# Estimation of Cortical and Cortico-Muscular Neural Connectivity and Non-Linear Interactions using a Non-Parametric Implementation of Mutual Information

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Supervisor: Prof.Dr.Bahman Honari

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# Declaration

I, the undersigned, declare that this work has not previously been submitted as an exercise for a degree at this, or any other University, and that unless otherwise stated, is my own work.

Kiruthika Velusamy

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Among various diseases of human body, neurological diseases are difficult to detect, manage and diagnose in the world of neuro-science. Over the past few decades, neurologists and researchers are progressing in detecting and diagnosing of neurological disorders. Various advanced technologies like electroencephalography and magnetoencephalography(EEG/MEG) assist the researchers to understand the undefined underlying pathological process.

By studying the relationship between cortical areas or interaction between two neurons aids in detection and diagnosis of the diseases.The neurologists examine the information transmission over the two areas. In this dissertation, estimating cortical connectivity and cortico- muscular connectivity using non-parametric methods to understand the information transmission. Many traditional methods such coherence and spectral density utilized to study linear interactions or properties. However, exploring non-linear properties with non-coordinate system would be challenging with traditional methods.

In this study, non-parametric implementation of mutual information utilized to estimate cortical connectivity and cortico-muscular connectivity and cross-validated against magnitude squared coherence. With Trinity Bio-medical Sciences neurological data, the EEG(C3,C4) and EMG(FDI) channels are employed to estimate the connectivity.

With density approximation method, mutual information is calculated and one of the

distance metrics used in this study is euclidean distance. Cross-mutual information theory is applied with time -lag ranging from 0 to 256 as per sample rate to understand the non-linear interaction between channels.

Cross-validated against bin-based approach and spectral coherence to study frequencies bands and estimate the connectivity. Alpha band is excluded because of volume conduction. This study might be helpful in assisting neurologist in examining specific cortical connectivity, movement associated disorders and in diagnosis of neurological diseases.

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# Chapter 1

# Introduction

In human body, the largest complex system which controls everything is brain. Because of the complex nervous system, neurological disorders are the most challenging to diagnose, manage and monitor in the world of medicine. Over the past few decades, neurologists and research scholars are advancing in the field of neuro-science towards the detection and diagnosis of neurological diseases with current technology and systems. On the recent report of World Health Organization[1],21% of the deaths are caused by neurological disorders. Every year, one billion people worldwide are affected by neurological disorders like epilepsy, Alzheimers disease and stroke to headache. These disorders affect the people worldwide.

Lately, various advanced diagnosis technologies such as Electrophysiollogical tests (Electroencephalography or EEG), computerised tomography (CT scan), magnetic resonance imaging (MRI scan), electromyography (EMG) and Magnetoencephalography (MEG) have been used to detect, manage and treat neurological disease and more. In McMackin R, et al[2], neuroimaging paved a way to understand pathogenesis and spread of the diseases. MRI and positron emission tomography may detect the changes in brain networks but underlying pathological process are poorly defined.

Neuro-degenerative diseases diagnosis involves clinicopathological correlation and histroical changes during the transmission of signals. These can be defined as structural and functional terms as altered patterns observed during neuro-motor connectivity. To study the brain connectivity and abnormal transmission of neurons, neurologists apply these advanced quantitative measures such as electroencephalography and magnetoencephalography(EEG/MEG).The recordings of EEG/MEG with 256 sensors and removal of artifacts has substantially in-

creased spatial resolution. These measurements assist in studying target regions like cortex and investigate about neuro-degenerative diseases.In this study, EEG and EMG/MEG are utilized to understand relation of the cortico-cortical connectivity and cortico -muscular connectivity.

## 1.1 Motivation

Many of neurological diseases such as Alzheimer disease,Parkinson's disease, tremor, dystonia, post-stroke movement disorders and hemiparesis are mostly cortex disorders associated with movements. Estimating neural activity between cortical areas and muscle areas aiding the neurologists to determine behavioral effects of disorders and proving feedback to rehabilitation mechanisms [3]. Approximation of cortico-muscular connectivity was initially reported between electromyography (EMG) and magnetoencephalography(MEG)[4]. However,estimation can provide better spatial solution by measuring between EEG and EMG.

Multi-variate time signals assist in investigating the relationship between concurrently recorded neurophysiological signals and to assess the information transmission between signals, giving insights into the function of the systems than studying paramters of single singnal.[5]. Traditional methods such as power spectrum, coherence give useful information in the study of interdependence between two signal and temporal coordination between cortical regions. However, these methods mainly measure linear connectivity, although neural connectivity may be nonlinear. For study of complex neurophysiological data, linear methods are inadequate.[6].

With advancement in information theory[7], Mutual information (MI), which applies the entropy of highorder statistics to approximate uncertainty, is a statistical measure of both linear and nonlinear dependencies between two time sequences. Mutual information calculation can be implemented by both parametric and non- parametric methods. For the higher dimensionlity data, Gaussian parametic implementations requires class densities assumption to make optimization tractable than non-parametric method.

Approximation of cortical and cortico-muscular connectivity using non-parametric implementation of mutual information provides better depiction about the abnormal activity between neurons and aiding the neurologists towards an advancement in diagnosing the neurological disorders associated with movements.

## 1.2 Research Question

Estimation of Cortical and Cortico-Muscular Neural Connectivity and Non-Linear Interactions using a Non-Parametric Implementation of Mutual Information

## 1.3 Research Challenge

The objectives put forth to address the research question are:

- The density approximation approach of calculating mutual information is computationally demanding than traditional bin-based approach.
- Tuning the smoothing parameter of the density approximation method for good results.
- The variation in h value may be different based on EEG-EEG and EEG-EMG signal values.

## 1.4 Scope of dissertation

The Kozachenko Leonenko estimator [7]as referred as density approximation method used in this study to estimate cortico connectivity and cortico-muscular connectivity. The non-parametric implementation of mutual information is applied to study the interdependence relationship between EEG-EEG and EEG-EMG signals. Comparing with traditional bin-based approach and cortical coherence for cross-validation for linear and non-linear interactions.

The data for the analysis, EEG- EMG data is provided by Trinity Bio-medical college sciences. The data consists of EEG -EMG channels of 8 healthy subjects with common 7 trials and time delay of 4s. Each trail includes 256 sample rate. To estimate mutual information using density approximation method, smoothing parameter value is calculated by simulating data and experimented with real-time data.

MATLAB is used to compute large data and estimate neural connectivity in this study.

## 1.5 Structure of dissertation

The thesis is organized as follows. Chapter 2 explains literature background and related work. Chapter 3 presents the methodology applied for the study followed by the analysis of simulated and experimental data conducted is presented. The Chapter 4 discusses the estimation against cortical coherence, The study concludes with summary, applications in neuroscience, conclusion and future works

# Chapter 2

# Literature review and Background study

In this chapter, the review of the literature on the neuro-electric signals (EEG and EMG) in studying the nervous system, applications of mutual information & information-theoretic measures for neural signal connectivity analysis and estimation of Mutual information(MI) is carried out. Separate research on each of the topics is conducted.

## 2.1 Neuro-electric signals (EEG and EMG) in Studying the Nervous System

Electrical signals encoding various forms of information can be observed at numerous levels of the complex nervous system.Most recent studies applies EEG and EMG to study the motion control during interaction between cerebral motor cortex and muscles.

Electroencephalogram (EEG) is a electrophysiological monitoring brain imaging technique and non-invasive method that applied to measure the voltage fluctuations induced by the mass electrical activity of neurons from electrodes placed on the scalp. [8].The recorded rhythmic activity are examined to find abnormalities in neural activity or electrical activity.

Electromyography (EMG) technique is applied to record the neural activity produced by motor muscles. EMG results assist the neurologist in finding nerve dysfunction, muscle dysfunction or problems with nerve-to-muscle signal transmission for psychogenic movement disorders such as (seizures, tremors)[9].

### 2.1.1 Relationship between EEG and EMG data (EEG-EEG Cortico-cortical and EEG-EMG cortico-muscular coherence)

The neurons in one cortical areas release signals to excite the target neurons in other cortical areas. The term ”cortico-cortical” refers to synchronization in neural activity during rest or action of tasks. In Thatcher, R.W et al [10], functional activity of cortical connections are studied using EEG coherence in Alzheimer's patients.

Cortical-cortico coherence might relate directly to treatment or indirectly reflect the change in task performance with treatment. Studying the actions produced by long distance connections and short length axonal connections in [11], explain the connectivity between right and left hemisphere. High alterations in EEG coherence compared with cortico-cortical areas to analyze the linear connectivity between cortical areas in dementia patients.

A synchrony in neural activity is reflected between primary cortex & motor regions and provides basis for rehabitation mechanism for post-stroke and dyskinesia patients. In Conway et al [12], reported that dynamic interactions are observed between the brain activities and motor tasks. In neuroscience, ”coherence” shows evidence of coupling between EEG and EMG signals. EEG-EMG coherence provides a measure of functional connectivity.

In particular, the cortico-muscular coupling strength was evaluated based on the EEG signals obtained from the primary motor cortex and EMG signals measured from upper arm of subjects. In [13] Krauth Richard et al, EEG-EMG coherence values are lower in post - stroke patient group than healthy subjects. However , there is quantifying reduction found in coherence after rehabilitation mechanism. First months patients are compared with motor-recovery patients aided the neurologist to evaluate cortico-musuclar coherence during the motor recovery.

Liu Jinbiao et al[14], studied cortico-muscular coherence and its applications to various neurological disorders such as pakinson's disease, post stroke, tremor and others. The motor functionality mostly derived from alpha and beta band of cortico- musular coherence.Analyzing healthy subjects with patients group ,it has been observed that , peak coherence value is usually seen within beta band in healthy subjects and for the movement disorder patients, it has been observed in alpha band.

## 2.2 Neuro-electric Signals for Neurological Diagnosis and Clinical Applications

Neuro-imaging techniques such as EEG and EMG are reliable,non-invasive, repeatable tests and applied in various neurological diagnosis and clinical applications. EEG & EMG synchorny can be quantified by various information theoretic methods such as coherence, mutual information and correlation. A study reported that there is significant decreased EEG synchony are found in Alzheimer patients[15].

EEG are utilized to extract features from linear and non-linear analysis of sampled EEG signals. A diagnosis based on EEG is employed to extract the features causing transient oscillations at low frequencies in Alzheimer's & dementia patients.[16]. Recorded EEG signals can quantify the information about periodic and rythmic patterns of specfic brain areas. In S.J.M smith[17] reported that EEG abnormal rhythmic patterns are useful in detection of dialysis dementia or encephalopathy.

The neural activity or electrical activity of voluntary muscle movements are mainly measured by EMG. A highly individual bio-signal, EMG is affected by neurological diseases and reveals any abnormal muscle contractions in standardized and temperate activities. In D Flament et al[18], EMG signal values showed low number of actions or bursts in pakinson's disease patient than normal health subjects. A study of EMG based robotic therapy for post-stroke patients[19], EMG -driven algorithm demonstrating better outcomes in re-habitation of post-stroke patients.

## 2.3 Applications of Mutual Information and Information-theoretic Measures for Neural Signal Connectivity Analysis

Among many mathematical or statistical methods to analyse the neural data,information theory most widely used over last 20 years. Information theory quantifies how much information a neurons carries[20]. Many of the neurologists employ information coding techniques to study the neural coding between response and stimuli. I(S;R) quantifies how much infor-

mation of uncertainty about stimulus can be gained from the observation of neural response.

$$I(S;R) = \sum_{S,R} p(r)\, p(r|s)\ \log_2 \frac{p(r|s)}{p(r)}$$

Unlike traditional methods coherence and correlation can measure linear interactions of neural responses, mutual information detects the linear and non-linear dependencies of the neural responses.

### 2.3.1 Neurophysiological studies

Wider applications of information theory can quantify the information about network connections, investigate the role of spike timing precision, correlations across neurons, and field potential fluctuations in the encoding of sensory information in neurophysiological data. In neurophysiological studies,researchers implement information theory techniques to study the sensory stimuli over each trail.Compared to other single trial analysis, information theory techniques are more efficient in quantifying the information carried over single trial. Information theory techniques can employed to find information of specific response and analyzing all features without assumption of specific feature are encoded.

Diagnosis of neurophysiological disorders involves mutual information to study underlying pathological facts. Information theoretic measures of network connection shows dynamic pattern in seizure patients. To assume global threshold for seizure movements, parameters are related to sensitivity and specificity to seizure-related precursory changes in neural activity are measured. Pairwise mutual information or cross mutual information employed to define the scope of threshold frequencies[21].

Similarly , Mutual information measures information with respect to frequency of two different responses to same stimulus and applied to information filtering of nervous system.Being able to deduce non-linear properties, mutual information employed to study the abnormal patterns in EEG for various neuro-physiological and clinical applications. In Davide Bernardi et al[22],mutual information applied to detect focal hand dystonia by comparing with beta band of healthy subjects. With information theory, researchers can address the problems of neural coding, processing neural information and more.

### 2.3.2 Applications in neuro-degenerative and neurological diseases

Information theory and mutual information has been extensively used in detection and diagnosis of neuro-degenerative diseases and neurological diseases such as Alzheimer's, post-stroke, dementia. Mutual information has been studied the evaluation of functional connectivity of the brain and the alterations in interactions between mild cognitive impairment (MCI) and AD[23].

Besides, mutual information measures the transmission of information between different cortical areas of patients suffering from Alzheimer's disease. Cortical connectivity are recorded through EEG and analyzed using Mutual information to find abnormal patterns in cortical connections. Additionally, mutual information has been effective measure in studying inter related brain network in neuro-degenerative diseases.

Combined with time-series analysis, auto mutual information of same sequence can be useful in account when characterizing the EEG signal. A predetermined time delay, cross mutual information between two different signals can quantify the amount of response carried over each signal.A study reported that auto-mutual information values are transformed and analyzed under receiver operating characteristic curve. The Sensitivity, specificity and accuracy values are obtained and it might be valuable to neurologists in treating AD[24].

There hasn't been standard measure of mutual information applied for the analysis of various neurological diseases. However, mutual information assists the neurologist to study the relationships and compare the values with healthy subjects.

## 2.4 Estimation Methods for MI

On the account of studying neural connectivity, mutual information can be estimated by either bin-based approach or k-nearest neighbors and kernels.

### 2.4.1 Bin-based approach

Bin-based approach mainly employ probability density function to select number of bins to build histograms.The binned method for calculating the mutual information uses discretization or partitioning the data values. For the better quantity, selecting number of bins chosen for the histogram based on the range of the data dictates the bin width[25]. Mainly bin-based

approach is used for finite discrete data series, calculated MI value may depend on binning.

The number of bins is calculated from estimated bin width h:

$$Number\ of\ bins = \lceil \frac{(max\ x - min\ x)}{h} \rceil$$

where max(x) is maximum value of sample x and min(x) is minimum value of sample x. For estimation of bins, most commonly used method is Sturge's rule

$$K = 1 + \log_2 n$$

For the probability distributions with high density data points, estimation of bias will be high. In Masimizu et al [26], empirical copula density are used to approximate the mutual information. The number of bins $m^2$ in the interval of $[0,1]^2$. To select m efficiently, AIC is given by the sum of the negative log likelihood and the number of unknown parameters.

$$AIC(m) = -2\ \frac{n}{m^2} \sum_{m}^{i=1} \sum_{m}^{j=1}\ C_m(\frac{i}{m}, \frac{j}{m}) \log_2 C_m(\frac{i}{m}, \frac{j}{m}) + 2J$$

With respect to calculating mutual information of spike train[**?**], Each spike train interval is converted into a word by binning the spikes for a bin width $\delta t$ and counting the number of spikes in each bin. The mutual information is calculated on the words rather than the spike trains with the probability of a given word estimated by counting how often it occurs in the data. The estimated mutual information approaches the true value slowly.

### 2.4.2 K- Nearest neighbours - KNN

Significant number of studies has been utilizing Kozachenko-Leonenko estimator for estimating mutual information for random variables which take values on a metric space.

One of the distance metrics used by Kozachenko-Leonenko estimator is K Nearest neighbours. In Shuyang Gao et al[27],KNN non paramteric method used to approximate entropy and mutual information. The free parameter k, defining the size of neighborhood to use in local density estimation. Using smaller k should be more accurate, but larger k reduces the variance of the estimate. KNN calculates the euclidean distance between each data points.

# Chapter 3

# Methodology

## 3.1 Implementation of Mutual information

In this study ,implementation of mutual information consists of estimation of entropy, volume, distance metrics and density approximation method.

### 3.1.1 Entropy and Mutual information in Information theory

In information theory[28], Entropy is defined as measure of uncertainty of discrete random variables.

$$H(X) = -\sum_{x \in \mathcal{X}} p(x)\ \log p(x)$$

where x is discrete random variable with alphabet $\mathcal{X}$ and p(x) probability mass functions. Entropy does not depend on the actual values taken by the random variable X, but only on the probabilities.

For n set of outcomesx1,x2,x3....N, entropy is estimated by

$$H(X) \approx -\frac{1}{N}\sum_{i=1}^{N} \log_2 p_X(x_i)$$

p(x) is unknown. In this study, data points are considered in metric space with no-coordinates. Based on [29], estimate of probabilities depend on the volumes which is measure of probability distribution.Considering a ball B(xi,V) with volume V is selected surrounding each data point;

The probability $P_k(xi)$that the ball B(xi,V) contains k points;

$$\langle K \rangle = NF_i$$

where Fi is the probability mass contained in B(xi,V).$\langle K \rangle$ contains the number of data points present in the ball equivalent to #[ B(xi,V)]. Then the entropy equation is formulated as

$$H(X) \approx -\log_2 N + \log_2 V + \frac{1}{N}\sum_{i=1}^{N} \log_2 \#[B(xi, V)]$$

Alternatively ,the number of points in the ball is considered in estimating probability than size of the ball. This equation can aiding in refrain from computing integrable manifold.

### 3.1.2 Estimating volume

Most of the data points are metric space than discrete space in calculating mutual information of neural activity. For the estimation of volume does not depend on coordinate measure. Mainly volume is calculated using the probability mass it contains

$$Vol\ B = P(x \in B)$$

Using the probability measure , number of points $\#[B(xi, V)]$ in the volume is equivalent to some integer h. so V=h/N. Mutual information is independent of measure used.There are two cases necessary to be considered.

- if one discrete variable is in discrete space and other random variable in metric space and it is considered as more general situation.
- if both of random variables are in metric space, estimate is derived using Kullback-Leibler (KL) divergence.

The equation of the mutual information is formulated as,

$$H(X) \approx \log_2 N + \log_2 \frac{h}{N} - \frac{1}{N}\sum_{i=1}^{N} \log_2 h = 0$$

.

### 3.1.3 MI between random variables in discrete and metric spaces

**Case 1: Random variables in discrete and metric spaces**

In neuro-science applications, stimuli are represented by discrete random variable and response is represented by values in metric space.Let S be a discrete set representing the stimuli and let R be a set of responses, which are recorded from the multiple neurons.

$$B_\epsilon(r) = \{t \in \mathcal{R} : d(r,t) < \epsilon\}$$

Each element of S is presented equally ,$n_t$. Let $n_s = |S|$ be the number of stimuli, Total number of data points present is N =$n_t n_s$. $B_\epsilon(r)$ is open ball around r with h points. The same measure of probabilities applied here. The estimate averaged over s

$$I(R;S) \approx \frac{1}{N}\sum_{i=1}^{N} \log_2 n_s \# \frac{[B(ri, \frac{h}{N})]}{h}$$

This estimation mostly applied for coordinated based quantities but it can extended to this situation also.

**Case 2: Random variables are in metric spaces**

If S stimuli and R response are both metric spaces, the marginal probability mass functions$P_R(r)$ and $P_S(s)$ with these measures entropy become zero.In this case, volume is estimated by measures from $P_R(r)$ $P_S(s)$ of marginal spaces. Thus, region which defines is square.

$$S(r_i, s_i, \frac{h1}{N}, \frac{h2}{N}) = \{(r,s) \in \mathcal{R} \times \mathcal{S} : r \in B_r(r_i, \frac{h1}{N}), s \in B_s(s_i, \frac{h2}{N})\}$$

The selection of h1 and h2 should be optimal.larger values reduce the accuracy of the estimation.

### 3.1.4 Distance Metrics

Various distance metrics are used to estimate the distance or transmission between two neuron responses. Euclidean, Manhattan, or van Rossum metric. In this study , euclidean distance is applied to measure the information transmission between two signals. The euclidean

distance between two responses are ,

$$d(p,q) = \sqrt{\sum_{i=1}^{n}(P_i - Q_i)^2}$$

One of the other metric to measure the distance between individual spike trains is calculated using the van Rossum metric, this calculates the distance between two spike trains u = (u1; u2; : : : ; un) and v= (v1; v2; : : : ; vm) as

$$d(u,v) = \sum_{i,j} e^{-}|u_i - u_j|/\tau + \sum_{i,j} e^{-}|v_i - v_j|/\tau - 2\sum_{i,j} e^{-}| - u_i - v_i|/\tau$$

Mutual information is independent of the choice of metric used. Mostly, euclidean distance is used to calculate mutual information to study about neural connectivity

### 3.1.5 Density approximation method

Calculating mutual information between two spike trains with no co-ordinate system are relatively difficult. Most of the random variables of spike trains takes values in metric space. Here, calculating mutual information faces two main difficulties; data in discrete values or integrable manifold; require large amount of data. These problems are addressed by simple KozachenkoLeonenko estimator which applies to metric space. One of the past methods, Traditional binned method uses discretization.to calculate mutual information by counting frequency number of words occur in the data. Converging to true value slowly and resulting large amount of words are the challenges faced while using binned method.

In conor[29], two relevant formulas are derived to calculate mutual information between metric space and between metric space; discrete space. KozachenkoLeonenko estimator, also called as density estimation method relies on smoothing parameter h which is nearest points in total number of data points in the volume of a ball.

The mutual information between two random variables U and V is given by

$$I(U;V) = \left\langle \log_2 \frac{P_{UV}(U,V)}{P_U(u)P_V(v)} \right\rangle$$

Where average with respect to joint distribution $P_{UV}(u,v)$ where u and v values are taken from U and V respectively. These joint distribution or probability distribution helps in

calculating mutual information by providing volume which is number of points are in ball rather than size of the ball. In KozachenkoLeonenko approach, data points are considered in pairs. Since spike trains have no good coordinate system, calculating volume of region would be difficult. The probability mass defines the volume of the region, the formula is given by

$$P_{UV}(u_i, v_i) \approx \frac{\#B}{VolB}$$

where B is a ball around the point $(u_i; v_i)$, B is the number of points in the ball and vol (V) is the volume of the ball. The probability mass function $< \#B >$ is

$$\langle \#B \rangle = \int P_{UV}(u, v) dV$$

Another approach to calculate volume instead of integrable manifold, P(U) and P(V) marginal distribution are used provide measure. Since the data points in pairs, for single data point $(u_i, vi)$; distance is calculated by either using K- nearest neighbour or Euclidean distance. Consider h nearest U- spike train interval to $u_i$:

$$C_U(u_i, v_i) = (u_j, v_j) : d(u_j, u_i) is one of the hsmallest U - distances$$

and the nearest h V -spike-train intervals to $v_i$:

$$C_U(u_i, v_i) = (u_j, v_j) : d(v_j = i, v_j) is one of the hsmallest v - distances$$

The Ball of the data point $(u_i, v_i)$ is calculated by calculating the area of number of points which lies closer to $u_i$ and number of points which are closer to $v_i$. is given by union of the data points given in these two regions and has volume of h2/n2.

$$C(u_i, v_i) = C_U(u_i, v_i) \cup C_V(u_i, v_i)$$

The number of points in region satisfying both U and V distance would be C# which has intersection of data points in both CU and CV where CU set contains corresponding data point and nearest h-1 data points to $(u_i, vi)$ when $u_i$ compared to $u_j$. where CV set contains corresponding data point and nearest h-1 data points to $(u_i, vi)$ when $v_i$ compared to $v_j$.

$$\#C(u_i, v_i) = \#[C_U(u_i, v_i) \cap C_V(u_i, v_i)$$

Case 1: If the two distributions are mutually dependent, mutual information measure is given by

$$I(U;V) \approx I_K L(\mathcal{P};h) = \frac{1}{n}\sum_{i=1} n \log_2 \frac{n\#[C(u_i,v_i)]}{h^2}$$

Case 2: If the two distributions are mutually independent, the probability is given by

$$prob(\#C(u_i,v_i)=r) = \frac{h-1r-1n-hh-r}{n-1h-1}$$

Where r =1 to h, r is urn constant and mutual information measure is given by

$$I_o(n,h) = \sum_{r=1}^{h} prob(\#C(u_i,v_i)=r)\log_2 \frac{nr}{h^2}$$

Where it is also called as upward bias in the estimate of mutual information. As the smoothing parameter approaches total number of points n, bias term becomes zero and it can be eliminated from the calculation.

$$I(U;V) \approx I(\mathcal{P};h) = I_K L(\mathcal{P};h) - I_0(n,h)$$

The bias term does not affected by range of smoothing parameter h. Final mutual information equation is given by maximizing $I(\mathcal{P};h)$over h.

### 3.1.6 Implementation in MATLAB

To facilitate study of the neural connectivity, MATLAB software has been used extensively in neuro-science field.Compared to other software and packages, MATLAB has been efficient in computing high dimensional data such as EEG  EMG data and analyze neural time-series data from electrode signal recordings.

In this study , implementation of mutual information function takes two EEG input signals with h parameter value. The signals are decimated by sampling rate with rate of sampling 8.The MATLAB package ”decimate” reduces the sample rate of x, the input signal, by a factor of r. The decimated signal taken as input and calculated size of array by ”size” MATLAB package.

```
function [MI] = Mutual_info(X1,Y1,k)
%klmi Calculates Mutual Information between x and y using the
%Kozachenko-Leonenko
%non-parametric methods (Houghton 2015)
%   x: N x 1
%   y: N x 1
N=size(X1,1);
% bias I0 mutual information
MI0=nan(1,N);
```

Figure 3.1: Implementation of mutual information

Initially , empty array mutual information is declared.As in the Fig 3.3, for the total number of data points, each $x_i$ point is replicated in another array to calculate the distance between each data point and neighbouring point by euclidean distance.With ”Sort” MATLAB package, indices of the closest points are sorted. This process is repeated for each point and indices of K- neighbouring points are taken. Similarly it has been performed for y signal , calculated array indices of $y_i$ points are taken.

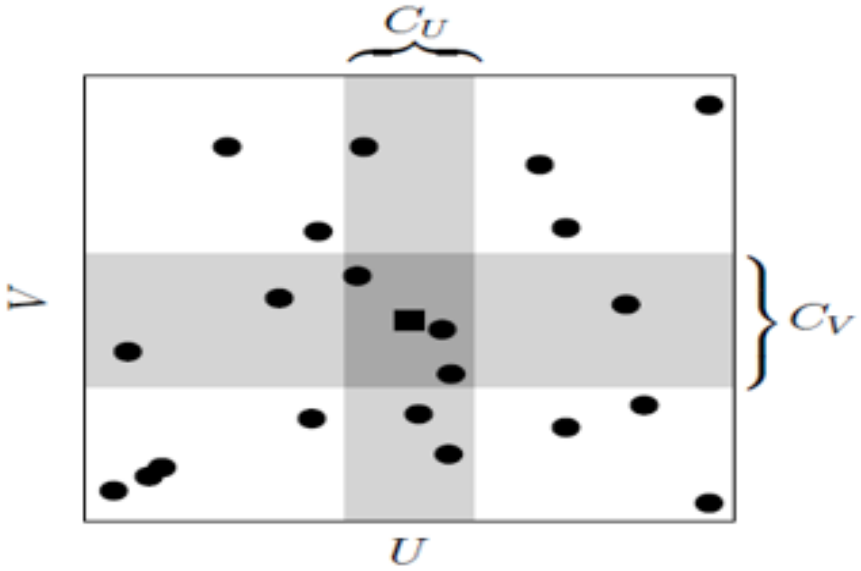


Figure 3.2: Intersection of Cu and Cv

The number of points in region satisfying both U and V distance would be C# which has

intersection of data points in both $C_U$ and $C_V$. For each data pair, array of intersection points calculated based on smoothing parameter h.

```
for ci=1:N
    X1i=X1(ci,:);
    dX=sqrt(sum((X1-X1i).^2,2)); %Distance between each point and xi
    [~,indexX1]=sort(dX); %indices for the sorted distances.
    CU=indexX1(1:(k+1)); %indices of the k nearest points to xi
    Y1i=Y1(ci,:);
    dY=sqrt(sum((Y1-Y1i).^2,2));%Distance between each point and yi
    [~,IndexY1]=sort(dY);%indices for the sorted distances.
    CV=IndexY1(1:(k+1));%indices of the k nearest points to xi
    % point which lie in the intersection of CU and CV
    no_of_points=intersect(CU,CV);
    MI0(ci)=length(no_of_points)/(k*k);
end
```

Figure 3.3: Finding the shortest distance of nearest h

If the two distribution of signals are mutually independent, bias term required to estimated.MATLAB toolbox ”symbolic” is applied in calculating dimensional computations of equations and applied to approximate large values of bias term.

```
if SymCalc>0
    syms sN sr sk integer positive
    sN=sym(N);% symbolic calculation of N
    sk=sym(k);% symbolic calculation of K
    syms sbias [1 k]
end
```

Figure 3.4: Symbolic calculation of N and H

The package ”nchoosek” returns a matrix containing all possible combinations of the elements of vector v taken k at a time. With ”nchoosek” package, bias term solved into possible combinations to avoid computing large value or infinity value. The bias term is removed from the original estimation of mutual information.

```
for r=1:k
    if SymCalc>0
        sr=sym(r);
        bias0(r)=nchoosek(sk-1,sr-1)./nchoosek(sN-1,sk-1).*nchoosek(sN-sk,sk-sr).*log2(sN*sr/(sk*sk));
    else
        %bias0(r)=factorial(N-1)./factorial(k-r)./factorial(r-1)./factorial(N-2*k+r)./factorial(k-r).
        %*log2(N*r/(k*k));
        bias0(r)=nchoosek(k-1,r-1)./nchoosek(N-1,k-1).*nchoosek(N-k,k-r).*log2(N*r/(k*k));
        % Bias calculation.
end
end
```

Figure 3.5: Calculation of Bias term

```
bias=double(sum(bias_I0));
MI=mean(log2(N.*MI0))-bias;
```

Figure 3.6: calculation of Mutual information

## 3.2 Experimental Data

The data for study is provided by department of Trinity bio medical sciences of Trinity College Dublin. Prof. Dr.Bahman Nasseroleslami & team collected the data from specfic group of helathy individual subjects to study the neural connectivity mainly cortico-cortical and cortico -muscular connectivity relastionships. The data obtained for this study includes 8 healthy subjects without any history of neuological disorders.

Each healthy subject data are anonymous. The EEG and EMG recording are included in each subject data. Mainly 4 EEG and 2 EMG channels data recording are obtained to study and estimate cortical connectivity. In this study, stimulated data are generated and performed various operations before proceeding into experimental real time data.

### 3.2.1 EEG

In the study, EEG is recorded by Synamps2 System , by an electrode cap with Ag/AgCl sintered ring electrode set. Considering earlobes and with a forehead location (AFz) as foundation. EEG is band-pass filtered between 0.01 and 400 Hz and digitally sampled at 2048 Hz and captured using SCAN software. Most of the EEG channels were recorded from the scalp electrodes.Before recording, value of contact impedance of the recorded electrodes were below 5 k

Collected EEG signals are converted into discrete data points to computing efficiently and for further studies. Each EEG channel data of each patient contains different number of trails with sample rate of 256.

The form of the data matrix as follows Three Dimensional c x t x s

c=6, no. of channels ($1 \rightarrow Cz, 2 \rightarrow Pz, 3 \rightarrow C4, 4 \rightarrow C3, 5 \rightarrow APB, 6 \rightarrow FDI$)

t: no. of trials( trial length 4s)

s: no. of samples in each trial

### 3.2.2 EMG

Simultaneously electromyogram(EMG) is recorded from the wrist extensors and signals from over the motor cortex in a human subject during maintained wrist extension[30]. These values are estimated with 4s of delay. The EMG plot has high peak value mostly ranges from 40 -100HZ. The EEG has a concentration of power at low frequencies and peak values

within range of 4 to 20 Hz. The EMG has more values in gamma band ranging from 20 to 400 Hz. The 95% confidence intervals have the same magnitude for both EEG and EMG.

The EMG channels are FDI and APB are with sample rate of 256 and different range of trails.

## 3.3 Calculation of Cortical Connectivity between 2 EEG Channels using Lagged (Cross-)Mutual Information

The implementation of cortico-cortical connectivity involves estimation of mutual information of two EEG signals C3 and C4. In the Fig 3.7, EEG cortex channels are depicted and for the study, similarly related C3 and C4 are considered.

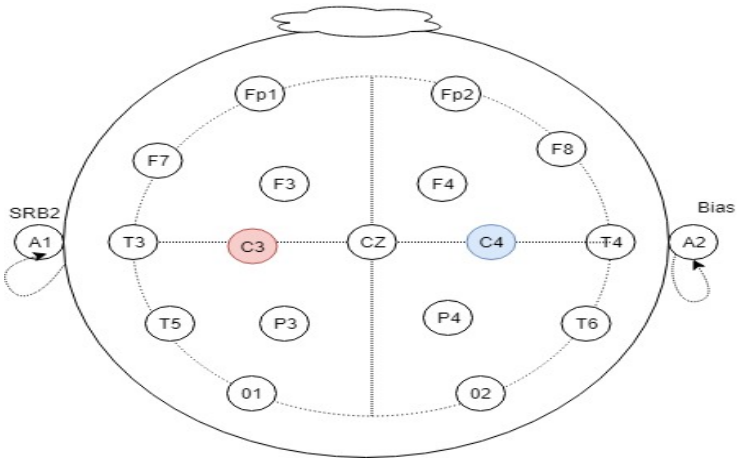


Figure 3.7: EEG channels diagram

First, the EEG signals are sampled down by decimate function and reduced dimension of the matrixThe MATLAB package ”decimate” reduces the sample rate of x, the input signal, by a factor of r.

```
function x= sampling(s,factorial)
    % Change the dimension of data
    s=permute(s,[3 2 1]);
    [~,m_cols]=size(s);
    temp=[];
    for i=1:m_cols
        % decimate the data
        sample=decimate(s(:,i),factorial);
        temp=[ temp sample];
    end
x=temp;
end
```

Figure 3.8: Sampling of Signals

Subsequent to sampling, each signal is shifted in time-phase by number of positions. For each trial, same process is repeated for sample rate of 256 times.Similarly it has been applied to second signal C4 by shifting the data points by backward.

```
function X= shi_signal_forward(x,no_pos)
[r c]=size(x);% rows and column
%shifts the data point  forward by no of positions
x=x(1:r-no_pos,:);
X=x;
end
```

Figure 3.9: Time phase forward shifting of signal

```
function Y=shi_signal_backward(y,no_pos)
[r c]=size(y);
%shifts the data point backward by no of positions
Y=y(no_pos+1:r,:);
end
```

Figure 3.10: Time phase backward shifting of signals

Additionally, mutual information is computed by using both bin-based approch and density approximation method for each time lag.

## 3.4 Calculation of Cortico-Muscular Coherence between EEG and EMG Channels using Lagged (Cross-)Mutual Information

Comparably, cortico-muscular coherence is also estimated by decimating the EEG C3 and EMG signal FDI.The time series analysis is applied by time-lagging of sample rate 256. The cross mutual information is calculated along with bin-based approach mutual information.

```
function [MI]=final_mi(x,y,k)
factorial=8;
x1=sampling(x,factorial);
y1=sampling(y,factorial);
sample=256;
mi=[];
bmi=[];
  for j = 0:256
           % time lag by one position forward lag on first signal c3
            fx = shi_signal_forward (x1, j);
            % time lag by one position forward lag on first signal(C4,FDI)
            by = shi_signal_backward(y1,j);
            fx = fx(:);
            by = by(:);
            %calculate mutual info for each time lag
            mi = [mi mutual_info(fx,by,k)];
            %calculate Bin-based MI for each time lag
            bmi = [bmi bmi(fx,by)];
            k = k;
   end
   ans = [mi ; bmi];
   k = k+100;

end
```

Figure 3.11: Calculation of mutual informatio with time lag

## 3.5 Comparison against Spectral Coherence

Coherence study the relation between two signals or any data. It is used to measure the power transfer between input and output of the system. In signal processing,spectral coherence is

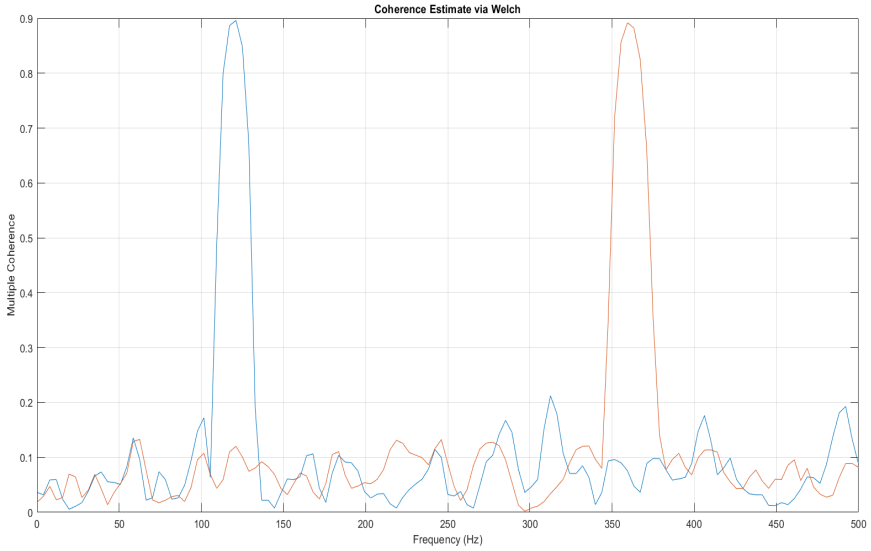


Figure 3.12: Coherence between x and y signals

applied to investigate the linear properties of the interaction between the cortex regions and muscles during specific task or movement.

The converted frequency components of EEG and EMG were analyzed to calculate band-specific auto-spectrum and cross-spectrum. The coherence also called as magnitude -squared coherence between signal x and y

$$C_xy(f) = \frac{|G_xy(f)|^2}{G_xx(f)G_yy(f)}$$

where Gxy(f) is the Cross-spectral density between x and y, and Gxx(f) and Gyy(f) the autospectral density of x and y respectively. The level of significance of the coherence value is determined based on the confidence limit shown as

$$confidence\ \ limit = (1 - (1 - \alpha)^{\frac{1}{L-1}}$$

MATLAB provides the coherence package to calculate magnitude squared coherence between two signals.

$$Cxy = mscohere(x, y)$$

$$cxy = mscohere(x, y, window, noverlap, f, fs)$$

In this study, mcohere package is used to calculate coherence between

- Between EEG channel C3 and EEG channel C4
- Between EEG channel C3 and EMG channel FDI

With respect to data matrix, $channel \times trails \times samplerate$, coherence is estimated by decimating with factorial value of 8 and with window sampling of 256.

**Case 1:Cortico - Cortical coherence :**

The coherence is studied between two EEG channels C3 and C4 with common trail of 7 and sample rate of 256. The mscohere package systematically calculates the coherence with time -lag and normalized frequency. In this study , it has been analyzed the alteration present in the each frequency band and coherence coefficient over time using the data from channel C3 and C4 with sample window of 256. Samples are taken into account without any overlap.

To examine the differences in the cortico-cortical relations, beta band( 8-14) is chosen to analyze the relation between C3 and C3 channel.Alpha band is avoided because of volume conduction and other factors. Most of the EEG values are in alpha and beta band [4-18HZ]. The cortico -cortical coherence provides information about the synchrony between signals from different electrodes or coils at each FFT frequency bin.Statistically cortico-cortical coherence values might be higher or most correlated as EEG cortex channels are very close to each other.The resultant matrix is symmetrical about with coherence values and frequency range. The following results might be helpful in comparing linear and nonlinear properties of neural network of neuological diseases.

$$[Cxy, F] = mscohere(C3, C4, hann(256), 0, 256)$$

The normalized frequency converted into atual frequency by multiplying ($\pi$) value(3.14) and sample rate of 256.

**Case 2:Cortico - musucular coherence :**

Corticomuscular coherence analysis is measure to study how cortical activities involved with the muscle movements and analyses the functional connection between brain motor cortex

regions and associated muscles.The EMG channels FDI and APB are measured during specific task or movement. The values of these signals can vary according to the movement or task. This might help neurologist to study specfic interactions of neural network.

The cortico muscular coherence is studied between EEG channel C3 and EMG FDI with common trail of 7 and sample rate of 256.Samples are taken into account without any overlap.The mscohere package systematically estimates the interactions between EEG and the coherence with time -lag and normalized frequency. The calculated coherence from channel C3 and FDI data with sample window of 256 has been analyzed to study the difference in the coherence coefficient for each frequency band over time.

To investigate the differences in the cortico-muscular relations, gamma band( 25-100hz) is chosen to analyze the relation between C3 and FDI channel.Alpha band is avoided because of volume conduction and other factors.EMG values are higher in beta and gamma bands. The cortico -muscular coherence provides information about the synchrony between brain cortex and associated muscles.

The cortico-muscular coherence value might be lower than cortico-cortical coherence because of signal response time and neuron feedback mechanism The resultant matrix is symmetrical about with coherence values and frequency range.

Estimating cortico-muscular coherence applicable to many neurological disorders with movement.

$$[Cxy, F] = mscohere(C3, FDI, hann(256), 0, 256)$$

The normalized frequency converted into atual frequency by multiplying ($\pi$) value(3.14) and sample rate of 256.

# Chapter 4

# Results

Results section lists the main results from this dissertation, and provides some insight and analysis into these results. Both tables and graphs are used to make the results data more digestible.For better computation and optimization , smoothing paramter h is varied over range of values to find optimal value. The better the optimal value of h, mutual information of density based approximation method is more closer to bin-based approach MI.

## 4.1 Cortico-cortical (EEG-EEG) connectivity

The main objective of this dissertation is estimating cortico-cortical connectivity with non-coordinate system. With substantial data, estimation of mutual information of EEG signals may result in better outcome in studying the relationship between these channels.

### 4.1.1 Estimation using MI

The significant focus paramter h , smoothing parameter is varied across 200-1000 for the cortico-cortical connectivity (EEG-EEG) estimation. Variation is compared with bin-based approach to find better approximation of mutual information by density approximation method. The mutual information is compared with spectral coherence to cross-validate outcomes of density method. From the Fig 4.1, it can be observed that when h value is 200, mutual information curves of both bin-based and density approximation are very distant to each other.

Following h values of 400 & 500, MI curves are getting more closer. Similar kind of pattern can be observed for the values of h above 700. The optimal value chosen for the

cortico-cortical connectivity (EEG- EEG) is 500. The optimal value for the K-nearest neighbour is 500.

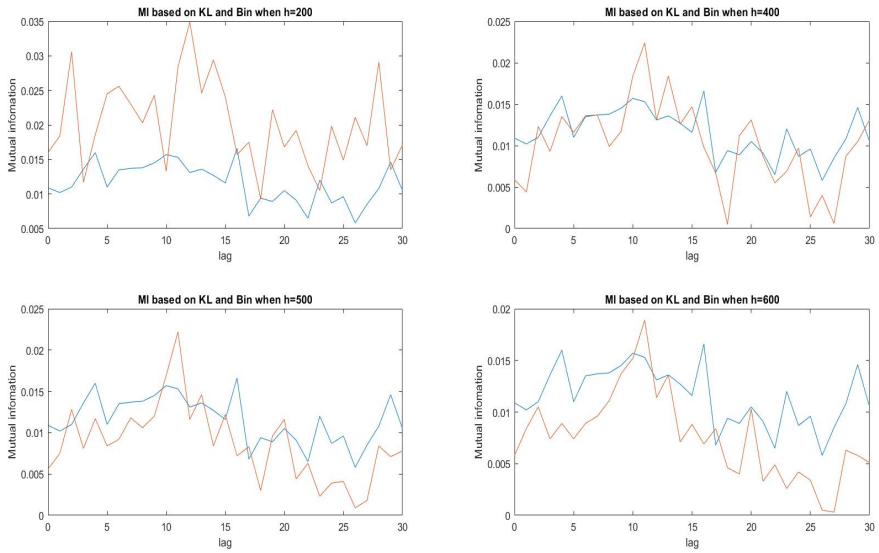


Figure 4.1: Variation of H (200,400,500,600) for the subject 102

With optimal value of h, mutual information is estimated for 8 healthy subjects. For the certainty and performance, common trial of 7 and sample rate of 256 is selected for the study. Following fig 4.3 shows the mutual information of bin-based , KL divergence(density-approximation method) and validated against spectral coherence.

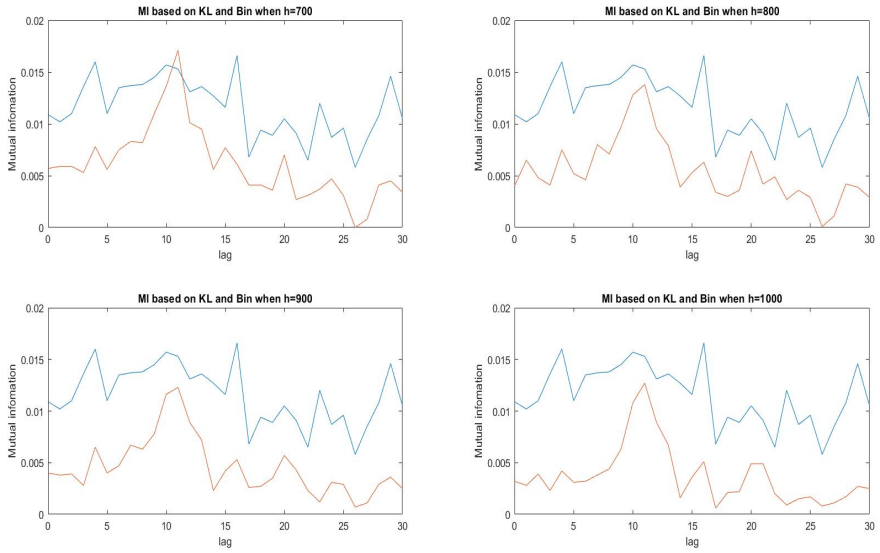


Figure 4.2: Variation of H (700,800,900,1000) for the subject 102

In this dissertation, alpha band is refrained from the study because volume conduction. Beta-band from 4 to 16 hz is considered to estimate connectivity and cross- validated against spectral coherence. There is significant peak value can be observed from both mutual information graph and coherence graph. As mutual information tends to provide non-linear properties, various non-linear interactions can be perceived from the fig 4.3 and 4.4.

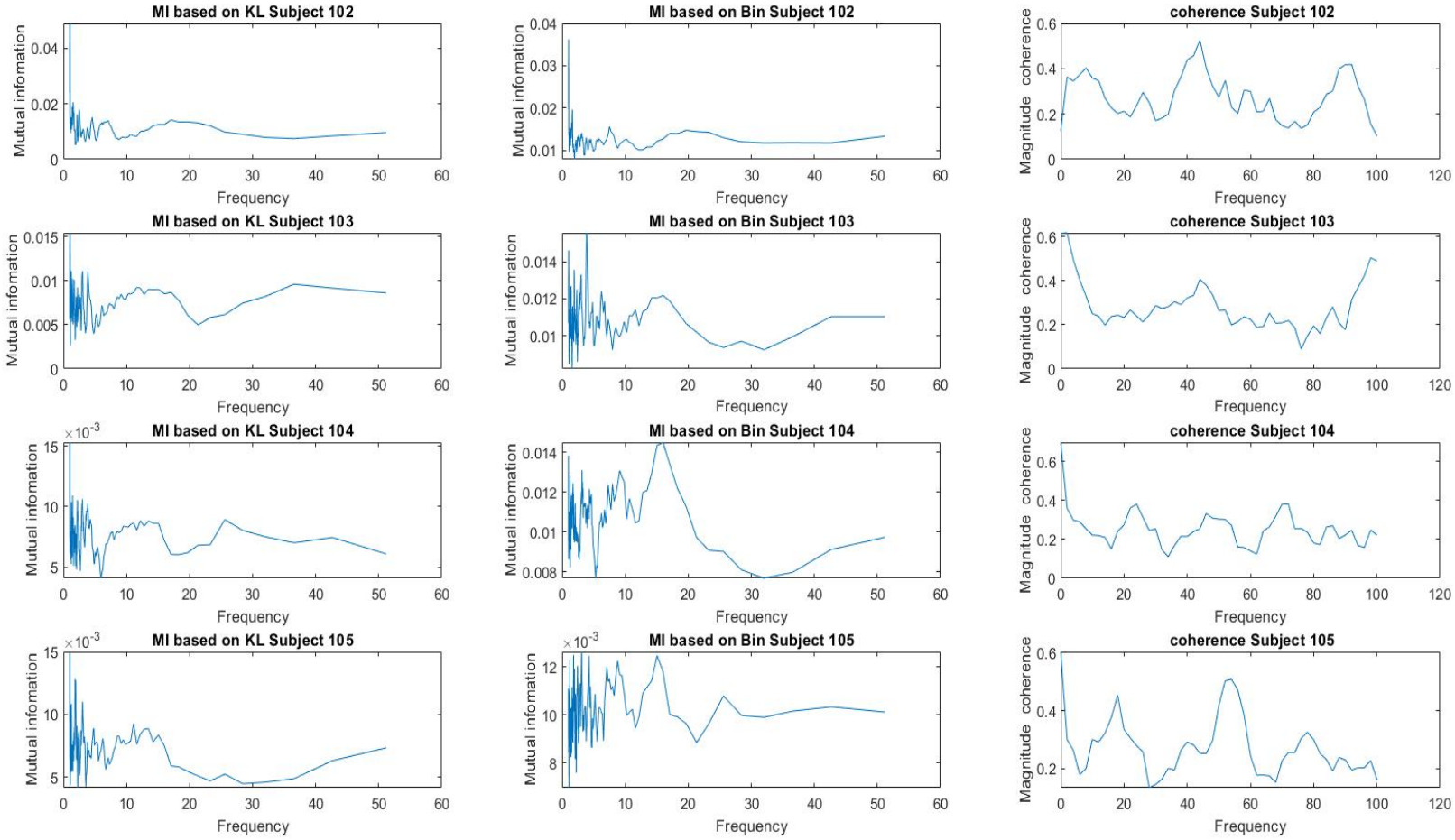


Figure 4.3: Mutual information of EEG-EEG channelsfor the subjects 102,103,104,105

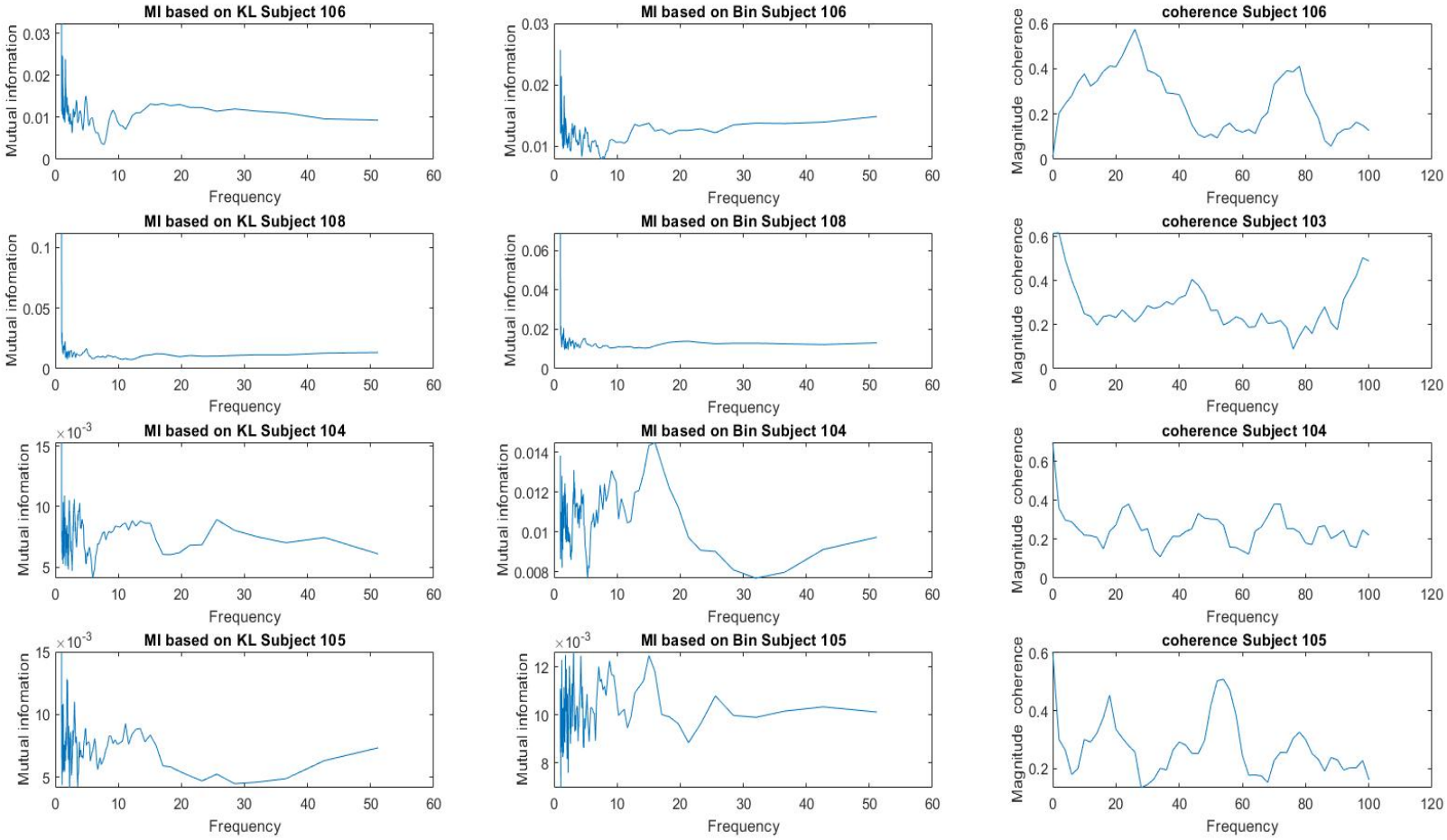


Figure 4.4: Mutual information of EEG-EEG channels for the subjects 106,108,111,112

### 4.1.2 Comparison against Spectral Coherence

The mutual information estimated by density approximation method is comapred with spectral coherence. To identify the differences in the cortico-cortical relations, beta band( 8-14) is chosen to analyze the relation between C3 and C4 channel.

The beta band of mutual information shows significant peak values similar to coherence. Spectral coherence shows linear properties of the signals and Initially mutual information has higher alpha band values.Alpha band is avoided because of volume conduction and other factors. Most of the EEG values are in alpha and beta band [4-20Hz]. The cortico -cortical coherence provides information about the synchrony between signals.

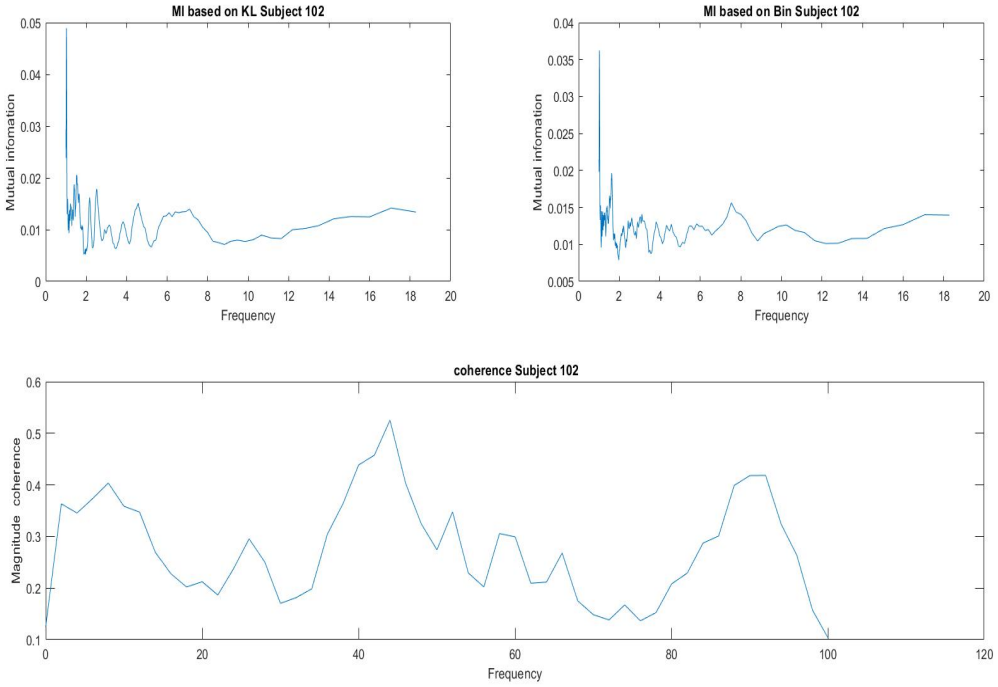


Figure 4.5: Mutual information VS Spectral coherence of Cortico-cortical connectivity

## 4.2 Cortico-muscular (EEG-EMG) connectivity

Estimating cortico-muscular connectivity with non-coordinate system is useful in various applications of neuroscience. With large data, calculation of mutual information of EEG and

EMG signals may be lower than cortico-cortical connectivity.

### 4.2.1 Estimation using MI

Similar to cortico-cortical , parameter is varied across 300-900 for the cortico-muscular connectivity (EEG-EEG) estimation. The bin-based approach mutual information is calculated along with KL divergence MI.The mutual information is compared with spectral coherence to cross-validate outcomes of density method.

From the Fig 4.6, variation of h values shows that when h=300, mutual information curves almost close to each other. The optimal value chosen as 400. The higher values of h, distance between two waves is increasing.

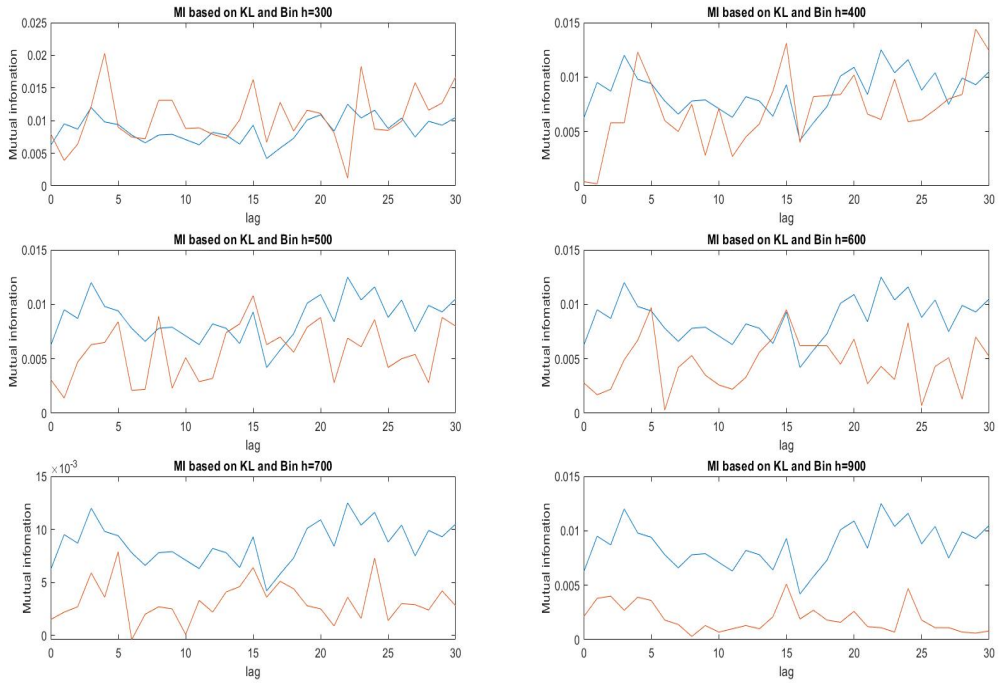


Figure 4.6: Variation of H (300,400,500,600,700,800,900) for the subject 102

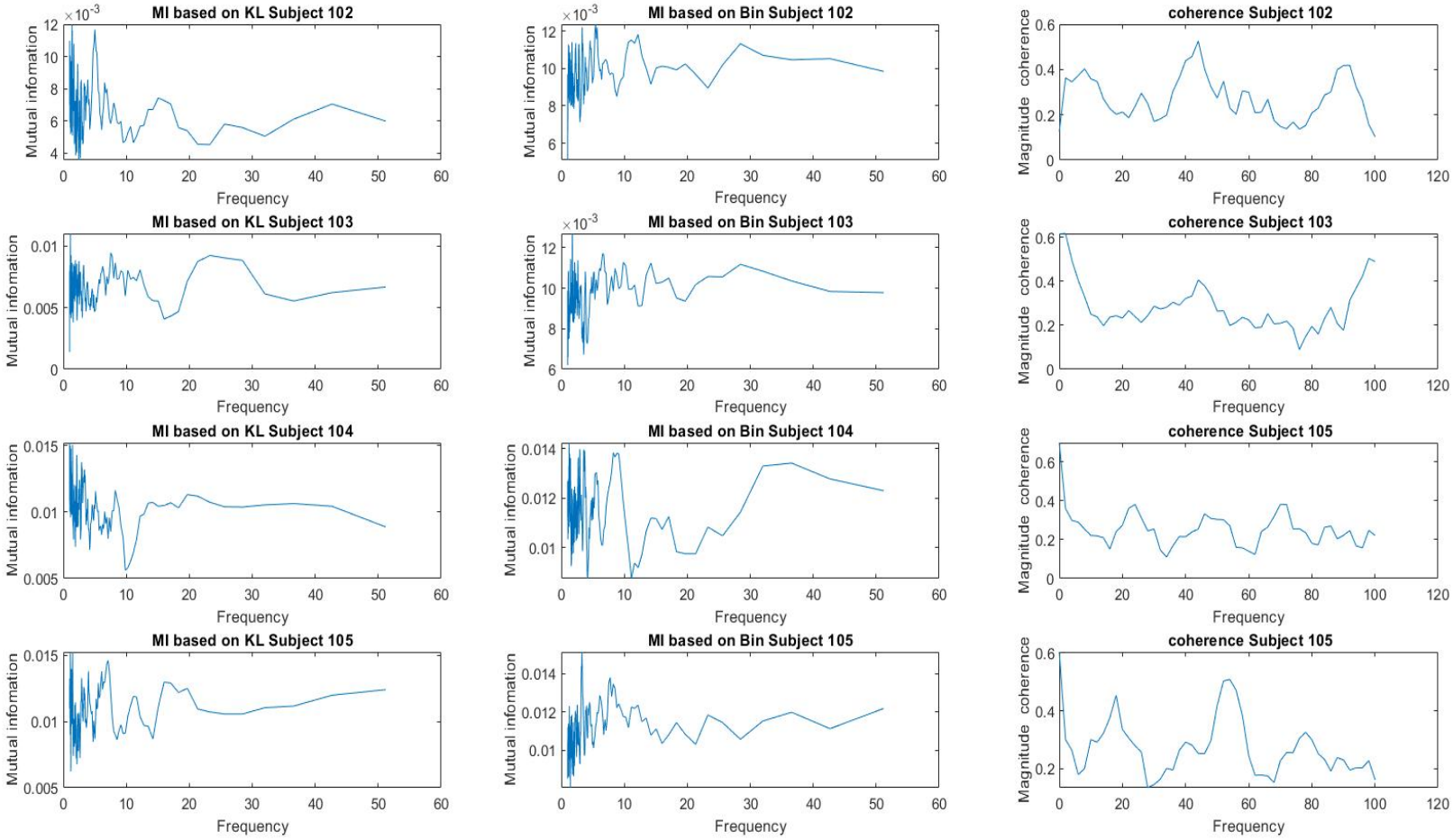


Figure 4.7: Mutual information of the EEG-EMG for the subjects 102,103,104,105

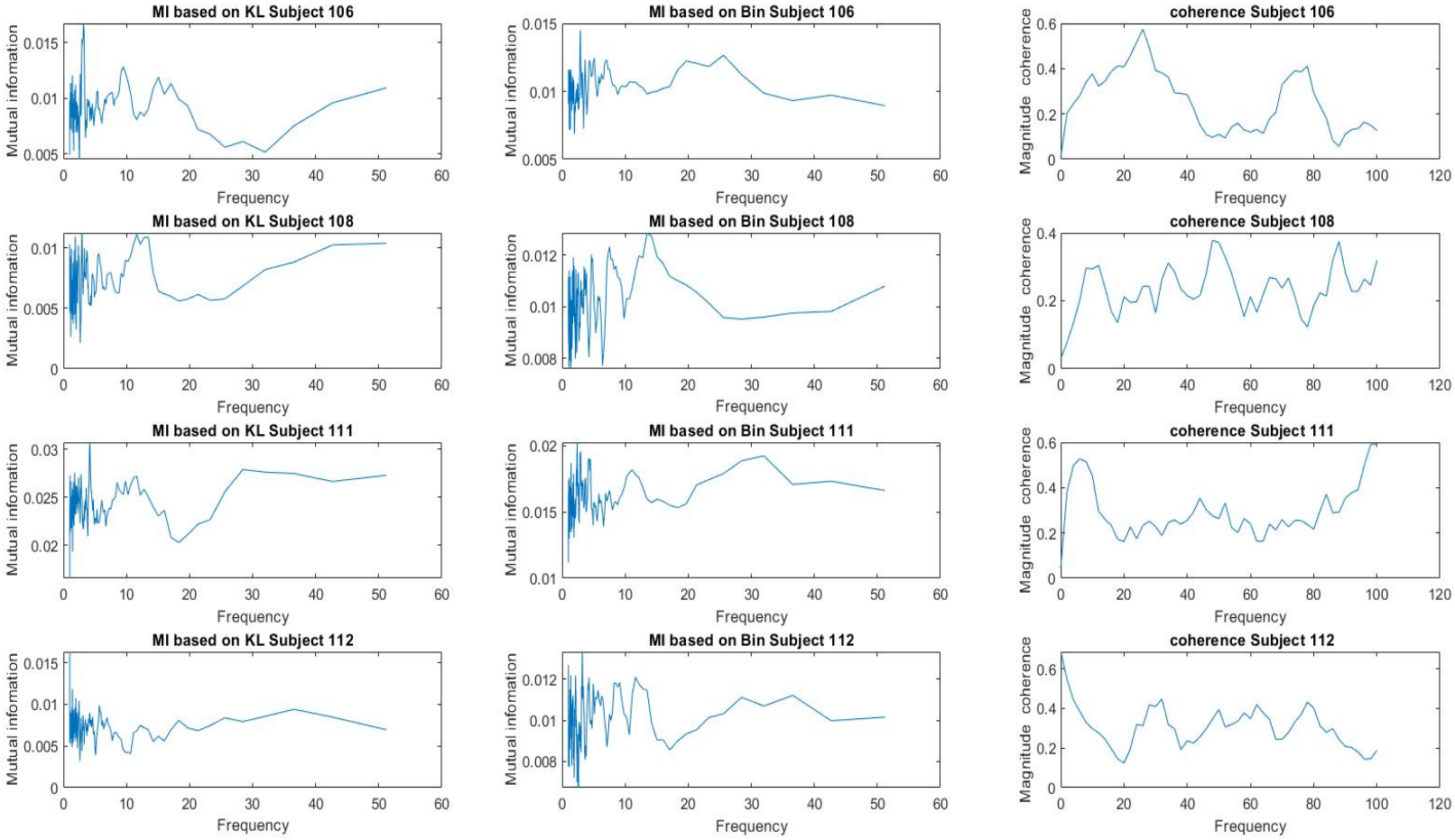


Figure 4.8: Mutual information of the EEG-EMG for the subjects 106,108,111,112

### 4.2.2 Comparison against Spectral Coherence

Similar to corticl connectivity estimation, cortico- muscular connectivity also estimated and cross validated against spectral coherence. The mutual information estimated by density approximation method is compared with spectral coherence. The differences are examined in the cortico-muscular relations, beta band( 8-14) is chosen to analyze the relation between C3 and FDI channel.

The beta band of mutual information shows significant peak values similar to coherence. Spectral coherence shows linear properties of the signals and Initially mutual information has higher alpha band values.Alpha band is avoided because of volume conduction and other factors. Most of the EMG values are in beta and gamma band [20-100Hz]. Because f

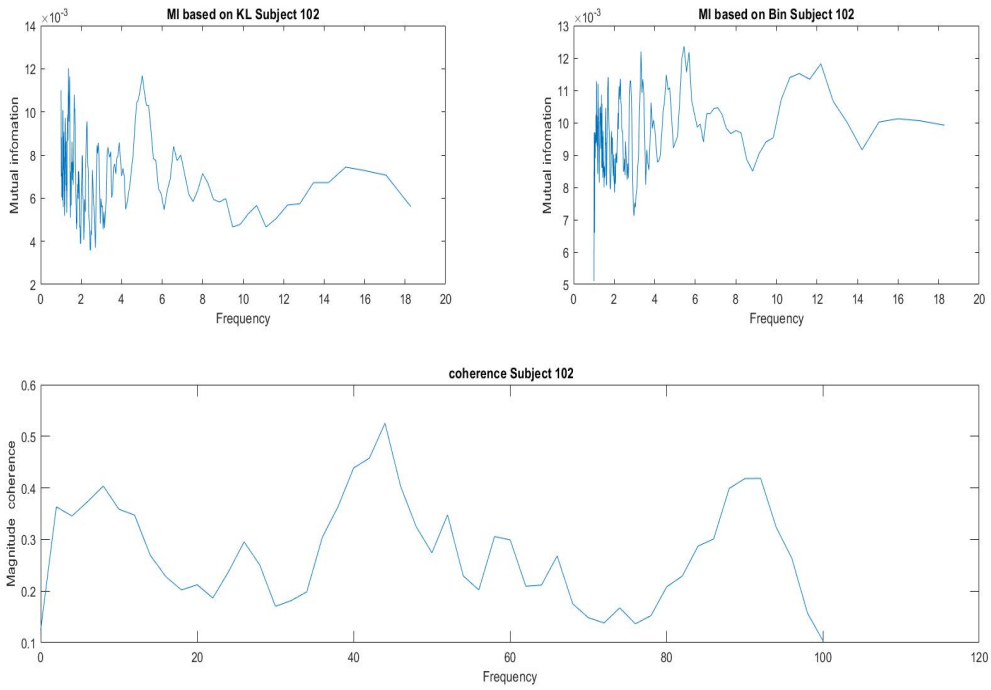


Figure 4.9: Mutual information VS Spectral coherence of Cortico-muscular connectivity

# Chapter 5

# Discussion and Conclusions

## 5.1 Summary of New Findings

In this study of estimating neural cortico-cortical connectivity and cortico-muscular connectivity, linear and non-linear properties of the interactions can be studied and employed in the diagnosis of neurological disorders.Mutual information of KL divergence is one of the efficient approach based on the proximity structure of the data;Various distance metrics can be employed to calculate the mutual information. The mutual information is independent of distance measures and not affected by probability measures. The findings as follows

- Systematically cortico-cortical connectivity might be higher than cortico-muscular connectivity because cortex regions are very close to each other.
- Cortico-muscular connectivity estimation provide information about the neural transmission about specfic channels or neurons invloved in movement state.
- As the data increases, smoothing parameter h also varies.

## 5.2 Non-linear interactions and the utility of MI-based Methods

The sensitive interactions in the brain network might be detected by traditional linear methods such as coherence and spectral density.To study the cognitive development and move-

ment, non-linear mutual information brings neurologist closer to computational models of cognition.

Additionally , non-linear methods can provide reliable evidence about the stimuli involved in the interaction and properties of the stimuli.Mutual information shows more variance about the information transmission between two regions than linear methods. One of the utility of MI based methods depict the virtually connected graph of brain network with interaction and might be helpful in identifying the regions associated with disorders.

## 5.3 Applications in neuroscience and neurological diagnostics

Many applications and studies of neuroscience utilize the mutual information to examine the interaction between regions and complex physiological data like EEG. Examining the connections of MI measures cognitive features and comparing interaction in AD patients and other types of dementia. This may be useful detecting neurological disorders in their early stage diagnosis and in monitoring progress of disease. Abnormal rhythmic pattern aids neurologist to identify the affected region of brain in post-stroke patients.

## 5.4 Limitation

This section lists the limitations in this dissertation. The other limitations as follows

- The analysis of EEG and EMG data can be applied to many other channels to study the relationship between cortico-muscular connectivity.
- The selection of optimal value h should be varied across many different channels with more data.
- The task or movement related to EMG data is unknown.It is difficult to study the measures related to specific task of patient during EMG recording.
- In neuroscience , certainty of standard measures of comparing mutual information is unavailable to the current neuologists.

- The density estimation approach is more computationally demanding than the binned approach;

## 5.5 Future Directions

Many neurologist struggling to set standard measure for the information transmission or measure of interaction between the neurons.By calculating the non-parametric mutual information paves way for comparing outcomes with healthy subjects.Estimation of neural connectivity and cortico-muscular connectivity might be useful in defining the standard measure for specific interaction between cortex channels or interaction between cortex - movement muscles. Hopefully, this study might be foundation for defining the standard measure. Additionally, optimizing h value across the channels and data might help to obtain better outcomes of the Mutual information.

## 5.6 Conclusions

The objective of this dissertation is to estimate cortical connectivity and cortico-muscular connectivity using non-parametric implementation of mutual information achieved successfully. Using auto and cross-mutual information, re-habitation & feedback mechanisms can be further improved serving specific purpose. Optimization of h value brings approximation of connectivity more closer in defining standard measure to compare with. By migrating the limitation , this study can move forward in new direction and can aid neurologist to explore the interactions.

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# Appendix

### Abbreviations

AMI - Auto Mutual Information
AD - Alzheimer's Disease
CCC - Cortico-Cortical Coherence
CMC - Cortico- Muscular coherence
CMI - Cross Mutual Information
EEG - Electroencephalography
EMG - Electromyography
KL - kozenko -Lenenko
KL - divergence - Kullback -Leibler divergence
KNN - K- Nearest Neighbours
MEG - Magnetoencephalography
MI - Mutual Information
PSD - Post Stroke Patients