Chemical & Physical Sciences
UNIVERSITY OF TORONTO
MISSISSAUGA

COLLOQUIUM SEMINAR TALK
TUESDAY, MARCH 13, 2018
12:10PM
KN 132

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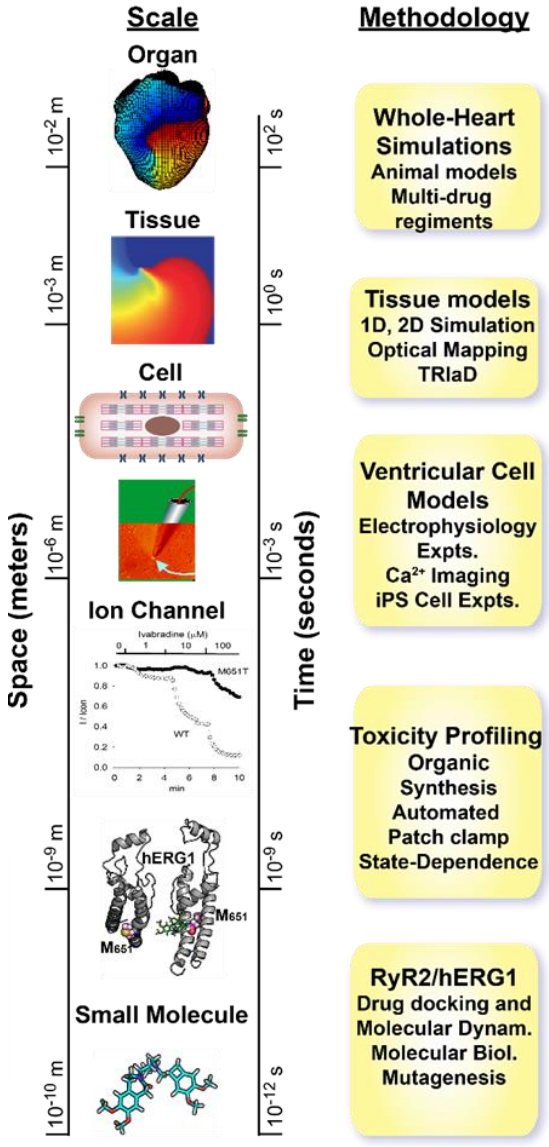
Modelling Drug Cardiotoxicity From Atom to Rhythms



Cardiotoxicity in the form of deadly abnormal rhythms is one of the most common and dangerous risks for drugs in development. Drug-induced proarrhythmia and prolongation of the QT interval have been so tightly associated that the QT interval has become widely accepted as a surrogate marker for arrhythmia. The problem with QT interval as a marker is that it is neither sensitive nor selective, resulting in many potentially useful drugs eliminated early in the drug discovery process including recent failures in clinical trials of retro-viral compounds. There is an urgent need for new approaches to screen and predict the effects of drugs on cardiac rhythms. I will present on the novel approach combining recently developed model cell lines derived from human cardiac myocytes and a panel of computational methods development to predict pIC50 of drug block to cardiac channels ranging from classical MD simulations, free energy simulations and then to machine-learning algorithms applied to drug interactions with various cardiac targets. Our work set the stage for predictions of how the fundamental mode of drug interaction with the promiscuous cardiac drug targets derived from each drug's unique structure activity relationship determines the resultant effects on cardiac electrical activity in cells and tissue. The modeling and simulation framework utilizes predictions from atomic scale cardiac ion channel structure simulations to generate kinetic parameters of for cellular models that capture dynamical interactions of drugs and target ion channels. The computational components are then integrated into predictive models and experimental measurements at the channel, cell and tissue scales to expose fundamental arrhythmia vulnerability mechanisms and complex interactions underlying emergent behaviors. This work demonstrates the feasibility and usefulness by applying the new framework to predict electro-toxicity in the heart for the prototype drugs.