Development of a 3D Computational Sheep Atria for the Study of Atrial Fibrillation

Timothy D. Butters[1], Oleg V. Aslanidi[2], Jicaho Zhao[3], Bruce Smaill[3], Henggui Zhang[1]

[1]University of Manchester, [2]King's College London, [3]Auckland Bioengineering Institute

Correspondance: Prof. Henggui Zhang, henggui.zhang@manchester.ac.uk.

Atrial fibrillation (AF) is the most common sustained arrhythmia in the developed world, affecting approximately 1.5% of its population [1]. The prevalence of AF increases with age, therefore in an ageing population AF is set to become a leading factor in mortality, morbidity and quality of life of the general population. Although AF is a common arrhythmia its genesis is not well understood, therefore further research to better understand the causes of the disease is paramount. Sheep are often used as experimental models to study cardiac diseases such as atrial fibrillation [2,3], but there are currently no species-specific mathematical models for the sheep atria.

Computer models provide a powerful tool for studying cardiac disease. In this study electrophysiologically detailed models were developed for different cell types of the sheep atria: the pectinate muscles (PM), crista terminalis (CT), right atrial appendage (RAA), Bachmann's bundle (BB), the left atrium (LA) and the pulmonary veins (PV). These single cell models were then incorporated into an anatomically detailed reconstruction of a sheep atria, which was segmented into the various cell types and contained detailed fibre orientation information throughout the tissue (Fig. 1A and 1B). This provided a computational platform that could be used to investigate the genesis of AF, and the importance of electrical heterogeneity and fibre structure on its sustainability.

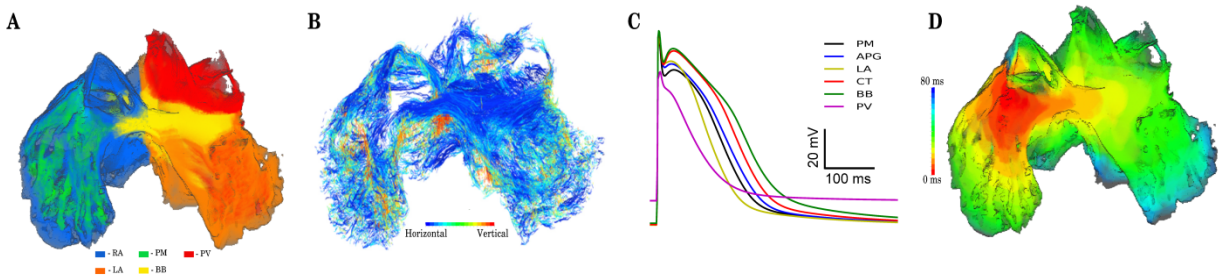

Fig. 1: (**A**) Reconstruction of the 3D sheep atria showing the different regions of the tissue. (**B**) The fibre structure of the reconstructed atria shown by the fibre angle to the horizontal plane. (**C**) Simulated action potentials of the different atrial cell types from the new sheep models. (**D**) Simulated activation map of the virtual 3D atria.

Although sheep are often used in an experimental setting, they are used at the tissue level as opposed to the single cell level. Therefore there is very little voltage clamp data available for individual currents, and so it was not possible to develop the cell models by fitting each modelled current to experimental data. Instead, the Ramirez *et al.* mathematical models of the canine atrium were used as a base for the new sheep models [4]. This model set includes detailed descriptions of cells in the right atrium, but does not include models for the fast conduction pathway of Bachmann's bundle, the left atrium, or the pulmonary veins. This model set was first expanded to describe these cell types using detailed experimental data from Li *et al.*, Ehrlich *et al.* and Burashnikov *et al.* [5-7]. The parameters of the RAA model were then altered so that the simulated action potential (AP) profile matched that of experimentally obtained AP recordings from the sheep atrium by Lenaerts *et al.* [8]. It was then assumed that the same current scaling factors used in the canine models to differentiate different cell types could be applied to the sheep model,

which produced a full set of atrial APs (Fig. 1C). The resting potential of the simulated RAA AP matches the measured value of -75 mV, as do the amplitude and APD_{90} (97 mV and 202 ms respectively) [8].

A 3D reconstruction of a sheep atria was generated using extended volume imaging [9], this was then segmented manually and the complex fibre structure of the tissue was extracted using an image based fibre tracking algorithm [9] (Fig. 1A and 1B). The single cell models were then incorporated into the geometry using a finite difference numerical scheme, and the tissue was stimulated from the sinoatrial node region. The resulting activation pattern is shown in Fig. 1D. The conduction velocities match well with experimental recordings, with values ranging from 0.8 m/s in the LA to 1.5 m/s in BB. The excitation pattern follows that of other species such as human and canine, where fastest conduction along the bundles of the PM, CT and BB are also seen.

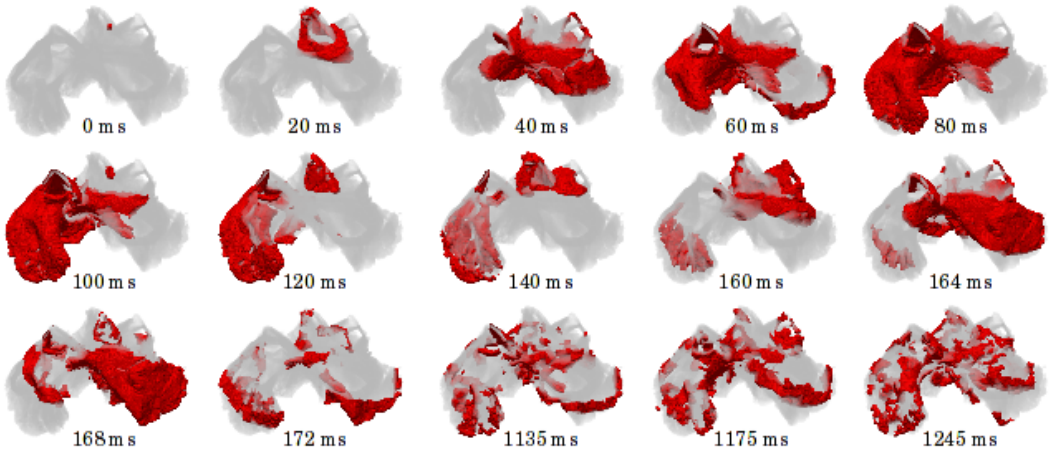

Fig. 2: Excitation pattern from a series of short coupled stimuli given in the pulmonary vein region (red shows depolarized tissue). The waves re-enter by rotating around the pulmonary vein sleeves (164 ms – 172 ms), they later break down into a fibrillatory pattern (1135 onwards).

The arrhythmogenic properties of the PV region were then investigated using a rapid pacing protocol. It has been previously suggested by Aslanidi *et al.* that atrial heterogeneity and anisotropy could be a possible mechanism for AF initiation [10, 11], so three rapid stimuli (cycle length 100 ms) were applied to the right anterior PV sleeve which is in a region of high anisotropy (Fig. 1B). This was carried out considering both the electrical heterogeneity and complex fibre structure of the atria (Fig. 2), just the electrical heterogeneity, and then just the fibre orientation where all tissue was simulated using the RAA model. AF was induced using this method for the two cases that considered the regional electrical differences. With no electrical heterogeneity it was not possible to induce AF.

As can be seen from Fig. 1C, a new set of atrial AP models has been developed that fit well with experimental measurements. This model set has been successfully incorporated into an anatomically detailed 3D reconstruction of a sheep atria. Conduction velocities within the virtual sheep atria are validated against experimental recordings, and the activation map follows the expected pattern with fast conduction along the fibre bundles of the PMs and BB.

This computational platform was then used to study the importance of electrical heterogeneity and anisotropy on the genesis and sustainability of AF. Fibrillation was induced by rapidly pacing the

pulmonary vein region under several conditions. It was found that AF can be induced when the electrical heterogeneity is modelled, regardless of whether or not the complex fibre structure is considered. However, when the fibre structure was ignored the fibrillatory patterns were very different, with fewer re-entrant wavelets forming and a more homogeneous pattern throughout the atria. When the electrical heterogeneity was ignored it was not possible to induce AF with the same pacing protocol. This shows that the differences in AP morphology in the atria are key for the genesis of AF, and the complex fibre structure is important for its development, which is in agreement with Aslanidi *et al*. [11]. Therefore, when using computational models to study cardiac arrhythmias such as AF, it is important to include biophysical details of both electrical regional differences and the tissue fibre structure. In summary, a novel species-specific computational platform of the sheep atria has been developed. This platform provides a powerful tool that can be used to study the mechanisms underlying the genesis of AF.

References:

1. Lip GYH, Kakar P, Watson T. Atrial fibrillation – the growing epidemic. Heart. 2007 93(5):542-543.

2. Tanaka K, Zlochiver S, Vikstrom KL et al. Spatial distribution of fibrosis governs fibrillation wave dynamics in the posterior left atrium during heart failure. Circ. Res. 2007 101(2):839-847.

3. Berenfeld O, Ennis S, Hwang E, et al. Time- and frequency-domain analyses of atrial fibrillation activation rate: The optical mapping reference. Heart Rhythm. 2011 8(11):1758-1765.

4. Ramirez RJ, Nattel S, Courtemanche M. Mathematical analysis of canine atrial action potentials: rate, regional factors, and electrical remodelling. Am. J. Physiol. Heart Circ. Physiol. 279:H1767-H1785, 2000.

5. Li D, Zhang L, Kneller J et al. Potential ionic mechanisms for repolarization differences between canine right and left atrium. Circ. Res. 2001 88:1168-1175.

6. Ehrlich JR, Cha TJ, Zhang L, et al. Cellular electrophysiology of canine pulmonary vein cardiomyocytes: action potential and ionic current properties. J. Physiol. 2003 551(Pt 3):801-813.

7. Burashnikov A, Mannava S, Antzelevitch C. Transmembrane action potential heterogeneity in the canine isolated arterially perfused right atrium: effect of IKr and IKur/Ito block. Am. J. Physiol. Heart Circ. Physiol. 2004 286:H2393-H2400.

8. Lenaerts I, Bito V, Heinzel FR, et al. Ultrastructural and functional remodelling of the coupling between Ca^{2+} influx and sarcoplasmic reticulum Ca^{2+} release in the right atrial myocytes from experimental persistent atrial fibrillation. Circ. Res. 2009 105:876-885.

9. Zhao J, Butters TD, Zhang H, Pullan AJ, LeGrice IJ, Sands GB, Smaill BH. An image-based model of atrial muscular architecture: effects of structural anisotropy on electrical activation. Circ Arrhythm Electrophysiol. 2012 5(2):361-70.

10. Aslanidi OV, Boyett MR, Dobrzynski H, et al. Mechanisms of transition from normal to re-entrant electrical activity in a model of rabbit atrial tissue: interaction of tissue heterogeneity and anisotropy. Biophys. J. 2009 96:798-817.

11. Aslanidi OV, Colman MA, Stott J, et al. 3D virtual human atria: a computational platform for studying clinical atrial fibrillation. Prog. Biophys. Mol. Biol. 2011 107:156-168.