

Assessing the Predictability of Real-Time Cardiac Digital Twins under Pathological Conditions

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Abstract

The clinical utility of cardiac digital twins (CDTs) critically depends on their ability to accurately predict an individual patient's response to medical interventions with high confidence. Performing an adequate assessment of their predictability becomes challenging when considering their computational costs, inherent model uncertainties and generalizability beyond baseline conditions. In this work, we present a calibrated CDT that produces electrocardiograms (ECGs) with high fidelity in near real-time and assess its predictability by evaluating manifestations of diagnostic ECG criteria when imposing common pathological conditions. In our evaluation, we demonstrate the accuracy and computational performance of the proposed CDT under baseline conditions and found that it reproduced 85% of expected diagnostic ECG criteria across all investigated pathological conditions. Our results provide initial evidence of CDT predictability towards previously unobserved conditions, thereby supporting the advancement of computational modeling in precision cardiology.

therefore crucial but challenging due to several implementation gaps. First, querying the vast parameter space of CDTs via many forward simulations is computationally infeasible with standard reaction-diffusion (RD) models [3], while calibrated CDTs remain subject to considerable uncertainty due to identifiability limits of the ECG [4,5]. Second, the incorporation of the cardiac conduction system is pivotal for reproducing key clinical markers in ECGs but inferring its exact topology is impossible with current non-invasive technologies [6]. Third, a deployment in clinical settings requires uncertainty quantification of CDTs, but assessment of their predictive capabilities beyond baseline conditions is difficult to perform and remains largely unexplored. Confronted with these challenges, current CDT frameworks resort to simplified modeling assumptions and restricted evaluation at the expense of their physical fidelity and generalizability. Accomplishing true clinical utility for CDTs requires high fidelity but computationally lean electrophysiology (EP) models enabling feasible calibration, incorporate a functionally realistic cardiac conduction system and demonstration of their validity beyond agreement with observations.

1. Introduction

Precision cardiology relies on key technologies for facilitating personalized therapies that are tailored to the biology of individual patients. CDTs – computational models of the heart combining patient-specific anatomical and clinical data within a mechanistic physiological framework – are emerging as one such promising technology. Assuming a strong coupling between *in silico* and *in vivo* hearts, a CDT can predict how a patient's heart will respond to medical interventions and risk factors, and thereby support the interpretation of clinical observations, risk stratification [1] and therapy planning [2] on an individual basis.

Establishing a strong coupling by calibrating CDT predictions to physical observations, foremost the ECG, is

We present an anatomically and mechanistically detailed model of human whole-heart EP that facilitates ECG prediction with high physical fidelity in near real-time. The CDT incorporates a realistic cardiac conduction system and was calibrated with carefully constrained anatomical and functional priors to accurately reproduce the P-wave, QRS-complex and T-wave morphologies of the subject's ECG during normal sinus rhythm (NSR). Its predictability was assessed by imposing intraventricular conduction disorders and tachy-arrhythmias and comparing model predictions against established ECG diagnostic criteria. We demonstrate that simulated manifestations of the pathologies are consistent with expected EP characteristics and ECG criteria.

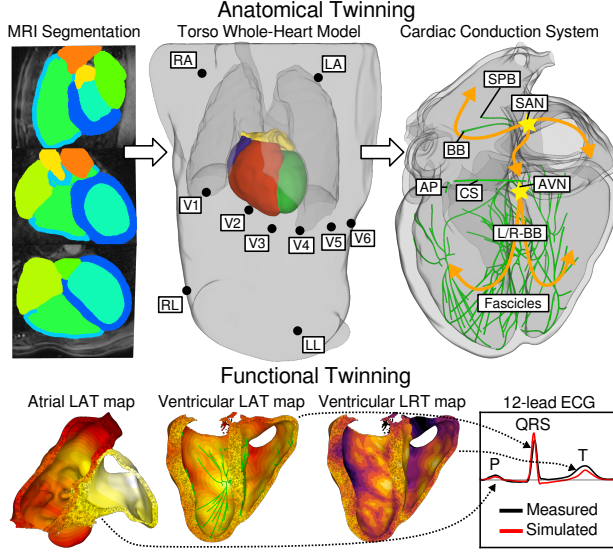


Figure 1. Components of the anatomical and functional twinning workflow employed for the proposed CDT.

2. Methods

2.1. Model Generation and Calibration

The anatomical and functional twinning workflow employed for generating the proposed CDT is depicted in Fig. 1. An anatomically accurate heart-torso model of a healthy subject was reconstructed from magnetic resonance imaging (MRI) data using a high fidelity anatomical twinning workflow [7] that was extended to cover the whole heart. The locations of key anatomical structures related to the cardiac conduction system, comprising of the sinoatrial node, inter-atrial connections, the coronary sinus, the atrioventricular node, the bundle branches and the ventricular fascicles, were manually identified based on the MRI data and profound anatomical prior knowledge [6]. In the subsequent functional twinning stage, the CDT was equipped with a mechanistic model of cardiac EP and calibrated to reproduce the subject's ECG under NSR. For this purpose, the Physics-Informed Eikonal (PIE) model [3], a computationally lean reduced-order EP model capable of simulating reentrant de- and repolarization patterns with high fidelity in near real-time, was employed. During calibration, PIE model attains physical fidelity by measuring action potentials and conduction velocities emerging within small-scale but high fidelity RD models and prescribes them as feature maps per myocardial region. To account for the heterogeneity of EP in the myocardial regions, these feature maps can be fine tuned per node, relative to their prescribed parameters, in order to precisely control de- and repolarization in the myocardium and therefore the emerging ECG.

To reproduce the clinically measured ECG from the subject under NSR, the EP of active myocardial regions was functionally characterized by the Courtemanche model [8] in the atria, the ToRORd model [9] in the ventricles and the Trovato model [10] in the his-purkinje system (HPS). Intra- and extra-myocardial regions were parameterized within a range of physiologically plausible EP properties, assembled from a comprehensive literature research [6, 11]. The PIE model was calibrated to match a baseline EP parametrization at a nominal basic cycle length of 600 ms using the ForCEPSS framework for standardized EP simulation [12]. To fit P, QRS and T segments of the ECG, the feature maps were fine-tuned using a Bayesian optimization scheme from the hyperparameter optimization framework Optuna [13]. In each optimization step, the error between the reference and the simulated ECG was quantified by the dynamic time warping (DTW) distance measure:

- The P-wave emerges from the depolarization pattern traversing the atria which starts at the sinoatrial (SA) node and spreads from the left to the right atrium via interatrial connections. Its morphology was reproduced by optimizing the conduction velocities (CVs) within the atria and the position of the interatrial connections.
- The QRS-complex results from the concurrent atrial repolarization and ventricular depolarization patterns where the latter is mediated by the HPS. Its morphology was matched by adjusting action potential duration (APD) maps within the atria, CV maps in the ventricles and the earliest activation sites of the HPS.
- The shape of the T-wave emerges from the ventricular repolarization gradients, which were tuned through the APD maps based on the apico-basal, transmural, circumferential components of the universal ventricular coordinates.

2.2. Model Evaluation

The fidelity of the calibrated CDT under baseline conditions was quantified by measuring the discrepancy between the simulated and the reference ECG under NSR using the DTW distance measure and the Pearson correlation coefficient (PCC). The predictability of the CDT beyond baseline conditions was assessed by imposing a diverse range of clinically common pathological cases spanning intraventricular conduction disorders and tachyarrhythmias and compare their characteristics in the simulated EP and ECGs against associated diagnostic criteria established in clinical practice. Specifically, these include left- and right bundle branch blocks, WPW syndrome, orthodromic AVRT and a monomorphic VT. The bundle-branch blocks were modeled by impeding the conduction per branch, causing an activation delay between

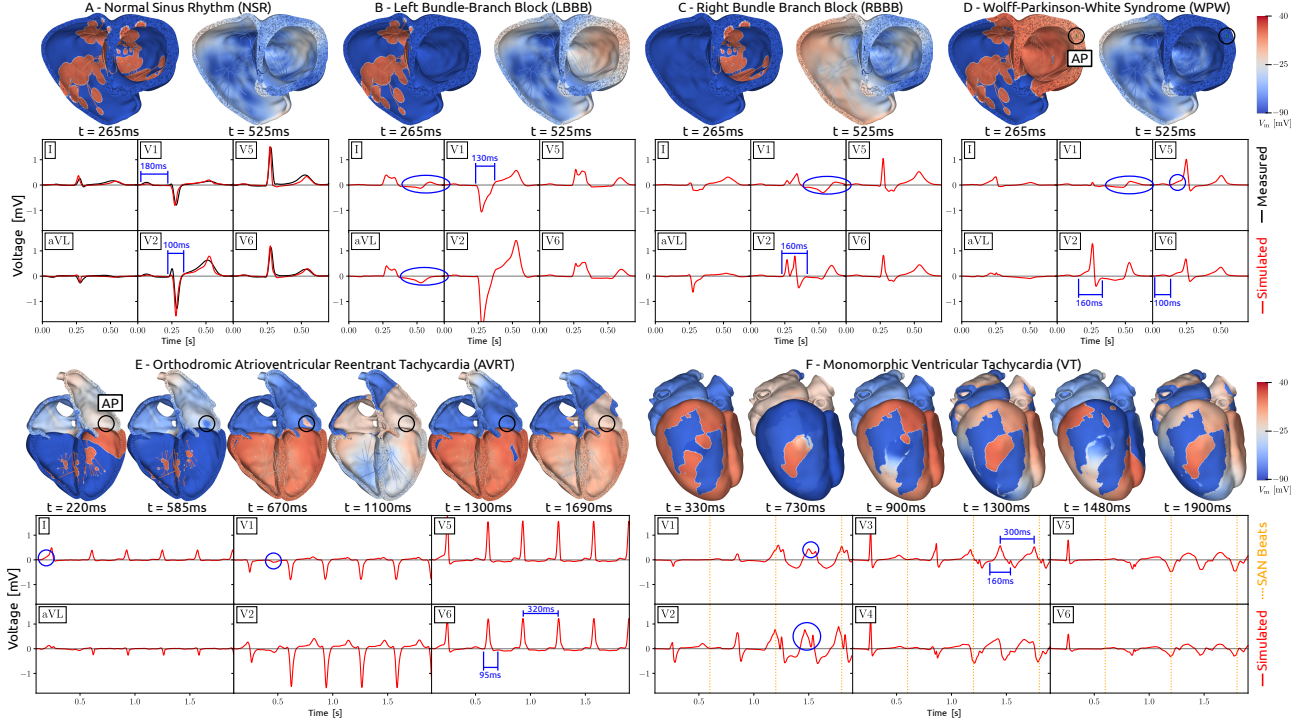


Figure 2. The transmembrane voltage maps at selected timesteps and the corresponding 12-lead ECGs at relevant leads produced by the CDT under (A) the NSR, (B) left bundle-branch block, (C) right bundle-branch block, (D) WPW syndrome causing ventricular pre-excitation, (E) orthodromic AVRT and (F) scar-induced monomorphic VT.

left and right ventricles, respectively. For the WPW syndrome and AVRT, an atrioventricular conduction leakage was implemented by inserting a concealed accessory pathway connecting the atria with the ventricular base at the outer left ventricular wall to cause pre-excitation of the left ventricle. The monomorphic VT was modeled by inserting an isthmus-shaped fibrotic scar surrounded by border-zone tissue with impaired EP into the left ventricular wall. An outer-loop topology VT was triggered by simulating an ectopic beat at the apical exit of the isthmus with an externally applied stimulus. For the NSR and each pathology, cardiac sources and corresponding ECGs were computed and the required duration of each simulation was measured. An ensemble of ECG diagnostic criteria for each pathology, given in Tab. 1, serves for estimating the predictability of the CDT based on the percentage of identified diagnostic criteria in the simulated ECGs.

3. Results

The calibration of the CDT required 54 minutes to complete with the employed framework and yielded a high correspondence with the reference ECG, achieving a DTW of 0.615 mV and a PCC of 0.878 averaged over all leads. The cardiac sources and corresponding ECGs computed by the CDT displayed in Fig. 2 show physiologically plausi-

ble de- and repolarization patterns and corresponding ECG morphologies across all pathological conditions. Overall, the model reproduced 22/26 or $\sim 85\%$ of expected diagnostic criteria of the pathological cases listed in Tab. 1. On average, single beat simulations lasting 700ms were computed within 30 ± 1 s, while multi-beat simulations over 2000ms required 176 ± 13 s.

4. Discussion and Conclusion

We presented a high fidelity ECG calibrated CDT that enables near real-time interrogation of EP responses to gain insight into the relationship between cardiac sources and their manifestation in ECG phenotypes. When perturbed with pathological conditions, the model predicted the majority of expected ECG diagnostic criteria, which represents initial evidence of CDT generalization capabilities beyond baseline conditions that strengthens the advancement of predictive modeling in precision cardiology.

Acknowledgments

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Table 1. Checklist of established ECG diagnostic criteria associated with healthy conditions under the NSR and each investigated pathological case.

(A) NSR	(B) LBBB	(C) RBBB
☒ P, QRS, T morphology	☒ QRS >120ms	☒ QRS >120ms
☒ Upright P-waves	☒ Broad monophasic R [I, aVL, V5-6]	☒ rSR' [V1-2]
☒ QRS in [75,110]ms	☒ deep and wide S [V1-3]	☒ Wide, slurred S [I, aVL, V5-6]
☒ Normal axis	☒ rS or QS complex [V1-2]	☒ Discordant ST-T
☒ PR in [120,200]ms	☒ No Q-waves [I, V5-6]	☐ Normal axis
	☒ Discordant ST-T	
(D) WPW	(E) Orthodromic AVRT	(F) Monomorphic VT
☒ Delta wave	☒ Delta Wave	☒ AV Dissociation
☒ PR <120ms	☒ 1:1 AV ratio	☒ Capture or fusion beats
☒ QRS >110ms	☒ RP in [70-120]ms	☐ Precordial concordance
☒ Secondary ST-T changes	☒ Retrograde P-waves	☒ QRS >120ms
	☒ Regular narrow tachycardia [150-250]bpm	☒ RSR' (left rabbit ear)
		☐ Extreme axis deviation

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