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*JACC Clin Electrophysiol*. Author manuscript; available in PMC 2025 May 03.

Published in final edited form as:

*JACC Clin Electrophysiol*. 2024 February ; 10(2): 359–364. doi:10.1016/j.jacep.2023.10.024.

# Toward Digital Twin Technology for Precision Pharmacology

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## Abstract

The authors demonstrate the feasibility of technological innovation for personalized medicine in the context of drug-induced arrhythmia. The authors use atomistic-scale structural models to predict rates of drug interaction with ion channels and make predictions of their effects in digital twins of induced pluripotent stem cell–derived cardiac myocytes. The authors construct a simplified multilayer, 1-dimensional ring model with sufficient path length to enable the prediction of arrhythmogenic dispersion of repolarization. Finally, the authors validate the computational pipeline prediction of drug effects with data and quantify drug-induced propensity to repolarization abnormalities in cardiac tissue. The technology is high throughput, computationally efficient, and low cost toward personalized pharmacologic prediction.

### Keywords

digital twins; dofetilide; hERG; iPSC-CMs; moxifloxacin

The study of the fundamental mechanisms of the human cardiac rhythm has long been limited by the study of approximated models of the heart and its environment. Here, we present a digital replica of the commercially available iCell Cardiomyocyte (Fujifilm Cellular Dynamics) and then use a digital-twin approach to predict drug effects that are validated by experimental data (Central Illustration). This digital-twin approach to

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Katherine Murray, MD, served as the Guest Associate Editor for this paper. William Stevenson, MD, served as the Guest Editor-in-Chief for this paper.

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prediction can be extended to screen on other genetic backgrounds, as it is increasingly evident that individual variability may be a key factor in determining the emergence of rare disease phenotypes in the setting of inherited and acquired disease as well as in predicting drug effects on heart rhythm for safety pharmacologic screening.

## METHODS

### SIMULATED ICELL CARDIOMYOCYTES, CELL LINE 01434 INDUCED PLURIPOTENT STEM CELL–INDUCED CARDIOMYOCYTE SPONTANEOUSLY BEATING ACTION POTENTIALS.

The Kernik in silico induced pluripotent stem cell–derived cardiomyocyte (iPSC-CM) immature baseline cells generated to represent iCell Cardiomyocytes, cell line 01434,[1-3] were used to generate 205 control-population cells. Cells were simulated by allowing the model parameters to vary within the SD of the experimental measurements[4] to obtain a Fridericia-corrected action potential duration at 90% repolarization rate (APD90cF)[5] of 220 to 357 ms, and the in silico data were compared with the experimental data.[5] APD90cF rate correction was used for spontaneously beating iPSC-CMs, as described by Blinova et al[5]:

$$\text{APD90cF} = \frac{\text{APD90}}{\sqrt[3]{\text{Beating interval}}}$$

where APD90 is the action potential duration at 90% repolarization rate. We also reconstructed digital twins of the long-QT syndrome type 1 (LQT1) population from Kernik et al[6] to match experimental measurements.[5] Dofetilide and moxifloxacin were applied to the same simulated cells that were used for nondrug simulations. The experimental published data[5] were collected in patient-specific LQT1 iPSC-CMs. Dofetilide (0.5-8 nM) and moxifloxacin (10-200 μM) were each used in 16 subjects.

### SIMPLIFIED MULTILAYER, 1-DIMENSIONAL RING SIMULATIONS.

We developed a novel multilayer, 1-dimensional ring model comprising a section of spontaneously beating iPSC-CMs to drive initiation of the depolarization of the multilayer ring. The ends of the 1-dimensional tissue model were connected by resistances to simulate gap junctions to allow continuous beating around the ring (ring 1, 165 cells; ring 2, 300 cells; ring 3, 500 cells) and a connected fiber between rings of 54 cells ($\Delta x = 0.01$ cm). The multilayer, 1-dimensional ring comprised 1,019 iPSC-CMs with 100 spontaneous beating cells (pacemaker) and 919 quiescent cells.

### ATOMISTIC-SCALE MODELING AND SIMULATION.

The Markov models of human ether-a-go-go–related gene (hERG) channel gating with drug binding and unbinding provided good agreement with experimental and clinical data, as previously described,[7] and were incorporated into the Kernik iPSC-CM model.[4] In that model, drug affinities as well as ingress and egress (“on” and “off”) rates for both neutral and charged dofetilide and moxifloxacin to open hERG channel model were computed using free energy and diffusion coefficient profiles from umbrella sampling allatom molecular dynamics simulations, as described previously.[7]

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## RESULTS

We combined atomistic-scale simulations to predict the rates of drug binding and unbinding to the hERG $K^+$ channel[7] into the Kernik computational model of the iPSC-CMs.[4] The model is derived from iCell Cardiomyocyte (cell line 01434) iPSC-CMs. A population of 205 digital twins of the iCell line were generated by allowing the model parameters to vary within the SD of the experimental measurements as in Kernik et al.[4] The cells beat spontaneously with a frequency (cycle length [CL]) of 500 to 2,000 ms in simulated and experimental systems.[5] We then validated the predicted iPSC-CM model outputs (ie, APD90cF) with experimental action potentials from iPSC-CMs (ie, ΔAPD90cF),[5] as show in Figure 1A.

We next digitally applied moxifloxacin to simulated iPSC-CMs and tracked ΔAPD90 relative to baseline (Figure 1B, left). The maximum plasma concentration of 6.6 μM[8] resulted in the application of 10 to 70 μM moxifloxacin in experiments. We then compared model output against experimental iPSC-CMs.[5] Finally, we applied dofetilide to the digital iPSC-CM population, assuming clinical maximum plasma concentration of 2.14 nM,[5,9] resulting in an effective concentration of 0.5 to 4 nM. In Figure 1B (right), we compare the predicted effects on simulated iPSC-CM ΔAPD90 against experiments. Figure 1C shows a comparison between experimentally recorded[5] and digital-twin representations of LQT1 mutation action potential waveforms.[4,6] Figure 1D shows the combined effect of 140 μM moxifloxacin (left) or 4 nM dofetilide on LQT1 example traces (right). As in experiments, some cells displayed early afterdepolarizations (purple, experiments; blue, simulations).

We next developed a simplified approach to test the propensity of each drug to cause arrhythmia in tissue, as spatial dimension is a prerequisite for arrhythmia.[10] We constructed a simplified multilayer, 1-dimensional ring that allows sufficient path length to enable testing of arrhythmia proclivity. We connected 1,019 digital cells randomly selected from the digital population (n = 17,319) in Kernik et al.[4] We constructed 10 cases, each with a different set of 1019 iCell iPSC-CM digital twins. The ends of the 1-dimensional tissue model were connected to allow continuous electric propagation through the multilayer ring of mature cells (nonspontaneous) following activation by 100 spontaneous beating cells (immature pacemaker).

In Figure 2A, is an exemplar snapshot of electric activity for the digital tissue twin in the absence of a drug, to serve as a control (10 simulations). In response to activation by the "pacemaker," the full ring quickly depolarizes (red) and then repolarizes (blue). Figure 2B shows the application of 2 nM dofetilide to the same model, resulting in the emergence of a different excitatory pattern with the development of a prolonged excitatory state and increased dispersion of repolarization in space, a surrogate for arrhythmia. We computed the time from activation until full repolarization as a proxy for cardiac CL. The model predicts 418 ± 63 ms with dofetilide, considerably longer than control (354 ± 27 ms). We also tracked the variance of the cardiac CL across 10 simulations as an indicator of spatial dispersion of repolarization. The model predicts that dofetilide promotes profound spatial dispersion of repolarization. In Figure 2C, we predict the effect of moxifloxacin (10 μM) in the same digital twins. With moxifloxacin, there is some prolonged repolarization

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heterogeneity (366 ± 34 ms) for n = 10 simulations compared with the drug-free case but considerably less than with dofetilide.

## DISCUSSION

New experimental platforms have allowed the linkage of genetic variants to mechanisms of disease that underlie disruption of normal cardiac physiology. As a result, we have gained a deeper mechanistic understanding of the emergence of specific cardiac phenotypes. However, there is not yet a clear way to understand the influence of individual genetic variability on susceptibility to drug-induced arrhythmias. The computational pipeline described here was able to predict different arrhythmia risks for 2 potent hERG blockers, dofetilide and moxifloxacin, and may constitute a first step toward personalized safety pharmacology.

A couple of important limitations of the approach here should be noted. Although the experimental[5] and simulated iPSC-CMs beat spontaneously with a frequency (CL) in the range of 500 to 2,000 ms, allowing predicted outputs to be directly compared with experimental measurements from spontaneously beating cells, we did not explore pacing frequencies outside that range. In our system, we match the predicted and measured data at the same rate over a broad range of frequencies, and the reported predictions shown in Figure 1 were corrected for rate.

The concentric-circle model in Figure 2 allows an extension of the path length in the simulations and the propagating impulse can move through one ring and into another and back again if: 1) excitation wavelength is shorter than the path length; and 2) current source is sufficient to excite the downstream sink. There are many conditions that can be tested in this geometry to predict the effects of these interactions, but here we tracked only the time it takes between excitation events (cardiac cycle) and the time from the start of impulse depolarization until the time the final cell repolarizes (a measure of dispersion).

The results can also be easily translated to a mature cardiac phenotype with simulation results classified into different risk categories using a machine learning pipeline.[11] As new approaches are critically important to attempt to solve long-standing problems related to the susceptibility of individuals to inherited and/or acquired cardiac arrhythmia, the technical innovation and associated source code presented here are freely available for use.

## FUNDING SUPPORT AND AUTHOR DISCLOSURES

This work was supported by National Heart, Lung, and Blood Institute (NHLBI) grants R01HL128537 (to Drs Clancy, Santana, and Vorobyov), R01HL152681 (to Drs Santana and Clancy) and U01HL126273 (to Drs Clancy and Yarov-Yarovy), NIH Common Fund Grant OT2OD026580 (to Drs Clancy and Santana), American Heart Association Career Development Award 19CDA34770101 and Oracle for Research fellowship (to Dr Vorobyov). All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

## ABBREVIATIONS AND ACRONYMS

**APD90** action potential duration at 90% repolarization rate

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| | |
|---|---|
| **APD90cF** | Fridericia-corrected action potential duration at 90% repolarization rate |
| **CL** | cycle length |
| **hERG** | human ether-a-go-go–related gene |
| **iPSC-CM** | induced pluripotent stem cell–derived cardiomyocyte |
| **LQT1** | long-QT syndrome type 1 |

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## PERSPECTIVES

### COMPETENCY IN MEDICAL KNOWLEDGE:

This study combines atomistic-scale simulations with a computational model of iPSC-CMs, providing valuable insights into the mechanisms of drug-induced arrhythmias. These insights can enhance our understanding of the factors contributing to arrhythmia development. By validating the predicted iPSC-CM model outputs against experimental data, the study demonstrates the reliability of the computational model in replicating real-world scenarios.

### TRANSLATIONAL OUTLOOK:

The study is an initial framework that can be extended for personalized safety pharmacology by predicting the individual arrhythmia risks of specific drugs. Future research can focus on expanding this approach to a broader range of drugs, allowing tailored drug safety assessments for individual patients. Future extension should include the integration of machine learning to classify drug-induced arrhythmia risk categories and to automate the categorization of drug safety, making it a practical tool for clinicians and drug developers.

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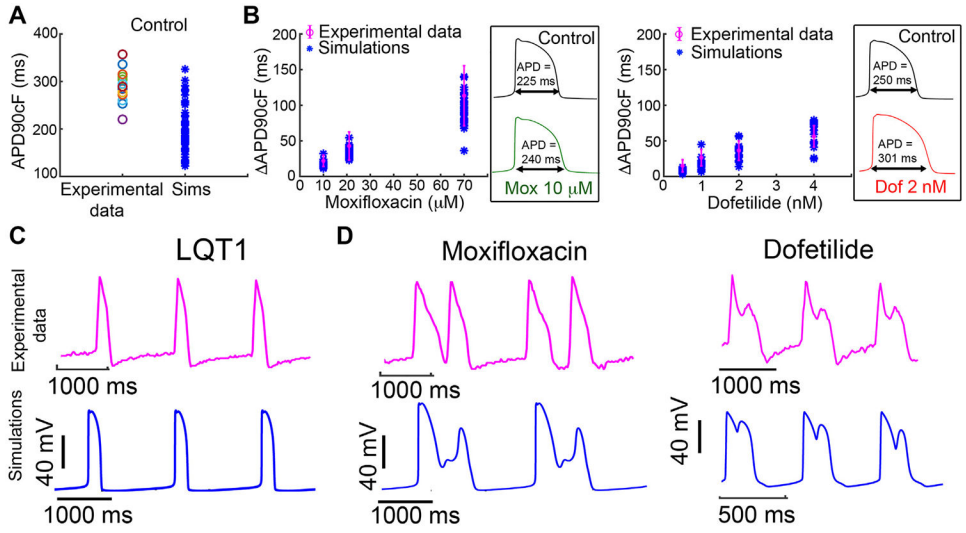



**FIGURE 1. Drug Screening in Digital Twins and Validation by Clinical and Experimental Data**

(A) Comparison of predicted effects of drugs on experimentally recorded iCell induced pluripotent stem cell–derived cardiomyocyte (iPSC-CM) action potential duration at 90% repolarization rate (APD90)[5] and digital-twin iPSC-CM APD90. We constructed 205 digital-twin iCell iPSC-CMs by randomly varying within the SDs of the experimental measurements.[4] (B) Comparison of simulated iPSC-CM ΔAPD90 to experimentally recorded iPSC-CMs for moxifloxacin (Mox) concentrations ranging from 10 to 70 μM (left) and a range of dofetilide (Dof) concentrations (0.5-4 nM). Example action potentials (APs) demonstrating the effect of moxifloxacin and dofetilide on AP morphology and duration from iCell digital twins are also shown. (C) Experiments (purple)[5] and digital twins (blue) of a long-QT syndrome type 1 (LQT1) mutation.[4,6] (D) LQT1 example traces with early afterdepolarizations after 140 μM moxifloxacin and 4 nM dofetilide. APD = action potential duration; APD90cF = Fridericia-corrected action potential duration at 90% repolarization rate; Sims = simulations.

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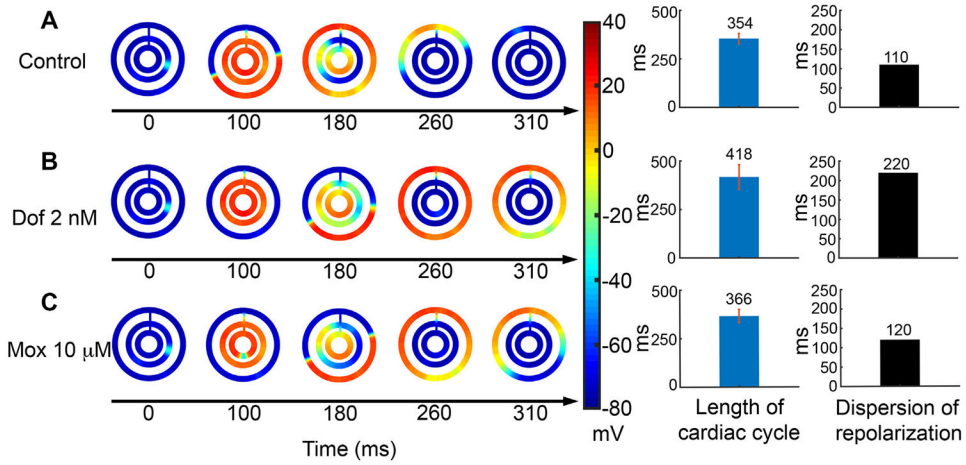
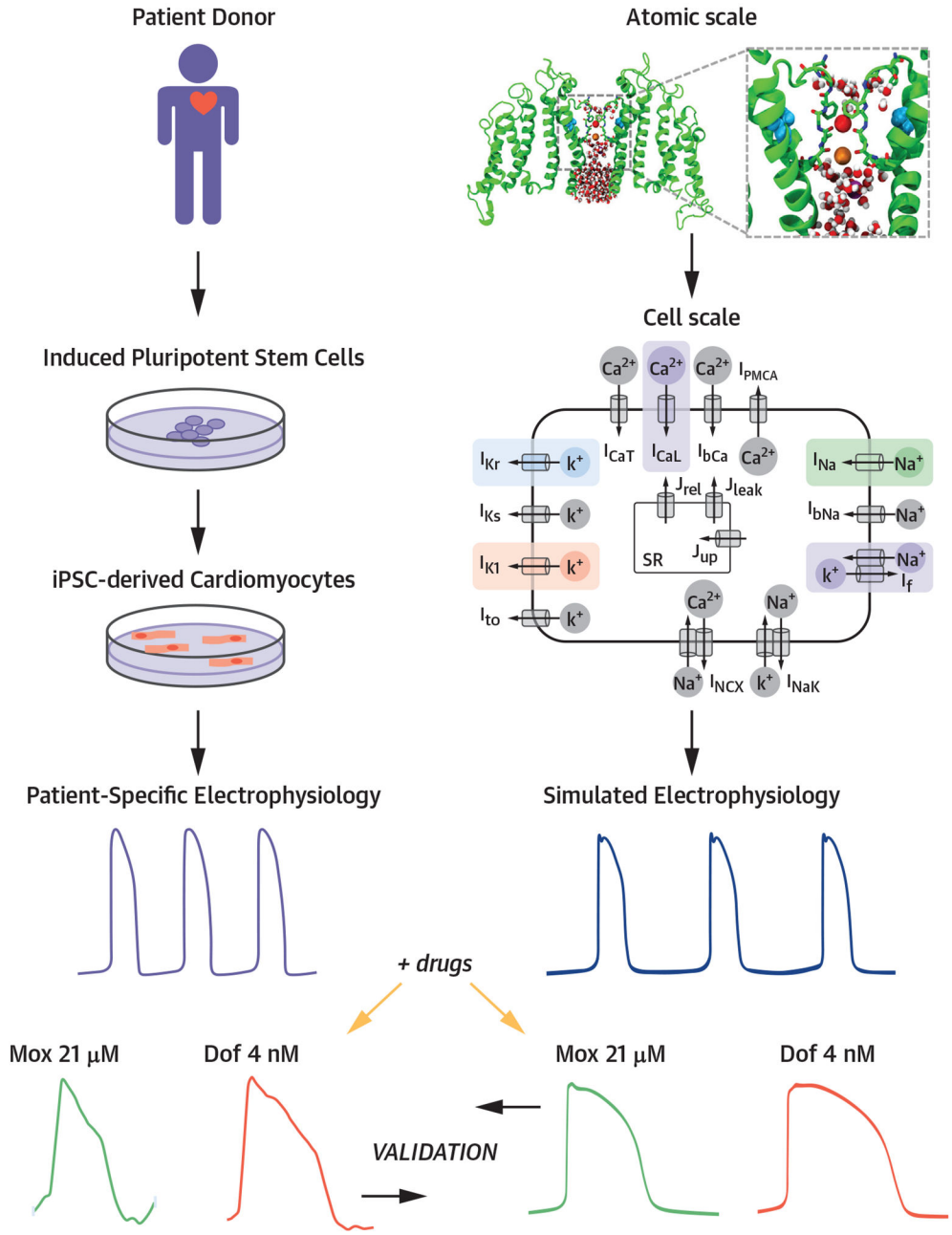



**FIGURE 2. Prediction of Initiation and Longevity of Arrhythmia Proclivity in an Idealized 1-Dimensional Digital Tissue Twin Model**

Shown is electric activity for a multiring, 1-dimensional digital tissue twin model comprising 1,019 induced pluripotent stem cell–derived cardiomyocyte digital twins connected by resistances to simulate gap junctions with 100 spontaneous beating cells driving depolarization. Each simulated tissue contained identical patterns of randomized spatial heterogeneity imposed by randomly varying within the SDs of the experimental measurements.[4] (A) Prediction of control case in the absence of drug (n = 10 simulations). (B) Predicted effect of the application of 2 nM dofetilide (Dof) (n = 10 simulations). (C) Application of 10 μM moxifloxacin (Mox) (10 simulations). The bar graphs on the right show proxy metrics for cardiac cycle length (left bars) and dispersion of repolarization (right bars; maximum – minimum cardiac cycle).

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**CENTRAL ILLUSTRATION. The Development of Digital Twins of iPSC-CMs Is a Step Toward the Prediction of Individual Responses to Drugs**

The left column shows the in vitro approach resulting in the differentiation of induced pluripotent stem cells (iPSCs) into iPSC-derived cardiomyocytes (iPSC-CMs) with patient-specific electrophysiology. The right column shows the computational pipeline from atomistic simulation structural model to predict drug–hERG channel kinetics that can then be incorporated into iPSC-CM digital twins, constituting a new high-throughput and low-cost approach to personalized drug screening. In the bottom row, digital outputs are compared with and validated by experiments[5] demonstrating the feasibility

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of the technology. Dof = dofetilide; hERG = human ether-a-go-go–related gene; Mox = moxifloxacin.