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Classifying the Electrophysiological Effects of Chronotropic Drugs on Human Induced Pluripotent Stem Cell-Derived Cardiomyocytes using Voltage Sensitive Dyes and Supervised Machine Learning

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The emergence of human induced pluripotent stem (hiPS) cell technology has expanded the possibilities for sourcing human cardiomyocytes (hiPS-CMs). Novel microscopy and analysis methods serve to accelerate development and validation of *in vitro* hiPS-CM models for drug screening. Voltage sensitive dyes (VSD) allow non-invasive, non-destructive, and longitudinal assessment of hiPS-CM electrophysiology at the sub-cellular membrane scale. In this study, we successfully use 2-photon microscopy to capture VSD signal at the cellular membrane scale generated from actively beating hiPS-CMs exposed to the chronotropic drugs, propranolol (10^{-5} M) and isoproterenol (10^{-7} M). We use SimFCS software, developed at the Laboratory for Fluorescence Dynamics at the University of California, Irvine, to remove motion artifact and assess the resultant signal over time. We are able to generate a waveform of VSD fluorescence that is representative of the changing membrane potential (i.e. the depolarization of an action potential). A number of characteristics of these waveforms are defined (upslope, maximum height, plateau height, downslope, peak width, and beat rate), compared across treatments, and shown to be significantly different between treatments. A supervised machine learning algorithm is then trained, validated, and the algorithm accuracy quantified using these data along with their known drug treatments. The algorithm that results can be used to predict which drugs hiPS-CMs have been exposed to given only their respective VSD waveforms. This study tests the hypothesis that VSDs may be used in conjunction with supervised learning to train an algorithm that is capable of automatically and accurately assessing, classifying, and predicting the membrane depolarization effects of chronotropic drugs.