in HEK293 cells showed that it does not generate any current (n=6). We utilized recently published computational models of the human atrial and ventricular action potential (Abraham et al., *J Mol Cell Cardiol.* 2010 and Grandi, *et al. J Mol Cell Cardiol.* 2010) to determine the effect that T322M has on cardiac Action Potential Duration (APD) stimulated at 1 Hz. A 100% reduction of I_{Ks} resulted in a prolonged APD in the atrial simulation but not the ventricular simulation. We incorporated a beta-adrenergic stimulation component into the ventricular model and found that reducing I_{Ks} by 100% in the modified simulation increased APD. We further modified the ventricular action potential simulation to compromise 'repolarization reserve' by reducing the rapidly-activating delayed-rectifier K^+ current or I_{Kr} component. This modification exacerbated that effect that 100% block of I_{Ks} had on ventricular APD. Based on these results we conclude that T322M prolongs the atrial APD in the absence of beta-adrenergic stimulation, and prolongs the ventricular APD in the presence of beta-adrenergic stimulation and a compromised repolarization reserve.

2362-Pos Board B348
A Mathematical Model Identifies Arrhythmia Susceptibility Factors in Mice with Heart Failure

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Tumor necrosis factor-α (TNF-α) is significantly elevated in the serum of patients with end-stage congestive heart failure and in the myocardium of patients with dilated cardiomyopathy and ischemic heart disease. This correlation suggests that the inflammatory cytokine TNF-α plays a significant role in promoting arrhythmias. To investigate the role of TNF-α, transgenic (TG) mice were generated with cardiac-specific overexpression of TNF-α which resulted in dilated cardiomyopathy, impaired Ca^{2+} dynamics, and increased mortality. In this study, we modified our model of mouse ventricular myocytes to account for the experimentally observed electrical remodeling. The resulting model demonstrated potential arrhythmogenic changes due to changes in action potential (AP) properties and cellular coupling. The simulated differences in action potential shape and duration were predominantly due to changes in the rapidly-inactivating transient outward K^+ current, $I_{Kto,f}$, and an ultra-rapidly activating K^+ current, I_{Kur}. The model incorporated experimental measurements of differences in Ca^{2+} handling in myocytes from wild type (WT) and TG mice: reduced $[Ca^{2+}]_i$ transients and slower Ca^{2+} sequestration by the sarcoplasmic reticulum (SR) in TG mice. The model also predicted that Ca^{2+} alternans developed at longer basic cycle lengths in TG compared to WT mice as observed experimentally. The greater susceptibility to Ca^{2+} alternans was attributed to a slower Ca^{2+} sequestration rate by the SR. Programmed stimulation with a premature impulse showed that longer S1-S2 intervals were effective at eliciting re-entry in TG vs. WT mice, suggesting a mechanism for the observed increase in the susceptibility of TG mice to re-entrant arrhythmias. A marked decrease of conduction velocity in TG mouse hearts was a major pro-arrhythmic mechanism in this mouse model of heart failure.

2363-Pos Board B349
Electrophysiological Modeling of Channelrhodophsin-2 in Cardiac Cells

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Purpose: With the recent interest in Channelrhodopsin-2 (Chr2) in neurological experiments, researchers have begun to investigate the utility of light-activated ion channels in other electrically active cell types, including human embryonic stem cell-derived cardiomyocytes (Abilez et al. 2010). However, the impact of Chr2 in action potential synchronization in cardiac cells is not yet fully realized, as neuronal and cardiac cells differ in electrical behavior. In the past, baseline electrophysiological models for normal neuronal and cardiac cells have been developed and recent attempts have been made to characterize Chr2 in neuron excitation control. However, these approaches do not capture the resulting ion channel current, nor have they been adapted for cardiac cells. By characterizing Chr2 currents within existing cell models, simulations can be conducted concurrently with experiments for principle validation and experiment optimization.
Methods: A kinetic model for Chr2 activation (Nikolic et al. 2006) was extended to an ion current formulation from current-voltage comparisons in the literature. This current was introduced into a ventricular cell model (ten Tusscher et al. 2003) and embedded in an implicit non-linear finite element framework (Wong et al. 2010) to perform simulations at cellular, tissue, and organ levels.
Results: To illustrate the features of our novel light-activated cell model, we present selected examples to show the benefits of concurrent modeling. At the cellular level, we explore the impact of photostimulation strength, duration, and frequency in Chr2-manipulated ventricular cells. At the tissue level, we evaluate the feasibility of using such manipulated cells as pacemakers in the heart.
Conclusion: By "transducing" cell models with Chr2, we can not only virtually probe characteristics of light-activated functional cells for novel applications of

Chr2 in cardiac cells and other electrically active cells, but also optimize experiments by qualitatively predicting experimental results.

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Using Regression-Based Model Analysis to Reconstruct and Predict Redundant Experimental Measurements

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The characterization of a heart cell's behavior generally involves a series of experimental measurements, some of which are relatively easy and others that require more involved experimental protocols. Because: 1) experimental studies can be time-consuming; and 2) it is not always possible to perform each measurement on a particular cell, there is a clear value in methods that can reliably distinguish between more informative and less informative experiments. Here we extend our previous studies that have analyzed several mathematical models of cardiac myocytes using parameter randomization and multivariable regression. The goal is to determine whether these techniques can be used to predict difficult-to-measure cellular outputs using a combination of a several easier-to-obtain measurements. Previously, we had devised a method to rank the cellular outputs in terms of their linear independence, choosing only to retain the most independent (good) outputs while rejecting the least independent (bad) outputs from the ranked list. Here, we use multivariable regression to derive a matrix whose elements indicate how changes in the 'good' outputs influence the 'bad' outputs. We found that most of the bad outputs could be specified with precision (R2 > 0.9 for 11 out of the 16 bad outputs). This implies that experiments to perform these measurements are unnecessary if the good outputs are already known. Moreover, in a few cases, a difficult-to-measure bad output could be well-predicted by a combination of a limited number of easier-to-measure outputs. The simulation results suggest that the information present in a more complicated cellular measurement may be reconstructed using a combination of easier measurements, thereby eliminating the need to painstakingly make these measurements. This method therefore shows great promise as a tool for model-driven experimentation.

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Stability and Self-Sustained Oscillations in a Ventricular Cardiomyocyte Model

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The Luo-Rudy I model, describing the electrophysiology of a ventricular cardiomyocyte, is associated with an 8-dimensional discontinuous dynamical system with logarithmic and exponential non-linearities depending on 15 parameters. By numerical approaches appropriate to bifurcation problems, sections in the static bifurcation diagram were determined. For different values of a steady depolarizing/hyperpolarizing current (I_{st}), the corresponding projection of the static bifurcation diagram in the (I_{st}, V) plane is complex, featuring three branches of stationary solutions delimited by two saddle-node bifurcation points. In addition, on the upper branch oscillations can occur within an I_{st} range $[-4.45, -0.51$ $\mu A/cm^2]$ where the Jacobian of the linearized system features two complex conjugated eigenvalues. Oscillations are either damped at a stable focus or amplified until the system trajectory is diverted to the lower branch of stable stationary solutions when reaching the unstable manifold of a homoclinic saddle. The middle branch of solutions is a series of unstable saddle points, while the lower one a series of stable nodes. For variable slow inward and K^+ current maximal conductances (g_{si} and g_K), in a range between 0 and 4-fold normal values, the dynamics is even more complex, and in certain instances self-sustained oscillations tending to a stable limit cycle appear. All these types of behavior were correctly predicted by linear stability analysis and bifurcation theory methods based on numerical continuation algorithms. Both unsustained oscillations, resulting in early after-depolarizations, and sustained oscillations may trigger dangerous ventricular arrhythmias by multiple mechanisms. In particular settings, e.g. for a normal g_K and one-fifth-of-normal g_{si}, these two arrhythmia-threatening conditions may occur simultaneously.

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Revisiting the Ionic Mechanisms of Early Afterdepolarizations in Cardiomyocytes: Predominant by Ca Waves or Ca Currents?

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Early afterdepolarizations (EADs) have been implicated in severe cardiac arrhythmias and sudden cardiac deaths. However, the mechanism(s) for EAD genesis, especially regarding the relative contribution of Ca wave vs. L-type Ca current ($I_{Ca,L}$), still remains controversial. In the present study, we systemically compared the properties of EADs in the following two pharmacological models: A) H_2O_2 (200 μM); B) Isoproterenol (100 nM) and Bay K 8644 (50 nM) (Iso+BayK). Membrane action potentials (APs) and Ca imaging were simultaneously recorded in isolated rabbit ventricular myocytes. We found that: 1) H_2O_2-induced EADs were facilitated by slow pacing rates, while