CORNELL UNIVERSITY

Joan and Sanford I. Weill Medical College

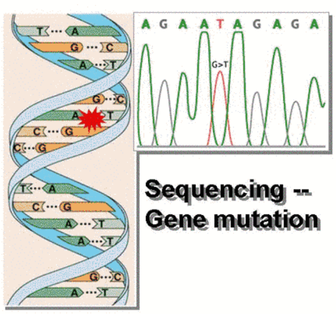
Math instead of mice

Genetics and arrhythmia mechanisms: Insights from theoretical models

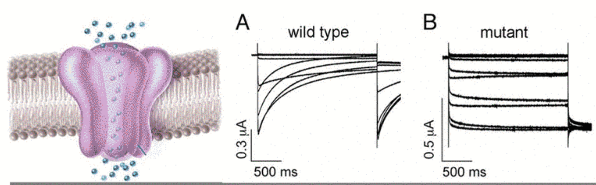
Department of Physiology and Biophysics

icb institute for computational biomedicine

Weill Medical College of Cornell University



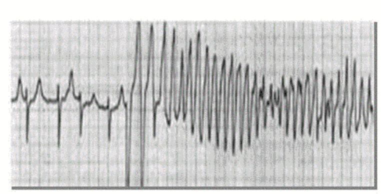
Sequencing -- Gene mutation



Channel recording -- Abnormal kinetics

How do mutations propagate as emergent dynamics to disrupt protein, cell and tissue behavior?

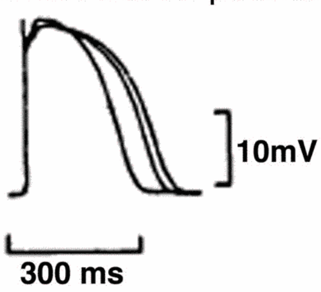
?



Abnormal ECG

Why math instead of mice?

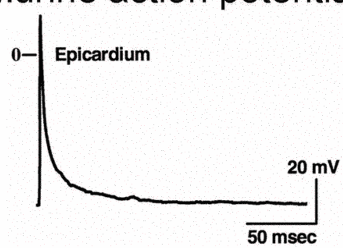
Human action potential



Franz, M.R. et al. J Clin Invest. 1988; 82(3): 972–979

QuickTime™ and a TIFF (Uncompressed) decompressor are needed to see this picture.

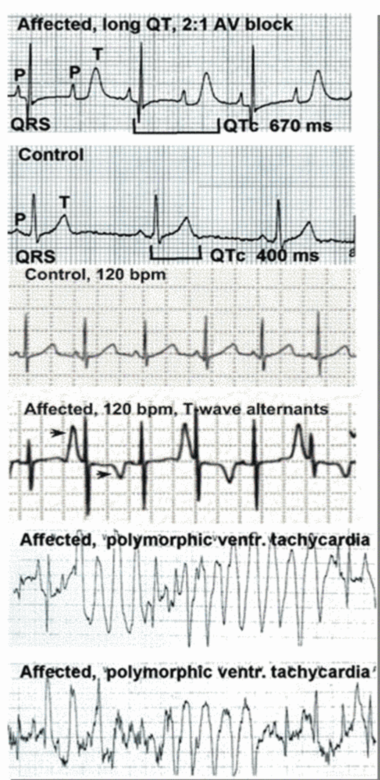
Murine action potential



≈300 grams
60-80 bpm

≈0.3 grams
500 bpm

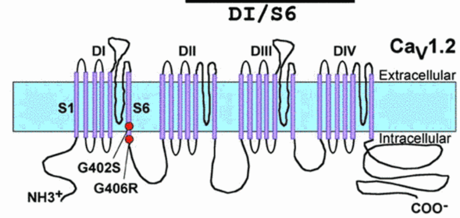
Anumonwo et al. Circ Res. 2001 Aug 17;89(4):329-35



Timothy Syndrome

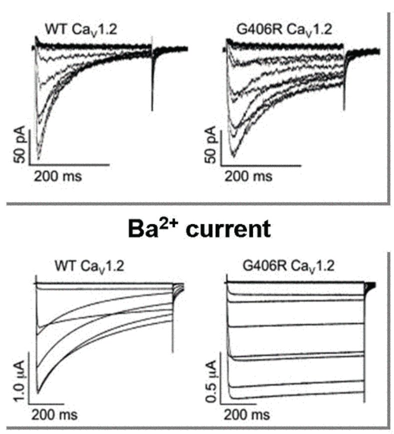
$Ca_V1.2$ mutations			S				R		
Human $Ca_V1.2$	V	L	**G**	V	L	S	**G**	E	F
Human $Ca_V1.1$	V	L	**G**	V	L	S	**G**	E	F
Human $Ca_V1.3$	V	L	**G**	V	L	S	**G**	E	F
Human $Ca_V1.4$	V	L	**G**	V	L	S	**G**	E	F
Human $Ca_V2.1$	V	L	**G**	V	L	S	**G**	E	F
Human $Ca_V2.2$	V	L	**G**	V	L	S	**G**	E	F
Human $Ca_V2.3$	V	L	**G**	V	L	S	**G**	E	F
Rat	V	L	**G**	V	L	S	**G**	E	F
Mouse	V	L	**G**	V	L	S	**G**	E	F
Chicken	V	L	**G**	V	L	S	**G**	E	F
Zebrafish	V	L	**G**	V	L	S	**G**	E	F
Fruitfly	I	L	**G**	V	L	S	**G**	E	F
Worm	V	L	**G**	V	L	S	**G**	E	F

DI/S6

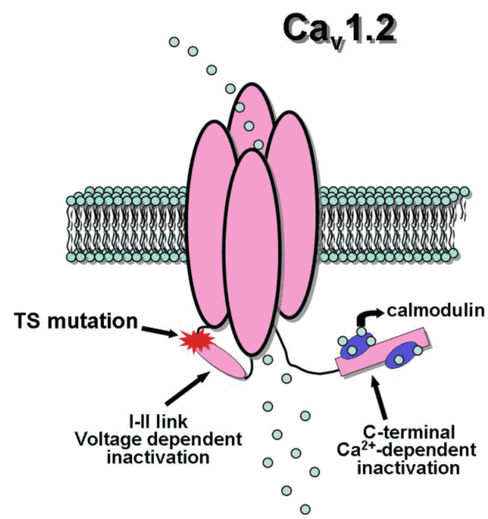


P.N.A.S. 2005 Jun 7;102(23):8089-96
Cell. 2004 Oct 1;119(1):19-31.

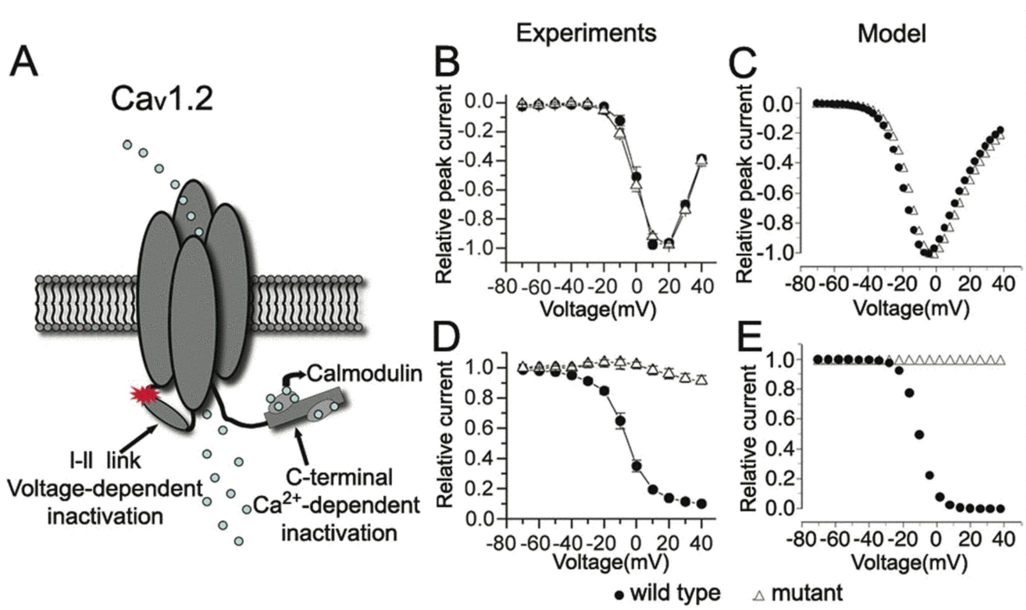
The TS mutation disrupts voltage-dependent inactivation of I_{CaL}



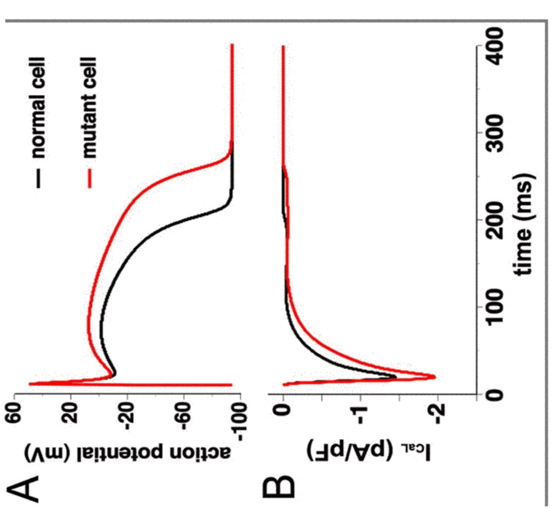
P.N.A.S. 2005 Jun 7;102(23):8089-96
Cell. 2004 Oct 1;119(1):19-31.



The Timothy Syndrome mutation eliminates voltage-dependent inactivation of $Ca_v1.2$

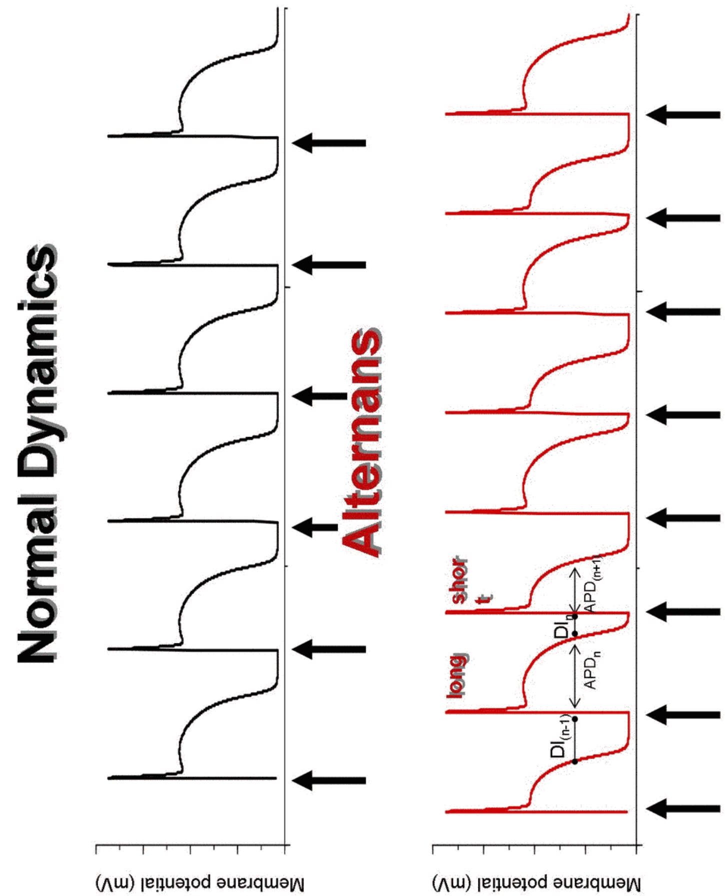


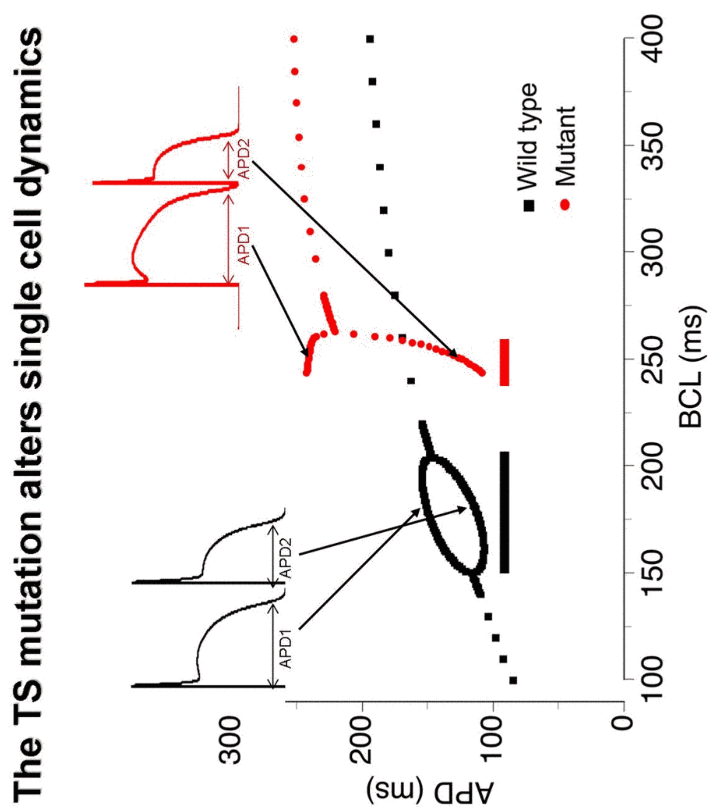
The TS mutation prolongs action potential duration (APD)

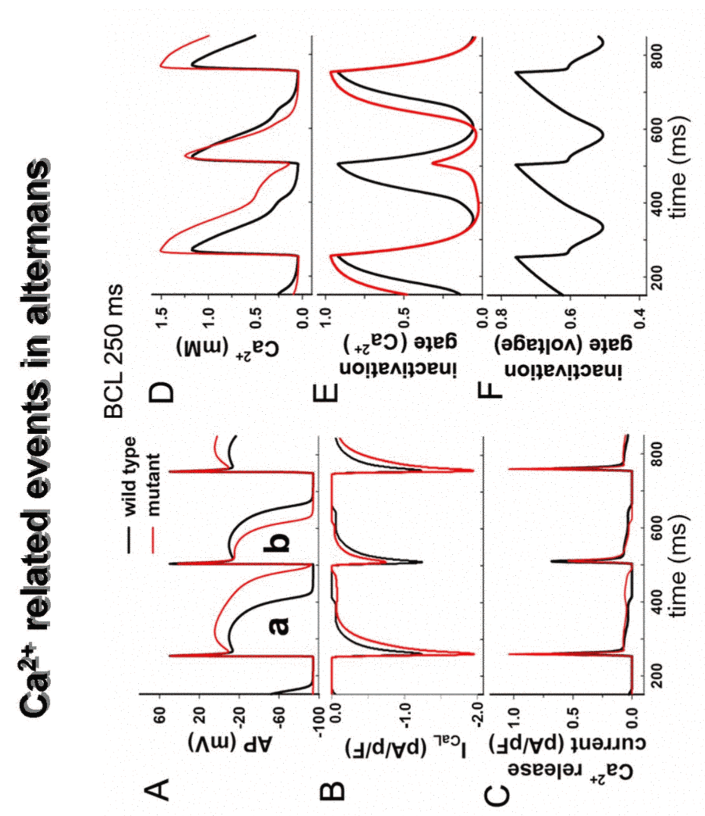


Physiological rate (BCL 500 ms)

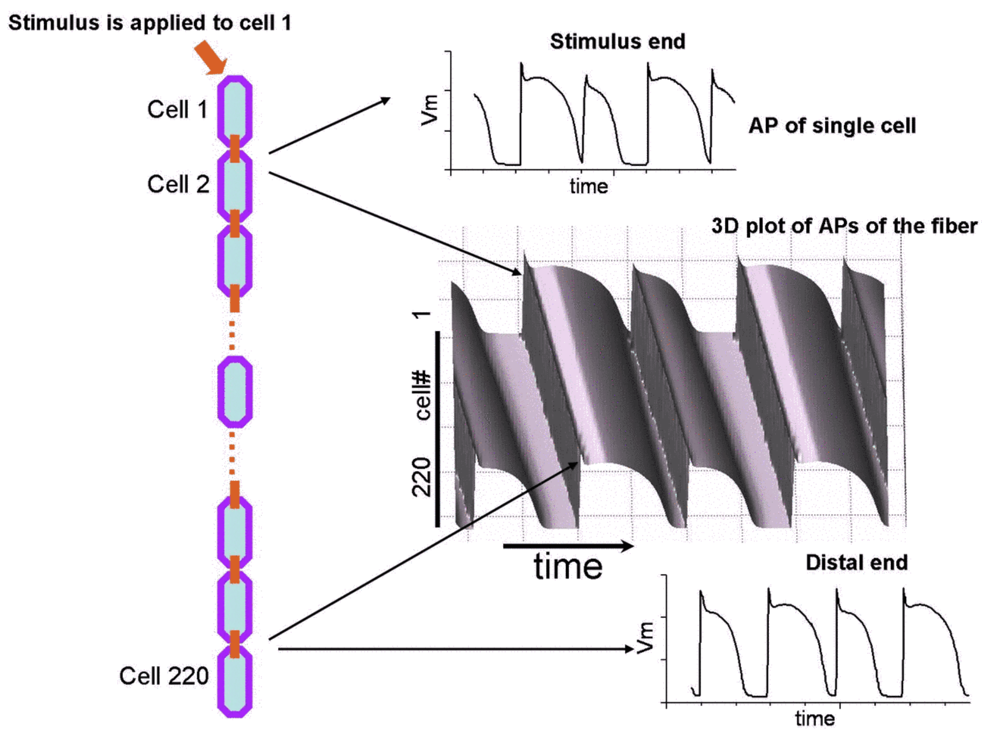
Fox JJ, McHarg JL, Gilmour RF Jr. Am J Physiol Heart Circ Physiol. 2002 Feb;282(2):H516-30.




The TS mutation alters single cell dynamics
APD1
APD2
APD (ms)
300
200
100
0
100
150
200
250
300
350
400
BCL (ms)
Wild type
Mutant


Ca2+ related events in alternans
BCL 250 ms
wild type
mutant
A
AP (mV)
B
ICaL (pA/pF)
C
Ca2+ release current (pA/pF)
D
Ca2+ (mM)
E
inactivation gate (Ca2+)
F
inactivation gate (voltage)
a
b
time (ms)
time (ms)

1-D Cardiac Fiber



The TS mutation shifts the window for discordant alternans ~70 ms

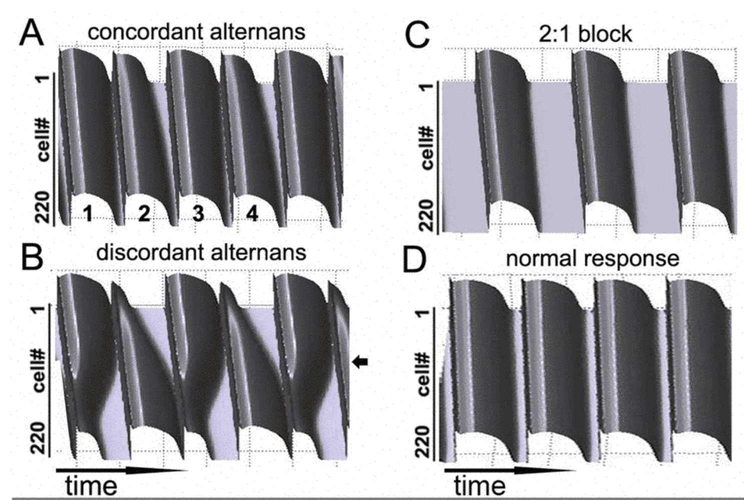
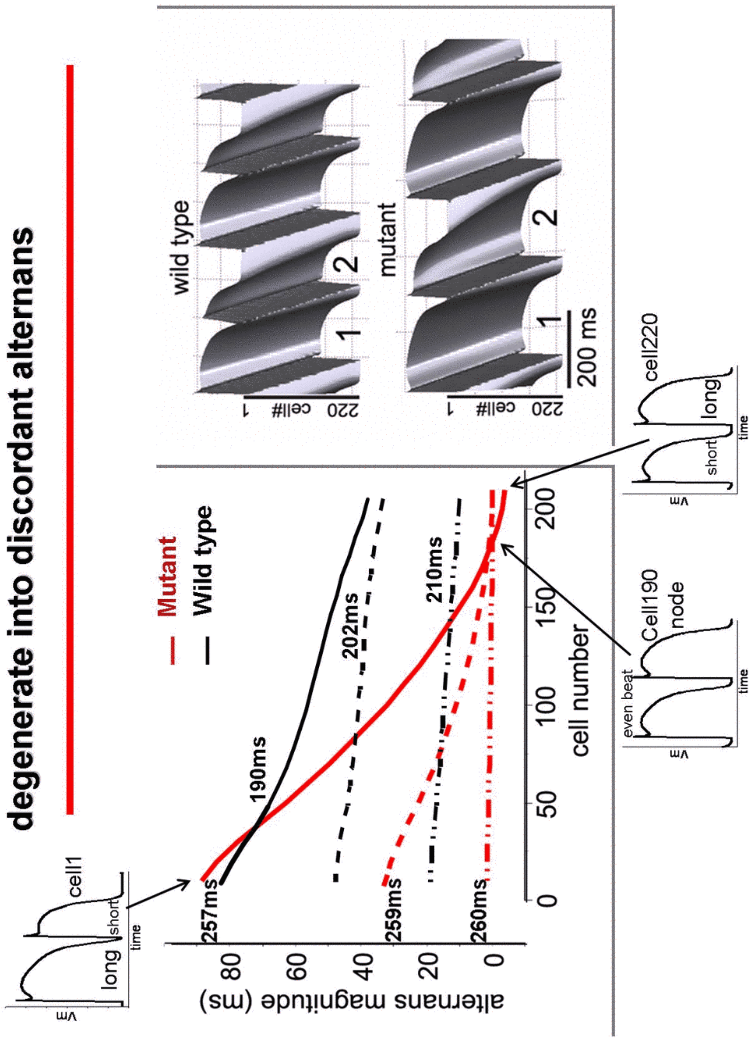


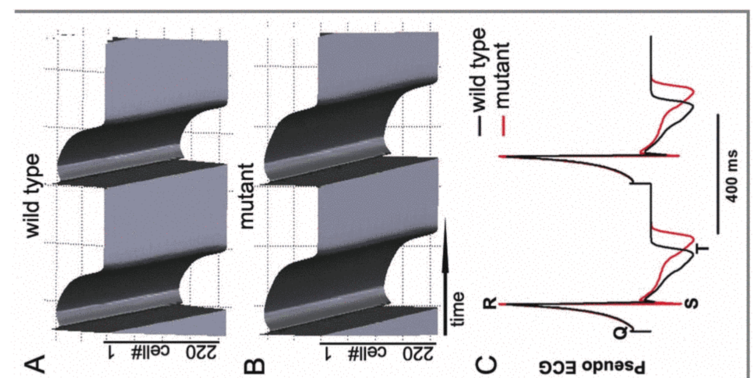
Table: Threshold BCL of arrhythmic events for fibers of normal and mutant cell

	Threshold BCL (ms)		
	Concordant Alternans	Discordant Alternans	2:1 block
Wild type	210	188	185
Mutant	259	257	249

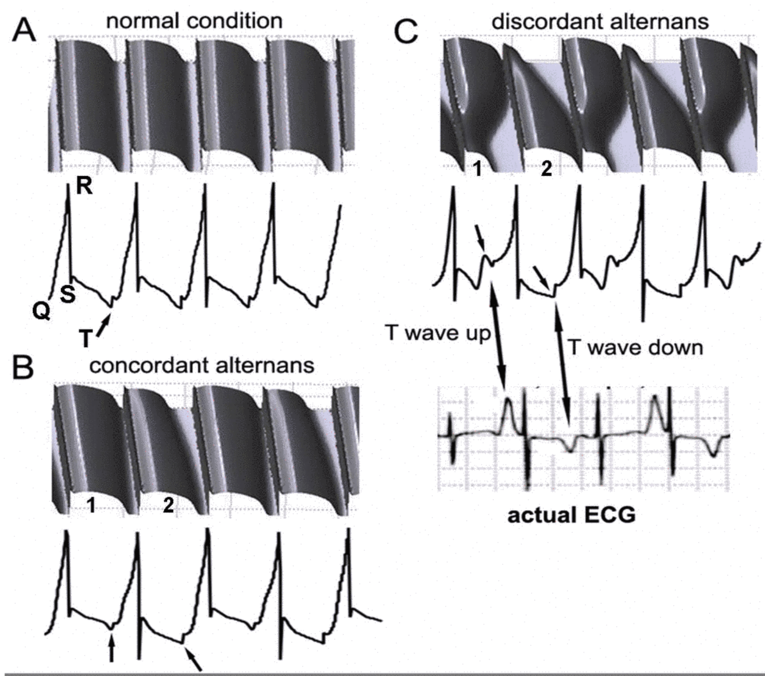
The TS mutation causes concordant alternans to rapidly degenerate into discordant alternans



QT interval prolongation



T-wave anomalies in computed ECGs



Summary

1 The TS mutation disrupts the rate-dependent dynamics in a single cardiac cell and promotes the development of alternans.

2 In coupled tissue concordant alternans is observed at much slower heart rates in mutant, and once initiated, rapidly degenerates into discordant alternans and conduction block.

3 The ECG computed from mutant tissue exhibits T-wave alternans and alternating T-wave inversion at physiologically relevant pacing rates.

Acknowledgements

Zheng I. Zhu Ph.D.

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

Alfred P. Sloan Foundation

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TIFF (Uncompressed) decompressor
are needed to see this picture.

The Lab

Zheng Zhu Ph.D.

Jun Xu Ph.D.

Ronit Vaknin

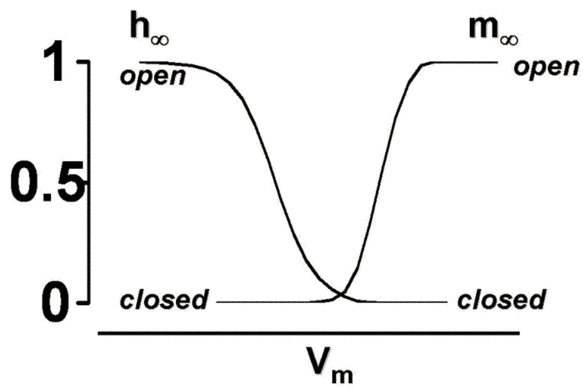
Detailed Na^+ channel gating models

- Usefulness - what can we learn?
- The relationship between implicit kinetic properties of channel gating and observed phenomena at other system scales.
- Non-equilibrium considerations
- Simulation of pharmacological interventions - predictive computable models.

The Hodgkin-Huxley framework

Variables h and m represent voltage dependent inactivation and activation gates

$$I_{Na} = m^3 h * g_{Na} * (E - E_{Na})$$



Markov models can incorporate mutations that affect discrete transitions

$$C \underset{b_1}{\overset{a_1}{\rightleftharpoons}} O \underset{b_2}{\overset{a_2}{\rightleftharpoons}} I$$

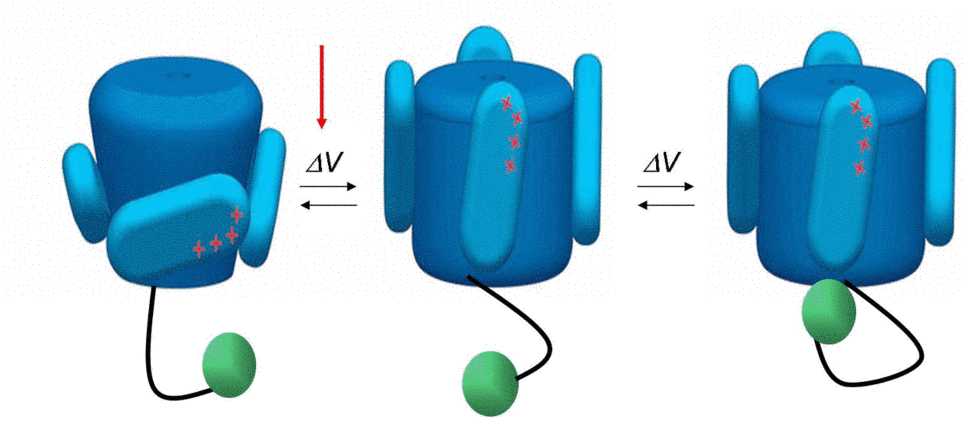


Figure adapted from Y. Jiang et al. Nature. 2003 May 1;423(6935):33-41.

Computation of state probabilities

$$C \underset{b_1}{\overset{a_1}{\rightleftharpoons}} O \underset{b_2}{\overset{a_2}{\rightleftharpoons}} I$$

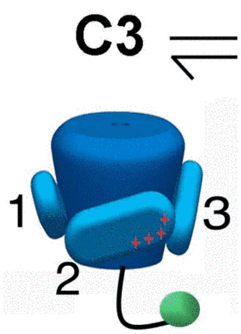
$$dP_i/dt = \sum_{j=1}^{N}[k_{ji} \bullet P_j(t,V_m)] - \sum_{j=1}^{N}[k_{ij} \bullet P_i(t,V_m)]$$

$dC/dt = P(O) \cdot b_1 - P(C) \cdot a_1$

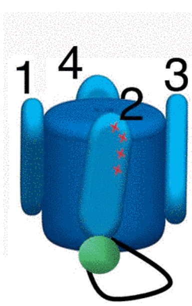
$dO/dt = P(C) \cdot b_1 + P(I) \cdot b_2 - (P(O) \cdot (a_2 + b_1))$

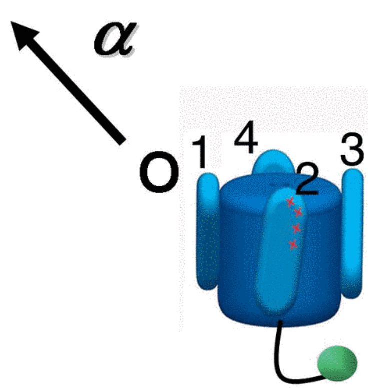
$dI/dt = P(O) \cdot a_2 - P(I) \cdot b_2$

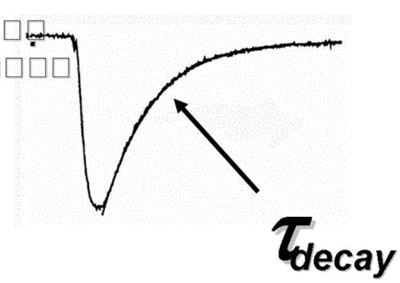
How do we build a model?



Extracting model parameters from experimental data





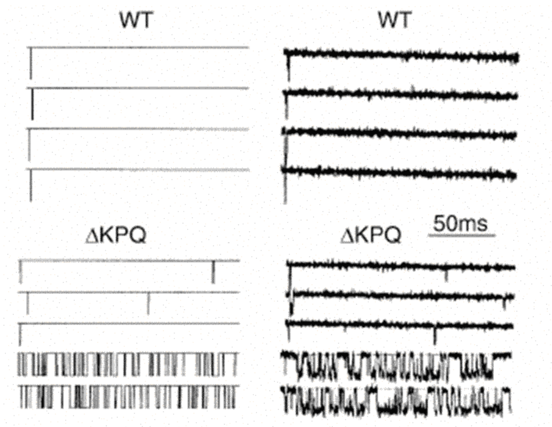


$$\tau_{decay} = 1 / \alpha$$

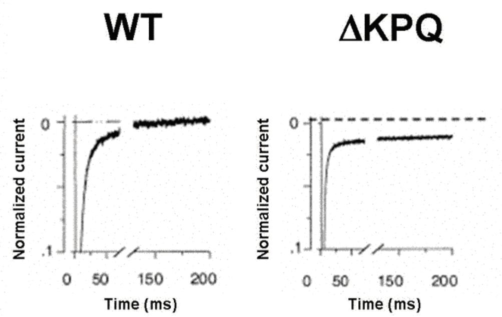
Kinetics of I_{Na}

Single channels

Simulation* Experiment**



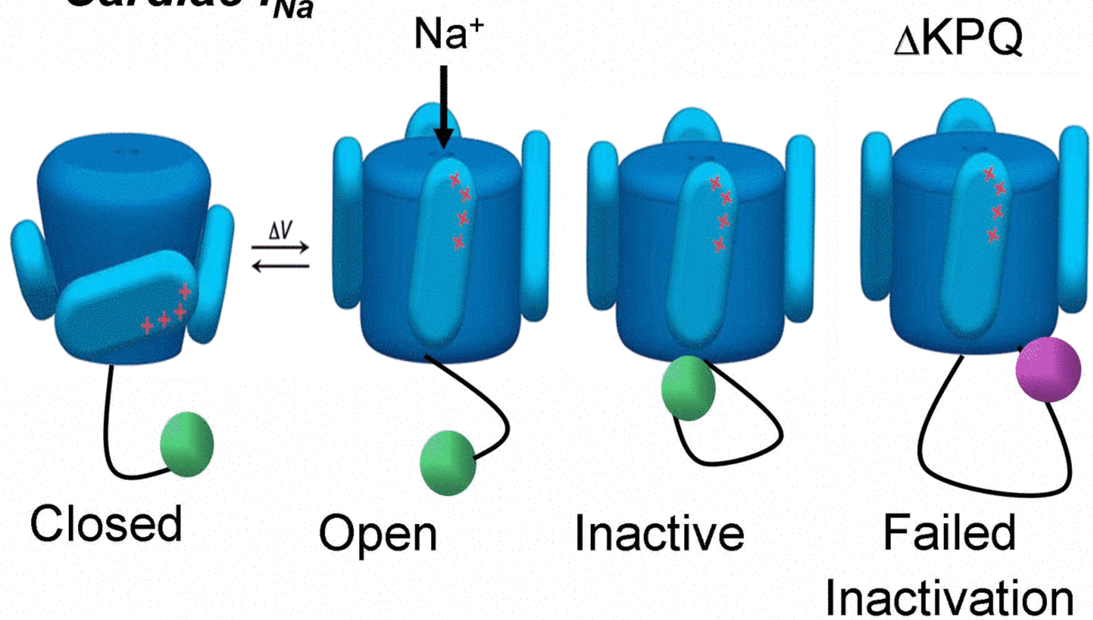
Whole cell***



* Clancy and Rudy. 1999. Nature. 400. 566-569.
**Chandra, Starmer and Grant. 1998. AJP. H1643-H1654

*** Bennett et al. 1995. Nature. 376. 683-685.

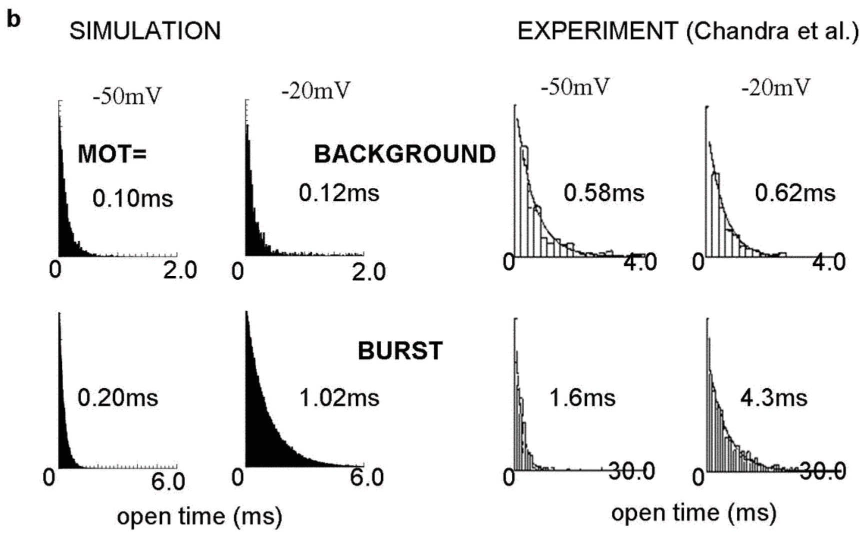
Cardiac I_{Na}



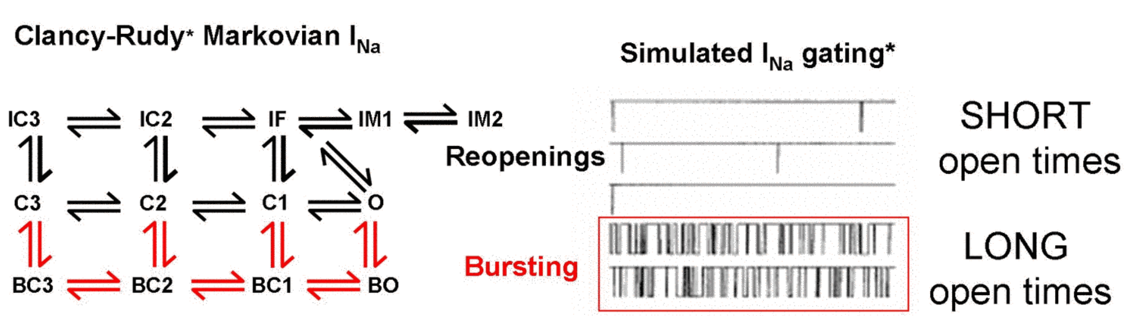
ΔKPQ channels may fail to inactivate

Multiple channel open times suggest “modal” gating

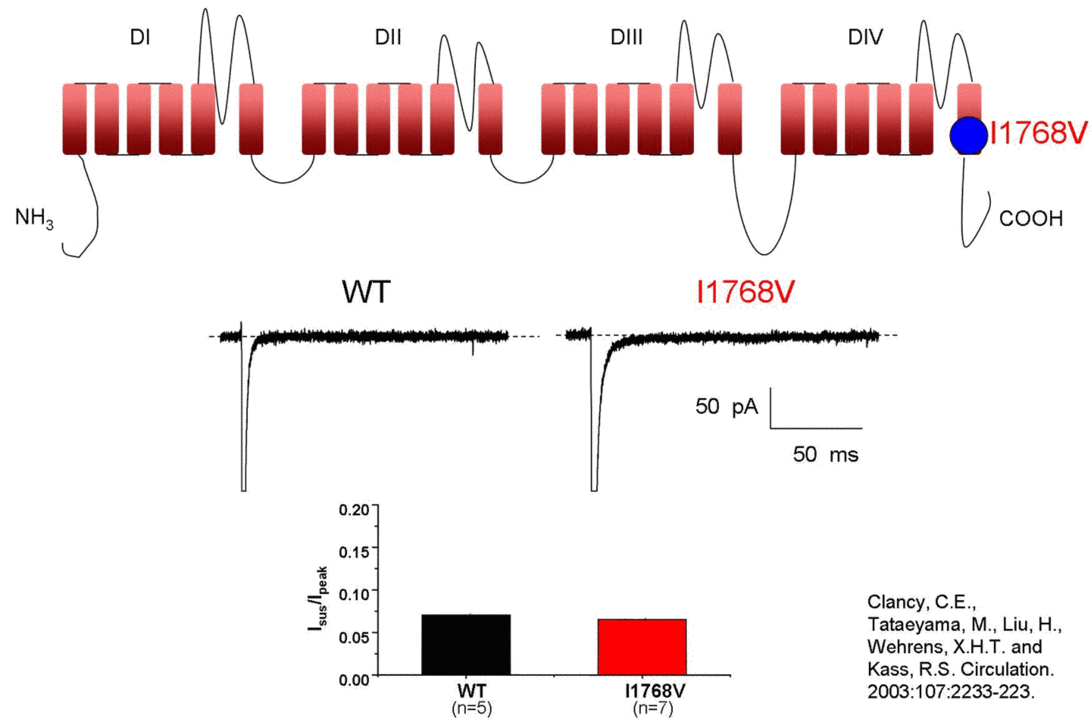
Two MOTs = two modes



Modeling kinetics of ΔKPQ I_{Na}

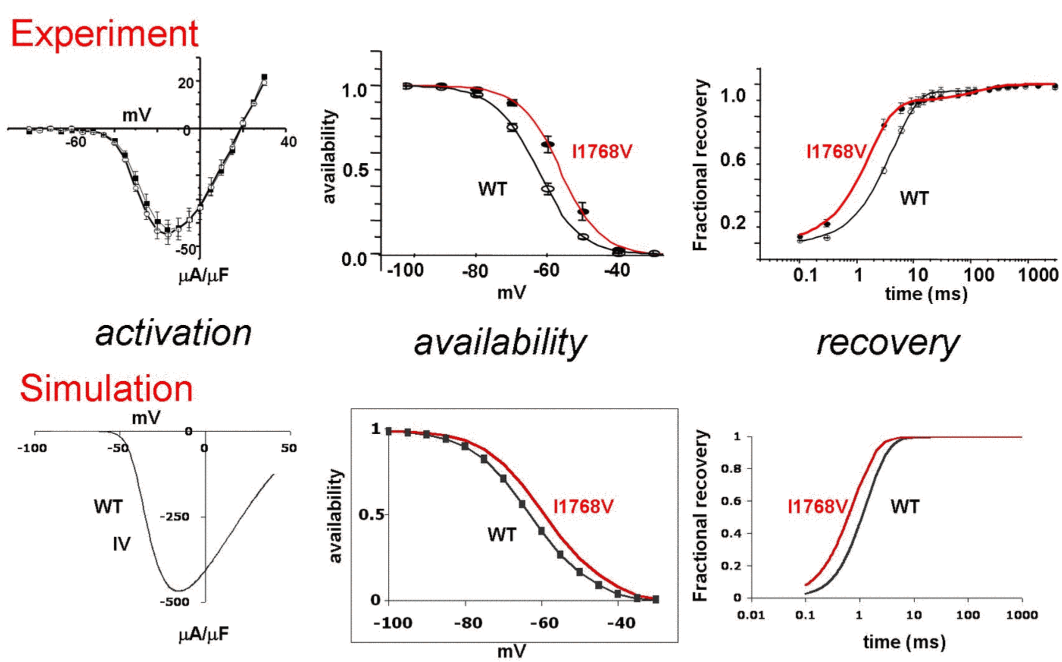


The I1768V Long-QT mutation lacks channel bursting



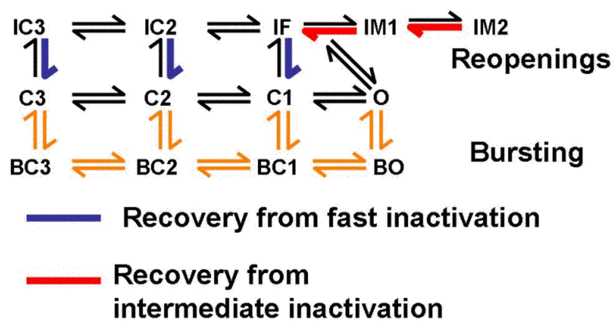
Clancy, C.E., Tataeyama, M., Liu, H., Wehrens, X.H.T. and Kass, R.S. Circulation. 2003:107:2233-223.

Kinetic properties of WT and I1768V cardiac I_{Na}

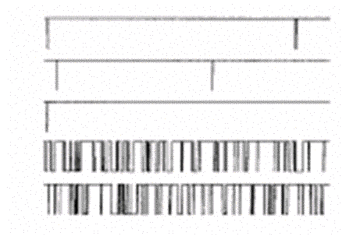


Background

Clancy-Rudy* Markovian I_{Na}

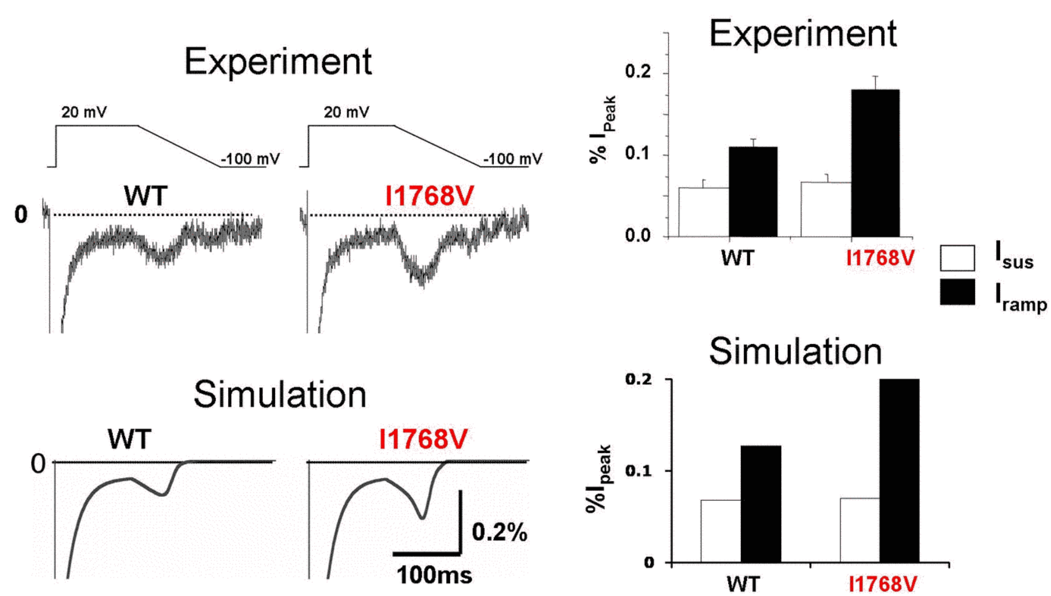


Simulated I_{Na} gating*



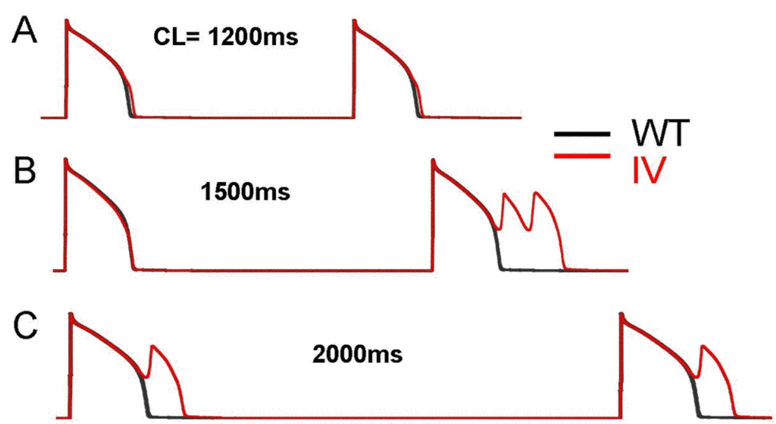
*Clancy and Rudy. Circulation: 2002:105:1208-1213.
Clancy and Rudy. 1999. Nature. 400. 566-569.

The I1768V mutation results in larger current during repolarization

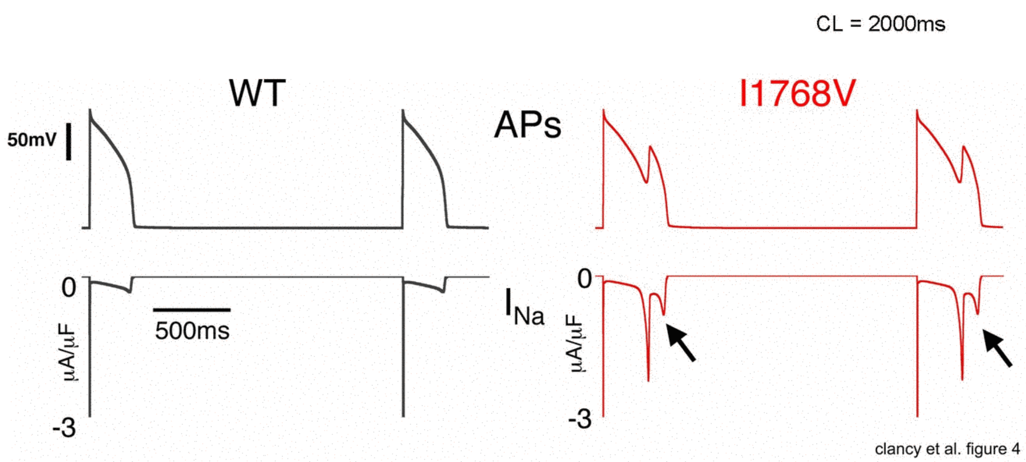


The I1768V mutation results in faster recovery from inactivation allowing for channel reopening during repolarization.

Channel reopenings disrupt the balance of current during repolarization and underlie arrhythmogenic EADs.



The mechanism of AP prolongation by I1768V

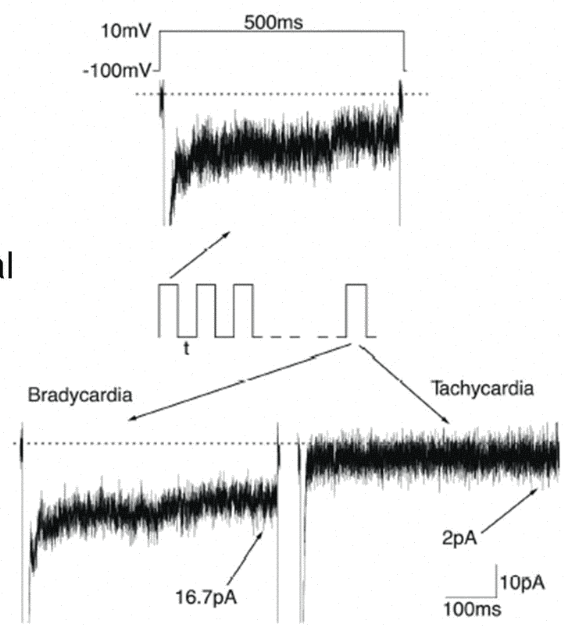


Summary

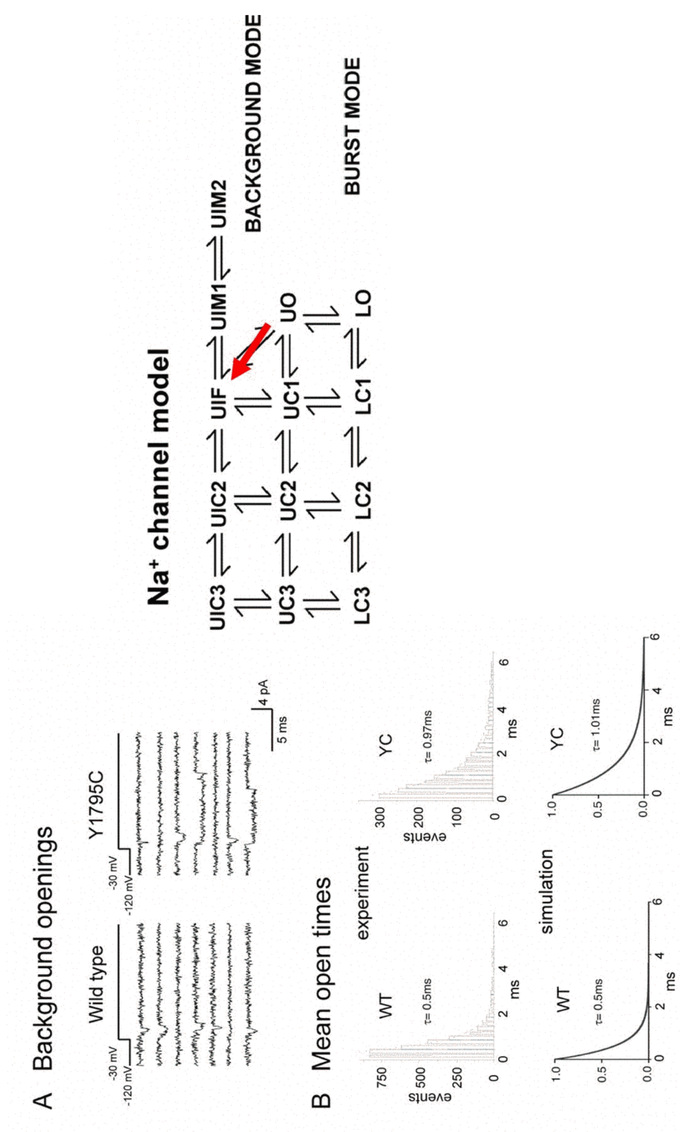
- Faster recovery from inactivation subsequent to channel opening results in *reopening* of a small population of channels.
- Background channel reopening results in the generation of late current during AP *repolarization*.
- Mutation induced alterations in channel gating during repolarization may underlie LQTs phenotypes.

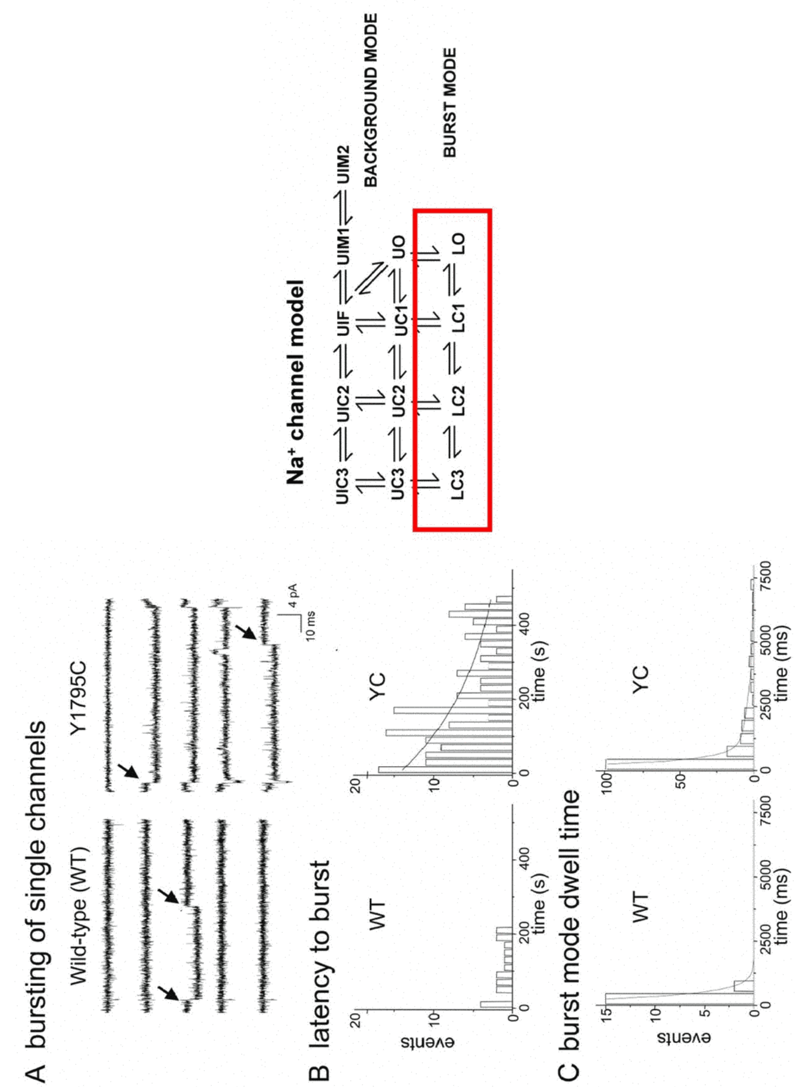
Mechanisms of rate dependence of LQT3 arrhythmias:

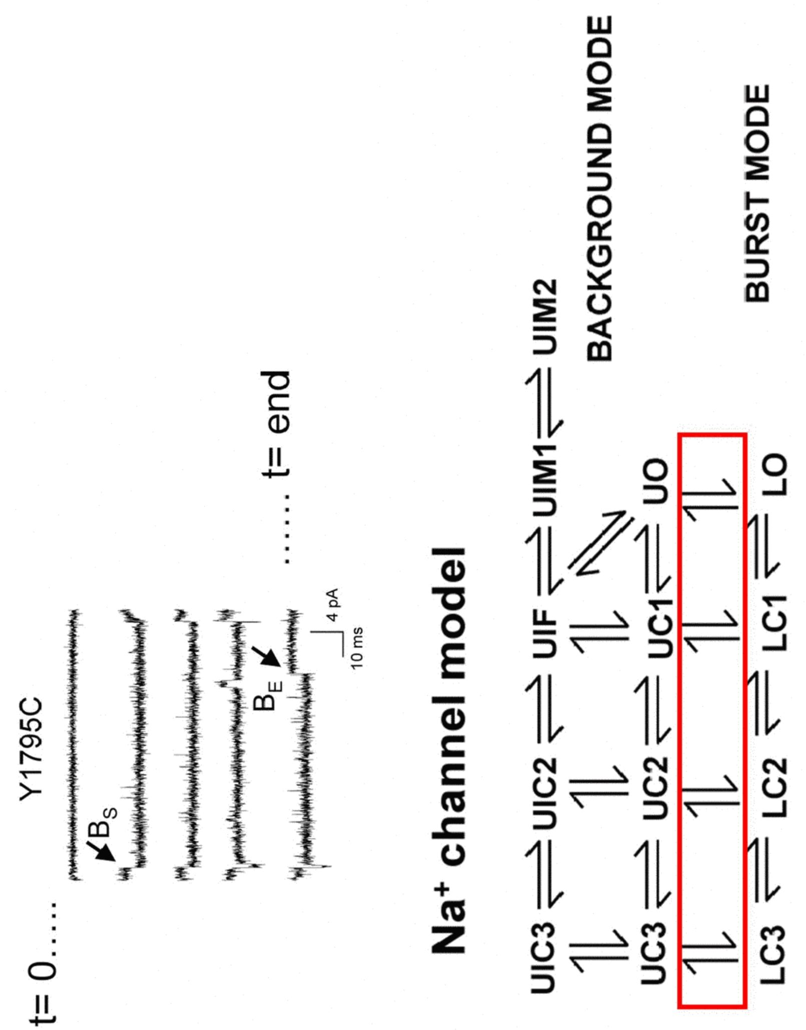
Insights from electrophysiological experiments and theoretical models.

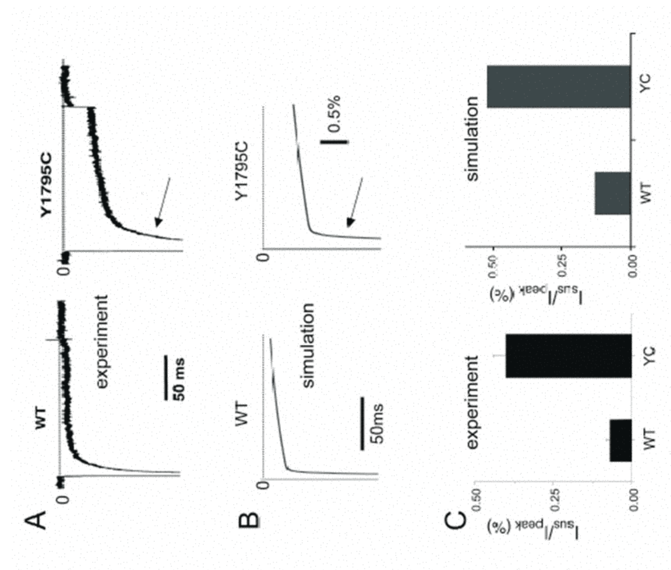


Clancy, C.E., Tataeyama, M. and Kass, R.S. Journal of Clinical Investigation. 2002:110:1251-1262.

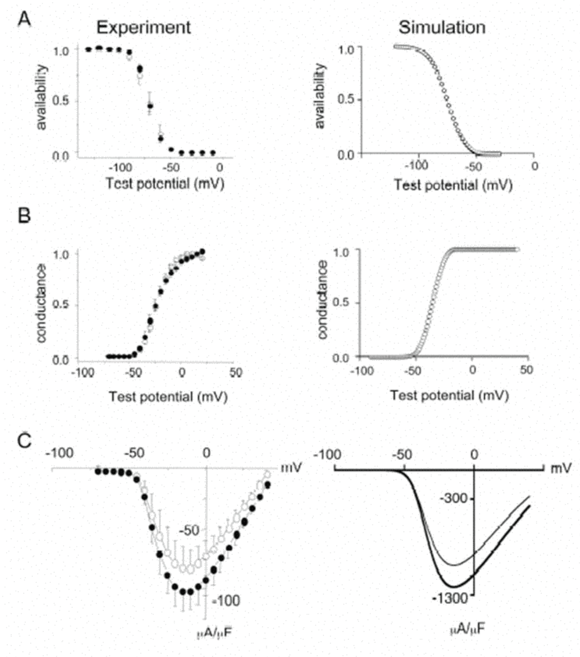

Na+ channel model
UIC3 UIC2 UIF UIM1 UIM2
UC3 UC2 UC1 UO
LC3 LC2 LC1 LO
BACKGROUND MODE
BURST MODE
A Background openings
Wild type
Y1795C
B Mean open times
experiment
simulation
WT
YC
τ= 0.5ms
τ= 0.97ms
τ= 1.01ms
events
ms

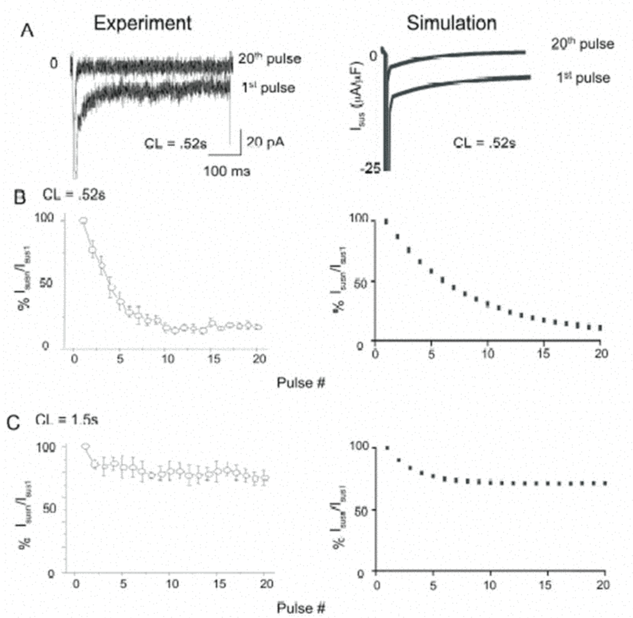

Na+ channel model
UIC3 UIC2 UIF UIM1 UIM2
UC3 UC2 UC1 UO
LC3 LC2 LC1 LO
BACKGROUND MODE
BURST MODE
A bursting of single channels
Wild-type (WT)
Y1795C
B latency to burst
C burst mode dwell time
WT
YC
events
time (s)
time (ms)


t= 0.....
Y1795C
B_S
B_E
4 pA
10 ms
...... t= end
Na+ channel model
UIC3
UIC2
UIF
UIM1
UIM2
UC3
UC2
UC1
UO
LC3
LC2
LC1
LO
BACKGROUND MODE
BURST MODE


A
WT
Y1795C
experiment
50 ms
B
simulation
0.5%
50ms
C
Isus/Ipeak (%)
0.50
0.25
0.00
YC

The Y1795C mutation does not affect other gating features





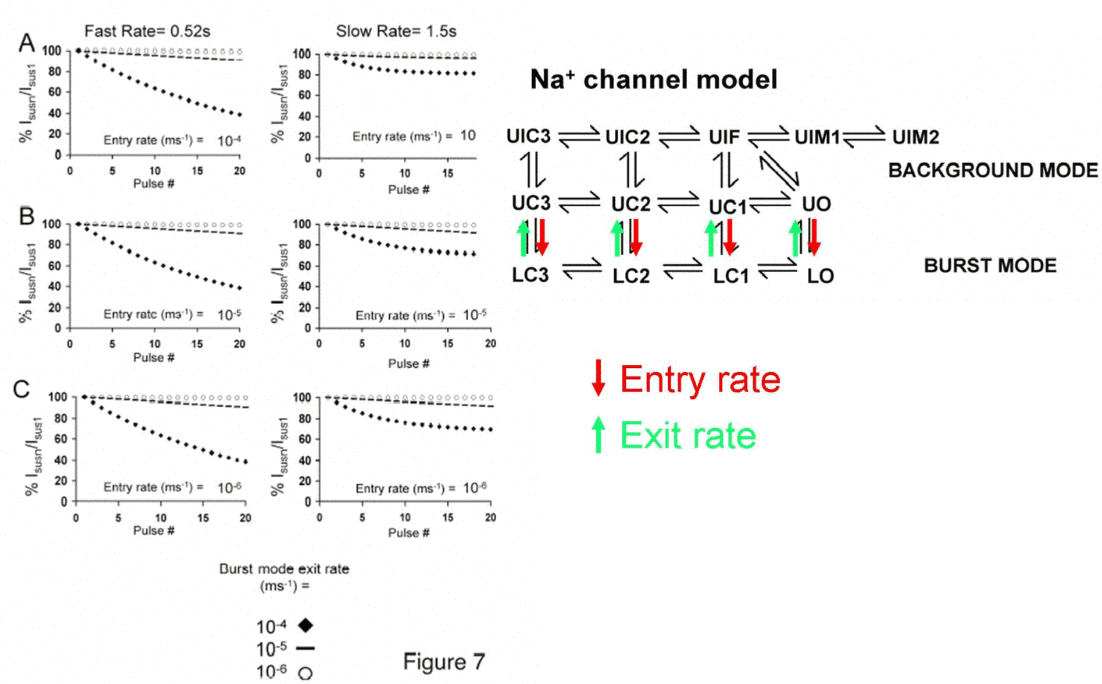


Figure 7

Acknowledgements

Robert S. Kass (Columbia University)

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Michihiro Tateyama (Columbia University)