



IBM

*Combination in vitro and in silico  
methodology for risk assessment  
of Long QT type 1 patients*

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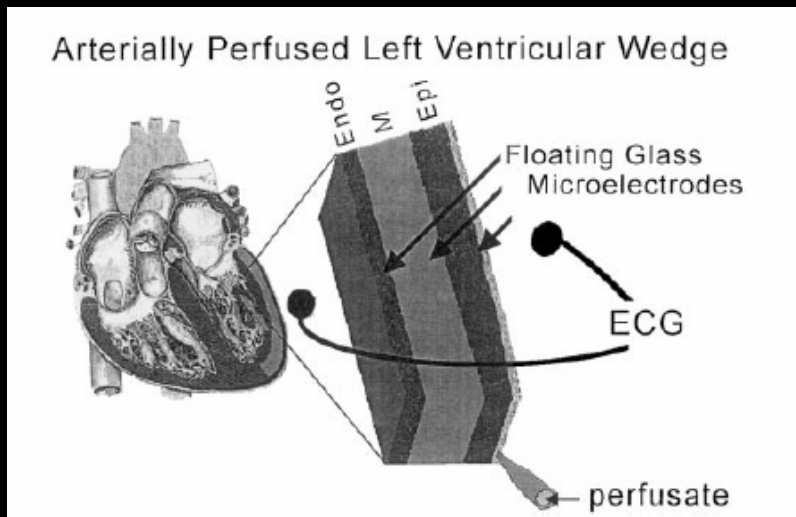
**Coeli M.B. Lopes, Arthur J. Moss**

**School of Medicine and Dentistry  
University of Rochester**

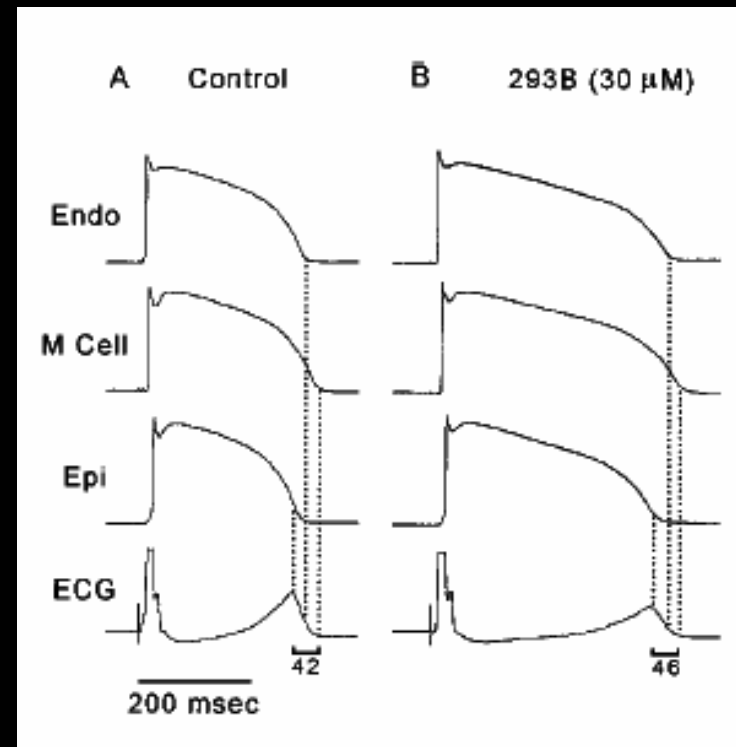
# Motivation-

- Visit by Dr. Arthur Moss to IBM Research
- U. or Rochester Team provide data on LQT1 mutants
  - Expression system
  - WT and two mutants (A and B)
  - Clinical outcomes
- IBM Team to do "blind" model study
  - Multiscale model of cardiac wedge
  - Predict ECG and QT prolongation effects

# Experimental ventricular wedge preparation



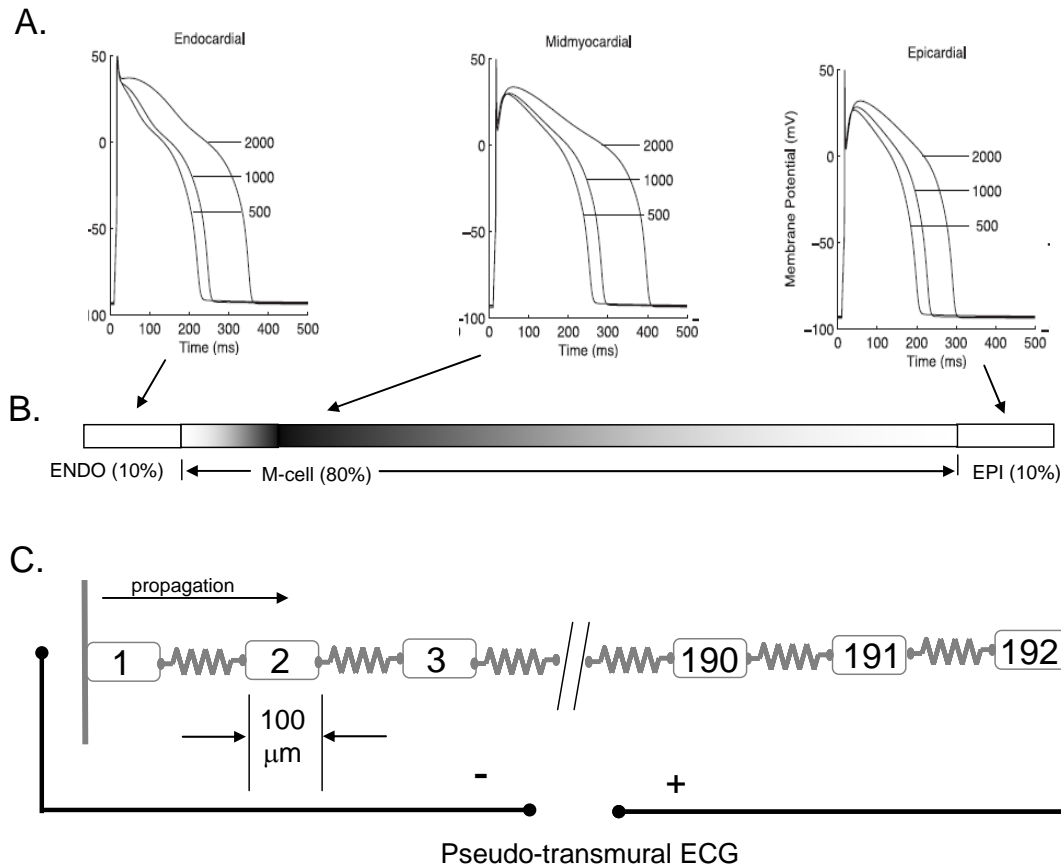
Yan, Shimizu, and Antzelevitch, 1998



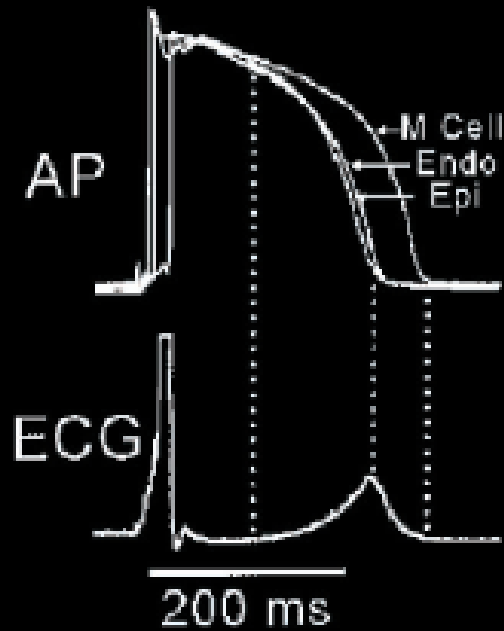
Shimizu and Antzelevitch, 1998

# Methods - Construction of 1-D Cable

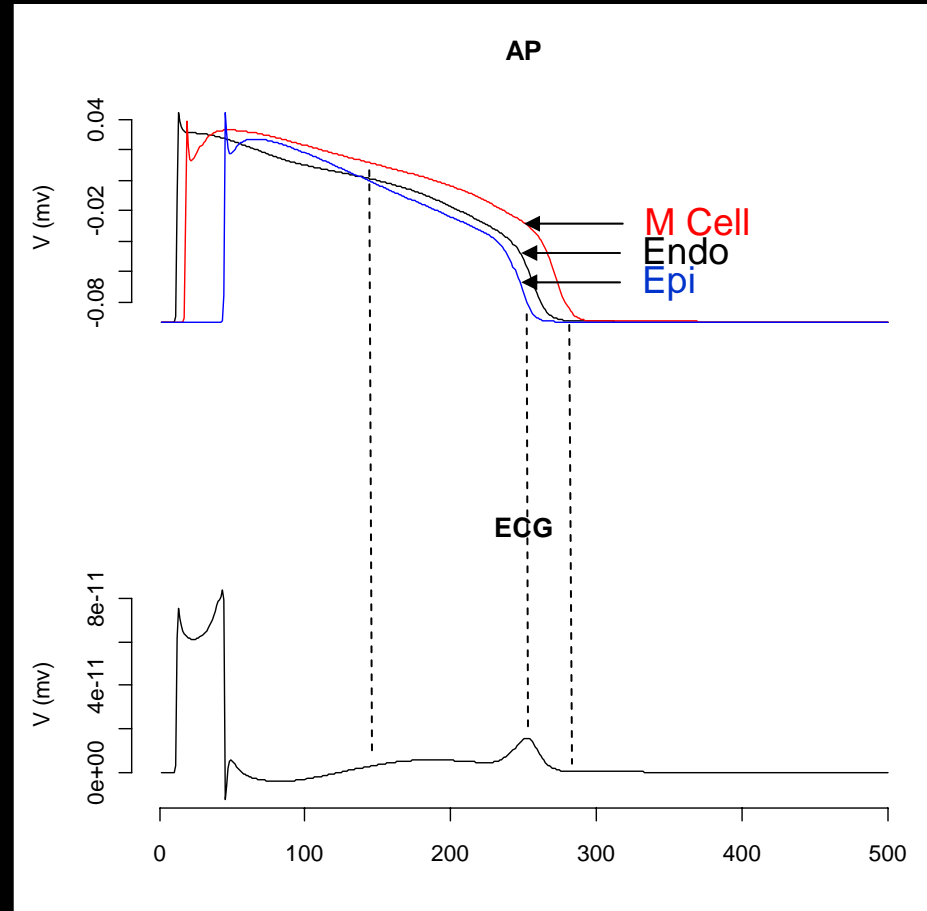
## Canine cell model from Flaim, Giles & McCulloch



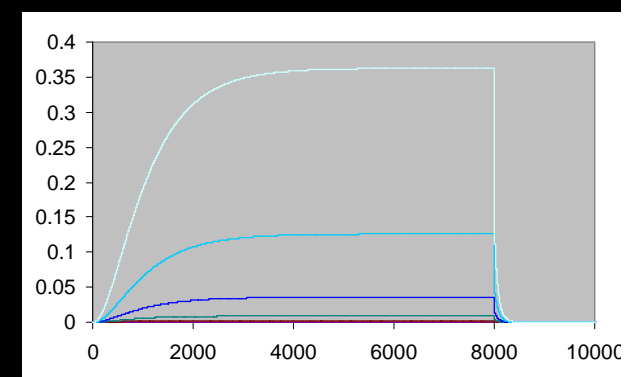
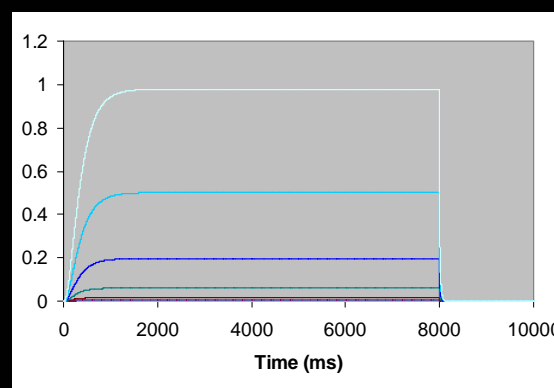
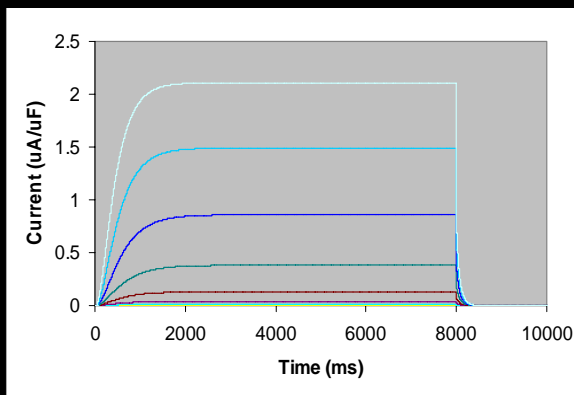
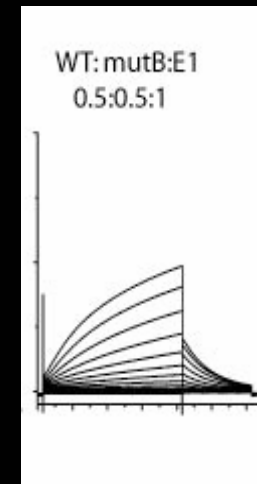
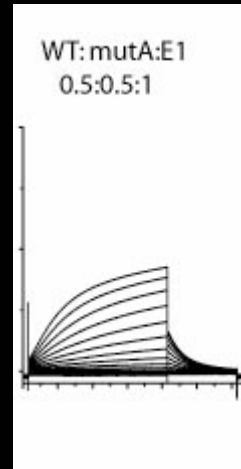
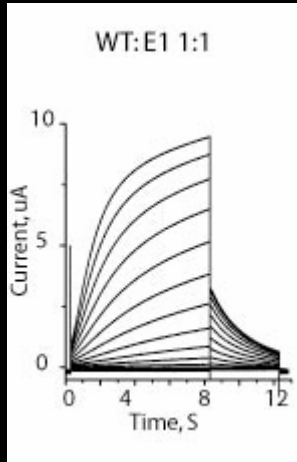
# Sample ECG signals for the WT case



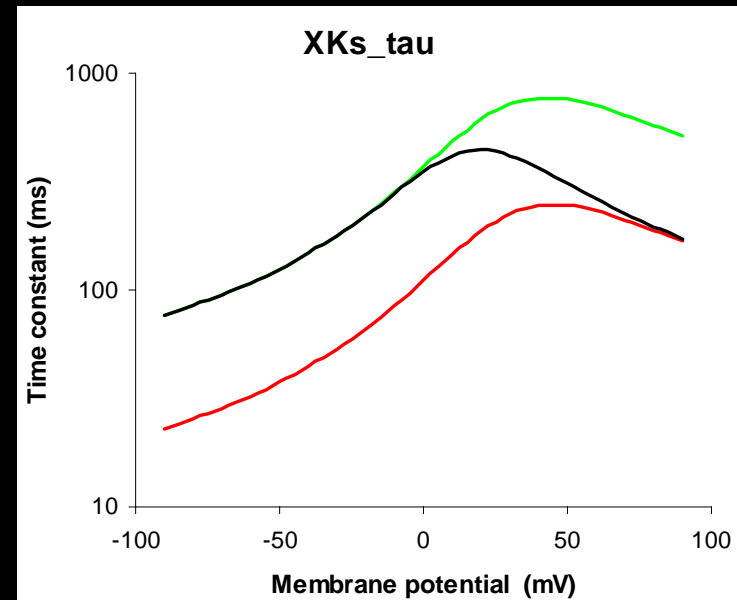
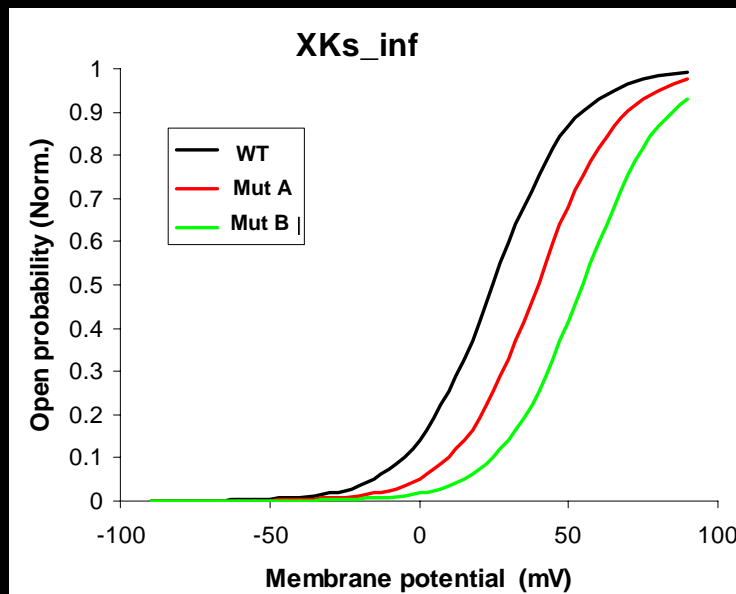
(Yan & Antzelevitch, 1998)



# WT vs. Mut A vs. Mut B versions of $I_{Ks}$

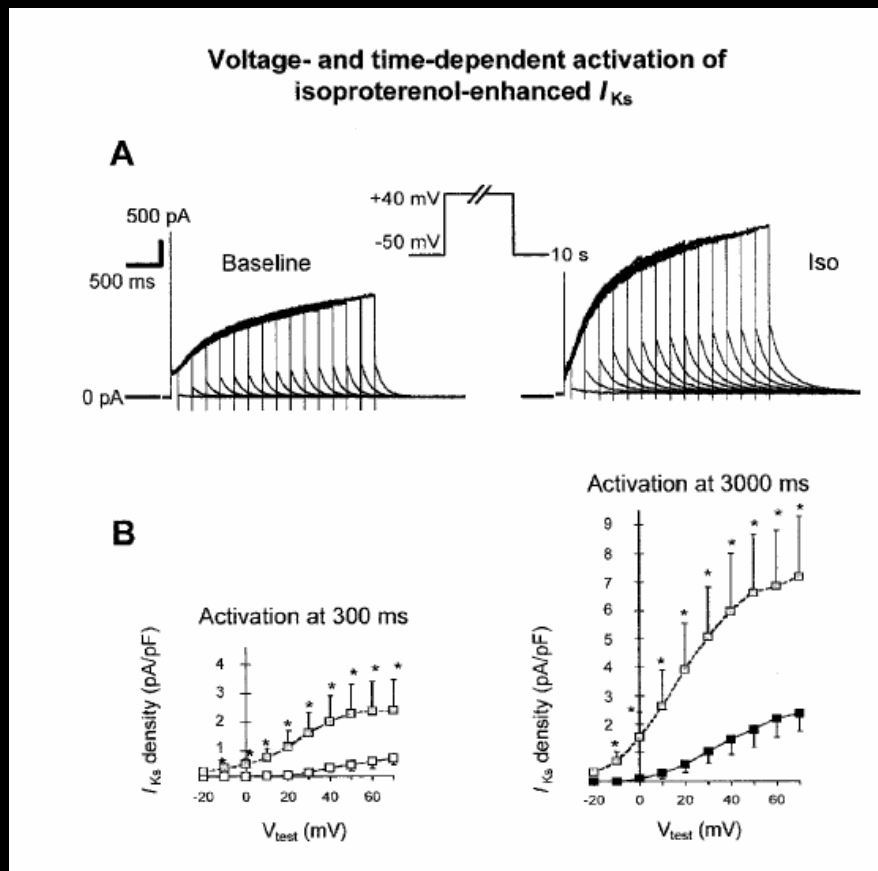


# Modeled gating variables as function of voltage for WT, Mut A and Mut B



$$\begin{aligned}
 I_{Ks} &= G_{Ks} \cdot \text{pow}(x_{Ks}, 2) \cdot (V - E_{Ks}) \\
 x_{Ks\_inf} &= 1 / (1 + \exp(-(V - 24.7) / 13.6)) \\
 a_1 &= 7.19e-5 \cdot (V - 10.) / (1 - \exp(-0.148 \cdot (V - 10.))) \\
 a_2 &= 1.31e-4 \cdot (V - 10.) / (\exp(0.0687 \cdot (V - 10.)) - 1.) \\
 \tau_{x_{Ks}} &= 1 / (a_1 + a_2)
 \end{aligned}$$

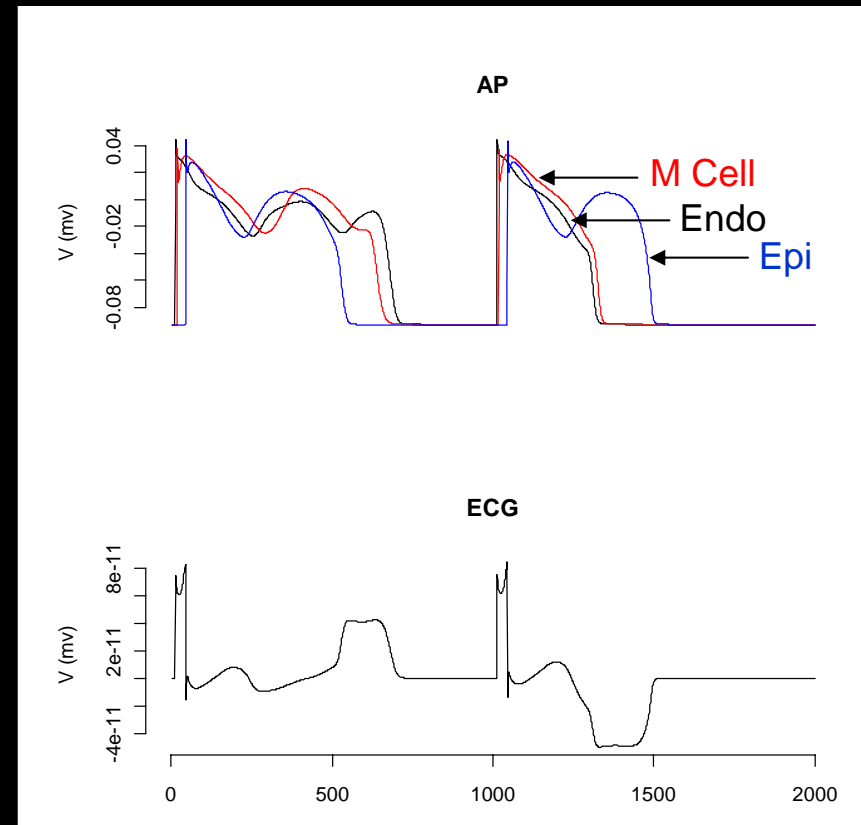
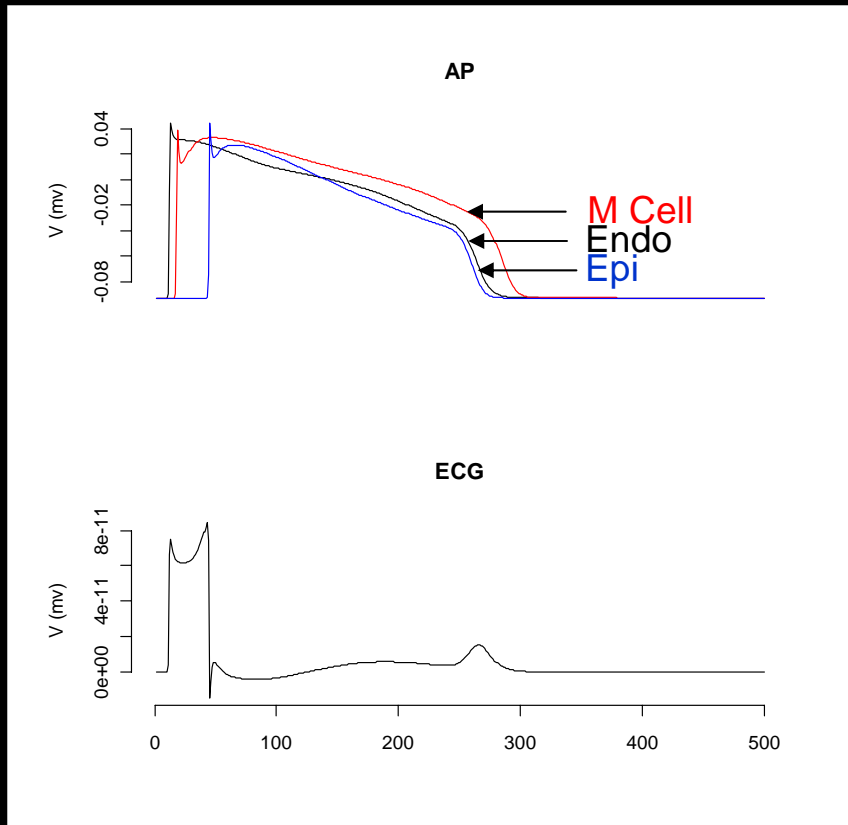
# Needed to model some $\beta$ -adrenergic effects



- GKs increased 4x
- xKs\_inf is shifted 30 mV to left
- GNaL increased 4x

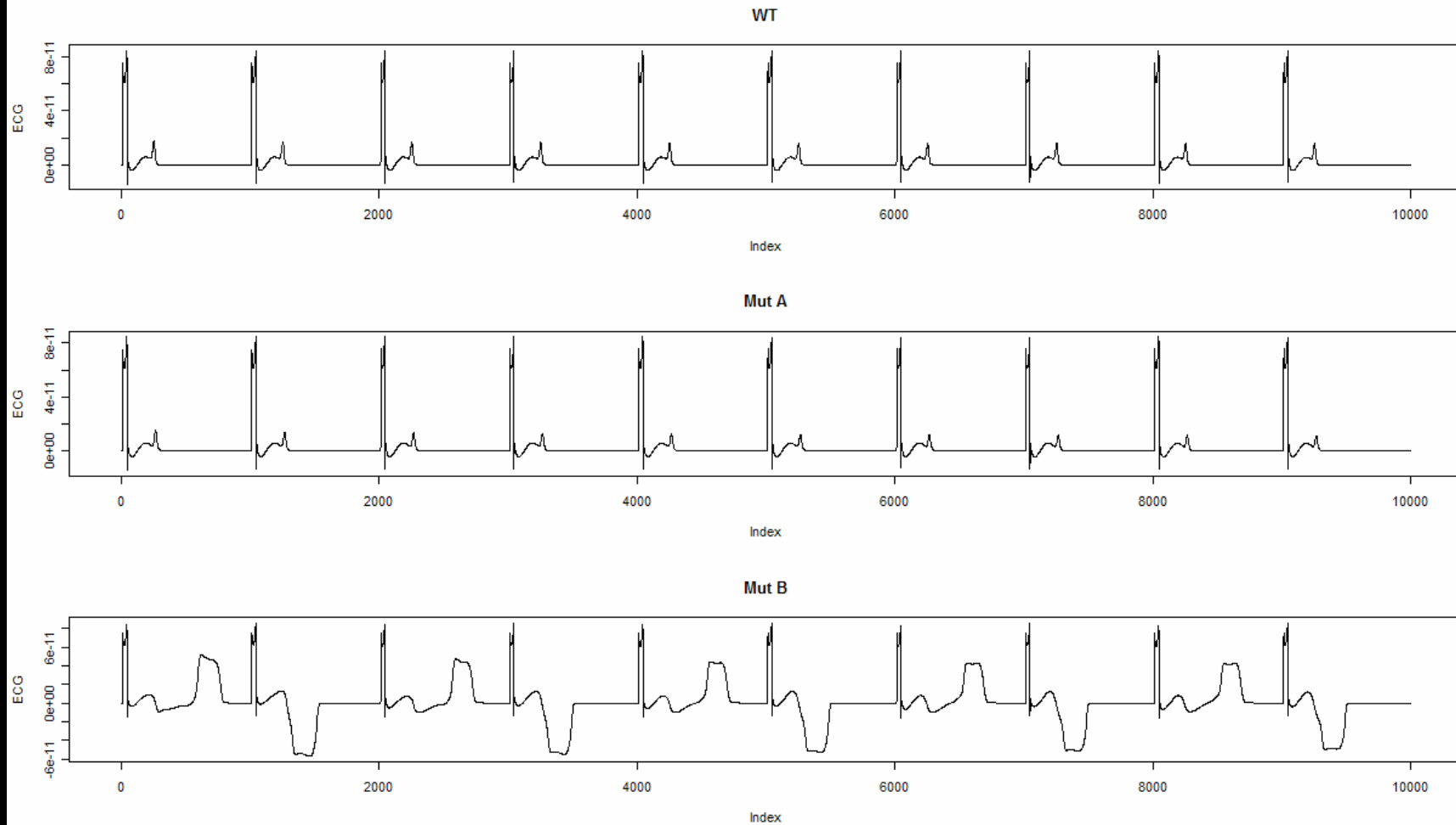
**Probing the Contribution of IKs to Canine Ventricular Repolarization: Key Role for  $\beta$ -Adrenergic Receptor Stimulation**  
 Paul G.A. Volders, Milan Stengl, Jurren M. van Opstal, Uwe Gerlach, Roel L.H.M.G. Spätjens, Jet D.M. Beekman, Karin R. Sipido and Marc A. Vos  
*Circulation* 2003;107:2753-2760; originally published online May 19, 2003;

# Transmural ECG of Mut A and Mut B



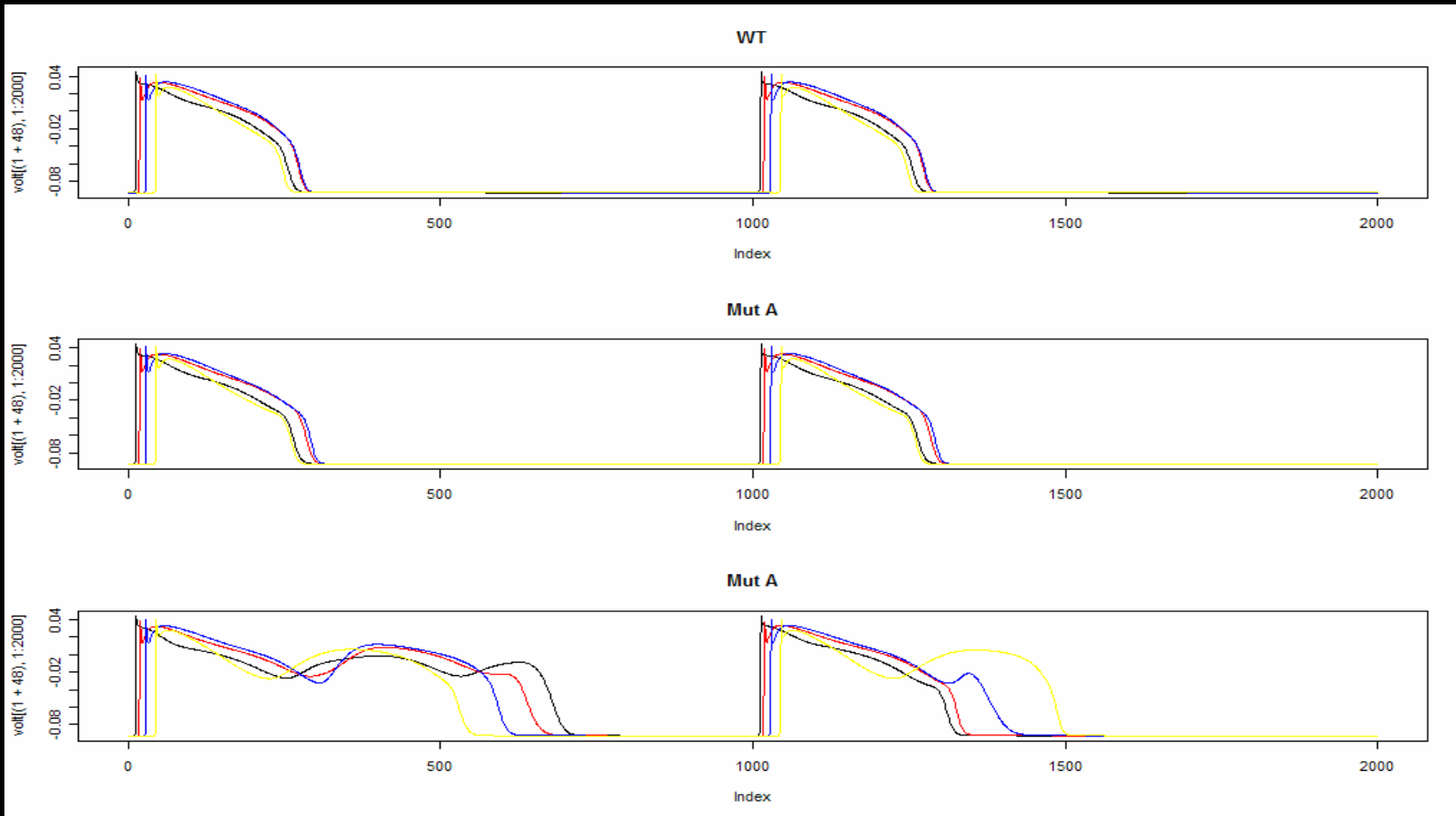
QT interval: 224ms(WT) 236ms(Mut A)

# ECG of WT, Mut A, and Mut



QT interval: 224ms(WT) 236ms(Mut A)

# AP shapes in WT, Mut A, Mut B



Black: Cell 1(100%); Red: Cell 38(80%); Blue: Cell 100(45%), Yellow: Cell 190(1%)

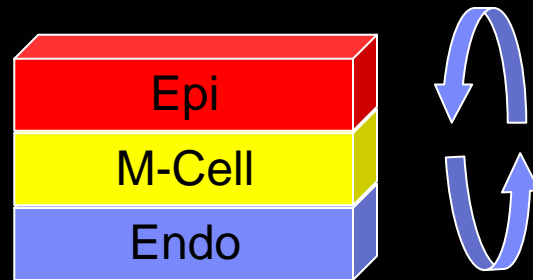
# Summary

- Physiological data from WT, Mut A and Mut B provided by U. of Rochester
- Incorporated into 1-D cable of canine wedge with FGM w/ added  $\beta$ -adrenergic effects
- Predicted Mut A has mild QT prolongation
- Predicted Mut B produce pronounced QT prolongation and T-wave alternans
- Qualitative match to clinical outcomes

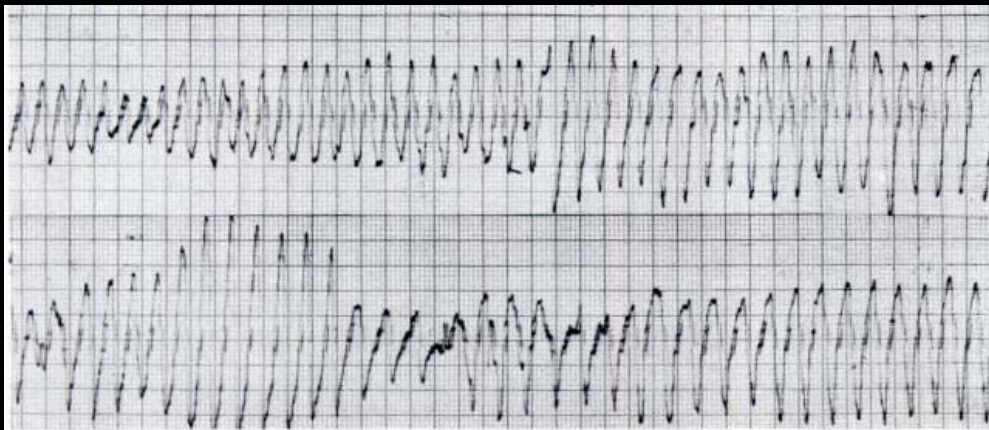
# Future Directions

- For 17 LQT1 mutations (clinical time dependent information > 10 patients for each)
- Refine 1-D model and  $\beta$ -effects
- 3-D Wedge
  - Blue Gene Supercomputer
  - Torsade de pointe ?
- Whole Heart ECG
- Real-time visualization and interaction with simulation

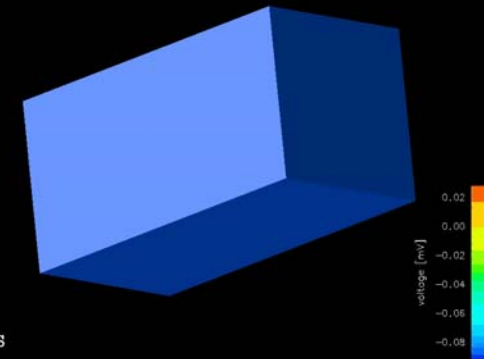
# Next step: Move to 3-D wedge model



**Torsade de pointe**



Carruth and Silverman, 1980



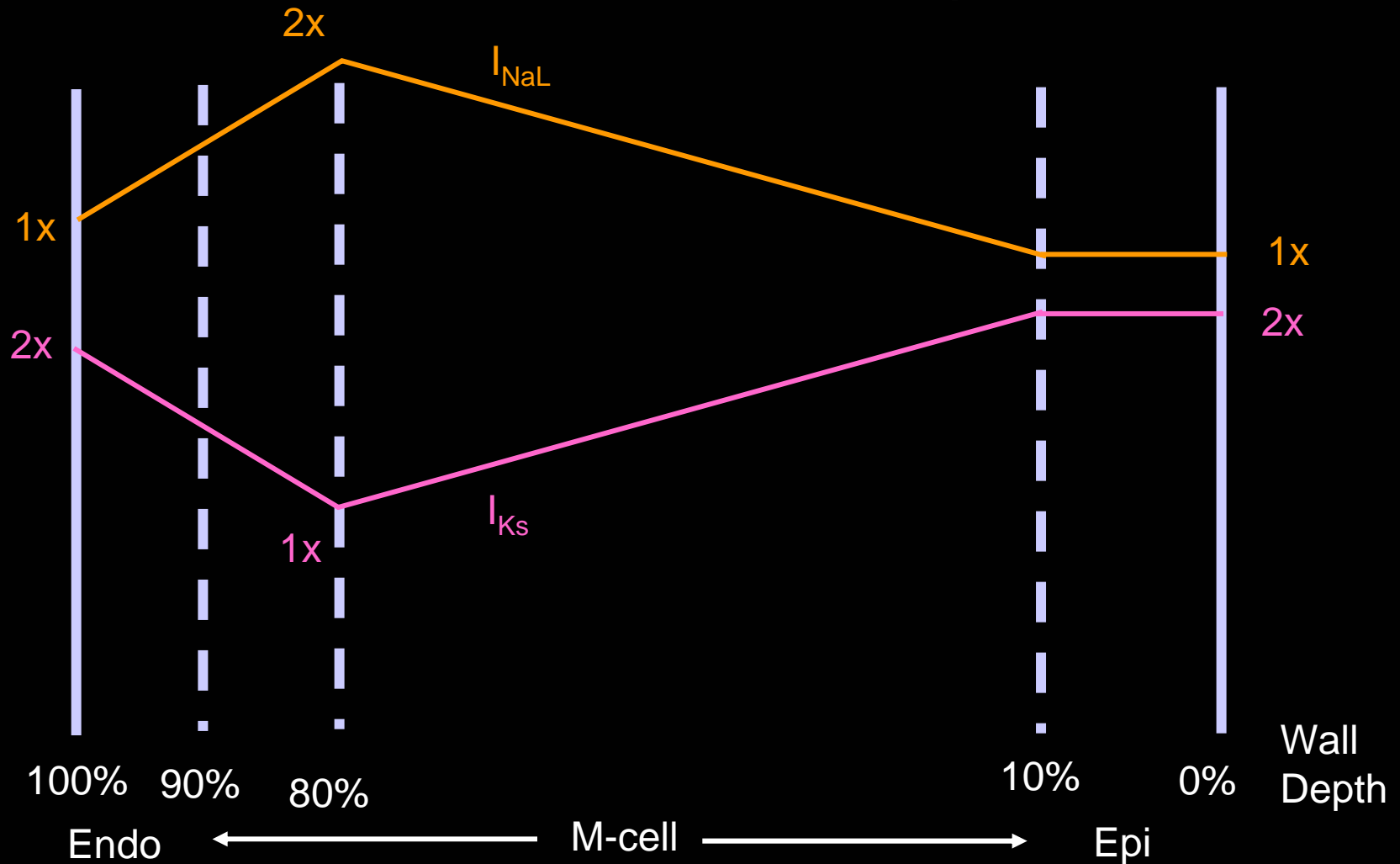
- 50x50x100 elements (=250 K)
- Slow conduction velocity
- Realistic size = 32 M elements



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# Schematic of membrane current profiles



# Sample APD distribution for the WT case

