Challenges Associated with Interpreting Mechanisms of Atrial Fibrillation

Abstract:

Determining optimal treatment strategies for complex arrhythmogenesis in atrial fibrillation (AF) is confounded by the lack of consensus on the mechanisms causing AF. Studies report a divergence of AF mechanisms, ranging from hierarchical drivers to anarchical multiple activation wavelets. Differences in reported AF mechanisms are likely because AF is recorded across diverse models, investigational tools, spatial scales and clinical populations. We review here different AF mechanisms, including anatomical and functional reentry; hierarchical drivers and anarchical multiple wavelets. We then describe different cardiac mapping techniques and analysis tools, including activation mapping, phase mapping, and fibrosis identification. We explain and review different data challenges, including differences between recording devices in spatial and temporal resolutions, spatial coverage and recording surface; and report clinical outcomes using different data modalities. Finally, we suggest future research directions for investigating the mechanisms underlying human AF.

Keywords:

Atrial Fibrillation, cardiac arrhythmia mechanisms, anatomical reentry, functional reentry, hierarchical drivers, triggered activity, anarchical multiple wavelets.

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Clinical Perspectives:

- Atrial fibrillation mechanisms include anatomical and functional reentry; hierarchical drivers that include reentry and triggered activity, and anarchical multiple wavelets.
- Data challenges, including differences between recording devices in spatial and temporal resolutions, spatial coverage and recording surface may account for differences in reported AF mechanisms.
- Identifying the properties of the atrial substrate responsible for sustaining an arrhythmia, for example, critical areas of fibrosis, may potentially be important for understanding the arrhythmia.
- Electrical mapping results need to be interpreted carefully, alongside other measures of the substrate, to identify the sustaining mechanisms of the arrhythmia.

1. Introduction:

Determining optimal treatment strategies for complex arrhythmogenesis in atrial fibrillation (AF) is confounded by the lack of consensus on the mechanisms causing AF. Fundamental to defining arrhythmogenic mechanisms of AF are the distinctions and interplay between functional features (determined by the electrophysiology of a cell) and structural features (determined by whether a structural or anatomical feature is critical to the existence and location of a source); and hierarchical and anarchical mechanisms (determined by whether an arrhythmia is perpetuated by discrete drivers or a universally distributed random phenomenon, respectively). Current discussions focus on whether myocardial activation in AF exhibits any organisation, and if it does, whether this organisation is due to functional or structural properties of the tissue. The hierarchical theory of AF proposes a degree of organisation in AF, sustained by discrete electrical drivers; whereas, the anarchical theory proposes that AF is sustained by a large number of randomly propagating, self-perpetuating activation wavelets without the presence of discrete electrical drivers [1], [2,3]. Differences in reported AF mechanisms may be because AF is recorded across diverse models, investigational tools, spatial scales and clinical populations, ranging from paroxysmal to permanent AF.

With this motivation, what follows is a series of definitions of the key mechanistic phenomena and classifications. This paper outlines the proposed potential mechanisms of AF; describes the different data modalities and analysis techniques used; indicates the challenges associated with interpretation of AF mechanisms and how these might be overcome; and suggests areas of future research. Throughout this review, possible explanations for divergent findings between studies are suggested.

2. Mechanisms of Atrial Fibrillation:

Here we briefly describe some of the concepts that are proposed to underlie *atrial fibrillation*, which is defined as a *high frequency turbulent electrical activity in the atria.* Sustained AF requires the presence of both a driver initiating the arrhythmia – consisting of either impulse initiation by automaticity or triggered activity, or reentrant activity – and a substrate that causes fibrillatory conduction. AF mechanisms depend on the degree of electrical and structural remodelling, which changes as AF progresses from paroxysmal

to persistent to permanent AF. This is described in detail in the review paper of Schotten et al. [1].

Proposed AF mechanisms include automaticity and triggered activity, which are both instances of abnormal impulse formation, as well as reentrant mechanisms. Both automaticity and triggered activity may initiate reentry, and manifest as waves emanating centrifugally from a focal source. While a single focus of automaticity is likely to be too slow to drive AF, recurrent triggered activity might maintain AF by continuously causing fibrillatory activity in the atria [4]. During paroxysmal AF, these electrical triggers and ectopic beats are frequently located in the pulmonary veins [5]. In this review, we focus on reentrant mechanisms, where *reentry* is defined as the *repetitive excitation of tissue by a recirculating wavefronts*. **Figure 1** shows several of the proposed mechanisms involved in atrial fibrillation initiation and maintenance. These mechanisms include the following classical AF mechanisms: (a) a single ectopic focus, (b) single circuit reentry, and (c) multiple wavelet reentry; as well as the following more recent mechanistic concepts: (a) stable rotors, (b) unstable fibrosis-linked rotors, and (c) epicardial-endocardial dissociation [6].

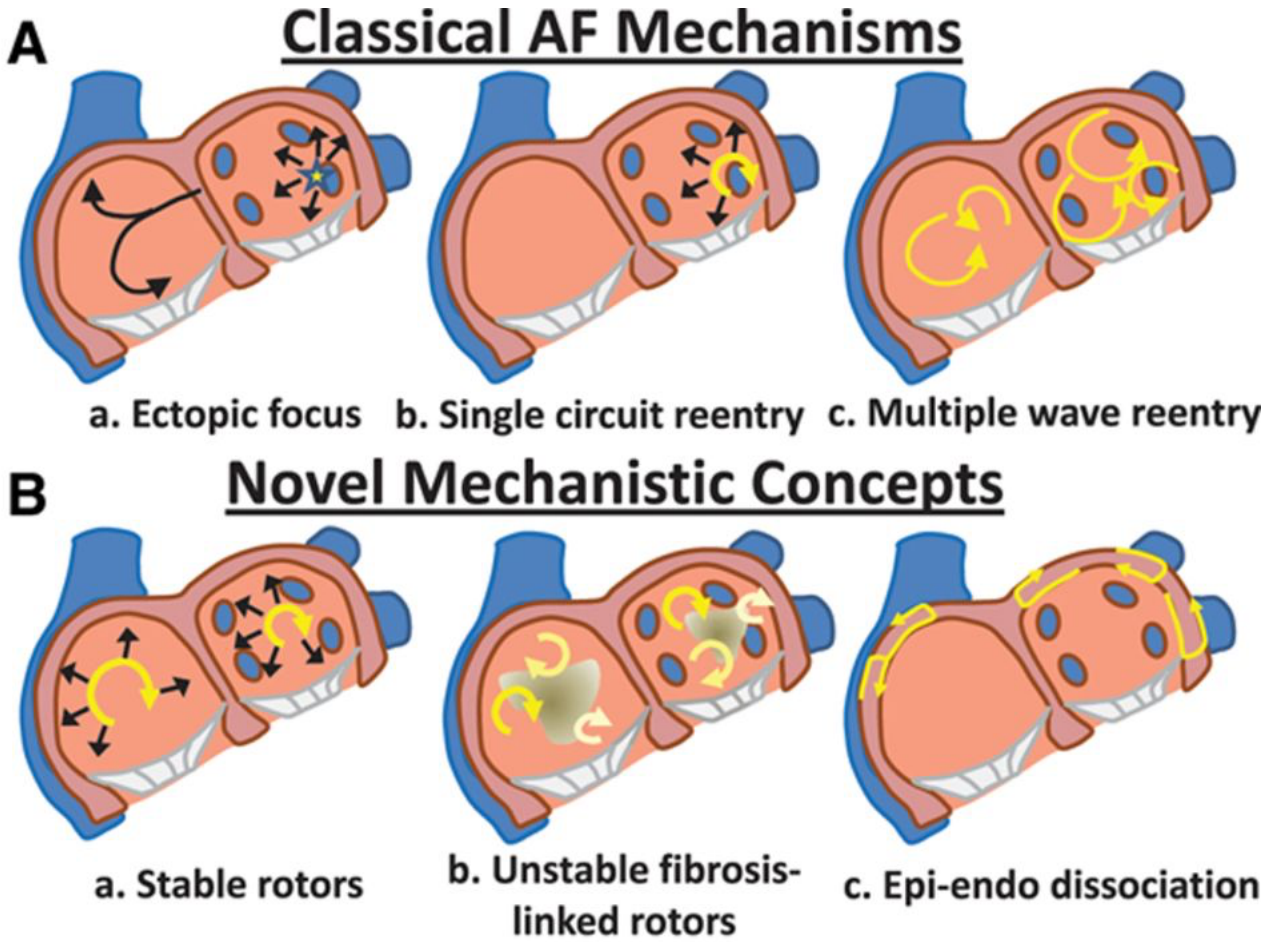

Figure 1: Mechanisms of Atrial Fibrillation.
(A) Classical AF mechanisms include: (a) Initiation from an ectopic focus (automatic or triggered activity); (b) Single circuit reentry; (c) Multiple wavelet reentry.
(B) More recently proposed AF mechanisms include: (a) Stable rotors; (b) Unstable fibrosis-linked rotors, where areas of fibrosis are shown in gray; (c) Epicardial-endocardial dissociation. From [6].

Arrhythmia initiation and maintenance, by mechanisms including reentry, depends on the *arrhythmia substrate*, which we define as *the electrophysiological and structural properties that underlie arrhythmia initiation and maintenance.* Features of this substrate may be anatomical or functional.

2.1.1 Anatomical reentry:

Anatomical reentry occurs when a wavefront of excitation propagates around an anatomical obstacle and reexcites myocardium that it has previously excited to form a reentrant circuit. Following on from Mayer's experiments in 1906 [7], Mines suggested a model of fixed anatomical reentry in 1913, based on experiments in atrial and ventricular ring-like preparations, which could be responsible for tachyarrhythmias in humans [8]. He showed that reentry around such a circuit required the product of the wave conduction velocity and refractory period (the *wavelength*) to be smaller than the length of the circuit (the *pathlength*). For example, macroreentry around cardiac structures, such as the tricuspid annulus (a cause of atrial flutter), occurs when this condition is satisfied, and the length of the path and the conduction velocity determines the cycle length of the activity [9].

Anatomical reentry may also occur at the micro-scale, with the movement of a wavefront around a small anatomical obstacle such as a small region of fibrosis sustaining fibrillatory conduction. As such, micro-anatomical obstacles anchor reentrant wavefronts; Tanaka et al. demonstrated that fibrosis in heart failure determines AF dynamics as reentrant sources anchor to areas of fibrosis in Langendorff-perfused HF sheep atria [10]. Hansen et al. used LGE-MRI imaging and dual optical mapping to show that re-entrant drivers anchor to micro-anatomic tracks maintaining AF [11,12].

All reentrant circuits, whether anatomical or functional (see below), must have an excitable gap, which *is the short time interval in the reentry cycle during which excitation by an external impulse is possible*. This gap can be partially excitable or fully excitable. Anatomical circuits can have a partially excitable gap when the wavelength just fits the pathlength

or a fully excitable gap when the wavelength is significantly shorter than the pathlength. **Figure 2A** shows a schematic reentry with a fully excitable gap.

2.1.2 Functional reentry:

Following on from Garrey's suggestion in 1914 that reentry could be initiated without an anatomic obstacle [13], in 1973 Allessie et al. provided the first direct experimental evidence that the presence of an anatomical obstacle is not necessary for reentry, demonstrating the existence of *functional reentry* [14]. We define *functional reentry* as *reentrant activity in the absence of a predetermined anatomical obstacle or circuit*. *Functional conduction block* occurs when *cardiac activation fails due to source-sink mismatch*.

Leading-circle mechanism

In 1973, Allesie et al. proposed the leading-circle theory in which a unidirectional block (due to a heterogeneous distribution of refractory period) causes an excitation wavefront to travel in a circular pathway [14]. In this theory, wavefronts also travel centripetally (towards the centre of the circle) and centrifugally (away from the centre). This theory is called leading-circle because there is a main circle which takes the path corresponding to the smallest possible circuit for which the path length equals the wavelength (approximately equal to the conduction velocity multiplied by effective refractory period) – centripetal wavefronts travelling over shorter circuits hit refractory tissue, while centrifugal wavefronts are dominated by the faster rate of the leading circle [15]. This is shown in **Figure 2B**. The leading circle theory does not have a fully excitable gap but must have a partially excitable gap. The leading-circle wavefront travels through partially refractory tissue, which reduces the conduction velocity, which in turn reduces the wavelength [16]. The central area is refractory because it is stimulated twice as fast as the leading circle activation by the centripetal wavefronts, leading to an unexcitable region. The inclusion of centripetal wavefronts in this model was motivated by the presence of low amplitude, short duration deflections; however, this observation is also compatible with contemporary spiral wave theory. The leading circle theory does not take into account the role of wavefront curvature, which is a very important component of rotors and the spiral wave mechanism.

Spiral wave theory

Spiral waves are ubiquitous in nature and excitable media; for example, spiral waves occur in chemical reactions (e.g. the Belousov-Zhabotinsky reaction), morphogenesis of amoeba [17], mitochondrial calcium waves in frog eggs [18] and chicken retina [19]. Spiral wave theory for cardiac arrhythmias was developed in theoretical studies performed by Krinsky in the USSR in the 1960s [20] and Winfree in the USA [21]. The first experimental evidence for the existence of spiral waves in cardiac tissue was from Davidenko et al. in sheep ventricular muscle [22]. *A rotor is a classification of functional reentry where wavefront curvature is the cause of wavelength being shorter than path length.* The *wave of excitation emitted by the rotor is a spiral wave in 2D, or a scroll wave in 3D* [23]. **Figure 2C** shows a spiral wave and **Figure 2D** shows a schematic scroll wave. The convex curvature of the wavefront increases towards and attains a critical value at the centre, and conduction velocity slows such that the wavefront cannot propagate into the core. The decrease in conduction velocity, action potential duration and wavelength due to electrotonic effects are illustrated in **Figure 2E**. At the centre, the wavefront curvature is so high that the wavefront source cannot provide enough current to depolarize the resting sink tissue ahead of it, causing rotation. As such, this core area is excitable but not excited, in contrast to the full refractory centre of the leading-circle theory. The *centre of rotation*, or *core*, is the *organizing centre of the spiral or scroll wave*.

The activation and repolarisation wavefronts meet each other at a non-excited point known as a phase singularity (PS), at which the phase of activation is undefined, and all excitation-recovery phases converge. **Figure 2E** shows the PS point where the wavefront and wave tail meet. A stationary rotor will have a PS that follows a circular trajectory; while meandering rotors have more complex trajectories. The trajectory of the PS path determines the diameter of the spiral wave core. The spiral wave theory has no fixed wavelength; wavelength also likely changes in the leading circle model as the reentrant wavefront moves from tranverse to longitudinal conduction in anisotropic tissue.

The mother rotor hypothesis proposes that AF is not entirely random, but that hierarchical periodic rotors drive the AF, acting as sources of high frequency wavefronts [24]. The leading-circle theory and spiral wave theory are different models to explain functional reentry. One of the key differences between the models is that they predict different responses to sodium channel blockade, with the leading circle predicting that reentry is promoted by

reducing the wavelength, while spiral wave theory predicts an antiarrhythmic action because of increased meander, increased core size and decreased critical curvature, which is consistent with experimental findings [15]. In addition, the leading circle theory does not explain the observation that wavelength is not reduced in several experimental models and many AF patients [25]. Kleber and Rudy state that a freely rotating wavefront in an excitation-diffusion system has to be spiral shaped because velocity must decrease from the edge to the centre of the wave to satisfy a constant period of rotation and because the velocity of a convex wavefront is less than the linear wavefront at the edge [16]. As such, leading circle theory was a historically considered mechanism, while spiral wave theory is a useful contemporary concept.

Wavefronts from a mother rotor may break into multiple wavefronts: *wavebreak occurs when a wavefront encounters an obstacle (for example scar tissue), leading to the formation of daughter wavefronts, or wavelets, and fibrillatory conduction.*

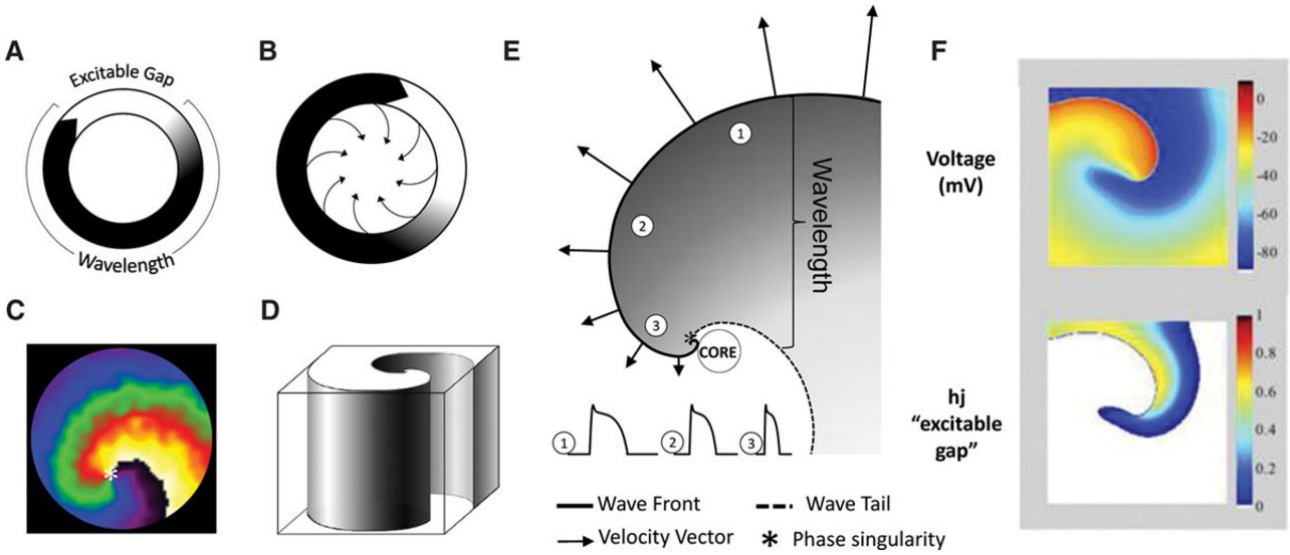

Figure 2: Reentry, leading circle and spiral mechanisms. From [26].

(A) Reentry around a ring (created by an anatomic obstacle). The wavelength shown in black is shorter than the pathlength and there is a fully excitable gap (white).
(B) Leading circle reentry around a functional obstacle with a refractory centre. Arrows indicate centripetal wavefronts.
(C) Example of a 2D spiral wave where the rotor tip is indicated by the white asterisk.
(D) Diagram showing a 3D scroll wave.
(E) Spiral wave conduction velocity (indicated by arrows), action potential duration and wavelength decrease towards the spiral wave core because of electrotonic ef-

fects. Example action potential traces are shown with a shorter action potential duration close to the core. Wavefront curvature becomes more pronounced near the centre of the spiral wave, or rotor, and there this a phase singularity where the wavefront and wave tail meet.

(F) Transmembrane voltage (top) and an estimation of the excitable gap (bottom) calculated as a product of the sodium current inactivation variables for a computational simulation.

Many studies report that AF re-entrant circuits are unstable [13], [27], [28] and of short duration [29], [30], which challenges the theory that discrete drivers sustain AF. An emerging novel hypothesis to explain how unstable re-entrant circuits may sustain AF is the idea of continuous phase singularity regeneration or "renewal", which was initially proposed by Dharmaprani et al. [31].

Multiple wavelets:

The *multiple wavelet hypothesis*, initially proposed by Moe and Abildskov in 1959, states that *AF is a disorganised anarchical atrial rhythm in which there are multiple random activation wavelets sustaining the activity, independent of the initiating event*. Moe et al. developed a computational model and predicted that at least 26 wavelets are required to sustain the arrhythmia. Experimental support for this hypothesis came from the Allessie group who found that between four and six wavelets were required to sustain turbulent atrial arrhythmia with the application of acetylcholine to dog hearts [32]. However, the multiple wavelet hypothesis does not explain the origin of the activity that causes the wavelets; if there were a small number of wavelets, then one would expect them to coalescence and annihilate AF [24].

The Cox-Maze surgical procedure aimed to terminate AF by using surgical incisions to reduce the atrial tissue mass below the critical circuit size required by multiple wavelet reentry [33]. In addition, computational modelling studies have investigated potential approaches for ablating multiple wavelet activation. For example, Carrick et al. simulated different ablation lesion sets to test the effects of ablation lesion length and multiple wavelet circuit density on ablation outcome, finding that applying ablation at regions of high circuit-density most efficiently decreased re-entry duration [34]. They then extended this to predict the most efficient distribution of ablation lesions for multiple wavelet activation[35].

2.1.3 Breakthrough activation:

Allessie et al. found no evidence for the presence of stable focal sources or rotors in a human epicardial mapping study using a high-resolution mapping catheter (interelectrode distance 2.25mm) during cardiac surgery [36]. Instead, they proposed a novel theory for the development of AF in structural heart disease, where the endocardium and epicardium of the atrium become electrically dissociated and epicardial break-through leads to fibrillatory waves [37]. *Electrical activation arising on the endocardial or epicardial cardiac tissue surface from transmural propagation through the cardiac tissue is termed breakthrough activation.* This breakthrough could be focal from the other surface of the heart, or due to transmural reentry. This represents a limitation of the endo-epicardial dissociation theory since it is difficult to determine whether it is a unique mechanism or a manifestation of transmural scroll waves [21]. Although how best to treat an AF substrate with endocardial-epicardial dissociation is an open question [38], recent studies by Jiang et al [39] and Piorkowski et al. [40] demonstrate the feasibility of AF catheter ablation based on epicardial and endocardial substrate mapping.

2.1.4 Classification of mechanisms:

Different studies group together different functional and anatomical mechanisms for the presentation and interpretation of their findings. For example, Weiss et al. classify the leading-circle and spiral wave theories as functional reentrant mechanisms, separately from anatomical reentry even when the rotor is anchored by an anatomical (fibrous tissue) core [4]. Richter et al. differentiates between anatomically anchored spiral waves and functional spiral waves, which may meander [41]. In contrast, Nattel et al. do not make this distinction and consider that the spiral wave theory also explains rotors anchored to anatomical obstacles, effectively considering all reentrant mechanisms together [42]. A rotor that is anchored to an anatomical obstacle that is large enough to become its centre of rotation cannot be distinguished from anatomical reentry. Similarly, Krogh-Madsen et al. classify reentry in their model as a mother rotor, even though it is anchored [43].

We suggest dividing mechanisms into abnormal impulse initiation and abnormal impulse conduction, following Hoffman and Rosen [44]. Using this classification, reentry is then a general subheading under abnormal impulse conduction that includes anatomical and functional reentry. Importantly, a rotor does not require an anatomical obstacle according to its definition; adding an obstacle will anchor a rotor but is not a necessary component

of its mechanisms. On the other hand, micro reentry around an anatomical obstacle need not be a rotor.

3. Cardiac mapping techniques:

Some of the divergence in mechanisms observed across studies may be due to the different analysis techniques used; as such, we review commonly used methodologies here.

3.1.1 Activation time mapping:

Charting local activation time from extracellular recordings (electrograms) on anatomical maps (electro anatomical mapping) are key to determining mechanisms of atrial flutters, tachycardias and slower regular rhythms, since they indicate the pattern of activation including electrical circuits and focal sources. However, activation time mapping for AF data is much more challenging since fractionation in the electrogram signals makes activation time assignment difficult, signals change continuously over time, and it is also difficult to select a suitable time window in which to display these maps. The local activation time of a unipolar electrogram is defined as the time of the maximum downslope because this has been shown to correspond to the time of maximum upstroke of the action potential and maximum sodium conductance, providing a biophysical basis for this choice of marker [45]. In contrast, the choice of marker for activation time of bipolar electrograms does not have a biophysical basis and varies between studies, with choices including the maximum absolute amplitude and the maximum derivative [46]. Unipolar electrograms represent a more local signal but are often contaminated by artifacts from the ventricles [47]; bipolar electrograms typically eliminate the ventricular signal, but their amplitude depends on wavefront direction [48].

The Schotten laboratory developed a technique to automatically assign activation times and reconstruct wavefronts from unipolar AF data [49]. *Activation time mapping analysis groups together similar local activation times into fibrillation waves.* Activation time maps can be post-processed to calculate conduction velocity maps [50], [51,52].

3.1.2 Electrogram features:

Techniques to analyse fibrillatory electrogram data include frequency analysis, such as dominant frequency or organisational index calculations [53]; fractionation scoring analysis

[54]; continuous electrical activity calculation [55]; gradient of activation calculation [56]; Shannon entropy analysis [57]; and peak-to-peak voltage calculation [58].

Features of the electrogram indicating properties of the underlying atrial structure may be identified and targeted during ablation with the aim of eliminating electrical drivers. Clinical mapping studies have used different measures to target electrical drivers including identifying sites of high dominant frequency (DF, the frequency with the highest power in the power spectrum obtained by applying the fast Fourier transform). DF analysis may be performed on invasive or non-invasive recordings; for example, Guillem et al. identified sites of maximal DF from non-invasive body surface potential mapping data [59]. Areas of high DF are thought to indicate areas of driver activity [60], and some clinical studies have targeted these areas. Sanders et al. demonstrated that ablating areas of high DF prolonged AF cycle length and increased AF termination for paroxysmal, but not persistent AF [53]. In advanced forms of AF, areas of slow activity are also important, and targeting areas of high DF is unlikely to provide sufficient ablation therapy. Jarman et al. found that areas of high DF are not spatiotemporally stable [61], suggesting that they do not represent a fixed driver. Salinet et al. suggest instead targeting areas that are repeatedly of high DF [62]. Shariat et al. propose using regional dominant frequency analysis to identify regions of wavebreak [63]. The RADAR-AF trial shows that ablating high-frequency sources - identified using DF analysis - together with PVI is not significantly different to using PVI alone [64]. This highlights that the usefulness of DF for targeting ablation is questionable because the arrhythmia mechanism is unstable [65], [66]. A key technical challenge for frequency mapping that needs to be taken into consideration is that the temporal resolution is limited by the short duration of cardiac recordings compared to the sampling rate.

Nademanee et al. proposed that fragmented electrograms represent areas where AF is perpetuated [54]. Ablation of complex fractionated atrial electrograms (CFAE) terminated AF in 95% of the patients in their study. However, other groups have failed to replicate this success [67,68]. One confounding factor is that there are different definitions of fractionated electrograms, with the clinically used electroanatomic mapping software using different algorithms to calculate CFAE scores, which have been shown to correlate poorly with each other and with conduction velocity and number of waves per AF cycle [69].

In addition, it is difficult to separate the mechanisms underlying electrogram morphology.

Narayan et al. mapped local refractoriness of atrial tissue using MAP catheters to classify the fractionation of bipolar electrograms, finding that far field signals account for 67% of fractionation, while other CFAE types include rapid localised AF sites (8%), spatial disorganisation (17%), and CFAE following AF acceleration, which is often accompanied by MAP alternans (8%) [70]. A high-density mapping study of patients during AF, sinus rhythm and paced rhythms showed that CFAE distribution is highly variable, and often caused by wave collision [71].

Electroanatomic mapping data may be processed to calculate the peak-to-peak amplitude of each bipolar electrogram signal across the atrium, to construct a spatial map of voltage. Areas of low voltage may identify regions of fibrotic tissue. Marcus et al. investigated the spatial distribution of voltage, demonstrating that AF patients exhibit more low voltage areas on the septal and posterior walls [58]. Jadidi et al. combined PVI ablation with ablation guided by electrogram voltage to show improved outcomes for persistent AF compared to PVI alone [72]. Box isolation of fibrotic areas (BIFA) is an ablation approach that applies patient-specific lesions surrounding areas of low voltage tissue [73]. One challenge associated with voltage mapping of bipolar electrogram signals is that the amplitude of bipolar electrogram signals depends on wavefront direction. Omnipolar mapping technology has the potential to overcome this limitation by providing an orientation-independent measure of voltage [74].

3.1.3 Phase mapping:

Despite fibrillation being a seemingly random process, Gray et al. developed a technique to analyse fibrillatory signals to translate periodicity in the signals into loops in a two variable state space that represents the system [75]. For phase mapping, the two variable system consists of the signal at a particular location plotted against a time delayed version of the signal. The phase angle is then measured as the angle around this trajectory for each point in the domain, and a spatial singularity in phase then corresponds to the centre of a rotating wave. This landmark paper revealed a degree of spatiotemporal organisation in fibrillation and the technique used to reveal this organisation is one method that can be used to locate the tip of spiral waves and analyse their dynamics. More recently, the Hilbert transform has been used to create a time delayed signal, and techniques have been developed for phase mapping of unipolar and bipolar electrogram data [76,77]. Topological rules enforce that the ends of wavefronts must either be connected to each other, to

boundaries or to phase singularities [78].

Phase mapping has been utilised by several clinical centres to guide ablation therapy. For example, the focal impulse and rotor modulation (FIRM) software applies phase mapping to basket electrode catheters to identify electrical drivers as ablation targets [79]. Noninvasive electrocardiographic imaging (ECGi) technologies consist of a vest of body surface electrodes for electrical recordings, together with an imaging scan to provide anatomical information, which are combined to construct detailed electro-anatomic maps [80]. Phase mapping has been applied to ECGi recordings to identify the spatiotemporal distribution of electrical drivers during AF, with ablation focussed on the high density regions [80]. The recent clinical review papers of Latchamsetty et al. and Mann et al. provide more details on electrical driver determination in AF [81] [82].

3.1.4 Activation vs phase mapping:

A potential advantage of phase mapping compared to activation mapping is that phase mapping does not assign particular importance to an activation point, which is advantageous for fractionated signals in which it is difficult to assign an activation time. Methodologies for constructing phase maps consist of both preprocessing and post-processing algorithms. Preprocessing steps may be employed to construct sinusoidal signals from atrial recordings prior to the application of the Hilbert transform to calculate phase. For example, Kuklik et al. developed a sinusoidal recomposition technique for unipolar electrograms in which an electrogram signal is expressed as a sum of sinusoidal wavelets of one period length [77]. Although this technique does not explicitly require activation times to be assigned to the signal, it assumes a constant cycle length for the signal to define the sinusoidal wavelets. Kuklik et al. compared cycle lengths calculated from times assigned to the unipolar signals to those calculated from the times of phase inversions and showed a good correlation [77]. Roney et al. developed a technique for phase mapping of unipolar or bipolar electrograms, which uses a sequence of filters and a variation of a pseudo-empirical mode decomposition technique to preprocess the signals prior to phase analysis [76]. Filtering the electrogram signals removes high frequency components of the signal, which may represent activation for fractionated signals.

Postprocessing steps include interpolation and extrapolation of either activation time recordings or phase values measured at a sparse arrangement of points either to a regular

grid or to the entire atrial surface. We previously demonstrated that the spatial resolution of AF data can significantly affect the interpretation of the underlying AF mechanism [83], which is a particularly important consideration when interpreting findings from low resolution recording devices [84]. Jacquemet investigated the effects of different phase interpolation techniques on false positive and negative phase singularity detections [85].

Clinically, both activation time and phase mapping techniques are challenging to apply to sequentially acquired AF recordings due to the temporal instability of AF. For globally acquired data, activation mapping is feasible but challenging due to electrogram fractionation and because it requires the choice of a time window in which to display activation wavefronts. Phase mapping has been successfully used to guide clinical ablation approaches [80], but requires specialistic analysis techniques. It is important to ensure that differences in findings between clinical centres are not because of differences in analysis techniques. Consequently, we recommend applying multiple analysis techniques to the same electrical dataset to increase confidence in findings; for example, using both activation and phase mapping or using alternative phase mapping techniques [3 86].

3.1.5 Fibrosis mapping:

Previous studies have demonstrated an association between atrial fibrillation driver location and fibrosis distribution: rotors are observed at the borders of patchy scar in clinical non-invasive electrocardiographic imaging (ECGi) studies [87] and in modelling studies [88]. As such, fibrotic areas represent an alternative target for catheter ablation. One of the challenges associated with clinical implementation of atrial LGE imaging is the requirement for standardized image processing techniques, and as such, Sim et al. published a standardized, reproducible open source platform for atrial fibrosis assessment [89]. Areas of fibrosis may be identified as areas of low-voltage and ablated (box isolation of fibrotic areas [73]), or using imaging data to identify areas of high LGE intensity. Kircher et al. compared applying PVI together with either linear ablation or ablation of low-voltage areas to find that ablating low voltage areas increased arrhythmia-free survival rate [90]. The DECAAF study showed that atrial fibrosis detected on LGE-MRI was independently associated with AF recurrence [91]. However, other studies found no correlation between LGE and rotors [92]. DECAAF II is a current clinical study investigating whether ablation guided by LGE-MRI is superior to PVI [93]. Chen et al. compared arrhythmogenic area location

identified as sites with spatio-temporal dispersion or continuous activity to low voltage areas and areas of increased intensity on LGE-MRI to find that most arrhythmogenic activities co-localised with low voltage areas, but there was less co-localisation with fibrosis identified using LGE-MRI [94]. Modelling studies may aim to select regions of fibrosis most likely to harbour reentrant drivers [95].

4. Data challenges:

4.1.1 Data modality:

For catheter ablation cases, different clinical centres use different catheters and electroanatomic mapping systems, each of which have their own advantages and disadvantages, which must be considered in data interpretation.

Contact mapping systems:

Multiple high-density electrode plaques have been used to map the epicardial atrial surface during surgery. For example, de Groot et al. used a spoon-shaped device with 244 unipolar electrodes (diameter, 3.6 cm; inter-electrode distance, 2.25 mm), as well as a rectangular array of 8x8 electrodes (interelectrode distance, 2.5 mm) to demonstrate the presence of focal fibrillation waves due to epicardial breakthrough [37]. In addition, Lee et al. collected simultaneous data from three epicardial electrode arrays with a total of 510 - 512 electrodes (total area of 92.85 cm^2), showing that wavefronts from foci or breakthrough maintained AF, with no evidence of reentry [27].

High-density mapping catheters offer high fidelity signals at good spatial resolution (2-6mm) but are limited in their coverage (2-3.5cm diameter) and so data have to be collected sequentially to construct a global map. These electrogram recordings may be processed to construct global maps of electrogram features, including dominant frequency values and fractionation indices. Both the Biosense Webster Carto and the Abbott Ensite Precision electroanatomic mapping systems offer toolboxes to assess electrogram fractionation using different algorithms [69], which may inform ablation strategies. Constructing activation maps from AF data in which activation patterns may be complex and continuously changing is challenging. To address these challenges, Mann et al. developed an al-

gorithm called RETRO-Mapping to detect wavefront propagation from sequential AF recordings [96].

The Rhythmia system has been used with the Orion mini-basket catheter to map atrial tachycardia to identify entrance and exit gaps at high resolution [97]. High density catheters can be used to identify missed pulmonary vein atrial connections after pulmonary vein ablation.

Recently, an omnipolar mapping technology, which provides orientation-independent measurements of cardiac activation and voltage, has been developed and integrated in the Abbott Ensite Precision electroanatomic mapping system [98]. The system uses a high-density grid of 16 equidistant electrodes (HD Grid Mapping Catheter Sensor Enabled, Abbott Technologies, Minneapolis, MN), with 3-3-3-mm spacing to provide improved localisation of scar, lesion gaps and wavefront collision [99]. Hong et al. utilised this catheter for mapping of the atria to differentiate between far-field and near-field signals and to assess bidirectional conduction block after pulmonary vein isolation [100].

Basket catheters record endocardial electrograms and offer a more global coverage; however, this coverage is limited to the atrial body and reduced by bunching of splines. For example, Laughner et al. measured interspline distances in the LA ranging from 1.5 to 121.2mm, with 1/3 of mapping electrodes exhibiting poor contact [84]. Focal Impulse and Rotor Modulation (FIRM) is a clinical mapping system that utilises a basket catheter and phase mapping technology to identify rotors and focal sources in patients undergoing ablation for AF [101]. The technology found that AF was sustained by an average of 2 – 3 rotors or focal sources, within areas of 2.2 ± 1.4 cm^2, which were then ablated [102]. The technology has shown an improved clinical outcome compared to conventional ablation in many studies; however, a recent study showed that catheter ablation of sites identified by FIRM mapping terminated AF in only a minority of patients [103]. The CARTOFINDER software within Carto may be used with basket mapping catheters to identify rotational and focal activation areas [104].

Non-contact mapping systems:

Non-contact electrode mapping systems - such as the dipole density mapping AcQMap system, which is used together with ultrasound imaging - offer a global coverage at a high resolution. The UNCOVER-AF 127-patient trial used AcQMap technology together with other ablation technologies to show promising results for freedom from AF at 1 year [105].

Body surface ECGi mapping has the advantage that it reconstructs signals from the epicardium of most of the left and right atria; however, it may not map the atrial septum and the pulmonary veins, and signals are smoothed during the inverse calculation. In addition, the technology does not map the endocardium.

Endocardial vs epicardial surface recordings:

The choice of endocardial or epicardial mapping will affect recordings, and might explain differences between, for example, findings from ECGi and basket mapping studies. For example, the electrical activity on the endocardium and epicardium of the atrium during AF have been shown to exhibit degrees of discordance, in which there are periods where the surfaces show the same wavefront pattern, and times when they have different wavefront patterns [106]. Hansen et al. found that intramural drivers were seen on sub-endocardial optical mapping, but these manifested as either reentry or breakthrough patterns on sub-epicardial mapping [11].

Differences between studies:

Recent clinical studies have published disparate findings on the mechanisms underlying AF. For example, the STARLIGHT clinical trial found no evidence of sustained rotational drivers, but instead persistent AF in these patients was sustained by multiple wavelets of activation [3]. Navara et al. demonstrated the existence of rotational and focal activation in PV antral regions for cases in which ablation terminated AF before complete PVI [86]. Honarbakhsh et al. used the CARTOFINDER technology together with a basket catheter to identify transient but repetitive focal or rotational drivers [107].

Ablation Approaches:

AF ablation approaches differ in their anatomical or electrical targets, as well as in the methodologies and recording devices utilised to identify these targets. PVI remains the cornerstone of AF ablation and ablation approaches for persistent AF typically include PVI together with other ablation lesions. Ablation approaches may target features of the electrogram signal; for example, Nademanee et al. pioneered the ablation of complex fractionated atrial electrogram (CFAE) signals, demonstrating a high success rate [54]. However, other clinical centres using CFAE ablation failed to replicate these outcomes, possibly due to the different aetiologies of fractionation [71]. An alternative ablation approach is to target areas of high frequency identified using dominant frequency analysis. However, the RADAR-AF trial showed that ablating high-frequency sources - identified using DF analysis - together with PVI was not significantly different to using PVI alone [64]. Ablation techniques that target specific electrogram features - including the degree of fractionation, spatiotemporal dispersion [56] or areas of dominant frequency - have the advantage that they can be applied to sequentially acquired recordings, from readily available catheters. The Star AF II trial found no improvement in ablation outcome with the addition of linear ablation or CFAE ablation to PVI for persistent AF patients [108].

Globally acquired recordings may be post-processed using phase mapping to identify electrical drivers that are targeted during ablation. This approach demonstrated promising success rates using basket catheters in the CONFIRM trial; however, other clinical centres showed varied outcomes using the technique [102]. Phase mapping has also been applied to non-invasive ECGi recordings to identify and target electrical drivers during AF [80]. These techniques require recording devices with global coverage and specialistic analysis techniques.

Alternatively, some ablation approaches target areas of fibrotic remodelling. These may be identified as regions of low voltage using sequential electrical mapping and electrically isolated using box isolation of fibrotic areas (BIFA) [73] or using imaging techniques; for example, DECAAF II is a clinical study investigating whether ablation guided by LGE-MRI is superior to PVI. Ablation approaches might also aim to modify the electrical size of the atria [109], or target specific anatomical structures [110].

4.1.2 Spatial and temporal resolution:

Recording modalities are typically limited in either resolution or coverage as explained in the previous section. We investigated how spatial resolution affects interpretation of AF recordings, expressing spatial resolution requirements as a linear function of the spatial wavelength, and found that high-density multipolar catheters provide sufficient resolution for rotor and focal source detection, but the basket catheter is prone to false rotor detections [83]. Aronis et al. considered the effects of multiple co-existing rotors on resolution requirements and found that including more than one rotor increased errors 10-fold, suggesting higher resolution requirements for cases with multiple drivers [111].

4.1.3 Data processing:

Correct processing of unipolar electrograms requires careful QRS subtraction [112]. Spatial interpolation of voltage will create problems if electrograms have different degrees of contact, and bipolar amplitude is direction dependent. Interpolation of phase does not have these problems; however, phase must be interpolated as a circular variable [83,85]. Pathik et al analysed basket catheter electrograms and report 2D rotors that are not present in 3D, suggesting that correctly incorporating distance between splines in 2D analysis is important [113]. Reliable detection of activation times for atrial electrograms during AF is challenging, particularly for fractionated signals.

4.1.4 Differentiating between mechanisms using limited data and interpolation:

Phase mapping including data interpolation will not be able to differentiate between a leading-circle and spiral way mechanism because both will appear as a spiral wave with a phase singularity after analysis.

The interpretation of phase mapping of conduction block requires particular care. Podziemski et al. demonstrate that analysis of conduction block data may result in phase singularities that are not due to rotational wavefronts [114]; an example is shown in **Figure 3** in which phase singularity locations coincide with lines of conduction block. Spiral waves with linear cores have been observed in both computational and experimental studies (1-2cm core size), which may appear similar to conduction along a line of block. Topologically, wavefronts must end on either a boundary or PS, so there will be a PS at the end of a wavefront moving along a line of block. Considering the rate of change of phase around a PS point, or the magnitude of conduction delay, may indicate whether the PS is at a

fixed rotor core or a conduction block line (that may be a linear core). In addition, Martinez-Mateu et al. showed using computational simulations that far-field components of unipolar electrograms make it difficult to distinguish between functional and anatomical re-entry [115]. An alternative interpretation of the findings of Podziemski et al. is motivated by the work of Arthur Winfree who states that rotors are seldom symmetric; the core of a rotor is often elongated because of the anisotropic properties of conduction (the long axis of the ellipse would be in the longitudinal direction of fast conduction) and described as an arc of functional conduction block [21].

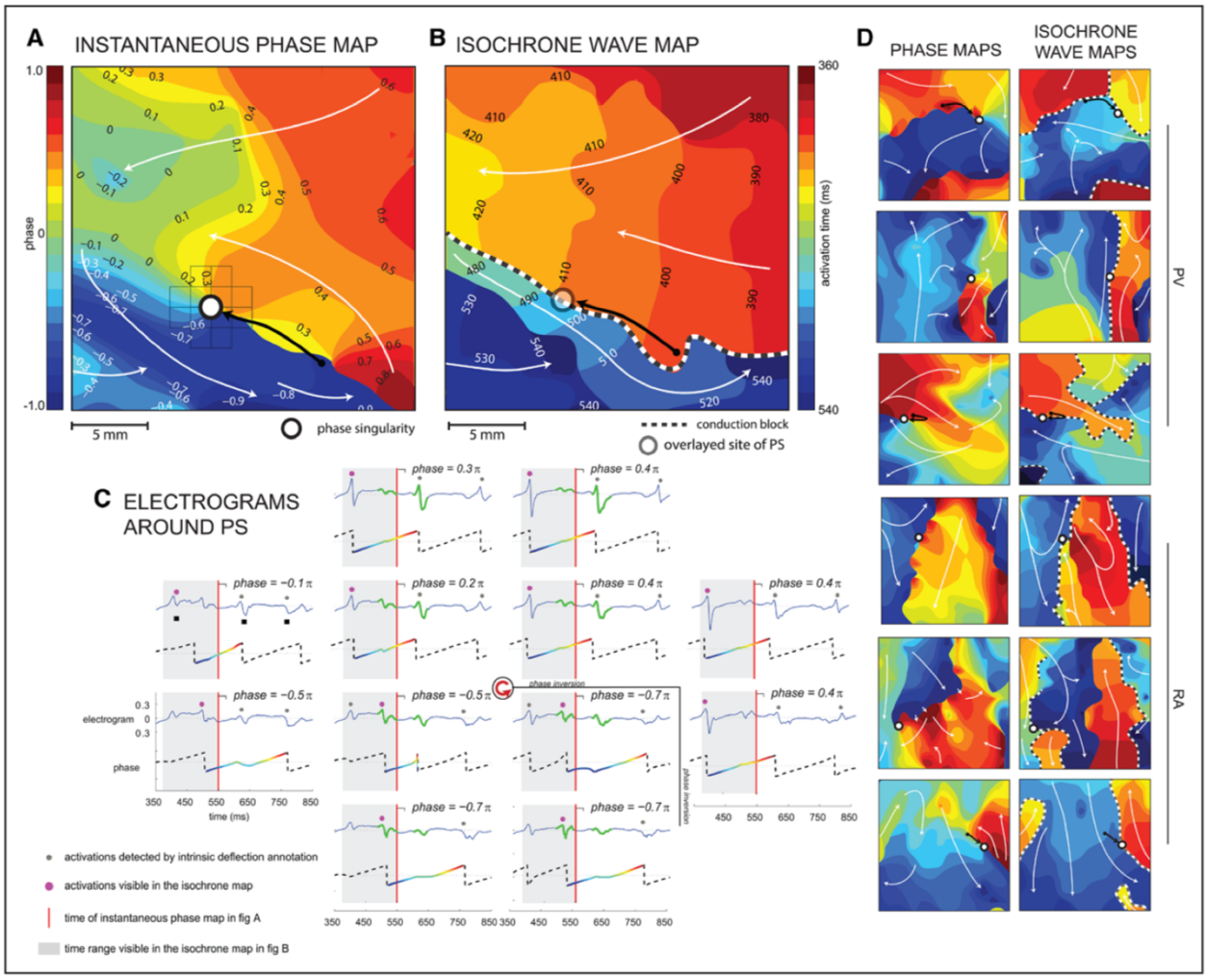

Figure 3: Phase singularities may occur at lines of conduction block. (A) A phase map corresponding to the isochrone wave map in (B). Circles indicate phase singularity locations; white arrows show propagation direction; black arrows shown the phase singularity trajectory; dashed lines indicate conduction block. (C) Electrograms around a phase singularity. (D) Example phase singularity detections for which corresponding isochrone maps show the phase singularity locations coincide with lines of conduction block. From

[114].

Luther et al. investigated reentry during atrial tachycardia using the rhythmia system and showed that pseudo-reentrant circuits often appear as stable rotational activation [116]. This is shown in **Figure 4** in which a secondary wavefront colliding with a partial rotational circuit gives the appearance of a complete rotational circuit. To correctly interpret arrhythmia mechanisms and to determine appropriate ablation approaches, it is important to differentiate between stable rotational activation and pseudo-reentrant circuits. This distinction is important for determining how ablation lines affect individual wavefronts during arrhythmia. During AF, there will be more wavefront collisions and conduction around lines of block, making correct interpretation even more complex.

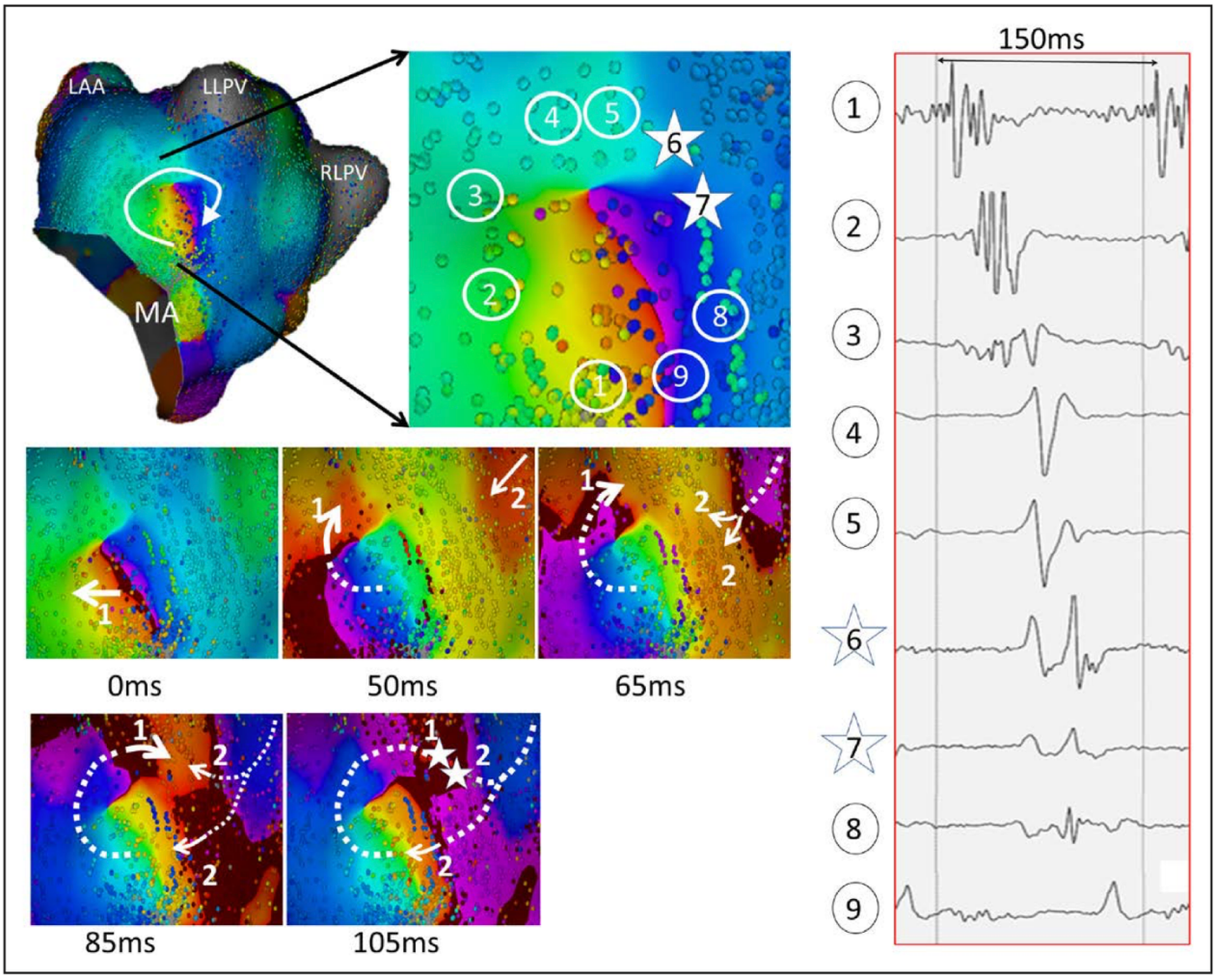

Figure 4: Pseudo-reentrant circuits composed of multiple wavefronts may appear as stable rotational activity. This example shows a carousel of activation on the posterior mitral annulus, mapped using the Rhythmia system, which appears to be stable rotational

activity. However, closely examining the activity shows there is a primary activation wavefront (marked 1) travelling through an area of slow condution (sites 1 – 3), which exhibit electrogram fractionation (right). A secondary wavefront (marked 2) collided with the primary wavefront, which is indicated by the split potentials at sites 6-7. This secondary wavefront then propagated to site 9, resulting in the appearance of complete rotation. LAA, left atrial appendage; LLPV, left lower pulmonary vein; MA, mitral annulus; RLPV, right lower pulmonary vein. From [116].

5. Future perspectives:

There are differences in opinion over how to classify reentrant mechanisms – for example whether leading-circle and spiral reentries should be separately classified, and whether a reentry anchored to a small structural obstacle should be considered to be an anatomical reentry or a functional spiral wave. We recommend following Hoffman and Rosen, dividing mechanisms into abnormal impulse initiation and abnormal impulse conduction [44]. Reentry is then a general subheading under abnormal impulse conduction that includes anatomical and functional reentry, with anatomical reentry around a central anatomical obstacle. A rotor does not require an obstacle according to its definition; adding an obstacle will anchor a rotor but is not a necessary component of its mechanisms. On the other hand, micro reentry around an anatomical obstacle need not be a rotor.

Interestingly, anchors caused by fibrotic remodelling could be anatomical (including micro-anatomical reentry caused by insulating collagen), or functional, due to the APD and CV properties of tissue in the presence of fibrosis; this is shown in **Figure 5** [117]. An ablation line from the centre of the reentrant circuit to a boundary of the tissue theoretically works for both anatomical and functional cases. Since the same ablation approach may work in either case, and we cannot differentiate between these mechanisms clinically, considering these mechanisms as hierarchical, as opposed to anarchical, could be a beneficial classification.

Ensuring the correct classification of phase singularities may prove crucial in their use for targeting ablations since wavefront break-up does not represent an equal target to a sta-

ble rotor. Targeting regions of the atria with a high probability of drivers may be a promising ablation strategy in the instance that drivers are an important AF mechanism. Increased understanding of the reason for this is warranted, including the development of methodologies for determining the relative importance of different drivers in the case of multiple drivers [118]. Perhaps, uncovering a degree of order in anarchical AF paves the way for identification of ablation targets. Thus, future studies into anarchical AF, to investigate whether any order exists, are paramount.

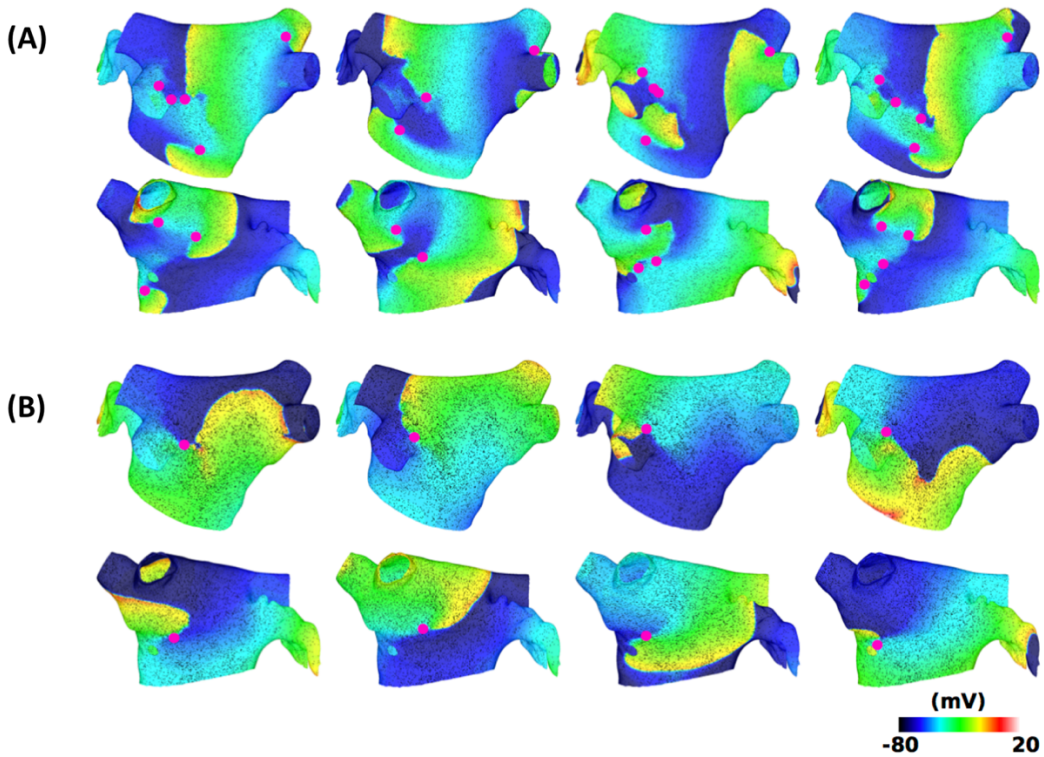

Figure 5: Type of fibrotic remodeling affects phase singularity locations, where anchors could be anatomical or functional.

(A) A model incorporating interstitial fibrosis, conduction slowing and ionic changes due to paracrine effects shows a large number of phase singularities (purple circles). Some of these are due to wavefront break-up close to the left inferior pulmonary vein.

(B) A model incorporating the same distribution of fibrotic remodeling but modelled as replacement fibrosis and conduction slowing shows fewer phase singularities with more stable reentry. From [117].

Ablation strategies for AF either target anatomical structures, use information on the structural substrate from imaging data or use information on the electrical substrate from

electroanatomic mapping. For example, Pambrun et al. systematically targeted the coronary sinus and the vein of Marshall; the PVs; any anatomical isthmus block regions, showing that this lesion set provides good short-term outcomes [110]. The DECAAF II clinical trial ablation strategy is to isolate areas of fibrotic tissue identified using LGE-MRI imaging [93]. Recent ablation approaches utilising electroanatomic mapping data include the Stochastic Trajectory Analysis of Ranked Signals (STAR) mapping approach, which identified early sites of activation and ablated these to produce a favourable clinical outcome [119]. Future research directions include how best to combine anatomical, structural and electrical measures to guide ablation therapy and to assess the additional benefit of mapping AF to provide patient-specific ablation approaches.

Understanding the tissue properties underlying AF is important for designing treatments aimed at limiting disease progression. Further studies linking the atrial substrate and arrhythmia, similar to that of [12], will advance the mechanistic understanding of AF and its ablation. The degree of reentrant driver meander may be decreased by both anatomical and electrophysiological properties (for example, by application of acetylcholine). Reentry anchor location and driver formation may also depend on electrophysiology [120], [121]; conduction velocity dynamics [122]; cardiac wavelength [123]; and anisotropy [51]. These tissue and electrophysiological properties each affect the electrogram signal but inferring these individual properties from the electrogram signal is challenging.

Simultaneous optical and electrical mapping will enable increased understanding of the relationship between electrogram and transmembrane voltage features [124]. In addition, detailed cellular level mapping of the electrical properties of the centre of reentrant activity, extending the study of [125], will enable identification of arrhythmia mechanisms, and will bridge the cellular and tissue levels.

Further clinical, basic science and computational studies investigating optimal ablation approaches for these different arrhythmia mechanisms are required. For example, Bayer et al. used computational modelling studies to suggest an alternative ablation approach that aims to streamline activation patterns [126]. Roney et al. performed a virtual pilot clinical study to use simulations to predict whether an extreme ablation approach of ablating interatrial connections would return the right atrium to sinus rhythm [127]. In addition, Weiss et al. examined the effects of ablation lesions on mother rotor activity, showing that ablation

at the core may convert the functional re-entry to a slower anatomical re-entry; while ablating from the core to a border interrupts the circuit and terminates the arrhythmia [4]. Finally, we recommend the design of new mapping catheters based on the resolution, data type and analysis methods discussed here.

Computational models of atrial arrhythmia have been utilised to offer important insights into arrhythmia mechanisms [127], [128], [129]. A recent pioneering study from the Trayanova laboratory identified patient-specific targets for AF for patients with a fibrotic substrate [130]. However, patient-specific modelling of AF is challenging due to the anatomical and structural complexity of the atria and the dynamic nature of the electrical substrate. Future research into improved methodologies for model construction, calibration and uncertainty quantification are required for aspects including: segmentation [89], anatomical structures [127], electrical and structural anisotropy [51], [131], [132], repolarisation heterogeneity and restitution [133], conduction heterogeneity [50], registration [134], fibrotic remodelling [117], and performing predictions on clinical timescales [135].

Identifying the properties of the atrial substrate responsible for sustaining the arrhythmia, for example, critical areas of fibrosis, may potentially be important for understanding the arrhythmia. Electrical mapping results need to be interpreted carefully, alongside other measures of the substrate, to identify the sustaining mechanisms of the arrhythmia.

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