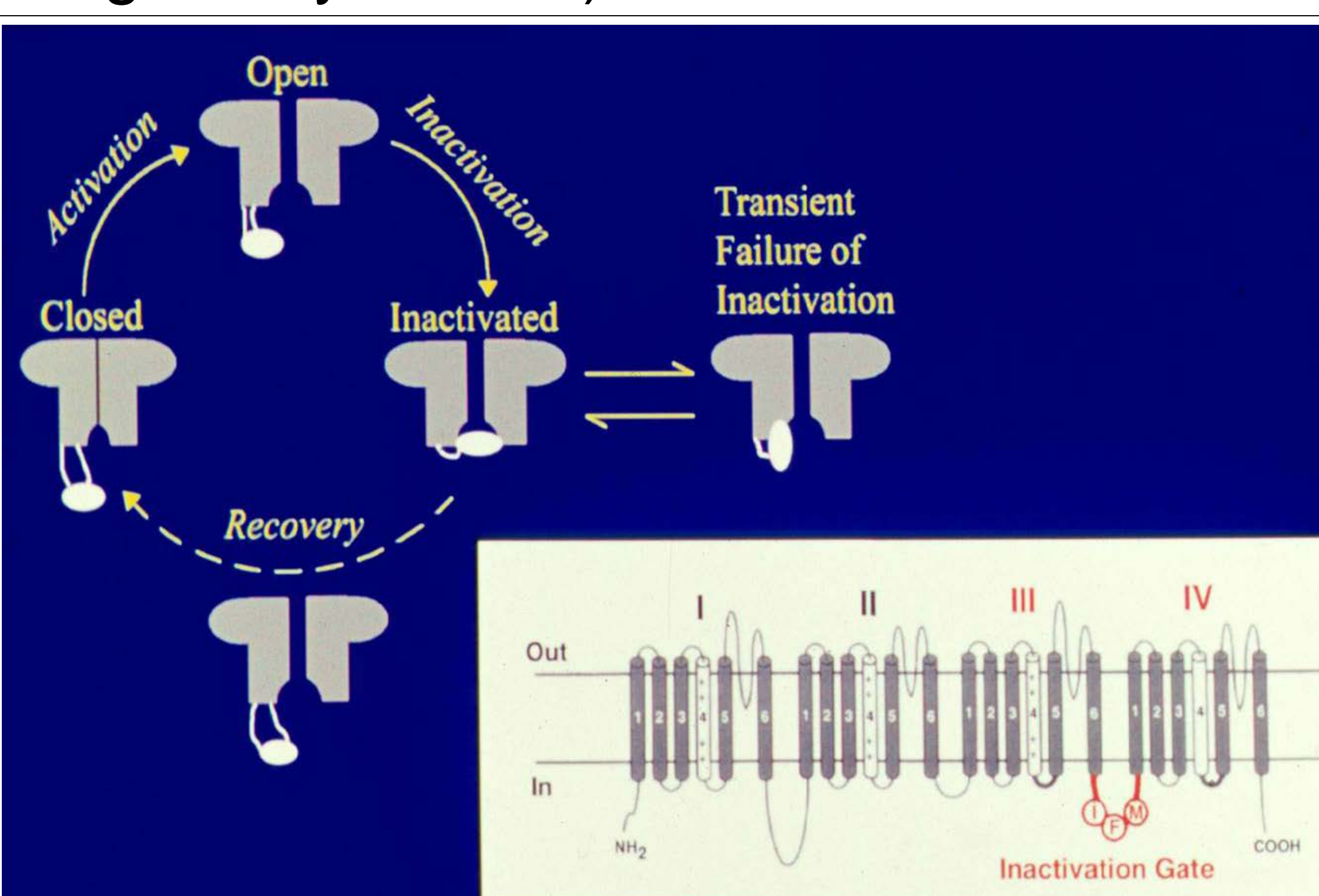


# Linking a genetic defect to its cellular phenotype in a cardiac arrhythmia

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**Abstract:** Advances in genetics and molecular biology have provided an extensive body of information on the structure and function of the elementary building blocks of living systems. Genetic defects in membrane ion channels can disrupt the delicate balance of dynamic interactions between the ion channels and the cellular environment, leading to altered cell function. As ion-channel defects are typically studied in isolated expression systems, away from the cellular environment where they function physiologically, a connection between molecular findings and the physiology and pathophysiology of the cell is rarely established. Here we describe a single-channel-based Markovian modeling approach that bridges this gap. We achieve this by determining the cellular arrhythmogenic consequences of a mutation in the cardiac sodium channel that can lead to a clinical arrhythmogenic disorder (the long-QT syndrome) and sudden cardiac death.

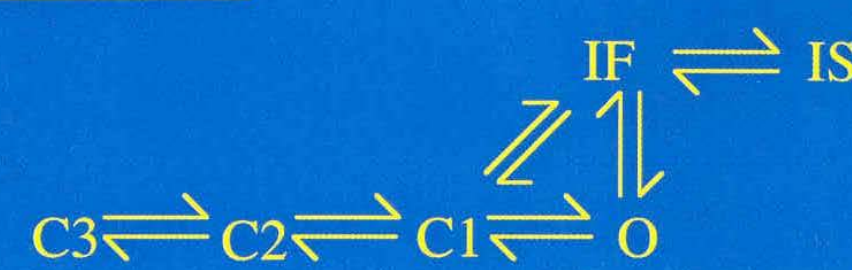


## Introduction

- The  $\Delta$ KPQ deletion mutation in the cardiac  $\text{Na}^+$  channel gives rise to the most severe form of long-QT syndrome (LQT3).
- The mutation affects a highly conserved portion of the III-IV linker known to be responsible for fast inactivation.
- The  $\Delta$ KPQ mutation gives rise to patient phenotypes marked by electrophysiological disturbances, syncope and sudden cardiac death.
- The development of arrhythmogenic episodes in LQT3 is correlated with bradycardia during sleep or relaxation.

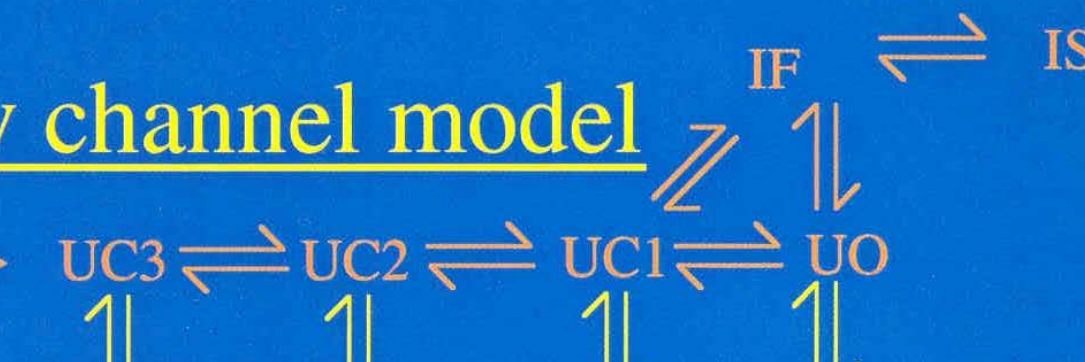
### Wild-type Markov channel model

- 3 closed states (C1, C2, C3)
- 1 open state (O)
- Fast and slow inactivation (IF, IS)



### $\Delta$ KPQ mutant Markov channel model

Background/Dispersed

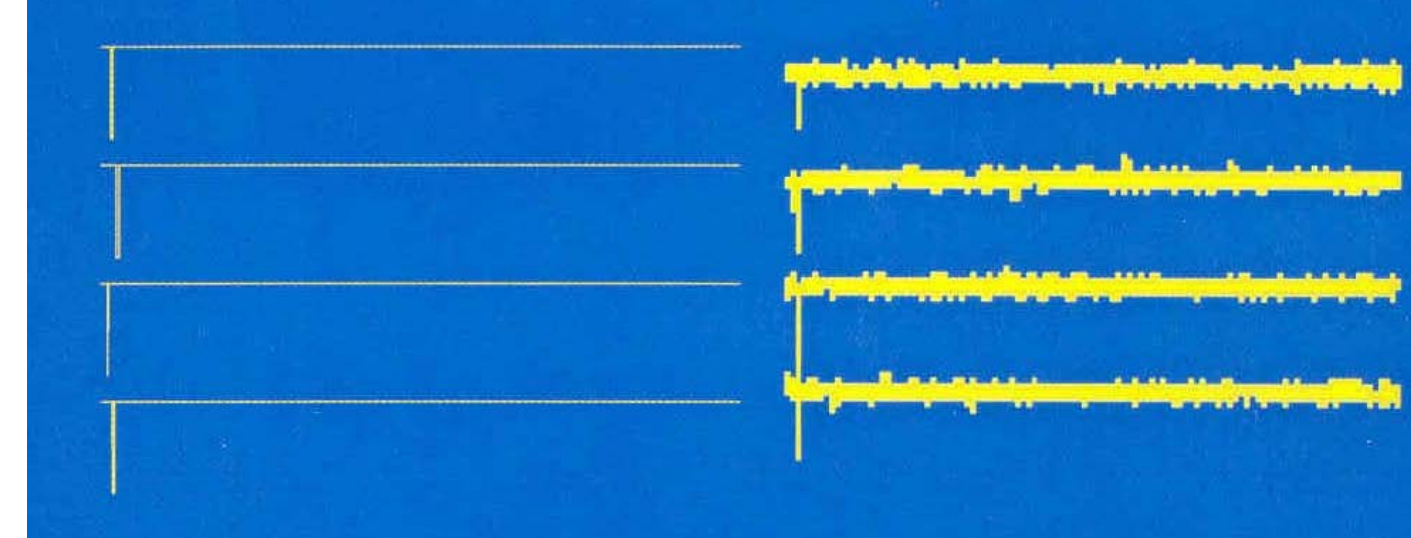


Burst Mode  
No inactivation



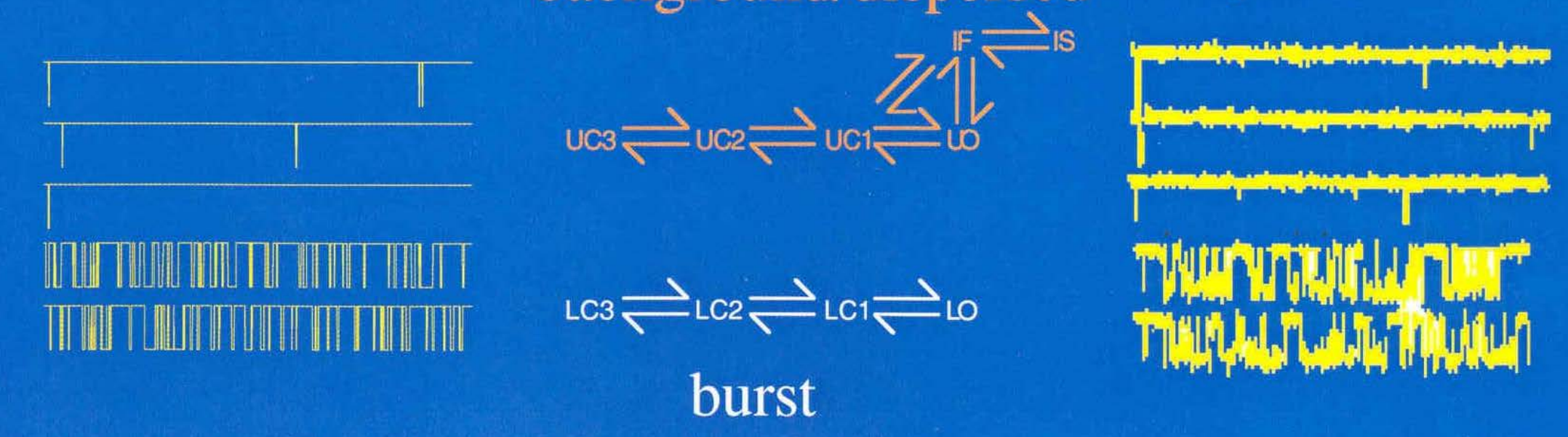
### Wild-type $\text{Na}^+$ channels

Simulation Experiment

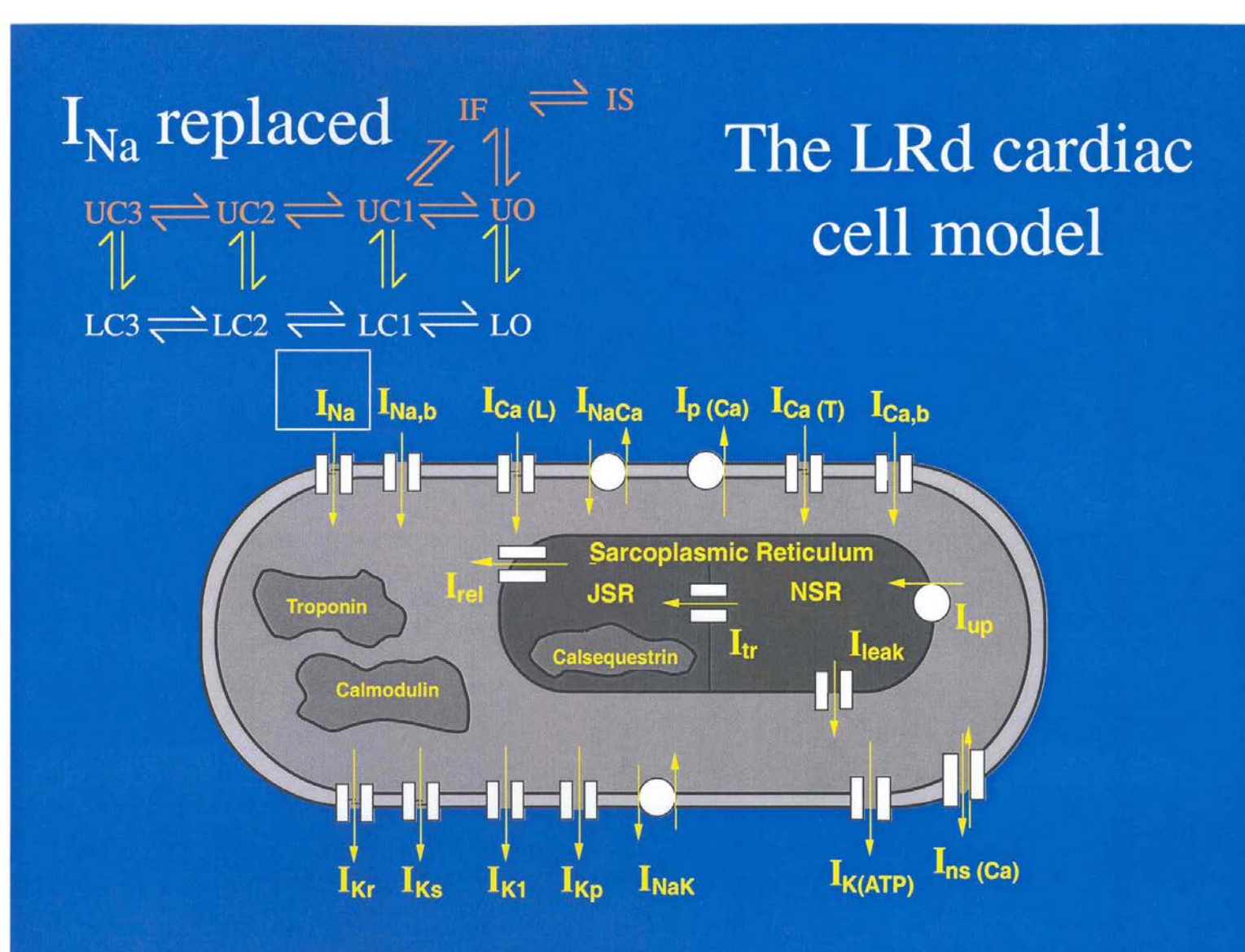


### $\Delta$ KPQ mutant $\text{Na}^+$ channels

Simulation background/dispersed Experiment



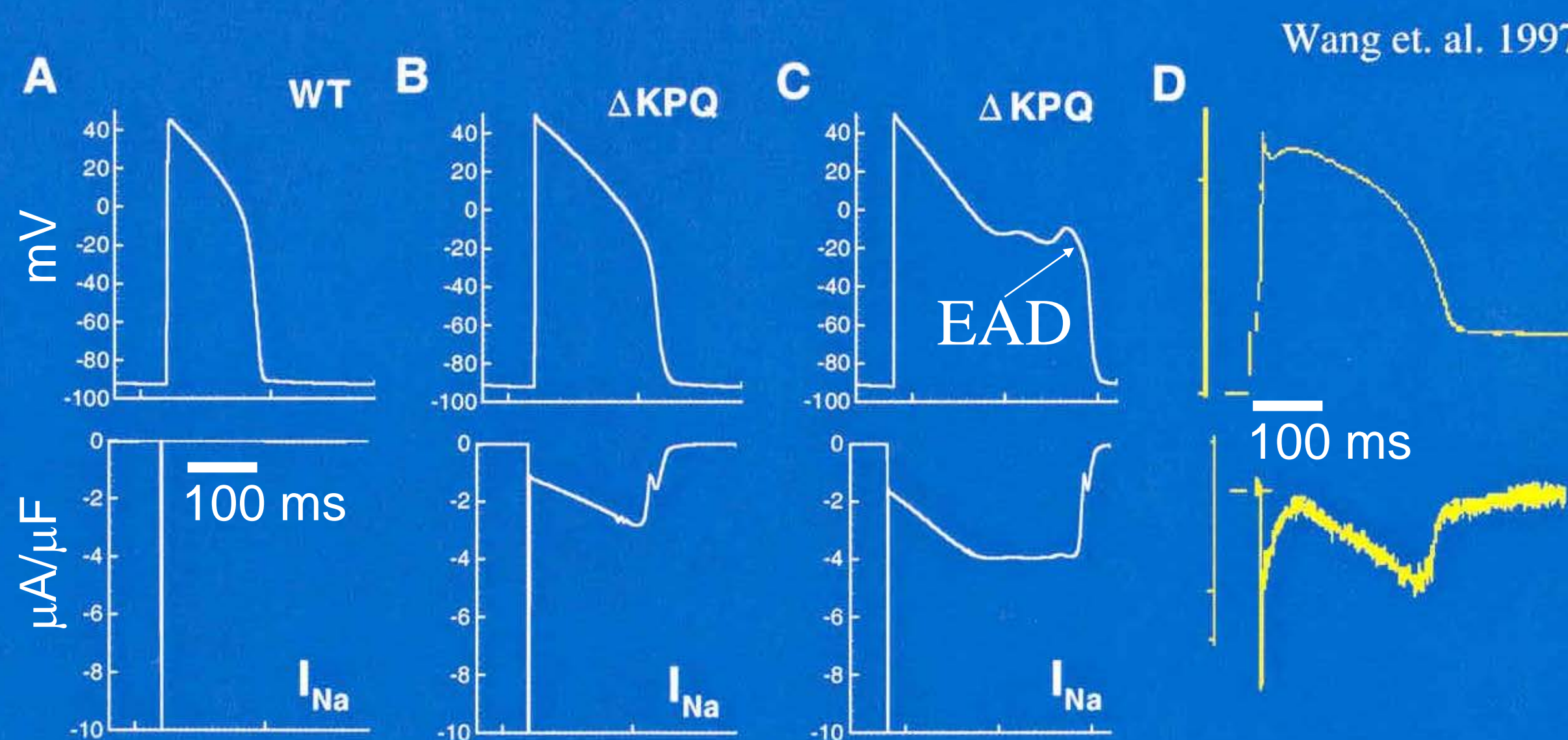
- In the background mode, mutant channels activate and recover from inactivation more quickly than wild-type (WT) channels.
- Faster activation of mutant channels leads to increased inactivation and faster decay of current.
- Increased rate of recovery of mutant channels leads to dispersed channel re-openings and a late component of  $I_{\text{Na}}$ .
- The likelihood of entry into the burst mode is very low but once mutant channels are in these states, return to background mode is unlikely.
- In the burst mode, mutant channels bounce back and forth between closed available states and a single open state contributing to late  $I_{\text{Na}}$ .



Wild-type and mutant channel models were incorporated into the Luo-Rudy model for action potential simulations.

### simulation

### experiment



- Persistent  $I_{\text{Na}}$  during the action potential plateau (B) prolongs the action potential duration (APD). Note close correspondence to experiment.
- Slowing the rate (C) results in further APD prolongation and early after-depolarizations (EADs).

## Conclusions

- Ion channel based models of cardiac cells can be used to investigate the effects of gene mutations on the whole cell.
- Transient failure of inactivation may give rise to a population of “bursting” channels.
- The  $\Delta$ KPQ mutation gives rise to a persistent inward current during the action potential plateau that prolongs APD and may give rise to EADs.

BCL=400ms

400ms

600ms

The 10<sup>th</sup> beat is shown after pacing at the indicated BCL.