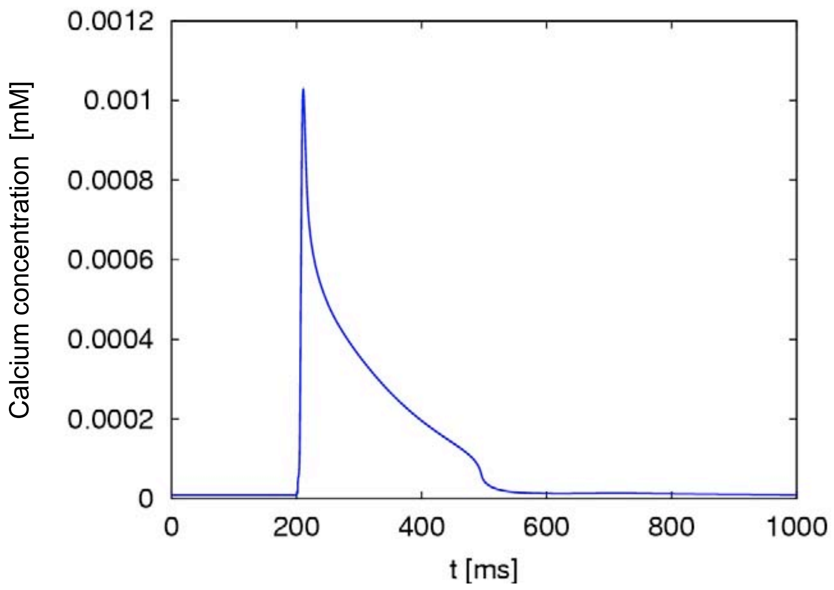
Noble-Kohl-Varghese-Noble Model 1998





Results of simulations for stimulus frequency of 1 Hz

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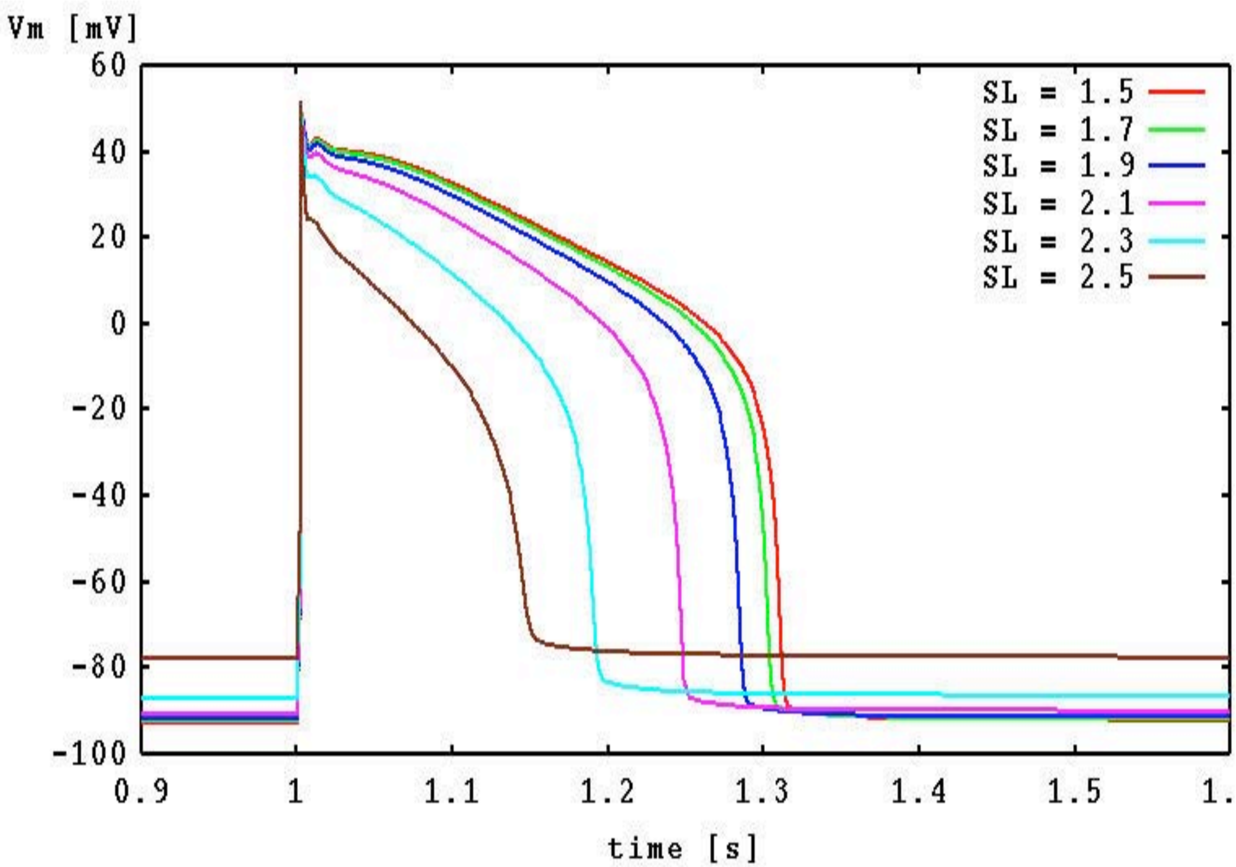
Prediction of Mechano-Electrical Feedback



Reduction of action potential duration (APD) by strain

Increase of resting voltage by strain

SL: sarcomere length

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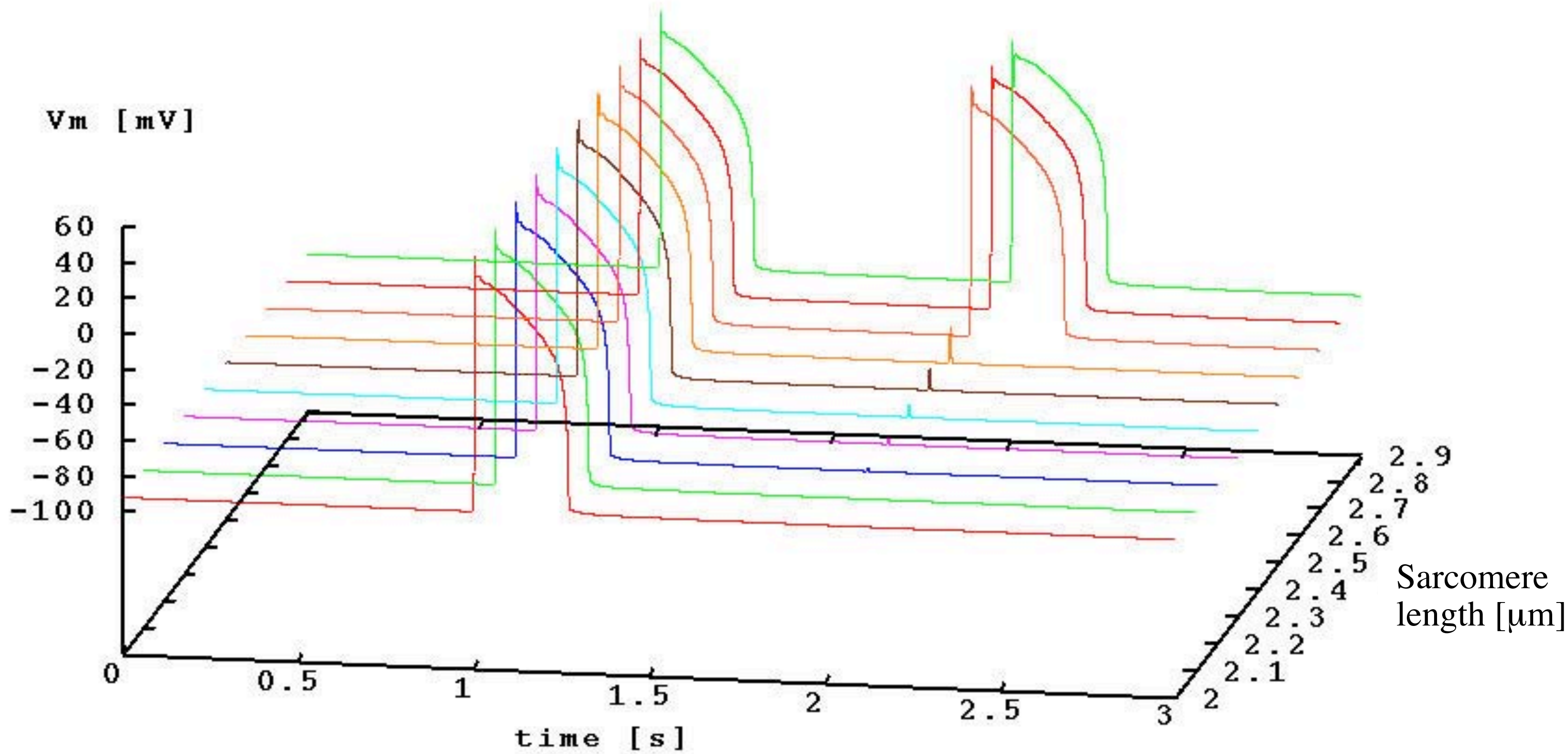
Prediction: Triggering of Action Potential by Strain



t=1 s: Electrical stimulus

t=2 s: Strain for 5 ms

Triggering of action potential for SL>2.7 μm

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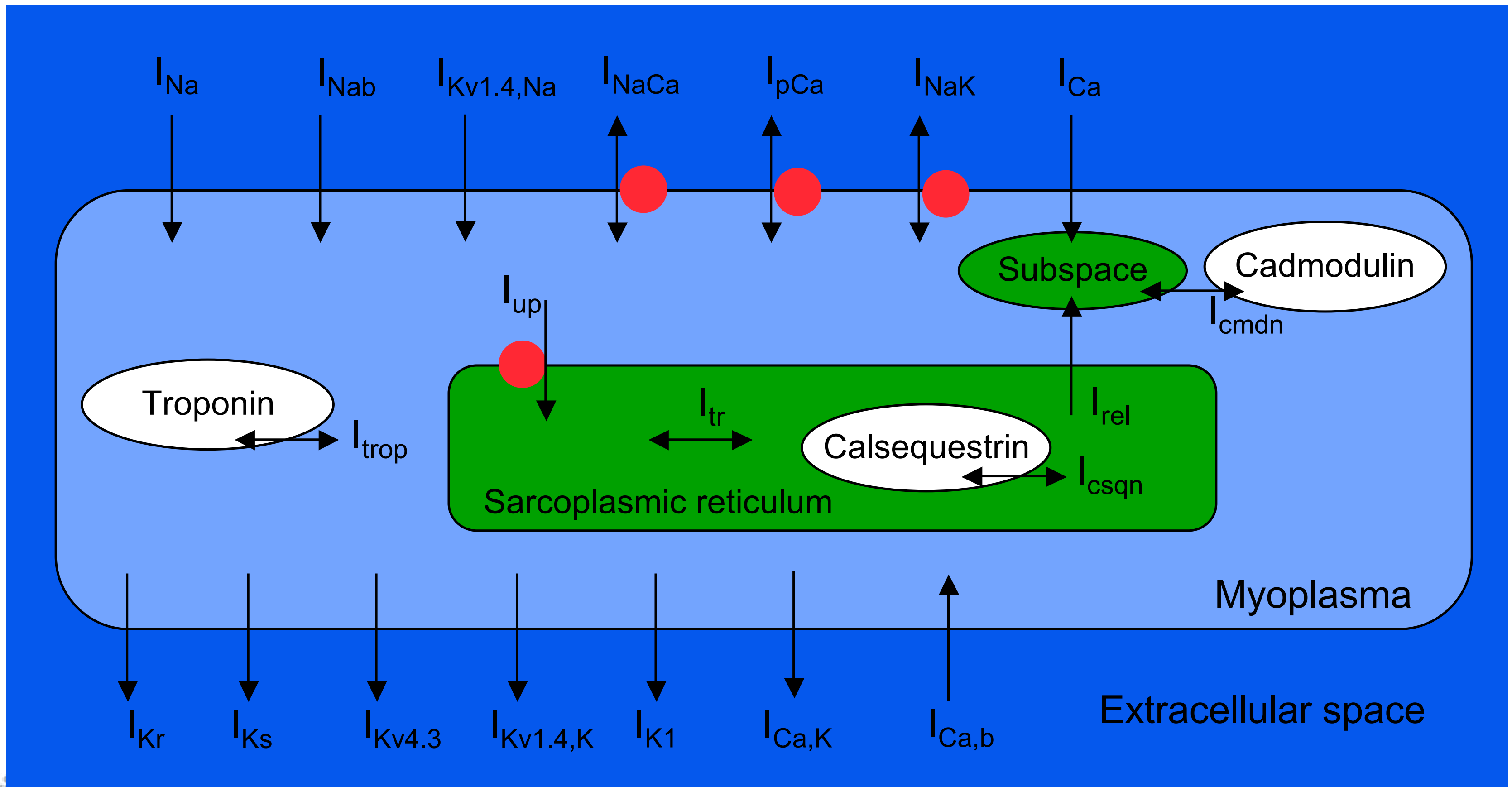
Iyer-Mazhari-Winslow Model 2004

Pump/exchanger **Compartment** **Ca-binding protein**



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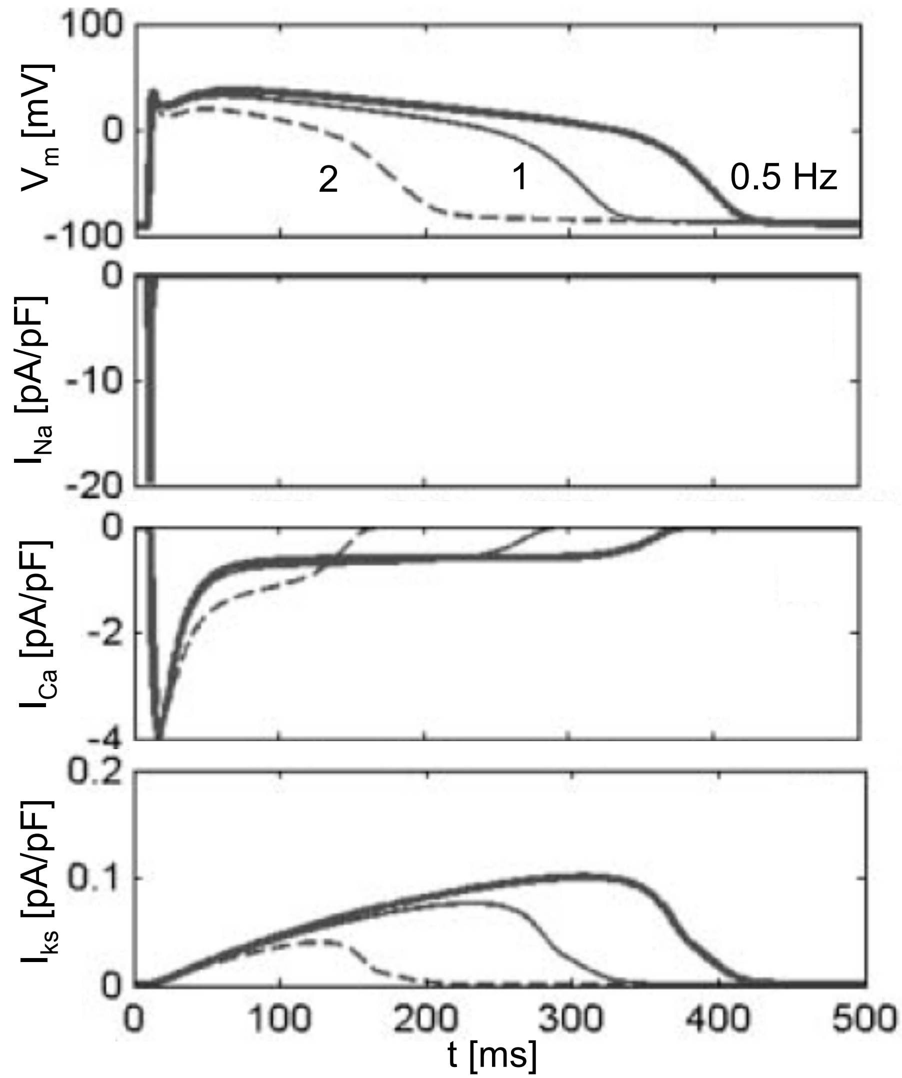
Reconstructed Voltage and Currents

Transmembrane voltage V_m

Fast sodium current I_{Na}

L-type calcium current I_{Ca}

Slow inward rectifying potassium current I_{Ks}



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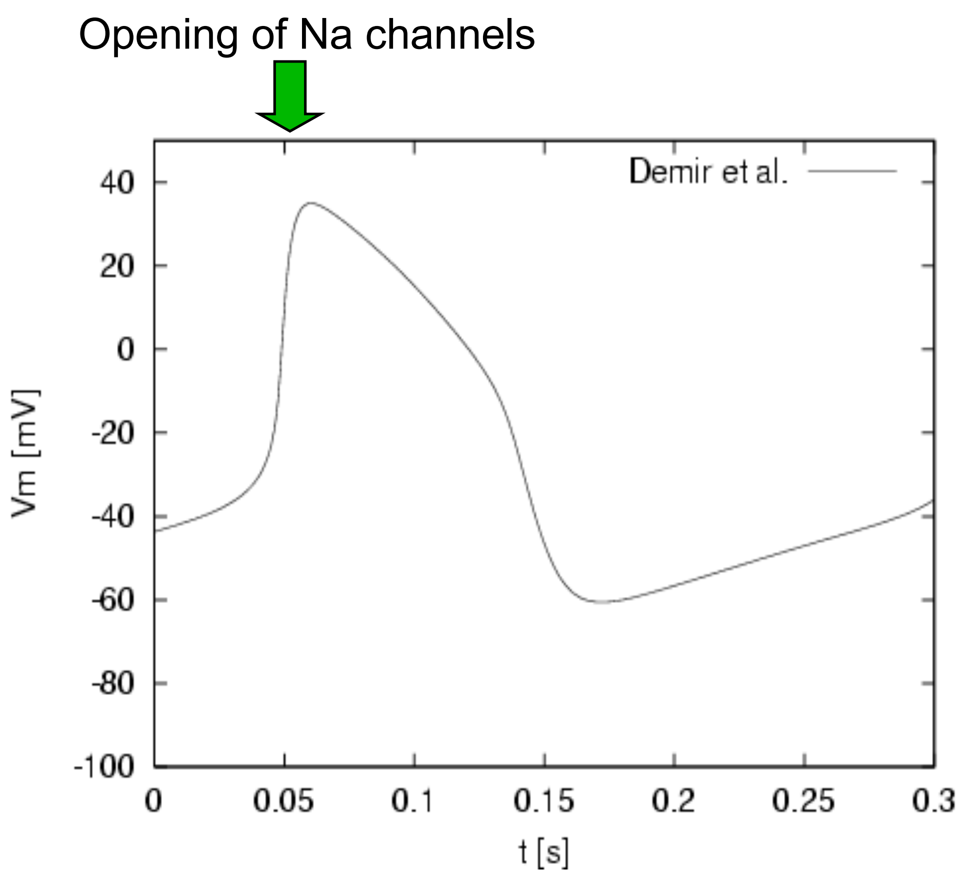
Electrophysiology of Mammalian Sinoatrial Node Cell



Depolarization starting at “resting voltage” (~-60 mV) leads to upstroke
Autorhythmicity with a frequency of ~3 Hz

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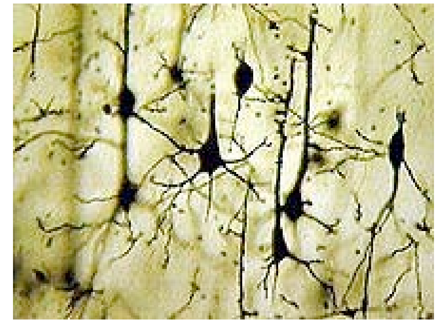
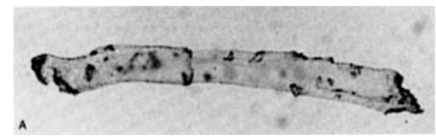
Modeling of Cardiac Myocytes versus Neurons





Geometry

- Spatial extend of neurons can be significantly larger than extend of myocytes
- Geometrical complexity of neurons can be significantly larger than complexity of myocytes

→ Assumption of isochronous properties of membrane typically used for single cardiac myocytes. Commonly, “0D” models.

→ 1-3D models typically used for single neurons

Membrane properties and transmembrane proteins

- Similar approaches applied for membrane modeling of myocytes and neurons
- Similar channels found, but significant differences of densities and properties

→ Adjustment by re-parameterization of conductivities and rate coefficients

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Group Work

Commonly, models represent behavior of cellular compartments with isochronous properties (0D)

Under which conditions is this description appropriate and when will it fail?

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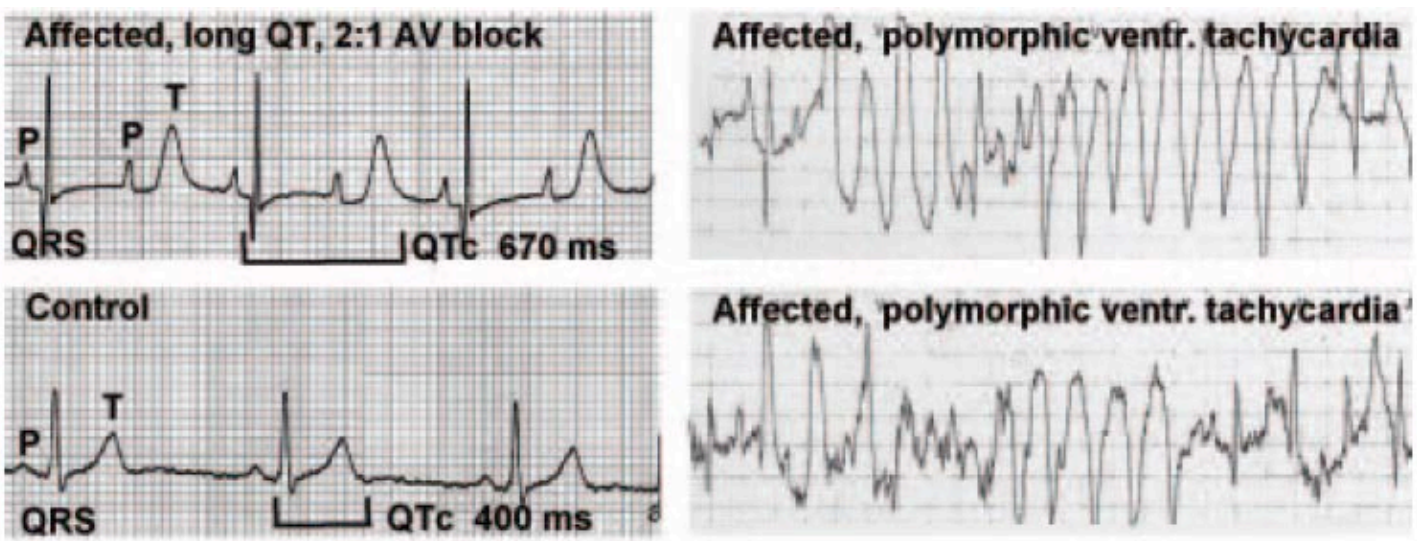
Timothy Syndrome



(Splawski et al, Proc Natl Acad Sci USA, 2005)

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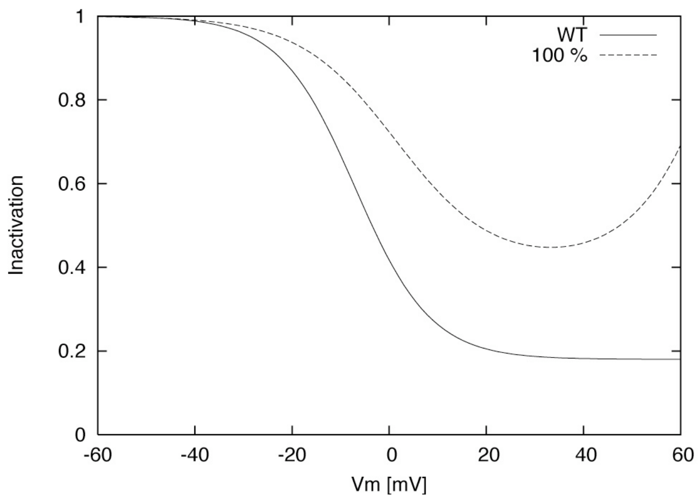
Modeling of Calcium Channel Mutation



Channel Modeling

Differences of steady state inactivation between wild type (WT) and mutated channels

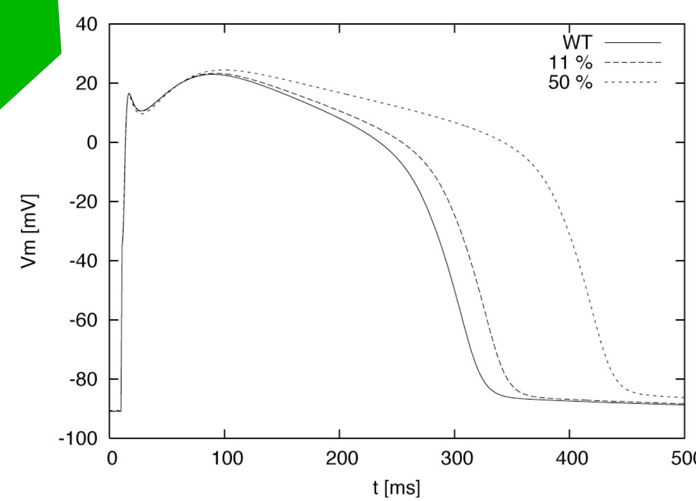
Numerical optimization

Integration in Myocyte Model

Prediction of course of transmembrane voltage in myocyte

Changes dependent on % of mutated channels

Significant increase of action potential duration (and intracellular calcium concentrations)



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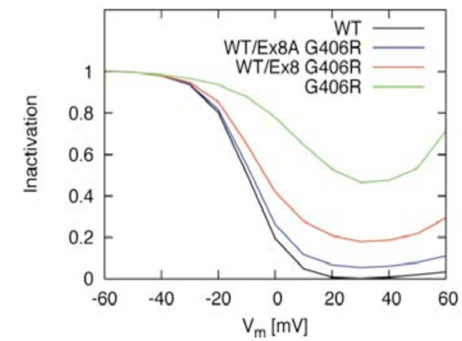
Calcium Channel Defect: Timothy Syndrome

Significant reduction of voltage-dependent inactivation of L-type calcium channels (Ca_v 1.2)

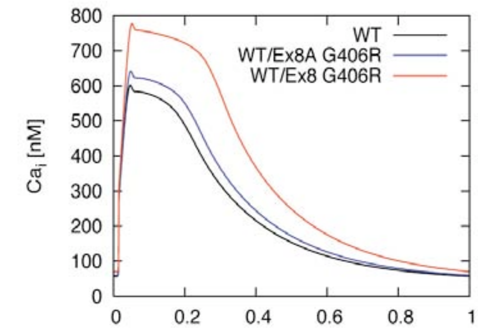
Characterization with
• electrophysiological studies in oocytes with normal (WT) and G406R Ca_v 1.2
• Prolonged QT time (LQT) in patient ECGs

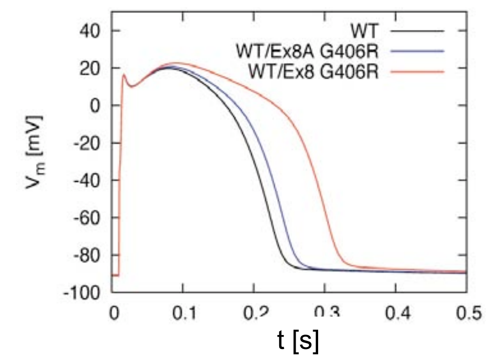
Prediction of cellular behavior with electrophysiological model of WT and G406R Ca_v 1.2

Ion channel



Ventricular myocyte





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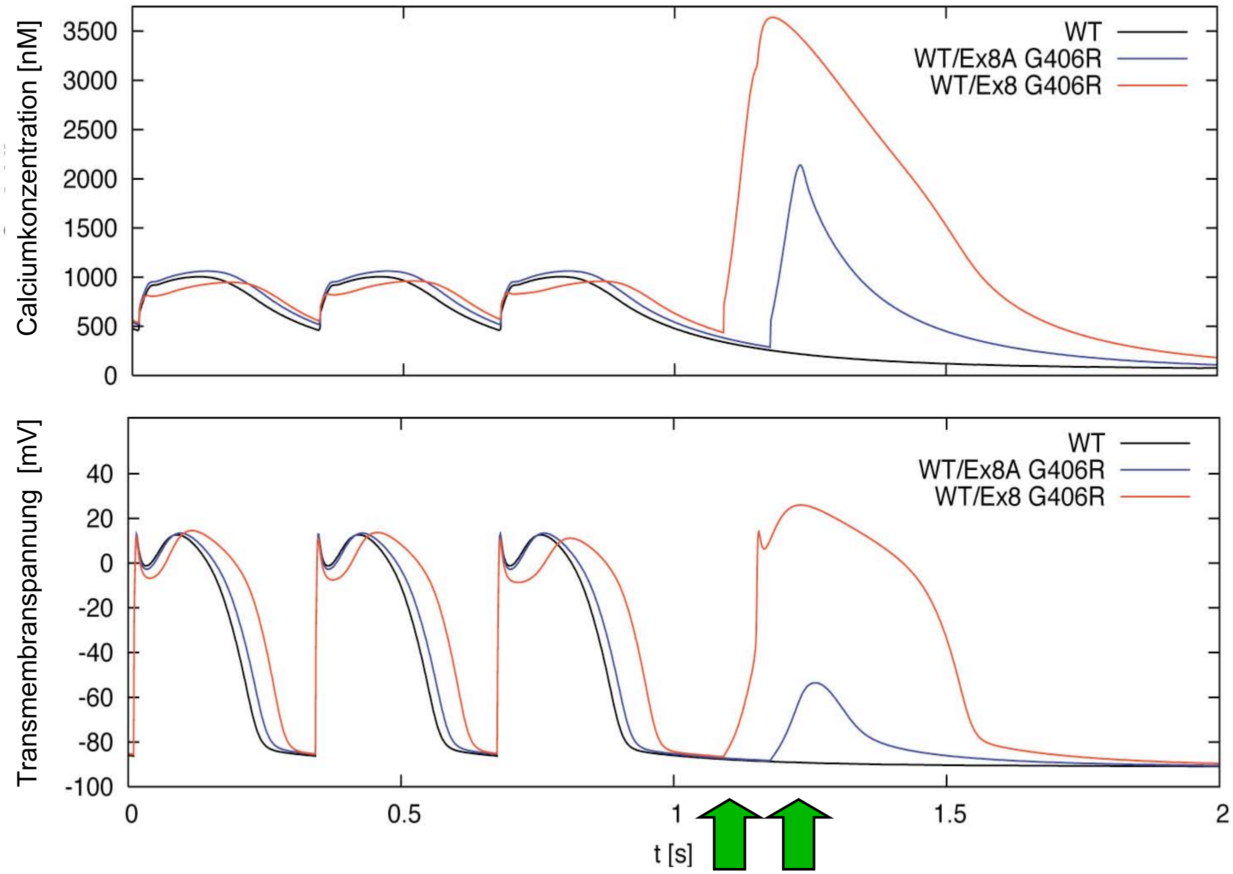
Timothy Syndrome: Increased Risk Of Arrhythmia

Protocol: Stimulus frequency of 3 Hz, pause



Spontaneous opening of sarcoplasmic release channel leads to delayed afterdepolarization!

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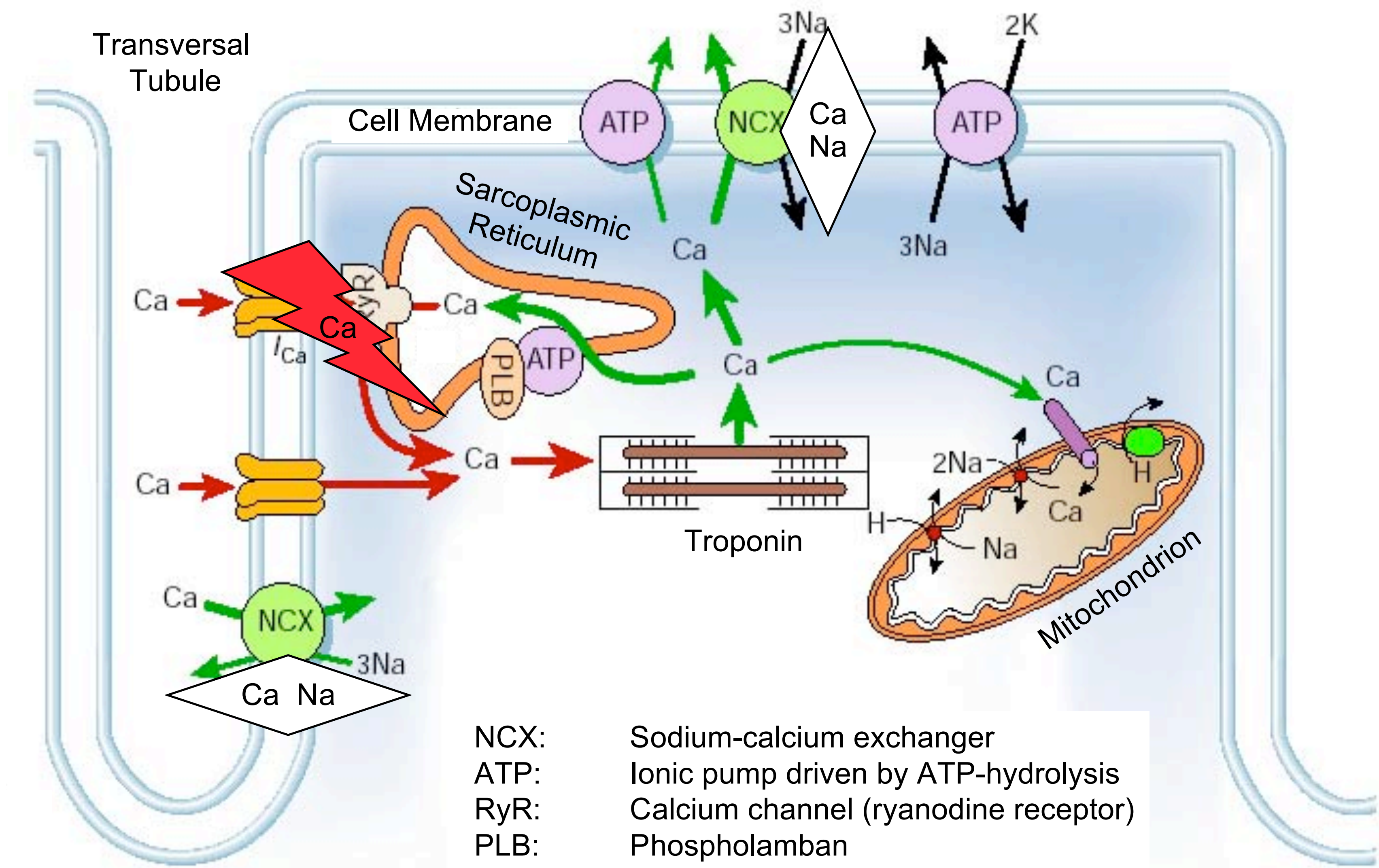
Cellular Electrophysiology: Calcium Regulation



NCX:	Sodium-calcium exchanger
ATP:	Ionic pump driven by ATP-hydrolysis
RyR:	Calcium channel (ryanodine receptor)
PLB:	Phospholamban

(Bers, Nature Insight Review Articles, 2002, modified)

Genetic Disease: Mutation of KCNQ1

Slow Inward Rectifying Potassium Current I_{Ks} { KCNQ1, KCNE1 }

KCNQ1

* Location of Mutation S4: Voltage sensing subunit

Mutations

- **S140G**
  Serine → Glycine
  found in family with hereditary atrial fibrillation
  (Chen et al., Science, 2003)
- **V141M**
  Valine → Methionine
  found in new born child with atrial fibrillation and short QT syndrome "de novo"
  (Kong et al., Cardiovasc. Res., 2005)

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Patient ECGs: Atrial Fibrillation

I, II, AVF, V1: Body surface leads HRA: High right atrium HBE: His-Bundle ECG

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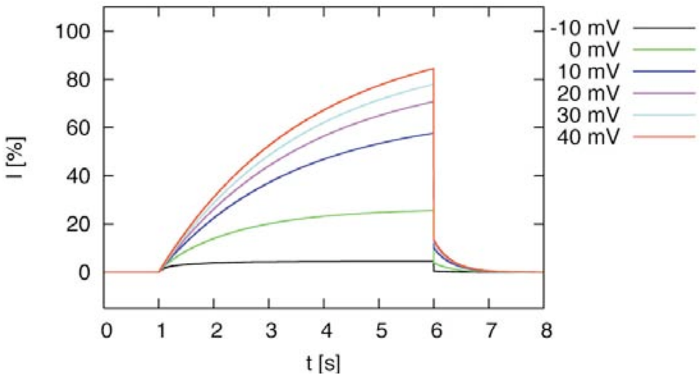
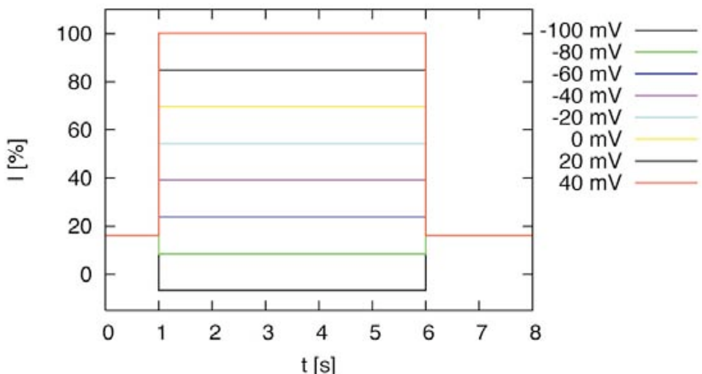
Mutation of Slow Inward Rectifying K-Current I_{Ks}

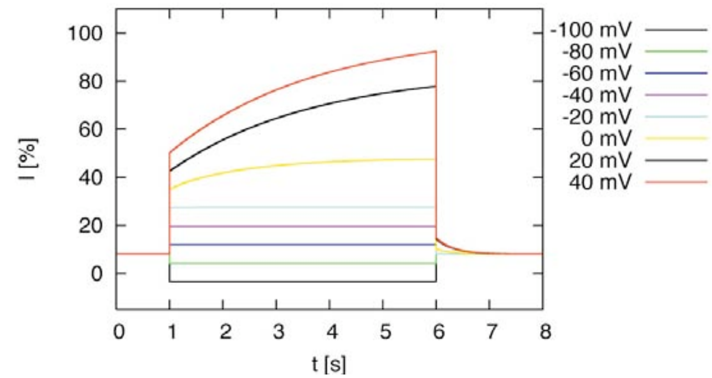
WT KCNQ1 + KCNE1



KCNQ1 with gain of function mutation + KCNE1
(S140G, V141M)



50 % WT / 50 % mutation



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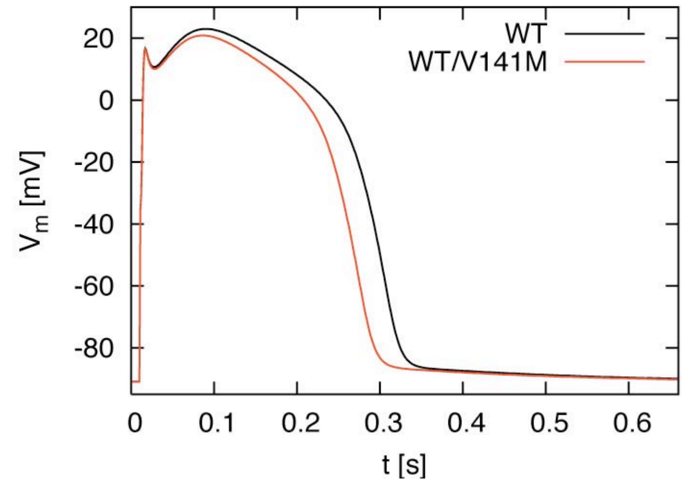
Prediction of Ventricular and Atrial Myocyte Behavior

Human ventricular myocyte at 1 Hz

Modified Iyer-Mazhari-Winslow model

APD ↓ - short QT syndrome
high risk for sudden cardiac death

(Hong et al, Cardiovasc. Res., 2005)

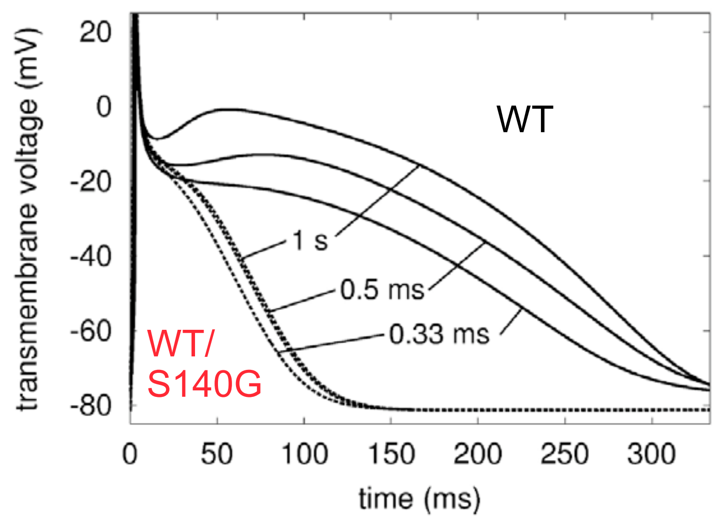


Human atrial myocyte at 1, 2, and 3 Hz

Modified Courtemanche-Ramirez-Nattel model

APD ↓↓ - facilitates atrial fibrillation

(Seemann et al, Proc. CinC, 2004)



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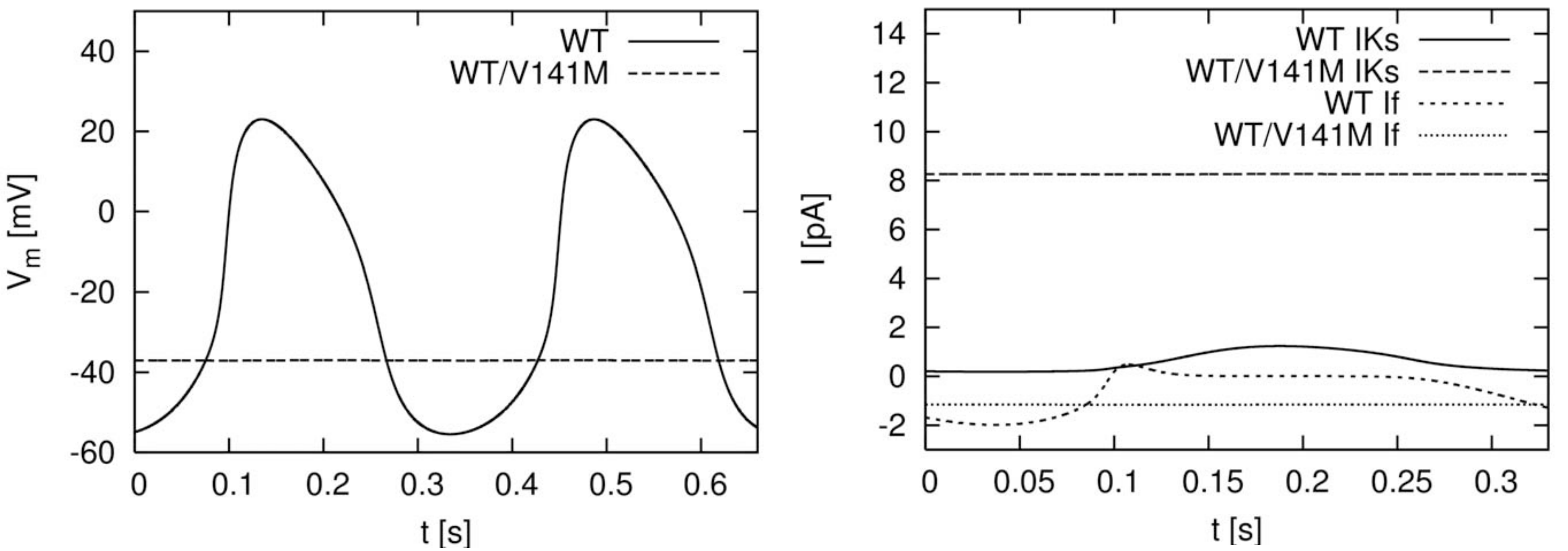
Prediction of Sinus Node Behavior



WT/V141M cells exhibit no autorhythmicity and a constant resting voltage of -37 mV

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Group Work

Imagine you are responsible for treatment of Timothy disease patients.

Which advice would you give these patients?

What type of drug would be helpful?

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