the myofibril being uniformly enshrouded by SR) is between 20-30% even as the heart rate ranged from 1 Hz to 5 Hz. The relatively small amount of SR coverage needed for economic control of Ca^{2+} is consonant with Berg and Purcell's (Biophysical Journal 20:193-219) classic finding that, as a consequence of the properties of diffusion, a small fractional covering of absorbers on the cell surface performs almost as well as when the surface is entirely covered by absorbers.

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Species-Specific Comparison of the Cardiac Sodium/Potassium Pump Based on a Minimal Biophysical Model

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The Na^+/K^+ ATPase (NKA) plays a critical role in maintaining the concentration gradients, across the plasma membrane, of potassium (which determines the cell's membrane potential) and sodium, the driving force behind crucial ion-exchange processes, including calcium extraction via the sodium/calcium exchanger. This function has been extensively studied, experimentally and by computational simulations, within the context of the excitation/contraction coupling in cardiac myocytes. An important source of complexity in these strongly couple systems is the significant species-dependent variability of physiological conditions under which NKA operates, particularly the intracellular sodium concentration $[Na^+]i$. For example, $[Na^+]i \sim 11$ mM in rat ventricular myocytes, and ~ 5 mM in guinea pig. An important question is whether (1) NKA is maintained across species and operates in different species-specific regimes; or (2) NKA shows significant species-dependent variations and hence participates directly in defining physiological conditions. Most existing models neglect this fundamental question by assuming a generic NKA formulation derived from disparate experimental sources. To address this problem, we propose a biophysical framework for characterizing NKA function, specifically designed for species-specific parameterization, and produce separate models for rat and guinea pig NKA, each parameterized from fully consistent data sets. We find that the apparent binding affinity for sodium in the rat is lower by a factor of approximately three, whereas the overall pump current magnitude is roughly doubled, relative to guinea pig. These trends mirror those for the $[Na^+]i$ differences, suggesting that NKA kinetics compensates or has adapted to its physiological conditions. Such comparisons allow an analysis of the relative influence of cellular components, ionic conditions, and the action potential on ion transport in cardiac contraction, and ultimately enable the quantification of variations in physiological function of NKA across biological contexts.

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Intermittent Early Afterdepolarizations Caused by Bistability

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Early afterdepolarization (EAD) is one of the main triggers for cardiac arrhythmias. The intracellular sodium concentration ([Na]i) is critical in regulating both intracellular calcium (Ca) homeostasis and membrane voltage (V). However, the role of [Na]i in the formation of early afterdepolarizations (EADs) is not completely understood. In this study, we applied mathematical modeling to show that slow [Na]i accumulation can lead to a novel form of aperiodic voltage dynamics where a sequence of action potentials (APs) with EADs occurs intermittently during regular periodic pacing. We find that these trains of EADs occur quasi-periodically and lead to intermittent EAD propagation and arrhythmias. The mechanism for these intermittent EADs can be traced to the subtle feedback between Na and Ca fluxes (especially via Na/Ca exchange (NCX) and Na/K-ATPase (IPump)) and their effect on the AP duration (APD). We analyzed the whole system by separating the slow [Na]i from the fast V-[Ca]i subsystem. We found that the fast subsystem exhibits bistability which leads to the observed EADs by forming hysteresis loops as [Na]i slowly accumulates and dissipates. That is, [Na]i can gradually decline during stable short APDs, but this gradually diminishes outward currents via IPump and INCX, which can result in abrupt APD prolongation with EADs. But that long APD gradually reverse the [Na]i decline, and shifts IPump and INCX more outward, which at some point abruptly prevents EADs and reverses APD prolongation. We argue that these intermittent EADs are robust and can occur at physiological [Na]i. Our study further provides a possible novel mechanism for the intermittency of cardiac arrhythmias.

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Diabetic Hyperglycemia Acutely Affects Action Potentials and Ionic Currents through CaMKII Activation on Rat Ventricular Myocytes

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Diabetes mellitus is a complex disease that involves cardiomyopathy and neuropathy. Ca^{2+}-Calmodulin dependent protein kinase II (CaMKII) is a nodal molecule that participates in many physiological and pathological processes in the heart. Diabetic hyperglycemia has been shown to activate CaMKII, through a novel modification of O-linked N-acetylglucosamine (O-GlcNAc) at S279, leading to cardiac arrhythmias at the whole heart/animal level. However, acute hyperglycemia affects specific ion channels and thus action potentials (APs) through O-GlcNAc activated CaMKII are still unclear. To investigate this question, we measured APs and ionic currents on freshly isolated rat ventricular myocytes under acute diabetic hyperglycemia challenge. Glucose (30mM) perfusion significantly reduced the AP amplitude ($82.7 \pm 5.7\%$ of control, n=8, p=0.011), depolarized the resting membrane potential (-79.8 ± 0.8 mV for control vs. -73.4 ± 1.8 mV for glucose, n=8, p=0.002), and prolonged the AP duration ($117.3 \pm 7.1\%$ of control, n=8, p=0.001) on rat myocytes whereas osmolality matched mannitol application did not change any AP parameters. KN-93 (10uM) pre-incubation abolished the glucose effects, indicating that acute glucose application changes cellular electrical activities via a CaMKII-dependent manner. Together, these data provide evidence for the arrhythmogenesis of acute hyperglycemia at the cellular level and suggest that CaMKII-modulated ionic currents are responsible for the hyperglycemic effects on APs.

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Transmural Gradient of I_{to} and I_{Nak} Profoundly Influence Ventricular Action Potential Duration

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The spatial distribution of transient outward K^+ current (I_{to}) and Na/K pump current (I_{NaK}) differ in ventricular epicardial, midmyocardial and endocardial cells in a gradually decreasing pattern called transmural gradient. Due to a lack of selective I_{to} blockers, it remains unclear whether changes in I_{to} alone affect action potential duration (APD) in the ventricle. In this study we use mathematical modeling to address the above question by modifying the kinetics of I_{to} and I_{NaK} on the framework of Hund-Rudy model to incorporate the transmural gradient. Model simulation results show that I_{to} of physiological values does not affect APD, but artificially increasing I_{to} above its normal value in the epicardium can prolong APD; further increasing I_{to} beyond a threshold cause collapsing of the AP plateau phase and abrupt shortening of APD. These model simulation results agree with the experimental data from using dynamic-clamp to manipulate I_{to} (Sun and Wang, *J Physiol* 564:411-419, 2006). Moreover, our simulation results show that the transmural gradient of Na/K pump also affects APD. Together, the I_{to} and Na/K pump affect the intracellular Na^+ and Ca^{2+} concentrations, which is manifest to influencing the late Na^+ current and Na^+/Ca^{2+} exchange current. Due to the interconnectedness of these currents to Na^+ and Ca^{2+} homeostasis, it is important to incorporate the transmural gradient of ion channels and transporters into mathematical models in order to understand their combined effects on modulating the AP properties across the myocardium. Our modeling platform will help to decipher how the transmural gradients can profoundly affect the cardiac conduction.

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Mechano-Chemotransduction in the Single Cardiac Myocyte Contracting in 3D Elastic Gel

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Objective: Mechanical stress under pathological conditions such as hypertension, infarction and fibrosis can cause heart failure and arrhythmias. However, little is known about the mechanotransduction mechanisms that underlie heart disease development due to previous lack of practical techniques to control the mechanical stress on single myocytes necessary for investigating at cellular and molecular levels. Here we use this system to study the mechanical load effects on modulating myocyte Ca^{2+} signaling and contraction dynamics. **Methods:** Recently, we developed a novel Cell-in-Gel system that allows control of mechanical load on single rabbit myocytes during excitation-contraction coupling in a 3D elastic gel matrix composed of polyvinyl alcohol (PVA) and tetravalent boronate-PEG crosslinker. The mechanical load can be controlled