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PREDICTING DRUG-INDUCED CARDIAC ARRHYTHMIAS USING ATOMISTIC SIMULATIONS

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EXECUTIVE SUMMARY

Induction of potentially deadly abnormal cardiac rhythms is one of the most common and dangerous risks of drugs in development and clinical use. Induction has been tightly associated with the loss of function of the cardiac ion channel protein hERG, which is responsible for transporting potassium ions out of the cell and restoring resting electric potential at the end of a heartbeat. This leads to the prolongation of the QT interval (the time of ventricular activity) on the ECG.

However, not all hERG-blocking and QT-prolonging drugs cause cardiac arrhythmias resulting in withdrawal of safe and efficient pharmaceuticals. The research team has developed a computational pipeline encompassing atomic and tissue scales that lets us estimate drug proclivity for arrhythmogenesis from its chemical structure. All-atom enhanced sampling molecular dynamics simulations of hERG–drug interactions simultaneously running on multiple Blue Waters nodes allowed the team to compute drug binding affinities and rates, which were used to predict emergent arrhythmias on a cardiac tissue scale.

RESEARCH CHALLENGE

Small-molecule pharmaceuticals form the basis of commonly used treatments for the majority of human aliments, and development of new safe and efficient drugs is a cornerstone of modern biomedical research. A challenging and yet unresolved problem plaguing these efforts is the lack of a robust and accurate method for the prediction of drug cardiotoxicity in the form of deadly heart rhythm disturbances. Such cardiac arrhythmias are often caused by a drug-induced blockade of potassium channel hERG, a major cardiac membrane-embedded ion transport protein [1]. hERG block leads to an increased duration of cardiac cell membrane voltage perturbation (so-called action potential), often manifesting as a prolongation of the QT interval on the ECG. The problem, however, is that not all hERG-blocking and QT-prolonging drugs cause arrhythmias, and currently there is no methodology that can predict drug proclivity for arrhythmogenesis from its chemical structure [2]. This has led to the withdrawal from development of potentially safe pharmaceuticals. To avoid this, the research team aims to develop a multiscale computational pipeline starting from state-dependent atomistic structural models of hERG–drug interactions all the way to functional kinetic models of cardiac cells and tissues, which would allow researchers to make such predictions. The enhanced sampling all-atom molecular dynamics (MD) simulations on Blue Waters are an integral part of this pipeline and allow the computation of drug affinities and rates, which are used as functional model parameters.

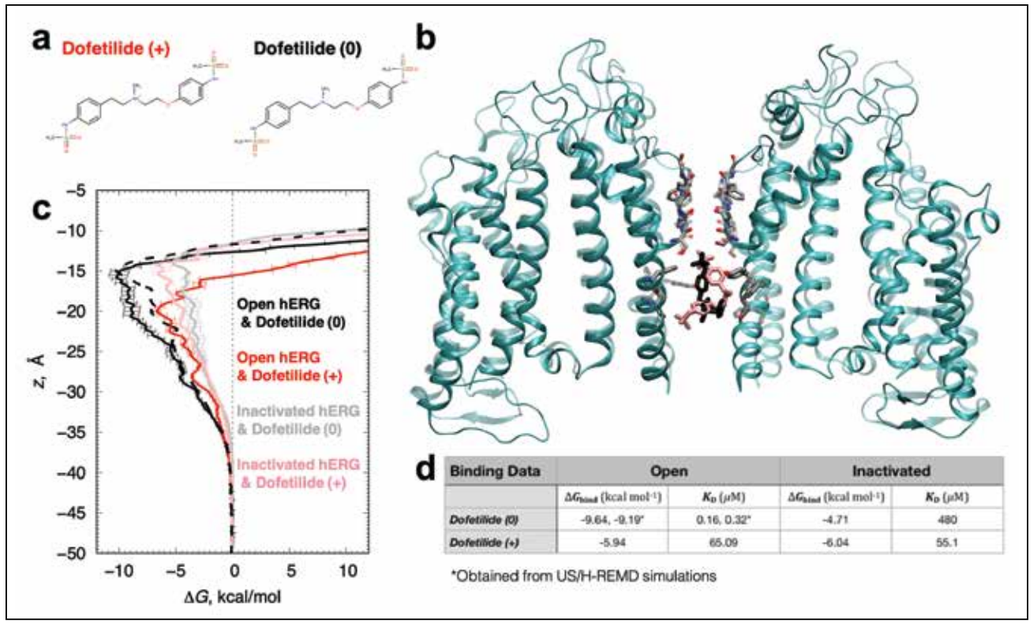

Figure 1: (a) Charged (0) and neutral (+) forms of dofetilide. (b) Open hERG (cyan ribbons) with dofetilide(0) bound (black) and inactivated hERG (semitransparent ribbons) with dofetilide(+) bound (pink). (c) Free energy (ΔG) profiles from the US/MD (solid) and US/H–REMD (dashed) simulations. (d) Computed binding free energies (ΔG_{bind}) and dissociation constants (K_d).

METHODS & CODES

The project's molecular systems of approximately 128,000 atoms consisted of the hERG protein built from a cryo-electron microscopy (cryo-EM) structure (PDB ID 5VA2) and embedded in a hydrated POPC (a phosphatidylcholine) lipid bilayer. The systems were assembled using CHARMM–GUI and simulated using NAMD with CUDA support on Blue Waters' XK nodes. After staged equilibration, umbrella sampling (US) and US–Hamiltonian-tempering replica exchange (US/H-RE) [3] MD simulations with 91 windows were used to study drug binding along the channel pore using 30 or 10 nanosecond-long production runs for each. Drug binding affinities were computed from free energy profiles, whereas drug ingress ("on") and egress ("off") rates were calculated based on diffusion coefficient profiles and from the ratio of "on" rates and affinities, respectively.

RESULTS & IMPACT

First, the team established that a cryo-EM hERG structure [4] likely represents an open conducting channel. The researchers also developed an inactivated hERG model by enforcing previously suggested N629 S620 intra-subunit hydrogen bonds [5] in restrained MD simulations, which also led to a distorted hERG selectivity filter conformation (Fig. 1b) thought to be important for inactivation [6]. In addition, the team developed atomistic CHARMM force field models of charged (+) and neutral (0) dofetilide (Fig. 1a). All-atom US/MD simulations revealed dofetilide binding in the channel pore, surrounded by hydrophobic F656 and Y652 residues (Fig.1b), known to be crucial for drug-induced hERG blockade [1]. Free energy profiles in Fig. 1c indicate more favorable binding for neutral dofetilide to the open hERG model compared to dofetilide(+) as well as inactivated state binding of both drug forms (compared to ΔG_{bind} in Fig. 1d). Both US/MD and US/H-REMD provided similar results (Fig. 1c and 1d) but at a fraction of computational cost for the latter. For open hERG, the team obtained a good agreement between experimental (3.5–11 μM [7–9]) and the team's computed (25±12 μM) drug affinities, K_d, accounting for drug form ratios at physiological pH. For inactivated hERG, experimental data suggest dofetilide binding in nanomolar range [7], but a much weaker affinity of 320±140 μM was computed. Thus, the inactivated hERG model likely is not representative of a channel state with high-affinity drug binding, and alternative models are actively being developed.

Importantly, the team computed "on" and "off" dofetilide rates for the open hERG model and directly used these values as parameters for their functional kinetic model of hERG–dofetilide interactions [10]. It was in turn integrated into the functional cardiac cell and tissue models, used to directly predict emergent arrhythmia indicators such as early afterdepolarizations in action potential profiles and beat-to-beat instabilities in computed pseudo-ECGs. The researchers' MD simulation-informed multiscale model provided excellent agreement for a range of experimental and clinical data, including a dose-dependent high pro-arrhythmia risk of dofetilide [10]. The team is working to utilize this pipeline for other hERG blocking drugs with different proclivities for arrhythmogenesis and, more importantly, suggest drug chemical modifications, which can alter its hERG interactions to ameliorate pro-arrhythmia risks but maintain their efficacy. Thus, the atomistic MD studies on Blue Waters helped the research group to develop and test a computational transferable protocol for robust prediction of drug cardiotoxicity based on its chemical structure, which can lead to faster and cost-effective development of safe and efficient pharmaceuticals and thus save human lives.

WHY BLUE WATERS

Access to Blue Waters' petascale architecture was indispensable for the success of these studies, since it allowed the team to efficiently conduct ~100 or more US/MD and US/H-REMD runs on GPU-equipped XK nodes at once, greatly reducing the total wall simulation time to just a few days and also permitting robust evaluation of simulation convergence.

PUBLICATIONS & DATA SETS

K. R. DeMarco *et al.*, "Atomistic modeling towards predictive cardiotoxicity," *bioRxiv*, p. 635441, 2019, doi: 10.1101/635441.