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Title Machine learning in drug development: Characterizing the effect of 30 drugs using Gaussian process regression, sensitivity analysis, and uncertainty quantification

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Abstract Text

An undesirable side effect of drugs are cardiac arrhythmias, in particular a condition called torsades de pointes. Current paradigms for drug safety evaluation are costly, lengthy, and conservative, and impede efficient drug development. Here we combine multiscale experiment and simulation, high-performance computing, and machine learning to create an easy-to-use risk assessment diagram to quickly and reliable stratify the pro-arrhythmic potential of new and existing drugs, see Figure 1. We capitalize on recent developments in machine learning and integrate information across ten orders of magnitude in space and time to provide a holistic picture of the effects of drugs, either individually or in combination with other drugs. We show, both experimentally and computationally, that drug-induced arrhythmias are dominated by the interplay of two currents with opposing effects: the rapid delayed rectifier potassium current and the L-type calcium current. Using Gaussian process classification, we create a classifier that stratifies safe and arrhythmic domains for any combinations of these two currents. We demonstrate that our classifier correctly identifies the risk categories of 23 common drugs, exclusively on the basis of their concentrations at 50% current block. Our new risk assessment diagram explains under which conditions blocking the L-type calcium current can delay or even entirely suppress arrhythmogenic events. Using machine learning in drug safety evaluation can provide a more accurate and comprehensive mechanistic assessment of the pro-arrhythmic potential of new drugs. Our study shapes the way towards establishing science-based criteria to accelerate drug development, design safer drugs, and reduce heart rhythm disorders.

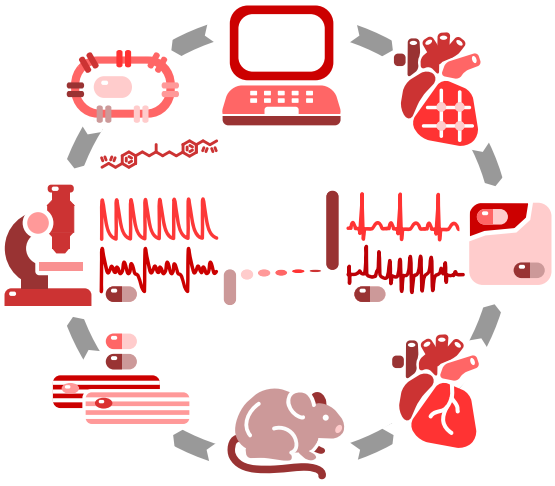

Figure 1. Hybrid computational-experimental approach to quickly and reliably characterize the pro-arrhythmic potential of existing and new drugs. We characterize calcium transients in ventricular cardiomyocytes in response to drugs, both computationally (top) and experimentally (bottom) and identify the ion channels that most likely generate early afterdepolarizations (left). We then screen the concentration space of the two most relevant channels and identify the classification boundary between the arrhythmic and non-arrhythmic domains using high performance computing and machine learning (center). We validate our approach using electrocardiograms, both computationally and experimentally, in whole heart simulations and excised Langendorff perfused hearts (right). We demonstrate the potential of our new classifier by risk stratifying 23 common drugs and comparing the result against the reported risk categories of these compounds.