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Time Evolution of ECoG Network Connectivity in Patients with Refractory Epilepsy

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Time Evolution of ECoG Network Connectivity in Patients with Refractory Epilepsy

Michael Joseph Selesko

A Thesis Submitted to the Graduate Faculty of
GRAND VALLEY STATE UNIVERSITY

In
Partial Fulfillment of the Requirements
For the Degree of

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Mike Selesko
Abstract

Epilepsy is a common neurological disorder that causes recurrent, unprovoked seizures. Focal, refractory epilepsy is characterized by seizures that start in a specific area in the brain and do not respond to antiepileptic medication. This study was conducted to characterize the connectivity of the focal brain region where seizures originate, known as the epileptogenic zone. Connectivity was measured from electrocorticogram (ECoG) recordings, during seizure events, using information theoretic measures mutual information (MI) and (TE). MI is the amount of information shared between two discrete random variables. TE is the directed information transfer between two discrete random variables. MI provides information about the strength of the connection and TE indicates the direction of information transfer. The analysis is performed in high frequencies, >30 Hz, in order to examine this spectral range of EEG activity, including events called high frequency oscillations (HFOs). The results show three trends in the connectivity of the epileptogenic zone. The first is that there is a reduction in the connectivity of the zone with the rest of the brain just after seizure onset. The second shows the connectivity increases just prior to the termination of the seizure. Finally, the third trend indicates that the direction of the information transfer during the seizure is from outside of the epileptogenic zone to inside. The epileptogenic zone is characterized by a disconnection at seizure onset, followed by a reconnection just prior to the seizure termination. The results show that the epileptogenic zone exhibits unique properties with respect to connectivity when compared to electrode sites from outside of the zone. These unique behaviors can help in accurately identifying the epileptogenic zone, thus leading to its successful removal.
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Abbreviations

**MI:** Mutual Information

**TE:** Transfer Entropy

**ECoG:** Electrocorticogram

**EZ:** Epileptogenic Zone

**COI:** Channels of Interest
Chapter 1

Introduction

1.1 Introduction

Epilepsy is a common neurological disorder that is characterized by recurrent, unprovoked seizures. Epilepsy can be classified as either generalized or focal epilepsy. In focal epilepsy, the seizure originates in a particular region of the brain, known as the epileptogenic zone, and then has the ability to spread to other regions [1], [2]. Epilepsy is initially treated with antiepileptic drugs (AED). When seizures persist despite the treatment with AED it is then classified as refractory epilepsy [3]. At this point, surgical removal of the epileptogenic zone is the gold standard for treatment. The focus of this study is on focal, refractory epilepsy.

The epileptogenic zone is the smallest region of the cortex that must be removed in order to eliminate the generation of seizures [2]. There is currently no consistent way to identify the boundaries of the epileptogenic zone and therefore the identification of other epileptic zones involved in seizures is determined via EEG recordings and brain imaging techniques [4]. The fact that the epileptogenic zone can only indirectly be identified means that the results of resective surgery vary from patient to patient. Success rates of resective surgery, meaning seizure freedom, range from 34% to 76% [5]. Network connectivity analysis can further aid in accurate identification of the epileptogenic zone.

Network connectivity is an area of study that looks at the relationships between
signals, such as the EEG recorded from patients with epilepsy. The network connectivity of EEG signals recorded from the epileptogenic zone have shown unique features compared to signals outside of this zone [6]–[15]. Mutual information (MI) and transfer entropy (TE) are information theoretic measure of network connectivity. MI is a measure of the strength of the correlation between two signals and TE is a similar measure that also provides information about the direction of the information flow. The present study was conducted in order to analyze how network connectivity changes, using MI and TE, with respect to the area identified by epileptologists as the seizure onset zone. The analysis was performed on electrocorticogram (ECoG) data provided by Spectrum Health’s Epilepsy Monitoring Unit in Grand Rapids, MI.

1.2 Purpose

The aim of this study is to characterize how network connectivity changes from seizure onset to seizure termination, specifically in channels of interest determined by the epileptologists at Spectrum Health’s Epilepsy Monitoring Unit. The channels are electrodes that record the electrical activity of neural assemblies in the brain. Channels of interest are identified as recordings from electrodes inside of the epileptogenic zone. The goal is to provide a tool for the epileptologists to aid in the accurate localization of the epileptogenic zone based on a network connectivity analysis. Ultimately, more knowledge of the epileptogenic zone will allow for more success in resective surgery for patients with focal, refractory epilepsy.

1.3 Scope

The aim of this study is to analyze how information transfer changes from seizure onset to termination. Mutual information (MI) is used to determined the amount of information shared between ECoG signals from two channels. The MI will be measured between all pairs of channels from three time points of interest: (1) 20 seconds prior to onset, (2) 10 seconds after onset, and (3) 10 seconds prior to termination. The MI after onset
and just before termination are compared to the MI just prior to onset to assess how MI changes throughout the seizure event, particularly in channels of interest (COI) identified by the epileptologists at the Epilepsy Monitoring Unit. The COI are located within the epileptogenic zone, which is the region of the brain that needs to be resected in order to produce seizure freedom. The next portion of the study examines how the direction of information transfer changes in channels of interest, from onset to termination, using the information theoretic measure transfer entropy (TE). TE is measured for multiple combinations of two types of paired channels: (1) one channel within and one channel outside of the epileptogenic zone, and (2) two channels outside of the epileptogenic zone. High frequency oscillations are considered biomarkers for locating the epileptogenic zone\[16\]. Therefore, high frequencies are of interest and the present study focuses on the following three frequency bands: (1) 125-250 Hz, (2) 62.5-125 Hz, and (3) 31.25-62.5 Hz. The analysis was done on 8 seizures over 3 different patients. The sampling frequency for each patient was at least 500 Hz in order to obtain the frequency bands of interest. For each patient, the seizure focus was determined to be located in the temporal lobe by epileptologists.

1.4 Assumptions

For this study, it is assumed that each seizure is its own independent event, not influenced by other seizure events. The independence assumption is important because it allows for the comparison among different patients. It is also assumed that the area determined by the epileptologists to be the seizure focus is in the epileptogenic zone. This area is known from the patient notes taken by the epileptologists during the presurgical process. The times identified by the epileptologists as the onset and termination times are taken to be the correct times for the purpose of identifying the points of interest.
1.5 Hypothesis

Previous studies have shown that the ECoG signals from channels within the epileptogenic zone become less connected as onset occur and as the seizure progresses toward termination, the connectivity of these channels increases with channels outside of the seizure onset zone [6–15]. This means at onset, the signals from within this zone show a decrease in coupling as the seizure begins, followed by an increase in coupling. This coupling is typically assessed using a coherence measure. Therefore, it is hypothesized that the MI of channels in the epileptogenic zone will show a unique pattern, decreasing after onset and increasing prior to termination. With respect to direction of the information flow, it is hypothesized that signals from within the epileptogenic zone will show a unique pattern throughout the seizure because it is clear that these signals behave differently than signals recorded outside of the epileptogenic zone.

1.6 Significance

The ultimate goal is to provide Spectrum Health with information to aid in identifying the area of the brain to resect in patients with epilepsy that does not respond to medication. The analysis of MI and TE within the epileptogenic zone should provide another tool for localizing the seizure focus. The unique patterns of connectivity within the focus should provide a better understanding for how seizures begin and terminate. A better understanding of how different areas of the brain communicate in epilepsy may provide valuable information for treatment and diagnosis. The mechanisms for how seizures start, propagate, and terminate are not well understood and the hope is that this research further progresses the knowledge of the nature of epilepsy.

1.7 Definitions

Mutual Information: The amount of information shared between two discrete random variables.
**Transfer Entropy**: The amount of directed information transfer between two discrete random variables.

**Epileptogenic Zone**: The area of cortical tissue that needs to be resected in order to produce complete seizure freedom.

**Channels of Interest**: Channels identified by epileptologists as being in the epileptogenic zone.
Abstract

Epilepsy is a common neurological disorder that causes recurrent, unprovoked seizures. Focal, refractory epilepsy is characterized by seizures that start in a specific area in the brain and do not respond to antiepileptic medication. This study was conducted to characterize the connectivity of the focal brain region where seizures originate, known as the epileptogenic zone. Connectivity was measured from electrocorticogram (ECoG) recordings, during seizure events, using information theoretic measures mutual information (MI) and (TE). MI is the amount of information shared between two discrete random variables. TE is the directed information transfer between two discrete random variables. MI provides information about the strength of the connection and TE indicates the direction of information transfer. The analysis is performed in high frequencies, >30 Hz, in order to examine this spectral range of EEG activity, including events called high frequency oscillations (HFOs). The results show three trends in the connectivity of the epileptogenic zone. The first is that there is a reduction in the connectivity of the zone with the rest of the brain just after seizure onset. The second shows the connectivity increases just prior to the termination of the seizure. Finally, the third trend indicates that the direction of the information transfer during the seizure is from outside of the epileptogenic zone to inside. The epileptogenic zone is characterized by a disconnection at seizure
onset, followed by a reconnection just prior to the seizure termination. The results show that the epileptogenic zone exhibits unique properties with respect to connectivity when compared to electrode sites from outside of the zone. These unique behaviors can help in accurately identifying the epileptogenic zone, thus leading to its successful removal.

2.1 Introduction

Epilepsy is a neurological disorder that is characterized by recurrent, unprovoked seizures. A seizure occurs when there is a hypersynchronous discharge of neurons in the cortex resulting from excitation neural activity overcoming inhibition activity [1]. Seizures are classified based on where they start in the brain. The two main categories are generalized seizures and focal seizures. Focal seizures occur in a specific network of cells on one side of the brain, whereas generalized seizures do not have a particular area of origin [17]. Epilepsy that results in focal seizures that do not respond to antiepileptic medication is known as focal, refractory epilepsy. This type of epilepsy can be evaluated for a resective surgery that targets the removal of the epileptogenic zone.

The epileptogenic zone is the "minimum amount of cortical tissue that must be resected to produce seizure freedom" [2]. The epileptogenic zone contains the seizure onset zone and the potential seizure onset zone. The seizure onset zone can be located presurgically using imaging and electrical recording techniques. However, the potential seizure onset zone does not initiate seizures until the seizure onset zone is removed and it is therefore impossible to locate [2]. This makes the outcome of resective surgery variable. The success rate of surgery has been reported to be anywhere from 34% to 76% [5]. Figure 2.1 illustrates the area of the brain that would have to be resected in order to produce seizure freedom.
The nature of the potential onset zone makes surgical outcomes unpredictable. The initiation and termination of seizures is not well understood and therefore, the location of the epileptogenic zone is difficult to determine. It is impossible to know how individual neurons within the brain are communicating during seizures because of the large number of neurons and their microscopic scale. Therefore, the analysis of network connectivity can offer insights into how different areas of the brain are communicating before (preictal), during (ictal), and after (postictal) a seizure on a macroscopic level.

Network connectivity is the analysis of how signals recorded from the brain interact, or communicate. There are functional and effective measures of connectivity. Functional connectivity measures how different neuronal assemblies are correlated over time. This provides information about the strength of the interaction of two temporal signals recorded from the brain. Effective connectivity results in information about the direction of the interaction of two signals [18]. The fact that seizures arise from hypersynchronous neural activity does not mean that the brain, on a macroscopic level, becomes more connected. In fact, it was been shown that the overall network of the brain at seizure onset becomes less connected [6]–[15]. Connectivity analysis of neuronal signals can be used to identify unique characteristics of signals from within the epileptogenic zone. There are many techniques for evaluating the connectivity of temporal signals [18]. However, information theoretic techniques are advantageous with respect to biomedical signals, such as neural activity, because they capture both linear and non-linear characteristics of a signal [19]. These measures are also non-parametric, meaning that the data is not prescribed.
to a specific model.

The aim of this study is to analyze if and how the connectivity of signals recorded from the epileptogenic zone differs from connectivity in signals outside of the epileptogenic zone. This would allow the epileptogenic zone to be better localized for improved surgical outcomes. Information theoretic measures, mutual information (MI) and transfer entropy (TE), are used to assess the strength of correlation and the direction of information transfer. The present study focuses on higher frequencies, >30Hz, due to the emergent research on the role that high frequency oscillations (HFOs) play in epilepsy [16], [20], [21]. The ultimate goal is to provide a better understanding of how connectivity in signals within the epileptogenic zone differ from those outside in order to provide epileptologists with another tool to aid in identifying which area of the brain to remove during resective surgery on patients with focal, refractory epilepsy.

2.2 Methods

2.2.1 Human Subject Data

The deidentified ECoG data was provided to Grand Valley State University by Spectrum Health’s Epilepsy Monitoring Unit (EMU). The data was collected during the pre-surgical analysis of patients with refractory epilepsy in order to help identify the potential region of the brain to surgically remove in order to eliminate the occurrence of seizures. In this study eight seizures from three different patients were analyzed. The ECoG recordings of two of the patients had a sampling frequency of 500 Hz, while the recordings from the other patient was 1000 Hz. The seizure onset for all three of the patients was localized to the temporal lobe.

2.2.2 Mutual Information and Transfer Entropy

Mutual information (MI) and transfer entropy (TE) are measures of connectivity derived from Claude E. Shannon’s theory of information [22]. The theory is based on the idea of entropy, which is a measure of the degree of uncertainty of a discrete random variable
Entropy is defined as

\[ H(X) = - \sum_{i=1}^{n} p_i \log_2 p_i, \]  

(2.1)

where \( X \) is a discrete random variable and \( p_i \) is the probability mass function for \( X \). The conditional entropy between two discrete random variables, \( X \) and \( Y \), is used to derive both MI and TE. The conditional entropy of one discrete random variable, \( X \), given another discrete random variable, \( Y \). It is defined as

\[ H(X|Y) = - \sum_{x} \sum_{y} p(x,y) \log_2 p(x|y). \]  

(2.2)

The MI between the two discrete random variables can be obtained using Equations 2.1 and 2.2,

\[ I(X,Y) = H(X) - H(X|Y) \]  

(2.3)

\[ = \sum_{x} \sum_{y} p(x,y) \log_2 \frac{p(x,y)}{p(x)p(y)}. \]  

(2.4)

The MI measure can be thought of as a reduction in uncertainty. Looking at Equation 2.3, it can be observed that if the discrete random variable \( X \) has a high level of entropy, or uncertainty, but the conditional entropy of \( X \) given \( Y \) is low, then the MI will be high. This can be interpreted as: knowing \( Y \) makes \( X \) less uncertain. It would therefore be concluded that \( X \) and \( Y \) share a certain amount of information, which can be calculated by Equations 2.3 and 2.4. It should also be noted that MI is a symmetric measure, \( I(X,Y) = I(Y,X) \), because it is simply a measure of the amount of information shared between two signals [24]. This is not a directional relationship. This value needs to be normalized in order to be compared with other values of MI. Linfoot has proposed a calculation to normalize MI values between 0 and 1 [25]. The normalization of MI is defined as

\[ I_{NL}(X,Y) = \sqrt{1 - e^{-2I(X,Y)}}. \]  

(2.5)

The exponential and square root functions are used so that when \( X \) and \( Y \) are independent, the exponential portion becomes 1 and thus the MI becomes 0. When MI is high,
the exponential will approach 0 and the normalized MI will go to 1. The estimation of
the probability distributions is most efficient when an adaptive binning process is used
\cite{26}. Details on the adaptive binning process are described in Section 3.2.2.

TE is an information theoretic measure based on the Granger causality, which is used
to attain information about the directional flow of information \cite{27}. TE takes into account
the past values of both X and Y and it is defined as

\[
TE_{X \rightarrow Y} = H(y_i | y_{i-t}) - H(y_i | y_{i-t}, x_{i-\tau})
\]

(2.6)

\[
= \sum_{y_i, y_{i-t}, x_{i-\tau}} p(y_i, y_{i-t}, x_{i-\tau}) \log_2 \frac{y_i | y_{i-t}, x_{i-\tau}}{y_i | y_{i-t}}
\]

(2.7)

where \(i\) represents a point in time, \(\tau\) and \(t\) are the time lags in the signals X and Y,
respectively, and \(k\) and \(l\) are the number of past values in X and Y, respectively \cite{19}. For the analysis of biomedical signals, \(t = k = l = 1\) is optimal \cite{19}. The value of 1
for these parameters are optimal for biomedical signals because the time series length
is typically short and the auto-correlation tends to decrease monotonically \cite{19}. TE
can also be interpreted as a reduction in uncertainty in a similar way as MI was. The
probability distributions of the random variables are estimated based on the Darbellay-
Vajda adaptive partitioning algorithm \cite{19}. This algorithm partitions the sample space
so that the distribution in each bin is independent.

### 2.2.3 Wavelet Decomposition

The discrete wavelet transform is used to decompose a signal at different time and fre-
quency resolutions. There is a trade-off between time and frequency resolution with this
transform. At higher frequencies, the time resolution becomes better at the expense of
the frequency resolution and vice versa for lower frequencies \cite{28}. The coiflet 1 mother
wavelet was used to perform the decomposition, as it has been shown to be optical for
EEG signal processing \cite{29}. The wavelet coefficients are obtained through a cascade of
high pass and low pass filters. The frequency bands of the wavelet coefficients of a 3-level
wavelet decomposition with respect to a 500 Hz sampling frequency are shows in Table
2.1. The frequency bands of interest are 31.25-62.2 Hz, 62.5-125 Hz, and 125-250 Hz in order to fit the >30 Hz criterion. Further description of wavelets used in this study can be found in Section 3.2.1.

Table 2.1: 3-level wavelet decomposition

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>Frequency Band</th>
</tr>
</thead>
<tbody>
<tr>
<td>d1</td>
<td>125 - 250 Hz</td>
</tr>
<tr>
<td>d2</td>
<td>62.5 - 125 Hz</td>
</tr>
<tr>
<td>d3</td>
<td>31.25 - 62.2 Hz</td>
</tr>
<tr>
<td>a3</td>
<td>0 - 31.25 Hz</td>
</tr>
</tbody>
</table>

2.2.4 Data Analysis

The goal is to observe how the connectivity of recordings from inside of the epileptogenic zone are different from recordings outside of this zone. This implies that there are two categories of channels, those within the zone and those outside of it. The epileptologists have identified channels of interest (COI) as those from within the epileptogenic zone based on their observation of the ECoG recordings. These channels typically exhibit high amplitude signals. MI and TE are measurements of connectivity between two channels, or pairs. Therefore, there are three possible combinations of pairs given the two categories defined above. These pairs will be referred to as Pair 1, Pair 2, and Pair 3 throughout the analysis and are defined in Table 2.2.

Table 2.2: Definitions of the three categories of channel pairs

<table>
<thead>
<tr>
<th>Pair Name</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pair 1</td>
<td>One channel within the COI and one outside of the COI</td>
</tr>
<tr>
<td>Pair 2</td>
<td>Two channels within the COI</td>
</tr>
<tr>
<td>Pair 3</td>
<td>Two channels outside of the COI</td>
</tr>
</tbody>
</table>

The analysis starts with the wavelet decomposition on the ECoG data to obtain the three frequency bands: 125-250 Hz, 62.5-125 Hz, and 31.25-62.5 Hz. The analysis
then spits into the MI analysis and the TE analysis. The block diagram in Figure 2.2 summarizes this process.

![Functional block diagram of the data analysis process.](image)

Figure 2.2: Functional block diagram of the data analysis process.

The analysis of the MI focuses on three time points of interest: (1) 20 seconds before seizure onset, (2) 10 seconds after onset, and (3) 10 seconds before seizure termination. The MI for each of these time points is labelled MI1, MI2, and MI3 respectively. MI was calculated over a five second window for each time of interest. The five second window was chosen in order to persevere stationarity. The objective with these three time points is to determine how MI changes just after onset and just prior to termination compared to the MI just before the seizure begins. In order to assess these changes, a percent change from MI1 was calculated for MI2 and MI3:

\[
\Delta MI_1 = \frac{MI_1 - MI_2}{MI_1}
\]  

(2.8)

and
\[
\Delta MI_2 = \frac{MI_1 - MI_3}{MI_1},
\]  

(2.9)

where \(\Delta MI_1\) is the percent change at onset and \(\Delta MI_2\) is the percent change at termination. A positive value for the percent change indicates that the MI has decreased from the first value and a negative result means that the MI has increased. This is done for each of the three sets of pairs defined previously (Table 2.2). A bootstrapping method was used to randomly select pairs for each of the three types. There are typically 4-7 channels that are in the epileptogenic zone for each patient and 60-70 located outside.

For each seizure, 10 random pairs of channels are selected for each of the three types of pairs. The MI is calculated for each randomly selected pair. The 95% confidence interval is then calculated for each pair based on a normal distribution. A confidence interval that does not include zero would then imply that the MI is different compared to the MI just before the seizure onset. This concludes the MI portion of the analysis, described by the left branch of the block diagram (Figure 2.2).

The TE portion of the analysis computes the TE in both directions and then takes the difference in order to obtain the direction of information flow. This is only done for Pair 1 and Pair 3 in order to analyze the directional connectivity from inside the epileptogenic zone to outside. Pair 2 is not of interest because the directional flow of information just within this zone is not likely to provide useful information for the purpose of this study. For Pair 1, \(\Delta TE\) is computed as \(\Delta TE = TE_{out} - TE_{in}\), where \(TE_{out}\) is the TE from the COI to a channel outside and \(TE_{in}\) is the TE from a channel outside to a channel within the COI. Therefore, a positive \(\Delta TE\) implies that the net flow of information is in the direction of in to out and a negative value implies the opposite. This is done for Pair 1 and Pair 3 in each of the eight seizures. The TE is computed during the seizure in four second time windows with 50% overlap. This was reduced from the 5 second window in order to create more observations for the runs test. A runs test is then done on the resulting \(\Delta TE\) values to determine whether there is a significant trend in the sign, positive or negative, during the seizure [30]. The results of the runs test provide a significance test for the pattern of the direction of the information flow. A p-value of
<0.05 indicates that the pattern of the sign of $\Delta TE$ is not random. This concludes the TE portion of the analysis.

2.3 Results

2.3.1 125 - 250 Hz Frequency Band

This portion of the analysis shows qualitative results for MI and TE for the representative subject, for one seizure. The representative subject is used to show general trends in the MI and TE throughout the seizure. The qualitative plots for MI and TE for the other subjects can be found in the Appendix. The global MI for all possible pairs of channels is depicted in Figure 2.3 for the three time points of interest: just prior to seizure onset (top), just after onset (middle), and just prior to termination (bottom). The COI are indicated on the in the red box around the labels. The COI show a general trend of a decrease in MI after onset and an increase just before termination.
The next step in the analysis was to look into how MI and TE change at three points in time related to seizure activity for each of the three categories of channel pairs. Figure

Figure 2.3: MI prior to onset (top), just after onset (middle) and just prior to termination (bottom) for the representative subject. Channels of interest are indicated on the y-axis.
2.4 shows MI (top) and TE (bottom) for each of the three pairs in the representative subject. With MI, Pairs 1 and 2, which both involve a COI, show a sudden decrease in the MI just after onset and a sharp increase in MI just before the seizure terminates. Pair 3 does not show either of these trends and overall, the MI between two channels outside of the COI appear to be unaffected by the seizure event. The change in TE also shows a unique trend with respect to Pair 1 when compared to Pair 3. With respect to Pair 1, the overall flow of information is in the direction of a channel outside of the COI to a channel within the COI. In Figure 2.4 this is observed as a negative value for $\Delta TE$. It is observed that during the seizure, Pair 1 shows all negative values and Pair 3 shows a more random pattern that alternates between positive and negative values. The next steps in the analysis were to determine the extent of these observed trends in the MI and TE.

![Figure 2.4: The MI and $\Delta TE$ for the representative subject. The MI between two channels is on top and the $\Delta$ TE is on the bottom for Pair 1 (left), Pair 2 (middle), and Pair 3 (right). The red line indicates the time of seizure onset and the green line marks seizure termination.](image)

The 95% confidence intervals for each of the three pairs are shown in Figure 2.5 for the percent change just after onset (left) and just before termination (right). These results come from the pooled MI across all seizures and patients using the bootstrapping method.
The percent change after onset shows that Pairs 1 and 2 are positive, meaning that there is a decrease in the MI, because the confidence intervals include all positive values. Pair 3 does not show a change in the MI. With respect to termination, there is a significant increase in MI just prior to termination, as it is the only pair where the confidence interval does not include zero. A negative percent change indicates an increase in MI. Overall, the analysis of the percent change in MI shows that pairs that include a COI show a significant change in MI at onset and termination, whereas pairs that do not include a channel in the COI do not show a significant change at either onset or termination.

![Figure 2.5: 95% confidence intervals for percent change in 125-250 Hz](image)

(a) Percent change after onset  
(b) Percent change prior to termination

The final part of the analysis was to investigate the trend in TE of net information flow into channels within the COI. Figures 2.6, 2.7, and 2.8 show a comparison of the $\Delta TE$ for Pair 1 and Pair 3 for an event in each of the three subjects that were analyzed. Figure 2.6 shows the results for Subject 1. Pair 1 clearly shows a pattern of information flow into the COI for the duration of the seizure while Pair 3 appears to show a random pattern during the seizure.
Subject 2 shows a similar trend for both Pairs as subject 1 (Figure 2.7). The only difference is that for Pair 1 in Subject 2 there are a few instances that show a positive $\Delta TE$ during the seizure.

Subject 3 shows a unique pattern in Pair 1 for $\Delta TE$ during the seizure when compared to Subjects 1 and 2. The direction of information flow is into the COI for the first two thirds of the seizure, and then reverses for the final part of the seizure before termination. Again, for Pair 3 there appears to be no real pattern.
The patterns of $\Delta TE$ observed during the seizure for Pairs 1 and 3 were quantitatively assessed by the runs test. A significant p-value ($< 0.05$) indicates that the pattern is not random, and there is an underlying trend. Table 2.3 shows the p-values from the runs test on each of the eight seizures analyzed for Pairs 1 and 3. An undefined p-value means that every value for $\Delta TE$ was negative, as is seen in Figure 2.6a.

Table 2.3: P-values of runs test for TE in 125-250 Hz. A "*" indicates a significant p-value. A "**" indicates that all TE measurements taken are in the same direction.

<table>
<thead>
<tr>
<th>Event</th>
<th>Pair 1</th>
<th>Pair 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event 1</td>
<td>Und.**</td>
<td>0.828</td>
</tr>
<tr>
<td>Event 2</td>
<td>Und.**</td>
<td>0.205</td>
</tr>
<tr>
<td>Event 3</td>
<td>Und.**</td>
<td>0.996</td>
</tr>
<tr>
<td>Event 4</td>
<td>0.0764</td>
<td>0.120</td>
</tr>
<tr>
<td>Event 5</td>
<td>Und.**</td>
<td>0.099</td>
</tr>
<tr>
<td>Event 6</td>
<td>Und.**</td>
<td>0.114</td>
</tr>
<tr>
<td>Event 7</td>
<td>1.26E-7*</td>
<td>0.542</td>
</tr>
<tr>
<td>Event 8</td>
<td>0.133</td>
<td>0.704</td>
</tr>
</tbody>
</table>

The results of the runs test show that, with respect to Pair 1, the sign of $\Delta TE$ was not a random pattern. With respect to Pair 3, all events show no trend for the sign of $\Delta TE$ during the seizure. Five events (1-3 and 5-6) show that all values of $\Delta TE$ were
negative during the seizure for Pair 1.

2.3.2 62.5 - 125 Hz Frequency Band

The MI matrices for the three time points of interest show a similar pattern in the 62.5-125 Hz frequency band as it did in the 125-250 Hz band for the representative subject (Figure 2.9). The COI, specifically C3 and C4, show a low MI at onset and an increased MI just prior to termination.
Figure 2.9: MI prior to onset (top), just after onset (middle) and just prior to termination (bottom) for the representative subject. Channels of interest are indicated on the y-axis.
The MI and TE of the three types of pairs in time again show a similar trend to the higher frequency band (Figure 2.10). There is a clear dip in the MI in Pairs 1 and 2 at onset, followed by an increase just prior to termination. The MI for Pair 3 does not show a change with the transition to the seizure. The ΔTE in Pair 1 is all negative during the seizure, whereas it appears random during the seizure for Pair 3.

![Figure 2.10: The MI and ΔTE for the representative subject. The MI between two channels is on top and the ΔTE is on the bottom for Pair 1 (left), Pair 2 (middle), and Pair 3 (right). The red line indicates the time of seizure onset and the green line marks seizure termination.](image)

The 95% confidence interval analysis of the percent change in this frequency band shows one significant difference from the 125-250 Hz band. This frequency band, the confidence interval for Pair 2 at onset includes zero. Therefore, it cannot be concluded that the MI for Pair 2 does not have a significant decrease after onset. The only conclusions that can be drawn are that MI for the Pair 1 category significantly decreases as seizure onset occurs and that Pair 2 shows a significant increase in MI just prior to seizure termination.
Figures 2.12, 2.13, and 2.14 show that the net flow of information during the seizure is into the COI for Pair 1 and random for Pair 3 across all subjects, as it was with the 125-250 Hz. Again, Subject 3 shows a unique pattern with the flow switching from inward to outward prior to termination.
The results of the runs test show that, for Pair 1, the pattern for $\Delta TE$ during the seizure is not random for six of the eight seizures, with four of these seizures having all negative values of $\Delta TE$ during the seizure. For Pair 3, the $\Delta TE$ does not show a significant pattern for any of the seizures across three patients (Table 2.4).
Table 2.4: P-values of runs test for TE in 62.5-125 Hz. A "*" indicates a significant p-value. A "**" indicates that all TE measurements taken are in the same direction.

<table>
<thead>
<tr>
<th>Event</th>
<th>Pair 1</th>
<th>Pair 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event 1</td>
<td>0.158</td>
<td>0.161</td>
</tr>
<tr>
<td>Event 2</td>
<td>Und.**</td>
<td>0.066</td>
</tr>
<tr>
<td>Event 3</td>
<td>Und.**</td>
<td>0.447</td>
</tr>
<tr>
<td>Event 4</td>
<td>Und.**</td>
<td>0.067</td>
</tr>
<tr>
<td>Event 5</td>
<td>0.002*</td>
<td>0.989</td>
</tr>
<tr>
<td>Event 6</td>
<td>Und.**</td>
<td>0.496</td>
</tr>
<tr>
<td>Event 7</td>
<td>0.0002*</td>
<td>0.932</td>
</tr>
<tr>
<td>Event 8</td>
<td>0.846</td>
<td>0.130</td>
</tr>
</tbody>
</table>

2.3.3 31.25 - 62.5 Hz Frequency Band

The final frequency band of interest is 31.25-62.5 Hz and it shows similar trends to the previous two bands that were analyzed. The MI matrices for the representative subject again show that the MI decreases in the COI at onset, followed by an increase prior to termination (Figure A.39).
Figure 2.15: MI prior to onset (top), just after onset (middle) and just prior to termination (bottom) for the representative subject. Channels of interest are indicated on the y-axis.
The MI and TE in time show the same trends as the previous two higher frequency bands for the representative subject. The MI decreases at onset when a COI is involved (Pairs 1 and 2) and does not show any trends when both of the channels are outside of the COI (Pair 3). The $\Delta TE$ again shows a net inward flow of information from channels outside of the COI to a channel in the COI and a more random pattern when observing two channels outside of the COI (Figure 2.16).

Figure 2.16: The MI and $\Delta TE$ for the representative subject. The MI between two channels is on top and the $\Delta TE$ is on the bottom for Pair 1 (left), Pair 2 (middle), and Pair 3 (right). The red line indicates the time of seizure onset and the green line marks seizure termination.

The analysis of the confidence intervals show the same trend as the 125-250 Hz band. At onset, there is a decrease in the MI in channels that are in the COI, which includes both Pair 1 and 2. This is shown by the fact that the confidence intervals for these two pairs only include positive values for the percent change (Figure 2.17a). With respect to the termination, Pair 2 is the only channel pair that shows a significant change in MI. This confidence interval only contains negative values, indicating that the MI increases just prior to termination for Pair 2 (Figure 2.17b).
The $\Delta TE$ shows the same trends as the previous two frequency bands. Across all three patients, the $\Delta TE$ shows that there is a net in flow of information to the COI (Pair 1) during the seizure, while there is a random pattern during the same time period for Pair 3 (Figures 2.18, 2.19, and 2.20). Subject 3 once again has the flip from inward to outward right before termination for Pair 3.

Figure 2.17: 95% confidence intervals for percent change in 31.25-62.5 Hz

(a) Percent change after onset

(b) Percent change prior to termination

Figure 2.18: Change in TE for Subject 1, Event 1 in 31.25-62.5 Hz

(a) $\Delta TE$ for Pair 1

(b) $\Delta TE$ for Pair 3
The runs test shows that for seven of the eight seizures the pattern of the $\Delta TE$ is not random and that in six of those seven the $\Delta TE$ is always negative during the seizure for Pair 1. Again, there was not a significant pattern observed for the $\Delta TE$ during any of the seizures for Pair 3 (Table 2.5).
Table 2.5: P-values of runs test for TE in 31.25-62.5 Hz. A "*" indicates a significant p-value. A "**" indicates that all TE measurements taken are in the same direction.

<table>
<thead>
<tr>
<th>Event</th>
<th>Pair 1</th>
<th>Pair 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event 1</td>
<td>Und.**</td>
<td>0.067</td>
</tr>
<tr>
<td>Event 2</td>
<td>Und.**</td>
<td>0.413</td>
</tr>
<tr>
<td>Event 3</td>
<td>Und.**</td>
<td>0.379</td>
</tr>
<tr>
<td>Event 4</td>
<td>Und.**</td>
<td>0.363</td>
</tr>
<tr>
<td>Event 5</td>
<td>0.057</td>
<td>0.137</td>
</tr>
<tr>
<td>Event 6</td>
<td>Und.**</td>
<td>0.624</td>
</tr>
<tr>
<td>Event 7</td>
<td>0.006*</td>
<td>0.930</td>
</tr>
<tr>
<td>Event 8</td>
<td>Und.**</td>
<td>0.988</td>
</tr>
</tbody>
</table>

2.4 Discussion

The aim of this study was to characterize the connectivity of channels of interest that were identified by epileptologists during their process of locating the region of the brain to surgically remove from patients with refractory epilepsy. The preliminary research and results indicated that there was a trend of a decrease in connectivity in the epileptogenic zone immediately following onset and an increase in connectivity just prior to termination. The focus of the study was on higher frequencies, >30 Hz, because of the growing evidence of the role of HFOs in the epileptic brain [16]. The results of the study found three main trends with respect to the connectivity of the epileptogenic zone. The first is that recordings from inside of the epileptogenic zone show a decrease in connectivity just after onset with both recordings from outside of this zone as well as from within the zone. The second is that recordings from inside of the epileptogenic zone show an increase in connectivity within the zone just prior to the termination of the seizure. The final observed trend is that the direction of information flow is from outside of the epileptogenic zone to inside during the seizure at these high frequencies.

The first trend is that recordings from inside of the epileptogenic zone showed a
decrease in connectivity during the transition from the preictal to ictal state. This is seen in the fact that the confidence intervals for Pairs 1 and 2 show a positive percent change in all frequency regions with the exception of Pair 2 in the 62.5-125 Hz range. It has previously been shown that the regions of the brain that are responsible for seizure initiation show a decrease in coupling with the other areas of the brain [31], [32]. A network analysis has also shown that the connectivity decreases as seizure onset occurs [6]. The results of this study show that the MI, a measure of functional connectivity, decreases in the epileptogenic zone as the seizure begins. The region of the brain where the seizure begins can be characterized by a disconnection with other regions in the brain in frequencies >30 Hz. The decreased connectivity and decoupling could indicate that the activity in that region may become chaotic during a seizure and lose its normal relationship with the rest of the activity of the brain.

The second trend shows that the functional connectivity of recordings from within the epileptogenic zone is increased from what it was during the preictal stage in the three frequency ranges analyzed. Although the MI for the Pair 1 category does not show an increase from the preictal stage, it does return to its original level, considering the fact that just after onset it showed a decrease in the MI. The pattern with functional connectivity progresses from a decrease in connectivity at onset to an increase in connectivity just before termination in high frequencies. Another study found a similar trend with respect to MI [33]. Stamoulis et al. found the same pattern in high frequencies that was observed in this study. The researchers also found the opposite pattern in lower frequencies, with MI being high at the beginning of the seizure and low just before termination. They suggest that high frequency interference may be a mechanism for seizure termination. High frequency activity may be responsible for cancelling out the synchronization that occurs at low frequencies at the onset of a seizure. A mechanism for this may be explained by the third observed trend.

The third trend found that direction of information flow is into the epileptogenic zone. In the results for Pair 1, the $\Delta TE$ generally showed a non-random pattern, with the values mainly being negative. However, for pairs of channels outside of the COI, there was never
a significant pattern with respect to the direction of the change in TE. This indicates that recordings from within the epileptogenic zone show a unique pattern across three patients and eight seizures that point to the idea that, at high frequencies, information flows from areas outside of the epileptogenic zone to within it. This net inward direction of the connectivity may be responsible for the high frequency interference proposed by Stamoulis et al. [33]. As the epileptogenic zone loses its connectivity with the rest of the brain at onset, the inward flow of information from these outer areas may be responsible for establishing its reconnection, resulting in the termination of the seizure. The unique pattern of this inward directed connectivity in the epileptogenic zone may also aid in the localization of the region where the seizure starts due to the fact that areas outside of the zone do not appear to show any type of pattern with $\Delta TE$.

The results of this study show that the channels identified by the epileptologists as being channels of interest in seizure initiation exhibit unique connectivity properties compared to other ECoG recordings from the brain. The connectivity of this region drops at seizure onset, followed by an increase in connectivity just before termination. These recordings also show that, at high frequencies, the flow of information is into the epileptogenic zone. This knowledge can potentially be used by epileptologists to help them identify the region of the brain that needs to be removed in order for the result to be seizure freedom. In addition to providing a tool for seizure localization, these findings can help shed light on how seizures occur and terminate, specifically the role that high frequency activity plays.

The present study only investigated the connectivity in high frequencies, $>30$ Hz. In the future, a comparison of these results with activity in lower frequencies may be important to understanding the significance of high frequency activity in seizures. Connectivity has been explored in lower frequencies, but the directional flow of information is not well understood [6–8]. The unique pattern of the $\Delta TE$ in the epileptogenic zone could be unique to high frequencies and provide evidence for its role in the idea of high frequency interference. Further work could support this by investigating the directional flow at lower frequencies. Another limitation of this work is that data was only analyzed from
three patients and eight seizures. The analysis was also only performed on recordings from patients with temporal lobe epilepsy. In the future, this should be expanded to include a larger and more diverse data set in order to confirm that these trends are applicable to other types of epilepsy. Finally, this study focuses in on the three categories of channels pairs and the comparisons between them. A more global approach that focuses on the connectivity of all combinations of channels at once may offer insights into how the connectivity is changing on a more macroscopic level during seizure events.

2.5 Conclusion

The results of this study found three main trends with respect to the network connectivity during a seizure in high frequencies, >30 Hz. The first trend was that the area of the brain involved in seizure initiation experiences a decrease in the level of connectivity with the rest of the brain. The second was that this same area of the brain shows that the connectivity increases just prior to seizure termination. Finally, the third trend shows that direction of information flow is from outside of the epileptogenic zone to inside during the seizure. The results show that seizures may generate in a particular area of the brain due to a disconnection from the rest of the brain. The seizure then only terminates as this area of the brain once again becomes connected to the outer areas. High frequency interference may be responsible for this reconnection. The inward flow of information at high frequencies may be a mechanism by which the epileptogenic zone is reconnected and the seizure is terminated. The goal was to characterize the connectivity of the epileptogenic zone. These three trends show that this zone does in fact exhibit unique connectivity properties during the seizure. The unique behavior of ECoG recordings from within the epileptogenic zone may provide information to epileptologists that can aid in the localization of seizure onset. This could potentially result in more successful surgical outcomes for patients with focal, refractory epilepsy.
Chapter 3

Extended Review of Literature and Extended Methodology

3.1 Extended Review of Literature

3.1.1 Epilepsy

3.1.1.1 Overview of Epilepsy

Epilepsy is a neurological disorder that is characterized by recurrent, unprovoked seizures. Unprovoked seizures do not have a known cause, such as alcohol withdrawal or a traumatic brain injury. A seizure is defined by a "hypersynchronous, excessive discharge of cortical neurons" \(^\text{[1]}\). In normal brain activity, there is a balance between excitation and inhibition. A seizure occurs when there is an imbalance between excitation and inhibition, with excitation becoming dominant. This can occur when excitation increases, inhibition decreases, or a combination of both \(^\text{[1]}\).

The International League Against Epilepsy (ILAE) classifies seizures based on three features: where the seizure begins in the brain, level of awareness during a seizure, and other features of seizures. Where the seizure begins is typically the first feature analyzed when classifying a seizure. Focal seizures begin in a particular area or network of cells on one side of the brain. Generalized seizures occur in networks on both hemispheres of the
brain. There are also cases in which the onset of the seizure is unknown. This is labelled as an unknown onset. The next step is to assess the level of awareness during a seizure. The level of awareness is summarized in Table 3.1.

Table 3.1: Level of Awareness [17]

<table>
<thead>
<tr>
<th>Level of Awareness</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal aware</td>
<td>If awareness remains intact, even if the person is unable to talk or respond during a seizure, the seizure would be called a focal aware seizure.</td>
</tr>
<tr>
<td>Focal impaired awareness</td>
<td>If awareness is impaired or affected at any time during a seizure, even if a person has a vague idea of what happened, the seizure would be called focal impaired awareness.</td>
</tr>
<tr>
<td>Awareness unknown</td>
<td>Sometimes it’s not possible to know if a person is aware or not, for example if a person lives alone or has seizures only at night. In this situation, the awareness term may not be used or it would be described as awareness unknown.</td>
</tr>
<tr>
<td>Generalized seizures</td>
<td>These are all presumed to affect a person’s awareness or consciousness in some way. Thus no special terms are needed to describe awareness in generalized seizures.</td>
</tr>
</tbody>
</table>

The other features of seizures are divided into motor and non-motor symptoms. The location of the seizure onset and propagation affect the symptoms in a focal seizure. Focal motor seizures can lead to twitching and jerking movements while focal non-motor seizures can result in changes in sensory perception, emotions, and thinking. Generalized motor seizures are are known as tonic-clonic seizures in which there is stiffening and jerking movements. Generalized, non-motor seizures are typically absences seizures [17]. The complete ILAE classification of seizures is shown in Figure 3.1.
Drug resistant, or refractory, epilepsy is a specific diagnosis of epilepsy that means a patient has continued seizures after the administration of antiepileptic drugs (AED). The ILAE officially defines drug resistant epilepsy as "when a person has failed to become (and stay) seizure free with adequate trials of two seizure medications" [3].

3.1.1.2 Resective Surgery and the Epileptogenic Zone

Resective surgery is a treatment for patients that have focal refractory epilepsy. The surgery involves removing a portion of the cortex that is involved in the initiation of epileptic seizures. This area of the brain is known as the epileptogenic zone. The epileptogenic zone is defined as "the minimum amount of cortical tissue that must be resected to produce seizure freedom" [2]. The determination of the epileptogenic zone is determined presurgically using various techniques to measure activity in the brain such as the electroencephalogram (EEG), electrocorticogram (ECoG), magnetoeencephalography (MEG), and functional magnetic resonance imaging (fMRI). Using these measurements, epileptologists presurgically determine five cortical zones that provide information about the location of the epileptogenic zone. These five zones are summarized in Table 3.2.

The actual seizure-onset zone is not necessarily equivalent to the epileptogenic zone. There are cases in which removal of the actual seizure-onset zone does not lead to the
Table 3.2: Cortical zones determined presurgically

<table>
<thead>
<tr>
<th>Cortical Zone</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irritative zone</td>
<td>Area of cortex which generates interictal spikes</td>
</tr>
<tr>
<td>Seizure-onset zone</td>
<td>Area of cortex that initiates clinical seizures</td>
</tr>
<tr>
<td>Symptomatogenic zone</td>
<td>Area of cortex which, when activated, produces the initial ictal symptoms or signs</td>
</tr>
<tr>
<td>Epileptogenic legion</td>
<td>Macroscopic lesion which is causative of the epileptic seizures because the legion itself is epileptogenic (e.g. cortical dysplasia) or by secondary hyperexcitability of adjacent cortex</td>
</tr>
<tr>
<td>Functional deficit zone</td>
<td>Area of cortex that is not functioning normally in the interictal period</td>
</tr>
</tbody>
</table>

elimination of seizures. There is typically an area adjacent to the actual seizure-onset zone, known as the potential seizure-onset zone, that can initiate seizures after the actual seizure onset zone is resected. These two zones are illustrated in Figure 3.2. The potential seizure-onset zone does not initiate seizures, but has the potential too, and it is therefore impossible to locate.

![Figure 3.2: The epileptogenic zone](image)

The surgically resected area in Figure 3.2 would have to include both the actual and potential seizure-onset zones in order to satisfy the definition of the epileptogenic zone. The epileptogenic zone is a subset of the resected portion. The accurate determination of the zones involved in epileptic seizures is crucial to a successful surgical outcome, complete freedom from seizures. In practice, the current techniques have limitations in allowing epileptologists to accurately identify the true epileptogenic zone. Surface EEG is good for providing an overall view of the electrical activity in the brain during a seizure, but has
poor spatial resolution because it is recording from the surface of the scalp. Invasive EEG recordings, such as ECoG, have better spatial resolution, but every region of the brain cannot be monitored. Epileptologists need to determine where to place the electrodes. If they do not place electrodes over regions that may be involved in the epileptogenic zone, then there is no way of capturing the entire area that needs to be resected. This is why a combination of measurement techniques are used to determine the area to be removed. Due to this, there is a subjective nature to the determination of the area of brain that needs to be surgically removed [2].

3.1.2 Electroencephalogram

The electroencephalogram (EEG) is a measure of the summation of field potentials produced by pyramidal neurons at surface of the brain. Pyramidal neurons are located in the cerebral cortex, the outer most layer of the cerebrum and are oriented perpendicular to the scalp, with the dendrites adjacent to the scalp. Post-synaptic potentials at the dendrites of the pyramidal neurons produce a field potential around the cell. The post-synaptic potentials can either be excitatory (EPSP) or inhibitory (IPSP) and the summation of these field potentials are recorded by the EEG electrode on the surface of the scalp. Therefore, one electrode records field potentials from thousands of pyramidal neurons. Figure 3.3 shows a field potential produced by a pyramidal neuron and recorded by an electrode.

![Figure 3.3: Field potential of a single pyramidal neuron](34)
The EEG signal is often analyzed in terms of its frequency components because it is the result of potentials from millions of neurons under the recording electrode, and thus unpredictable and aperiodic. The EEG signal can be separated into frequency bands depending on the state of interest of the brain [34]. The frequency bands and their associated states are summarized in Table 3.3.

Table 3.3: Frequency bands of EEG signal

<table>
<thead>
<tr>
<th>Wave</th>
<th>Frequency Range</th>
<th>Associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delta</td>
<td>0.5-4 Hz</td>
<td>Deep Sleep, serious brain disorders, waking state [34]</td>
</tr>
<tr>
<td>Theta</td>
<td>4-8 Hz</td>
<td>Emotional stress, creative inspiration, and deep meditation [34]</td>
</tr>
<tr>
<td>Alpha</td>
<td>8-13 Hz</td>
<td>Typically in occipital lobe, when eyes are closed, state of relaxation [34]</td>
</tr>
<tr>
<td>Beta</td>
<td>13-30 Hz</td>
<td>When the mind is engaged in mental activities [34]</td>
</tr>
<tr>
<td>Gamma</td>
<td>&gt;30 Hz</td>
<td>Various cognitive and motor functions [34]</td>
</tr>
</tbody>
</table>

The EEG is a useful tool for analyzing the activity of the brain. However, there are limitations because the recording electrodes are on the surface of the scalp. The actual signal recorded from the electrodes thus must traverse the dura, skull, and skin. This results with issues in the integrity of the signal, specifically with spatial resolution and the impact of artifacts. In order to combat these obstacles, electrodes can be placed directly on an exposed portion of the cortex through an operative procedure that involves removing a portion of the skull to expose the cortex. The technique of recording signals from electrodes directly on the exposed cortex is known as electrocorticography (ECoG). This technique is frequently used by surgeons to determine the epileptogenic zone in patients with refractory epilepsy.

3.1.3 Network Connectivity

3.1.3.1 Overview of Network Connectivity

Network connectivity, when applied to signals measured from the brain, is an area of study that seeks to measure interactions between areas in the brain. Network connectivity can
be subdivided into three categories: structural, functional, and effective [18].

Structural connectivity is how individual neurons and groups of neurons are physically connected throughout the brain. This type of connectivity is hard to assess because synaptic connections are dynamic in that new connections are constantly formed and others are eliminated. These structural connections are difficult to visualize. For this reason, functional and effective connectivity are examined through different measures of activity in the brain, such as the EEG.

Functional connectivity is the measure of the "temporal correlation among the activity of different neural assemblies" [18]. This type of connectivity can be measured, using signal processing techniques, to determine the correlation between signals from different areas of the brain. The important thing to note with functional connectivity is that it is only a measure of the strength of a connection between two signals. There is no information about the direction of the communication. Functional connectivity can be further broken down into linear coupling and nonlinear coupling. Linear based techniques of functional connectivity are based on coherence, typically Magnitude Squared Coherence and Wavelet Coherence [18]. Nonlinear techniques are often used because processes within the brain have nonlinear characteristics. These techniques are based on phase synchronization. A third group of techniques, outside of linear and nonlinear, can also be used to assess connectivity. These techniques are based on information theory, which is sensitive to both linear and nonlinear models. Mutual information is an information based technique that is used to assess functional connectivity.

The third measure of network connectivity is effective connectivity, which is "the direct or indirect influence that one neural system exerts over another" [18]. This category differs from functional connectivity in two ways. An effective connectivity measure provides information about the direction of the coupling, unlike functional connectivity. The second difference is that effective connectivity measures indirect, as well as direct, coupling between two signals. There are two main categories that measures of effective connectivity fall under. One is a data-driven estimate which is a direct estimate of the connectivity based on signals recorded from different areas in the brain. The other cat-
egory is a model-based approach, which uses a combination of structural and functional connectivity. The model-based approach requires knowledge, or a hypothesis, about an existing neurobiological model based on the structural connectivity. The model is then tested using functional connectivity. The data-driven techniques use signals measured from the brain. Techniques include partial directed coherence, the directed transfer function, and transfer entropy. Transfer entropy is an information-based technique, so it does not require the assumption of a linear or nonlinear model [18].

3.1.3.2 Review of Network Connectivity in the Epileptic Brain

Seizures are typically thought of as events that are the result of hypersynchronous neural activity [35]. On the microscopic level, this is true. Groups of neurons must be firing synchronously in order to produce the high amplitudes seen in the EEG signal that are characteristic of a seizure. However, this should not be confused with the macroscopic level. Groups of neurons in different areas of the brain are not necessarily synchronous. Network analysis of the brain can provide important information about the how and why seizures start, spread, and terminate. This type of analysis can also aid in the identification of the seizure onset zone in cases of focal epilepsy.

The onset of a seizure is characterized by low-amplitude, high-frequency rhythms of the EEG signal, often in the epileptogenic zone [36]. These rhythms are known as ”beta buzz.” Recent research into network connectivity in epileptic brains has shown that a seizure may be characterized by decoupling between different brain regions at seizure onset [6]–[8]. In high frequencies, in the range of 80 to 200 Hz, decoupling is also seen among brain regions [37]. However, there is also research that shows brain areas become more connected at lower frequencies at onset [9].

As the seizure propagates, the recorded EEG signal transitions to higher-amplitude, slower rhythms. The coupling as the seizure propagates seems to depend on the measure of connectivity that is used. Linear measures of correlation show that the brain regions remain decoupled during the propagation of the seizure [7], [8]. Other measures, such as phase correlations and synchronization likelihood, show that brain regions begin to
become more coupled during the period of seizure propagation \cite{9, 10}.

Seizure termination is not as well studied as the seizure onset and propagation. The end of the seizure is characterized by large-amplitude, slower-frequencies EEG signals. The connectivity between brain regions increases as the seizure terminates, meaning that the EEG signals have a higher degree of coupling as the seizure terminates compared to the seizure onset \cite{7, 12}. The coupling in higher frequencies (80-200 Hz) is also shown to increase as the seizure terminates \cite{13}.

The identification of the seizure onset zone is important in order for resective surgery to be successful. Investigation of the connectivity in this region could provide valuable information in identifying the appropriate region of the brain to remove. Research shows that the seizure onset zone becomes isolated just prior to the seizure onset and its connectivity with other brain regions progressively strengthens as the seizure progresses \cite{14}. Another study shows that the seizure onset zone becomes isolated just after onset and is the most connected just prior to termination \cite{15}. The seizure onset goes from more isolated to more connected as the seizure progresses from onset to termination, however the timing of the isolation remains unclear.

Overall, connectivity analyses show that the neuronal network in the epileptic brain shift from a weakly connected network at onset to a more strongly connected network at termination. The seizure onset zone shows unique characteristics of connectivity. The onset zone progresses from an isolated area to a more connected area as the seizure progresses. Network connectivity analysis of the epileptic brain can provide insights into how a seizure initiates, propagates, and terminates. This information can help in identification of the seizure onset zone and provide a better understanding of how seizures initiate, propagate, and terminate in the brain.

3.1.4 Information Theory

Information theory is a field that was first described in Claude E. Shannon’s paper, "A Mathematical Theory of Communication," in 1948 \cite{22}. The concept of entropy is at the heart of Shannon’s Theory of Communication, known as Shannon entropy. This is a
completely different concept than the idea of entropy in thermodynamics. In information theory, entropy is the measure of information and can be thought of as a degree of uncertainty \cite{23}. In a communication system there is an information source, that sends the information, and receiver of the information. Entropy is a measure of the amount of information that is sent from the source to the receiver. At the source, there are a finite amount of messages that can be sent, each with their own probability. The amount of information sent by the source depends on the probability distribution of the messages. An analogy used by John R. Pierce about a coin toss illustrates the meaning of the measure of entropy \cite{23}.

A fair coin toss has an equal probability of landing on heads or tails, which is 50%. In this case, the message is the result of the coin toss, heads or tails. The formula to calculate entropy based on a probability distribution is defined in Equation \ref{3.1}.

\[
H = \sum_{i=1}^{n} p_i \log_2 p_i \tag{3.1}
\]

When the coin toss is fair, the entropy works out to be 1 bit. The unit of entropy is bits, which is a reference to the number of bits that it would take to transmit the information. It is important to note that entropy does not need to take on an integer value through, meaning that the unit of bits is a theoretical measure. If the probability of heads is say 100%, then the entropy comes out to be zero bits. The entropy for varying probabilities of a coin toss resulting in heads is shown in Figure \ref{3.4}.
The plot of the entropy shows that the highest amount of information is transferred when the coin toss has an equal probability of landing on heads or tails. This makes sense intuitively because the most amount of uncertainty exists when there is an equal probability. If, say, there was a 99% chance of the coin landing heads, there is not much uncertainty about the outcome of the coin toss. In a communication sense, the receiver does not gain a lot of information from the message of such a coin toss, because the receiver knows that the message will likely contain the heads value.

The concept of entropy is the basis for the field of information theory and understanding it allows for a better understanding of more complicated measures, such as mutual information and transfer entropy, which are based on entropy and joint entropy. These information theoretic ideas provide quantitative measures for how much information two signal sources share and in what direction they are sharing the information.

3.1.5 High Frequency Oscillations

High frequency activity in the EEG signal has recently been identified as a potential biomarker for epileptic tissue. This frequency component of the EEG signal is known as High Frequency Oscillations (HFOs) and consists of frequencies greater than 80 Hz.
HFOs can be further divided into two subgroups, ripples (80-250 Hz) and fast ripples (250-600 Hz). Neurons in the epileptic tissue respond to subthreshold stimuli and result in an action potential firing that spreads to interconnected neurons. This activity synchronizes, resulting in the presence of HFOs in the recorded EEG signal [16].

Ripples and fast ripples are associated with normal physiological activity in the brain and abnormal activity in the epileptic brain [16]. These HFOs are shown to occur at an increased rate within the seizure onset zone [20]. A differentiation can also be made between ripples and fast ripples when assessing the epileptogenic zone. Areas of the brain that contain more ripples than fast ripples have been shown to be more successful targets of surgery [21]. HFOs are being used to determine the anatomical locations of the epileptogenic zone. The changing connectivity at these higher frequencies can also aid in determining the area of the brain to resect in order for a successful surgery. The coupling of higher frequencies (80-200 Hz) has been shown to decrease at onset and then increase at seizure termination [13].

3.2 Extended Methodology

3.2.1 Wavelet Decomposition

The wavelet transform, like other transforms such as the Fourier transform, transforms a signal in time into a signal that provides more information. The wavelet transform remaps a signal so that information about both time and frequency are available. This is similar to the idea of the Fourier transform, in which a signal in time is transformed into a signal that provides information about the frequency content of the original signal. In the Fourier transform sinusoidal functions are used to probe the signal in order to determine the coefficients that can be used to obtain the frequency information. The difference with the wavelet transform is that the function used to probe the signal has a finite duration, known as a wavelet. The original wavelet is known as the mother wavelet. The mother wavelet is then scaled in order to probe the different frequencies in the signal.
The equation for the continuous wavelet transform (CWT) is given in Equation 3.2.

\[ W(a, b) = \int_{-\infty}^{\infty} x(t) \frac{1}{\sqrt{|a|}} \Psi \ast \left( \frac{t - b}{a} \right) dt \]  

(3.2)

where \( a \) represents the scale, which corresponds to frequency, and \( b \) is the translation factor, which corresponds to time. This transformation results in coefficients that contain information about the time and frequency components of the original signal. The unique aspect of the wavelet transformation is that the frequency and time resolutions are not constant. At high frequency, the time window is short, in order to capture the higher frequencies. This means that the time resolution is good at higher frequencies, but the frequency resolution is not as good. The opposite is true for low frequencies [28].

The CWT is often redundant, meaning that it is over-sampled because it is continuous. More than enough coefficients are produced in the CWT to specify the signal. The discrete wavelet transform (DWT) is often used to obtain the wavelet coefficients using discrete values for the scaling and translation factors. The DWT can be described in terms of a filter bank. An example signal, \( x[n] \), sampled at 100 Hz can be used to describe the idea of the filter bank. The signal is passed through the filter bank shown in Figure 3.5.

![Wavelet decomposition filter bank](image)

Figure 3.5: Wavelet decomposition filter bank

In this case, a 3-level decomposition is used to obtain the wavelet coefficients, \( d \) and \( a \). Each coefficient represents the signal in the frequency band as shown in Figure 3.5. The frequency bands are dependent on the sampling frequency. The first coefficient, \( d1 \), will always be \( \frac{fs}{4} \) to \( \frac{fs}{2} \) Hz.
The Fourier transform is often not enough when analyzing biological signals, which are inherently non-stationary and therefore the frequency components change over time. The wavelet transform is a more appropriate transform when dealing with biological signals, such as the EEG. The proper mother wavelet needs to be chosen in order to capture the characteristics of the signal to be analyzed. The decision of the mother wavelet should not be arbitrary. An analysis of the Haar, Daubechies, Coiflet, and Biorthogonal wavelet families found that the Coiflet 1 mother wavelet was the most suitable for signal processing of epileptic EEG signals [29]. The Coiflet 1 wavelet is shown in Figure 3.6.

Figure 3.6: Coiflet 1 mother wavelet

The Coiflet 1 wavelet provided the best accuracy in classifying epileptic EEG signals because the support width of the mother wavelet is similar to the EEG signal and it has a compact filter length [29].

The number of levels of decomposition depends on the sampling frequency and the frequencies of interest. The goal is to assess connectivity in higher frequencies, the gamma band and HFOs. The sampling frequency of the ECoG recording is 1000 Hz. Therefore, a 4-level decomposition is needed to obtain the frequencies of interest. The frequency bands of a 4-level decomposition with a sampling frequency of 1000 Hz are provided in Table 3.4. Frequencies in the delta, theta, alpha, and beta bands are not analyzed and therefore are not necessary to resolve in the wavelet decomposition, which saves compute time.
Table 3.4: 4-level wavelet decomposition

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>Frequency Band</th>
</tr>
</thead>
<tbody>
<tr>
<td>d1</td>
<td>250 - 500 Hz</td>
</tr>
<tr>
<td>d2</td>
<td>125 - 250 Hz</td>
</tr>
<tr>
<td>d3</td>
<td>62.5 - 125 Hz</td>
</tr>
<tr>
<td>d4</td>
<td>31.25 - 62.2 Hz</td>
</tr>
<tr>
<td>a4</td>
<td>0 - 31.25 Hz</td>
</tr>
</tbody>
</table>

3.2.2 Mutual Information

Mutual information (MI) is an information theoretic measure that quantifies the amount of information shared between two time series, X and Y. The measure is based on the idea of entropy, which can be thought of as the degree in uncertainty. The entropy of a time series was defined in Equation 3.1. When dealing with two time series, the entropy of a time series X, given a second time series Y is known as the conditional entropy, which is based on the joint probability of X and Y as well as the probability of X, given Y:

\[
H(X|Y) = - \sum_x \sum_y p(x,y) \log_2 p(x|y)
\] (3.3)

The joint entropy of two time series is just based on their joint probability:

\[
H(X,Y) = - \sum_x \sum_y p(x,y) \log_2 p(x,y)
\] (3.4)

Given the conditional and joint entropy of two time series, X and Y, the mutual information can be defined as

\[
I(X,Y) = H(X) - H(X|Y)
\] (3.5)

\[
= H(X) + H(Y) - H(X,Y)
\] (3.6)

\[
= \sum_x \sum_y p(x,y) \log_2 \frac{p(x,y)}{p(x)p(y)}.
\] (3.7)

MI is best thought of as a reduction in uncertainty. MI for two time series, X and Y, will be high when the individual sum of the entropies of the two signals is much greater than the joint entropy. This means that the uncertainty is reduced when the two signals are
observed jointly. Looked at another way, knowing past values of Y makes the prediction of future values of X better than just knowing past values of X. In other words, the MI measures the average number of bits of X that can be predicted by also measuring Y [24].

The value obtained from Equation 3.7 is unique to the entropy of the signal of interest. Therefore it is necessary to perform a normalization of the MI in order compare between multiple pairs of signals. Linfoot has proposed a normalization of the MI so that the values range from 0 to 1 [25]. The normalization is defined as

$$I_{NL}(X,Y) = \sqrt{1 - e^{-2I(X,Y)}}$$

The normalized MI is obtained for all combinations of channel pairs which results in a MI matrix. The MI for each channel pair is obtained using a MATLAB toolbox, MIDER, developed by Villaverde et al. [38]. In order to obtain the the MI, the probability distribution needs to be estimated. This is typically done by creating equally sized bins and estimating the probability distribution by counting the experimental data in each bin. The number of bins to use in the estimation of MI depends on each signal, but MI is sensitive to the number of bins used [26]. There are some rules of thumb for choosing the number of bins, but an adaptive binning process has been shown to be the most successful [26]. In the adaptive binning method developed by Cellucci et al., the size of each bin is not uniform. The size of each bin is adjusted so that each bin contains the same number of data points. This method is employed in the MIDER toolbox in order to create a more reliable measure of MI.

### 3.2.3 Transfer Entropy

Transfer entropy (TE) is an information theoretic analog of the Granger causality [27]. Granger causality asserts that if a signal, X, "Granger-causes" a second signal, Y, if knowing past values of X makes it easier to predict future values of Y than just knowing past values of Y alone. TE, like MI, can be thought of in terms of a reduction in uncertainty. It is based on the probability distributions of the two signals, X and Y.
Transfer entropy is defined as:

\[ TE_{X \rightarrow Y} = H(y_i | y_{i-t}) - H(y_i | y_{i-t}, x_{i-\tau}) \]  \hspace{1cm} (3.9)

\[ = \sum_{y_i,y_{i-t},x_{i-\tau}} p(y_i,y_{i-t},x_{i-\tau}) \log_2 \frac{y_i | y_{i-t}, x_{i-\tau}}{y_i | y_{i-t}} , \]  \hspace{1cm} (3.10)

where \( i \) represents a point in time, \( \tau \) and \( t \) are the time lags in the signals \( X \) and \( Y \), respectively, and \( k \) and \( l \) are the number of past values in \( X \) and \( Y \), respectively [19]. By the definition in Equation 3.9, information flows from \( X \) to \( Y \) if the uncertainty of future values of \( Y \), given past values of \( Y \), is reduced by also knowing past values of \( X \). It should be noted that \( TE \) cannot be negative because conditioning on past values of \( X \) will not increase the uncertainty.

As with MI, the estimation of \( TE \) requires the data to be binned in order to determine the probability distribution of the data. An adaptive partitioning approach provides a stronger estimation of the \( TE \) as it did with MI (3.2.2). Lee et al. implement a calculation for \( TE \) in MATLAB that uses the Darbellay-Vajda adaptive partitioning algorithm to estimate the probability distribution [19].

### 3.2.4 Runs Test

The runs test is used to determine whether a sequence of observations statistically independent or if there is an underlying trend. A runs test can be performed on a sequence of data in which the data can take on a value of one of two mutually exclusive categories. For example, the two categories could be whether a value is greater than zero (+) or less than zero (-). In a sequence, a run is defined as a series of identical observations. An example with a sequence of 20 observations is shown in Figure 3.7.

![Figure 3.7: Runs Test](image)
In this example there would be 12 runs. A sequence of observations would be considered independent if the probability of an observation does not change from one observation to the next. The number of runs can be described by a random variable, \( r \), which has a sampling distribution with a mean and variance:

\[
\mu_r = \frac{2N_1N_2}{N} - 1
\]

\[
\sigma^2_r = \frac{2N_1N_2(2N_1N_2 - N)}{N^2(N - 1)}
\]

where \( N_1 \) and \( N_2 \) are the number of plus and minus signs respectively and \( N \) is the total number of observations. The significance test is based on this sampling distribution. The null hypothesis would be that there is no underlying trend and the sequence is random. The null hypothesis would be rejected, at the specific significance level, if there are too many runs or there are too few runs. A rejection of the null hypothesis means that there is an underlying trend in the sequence of observations. While MI is a non-directional measure of the strength of the connection, TE is a directional connectivity measure.
Appendix A

Figures

A.1 Subject 1

Figure A.1: Subject 1 Seizure 2 MI prior to onset (left), just after onset (middle) and just prior to termination (right). Channels of interest are indicated on the y-axis. 125-250 Hz.
Figure A.2: Subject 1 Seizure 2 MI prior to onset (left), just after onset (middle) and just prior to termination (right). Channels of interest are indicated on the y-axis. 62.5-125 Hz.

Figure A.3: Subject 1 Seizure 2 MI prior to onset (left), just after onset (middle) and just prior to termination (right). Channels of interest are indicated on the y-axis. 31.25-62.5 Hz.

Figure A.4: Subject 1 Seizure 2 MI prior to onset (left), just after onset (middle) and just prior to termination (right) for the representative subject. Channels of interest are indicated on the y-axis. 62.5-125 Hz.
Figure A.5: Subject 1 Seizure 2 (62.5-125 Hz)

Figure A.6: Subject 1 Seizure 2 (31.25-62.5 Hz)
Figure A.7: Subject 1 Seizure 3 MI prior to onset (left), just after onset (middle) and just prior to termination (right). Channels of interest are indicated on the y-axis. 125-250 Hz.

Figure A.8: Subject 1 Seizure 3 MI prior to onset (left), just after onset (middle) and just prior to termination (right). Channels of interest are indicated on the y-axis. 62.5-125 Hz.

Figure A.9: Subject 1 Seizure 3 MI prior to onset (left), just after onset (middle) and just prior to termination (right). Channels of interest are indicated on the y-axis. 31.25-62.5 Hz.
Figure A.10: Subject 1 Seizure 3 (125-250 Hz)

Figure A.11: Subject 1 Seizure 3 (62.5-125 Hz)
A.2 Subject 2

Figure A.13: Subject 2 Seizure 1 MI prior to onset (left), just after onset (middle) and just prior to termination (right). Channels of interest are indicated on the y-axis. 125-250 Hz.
Figure A.14: Subject 2 Seizure 1 MI prior to onset (left), just after onset (middle) and just prior to termination (right). Channels of interest are indicated on the y-axis. 62.5-125 Hz.

Figure A.15: Subject 2 Seizure 1 MI prior to onset (left), just after onset (middle) and just prior to termination (right). Channels of interest are indicated on the y-axis. 31.25-62.5 Hz.
Figure A.16: Subject 2 Seizure 1 (125-250 Hz)

Figure A.17: Subject 2 Seizure 1 (62.5-125 Hz)
Figure A.18: Subject 2 Seizure 1 (31.25-62.5 Hz)

Figure A.19: Subject 2 Seizure 2 MI prior to onset (left), just after onset (middle) and just prior to termination (right). Channels of interest are indicated on the y-axis. 125-250 Hz.
Figure A.20: Subject 2 Seizure 2 MI prior to onset (left), just after onset (middle) and just prior to termination (right). Channels of interest are indicated on the y-axis. 62.5-125 Hz.

Figure A.21: Subject 2 Seizure 2 MI prior to onset (left), just after onset (middle) and just prior to termination (right). Channels of interest are indicated on the y-axis. 31.25-62.5 Hz.
Figure A.22: Subject 2 Seizure 2 (125-250 Hz)

Figure A.23: Subject 2 Seizure 2 (62.5-125 Hz)
Figure A.24: Subject 2 Seizure 2 (31.25-62.5 Hz)

Figure A.25: Subject 2 Seizure 3 MI prior to onset (left), just after onset (middle) and just prior to termination (right). Channels of interest are indicated on the y-axis. 125-250 Hz.
Figure A.26: Subject 2 Seizure 3 MI prior to onset (left), just after onset (middle) and just prior to termination (right). Channels of interest are indicated on the y-axis. 62.5-125 Hz.

Figure A.27: Subject 2 Seizure 3 MI prior to onset (left), just after onset (middle) and just prior to termination (right). Channels of interest are indicated on the y-axis. 31.25-62.5 Hz.
Figure A.28: Subject 2 Seizure 3 (125-250 Hz)

Figure A.29: Subject 2 Seizure 3 (62.5-125 Hz)
A.3 Subject 3

Figure A.30: Subject 2 Seizure 3 (31.25-62.5 Hz)

Figure A.31: Subject 3 Seizure 1 MI prior to onset (left), just after onset (middle) and just prior to termination (right). Channels of interest are indicated on the y-axis. 125-250 Hz.
Figure A.32: Subject 3 Seizure 1 MI prior to onset (left), just after onset (middle) and just prior to termination (right). Channels of interest are indicated on the y-axis. 62.5-125 Hz.

Figure A.33: Subject 3 Seizure 1 MI prior to onset (left), just after onset (middle) and just prior to termination (right). Channels of interest are indicated on the y-axis. 31.25-62.5 Hz.
Figure A.34: Subject 3 Seizure 1 (125-250 Hz)

Figure A.35: Subject 3 Seizure 1 (62.5-125 Hz)
Figure A.36: Subject 3 Seizure 1 (31.25-62.5 Hz)

Figure A.37: Subject 3 Seizure 2 MI prior to onset (left), just after onset (middle) and just prior to termination (right). Channels of interest are indicated on the y-axis. 125-250 Hz.
Figure A.38: Subject 3 Seizure 2 MI prior to onset (left), just after onset (middle) and just prior to termination (right). Channels of interest are indicated on the y-axis. 62.5-125 Hz.

Figure A.39: Subject 3 Seizure 2 MI prior to onset (left), just after onset (middle) and just prior to termination (right). Channels of interest are indicated on the y-axis. 31.25-62.5 Hz.
Figure A.40: Subject 3 Seizure 2 (125-250 Hz)

Figure A.41: Subject 3 Seizure 2 (62.5-125 Hz)
Figure A.42: Subject 3 Seizure 2 (31.25-62.5 Hz)
Appendix B

Code

B.1 Scripts

B.1.1 MIMatrices.m

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% Author : Mike Selesko
% Filename : MI Matrices.m
% %
% Description: This script file computes the MI between all channels at
% three time points of interest: 20 seconds before seizures, 10 seconds
% into seizure, and 10 seconds before seizure termination. This is done on
% the wavelet coefficients corresponding to the following frequency ranges:
% 125−250 Hz, 62.5−125 Hz and 31.25−62.5 Hz.
% %
% Functions Used:
% seizureTimeInfo (Custom)
% wavelet3 (Custom)
% MyMider (MIDER Toolbox)
% PlotMI (Custom)
% % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % %
% Add the necessary paths
addpath( '\fileserv\biomed\C:\Drive\eegData\Mike_Selesko\MATLAB\Functions ');
addpath( '\fileserv\biomed\C:\Drive\eegData\Mike_Selesko\MATLAB\Mider ');
addpath( 'W:\MatLab\Associated\Files\Chapter11 ');
addpath( '\fileserv\biomed\C:\Drive\eegData\Mike_Selesko\MATLAB\KernelMI ');
addpath( '\fileserv\biomed\C:\Drive\eegData\Mike_Selesko\MATLAB\TransferEntropy ');

clear all; % Clear the workspace

% Load in the sampling frequency, channel names, and data matrix
load Fs.mat % Sampling Frequency
load Channels.mat % Channel Names
load Data.mat % Data matrix

% Remove the EEG mark channels from channel array (SPECIFIC FOR EACH
% SEIZURE)
channels = [1 19 21 37 42 43 46 65];
Channels = Channels(channels);

% Specify the start and end points of the seizures (SPECIFIC FOR EACH
% SEIZURE)
[n_seizStart n_seizEnd seizDuration] = seizureTimeInfo([19 24 9], [19 25 23], [18 57 45], Fs);

% Take 2 mins before and 2 mins after the seizure
start = n_seizStart - 120*Fs;
finish = n_seizEnd + 120*Fs;
newData = Data(n_seizStart-120*Fs: n_seizEnd+120*Fs, :);
clear Data

% Clear the original data matrix

% Set new seizure start and end time based on new, smaller data matrix
n_seizStart = n_seizStart - start;
n_seizEnd = n_seizEnd - start;

% 3 Level Wavelet Decomposition for Fs = 500 Hz:
% d1 > 125 - 250 Hz
% d2 > 62.5 - 125 Hz
% d3 > 31.25 - 62.5 Hz
% a3 > 0 - 31.25 Hz
[d1, d2, d3, a3] = wavelet3(newData, Channels);

% Mutual Information Matrices
% Generate the MI matrices at each of the time points of interest for each
% of the wavelet coefficients
% MI1: Before onset (20 Seconds before)
% MI2: Right after onset (10 seconds into)
% MI3: Right after termination (10 seconds before termination)

% 125 - 250 Hz
MI1 = MyMider(d1(n_seizStart-20*Fs: n_seizStart-15*Fs,:));
MI2 = MyMider(d1(n_seizStart+10*Fs: n_seizStart+15*Fs,:));
MI3 = MyMider(d1(n_seizEnd-10*Fs: n_seizEnd-5*Fs,:));
M11_d1 = MI1.MI1;
M12_d1 = MI2.MI1;
M13_d1 = MI3.MI1;

% 62.5 - 125 Hz
% Use MIDER to obtain the MI matrices at the time points of interest
MI1 = MyMider(d2(n_seizStart-20*Fs: n_seizStart-15*Fs,:));
MI2 = MyMider(d2(n_seizStart+10*Fs: n_seizStart+15*Fs,:));
MI3 = MyMider(d2(n_seizEnd-10*Fs: n_seizEnd-5*Fs,:));

% Get normalized MI
M11_d2 = MI1.MI1;
M12_d2 = MI2.MI1;
M13_d2 = MI3.MI1;

% Plot the MI Matrices
B.1.2 MIandTEPairs.m

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
% Author: Mike Selesko
% Filename: MIandTEPairs.m
%
% Description: This script calculates the MI and difference in TE between
% three types of pairs of channels: (1) one COI and one non-COI, (2) two COI
% and (3) two non-COI. This is done for 4 second time windows with 50%
% overlap. The MI and TE are then plotted as bar graphs with the start and
% end of the seizure indicated on the plot.
%
% Functions Used:
% seizureTimeInfo (Custom)
% wavelet3 (Custom)
% direction (Custom)
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%

addpath ('\fileserv\biomed\C_Drive\eegData\Mike_Selesko\MATLAB\Functions');
addpath ('\fileserv\biomed\C_Drive\eegData\Mike_Selesko\MATLAB\Mider');
addpath ('\W\MatLab\Associated_Files\Chapter_11');
addpath ('\fileserv\biomed\C_Drive\eegData\Mike_Selesko\MATLAB\KernelMI');
addpath ('\fileserv\biomed\C_Drive\eegData\Mike_Selesko\MATLAB\TransferEntropy');

clear all;  \ Clear the workspace

load Fs.mat  \ Sampling Frequency
load Channels.mat % Channel Names
load Data.mat % Data matrix

% Remove the EEG mark channels from channel array (SPECIFIC FOR EACH SEIZURE)
channels = [1:19 21:37 42:43 46:65];
Channels = Channels(channels);

% Specify the start and end points of the seizures (SPECIFIC FOR EACH SEIZURE)
[n_seizStart n_seizEnd seizDuration] = seizureTimeInfo([19 24 9], [19 25 23], [18 57 45], Fs);

% Take 2 mins before and 2 mins after the seizure
start = n_seizStart -120*Fs;
finish = n_seizEnd +120*Fs;
newData = Data(n_seizStart-120*Fs:n_seizEnd+120*Fs,:);
clear Data % Clear the original data matrix

% Set new seizure start and end time based on new, smaller data matrix
n_seizStart = n_seizStart -start;
n_seizEnd = n_seizEnd -start;

% 3 Level Wavelet Decomposition for Fs = 500 Hz:
% d1 -> 125 - 250 Hz
% d2 -> 62.5 - 125 Hz
% d3 -> 31.25 - 62.5 Hz
% a3 -> 0 - 31.25 Hz
[d1, d2, d3, a3] = wavelet3(newData, Channels);

n_start = 1;
n_end = n_seizEnd + 60*Fs;

% Find index for the channels to be analyzed
COI1 = find(Channels == "C3")
outCOI1 = find(Channels == "A1")
COI2 = find(Channels == "C1")
outCOI2 = find(Channels == "B1")

% Find the MI and difference in TE between the three types of pairs
% 125 - 250 Hz
[Mxy1, DeltaTE1, t_index] = direction(n_start, n_end, d1, COI1, outCOI1, Fs); % Pair 1
[Mxy2, DeltaTE2, t_index] = direction(n_start, n_end, d1, COI1, COI2, Fs); % Pair 2
[Mxy3, DeltaTE3, t_index] = direction(n_start, n_end, d1, outCOI1, outCOI2, Fs); % Pair 3

% Plot the MI and the difference in TE
figure(1);
subplot(2,3,1);
bar(t_index, Mxy1); ylim;
set(gca, 'XTick', t_index(1:20:end), 'FontSize', 5);
set(gca, 'YTick', ylim, 'FontSize', 5);
xlabel('Time (s)', 'FontSize', 8, 'FontWeight', 'bold'); ylabel('MI', 'FontSize', 8, 'FontWeight', 'bold');

subplot(2,3,4);
bar(t_index, DeltaTE1); ylim;
set(gca, 'XTick', t_index(1:20:end), 'FontSize', 5);
set(gca, 'YTick', ylim, 'FontSize', 5);
xlabel('Time (s)', 'FontSize', 8, 'FontWeight', 'bold');
legend([h1 h2], { 'Onset', 'Termination' }); xlim([0 (n_end/Fs + 110)]); set(gca,'XTick',(t(index (1):20 t(index (end-1)))),'FontSize',5);
title({'\Delta TE from } Channels COI1, Channel2 \( (125 \omega 250Hz) \), 'FontSize',8);
ylabel({'\Delta TE', 'FontSize', 8, 'FontWeight', 'bold'}); xlabel({'Time(s)', 'FontSize', 8, 'FontWeight', 'bold'});

subplot(2,3,2);
bar(t_index, Mlxy_2); yl = ylim;
h1 = line([120 120], [yl(1) yl(2)], 'Color', 'r', 'LineWidth', 0.75);
h2 = line([1 index (end)-60 t_index (end)-60], [yl(1) yl(2)], 'Color', 'g', 'LineWidth', 0.75);
legend([h1 h2], { 'Onset', 'Termination' }); xlim([0 (n_end/Fs + 110)]);
set(gca,'XTick',(t(index (1):20 t(index (end-1)))),'FontSize',5);
title({'MI between channels } Channels COI1, Channel2 \( (125 \omega 250Hz) \), 'FontSize',8);
ylabel({'MI', 'FontSize', 8, 'FontWeight', 'bold'}); xlabel({'Time(s)', 'FontSize', 8, 'FontWeight', 'bold'});

subplot(2,3,5);
bar(t_index, DeltaTE_2); yl = ylim;
h1 = line([120 120], [yl(1) yl(2)], 'Color', 'r', 'LineWidth', 0.75);
h2 = line([1 index (end)-60 t_index (end)-60], [yl(1) yl(2)], 'Color', 'g', 'LineWidth', 0.75);
legend([h1 h2], { 'Onset', 'Termination' }); xlim([0 (n_end/Fs + 110)]);
set(gca,'XTick',(t(index (1):20 t(index (end-1)))),'FontSize',5);
title({'\Delta TE from } Channels COI1, Channel2 \( (125 \omega 250Hz) \), 'FontSize',8);
ylabel({'\Delta TE', 'FontSize', 8, 'FontWeight', 'bold'}); xlabel({'Time(s)', 'FontSize', 8, 'FontWeight', 'bold'});

subplot(2,3,3);
bar(t_index, Mlxy_3); yl = ylim;
h1 = line([120 120], [yl(1) yl(2)], 'Color', 'r', 'LineWidth', 0.75);
h2 = line([1 index (end)-60 t_index (end)-60], [yl(1) yl(2)], 'Color', 'g', 'LineWidth', 0.75);
legend([h1 h2], { 'Onset', 'Termination' }); xlim([0 (n_end/Fs + 110)]);
set(gca,'XTick',(t(index (1):20 t(index (end-1)))),'FontSize',5);
title({'MI between channels } Channels COI1, Channel2 \( (125 \omega 250Hz) \), 'FontSize',8);
ylabel({'MI', 'FontSize', 8, 'FontWeight', 'bold'}); xlabel({'Time(s)', 'FontSize', 8, 'FontWeight', 'bold'});

subplot(2,3,6);
bar(t_index, DeltaTE_3); yl = ylim;
h1 = line([120 120], [yl(1) yl(2)], 'Color', 'r', 'LineWidth', 0.75);
h2 = line([1 index (end)-60 t_index (end)-60], [yl(1) yl(2)], 'Color', 'g', 'LineWidth', 0.75);
legend([h1 h2], { 'Onset', 'Termination' }); xlim([0 (n_end/Fs + 110)]);
set(gca,'XTick',(t(index (1):20 t(index (end-1)))),'FontSize',5);
title({'\Delta TE from } Channels COI1, Channel2 \( (125 \omega 250Hz) \), 'FontSize',8);
ylabel({'\Delta TE', 'FontSize', 8, 'FontWeight', 'bold'}); xlabel({'Time(s)', 'FontSize', 8, 'FontWeight', 'bold'});

savefig('figure(1)', 'TE_01');
toc;

\% 62.5 - 125 Hz
tie;

[MIy_1,DeltaTE_1, t_index] = direction(n_start, n_end, d2, COI1, COI1, Fs); \% Pair 1
[MIy_2,DeltaTE_2, t_index] = direction(n_start, n_end, d2, COI1, COI2, Fs); \% Pair 2
[MIy_3,DeltaTE_3, t_index] = direction(n_start, n_end, d2, COI1, COI2, Fs); \% Pair 3

\% Plot the MI and the difference in TE
figure(2);
subplot(2,3,1);
bar(t_index, MIy_1); yl = ylim;
h1 = line([120 120], [yl(1) yl(2)], 'Color', 'r', 'LineWidth', 0.75);
h2 = line([1 index (end)-60 t_index (end)-60], [yl(1) yl(2)], 'Color', 'g', 'LineWidth', 0.75);
legend([h1 h2], { 'Onset', 'Termination' }); xlim([0 (n_end/Fs + 110)]);
set(gca,'XTick',(t(index (1):20 t(index (end-1)))),'FontSize',5);
title({'MI between channels } Channel COI1, Channel2 \( (62.5 \omega 125Hz) \), 'FontSize',8);
ylabel({'MI', 'FontSize', 8, 'FontWeight', 'bold'}); xlabel({'Time(s)', 'FontSize', 8, 'FontWeight', 'bold'});
% Plot the MI and the difference in TE
figure(3);
subplot(2,3,1);
bar(t_index, DeltaTE_1); yl = ylim;
h1 = line([120 120], [yl(1) yl(2)], 'Color', 'r', 'LineWidth', 0.75);
h2 = line([t_index(end) - 60 t_index(end) - 60], [yl(1) yl(2)], 'Color', 'g', 'LineWidth', 0.75);
legend([h1 h2], ['Onset', 'Termination']); xlim([0 (n_end/Fs + 110)]);
set(gca, 'XTick', (t_index(1):20:t_index(end-1)), 'FontSize', 5);
title(['\Delta TE from – Channels(COL1) \omega – Channels(outCOL1) \omega(62.5$\rightarrow$125 Hz)'], 'FontSize', 8);
ylabel('MI', 'FontSize', 8, 'FontWeight', 'bold'); xlabel('Time(s)', 'FontSize', 8, 'FontWeight', 'bold');

subplot(2,3,2);
bar(t_index, Mlxy_2); yl = ylim;
h1 = line([120 120], [yl(1) yl(2)], 'Color', 'r', 'LineWidth', 0.75);
h2 = line([t_index(end) - 60 t_index(end) - 60], [yl(1) yl(2)], 'Color', 'g', 'LineWidth', 0.75);
legend([h1 h2], ['Onset', 'Termination']); xlim([0 (n_end/Fs + 110)]);
set(gca, 'XTick', (t_index(1):20:t_index(end-1)), 'FontSize', 5);
title(['\Delta MI_between_channels – Channels(COL1) \omega – Channels(COL2) \omega(62.5$\rightarrow$125 Hz)'], 'FontSize', 8);
ylabel('MI', 'FontSize', 8, 'FontWeight', 'bold'); xlabel('Time(s)', 'FontSize', 8, 'FontWeight', 'bold');

subplot(2,3,3);
bar(t_index, Mlxy_3); yl = ylim;
h1 = line([120 120], [yl(1) yl(2)], 'Color', 'r', 'LineWidth', 0.75);
h2 = line([t_index(end) - 60 t_index(end) - 60], [yl(1) yl(2)], 'Color', 'g', 'LineWidth', 0.75);
legend([h1 h2], ['Onset', 'Termination']); xlim([0 (n_end/Fs + 110)]);
set(gca, 'XTick', (t_index(1):20:t_index(end-1)), 'FontSize', 5);
title(['\Delta MI_between_channels – Channels(outCOL1) \omega – Channels(outCOL2) \omega(62.5$\rightarrow$125 Hz)'], 'FontSize', 8);
ylabel('MI', 'FontSize', 8, 'FontWeight', 'bold'); xlabel('Time(s)', 'FontSize', 8, 'FontWeight', 'bold');

subplot(2,3,4);
bar(t_index, DeltaTE_2); yl = ylim;
h1 = line([120 120], [yl(1) yl(2)], 'Color', 'r', 'LineWidth', 0.75);
h2 = line([t_index(end) - 60 t_index(end) - 60], [yl(1) yl(2)], 'Color', 'g', 'LineWidth', 0.75);
legend([h1 h2], ['Onset', 'Termination']); xlim([0 (n_end/Fs + 110)]);
set(gca, 'XTick', (t_index(1):20:t_index(end-1)), 'FontSize', 5);
title(['\Delta TE from – Channels(COL1) \omega – Channels(outCOL1) \omega(62.5$\rightarrow$125 Hz)'], 'FontSize', 8);
ylabel('TE', 'FontSize', 8, 'FontWeight', 'bold'); xlabel('Time(s)', 'FontSize', 8, 'FontWeight', 'bold');

subplot(2,3,5);
bar(t_index, DeltaTE_3); yl = ylim;
h1 = line([120 120], [yl(1) yl(2)], 'Color', 'r', 'LineWidth', 0.75);
h2 = line([t_index(end) - 60 t_index(end) - 60], [yl(1) yl(2)], 'Color', 'g', 'LineWidth', 0.75);
legend([h1 h2], ['Onset', 'Termination']); xlim([0 (n_end/Fs + 110)]);
set(gca, 'XTick', (t_index(1):20:t_index(end-1)), 'FontSize', 5);
title(['\Delta TE from – Channels(outCOL1) \omega – Channels(outCOL2) \omega(62.5$\rightarrow$125 Hz)'], 'FontSize', 8);
ylabel('TE', 'FontSize', 8, 'FontWeight', 'bold'); xlabel('Time(s)', 'FontSize', 8, 'FontWeight', 'bold');

subplot(2,3,6);
bar(t_index, DeltaTE_4); yl = ylim;
h1 = line([120 120], [yl(1) yl(2)], 'Color', 'r', 'LineWidth', 0.75);
h2 = line([t_index(end) - 60 t_index(end) - 60], [yl(1) yl(2)], 'Color', 'g', 'LineWidth', 0.75);
legend([h1 h2], ['Onset', 'Termination']); xlim([0 (n_end/Fs + 110)]);
set(gca, 'XTick', (t_index(1):20:t_index(end-1)), 'FontSize', 5);
title(['\Delta TE from – Channels(outCOL1) \omega – Channels(outCOL2) \omega(62.5$\rightarrow$125 Hz)'], 'FontSize', 8);
ylabel('TE', 'FontSize', 8, 'FontWeight', 'bold'); xlabel('Time(s)', 'FontSize', 8, 'FontWeight', 'bold');
savefig('figure(2)', 'TE_62');
toc;
h2 = line ([t_index(end)−60 t_index(end)−60], [yl(1) yl(2)], 'Color', 'g', 'LineWidth', 0.75);
legend ([h1 h2], [Onset 'Termination']); xlim([0 (n_end/Fs + 110)));
set(gca, 'XTick'.(t_index(1):20: t_index(end−1)), 'Fontsize', .5);
title (['MI' Channels{COI1}, _End_ Channels{outCOI1}, _31.25−62.5_Hz'], 'FontSize', .8);
ylabel (['MI', 'Fontsize', 8, 'FontWeight', 'bold']); xlabel (['Time(s)', 'FontSize', 8, 'FontWeight', 'bold']);

subplot (2,3,4);
bar(t_index, DeltaTE1); yl = ylim;
h1 = line ([120 120], [yl(1) yl(2)], 'Color', 'r', 'LineWidth', 0.75);
h2 = line ([t_index(end)−60 t_index(end)−60], [yl(1) yl(2)], 'Color', 'g', 'LineWidth', 0.75);
legend ([h1 h2], [Onset 'Termination']); xlim([0 (n_end/Fs + 110)));
set(gca, 'XTick'.(t_index(1):20: t_index(end−1)), 'Fontsize', .5);
title (['\Delta TE from_ Channels{COI1} _End_ Channels{outCOI1} _31.25−62.5_Hz'], 'FontSize', .8);
ylabel (['\Delta TE', 'FontSize', 8, 'FontWeight', 'bold']); xlabel (['Time(s)', 'FontSize', 8, 'FontWeight', 'bold']);

subplot (2,3,2);
bar(t_index, Mxy2); yl = ylim;
h1 = line ([120 120], [yl(1) yl(2)], 'Color', 'r', 'LineWidth', 0.75);
h2 = line ([t_index(end)−60 t_index(end)−60], [yl(1) yl(2)], 'Color', 'g', 'LineWidth', 0.75);
legend ([h1 h2], [Onset 'Termination']); xlim([0 (n_end/Fs + 110)));
set(gca, 'XTick'.(t_index(1):20: t_index(end−1)), 'Fontsize', .5);
title (['\Delta M from_ Channels{COI1} _End_ Channels{COI2} _31.25−62.5_Hz'], 'FontSize', .8);
ylabel (['\Delta M', 'FontSize', 8, 'FontWeight', 'bold']); xlabel (['Time(s)', 'FontSize', 8, 'FontWeight', 'bold']);

subplot (2,3,5);
bar(t_index, DeltaTE2); yl = ylim;
h1 = line ([120 120], [yl(1) yl(2)], 'Color', 'r', 'LineWidth', 0.75);
h2 = line ([t_index(end)−60 t_index(end)−60], [yl(1) yl(2)], 'Color', 'g', 'LineWidth', 0.75);
legend ([h1 h2], [Onset 'Termination']); xlim([0 (n_end/Fs + 110)));
set(gca, 'XTick'.(t_index(1):20: t_index(end−1)), 'Fontsize', .5);
title (['\Delta TE from_ Channels{COI2} _End_ Channels{outCOI2} _31.25−62.5_Hz'], 'FontSize', .8);
ylabel (['\Delta TE', 'FontSize', 8, 'FontWeight', 'bold']); xlabel (['Time(s)', 'FontSize', 8, 'FontWeight', 'bold']);

subplot (2,3,3);
bar(t_index, Mxy3); yl = ylim;
h1 = line ([120 120], [yl(1) yl(2)], 'Color', 'r', 'LineWidth', 0.75);
h2 = line ([t_index(end)−60 t_index(end)−60], [yl(1) yl(2)], 'Color', 'g', 'LineWidth', 0.75);
legend ([h1 h2], [Onset 'Termination']); xlim([0 (n_end/Fs + 110)));
set(gca, 'XTick'.(t_index(1):20: t_index(end−1)), 'Fontsize', .5);
title (['\Delta M from_ Channels{outCOI1} _End_ Channels{outCOI2} _31.25−62.5_Hz'], 'FontSize', .8);
ylabel (['\Delta M', 'FontSize', 8, 'FontWeight', 'bold']); xlabel (['Time(s)', 'FontSize', 8, 'FontWeight', 'bold']);

subplot (2,3,6);
bar(t_index, DeltaTE3); yl = ylim;
h1 = line ([120 120], [yl(1) yl(2)], 'Color', 'r', 'LineWidth', 0.75);
h2 = line ([t_index(end)−60 t_index(end)−60], [yl(1) yl(2)], 'Color', 'g', 'LineWidth', 0.75);
legend ([h1 h2], [Onset 'Termination']); xlim([0 (n_end/Fs + 110)));
set(gca, 'XTick'.(t_index(1):20: t_index(end−1)), 'Fontsize', .5);
title (['\Delta TE from_ Channels{outCOI1} _End_ Channels{outCOI2} _31.25−62.5_Hz'], 'FontSize', .8);
ylabel (['\Delta TE', 'FontSize', 8, 'FontWeight', 'bold']); xlabel (['Time(s)', 'FontSize', 8, 'FontWeight', 'bold']);
savelig(figure(3), 'TE03');

B.1.3 MIPercentChange.m

% Author: Mike Selisko
% Filename: MI_PctChange.m

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% Description: This script calculates the MI between three types of pairs
% of channels: (1) One COI and one non-COI, (2) two COI and (3) two non-COI.
% The pair combinations are randomly generated. The MI is calculated just
% before onset, just after onset, and just before termination. The percent
% change for onset and termination is calculated as a change from the
% baseline MI from before the seizure onset. This is done in three
% frequency ranges: 125–250 Hz, 62.5–125 Hz, and 31.25–62.5 Hz.

% Functions Used:
% seizureTimeInfo (Custom)
% wavelet3 (Custom)
% MyMider (MIDER Toolbox)

% Add the necessary paths
addpath('fileserv\biomed\C_Drive\eegData\Mike_Selosko\MATLAB\Functions');
addpath('fileserv\biomed\C_Drive\eegData\Mike_Selosko\MATLAB\Mider');
addpath('W:\MatLab\Associated_Files\Chapter_11');
addpath('fileserv\biomed\C_Drive\eegData\Mike_Selosko\MATLAB\KernelMI');
addpath('fileserv\biomed\C_Drive\eegData\Mike_Selosko\MATLAB\TransferEntropy');

clear all; % Clear the workspace

% Load in the sampling frequency, channel names, and data matrix
load Fs.mat % Sampling Frequency
load Channels.mat % Channel Names
load Data.mat % Data matrix

% Remove the EEG mark channels from channel array (SPECIFIC FOR EACH
% SEIZURE)
channels = [1:19 21:37 42:43 46:65];
Channels = Channels(channels);

% Specify the start and end points of the seizures (SPECIFIC FOR EACH
% SEIZURE)
[n_seizStart n_seizEnd seizDuration] = seizureTimeInfo([19 24 9], [19 25 23], [18 57 45], Fs);

% Take 2 mins before and 2 mins after the seizure
start = n_seizStart - 120*Fs;
finish = n_seizEnd + 120*Fs;
newData = Data(n_seizStart - 120*Fs:n_seizEnd+120*Fs,:);
clear Data % Clear the original data matrix

% Set new seizure start and end time based on new, smaller data matrix
n_seizStart = n_seizStart - start;
n_seizEnd = n_seizEnd - start;

% 3 Level Wavelet Decomposition for Fs = 500 Hz:
% d1 -> 125 – 250 Hz
% d2 -> 62.5 – 125 Hz
% d3 -> 31.25 – 62.5 Hz
% a3 -> 0 – 31.25 Hz
[d1, d2, d3, a3] = wavelet3(newData, Channels);

%% Mutual Information Matrices
% Generate the MI matrices at each of the time points of interest for each
% of the wavelet coefficients
% MI1: Before onset
% MI2: Right after onset
% MI3: Right after termination

MI1 = MyMider(d1(n_seizStart−20∗Fs:n_seizStart−15∗Fs,:));
MI2 = MyMider(d1(n_seizStart+10∗Fs:n_seizStart+15∗Fs,:));
MI3 = MyMider(d1(n_seizEnd−10∗Fs:n_seizEnd−5∗Fs,:));
MI1_d1 = MI1.MI1;
MI2_d1 = MI2.MI1;
MI3_d1 = MI3.MI1;

MI1 = MyMider(d2(n_seizStart−20∗Fs:n_seizStart−15∗Fs,:));
MI2 = MyMider(d2(n_seizStart+10∗Fs:n_seizStart+15∗Fs,:));
MI3 = MyMider(d2(n_seizEnd−10∗Fs:n_seizEnd−5∗Fs,:));
MI1_d2 = MI1.MI1;
MI2_d2 = MI2.MI1;
MI3_d2 = MI3.MI1;

MI1 = MyMider(d3(n_seizStart−20∗Fs:n_seizStart−15∗Fs,:));
MI2 = MyMider(d3(n_seizStart+10∗Fs:n_seizStart+15∗Fs,:));
MI3 = MyMider(d3(n_seizEnd−10∗Fs:n_seizEnd−5∗Fs,:));
MI1_d3 = MI1.MI1;
MI2_d3 = MI2.MI1;
MI3_d3 = MI3.MI1;

Randomize Channels for Analysis and get % change values (10 runs)

for i = 1:10
    % Separate the channels of interest from those outside the COI
    COI = Channels([33:36 41:42]);
    nonCOI = Channels([1:14 23:24]);

    % Randomly choose channels for the analysis
    % Pair 1: One COI, One non-COI
    COI1 = find(Channels == string(COI(randi(length(COI),1))));
    nonCOI1 = find(Channels == string(nonCOI(randi(length(nonCOI),1))));

    % Pair 2: Two COI
    COI1a = find(Channels == string(COI(randi(length(COI),1))));
    COI1b = find(Channels == string(COI(randi(length(COI),1))));
    while COI1a == COI1b
        COI1b = find(Channels == string(COI(randi(length(COI),1))));
    end

    % Pair 3: Two non-COI
    nonCOI1a = find(Channels == string(nonCOI(randi(length(nonCOI),1))));
    nonCOI1b = find(Channels == string(nonCOI(randi(length(nonCOI),1))));
    while nonCOI1a == nonCOI1b
        nonCOI1b = find(Channels == string(nonCOI(randi(length(nonCOI),1))));
    end

    % Pair 1: One COI and One non-COI
    percentChangeMI_Pair1a_d1(i) = (MI1_d1(COI1,nonCOI1) − MI2_d1(COI1,nonCOI1)) / MI1_d1(COI1,nonCOI1);
    percentChangeMI_Pair1b_d1(i) = (MI1_d1(COI1,nonCOI1) − MI3_d1(COI1,nonCOI1)) / MI1_d1(COI1,nonCOI1);
    percentChangeMI_Pair1a_d2(i) = (MI1_d2(COI1,nonCOI1) − MI2_d2(COI1,nonCOI1)) / MI1_d2(COI1,nonCOI1);
    percentChangeMI_Pair1b_d2(i) = (MI1_d2(COI1,nonCOI1) − MI3_d2(COI1,nonCOI1)) / MI1_d2(COI1,nonCOI1);
    percentChangeMI_Pair1a_d3(i) = (MI1_d3(COI1,nonCOI1) − MI2_d3(COI1,nonCOI1)) / MI1_d3(COI1,nonCOI1);
    percentChangeMI_Pair1b_d3(i) = (MI1_d3(COI1,nonCOI1) − MI3_d3(COI1,nonCOI1)) / MI1_d3(COI1,nonCOI1);

    % Pair 2: Two COI
percentChangeMI_Pair2a_d1(i) = (MI1_d1(COI2a, COI2b) - MI2_d1(COI2a, COI2b)) / MI1_d1(COI2a, COI2b);
percentChangeMI_Pair2b_d1(i) = (MI1_d1(COI2a, COI2b) - MI3_d1(COI2a, COI2b)) / MI1_d1(COI2a, COI2b);
percentChangeMI_Pair2a_d2(i) = (MI1_d2(COI2a, COI2b) - MI2_d2(COI2a, COI2b)) / MI1_d2(COI2a, COI2b);
percentChangeMI_Pair2b_d2(i) = (MI1_d2(COI2a, COI2b) - MI3_d2(COI2a, COI2b)) / MI1_d2(COI2a, COI2b);
percentChangeMI_Pair2a_d3(i) = (MI1_d3(COI2a, COI2b) - MI2_d3(COI2a, COI2b)) / MI1_d3(COI2a, COI2b);
percentChangeMI_Pair2b_d3(i) = (MI1_d3(COI2a, COI2b) - MI3_d3(COI2a, COI2b)) / MI1_d3(COI2a, COI2b);

% Pair 3: Two non-COI
percentChangeMI_Pair3a_d1(i) = (MI1_d1(nonCOI3a, nonCOI3b) - MI2_d1(nonCOI3a, nonCOI3b)) / MI1_d1(nonCOI3a, nonCOI3b);
percentChangeMI_Pair3b_d1(i) = (MI1_d1(nonCOI3a, nonCOI3b) - MI3_d1(nonCOI3a, nonCOI3b)) / MI1_d1(nonCOI3a, nonCOI3b);
percentChangeMI_Pair3a_d2(i) = (MI1_d2(nonCOI3a, nonCOI3b) - MI2_d2(nonCOI3a, nonCOI3b)) / MI1_d2(nonCOI3a, nonCOI3b);
percentChangeMI_Pair3b_d2(i) = (MI1_d2(nonCOI3a, nonCOI3b) - MI3_d2(nonCOI3a, nonCOI3b)) / MI1_d2(nonCOI3a, nonCOI3b);
percentChangeMI_Pair3a_d3(i) = (MI1_d3(nonCOI3a, nonCOI3b) - MI2_d3(nonCOI3a, nonCOI3b)) / MI1_d3(nonCOI3a, nonCOI3b);
percentChangeMI_Pair3b_d3(i) = (MI1_d3(nonCOI3a, nonCOI3b) - MI3_d3(nonCOI3a, nonCOI3b)) / MI1_d3(nonCOI3a, nonCOI3b);

end

% Store Onset Results
filename = "Sub1_Event1_Onset.xlsx";
xlswrite(filename, header, sheet1);
xlswrite(filename, percentChangeMI_Pair1a_d1', sheet1, 'B2');
xlswrite(filename, percentChangeMI_Pair1a_d2', sheet1, 'B2');
xlswrite(filename, percentChangeMI_Pair1a_d3', sheet1, 'B2');
xlswrite(filename, percentChangeMI_Pair2a_d1', sheet1, 'B12');
xlswrite(filename, percentChangeMI_Pair2a_d2', sheet1, 'B12');
xlswrite(filename, percentChangeMI_Pair2a_d3', sheet1, 'B12');
xlswrite(filename, percentChangeMI_Pair3a_d1', sheet1, 'B22');
xlswrite(filename, percentChangeMI_Pair3a_d2', sheet1, 'B22');
xlswrite(filename, percentChangeMI_Pair3a_d3', sheet1, 'B22');
xlswrite(filename, pair1, sheet1, 'C2-C11');
xlswrite(filename, pair2, sheet1, 'C12-C21');
xlswrite(filename, pair3, sheet1, 'C22-C31');
xlswrite(filename, subj, sheet1, 'D2-D31');
xlswrite(filename, header, sheet2);
xlswrite(filename, percentChangeMI_Pair1a_d2', sheet2, 'B2');
xlswrite(filename, percentChangeMI_Pair1a_d3', sheet2, 'B2');
xlswrite(filename, percentChangeMI_Pair2a_d2', sheet2, 'B12');
xlswrite(filename, percentChangeMI_Pair2a_d3', sheet2, 'B12');
xlswrite(filename, percentChangeMI_Pair3a_d2', sheet2, 'B22');
xlswrite(filename, percentChangeMI_Pair3a_d3', sheet2, 'B22');
xlswrite(filename, pair1, sheet2, 'C2-C11');
xlswrite(filename, pair2, sheet2, 'C12-C21');
xlswrite(filename, pair3, sheet2, 'C22-C31');
xlswrite(filename, subj, sheet2, 'D2-D31');
xlswrite(filename, header, sheet3);
xlswrite(filename, percentChangeMI_Pair1a_d3', sheet3, 'B2');
xlswrite(filename, percentChangeMI_Pair2a_d3', sheet3, 'B12');
xlswrite(filename, percentChangeMI_Pair3a_d3', sheet3, 'B22');
xlswrite(filename, pair1, sheet3, 'C2-C11');
xlswrite(filename, pair2, sheet3, 'C12-C21');
xlswrite(filename, pair3, sheet3, 'C22-C31');
xlswrite(filename, subj, sheet3, 'D2-D31');

% Store Termination Results
filename = "Sub1_Event1_Term.xlsx";

96
% Author: Mike Selesko
% Filename: TERunsTest.m
% Description: This function randomly chooses channels for Pair 1 and Pair 3 and computes the TE in both directions. The difference in TE is then taken and a runs test is performed on the sequence during the seizure to determine if there is a pattern in the sequence of positive and negative values of the difference in TE.
% Functions Used:
% seizureTimeInfo (Custom)
% wavelet3 (Custom)
% deltaTE (Custom)

% Add the necessary paths
addpath ('\fileserv\biomed\C_Drive\eegData\Mike_Selesko\MATLAB\Functions');
addpath ('\fileserv\biomed\C_Drive\eegData\Mike_Selesko\MATLAB\Mider');
addpath ('\W:\MatLab\Associated_Files\Chapter_11');
addpath ('\fileserv\biomed\C_Drive\eegData\Mike_Selesko\MATLAB\KernelMI');
addpath ('\fileserv\biomed\C_Drive\eegData\Mike_Selesko\MATLAB\TransferEntropy');

clear all;  % Clear the workspace

send_msg (\{2489102059\}, 'MATLAB', 'Program is Done', 'AT&T');
% Load in the sampling frequency, channel names, and data matrix
load Fs.mat  % Sampling Frequency
load Channels.mat  % Channel Names
load Data.mat  % Data matrix

% Remove the EEG mark channels from channel array (SPECIFIC FOR EACH
% SEIZURE)
channels = [1:19 21:37 42:43 46:65];
Channels = Channels(channels);

% Specify the start and end points of the seizures (SPECIFIC FOR EACH
% SEIZURE)
[n_seizStart n_seizEnd seizDuration] = seizureTimeInfo([19 24 9], [19 25 23], [18 57 45], Fs);

% Take 2 mins before and 2 mins after the seizure
start = n_seizStart - 60*Fs;
finish = n_seizEnd + 60*Fs;
newData = Data(start-120*Fs:n_seizEnd+120*Fs,:);
clear Data  % Clear the original data matrix

% Set new seizure start and end time based on new, smaller data matrix
n_seizStart = n_seizStart - start;
n_seizEnd = n_seizEnd - start;

% 3 Level Wavelet Decomposition for Fs = 500 Hz:
% d1 -> 125 - 250 Hz
% d2 -> 62.5 - 125 Hz
% d3 -> 31.25 - 62.5 Hz
% a3 -> 0 - 31.25 Hz
[d1, d2, d3, a3] = wavelet3(newData, Channels);

% Separate the channels of interest from those outside the COI
COI = Channels([33 36 41 42]);
nonCOI = Channels([1 14 23 24]);

% Randomly choose channels for the analysis
COI1 = find(Channels == string(COI(randi(length(COI),1))));
outCOI1 = find(Channels == string(nonCOI(randi(length(nonCOI),1))));
outCOI2 = find(Channels == string(nonCOI(randi(length(nonCOI),1))));

% Pair 1: One in COI and one out
% 125 - 250 Hz
[before1_d1, during1_d1, after1_d1] = deltaTE(d1, COI1, outCOI1, n_seizStart, n_seizEnd, n_seizEnd+60*Fs, Fs);
% 62.5 - 125 Hz
[before1_d2, during1_d2, after1_d2] = deltaTE(d2, COI1, outCOI1, n_seizStart, n_seizEnd, n_seizEnd+60*Fs, Fs);
% 31.25 - 62.5 Hz
[before1_d3, during1_d3, after1_d3] = deltaTE(d3, COI1, outCOI1, n_seizStart, n_seizEnd, n_seizEnd+60*Fs, Fs);

% Pair 3: Two Outside COI
% 125 - 250 Hz
[before3_d1, during3_d1, after3_d1] = deltaTE(d1, outCOI1, outCOI2, n_seizStart, n_seizEnd, n_seizEnd+60*Fs, Fs);
% 62.5 - 125 Hz
[before3_d2, during3_d2, after3_d2] = deltaTE(d2, outCOI1, outCOI2, n_seizStart, n_seizEnd, n_seizEnd+60*Fs, Fs);
% 31.25 - 62.5 Hz
[before3_d3, during3_d3, after3_d3] = deltaTE(d3, outCOI1, outCOI2, n_seizStart, n_seizEnd, n_seizEnd+60*Fs, Fs);
```matlab
[h, p1(1)] = runtest(during1_d1, 'Tail', 'left');
[h, p1(2)] = runtest(during1_d2, 'Tail', 'left');
[h, p1(3)] = runtest(during1_d3, 'Tail', 'left');
[h, p3(1)] = runtest(during3_d1, 'Tail', 'left');
[h, p3(2)] = runtest(during3_d2, 'Tail', 'left');
[h, p3(3)] = runtest(during3_d3, 'Tail', 'left');

% Write to excel
header = {'', 'Pair_1', 'Pair_3'};
filename = 'RunsTest.xlsx';
xlswrite(filename, header, 'Sheet1');
xlswrite(filename, p1', 'Sheet1', 'B2');
xlswrite(filename, p3', 'Sheet1', 'C2');
```

## B.2 functions

### B.2.1 deltaTE.m

```matlab
function [before, during, after] = deltaTE(x, source_i, sink_i, onset, term, n_end, Fs)

% Inputs
% onset: start point
% n_end: end point
% x: data matrix
% source_i: index for the source signal
% sink_i: index for the sink signal
% Fs: sampling frequency
%
% Outputs
% before: TE before the seizure
% during: TE during the seizure
% after: TE after the seizure
%
% Description: This function outputs three vectors of the difference in transfer entropy between a pair of channels. The three vectors are the difference in TE before, during and after the seizure.

ord = 3;
t = 1;
Tau = [3:10];

% Delta TE before Seizure
n = 1; j = 1;
while n < onset
    source = x(n:n+4*Fs, source_i);
sink = x(n:n+4*Fs, sink_i);

    [Txy, a, v] = transferEntropyPartition(source, sink, 2, 2);
    [Tyx, a, b] = transferEntropyPartition(sink, source, 2, 2);
    before(j) = Txy - Tyx;
    n = n + 2*Fs;
j = j + 1;
end

% Delta TE during Seizure
```
n = onset; j = 1;

while n < term
    source = x(n:n+4*Fs,source_i);
sink = x(n:n+4*Fs,sink_i);

    [Txy,a,v]=transferEntropyPartition(source,sink,2,2);
    [Tyx,a,b]=transferEntropyPartition(sink,source,2,2);
during(j) = Txy - Tyx;
n = n + 2*Fs;
j = j + 1;
end

during(j) = Txy - Tyx;
n = n + 2*Fs;
j = j + 1;
end

B.2.2 direction.m

function [MIxy,DeltaTE,t_index] = direction(n_start,n_end,x,source_i,sink_i,Fs)
%
% Inputs
% n_start: start point
% n_end: end point
% x: data matrix
% source_i: index for the source signal
% sink_i: Index for the sink signal
% Fs: sampling frequency
%
% Outputs
% MIxy: mutual information vector
% DeltaTE: Change in TE vector
% t_index: time vector for plotting
%
% Description: This function outputs vectors for mutual information, the directionality constant from PCMI, and the change in transfer entropy for a source channel and a sink channel to determine the direction of information flow from time n_start to n_end.

t_index(1) = 0;
i = 1;
j = 1;

ord = 3;
t = 1;
Tau = [3:10];

while n_start < n_end
    % Window data
    source = x(n_start:n_start+4*Fs,source_i);

    [Txy,a,v]=transferEntropyPartition(source,sink,2,2);
    [Tyx,a,b]=transferEntropyPartition(sink,source,2,2);

during(j) = Txy - Tyx;
n = n + 2*Fs;
j = j + 1;
end

end
sink = x(n_start:n_start+4*Fs, sink_i);

%output = MyMider(x(n_start:n_start+5*Fs,:));
%MI = output.MI;

% Get mutual information and transfer entropy
[Txy(j), a, v] = transferEntropyPartition(source, sink, 2);
[Tyx(j), a, b] = transferEntropyPartition(sink, source, 2);

%MIxy(j) = MI(source_i, sink_i);

% Update the starting point
n_start = n_start + 2*Fs;

% Update the Time Index
if i == 1
    t_index(i) = 0;
else
    t_index(i) = t_index(i-1) + 2;
end

% Increment indices
i = i + 1;
j = j + 1;

end
DeltaTE = Txy - Tyx;
MIxy = 0;
end

B.2.3 plotMI.m

function plotMI(MI, MI_title, Channels, tickSize, titleSize, axisLabelSize)

% Inputs
% MI: mutual information matrix
% MI_title: string for the title of the plot
% Channels: vector with channel names
% tickSize: integer for axis tick size
% titleSize: integer for font size of the title
% axisLabelSize: integer for font size of the axis labels
%
% Description: This function plots a MI matrix as a heat plot
setColorbar(0, 1, 'MI', 0, 0);
MI_heatPlot(MI_title, MI, Channels);
imagesc(MI);
colorbar('EastOutside'); caxis([0 1]);
set(gca, 'XTick', 1:(length(Channels)), 'XTickLabel', Channels, 'FontSize', tickSize, ...
    'Color', 'k', 'FontWeight', 'bold');
set(gca, 'YTick', 1:(length(Channels)), 'YTickLabel', Channels, 'FontSize', tickSize, ...
    'Color', 'k', 'FontWeight', 'bold');
xtickangle(90);
title(MI_title, 'FontSize', titleSize);
xlabel('Channels', 'FontSize', axisLabelSize); ylabel('Channels', 'FontSize', axisLabelSize);
end
B.2.4 seizureTimeInfo.m

% Function name: seizureTimeInfo(startTime, endTime, fileStartTime, samplingFreq)
% Inputs
% startTime: vector for seizure start time in the form [Hr Min Sec]
% endTime: vector for seizure end time in the form [Hr Min Sec]
% fileStartTime: vector for file start time in the form [Hr Min Sec]
% samplingFreq: sampling frequency
% Example for time vector form:
% 21:30:05 =====> [21 30 5]
% Description: This function takes in the start times of the seizure (startTime) and
% the file (fileStartTime) as well as the duration of the seizure
% (seizureDuration). The function also takes in the sampling frequency.
% The function outputs the starting data point of the seizure and the data
% point of the end of the seizure.

function [n_seizureStart n_seizureEnd duration] = seizureTimeInfo(startTime, endTime, fileStartTime, samplingFreq)

% Convert the times into seconds
fileStartTime = fileStartTime(1)*3600 + fileStartTime(2)*60 + fileStartTime(3);
seizureStartTime = startTime(1)*3600 + startTime(2)*60 + startTime(3);
seizureEndTime = endTime(1)*3600 + endTime(2)*60 + endTime(3);

% Convert the seconds into data points using sampling frequency.
% n_seizureStart = (seizureStartTime - fileStartTime) * samplingFreq;
% n_seizureEnd = (seizureEndTime - fileStartTime) * samplingFreq;
% duration = seizureEndTime - seizureStartTime;
end


B.2.5 wavelet3.m

function [d1, d2, d3, a3] = wavelet3(Data, Channels)

% Inputs:
% Data: data matrix
% Channels: Cell array of channel names
% Outputs:
% d1: 1st wavelet coefficient
% d2: 2nd wavelet coefficient
% d3: 3rd wavelet coefficient
% Description: This function takes in a data matrix and performs a 5
% level wavelet decomposition using the coiflet 1 mother wavelet.

dwtmode('ppd'); % Periodically pad
for i = 1:length(Channels)
    [W(:, i), L(:, i)] = wavedec(Data(:, i), 9, 'coif1');
    d1(:, i) = wrcoef('d', W(:, i), L(:, i), 'coif1', 1); % 250 - 500 Hz
    d2(:, i) = wrcoef('d', W(:, i), L(:, i), 'coif1', 2); % 125 - 250 Hz
    d3(:, i) = wrcoef('d', W(:, i), L(:, i), 'coif1', 3); % 62.5 - 125 Hz
    a3(:, i) = wrcoef('as', W(:, i), L(:, i), 'coif1', 5);
end
end
**B.2.6 wavelet5.m**

```matlab
function [d1, d2, d3, d4, d5, a5] = wavelet5(Data, Channels)

% Inputs:
% Data: data matrix
% Channels: cell array of channel names
% Outputs:
% d1: 1st wavelet coefficient
% d2: 2nd wavelet coefficient
% d3: 3rd wavelet coefficient
% d4: 4th wavelet coefficient
% d5: 5th wavelet coefficient

% Description: This function takes in a data matrix and performs a 5-level wavelet decomposition using the coiflet 1 mother wavelet.

dwtmode('ppd');  % Periodically pad
for i = 1:length(Channels)
    [W(:,i),L(:,i)] = wavedec(Data(:,i),9,'coif1');
    d1(:,i) = wrcoef('d',W(:,i),L(:,i),'coif1',1);  % 250 - 500 Hz
    d2(:,i) = wrcoef('d',W(:,i),L(:,i),'coif1',2);  % 125 - 250 Hz
    d3(:,i) = wrcoef('d',W(:,i),L(:,i),'coif1',3);  % 62.5 - 125 Hz
    d4(:,i) = wrcoef('d',W(:,i),L(:,i),'coif1',4);  % 31.25 - 62.5 Hz
    d5(:,i) = wrcoef('d',W(:,i),L(:,i),'coif1',5);  % 15.625 - 31.25 Hz
    a5(:,i) = wrcoef('as',W(:,i),L(:,i),'coif1',5);
end
end
```

**B.2.7 transferEntropyPartition.m**

```matlab
function [T nPar dimPar] = transferEntropyPartition(X,Y,t,w)

% This function computes the transfer entropy between time series X and Y, with the flow of information directed from X to Y. Probability density estimation is based on the Darbellay-Vajda partitioning algorithm.

% Inputs:
% X: source time series in 1-D vector
% Y: target time series in 1-D vector
% t: time lag in X from present
% w: time lag in Y from present

% Outputs:
% T: transfer entropy (bits)
% nPar: number of partitions
% dimPar: 1-D vector containing the length of each partition
% (same along all three dimensions)

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% This program is free software: you can redistribute it and/or modify
```
fix block lengths at 1
l=1; k=1;
X=X(:,1)'; Y=Y(:,1)';

% go through the time series X and Y, and populate Xpat, Ypat, and Yt
Xpat=[]; Ypat=[]; Yt=[];
for i=max([1+l+k+w]):min([length(X) length(Y)])
    Xpat=[Xpat; X(i-l-t+1:i-t)];
    Ypat=[Ypat; Y(i-k-w+1:i-w)];
    Yt=[Yt; Y(i)];
end

% ordinal sampling (ranking)
Nt=length(Xpat);
[B, IX]=sort(Xpat);
Xpat(IX)=1:Nt;
[B, IX]=sort(Ypat);
Ypat(IX)=1:Nt;
[B, IX]=sort(Yt);
Yt(IX)=1:Nt;

% compute transfer entropy
partitions=DVpartition3D(Xpat, Ypat, Yt, 1:Nt, 1:Nt, 1:Nt);
nPar=length(partitions);
dimPar=zeros(nPar,1);
for i=1:nPar
    dimPar(i)=partitions(i).Xmax-partitions(i).Xmin+1;
end
T=0;
for i=1:length(partitions)
    a=sum(partitions(i).Xmin & Xpat<partitions(i).Xmax & ... 
        & Ypat<partitions(i).Ymin & Ypat<partitions(i).Ymax)/Nt;
    b=sum(Ypat<partitions(i).Ymin & Ypat<partitions(i).Ymax)/Nt;
    c=sum(Ypat<partitions(i).Ymin & Ypat<partitions(i).Ymax)/Nt;
    d=(partitions(i).Ymax-partitions(i).Ymin+1)/Nt;
    T=T+a*log2((a*d)/(b*c));
end

B.2.8 DVpartition3D.m

function partitions=DVpartition3D(X,Y,Z,Xmin,Xmax,Ymin,Ymax,Zmin,Zmax)
This function implements the Darbellay-Vajda partitioning algorithm for a 3D space in a recursive manner. In order to support recursion, each function call should specify a sub-space where partitioning should be executed. It is assumed that X, Y, and Z are ordinal (ranked, starting from 1) samples.


Inputs:
- X: 1-D vector containing coordinates in the first dimension
- Y: 1-D vector containing coordinates in the second dimension
- Z: 1-D vector containing coordinates in the third dimension
- Xmin: lower limit in the first dimension
- Ymin: lower limit in the second dimension
- Zmin: lower limit in the third dimension
- Xmax: upper limit in the first dimension
- Ymax: upper limit in the second dimension
- Zmax: upper limit in the third dimension

Outputs:
- partitions: 1-D structure array that contains the lower and upper limits of each partition in each dimension as well as the number of data points (N) in the partition

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\begin{verbatim}
alpha = 0.05;

idx = X > Xmin & X < Xmax & Y > Ymin & Y < Ymax & Z > Zmin & Z < Zmax;
Xsub = X(idx);
Ysub = Y(idx);
Zsub = Z(idx);

Xdiv = floor(mean([Xmin Xmax]));
Ydiv = floor(mean([Ymin Ymax]));
Zdiv = floor(mean([Zmin Zmax]));

N = [sum(Xsub & X < Xdiv & Ysub & Y < Ydiv & Zsub & Z < Zdiv) sum(Xsub & X < Xdiv & Ysub & Y < Ydiv & Zsub & Z > Zdiv) ... sum(Xsub & X < Xdiv & Ysub & Y > Ydiv & Zsub & Z < Zdiv) sum(Xsub & X < Xdiv & Ysub & Y > Ydiv & Zsub & Z > Zdiv) ... sum(Xsub & X > Xdiv & Ysub & Y < Ydiv & Zsub & Z < Zdiv) sum(Xsub & X > Xdiv & Ysub & Y < Ydiv & Zsub & Z > Zdiv) ... sum(Xsub & X > Xdiv & Ysub & Y > Ydiv & Zsub & Z < Zdiv) sum(Xsub & X > Xdiv & Ysub & Y > Ydiv & Zsub & Z > Zdiv)];
\end{verbatim}
T = \sum \left( \frac{\text{mean}(N) - N}{\text{mean}(N)} \right)^2 / \text{mean}(N). \% \text{ has been corrected to include a normalization factor in the denominator}

partitions = \text{struct}('Xmin',{}, 'Xmax',{}, 'Ymin',{}, 'Ymax',{}, 'Zmin',{}, 'Zmax',{}, 'N',{});

if T > \text{icdf('chi2',1-alpha,7)} && Xmax = Xmin && Ymax = Ymin && Zmax = Zmin
  if N(1) = 0
    partitions = [partitions DVpartition3D(X,Y,Z,Xmin,Xdiv,Ymin,Ydiv,Zmin,Zdiv)];
  end
  if N(3) = 0
    partitions = [partitions DVpartition3D(X,Y,Z,Xmin,Xdiv,Ymin,Ydiv+1,Ymax,Zmin,Zdiv)];
  end
  if N(2) = 0
    partitions = [partitions DVpartition3D(X,Y,Z,Xdiv+1,Xmax,Ymin,Ydiv,Zmin,Zdiv)];
  end
  if N(4) = 0
    partitions = [partitions DVpartition3D(X,Y,Z,Xdiv+1,Xmax,Ydiv+1,Ymax,Zmin,Zdiv)];
  end
  if N(5) = 0
    partitions = [partitions DVpartition3D(X,Y,Z,Xmin,Xdiv,Ymin,Ydiv,Zdiv+1,Zmax)];
  end
  if N(7) = 0
    partitions = [partitions DVpartition3D(X,Y,Z,Xmin,Xdiv,Ydiv+1,Ymax,Zdiv+1,Zmax)];
  end
  if N(6) = 0
    partitions = [partitions DVpartition3D(X,Y,Z,Xdiv+1,Xmax,Ymin,Ydiv,Zdiv+1,Zmax)];
  end
  if N(8) = 0
    partitions = [partitions DVpartition3D(X,Y,Z,Xdiv+1,Xmax,Ydiv+1,Ymax,Zdiv+1,Zmax)];
  end
else
  sum(idx) = 0
  partitions(1).Xmin = Xmin;
  partitions(1).Xmax = Xmax;
  partitions(1).Ymin = Ymin;
  partitions(1).Ymax = Ymax;
  partitions(1).Zmin = Zmin;
  partitions(1).Zmax = Zmax;
  partitions(1).N = sum(idx);
end
Bibliography


