Development and Validation of a Cellular Automaton Framework for Simulating Heterogeneous Ventricular Restitution Dynamics and Functional Re-entry

Giada S Romitti[1], James A Coleman[2], Alejandro Liberos[1], Ignacio García-Fernández[1], Miguel Lozano[1], Miguel Rodrigo[1], Alfonso Bueno-Orovio[2]

[1] Computational Multiscale Simulation Lab (CoMMLab), Department of Computer Science and Department of Electronic Engineering, Universitat de València, Valencia, Spain
[2] Department of Computer Science, University of Oxford, Oxford, United Kingdom

Abstract

The elevated computational cost of high-fidelity cardiac simulations often limits their clinical utility. We developed and validated an efficient cellular automaton (CA) framework to model functional ventricular arrhythmias and handle electrophysiological variability.

By embedding the biophysically detailed ToR-ORd model into the CA via action potential duration (APD) and conduction velocity restitution properties, we extend the population-of-models paradigm to a CA environment for the first time. Hypertrophic cardiomyopathy served as a validation exemplar for large-scale simulations of intra-individual variability.

The framework accurately captured the electrophysiol-ogical diversity of the underlying biophysical population, with mean average errors of 1.39–6.18 ms (<2.3% relative error) in APD reconstruction. Under complex S1-S5 pacing, the CA reproduces 96% of stimuli with high fidelity (5.9% mean APD error) and captures complex functional re-entrant patterns, such as ventricular tachycardia, consistent with full biophysical simulations.

These results demonstrate that the proposed CA model can retain high-fidelity predictive power while enabling rapid, population-based arrhythmia risk assessment at scale across diverse cardiac pathologies.

1. Introduction

The computational cost of biophysically detailed models remains a primary constraint for large-scale clinical applications, particularly when investigating the functional substrates of complex arrhythmias. Despite this, computational arrhythmia modelling holds considerable potential to advance mechanistic insights into sudden cardiac death, with important implications for clinical risk stratification [1]. To bridge the gap between high-fidelity mechanistic depth and clinical feasibility, there is an increasing need for efficient reduced-order approaches that retain key properties of interest. Cellular automata (CA) offer a promising alternative, enabling efficient simulations while preserving key electrophysiological properties relevant to arrhythmogenesis [2, 3]. However, while careful consideration of cellular variability is critical for accurate arrhythmia modelling, it has remained largely unaddressed in CA frameworks.

To address this gap, we extend our CA framework to incorporate heterogeneous ventricular restitution effects, thereby enabling the modelling of functional re-entry. Specifically, we integrated the biophysically detailed ToR-ORd model into the CA, characterizing its behaviour through action potential duration (APD) and conduction velocity (CV) restitution properties. The framework was then expanded using a population-of-models approach [4], allowing the study of electrophysiological diversity at scale. To our knowledge, this marks the first application of a CA model to construct restitution-based populations, enabling the exploration of electrophysiological variability at a fraction of the traditional computational cost.

Finally, we demonstrate the utility of this framework by examining arrhythmia mechanisms in hypertrophic cardio-myopathy (HCM), a disease condition affecting 1 in 500 individuals and a leading cause of sudden cardiac death [5]. By comparing functional re-entry in the CA model against its monodomain equivalent, we provide a robust and scalable platform for exploring arrhythmogenesis in inherited heart disease and beyond.

2. Material and Methods

2.1. Calibration of CA restitution features

To calibrate and validate the CA model, we performed monodomain simulations using the ToR-ORd ventricular action potential model [6] implemented in MonoAlg3D [7]. To account for variable degrees of slowed repolarisation in HCM, eight scenarios were simulated by combining transmural cell types (endocardial and epicardial) and ionic remodelling severity (Control, Moderate, Severe, Extreme), as in previous work [1].

Restitution properties were quantified for both APD and CV using S1–S2 protocols. Simulations were conducted on a 1D cable (70 mm; Δx=0.1 mm). Each case was initialized to steady-state over 250 beats, and S1-S2 restitution properties computed over a broad range of cycle lengths ($S1 \in \{300{:}20{:}500, 600{:}100{:}1000\}$, $S2 \in \{200{:}20{:}1100\}$ ms), yielding a total of 5,888 simulations.

APD restitution was modeled by a double-exponential surface capturing the dependence of APD^{n+1} on both the preceding diastolic interval (DI^n) and APD (APD^n), accounting for recovery kinetics and memory effects [3] (Figure 1A-B). This formulation implicitly incorporates tissue refractoriness by anchoring the restitution properties to the minimum DI^n (effective refractory period) supported by the biophysical ToR-ORd model, ensuring consistency with the underlying recovery dynamics [3]. CV restitution was modeled via exponential relationships with DI^n [2] (Figure 1C). Biomarkers were evaluated at cable locations selected to minimize boundary effects.

The CA framework follows an event-driven formulation [2], where tissue elements are represented as binary states (inactive/active) and activation times are computed via a fast-marching scheme driven by CV restitution. To visualize and track cellular activity, a "lifetime" variable was assigned to each element to track activation duration.

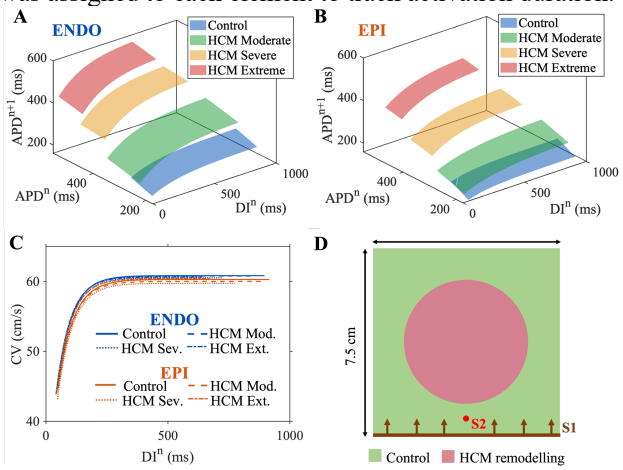

Figure 1. (A) ENDO and (B) EPI transmural APD restitution surfaces (APD^{n+1}); (C) CV restitution curves; (D) 2D simulation domain for arrhythmia induction.

2.2. CA extension to population of models

To reconstruct the continuous electrophysiological space of the biophysical population, we developed a parametric interpolation framework. This approach allows the CA to represent any intermediate cellular phenotype by interpolating between reference restitution surfaces (e.g., HCM Moderate–Severe). For a given model within the biophysical population, a consistent parametric interpolation ($\alpha \in [0,1]$) was applied to both the (DI^n, APD^n) domain and the corresponding APD^{n+1} values within the overlapping physiological range. Interpolated values were then fitted using a double-exponential surface, preserving nonlinear restitution dynamics and smooth transitions between scenarios.

To validate the interpolation accuracy, the interpolated surfaces were compared against ground-truth monodomain data. Specifically, we identified the ionic configurations corresponding to each target APD and applied an S1-S2 pacing protocol to these configurations. This allowed us to reconstruct the "ground-truth" restitution properties and verify their consistency against the interpolated ones.

2.3. Electrophysiological stimulation protocols and arrhythmia validation

The proposed CA model was validated using a two-step process. First, cable-level validation was performed under complex pacing protocols to assess the CA ability to capture rapid changes in excitation frequency. Simulations were conducted on the same 1D domain used for restitution extraction. All eight scenarios were evaluated under an unseen S1-S5 protocol (3×S1 at 1000 ms, 1×S2 at 800 ms, 2×S3 at 600 ms, 1×S4 at 400 ms, and 3×S5 at 500 ms).

Second, tissue-scale re-entry dynamics were examined by comparing CA inducibility with monodomain counterparts on a 7.5×7.5 cm² domain containing a central circular HCM-remodeled zone (2.5 cm radius; Figure 1D). Simulation outcomes were categorized into four responses following [1]: (i) failed ectopic propagation, (ii) successful propagation without reentry, (iii) premature ventricular complex (PVC) couplets (single reentrant beat), and (iv) ventricular tachycardia (VT; ≥2 reentries).

3. Results

3.1. Cable validation: CA accurately reproduces complex pacing protocols

The CA produced both APD and CV decreases with higher pacing rates, reflecting the ion channel recovery kinetics of the ToR-ORd model (Figure 1A-C). Moreover, the CA preserved the physiological transmural gradient, with longer APD in endocardial versus epicardial cells [6] (Figures 2 and 3). While the biophysical model required 250 beats for stabilization, the CA achieved steady-state in less than 5 beats.

When evaluated against the monodomain biophysical model using the complex S1-S5 protocol, the CA achieved concordant activation in 77 out of 80 stimuli (96%), with a mean APD error of 5.9% (Figure 2). Notably, this included the correct reproduction of 7 non-capture events, in which stimuli applied during the refractory period failed to trigger an activation, confirming that the CA faithfully replicates the biophysical limits of tissue excitability.

Minor discrepancies occurred only at extremely small

DIs under strong APD protraction (HCM Severe/Extreme), where the CA's discrete propagation threshold differs from the marginal excitability of the biophysical model. Overall, the CA faithfully reproduces the main trends observed across all scenarios at only a fraction of the computational cost (approximately 1.3% of the biophysical simulation time, representing a 75× speedup [3]).

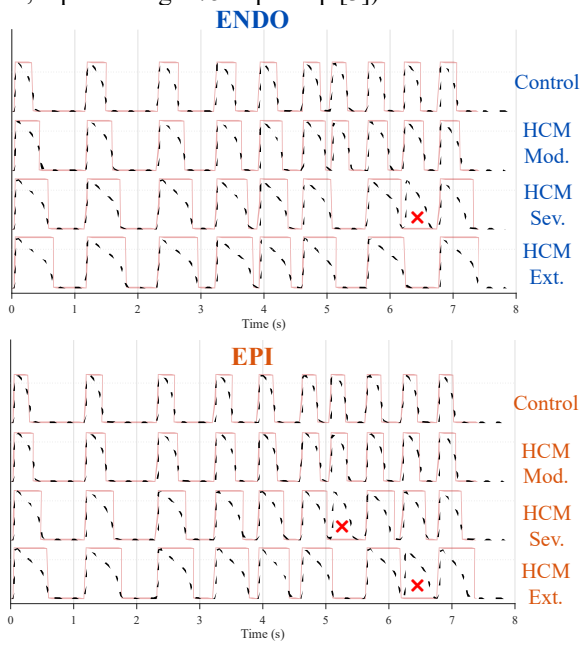

Figure 2. Stacked membrane potentials for ENDO (top) and EPI (bottom) scenarios. ToR-ORd model simulations (black) are compared with corresponding cellular automaton states (pink, rescaled to the same range).

3.2. Interpolated restitution surfaces accurately reproduce biophysical dynamics

The proposed interpolation strategy, designed to enable variable APD prolongation while capturing cell variability through a population-like approach, successfully generated comprehensive restitution surfaces at all intermediate levels of remodeling. The evaluation encompassed four diverse remodeling stages: 40% HCM Moderate–Severe (ENDO), 68% HCM Severe–Extreme (ENDO), 19% HCM Moderate–Severe (EPI), and 88% HCM Severe–Extreme (EPI). Mean absolute APD errors ranged from 1.39 ms (ENDO Severe–Extreme) to 6.18 ms (EPI Moderate–Severe), with relative errors consistently below 2.3% and peak local deviations remaining under 10 ms.

Representative interpolated examples for both ENDO (Severe-Extreme) and EPI (Moderate-Severe) scenarios are shown in Figure 3, including action potentials (Figure 3A,D), comparisons between interpolated and biophysical restitution surfaces (Figure 3B,E), and the corresponding restitution error maps (Figure 3C,F). Error patterns were consistent across all cases, with minor deviations primarily localized at short DI^n at high pacing rates. In all cases, errors remained uniformly low across the DI^n range (Figure 3C,F). Differences in restitution slope were small (≤0.03; relative error), indicating preservation of key dynamical properties such as APD sensitivity and alternans onset.

Pointwise error distributions were narrow and centered around zero for all remodeling levels. Small shifts in mean error observed in specific ENDO and EPI configurations were associated with low variance, suggesting the absence of significant systematic biases. Overall, the framework accurately reproduces the main features of the underlying biophysical behavior of HCM progression, enabling CA simulations of populations of models in health and disease.

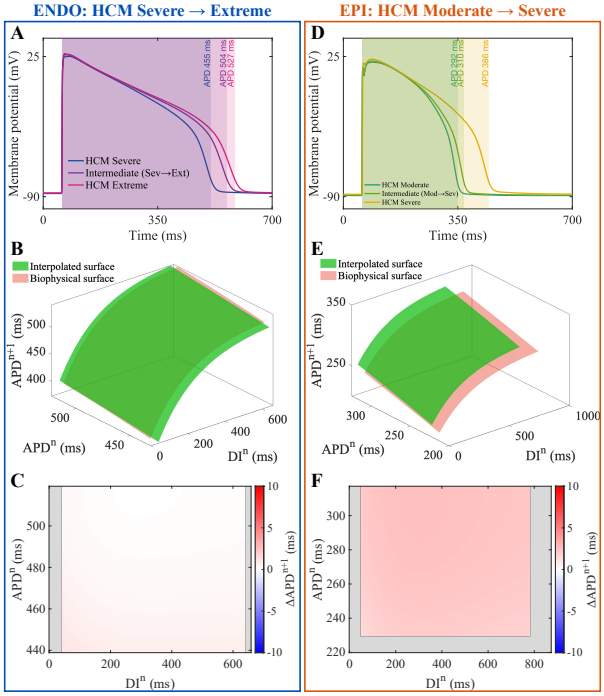

Figure 3. Interpolation performance in representative ENDO (left, Severe–Extreme) and EPI (right, Moderate–Severe) cases. (A, D) Membrane potential curves. (B, E) Restitution surfaces. (C, F) Error maps ($\Delta APD^{n+1} = APD^{n+1}_{interpolated} - APD^{n+1}_{biophysical}$).

3.3. 2D tissue validation: CA reproduces functional re-entry mechanisms

The functional accuracy of the CA framework was further validated by comparing its emergent arrhythmic behavior against high-fidelity biophysical simulations under S1-S2 pacing. Across the population of models, the CA successfully reproduced the four categorical responses of wavefront conduction (failed ectopic, propagation with no re-entry, PVC couplets, and VT). Figure 4 illustrates a representative case of VT induction, where the CA model consistently replicated the same qualitative dynamics and activation pathways of its biophysical analogue. Notably, the framework captures key features such as breakthrough points and wavefront curvature during interaction with the

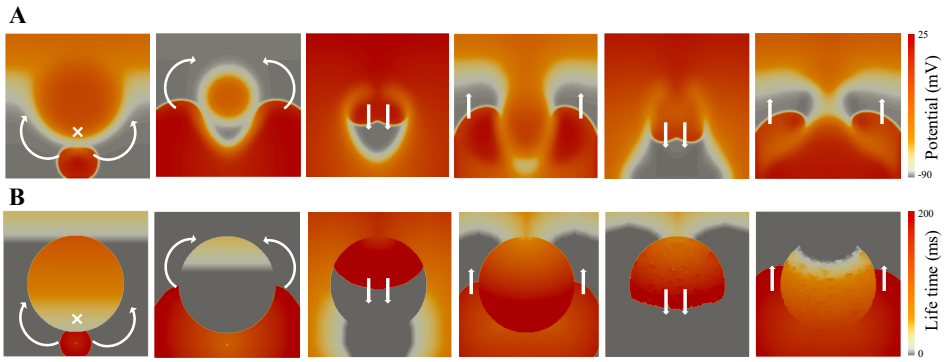

Figure 4. Representative tissue simulations following S2 stimulation, illustrating VT induction in (A) monodomain snapshots (transmembrane potential) and (B) CA simulations (activation times expressed via lifetime).

HCM-remodeled region.

Critically, while CA models have largely been limited to simulating anatomical re-entry (e.g., around fixed scars [2]), these results demonstrate that our framework enables the investigation of functional re-entry supported by heterogeneous repolarization substrates. This advance confirms that the CA can reliably replace biophysical models in large-scale studies of arrhythmia mechanisms triggered by electrophysiological remodeling.

4. Conclusions and Discussion

This work extends a CA framework [3] to translate complex ventricular biophysics into a computationally efficient environment. By integrating ToR-ORd-derived kinetics, the proposed model enables, for the first time, the accurate simulation of functional re-entries driven by heterogeneous repolarization substrates, a phenomenon traditionally limited to high-fidelity biophysical solvers. A core innovation is the integration of ionic variability directly into the CA architecture. Unlike conventional CA, our strategy incorporates a population-based approach to represent electrophysiological diversity within the substrate. The resulting framework is inherently scalable, providing a practical platform for large-scale investigations of inter-subject variability.

The framework was validated in dual-stage process. Under complex S1–S5 pacing, the CA achieved 96% accuracy in capturing beat-to-beat dynamics, replicating not only APD and CV restitution but also refractory-induced activation failures. At the tissue level, it successfully reproduced the full spectrum of arrhythmic outcomes observed in biophysical benchmarks [1], including the emergence of sustained VT. Moreover, the model achieves steady-state stabilization in less than 5 beats, and an estimated 75-fold reduction in execution time, enabling efficient large-scale and real-time simulations.

Building on this validation, future efforts can now focus on systematically exploring a broader parameter space. Its computational efficiency makes it particularly suitable for high-resolution S1–S2 inducibility and vulnerability window studies, which remain computationally prohibitive for high-fidelity solvers. By delivering accurate results with negligible overhead, this framework enhances the feasibility of large-scale screenings and represents a step towards rapid, personalized arrhythmic risk assessment.

Acknowledgments

This work was funded by grants PID2023-148702OB-100 (MCIU/AEI 10.13039/50110001103), EraNet PCI2024-153442 (FEDER, UE), and CIAICO/2024/247 (Consolidados 2024, Generalitat Valenciana). This work acknowledges further support from the SMASH-HCM project under Innovate UK grant 10110728.

References

[1] J. A. Coleman et al., “Effects of ranolazine on the arrhythmic substrate in hypertrophic cardiomyopathy,” *Front. Pharmacol.*, vol. 15, Art. no. 1379236, 2024.

[2] D. Serra et al., “An automata-based cardiac electrophysiology simulator to assess arrhythmia inducibility,” *Mathematics*, vol. 10, no. 8, Art. no. 1293, 2022.

[3] G. S. Romitti et al., “Implementation of a cellular automaton for efficient simulations of atrial arrhythmias,” *Med. Image Anal.*, Art. no. 103484, 2025.

[4] O. J. Britton et al., “Experimentally calibrated population of models predicts and explains intersubject variability in cardiac cellular electrophysiology,” *Proc. Natl. Acad. Sci. U.S.A.*, vol. 110, no. 23, 2013.

[5] M. Lorenzini et al., “Mortality among referral patients with hypertrophic cardiomyopathy vs the general European population,” *JAMA Cardiol.*, vol. 5, no. 1, pp. 73–80, 2020.

[6] J. Tomek et al., “Development, calibration, and validation of a novel human ventricular myocyte model in health, disease, and drug block,” *elife*, vol. 8, Art. No. e48890, 2019.

[7] L. A. Berg et al., “Toward cardiac electrophysiology digital twins with an efficient open source scalable solver on GPU clusters,” *Scientific Reports*, 2026.

Address for correspondence:

Giada Sira Romitti
Av. de l’Universitat, s/n. 46100, Burjassot (Valencia, Spain).
giada.romitti@uv.es