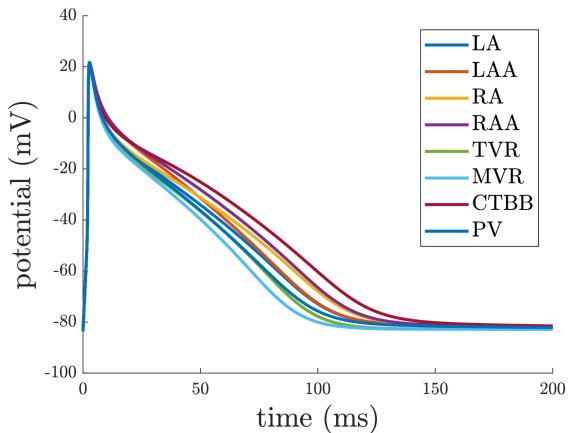


## **Supplementary Material**



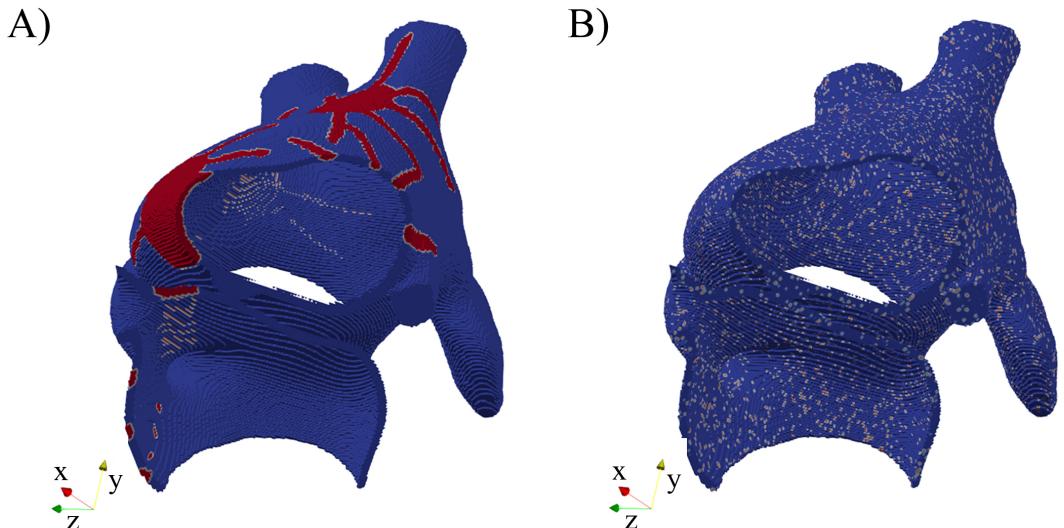
**Figure S1.** APs corresponding to the different electrophysiological regions in the 3D biatrial models.

**Table S1.** Longitudinal conductivity ( $L_{CV}$ ) and transverse-to-longitudinal conductivity ratio ( $T/L_{CR}$ ) values for the different atrial regions.

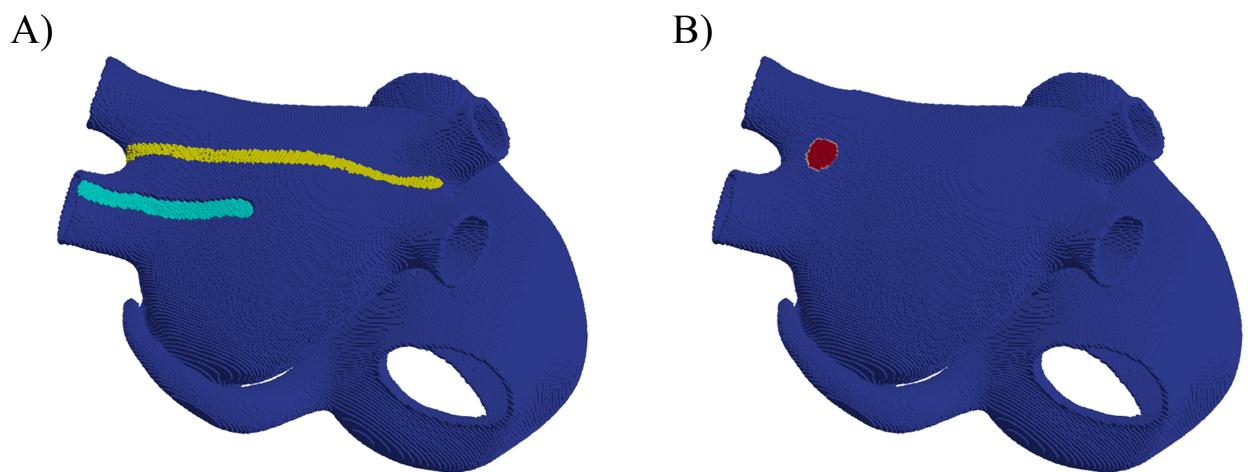
| Region | $L_{CV}$ (S) | $T/L_{CR}$ |
|--------|--------------|------------|
| RA     | 0.0030       | 0.35       |
| CT     | 0.0085       | 0.15       |
| PV     | 0.0017       | 0.50       |
| BBPM   | 0.0075       | 0.15       |
| IST    | 0.0015       | 1.00       |
| SAN    | 0.0008       | 1.00       |
| FO     | 0.0000       | 1.00       |
| CS     | 0.0060       | 0.5        |
| LA     | 0.0030       | 0.25       |
| LFO    | 0.0075       | 0.15       |

## **REFERENCES**

Abdollahpur, M., Holmqvist, F., Platonov, P. G., and Sandberg, F. (2021). Respiratory Induced Modulation in f-Wave Characteristics During Atrial Fibrillation. *Frontiers in Physiology* 12, 653492. doi:10.3389/fphys.2021.653492



**Figure S2.** Sections of the left atrium for the  $\mathcal{O}_{08}$  model (A) and  $\mathcal{D}_{08}$  model (B). In the  $\mathcal{O}_{08}$  the ACh release nodes (red) are concentrated in the 2 most external layers of the mesh, while in the  $\mathcal{D}_{08}$  model they are uniform randomly distributed in all the three node layers.



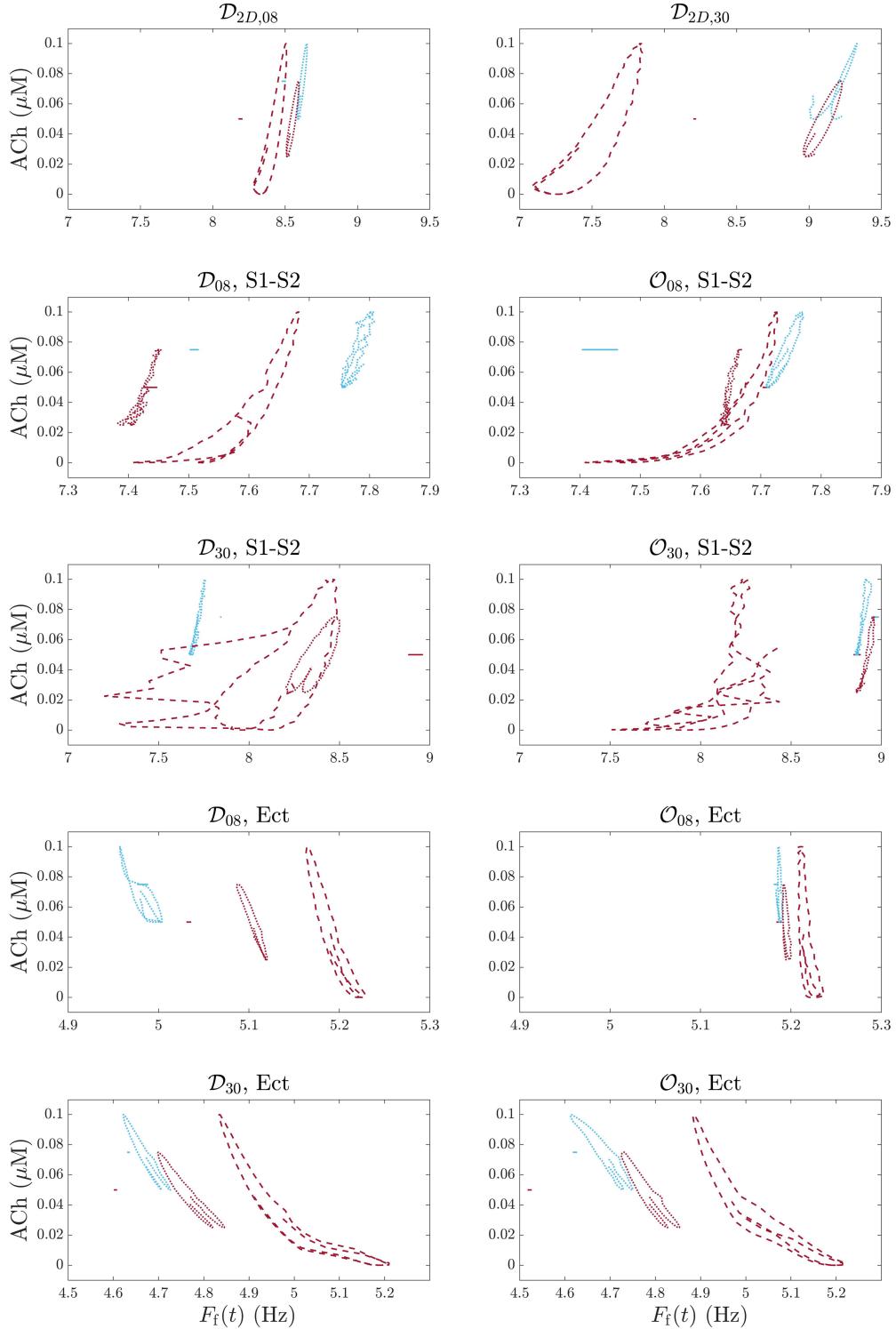
**Figure S3.** A) Location of the S1 stimulation (yellow region) and of the S2 stimulation (cyan region). B) Location of ectopic beats stimulation (red region)

**Table S2.** Results from clinical data ( $\mathcal{B}$ : baseline,  $\mathcal{CR}$ : Controlled Respiration,  $\mathcal{PA}$ : Post Atropine). (\*) indicates significant differences to  $\mathcal{B}$  and (●) indicates significant differences to  $\mathcal{CR}$ . The quality of baseline signals of patient f was too low to evaluate  $\Delta F_f^{\mathcal{B}}$  and  $\bar{F}_f^{\mathcal{B}}$ . Table adapted from Abdollahpur et al. (2021).

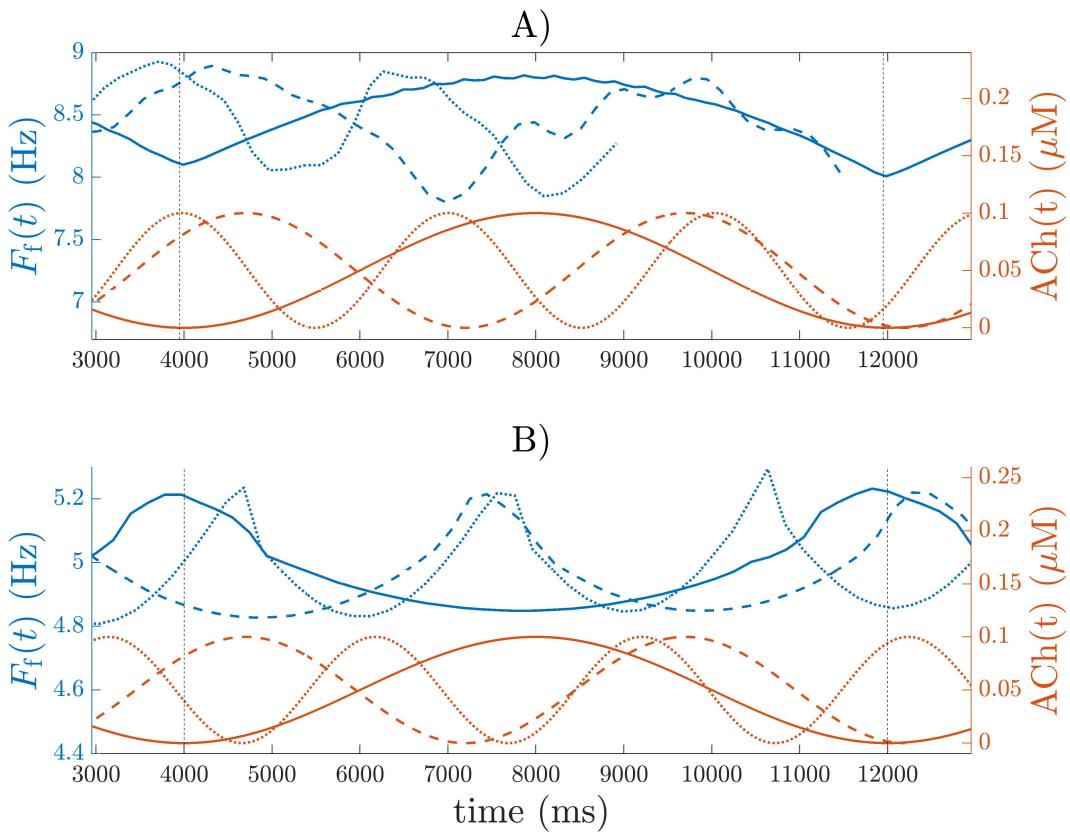
| Patient | $\Delta F_f^{\mathcal{B}}$ (Hz)       | $\Delta F_f^{\mathcal{CR}}$ (Hz)       | $\Delta F_f^{\mathcal{PA}}$ (Hz)       | $\bar{F}_f^{\mathcal{B}}$ (Hz) | $\bar{F}_f^{\mathcal{CR}}$ (Hz) | $\bar{F}_f^{\mathcal{PA}}$ (Hz) |
|---------|---------------------------------------|--|--|--------------------------------|---------------------------------|---------------------------------|
| a       | $0.16 \pm 0.06$                       | $0.17 \pm 0.09^*$                      | $0.16 \pm 0.08^{\bullet}$              | $6.84 \pm 0.43$                | $6.67 \pm 0.45^*$               | $6.71 \pm 0.41^{\bullet*}$      |
| b       | $0.13 \pm 0.06$                       | $0.16 \pm 0.08^*$                      | $0.13 \pm 0.07^{\bullet}$              | $6.17 \pm 0.35$                | $6.31 \pm 0.37^*$               | $6.46 \pm 0.36^{\bullet*}$      |
| c       | $0.16 \pm 0.08$                       | $0.17 \pm 0.08^*$                      | $0.14 \pm 0.07^{*\bullet}$             | $6.57 \pm 0.43$                | $6.75 \pm 0.39^*$               | $6.36 \pm 0.43^{\bullet*}$      |
| d       | $0.16 \pm 0.08$                       | $0.19 \pm 0.10^*$                      | $0.19 \pm 0.10^*$                      | $7.68 \pm 0.51$                | $7.39 \pm 0.54^*$               | $7.57 \pm 0.54^{\bullet*}$      |
| e       | $0.14 \pm 0.07$                       | $0.21 \pm 0.10^*$                      | $0.21 \pm 0.12^*$                      | $7.46 \pm 0.46$                | $7.29 \pm 0.49^*$               | $7.14 \pm 0.48^{\bullet*}$      |
| f       | -                                     | $0.17 \pm 0.08$                        | $0.16 \pm 0.08^{\bullet}$              | -                              | $5.91 \pm 0.41$                 | $5.96 \pm 0.42^{\bullet}$       |
| g       | $0.15 \pm 0.08$                       | $0.17 \pm 0.07^*$                      | $0.17 \pm 0.07^*$                      | $7.73 \pm 0.43$                | $8.11 \pm 0.44^*$               | $7.98 \pm 0.43^{\bullet*}$      |
|         | $\Delta \bar{F}_f^{\mathcal{B}}$ (Hz) | $\Delta \bar{F}_f^{\mathcal{CR}}$ (Hz) | $\Delta \bar{F}_f^{\mathcal{PA}}$ (Hz) | $\bar{F}_f^{\mathcal{B}}$ (Hz) | $\bar{F}_f^{\mathcal{CR}}$ (Hz) | $\bar{F}_f^{\mathcal{PA}}$ (Hz) |
| Average | $0.15 \pm 0.01$                       | $0.18 \pm 0.02$                        | $0.17 \pm 0.03$                        | $7.07 \pm 0.64$                | $6.93 \pm 0.73$                 | $6.88 \pm 0.71$                 |

**Table S3.** Comparison of results obtained from the transmembrane voltage (AP) traces and from pseudo-ECGs, in terms of  $\bar{F}_f$ .

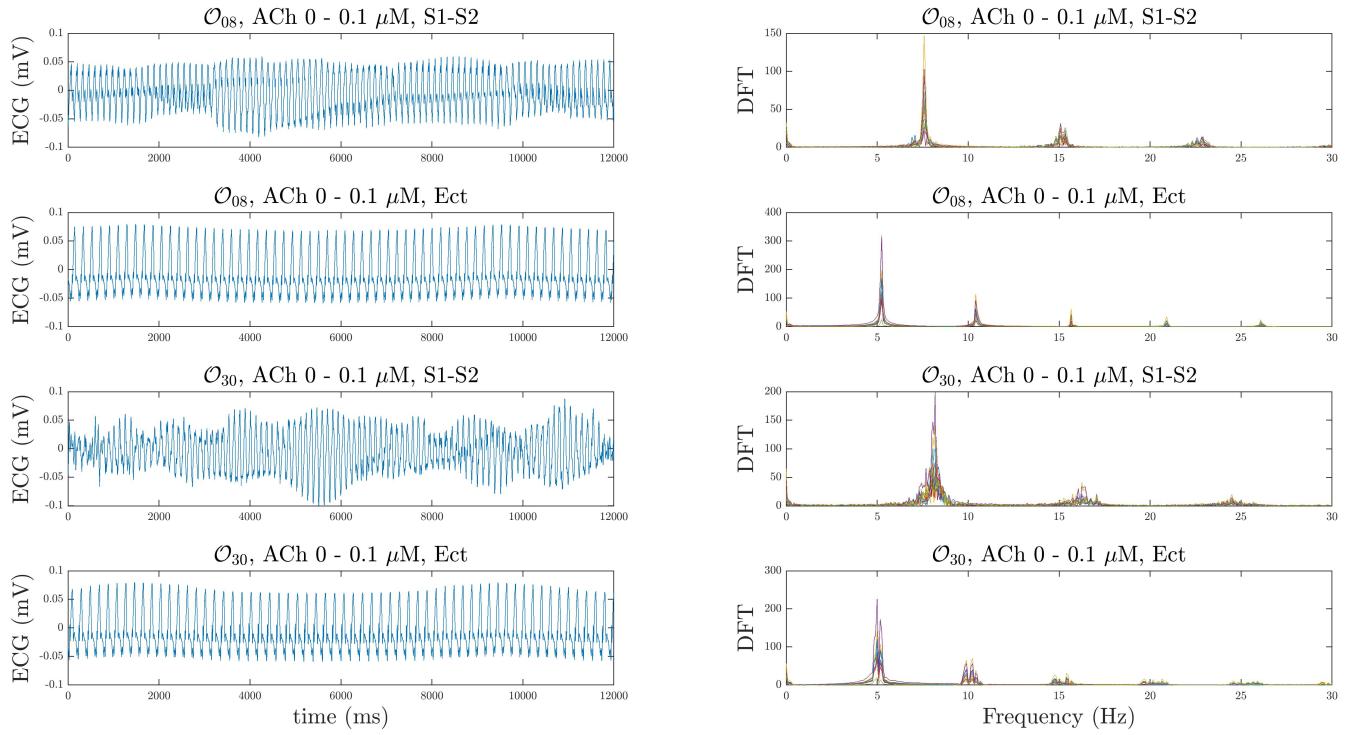
|                          | $\bar{F}_f$ from AP (Hz) | $\bar{F}_f$ from ECG (Hz) |
|--------------------------|--------------------------|---------------------------|
| $\mathcal{O}_{08}$ S1-S2 | 7.66                     | 7.67                      |
| $\mathcal{O}_{08}$ Ect   | 5.21                     | 5.25                      |
| $\mathcal{O}_{30}$ S1-S2 | 8.04                     | 8.00                      |
| $\mathcal{O}_{30}$ Ect   | 4.99                     | 5.01                      |



**Figure S4.**  $F_f(t)$  versus  $ACh(t)$  for  $\mathcal{D}_{2D,08}$  and  $\mathcal{D}_{2D,30}$  (first row),  $\mathcal{D}_{08}$  and  $\mathcal{O}_{08}$  (second row) and  $\mathcal{D}_{30}$  and  $\mathcal{O}_{30}$  (third row) and application of the S1-S2 protocol,  $\mathcal{D}_{08}$  and  $\mathcal{O}_{08}$  (fourth row) and  $\mathcal{D}_{30}$  and  $\mathcal{O}_{30}$  (fifth row) and application of a train of ectopic beats. Light blue/dark red represents  $\overline{ACh}=0.075/\overline{ACh}=0.05 \mu\text{M}$ . Solid/dotted/dashed lines represent  $\Delta\text{ACh}$  values of  $0.0/0.05/0.1 \mu\text{M}$ .



**Figure S5.** A) Results from 2D tissue simulations with  $\mathcal{D}_{2D,30}$  spatial configurations of ACh release. B) Results from 3D biatrial simulations with  $\mathcal{D}_{30}$  spatial configurations of ACh release and application of a train of ectopic beats.  $F_f(t)$  (blue) and  $ACh(t)$  (red) are plotted in both panels for  $\overline{ACh} = 0.1 \mu M$ . Solid/dashed/dotted lines represent different ACh concentration modulation frequencies (0.125/0.20/0.33 Hz, respectively). In panel A), both the 0.20 Hz and 0.33 Hz frequencies of ACh modulation resulted in premature rotor extinction at the tissue borders.



**Figure S6.** Left column) ECG signal from one of the 12 electrodes. Right column) Module of the Discrete Fourier transforms (DFT) of the 12 pseudo-ECG signals.