Digital Twins for Atrial Fibrillation Including Fibrosis Infiltration Characterized from Voltage Measurements

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Abstract

Atrial fibrillation (AF) catheter ablation is associated with high recurrence rates. Personalized computational models, or digital twins (DTs), offer a framework to optimize these procedures through patient-specific ablation planning. Given its key role in arrhythmia maintenance, fibrosis characterization is essential for the predictive fidelity of these models.

We propose a methodology to estimate fibrotic distribution from intracavitary electrical recordings. Simulations of atrial tissue across varying fibrosis levels (0-35%) were conducted to generate endocardial bipolar electrograms and quantify the peak-to-peak voltage (Vpp). From these, a calibration function (R^2=0.94) was established to correlate Vpp with fibrotic burden.

This function was applied to clinical data from three patients to generate personalized substrate maps, differentiating healthy tissue (>0.25 mV), scar (<0.1 mV), and interstitial fibrosis. This methodology was integrated into our established workflow for electrophysiologically informed DTs, which are anatomically and functionally characterized to patient-specific biomarkers (cycle length and conduction velocity).

These models would enable the development of model-guided ablation strategies tailored to the individual structural characteristics of each patient.

1. Introduction

Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia worldwide, affecting approximately 37.6 million people. However, catheter ablation, one of the main treatments alongside drug therapy, yields suboptimal results, with a high recurrence rate. Digital twins (DT), computational models integrating patient-specific data, have emerged as a promising tool for optimizing procedural success by simulating personalized ablation strategies.

Previously, we developed a workflow to generate electrophysiologically characterized DTs from intracavitary AF electrograms (EGMs) [1]. While allowing precise functional characterization, these models lacked fibrotic substrate representation. In fibrotic regions, conduction velocity (CV) is locally reduced, and wavefront disruption occurs, which sustains reentrant activity and perpetuates fibrillation. Given the role of fibrosis distribution in AF maintenance, incorporating it directly into computational models may be beneficial.

Fibrosis is typically detected via image intensity ratio (IIR) in late gadolinium-enhanced magnetic resonance imaging (LGE-MRI) [2] or voltage maps from intracavitary electrical recordings [3]. Previous studies have linked IIR to different degrees of fibrosis [2], but voltage-based strategies often focus only on non-conductive low-voltage areas (<0.5 mV in sinus rhythm; <0.25 mV in AF [4]). Modeling varied fibrotic infiltration based on measured voltage remains unstudied.

This study aims to customize and incorporate patient-specific atrial fibrosis into our DT workflow. We calibrated the relationship between regional fibrosis percentage and local voltage during simulated AF episodes and then used this calibration to construct patient-specific, fibrosis-infiltrated simulations of AF.

2. Materials and methods

2.1. Two-dimensional tissue simulations

A 50x50x3 mm atrial tissue patch (63,072 nodes; inter-nodal distance: 0.62 ± 0.12 mm) was used to generate atrial substrates varying the degree of fibrosis infiltration ({0, 5, 10, 15, 20, 25, 30, 35} %). A uniform fiber direction (FD) was assigned parallel to the x-axis. Fibrosis distribution was implemented using the fibrosis pattern generation algorithm proposed by Romitti et al. [5], which provides fibrosis patterns aligned with the fiber direction. This algorithm drives fibrotic starting from an initial set of seeds (300 in this case) based on a probabilistic rule governed by the angle between the local FD and the vectors connecting a node to its neighbors (Figure 1a). Fibrosis levels were

capped at 35%, as higher percentages resulted in conduction block, behaving as scar.

Non-fibrotic nodes were modeled under persistent AF (PsAF) conditions using Koivumaki's cellular model [6], incorporating pathological modifications as described in [7]. For fibrotic tissue, the PsAF model was modified using the approach described by Romitti et al. [5], which is an adaptation of the work by Martinez et al. [8]. This model involves disconnecting 30% of randomly selected fibrotic nodes and applying ionic remodeling to the remaining 70% to simulate the effect of the TGF-β1 protein (Figure 1b).

AF episodes (4 s duration) were simulated using an S1-S2 pacing protocol (a train of seven S1 pulses at 5 Hz followed by a precisely timed S2 pulse) to induce self-sustained reentrant activity (Figure 1c). In models with fibrosis levels exceeding 10%, sustained reentry could not be maintained. Therefore, an additional protocol involving periodic stimulation at 2 Hz from the left margin was applied to assess propagation along the fiber axis in all models (Figure 1e).

Electrical propagation was governed by the monodomain equation and solved using a GPU-based platform with a time step of 20µs.

2.2. Voltage measurement in electrograms

To quantify the relationship between intracavitary voltage and the degree of fibrosis, 25 pairs of orthogonal bipolar EGMs (EGM_x EGM_y), were calculated per simulation. Virtual bipolar electrodes (3 mm spacing) were positioned 1 mm from the endocardium (Figure 1a). The local peak-to-peak voltage (Vpp) was measured for each EGM pair. In AF simulations, the final second was analyzed. Vpp per activation was measured across both axes, and the maximum value obtained between the two components was used (Figure 1d). In pacing simulations, Vpp was derived from the last stimulus using only the EGM_x component (Figure 1f), as it aligned with the propagation direction. Overall substrate was characterized by the median Vpp from all electrodes and protocols.

Finally, the Vpp measurements were normalized between 0 mV and 0.25 mV, an established healthy tissue threshold [4]. These values were regressed against fibrosis percentages to derive the final calibration function.

2.3. Fibrosis personalization

The calibration function was applied to characterize the fibrotic distribution in three AF patients from Hospital Clínico San Carlos (Madrid, Spain). High-density, 30 s intracavitary bipolar recordings were obtained during AF using an Octaray catheter (Biosense Webster; 24 electrodes), ensuring comprehensive left atrial coverage.

Local Vpp was quantified within 300 ms windows (ensuring at least one atrial activation), and the median

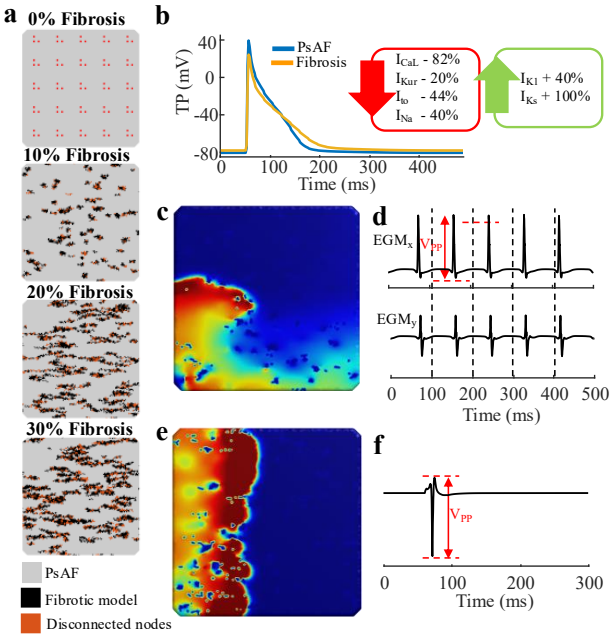

Figure 1. a) Fibrosis models at 0% (with electrode placement), 10%, 20%, and 30%. b) PsAF vs. fibrotic action potential curves and fibrosis ionic changes. c-f) Propagation maps and Vpp quantification for AF (c, d) and pacing (e, f) protocols.

value was calculated for each electrode location. These estimates were projected onto the patient-specific atrial geometry reconstructed from computed tomography imaging. To assign values to the mesh, a weighted average of the three nearest Vpp measurements was calculated for each node, using the inverse distance squared as the weighting factor. Finally, projected Vpp values were smoothed using a 3D Gaussian filter ($\sigma = 2$).

Nodal Vpp values were transformed into regional fibrosis percentages, representing the probability of a node being fibrotic, via the calibration function. To model the spatial distribution of the lesions, a modified version of the fibrosis pattern generation algorithm was implemented. Initial seeds were randomly distributed within the fibrotic regions with a density proportional to the extent of the affected area (50 seeds/1% of fibrotic surface). A node was ultimately designated as fibrotic if the stochastic parameter generated by the algorithm exceeded the complement of the node's fibrosis probability.

2.4. Integration into the DT workflow

The developed methodology for identifying fibrotic and scar regions was integrated into an established workflow for generating electrophysiologically informed DTs [1]. In this framework, cycle length (CL) and CV were estimated locally from the clinical electrograms recorded during AF episodes. Using a calibration study, the cellular model (in terms of electrical remodeling) and the propagation model

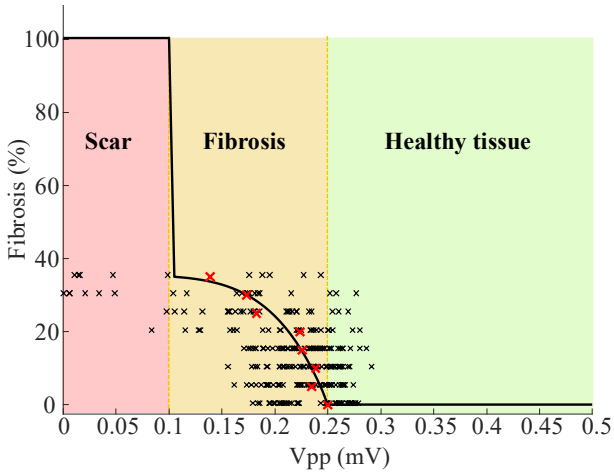

Figure 2. Calibration function obtained that relates Vpp to the percentage of fibrotic tissue.

(in terms of diffusion) are adapted for each simulated node based on the measured biomarkers. Finally, the scar was modeled by disconnecting the corresponding nodes, and fibrosis was modeled by randomly disconnecting 30% of the nodes and applying the ionic changes associated with fibrotic tissue remodeling to the remaining 70%.

Using the obtained models, AF simulations were performed by applying a protocol of increasing frequencies from 12 points covering the atrial surface [1], and the CL and CV obtained in the simulations were evaluated to compare them with those measured from clinical signals.

3. Results

3.1. Calibration function

The relationship between Vpp and the percentage of fibrosis was characterized by fitting the measured data to a power function ($R^2 = 0.94$):

$$fibrosis\ (\%) = -431 \cdot {V_{PP}}^{5.13} + 0.35$$

Following established clinical criteria [4], a threshold of 0.1 mV was set to identify dense scar, defined as electrophysiologically inactive tissue. Conversely, Vpp values exceeding 0.25 mV were classified as healthy myocardial tissue. Figure 3 illustrates the resulting calibration curve correlating Vpp with the fibrotic burden.

3.2. Fibrosis distribution

Figure 3 illustrates the patient-specific fibrosis distributions derived from the calibration curve for the three subjects analyzed. Following the established methodology, nodes with voltage measurements exceeding 0.25 mV were modeled as healthy tissue, while those below 0.1 mV were classified as scar. Substrate with intermediate values (0.1 - 0.25 mV) was categorized as either fibrotic or healthy based on the stochastic pattern generation algorithm and the local probability assigned by the calibration function.

Patient 1 exhibited a scar affecting 13.6% of the atrial surface, while fibrotic infiltrations covered 7.3%. The fibrosis and scar were primarily localized to the posterior wall, including the left pulmonary veins (PVs) and the anterior wall. Patient 2 presented the most extensive structural modification, with dense scar reaching 20% of the atrial surface. This scar was predominantly located around the PVs attributed to a previous ablation procedure, resulting in complete electrical isolation. Additionally, fibrotic infiltrations in this patient accounted for 8.37% of the surface. In contrast, Patient 3 showed minimal substrate modification, with no scarring and fibrotic infiltration of only 0.47%.

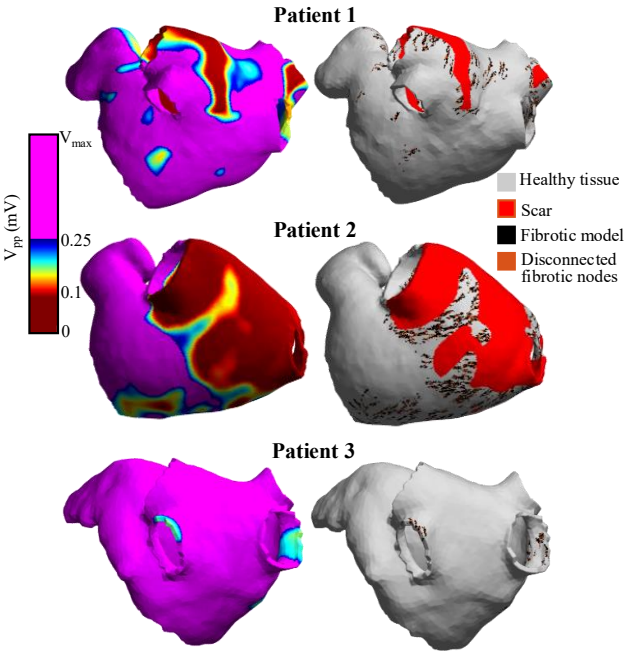

Figure 3. On the left, Vpp maps projected onto the atrial geometry of the three patients. On the right, estimated fibrosis distribution.

3.3. Digital twins with fibrosis

Figures 4a and 4b show a comparison of CL and CV values measured from clinical signals and those obtained in simulations using our DTs. The DTs incorporating fibrosis were able to reproduce clinical biomarker values both globally and regionally. Panels c and d show, as an example, the spatial distribution of biomarkers for patient 1. It was observed that the DT could reproduce local variations, such as an area of faster conduction near the right superior pulmonary vein.

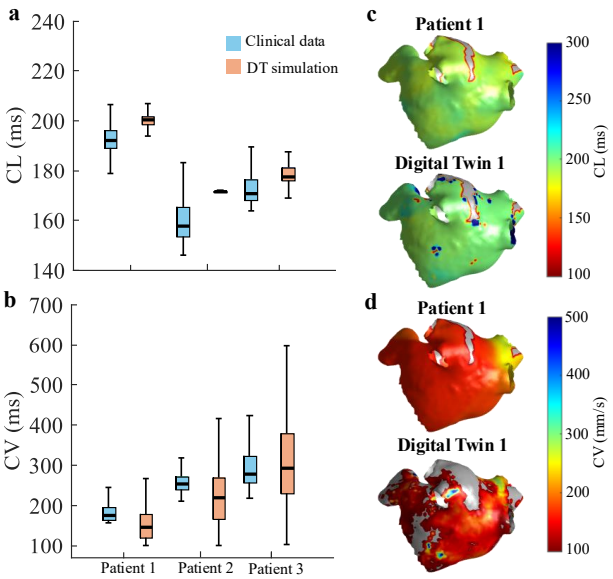

Figure 4. a) CL distributions measured in clinical signals and in DTs. b) Same for CV. c) Spatial distribution of CL for patient 1 and its DT. D) Same for CV.

4. Discussion

In this work, we developed a methodology to personalize atrial models by incorporating patient-specific fibrosis distributions derived from intracavitary voltage measurements during AF episodes. A calibration study was conducted to characterize the relationship between the regional fibrosis percentage in a tissue patch and the resulting Vpp during wavefront propagation. The derived calibration function enabled the generation of personalized models for three AF patients, successfully differentiating among healthy tissue, scar, and fibrotic regions. Notably, this approach allowed for the identification of both localized fibrotic infiltrations and an extensive scar resulting from a prior ablation procedure.

This methodology was integrated into an established DT workflow, facilitating a level of structural personalization that extends beyond conventional low-voltage area detection [3]. By leveraging these digital twins, we performed patient-specific simulations that closely reflect the individual's unique arrhythmogenic phenotype. These advanced models provide a robust platform for virtual therapy testing and outcome prediction, potentially aiding in the strategic planning of ablation procedures to enhance clinical success rates.

This study presents a preliminary framework that warrants further validation in a larger patient cohort. Future efforts will focus on comparing the generated fibrosis maps with alternative modalities, such as LGE-MRI, and quantifying the gain of integrated fibrosis characterization compared to simpler, non-fibrotic models.

Acknowledgments

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