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simulations of membrane-embedded solutes has, in general, been drastically underestimated.

### 1072-Plat
**Evaluating CHARMM Additive and Drude Polarizable Force Fields Through QM/MM Computations of the Vibrational Stark Effect**
**Ashley L. Ringer**, Alexander D. MacKerell Jr.
University of Maryland, Baltimore, Baltimore, MD, USA.
The proper description of the electric environment of macromolecules is a critical challenge for force field methods. To test and validate the CHARMM force field's ability to describe this electric environment combined QM/MM calculations have been used to calculate the vibrational Stark effect (VSE). The Stark effect refers to the characteristic shift of a specific vibrational frequency upon the introduction of an electric field. In this work, we develop a first principles methodology to compute Stark shifts using correlated electronic structure techniques and validate this approach by computing the Stark shift of a model VSE probe, acetonitrile, in several solvents. The solvent environment around the probe is sampled through 20 ns molecular dynamics simulations of each molecule surrounded by several hundred explicit solvent molecules. From these simulations, two hundred snapshots of the probe with the solvent environment are collected for the QM/MM analysis. Several QM/MM computational schemes are compared for calculating the vibrational spectrum of the VSE probe in the field created by the solvent molecules, which are treated as MM atoms with the CHARMM force field. From these computations, an average Stark shift is determined for each probe molecule and compared to experimental measurements. This information can be directly related to the electric field surrounding the probe molecule, and therefore may be used as a direct test of the ability of a force field to reproduce the electric field around those functional groups. Information from these calculations will act as the basis for additional optimization of the force field to more accurately represent the electric fields in macromolecules.

### 1073-Plat
**Thermal, Chemical and Mechanical Stability of HPV L1 VLP Vaccines: A Multiscale All-Atom Simulation Study**
**Harshad Joshi**, Peter Ortoleva.
Indiana University, Bloomington, IN, USA.
Recently Virus-like-Particles (VLPs) have been used as vaccines against viral diseases. It is the structural similarity of VLPs, and the surface proteins (epitopes) that evokes a neutralizing antibody response. We present a novel computational approach which may ultimately be applied in cell-free synthesis of VLP-based vaccines that are stable over wide range of external environmental conditions (e.g. temperature). Moreover, we aim to construct VLPs that can be stored and dressed later with different epitopes depending on the target virus, addressing wide range of viral diseases in a fast, cost-effective manner in unfolding pandemic scenarios.
Here we present computational studies on VLPs constructed from a major capsid protein (L1) of human papilloma virus (HPV). The thermal stability and structural dynamics of these VLPs was studied using our novel multiscale all-atom approach. We probed mechanical stability via a bottom-up approach starting from major L1 protein going eventually up to the complete VLPs. External force was applied to each of these systems to probe their response to external tension. We have found the unfolding pathways of L1 proteins. Forces were applied to probe the strength of interface interactions between (1) L1 proteins and (2) pentameric assemblies of these protomers that form the subunits of a complete VLP. Finally we performed fully atomistic force-probe MD simulations of the complete VLPs in explicit solvent. Forces were applied at different positions on the viral surface. A detailed picture of the spatial distribution of elastic constants and yielding forces was obtained.
All these results together helped us to understand thermal, chemical and mechanical stability of HPV VLPs. These will be used to make appropriate predictions of mutations in the structures to achieve our long term goal of constructing more stable VLPs.

## PLATFORM AE: Cardiac Electrophysiology

### 1074-Plat
**Mechanisms of hERG Potassium Channel Enhancers**
**Chia-Wei Lin**[1], Xueying Cao[1], Robert Penland[2], Laszlo Urban[1], Gul Erdemli[1].
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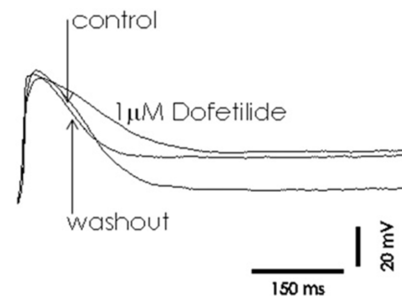
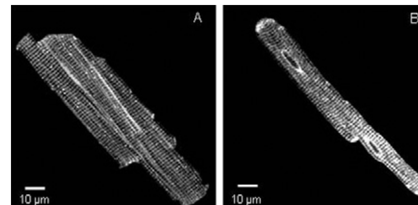
[2]Novartis Pharmaceuticals Corporation, Cambridge, MA, USA.
Mutations in the human Ether-à-go-go related gene (hERG) potassium channel and hERG channel blockers offer tools for studying structural, biophysical and functional properties of the channel. However, the current understanding of how the hERG channel opens and closes is still incomplete. Here, we used alternative chemical tools, hERG channel enhancers, to study the hERG channel gating. RPR260243 drastically slowed down the deactivation rate whereas NS-1643 accelerated the activation rate. Neither enhancers changed the open probability of the inactivation gate. In contrast, PD-307243 only affected the inactivation by positively shifting its open probability curve without changing the activation properties. Because these enhancers have been shown to have different binding sites, we hypothesized that a novel binding site might exist for previously unrecognized hERG channel blockers. By using substructures of the 3 hERG channel enhancers for a cheminformatics search, we discovered several Novartis hERG blockers that likely overlap with the enhancer binding sites. These findings demonstrate the possible utilization of hERG channel enhancers to explore channel biophysics and uncover different classes of novel hERG channel blockers that may escape from traditional detection methods such as dofetilide-related radioligand binding.

### 1075-Plat
**Automated Patch Clamp with Current Clamp: Action Potential Recordings from Stem Cell Derived Cardiomyocytes**
**Sonja Stoelzle**, Alison Haythornthwaite, Claudia Haarmann, Cecilia Farre, Rodolfo Haedo, Andrea Brüggemann, Michael George, Niels Fertig.
Nanion Technologies, Munich, Germany.
Automated planar patch clamp devices, with their higher throughput and high data information content, are finding their place in the market for making high quality electrophysiological measurements.
Ease of use and higher data throughput make these devices ideal tools for ion channel screening and safety testing. The ability to record from stem cell derived cardiomyocytes in both voltage and current clamp modes on an automated patch clamp platform is an important advancement in ion channel screening and safety testing. Using a planar patch clamp workstation, currents mediated by $K^+$, $Na^+$ and $Ca^{2+}$ channels could be recorded from stem cell derived cardiomyocytes in the voltage clamp mode. In the current clamp mode, action potentials could be recorded for the first time on a planar patch clamp device. The built-in temperature control allowed for pharmacology on action potentials (see figure) both at room temperature and 35°.
The use of stem cell derived cardiomyocytes in safety testing is becoming increasingly important. The ability to test compounds on ion channels in both voltage and current clamp modes, as well as at different temperatures, may be crucial for future safety testing.




### 1076-Plat
**STIM1 in Rat Ventricular Myocytes**
**Guiling Zhao**, W.Jonathan Lederer.
Center for Biomedical Engineering and Technology and Department of Physiology, University of Maryland School of Medicine, Baltimore, MD, USA.
The $Ca^{2+}$ binding protein STIM1 is located primarily in the sarcoplasmic and endoplasmic reticulum. It is thought that STIM1 plays a critical role in activating $Ca^{2+}$ release activated $Ca^{2+}$ channel (CRAC) in non-excitable cells such as T lymphocytes and may also be important in excitable cells such as skeletal muscle and smooth muscle cells. However, it is not clear yet if STIM1 is expressed and functions in adult rat ventricular myocytes. Figure A shows STIM1 immunofluorescence and Figure B shows STIM1-mcherry fluorescence expressed in cultured rat ventricular myocytes. Both show a similar pattern of STIM1 localization, primarily at the Z-disk of the ventricular myocyte. Fluorescence recovery after photobleaching shows that STIM1 moves readily with the S/ER network. While there is no obvious need for store-operated $Ca^{2+}$ channels (SOCs) in ventricular myocytes, the clear presence of STIM1 suggests that an as yet undiscovered function of this $Ca^{2+}$ binding protein in ventricular myocytes is likely to be discovered. We are now examining the electrophysiological and $Ca^{2+}$ signaling functions of STIM1 in mammalian (rat and mouse) ventricular myocytes.



A. Immunostaining shows STIM1 is expressed in rat ventricular myocyte; B. Over expression of STIM1-mCherry in cultured (48 h) rat ventricular myocyte.