# Supplemental Material for Left atrial appendage electrical isolation reduces atrial fibrillation recurrences: a simulation study

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# S1 Computational model of AF

A structurally detailed model of the human atria, extensively described previously <sup>1</sup> , was used
in this study. The global geometry was reconstructed using magnetic resonance image data of
a subject with normal atria. Additional anatomical structures and properties, such as wall
thickness heterogeneities, twenty pectinate muscles, Bachmann's Bundle, interatrial bundles,
and the crista terminalis, and left atrial appendage trabeculated network were added
manually. <sup>2</sup> One to three layers of fiber orientations manually included in the model based on
anatomical studies using a combination of manual editing and computer algorithms. 1 These
structures are considered to play a key role in AF initiation and maintenance. 3, 4
Simulations were performed with a second-order accurate finite-difference method <sup>5</sup> on a
hexahedral mesh at 0.2mm resolution including of approximately 5 million nodes.
Differential equations for potentials and ion concentrations were integrated with the forward
Euler method and gating variables with the Rush-Larsen method <sup>6</sup> using a time step of
0.01ms. The implementation of the boundary conditions is implicit in the formulation of
Saleheen and Ng. <sup>7</sup> . Simulations were performed with a monodomain reaction-diffusion
model using the propag-5 software <sup>8</sup> and run on a Cray XC50 supercomputer with GPU
support.
The material properties for the atria were set to produce an approximately normal P wave in
case of sinus rhythm. <sup>2</sup> The effective monodomain conductivities along and across the fiber

- are given in Table S1. The tissue surface to volume ratio was 800 cm<sup>-1</sup> throughout the atrial myocardium.
- Ionic currents for each node were described by the Courtemanche-Ramirez-Nattel model.<sup>9</sup>
- Changes in ionic currents caused by AF were incorporated by setting the conductivities for
- $I_{to}$ ,  $I_{Ca,L}$ , and  $I_{K1}$  at 40%, 35%, and 200% of their normal values, respectively. <sup>10</sup>

#### **S2** Fibrosis distribution

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- Fibrosis patterns similar to those obtained from LGE-MRI were generated with an algorithm
- that produces spatially-correlated, anatomy-tailored random fields (Figure S1). 1, 11
- The fibrosis was distributed within the atrial wall, while the endocardial bundles remain
- intact. The spatial distribution of fibrosis was uneven, with patches or island presenting
- higher degree of fibrosis. Such distribution was based on spatially correlated, anatomy-
- tailored random fields (Figure S1). <sup>1, 11, 12</sup> Fibrotic elements were assumed to be electrically
- active and conductive along the fiber direction and electrically isolated in the transverse
- direction (Table S1). The fibrosis was modelled in this way to represent the loss of side-to-
- side electrical connections between atrial muscle bundles found by Spach et al. in fibrotic
- atrial tissue. 13 Simulations were performed without fibrosis, with moderate fibrosis, and with
- severe fibrosis, in which 0%, 50%, and 70% of elements were fibrotic as described earlier. <sup>1</sup>

## S3 AF initiation in pre- and post-catheter ablations

- In order to assess the likelihood of AF initiation, both before and after catheter ablations, 20
- pacing locations were selected in both atria, including the area between the PVs, left atrium
- (LA), left atrial appendage (LAA), right atrial appendage (RAA), coronary sinus, superior
- caval vein (SCV), inferior caval vein (ICV), and right atrium (RA). These points were
- selected based on reported possible sources of extra-PV ectopic focal activity in AF

patients.<sup>14</sup> All pacing points, except the one located on the LAA were located outside the ablated area. As a consequence, in simulations with LAAI the AF initiation rates were corrected by excluding simulations in which pacing point was located in the LAA. In each simulation one pacing point were selected. The stimulation protocol consisted of a 2 seconds incremental pacing from a selected location, in which a train of stimuli with progressive reduction in pacing interval was applied, followed by 3 seconds of simulation with no pacing.

### S4 Definition of a successful AF initiation

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The outcome of the stimulation protocol was analyzed in terms of the type of self-sustained 58 rhythm after 2 seconds of stimulations. In the presence of no activity, the initiation was 59 considered unsuccessful. Otherwise, a distinction between AF and atrial flutter (AFL) was 60 made, with the latter not being considered a successful AF initiation. To differentiate between 61 AF and AFL conduction patterns, we computed 12-leads ECGs from the simulated atrial 62 electrical activity. To construct the ECGs, the atrial model was incorporated into an 63 inhomogeneous torso model including lungs and intracavitary blood masses. Body surface 64 potentials were simulated using a bi-domain equation solved at 1-mm resolution.<sup>2</sup> 65 In all 12-lead ECGs, after the pacing periods, we detected positive fibrillation wave peaks 66 and calculated fibrillation cycle length (FCL) as the time interval between two successive F-67 wave peaks (Figure S2-A). These FCL lengths were used to generate Poincaré plots (Figure 68 S2-B &C). The FCL were described as a vector  $FCL = [l_1, l_2, ..., l_N]$ , where  $l_i$  is the *i*th FCL. 69 Each Poincaré plot is composed of the points of  $l_i$  on the x-axis versus  $l_{i+1}$  on the y-axis. 70 The point cloud dispersion (PCD) in Poincaré plots was used as a sensitive parameter 71 describing the regularity of activations and to differentiate between AFL and AF simulations. 72 PCD were calculated using as an averaged Euclidean distance of each point in a point cloud 73 to the point cloud centroid: 74

$$PCD = \frac{1}{N-1} \sum_{i=1}^{N-1} \sqrt{(l_i - c_x)^2 + (l_{i+1} - c_y)^2}$$
 (1)

where  $C(c_x, c_y)$  is the centroid of the point cloud in Poincaré plot. Finally, by applying an

arbitrary threshold to the PCD we classified AF conduction patterns in simulations from

AFL. All algorithms were developed in Matlab (v. R2016a, Mathworks).

Figure S3 illustrates representative conduction patterns of simulations and corresponding

three-lead ECG in the control group with three different degrees of fibrosis. In the absence of

fibrosis AF was not inducible while in moderate and severe fibrosis the stimulation of the

atria resulted in AF induction. Figure S4 shows activation patterns in PVI + LAAI

simulations and corresponding ECGs without fibrosis, with moderate fibrosis, and with

severe fibrosis. In these examples, AF was inducible only in severe fibrosis but not without or

in moderate fibrosis.

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#### S5 Detection and tracking fibrillation waves

- A fibrillation wave was defined as a contiguous volume in which all nodes had
- transmembrane voltages above -60mV. The number of waves was calculated at each
- millisecond of simulated time.
- 89 Fibrillation waves were tracked in both time and space, as described in our previous study. 15
- Briefly, the temporal dynamics of waves can be described by three events:
- Generation: appearance of a new wave due to a wave breaking up into two or more waves.
  - Fusion: the fusion of two or more waves into one wave as they merge with each other.
- Extinction: the extinction of a wave, because either it hits a boundary or runs into unexcitable tissue.

## **S6 Statistics**

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All statistical analyses were performed using GraphPad Prism software version 8.0. All values were expressed as the mean  $\pm$  SD. Statistical tests were performed to compare the effect of two parameters, fibrosis levels and ablation patterns, in AF initiation rate, using Two-Way ANOVA followed by post hoc Bonferroni test. A value of P < 0.05 was considered significant.

## Figure legends:

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**Figure S1:** Posterior and anterior view of the atria with patchy fibrosis. A) Patchy fibrosis 104 model, 50% fibrotic (anterior view). B) Patchy fibrosis model, 50% fibrotic (posterior view). 105 C) Cross sectional view of the atrial geometry demonstrating fibrosis distribution within the atrial wall. 107 Figure S2: Local electrograms recorded during simulated AF episodes at 4 different point on 108 both atria (E1-E4) and 2 ECG leads (II and V1). 109 Figure S3: Atrial tachycardia patterns. A) An example of simulated lead II ECG in a 110 simulation with atrial fibrillation conduction pattern. Red stars indicate the positive peak of 111 the fibrillation wave. B) Corresponding Poincaré plot generated from the ECG presented in 112 section A. C) An example of ECGs (Lead I, II, and V1) and corresponding Poincaré plots in a 113 simulation with flutter conduction pattern. D) An example of ECGs and corresponding 114 Poincaré plots in a simulation with a fibrillation conduction pattern. 115 Figure S4: AF initiation in control simulations. A) Consecutive snapshots of conduction 116 patterns and corresponding three ECG leads (II, V1, and V3) in control simulations with no, 117 moderate, and severe fibrotic simulations. 118 Figure S5: AF initiation in ablation simulations. Series of conduction pattern snapshots in 119 simulations with pulmonary vein isolations accompanied by LAA isolation and their 120 corresponding three ECG leads (II, V1, and V3) without, with moderate, and with severe 121

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fibrosis.

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**Table S1.** Tissue conductivity parameters ( $\sigma$ ) used in the simulations. The units are mS/cm.

The subscript 'i' stands for intracellular, 'e' for extracellular, 'L' for longitudinal, 'T' for transverse (within a tissue sheet) and 'C' for across-sheet.

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	material	$\sigma_{iL}$	$\sigma_{iT}$	$\sigma_{iC}$	$\sigma_{eL}$	$\sigma_{eT}$	$\sigma_{eC}$	
	wall	3.0	0.3	0.3	3.0	1.2	1.2	
	iso	1.5	1.5	1.5	1.5	1.5	1.5	Γ

iso	1.5	1.5	1.5	1.5	1.5	1.5	0.75	0.75	0.75
BB	9.0	0.3	0.3	9.0	1.2	1.2	4.5	0.24	0.24
fibrotic	3.0	0.0	0.0	3.0	1.2	1.2	1.5	0	0

 $G_{mL}$ 

1.5

 $G_{mT}$ 

0.24

 $G_{mC}$ 

0.24

**Table. S2** Atrial Fibrillation Cycle length (AFCL) in simulations with different ablation patterns (\* P Value < 0.05).

Simulation groups Fibrosis	Control	PVI	вох	PVI + LAAI	BOX + LAAI
without	149±3.2ms	154± 2.3ms*	155± 2.7ms*	163± 2.4ms*	167± 2.7ms*
moderate	142± 3ms	149± 2ms*	153± 4.1ms*	157± 3ms*	158± 4.1ms*
severe	139± 2.4ms	146± 1.9ms	$148 \pm 3.4 \text{ms}$	151 ± 2.5ms*	152 ± 3.4ms*











