ANALYSIS AND VISUALIZATION OF ATRIAL FIBRILLATION ELECTROGRAMS USING CROSS-CORRELATION

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ABSTRACT

CONRAD GEIBEL: Analysis and Visualization of Atrial Fibrillation Electrograms using Cross-correlation. (Under the direction of David Lalush, Ph.D.)

Despite many recent studies into the behavior of the complex fractionated atrial electrograms (CFAEs) that characterize atrial fibrillation, there has been relatively little success in analyzing them to reliably identify and ablate the rotor sources of atrial fibrillation in real time. The objective of this study is to propose a new method of analyzing and displaying CFAE signals to help cardiologists identify likely rotors during ablation procedures. This method uses cross-correlation to compare the electrograms collected at individual electrodes, and calculates the time lead/lag for each electrode compared to a local reference. The results of the analysis are displayed on a 3D color map using coordinate data collected alongside the electrogram data.

Atrial fibrillation CFAE data was collected from patients with one of two different types of electrode catheter, and a data set from a patient with atrial flutter was evaluated using the same methods. The cross-correlation method was confirmed to be working as designed when the atrial flutter lead/lag color map matched the one created by the cardiologists who collected the data. Several AF wave fronts were identified in the data as a lead to lag shift. By varying the length of electrogram data used through the analysis, it was determined that CFAEs have irregular timing and cannot easily be compared in large time sections versus smaller time sections. The unstable CFAE timing also led to the conclusion that nonlocal references cannot accurately correlate with the data, which may be due to the unpredictable flow of activation waves in the heart. The irregular timing of many of the electrograms points to regularity of
CFAEs in an area as a potential indicator of rotor centers. Collecting the data using unipolar electrodes rather than bipolar electrodes was found to give much better results, with many instances of wave front activity found, as well as better agreement between large and small sections in some cases. With its ability to identify AF wave fronts, this method has potential as a tool to be used to locate and identify likely AF sources in real time.
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1. INTRODUCTION

Atrial Fibrillation (AF) is an arrhythmia, or abnormal heartbeat, involving the disorganization of electrical impulses within the atria of the heart. This disorganization prevents the atria from contracting normally and results in a decrease in heart efficiency as well as increased risk of blood clot formation. Atrial fibrillation can be paroxysmal or persistent. Paroxysmal AF occurs randomly and for a limited amount of time before the heart returns to normal sinus rhythm. It is typically easier to treat than persistent AF. Atrial fibrillation is identified as persistent when the condition maintains itself constantly without intervention, and is the focus condition of this study. There has been extensive discussion over the last century as to the mechanism that initiates and maintains atrial fibrillation. A current theory among scholars is that atrial fibrillation is regularly driven by electric “rotors” within the cardiac tissue. These sources are characterized by a large wavefront that revolves around a single point in the center of the rotor, called a “phase singularity”. Smaller wavefronts called wavelets split off from the rotating wavefront as refractory tissue or other wavelets are encountered, causing the chaotic fibrillation that prevents contraction. These rotor sources are highly organized, but the disordered daughter wavelets overcome this regularity in far-field tissue that is not near the source.

Ablation is the surgical treatment method used for AF patients, and involves using high energy to remove or deactivate conductive tissues in the heart, with the intent of controlling the flow of electrical impulses. Current ablation procedures typically involve standardized practices such as pulmonary vein isolation (PVI) or linear ablation. These practices have a very high success rate for treating paroxysmal AF, but they are not as effective on patients with persistent
When the standardized ablation methods are unsuccessful, additional ablation involving the analysis of the complex fractionated atrial electrograms (CFAEs) is pursued. Success rates of these procedures vary substantially between reports, and there is not yet a standardized and reliable method of analyzing the atrial electrograms to locate the rotor sources. Currently many cardiologists resort to a “trial-and-error” method where they ablate in places of intense chaos and observe for any change in the CFAEs. The cardiologists ablate as much as necessary to bring the CFAEs into organization and terminate the fibrillation, which is inefficient and increases the risk of harm to the patient.

To change the current practices and increase both the efficiency and safety of ablation procedures, a reliable and standardized method of evaluating atrial electrograms to locate rotor sources must be developed. This thesis project is aimed at creating and evaluating a novel method for analyzing CFAEs and determining wavefront activity with an active mapping technique. Analysis and display programs were built in Matlab using electrogram data collected from persistent AF patients using small multi-electrode catheters. An analysis methodology was developed that compared the electrogram collected at an electrode with that of a local “reference” electrode and used cross-covariance calculations to determine the time difference, or lag, between the impulses of each electrogram. After finding the time lag for each individual electrode, a 3D color map could be created using collected coordinate data. These color maps would show the different time lag at each electrode and allow visualization of the wavefront activity over the time period of the collected electrograms.

Although it is not implemented in this study, the eventual objective would be to use these analysis and visualization methods in a real-time active mapping approach, where the cardiologist applies a small multi-electrode catheter to multiple places on the atrial wall, and
each time the program would process the electrical activity into a visualized color map showing
the wavefront. The wavefront activity would be used to follow the wavefronts and determine
their origins at the rotor sources. The mapping catheter would be used alongside the ablation
catheter, so that rotors could be eliminated as soon as they are located, as opposed to current
CFAE studies. The current procedures often perform a data collection procedure, and then they
process the data and determine rotor locations afterwards. On a later date they would try to use
the mapping results in an ablation procedure. Performing the planning and ablation procedures
separately is not always successful, however, since rotors can migrate over time. Unless the
ablation is performed very soon after the data collection, there is a chance of the rotor being
missed due to migration. If the rotors could be located without unnecessary ablation, the
surgery would cost less in time and energy, as well as reducing risk for the patient.

The methodology of this project is unique in its use of small multi-electrode catheters and
goal of an active mapping approach where the ablation occurs in synchronization with the
cardiac mapping. Most AF mapping studies use large, low resolution electrode arrays, such as
basket catheters. These catheters would collect electrograms from the entire heart chamber
with relatively low resolution. Although the researchers using these were able to allegedly
locate rotor centers, these locations may not have been completely accurate or their sizes could
have been overestimated because of the low resolution. The small multi-electrode catheters
used in this study have a much better potential spatial resolution than larger catheters, which
will allow the cardiologist to locate the rotor center with greater accuracy. The small size of the
catheters in the study also allows ease of movement within the chamber and the possibility of
ablating a rotor immediately after it is located with the mapping catheter.
The second section of this thesis discusses the background of atrial fibrillation, the prevailing theories of its maintenance, current methods used to treat it, and examples of methods for analyzing CFAEs. Section three describes the novel method for analyzing electrograms collected during AF, with the goal of developing a real-time localized measurement of conduction impulses in the atrium during surgery. Section four explains the results obtained in the analysis of three distinct data sets using the methods described in Section three. The final section discusses conclusions that were drawn from the data and the potential implications for the methodology based upon the results.
2. BACKGROUND

2.1 Atrial Fibrillation

Fibrillation is a in which the electrical signals become chaotic within the cardiac muscle. When it occurs, the muscle tissue becomes uncoordinated, with small areas contracting at random intervals. The affected chambers cannot contract normally in this state; they can only shake, or fibrillate. Very little, if any, blood can be pumped through a fibrillating heart chamber. Fibrillation can occur in either the atria of the heart or in the ventricles. Ventricular fibrillation (VF) is a very serious condition. Without the pumping of the ventricles, blood cannot be circulated throughout the body, and the patient can die within a few minutes without treatment. Atrial fibrillation (AF) is not as serious of a condition as VF. Because of the continued pumping of the ventricles, blood is still pushed passively through the atria. Without the aid of the atria, though, the heart pumps at 20-30% lower efficiency. In a normal heartbeat, the ventricles contract in response to electrical impulses that travel through the atria from the sino-atrial (SA) node. In the case of AF, however, the electrical impulses in the atria are disorganized. The impulses reach the ventricles more often and more chaotically, resulting in a faster, irregular heart rate in the patient, as seen in Figure 2.1 below.
In the figure, the fibrillating heart beats faster and more irregularly because of all the individual impulses reaching the atrioventricular node from the individual chaotic circuits. In a normal heart only one primary impulse wave reaches the atrioventricular node, allowing the ventricles to beat in time with the atria.

It is uncommon for both AF and VF to occur within the same patient at the same time, though it is not impossible. The muscle tissue in the atria and ventricles are similar, and it is widely held that the same mechanisms cause fibrillation in both AF and VF.

Although there are several prevailing theories as to the cause and mechanism of atrial fibrillation, they all agree that re-entry plays a critical part in fibrillation. Whenever an electrical impulse passes through an area of muscle tissue, that area enters a refractory state that cannot conduct electricity for a certain amount of time. In a normal heart, the electrical impulse travelling through the chamber will dissipate when it reaches the other side of the chamber because all of the tissue around it is refractory and conduction is blocked. Some portions of the heart tissue come out of refractoriness earlier than other portions, creating a mosaic of refractory and non-refractory tissues. In certain situations, the electrical impulses in the heart may not follow the normal pathway. An impulse can encounter anatomical or functional obstacles in the heart tissue, such as a small area of refractory tissue, and the impulse would split or travel around it. After interacting with this obstacle, one or more electrical impulses will
be travelling in new directions. These irregular impulses can travel throughout the heart chamber, blindly following the tissue wherever it is not in a refractory state. If they encounter another area of refractory tissue, then they will split around that and create even more impulses or they will dissipate. Some electrical waves will find pathways of non-refractory tissue between refractory areas. The impulses will travel in a chain reaction of smaller waves called wavelets as they encounter different areas of refractory tissues within the chamber, and these chain reactions can create long pathways. In some cases, the pathways can even travel back to an earlier point in the pathway and create a circuit.

This circuit will end immediately if the tissue is still in a refractory state, but if the tissue has reverted back to an excitable state, then the pathway can restart all over again, following the same or a similar pathway. This event is referred to as a “re-entrant circuit”. If the pathway is sufficiently long, then the circuit will have a gap of non-refractory tissue between the beginning and tail of the impulse wave following it. The impulse can follow the same exact pathway each time it goes around the circuit, and remain stable. In this case the condition is a flutter, rather than a fibrillation. A comparison between long and short reentrant pathways using strips of cardiac muscle is shown in figure 2.2 below. In the normal pathway, the impulse reaches a refractory start point, terminating the impulse just as the impulse reaches the bottom of the chamber wall in a healthy heart. The long pathway has a gap of non-refractory tissue that allows it to continue the loop indefinitely.
On the other hand, shorter pathways can have the problem of the impulse reaching itself, with little or no non-refractory gap. When the impulse reaches the refractory tissue from earlier in the circuit, it will usually split around it, creating a new wavelet that travels off in a different direction. The resulting re-entrant circuit is unstable and creates many disorganized wavelets that interfere with other waves and wavelets throughout the heart chamber. This situation leads to fibrillation.

2.2 Theories of Atrial Fibrillation Maintenance

2.2.1 Circus Movement

Starting in the early 20th century there were two prevailing theories for the maintenance of atrial fibrillation, Lewis’s circus movement theory and the ectopic foci theory. Circus movement was first hypothesized by Lewis in 1921. He believed that a single circuit could form in a chamber of the heart that would interfere with the normal sinus rhythm waves from the SA node and cause flutter or fibrillation. Lewis’s theory of “circus movement” suggested the phenomenon of re-entry, described in Section 2.1, as the mechanism for atrial fibrillation maintenance.
This figure shows a step by step process of the start and maintenance of “circus movement” in muscle rings. The wavefront starts at (1), continuing until it reaches a “circus” state at (5).

2.2.2 Ectopic Foci

Ectopic Foci are excitable areas of cardiac tissue that can fire of their own volition and interfere with the sinus rhythm. In normal sinus rhythm, the SA node usually suppresses the ectopic foci due to the higher impulse rate of the SA node. However, in the instance of an ectopic focus with a superior fire rate to that of the SA node, the focus can overcome the SA node signal and interfere with normal heart function. If an ectopic focus starts firing at a fast, regular rate, then it can create a regular electrical “wave” from this point. The wave it creates will not follow normal cardiac circuits, and can result in a reentrant circuit that triggers AF.

The theories of ectopic foci versus circus movement were disputed throughout the 20th century. Studies by Prinzmetal and Scherf in the 1950’s found evidence of focal beats in AF. They believed that AF was driven by one or more focal beat sources rather than circus movement. Both studies concluded that their results refuted Lewis’s theory. The debates surrounding the ectopic focus theory were not resolved until 1998, when a study by Haissaguerre et al. provided definite evidence of focal beats originating around the pulmonary veins during atrial fibrillation. Haissaguerre’s discovery led to the development of the pulmonary vein isolation (PVI) method of ablation that is commonly used today to treat atrial fibrillation.
2.2.3 Multiple Wavelet Hypothesis

Atrial fibrillation is inherently unstable due to the frequent splitting of waves and creation of wavelets. In 1950s, Gordon Moe proposed a third theory for the mechanism of atrial fibrillation, the multiple wavelet hypothesis\(^9\). According to his hypothesis, once AF is established it is “self-sustained and independent of its initiating agency” (Moe, 1959)\(^9\). Moe believed that atrial fibrillation is too chaotic of a condition for it to last for years at a time under the circus movement or ectopic focus mechanisms\(^8\). He envisioned fibrillation as the result of “randomly wandering wavefronts, ever changing in number and direction.” (Moe, 1956). \(^8\)

There was little evidence to support multiple wavelet hypothesis other than Moe’s computer simulations in 1962\(^11\), until a study was performed by Allessie et al. 21 years later\(^10\). Allessie’s group mapped the wavefront spread in the atria during fibrillation and discovered multiple propagating wavelets maintaining the chaotic atrial activity. Their results showed that the number of wavelets necessary to maintain the arrhythmia is 4 to 6\(^10\) rather than the over 26 predicted by Moe’s simulations\(^11\). Allessie’s observations, alongside several other animal and human studies, led to the development of Cox’s surgical MAZE procedure for treating AF\(^12\).

Figure 2.4\(^49\) shows the schematic of the Cox-Maze IV procedure, which is a more recent version of Cox’s original surgical MAZE procedure and combines both radiofrequency ablation and surgical incisions to treat AF.
2.2.4 Leading Circle Theory

In 1973, Allessie et al. made the discovery of reentrant circuits that would develop in the heart without obstacles. In these cases, as the circuit continued around in a “circle” the center would be barraged by centripetal wavelets, causing it to be in a state of constant refractoriness. As the center remained refractory, it would act as a functional obstacle and the reentrant circuit could continue to maintain the arrhythmia. This suggested mechanism was dubbed the “leading circle” theory of AF. While similar to Lewis’s earlier circus movement theory, it was different in that it did not require an anatomical obstacle, the circulating wave intrudes upon itself, and it has a shorter cycle length than circus movement. Figure 2.5 below shows the leading circle concept. The leading circle’s primary pathway is shown by the bold back arrow, with the centripetal wavelets going in towards to refractory center. This circuit will also split wavelets towards the outside to the rest of the atrium.
Figure 2.5 - Diagram of the Leading Circle Mechanism of AF

The arrows in the figure show the wavefront paths and directions in the leading circle mechanism. The rotor itself is shown as the large arrow, while the smaller arrows are the daughter wavelets that keep the center in a non-refractory state. The gray area is the gap of refractory tissue that allows the circle to continue indefinitely.

The leading circle theory prevailed for about 20 years before researchers found problems with it. Due to the refractoriness of the leading circle’s center, it would be impossible for the circulating wavefront to intrude upon it, and the circuit would be fixed in a single location. However, several high-resolution studies found evidence of reentrant circuits drifting during AF. If the reentrant circuits followed the leading circle mechanism as described by Allessie, then this drifting would not have occurred.

2.2.5 Mother Rotor Theory

To address the issues with the leading circle theory, researchers suggested that fibrillation is driven by a spiral wave rather than a circulating wave in a circuit. Spiral waves had been studied in other muscle tissues of the body, though no extensive testing had been done into whether these spiral waves occurred in the heart. These spiral waves are called such in 3D applications, but when working with 2D applications, such as the endocardial surface, they look like and are called rotor waves.
Figure 2.6 shows the basic mechanism of an atrial rotor. The initial step of the rotor mechanism is a wave break after the interaction of a wavefront with a functional or anatomical obstacle, such as another wavefront. The process occurs following the S1-S2 protocol, which proceeds as follows:

(i) The S1 wave is followed by a perpendicular S2 wave.

(ii) If S2 is initiated before the tail of S1 exits the refractory state, then S1 acts as an obstacle to S2 at the intersection point.

(iii) S2 turns into a rotating spiral wave, with the center at the point of intersection.

After the rotor initiates, it maintains itself in a process similar to the S1-S2 protocol. As the spiral wave travels around, any obstacles encountered (tissues in a refractory state) cause it to split and create wavelets. These wavelets then travel throughout the atria, interfering with normal electrophysiological pathways and starting fibrillation of the chamber.

The center of the spinning rotor is found as a “phase singularity”, which is the point where the phase of all points around it add up to \(2\pi\). The phase singularity is marked by the point where the red and black wavefronts meet in Figure 2.6. In recent years, high resolution mapping and computer modeling has led to a resurrection of Lewis’s original circus movement.
theory with modifications. Several mapping studies of AF have found a single or a small number of rapidly spinning sources maintaining the fibrillation\textsuperscript{17-19}. However, these sources are not Lewis’s waves that travel in a ring; they are rotors that spin around a phase singularity. Although the wavelets cause electrical chaos in the heart, the rotor that maintains fibrillation will often be highly periodic and organized\textsuperscript{20}.

2.3 Current Ablation Strategies and their Issues

2.3.1 Pulmonary Vein Isolation

Ablation strategies targeting the pulmonary veins are the foundation of AF ablation procedures\textsuperscript{45}. Initial treatments attempted to ablate focally within the PVs, but this method was abandoned in favor of complete electrical isolation of the PVs by creating a full circle of ablation around each, which resulted in much lower recurrence of fibrillation. The isolation of each individual PV is typically called pulmonary vein isolation (PVI). A study by Pappone et al. proposed a method of circumferential PV ablation called PV antral ablation\textsuperscript{21}. Using radiofrequency energy close to the cardiac surface, they were able to reduce local electrogram amplitude by over 80%, creating a reduction but not complete block of electrical signals. Reducing the signal strength by this amount would interfere with chaotic wavelets from AF sources while allowing the normal heart beat wavefronts from the SA node to pass through.

Arentz et al. determined that conduction block of the entire area around both PVs, called pulmonary vein antral isolation (PVAI) is more effective than isolation of individual pulmonary veins\textsuperscript{22}. It is vital that a continuous circumferential line is created around both ipsilateral PVs, and the line must have full electrical block for effective treatment\textsuperscript{23}. Figures 2.7\textsuperscript{21} and 2.8\textsuperscript{22} show the lines of ablation followed in PVI versus PVAI. Since PVAI isolates a larger area
than PVI, it cuts off the AF sources that can form in the area around the PVs, rather than only the sources that form in the PVs.

Figure 2.7 (Left) – Ablation spots of Pappone et al.’s PV Antral Ablation (PVI) 21

Figure 2.8 (Right) – Ablation spots of Arentz et al.’s PV Antral Isolation (PVAI) 22

Although PVI/PVAI is a very effective treatment for paroxysmal AF, it is not as effective for patients with persistent or long-standing AF 45. Studies have shown that after a single procedure of PVI success rates ranged from 21-22% at almost 2 years 24. PVAI has been shown to have greater success than PVI, with studies claiming success rates of 36% to 43.2% for a single procedure of PVAI for patients with long-standing AF 25-26. Despite its lower success in treating...
persistent AF, PVAI has become the preferred initial ablation strategy for all AF patients, both paroxysmal and persistent45.

2.3.2 Linear Ablation

Linear ablation involves creating linear lesions in the atrial tissue in order to modify the macro-reentrant circuits involved in maintaining AF23. The procedure usually includes a roof line connecting the left and right superior pulmonary veins and a mitral line connecting the mitral annulus to the left inferior pulmonary vein23. Linear ablation is an evolution of the MAZE procedure, an early surgical treatment for AF where the cardiac muscle is cut in a “maze” pattern to control the flow of electrical waves within the atria and prevent reentrant circuits from developing12. Studies have shown that re-entrant atrial tachycardia is likely to occur in patients again after PVI treatment without the addition of linear ablation23.

Figure 2.9 – Example of Roof and Mitral Isthmus Lines in Linear Ablation50
This figure shows a 3D map of roof and mitral isthmus line ablations performed in a study by Scharf et al. Each red dot marks the location of an ablation lesion that was placed there.

Linear ablation can be challenging to perform, since bidirectional block must be achieved across all lines to have effective lesions23. If complete linear block is not achieved in surgery, then there is an increased chance of reentrant atrial tachycardia developing after the procedure23. Linear ablation is often used in addition to PVI, PVAI, or electrogram-based ablation, and not on its own. An investigation by Willems et al. found that patients who undergo
linear ablation in addition to PVI have a much lower recurrence of AF than patients who only undertake PVI.\(^{28}\)

2.3.3 Complex-Fractionated Atrial Electrograms

AF ablation research has become increasingly focused on the analysis of complex-fractionated atrial electrograms (CFAEs). CFAEs are collected from the atrial tissue during fibrillation and represent areas of “slow conduction, wavefront collision, conduction block, or anchor points for reentrant circuits.” (Letsas, 2011)\(^{45}\). Cardiologists want to analyze these signals to determine the source(s) maintaining the fibrillation and disrupt them to terminate AF. End points for CFAE ablation include complete elimination of the CFAE or slowing and organization of the local electrograms.\(^{30}\) Figure 2.10\(^{31}\) below, taken from a paper by Oral et al.\(^{31}\), shows different CFAEs obtained from a patient with AF. CFAEs will sometimes exhibit periods of relatively stable, rapid activity as seen in electrogram A. The wavelets can also collide and travel so chaotically that the electrograms show little meaningful activity without filtering, such as in electrogram B.

![Figure 2.10 – Examples of CFAEs from Study by Oral et al.\(^{31}\)](image)

There is not yet a reliable technique for accurately analyzing CFAEs in ablation procedures, which limits its usefulness. Several studies have been performed using CFAE ablation, but they have gotten mixed results, with success rates ranging from 33% to 95%\(^{30-31}\).
There has also been research into the use of CFAE ablation in addition to PVI or PVAI. In these investigations, CFAE ablation was performed immediately following treatment with PVI/PVAI. Studies by Elayi et al.\textsuperscript{32}, Brooks et al.\textsuperscript{24}, and Kong et al.\textsuperscript{27} experienced improved success rates when using this method. On the other hand, outcomes by Oral et al.\textsuperscript{25} and Bencsik et al.\textsuperscript{33} reported little or no improvement after using CFAE ablation in addition to PVI or PVAI. Another factor to be considered with these studies is that CFAE ablation significantly increased the procedural time and energy, which increased costs and danger for the patient\textsuperscript{27}.

### 2.3.4 Stepwise Catheter Ablation Approach

According to the Bordeaux group\textsuperscript{37}, the optimal stepwise catheter ablation approach for persistent AF includes:

(i) PVI as the initial step, along with isolation of the superior vena cava and coronary sinus.\textsuperscript{37}

(ii) Electrogram-based ablation aiming at CFAEs and electrograms with large activation gradients.\textsuperscript{37}

(iii) Final target site should be linear ablation of the mitral isthmus line and left atrial roof line.\textsuperscript{37}

(iv) If AF still persists, the right atrium is targeted for ablation if there is evidence that a source for AF exists in those areas.\textsuperscript{37}

Using this method, the Bordeaux group reported termination of AF in 87% of patients, and lack of AF in 95% of patients after an 11-month follow up\textsuperscript{37}. Another stepwise procedure study by Rostock et al. found a single procedure success rate of 38% at 20 months, but it was improved to 81% success with the addition of repeat procedures\textsuperscript{39}. 
2.4 Ablation Procedure Used by Cardiologists at UNC Chapel Hill

Atrial ablation procedures are performed regularly at UNC Chapel Hill. Dr. Mounsey and Dr. Gehi of UNC Cardiology have extensive experience with the treatment of atrial fibrillation and were collaborated with over the course of this project. They use a modified stepwise procedure for AF ablation that was explained in their published study from 2012, and is summarized below:

1) As with most other ablation procedures, the first ablation performed is pulmonary vein antral isolation (PVAI). PVAI lesions are placed until complete block can be confirmed.

2) A linear ablation of the roof line is performed.

3) After the first two ablations, a decapolar mapping catheter is used to collect electrograms from the atrial wall. The cardiologist places lesions in the area of any electrograms that are identified as CFAEs.

4) Coronary sinus isolation is performed, where linear lesions are placed adjacent to and within the coronary sinus until the atrial activity within it disappears.

5) A mitral isthmus linear ablation line is created.

6) The final ablation is the isolation of the superior vena cava.

7) The procedure is considered complete at any point if sinus rhythm has returned and AF cannot be induced again. If the treatment reaches this stage and the cycle length of the fibrillation is significantly slower, then the procedure is complete.

8) The patient’s condition could also be reduced to atrial flutter or tachycardia, which would be fixed using further ablation.
9) Patients still exhibiting fibrillation after the procedure are treated with anti-arrhythmic medicines to control the fibrillation.

Using these methods, the cardiologists reported an AF recurrence rate of 27.3% for paroxysmal AF patients and 18.8% for persistent AF patients with repeat procedures after 56 weeks.

2.5 Significance of this Project

The objective of this study is to develop and examine a novel method of actively analyzing CFAEs and determining wavefront direction in real time using small multi-electrode catheters. Data would be collected from an area in the atrial wall during fibrillation using a small multi-electrode catheter, such as a spiral catheter or loop catheter. The data would be analyzed using an electrogram comparison method, and wavefront shape and direction in the data collection area would be displayed on the computer for the cardiologist’s perusal. Using this knowledge about wavefront behavior, it is hoped that the method could be used multiple times in order to “triangulate” the center of the rotor source in the atrial wall. If the cardiologist is able to locate the rotor center, then the rotor area could be ablated to potentially terminate the fibrillation.

AF is usually not immediately dangerous to the patient, but patients with AF have a five-fold increase in the risk of stroke compared to people without AF. This risk increases drastically with age, reaching up to 23.5% in AF patients aged 80-89. Even with the relatively high success rates of ablation procedures, many of the patients with “successful” treatments must remain on at least one antiarrhythmic drug. Using antiarrhythmic drugs is not necessarily an ideal situation since, as with many prescription medications, there can be unintended side effects. Most antiarrhythmic drugs affect the entire heart rather than only the atria. Ventricular side
effects can occur while taking the drugs including proarrhythmic events, negative inotropy, and torsades de pointes\textsuperscript{42-43}.

Relatively little progress has been made in improving ablation treatments since the adoption of pulmonary vein isolation. The reason for this lack of progress is that no consistently accurate methods have been developed for analyzing CFAEs. According to the prevailing mother rotor theory, the rotors will be an organized source within the disorder of fibrillation. If one is able to analyze the CFAEs during atrial fibrillation correctly then one can pinpoint the rotors, or rotor migration pathways, and ablate them.

However, without a definitive method of locating rotors in the atria, cardiologists must resort to trial and error in order to terminate AF. Currently, cardiologists use trial and error to try and guide the fibrillatory pathways into a controllable loop by ablating spots that exhibit CFAEs. Once the fibrillation is constricted to a single pathway, the tissue along the entire pathway area is ablated in order to eliminate the fibrillation. The trial and error methods are not always successful, and patients’ hearts are often ablated more than would be necessary if the rotors could be located. Catheter ablation carries certain risks at any point, such as bleeding at the ablation site or perforation of the heart muscle, and ablating more than necessary increases these risks\textsuperscript{51}.

Developing an easier, more reliable method of locating rotors during AF would have a profound effect on the clinical practice of ablation. With a consistent, real-time method for analyzing CFAEs, it would become easier for cardiologists to find and ablate rotors in a patient. If cardiologists do not have to use trial and error to treat the patient, then they can ablate only at the minimum necessary spots rather than ablate all throughout the heart. Less ablation on the patient creates less scar tissue, which is safer for the patient. It would also speed up surgeries immensely and could reduce the costs and risks associated with ablation surgery.
2.6 Previous Procedures for Analyzing CFAEs

2.6.1 Sanders et al. – Dominant Frequency Analysis

Rotors are attractive as focal points for ablation, since they are a strong periodic point source among all of the chaotic CFAEs. Early studies into locating these rotors, such as an experiment by Sanders et al. in 2004[^44], used dominant frequency (DF) analysis to translate the CFAE signals in AF patients. They believed that the areas with the highest DF would be closest to the rotors driving AF, and should be the key targets for ablation.

Sanders’ group performed electroanatomic mapping on 32 AF patients (19 paroxysmal, 13 persistent), and they were put through ablation surgery. The dominant frequency was then calculated for each electrode point by an investigator who was blinded to the results of the surgery. The calculated results were used to create a DF map of the atria and CS. In order to assess the hypothesis, DF maps for each patient were compared with the results for that patient’s ablation surgery.

In their results, the changes in AF cycle length (AFCL) during ablation were observed as effects of ablation. The AFCL would increase significantly when ablation occurred at high DF sites, but AFCL remained unchanged when ablation occurred in other areas. During the surgery, AF was terminated in 17 of the 19 paroxysmal AF patients, but there was not termination in any of the persistent AF patients. It was observed that more of the high DF areas in paroxysmal patients occurred in or around the PVs than in persistent patients. Most of the successfully treated patients had high DF sites only in or around the pulmonary veins. To account for the lack of success in persistent AF patients, Sanders pointed out that there were more high DF sites in the atria of the patients than were ablated in the surgery.

The conclusion of the study was that these high DF sites participate in the maintenance of AF, since ablation of these sites resulted in an increase of the AFCL of some patients, as well
as termination of AF in a number of paroxysmal AF patients. Although this method of CFAE analysis looked promising, it has not proven to be very reliable in practice. Later studies have also found significant variability in DF patterns of fibrillation, such as the study by Nash in 2006\textsuperscript{17}.

2.6.2 Nash et al. – Phase Analysis of Wavefronts

It is widely thought that the mechanisms for atrial and ventricular fibrillation are very similar, if not the same. Both VF and AF studies were researched for this project. Nash et al. performed a study 2006 where phase analysis and DF analysis were used to study the wavefronts and rotors in VF\textsuperscript{17}. They decided to use phase analysis “because it provides a way of identifying reentrant sources that is robust in the presence of noise and changing signal morphology.” (Nash, 2006)\textsuperscript{17}.

In the study, electrograms of the ventricles of the heart during 20–40 sec episodes of VF in 10 patients were recorded. An electrode sock was used to record 256 electrograms spread across both ventricles. The electrogram data was filtered and processed to determine the dominant frequency for each electrode and obtain a DF map of the ventricles. In order to visualize the wavefronts, several steps were taken. In general, a phase plot is created by graphing two state variables against one another in a system. For this study, the electrogram voltage was plotted against the Hilbert transform of itself. There was a phase plot for each electrode, and they calculated the phase at each time point using the plots. A topological charge technique\textsuperscript{47} was used to identify the phase singularities, which correspond to rotor centers, and an active-edge technique\textsuperscript{48} was used to visualize the wavefronts.

Nash et al. had a number of interesting observations. There were three distinctly different DF patterns identified among the 10 patients. The homogeneous/static DF structure (2 patients) was characterized by low variability of DF across the test area, as well as little change
in the pattern over time. The heterogeneous/mobile structure (2 patients) had significantly more DF variability across the electrode field. This pattern would also change with time. The heterogeneous/static structure (6 patients) exhibited a spatially varied DF map that remained relatively unchanged over time. The variability observed in the different DF maps did not support the conclusion made by Sanders et al. a year before. The DF maps did not consistently relate to the phase analysis results and the three structures shows that person to person variability will exist when mapping DF.

Figure 2.11 – Nash’s Findings of Reentrant Activity in a Patient’s VF

This figure shows the rotor moving over time in the span of a single revolution. The top set of color maps shows the relative voltage pattern within the heart at that time point, while the second set of maps shows the relative phase for each electrode, where the lagging electrodes are red and leading are blue. Using computational methods, Nash et al. created the third set of maps, which shows the path of one of the rotor’s wavefront arms.
Epicardial reentry was observed in all patients using the phase analysis method, an example of which is shown in Figure 2.11\textsuperscript{17}. The number of phase singularities found in the study remained low, lending credence to the mother rotor theory. However, the VF would sometimes devolve into large, chaotic, reentrant waves, similar to what one would find in Moe’s multiple wavelet mechanism of fibrillation. This behavior would usually prevail for several cycles, and then return to a more organized rotor mechanism. Nash concluded that both mother rotor and multiple wavelet mechanisms can maintain VF, and they are not mutually exclusive.

2.6.3 Narayan et al. – Cycle-to-Cycle Analysis using Basket Catheter Electrodes

The concept of an electrogram comparison method of determining wavefront activity between electrodes is not entirely new. A very recent study into analyzing CFAEs was published by Narayan et al. in 2012\textsuperscript{52}. According to Narayan, “there has been no direct evidence for localized sources in human AF using traditional methods” (Narayan, 2012)\textsuperscript{52}, even though several successes have occurred using animal models. A novel time-based approach utilizing repolarization and conduction dynamics was suggested as a method to characterize and locate rotor and focal sources of AF.

The data collection in this study began by collecting repolarization dynamics information using a monophasic action potential (MAP) catheter. Monophasic action potentials are the extracellular potentials that are measured by applying mechanical load to a cell\textsuperscript{54}. These potentials peak during repolarization of the tissue, which allows one to measure and define the repolarization dynamics during the heart activity\textsuperscript{54}. Unipolar electrograms are not able to separate far-field AF activity from local AF activity\textsuperscript{53}. However, MAPs can define the local depolarization and repolarization, which allows one to “identify signals as far field if they are dissociated from local action potentials or fall too early within repolarization to activate local tissue.” (Narayan, 2011)\textsuperscript{53}
Simultaneous to the MAP collection, 64 pole basket catheters were used to collect unipolar electrograms from multiple sites throughout the left atrium. The electrograms were recorded as unipoles and filtered at 0.05 to 500 Hz. The electrograms were also recorded as overlapping bipoles to reduce far-field artifact. Data was collected from 49 AF patients total, 20 of which had electrograms recorded from both the left and right atria rather than only the left atrium. These patients had a mix of paroxysmal and persistent AF, and any patients without active AF at the start of the data collection had it induced through external pacing.

AF activation maps were created from the data by analyzing the unipolar electrograms to build “movies” of the AF activation cycles. Each “frame” of the movie was a plot of the voltage at each electrode location at a time point. These frames were made for multiple time points to build an animation of the changing voltage. Isochronal maps were also created to illustrate single cycle snapshots of AF. In isochronal maps, each electrode has a color coded value based upon its time shift in relation to a reference signal. Electrodes of the same time shift, and therefore color, are called isochrones. These isochrones help the viewer to identify the wavefront action in the period of time studied, as seen in Figure 2.12. The isochronal maps and AF movies were used to identify both rotors and focal beats. The rotors were identified as locations of rotating wavefronts around a single point while focal beats were identified as locations of general wavefronts traveling out from a single point. These events had to persist for at least 50 AF cycles before being marked as rotors or focal beats.
Figure 2.12 – Left Atrial Rotor Source (Left) and Focal Beat Source (Right)\textsuperscript{52}

This figure shows examples of rotor sources and focal beat sources found using the mapping methods. The colors represent the time lag after a reference, represented by the red color in both plots. The white arrows show the predicted direction of the AF impulses based upon the isochrones results. The rotor source in the left map was located in a persistent AF patient, while the focal beat source in the right map was located in the left atrium of a patient with paroxysmal AF.

Narayan’s computational mapping method was able to identify rotors or focal beats during AF in 47 of the 49 patients. The number of AF sources located in patients with persistent AF was typically higher than the number of sources located in patients with paroxysmal AF. The number of rotors located was higher than the number of focal beats, with a ratio of 57 rotors to 11 focal beats. It was also observed that 27\% of the AF sources in were located in the right atrium. Narayan et al. made several conclusions from these results. The greater number of sources in persistent AF patients was believed to explain the greater difficulty in treating persistent AF compared to paroxysmal AF. Also, the presence of right atrial sources were believed to “explain the 70-80\% “ceiling” in AF ablation success in current studies” (Narayan, 2012)\textsuperscript{52}. 
Despite the apparent success of Narayan et al.’s study, it is believed that the use of basket catheters has several disadvantages. In addition to the low spatial resolution of the basket catheters, no ablation can be completed while collecting data using them. It is believed that a smaller, more mobile catheter may be better to map the activity and find likely AF sources. AF sources can change location over time (ref from earlier). The rotor and focal sources located using Narayan’s methods could change location after data collection, and subsequent ablation procedures after mapping may not be successful. A mobile multi-electrode catheter could be used in conjunction with ablation to locate likely AF sources in the patient, and then immediately ablate those areas. In this thesis, a similar electrogram comparison based mapping method will be explored that utilizes a smaller multi-electrode catheter as opposed to a large basket catheter.
3. METHODS

AF Lag Analysis and Visualization

![Flowchart of Entire Procedure for Collection, Analysis, and Visualization of Data](image)

**Figure 3.1. Flowchart of Entire Procedure for Collection, Analysis, and Visualization of Data**

### 3.1 Data Collection

Data collection was performed by Drs. Gehi and Mounsey of UNC – Chapel Hill Cardiology over the course of the past year. Data was collected from patients that came in for their previously scheduled ablation procedures. This ablation procedure was described previously in Section 2.4. Before the actual catheter ablation, a multi-electrode catheter was
held against the left atrial wall for several seconds while recording the electrogram at each electrode. The process was repeated at least 10 times in order to collect data from all around the left atrium. A parallel 3D positioning system was able to record the positions of the catheter electrodes at each of the data collection positions and store them, along with the collected electrograms, in an EP WorkMate System from St. Jude Medical. The system allowed the cardiologists to collect the data from patients and store it electronically on the system’s hard drive.

In order to transfer the collected data from the EP Workmate System, the data for each position had to be saved individually to a separate flash drive, which was then used to transfer the data to PC.
3.1.1 Data Sets

There were three data sets used in this project to develop and test the analysis algorithms. These data sets are referred to as the Initial, Flutter, and Unipolar data sets.

<table>
<thead>
<tr>
<th>Data Set</th>
<th>Details</th>
</tr>
</thead>
</table>
| Initial   | • 10 bipole electrode spiral catheter (Livewire Spiral HP Catheter, St Jude)  
• Collected data at 16 different positions in atrial wall (A-P).  
• Electrogram data collected for 10 sec at each position.  
• Sampling Frequency = 2 kHz |
| Flutter    | • Single bipolar electrode catheter  
• Collected data at 31 different positions in atrial wall.  
• Electrogram data collected for 8 to 12 seconds at each position  
• 5 bipole electrode loop catheter placed in atrial appendage for reference signal.  
• Sampling Frequency = 2 kHz |
| Unipolar  | • Unipolar circumferential decapolar mapping catheter  
• Collected data at 13 different positions on the atrial wall (A-M).  
• Electrogram data collected for 5 to 15 seconds at each position  
• Sampling Frequency = 2 kHz  
• Collection Filtering = Bandpass with limits at 1Hz and 50Hz |

Table 3.1. Characteristics of Data Sets Used
3.1.2 Transfer Data from EP WorkMate System to Matlab

The first step that was taken for each data set was to transform the data from the EP WorkMate System at the hospital into a manipulable form in Matlab. The data was imported to the PC as a large collection of text files, with each text file containing the data for a single electrogram. Each electrogram that the system recorded has its own unique name. The 3D coordinate data was exported in a single large .csv document, with x, y, and z coordinates for each electrode, and a different set of coordinates for each position.

When the data was obtained in its text file form from the cardiologists, a program was used to import the electrogram data from the text files into Matlab matrices that could be manipulated. In the program, native Matlab functions are used to first open the text file in Matlab, then to scan through it, taking data and re-saving the data as a Matlab variable. This process is repeated for all electrodes at all positions. The program puts all the data together into a matrix for each catheter, with a row for each electrode/electrode pair in the catheter. There is a different matrix created for each catheter position. For example, in ObtainInitialData.m, 16 different matrices are created, labeled A-P for the 16 different positions, and each of these matrices has 10 rows, for each of the 10 electrode bipoles in the catheter.

After importing the electrogram data, the program imports the 3D positioning data using the same reading procedure as was used for the electrode data. After importing both the electrogram and coordinate data, the matrices for each position are combined into a structure for that position.

This series of import programs was used for all three data sets, with few changes between each program. The only notable change was for the flutter data, which was recorded as 31 different single electrode positions. The flutter program imports all of the electrogram data as a single matrix, with each row representing one of the 31 positions.
3.2 Matlab Data Processing and Analysis

3.2.1 Filtering and Pre-Analysis Calculations

The analysis program starts by filtering the data to remove unwanted artifact and noise. Most of the filters used in these programs are Gaussian low-pass filters. They are created using the steps outlined in the table below:

<table>
<thead>
<tr>
<th>Data Set</th>
<th>Filtering Procedure</th>
</tr>
</thead>
</table>
| Initial       | 1) Electrogram data and coronary sinus reference data are filtered using the same filters.  
               | 2) Data is normalized by subtracting the mean value of electrogram. It is then half-wave rectified to keep only positive values. 
               | 3) Gaussian (80 points, $\alpha = 4$) low-pass FIR filter is used. 
               | 4) Gaussian (60 points, $\alpha = 4$) low-pass FIR filter is used. |
| Flutter        | 1) Electrode data and coronary sinus reference data are filtered the same amount.  
               | 2) Gaussian (80 points, $\alpha = 4$) low-pass FIR filter is used. 
               | 3) Gaussian (60 points, $\alpha = 4$) low-pass FIR filter is used. |
| Unipolar      | 1) Butterworth high-pass IIR filter (30 order, $f_c = 4Hz$) is used.  
               | 2) Gaussian (130 points, $\alpha = 4$) low-pass FIR filter is used. 
               | 3) Gaussian (80 points, $\alpha = 4$) low-pass FIR filter is used. |

Table 3.2. Filtering Characteristics for each Data Set
Figures 3.2-3.3. Unfiltered versus Filtered Electrograms for Position A of Unipolar Data Set

After the filtering is complete, the program does several calculations using the 3D mapping coordinates. First the midpoint is determined between the two electrodes that composed each bipole electrode. This calculation was only necessary for the electrogram data in the Initial data set and the atrial appendage reference data, since all the other data was collected with unipolar electrodes. After midpoint calculation the program establishes the distance between each electrode or each bipole midpoint, which will be used later in the analysis.

The primary lag analysis is performed using the entire data set, called the Sect0 analysis. Details for the Sect0 electrograms of each data set are shown in Table 3.2 on the next page:
<table>
<thead>
<tr>
<th>Data Set</th>
<th>Sections</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>Sect0 (1 section)</td>
<td>Full electrogram length is 20000 pts. (10 seconds @ 2kHz)</td>
</tr>
<tr>
<td>Flutter</td>
<td>Sect0 (1 section)</td>
<td>Full electrogram length is 15000 pts. (8 seconds @ 2kHz)</td>
</tr>
</tbody>
</table>
| Unipolar | Sect0 (1 section) | Each Position has a different electrogram length:  
A. 29583 pts. (14.8 sec @ 2kHz)  
B. 32602 pts. (16.3 sec)  
C. 24624 pts. (12.3 sec)  
D. 10627 pts. (5.3 sec)  
E. 8951 pts. (4.5 sec)  
F. 14677 pts. (7.3 sec)  
G. 13547 pts. (6.8 sec)  
H. 15514 pts. (7.8 sec)  
I. 20325 pts. (10.2 sec)  
J. 11972 pts. (6.0 sec)  
K. 9892 pts. (5.0 sec)  
L. 13636 pts. (6.8 sec)  
M. 11317 pts. (5.7 sec) |

Table 3.3. Electrogram Sections for Sect0 Analysis.

3.2.2 Sect0 Electrogram Lag/Lead Analysis

The first step in the lag analysis part of the program is to calculate the cross-covariance between the electrode electrogram and the reference electrogram for each electrode at each position using the xcov() function. The reference electrogram used was different for each data set. In the Initial and Unipolar data sets, the reference was a local electrogram. The first electrode was used as the reference for almost all cross-covariance calculations. For positions C & O and position F of the Initial data set, the reference electrodes were electrode 2 and electrode 4, respectively. These alternative references were used because of low signal quality in other electrograms for these positions. The atrial appendage electrograms were used as the references for the Flutter data set. Because these electrograms were collected at different times for the Flutter data set, there is a unique atrial appendage reference signal for each individual electrode. In the calculation of the cross-covariance, the program offsets the reference data by a certain amount, calculating the cross-covariance at each point of offset. For example, if the
offset length is set to 250, then the cross-covariance will be calculated 501 times, one for each point between +250 and -250 offset. For the Initial and Unipolar data sets, a ±250 point offset was used for all iterations. For the Flutter data set, ±600 point offset was used for all iterations. In the selected data sections of the Unipolar data set, a ±200 point offset was used.

![Figure 3.4. Comparison of Electrograms and their Associated Cross-Covariance Curve](image)

This figure contains the 5th electrode electrogram overlaid on the reference electrogram for Position A of the Unipolar data set. The cross-covariance curve above the electrograms shows peaks at places where the electrograms would match up if electrode electrogram was shifted by that amount.

The next step of the analysis determines at which offset the cross-covariance is strongest for each electrode and defines the overall time lag between that electrode and the reference electrode. The program searches point by point through derivative of each cross-covariance curve to find any zero-crossing from positive value to negative values, which represent a peak in the original cross-covariance curve. The program then uses the metric mean value for each peak to determine which offset has the most agreement between the electrode and the reference.

Once the program determines the lag offset for every electrode, a smoothing step is performed on the data. In the Initial data sets, the program recalculates the lag value by taking into account the value of lead/lag at each other electrode. This calculation was initially used for the Unipolar data set as well, but later on in the project it was decided that the data set did not
need a smoothing step. In the Flutter data set, the electrograms were so organized (See Figures 4.8-4.9) that the cross-covariance peaks representing the next and the previous period were close to the same strength. Some of the lag values would be recorded as the opposite lag compared to the other electrodes surrounding it, and a smoothing step was designed to fix these outliers. For each electrode, the program counts the numbers of lagging/leading electrodes nearby, and if the majority of the nearby electrodes have an opposite time lag than the target electrode, then the lag for that electrode is changed to the next highest lag determined using the metric mean. In almost all cases this next highest lag was the opposite lag peak.

3.2.3 Multi-Section Analyses

Separate analysis iterations were performed by splitting the electrograms up into multiple sections, then performing the lag analysis on each individual section. The Initial and Flutter data sets were split up into Sect0, Sect2, and Sect4 analyses, while the Unipolar data had an additional SectS analysis. The details for each of the individual analyses are shown on Table 3.4.
<table>
<thead>
<tr>
<th>Data Set</th>
<th>Sections</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>Sect0 (1 section)</td>
<td>Full electrogram length is 20000 pts. (10 seconds @ 2kHz)</td>
</tr>
<tr>
<td></td>
<td>Sect2 (2 sections)</td>
<td>Each section is half the length of Sect0.</td>
</tr>
<tr>
<td></td>
<td>Sect4 (4 sections)</td>
<td>Each section is one fourth the length of Sect0.</td>
</tr>
<tr>
<td>Flutter</td>
<td>Sect0 (1 section)</td>
<td>Full electrogram length is 15000 pts. (8 seconds @ 2kHz)</td>
</tr>
<tr>
<td></td>
<td>Sect2 (2 sections)</td>
<td>Each section is half the length of Sect0.</td>
</tr>
<tr>
<td></td>
<td>Sect4 (4 sections)</td>
<td>Each section is one fourth the length of Sect0.</td>
</tr>
<tr>
<td>Unipolar</td>
<td>Sect0 (1 section)</td>
<td>Sections that look particularly good/regular are selected for each position:</td>
</tr>
<tr>
<td></td>
<td>Sect2 (2 sections)</td>
<td>Each section is half the length of Sect0.</td>
</tr>
<tr>
<td></td>
<td>Sect4 (4 sections)</td>
<td>Each section is one fourth the length of Sect0.</td>
</tr>
<tr>
<td></td>
<td>SectS (1 section)</td>
<td>Each Position has a different electrogram length:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N. 29583 pts. (14.8 sec @ 2kHz)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>O. 32602 pts. (16.3 sec)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P. 24624 pts. (12.3 sec)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Q. 10627 pts. (5.3 sec)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R. 8951 pts. (4.5 sec)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S. 14677 pts. (7.3 sec)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T. 13547 pts. (6.8 sec)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>U. 15514 pts. (7.8 sec)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>V. 20325 pts. (10.2 sec)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>W. 11972 pts. (6.0 sec)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>X. 9892 pts. (5.0 sec)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Y. 13636 pts. (6.8 sec)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Z. 11137 pts. (5.7 sec)</td>
</tr>
<tr>
<td></td>
<td>A. pts. 8000:12000 (sec 4-6 @ 2kHz)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B. pts. 18000:22000 (sec 9-11)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C. pts. 2000:4600 (sec 1-2.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>D. pts. 2000:6000 (sec 1-3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>E. pts. 1000:5000 (sec 0.5-2.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>F. pts. 1000:2500 (sec 0.5-1.25)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>G. pts. 3800:5800 (sec 1.9-2.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>H. pts. 2200:4000 (sec 1.1-2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>I. pts. 9100:11400 (sec 4.55-5.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>J. pts. 4800:6400 (sec 2.4-3.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>K. pts. 3200:6600 (sec 1.6-3.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>L. pts. 9300:11300 (sec 4.65-5.65)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M. pts. 1200:2880 (sec 0.6-1.44)</td>
<td></td>
</tr>
</tbody>
</table>

Table 3.4. Electrogram Sections for Each Analysis Iteration.

The lag analysis procedure for each of the other analyses is almost identical to the Sect0 analysis described in Section 3.3.2. The SectS electrograms were analyzed as single sections, so there were no changes made to the analysis. An addition to the multi-section analyses Sect2 and Sect4 is that the standard deviation is calculated for each set of results, which helps to give a better idea of how stable an electrogram remains throughout the data collection period.
average standard deviation is also calculated for each position and the positions are sorted into a list of least average standard deviation to greatest. Average standard deviation was not calculated for the Flutter data sets, since there is only one position.

In the display program, color maps are used to show the different lag values for electrodes on a 3D map. To ensure accurate visualization and comparison of the data, the limits for these color maps are calculated in the analysis program. A first set of limits is calculated using the Sect0, Sect2, and Sect4 data results. A second set of color limits was created for the Unipolar data set using only the Sect5 data results.

3.3 Matlab Mapping and Visualization of Results

A display program was designed that would give the user several options of which analysis results to view, and to show those to the user in an understandable format. After choosing which of the positions they want to view by entering a position A-P (A-M in Unipolar data set; unused in Flutter data set), the electrode electrograms and reference electrograms for that position are formatted for easier viewing. By offsetting each electrogram vertically, the plots are made to look similar to an ECG chart. An ECG chart is a common tool used by cardiologists, and showing the data in this manner would help them to more easily understand the visualized electrograms.

After the position is locked, the different display options are printed onto the command window of Matlab and the user inputs what data they wish to view. The options available for each data set are shown on Table 3.5 on page 36.
<table>
<thead>
<tr>
<th>Position</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Data Set</td>
<td>1. Electrode Data Chart</td>
</tr>
<tr>
<td></td>
<td>2. Lag Map for this Position</td>
</tr>
<tr>
<td></td>
<td>3. X-Cov Plots for this Position</td>
</tr>
<tr>
<td></td>
<td>4. X-Cov Plots vs. Shifted Chart</td>
</tr>
<tr>
<td></td>
<td>5. List of Least Noise Positions</td>
</tr>
<tr>
<td></td>
<td>6. All positions on one graph</td>
</tr>
<tr>
<td></td>
<td>9. Choose New Position</td>
</tr>
<tr>
<td></td>
<td>0. Terminate Program</td>
</tr>
<tr>
<td>Flutter Data Set</td>
<td>1. Electrode Data Chart</td>
</tr>
<tr>
<td></td>
<td>2. Lag Map</td>
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<tr>
<td></td>
<td>3. X-Cov Plots</td>
</tr>
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<td></td>
<td>4. X-Cov Plots vs. Shifted Chart</td>
</tr>
<tr>
<td></td>
<td>9. Choose New Position</td>
</tr>
<tr>
<td></td>
<td>0. Terminate Program</td>
</tr>
<tr>
<td>Unipolar Data Set</td>
<td>1. Electrode Data Chart</td>
</tr>
<tr>
<td></td>
<td>2. Lag Map for this Position</td>
</tr>
<tr>
<td></td>
<td>3. Display X-cov plot for each electrode</td>
</tr>
<tr>
<td></td>
<td>4. X-Cov Plots vs. Shifted Chart</td>
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<td></td>
<td>5. List of Least Noise Positions</td>
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<td></td>
<td>6. All positions on one graph</td>
</tr>
<tr>
<td></td>
<td>7. Dominant Frequency Analysis of Sect0</td>
</tr>
<tr>
<td></td>
<td>9. Choose New Position</td>
</tr>
<tr>
<td></td>
<td>0. Terminate Program</td>
</tr>
</tbody>
</table>

**Table 3.5. User Options for the Different Display Programs**

Each option is covered in more detail in the following list.

**Option 1 – Electrogram Plots**

The first option involves the display of the electrogram data in ECG chart form. In the Initial data set, the program only plots the rectified and filtered data. An example of an electrogram plot can be seen in Figure 4.1 of the Results section.

**Option 2 – Lag Result Maps**

Selection of the second option results in plots of the lead/lag times for the different electrodes in 3D space. These plots contain points in 3D space representing the different electrodes, and each electrode has a color based upon its respective lead/lag data result. For the
Initial and Unipolar data set there are lines connecting the different electrodes, to show how the catheter was shaped during data collection. Examples for these plots can be found in Figures 4.4 and 4.35-37 of the Results section.

Option 3 – Individual Cross-covariance Plots

With the third option the program plots the cross-covariance (xcov) curves for each section in a data set. These plots also contain bar graphs of the metric mean for each peak in the xcov curves, which allows the user to check that the program is working correctly and determining the correct peak as strongest in the xcov plot.

Option 4 – Overlaid and Shifted Electrogram Figures

The fourth section causes the program to plot the electrogram for each electrode, overlaid onto an electrogram for the reference electrode. The cross-covariance curve is plotted in a separate graph on each figure, as well as another electrogram plot. The new electrogram plot contains the reference electrogram graphed on top of the electrode electrogram, but the electrode electrogram is shifted by the amount determined to be the lag offset in the analysis program. If the lag was chosen correctly, then the shifted electrode electrogram and the reference electrogram will match one another closely. These overlaid electrograms provide an easier visualization of whether the analysis program is working correctly.

Option 5 – List of Least Std Deviation Positions

When the user selects option 5, the ranked lists of lowest standard deviation positions from the analysis program are displayed. The list for the Sect2 and Sect4 are all displayed in sequence on the command window.

Option 6 – Plot All Positions on One Graph

The sixth choice displays the lag maps for every position in a data group. Each map is created using the same methods as in option 2. Along with the lag map, another figure
containing checkboxes for each position is displayed to the user. Using this input, the user can select particular positions to show or hide, and press a button to redraw the map with only the selected positions. For Sect2 and Sect4 data, a multi-position lag map and checkbox control figure are created for each individual section. Both Options 5 and 6 are not available for the Flutter data set, since this data set only had one position.

*Option 7 – Dominant Frequency Analysis*

A dominant frequency analysis is performed on each position in the Sect0 analysis of the Unipolar data set. The analysis is performed using the fast Fourier transform (FFT) and power spectrum analysis. The dominant frequency for each electrode was calculated in the analysis program, and this list of dominant frequencies can be displayed in a list format similar to Option 5.

*Option 9 & 0 – Restart or Terminate the Program*

Selecting option 9 puts the program back into its initial state and allows the user to select a new position to view. Option 0 causes the program to exit the program, as well as close any open figures.
4. RESULTS

4.1 Initial Data Set

The Initial data set was the first one collected by the cardiologists and analyzed, so this data set was used to create the analysis method and Matlab programs. Although the atrial fibrillation impulses could be discerned after filtering, the data positions were characterized by either low amplitude or high noise.

4.1.1 Filtering Results and Signal Quality

The spiral catheter used in the Initial data collection is larger and more unwieldy than smaller conventional catheters. The cardiologist had difficulty holding the spiral catheter against the atrial wall during AF and obtaining a good signal on all of the catheter electrodes.

![Figure 4.1. Bipolar Electrograms for Position B of Initial Data Set](image)

One of the issues with the data was low signal amplitude. Refer to position B data in Figure 4.1. The electrograms for the 3rd, 4th, 5th, 9th and 10th electrodes all had very low
amplitude signals. Figure 4.2 below compares the electrograms from the 2\textsuperscript{nd} and 3\textsuperscript{rd} electrodes, in which one can see very small peaks in the 3\textsuperscript{rd} electrogram that match with the larger peaks in the 2\textsuperscript{nd} electrogram. These peaks are difficult for the program to tell from any noise peaks, such as those seen around 6500 ms in the 3\textsuperscript{rd} electrogram. The program had difficulty in differentiating the AF impulses from noise in these low amplitude signals, since the noise peaks were almost as large as the AF peaks in many cases.

**Figure 4.2. Comparison of Electrograms 2 & 3 from Position B**

Not only was low signal amplitude a problem in some positions, but high noise was an issue in the others. Figure 4.3 shows that there was significant noise on each electrogram for Position I and these peaks were often irregularly shaped.
Figure 4.3. Electrograms for Position I of the Initial Data Set

For example, the 9th electrode electrogram contained periods of large, easily distinguishable peaks, but also contained periods where the peaks are indistinguishable from noise. The extra peaks from noise made the analysis much more difficult, since many false cross-covariance peaks were obtained in the analysis that had to be evaluated to determine the correct time lag.

This high noise can be attributed in part to the low amplitude of the electrograms. Filtering the low amplitude electrograms enough to eliminate the noise would have removed much of the desired AF signal strength, so all of the noise could not be filtered out.
4.1.2 Single-section (Sect0) Analysis

Figure 4.4. Sect0 Lag Map for Position B
This figure shows the lag analysis results for position B. In the 3D lag analysis map, the time lag is shown as a function of color. There is a color map on the side of the figure that shows which amount of lag goes with which shade of color. In the map, the positive values mean that the electrode signal lags behind the reference, while the negative values mean that the electrode signal leads the reference.

Despite the low amplitude of many of the electrograms collected at position B, the lag analysis presented a promising map. One can see a shift from dark red at one side of the spiral catheter, representing where the signal is the most behind the distal reference electrode, to the dark blue section at the opposite side of the spiral, representing where the signal leads the reference electrode the most. There is a gradual shift from dark red to dark blue across the catheter, but there is an out of place dark red lag in the center electrode. If one imagines a line of the wavefront traveling across the spiral in Figure 4.4, then the center electrode should be light orange or yellow, representing a smaller amount of lag. Though the wavefront passing through this position could have been irregularly shaped, it is also possible that the low amplitude of the 10th electrode pair, seen in Figure 4.1, caused the program to calculate an
inaccurate lag value for the center electrode. The ambiguity of this result illustrated the need for a method to assess signal quality in terms of how regular a signal is and how stable its frequency remains over time.

Figure 4.5. Cross-Covariance Analysis for Electrode Pair 8 in Position B
This figure is an example of the cross-covariance (xcov) curve obtained at the 8th electrode pair for Position I. It also shows the electrode electrogram (green) compared to the reference electrogram (blue) in two plots. The top plot shows the electrograms as they were recorded, while the bottom plot shifts the electrode electrogram by the amount determined by the program to be the time lag between the two. The time lag was determined as the highest peak in the cross-covariance curve on top. Since the highest peak was at -17.5ms, so the green electrogram was shifted to the left by 17.5ms in the bottom plot.

The xcov analysis results for position B, which had a promising wavefront result (Figure 4.4), did not show as much agreement as expected. Figure 4.5 shows the cross-covariance (xcov) curve and overlaid electrograms for the 8th electrode pair of Position B. The lag map had looked like a good wavefront example. Although the analysis seemed to match the peaks better for this electrode and position than it did in Figure 4.6, irregularity in the AF impulses could still be seen. The low amplitude and noise problems in this data set likely contributed to the poor lag analysis results. It also led to the conclusion that it was too difficult to get a good electrical contact with
the atrial wall using the LiveWire spiral catheter. It was decided that using different electrode
catheters for subsequent data sets was necessary.

4.2 Flutter Data Set

With the imperfect lag analysis results and irregularities in signal frequency for the Initial Data set, it was decided that testing the analysis methods on a controlled set of data would be a logical next step for the investigation. Atrial flutter, as mentioned in the Background, is a more organized form of cardiac reentry, the driving force of atrial fibrillation. Flutter is driven by a reentrant circuit or rotor, but without the splitting off of wavelets that cause chaos in the cardiac tissue. The Flutter data set was collected from a patient with atrial flutter and analyzed using the same general methods as the Initial data set.

4.2.1 Filtering and Signal Quality

Figure 4.6. Electrograms for Electrodes 1-15
The electrograms for the 31 electrodes in the Flutter data set are shown in Figures 4.6 and 4.7 on the previous page. Except for some artifact or noise in the electrogram for the 5th electrode, the signals generally had very low noise, if any. The signals also had varying amplitudes between high-amplitude, easily recognizable signals and low-amplitude signals that could barely be seen in places. A good representation of the different amplitudes is shown in Figure 4.8 below, which shows a section of the electrograms for the 7th, 8th, 9th, and 10th electrodes. Although the 9th and 10th electrograms were much smaller than the larger electrograms of the 7th and 8th electrodes, there was little enough noise that the program could still recognize the flutter impulses in the electrograms.
Figure 4.8. Example of Amplitude Variation in Flutter Electrograms

Figure 4.9. LASSO Reference Electrograms, Electrodes 1-15
Figures 4.9 and 4.10 show the reference electrograms for each of the electrodes. They were collected from the atrial appendage with a LASSO catheter. The reference electrograms were generally higher amplitude than their associated electrode electrogram, as well as having very low noise after filtering.
4.2.2 Single-section (Sect0) Analysis

These figures show the lag analysis results for the flutter data as a single section. The electrodes covered most of the inner wall of the atrium, with the yellow section being near the reference electrodes in the left atrial appendage. Figure 4.11 shows the atrium from the front, while 4.12 and 4.13 are the same plot rotated 90° to the right or 45° to the left and up, respectively. These other rotations show that the electrode positions covered the entire endocardial wall of the left atrium.
The bulk of the electrodes in Figures 4.11-4.13 were either dark red or dark blue, with the electrogram either lagging behind or leading ahead of the reference signal, respectively. These lagging and leading electrodes were grouped together, with no outlier electrodes in the middle of a group. At the right side of the map is the area where the atrial appendage was located. The electrograms in this area had much more mild lag since they were spatially closer to the reference electrode.

Mean/Stddev Lag for 1 Section

![Figure 4.14. Lag Results Map without Smoothing Step Enabled](image)

*Figure 4.14. Lag Results Map without Smoothing Step Enabled*

*This figure is showing the same results as those seen in Figure 4.11, except for the deactivation of the smoothing step in the analysis. The circled electrodes are those that do not match the results in 4.11.*

Observe Figure 4.14, which shows the 3D lag map without the smoothing step in the analysis. There were several outlier electrodes on the lower area of the atrium that show lead rather than lag that their surrounding electrodes show. This disagreement between electrodes is
not seen when the smoothing step is used in Figure 4.13, and provides evidence that the smoothing step is working as intended.

Figure 4.15A-B. Comparison of Flutter Lag Results with Activation Map Created by Cardiologists

Comparison between the Flutter lag results and an activation map created by the cardiologists using the EP Workmate System. The lag results map in 4.15A is a representation of the single-section lag results, except the color axis is reversed to match the color axis of the activation map in 4.15B. The matching electrode positions were labeled on both 4.15A and 4.15B.

When compared, the Flutter lag results and activation map match one another relatively well. There was a division separating the lagging and leading sections in a line going from electrodes O through E in both the lag results and the activation map. However, there was a difference in the border on the lower half of the atrium. In the activation map, electrodes E, H, Y, W, X, and EE were all leading the reference, but in the lag results the electrodes were lagging behind the reference. Despite these differences, both the lag results and the activation map relatively match one another, showing distinct lagging and leading sections.
Figures 4.16 and 4.17 above show the xcov curves as well as the overlaid electrograms for the 30th and 7th electrodes versus their respective references. Other electrodes all had similar results to those shown above; electrodes 30 and 7 were chosen because their electrograms...
show one of the smallest and one of the largest amplitude signals, respectively. The analysis found impulses both before and after each reference electrogram impulse for every catheter electrode, represented by peaks in the xcov curve. These peaks often had very similar amplitude, but the metric mean method of analyzing peak strength was able to determine which peak represented stronger agreement between the two electrograms. As seen in the overlaid electrograms plots, the time lead or lag determined by the analysis was very accurate. The shifted electrogram in the bottom plot matches up very closely with the reference electrogram. Because of the accurate matching between the time-shifted electrode electrogram and the reference electrogram seen in Figures 4.16 and 4.17, it was decided that the lag analysis method created in this study was working as designed and should be a viable method for analyzing atrial fibrillation electrical signals.

It is interesting to note the double peaks in the cross-covariance curves of Figure 4.18-19. After studying the data, it was discovered that these are caused because the reference electrode actually has two peaks. It initially looked as if the reference waveform was composed of a periodic single peak and trough in the electrograms of Figures 4.11-12, but in Figures 4.18-19 showed that there is a second peak following the trough in the waveform. Although this second peak is not as large as the first peak, it is still large enough that it creates a positive cross-covariance value between the electrode and reference electrograms. Although this behavior was noted, it was not investigated further.

One important observation for this data set was that the signal had a very stable frequency. Atrial flutter is very organized due to its lack of roaming wavelets, and this organization made it easier for the analysis program to determine the proper time lead/lag between the electrode and atrial appendage reference. The lack of regularity in the earlier Initial data set was likely a contributing factor to error in the Initial analysis results. The irregularity in
the Initial signal was believed to be caused by the wavelets that split off from the rotor source during AF. The wavelets would introduce signal interference and alter the AF impulses all throughout the chamber. It would be reasonable to assume that the irregularity in the local electrograms also existed in the rest of the atrium. Early in the investigation, a nonlocal reference in the coronary sinus (CS) was considered to be used as a reference for all of the positions in the Initial data set. However, the wavelet behavior in AF creates irregularity in the signals, and these irregularities would become increasingly difficult to predict as distance between the reference and data electrode increased. It was concluded that though a nonlocal reference may be suitable for atrial flutter analysis, it should not be used to analyze atrial fibrillation.

4.3 Unipolar Data Set

After the high noise and low amplitude of the electrograms in the Initial data set, it was predicted that using bipolar electrodes in such close proximity was removing not only the ventricular artifact, but also much of the amplitude from the AF impulses themselves. To test this hypothesis, the next set of data was collected using 10 unipolar electrodes in a circumferential decapolar mapping catheter as opposed to using the 10 bipolar electrode pairs of the spiral catheter. These electrodes would pick up everything that they detected, including any artifact coming from the other chambers of the heart. This set of data was designated under the name Unipolar.

4.3.1 Filtering and Signal Quality

After filtering was completed as described in the Methods section, a definite sinusoidal signal was obtained that appeared to represent the AF impulses.
Figure 4.18. Unfiltered Position A Electrograms from Unipolar Data Set

Figure 4.18 contains a plot of the unfiltered data collected at Position A. There is extensive noise in the signal, as well as regular peaks from the ventricular beats of the heart. In some places the AF impulses can be seen riding the electrogram, but there is too much artifact and noise for any analysis to be performed. The filtered electrogram for this position is shown below on Figure 4.19.

Figure 4.19. Filtered Position A Electrograms from Unipolar Data Set
The filtered electrograms looked much more like sinusoidal signals after the filtering was performed. Although the noise could not be taken out completely, one could easily see the periodic AF impulse signal that had been covered up by the noise and artifact before. It is interesting to observe that the AF impulses seemed cycle through periods of regularity and irregularity. For example, in Position A there were periods of regular, large amplitude impulses at around 4-6 seconds, 8-10 seconds, and 13-15 seconds. This cycling could have been due to migration of the rotor to be closer to the collection position, or could have been periods of time when wavelets were not colliding in that area as frequently so that only the rotor impulses were travelling across the catheter area. Relatively clear, sinusoidal electrograms were obtained for most of the 13 positions collected in this data set. Below are shown the unfiltered and filtered electrograms for Position J.

![Figure 4.20. Unfiltered Position J Electrograms from Unipolar Data Set](image-url)
The Position J electrograms did not have as much artifact or noise as the Position A data. Compared to the earlier position, it is much easier to see the AF impulses on top of the unfiltered electrograms, though filtering was still needed before analysis could be performed. In Figure 4.21, the electrograms are more regular, without the cycling between different frequencies and amplitudes of signal that was observed in the Position A results.

4.3.2 Single-section (Sect0) Analysis

Given the higher quality of the electrograms for the Unipolar data set compared to those of the Initial data set, it was expected that the lag maps for the Unipolar data positions would look more consistent than those created in earlier data analyses.
Figure 4.22. Sect0 Lag Results Map for Position A

This figure shows the lag analysis results for the Position A electrograms using the same methodology as for the initial data set (see Figure 4.4). For the Unipolar Data set, the reference electrode was made bigger than the other electrodes in the map to allow easy identification by the user. The black arrow shows a prediction of the wavefront movement through the catheter area.

The blue leading and red lagging sections were grouped together in Figure 4.22, and the electrodes near the reference all matched with close to zero lag. This grouping of electrograms indicated a definite shift from leading to lagging. It appeared that the wave front came in from the middle electrodes of the catheter, and moved around towards the reference end of the catheter before turning and going through the electrodes at the terminal end of the catheter (opposite end from the reference).

The signature of a wavefront passing through was found for almost all of the positions. In Figure 4.23 below, the lag analysis results are shown on the color map for position J, whose electrograms were seen above in Figure 4.21.
Figure 4.23. Sect0 Lag Results Map for Position J

The figure shows the single section lag results for position J, presented in the same fashion as the results on Figure 4.22.

A definite shift showing the path of the wavefront was also seen in this position. According to the data, it appeared as if the wave front entered the catheter area from a spot on the terminal arm around the 4th electrode. It then proceeded across the catheter before leaving around the 8th and 9th electrodes. The wave front path looked more like a revolving shift than a straight across shift, as seen in the arrow on the figure. This revolving shift indicated that the center of rotation was in a direction between the 6th and 7th electrodes of the catheter. The revolving wave front could potentially be used to know that a rotor was close to position J, and in the direction between the 6th and 7th electrodes. These observations foreshadow a potential use of this analysis procedure as a way to triangulate rotor center locations, rather than merely knowing when the catheter has been placed on top of one.

The higher signal to noise ratio, as well as the lag maps that displayed coherent wavefront activity, lent support to the hypothesis that the bipolar electrodes of the Initial data
set were eliminating important AF signal data, and that unipolar data collection and filtering may be a better method for collecting data during atrial fibrillation.

Not only did the Unipolar data set yield lag maps with coherent wavefront activity, but the cross correlation analysis encountered no problems with confusion between peaks in this data set.

Figure 4.24. Cross-Covariance (xcov) Curves for Each Electrode of Position A
This figure shows the cross-covariance curve created for each electrode when compared to the reference electrode. The results follow the electrode order horizontally, so 1-5 are on top and 6-10 are on bottom. A DataTip shows the time lag determined for each electrode as the value of X in its xcov curve.

All of the cross-covariance plots created contained only a single positive peak centered at a lag value other than zero. The vertical bars at each peak in Figure 4.24 represent the lag strength, which is the maximum possible value for all electrodes since there was only one peak each.

4.3.3 Selected-section (SectS) Analysis

Although analysis of the entire period of the collected electrograms for the Unipolar data set yielded promising results, it was not certain that this data could be trusted as a whole. The AF data electrograms collected in the Initial and Unipolar datasets were still more noisy and
irregular than those obtained from the atrial flutter patient in the Flutter data electrograms. Also, the “cycling” action of the unipolar electrograms in Figures 4.17 and 4.19 needed to be considered and investigated. As an additional test of the regularity of the AF signal in the Unipolar data set, the electrograms for each section were observed and a section containing the most stable data was isolated. The most stable area of the data was determined (by the human eye) by answering the question, “Which time period has the most regularity among all of the electrograms?” A selected section was obtained for each position. The endpoints and length of each of these selected sections was detailed earlier in Table 3.3 of the Methods section. The selected sections for Positions A and J are shown below.

**Figure 4.25. Selected Data Section for Position A**

This figure shows the selected data section for Position A. The selected section was cut from the single section electrogram, beginning at 4 sec and ending at 6 sec to cover a 2 sec span.
Figure 4.26. Selected Data Section for Position J

Similar to Figure 4.25, this selected data section was cut from the position J electrogram starting at 2.4 sec and ending at 3.2 sec to over a 0.8 sec span. It is shorter than the previous in Figure 4.25 because of the shorter overall length of the position J electrogram compared to the length of the position A electrogram.

As can be seen in Figures 4.25 and 4.26, the selected electrograms were fairly regular, with similar waveforms between each electrode, which were expected to allow the time lag between electrodes to be calculated with limited error.
Figure 4.27. Comparison of Sect0 (Left) and SectS (Right) Lag Maps for Position A

The figure compares the lag results when using the entire electrogram (Sect0) and the lag results when using only the selected data section (SectS) for position A. The Sect0 Results are on the left and the SectS on the right.

Using the Position A selected electrogram, the lag results in Figure 4.27 were acquired.

The figure shows both the Sect0 and the SectS lag results side by side for ease of comparison.

Despite the assumed irregularity of the data, the lag results for the entire time series almost exactly match those obtained for only the selected time series. There is only a minor difference in lag value between the 7th electrodes in each map.
Figure 4.28. Comparison of Sect0 (Left) and SectS (Right) Lag Maps for Position J

The figure is similar to 4.27 in that it compares the lag results of Sect0 and SectS. This figure shows the comparison for position J of the Unipolar data set.

The lag results in Figure 4.28 were obtained in the Position J analysis. Again, the lag map for the Sect0 data closely resembles the lag map for the SectS data. However, the two lag maps do not agree quite as completely as they did with the Position A data. The SectS electrodes seem to consistently show more negative lag (higher lead) than their corresponding Sect0 electrodes, with the exception of the electrodes 1 and 2. This agreement between the Sect0 and SectS results was seen in many of the positions, including positions A, B, C, D, F, H, J, K, and M.

The fact that the analysis of a selected section matches the analysis of the entire data set indicates that the conduction patterns remained fairly stable over the time period, and the Unipolar electrograms were more regular than initially hypothesized.

4.4 Effects of Varying Section Sizes on Analysis Results

Other studies of atrial fibrillation, such as the Narayan studies in 2010-2012\textsuperscript{52,53}, analyzed the electrogram signals peak by peak rather than evaluating the entire set of collected
data in a single section. In a fashion similar to Narayan’s, the analysis program was designed to process the data in several different iterations, each with the data split up into a different number of sections, ranging from 1 section to 4 sections. It was expected that this method could be used as a measure of the regularity or stability of the AF signal, where a stable signal would exhibit similar lag results for each of the smaller sections.

4.4.1 Initial Data Set

The Initial data set was used to develop the code for analyzing the data in sections, and therefore was the first set of data tested with these methods. Due to the high noise and limited signal consistency discovered in the analysis of the single section data, it was hypothesized that the multi-section results would not agree very well, if at all. All of the positions were analyzed, but Position B was already covered earlier in Section 4.1 of the Results, so it will be used as an example.

Position B had some fairly low amplitude electrograms in comparison to other positions, but the single section analysis results (Figure 4.4) looked promising with their definite lag shift.
Figure 4.29a & b. Two-section Lag Result Maps for Position B (a = left; b = right)
The figure contains the lag results map for each individual section of the position B Sect2 analysis. The result on the left plot (a) was obtained from analysis of seconds 0-5 of the collected electrograms, while the result on the right plot (b) was obtained from analysis of seconds 5-10 of the collected electrograms. Other than this change the lag maps are set up with the same methodology as earlier ones.

The Sect2 result maps for position B are shown in Figure 4.29. The sections did not agree very strongly, with several differences observed. There were some similarities between the first section analysis on Figure 4.29a and the Sect0 analysis in Figure 4.4, but not enough to say that they exhibited the same behavior.
Figure 4.30a-d. Four-section Lag Result Maps for Position B
The figure contains the lag results map for each individual section of position B Sect4 analysis. The map in the top-left plot (a) was obtained from analysis of seconds 0.0-2.5 of the collected electrograms, the top-right plot (b) was obtained from analysis of seconds 2.5-5.0 of the collected electrograms, the bottom-left plot (c) was obtained from analysis of seconds 5.0-7.5 of the electrograms, and the bottom-right plot (d) was obtained from analysis of seconds 7.5-10.0 of the electrograms. Other than the data used, lag maps are set up with the same methodology as earlier ones.

The Sect4 analysis results in Figure 4.30 did nothing to debunk the earlier multi-section results. The electrodes changed their results greatly from section to section, showing no stable activity over the 10 seconds of collected data.

This disagreement between sections was confirmed in all of the collection positions. It was also predicted that even though none of the Sect2 or Sect4 data maps matched the Sect0 map, it was possible that one could average the different section results together for each electrode, and the averaged map would be close to the Sect0 results.
Figure 4.31-4.33. Average Lag Maps for Sect0, Sect2, and Sect4 Analyses of Position B

Figures 4.31, 4.32, and 4.33 show the mean lag results for the Sect0, Sect2, and Sect4 data, respectively, at position B. On the Sect2 and Sect4 analyses, the standard deviation between sections for each electrode is plotted on its respective electrode. A low standard deviation indicates agreement between sections, while a high value indicates disagreement.

Contrary to expectations, the averaged sections did not result in lag maps that agreed with the single section analysis. The Sect2 map agreed with the Sect0 data in some respects, but there was still a large amount of error. The Sect4 map did not match either of the other maps. It was observed that as the number of sections was increased, the mean lag results would become increasingly mild. In Figure 4.31, the lag and lead values are much more extreme than those seen in Figure 4.33. This difference was caused by the larger amount of disagreement between
sections when there are more sections. In Figure 4.30 many electrodes would switch back and forth between lagging and leading over time, and these negative and positive results would cancel one another out when the mean was calculated between the sections. The data behaved as expected when split into smaller sections, as seen in the example figures. Due to the high amount of noise and lack of stability, the separated sections barely agreed with one another, often switching back and forth between lagging and leading with the successive sections. These results add additional evidence that the AF impulses were unstable and without a regular frequency. This conclusion cannot be stated as fact, since the disagreement between sections could be merely another casualty of the high noise in the Initial data set.

4.4.2 Flutter Data Set

With the stability of the electrograms found in the analyses of the Flutter data set, explored in Section 4.3, it was expected that the multi-section lag results would agree with one another. The multi-section analyses would be further proof of the regularity and stability of the electrograms collected during atrial flutter.
Figure 4.34a-b. Sect2 Lag Result Maps for Flutter Data Set (a = left; b = right)

Similar to Figure 4.29, 4.34a and 4.34b show the Flutter lag results for the first and second half of the data electrograms, respectively.

The lag results map for the Sect2 analysis is shown above in Figure 4.34. Contrary to expectations, the maps for the two sections did not agree. While the second section showed a result similar to that found for the single section analysis in Figure 4.13, the first section yielded electrodes that almost entirely lead the reference. There were outlier electrodes found in the second section map as well, despite the additional smoothing steps in the Flutter analysis.
Figure 4.35a-d. Sect4 Lag Result Maps for Flutter Data Set

Similar to Figure 4.30, 4.35a-d show the Flutter lag results for seconds 0-2, 2-4, 4-6, and 6-8 of the original electrograms, respectively.

The Sect4 analysis iteration, the results of which are shown in Figure 4.35, also showed substantial variability between sections. The first section had results that agreed well with the Sect0 analysis, and the fourth section agreed somewhat, though with a larger portion of lagging electrodes than in the others. The second section was observed to be similar to the second section of the Sect2 analysis, which is unexpected because they did not use the same electrograms.
Figure 4.36-4.38. Sect2 and Sect4 Average Lag Maps for Flutter Data Set

Figures 4.36, 4.37, and 4.38 show the mean lag results for the Sect0, Sect2, and Sect4 analyses of the Flutter data set, respectively. On the Sect2 and Sect4 analyses, the standard deviation between sections for each electrode is plotted above its respective electrode. A low standard deviation indicates agreement between sections, while a high value indicates disagreement. The color scale is the same for all maps.

Figures 4.36-4.38 the mean lag maps do not agree, just as expected with such variability in the different sections. However, the mean lag maps match one another better than the mean lag maps for the Initial data set did. In all three maps, the electrodes in the top section of the atrium were primarily leading the reference, just as they were in the Sect0 analysis. The most
disagreement was observed in the inferior atrial electrodes, seen as yellow or pale green in the color maps. These electrodes had both lagging and leading results in different sections, which canceled one another out when the mean was calculated. One could also identify these electrodes by looking at their standard deviations. The higher standard deviation electrodes had disagreement between sections, while the electrodes with little variability between sections had smaller standard deviation.

It is believed that these results do show regularity, in fact there could have been too much regularity for this analysis. There was so much agreement between the reference and electrode that the program could not tell whether the electrode was leading or lagging, since both the leading and lagging peaks would match up very well with the reference. At first these results were disturbing, since disagreement between sections would mean that the signal was not stable, and the hypothesis was proven wrong. On the other hand, it is likely that this variability occurred because the Flutter electrograms were too stable, rather than unstable. As seen in the electrograms of the electrodes and their references, Figures 4.6-4.7 and 4.9-4.10, the flutter impulses were all very similar to one another in both the reference and the electrodes. There was very little differentiation in the signal for the program to lock onto as an anchor, so it had difficulty in determining whether an electrode peak was supposed to match up with the reference peak that occurred later than it or the one that occurred before it. As observed earlier, most of the cross-covariance (xcov) curves had two large peaks at a lagging point and a leading point that were often very close in amplitude. The smoothing step was added to the analysis in order to fix single electrodes that did not agree with the ones surrounding it, but it would not have fixed large areas. In fact, it could have made them worse by changing the correct electrodes to match the surrounding erroneous ones.
In order to show the difference that the smoothing step made on the data, the Sect2 analysis was performed with the smoothing step disabled. Other than the lack of smoothing, these results are shown with the same methodology as those of Figure 4.34.

Figure 4.39 shows the differences that the smoothing step made when one compares it to Figure 4.34. The primary area of disagreement was the inferior part of the atrium, which was overwhelmingly leading in Figure 4.34a and overwhelmingly lagging in Figure 4.34b. This disagreement is not seen in Figure 4.39. Many more electrodes agree with one another in Figure 4.39 than in Figure 4.34, including the inferior section. Only two individual electrodes do not match, but these differences were sufficient to cause the smoothing step to draw completely different conclusions as to what the data should look like in that area. For the most part, however, the smoothing step was effective in eliminating single outlier electrodes.
The fact that most of the electrodes were either lagging or leading by the same amounts in Figures 4.36, 4.34, and 4.35 is evidence that the Flutter data was stable and regular, even if there was variability between lagging or leading in many of the electrodes. This situation lead to the belief that this analysis method may not be the best to use for very regular, stable conditions like atrial flutter, though it could work better in an idealized atrial fibrillation system that has low noise like the Flutter data set and a small amount more variation in frequency that the program could use as an anchor to compare electrograms.

4.4.3 Unipolar Data

When the Unipolar data set was obtained, the multi-section analysis had been performed on a high noise and chaotic data set with the Initial data, and on a very low noise and stable data set with the Flutter data. Neither of these data sets yielded multi-section results that had multiple sections in agreement with one another. The Unipolar AF electrograms, examples of which are in Figures 4.21 and 4.23, were observed to have a higher signal-to-noise ratio than those of the Initial data set. They also had some variation in frequency over the course of the data collection, which could serve as an anchor to avoid the errors observed in the multi-section analysis of the Flutter data set. Like the Initial data set, the positions covered earlier in the results section, Positions A and J, will be shown as examples of the Unipolar multi-section analysis results.
The Sect2 analysis for position A yielded the color maps in Figure 4.40 above. These two lag maps matched one another much more closely than lag maps from either the Initial or Flutter data sets. The area with the most negative lead is at the 5th electrode in both plots, indicating that the wavefront enters from that direction, and the lag is greatest at the terminal end, indicating that the wavefront left from that direction. This behavior is similar to that observed in the lag map of the single section analysis on Figure 4.24.
Figure 4.41a-d. Sect4 Lag Analysis Maps for Position A
This figure houses the lag results for each of the four individual sections obtained for Position A of the Unipolar data set. Figure 4.41a (top-left) was obtained using seconds 0-3.7, 4.41b (top-right) was obtained using seconds 3.7-7.4, 4.41c (bottom-left) was obtained using seconds 7.4-11.1, and 4.41d (bottom-right) was obtained using seconds 11.1-14.8, of the data electrograms.

The Sect4 analysis in Figure 4.41 yielded lag maps that mostly matched one another in wavefront behavior. In the second, third, and fourth sections, the wavefront entered at around the 5th electrode, which had the lowest lag, while exiting at the terminal electrode, which had the highest lag, just like in the Sect0 and Sect2 analyses. The first section appeared to have a similar grouping of electrodes as the other sections, but the area around the 5th electrode was not the lowest lag section. Even though some sections seemed to be scaled at different amounts, their behavior was still similar, which indicated the same wavefront behavior.

The mean lag maps were also created for the Unipolar data, and the maps for position A are shown below in Figures 4.42, 4.43, and 4.44 for the Sect0, Sect2, and Sect4 analyses, respectively.
Figures 4.42, 4.43, and 4.44 show the mean lag results for the Sect0, Sect2, and Sect4 analyses of the Position A Unipolar Data, respectively. On the Sect2 and Sect4 analyses, the standard deviation between sections for each electrode is plotted above its respective electrode. A low standard deviation indicates agreement between sections, while a high value indicates disagreement. The color scale is the same for all maps.

All three mean lag maps showed similar behavior, as expected from the individual section results discussed earlier. The Sect0 and Sect2 mean lag maps agreed together almost exactly, with the same wavefront direction coming in from the middle of the catheter and leaving through the terminal electrode. The Sect4 mean lag map was found to be almost the same as the other maps, with the exception of the 7th electrode, which had a very negative lag...
compared to the Sect0 and Sect2 maps. This error likely occurred because the lag value for the 7th electrode in the fourth section was an outlier with a very negative lag value that threw off the 7th electrode value when averaging the sections together. If one ignored the outlier electrode, then the wavefront behavior would look very similar to the Sect0 and Sect2 results.

Figure 4.45a-b Sect2 Lag Result Maps for Position J of Unipolar Data Set (a = left; b = right)
Similar to Figure 4.41, this figure shows the Sect2 analysis results for Position J of the Unipolar Data Set. The results in 4.45a were obtained using seconds 0.0-3.0 of the electrograms and the results in 4.45b were obtained using seconds 3.0-6.0 of the electrograms.

Comparable to the position A results in Figure 4.41, the Sect2 position J maps show similar lag shift and therefore wavefront activity, but there are different value scales for each, with the first section being more negative and the second section being more positive. Also, the terminal electrode disagrees between the two sections; it is believed the second section is correct since it matches the Sect0 data in Figure 4.47 more accurately.
Figure 4.46. Sect4 Lag Result Maps for Position J of Unipolar Data Set
This figure houses the lag results for each of the four individual sections obtained for Position J of the Unipolar data set. Figure 4.46a (top-left) was obtained using seconds 0-1.5, 4.46b (top-right) was obtained using seconds 1.5-3.0, 4.46c (bottom-left) was obtained using seconds 3.0-4.5, and 4.46d (bottom-right) was obtained using seconds 4.5-6.0, of the data electrograms.

Also similar to the position A results, the Sect4 lag maps in Figure 4.46 did not match one another as well as in the Sect2 data. While the second and fourth sections exhibited activity similar to the first and second sections of the Sect2 analysis, the first and third sections showed different wavefront behavior. In these sections, the highest lag was at the ends of the catheter, while the lowest lag was in the middle, suggesting a straight shift that started at the middle of the catheter and traveled through to the ends. The terminal end of the first section did not match that of the third section, with a much lower lag than expected. This behavior was likely caused by the same electrogram event as that which caused the error observed in the first section of the Sect2 analysis. The fact that the wavefront behavior switched back and forth between sections was interesting, and supports the “cyclical” action observed in the Unipolar electrograms.
Figures 4.47-4.49. Sect0, Sect2, and Sect4 Average Lag Maps for Position J

Figures 4.47, 4.48, and 4.49 show the mean lag results for the Sect0, Sect2, and Sect4 analyses of the Position J Unipolar Data, respectively. On the Sect2 and Sect4 analyses, the standard deviation between sections for each electrode is plotted on its respective electrode. Other than the results themselves, there are no other differences in the plots from earlier lag maps.

Despite the disagreement between sections in the position J analysis, the averaged lag maps in Figures 4.47, 4.48, and 4.49 agreed with one another very well. Similar to the position A analysis, the Sect0 and Sect2 mean lag maps matched almost exactly, while there were differences in two electrodes in the Sect4 mean lag map. Compared to both the Initial and Flutter data sets, the multi-section analyses of the Unipolar data had superior agreement.
between sections. This improved agreement indicates that the Unipolar electrograms were more organized than the noisy Initial electrograms. It also suggests that the analysis method is better able to calculate time lag in a signal that has at least low frequency change over time, compared to a completely organized signal like that analyzed in the Flutter data set.
5. CONCLUSION

The purpose of this project was to develop and evaluate a signal processing and data analysis procedure for a novel real-time active mapping methodology in atrial ablation procedures. After collection of data from two persistent AF patients and one atrial flutter patient, separate but analogous analysis and visualization programs were used in Matlab to analyze the collected electrograms. In the analysis programs, the time lag between AF impulses of different electrograms was calculated. These analysis results were used in the visualization programs to create 3D color maps that showed the time lag between each electrode and an established reference electrode. The maps, along with comparison plots of the separate electrograms, were studied to evaluate the program’s ability to find moving wavefronts or electrical rotors within the data, as well as evaluate characteristics of the AF signal. The conclusions drawn from these studies are discussed below.

The most noticeable results from the Initial data set analysis were related to signal quality. Many of the electrograms collected in the Initial data set either had low signal amplitude, high noise, or both. This lack of signal quality was reflected in the lack of cohesive wavefronts in the analysis results, and there were a couple of possible explanations for it. The initial conclusion, supported by cardiologist observations, was that the spiral catheter was difficult to press against the atrial wall to collect the data. The tenuous contact with the atrial wall would have resulted in low amplitude signals, as well as high noise in the collected electrograms. Another explanation for the low signal quality was the use of bipolar electrode pairs to collect the data, rather than unipolar electrodes. Bipolar electrodes collect data by subtracting the signal
collected in one electrode from that collected in the other electrode, which should remove most, if not all, of the background noise and external artifact. After observing the low signal quality in the Initial data set, it was believed that the bipolar electrode pairs could have been removing a large amount of the target AF signals and causing the low amplitude signals. The irregularity of the electrograms, as well as the disagreement between sections in the Sect2 and Sect4 analyses, supported the conclusion that the AF electrograms had an unstable frequency. This deduction was not certain since it was also possible that the disagreement was another result of the high noise in the Initial data set.

With the low quality signals and results obtained in the Initial data set, data collected from a patient with atrial flutter was analyzed using the same methods to test the analysis on a controlled data set. The electrograms from this data set had much less noise than those obtained in the Initial data set, and the analysis had no problem determining an accurate time lag between them. It was concluded that the analysis program was working as intended, so the inaccuracies observed in the earlier analyses must have been due to the lower signal quality in the Initial data set. The high regularity of electrograms in the Flutter data proved how unstable the AF electrograms in the Initial data were. Although a fairly accurate lag map was found when analyzing the data as a single section, significant disagreement between sections in the Sect2 and Sect4 analyses revealed that the Flutter data set was perhaps too regular, confusing the analysis program as to whether each electrode was lagging behind or leading the reference electrode. This situation lead to the belief that this lag analysis method may not be optimal for very stable conditions like atrial flutter. It could work better in an idealized atrial fibrillation system that has low noise like the Flutter data set and a small amount more variation in frequency that the program could use as an anchor to compare electrograms. The differences in frequency stability between the Initial and Flutter data sets revealed the effects of the wavelets.
that only occur in atrial fibrillation. Since the wavelet effects cannot be easily predicted, it was decided that a nonlocal reference could not be used for this atrial fibrillation study.

The Unipolar analysis was performed to explore whether unipolar electrodes collect higher quality electrograms than bipolar electrode pairs, and theory was supported by the lower noise and higher amplitude of the Unipolar electrograms when compared to those of the Initial electrograms. Coherent wavefronts found using the analysis methods also indicated that the analysis methods were working correctly for the Unipolar data set. It is believed that the “revolving” wavefront activity observed in the lag maps revealed their possible use to tell the direction in which the rotor was located. The similarities between the SectS and the Sect0 analyses indicated that the unipolar electrograms could have been more stable than initially believed. Compared to both the Initial and Flutter data sets, the multi-section analyses of the Unipolar data had superior agreement between sections. This improved agreement indicates that the Unipolar electrograms were more organized than the noisy Initial electrograms. It also suggests that the analysis method is better able to calculate time lag in a signal that has at least a small amount of frequency change over time, compared to a completely organized signal like that analyzed in the Flutter data set.

A key conclusion was that unipolar electrodes obtain higher quality AF electrograms than bipolar electrodes. Similar studies in the future may think to use bipolar electrodes to collect their data, since bipolar electrograms and instrumentation amplifiers are often used to collect biological data, but with the knowledge obtained in this study they would know that unipolar electrodes work better for small data collection areas. The wavelet effects that prevented nonlocal reference electrodes from being used could indicate that local references may be better than nonlocal references in future AF studies that use electrogram comparison. The most
important conclusion drawn from this project is that the proposed method seems to be able to model the wavefront activity in 3D space for a given set of electrograms, as seen in both the Flutter and Unipolar data sets. The analysis procedure has potential to be used in a real-time active mapping procedure, and should be studied further to continue development.

This project laid a foundation for the signal analysis methods to be used in an eventual real-time active mapping procedure for atrial fibrillation. A reasonable next step would be to perform another study with more data sets and armed with the knowledge gained from the first study. After this study, the main question that needs to be asked is whether the analysis method can find rotor locations, and what they would look like on the lag result maps. The aim of a second study would be to find examples of the lag map at actual rotor locations. After establishing credibility for the signal analysis procedure, the next step would be to streamline the data collection and analysis so that one could collect data for the program and perform the analysis at the same time. The data collection could then be guided by the lag map results to locate rotors in the patient in semi-real time. This methodology could be further confirmed under controlled conditions by testing it on an animal model of AF. Through several studies, this analysis approach could eventually be developed into a real-time active mapping procedure for atrial fibrillation ablation.


