Atrial Fibrillation: How to Move Forward in This Complex Arrhythmia

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Abstract

Atrial fibrillation (AF) is typically classified by episode duration (paroxysmal, persistent, long-standing persistent, and permanent). Multiple mechanisms have been proposed underlying AF (multiple rotors, focal sources, wavelet hypothesis, epi-endo dissociation, micro reentry, ...). However, despite extensive study, pulmonary vein isolation (PVI) remains the only proven ablation treatment for paroxysmal AF. This work aims to address critical challenges to progress AF research. 1. Complexity: The trend towards increasingly complex models, such as digital twins, raises the question of whether we fully understand simpler models. We revisit a fundamental theorem in atrial tachycardia that was overlooked for more than three decades despite existing evidence, suggesting that simpler models may still hold untapped insights. 2. Open Source Code: Limited availability of open-source codes for analyzing AF data impedes research, while many companies restrict access to their proprietary tools. 3. Data Accessibility: The scarcity of publicly available datasets, due to privacy concerns and reluctance to share, hampers progress. 4. Heterogeneity: AF might be highly variable, with different pathologies manifesting as AF, suggesting that uniform treatment approaches may not be suitable.

This work aims to challenge existing paradigms and advocate for a collaborative and transparent approach to AF research.

1. Introduction

AF has been extensively studied for decades, typically classified by episode duration: paroxysmal, persistent, persistent, and permanent AF.

For paroxysmal AF, Haissaguerre et al. [1] discovered that it is triggered by irregular ectopic activity originating in the pulmonary veins and demonstrated that pulmonary vein isolation (PVI) is an effective way to treat paroxysmal AF. However, the mechanisms underlying persistent AF are less well understood, leading to a relatively low success rate of around 50% [2].

Various mechanisms have been proposed and supported by experimental studies, clinical observations, and computer simulations. The hypothesized mechanisms include: **1. The multiple wavelet theory** hypothesises that AF is maintained by multiple independent reentrant wavelets which change position, shape, size and number with each successive excitation [3]. **2. The mother rotor** fibrillation hypothesis [4] suggests that one fast stationary or meandering rotor in one region of the heart generates additional wavebreaks in the surrounding tissue producing a pattern on fibrillatory conduction. This may resemble multiple wavelet activation patterns. **3. The multiple rotor theory**, which suggests that stable [5] or meandering rotors[6] are responsible for the maintenance of AF. **4. The double layer hypothesis** suggests that persistent AF can cause complete electrical dissociation between the atrial endocardial and epicardial surfaces. The maintenance of AF is then regulated by breakthroughs of the remaining connections between these two layers [7]. **5. The micro-anatomic intramural reentry hypothesis** suggests that AF may be driven by spatially and temporally stable intramural reentry rotating through the pectinate bundle [8].

Despite the variety of proposed mechanisms, the exact cause of persistent AF remains unclear, and ablation treatment has not shown benefits beyond PVI, which highlights the need for further research to improve treatment outcomes. In this work, we will suggest four critical challenges to advance AF research.

2. Model complexity

First, models are becoming increasingly complex. They now incorporate detailed, patient-specific anatomical structures, include fiber orientation, fibrotic and adipose tissues, etc. These models are sometimes coupled with cardiac mechanics, also increasing complexity. However, even a basic simulation of rotor induction using OpenCARP reveals significant differences between the different atrial and ventricular cardiac models, as shown in Figure 1. This shows that we should be cautious with using these models, and always explore the effect of different models on the simulations we perform.

Even the simplest models can unveil entirely new mechanisms. Our group aimed to investigate the most simple arrhythmia, namely AT, using the simplest model possible: a

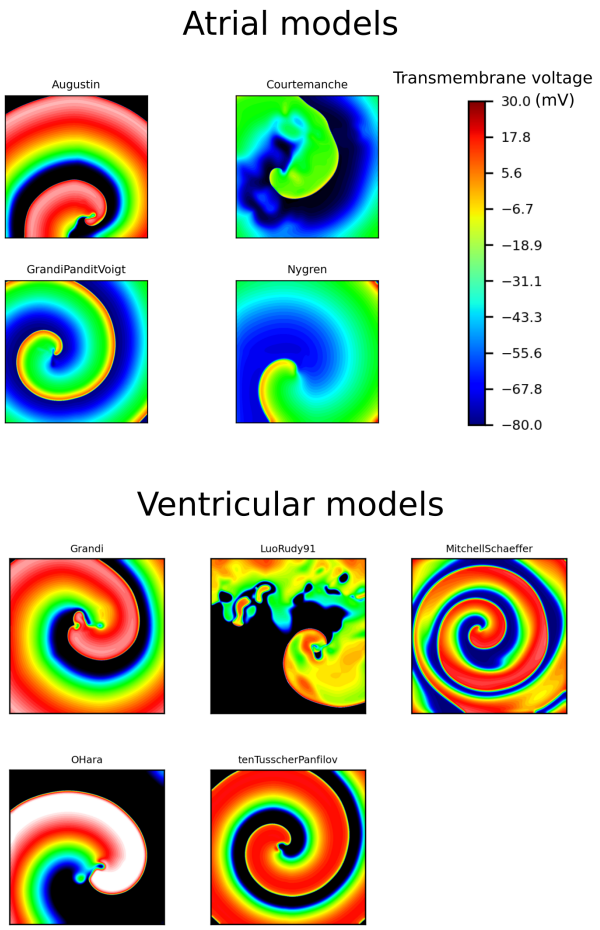

Figure 1. Different simulated atrial and ventricular models show very different behaviour.

sphere with holes. Topologically, the left atrium (LA) and right atrium (RA) are indeed equivalent with spheres with openings. These natural boundaries include the left pulmonary veins (LPV), right pulmonary veins (RPV), and mitral valve (MV) for the LA, and the tricuspid valve (TV), inferior vena cava (IVC), and superior vena cava (SVC) for the RA. Additional non-conducting tissue can be conceptualized as creating extra boundaries within this spherical model.

We discovered that when reentry is induced in this model, it consistently occurs in pairs: a clockwise rotation is always accompanied by a counterclockwise one. This phenomenon can be described mathematically using the topological charge, defined by

$$I = \frac{1}{2\pi} \oint_C \vec{\nabla}\phi \cdot d\vec{\ell} \tag{1}$$

where the sum of the topological charges around all boundaries must equal zero. This principle, known as the index theorem, was first described by Winfree et al. in 1988 and later by Davidsen et al. in 2004 [9, 10]. Despite its long-standing existence, it has been overlooked in the context of AT based on reentry, where the dominant belief has been that a single reentry loop drives the arrhythmia [11]. Traditionally, ablation of this single loop was thought to terminate the AT. However, we found that both boundaries containing reentry must be connected to stop the AT. Otherwise, it will persist and transform into a usually slower AT.

The second reentry loop has been overlooked for the past 30 years because it often does not complete a full rotation and was dismissed as a passive or bystander loop, considered irrelevant for ablation therapy. This incomplete rotation occurs because the second loop collides with the primary complete reentry loop. Furthermore, entrainment mapping, which only identifies complete rotations, does not detect these incomplete loops and yields long post-pacing interval values for them. However, we found that the second incomplete reentry loop is equally significant as the dominant driving loop of the arrhythmia.

We validated our theory through 572 simulations and 131 clinical cases, all of which corroborated the index theorem and aligned with our ablation predictions. Additionally, we have enhanced our software package, Directed Graph Mapping, which applies network theory to analyze cardiac arrhythmias, by integrating new algorithms that automatically identify the critical boundaries that require connection by ablation to terminate the AT.

By adopting a simplified approach, we developed a novel ablation therapy for AT and discovered fundamental principles that have been overlooked for the past 30 years [12]. This demonstrates the enduring value of investigating elementary models, as they can yield transformative insights that complex approaches may obscure.

3. Open Source Code

In the field of cardiac research, there remains a strong culture of developing in-house code, and researchers often need to recreate methodologies from scratch, a process that is arduous and time-consuming. In addition, companies such as Biosense Webster, Boston Scientific, Abbott, and several new market entrants provide proprietary software to guide ablation therapy by analyzing electroanatomical data. This proprietary nature limits broader access and collaboration.

However, the primary goal of scientific research, especially in healthcare, is to positively contribute to society by improving healthcare delivery and improving our understanding of conditions such as cardiac arrhythmia. Given the financial constraints faced by many research institutions, adopting an open source approach can facilitate resource sharing among a broader scientific community and

democratize access to healthcare innovations, particularly for lower-income countries. Open source practices not only promote the sustainability of scientific research, but also align with the principles of public funding, ensuring that publicly financed research benefits society in general, rather than a select few.

Fortunately, the number of open-source projects is gradually increasing. For example, in the realm of computer simulations, there is a growing community of open source users and contributors, thanks to initiatives like OpenCARP. For the analysis of ECG data, there is a growing community around Physionet (physionet.org). Some cardiac research groups, like the Cardiac Electro-Mechanics Research Group (Imperial College London & King's College London), are making strides by providing open-source code on their respective web pages. However, resources in the field are still scattered across various sites, lacking centralized repositories. In contrast, fields such as neuroscience are significantly ahead, with numerous open-source projects consolidated on platforms like the Brain/Minds Data Portal (dataportal.brainminds.jp), Brainlife (brainlife.io), and the Allen Brain Map (portal.brain-map.org), which serve as comprehensive repositories for shared data and tools.

Overall, the cardiac research community needs to embrace a more open and collaborative approach to accelerate innovation in our field. Open source projects can contribute to increased sustainability, reproducibility, transparency, collaboration, flexibility, and longevity of research projects. In addition, a centralized platform would greatly facilitate the sharing and accessibility of software, foster collaboration, and accelerate advancements in the field.

In this light, we are currently preparing the open source version of Directed Graph Mapping called OpenDGM. OpenDGM introduces a novel modular framework, redesigned from the proprietary DGM package [13]. This package will be able to preprocess data from the large mapping companies, as well as simulated datasets. It mainly uses network theory in its data processing capabilities, but also has other capabilities like a phase mapping, and features an extensive visualization module.

4. Data availability

Another significant challenge in our field is the accessibility and availability of comprehensive datasets. Physionet remains the largest data-sharing initiative, offering a vast array of ECG datasets for research. Other resources such as the Cardiac Atlas Project (cardiacatlas.org) provide cardiac imaging examinations along with associated models and derived measurements. Personalize AF (personalizeaf.net) hosts computer-generated datasets, and various research groups offer additional datasets on their websites. Despite these resources, there is still a lack of a centralized platform that aggregates all these datasets, making it difficult to navigate and access the wealth of data available across multiple websites.

Clinical electro-anatomical mapping data is rarely accessible, primarily due to GDPR constraints and patient privacy concerns. Similarly, experimental data from animal studies is rarely shared openly, despite not being subject to these regulatory restrictions.

In contrast, neuroscience has made significant strides compared to our field, demonstrating a clear ability to overcome GDPR-related challenges. Platforms like OpenNeuro (openneuro.org) host over 1,164 public datasets, including MRI, PET, MEG, EEG, and iEEG data. Brainlife (brainlife.io) offers numerous datasets, including human data, and supports scientific reproducibility with 'Open Services', providing apps for data analysis and integration into larger workflows. Additionally, the Brain/Minds Data Portal (dataportal.brainminds.jp) features experimental datasets from marmosets, and the Allen Brain Map (portal.brain-map.org) offers extensive animal and human data collections.

Therefore, there is a clear need for similar platforms in our field. Open data platforms enable researchers to validate findings, conduct meta-analyses, and build upon existing work without replicating costly and time-consuming experiments, thereby accelerating the pace of discovery and facilitating cross-disciplinary insights. By adhering to the FAIR principles - Findability, Accessibility, Interoperability, and Reusability - these platforms ensure that data is well-organized, easily discoverable, and accessible to both humans and machines. This approach promotes the use of standardized formats and metadata, enhancing the potential for diverse datasets to be combined and reused in new studies. Ultimately, open data sharing not only democratizes access to scientific knowledge but also fosters an ecosystem where data can be seamlessly integrated and leveraged for novel research questions, leading to more robust and impactful scientific outcomes.

5. Heterogeniety of AF

Currently, AF is catergorized based on its duration (paroxysmal, persistent, long-standing persistent, and permanent). However, there is increasing recognition that current AF could encompass multiple, distinct subtypes, each characterized by unique pathophysiological mechanisms [14]. This complexity is not surprising, considering that the diagnosis of AF is based on the analysis of the ECG, a one-dimensional signal that reflects the collective behavior of millions of electrically active cardiac cells. The reduction of such complex, multidimensional cellular inter-

actions into a singular diagnostic category may overlook the diverse underlying processes, necessitating a more nuanced approach to classification and treatment. Identifying and classifying these subtypes of AF could pave the way for more targeted and effective therapies. It is plausible that mechanisms such as multiple rotors, focal sources, wavelet hypotheses, epi-endo dissociation, and micro reentry may all be present, but their prevalence could vary depending on the specific AF subtype or patient population. However, achieving this level of precision in diagnosis and treatment requires a deeper understanding of the unique mechanisms driving each subtype, along with the development of advanced diagnostic tools capable of distinguishing between them accurately. As mentioned earlier, open source initiatives and data sharing can greatly support these efforts by enabling collaboration and providing access to diverse datasets and tools. This will accelerate the identification and classification of AF subtypes, leading to more personalized and effective treatments.

6. Conclusion

In this paper, we propose four strategies to improve our understanding of cardiac arrhythmias such as AF. First, we emphasize the value of simplifying complex models by applying fundamental principles, such as the index theorem, which has yielded new insights in AT. Our findings challenge the conventional view that a single reentry loop drives AT, instead showing that reentry loops typically occur in pairs. Second, we advocate for the establishment of comprehensive open source frameworks and data-sharing platforms to facilitate collaboration, validation, and reproducibility in AF research. Such resources could accelerate innovation and lead to more personalized and effective therapies. Finally, we recommend exploring the potential existence of different subtypes of AF based on underlying mechanisms rather than just episode duration, which could allow for more targeted treatment strategies.

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