# BE6003/Physiol 6003

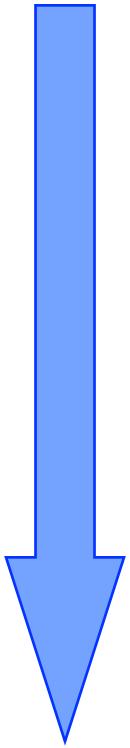
# Cellular Electrophysiology and Biophysics

## Modeling of Cellular Electrophysiology

CVRTI

**Frank B. Sachse,** University of Utah

# Overview



- Modeling of Cardiac Myocytes
  - Background
  - Examples
- Impact of Ion Channel Mutations on Cellular Electrophysiology
  - Timothy Syndrome
  - Short QT

Group work

Group work

Group work

CVRTI

# Group Work

Summarize major points from review paper!

CVRTI

# Electrophysiological Models of Cells: Motivation

Description of
Insights into
Prediction of
} electrophysiological phenomena

**Applications**

- Modeling
  - Integration in conduction models
  - Integration with other types of cellular models, e.g. of metabolism and force development
  - Testbed for ion channel models
- Therapy
  - Parameterization and optimization of electrical nerve stimulators, defibrillators, and pace maker
    - electrode material, shape and position
    - signal
  - Development, evaluation and approval of pharmaceuticals
- Teaching and training in cardiology, bioengineering, and pharmacology

CVRTI

# Microscopic Cellular Anatomy

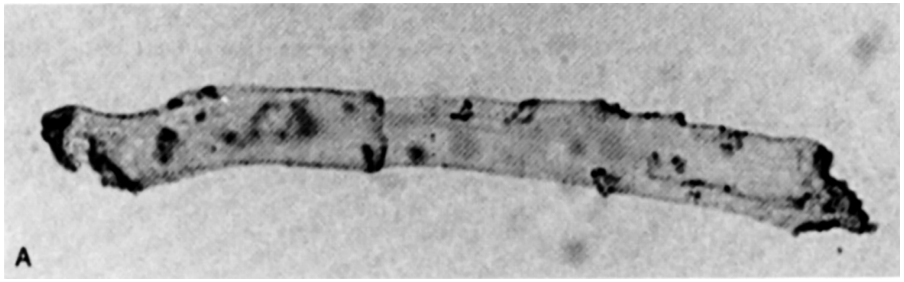
## Myocyte of ventricular myocardium

cylinder-shaped

length: 60-120 µm

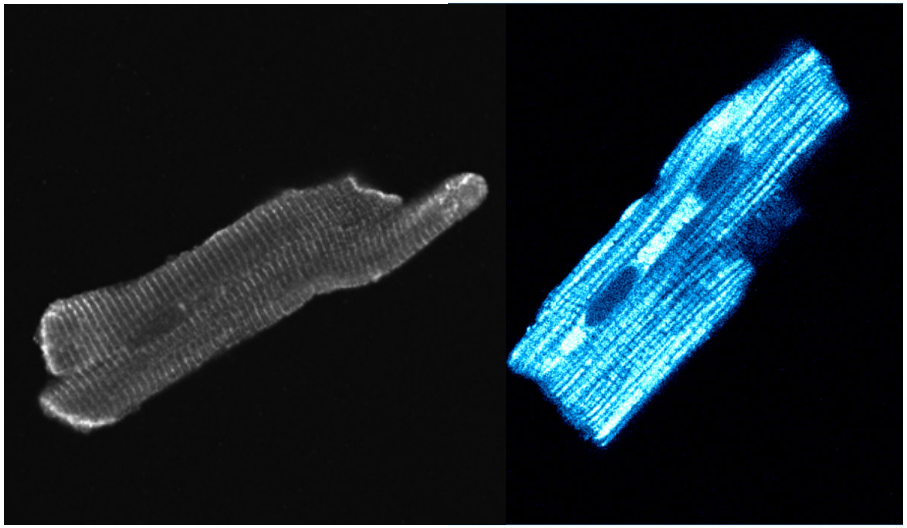
diameter: ca. 8-15 µm

(Hoyt et al. 89)




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

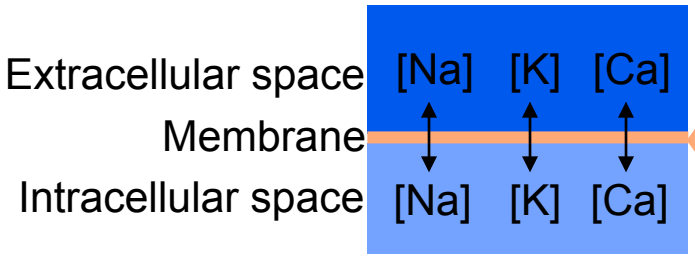
- cylinder-
- spindle-
- brick and
- rod-shaped



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

CVRTI

# Electrophysiology of Cardiac Myocytes: Basics




Time and voltage dependent, ion selective ion channels

**Depolarization:**

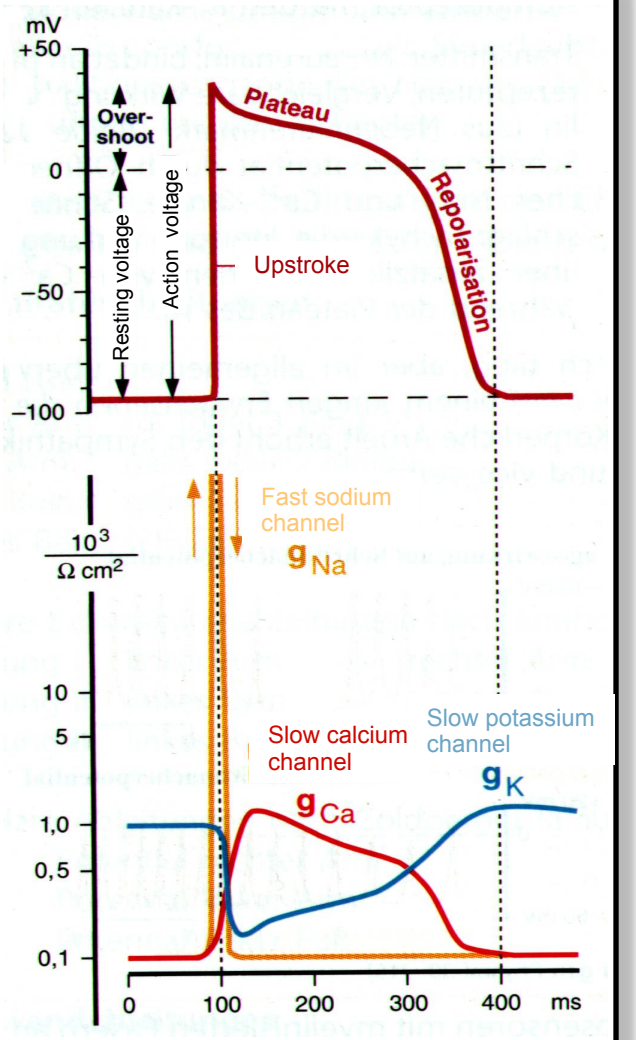
After reaching of threshold voltage:
Fast temporary increase of $g_{Na}^{+}$

**Plateau phase:**

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

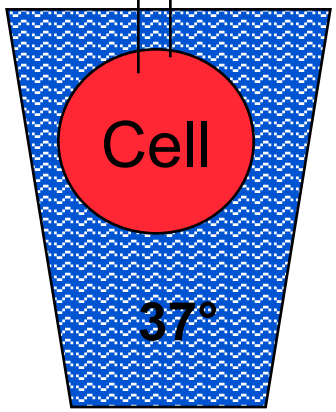
**Repolarization:**

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




CVRTI

# Development of Electrophysiological Cell Models




Measuring system

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

Measurement data

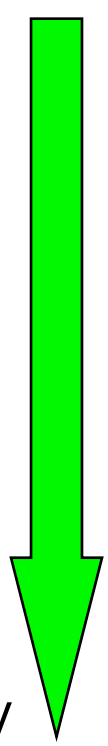
Action voltage, membrane currents,
conductivities, ion concentration,
membrane capacitance
length, volumes
…

Mathematical model

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

CVRTI

# Models of Cellular Electrophysiology

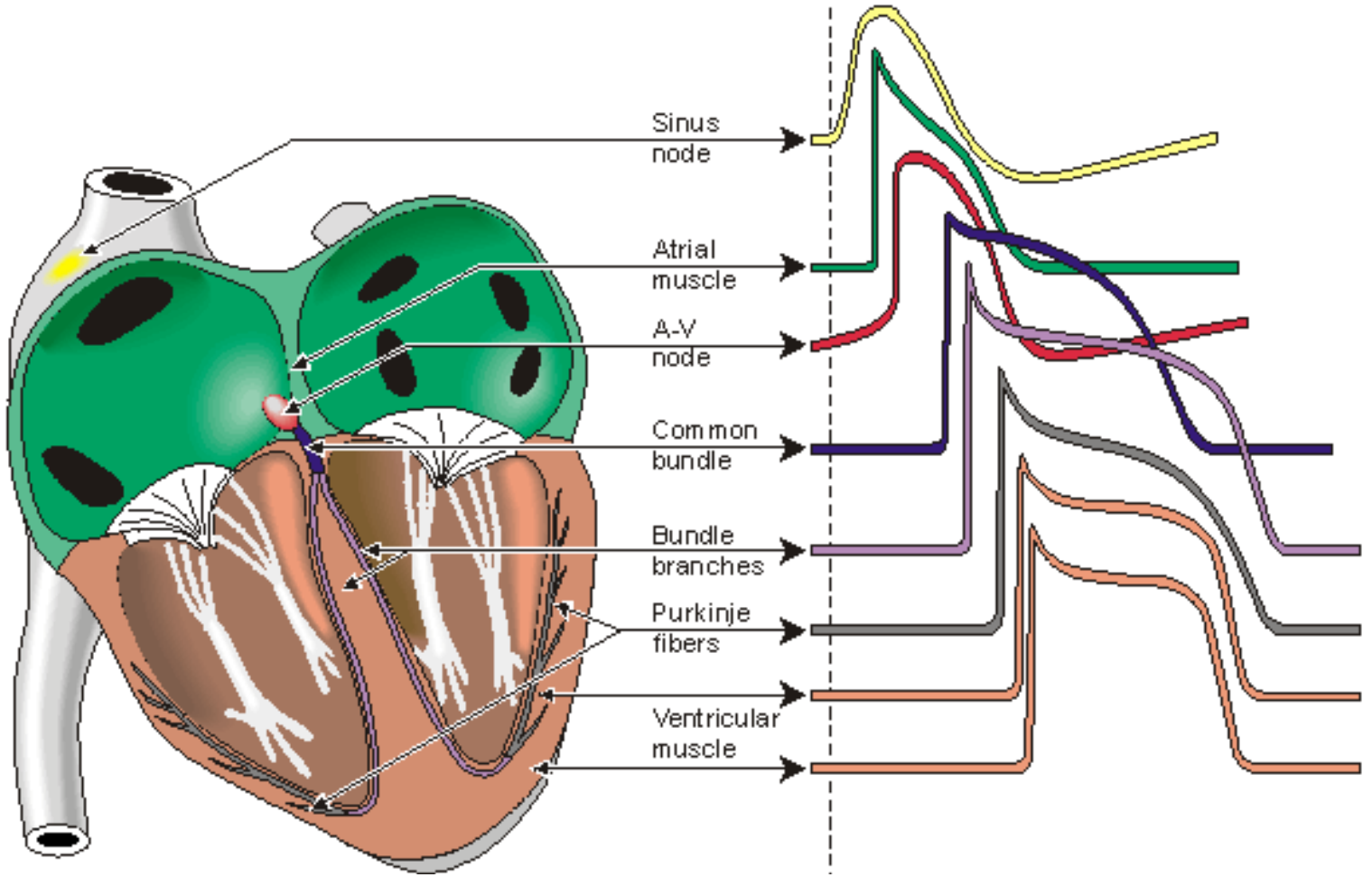



| | | |
|---|---|---|
| • Hodgkin-Huxley | axon membrane | giant squid |
| • Noble | Purkinje fiber | - |
| • Beeler-Reuter | ventricular myocyte | mammal |
| • DiFrancesco-Noble | Purkinje fiber | mammal |
| • Earm-Hilgemann-Noble | atrial myocyte | rabbit |
| • Luo-Rudy | ventricular myocyte | guinea 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 |
| … | | |

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

CVRTI

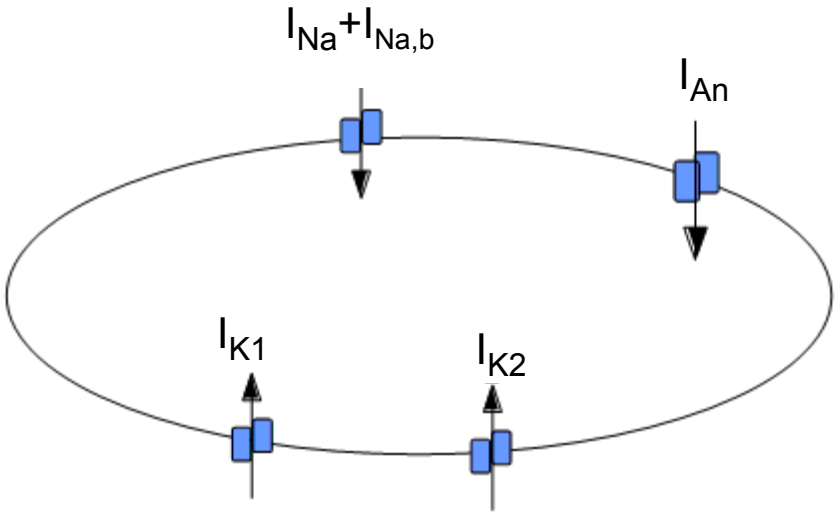
# Transmembrane Voltages Measured at Different Positions




(Malmivuo and Plonsey, Bioelectromagnetism)

CVRTI

# Noble Model 1962: Model of Purkinje Fiber




Membrane currents

$$i_m = i_{Na} + i_{Na,b} + i_{K1} + i_{K2} + i_{An}$$

CVRTI

# Noble Model 1962: Currents

Two different $Na^+$ currents:
1. Voltage dependent, quickly activating and inactivating

$$i_{Na} = g_{Na}(V_m - E_{Na})$$
$$g_{Na} = \bar{g_{Na}}\, m^3 h$$

2. Background current with constant conductance

$$i_{Na,b} = g_{Na,b}(V_m - E_{Na})$$

Background anion current with constant conductance

$$i_{An} = g_{An}(V_m - E_{An})$$

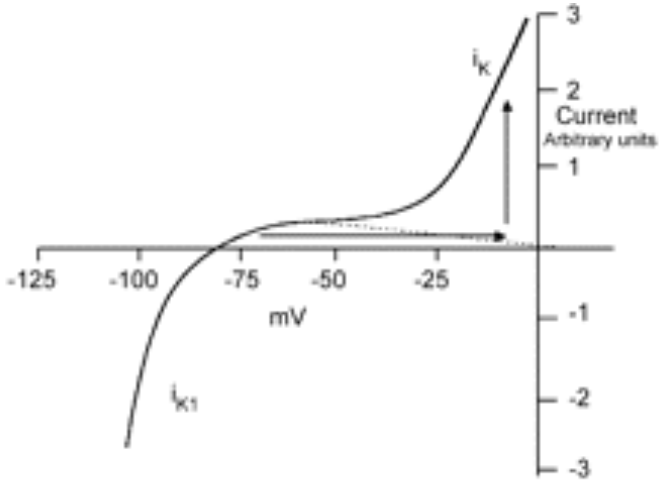
CVRTI

# Noble Model 1962: Potassium Currents

1. Voltage dependent, instantaneous

$$i_{K1} = g_{K1}(V_m - E_K)$$

$$g_{K1} = 1.2\, e^{-\frac{V_m}{50}} + 0.015\, e^{\frac{V_m+90}{60}}$$




2. Time dependent, ~classic HH $K^+$ current but with long time constant, i.e., 100x longer than in nerve. "Delayed rectifier" because it is slow and primarily outward.

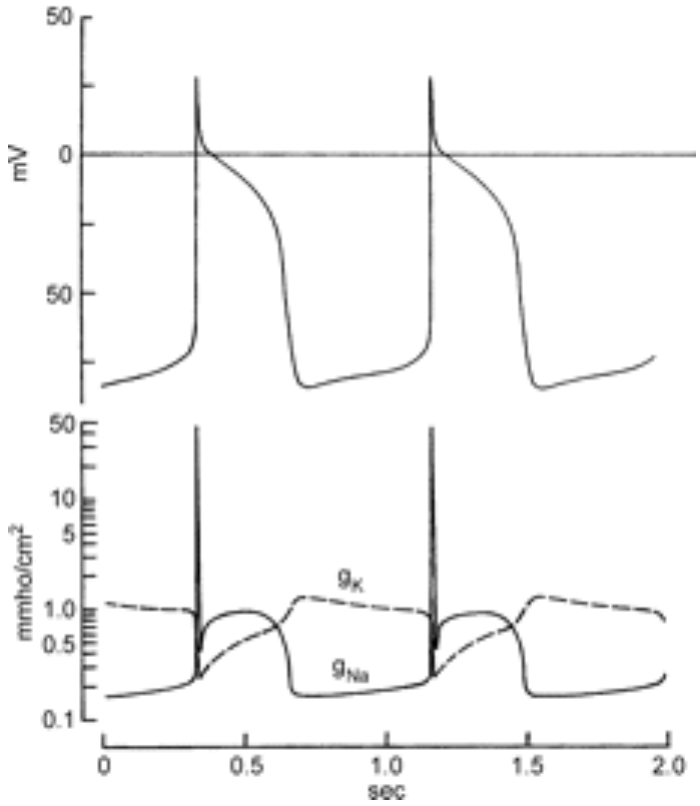
$$i_{K2} = g_{K2}(V_m - E_k)$$

$$g_{K2} = \bar{g_{K2}}\, n^4$$

CVRTI

# Noble Model 1962: Results

"So my research day started at 1:30 a.m.; a quick coffee, and then two hours at the *Mercury* computer. Then on to the slaughterhouse at 5 a.m. to pick up the sheep hearts with which the day's experiments would be done. Those experiments sometimes lasted until the time came to return to programming *Mercury*. I think that experience completely wrecked my circadian rhythms, but let's return to that kind of rhythm later in this chapter." Denis Noble. The Music of Life: Biology beyond the Genome. (Oxford University Press, USA, 2006). Page 61.



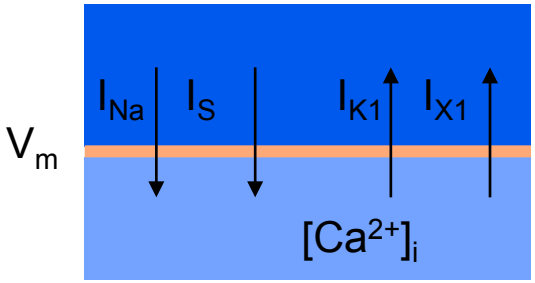

- Modeled pacemaker activity without explicit oscillator
- Physiologically incorrect
  - Developed before voltage clamp of cardiac cells
  - Plateau produced by Na rather than Ca current, which was missing

CVRTI

# 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

CVRTI

# Beeler-Reuter: Current Equations

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

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

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

$i_{X1}, i_{Na}, i_{K1}, i_s$: Current densities [μA/cm$^2$]

$V_m$: Transmembrane voltage [mV]

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

$g_s$: Conductivity [mS/cm$^2$]

$g_{Na}$: Conductivity of open Na channels [mS/cm$^2$]

$g_{NaC}$: Conductivity of closed Na channels [mS/cm$^2$]

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

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

$\left[Ca^{2+}\right]_i$: Concentration of intracellular calcium [mmol/cm$^3$]

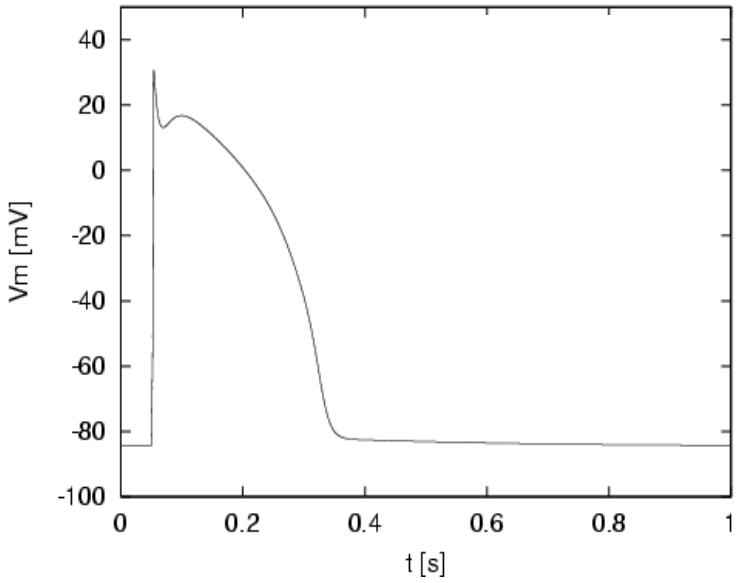
CVRTI

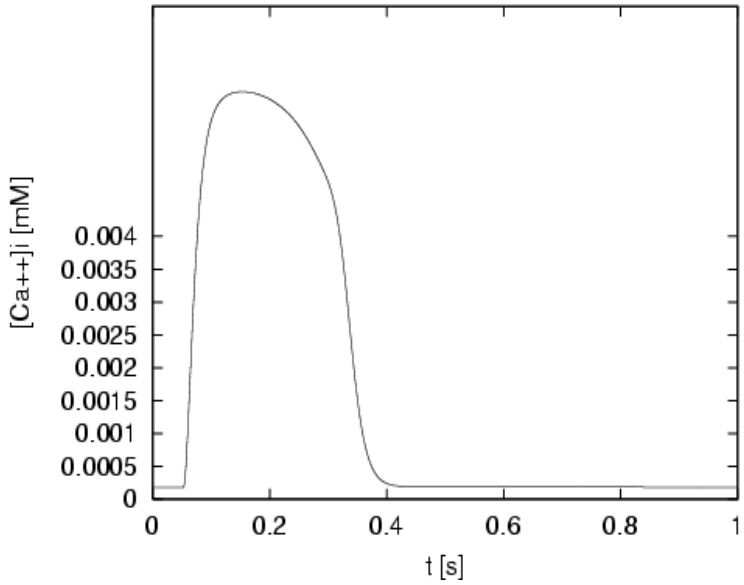
# Beeler-Reuter: Equations for Currents and Concentrations

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

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

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




Results of simulations for stimulus frequency of 1 Hz

CVRTI

# Luo-Rudy Model 1991/94

Electrophysiological model of ventricular myocyte membrane from guinea pig

Parameterization by measurement with clamp techniques

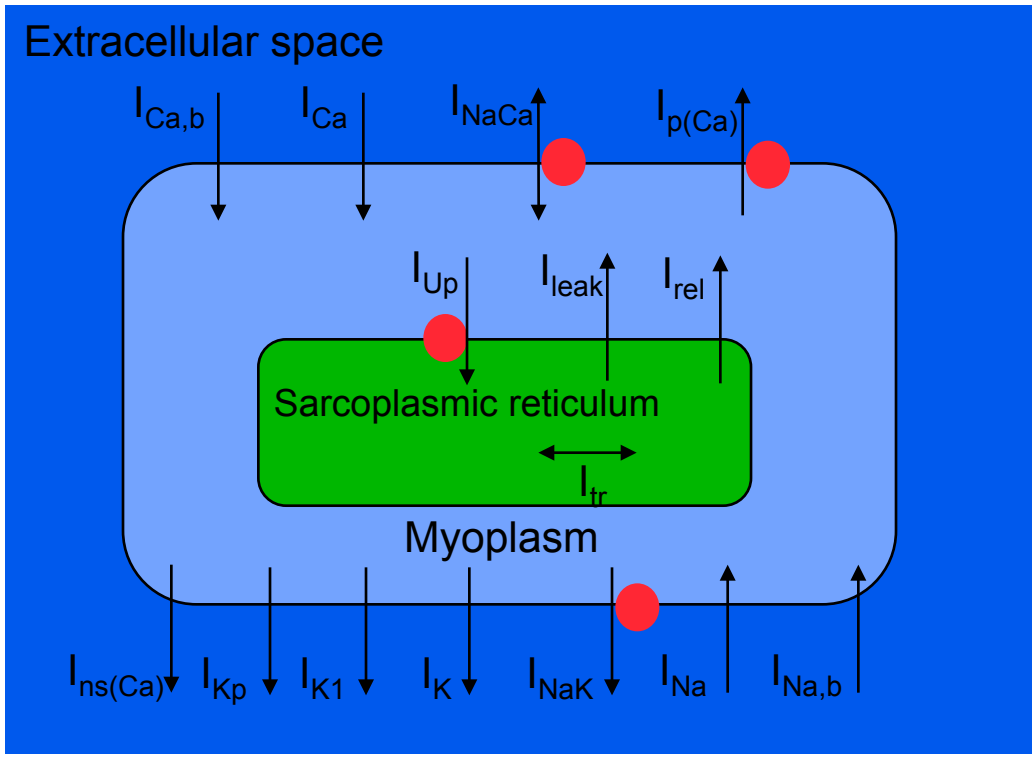
- Phase I: 1991
- Phase II: 1994

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
  …

CVRTI

# Luo-Rudy Model




Pump

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

CVRTI

# Cellular Electrophysiology: Normal and Failing

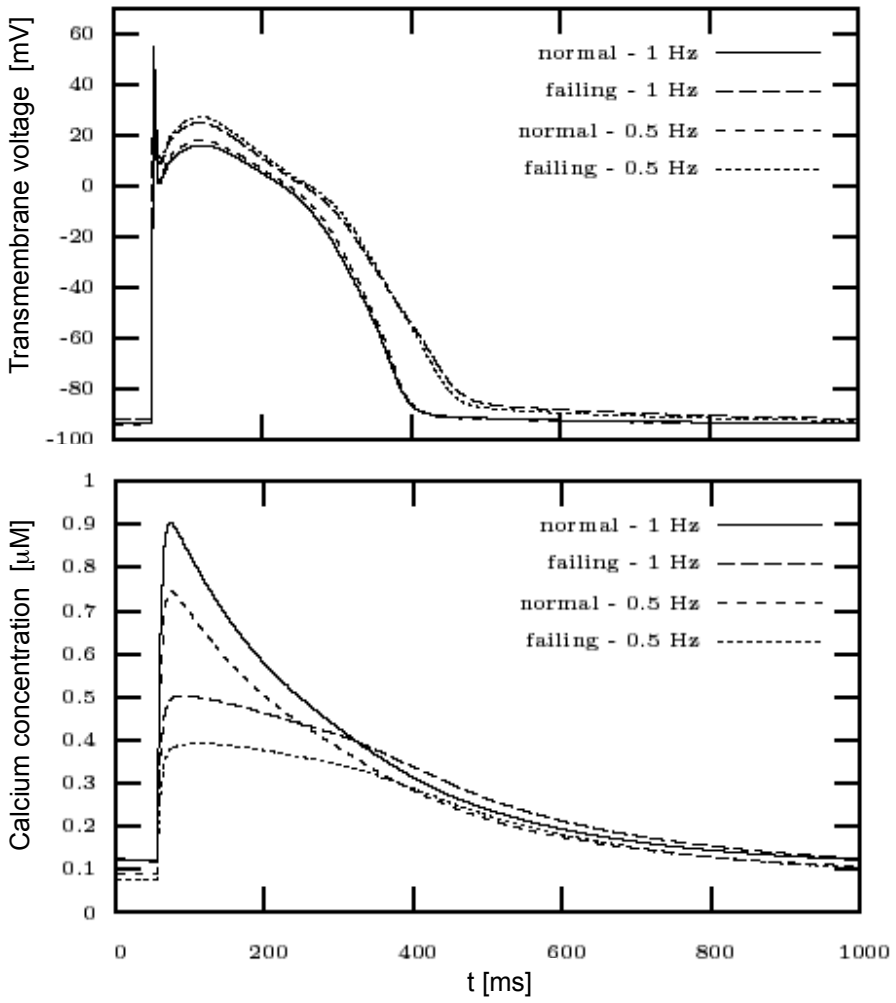
Simulation of normal and failing human ventricular myocytes with modified Priebe-Beuckelmann model

Pathology: Hypertrophy

Significant changes of density of proteins relevant for calcium transport:

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

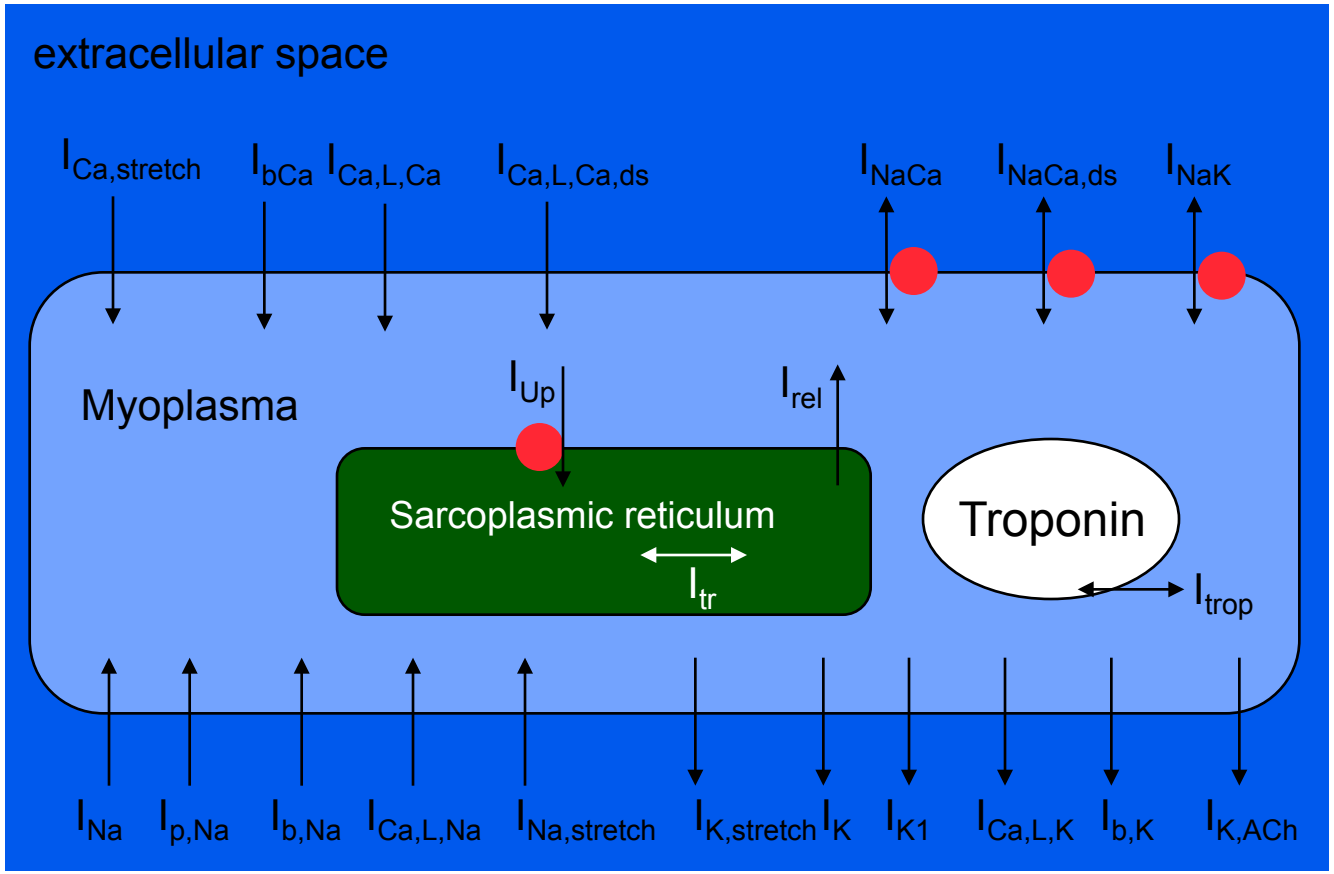
(Sachse et al, JCE, 2003)




CVRTI

# Noble-Kohl-Varghese-Noble Model 1998

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




pump

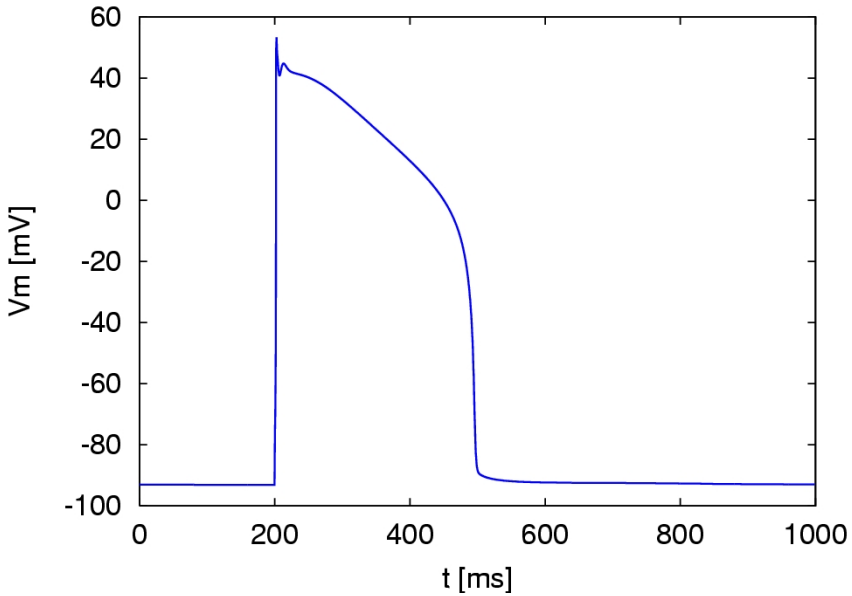
**Geometry**
cylinder-shaped
length: 74 μm
radius: 12 μm

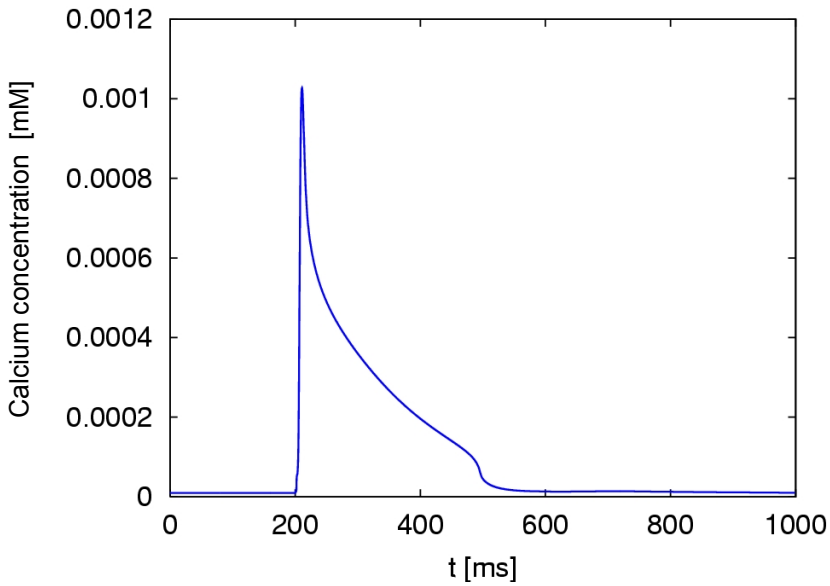
**Mechano-electrical feedback** by stretch activated ion channels

**Neural influence** by transmitter activated ion channels etc.

CVRTI

# Noble-Kohl-Varghese-Noble Model 1998

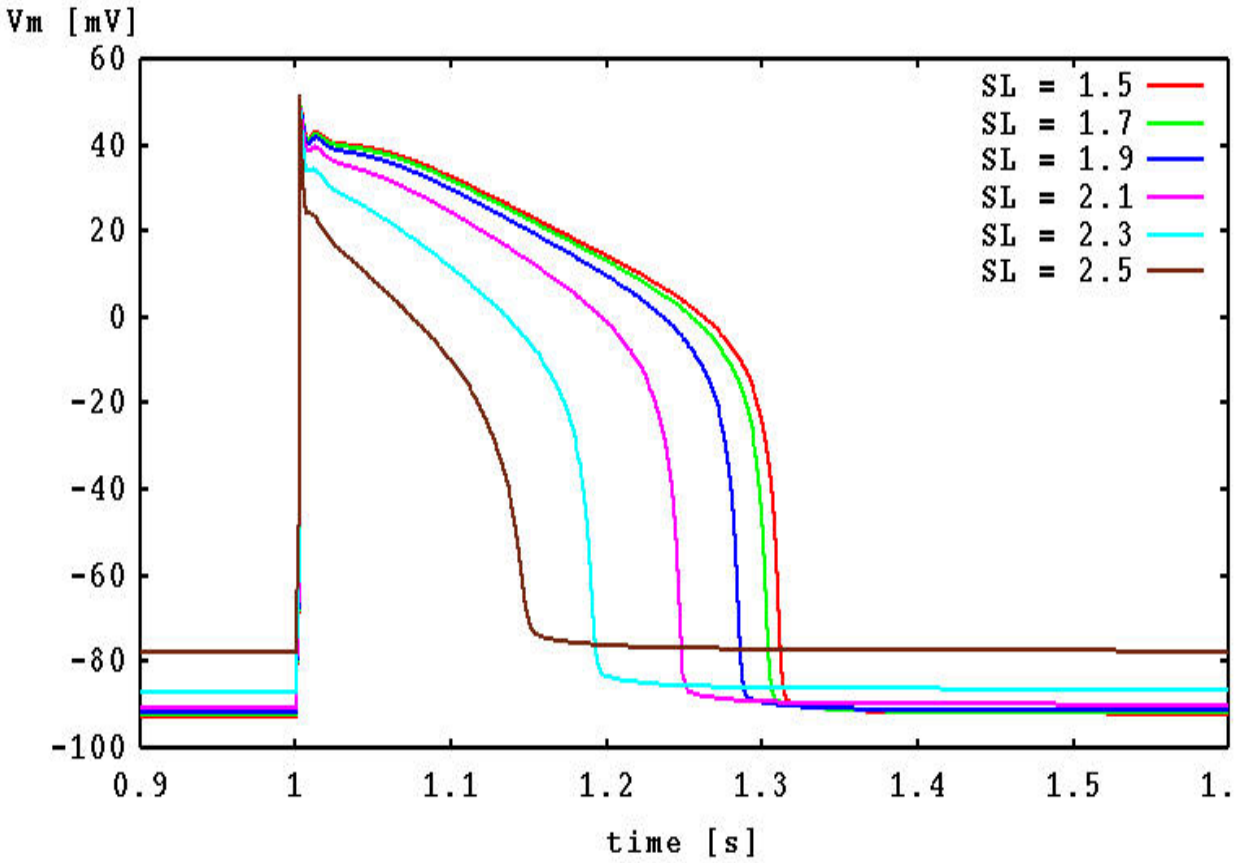



Results of simulations for stimulus frequency of 1 Hz

CVRTI

# Prediction of Mechano-Electrical Feedback



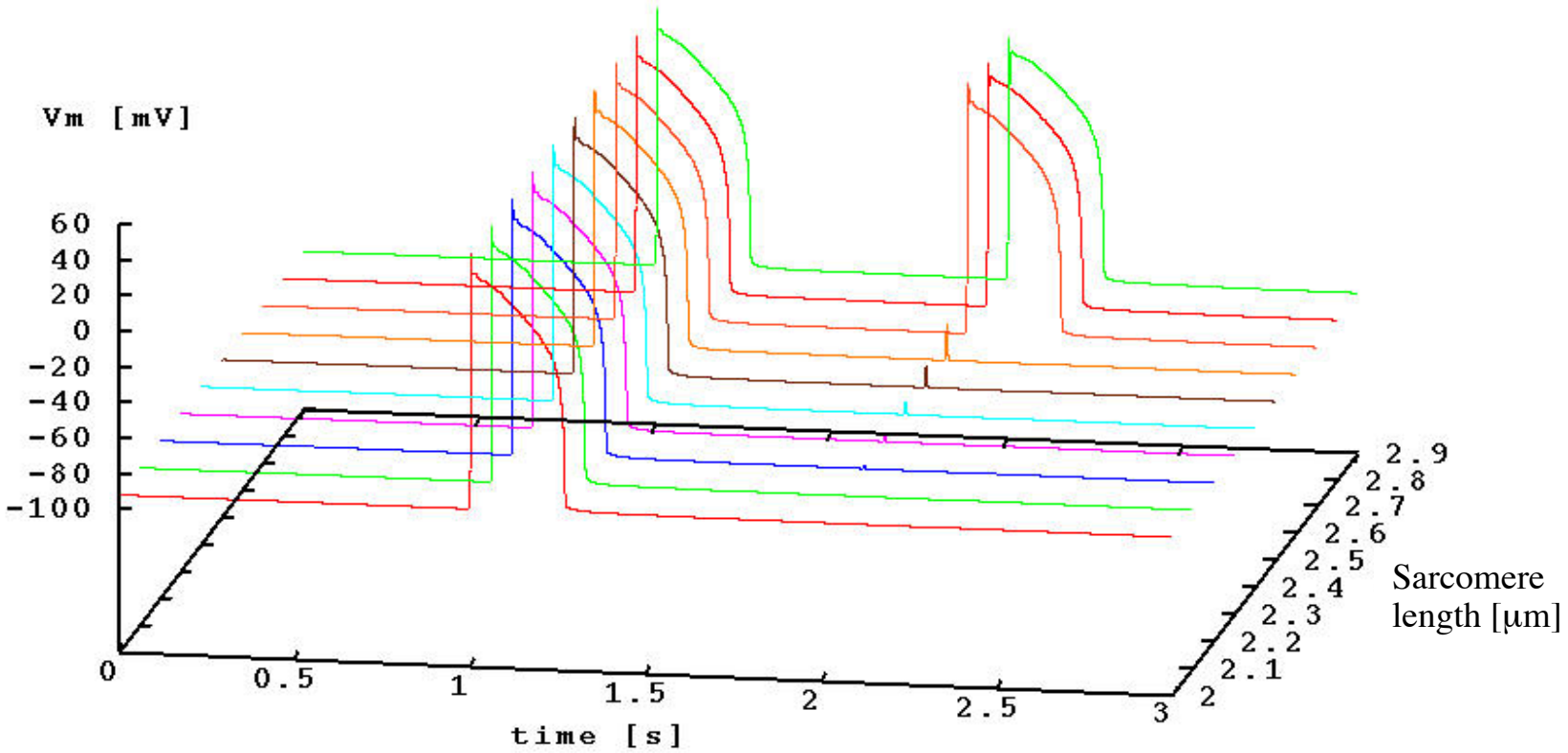

Reduction of action potential duration (APD) by strain

Increase of resting voltage by strain

SL: sarcomere length

CVRTI

# Prediction: Triggering of Action Potential by Strain



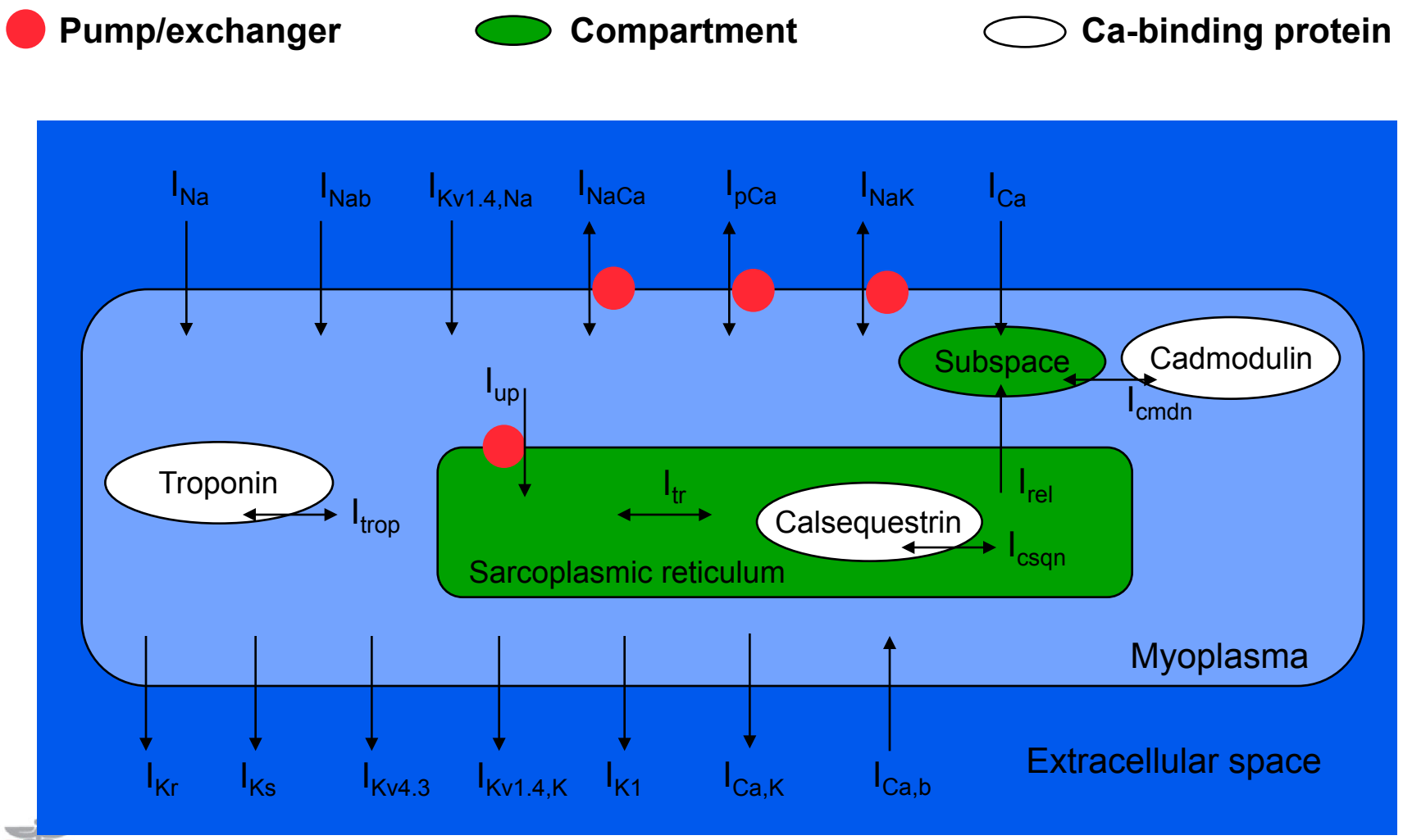

t=1 s: Electrical stimulus

t=2 s: Strain for 5 ms

Triggering of action potential for SL>2.7 μm

CVRTI

# Iyer-Mazhari-Winslow Model 2004




CVRTI

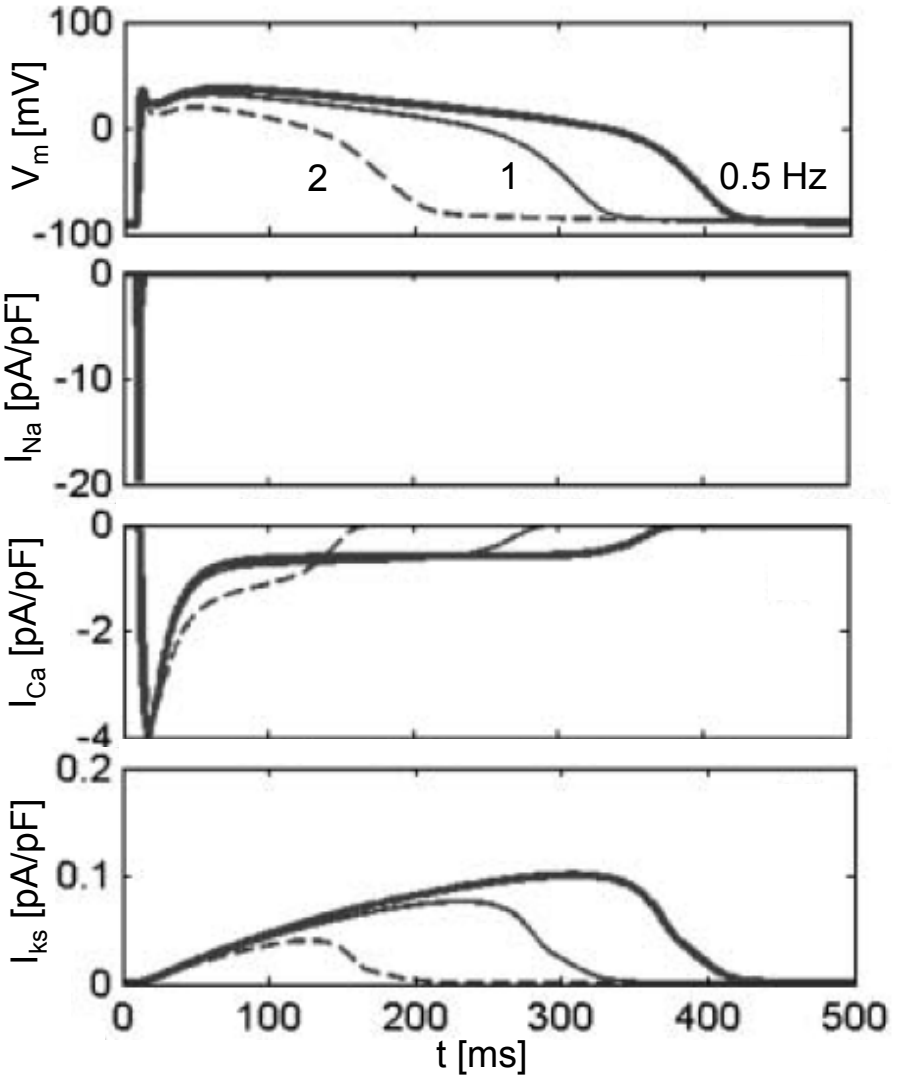
# Reconstructed Voltage and Currents

Transmembrane voltage $V_m$

Fast sodium current $I_{Na}$

L-type calcium current $I_{Ca}$

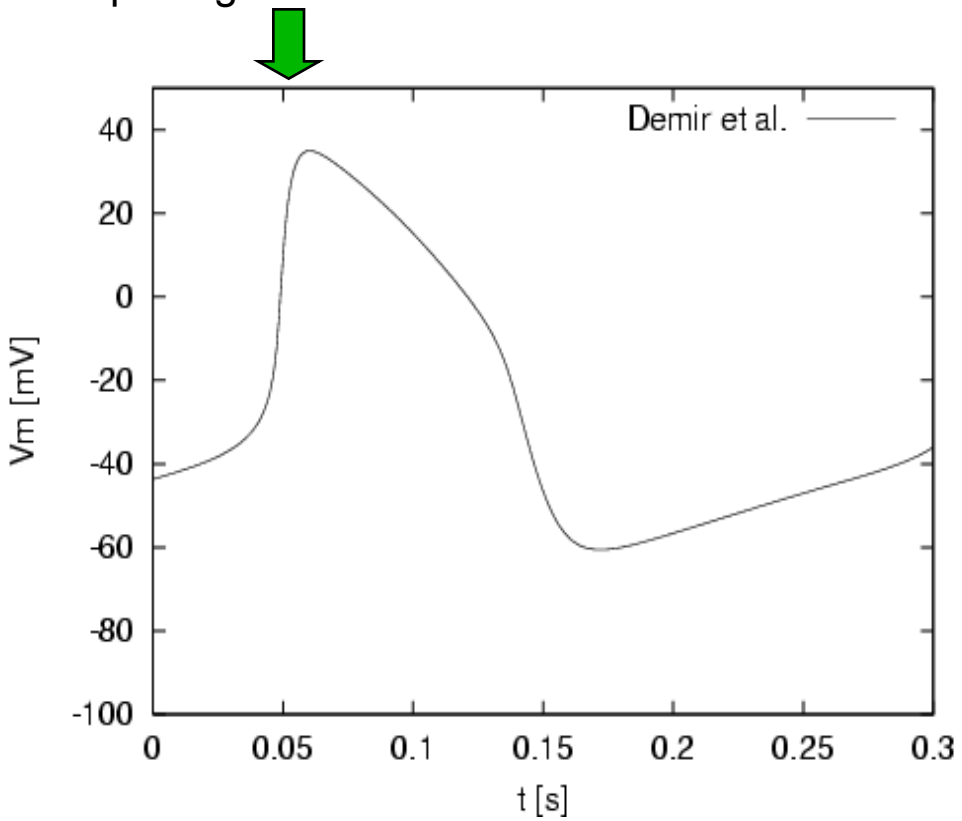
Slow inward rectifying potassium current $I_{Ks}$




CVRTI

# Electrophysiology of Mammalian Sinoatrial Node Cell

Opening of Na channels



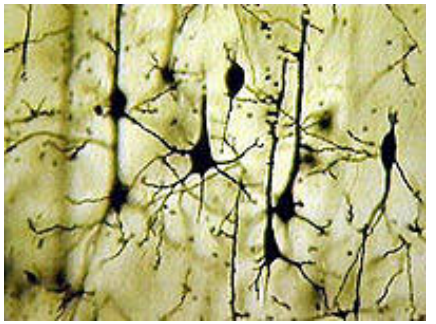

Depolarization starting at “resting voltage” (~-60 mV) leads to upstroke
Autorhythmicity with a frequency of ~3 Hz

CVRTI

# 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

CVRTI

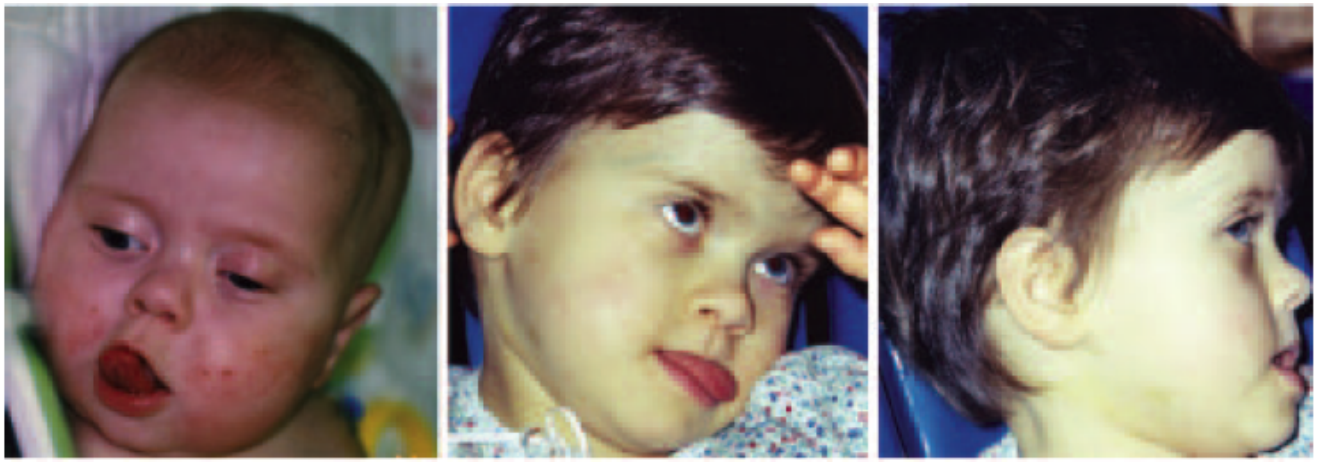
# Group Work

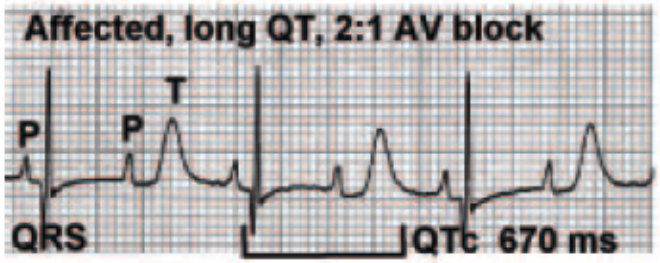
Commonly, models represent behavior of cellular compartments with isochronous properties (0D)

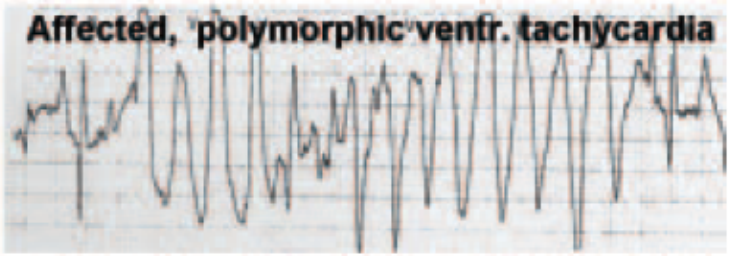
Under which conditions is this description appropriate and when will it fail?

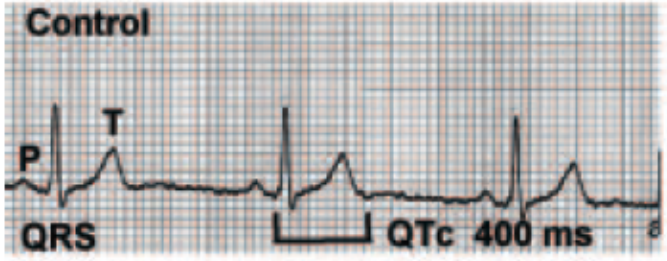
CVRTI

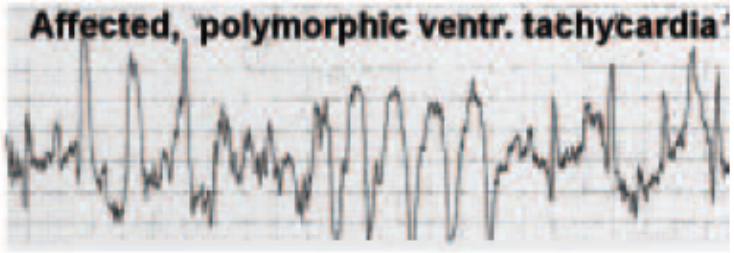
# Timothy Syndrome





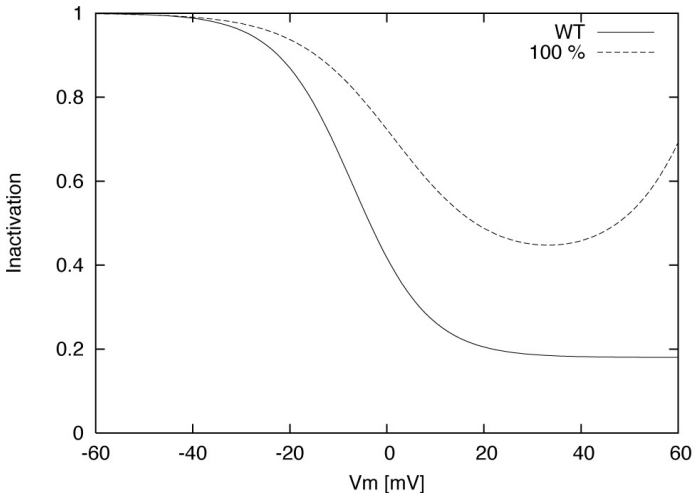




CVRTI

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

# Modeling of Calcium Channel Mutation




## Channel Modeling

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

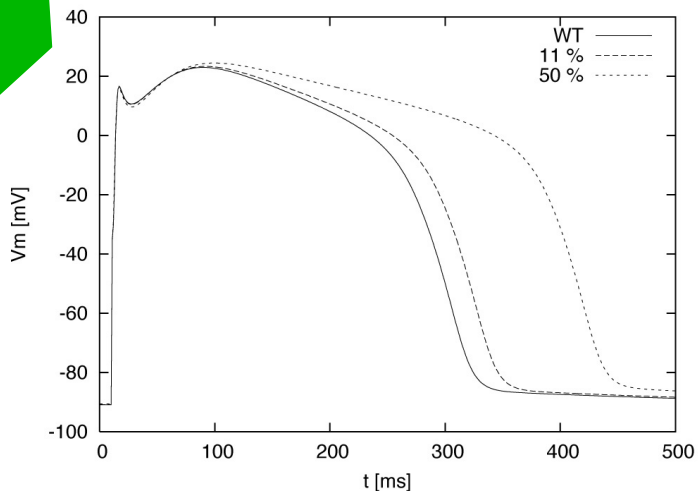
Numerical optimization

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)




CVRTI

# Calcium Channel Defect: Timothy Syndrome

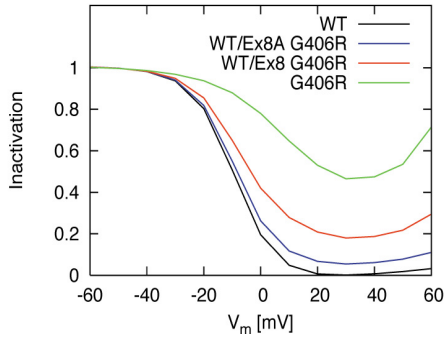
Significant reduction of voltage-dependent inactivation of L-type calcium channels ($Ca_v$ 1.2)

**Characterization with**

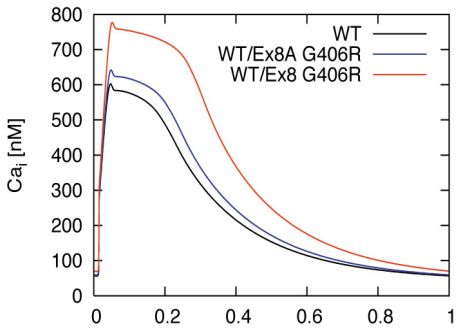
- electrophysiological studies in oocytes with normal (WT) and G406R $Ca_v$ 1.2
- Prolonged QT time (LQT) in patient ECGs

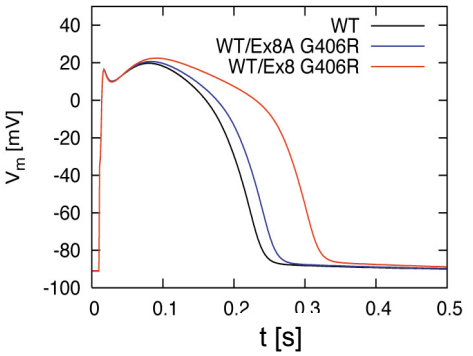
Prediction of cellular behavior with electrophysiological model of WT and G406R $Ca_v$ 1.2

Ion channel




Ventricular myocyte

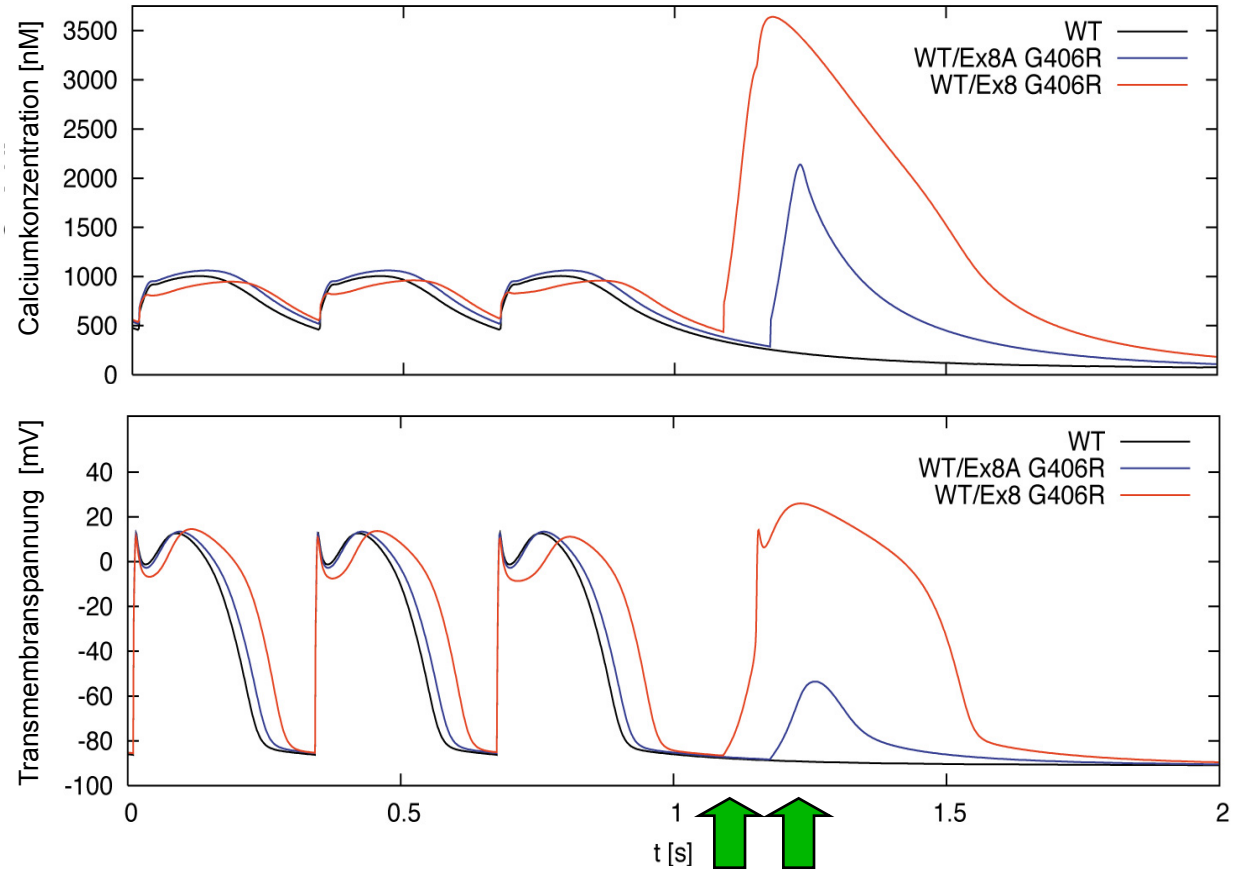



CVRTI

# Timothy Syndrome: Increased Risk Of Arrhythmia

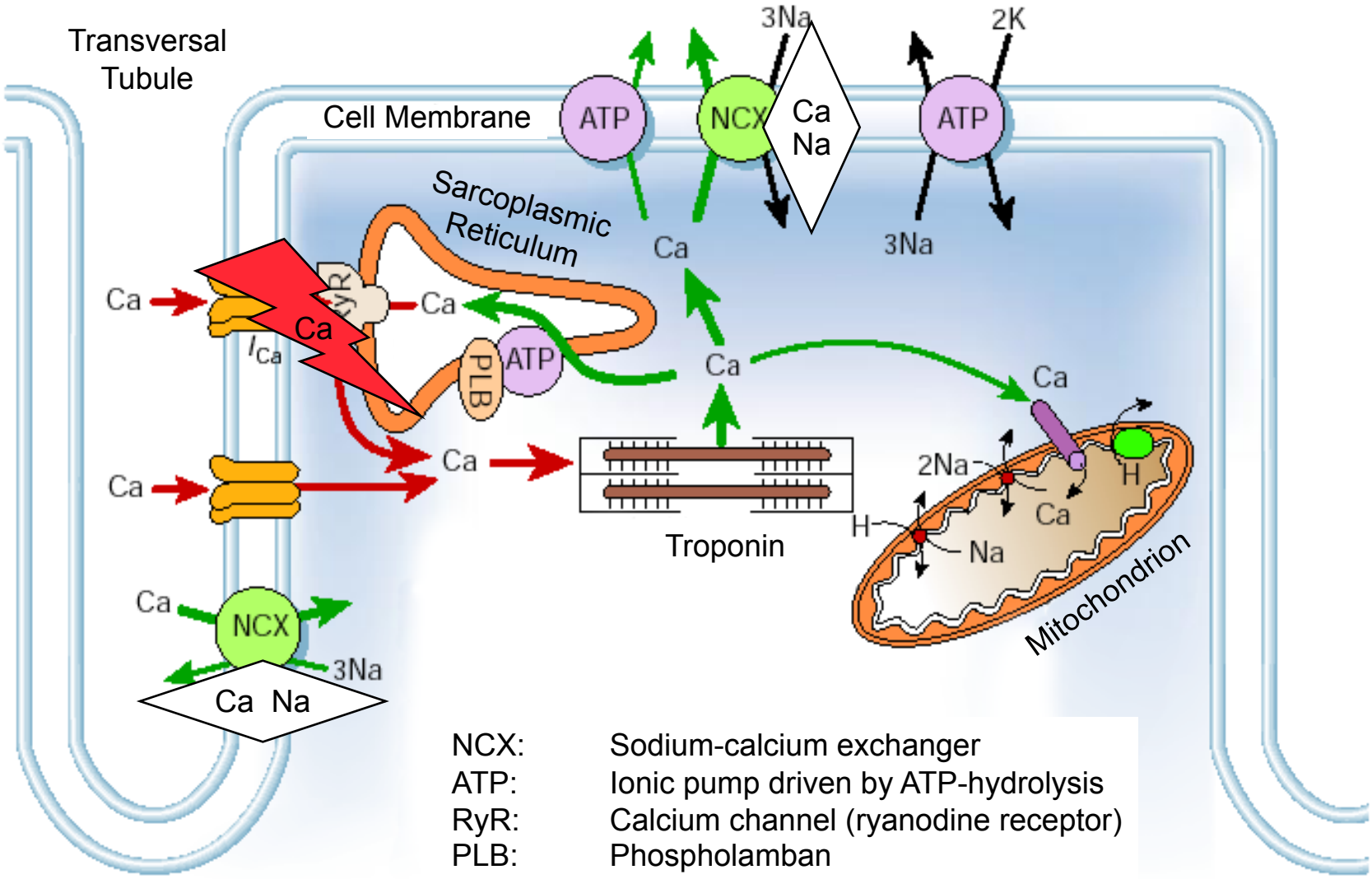
Protocol: Stimulus frequency of 3 Hz, pause




Spontaneous opening of sarcoplasmic release channel leads to delayed afterdepolarization!

CVRTI

# 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

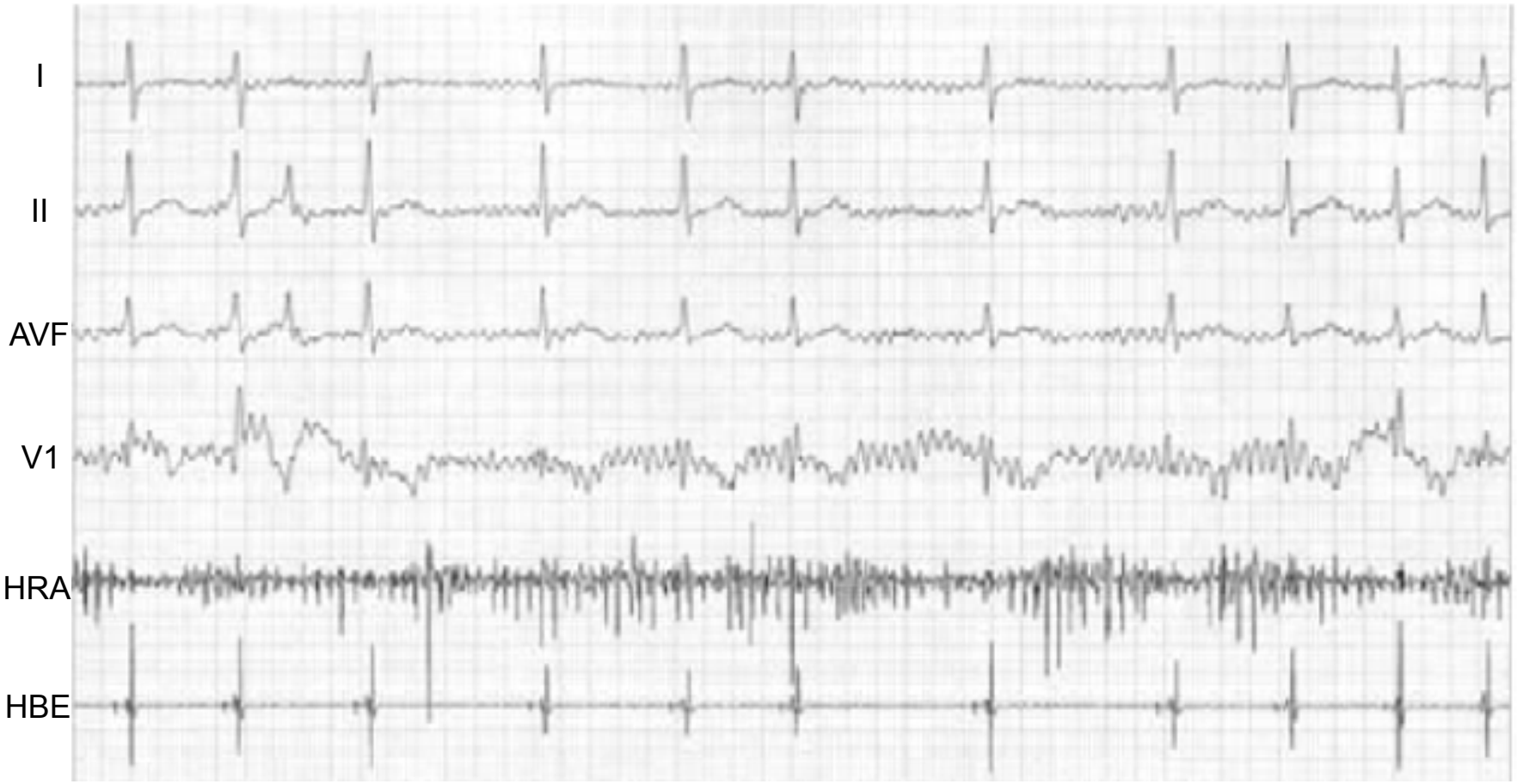

**Mutations**

- **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)

* Location of Mutation S4: Voltage sensing subunit

CVRTI

# Patient ECGs: Atrial Fibrillation

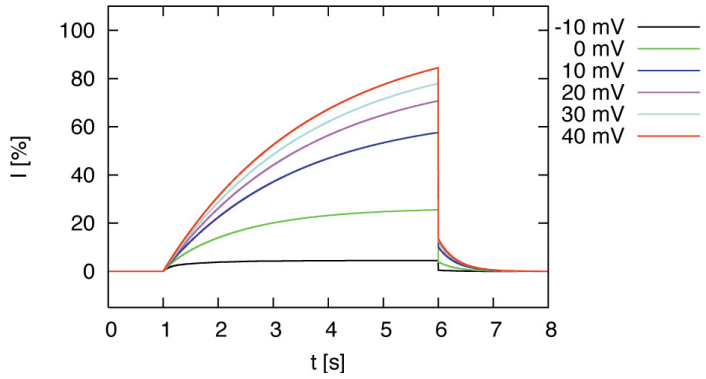



I, II, AVF, V1: Body surface leads HRA: High right atrium HBE: His-Bundle ECG

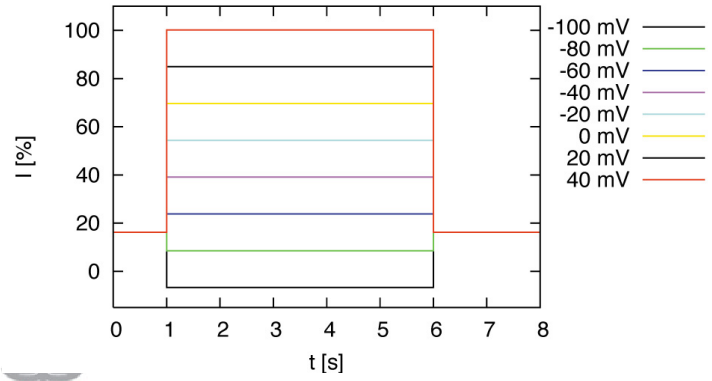
CVRTI

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

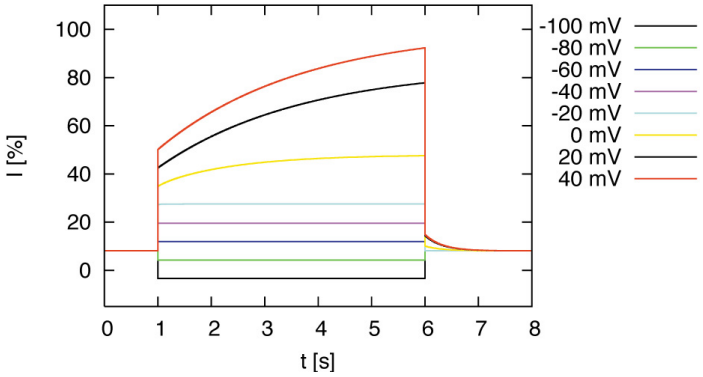
WT KCNQ1 + KCNE1




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




50 % WT / 50 % mutation




CVRTI

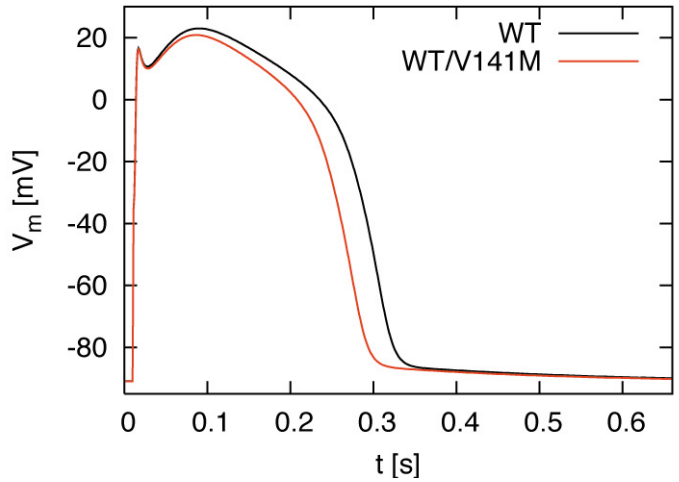
# Prediction of Ventricular and Atrial Myocyte Behavior

**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)

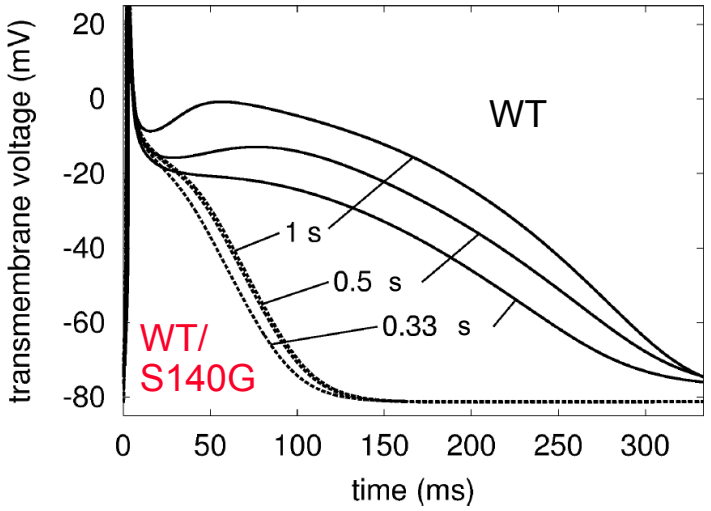



**Human atrial myocyte at 1, 2, and 3 Hz**

Modified Courtemanche-Ramirez-Nattel model

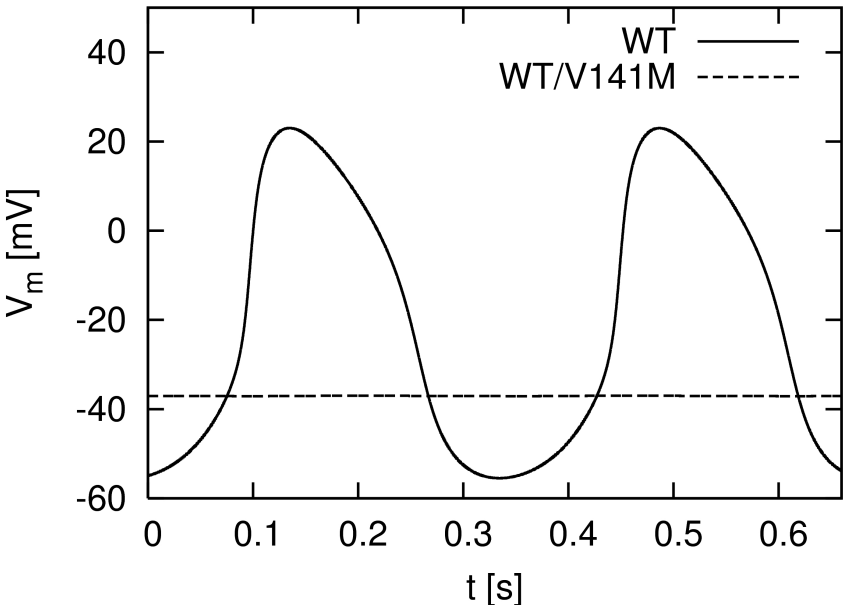
APD ↓↓ - facilitates atrial fibrillation

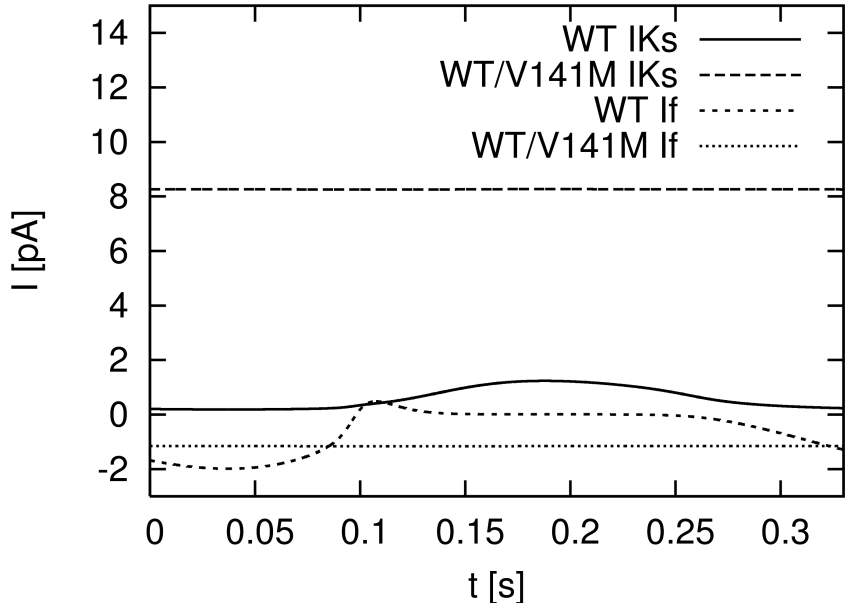
(Seemann et al, Proc. CinC, 2004)




CVRTI

# Prediction of Sinus Node Behavior




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

CVRTI

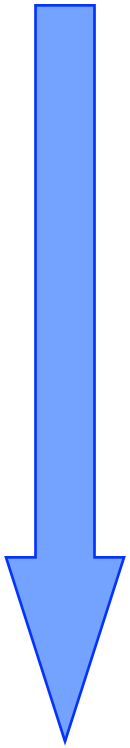
# Group Work

Imagine you are responsible for treatment of a Short QT patient.

What type of drug and/or implant could be helpful?

How would you apply modeling to support your decision?

# Summary



- Modeling of Cardiac Myocytes
  - Background
  - Examples
- Impact of Ion Channel Mutations on Cellular Electrophysiology
  - Timothy Syndrome
  - Short QT

CVRTI