

# **ABSTRACT OF THE DISSERTATION**

## **KCNQ1/KCNE1 Interaction in the Cardiac IKs Channel and its Physiological Consequences**

by

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Dynamic conformational changes of ion channel proteins during activation gating determine their function as carriers of current. The relationship between these molecular movements and channel function over the physiological timescale of the action potential (AP) has not been fully established due to limitations of existing techniques. We constructed a library of possible cardiac IKs protein conformations and applied a combination of protein segmentation and energy linearization to study this relationship computationally. Simulations reproduced the effects of the beta-subunit (KCNE1) on the alpha-subunit (KCNQ1) dynamics and function, observed in experiments. Mechanistically, KCNE1 increased the probability of “visiting” conducting pore conformations on activation trajectories, thereby increasing IKs current. KCNE1 slowed IKs activation by impeding the voltage sensor (VS) movement and reducing its coupling to pore opening. Conformational changes along activation trajectories determined that the S4-S5 linker (S4S5L) plays an important role in these modulatory effects by KCNE1. Integration of these molecular structure-based IKs dynamics into a model of human cardiac ventricular myocyte, revealed that KCNQ1-KCNE1 interaction is essential for normal AP repolarization.