

# Impact of Fibrosis Border Zone Characterisation on Fibrosis-Substrate Isolation Ablation Outcome for Atrial Fibrillation

Shaheim Ogbomo-Harmitt<sup>1</sup>, Ahmed Qureshi<sup>1</sup>, Andrew King<sup>1</sup>, Oleg Aslanidi<sup>1</sup>

<sup>1</sup>School of Biomedical Engineering and Imaging Sciences, King's College London, United Kingdom

## Abstract

Atrial fibrillation (AF) is globally the most common type of cardiac arrhythmia and is a precursor for serious conditions such as stroke. The success rate of AF treatments, such as catheter ablation (including the current gold standard, pulmonary vein isolation), is suboptimal, warranting better strategies. Fibrosis-substrate isolation ablation (FISA) is a promising new ablation strategy currently showing success in clinical trials. However, to perform FISA, the left atrial (LA) fibrosis border zone (FBZ) needs to be characterised. This study investigates the impact of FBZ characterisation on FISA outcomes for AF simulated using 10 patient-specific 3D LA models. Simulations show that (i) including a large amount of FBZ tissue within FISA lesions can increase the success of AF termination, and (ii) FISA is more effective for patients with Utah fibrosis stages III and IV. These results can help clinicians to improve the stratification of AF patients and the implementation of the FISA strategy.

## 1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia globally and can cause stroke, heart failure, and dementia [1]. Catheter ablation (CA) for AF has emerged as an effective rhythm-control strategy, performed in multiple clinics worldwide [2]. Pulmonary vein isolation (PVI) is the common ablation strategy that involves wide-area circumferential ablation of the pulmonary veins to target the initial AF triggers. However, the single procedure success of PVI for persistent AF is 30% [2].

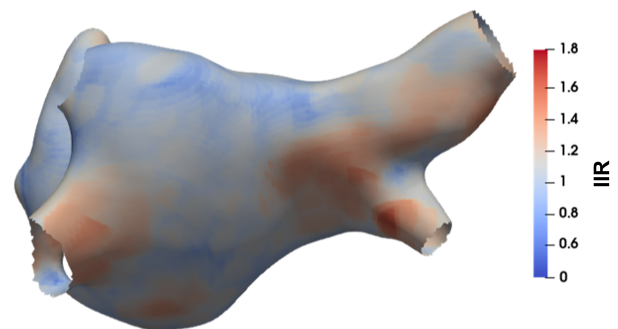
Hence, new ablation strategies have been investigated to improve the outcomes of CA treatment. Fibrosis-substrate isolation ablation (FISA) is a strategy currently in clinical trials to surpass the success rate of PVI [3].

Several studies have tested this strategy clinically and reported a higher single procedure success rate than PVI. However, there are nuances in how studies have characterised the threshold of fibrosis border zone (FBZ), which potentially can affect the FISA outcome. Therefore, this in-silico study investigates the impact of the FBZ threshold characterisation on AF termination by FISA.

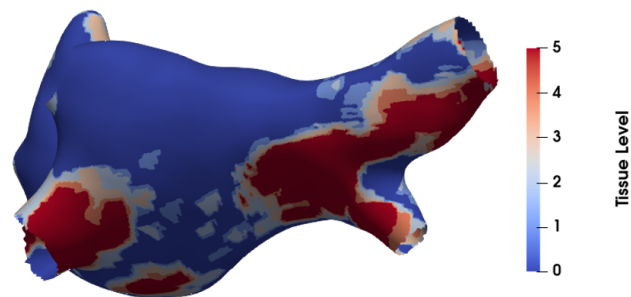
## 2. Methods

### 2.1. Data and Preprocessing

The surface left atrial (LA) meshes for 10 patients were obtained from a study by Roney et al., which includes the image intensity ratio (IIR) data from the late gadolinium-enhanced (LGE) MRI and patient-specific fibre orientation from a registered LA fibre orientation atlas (Figure 1) [4]. The virtual cohort consisted of 2 Utah stage IV, 3 Utah stage III, 4 Utah stage II and 1 Utah stage I patients.



**Figure 1.** 3D surface LA mesh with IIR data from corresponding MRI image.



**Figure 2.** 3D surface LA mesh after IIR data thresholding (fibrosis = red, healthy tissue = blue and FBZ is intermediate colours in between red and blue).

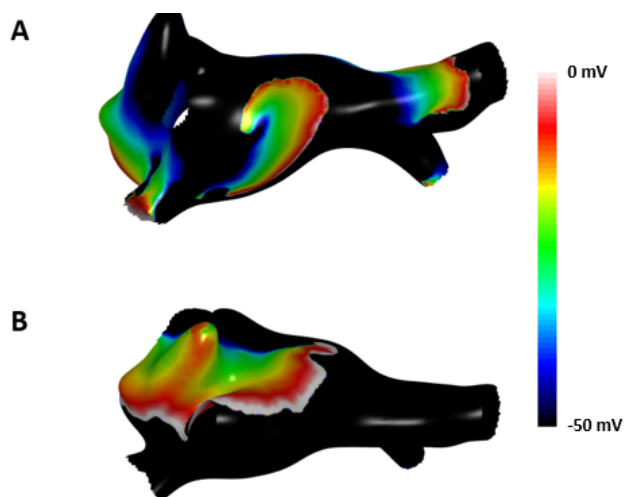
The 10 LA meshes were then thresholded to differentiate atrial tissue into levels characterised by the prevalence of fibrosis. Healthy tissue (level 0) was characterised by mesh elements with less than  $1.08 > \text{IIR}$ , whereas dense fibrotic tissue was determined by  $\text{IIR} > 1.24$  (level 5) [5]. The IIR values within the healthy and the FBZ were split into four discrete tissue levels (levels 1-4) (Figure 2) [6].

## 2.2. Fibrosis Modelling

To model fibrotic tissue, healthy tissue (level 0) was assigned the longitudinal conductivity of 0.4 S/m and transverse 0.1 S/m [7]. Meanwhile, using the square root proportional relationship of conduction velocity (CV) and conductivity [8], the conductivity of FBZ (levels 1-4) and dense fibrosis (level 5) was found by reducing the CV by one-sixth in ascending order of tissue level and then calculating the respective conductivity.

## 2.4. AF simulation

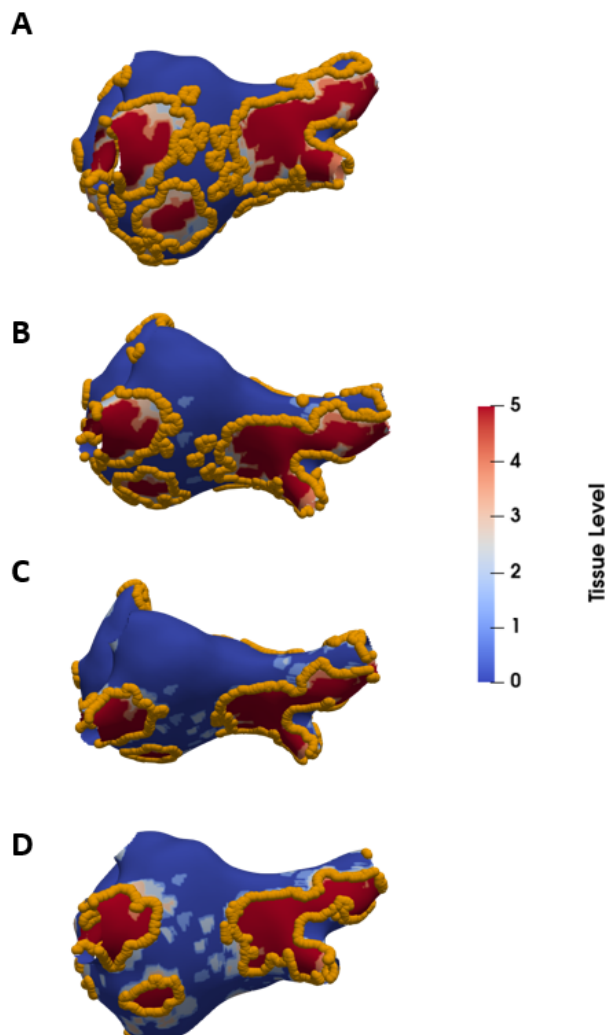
Electrophysiological simulations were run using the openCARP simulator, with the monodomain model for excitation propagation. AF was initiated using the phase singularity distribution (PSD) method to simulate two AF scenarios [9,10]. Scenario 1 was initiating a rotor at the left superior pulmonary vein, while scenario 2 was initiating a rotor on the LA's anterior (Figure 3). To model chronic AF ionic remodelling, a variant of the Courtemanche ionic model by Loewe et al. was implemented, and a 168 ms cycle length was set for the PSD AF initiation [11].



**Figure 3.** Example of voltage propagation maps on 3D LA surface mesh for AF scenarios 1 (A) and 2 (B).

## 2.3. Catheter Ablation Modelling

Four different FISA strategies were investigated in this study, where each strategy ablated each FBZ level 1-4 (Figure 4). The ablation lesions were modelled as spheres to replicate the tip of the catheter; the sphere radius matched the radius of catheters used in clinics (1.75 mm).



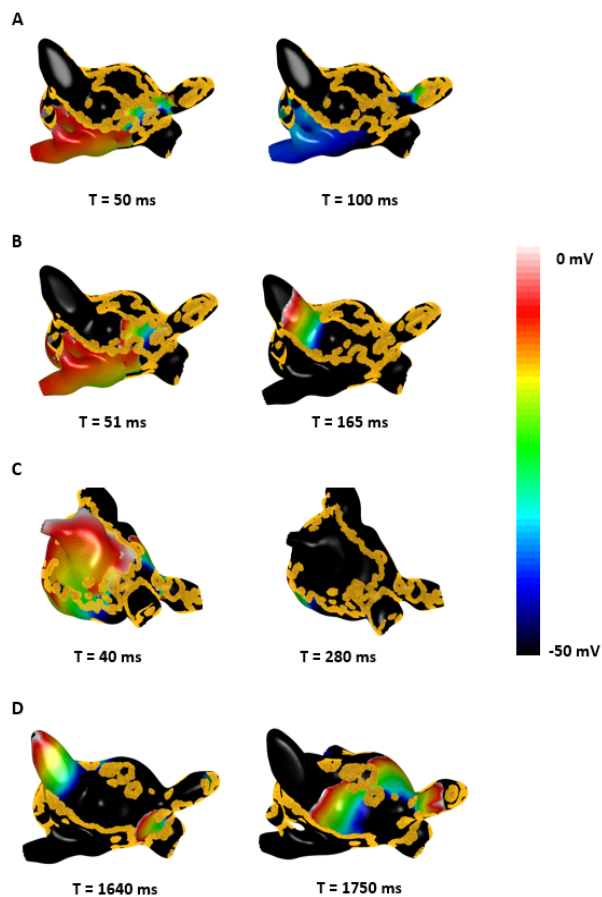
**Figure 4.** 3D LA surface mesh with FISA lesions (orange) applied at FBZ levels 1-4 (A-D, respectively).

The conductivity of ablation lesions on the LA model was set to  $1e-10$  S/m in the longitudinal and transverse directions. The in-silico FBZ ablation pipeline begins with a 10s initial simulation of a given AF scenario, then with the last variable states of the initial simulation are saved and, after FISA lesions are applied, used as the initial conditions for a 2s simulation of the ablated LA model. The ablation success was defined as the termination of AF.

## 3. Results

Overall, FISA with FBZ of levels 1 & 2 performed the best

for AF scenario 1. For AF scenario 2, ablation with FBZ of level 1 was the most successful. FISA with FBZ of level 4 terminated AF the least across the AF scenarios (Table 1).



**Figure 5.** Example of LA voltage propagation maps post-ablation for FISA of a single subject for each FBZ level 1-4 (A-D). Post-ablation times are shown in the images; orange = FISA lesions.

Figure 4 reflects the effectiveness of each FISA strategy. When the ablated FBZ is set to level 4, the reentry waves (rotors) are not fully encapsulated within the ablation lesions, allowing them to propagate throughout the LA tissue and sustain AF (Figure 5D). Meanwhile, when the FISA FBZ are levels 1, 2 or 3, rotors are constricted within a relatively small region which blocks its path and terminates AF (Figure 5A, 5B and 5C).

However, Utah fibrosis stage did affect the outcome of FISA, as reflected in Table 2, as subjects with Utah stages III & IV had a high number of successful AF termination post-ablation than subjects with Utah stages I & II.

When ablated FBZ was set to level 2, FISA successfully terminated AF for all subjects with Utah stages I & II. Alternatively, ablation of FBZ levels 1 and 3 terminated AF in between 4 and 5 out of 5 Utah stages I & II subjects; ablation of FBZ level 4 successfully terminated AF

between 2 and 3 of the Utah stages I & II subjects.

**Table 1.** Number of successful FISA AF terminations (out of 10) for each ablated FBZ level and AF scenario.

FBZ level	AF Scenario 1 (n = 10)	AF Scenario 2 (n = 10)
1	6	8
2	7	7
3	7	5
4	5	3

**Table 2.** The number of successful FISA AF terminations for each ablated FBZ level, AF scenario and Utah stage.

Utah Fibrosis Stage	Ablated FBZ level	AF Scenario 1	AF Scenario 2
I & II (n = 5)	1	2	3
	2	2	2
	3	3	1
	4	2	1
III & IV (n = 5)	1	4	5
	2	5	5
	3	4	4
	4	3	2

## 4. Discussion

This study investigates the impact of FBZ characterisation on in-silico FISA outcomes for AF. These results show that AF termination is more successful when FISA is applied to FBZ levels 1 and 2 (i.e., the outer borders of fibrosis).

Meanwhile, at the ablation of FBZ level 4, where the border zone is closest to the dense fibrosis, FISA AF termination was the least successful, as the ablation lesions did not encapsulate the rotors sustaining AF. A study by Morgan et al. supports this result by showing that reentrant drivers (RDs) of AF were stabilised within the FBZ due to its slow conductive properties. Furthermore, the study showed that the RDs propagated around fibrosis levels 3 and 4 [6]. Therefore, the FISA lesions must encapsulate tissue level 3 as a minimum to contain the rotors within the lesions. Our study supports this, as FISA AF termination outcomes are similar for ablating FBZ levels of 1,2 and 3. Our results also show that the FISA can be more effective if the ablated FBZ tissue level is lower than 3. This result can be vital for clinicians as ablating more FBZ tissue could improve patient outcomes for FISA.

Our results also highlight that FISA is more effective for patients with Utah fibrosis stages III & IV, than those with stages I & II. Therefore, using MRI preprocedural scans of the LA, clinicians could potentially assess if the FISA treatment will be effective for the patient. Furthermore, the results of the DECAFF II study focused on ablating the perimeter of the dense fibrosis or dense fibrosis completely [3]. We hypothesise that fibrosis-

guided ablation successful outcomes will be higher if the ablation lesions specifically target the FBZ tissue. We also note that definition of dense fibrosis and FBZ from LGE MRI can be very sensitive to the method used, which may explain discrepancies between different studies [12].

Limitations of the study include the lack of the LA model validation with patient electroanatomical mapping (EAM) data, and lack of consideration of the atrial wall thickness that can also affect the rotor dynamics [13,14].

Therefore, future work should focus on applying the methodology of this study to a larger patient cohort, running more AF scenarios and ablation strategies and applying patient EAM data to validate the results further. Moreover, deep learning techniques can be applied to improve ablation strategy selection for each patient [15].

## Conclusion

In summary, we have investigated the impact of FBZ characterisation on FISA outcomes for AF. Our results show that FISA that includes a large amount of FBZ tissue within its ablation lesions can increase the success of AF termination. In addition, we also show that FISA is more effective for patients with Utah fibrosis stages III & IV.

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## Address for correspondence:

Shaheim Ogbomo-Harmitt  
School of Biomedical Engineering and Imaging Sciences, King's College London, 3rd Floor Lambeth Wing, St Thomas' Hospital, London, SE1 7EH, UK  
shaheim.ogbomo-harmitt@kcl.ac.uk