Exploring Atrial Fibrillation Through Computational Models: Clinical Applications, Mechanisms, and Advancements in Tools

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Abstract

Atrial fibrillation (AF) is the most common cardiac arrhythmia, characterized by a fast and irregular heart rate. Computer modelling has been playing an ever more important role in understanding AF. This review showcases research from the past two years from a variety of aspects relevant to computational modelling of AF. Beginning with research that is directly relevant in clinical settings, such as antiarrhythmic drugs, ablation techniques and blood clot modelling. This is followed by studies that aim to understand the underlying mechanisms behind AF, including influence from fibrosis, fatty tissue, and atrial model size and makeup. The last section features literature on techniques, methodologies and tools that are relevant to AF modelling, such as diffusion algorithms, imaging, and artificial intelligence.

1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia which is characterized by a fast and irregular heartbeat [1]. It is a result of abnormal action potential wave traversal through the muscle fibers of the atria. This can either be due to spontaneous triggered activity, or a continually rotating wave-front (reentry) [2,3]. Reentries can be formed around an anatomical opening (macro-reentry) or be due to heterogeneity or anisotropy in the atria (micro-reentry). A key factor of AF is its self-deteriorating nature, i.e., its occurrence promotes changes in the atria that further perpetuate AF, referred to as atrial remodeling [4]. This can take the form of changes in ionic currents, affecting the action potential refractory period, or structural changes, such as deposition of excess collagen, known as fibrosis. Two common treatments for AF are anti-arrhythmic drugs and ablation [5].

Computer modeling is an effective tool for studying AF. When these models incorporate personalized patient data from sources such as magnetic resonance imaging (MRI) [6], computed tomography (CT) imaging [7] and local impedance measurements [8], they are classified as patient specific computer models, or digital twins [1,9]. These patient specific data are used in forming a 3D reconstruction of human atria, either as a bilayer (the surfaces of the atrial shape) or as the whole volume [10], capturing fibrotic or scarred areas [6,7].

Artificial intelligence (AI) is starting to play an ever more significant role in medicine [11]. It has become practical with recent computational advances and often outperforms conventional approaches. The wide uses for AI in atrial physiology have ranged from assistance in analyzing and labelling medical images [12] to enhancing the understanding of computer simulation results [3,13].

This review highlights recent research related to computational modeling of AF. The first section focuses on clinically relevant modeling, the second section has a focus on modeling of the underlying atrial physiology responsible for AF, the last section looks at research on relevant processes, methodologies, and tools such as AI.

2. Clinically Relevant Modelling

Computer modelling can simulate a variety of atrial physiology, from cellular-level currents to tissue-level electrophysiology and chamber blood flow. Simulations increase our understanding of the underlying physiology of AF and by incorporating patient specific data they can become more clinically relevant. Digital twins have the potential to offer unparalleled understanding and allow for exploration of alternative treatments in a patient specific manner [9]. Trayanova et al. [1] reviewed the current state of cardiac digital twins, highlighting the advances made towards bringing them into clinical settings. Building on this concept, a large collection of digital twins could be used to conduct clinical trials entirely through computer modelling. Given that computer modeling allows easy isolation of variables, in-depth analysis and perfect repeatability, digital twins and their clinical trials will potentially revolutionize the field of cardiac physiology and AF healthcare.

Complete digital twins are not yet possible, but large *in silico* trials have been demonstrated. Dasi et al. [14] used 800 atria in an *in silico* drug trial. Variations in the atrial models were based on and validated with clinical measurements. Drug administration was modelled with

electrophysiological changes, and then AF was initiated and analyzed, enabling them to suggest several different drug treatments for various AF characteristics. Following this paper, the same group then ran an 800 atria trial with both drug and ablation therapy [5]. Pulmonary vein isolation [5] was applied to these atria, 522 of which were still able to sustain AF. Twelve supplementary treatments were then given to these 522 models, including established and novel ablations, and drugs (alone and with ablation). This trial study showed differing efficacy of treatments based on the characteristics of the atria.

Ablation is effective in early AF stages; however, it is suboptimal for persistent or long-standing persistent AF [15], and so remains a focus in computer modelling [3,13,16,17]. Bifulco et al. [3] simulated pulmonary vein isolation and did not show significant improvement in reducing arrhythmias, however, the results did show that before ablation, the atria mostly had functional reentries, while after ablation the majority of reentries were anchored to anatomical openings or ablation scars. Dasi et al. [5] demonstrated that by supplementing common ablation techniques with a small additional ablation that breaks right atrial (RA) tricuspid macro-reentries, the success rate increases by approximately 50%. Best success rates occurred when this supplementary procedure was combined with substrate-based ablation of patient specific fibrotic areas. These findings were in general agreement with clinical results [5].

Another study sought to improve this substrate-based ablation [16]. They compared ablating dense fibrotic patches with ablating dense fibrosis patches + their bordering diffuse fibrosis. The authors found that isolating the fibrotic border zone + dense fibrosis significantly helped the ablation success rate, and that substrate-based ablation like this is more effective for patients with higher fibrosis percentages.

While AF itself is not life threatening, it greatly increases the risk of stroke [18]. Computer modelling of left atrial (LA) blood flow can elucidate the process of blood clot formation due to the presence of the LA appendage (LAA) and impaired myocardial mechanical activity during AF. Qureshi et al. [18] performed fluid dynamics simulations during a healthy heartrate and during AF. Three key aspects to blood clot formation were simulated, blood stasis, endothelial damage, and hypercoagulability (collectively called Virchow's triad). In comparison to the healthy case, the AF conditions had a lower flow velocity, larger and slower vortices, and significantly more endothelial damage. The healthy case washed away the damage induced coagulants with every passing cardiac cycle, while the slower blood velocities during AF caused uninterrupted clot growth in the LAA. These simulations can provide clinicians with a deeper understanding of stroke risks on a per patient basis. A follow-up study [19] used global sensitivity analysis to gain understanding of the contributions of inlet velocity, coagulant initial conditions, and a biochemical constant. Using 160 2D fluid dynamics simulations of the four common LAA morphologies, they found that initial conditions of coagulants were the biggest contributors to blood clot formation across all LAAs, while the impacts of the other factors were dependent on LAA morphology.

3. Modelling Atrial Physiology

Fibrosis is one of the most significant contributors to AF progression. Its effects on the atrial pathophysiology have been extensively studied with computer simulations [2,6,15,20]. Ogbomo-Harmitt et al. followed up the fibrotic border zone ablation study [16] with a more extensive look at its impact on AF [15]. Healthy tissue, dense fibrosis, and four more fibrosis levels (representing the fibrotic border zone) were derived from MRI voxel intensities. Simulations were performed with and without the fibrotic border zone. They found that the fibrotic border zones slowed down conduction in reentry phase singularity areas, and increased the reentry frequency, while decreasing the total number of phase singularities. The simulations with the fibrotic border zone had reentries deeper inside dense fibrosis, indicating that the border zones guided them in that direction. These slow conduction velocity regions that anchor reentries can then be identified as potential ablation targets.

Fibrosis is not the only substrate that affects conduction, Chahine et el. [6] investigated both obesity and atrial fibrosis. They set out to investigate if atrial epicardial fatty tissue can be linked to body mass index or the volume and fibrosis of the LA. Using 3 MRI scans, they found that epicardial fat was significantly correlated with all three aspects, however, the location of the LA epicardial fat and fibrotic regions did not appear to show any clear overlap. In a follow-up study [20], computer simulations were used to understand how reentries are affected by fibrosis and epicardial fat. They found that epicardial fat inclusion led to better agreement with the respective patient's clinical results. In their simulations, 83% of reentries were micro-reentries, of which 73% anchored to regions that contained both fat and fibrosis.

The contribution of atrial fibrosis in AF maintenance is a common topic of study, Colman et al. [2] examined the lesser studied role of fibrosis in AF genesis. Using simulations performed on both 2D and 3D atrial tissue models, they found that along with maintaining AF, patchy fibrosis can also help generate it. Namely through reducing electrical loading on tissue regions, helping the spontaneous AF trigger site excitation to be more robust.

Along with self-initiation, AF can also self-terminate. Dharmaprani et al. [21] investigated this and showed that the termination time follows a power law relationship with atrial size and correlation length [21]. This insight gives more predictive power when determining potential AF behavior in research and clinical settings. Many of the

previously mentioned studies used LA-only models in simulations. The LA is often the focus of AF simulation studies, so as a simplification, the RA gets excluded [4]. Diaz et al. [4] released a study that showed the importance of RA inclusion in AF simulation studies. The study tests the vulnerability to arrhythmias given the presence or absence of the RA. Eight patient specific atria were used and simulations were performed on biatrial models and LA-only models. The study also incorporated three different levels of AF induced atrial remodeling, healthy, mild and severe, modelled by varying ionic currents, fibrosis level and conductivity. They found that adding the RA increased arrhythmia rates by 116% and 29% in mild and severe remodeling cases, respectively.

4. Modelling Tools and Methodologies

Medical imaging is important clinically, its importance is reflected in the breadth of research involving it [6,7,12,13,15,18]. Two prominent imaging technologies are MRI and CT. Due to its ability to indicate fibrotic areas, MRI remains popular, alternatively, CT also sees usage in all stages of cardiac clinical care and is known for its greater resolutions. Bodagh et al. [7], in a review, covered the current and potential applications of CT in cardiac clinical settings and computer simulations, and its potential to improve patient specific medical intervention and their outcomes. In the future, CT has the potential to obtain accurate representations of epicardial fat, atrial structure, and wall thickness for atrial models.

There are methods other than MRI that can identify fibrotic areas. Local impedance measurements, an emerging technique used to gauge the healthiness of atrial tissue (presence of scar/fibrosis) was studied by Anton et al. [8]. To make these measurements, contact force is needed on the area of interest, but the effect of contact force itself on local impedance is not well understood. A clinically validated model was used to simulate catheter contact force on atrial tissue of varying thickness and healthiness. They found that impedance increases with contact force, and tissue thickness and healthiness, ultimately concluding that a combination of known contact force and local impedance is effective at differentiating healthy tissue from scar tissue.

Simulation studies have become larger with improving computer hardware but can still be bottlenecked by manual pre-processing steps. In the previously mentioned *in silico* clinical trial studies the large numbers of atrial models were noteworthy [5,14]. Recently, Roney et al. [10] presented an open-source pipeline to produce 1000 biatrial bilayer and volumetric models in a quick and reproducible way. In addition, they investigated the effects on AF dynamics from fibrosis, fibers and model reconstruction method (bilayer/volumetric). Concluding that volumetric and bilayer models (from the same MRI) result in different AF patterns, but that they can be brought closer together with the inclusion of fibrosis.

Using the finite element method to solve equations for the bidomain formulation of atrial tissue is a standard and accurate way simulations are performed. Nagel et al. [22] investigated the effects of model simplifications, while taking note of the resulting performance and accuracy relative to the bidomain finite element method. They were able to find performant and accurate alternatives, namely the Eikonal and boundary element methods.

The previously mentioned fluid dynamics studies [18,19] showed the value of modelling AF physics beyond the typical tissue electrophysiology simulations. Gerach et al. [17] used an electromechanical whole-heart model to investigate the effect of standard atrial ablation on the heart's function. Presence of ablation scars reduced both atrial and ventricular stroke volumes. It also increased the LA's pressure by 20% during systole. This multiphysics simulation shows that while ablation treats AF, it does come at the cost of cardiac efficiency.

The potential of AI in cardiac electrophysiology cannot be understated. In a review, Kabra et al. [11] highlighted how it has been used in relation to arrhythmias, its challenges, and its future potential. The wide range of AI applications include assistance with and improvement of implantable and wearable medical devices, improved electrocardiogram interpretations and ablation targets. For example, noting that fibrosis is important for understanding ablation outcomes and that its identification can be manually intensive, Ogbomo-Harmitt et al. [12] proposed the use of AI to identify fibrosis scar in MRI scans. Using a multi-stage AI pipeline, they achieved state of the art accuracy in a challenge evaluation test.

Patterns that are unrecognizable by the human eye or are difficult, if not impossible, to describe analytically, can be picked up by AI. However, the reasoning behind its output is not human interpretable, which is not well suited for the field of medicine. Therefore, interpretability of neural networks remains an active area of research. Ogbomo-Harmitt et al. [13] looked at using AI to assist in improving persistent AF post-ablation success, and its implications in clinical settings. Simulations were performed on 187 LA models, having three different types of ablations administered for each, and AI was used for predicting the strategy success. Feature attribution map methods were used to investigate AI model interpretability. The feature attribution maps highlighted regions that were shown to be proarrhythmic in the simulations. Ultimately concluding that interpretability is useful for AI to be seen as a useful and trustable tool for assistance in clinical practice.

Bifulco et al. [3] performed simulations on human persistent AF LA under both pre- and post-ablation conditions. They sought to understand why AF reoccurs after ablation through interpretable AI. In post-ablation LA that experienced AF reoccurrence, non-conductive regions (fibrosis/scar) were labelled as proarrhythmic if a reentry anchored to them or non-proarrhythmic otherwise. Given

these labels and spatial measurements of the non-conductive regions (such as perimeter and area), a random forest classifier was trained. The results were made interpretable by using the SHAP [3] approach to ascertain relative contributions of the spatial features towards a given proarrhythmic or non-proarrhythmic outcome. Finding that non-conductive region perimeter was most influential in predicting arrhythmogenicity.

5. Conclusions

Our understanding of AF has been greatly increased by computer modelling of underlying atrial pathophysiology (fibrosis, epicardial fat and blood clot formation) and its treatments (drug and ablation therapy). With the use of personalized models, the promise of digital twins and *in silico* clinical trials, computer modelling is becoming increasingly relevant clinically. Pathophysiology studies highlight the importance of atrial size and the presence of the RA and epicardial fat on AF behavior in computer simulations. Imaging technologies, MRI and CT, already see wide usage in research and clinical practice, with the addition of emerging supplementary techniques such as local impedance measurements and AI, their role is set to further increase in prominence. The advancements of AI and its interpretability have accelerated the progress of computer modelling towards the medical ideal of precise patient specific treatments.

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