Chapter 5

Computer-Aided Clinical Decision Support Systems for Atrial Fibrillation

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Additional information is available at the end of the chapter

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Abstract

Clinical decision support systems (clinical DSSs) are widely used today for various clinical applications such as diagnosis, treatment, and recovery. Clinical DSS aims to enhance the end-to-end therapy management for the doctors, and also helps to provide improved experience for patients during each phase of the therapy. The goal of this chapter is to provide an insight into the clinical DSS associated with the highly prevalent heart rhythm disorder, atrial fibrillation (AF). The use of clinical DSS in AF management is ubiquitous, starting from detection of AF through sophisticated electrophysiology treatment procedures, all the way to monitoring the patient's health during follow-ups. Most of the software associated with AF DSS are developed based on signal processing, image processing, and artificial intelligence techniques. The chapter begins with a brief description of DSS in general and then introduces DSS that are used for various clinical applications. The chapter continues with a background on AF and some relevant mechanisms. Finally, a couple of clinical DSS used today in regard with AF are discussed, along with some proposed methods for potential implementation of clinical DSS for detection of AF, prediction of an AF treatment outcome, and localization of AF targets during a treatment procedure.

Keywords: clinical decision support systems, atrial fibrillation, cardiac signal processing, machine learning, Bayesian filtering

1. Introduction

Decision support systems (DSSs) are computer systems that assist in making logically and strategically appropriate decisions for complex tasks [1]. DSSs are used in a variety of applications such as making a financial decision, an administrative decision, a scientific, or even

in making engineering-based decisions (e.g., process control in manufacturing and clinical diagnosis) [2–6]. Highly sophisticated DSSs that are being built today not only play the role of offering opinions to the users for them to make a decision, but they also learn from previous instances and from manually corrected mistakes aiming to offer better decisions in future. Research on DSS today is focused on improving their reliability so that they can perform major decision making without a human in the loop. Although DSS can solve very elementary problems, they are specifically used to solve complex semistructured and unstructured problems in a fully automated or a semiautomated fashion [7, 8].

Studies on the development of DSS gained attention in the 1960s and the first experimental study was reported by Ferguson and Jones in 1969 [7, 9]. There were many simultaneous advancements in the field of engineering, data analytics, and artificial intelligence (AI), which supported the enhancement of DSS. Several applications of DSS were developed during that period. A DSS was designed for business intelligence that used a business analytic model to provide advice to administrative authorities on critical planning decisions for the company [10]. A DSS was built for implementing a digital library to automatically search and fetch books and documents electronically from the library database based on manually entered query tags [11]. An engineering-based DSS would be any expert system used for solving complex mathematical problems, for example, symbolic automatic integrator commonly called SAINT was such an expert system that was developed in the beginning of the era of practical AIs. It was used to perform symbolic mathematical integrations using heuristic methods [12]. A DSS called Brandaid was developed in 1975 to solve problems in the field of marketing, which includes decisions on advertising and promotion [13]. Later, different innovative methodologies were put to use to develop the DSS; this led to different categories of them based on the methods/tasks that the DSS performs [14].

The modern-day DSS employ complex algorithms with highly interactive graphical user interfaces, thus increasing the flexibility of use. Today, for major industrial applications, a combination of all the types of DSS is also incorporated. The technology to help improve DSS is highly evolving, such as better communication protocols, wireless and mobile devices, improved operating systems for smart phones that supports powerful software applications, efficient and fast signal and image processing algorithms, improved machine learning, and artificial intelligence techniques. More improvements are underway in the future with more reliable algorithms in order to increase the robustness of the DSS with the aim of getting their abilities as close to human-made decisions [15].

1.1. Clinical decision support systems

A DSS that supports decision-making tasks related to medical and healthcare benefits is a clinical decision support system (clinical DSS) [16–18]. A considerable part of clinical DSS is a knowledge-driven DSS [8] that has the ability to understand clinical problems and provide reliable suggestions and directions to physicians and patients. The medical tasks requiring the assistance of a clinical DSS can be a simple patient database management using a data-driven DSS [8], to as complex as, making real-time decisions while performing a surgery using a knowledge-driven DSS. Clinical DSS is primarily employed only to enhance decision

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making in the clinical routine, and not to give the machine the authority of a clinician. A common clinical DSS widely used today is a computer-aided diagnosis system, which assists the doctors in making the diagnosis for a patient [19, 20]. Physicians and other medical practitioners make critical decisions generally based on their knowledge and medical expertise, but with the implementation of clinical DSS they get suggestions that are more logical, which can thus be considered as an additional opinion to their personal ones. Some important advantages of clinical DSS are that it provides increase in quality of service to the patients, it helps in avoiding human errors during the process of diagnosis or treatment, and it improves efficacy of treatment procedures. It is believed that clinical DSS has the potential to improve health care although evaluation of clinical DSS has shown only equivocal results. A review of the clinical DSS in the context of evaluation can be found in the article by Kaplan and group [21].

A well-known project of clinical DSS was developed in the early 1970s at Stanford University called the MYCIN [4]. It was an expert system developed mainly to support the treatment of blood diseases and bacterial infections. It is a rule-based AI meaning that it was designed to work based on a set of rules that is defined in a grammar, and there is an action output defined for every input in the grammar. This way the system outputs the diagnosis of an infection, based on the given input set of patient symptoms. It also tries to perform additional diagnosis by suggesting relevant laboratory tests before arriving at a conclusion on the treatment procedure. In addition to diagnosis, MYCIN was designed to provide recommendations of antibiotics and other medications with the right dosage suitable for the patient. This clinical DSS used about 500 rules in order to process its decision, which is said to be most of the times acceptable compared to the decisions made by medical experts.

A number of clinical DSSs exist in the field of medical imaging [22, 23]. Medical imaging is a key tool to diagnosis of most of the diseases today. The method of imaging may be of a wide variety, such as magnetic resonance imaging (MRI), computerized axial tomography (CAT), and ultrasound imaging. Each of these image output has distinct characteristics, and hence its respective purpose of diagnosis. For example, the characteristic of a CAT technique is that it enhances the soft tissues and is hence used to examine diseases related to soft organs such as a liver tumor. Most of the imaging tools and concomitant software available fall under computer-aided diagnosis. A computer-aided diagnosis system can still be considered as a clinical DSS since they assist in decision making for the radiologists and other clinicians. A fully automated computer-aided diagnosis can be created but cannot be completely relied upon unless they have high accuracy (i.e., high sensitivity and specificity). The computer systems used in acquisition of these images itself are a component of a clinical DSS. An image diagnosis system that performs automatic analysis of a medical image or a series of images to detect abnormalities specific to a disease through image processing techniques is an automated computer-aided diagnosis; developing algorithms for this operation is a critical area of research. There are several systems today for automatic detection of lesion sites in a CAT image for mammary cancer and lung cancer [24]. Apart from the above-mentioned systems, there are various clinical DSS algorithms that are being developed today for different purposes and applications [24–27].

This chapter is devoted to introducing clinical DSS specific to the systems used in the field of cardiac electrophysiology (EP) to treat a condition called atrial fibrillation (AF). AF is a highly

prevalent heart rhythm disorder affecting over 2.7 million people in USA annually [28] and over 30 million people worldwide [29]. It also increases the risk of stroke [28], and hence is a serious health concern leading to frequent hospitalizations and deaths. AF is basically caused due to disorganization of the electrical signals in the atria. There are several mechanisms associated with AF, and based on one or more of these mechanisms there are various treatment methods to control AF. Some of these treatment methods are discussed later in this chapter.

Intelligent computer systems are used throughout the process of assisting AF patients. In general, there are three major tasks involved in AF therapy: diagnosis of AF, treatment of AF, and monitoring/follow-up. Each of these tasks is assisted by sophisticated clinical DSS in order to ease the respective process and also to prevent overlooking of any important issues. Most of the algorithms used for EP procedures are mostly signal processing based, i.e., the electrical signals from the heart (see Section 2.1) are analyzed to extract information and derive inferences. These algorithms are designed to address the challenges in the management of AF therapy such as detection of AF episodes, prediction of a treatment outcome, and localization of AF targets during catheter ablation procedure. This chapter hence focuses on the clinical decision support technologies that are available today for AF management and some proposed algorithms for potential clinical DSS implementations. A background on atrial fibrillation and some relevant concepts are discussed in Section 2, followed by a discussion of some of the developed algorithms.

2. Background

The heart forms the major part of the circulatory system in the human body. It is essentially a blood pump that regulates oxygenated and deoxygenated blood. The upper chambers of the heart, the atria, and the lower chambers, the ventricles, both contract following a particular rhythm of synchrony. Such a healthy contraction rhythm is called a normal sinus rhythm (NSR). Any anomaly in this rhythm leads to a cardiac arrhythmia and AF is one of the common types. This section presents an introduction to the mechanisms behind the heart's function, an introduction to cardiac arrhythmia and AF, and finally some treatment options available for AF.

2.1. Electrical system of the heart

The contraction of the heart chambers are essentially triggered by electrical signals propagating along the myocardium [30]. As shown in **Figure 1**, a location called the sinoatrial node (SA node) is present in the right atrium and it produces the necessary stimulus for the cardiac cells to get activated. The cardiac cells possess the characteristic of producing action potentials (APs, special type of voltage signals) due to ion exchange mechanisms, when sufficient external stimulus is applied to it. A phase of this AP where the transmembrane potential (TMP) reaches its peak due to intracellular mechanisms in turn causes the cell to contract; this produces the myocardial contraction. The signals from the SA node propagate following the distinct NSR pathway to create the rhythmic contraction synchrony between the atria and the ventricles. The signals from the right atrium propagate to left atrium (LA) through intraatrial

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pathways called Bachmann's bundle. The signals exiting the atria are then delayed by the atrioventricular node (AV node) before passing into the ventricles. AV node is the only electrical junction of the atria and ventricles. The signals are then distributed across the ventricles through the Purkinje fibers. Hence, during an NSR, the signals take this specific pathway in an organized fashion, indicating a healthy cardiac rhythm. The TMP in a part of tissue collectively results in an electrogram (EGM) signal when measured using a voltage sensing electrode. The effect of the TMPs when measured using electrodes placed on the chest surface as opposed to those on the tissue itself produces surface electrocardiogram (ECG). More about these signals are discussed further.

2.1.1. Characteristics of ECG

A human ECG signal has a unique characteristic of what is called as PQRST complex that refers to the morphology of any ECG. The activations during NSR phase creates the PQRST complex shown in **Figure 2**. P, Q, R, S, T, are the labels given to specific activation peaks in ECG which are the P-wave, QRS complex, T-wave, and the less common U-wave [31]. The P-wave corresponds to the depolarization of the cells in the atria. The next part is the QRS complex and it represents the activations that cause the ventricles to contract. This is the most important part of the PQRST complex since it corresponds to systolic interval and is used for determining heart rate. Finally, the T-wave is said to occur due to the repolarization of the ventricles. Some theories suggest that the U-wave could also be due to repolarization of the

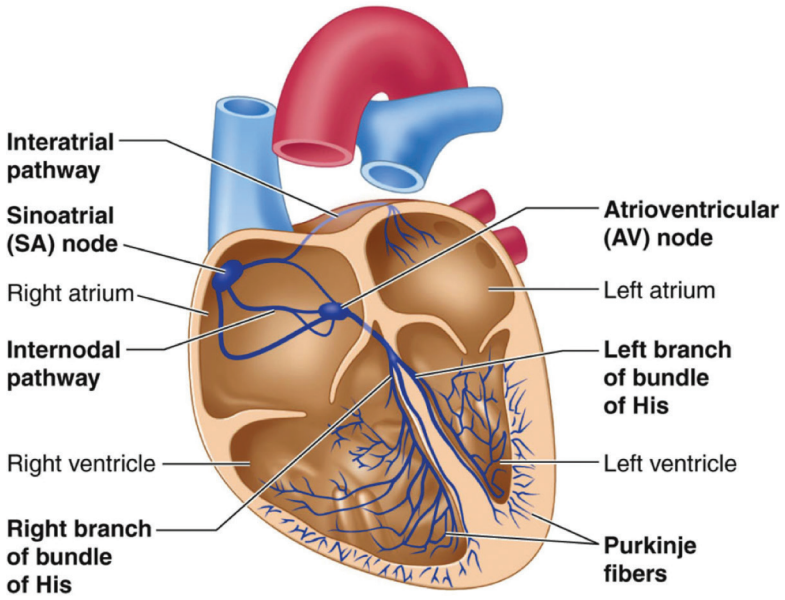

Figure 1. Electrical conduction system of the heart: The figure illustrates the different electrical nodes and muscle fibers that play a role in the electrical conduction system. It also represents the NSR pathway.

ventricles [32]. During NSR, the deflections of each wave starting from P-wave all the way to T-wave occur with the exact same signal polarities. As seen from **Figure 2**, the QRS complex has larger amplitude of deflection from the isoelectric line because of the larger mass of the ventricle cells that is getting depolarized.

Professionals trained in ECG interpretation would be able to detect even minor variations in the ECG signals. The idea of a clinical DSS here would be to assist such professionals by automatically interpreting the ECG. Any abnormality such as an arrhythmia or coronary heart disease can be detected using the ECG morphology. In case of AF, then the ECG demonstrates high heart rate along with absence of P-waves.

2.1.2. Intracardiac electrograms

Intracardiac electrograms (EGMs) are the signal obtained from locations of the myocardium. In general, they are recorded from the following regions using cardiac catheters: the high right atrium, coronary sinus, bundle of His, and the apex. The leads are placed at these locations and the outputs are arranged in such a way that a sequential activation is seen during NSR. This way the clinicians could easily confirm the pathway starting from SA node all the way to apex. EGMs, just like the ECGs, have its characteristic properties and can be used to determine abnormalities.

In general, there are two measurement configurations by which the EGMs can be represented, namely, the unipolar and the bipolar (refer **Figure 3**) [33]. Unipolar EGMs are those that are recorded using a single electrode catheter or the EGMs obtained from each electrode separately

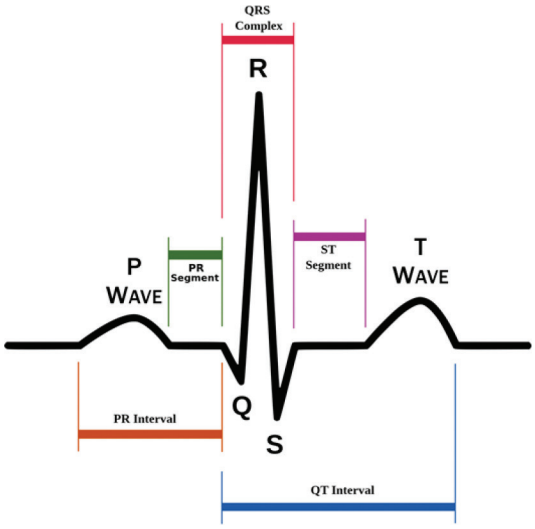

Figure 2. PQRST complex of surface ECG: This figure shows the general representation of the different complexes in a surface ECG. P-wave is due to atrial depolarization, QRS is due to ventricle depolarization and T-wave is associated with ventricular repolarization [34].

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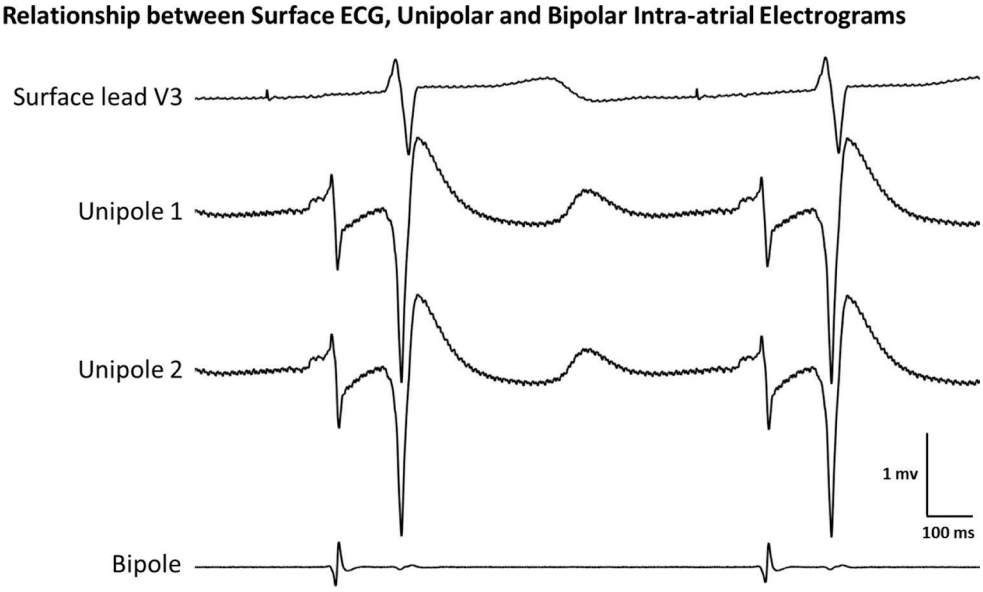

Figure 3. Relationship between different types of electrograms: The top-most plot is the surface lead which illustrates the QRS complex. The next two signals are two closely spaced unipoles; the far-field ventricular activations can be clearly seen in them. The last signal is the resultant bipole of the two unipoles in the figure. It can be clearly seen that the ventricular activations gets canceled giving rise to atrial activations alone. Also, the baseline noise present in unipoles is removed in the bipole signal.

from a multipole catheter. Bipolar EGMs are those that are obtained with respect to a nearby reference. The two types of EGMs have its own benefits and limitations [30]. Unipolar EGMs are very helpful in determining the wave direction using Einthoven's convention of positive and negative deflections [35], since it preserves the properties of the raw activation signals. It is also useful in determining conduction velocity and the signal amplitude. Bipolar EGMs do not preserve any of the information such as the wave direction because it is calculated with a reference and hence the signals might cancel out giving rise to a peak at an activation time different from unipolar and also might result in different deflection polarities. However, bipolar EGMs are an excellent means of removing noise and far-field effects which, in often case, are the most challenging criteria that hides the local activations present in an EGM. For example, the bipoles calculated in the LA will cancel out any activation that has occurred due to ventricular depolarization resulting in successful capture of the local atrial activations in the LA.

2.2. Cardiac arrhythmia and introduction to AF

Cardiac arrhythmia is a condition occurring when there is a perturbation in the NSR activity. The NSR pathway could go wrong in several ways resulting in several types of arrhythmias that are defined based on the abnormality mechanism [36]. Broadly speaking, the general types of arrhythmias are tachycardia and bradycardia. Tachycardia is the condition where the heart rate is higher than the normal, and bradycardia is its counterpart (lower heart rate).

Atrial tachycardia is a common arrhythmia which is caused by a rapidly periodically firing focus that could be located anywhere in the atrial myocardium. It is mostly treated by catheter ablation (see Section 2.3.4) and has a relatively high success rate of 90% after repeated procedures [37]. Another well-known atrial tachyarrhythmia and that that is also closely related to AF, is atrial flutter. Similar to AF, it results in a rapidly beating atria but it has its own mechanism causing it. The mechanism is said to be a single reentrant circuit mostly originating in the right atrium. With respect to the atrial arrhythmias, AF could be grouped as a tachyarrhythmia but the difference between AF and atrial tachycardia is that the rapid beating is not as regular as the tachycardia, in fact there is no beating at all–the atria during AF simply randomly quivers due to chaotic signals as shown in **Figure 4**.

Symptoms of AF include palpitations, unconformable flip-flopping in the chest, physical weakness, dizziness, shortness of breath, chest pain, and syncope. Some risks involved in AF in addition to stroke are, heart failure, high blood pressure, and lung disease. There are different types of AF categorized based on the duration of AF episodes. From a clinical standpoint, according to the established consensus [37], some of the types of AF are paroxysmal, persistent, and permanent AF. Paroxysmal AF is defined as recurrent AF (≥two episodes) that involves spontaneous termination within 7 days. Persistent AF is defined as continuously occurring episode that is sustained for more than 7 days. Finally, permanent AF, which is a rare condition, is when the physician and the patient together take the decision of not undergoing any procedures to control the AF, and so the patient permanently stays in AF.

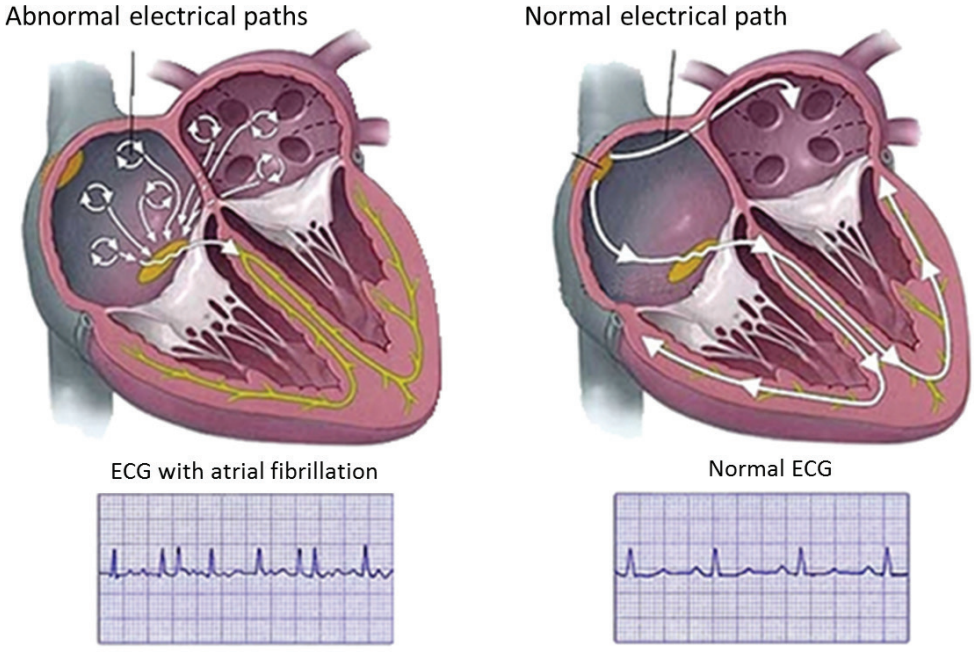

Figure 4. Atrial fibrillation vs normal sinus rhythm: The figure illustrates the disorganization of the signals in atria during AF (shown on the left), in contrast to the regular path of the signal during NSR (shown on the right).

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2.3. Methods of AF treatment

The results of several scientific and clinical studies on AF have led to the development of many mechanistic and nonmechanistic approaches for treating AF. Every treatment procedure has its own benefits and limitations. So, the treatment method that gives the maximum patient outcome is what is followed widely. Each treatment also has its specific endpoint, however, the ultimate goal of any treatment is to successfully terminate AF and restore sinus rhythm. Some common treatment methods are discussed below.

2.3.1. Pharmocological therapy

The studies on different ionic mechanisms of the cardiac cells and how they are related to the arrhythmia (e.g., formation of AP alternans), have led to the development and synthesis of various rate-control and rhythm-control drugs. They directly interact with the ion channels, and control and regulate the exchanges in order to maintain a normal AP thus maintaining NSR. The antiarrhythmic drugs are categorized into various classes based on the behavior of the drug on different ion channels. Class-I drugs are related to sodium channels, e.g., quinidine. Class-II are effective beta blockers, e.g., propranolol. Class-III type interacts with potassium channels and prolongs the action potentials, e.g., sotalol, and Class-IV helps in regulating the calcium channels, e.g., diltiazem. Class-III is a commonly prescribed antiarrhythmic for the fact that it prolongs the AP, increases the refractory period, and so the AP cannot be fired instantly, thus preventing reentries. Some popular Class-III drugs are amiodarone and dofetilide. Unfortunately, the drugs may not be much effective as a standalone AF treatment especially for patients showing poor response [38], and it might also produce some side effects for the patients.

2.3.2. Direct current electrical cardioversion

Direct current electrical (DCE) cardioversion or simply cardioversion, is the procedure by which an electric voltage is applied to the chest at particular instants of the heart beat in order to reset the rhythm back to NSR [39]. The electric shock at a specific power is applied to the chest using electrode patches to the patient under anesthesia. The power is decided according to the intensity of AF. The shock is provided in such a way that it synchronizes with the R-wave of the PQRS complex, mainly because the atria would have passed the refractory period during R-wave, and the application of the current will excite the cells and start a fresh cardiac cycle. This treatment, most of the time terminates AF immediately, however, some patients experience AF episodes return after cardioversion. Hence, it is important for the clinician to make a reliable decision on whether or not the patient would benefit from DCE cardioversion therapy.

2.3.3. Open-heart maze procedure

The maze procedure is a surgical treatment by which lesions are created using incisions to various regions of the myocardium after opening up the chest. The treatment technique was introduced by James Cox in 1991 [40]. The lesion set resembles the structure of a maze, which gives it the name. The lesions basically are designed in such a way that the signals in the atrium do not form a reentry. The maze procedure has proved to be effective in terminating

AF; however, it is highly invasive and is normally provided for patients who undergo an open-heart surgery as part of their treatment for other types of heart complications.

2.3.4. Catheter ablation therapy

Catheter ablation therapy is a method by which ablation lesions are formed using radio frequency (RF) energy delivered via a catheter. The conventional catheter ablation procedure for AF today is the pulmonary vein isolation (PVI). In PVI, the lesions are formed around the PV ostia with the aim of electrically isolating the PVs from the rest of the left atrium. The PVI came into existence because of the pioneering discovery by Haissaguerre et al. that some ectopic triggers from the PVs enter the atrium and maintains AF [41] (illustrated in **Figure 5**). Some studies also suggest that these focal triggers could initiate non-PV AF drivers as shown in **Figure 5**. More about these non-PV drivers are discussed in Section 3. PVI showed remarkable increase in success rate of AF treatment and hence was adopted as the standard procedure by clinicians across the globe. There was also improvement over the traditional PVI that proposed only lesions around PV ostia. A strategy called the circumferential ablation was introduced which defined the lesions around the antrum of the PVs as opposed to the ostia [42]. In addition to circumferential ablation, a linear lesion set was proposed, which appeared to produce better outcome in clinical studies. Some of these non-PV lesions consisted of roof line, lines at mitral isthmus, and lines in between the PV pairs. PVI is mostly the primary strategy, and linear lesions are mostly preferred as a strategy in addition to PVI. However, what ablation to perform on top of PVI is disputable and is decided mostly based on the patient's individual atrial and AF properties.

Catheter ablation treatment combined with antiarrhythmic drug therapy is followed widely today. However, the treatment is not completely successful. Many patients experience recurrence of AF after the first procedure. Multiple repetitions of the procedure have to be performed especially for persistent AF patients, to control the recurrence. After a single pro-

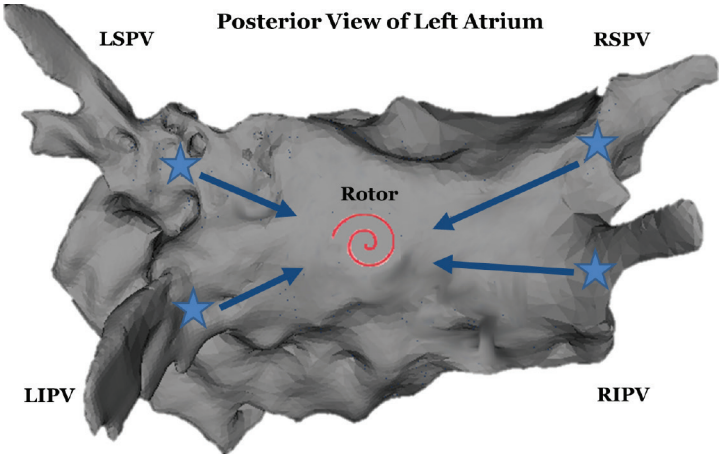

Figure 5. PV triggers initiating AF (posterior view): Figure illustrates the ectopic focal triggers originating from the PVs eventually initiating spiral waves in the LA wall, thus initiating and sustaining AF. LSPV: left superior pulmonary vein; RSPV: right superior pulmonary vein; LIPV: left inferior pulmonary vein; RIPV: right inferior pulmonary vein.

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cedure, late recurrence of AF occurs between 11 and 29%, and after repeated procedures, it occurs between 7 and 24% [37]. A widely accepted reason for the recurrence is the reconnection of the PVs, however, there are also theories suggesting that the recurrence could be due to the arrhythmogenic sources (especially functional sources) existing outside the PVs, which are not addressed by the current catheter ablation procedure.

3. Computer-aided technologies for atrial fibrillation

The clinical DSS is largely used during an AF ablation procedure. In order to ablate different regions of the LA, it is necessary to have a visualization of both the atrium and the catheter's location. The fluoroscopy technique which produces a real-time image of the catheter and the atrial structures was used initially for visualization. However, fluoroscopy uses X-rays, and prolonged exposure is harmful for the patient as well as for the clinicians performing the procedure. In order to reduce the fluoroscopy time, a novel technology called the electroanatomic mapping was introduced. Electroanatomic mapping is a technique where the clinician maneuvers a mapping catheter across the LA endocardium and the computer produces a three-dimensional virtual map of the LA endocardium. This mesh structure displays the LA anatomic structures along with the PVs (the atrial structure shown in **Figure 5** is a mesh produced by such a mapping system). In addition, the electroanatomic mapping systems have the function to display the real-time catheter position on the mesh. This makes it possible for the clinician to ablate anywhere using the 3D mesh as the reference. Some electroanatomic mapping systems available in the market are “CARTO” by Biosense Webster Inc., “EnSite NaVx” by St. Jude Medical, and “Rhythmia” by Boston Scientific. Electroanatomic mapping systems not only produce the mesh structure, but also are capable of performing several other interesting functions that help clinicians to make ablation decisions. One such feature is the activation map. As the name “electroanatomic mapping” suggests, the map shows anatomy as well as the electrical activations in the form of a voltage map with color codes. This largely helps in treating atrial tachycardia, the clinician can see in the electroanatomic map and visualize where the earliest activation occurred, and then perform ablation accordingly. Further, the system displays the ablation lesions on the mesh with a unique color code that is varied based on the power delivered by the RF catheter. This helps the clinician to ensure that the tissue was sufficiently cauterized to stop the conduction at that location.

The mapping catheters that are used to construct the electroanatomic mesh are specialized diagnostic catheters known as a multipole diagnostic catheter (MPDC) (some types of MPDCs are shown in **Figure 6**). It consists of multiple nodes with voltage sensitive electrodes. These electrodes are arranged in a particular geometric shape which differs between different MPDC types. Some common MPDCs are Lasso and Pentaray both by Biosense Webster, FirMap (Abbott EP), Constellation (Boston scientific), Achieve (Medtronic), and Advisor (St. Jude Medical). A major feature of the MPDCs is that the electrodes can record the EGMs when they are placed in contact with the tissue. Hence, the MPDC is placed in different endocardial locations to build the mesh structure and also to obtain the EGMs. These EGMs can further be used to perform non-PV ablation. As stated earlier, PVI is not completely successful, and in order to improve the success, non-PV targets should be determined and ablated. For example,

Figure 6. Different types of MPDCs: Figure shows the various types of MPDCs, which are used for generating electroanatomic maps and for recording information from the endocardium. The top one is a 20 unipole Lasso catheter, the bottom-left is a Basket catheter and the bottom-right one is a Pentaray catheter. Image reproduced from Ref. [33].

some studies showed the presence of slow conduction regions in the myocardium, which when ablated, terminated AF in their studies [43]. These sites can be identified by recording the EGMs, which, based on a specific definition, could be characterized as what is called as complex fractionated atrial electrograms (CFAEs). CFAE ablation was the first EGM-based (mechanistic) non-PV ablation, while all other strategies are anatomy based (nonmechanistic), in the sense that they do not require any functional quantities such as the EGMs to determine whether or not to ablate that site. Based on the above concept, some mapping systems were installed with a feature to automatically compute CFAE sites, and indicate them on the mesh, for the clinicians to make the ablation decision about CFAE. However, in current clinical practice, CFAE ablation is not very common, possibly because of some controversial results reported by some studies [37, 44]. This demonstrates the need for determining the "real" non-PV targets which play a role in AF maintenance. Traditionally, in AF studies performed in the past using physical experiments and computer simulations, several studies have demonstrated circular and spiral patterns of electrical waves propagating along the tissue during AF [45–48]. The AF spiral waves were termed as rotors which later gained more attention among researchers in the field. Rotors consist of a wavefront and a wavetail, and they may rotate about a functional center (**Figure 7**). The gap between the front and the tail is the wavelength of the rotor. A rotor propagates with a conduction velocity, and rotates following a periodic cycle length (the velocity vectors at the wavefront of a rotor are illustrated in **Figure 7**). Rotors can also form wave breaks that eventually lead to multiple chaotic spiral waves. Rotors were initially encountered only in animal studies. For the first time, they were claimed to be observed in human clinical studies by Narayan et al. [49]. In addition to finding rotors, their study also reports observation of some ectopic foci outside the PVs, and that they act as AF drivers. The technique that revealed the presence of rotors using the EGM in humans is called phase mapping [49]. According to this technique, the EGMs are collected simultaneously at

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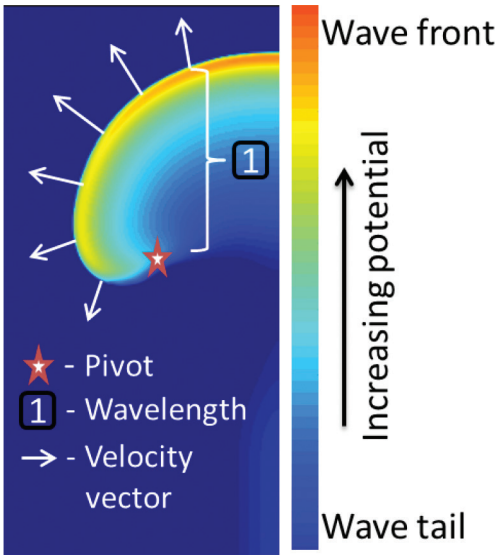

Figure 7. Propagation of a rotor wave: The different components of a rotor wave are illustrated in the figure. The arrows points in the direction of the wavefront propagation. Image recreated based on the work in reference [50].

different LA locations using a basket type MPDC (shown in **Figure 6**), and the signals are processed using Hilbert transform in order to obtain a map of the spatiotemporal variation of the signal phase. This phase map showed progressive change of phase in a circular pattern around a core called as the phase singular, thus demonstrating the characteristic of a rotor. The method of Hilbert transform that is used to obtain the phase map has also been used in different contexts of fibrillation in earlier studies [51, 52]. The algorithm/ablation procedure used by Narayan et al. was called focal impulse and rotor modulation (FIRM). Based on the outcome of the clinical studies on FIRM-guided ablation and several other follow-up studies, the FIRM algorithm was found to be effective, especially when combined with PVI [53]. The FIRM technology was later commercialized as a clinical diagnosis system for AF, now owned by Abbott Electrophysiology.

While whether or not the rotors are the primary AF drivers, is a topic still under investigation, developing novel algorithms for identifying and localizing rotors have been a critical area of research in the community. Several methods were introduced to help map rotors using engineering techniques in both time and frequency domain [54–58]. Some of these methods are specifically designed to use conventional MPDCs such as a Lasso catheter, aiming to outperform the limitations of the current EP systems available for identifying rotors.

As opposed to the time domain approach of phase mapping, there were also some frequency domain approaches, one of which is called the dominant frequency (DF) mapping. According to the DF mapping technique, the fast Fourier transform (FFT) of the signals at various locations is computed, and the highest frequency from the FFT plot at each location is considered as the DF for the respective location. When the DFs at various regions of the atrium were investigated, the frequency distribution showed organization and was said to

have high values in the left atrium [50]. However, there are some studies suggesting that DF is not an effective method to analyze AF [37].

The workstations available today in the EP labs consists of all the components required to assist the clinicians during an ablation procedure, such as the electroanatomic mapping software, mapping and ablation catheters, imaging devices such as fluoroscopy and ultrasound, and other associated software such as the FIRM mapping, DF mapping, and CFAE mapping. Therefore, EP workstation is the best example of a clinical DSS, without which the ablation procedures is nearly impossible to perform today. This demonstrates the significance of clinical DSS not only in AF, but also in general clinical cardiac electrophysiology.

3.1. Developed methods of clinical decision making for AF

As discussed earlier, clinical DSSs play an important role in AF ablation treatment. This section presents a detailed discussion of some techniques and algorithms developed by our group that could be potentially implemented in a clinical DSS to assist a clinician for managing AF patients. A schematic diagram of the various EP systems along with the integration of one of the developed clinical DSS system is illustrated in **Figure 8**.

The role of clinical DSS in AF could be categorized into three important tasks:

- Detection of AF from the surface ECG for AF therapy management.
- Prediction of successful postcardioversion patients with persistent AF.
- Identification of successful ablation targets from EGM signals.

The above three tasks quite covers the necessary tasks required for AF management today. All the algorithms mentioned below were implemented in MATLAB (The MathWorks, Inc., Natick, MA, USA).

3.1.1. Detection of AF from surface ECG for AF therapy management

Rate control and rhythm control are two strategies for treatment of AF. The goal of rhythm control is to convert an arrhythmic condition to NSR, and that of rate control is to slow down the heart rate when it increases due to AF. Catheter ablation therapy is an example of rhythm control method. Although catheter ablation is a commonly preferred treatment, at an initial stage of AF, doctors recommend rate control therapy. It could be performed using rate control drugs or cardiac pacemakers.

Detection of AF is a crucial operation for providing timely and appropriate treatment for the patient. AF detection techniques mostly involve application of signal processing algorithms to ECG signals [59]. There are two major types of methods for detecting AF, first, by calculating the R-R interval (RRI), which represents the heart rate. Majority of the methods in the literature are based on RRI [60–68]. Another approach is by using RRI in combination with atrial activity (AA) analysis, which uses heart rate along with atrial ECG pattern. However, in rate controlled patients, the heart rate is externally controlled, in which case, the algorithms that are based on rate will fail to detect AF [69, 70]. Currently available methods working based

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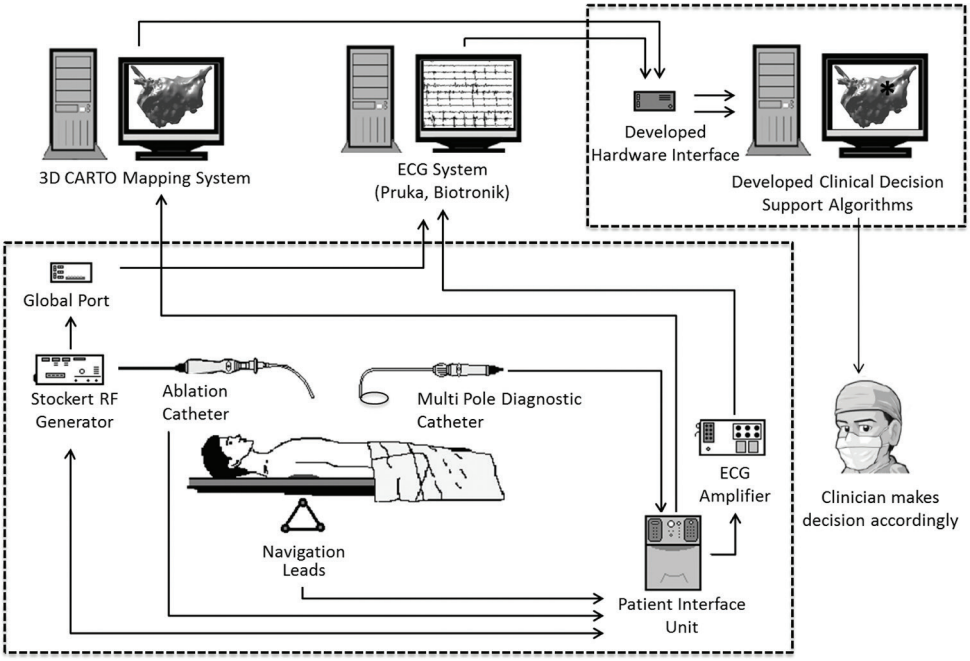

Figure 8. Schematic of a clinical DSS for AF: The figure shows a schematic of the different components of a typical EP laboratory, integrated with the developed clinical DSS algorithm. The computer screen of the developed DSS illustrates an example of ablation target localization, where the asterisk indicates the estimated rotor location as would be produced by the algorithm described in Section 3.1.3.

on AA exclusively, do not perform well [71]. AA analysis is more complicated in rate-controlled patients and could result in false diagnosis mainly because of the low voltage nature of the AA signals compared to the ventricle activities. The idea that the absence of P-waves is a major indicator of AF is used in most of the AF detection algorithms. However, ECG is a nonstationary signal and P-waves have relatively less amplitude, so the algorithms using P-wave detection encounter many challenges. In this section, we discuss a robust algorithm that we developed for automatic AF detection. The algorithm is independent of heart rate, and is suitable for rate-controlled patients with paroxysmal AF. The algorithm is capable of fast and reliable detection of AF by using minimum cardiac cycles (heart beats).

The algorithm essentially uses short ECG signals, and applies a feature extraction and machine learning approach to detect whether or not an abnormality exists in the signal. A block diagram of the developed system is shown in **Figure 9**.

The input signal is first subjected to preprocessing. The preprocessing step consists of a third-order Butterworth bandpass filter in order to reduce noise. The poles are designed to be at 0.5 and 50 Hz. For each heartbeat, nine features are extracted out of which three are statistical features and the rest are morphological features. The statistical features include variance, skewness, and kurtosis. The morphological features are calculated as the average amplitude

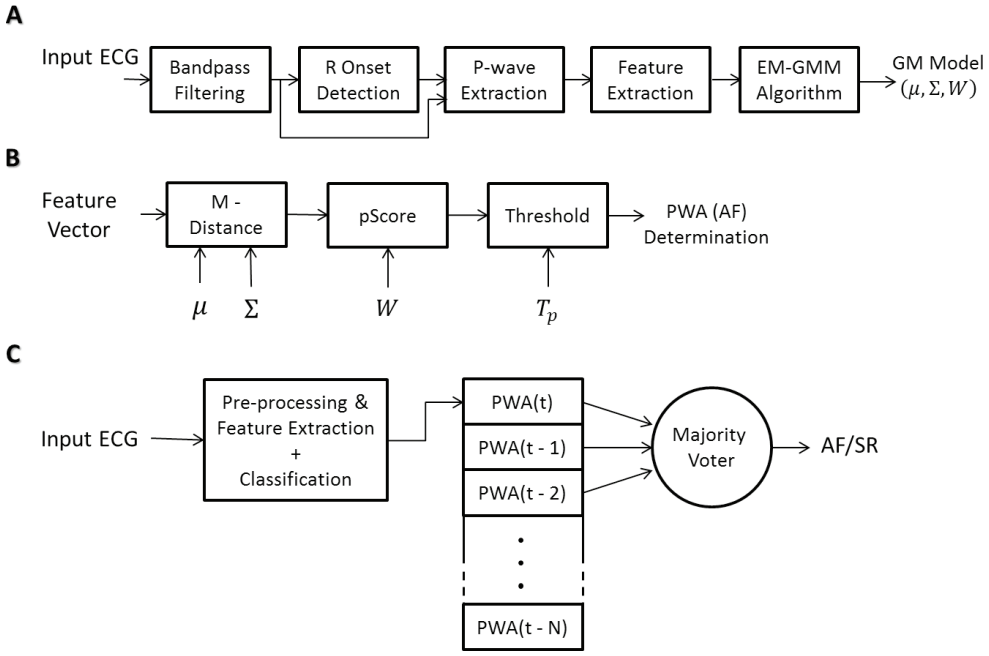

Figure 9. AF detection method: Figure shows the block diagram of the developed method of AF detection. PWA = P-wave absence, M-distance = Mahalanobis distance. A, Feature extraction and training; B, classification; C, majority voter post-processing.

of the P-wave at different intervals (i.e., first 20 ms or last 10, 20, 20, or 30 ms). A statistical model using a multivariate Gaussian mixture model (GMM) is created using the distribution of the NSR P-wave features. To generate the training model, the expectation-maximization (EM) algorithm is iteratively applied [72]. For the testing phase, the same preprocessing is performed and the same features are extracted, but now a majority vote of seven heart beats is employed in order to classify whether the test signal represents An NSR or AF. The algorithm is evaluated on the MIT-BIH AF Database from Physiobank [73]. The dataset includes 25 long-term (10 h) ECG recordings with AF (23 paroxysmal and 2 persistent) and contains 299 AF episodes (about 93.4 h). The proposed algorithm demonstrated that it is capable of classifying AF with a very high sensitivity of 98.08%. The sensitivity was highest among the compared algorithms (see **Table 1**). The specificity was 91.66% which had the second lowest classification error comparatively, which is a significant performance considering that the other methods are RRI-based approaches.

3.1.2. Prediction of successful postcardioversion patients with persistent AF

As discussed earlier, DCE cardioversion is one of the treatment options available, in which an electric shock is applied to the chest at certain intervals in order to restore NSR. This treatment however does not have a high long-term success rate, although it has more than 90% procedure success. A more well-defined method to evaluate the effectiveness, and hence

Algorithm	Year	Method	WL (seconds)	Se (%)	Sp (%)	PPV (%)	Err (%)
Moody et al.*	1983	RRI	60	93.58	–	85.92	–
				87.54	95.14	92.29	7.88
Cerutti et al.*	1997	RRI	90	93.3	–	94.4	–
				96.10	81.55	75.76	16.62
Tatento et al.*	2001	RRI	50	94.4	97.2	96.1	–
				91.20	96.08	90.32	5.32
Logan et al.*	2005	RRI	120	96	89	–	–
				87.30	90.31	85.72	10.89
Lake et al.	2011	RRI	12	91	94	–	–
Couceiro et al.*	2008	RRI + PWA	60	93.80	96.09	–	–
				96.58	82.66	78.76	11.77
Babaezaideh et al.*	2009	RRIRRI/PWA	>60	91	96	86	–
				89	96	88	–
Dash et al.†	2009	RRI	128 beats	94.4	95.1	–	–
Huang et al.†	2011	RRI	101 beats	96.1	98.1	–	–
Proposed algorithm	2014	PWA	1 beat	89.37	89.54	72.40	11.34
			7 beats	98.09	91.66	79.17	6.88

Unreported performance measures are displayed as a dash. Se = Sensitivity, Sp = Specificity, PPV = Positive predictive value, Err = Error rate.

*Additional algorithm evaluation completed by Larburu et al. is shown on the second row. Optimal window length (WL) was determined by Larburu et al.

†Results include additional processing for the purpose of ectopic beat filtering.

Table 1. Comparison of AF detection algorithms including additional evaluation performed by Larburu et al. [74].

predict the likelihood of maintaining NSR after cardioversion for patients who are about to undergo cardioversion, is important, so that the risks involved in cardioversion can be assessed [75]. If such a prediction can be performed, then the doctor could make a decision accordingly on whether to give the patient a cardioversion or not.

This section presents a novel computational method to perform signal analysis of AF patient ECG recorded before cardioversion and predict what the success of the treatment would be. A block diagram of the developed system is shown in **Figure 10**.

The method comprises preprocessing, extraction of features, classification, and then validation. The preprocessing is to remove the noise and the isoelectric line perturbations, for which a bandpass filter with cut off frequencies of 0.01 and 50Hz were applied. Following this, AA is extracted from the QRST complex using an average beat subtraction technique. There are a total of seven features extracted from the AA signals. The extracted features are calculated from the matching pursuit (MP) time-frequency representation of the AA signals [76]. A classifier based on quadratic discriminative analysis (QDA) is trained using the extracted features from the training data. The trained classifier was evaluated on an ECG data [77]

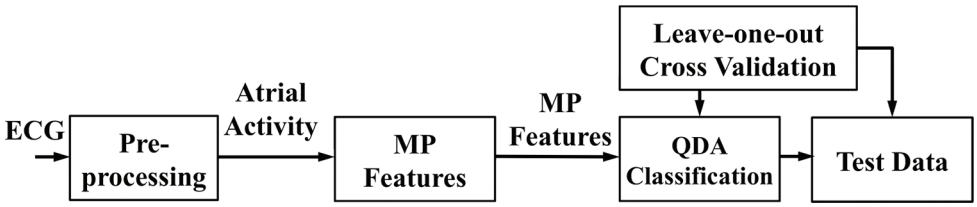

Figure 10. Prediction of cardioversion outcome: Figure shows the block diagram of the developed prediction method.

with 40 persistent AF patients who had a successful external DCE cardioversion therapy, but after 2-week follow-up, 20 patients had maintained NSR (AF-free) and 20 had a relapse of AF (AF-relapse). A leave-one-out cross-validation classification produced an outcome of 100% sensitivity and 95% specificity. Compared to the relevant methods in the literature (see **Table 2**), the proposed method resulted in the highest sensitivity and specificity values in predicting the success of DCE cardioversion in AF patients.

3.1.3. Identification of successful ablation targets from EGM signals

Catheter ablation is the most commonly preferred treatment for AF. However, the success rate of the procedure is only suboptimal due to recurrence of AF especially with persistent type patients. The arrhythmogenic rotors existing outside the PVs could be a potential target for ablation. However, in today's clinical practice there is no well-defined method to find the location of these rotors. Hence, a system that could estimate the rotor location and hence guide the clinician to the targets would be a significant clinical DSS for AF ablation in today's clinical scenario.

Method	Study size	Significance	Sensitivity	Specificity
P-wave duration, 1997 [78]	35	0.001	73%	71%
Heart rate variability, 2001 [79]	93	–	76%	90%
Fibrillatory rate, 2003 [80]	44	0.021	–	–
Clustering of RR intervals, 2004 [81]	66	0.034	–	–
P-wave duration, 2005 [82]	118	0.0001	72%	77%
P-wave duration, 2006 [83]	122,493	0.02	90%	21%
Fibrillatory rate, 2006 [84]	175	0.0001	79%	80%
Fibrillatory rate, 2006 [85]	54	0.002	–	–
Harmonic decay, 2006 [85]	54	0.0004	92%	47%
Sample entropy, 2006 [86]	66	0.02	–	–
Wavelet transform, 2007 [87]	30	–	100%	89%
P-wave dispersion, 2011 [88]	26	0.001	86%	95%
Wavelet sample entropy, 2008 [89]	40	–	95%	93%
Proposed MP-based method, 2014	40	0.005	100%	95%

Table 2. Comparison of signal processing methods.

The developed method is a novel probabilistic approach to localize rotors [90]. The relevant methods available in the literature for locating rotors involve deterministic, noniterative solutions using time-domain and frequency-domain characteristics [54–58]. The developed method uses a Bayesian filtering approach to search for the rotors by iteratively guiding an MPDC toward the center of a rotor. The algorithm was evaluated using a 2D realistic atrial tissue simulation. We developed a numerical simulation of a 10 cm × 10 cm 2D atrial tissue with a spatial resolution of 0.025 cm and sampling frequency of 500 Hz, using the Nygren human atrial cell model [91]. The numerical simulation was written using FORTRAN programming, and the visualization of the output was implemented in MATLAB. A single stable rotor was initiated and a standard 20 pole Lasso catheter (Biosense Webster, Diamond Bar, CA, USA) was simulated, from which the bipolar EGMs were obtained.

As shown in **Figure 11**, the method uses the discrete search space and some EGM characteristics as input, and gives the probability distribution of the presence of rotor in the search space, from which the rotor location can be estimated as the output. The 2D tissue is the bounded search space and it is discretized to form a grid, the coordinates of which is the first input to the algorithm. The center of the Lasso can be placed anywhere on this grid space. When a catheter is placed at a location, the following EGM characteristics are computed, which is the second input: the first activated bipole (FAB) and the rotor propagation ratio (RPR). FAB denotes the label number of the bipolar electrode of the Lasso that gets activated earliest by the rotor's wavefront. It is mathematically represented by Φ. RPR, represented by Φ, is the ratio of the two following characteristics: total conduction delay and cycle length, the definition of which can be found in the publication of our preliminary studies using both simulation and real clinical data [54].

The overall proposed idea is that the clinician places the catheter at any arbitrary endocardium location and records the EGMs. Then the system calculates FAB and RPR from these EGMs. The search space is discretized and now, both the inputs to the Bayesian algorithm are kept ready. The system first checks if the current catheter location is already a rotor center or not. This is performed using the EGM characteristics and the mathematical criterion, $\tau \simeq 1$, that is established for rotor convergence in our previous work [54]. If it is already a

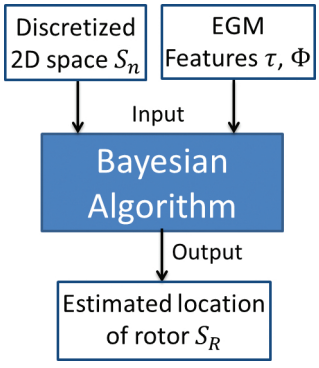

Figure 11. Overview of the guidance algorithm—The inputs are the search space and the two EGM characteristics, RPR (τ) and FAB (Φ) and the output is the estimated location of rotor.

rotor center, then, the clinician is advised to perform ablation, however, if it is not a rotor, i.e., if the convergence condition is not satisfied, then the inputs are provided to the developed algorithm to estimate a high probability location. The clinician then moves the catheter to this new location. This completes one iteration of the catheter-guidance algorithm. The EGMs are recorded again at the new location, and the convergence condition is checked again. If a rotor center is still not found, the new EGMs are processed by the algorithm to output a new estimate, and the catheter is moved by the clinician to this location. This process is repeated until a rotor is located, i.e., until the convergence condition is satisfied. The results of the developed algorithm demonstrate that the time taken to reach convergence is minimized during every iteration. This is mainly because of the updating steps of the recursive Bayesian filter, which tends to decrease the variance of the posterior distribution with increasing iterations.

The Bayesian algorithm uses the traditional Bayes theorem formulation which states that the posterior is proportional to the product of the prior and the likelihood. The posterior probability is nothing but the probability distribution of the presence of rotor in the search space. Here, the task is to determine the likelihood, and for that the EGM characteristics are used. The likelihood in our algorithm is defined as a function of two separate likelihood functions which are each a function of the features calculated from the local EGM recording. The prior is considered to be uniform distribution, meaning that the rotor could be present anywhere on the search space initially. However, in future, the prior could be tuned to any particular distribution according to clinicians' expertise and the information from cardiac anatomy. Finally, the algorithm uses the maximum *a posteriori* technique on the posterior distribution to determine the estimated location of a rotor center. This is the procedure during the first iteration; during the second one, the posterior from the previous step becomes the new prior in the Bayesian formulation, and the estimation is carried out again. This process continues until we converge.

Such an iterative framework makes the guidance to be adaptive, which could be much useful to tackle the dynamic nature of rotors. The results of our algorithm are highly promising. The algorithm was tested by placing the catheter in all the possible grid locations on the 2D simulated tissue. The algorithm achieved 100% convergence, and it took 3.37 ± 1.05 (mean ± sd) number of steps to find a rotor center. In order to assess the usefulness of the developed method, we compared it to a possible method for searching for rotors that could be used in current clinical practice using a Lasso MPDC. It is an unguided approach carried out by randomly placing the catheter at different locations of the atrium, and checking for convergence at each location. After a couple of placements, if the rotor is not found, the clinician might simply abort the manual search. We implemented this strategy on the simulation, with 20 iterations as the threshold. The convergence in the unguided case was only 34% and the number of steps, mean ± sd was 6.58 ± 3.72. This demonstrates the significance of the developed guidance strategy for implementation in a clinical setting.

Some examples of the catheter guidance implemented in MATLAB, is shown in **Figure 12**. The initial arbitrary location of the catheter is s1, and the catheter is advanced (as "dictated" by the algorithm) through s2, and finally converges at s3, which happen to be the rotor center.

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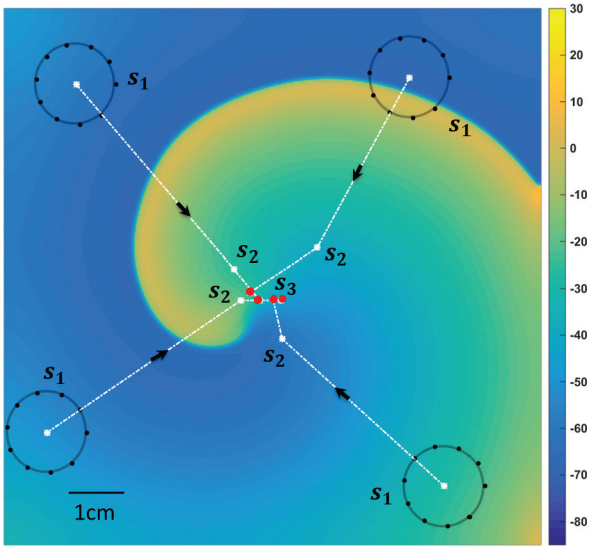

Figure 12. Some examples of the catheter-guidance paths using the proposed algorithm on the simulation—Each path is indicated from the first step, s1, to the rotor-convergence location in s3.

The algorithm's robustness can be clearly seen in the figure, with two major observations: First, the adaptive nature from the distance of the jump; the jump from s1 to s2 is always longer than the subsequent jumps, which means that the method tries to take shorter steps when it "feels" that it is getting close to a rotor center. The second observation is the adaptivity with respect to the direction; the direction of the path diverts toward the center of the rotor with increasing iterations. Additionally, it is also seen that the convergence points (red dots in the figure) are very close to the center (according to the developed simulation). The developed algorithm however is only a preliminary design and has to be improvised in future to tackle practical scenarios such as heterogeneous wave propagation, rotors with different cycle lengths, rotors with meandering center, etc.

4. Conclusion

This chapter reviewed some of the clinical decision support systems that have been developed and used in the therapy management of AF patient. Specifically, we discussed methods for detection of AF episodes from surface ECG signals, prediction of the success of DCE cardioversion from ECG signals, and identification of ablation targets for AF catheter ablation. The clinical DSS development is taking place in the right pace, the research field is witnessing promising methods that could turn into reliable clinical DSS technologies to assist the clinicians in the process of AF treatment and management in order to enhance the health of millions of patients afflicted by this debilitating rhythm disorder so that they can live longer and more fulfilling lives.

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Conflict of interest

The authors declare no conflict of interests.

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