MODELING CLASSIFICATION NETWORK OF ELECTROENCEPHALOGRAPHIC ARTIFACTS AND SIGNALS ASSOCIATED WITH DEEP BRAIN STIMULATION

By

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ABSTRACT OF THE THESIS

Modeling Classification Network of Electroencephalographic Artifacts and Signals Associated with Deep Brain Stimulation

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In the last decade, network science has been widely applied in engineering, financial, management and biological systems. The study of network has emerged as a useful tool to investigate complex systems with interdependent components because a new set of theoretical tools and practical techniques have been developed to analyze data that can be modeled as networks. The growing interest in network analysis encompasses the study of social media network structure, protein interaction network, and human brain functional network. The objective of this study is to develop a new reliable framework for classifying network data evolved over time. In particular, this research conducts a study on electroencephalographic (EEG) data as a form of multivariate time series modeled as a network during a period of time in which a treatment procedure called deep brain stimulation (DBS) is either set to be on or off.

DBS is a procedure used to treat symptoms of neurological movement and neuropsychiatric disorders—most commonly for patients with Parkinson's disease (PD) who do not respond well to medication. The procedure involves the use of a surgically

implanted, battery operated neurostimulator to send electrical stimulation to targeted areas in the brain, and in PD, the brain areas targeted for stimulation are selected because the role that they are thought to play in controlling movements. Currently, conventional DBS therapy is not suitable to be individualized: DBS is only able to deliver stimulation continuously and the DBS setting, such as amount of stimulation delivered, is adjusted based on a trial-and-error process involving subjective clinical assessment. If DBS is able to deliver an adequate amount of stimulation only when it is necessary for an individual patient based on quantitative measurement, adjusting DBS setting will become a more objective process and the therapy will become more effective with less side effect. For such an adaptive DBS to be realized, a detectable feedback signal must be identified that can be used to adjust DBS setting in a feedback control system. Currently, there is lack of such definitive signals that are thought to be reliable as the basis for feedback.

Electroencephalographic (EEG) recording is a clinical and electrophysiological monitoring tool used by physicians to diagnose and monitor patients with neurological conditions. EEG measures regional electrical activity of the brain of an individual in the form of a multivariate time series dataset. Because EEG has high temporal resolution on the order of milliseconds, it has a unique potential to measure feedback signals for DBS to operate in a feedback control system.

In this study, a classification framework is developed to identify whether or not a set of EEG signals and its frequency components can be used to develop classifier for identifying EEG signals belonging to a state when the DBS is on vs. a state when the DBS is off. In particular, the framework applies binary classifiers to features derived from networks constructed based on the multivariate EEG data. The first part of this study attempts to apply the classification framework by focusing on physiological frequency ranges with three different binary classifiers including logistic regression, least absolute shrinkage and selection operator (LASSO), and a new method known as principal component stepwise selection logistic regression (PCSSLR) that is developed in this thesis. The second part attempts to identify potential biomarkers to be used as feedback control signals for an adaptive DBS device. The results of both parts will help to address the question of whether or not EEG data can be used to detect feedback signals for use in adaptive DBS feedback control system and to establish a modeling framework to develop similar classifier for performing statistical classification based on network features to identify which group a temporal signal belongs to.

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Chapter 1 Introduction

1.1 Network and Brain Functional Connectivity

Network science has been increasingly applied to study complex systems. Example of systems that have recently been studied as networks include protein interaction network, communication network, infrastructure network, social medial network, financial network, and brain functional network [1]. A better understanding of the dynamics of these networks and the interrelationships of their components can be important because network features may reveal precursors of changes of the networks that are not easily detectable otherwise [1]. In the past decade, the understanding of networks has been applied in many different applications because a new array of tools and practical techniques has been developed to map and analyze networks [2]. In application s to understand different disease mechanism, for example, it is generally accepted now that it is not enough to identify the list of all genes associated with a genetic disease. It is believed that it is also important to map the detailed connection of the cellular components that are influenced by such genes [2]. Brain functional connectivity network is another example of networks that have recently been analyzed to reveal discriminating network-based features using scalp EEG recordings. In this study, EEG data are used to construct brain functional network for developing a classifier of a binary state related to a treatment procedure known as deep brain stimulation (DBS). Such a classifier may reveal features that can be used as potential biomarkers to assess treatment effects of deep brain stimulation and, ultimately, lead to the realization of reliable feedback control system of DBS in Parkinson’s disease (PD).

1.2 Electroencephalography (EEG)

Electroencephalographic (EEG) recording is a clinical tool used by physicians to diagnose and monitor patients with neurological disorders [3]. An EEG recording records electrical activity of the brain of an individual in the form of a multivariate time series dataset. It is especially important for patients with epilepsy. Abnormalities in EEG recording are used in clinical setting to confirm diagnosis of epileptic seizures [4]. In addition, accurate interpretation of EEG data by physicians is the key to monitoring other disorders including sleep disorders, coma and brain death [3].

1.2.1 Electroencephalographic Artifacts

EEG recordings can become contaminated by data captured from non-cerebral signals. The recordings often include electrical activity of both cerebral and non-cerebral origin [5]. The recoding activity that is not of cerebral origin is called artifact. EEG signals are susceptible to different types of artifacts, including ocular, muscular, movement and environmental types. An EEG recording contaminated with artifacts reduces its interpretability by clinicians and neurologists [6].

To overcome this problem, existing diagnostic systems commonly depend on experienced clinicians to manually select artifact-free epochs from EEG recording. The clinicians would use only the artifact-free epoch from the EEG data to interpret the EEG signals from the patients. In addition, different approaches of recognition, source identification, and elimination of artifacts have also been developed to reduce misinterpretation of EEG recordings contaminated with different types of artifacts [7].

1.3 Deep Brain Simulation (DBS)

In recent years, deep brain stimulation neurostimulator (DBS) implant has become increasingly common among patients with neurological and psychiatric disorders [8]. The DBS implant is a medical device that sends electrical impulses in the brain for treatment of movement and psychiatric disorder. Implanting a DBS involves surgical placement of electrodes into a number of specific anatomical structures including the ventrointermediate nucleus of the thalamus (VIM), globus pallidus internus (GPi), and subthalamic nucleus (STN) of the patient's brain [9]. This procedure has been approved as treatment for treatment-refractory Parkinson's disease and medication-resistance form of major depressive disorder.   In Europe and Canada, deep brain stimulation has also been approved by regulatory agencies to use as treatment to control epileptic seizures.

1.3.1 Deep Brain Stimulation and Electroencephalographic Aliasing Artifacts

Deep brain stimulation neurostimulator, however, has been shown to induce a peculiar form of aliasing artifacts in EEG recordings [10]. Jech at al. (2006) described these artifacts as distinctive vertical lines in power spectrum of EEG recordings contaminated with DBS-induced artifacts [8] that overlap with cerebral waveforms in frequency spectral density. These vertical lines occur at dominant frequencies that are harmonics of the stimulation frequency programmed for the DBS neurostimulator and occur due to aliasing [10]. Because there are indications that U.S. Food and Drug Administration will approve deep brain stimulation procedure as a treatment option to control seizure for patient with epilepsy in the United States., more patients with epilepsy, who would normally require EEG monitoring their conditions, will likely receive deep brain stimulation as a treatment option. However, DBS treatment will introduce EEG artifacts that overlap with cerebral waveforms in EEG recordings for this group of patients and significantly interfere with accurate interpretation of such EEG recordings by neurologists.

1.3.2 Aliasing Artifact

Aliasing is an undesirable effect arising from discrete-time sampling. The Nyquist theorem states that at least twice the frequency of input signals are needed to accurately define the signals. To accurately measure frequency (f) of a signal, it is necessary to use a sampling rate that is at least 2f. If a sampling rate (2f) is used to measure a signal at frequency greater than f, the measured signals will contain aliasing artifacts [10]. This situation is relevant to DBS-induced aliasing artifacts because DBS electrical stimulation frequency of many clinical cases is programmed at a frequency just above the Nyquist frequency given a normal EEG sampling rate of 200Hz. For example, if DBS device is programmed to deliver electrical pulse at stimulation frequency of 105 Hz, DBS artifacts in EEG recordings will likely appear.

Aliasing artifacts are false signals. This kind of artifacts has frequencies appear as mirror images of the original frequency and its harmonics around the Nyquist frequency as illustrated in Figure 1.

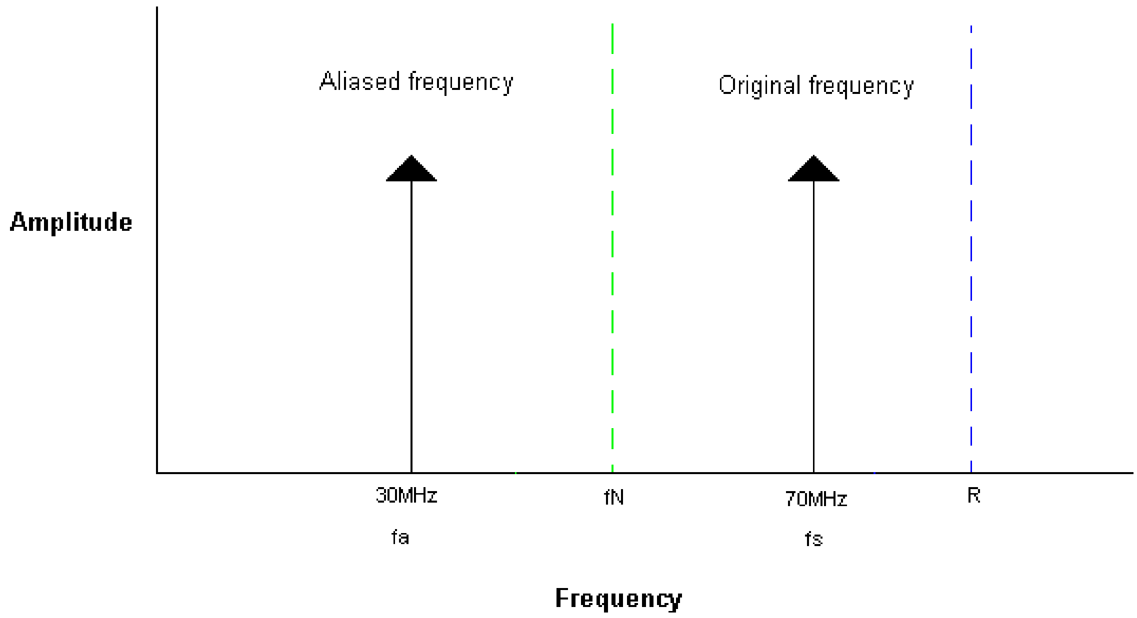

Figure 1. Stylized illustration of aliasing artifacts due to undersampling.

In Figure 1, the aliased signal has frequency fa which occurs due to aliasing effect of the original signal which has frequency of 70 MHz. In this illustration, R is the sampling frequencies at 100Hz and fN is the Nyquist frequency at 50Hz.

The frequency of the aliased signal can be predictable and is found by

$$fa=|R\,n - fs|$$

where fa is aliased frequency, n is an integer multiple of sampling rate R and fs is frequency of the signals or its harmonic frequencies [10].

1.3.3 Frequencies of Electroencephalographic Aliasing Artifact Associated with Deep Brain Stimulation

DBS artifacts consist of alias frequencies derived from the stimulator frequency and its harmonics [10]. According to Nyquist sampling criterion, when the sampling rate is not sufficiently high to capture a signal, alias frequencies can be predicted based on the signal frequency of interest and its harmonics. In the case of DBS artifacts in EEG data, it was shown that alias frequencies can be predicted up to a variable degree of accuracy [10]. However, predictability of the energy level of such kind of artifact remains elusive. Different EEG channels may have different patterns of alias, reflecting differences in how DBS signals are perceived at each electrode location due to volume conduction of inhomogeneous tissue.

Because of the sampling rate of 200 Hz, if the programmed DBS stimulation frequency is over 100 Hz, a series of aliasing artifact may appear in the sampled EEG time series data. For example if a DBS implant is programmed to stimulate at 105 Hz, then the following aliased frequencies may appear in any EEG electrode recording.

105 Hz Signal			210 Hz Signal			420 Hz Signal		
F	N	Fa*(N)<100Hz	F	N	Fa*(N)<100Hz	F	N	Fa*(N)<100Hz
105	1	94.95	210	1	10.1	420	2	20.2
210	1	10.1	420	2	20.2	840	4	40.4
315	2	84.85	630	3	30.3	1260	6	60.6
420	2	20.2	840	4	40.4	1680	8	80.8
525	3	75.75	1050	5	50.5			
630	3	30.3	1260	6	60.6			
735	4	65.65						
840	4	40.4						
945	5	55.55						
1050	5	50.5						
1156	6	44.45						
1261	6	60.6						

The aliased artifacts distort the underlying cerebral signals captured in EEG recordings. The most prominent issue occurs if aliased artifacts occurs among the alpha band (7-13 Hz) and beta band (13-31Hz) because these frequencies overlap with cerebra signals that can be captured in EEG recordings. The overlapping of the aliasing artifacts and cerebral signals can lead to difficulty for physicians to accurately interpret findings from EEG recordings, potentially leading to either false positive or false negative diagnoses.

In this study, a proposed classification framework will be applied to such aliasing EEG artifacts associated with DBS at specific frequency ranges. These aliasing artifacts will be used as a first attempt to develop a classifier that discriminate an EEG time segment associated with the DBS-on state from the DBS-off state.

1.4 Physiological EEG Frequency Bands

Most of the cerebral signals captured in clinical EEG recordings are within 1- 20Hz. Waveforms observed in EEG recordings are subdivided into frequency bands.

Bands	Frequency (Hz)
Alpha	7-13
Beta	13-31
Gamma	32+

These cerebra signals are directly related to the physiological state of a patient. In this study, the propose classification framework will be applied to these the alpha and beta frequency bands. The application of the classification framework will attempt to develop a classifier that can discriminate an EEG time segment associated with the DBS-on state from the DBS-off state.

1.5 Electrodes Placement

EEG recording is performed by placing electrodes on the scalp of an individual. The placement of the EEG electrodes in a clinical setting follows the 10-20 system convention. This system was developed to ensure standardized EEG recordings that can be compared over time and among patients [6]. The electrode names included in this convention are Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, and O2. Figure 2 shows the 10-20 system map of the electrodes. In a clinical setting, the actual EEG data read by clinicians are channels data which are calculated as the difference between a given pair of neighboring electrode in order to eliminate some amounts of artifacts. For example, the Cz-Pz channel represents the difference of the data recorded for electrode Cz and electrode Pz.

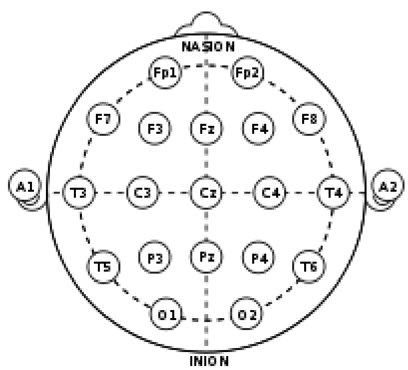

Figure 2. 10-20 system used in placement of EEG electrodes

1.6 Binary Classifier

There is a number of methods that are commonly used to developed binary classifier. In this study, the following methods are used to train and test the classification model.

1.6.1 Logistic regression

Logistic regression estimates the relationship between the dependent variable and the independent variables by applying the logistic function to estimate probability of a data point belonging to a class represented by the dependent variable. For binary classification problem, the dependent variable can take either one of two values representing the classes.

Given m independent variables, the logistic regression uses the following logistic function to estimate the probability of the dependent variable to be either one of the two classes.

$$F(x) = \frac{1}{1 + e^{-(\beta_0 + \beta_1 x_1 + \cdots + \beta_m x_m)}}$$

Chapter 2 Literature Review

2.1 EEG Brain Functional Connectivity Networks

In order to model and analyze EEG data, a number of recent studies have applied network science to model EEG data as complex brain functional connectivity networks. Zeng et al constructed EEG connectivity network from EEG data with characteristics of mean clustering coefficient and path length to assess whether or not such complex network-derived biomarkers can be effectively used to track cognitive impairment of patients with diabetes [11]. Jalili used correlation of EEG data from healthy subjects to construct binary connectivity network and computed global and local efficiency in order to compare and contrast network characteristics of left and right cerebral hemispheres [12]. Tóth et al analyzed brain connectivity network using EEG recordings with phase synchronization in different frequency bands to identify potentially predictive characteristic feature of mild cognitive impairment [13]. Sargolzaei et al proposes developing a method based on brain functional connectivity networks using scalp EEG data to classify whether a pediatric patient has epilepsy or not [14].

2.2 Biomarkers of Parkinson’s Disease and Deep Brain Stimulation

A number of studies have established from Parkinson’s disease (PD) patient receiving DBS that power spectra tend to show high level of synchronization activity over the range of 13 – 30 Hz when recorded in the off-medication state [15]. Studies have shown that beta activity is suppressed with levodopa treatment and DBS treatment [15]. These studies point to an example of a potentially universal signal that can be used to discriminate effects of DBS treatments in patients with PD.

2.3 Existing Studies of Inter-channel Relation Analysis of EEG Data

Inter-channel similarity and dissimilarity of EEG data are traditionally analyzed using several different numerical metrics. The common methods to calculate associations in neurophysiological records are described in the following section. These methods include linear correlation, coherence, mutual information and phase lag index [4].

2.3.1 Linear Correlation

The most common method applied in the literature to estimate inter-EEG-electrode relation is linear correlation in the time domain [4]. It is widely used to measure correlation between spikes discharges in microelectrodes studies. The correlation between two discretized EEG signals, x(t) and y(t), is defined by Pearson correlation coefficient

$$\rho_{xy} = \frac{cov[x(t), y(t)]}{\sqrt{var[x(t)]}\,\sqrt{var[y(t)]}}$$

$$\rho_{xy} = \frac{\sum_{k=1}^{N}(x(k)-\bar{x})(y(k)-\bar{y})}{\sqrt{\sum_{k=1}^{N}(x(k)-\bar{x})^2\sum_{k=1}^{N}(y(k)-\bar{y})^2}}$$

Linear correlation compares the amplitudes of the signals in order to quantify the co-movement of the data series over a measurement domain such as temporal domain.

Pearson correlation coefficient estimates association between any two sets of data sets and is bounded from -1 to 1. A value of -1 implies a perfect inverse linear relation between the two data sets whereas a value of 1 signifies a perfect direct linear relation.

2.3.1.1 Limitation

The major limitation of linear correlation is that it measures only linear relations. Non-linear relation between two given signals is usually not sensitive enough to be detected as significant association by the use of linear correlation. Thus, the use of Pearson correlation coefficient may underestimate association between two EEG electrode recordings if the EEG recordings exhibit nonlinear relation. Several studies, however, have found that linear correlation can perform as well as other nonlinear association measures when applied to neurophysiological data [16]. Linear correlation of a sampled set of data also does not converge to one finite value if the data sets are not stationary. The estimate of correlation using Pearson correlation coefficient changes over time if the underlying x(t) and y(t) have means and variances change over time.

2.3.2 Coherence

Coherence is a measure of association of two signals in the frequency domain using cross-spectrum and power spectral density functions [4]. Coherence quantifies how similar two signals are in terms of phase difference and frequency.

Coherence between two discretized EEG signals x(t) and y(t) is defined as

$$Coh_{xy}(f) = \frac{|\, P_{xy}(f)|^2}{P_{xx}(f)P_{yy}(f)}$$

where P_{xy} is the cross-spectral density of signal x and signal y, P_{xx} and P_{yy} are the power spectral density functions of x(t) and y(t).

Coherence estimates is a function of frequency and has values over the range of [0,1]. Coherence indicates how well a signal x corresponds to another signal y at a given frequency.

If two sinusoidal signals are perfectly coherent, then the two signals can result in stationary interference.

2.3.3 Mutual Information

Mutual Information (MI) measures association between two signals based on information theory [4]. MI quantified the amount of information that are known about a signal, x, with the use of another signal y. An estimate of MI (x,y) measures the amount of uncertainty reduction in a signal x due to what is already known about the signal y. MI of two discrete signals x and y is defined as

$$MI(x,y) = \sum_{y \in Y} \sum_{x \in X} p(x,y) \log\left(\frac{p(x,y)}{p(x)p(y)}\right)$$

where $\mathrm{p}(\mathrm{x},\mathrm{y})$ represents the joint probability distribution function of x and y, $\mathrm{p}(\mathrm{x})$ and $\mathrm{p}(\mathrm{y})$ are the marginal probability distribution of x and y.

Given x and y are independent, MI(x,y) = 0. If x is a function of y and there is no uncertainty in this functional relation, MI (x,y) is equal to the amount of uncertainty contained in x or y alone. Specifically, this amount of uncertainty is represented as information entropy $H(x) = -\sum_{i=1}^{n} P(x_i) log P(x_i)$ for x or $H(y) = -\sum_{i=1}^{n} P(y_i) log P(y_i)$ for y. MI is lower bounded by 0. Its upper bound depends on entropy of x or y such that

$$I(x,y) \leq \min[H(x), H(y)].$$

2.3.4 Phase Lag Index

Phase lag index (PLI) measures asymmetry of phase difference distribution between two signals calculated based on instantaneous phases. In EEG recordings, PLI is known to be less affected by influence of volume conduction due to signal sources that generate large electrical fields that propagate to more than one electrode [17].

In particular, PLI measures statistical interdependencies between two signals by focusing on the strength of association due to consistent and nonzero phase lag between the signals that cannot be explained by volume conduction from a single strong source [18]. PLI is defined as

$$\Phi \equiv |< sgn[\sin(\Delta\phi(t_k))] >|$$

where < g > represent average of all element of g and $\Delta\phi$ is the phase different between two signals for each time point k. PLI has value ranges over the interval [0,1]. A PLI value of 1 indicates phase differences due to interactions not relating to volume conduction and noise.

2.4 Existing Studies of Network Analysis

A large number of existing studies involved with EEG data focus on using undirected networks to gain insight of network characteristics [19]. An undirected network is defined with a set of nodes and links with no specific orientation. A link represents a quantitative measure of relation between two nodes. The link from a node of x to a node y is identical to the link from the node of y to the node of x in an undirected network.

In the context of EEG data, nodes may represent the channels that capture signals from the brain while channels represent brain region. Link may represent connections between channels or brain regions. These connections can be quantified using a range of metric. Existing studies have used different inter-relation methods to quantify association among EEG channels or brain region. These methods include linear correlation, coherence, mutual information and phase lag index [4].

In order to construct a network for EEG data, a connectivity matrix

$$A = [a_{ij}]$$

is used to quantify all connection among the EEG-related nodes. Two different types of connectivity matrix are used in existing studies.

2.4.1 Binary Network

A binary network is constructed by converting a connectivity matrix using a threshold. Specifically, a_{ij} is set to be 1 if the underlying interrelation measures between node i and node j is > τ where τ is a pre-defined threshold, and 0 otherwise. Because a pre-defined weight is used as threshold, this method is known as hard thresholding [19]. Hard thresholding the interrelationship measure results in an unweighted network. Because hard thresholding encode connections between nodes in a binary fashion, it is sensitive to the choice of the threshold.

2.4.2 Weighted Network

A weighted network is constructed with links that have weights assigned. Specifically, a_{ij} is set to have a quantitative value assigned. Unlike in a binary network, the connectivity matrix does not only have value of 0 or 1. Rather, the connectivity matrix has values within a range. In practice, the connection matrix is normalized based on the mean weights in the matrix such that each a_{ij} can represents a Z-score calculated based on the mean and standard deviation of all a_{ij} [19].

2.4.3 Relevant Network Measures from Existing Studies

Network measures can be used to detect patterns of electrical signals and artifacts of EEG recordings. The following describe the mathematical definitions of network measures commonly used to quantify EEG-based binary and undirected network [19].

2.4.3.1 Basic Notation and Concept

Given N is a set of all nodes in the network, n is the total number of nodes, L is the set of links in the network, and l is number of links. (I, j) is link between nodes i and j where both i and j are in the set of N. a_{ij} is the connection measure between i and j such that $a_{ij} = 1$ where (i,j) exists and $a_{ij} = 0$ otherwise [19]. The number of links, l, is defined as

$$l = \sum_{i,j \in N} a_{ij}$$

2.4.3.2 Degree

Degree is the number of links connected to a node and is defined as

$$k_i = \sum_{j \in N} a_{ij}$$

2.4.3.3 Shortest path

Shortest path is a quantity used to measure integration of the network. The shortest path between node i and j is defined as

$$d_{ij} = \sum_{a_{uv} \in g_{i \leftrightarrow j}} a_{uv}$$

where $g_{i \leftrightarrow j}$ is the shortest path between node i and j.

2.4.3.4 Number of Triangles

Number of triangles is a quantity used to measure segregation of network. The number of triangles around a node i is defined as

$$t_i = \frac{1}{2} \sum_{j,h \in N} a_{ij} a_{ih} a_{jh}$$

2.4.3.5 Segregation Metrics

2.4.3.5.1 Clustering coefficient

Clustering coefficient of a network can be defined as

$$C = \frac{1}{n} \sum_{i \in N} C_i = \frac{1}{n} \sum_{i \in N} \frac{2t_i}{k_i(k_i - 1)}$$

where C_i is the clustering coefficient of node i. A clustering coefficient of a node i measures the degree to which nodes in a graph tend to cluster together.

2.4.3.5.2 Efficiency

Efficiency of a network measures how efficiently the network exchanges information. The local efficiency of a node i characterizes how well information is exchanged by its neighbors even if the node is removed.

$$E_{loc} = \frac{1}{n}\sum_{i\in N} E_{loc,i} = \frac{1}{n}\sum_{i\in N} \frac{\sum_{j,h\in N, j\neq i} a_{ij}a_{ih}\left[d_{jh}(N_i)\right]^{-1}}{k_i(k_i - 1)}$$

where $E_{loc,i}$ is local efficiency of node i, and $d_j, h(N_i)$ is the length of shortest path between j and h that contains only neighbors of i.

2.4.3.5.3 Modularity

Modularity of a network measures strength of a subdivision of a network. Network with high modularity has many connections between nodes within modules but only sparse connections between nodes in different modules.

$$Q = \frac{1}{l}\sum_{i,j\in N}\left(a_{ij} - \frac{k_i k_j}{l}\right)\delta_{m_i,m_j}$$

where m_i is module containing node i and $\delta_{m_i,m_j} = 1$ if $m_i = m_j$, and 0 otherwise.

2.4.3.6 Centrality Metrics

Centrality metrics are used to identify the node that is the most important for a given network.

Closeness centrality is defined as

$$L_i^{-1} = \frac{n-1}{\sum_{j\in N, j\neq i}\{d_{ij}\}}$$

Betweenness Centrality is defined as

$$b_i = \frac{1}{(n-1)(n-2)} \sum_{h,j \in N, h \neq j, h \neq i, j \neq i} \frac{\rho_{hj}(i)}{\rho_{hj}}$$

where ρ_{hj} is the number of shortest path between h and j, and ρ_{hj} is the number of shortest path between h and j that pass through i.

2.4.3.7 Measure of Resilience

Degree of distribution defines the cumulative degree distribution of the network

$$P(k) = \sum_{k' \geq k} p(k')$$

where $p(k')$ is the probability of a node having degree k'.

2.5 Limitations and Challenges

To analyze physiological alpha band, beta band and aliasing artifacts of DBS, it is necessary to isolate signals around the few artifactual frequencies. Many existing studies of inter-channel relation of EEG data apply linear correlation of magnitude of signal in the time domain. Since the raw EEG data consist of signals as a mixture of a spectrum of many frequencies, results obtained from analyzing network characteristics of raw EEG data are based on all available frequencies including both cerebral electrical signal and non-cerebral artifacts. As a result, time-based linear correlation and mutual information are not directly applicable to analyze EEG data of a particular frequency range.

2.6 Open Problems

Network analysis is a useful approach to analyze connection measurement among EEG multi-channel data set as a complex system with inter-related components.

- In order to model network effects specific related to alpha band, beta band and aliasing artifacts in EEG signals that are associated with DBS, an alternative modeling framework, including metrics and workflows, is needed.
- In the context of DBS-associated effects, comparing network constructed with EEG data recorded while DBS was on and off for different physiological frequency ranges of alpha and beta bands may lead to insights of which combination of frequency ranges and channels may be used as potential biomarkers for the purpose of elucidating behavior of the EEG data as a network system.

Chapter 3 Research Objective and Problems

3.1 Framework of Developing Classifier for EEG Networks

The overall motivation of this study is to contribute to identify potential biomarkers that can be used as feedback signals in a DBS feedback control system. An objective to achieve is to develop a framework to analyze the EEG segments over a particular frequency ranges as a network system. A modeling framework suitable to capture behavior of EEG signals over time would likely lead to better classification performance of EEG segments associated with DBS. In developing such a modeling framework, it is important to recognize that both prediction results and interpretability of the prediction results are important to clinicians. Figure 3 summarizes the general process of developing and applying such a classification modeling framework.

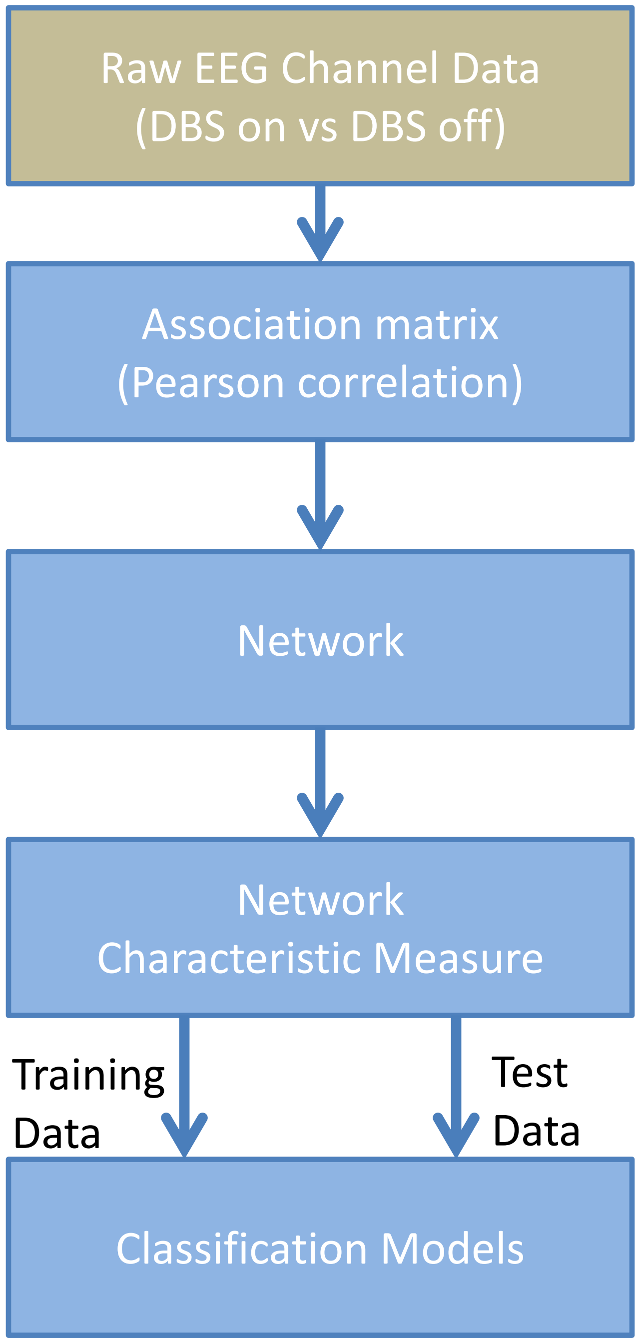

Figure 3. Conceptual illustration of workflow involved in developing classification model using EEG channel data and network information to differentiate DBS-on vs. DBS-off state.

One relevant proposed idea to overcome the limitation of time-based correlation as a metric of association among EEG channels is to propose a new metric to measure association among EEG channel data that would focus on only the effect of EEG data over a particular frequency range. In this thesis, a metric that is being developed is based on Pearson correlation coefficient that is computed over the frequency domain rather than over the time domain.

The EEG recordings with DBS artifacts using 10-20 EEG system consist of temporal data recorded from 18 channels. Using Pearson correlation coefficient of 1-minute discrete Fourier transform spectrum of original 19 electrode recordings with 200 Hz sampling rate, it has been demonstrated in a previous study conducted hat there can be significant correlation among subsets of these 19 EEG electrode data using clinical data obtained from neurology cases. In addition, the correlation coefficient is time-varying. However, the Pearson correlation coefficients previously investigated measure spectrum correlation based on the entire spectral range of 0 – 100 Hz. Thus, the analysis did not specifically address correlation of the frequencies at which alpha activity, beta activity or DBS artifacts occur. In this study, specific frequency range corresponds to alpha activity, beta activity and DBS artifacts are selected separately to develop networks based on correlation among the selected frequency range. These networks are then used to derive network metrics to be used as features in developing classification model for differentiating EEG data recorded while DBS is on versus DBS is off. The resulted classification model will lead to biomarkers for identifying effects of DBS on physiological frequency range of EEG recordings and/or brain activity as recorded by EEG devices.

3.2 Classification of EEG Data Using Network Characteristics

A main objective is to apply the proposed framework to model and to classify EEG data into DBS-on versus DBS-off based on characteristics of network constructed using association matrices focusing on isolating effects of alpha band, beta band and potential DBS aliasing artifact frequency ranges. The association metrics used in this study is Pearson correlation in frequency domain. Frequency based correlation can isolate effects of a particular frequency ranges from EEG channel data. The classification model is built by using training and testing EEG data sets focusing on network characteristic of clustering coefficient because clustering coefficient has previously been shown to lead to good binary classification performance for distinguishing EEG frequency correlation network into DBS-on or DBS-off states. The end result is a classification model that can be used to predict if a particular EEG data set was recorded while a DBS device is on or off. The classification framework based on association among EEG channel data would represent method to isolate network features that are likely to be important in assessing treatment effects of DBS in patients with Parkinson's disease.

3.2.1 Classification Models based on Artifacts

The classification framework is applied to attempt to use specific correlation of DBS artifacts among the 18 channel dataset to develop a classifier. The correlation analysis is applied to a narrow range of frequencies around the artifactual frequencies such as 10.1Hz, 20.2Hz, 30.3Hz and 40.4Hz. The result would demonstrate associations among artifacts in the 18 channel recordings. Since the characteristic of these artifacts are unique when DBS is on, the classifier developed should indicate predictive relationship that can be used in classifying EEG data into DBS-on versus DBS-off categories. The result of this part of the study will serve as a baseline control for comparing binary classifier performance with those resulted from physiological frequency bands.

An objective criterion to assess relative performance of binary classifiers is Area Under Curve (AUC) of the corresponding Receiver Operating Characteristic (ROC) curve of the binary classifiers.

3.2.2 Receiver Operating Curve (ROC) and Area Under the Curve (AUC)

3.2.2.1 Receiver Operating Curve (ROC)

Receiver Operating Characteristic (ROC) curve is a graphical tool that shows the performance of a binary classifier. More specifically, a ROC curve is created by plotting True Positive Rate (TPR) against False Positive Rate (FPR) for various thresholds that are used to obtain the binary classification result of a binary classifier. A ROC curve is used for various purposes. This kind of plot provides

1) An analytical tool to select an optimal threshold to apply for creating binary classification result of a binary classifier; and
2) An indicator of relative performance of a binary classifier over the range of possible threshold.

In this study, ROC is used to evaluate and compare the binary classification performance of different binary classifier over the range of all possible thresholds. Such an evaluation will be useful to assess the binary classification performance of a given classifier over all possible range of cutoffs for the purpose of binary classification.

In an ROC curve, a completely random guess would result in a point along the diagonal line from the bottom left to the top right corners. This diagonal line is also known as line of no-discrimination. The perfect binary classifier with the best possible prediction result would give a point in the upper left corner of the ROC space with 0% FPR and 100% TPR. An example ROC curve is show in Figure 4.

3.2.2.2 Area Under the Curve (AUC)

Area Under the Curve (AUC) is the normalized area between the ROC curve and x-axis of the ROC space. The AUC of a binary classifier can be used to quantify the binary classification performance of a binary classifier. AUC ranges from 0 to 1. An AUC of 1 indicates that a binary classifier has a perfect binary classification performance and an AUC of 0.5 indicates a binary classifier has a random classification performance. An illustration of AUC is shown in Figure 4.

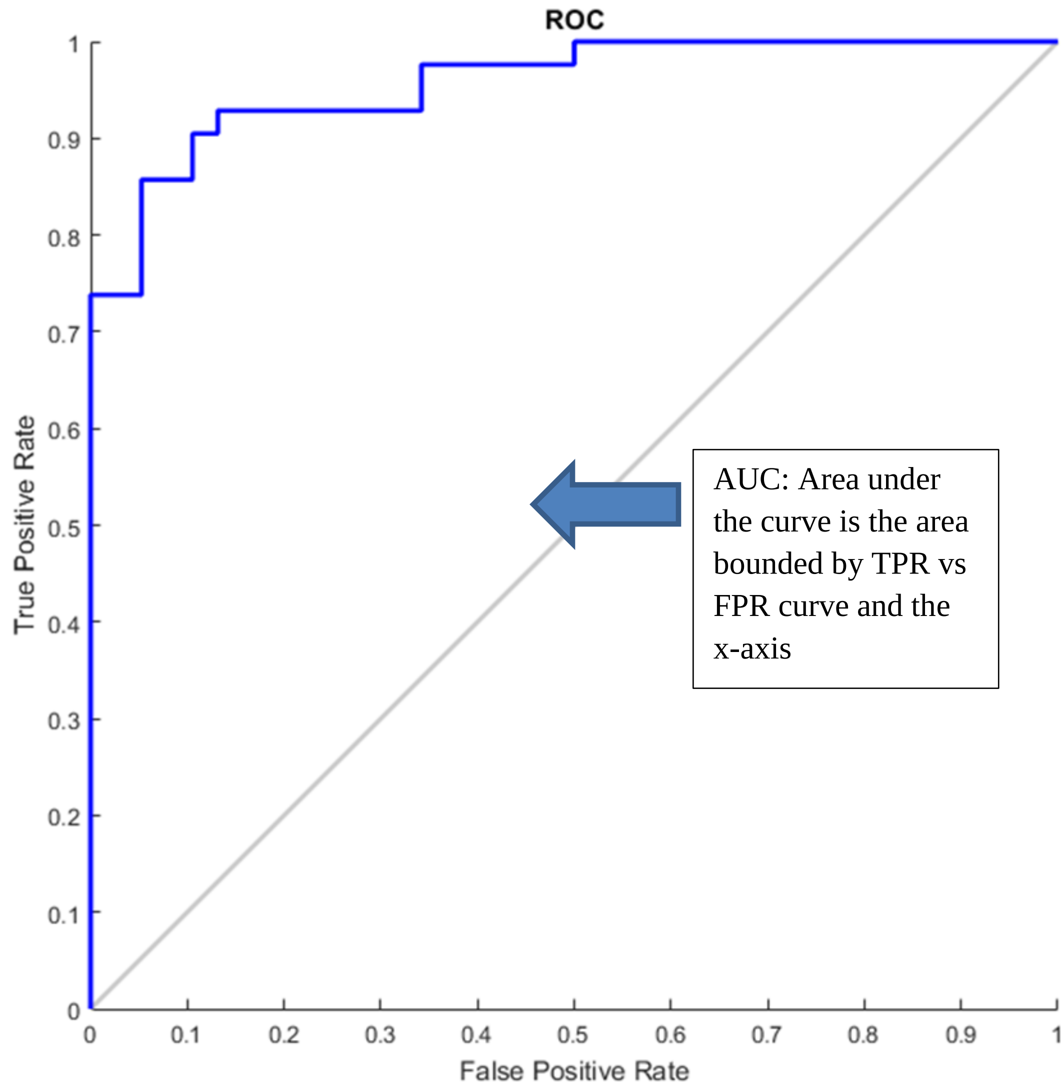

Figure 4. Example Receiver Operating Curve and illustration of Area Under the Curve.

3.2.3 Classification Model based on Physiological Frequency Ranges

After applying the classification framework to example EEG artifacts related to DBs, the same classification framework is applied to alpha frequency band and beta frequency band to attempt to build a binary classifier for DBS on and off state based on frequency ranges with physiological significance. The alpha band consists of signal over 7-13 Hz and the beta band consists of brain activity over 13-31 Hz. The result of a classifier that can discriminate DBS-on vs. DBS-off state would likely point to network features of alpha or beta activities over different brain regions that can be used to assess treatment effects of DBS for patients with Parkinson’s disease.

Chapter 4 Research Data

De-identified set of EEG recording (12 hours duration) from a patient undergoing chronic bilateral subthalamic nucleus (STN) DBS treatment for Parkinson's disease is used in this study. Of the 12 hours of EEG recording, 6 hours of recording were recorded while DBS was on and 6 hours of data were recorded while DBS was off. The DBS was performed with an implanted Medtronic Activa PC deep brain stimulator [10]. The EEG data was acquired using a Nihon Kohden EEG-1200 system.

4.1.1 Clinical EEG Data and DBS Aliasing Artifact

Recognition of DBS artifacts is essential in understanding the importance of these artifacts. An example of EEG recordings before and after DBS was turned off is shown in Figure 5.

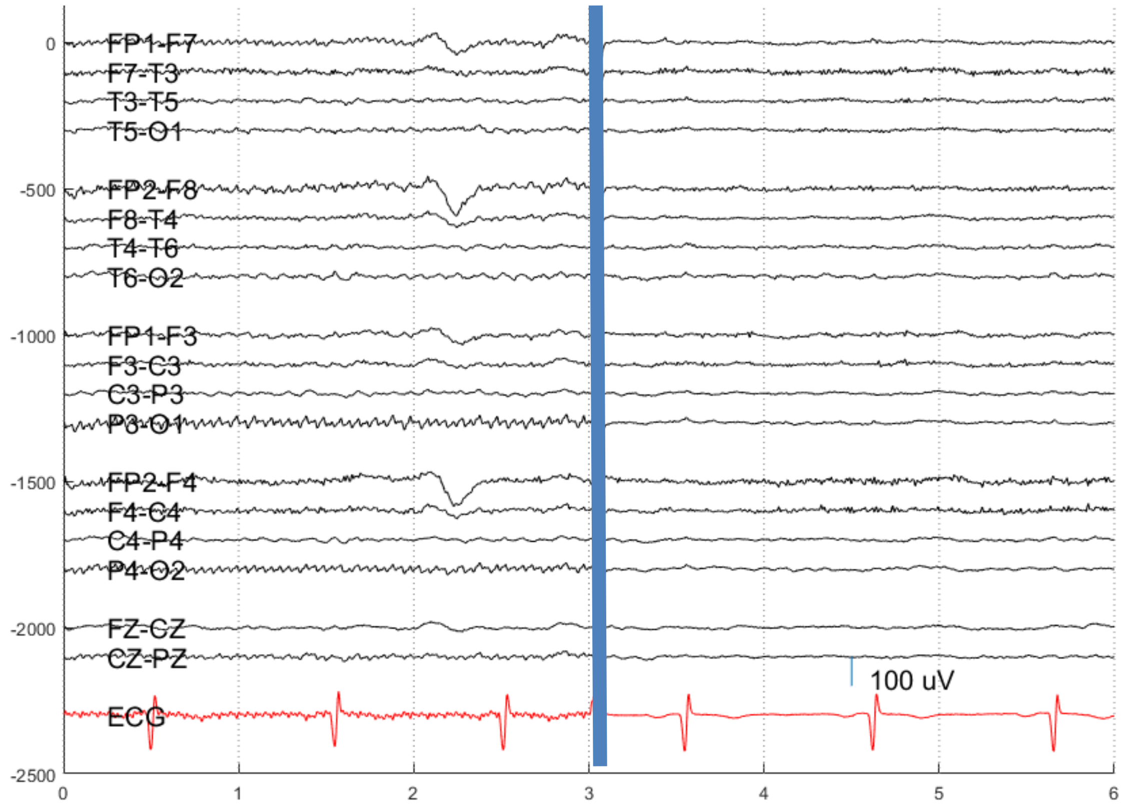

Figure 5. EEG Recording with DBS turned on and DBS turned off. The blue vertical line separates the 18-channel EEG data when the DBS was turned on versus when the DBS was turned off. Note that 10 Hz artifacts in Fp2-F8, P4-O2 and P3-O1 channels are especially noticeable.

According to Figure 5, the DBS aliasing artifacts observed for this EEG recording were diffuse and especially visible with 10 Hz frequency. Converting the signals into frequency-based signal using fast Fourier transform reveals frequency characteristics of the EEG recordings contaminated with DBS-induced aliasing artifacts as shown in Figure 6 [10].

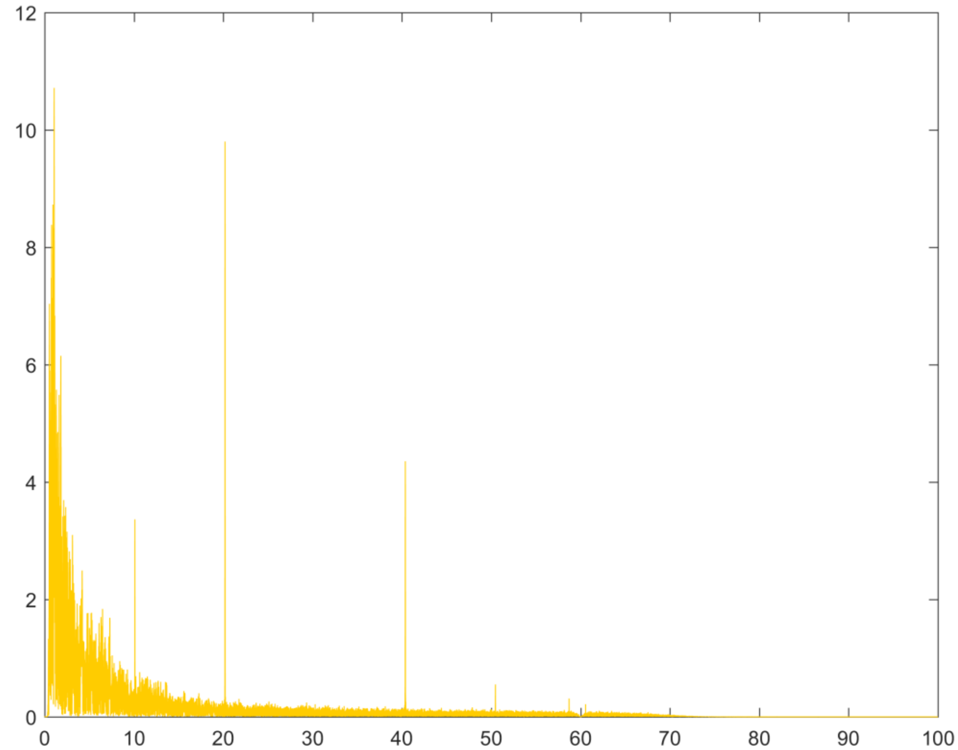

Figure 6 Example of EEG channel data in frequency domain. Notice the vertical artifactual signals at approximately 10Hz, 20 Hz, and 40 Hz.

Figure 7shows the spectrum of the EEG data for each channel. The vertical lines are the DBS aliasing artifacts. These artifacts are prominent when DBS is on. When DBS is off, the artifacts are no longer visible in EEG spectrum in shown in Figure 8.

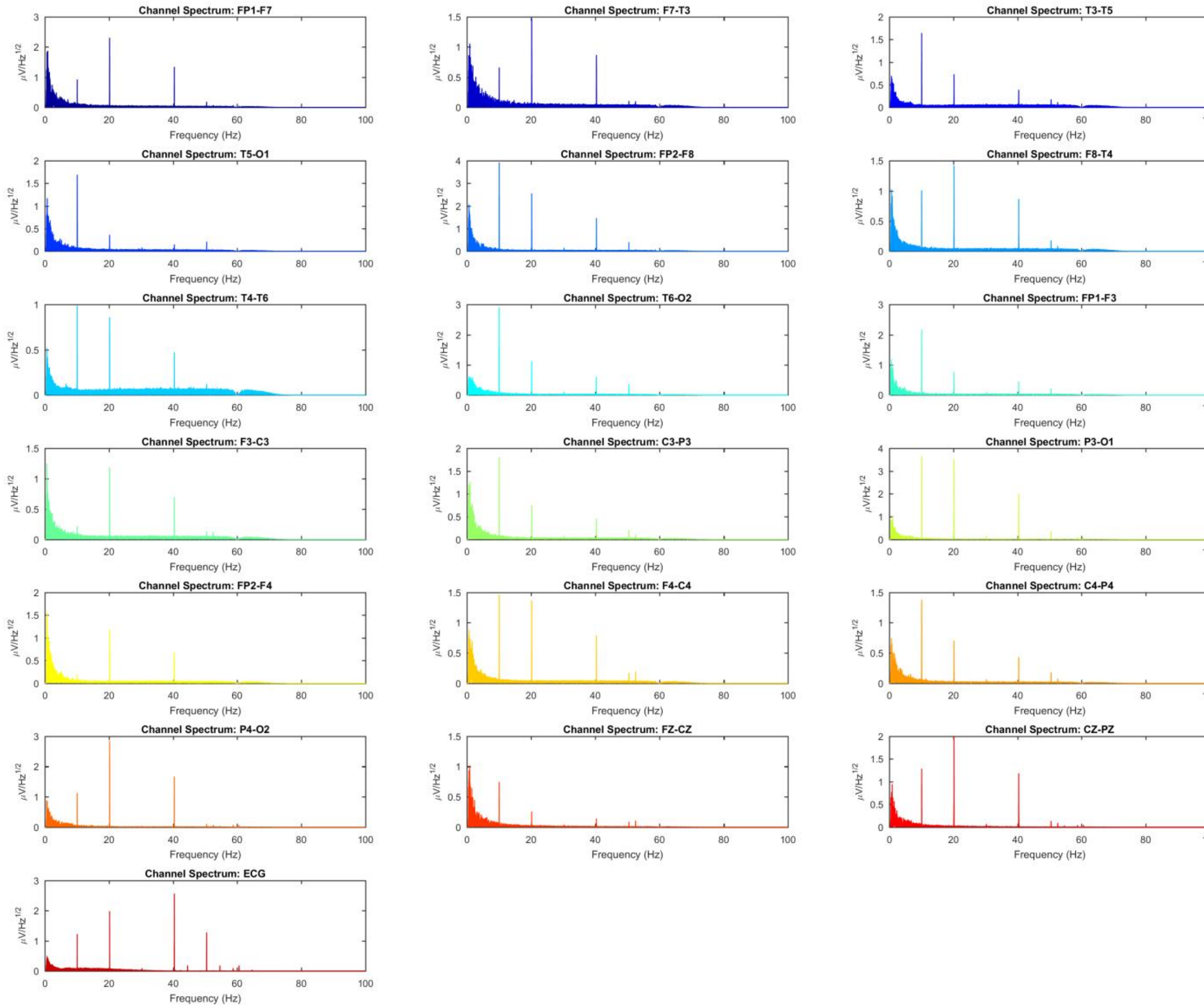

Figure 7 Spectral density estimate of EEG data with DBS-on over an approximately 6-hour period.

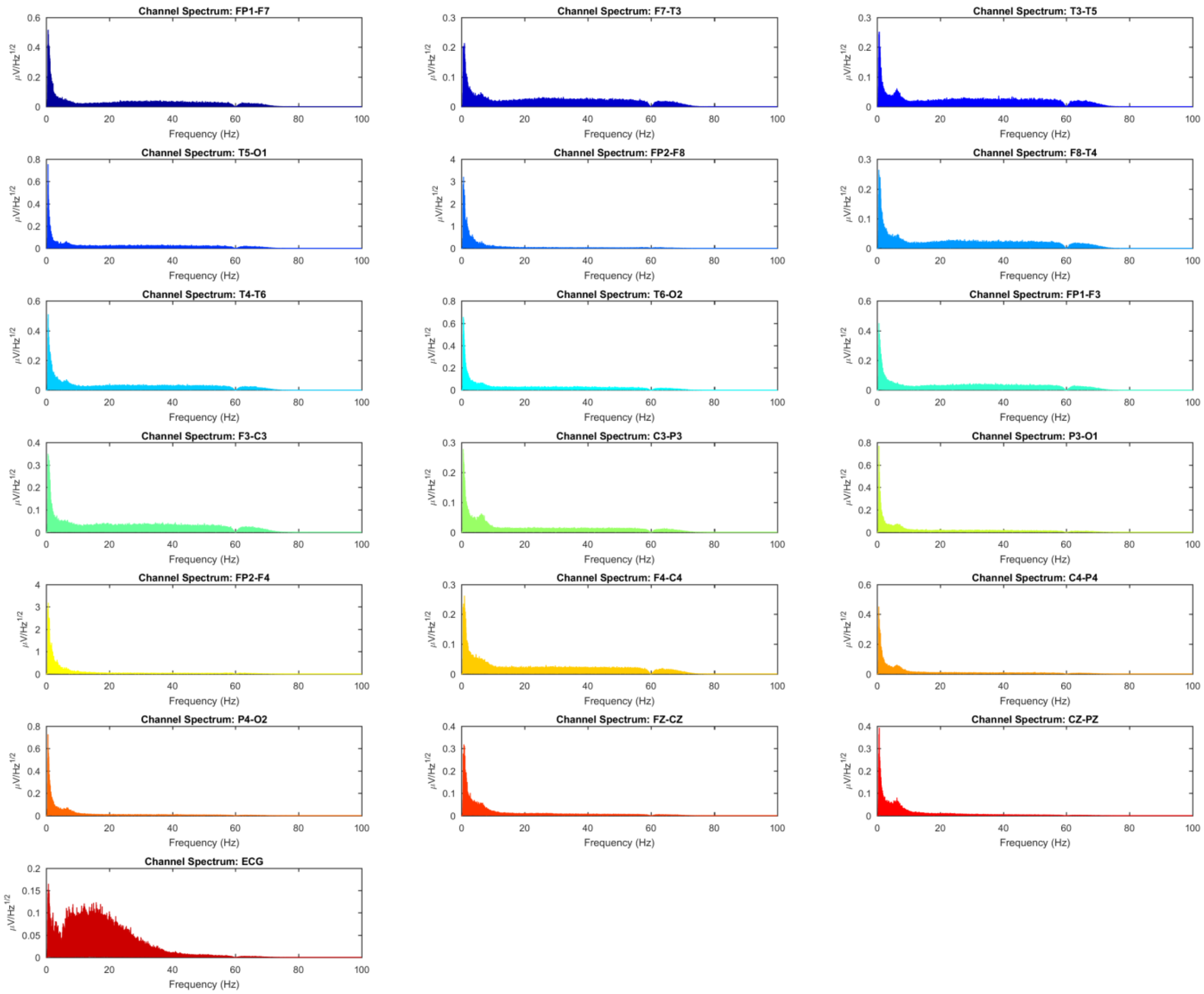

Figure 8 Spectrum of EEG signals with DBS-off over an approximately 6-hour period.

Chapter 5 Research Methods

5.1 Modeling Framework for Research Problem

To quantitatively measure dependency among the electrode signals, a newly proposed method to measure association in frequency among discretized signals is used. Specifically, Pearson correlation coefficient of EEG electrode signals over a range of frequency in the discrete Fourier transform (DFT) of the original EEG data is estimated for 6-minute time window sample. The range of frequency of interest corresponds to the artifactual frequencies resulted from aliasing effects of DBS signals and physiological frequency ranges with artifact removed. A 6-min data sample consists of 72,000 data points for each of the 19 channel data set.

A modeling framework is developed as summarized in Figure 9. The steps are summarized as followed:

- The multi-channel EEG data is processed into 6-min time segments for both DBS-on and DBS-off labelled dataset.
- Two thirds of data from DBS-on and DBS-off group is retained as training set and the rest as test set.
- Pearson correlation coefficient is used to construct association matrix among channel data for each 6-min EEG segment. The association metrics are calculated based on a small range of frequency around the artifactual frequencies for modeling artifact effects and on the physiological frequency ranges with artifactual frequency range removed. For the dataset used, the artifactual

frequencies are 10.1 Hz, 20.2 Hz, 30.3 Hz and 40.4 Hz. The association metrics are also calculated based on 4 subsegments of the physiological frequency range including alpha bands (7Hz -9 Hz, 11Hz-13 Hz) and beta band (13Hz-19Hz, 21-29Hz).

- Based on the association matrix, construct binary undirected network.
- A set of network measures are computed for each channel for each 6-min EEG segment. Results derived from network can be compared among networks constructed over different frequency ranges. In this thesis study, the network measure of clustering coefficient is used as the predictor variables in the binary classifier of EEG data recorded when DBS is on vs. DBS is off.
- For each 6-second EEG segment, several binary classifier models including logistic regression and other models (which will be introduced in section 7) are used to train the model separately for each network characteristics. The response variable in each of these models is a binary variable represents the state of the DBS system with 1 assigned for DBS-on and 0 assigned for DBS-off. The predictor variables are network metric of clustering coefficient of each channel i. The resulting binary classifier consists of model coefficient B_i , which is regression coefficients corresponding to each channel i.
- After a model is developed with the regression coefficients trained, the model is evaluated for its classification performance based on the remaining one thirds test dataset with the use of ROC curve and AUC.

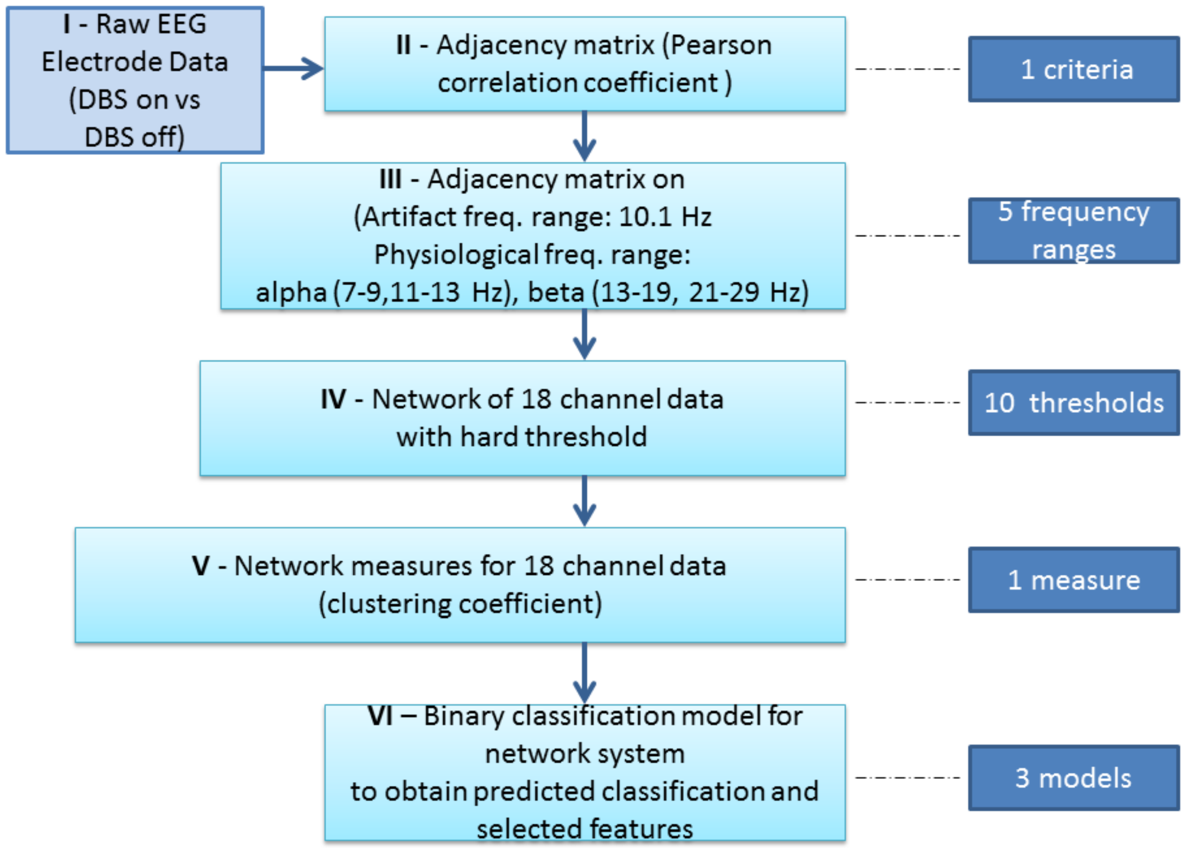

Figure 9. Modeling framework for processing and computing network measures as independent variables to model class labels of EEG data

5.1.1 Model Training Procedure

In order to assess binary classifier performance, the network measured derived from the EEG data are randomly split into training and test set. The training set consists of 2/3 of original data and the test set consists of 1/3 of the original data.

Using the training set, a binary classifier is developed and its performance is assessed using the test dataset. More specifically, the Area Under Curve (AUC) of the receiver operating characteristics (ROC) curve is used as a quantitative measure of classification performance of the binary classifier. AUC is selected to be used as objective measure of binary classification performance.

The cross validation is repeated 1,000 times for each combination of model, frequency range and Pearson correlation. Each cross validation run is done by randomly splitting the original data into different training set and test set. For each of the random split, AUC is calculated. The distribution of all AUCs calculated from 1,000 random data splits is visualized using boxplot. The corresponding features selected among the 1,000 runs are examined.

Chapter 6 Challenges Encountered

Logistic regression is used as an initial attempt to address the question of whether or not it is possible to develop a binary classifier based on clustering coefficients of the EEG-frequency-based network for the purpose of separating EEG data into DBS-on and DBS-off classes. Two objectives are generally recognized to be important in developing binary classifier for the purpose of clinical application. One objective is prediction accuracy. A second objective is interpretation of the model for the purpose of identify important factors that may serve as potential biomarkers.

6.1 A Simple Binary Classifier: Logistic Regression Model

Given m independent variables, the logistic regression uses the following logistic function to estimate the probability of the dependent variable to be either one of the two classes.

$$F(x) = \frac{1}{1 + e^{-(\beta_0 + \beta_1 x_1 + \cdots + \beta_m x_m)}}$$

where x_i represents the clustering coefficient of each EEG channel which records electrical activity from a particular brain region. This research study focuses on using clustering coefficients calculated based on the networks derived from data of EEG channel as an example network measure to investigate binary classification of EEG frequency based network.

6.1.1 Comparison of Logistic Regression Training and Test Set Classification Performance Based on Clustering Coefficients: ROC Curve's AUC vs. Pearson Correlation

For each of the frequency range of interest, 1,000 samples of training and test data sets were randomly drawn from the original six-minute EEG data. For each training and test data set, a logistic regression model was trained and tested in order to examine binary classification performance.

6.1.1.1 Alpha Wave (7-9 Hz)

The summary result of classification performance in terms of ROC curve's AUC distribution for selected value of Pearson correlation coefficient used as thresholds to construct undirected EEG/brain network based on channel data for 7-9 Hz frequency range is shown in Figure 10 . For the detailed comparison classification performance of the training datasets and that of the test datasets focusing on only one Pearson correlation value, the distributions of corresponding ROC curve's AUC for the 1,000 sampling iterations are show in Figure 11 to Figure 20 . The Pearson correlations used to construct the EEG frequency network are 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9 and 1. Below each of the boxplots of AUC distributions for training and test sets, a table summarizes the median AUC and mean AUC of training and test set, difference and percentage of difference between test set's median and mean AUC with respect to training set's AUC presented.

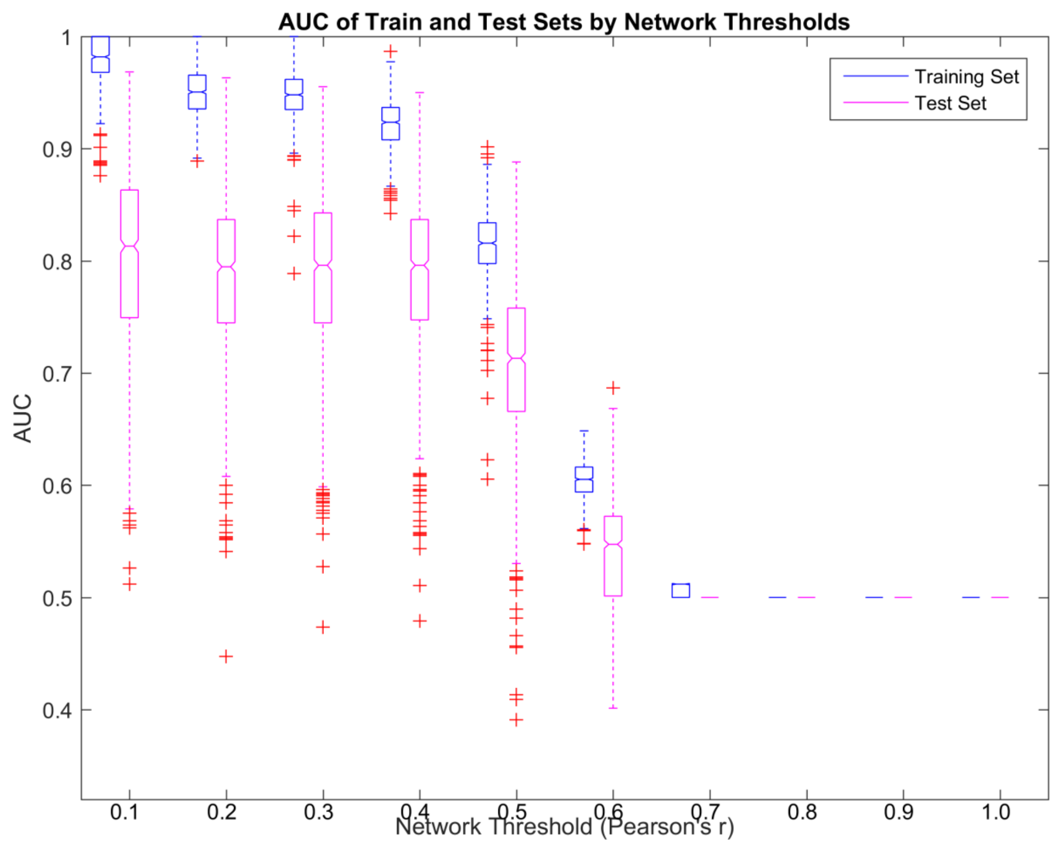

Figure 10. Training and test set classification performance of logistic regression models over range of Pearson correlations used to construct EEG network for frequency of 7-9 Hz.

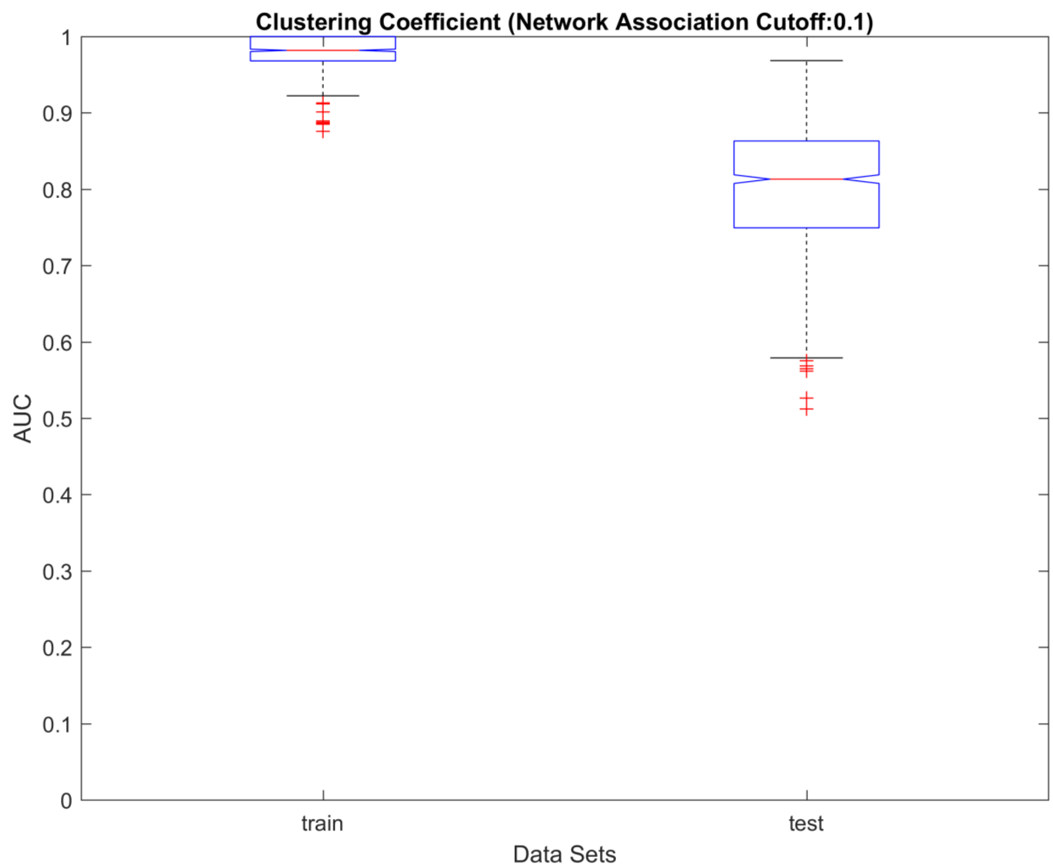

Figure 11. Training and test set classification performance of logistic regression models for EEG network constructed using Pearson correlation threshold of 0.1 over frequency range of 7-9 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.1)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.9818	0.8132	-0.1687	-17.18%
Mean	0.9809	0.8035	-0.1774	-18.08%
Standard Deviation	0.0196	0.0794	0.0598	304.98%

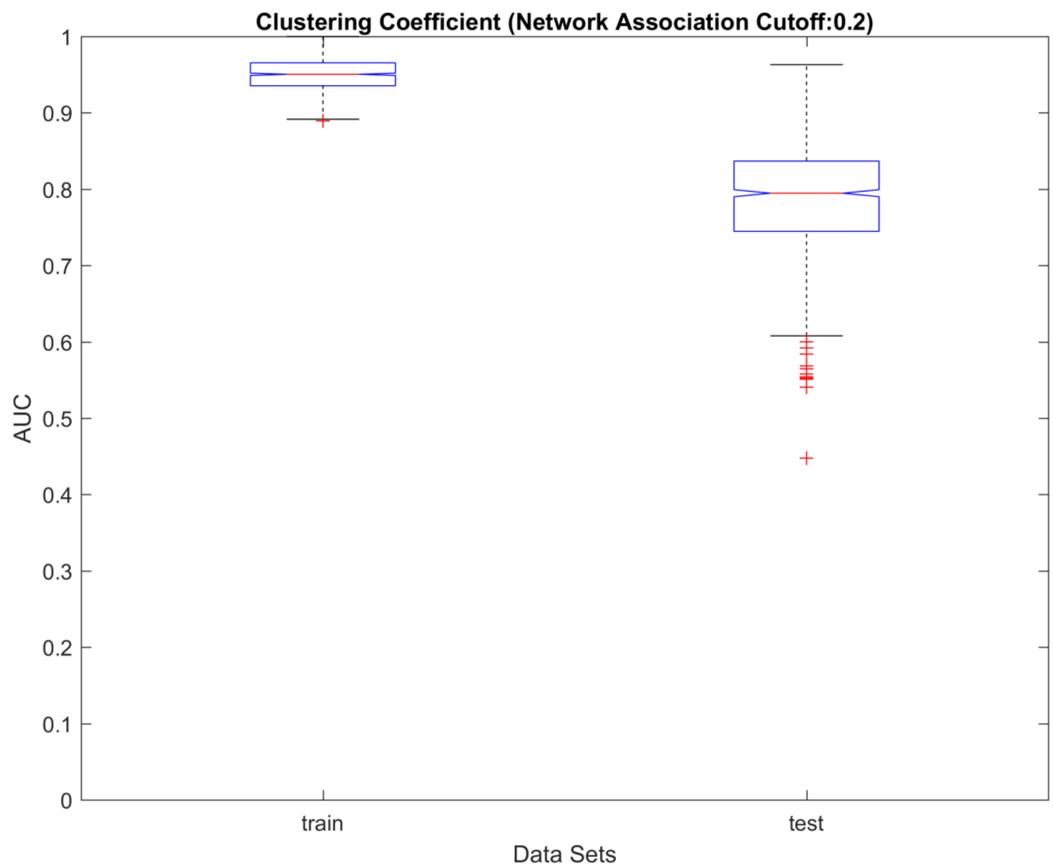

Figure 12. Training and test set classification performance of logistic regression models for EEG network constructed using Pearson correlation threshold of 0.2 over frequency range of 7-9 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.2)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.9505	0.7947	-0.1558	-16.39%
Mean	0.9507	0.7875	-0.1632	-17.16%
Standard Deviation	0.0218	0.0701	0.0482	220.72%

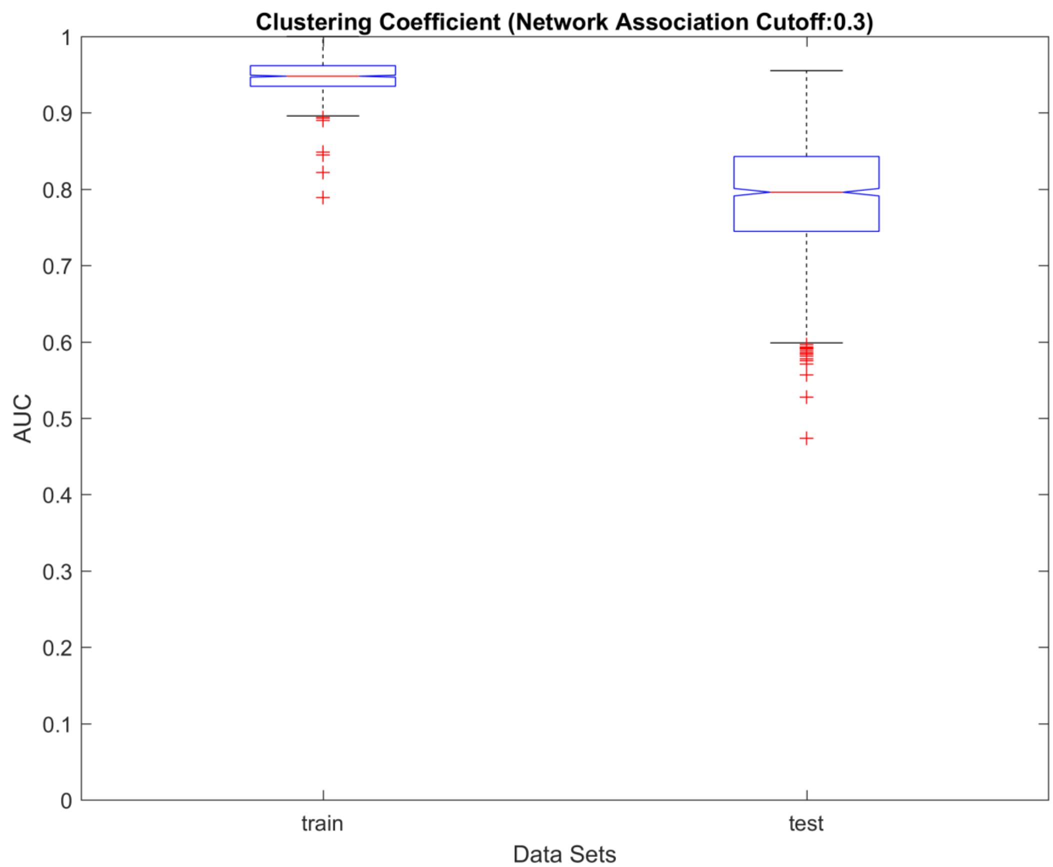

Figure 13. Training and test set classification performance of logistic regression models for EEG network constructed using Pearson correlation threshold of 0.3 over frequency range of 7-9 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.3)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.948	0.7961	-0.1519	-16.03%
Mean	0.9472	0.7911	-0.1561	-16.48%
Standard Deviation	0.0217	0.0728	0.0511	235.25%

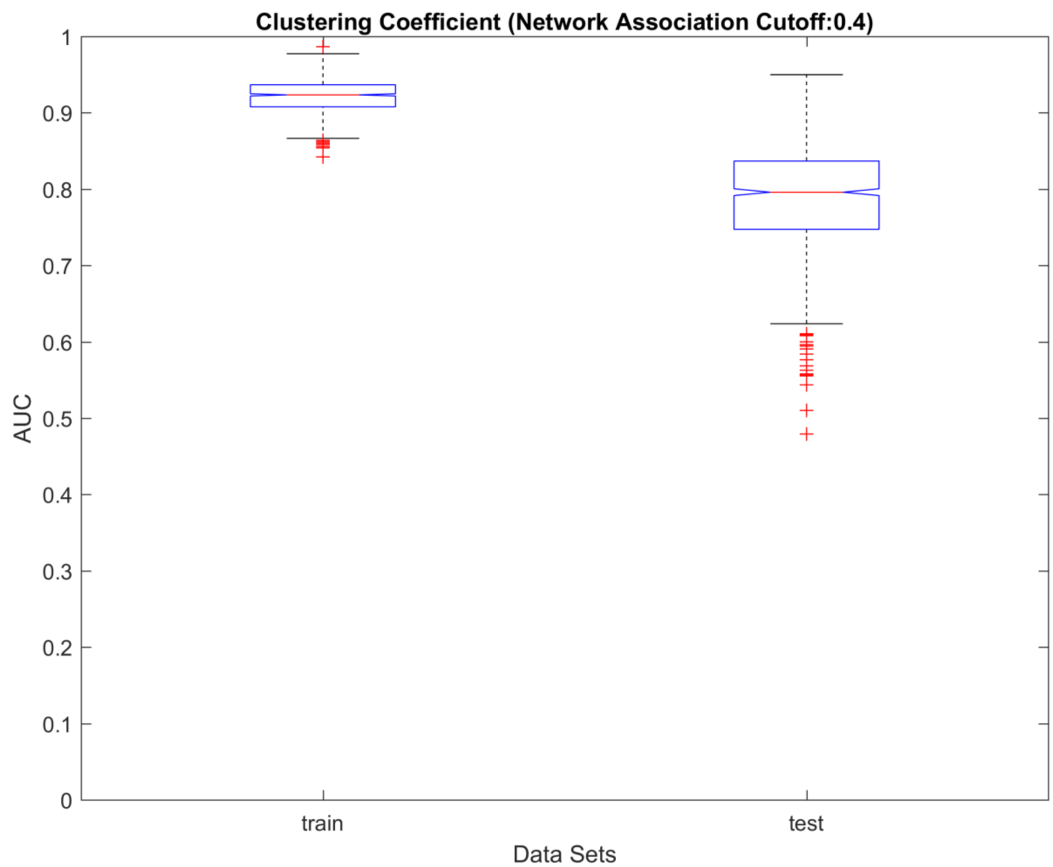

Figure 14. Training and test set classification performance of logistic regression models for EEG network constructed using Pearson correlation threshold of 0.4 over frequency range of 7-9 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.4)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.9236	0.7961	-0.1275	-13.81%
Mean	0.9227	0.7896	-0.1331	-14.42%
Standard Deviation	0.0215	0.0692	0.0477	221.89%

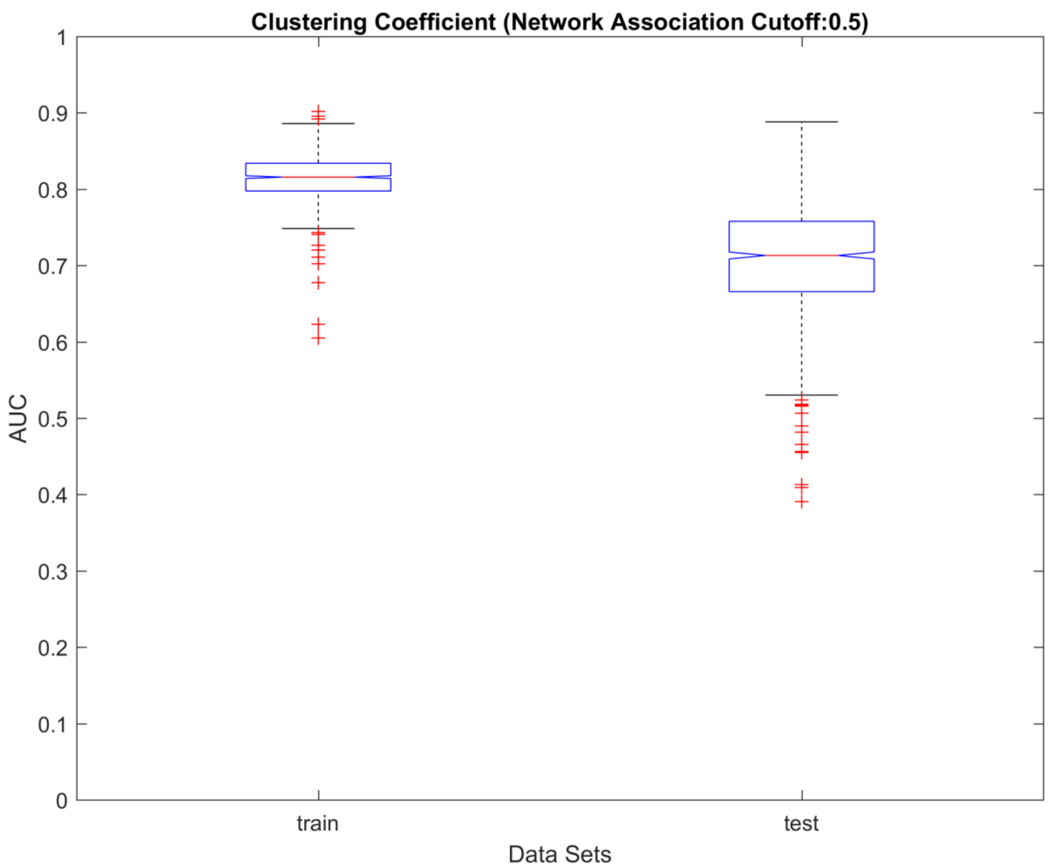

Figure 15. Training and test set classification performance of logistic regression models for EEG network constructed using Pearson correlation threshold of 0.5 over frequency range of 7-9 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.5)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.8158	0.7132	-0.1026	-12.58%
Mean	0.8152	0.7088	-0.1064	-13.05%
Standard Deviation	0.0289	0.0725	0.0436	151.05%

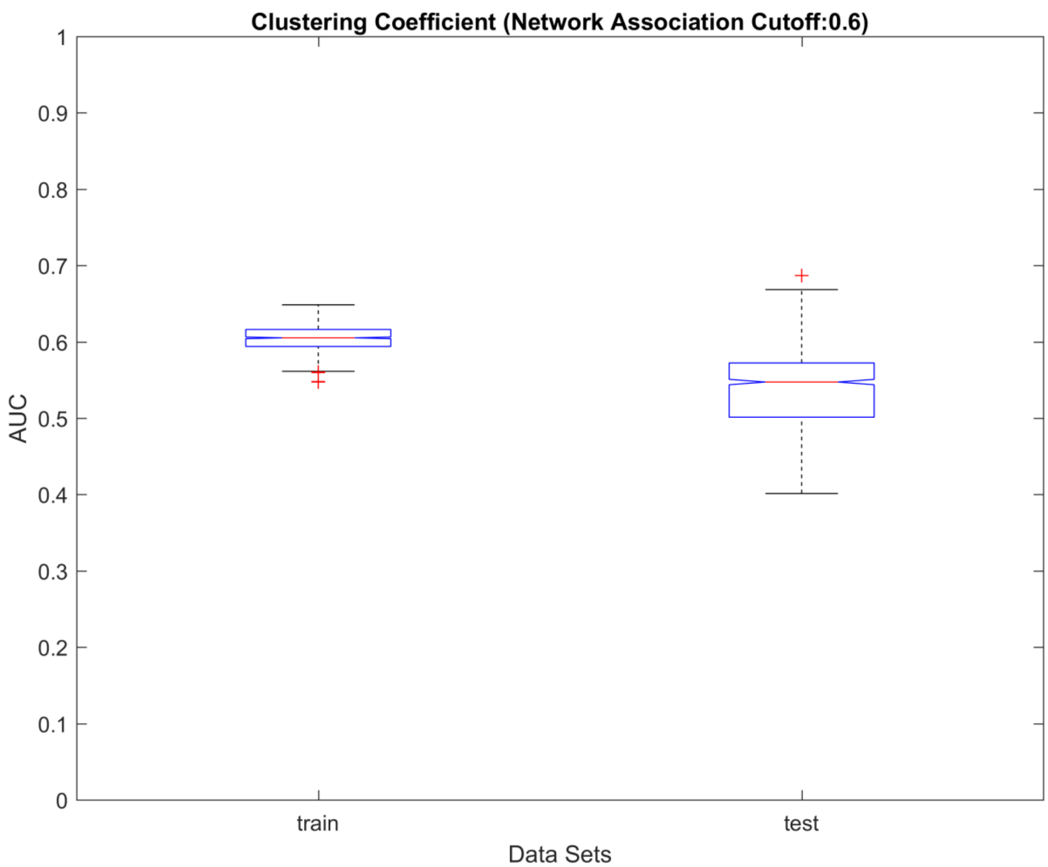

Figure 16. Training and test set classification performance of logistic regression models for EEG network constructed using Pearson correlation threshold of 0.6 over frequency range of 7-9 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.6)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.6053	0.5474	-0.0579	-9.57%
Mean	0.6031	0.5391	-0.0639	-10.6%
Standard Deviation	0.0176	0.0466	0.0289	164.15%

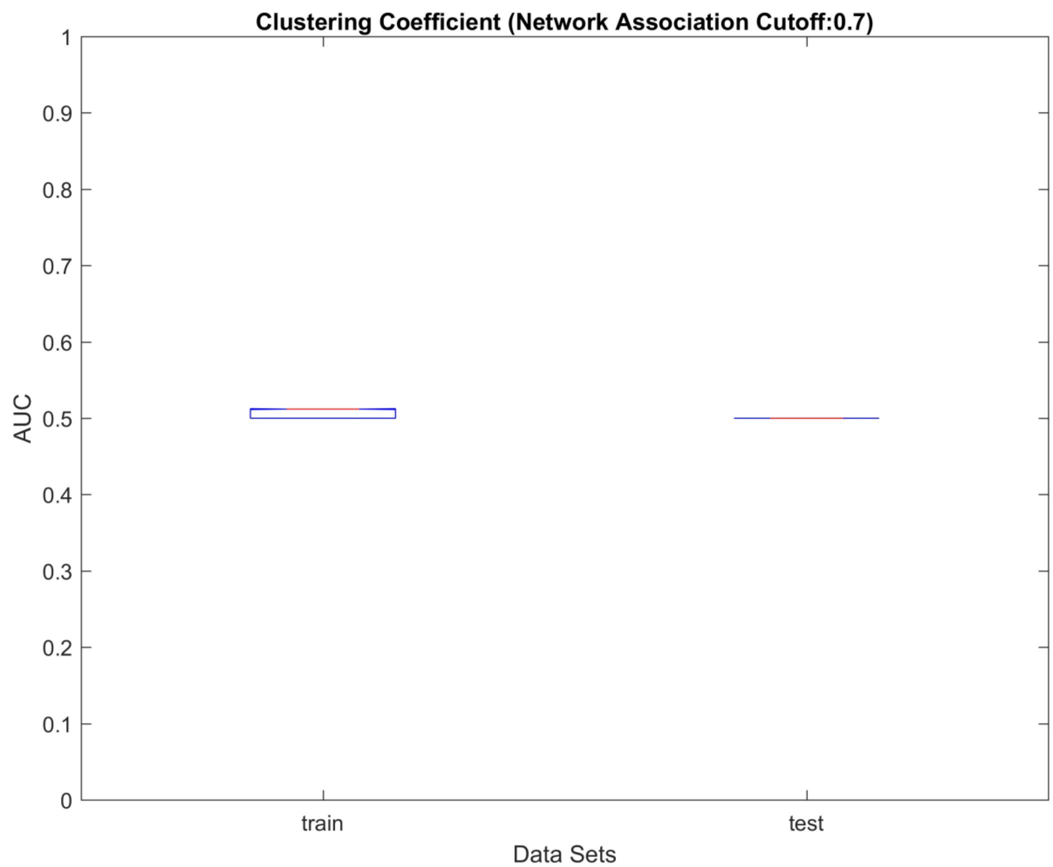

Figure 17. Training and test set classification performance of logistic regression models for EEG network constructed using Pearson correlation threshold of 0.7 over frequency range of 7-9 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.7)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5119	0.5	-0.0119	-2.33%
Mean	0.5082	0.5	-0.0082	-1.6%
Standard Deviation	0.0055	0	-0.0055	-100%

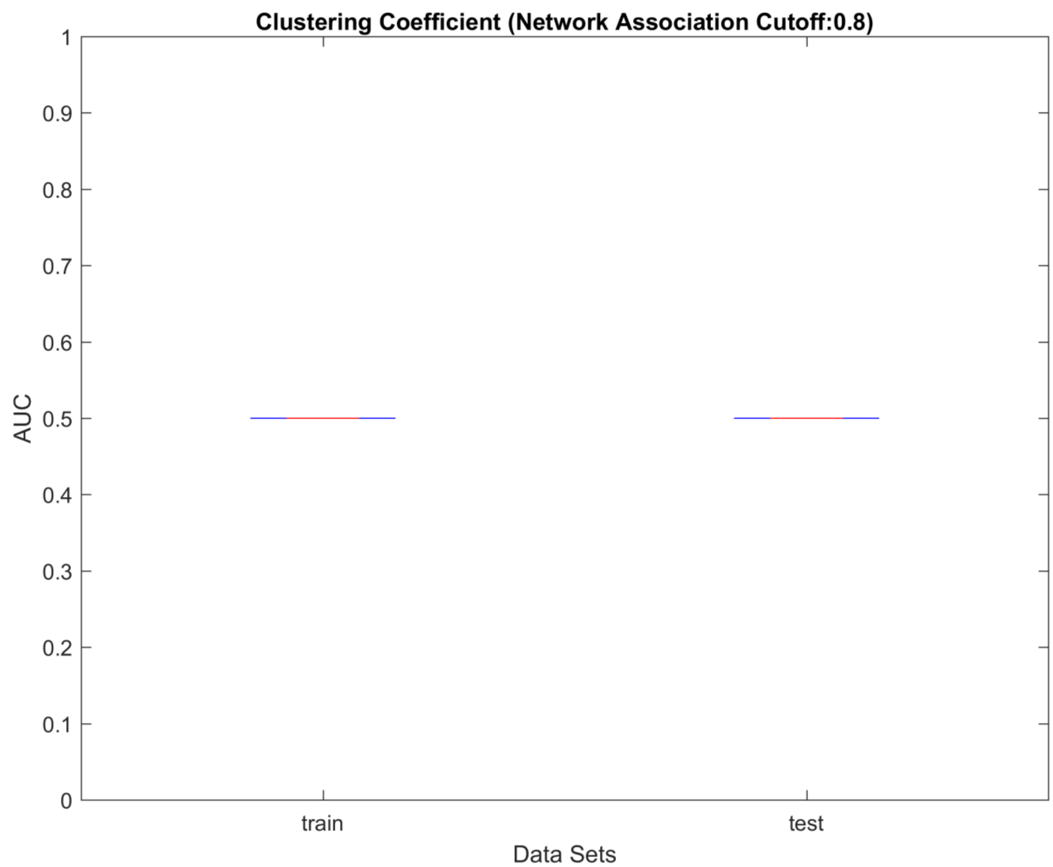

Figure 18. Training and test set classification performance of logistic regression models for EEG network constructed using Pearson correlation threshold of 0.8 over frequency range of 7-9 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.8)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5	0.5	0	0%
Mean	0.5	0.5	0	0%
Standard Deviation	0	0	0	0%

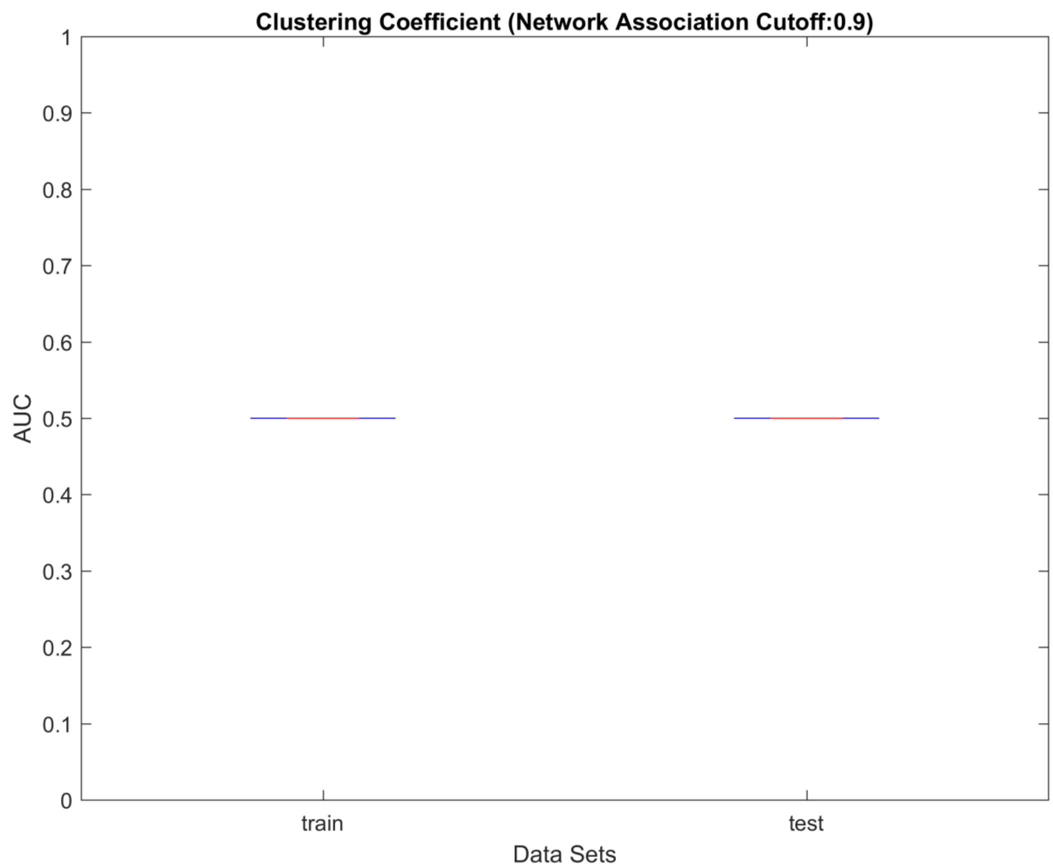

Figure 19. Training and test set classification performance of logistic regression models for EEG network constructed using Pearson correlation threshold of 0.9 over frequency range of 7-9 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.9)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5	0.5	0	0%
Mean	0.5	0.5	0	0%
Standard Deviation	0	0	0	0%

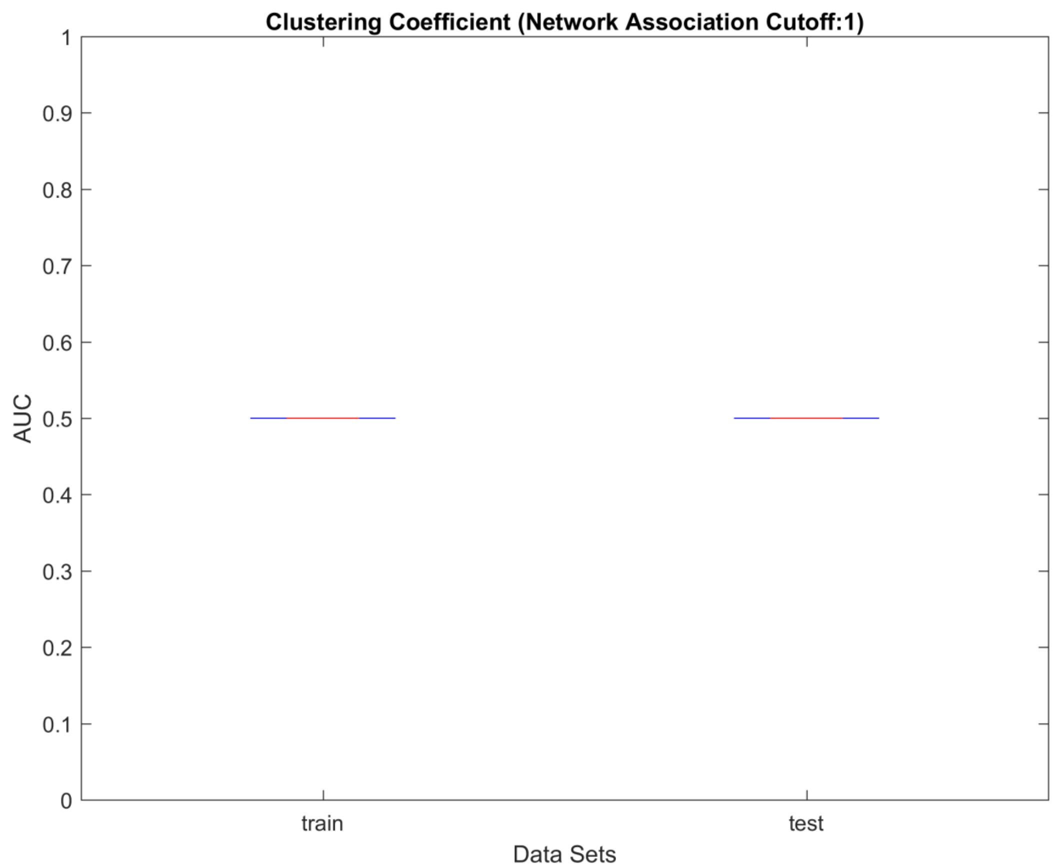

Figure 20. Training and test set classification performance of logistic regression models for EEG network constructed using Pearson correlation threshold of 1 over frequency range of 7-9 Hz.

	ROC Curve's AUC (Network Association Threshold: 1)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5	0.5	0	0%
Mean	0.5	0.5	0	0%
Standard Deviation	0	0	0	0%

6.1.2 Unsatisfactory Classification Results

For the network metric of clustering coefficients derived from the EEG data, logistic regression does not result in a statistically robust and parsimonious model even though the AUC distribution indicates relatively good performance.

With a more detailed examination, it can be observed that the relevant logistic regression modeling results for binary classification of the EEG network data have at least some regression coefficients not having sufficient power to reject null hypothesis of $\beta_i = 0$. The test statistics is $W = \frac{(\widehat{\beta_\iota}-0)}{SE(\widehat{\beta_\iota})}$ where SE represents the standard error of β_i.

The hypothesis test results correspond to the test statistics of $W = \frac{(\widehat{\beta_\iota}-0)}{SE(\widehat{\beta_\iota})}$ that are not extreme enough to be considered significant at 0.05 level. For these non-significant p-values (> 0.05), the corresponding $\widehat{\beta_\iota}$ is considered to be no different than 0 due to either one of the following two reasons:

- $\widehat{\beta_\iota}$ is very close to 0.
- $SE(\widehat{\beta_\iota})$ is very large

In addition, all predictor variables are retained by modeling the network measure data using a logistic regression approach. The process of training a logistic regression model does not result in selecting a subset of most relevant predictor variables. Selecting a subset of independent variables in the model developed is an important consideration for identifying potential biomarkers using EEG data. In addition, feature selection can also simplify the trained model to make the model easier to interpret.

Because the logistic regression models trained and tested result in good overall classification performance but many coefficients have non-significant p-value, the dataset may exhibit multicollinearity characteristic.

6.1.3 Example of Network Metric EEG Data with Multicollinearity

Figure 21 is an example correlation matrix of the clustering coefficients of EEG data. Given correlation value of at least 0.4 considered to represent high degree of correlation, the correlation matrix shows that there are pairs of EEG channels that have relative high level of correlation coefficients of their clustering coefficients. The network association threshold is 0.2.

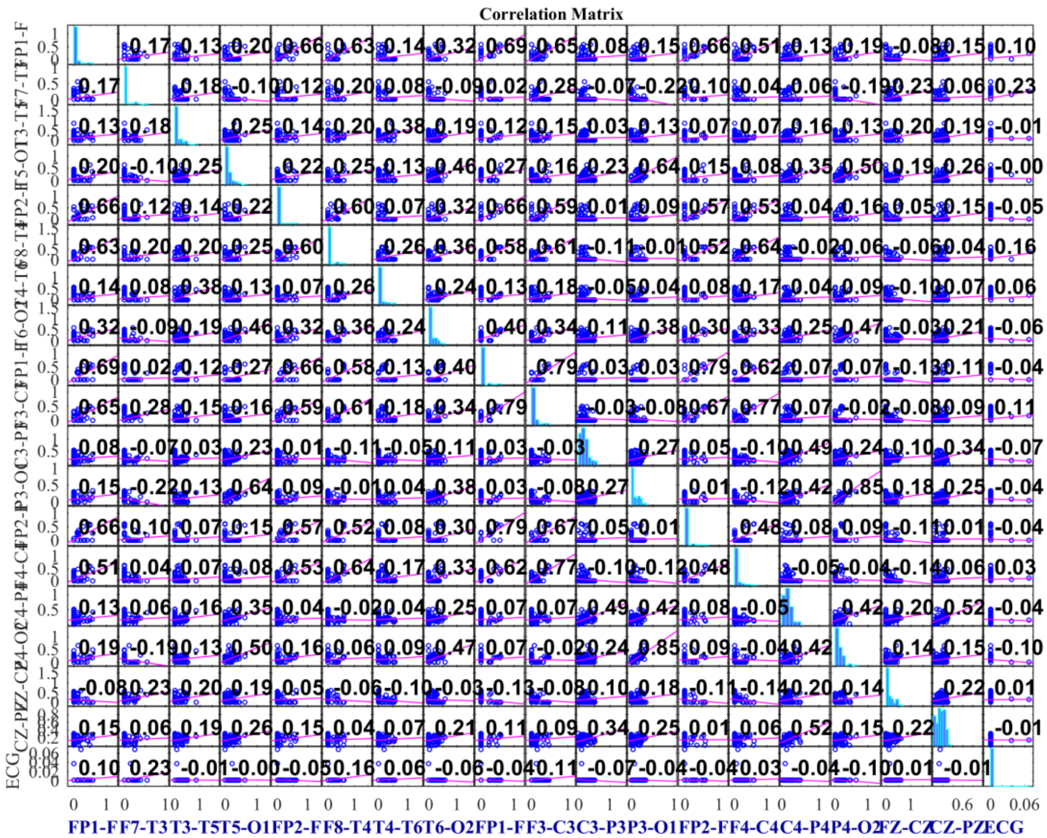

Figure 21. Example of correlation matrix of predictor variables (clustering coefficients) that are used to construct binary classifier. Based on a criteria of pairwise correlation of 0.4 or above as indicator of high level of multicollinearity, the predictor variables exhibit relatively high level of pairwise correlation.

6.1.3.1 Variance Inflation Factor (VIF)

Variance inflation factor is an indicator that can be used to quantify the degree of multicollinearity in the predictor variables used to build a generalized regression model including logistic regression model. It measures how much the variance of an estimated regression coefficient ($\widehat{\beta\_\iota}$) is increased due to correlation with other predictors in the model. More specifically, VIF is defined as

$$VIF = \frac{1}{1 - R_j^2}$$

where R_j^2 is the coefficient of determination of the following regression model:

$$X_j = c + \sum_{i \neq j} \alpha_i X_i$$

where X_j is the jth predictor variable in the regression model that is used to construct a binary classifier. A VIF($\widehat{\beta}_J$) of 1 indicates that X_j is orthogonal to all other predictor variables in the model. A VIF($\widehat{\beta}_J$) > 1 indicates that X_j is not orthogonal to all other predictor variables. The square root of VIF shows the number of multiples that standard error associated with coefficient of the relevant predictor variable compared with what it would be if the predictor variable were uncorrelated with all other predictor variables in the model. A generally acceptable rule that degree of multicollinearity is high if VIF($\widehat{\beta}_J$) > 5.

For the example data shown in Figure 21 , VIF for all predictor variables is shown in Figure 22. The VIF plot shows that there are multiple predictor variables with VIF > 5. The combination of these VIF indicates that the predictor datasets as a whole has serious multicollinearity issue.

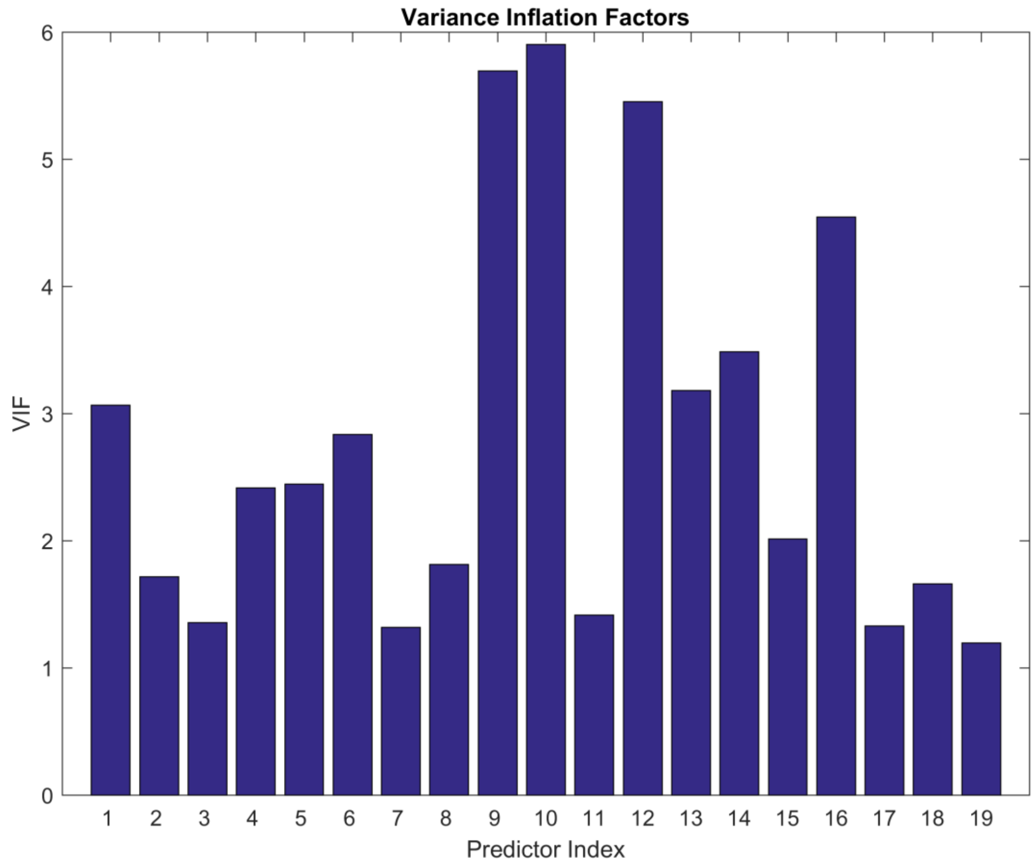

Figure 22. Variance inflation factor of example network metric (clustering coefficient) of EEG data.

6.2 Existing Studies of Modeling Multidimensional EEG Data with Multicollinearity Characteristics

Multicollinearity refers to a situation in which two or more predictor variables in a regression model are highly correlated. When a multidimensional dataset that is used exhibits multicollinearity, one or more variables of the dataset can be linearly predicted from the other variables to a high degree of accuracy.

Multicollinearity can lead to problem of interpreting multivariate models with predictor variables that are correlated with each other. More specifically, McFarland specifically discusses one issue with multicollinearity is the potential difficulty of interpretation of the regression weights [20]. According to McFarland, the weight of a given EEG spectral feature in a regression model is affected both by the covariance of the feature itself and the covariance with other features in the model. EEG features that are used as predictor variables that correlate less with other predictor variables in a regression model would tend to have larger weights than EEG features that are highly correlated with other EEG features in the model. This issue of interpretation persists even for cases in which the predictor variables have the same scale. Because of the difficulty of interpretation, the possible impact of multicollinearity should be considered when interpreting the regression weights of a regression model.

6.3 Modeling Challenges – Multicollinearity

In modeling classification of binary classes using multiple variables, a commonly used method is to use all variables as possible predictor variables in a logistic regression model. However, the outcome of developing a model is highly dependent on correlation structure among predictive variables. This is especially the case given the objectives of developing binary classifier in this study are both prediction and interpretation of the modeling results. Because inference involved in training classifier assumes that all predictive variables are uncorrelated, any high degree of correlation among the predictive variables may seriously violate such assumptions. When the covariates in the model are not independent from one another, multicollinearity problems arise in developing the model, which can lead to biased coefficient estimation and a loss of power. [21]

Multicollinearity is a characteristic of independent variables in a statistical model. With multicollinearity present, some independent variables in a multiple logistic regression model are highly correlated. A challenging of modeling the EEG derived network measures is to overcome the effect of high level of multicollinearity attributed to the network measures of the EEG channels when the dataset exhibits strong multicollinearity.

6.3.1 Modeling Issues Due to Multicollinearity

Multicollinearity makes it challenging to meaningfully model a dataset. The following issues are attributed to multicollinearity:

a) Basic assumption of regression model is violated

Logistic regression model assumes that all independent variables are linearly independent from each other. With two or more independent variables correlated with each other, a logistic regression model does not give valid results about a particular individual independent variable.

b) Interpretation of the model's regression coefficient are misleading

A regression coefficient estimate is supposed to specify the effect of one unit change in one independent variable holding all other independent variables constant. With multicollinearity, it is not possible to hold all independent variables constant while increasing the value of an independent variable that is correlated with other independent variables by one unit.

c) Standard errors of the regression coefficients tend to be large

The standard errors of affected logistic regression coefficients of are large, resulting in test statistics of $W = \frac{(\widehat{\beta_i} - 0)}{SE(\widehat{\beta_i})}$ to be small. This makes it more difficult to reject a false null hypothesis that $\beta_i = 0$. As a result, type II error is more likely to occur for the affected logistic regression coefficients.

d) Overfitting

Overfitting of the logistic regression model can occur if there is redundancy in the dataset. As a result, small change of the independent variables may lead to large changes in affected logistic regression coefficients.

For logistic regression coefficients with p-value less than 0.05, the meaning of the p-value is not useful in identifying important variables because

- The test done is based on testing a particular regression coefficient given all other variables are also in the model. Thus, all regression coefficients would still need to be retained in the model in order to make classification prediction. Thus, no subset of predictor variables is identified as a result.
- If another logistic regression model is developed using only the corresponding subset of independent variables with regression coefficients that are less than 0.05, the resulted regression model can result in insignificant p-value (> 0.05) for the regression coefficients of these remaining independent variables.

6.3.2 Minimum p-value in Each Model

P-value is the probability of getting a result equal to or more extreme than what we observed if H_O is true. Within the context of assessing regression coefficient of β_i, H_O represents the hypothesis test that $\beta_i = 0$. If the p-value is lower than a pre-defined limit, then it is customary to reject H_O and conclude that there is statistical evidence that $\beta_i \neq 0$. .

An experiment was conducted for developing logistic regression models for 100 randomly select training sets of the EEG network data for 11-13 Hz frequency range. For each the model developed, the minimum p-value among 20 logistic regression coefficients of the 20 predictor variables is selected. These selected minimum p-values are then compared with a cut off value of 0.05.

The experiments were repeated six times. The following shows the number of models with at least one p-value that are less than 0.05 for each of the six experiments.

27, 33, 23, 36, 28, 34

Out of 6 experiments of 100 randomly select dataset, the corresponding model developed have only on average 30.2 dataset that have at least one minimum p-value less or equal to 0.05. This results show that the dataset potentially have dimensions that are correlated with each other to a large degree.

6.3.3 β_i with Significant p-value (10 examples)

Another experiment would illustrate the modeling challenge. An experiment was run to examine samples of β_i with significant p-value at 0.05 level using EEG network data for 11-13 Hz frequency range. The following shows a sample set result of developing logistic regression using 10 different training sets and applying the resulted models to the corresponding test set.

1. 2 3 4 6 7 15 16
2. 0 2 4 11 16
3. No Significant p-value
4. No Significant p-value
5. 16
6. No Significant p-value
7. No Significant p-value
8. No Significant p-value
9. No Significant p-value
10. 4 7 16

As seen from the sample result, it is possible for no independent variables with logistic regression coefficient that are significant at 0.05 level. For those models that do have significant p-values, the independent variables with the regression coefficient that are significant vary from one model to another.

In conclusion, modeling the data using logistic regression indicates the data contains characteristic of multicollinearity. The effect of multicollinearity lead to serious violation of assumptions required to develop an appropriate and meaningful logistic regression model. Depending on the dataset, applying simple logistic regression model may lead to statistically invalid results, which would lead to model overfitting. The resulting model is not statistically robust and not parsimonious. In addition, logistic regression model does not perform variables selection, and thus all β_i with non-significant and significant p-value are needed to estimate classifier response variable of the logistic regression model. A research objective is to overcome these challenges inherent in the EEG-data derived network metrics.

Chapter 7 Research Results and Analysis

7.1 Alternative Binary Classification Models

Because the EEG network datasets exhibit multicollinearity characteristic, simple logistic regression modeling approach may not result in statistically robust classification results with respect to the objectives of the current study. As a result, alternative binary classification modeling approaches are examined to attempt to address the question of whether or not additional binary classifiers can be developed in order to compare binary classification results derived from different binary classification modeling approaches.

7.1.1 Model Formulation: Modeling Methodology for EEG Data with Multicollinearity - Principal Component Stepwise Selection Logistic Regression (PCSSLR)

A new modeling approach, Principal Component Stepwise Selection Logistic Regression (PCSSLR), is developed specifically for this study for the binary classification step of the modeling framework. PCSSLR is developed to overcome potential multicollinearity effects of the network metrics of the EEG data. This new modeling approach is applied in step VI of the modeling framework and the corresponding results are compared with results derived using LASSO.

PCSSLR is developed to attempt to overcome challenges of obtaining more satisfactory results in predicting classes of DBS on vs DBS off given only the connectivity metrics derived from EEG electrode data. Logistic regression is a component of this modeling approach, but additional steps are added to prepare the data that are modeled to overcome multicollinearity.

The steps of PCSSLR are:

1. Derive principal components from the training data (PC step)

   The step linearly transforms training data to corresponding data in the principal component space. Because each principal component is independent and orthogonal from each other, this linear transformation solves the problem of correlation among linearly dependent independent variables related to multicollinearity. In a sense, this step imposes constraint on the original features to require the newly linearly transformed features to be independent of each other.

2. With stepwise forward selection (SS step)

   Starts with zero independent linearly transformed variable, this step tests whether the addition of one more transformed variable would improve the model based on error rate. The transformed variables that lead to models with the least errors would be added to the model at each stepwise selection iteration. This feature selection step would stop when overall model error cannot be improved beyond a predefined tolerate level.

3. Develop final logistic regression model (LR step)

   Using the selected independent variables identified in step 2 to estimate a final logistic regression model. The resulted logistic regression model would have all regression coefficients that are significant partly because features are transformed into linearly independent variables by step 1 and the resulted model is parsimonious because feature selection has been performed by step 2.

When testing the model using test set, the same PCSSLR steps are performed. For the PC step, the original principal component loadings (weights, w) are multiplied with each new test data to obtain linearly transformed data (X') X'$= w\, X$. For the LR step, Logistic Regression coefficients (β_i) are estimated. These coefficients are multiplied with linearly transformed data (X') to arrive at estimated logistic regression output (y).

PCSSLR is a method to identify important features and to impose constraints on dataset which exhibits multicollinearity in order to develop a generalized linear model with regression coefficients that are statistically valid without explicitly solving a minimization problem (LASSO).

7.1.1.1 Modeling Data Using PCSSLR

The modeling results give good or better AUC performance that simple logistic regression for modeling the network metric data derived from the EEG data obtained with DBS on vs DBS off. The final logistic regression model is more parsimonious due to use of stepwise selection than simple logistic regression.

The following shows an example of the final logistic regression coefficients. The model consists of 8 independent variables and 1 constant term, all of which leads to significant p-values (<0.05) of the corresponding hypothesis test.

p-values of regressions coefficients:

0.0086 0.0042 0.0062 0.0012 0.0055 0.0425 0.0006 0.0009 0.0073

7.1.2 Least Absolute Shrinkage and Selection Operator (LASSO)

LASSO is a method that performs both regularization and variable selection. This method is often used in the machine learning community for modeling multi-dimensional data with correlated covariates. LASSO can be used to

- Identify important features
- Reduce number of predictors
- Improve model predictive error compared to ordinary least square regression

The LASSO is formulated as followed

$$\min_{\mathrm{B}_0, \mathbf{B}} \left\{ \frac{1}{N} \|y - \mathrm{B}_0 - \boldsymbol{X}\mathrm{B}\|_2^2 \right\} \textit{ subject to } \|\mathrm{B}\|_1 \le t$$

which can be expressed in Lagrangian form:

$$\min_{\mathrm{B}_0, \mathbf{B}} \left\{ \frac{1}{N} \|y - \mathrm{B}_0 - \boldsymbol{X}\mathrm{B}\|_2^2 + \lambda \|\mathrm{B}\|_1 \right\}$$

Notice that for every t, there is a corresponding λ in the Lagrangian form.

LASSO seeks to find the solution of $(\mathrm{B}_0, \mathbf{B})$ such that the L1 norm of **B** is minimized with the given Lagrangian factor and the deviance of the model compared to the data $\|y - \mathrm{B}_0 - \boldsymbol{X}\mathrm{B}\|_2^2$ is minimized. As λ increases, the number of nonzero coefficients $(\mathrm{B}_0, \mathbf{B})$ would decrease.

LASSO has the following characteristics:

a) Original Predictors are retained (no linear transformation)

   As a result, more physiologically relevant interpretation (brain-regions related insights) can be made for the independent variables.

b) Minimize estimated errors to result in the best estimate of regression coefficient.

A typical analysis of LASSO involves with identifying the model parameter, λ, which gives a low deviance with respect to the data. For a particular value of λ, non-zero coefficients in the linear model are the solutions to the minimization problem.

For one training data randomly selected using EEG network data for 11-13 Hz, LASSO estimates the following coefficients as non-zero for λ that gives cross-validation error within 1 standard deviation of the minimum cross-validation error.

Index of coefficients identified:

4 15 18 19

The value of λ which leads to cross-validation error within 1 standard deviation of the minimum and a minimum number of coefficient is shown in Figure 23.

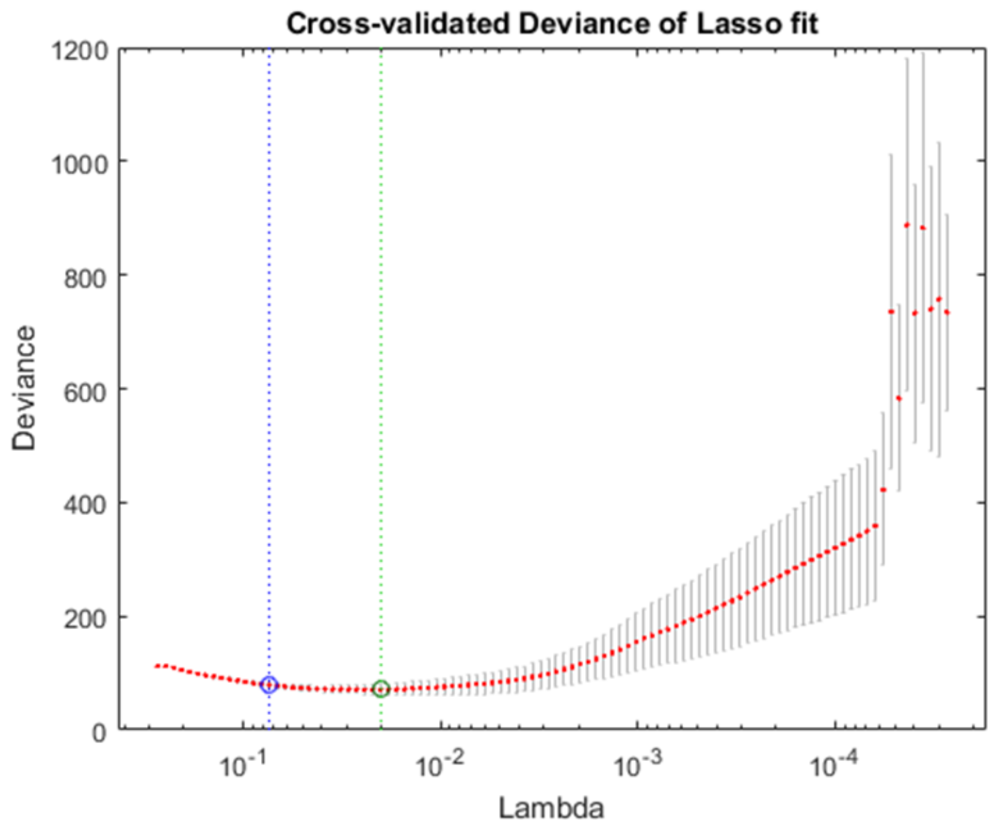

Figure 23. Example of cross validation errors for selected value of λ for solutions that satisfies the minimization problem of LASSO.

In this thesis study, classification results derived using LASSO will be used to compare with those derived using PCSSLR and logistic regression.

7.2 Characteristics of EEG Network Data

7.2.1 Data for Training and Testing Classifier

Before deriving EEG network, the EEG data are pre-processed into 6-minute time segments. This leads to 62 time segments in the DBs-on group and 57 time segments in the DBS-off group. For each network features used to develop a classifier, 2/3 of data set is used as training set and 1/3 of data set is used as test set. This results in 80 time segments in the training set and 39 time segments in the test set.

7.2.2 Example Association Matrix

An example association matrix developed based on frequency-based Pearson correlation coefficients calculated for all given pair of EEG electrode data is shown in Figure 24.

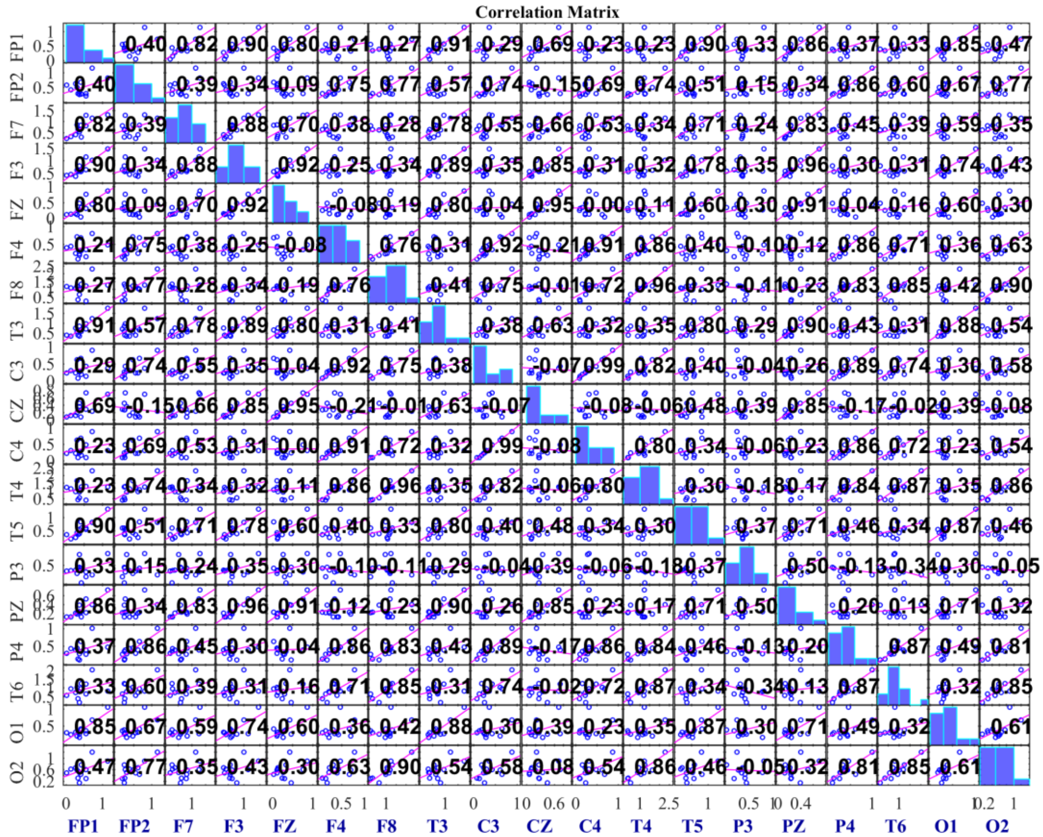

Figure 24. Example association matrix for a 6-minute time segment with DBS-on for frequency range near 10.1 Hz

7.2.3 Example EEG Network

An example EEG binary and undirected network constructed using an association matrix with arbitrary hard thresholding of 0.6 and DBS-on is presented in Figure 25. The lines in Figure 25 represents links with association metrics defined based on Pearson correlation coefficient for frequency range around 10.1 Hz computed between all pairs of 18 channel data

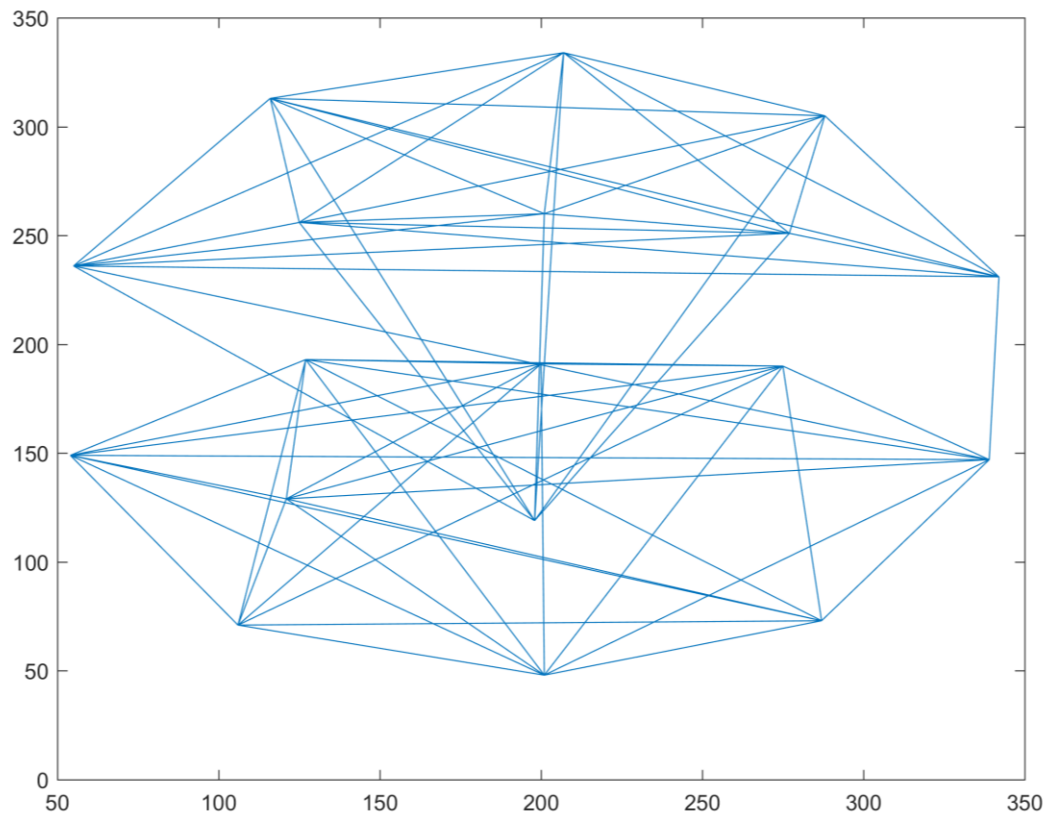

Figure 25. Example network constructed based on association matrix of a 6-minute EEG segment for frequency range around 10.1 Hz. Network features are computed based on this type of EEG network.

7.3 Modeling and Analysis Results

7.3.1 Model Classification Performance (Classifier based on Artifacts)

7.3.1.1 Network Clustering Coefficient (10.1Hz)

The classification performance of the test data set of the classifier model with network clustering coefficient is shown in Figure 26 as a receiver operating characteristic curve for 6-minute time segment. The corresponding confusion matrix is listed below.

The result of this classifier shows the model shows a good performance to discriminate EEG data with DBS-on from EEG data with DBS-off.

	Predicted DBS off	**Predicted DBS on**
DBS off	18	1
DBS on	0	20

Fraction of samples misclassified: 0.0256

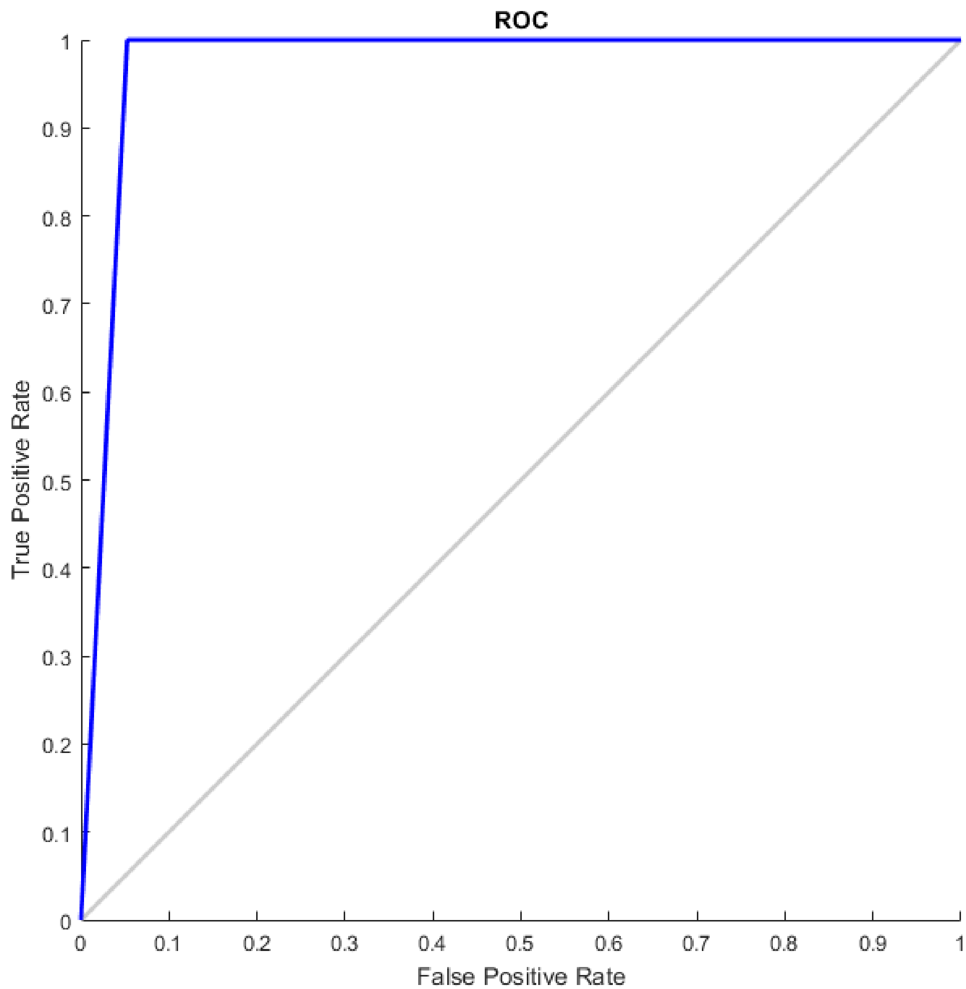

Figure 26 Receiver operating characteristic curve of DBS-on and DBS-off classifier developed using clustering coefficient of individual EEG channel as predictor variable.

7.3.2 Physiological Frequency Range Classification Modeling

The modeling framework is applied to derive network based on Pearson correlation coefficient for physiological range of frequency over 6-minute interval. These frequency ranges include alpha (7-13 Hz) and beta (13-31 Hz) bands. The network measures can be used to characterize the network for a particular period of time. These network measures are used to train classifier for binary classes of network activities that occur during DBS-on session or DBS-off session. The classifier performance is assessed using ROC curve and AUC. The classifier modeling will result in identification of potential and unique EEG biomarkers which can indicate treatment effect of DBS on EEG recording and brain activity.

Most of the cerebral signals captured in clinical EEG recordings are within 1- 20Hz. Waveforms observed in EEG recordings are subdivided into frequency bands.

Bands	Frequency (Hz)
Alpha	7-13
Beta	13-31
Gamma	32+

7.3.3 Example Receiver Operating Characteristics (ROC) Curve of Training and Test Set

Classification model is developed for physiological frequency range. The physiological frequency range corresponds to cerebral signals that are directly related to physiological state of a patient. The physiological frequency ranges are divided into 4 segments. To remove effect of artifact, each segment is specifically divided to exclude artifactual frequency range around 10.1 Hz, 20.2 Hz and 30.3Hz.

In this research study, the propose classification framework is applied to the alpha and beta frequency bands. The application of the classification framework will attempt to develop a classifier that can discriminate an EEG time segment associated with the DBS-on state from the DBS-off state. More specifically, the frequency bands are divided into 4 segments to isolate non-artifacts effects that are known to occur at 10.1 Hz, 20.2 Hz, and 30.3 Hz.

Segments	**Frequency Range (Hz)**
Alpha 1	7 <= frequency < 9
Alpha 2	11 < frequency < 13
Beta 1	13<= frequency < 19
Beta 2	21 < frequency < 29

For each data split sample, the data set is randomly divided into 2/3 for training set and 1/3 for test set. Using training set data, attempts were made to develop a model with good prediction for the test set. Examples of ROC curve for the training set of one sample of cross validation data set is shown in Figure 27. The corresponding ROC curve for the test set is shown in Figure 28.

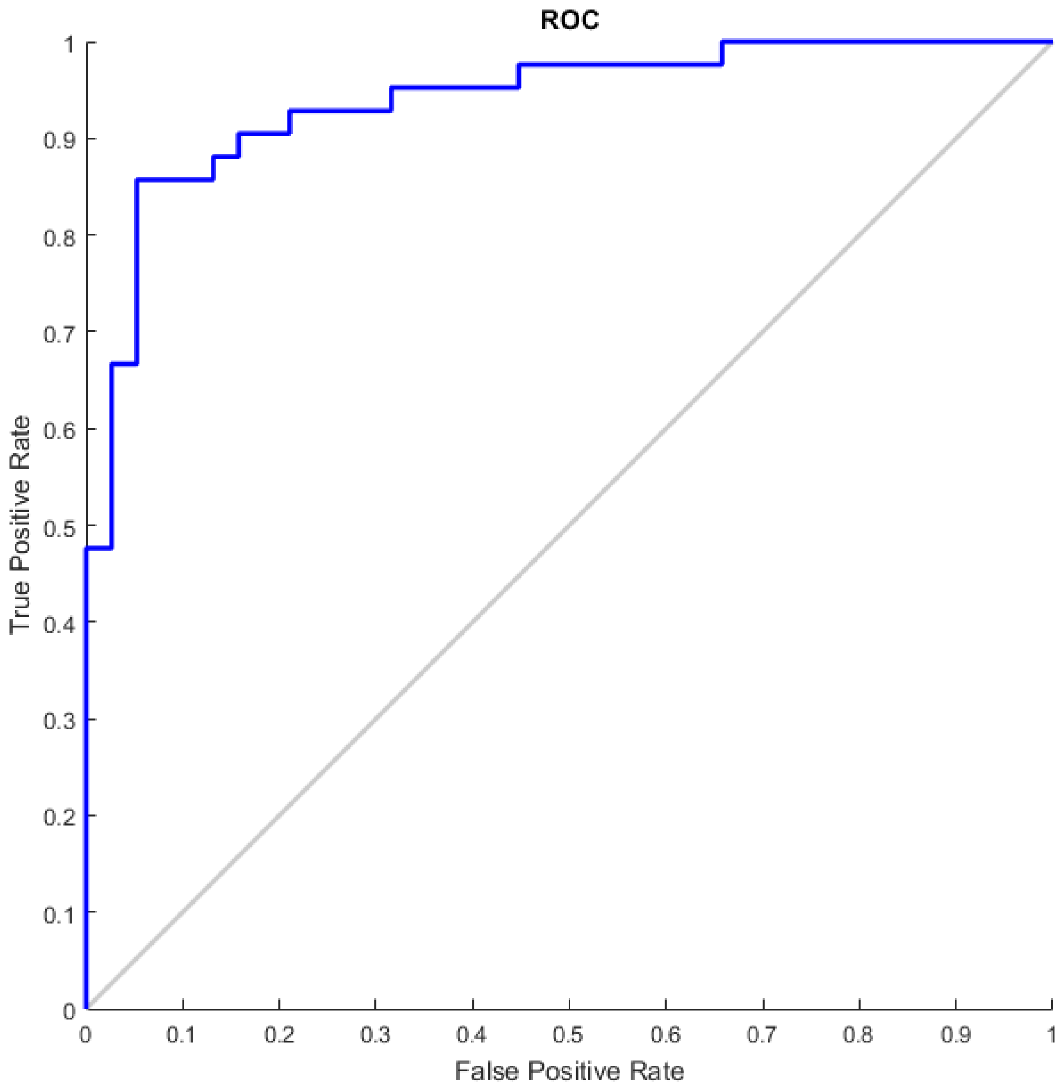

Figure 27 Example ROC curve of training data set.

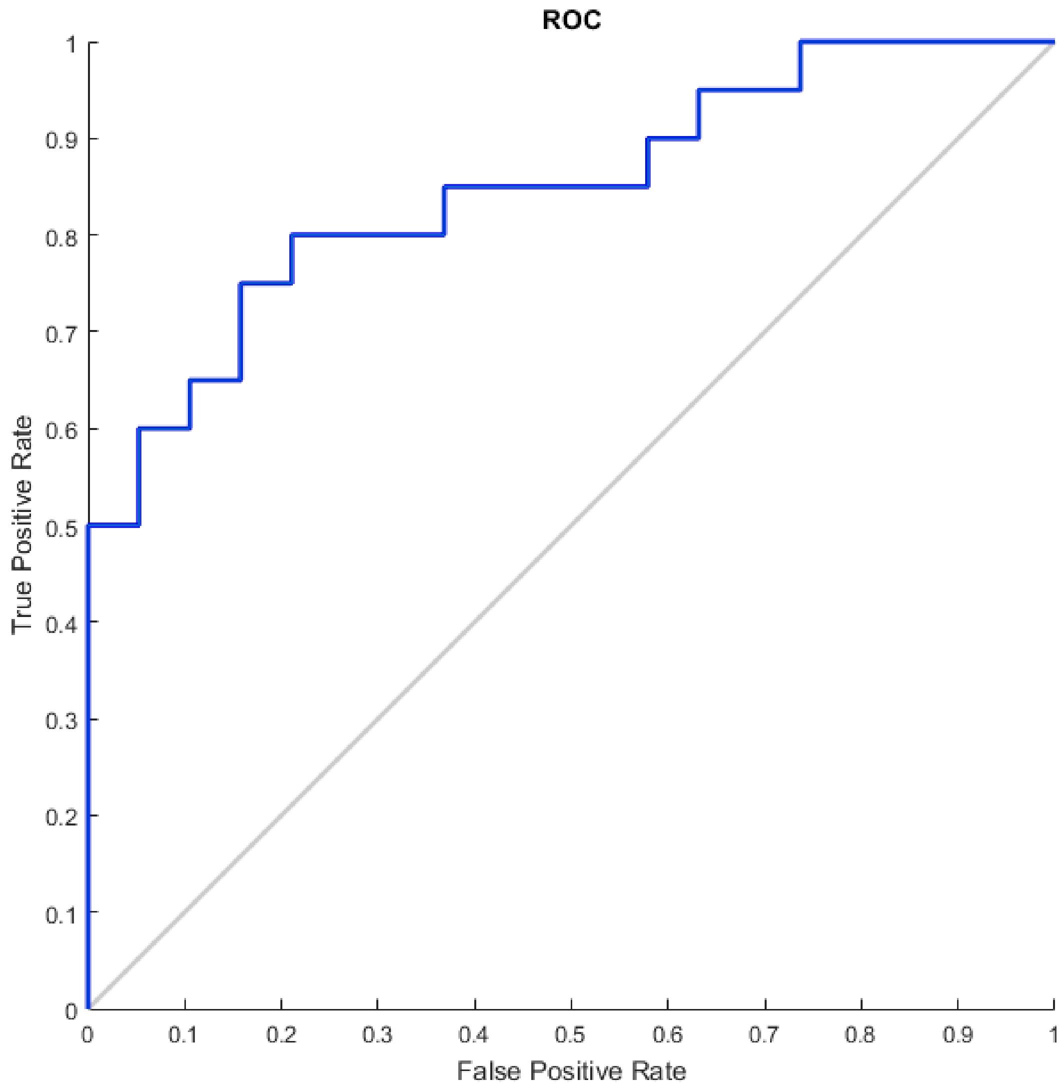

Figure 28 Example ROC curve of test data set.

7.3.4 Comparison of PCSSLR Training and Test Set Classification Performance Based on Clustering Coefficients: ROC Curve's AUC vs. Pearson Correlation

One split of the original data leads to one set of training and data. The training data are used to develop model that would result in one AUC for the ROC curve. Since PCSSLR uses a forward selection step, only a subset of the original full set of predictor variables would be included in the model developed. Based on the 1,000 samples derived using the cross validation method, 1,000 set of AUC and ROC curves are resulted.

7.3.4.1 Alpha Wave (7-9 Hz)

The summary result of classification performance in terms of ROC curve's AUC distribution for selected value of Pearson correlation coefficient used as thresholds to construct undirected EEG/brain network based on channel data for 7-9 Hz frequency range is shown in Figure 29. For the detailed comparison classification performance of the training datasets and that of the test datasets focusing on only one Pearson correlation value, the distributions of corresponding ROC curve's AUC for the 1,000 sampling iterations are show in Figure 30 to Figure 39 . The Pearson correlations used to construct the EEG frequency network are 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9 and 1. Below each of the boxplots of AUC distributions for training and test sets, a table summarizes the median AUC and mean AUC of training and test set, difference and percentage of difference between test set's median and mean AUC with respect to training set's AUC presented.

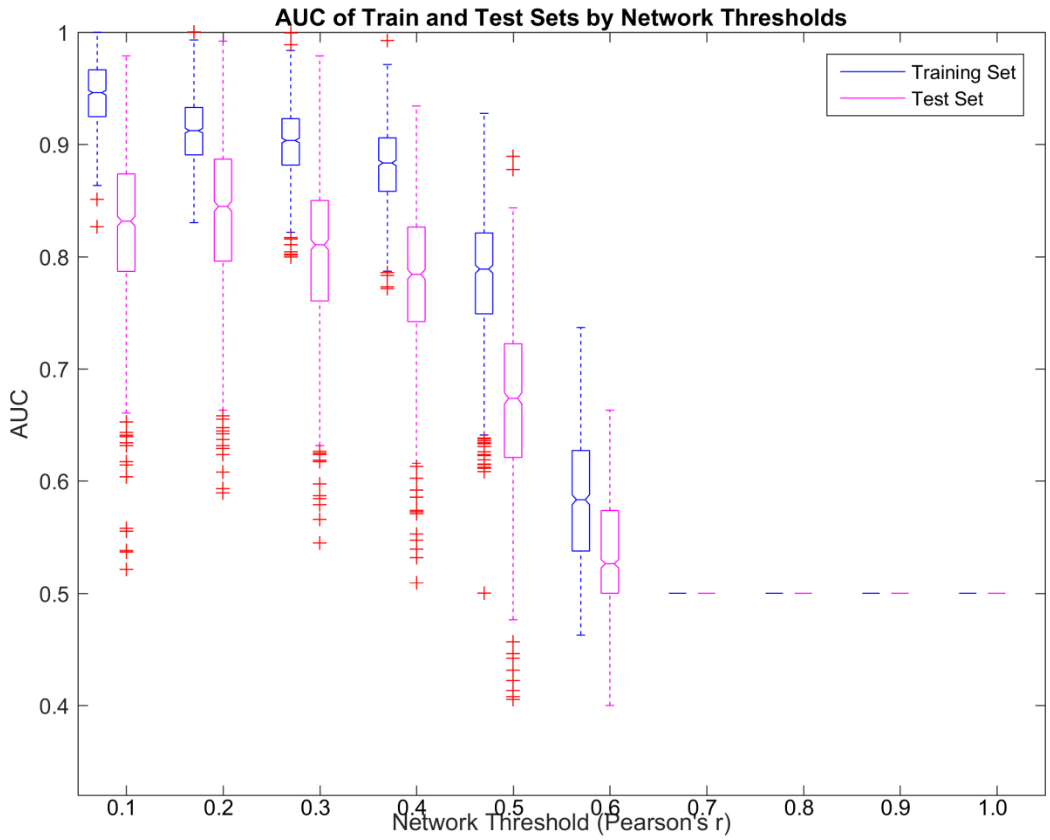

Figure 29. Training and test set classification performance of PCSSLR over range of Pearson correlations used to construct EEG network for frequency of 7-9 Hz.

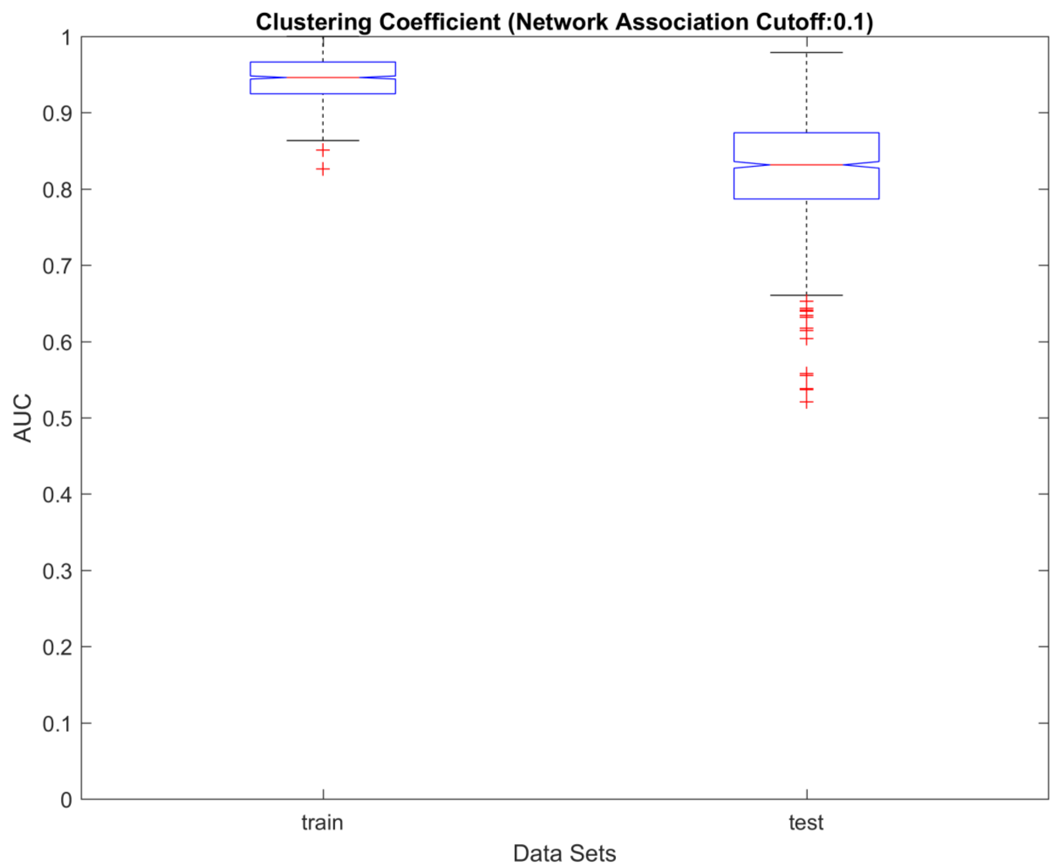

Figure 30. Training and test set classification performance of PCSSLR for EEG network constructed using Pearson correlation threshold of 0.1 over frequency range of 7-9 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.1)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.9461	0.8316	-0.1145	-12.11%
Mean	0.9457	0.8259	-0.1198	-12.67%
Standard Deviation	0.0299	0.0684	0.0385	128.75%

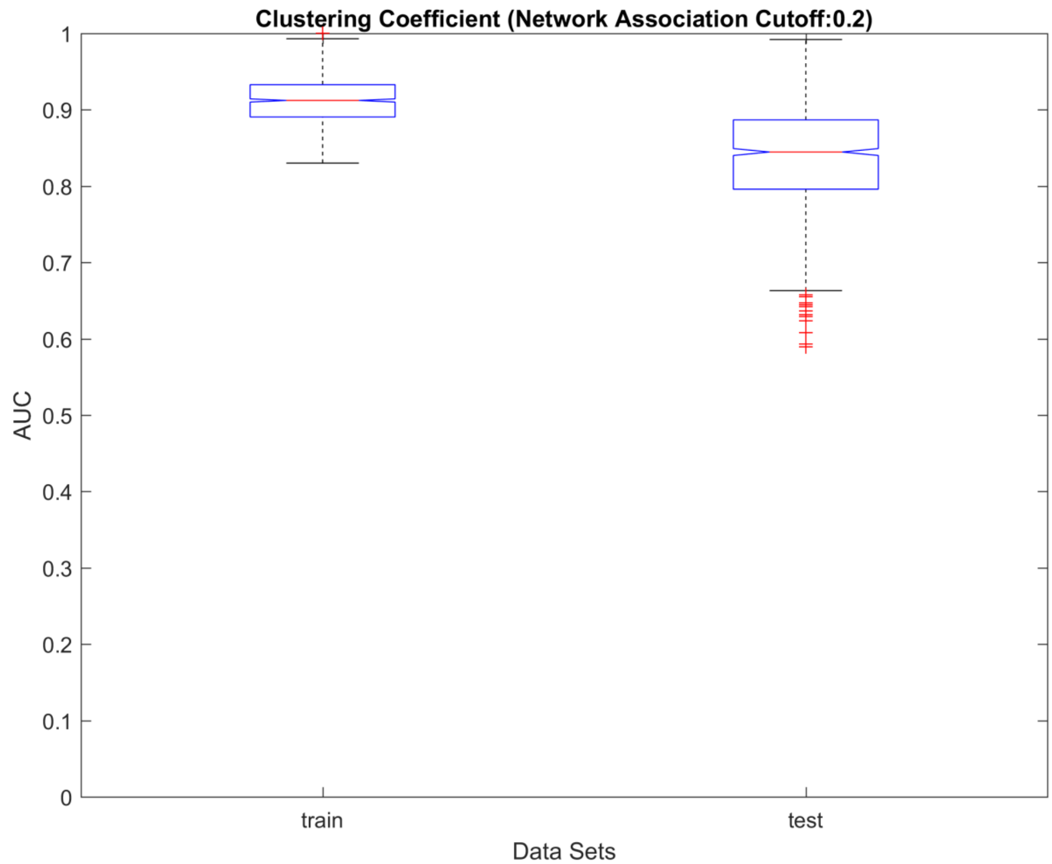

Figure 31. Training and test set classification performance of PCSSLR for EEG network constructed using Pearson correlation threshold of 0.2 over frequency range of 7-9 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.2)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.9123	0.8447	-0.0675	-7.4%
Mean	0.9116	0.8384	-0.0732	-8.03%
Standard Deviation	0.0292	0.0667	0.0375	128.46%

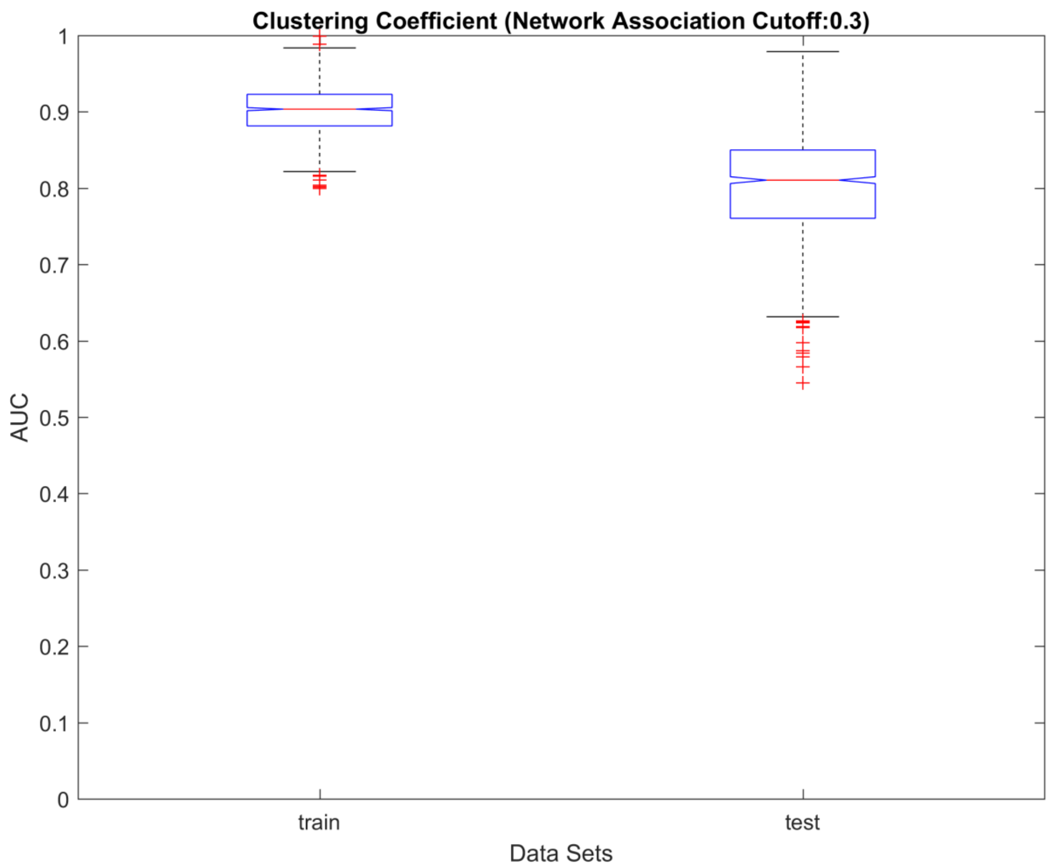

Figure 32. Training and test set classification performance of PCSSLR for EEG network constructed using Pearson correlation threshold of 0.3 over frequency range of 7-9 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.3)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.9035	0.8105	-0.093	-10.29%
Mean	0.902	0.8025	-0.0996	-11.04%
Standard Deviation	0.0319	0.0654	0.0335	104.96%

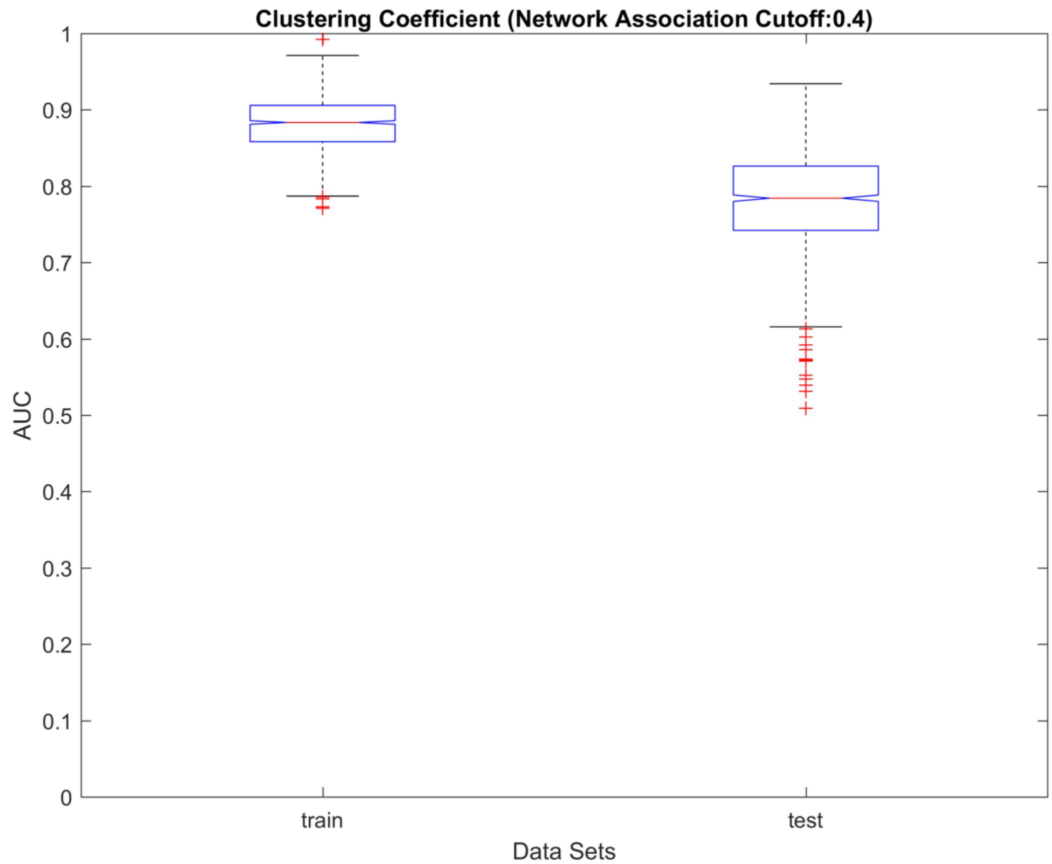

Figure 33. Training and test set classification performance of PCSSLR for EEG network constructed using Pearson correlation threshold of 0.4 over frequency range of 7-9 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.4)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.8835	0.7842	-0.0992	-11.23%
Mean	0.8817	0.78	-0.1017	-11.54%
Standard Deviation	0.0343	0.0657	0.0315	91.81%

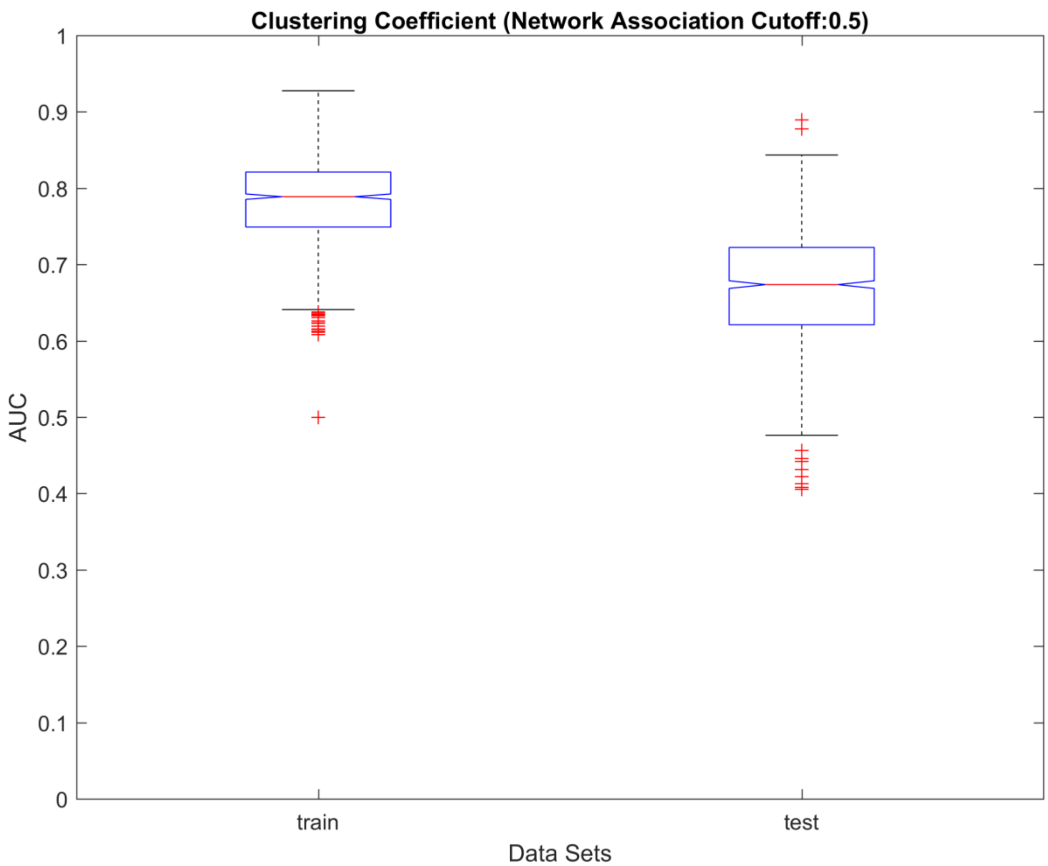

Figure 34. Training and test set classification performance of PCSSLR for EEG network constructed using Pearson correlation threshold of 0.5 over frequency range of 7-9 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.5)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.7888	0.6737	-0.1152	-14.6%
Mean	0.7823	0.6679	-0.1144	-14.63%
Standard Deviation	0.0563	0.0768	0.0206	36.51%

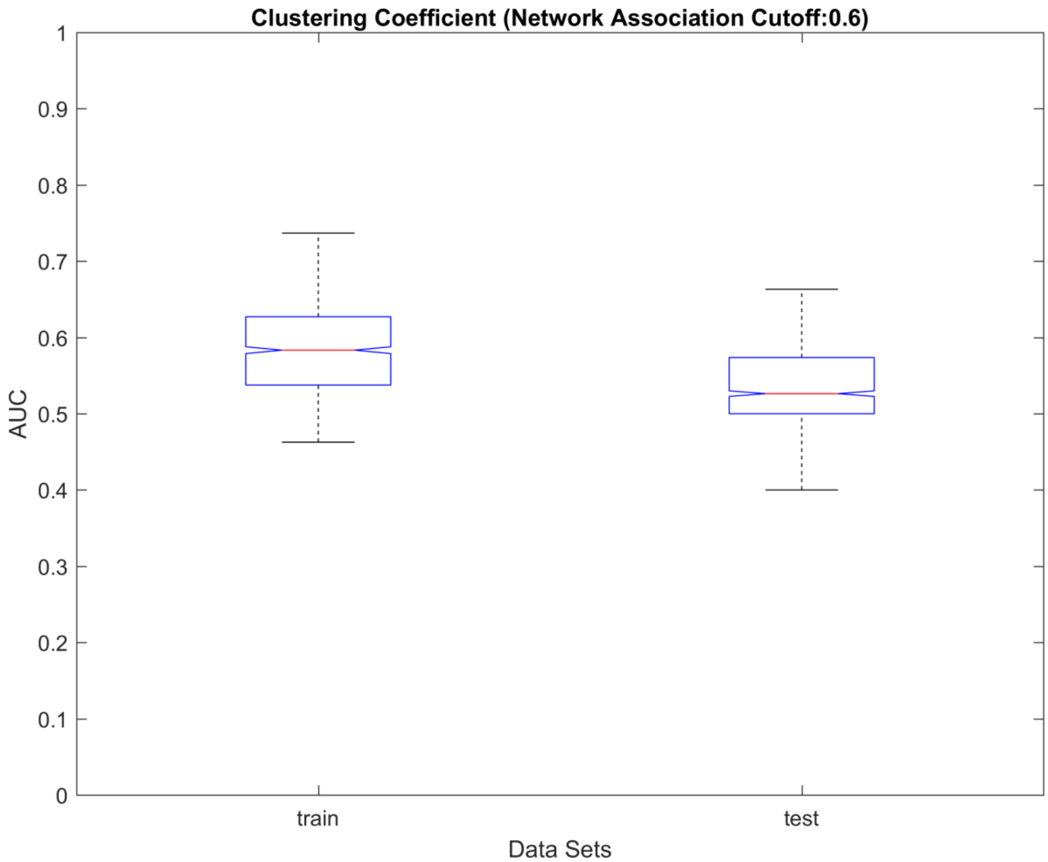

Figure 35. Training and test set classification performance of PCSSLR for EEG network constructed using Pearson correlation threshold of 0.6 over frequency range of 7-9 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.6)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5833	0.5263	-0.0570	-9.77%
Mean	0.5816	0.5384	-0.0431	-7.42%
Standard Deviation	0.0557	0.0433	-0.0124	-22.22%

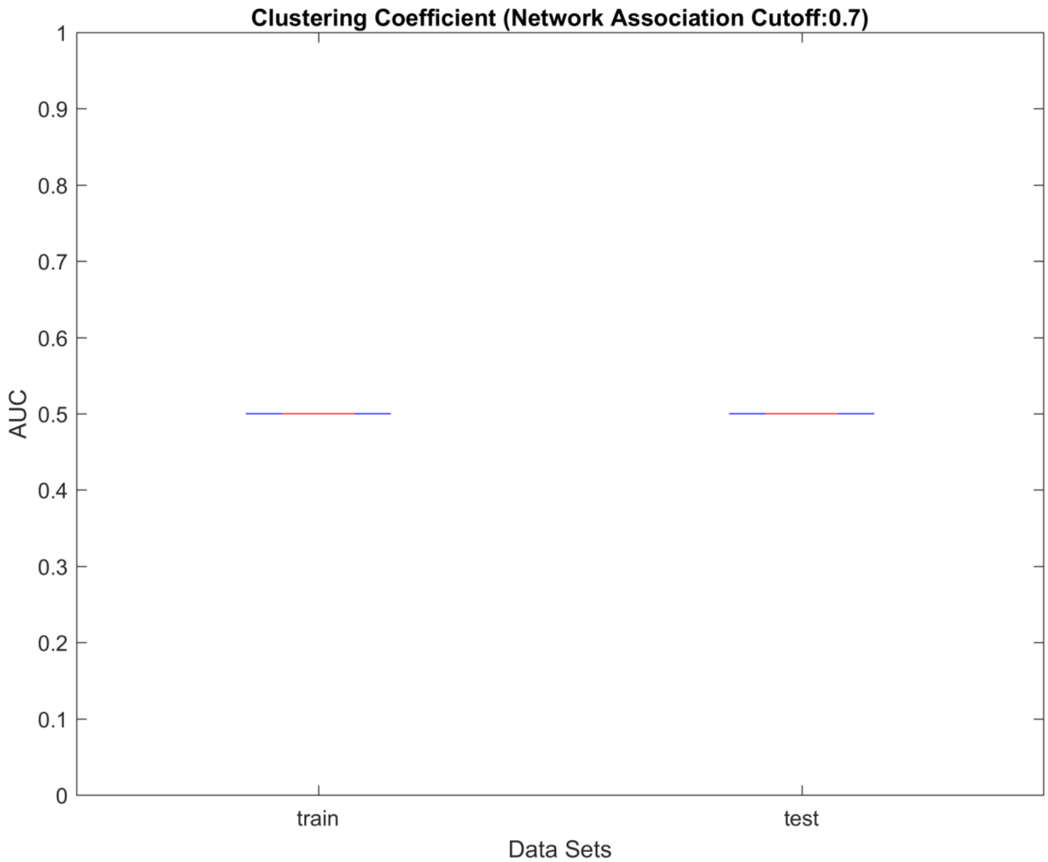

Figure 36. Training and test set classification performance of PCSSLR for EEG network constructed using Pearson correlation threshold of 0.7 over frequency range of 7-9 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.7)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5	0.5	0	0%
Mean	0.5	0.5	0	0%
Standard Deviation	0	0	0	0%

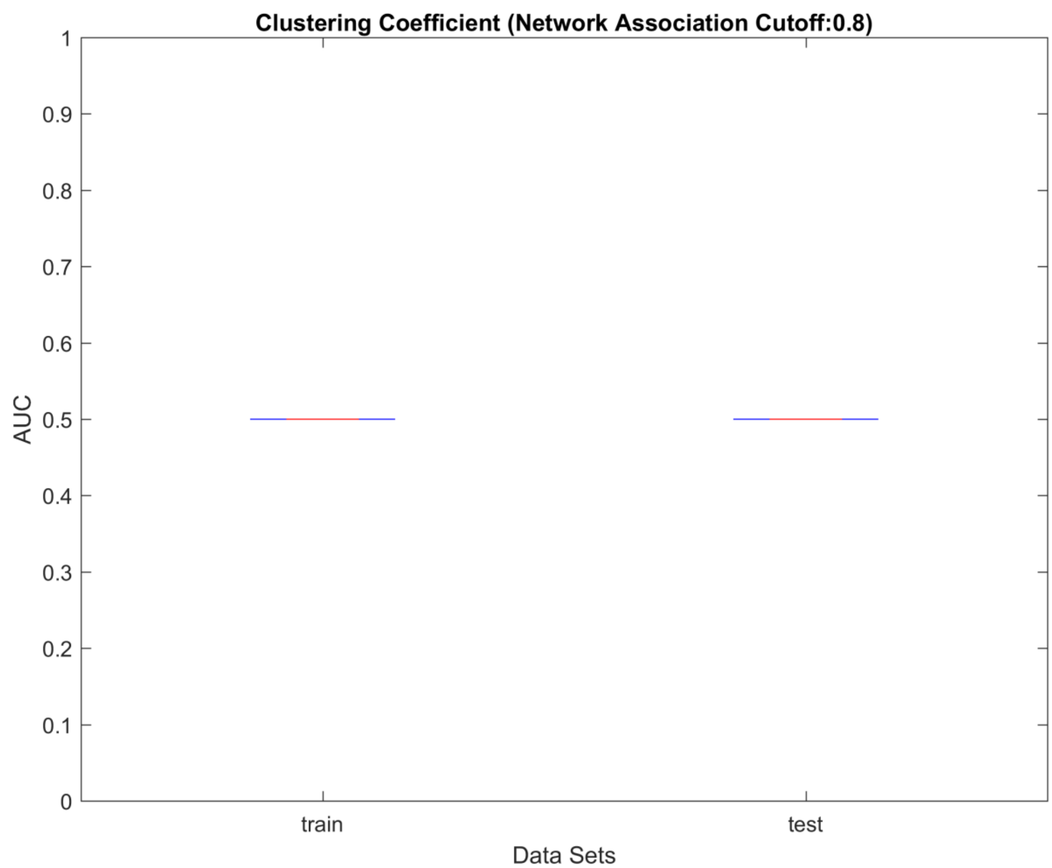

Figure 37. Training and test set classification performance of PCSSLR for EEG network constructed using Pearson correlation threshold of 0.8 over frequency range of 7-9 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.8)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5	0.5	0	0%
Mean	0.5	0.5	0	0%
Standard Deviation	0	0	0	0%

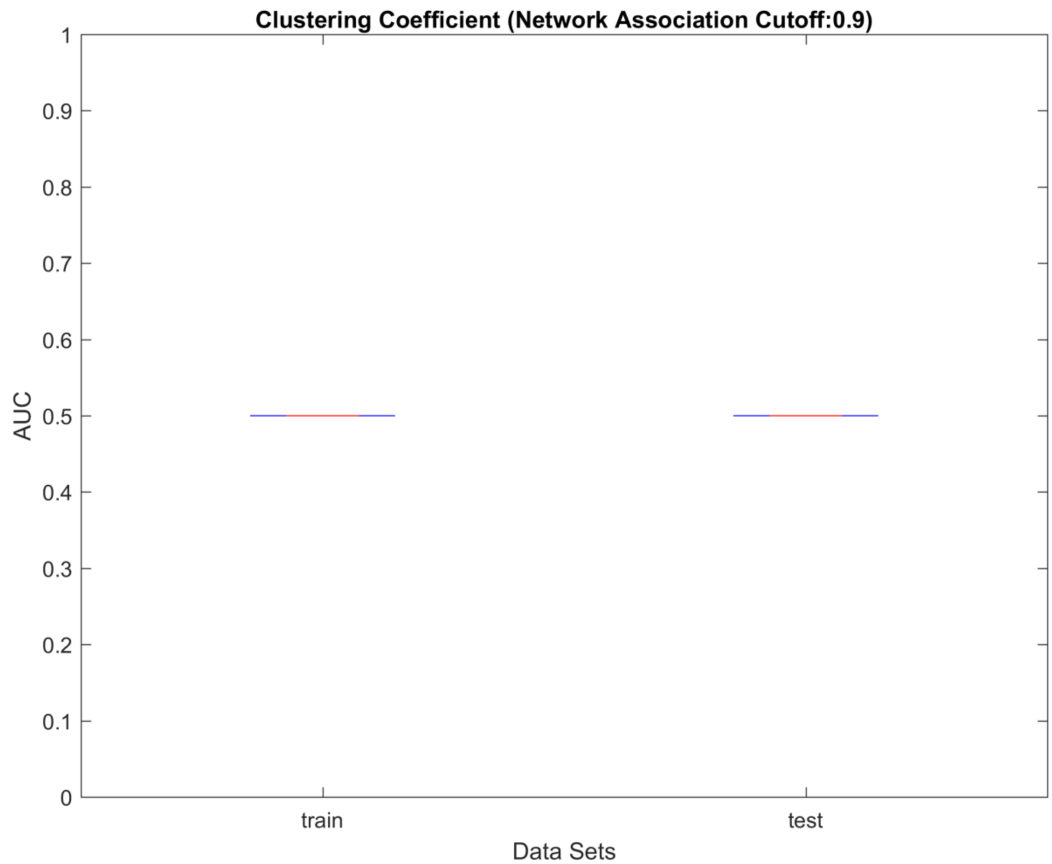

Figure 38. Training and test set classification performance of PCSSLR for EEG network constructed using Pearson correlation threshold of 0.9 over frequency range of 7-9 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.9)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5	0.5	0	0%
Mean	0.5	0.5	0	0%
Standard Deviation	0	0	0	0%

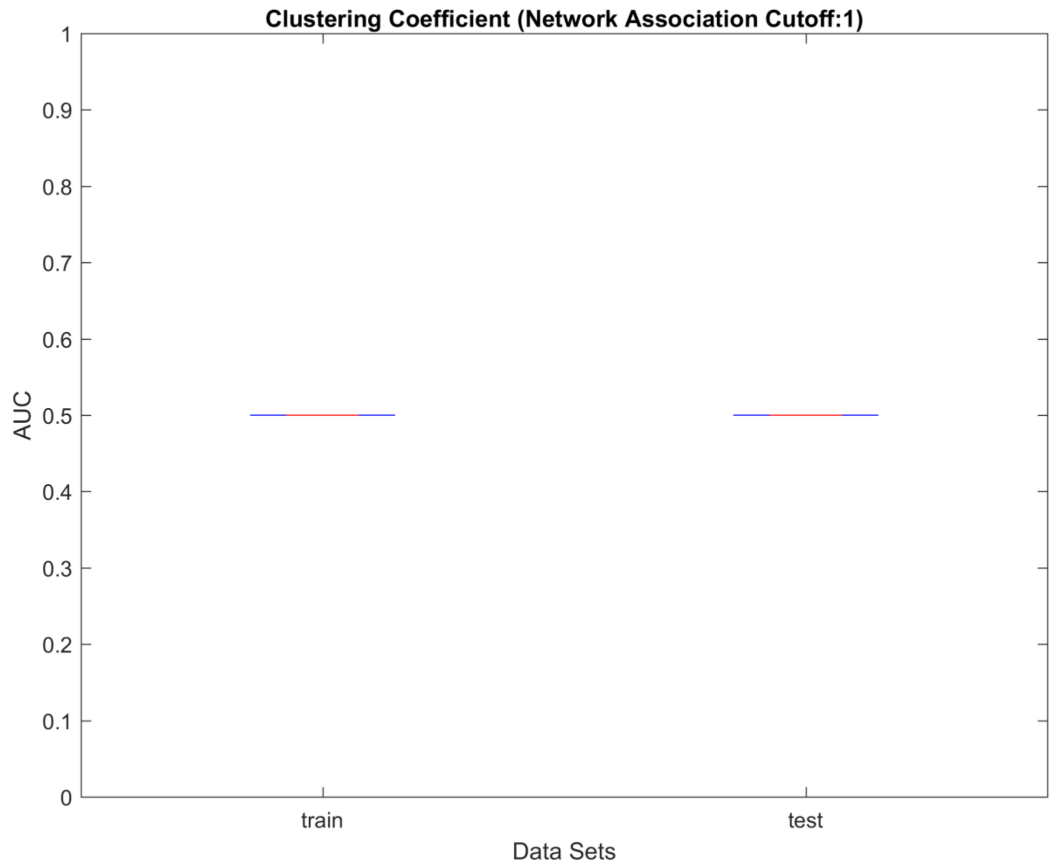

Figure 39. Training and test set classification performance of PCSSLR for EEG network constructed using Pearson correlation threshold of 1 over frequency range of 7-9 Hz.

	ROC Curve's AUC (Network Association Threshold: 1)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5	0.5	0	0%
Mean	0.5	0.5	0	0%
Standard Deviation	0	0	0	0%

7.3.4.2 Alpha Wave (11-13 Hz)

The summary result of classification performance in terms of ROC Curve's AUC distribution for selected value of Pearson correlation coefficient used as thresholds to construct undirected EEG/brain network based on channel data for 11-13 Hz frequency range is shown in Figure 40. For the detailed comparison classification performance of the training datasets and that of the test datasets focusing on only one Pearson correlation value, the distributions of corresponding ROC curve's AUC for the 1,000 sampling iterations are show in Figure 41 to Figure 50. The Pearson correlations used to construct the EEG frequency network are 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9 and 1. Below each of the boxplots of AUC distributions for training and test sets, a table summarizes the median AUC and mean AUC of training and test set, difference and percentage of difference between test set's median and mean AUC with respect to training set's AUC is presented.

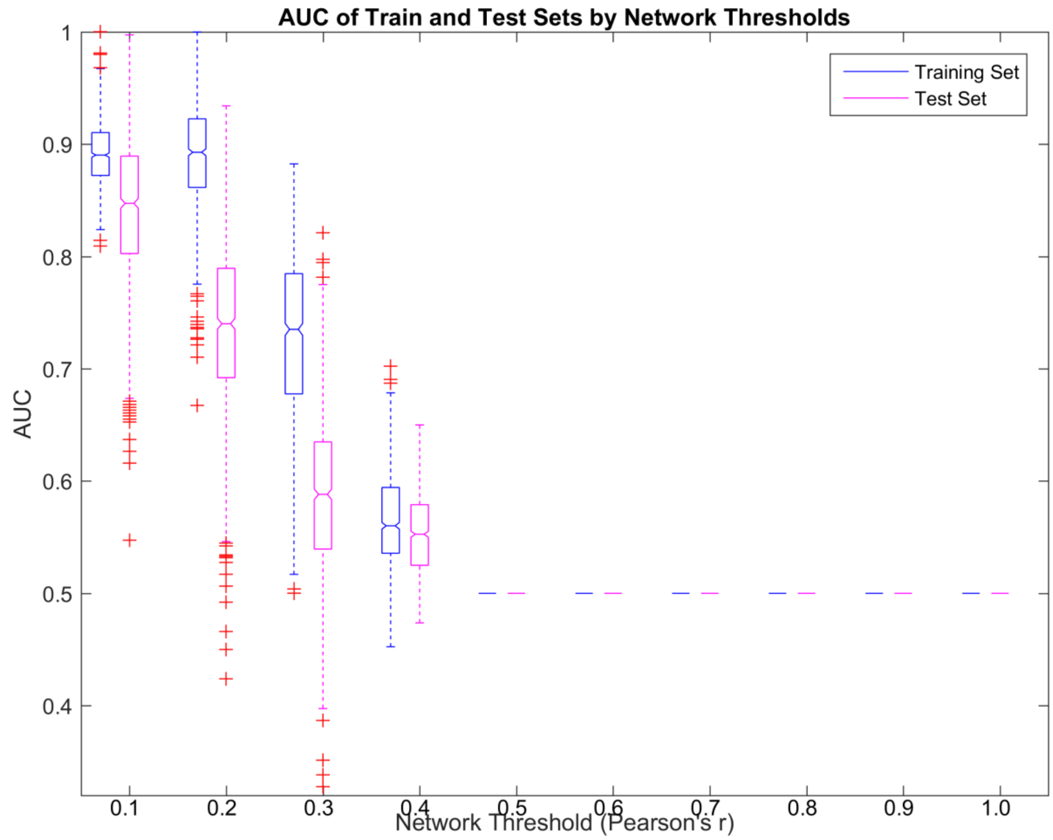

Figure 40. Training and test set classification performance of PCSSLR over range of Pearson correlations used to construct EEG network for frequency of 11-13 Hz.

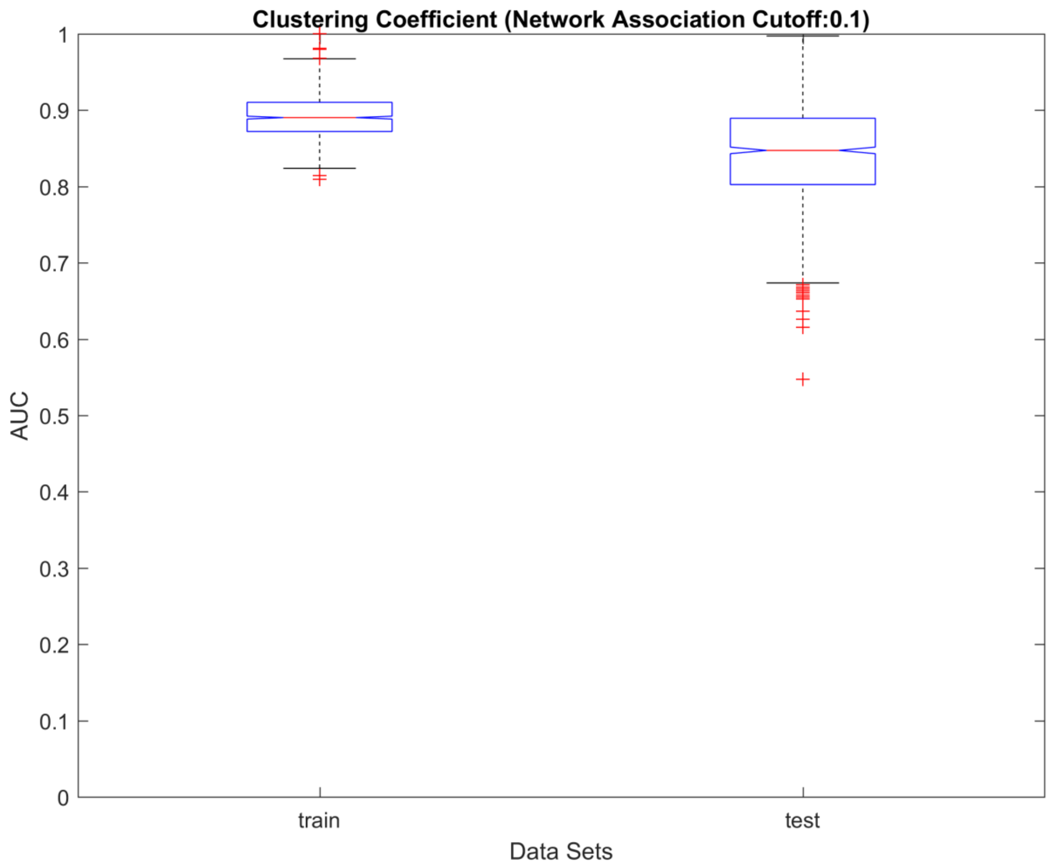

Figure 41. Training and test set classification performance of PCSSLR for EEG network constructed using Pearson correlation threshold of 0.1 over frequency range of 11-13 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.1)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.8904	0.8474	-0.043	-4.83%
Mean	0.8921	0.8446	-0.0475	-5.32%
Standard Deviation	0.029	0.0646	0.0356	123.03%

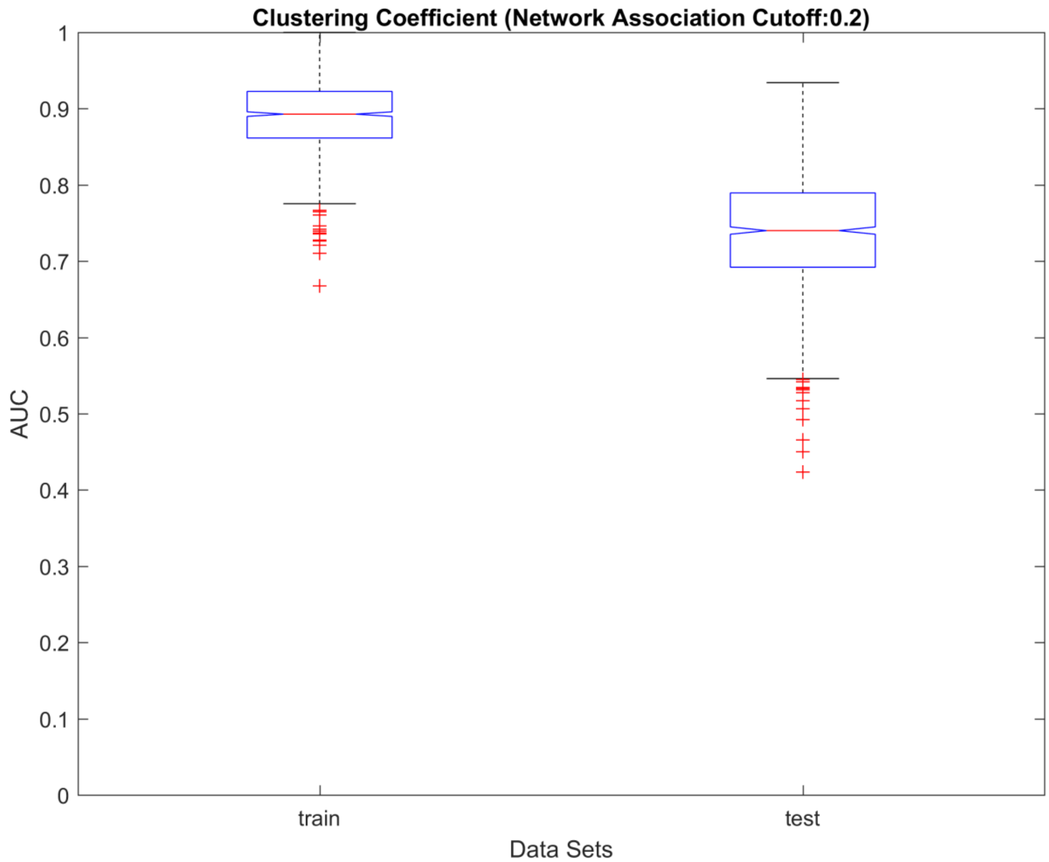

Figure 42. Training and test set classification performance of PCSSLR for EEG network constructed using Pearson correlation threshold of 0.2 over frequency range of 11-13 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.2)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.8929	0.7401	-0.1527	-17.11%
Mean	0.8889	0.7374	-0.1515	-17.04%
Standard Deviation	0.048	0.075	0.0271	56.39%

¶

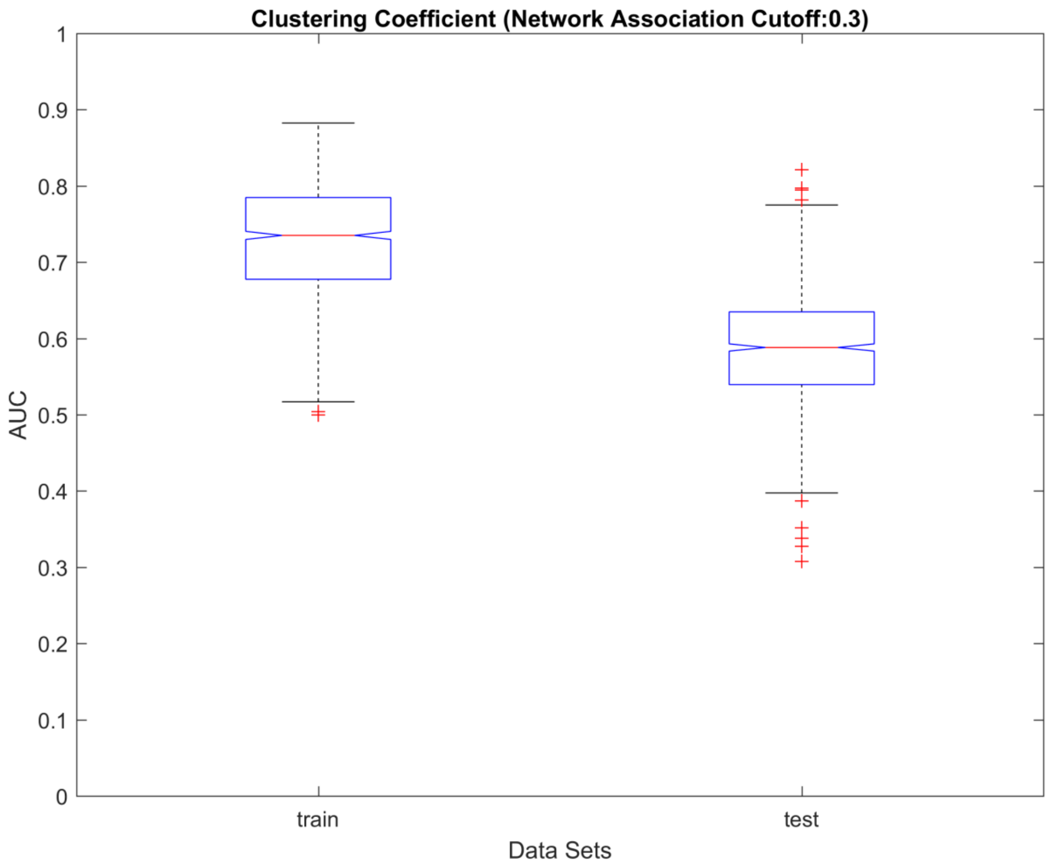

Figure 43. Training and test set classification performance of PCSSLR for EEG network constructed using Pearson correlation threshold of 0.3 over frequency range of 11-13 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.3)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.7351	0.5882	-0.147	-19.99%
Mean	0.7242	0.5864	-0.1377	-19.02%
Standard Deviation	0.0777	0.0765	-0.0013	-1.63%

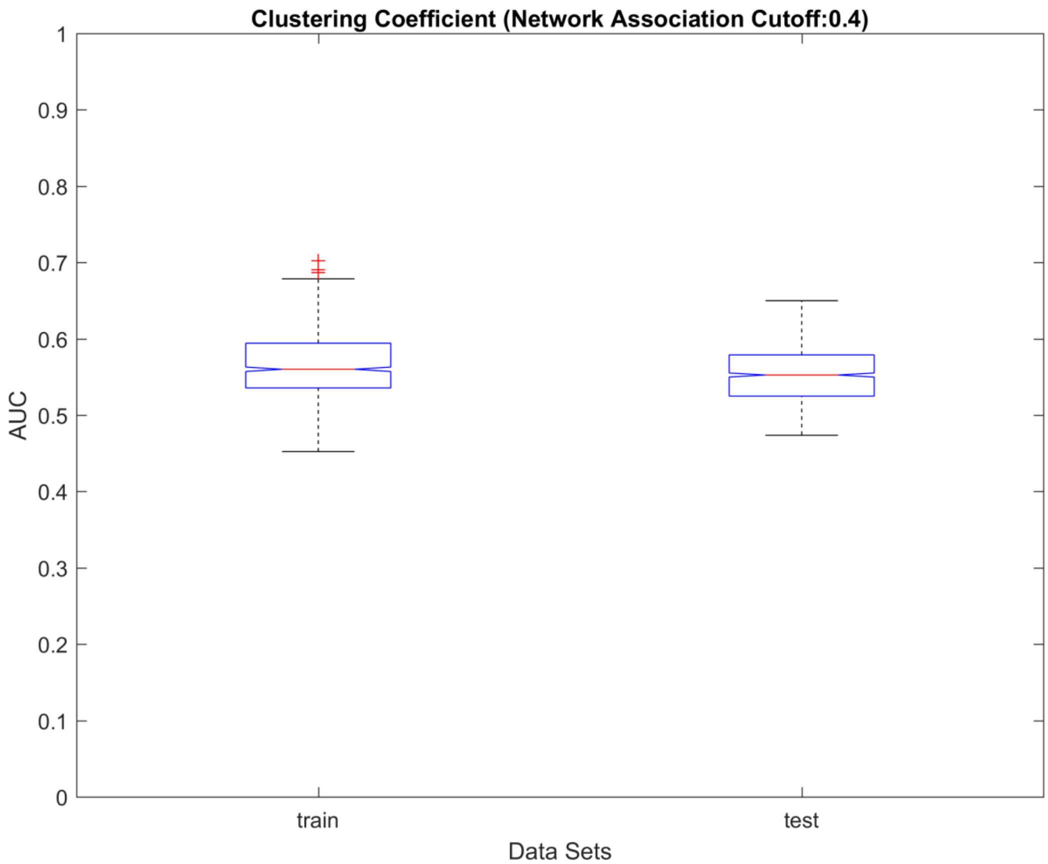

Figure 44. Training and test set classification performance of PCSSLR for EEG network constructed using Pearson correlation threshold of 0.4 over frequency range of 11-13 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.4)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5602	0.5526	-0.0075	-1.34%
Mean	0.5628	0.5564	-0.0064	-1.14%
Standard Deviation	0.0405	0.0366	-0.0039	-9.66%

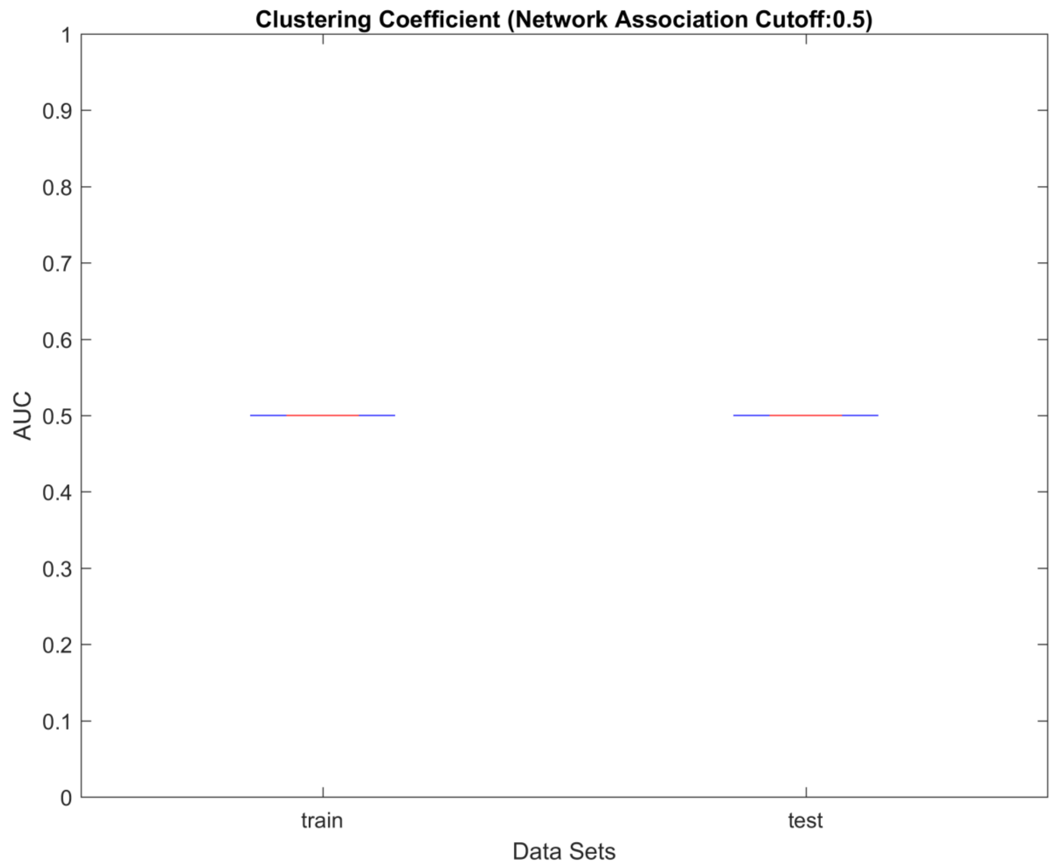

Figure 45. Training and test set classification performance of PCSSLR for EEG network constructed using Pearson correlation threshold of 0.5 over frequency range of 11-13 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.5)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5	0.5	0	0%
Mean	0.5	0.5	0	0%
Standard Deviation	0	0	0	0%

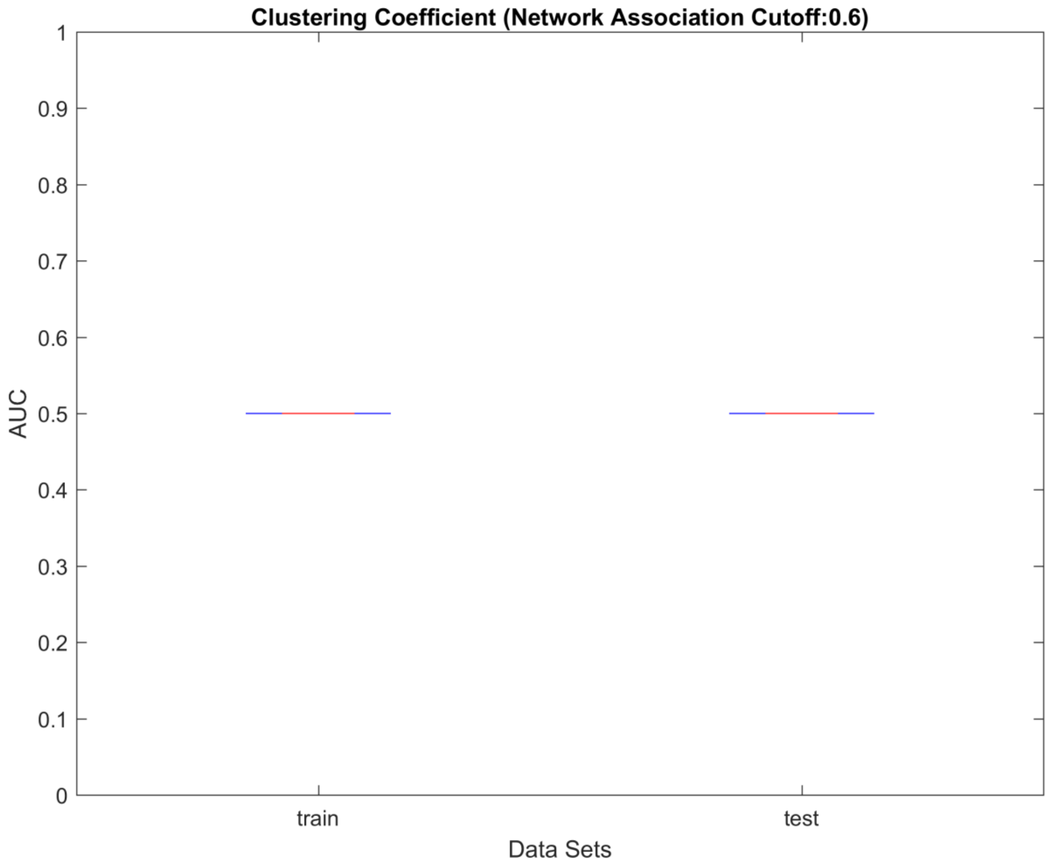

Figure 46. Training and test set classification performance of PCSSLR for EEG network constructed using Pearson correlation threshold of 0.6 over frequency range of 11-13 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.6)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5	0.5	0	0%
Mean	0.5	0.5	0	0%
Standard Deviation	0	0	0	0%

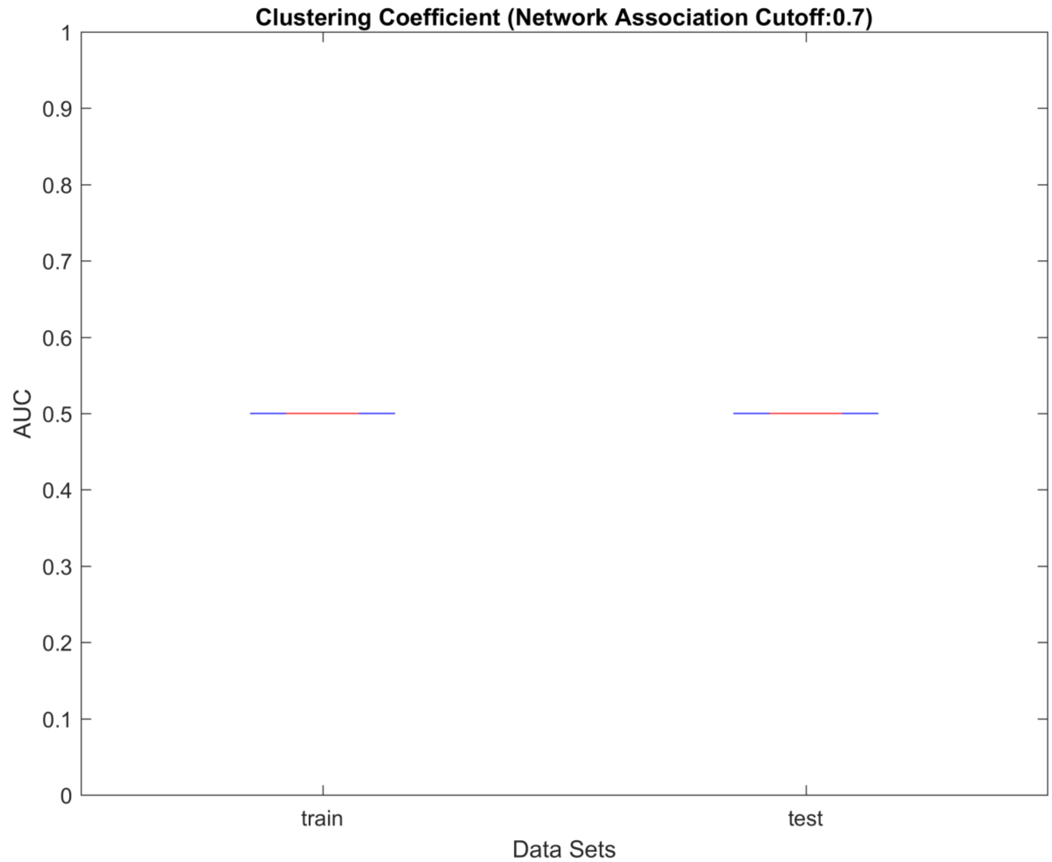

Figure 47. Training and test set classification performance of PCSSLR for EEG network constructed using Pearson correlation threshold of 0.7 over frequency range of 11-13 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.7)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5	0.5	0	0%
Mean	0.5	0.5	0	0%
Standard Deviation	0	0	0	0%

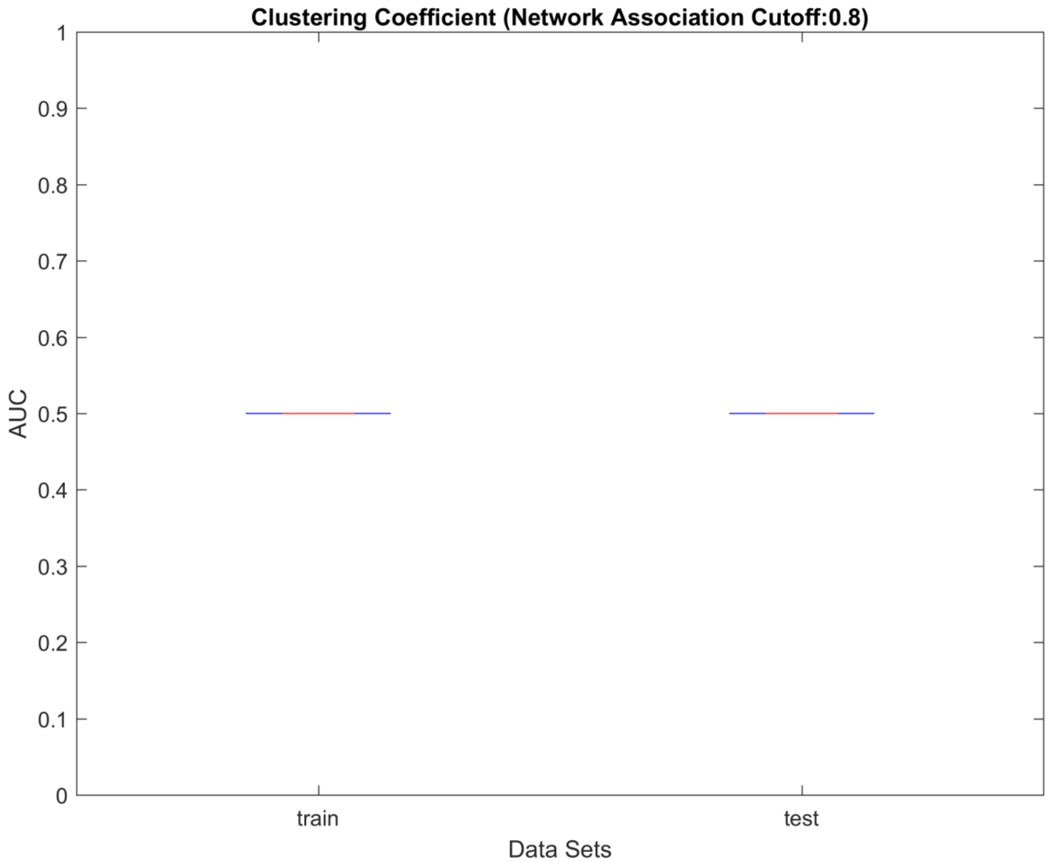

Figure 48. Training and test set classification performance of PCSSLR for EEG network constructed using Pearson correlation threshold of 0.8 over frequency range of 11-13 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.8)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5	0.5	0	0%
Mean	0.5	0.5	0	0%
Standard Deviation	0	0	0	0%

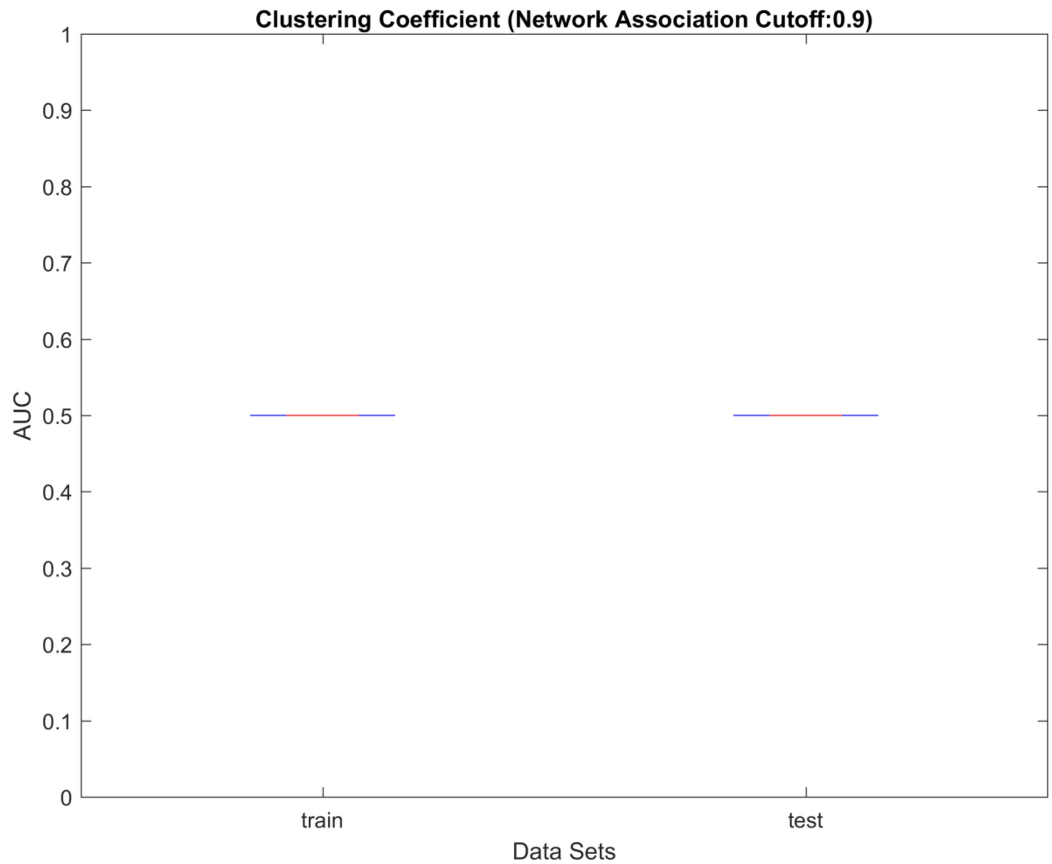

Figure 49. Training and test set classification performance of PCSSLR for EEG network constructed using Pearson correlation threshold of 0.9 over frequency range of 11-13 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.9)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5	0.5	0	0%
Mean	0.5	0.5	0	0%
Standard Deviation	0	0	0	0%

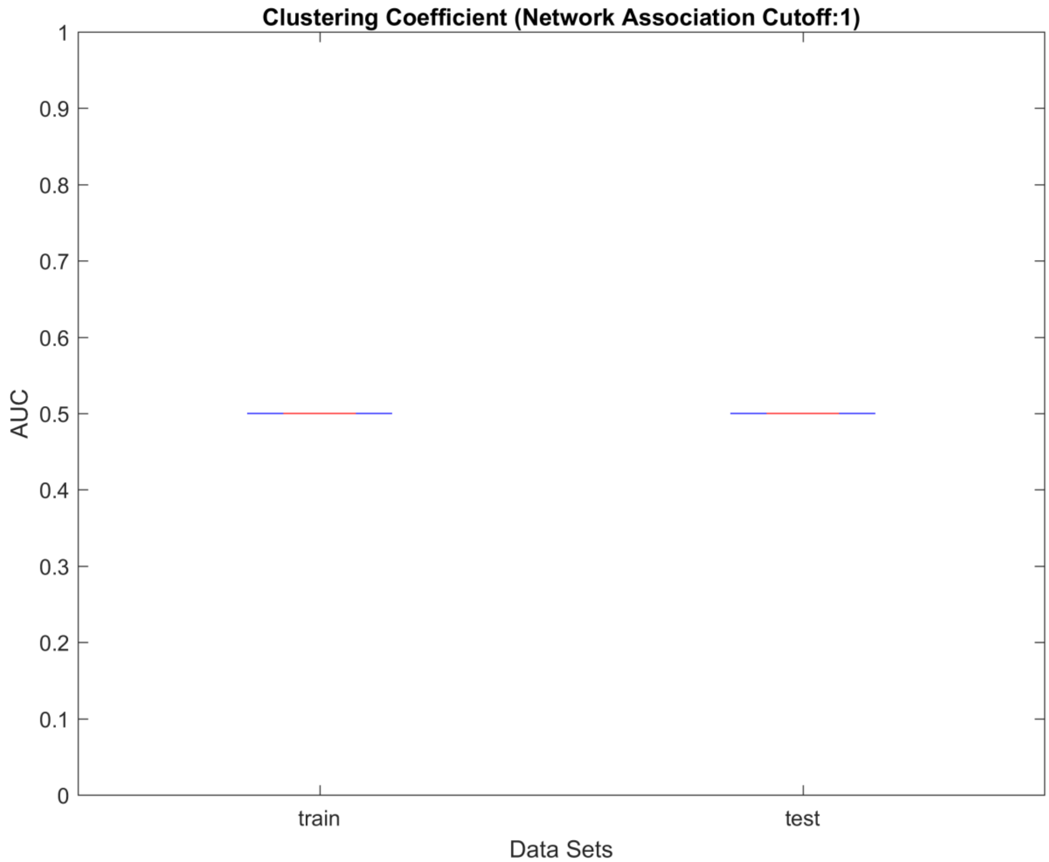

Figure 50. Training and test set classification performance of PCSSLR for EEG network constructed using Pearson correlation threshold of 1 over frequency range of 11-13 Hz.

	ROC Curve's AUC (Network Association Threshold: 1)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5	0.5	0	0%
Mean	0.5	0.5	0	0%
Standard Deviation	0	0	0	0%

7.3.4.3 Beta Wave (13-19 Hz)

The summary result of classification performance in terms of ROC Curve's AUC distribution for selected value of Pearson correlation coefficient used as thresholds to construct undirected EEG/brain network based on channel data for 13-19 Hz frequency range is shown in Figure 51 . For the detailed comparison classification performance of the training datasets and that of the test datasets focusing on only one Pearson correlation value, the distributions of corresponding ROC curve's AUC for the 1,000 sampling iterations are show in Figure 52 to Figure 61 . The Pearson correlations used to construct the EEG frequency network are 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9 and 1. Below each of the boxplots of AUC distributions for training and test sets, a table summarizes the median AUC and mean AUC of training and test set, difference and percentage of difference between test set's median and mean AUC with respect to training set's AUC is presented.

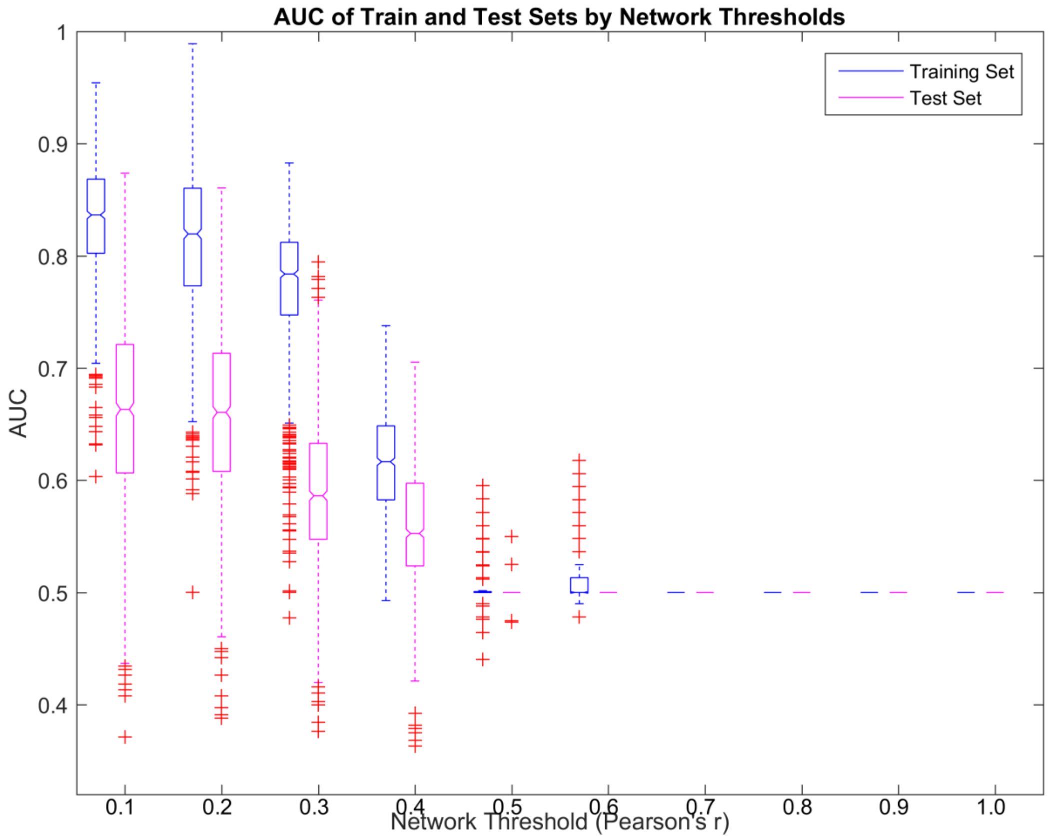

Figure 51. Training and test set classification performance of PCSSLR over range of Pearson correlations used to construct EEG network for frequency of 13-19 Hz.

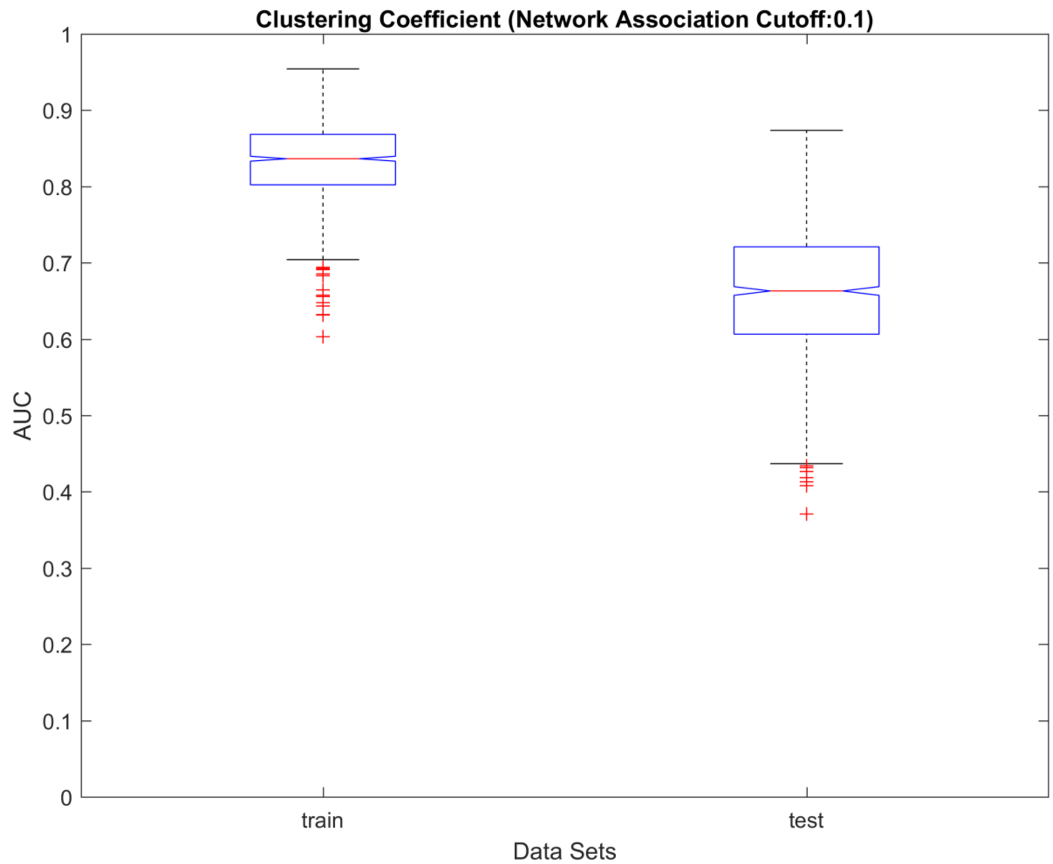

Figure 52. Training and test set classification performance of PCSSLR for EEG network constructed using Pearson correlation threshold of 0.1 over frequency range of 13-19 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.1)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.8365	0.6632	-0.1733	-20.72%
Mean	0.8327	0.66	-0.1727	-20.74%
Standard Deviation	0.0517	0.0808	0.0291	56.34%

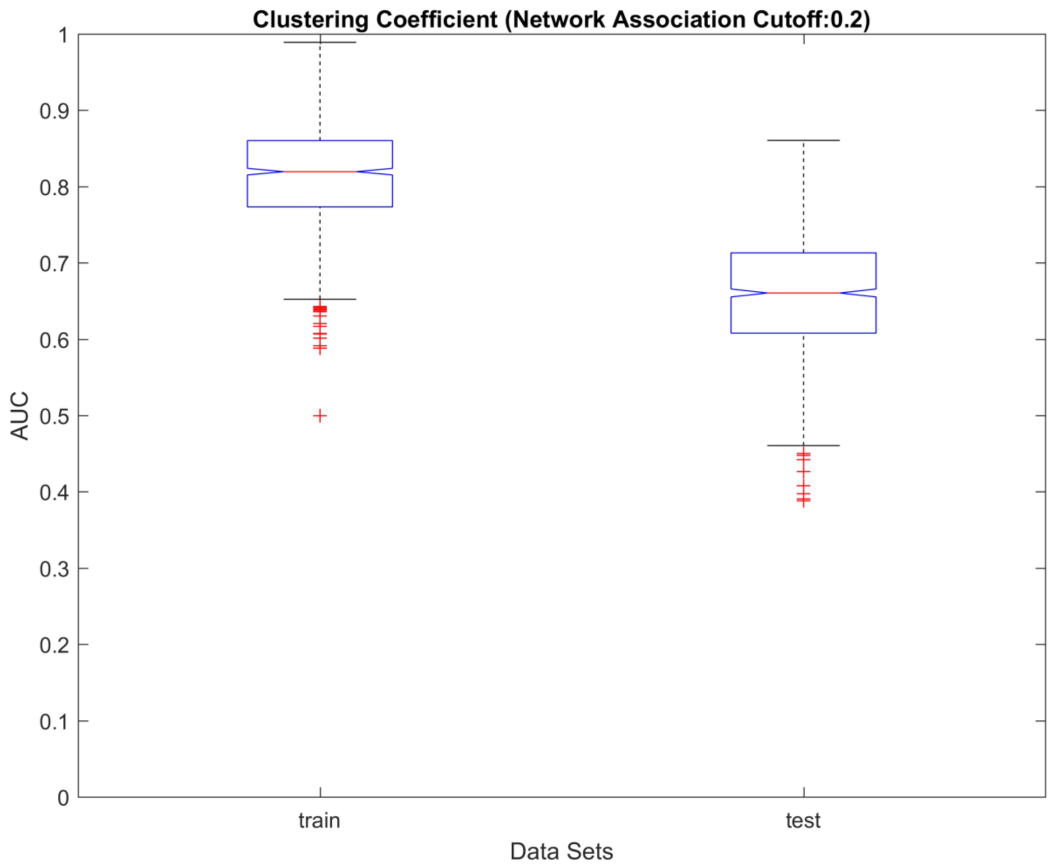

Figure 53. Training and test set classification performance of PCSSLR for EEG network constructed using Pearson correlation threshold of 0.2 over frequency range of 13-19 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.2)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.8195	0.6605	-0.159	-19.4%
Mean	0.8133	0.6577	-0.1555	-19.12%
Standard Deviation	0.068	0.0787	0.0107	15.77%

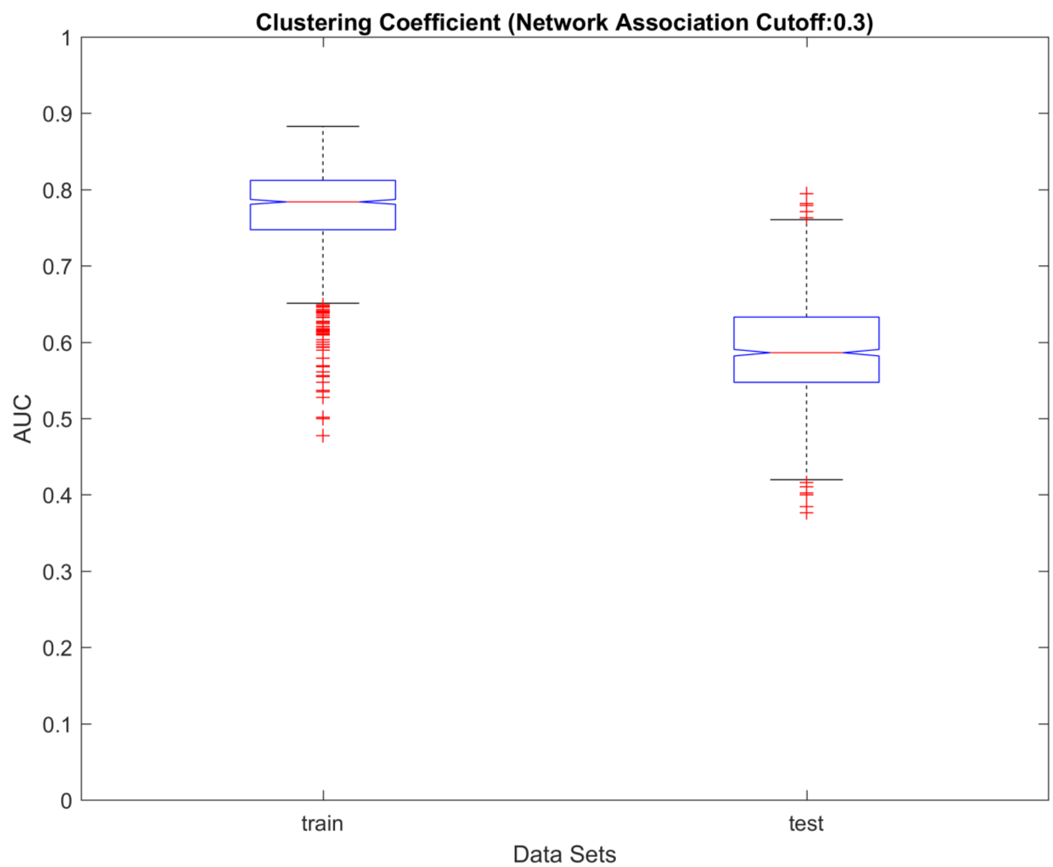

Figure 54. Training and test set classification performance of PCSSLR for EEG network constructed using Pearson correlation threshold of 0.3 over frequency range of 13-19 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.3)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.7838	0.5862	-0.1977	-25.22%
Mean	0.7642	0.5899	-0.1743	-22.8%
Standard Deviation	0.0761	0.0668	-0.0093	-12.23%

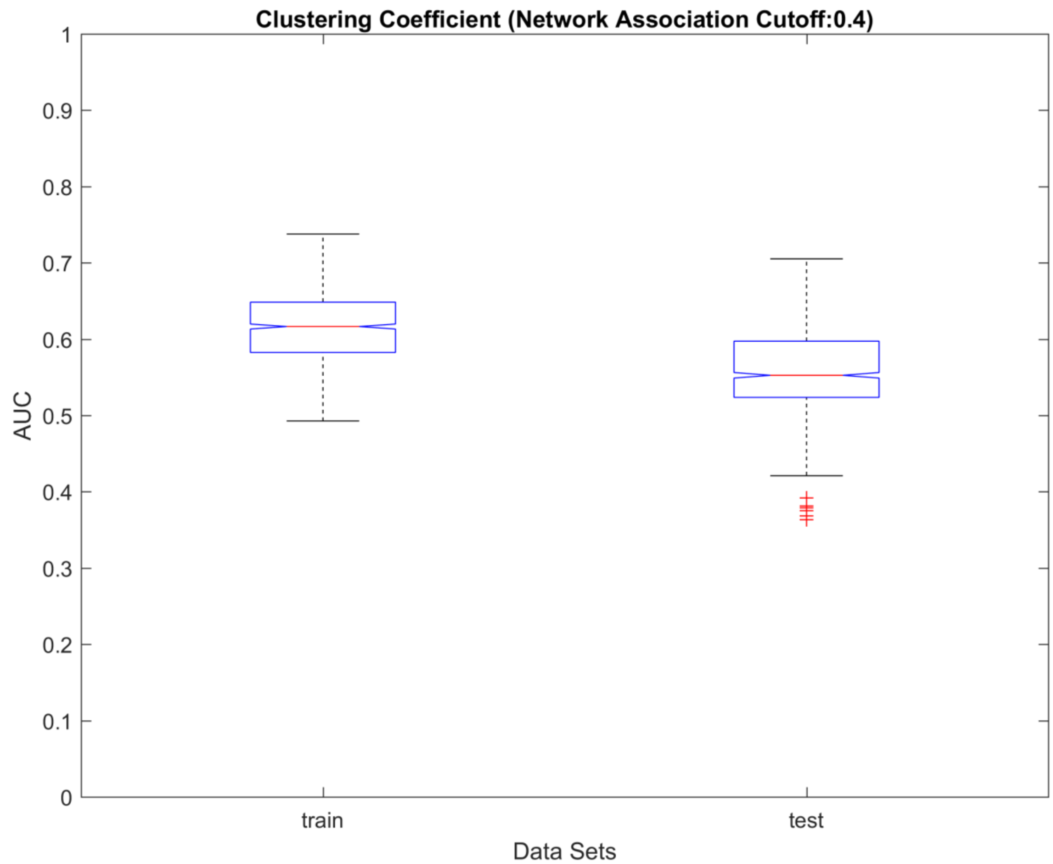

Figure 55. Training and test set classification performance of PCSSLR for EEG network constructed using Pearson correlation threshold of 0.4 over frequency range of 13-19 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.4)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.6165	0.5526	-0.0639	-10.37%
Mean	0.6083	0.5585	-0.0498	-8.19%
Standard Deviation	0.0536	0.0514	-0.0021	-4.01%

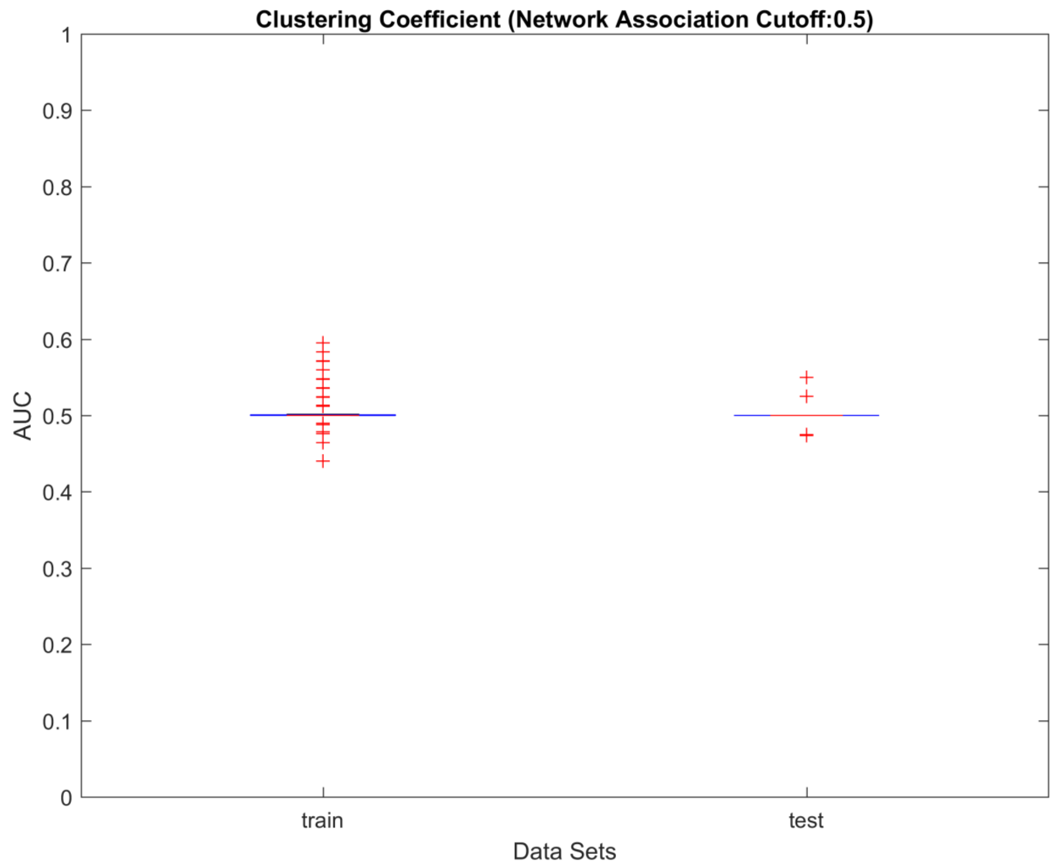

Figure 56. Training and test set classification performance of PCSSLR for EEG network constructed using Pearson correlation threshold of 0.5 over frequency range of 13-19 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.5)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5	0.5	0	0
Mean	0.5082	0.4969	-0.0113	-2.22%
Standard Deviation	0.0181	0.014	-0.0041	-22.54%

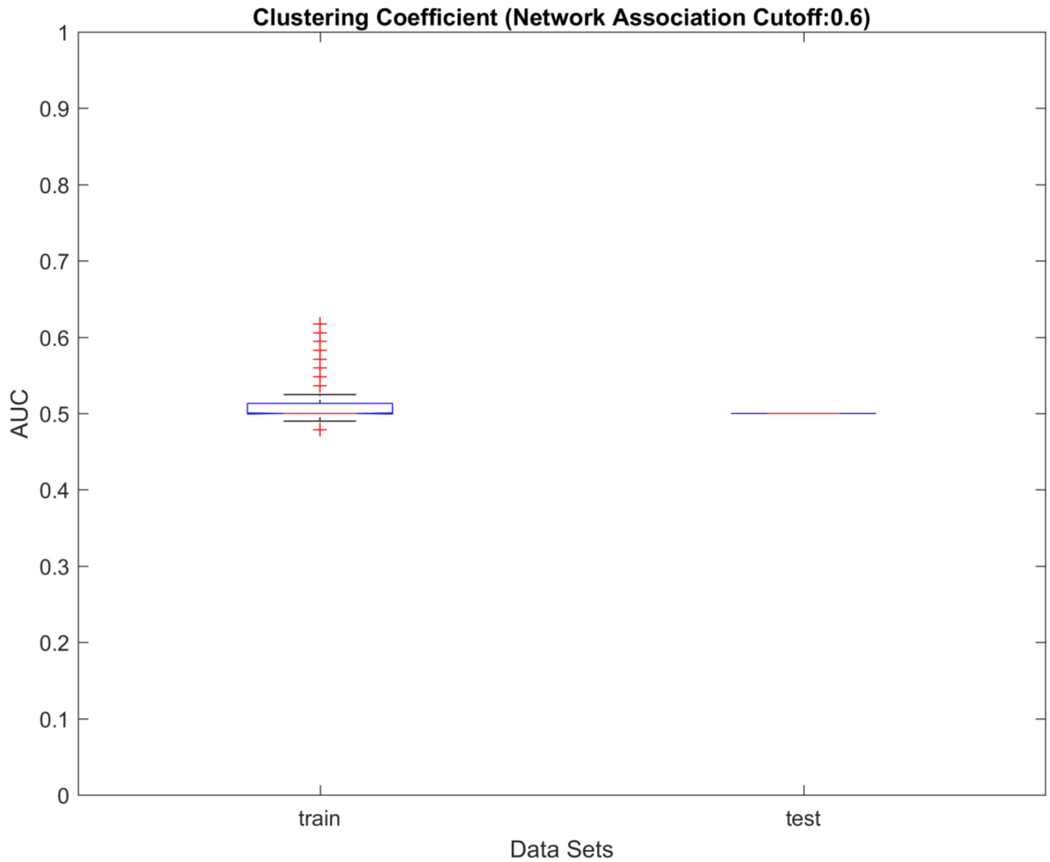

Figure 57. Training and test set classification performance of PCSSLR for EEG network constructed using Pearson correlation threshold of 0.6 over frequency range of 13-19 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.6)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5	0.5	0	0
Mean	0.5098	0.5	-0.0098	-1.92%
Standard Deviation	0.0195	0	-0.0195	-100%

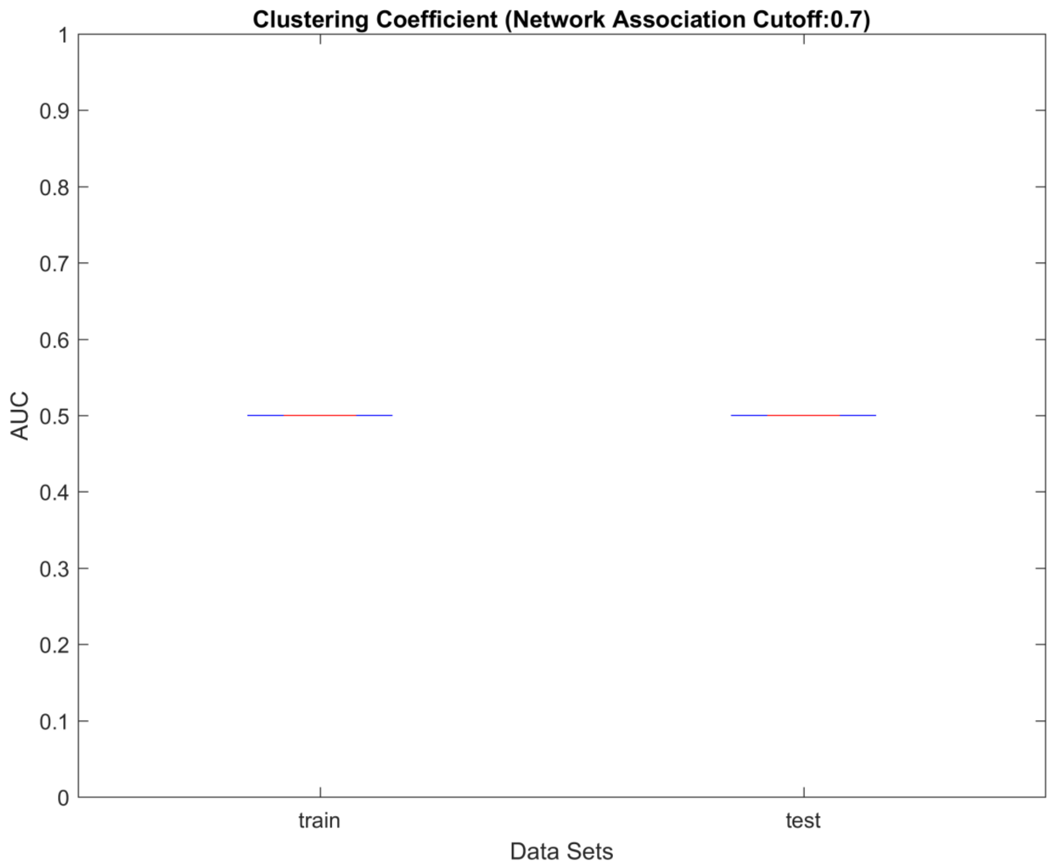

Figure 58. Training and test set classification performance of PCSSLR for EEG network constructed using Pearson correlation threshold of 0.7 over frequency range of 13-19 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.7)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5	0.5	0	0%
Mean	0.5	0.5	0	0%
Standard Deviation	0	0	0	0%

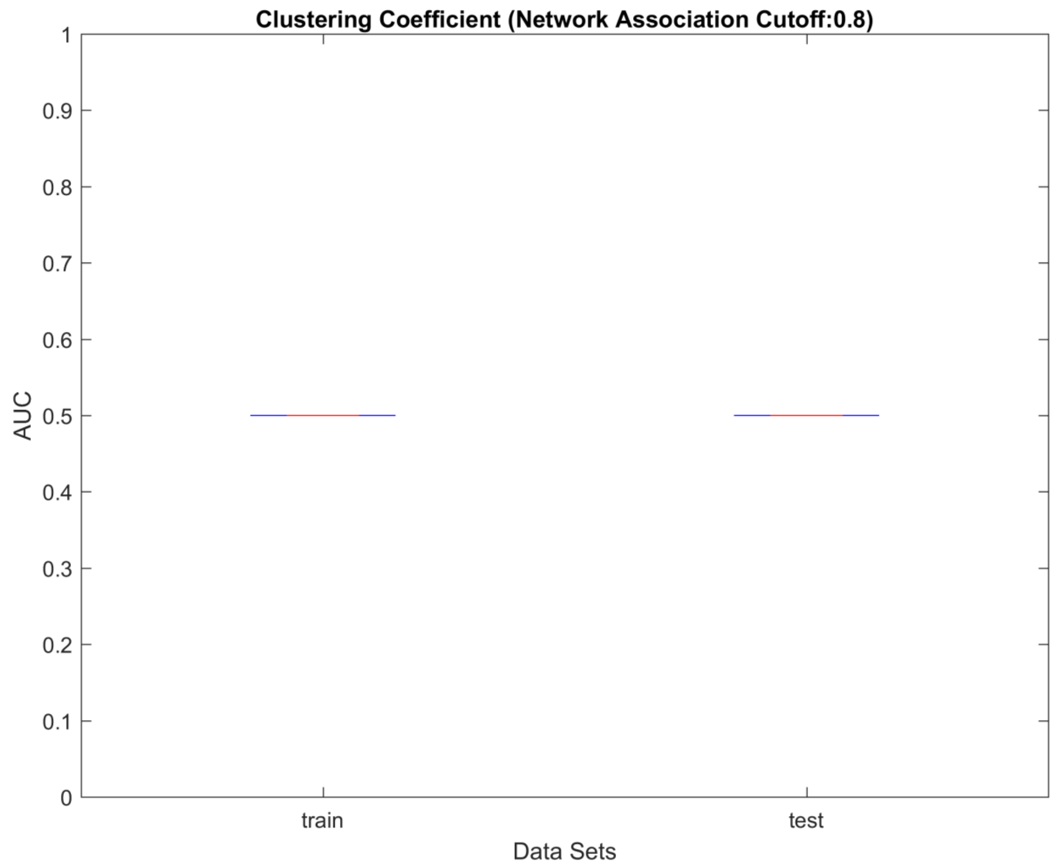

Figure 59. Training and test set classification performance of PCSSLR for EEG network constructed using Pearson correlation threshold of 0.8 over frequency range of 13-19 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.8)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5	0.5	0	0%
Mean	0.5	0.5	0	0%
Standard Deviation	0	0	0	0%

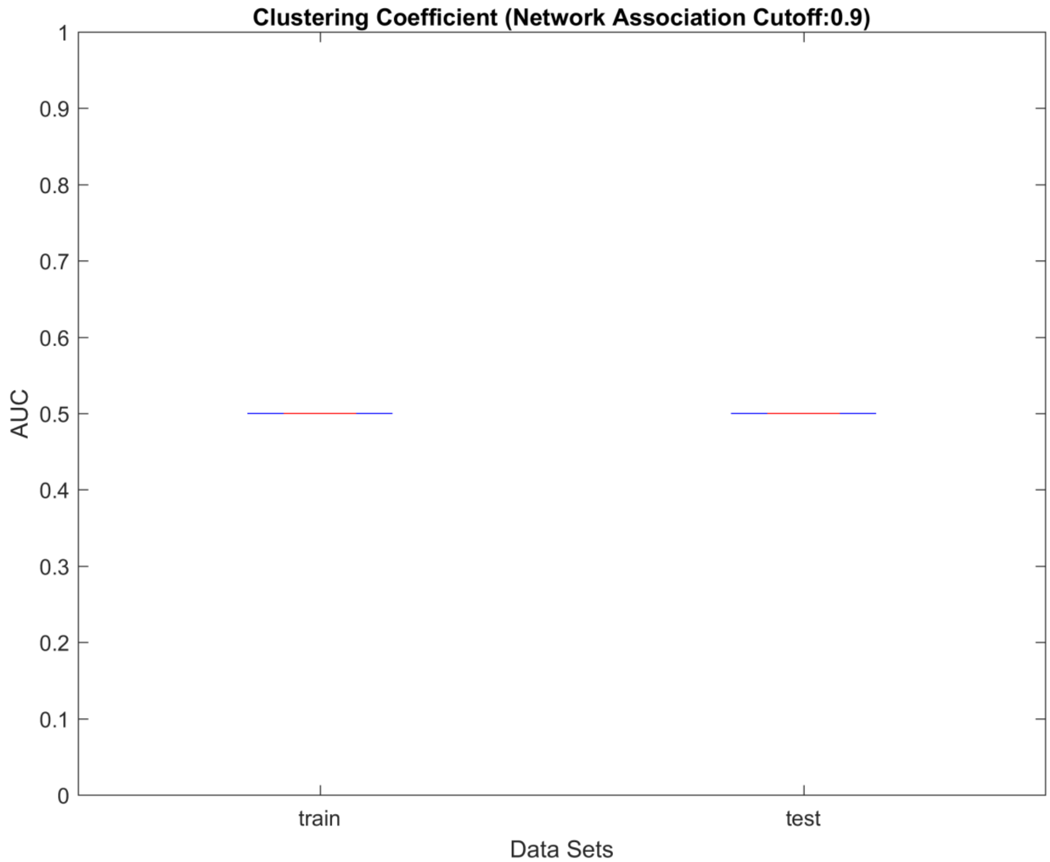

Figure 60. Training and test set classification performance of PCSSLR for EEG network constructed using Pearson correlation threshold of 0.9 over frequency range of 13-19 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.9)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5	0.5	0	0%
Mean	0.5	0.5	0	0%
Standard Deviation	0	0	0	0%

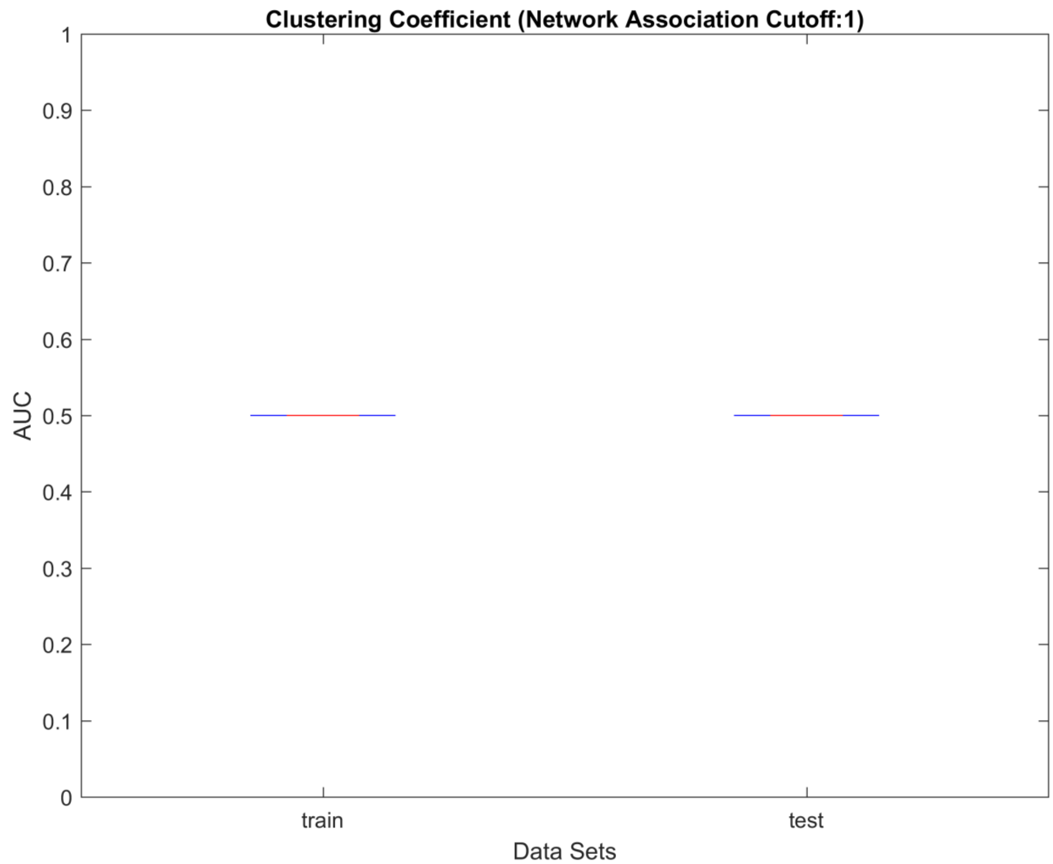

Figure 61. Training and test set classification performance of PCSSLR for EEG network constructed using Pearson correlation threshold of 1 over frequency range of 13-19 Hz.

	ROC Curve's AUC (Network Association Threshold: 1)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5	0.5	0	0%
Mean	0.5	0.5	0	0%
Standard Deviation	0	0	0	0%

7.3.4.4 Beta Wave (21-29 Hz)

The summary result of classification performance in terms of ROC Curve's AUC distribution for selected value of Pearson correlation coefficient used as thresholds to construct undirected EEG/brain network based on channel data for 21-29 Hz frequency range is shown in Figure 62. For the detailed comparison classification performance of the training datasets and that of the test datasets focusing on only one Pearson correlation value, the distributions of corresponding ROC curve's AUC for the 1,000 sampling iterations are show in Figure 63 to Figure 72 . The Pearson correlations used to construct the EEG frequency network are 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9 and 1. Below each of the boxplots of AUC distributions for training and test sets, a table summarizes the median AUC and mean AUC of training and test set, difference and percentage of difference between test set's median and mean AUC with respect to training set's AUC is presented.

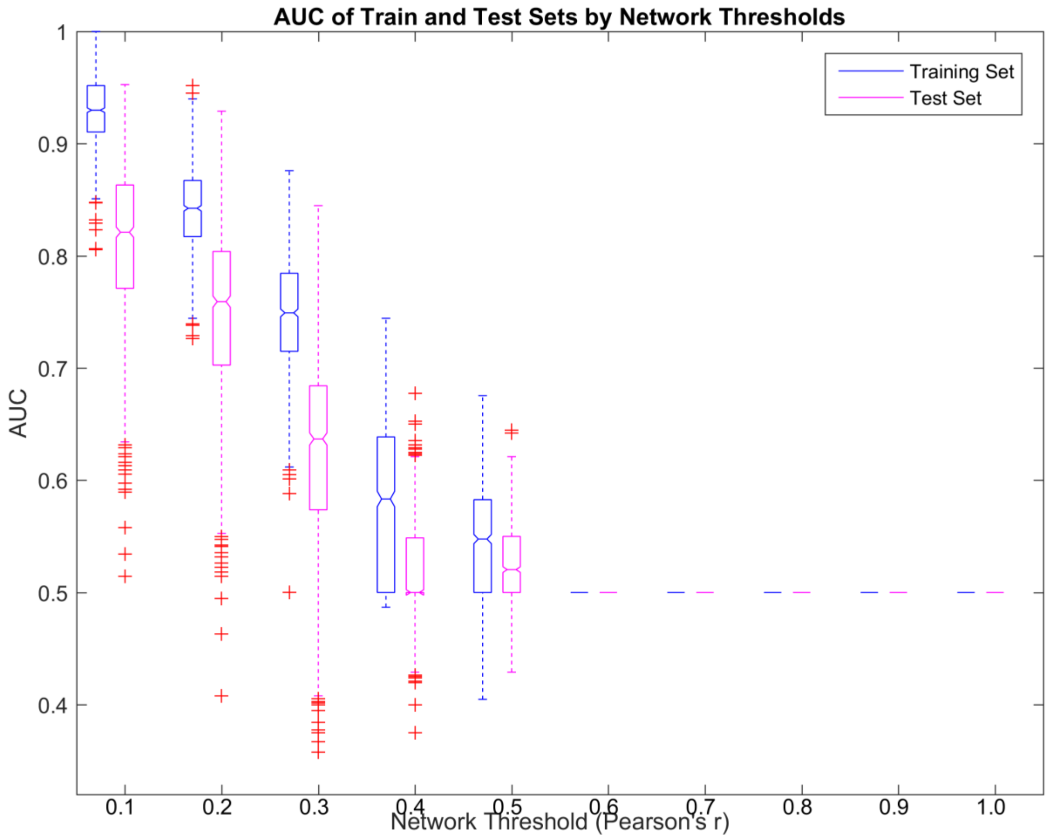

Figure 62. Training and test set classification performance of PCSSLR over range of Pearson correlations used to construct EEG network for frequency of 21-29 Hz.

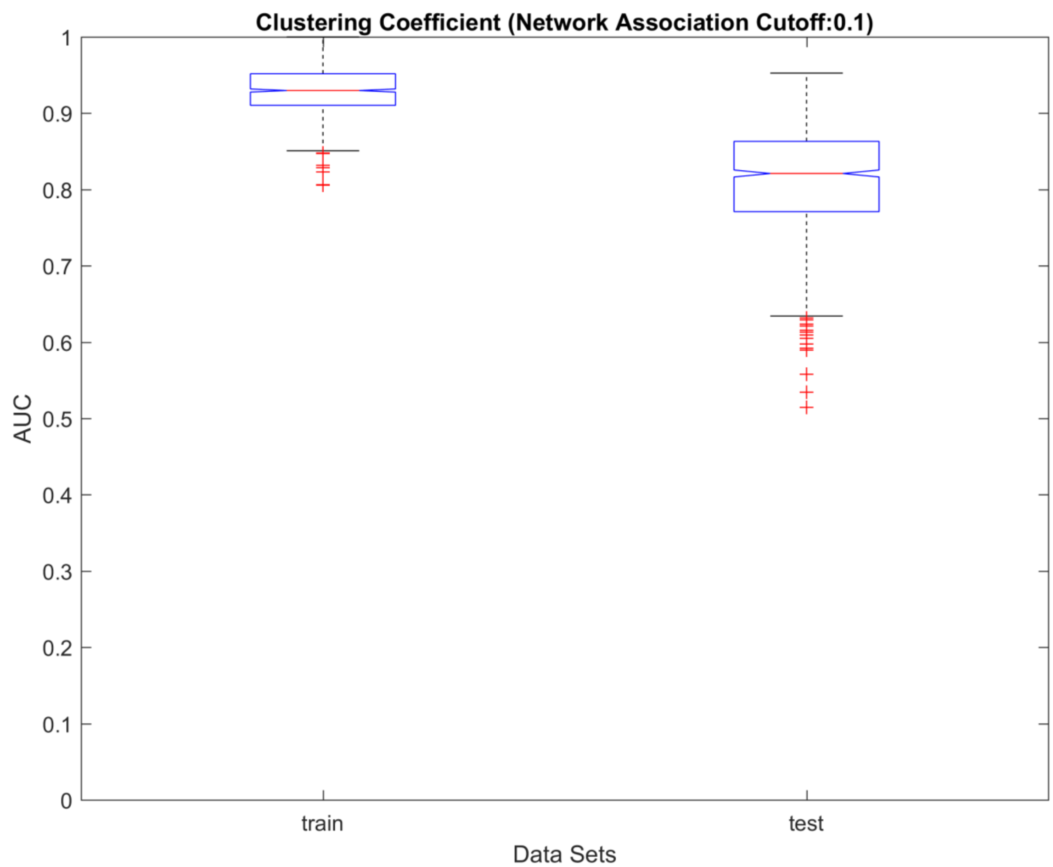

Figure 63. Training and test set classification performance of PCSSLR for EEG network constructed using Pearson correlation threshold of 0.1 over frequency range of 21-29 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.1)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.9298	0.8211	-0.1088	-11.7%
Mean	0.9305	0.8112	-0.1192	-12.82%
Standard Deviation	0.0319	0.0673	0.0354	110.83%

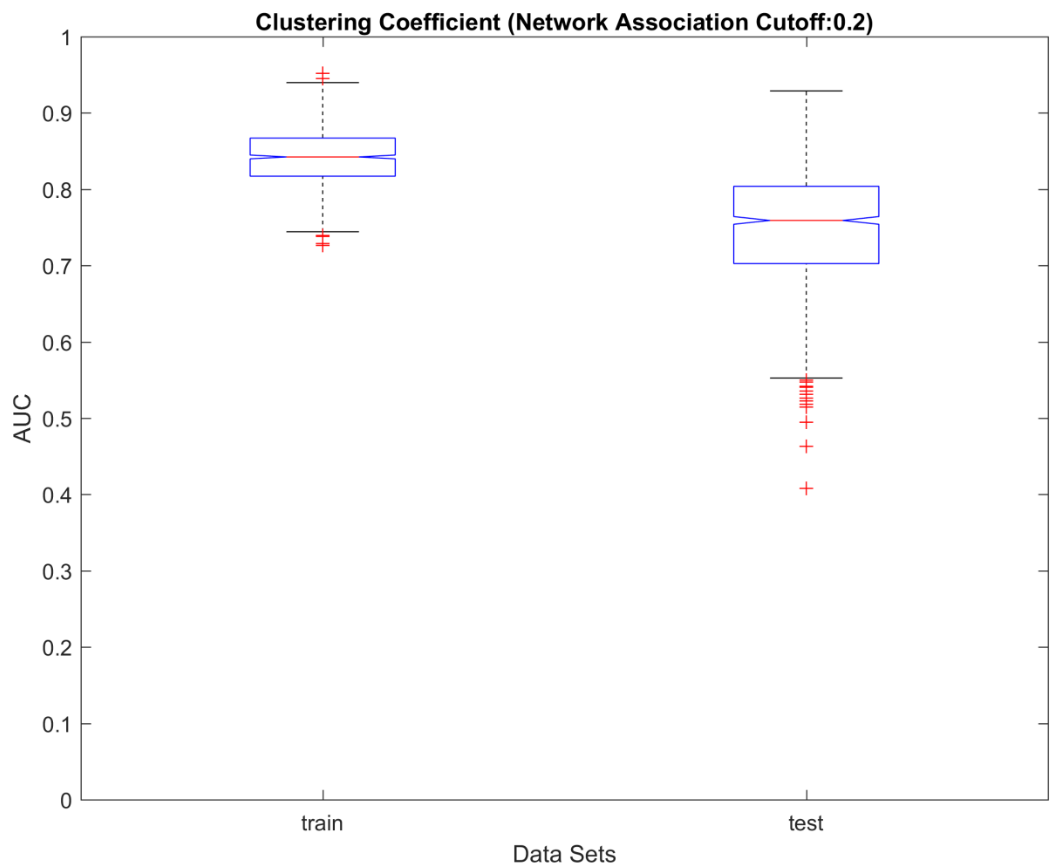

Figure 64. Training and test set classification performance of PCSSLR for EEG network constructed using Pearson correlation threshold of 0.2 over frequency range of 21-29 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.2)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.8424	0.7592	-0.0832	-9.88%
Mean	0.8424	0.7505	-0.0918	-10.9%
Standard Deviation	0.0363	0.0773	0.041	112.84%

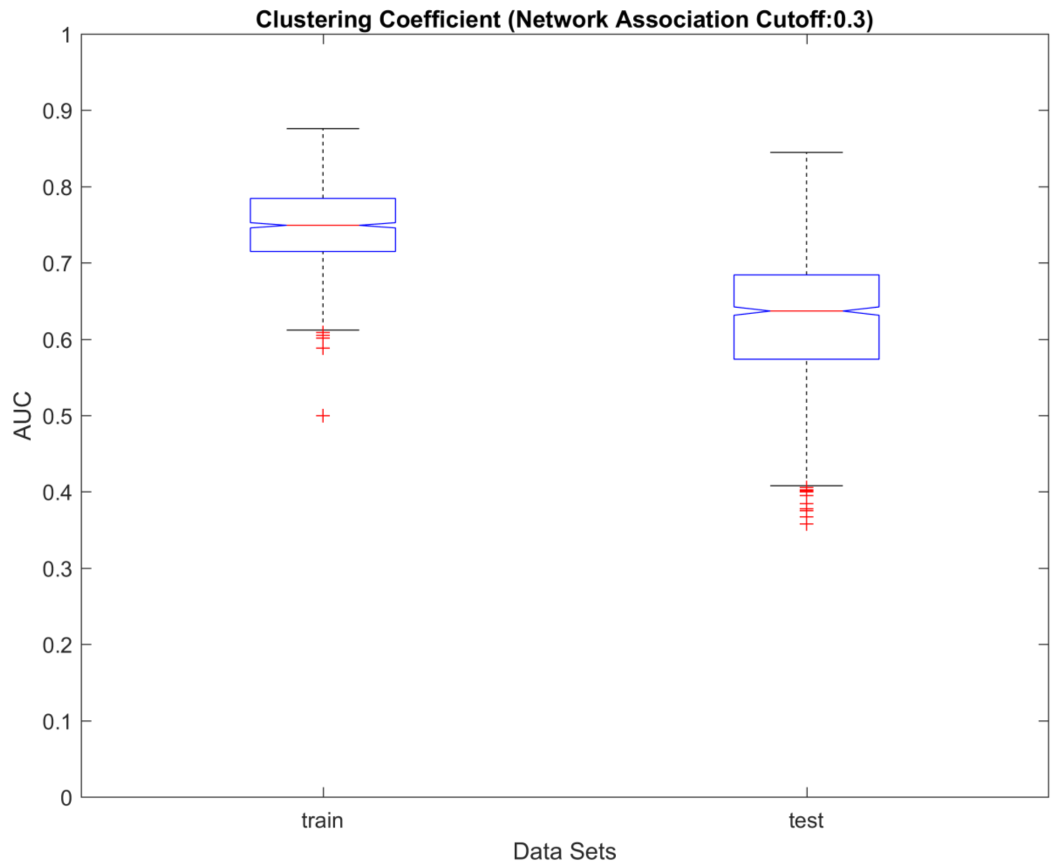

Figure 65. Training and test set classification performance of PCSSLR for EEG network constructed using Pearson correlation threshold of 0.3 over frequency range of 21-29 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.3)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.7492	0.6368	-0.1124	-15.0%
Mean	0.7486	0.6248	-0.1237	-16.53%
Standard Deviation	0.0527	0.0839	0.0312	59.08%

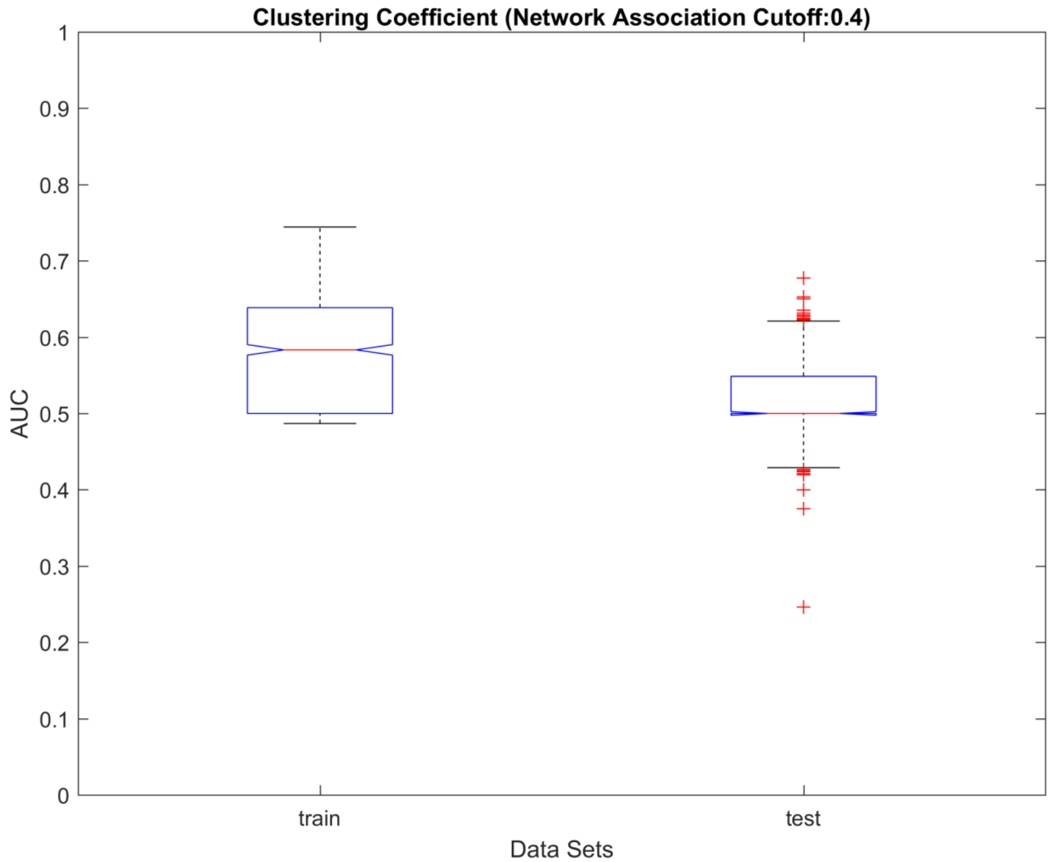

Figure 66. Training and test set classification performance of PCSSLR for EEG network constructed using Pearson correlation threshold of 0.4 over frequency range of 21-29 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.4)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5833	0.5	-0.0833	-14.29%
Mean	0.5811	0.5214	-0.0597	-10.27%
Standard Deviation	0.0694	0.0419	-0.0275	-39.6%

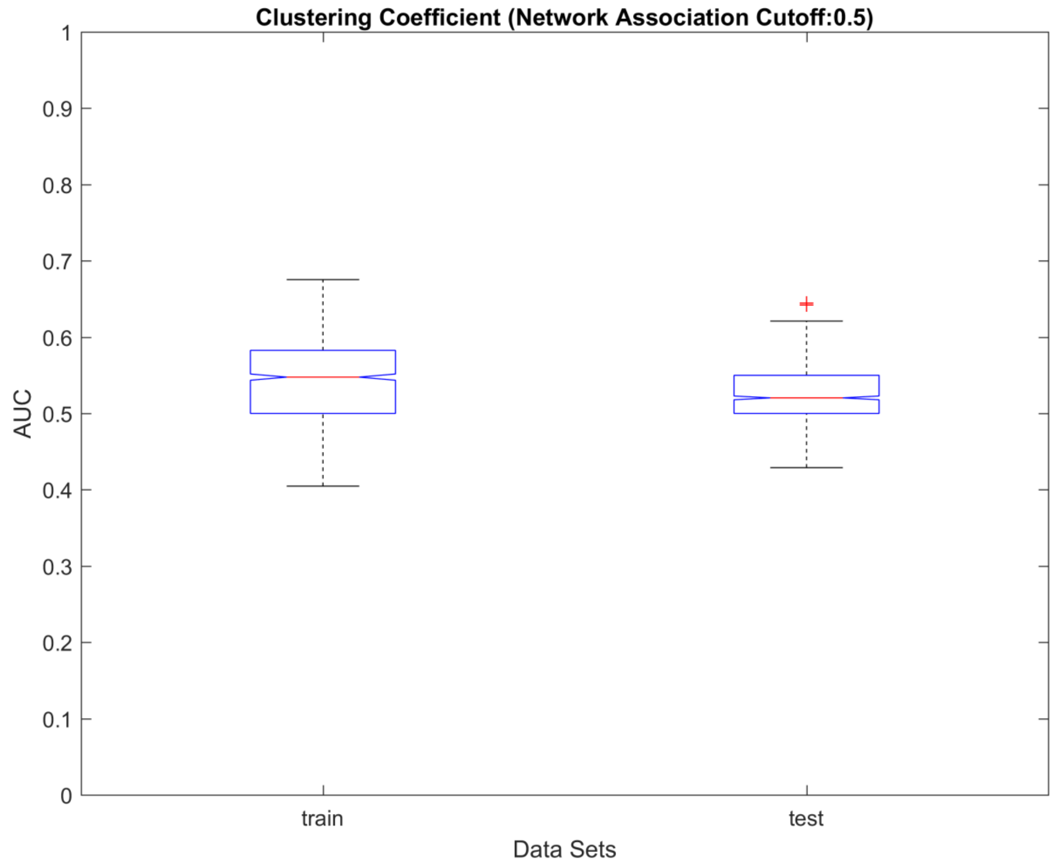

Figure 67. Training and test set classification performance of PCSSLR for EEG network constructed using Pearson correlation threshold of 0.5 over frequency range of 21-29 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.5)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5476	0.5204	-0.0272	-4.97%
Mean	0.5468	0.5239	-0.0229	-4.19%
Standard Deviation	0.0453	0.0369	-0.0084	-18.51%

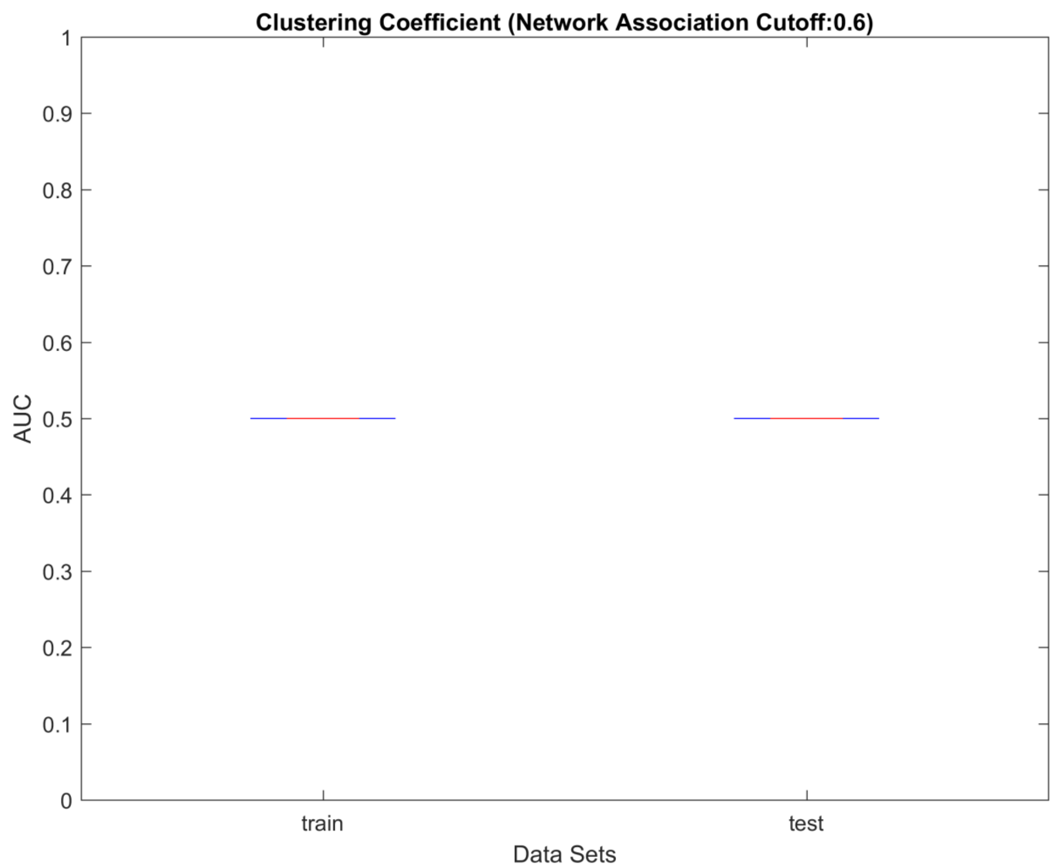

Figure 68. Training and test set classification performance of PCSSLR for EEG network constructed using Pearson correlation threshold of 0.6 over frequency range of 21-29 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.6)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5	0.5	0	0%
Mean	0.5	0.5	0	0%
Standard Deviation	0	0	0	0%

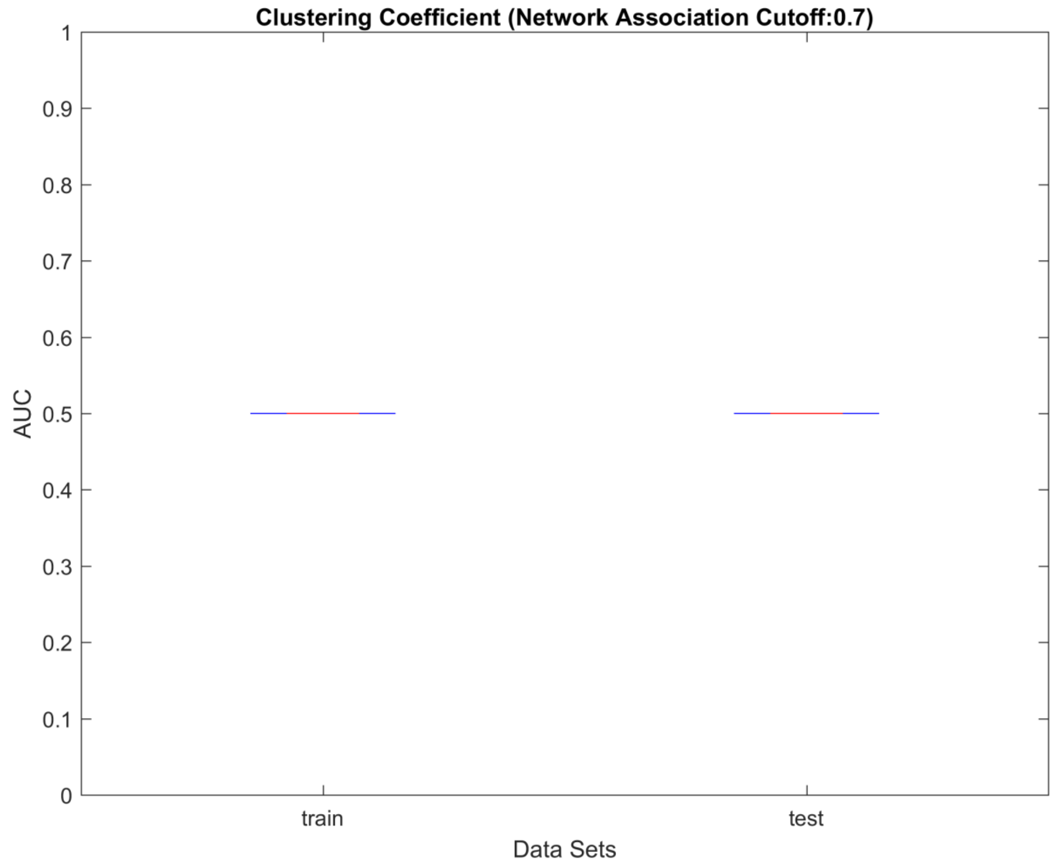

Figure 69. Training and test set classification performance of PCSSLR for EEG network constructed using Pearson correlation threshold of 0.7 over frequency range of 21-29 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.7)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5	0.5	0	0%
Mean	0.5	0.5	0	0%
Standard Deviation	0	0	0	0%

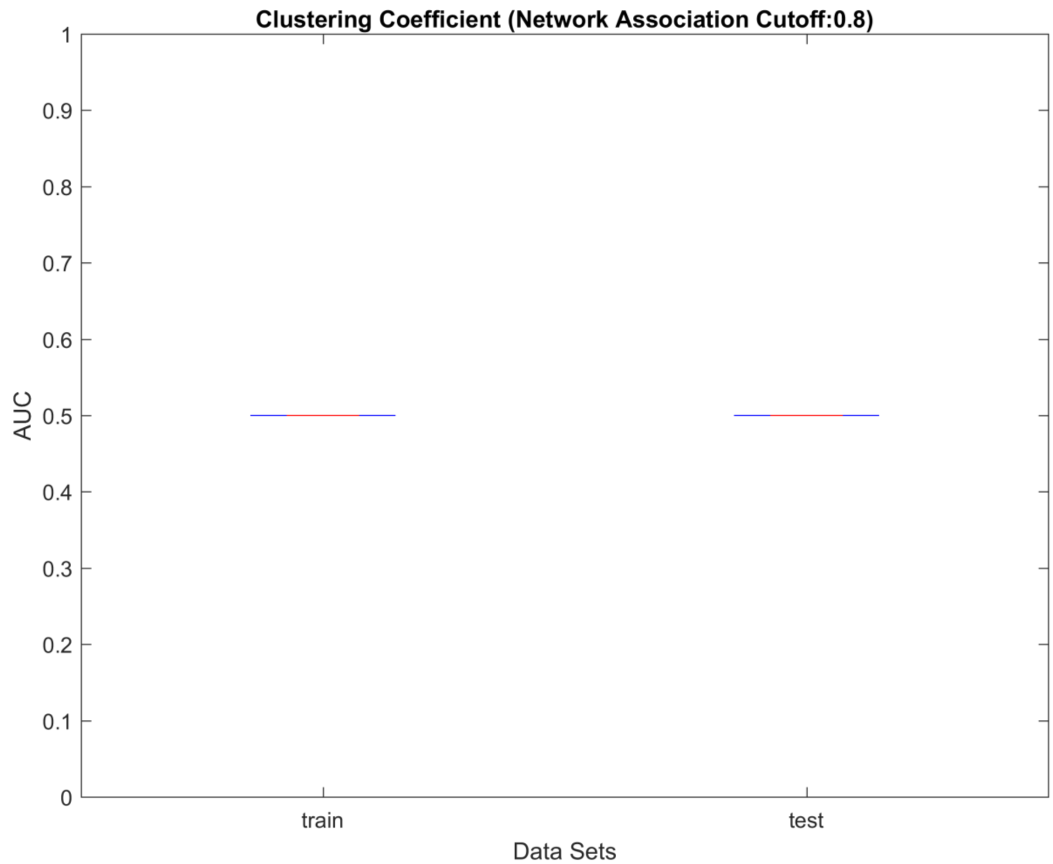

Figure 70. Training and test set classification performance of PCSSLR for EEG network constructed using Pearson correlation threshold of 0.8 over frequency range of 21-29 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.8)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5	0.5	0	0%
Mean	0.5	0.5	0	0%
Standard Deviation	0	0	0	0%

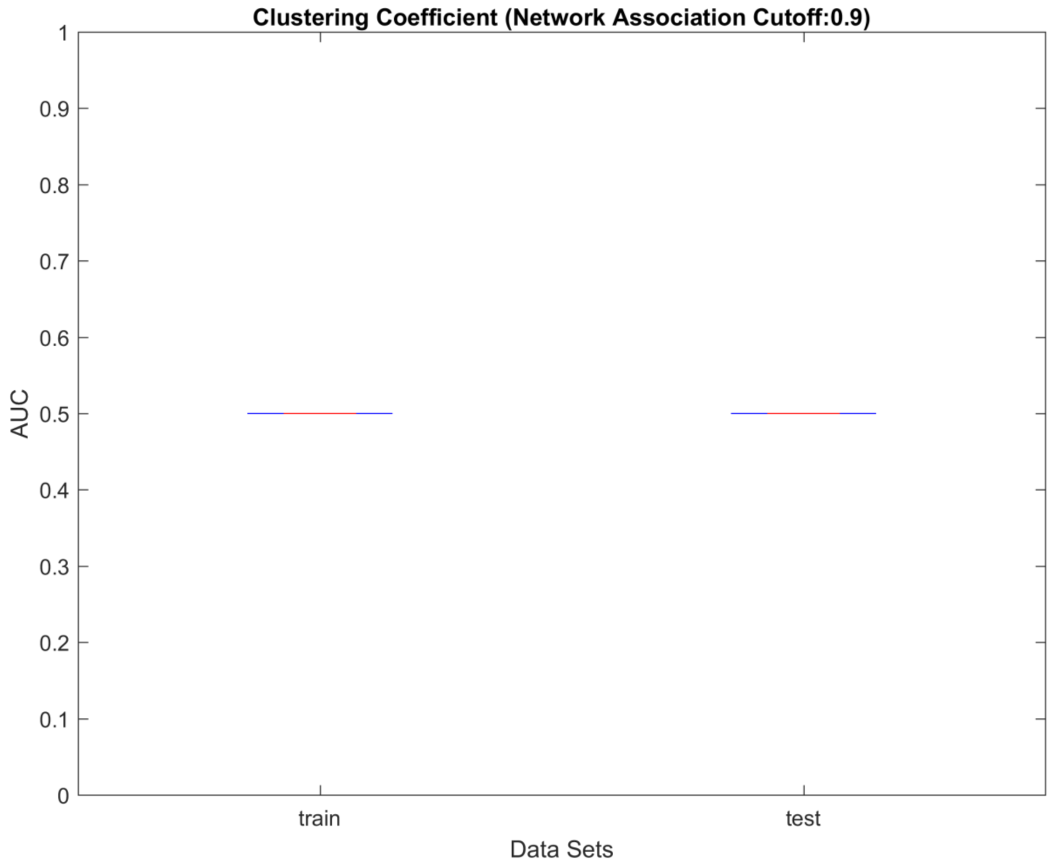

Figure 71. Training and test set classification performance of PCSSLR for EEG network constructed using Pearson correlation threshold of 0.9 over frequency range of 21-29 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.9)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5	0.5	0	0%
Mean	0.5	0.5	0	0%
Standard Deviation	0	0	0	0%

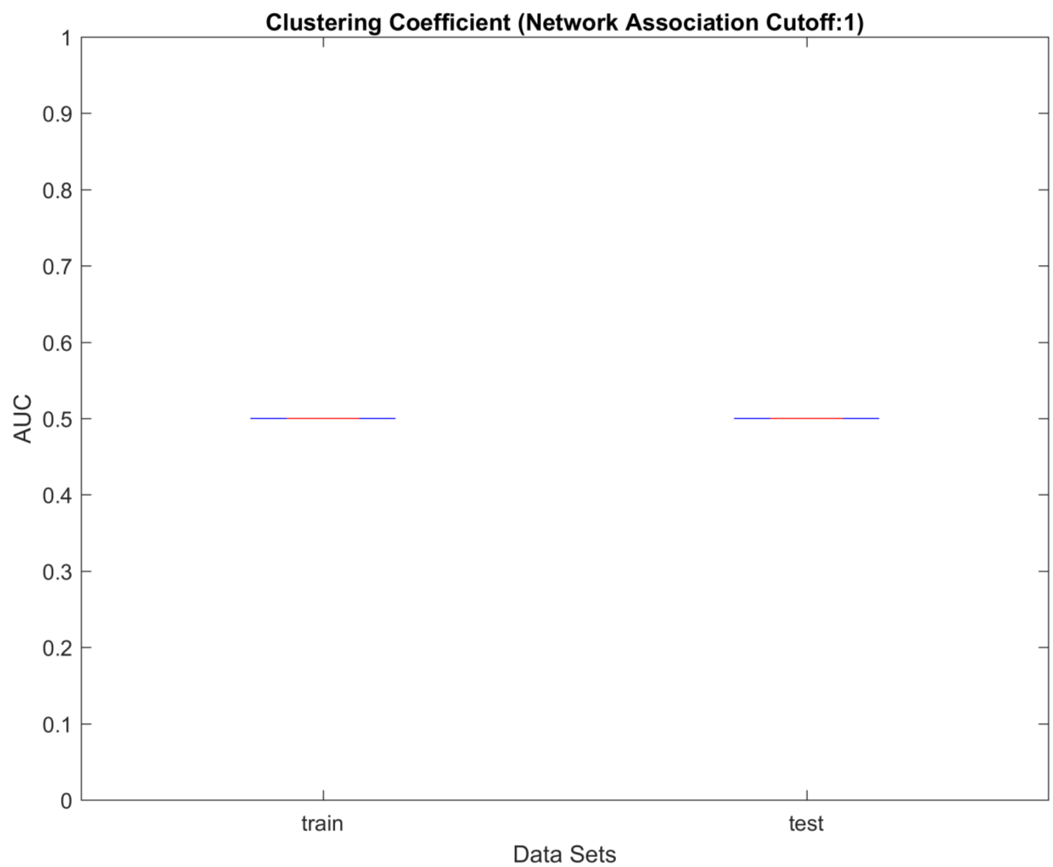

Figure 72. Training and test set classification performance of PCSSLR for EEG network constructed using Pearson correlation threshold of 1 over frequency range of 21-29 Hz.

	ROC Curve's AUC (Network Association Threshold: 1)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5	0.5	0	0%
Mean	0.5	0.5	0	0%
Standard Deviation	0	0	0	0%

7.3.5 Comparison of LASSO Training and Test Set Classification Performance Based on Clustering Coefficients - ROC Curve's AUC vs. Pearson Correlation

In order to develop LASSO binary classifier for the EEG frequency network data, λ corresponding to average minimum 10-fold cross validation error is used to select the final binary classifier for each training and test data set split.

7.3.5.1 Alpha Wave (7-9 Hz)

The summary result of classification performance in terms of ROC curve's AUC distribution for selected value of Pearson correlation coefficient used as thresholds to construct undirected EEG/brain network based on channel data for 7-9 Hz frequency range is shown Figure 73. For the detailed comparison classification performance of the training datasets and that of the test datasets focusing on only one Pearson correlation value, the distributions of corresponding ROC curve's AUC for the 100 sampling iterations are show in Figure 74 to Figure 83 . The Pearson correlations used to construct the EEG frequency network are 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9 and 1. Below each of the boxplots of AUC distributions for training and test sets, a table summarizes the median AUC and mean AUC of training and test set, difference and percentage of difference between test set's median and mean AUC with respect to training set's AUC presented.

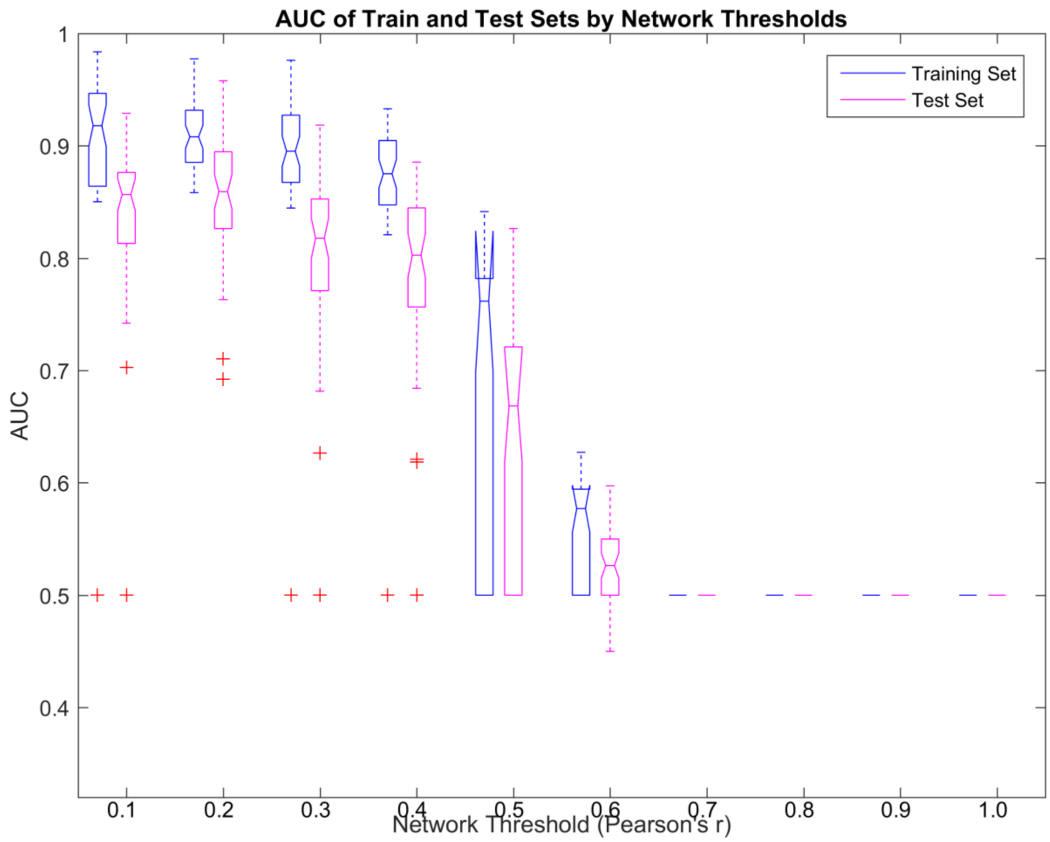

Figure 73. Training and test set classification performance of LASSO over range of Pearson correlations used to construct EEG network for frequency of 7-9 Hz.

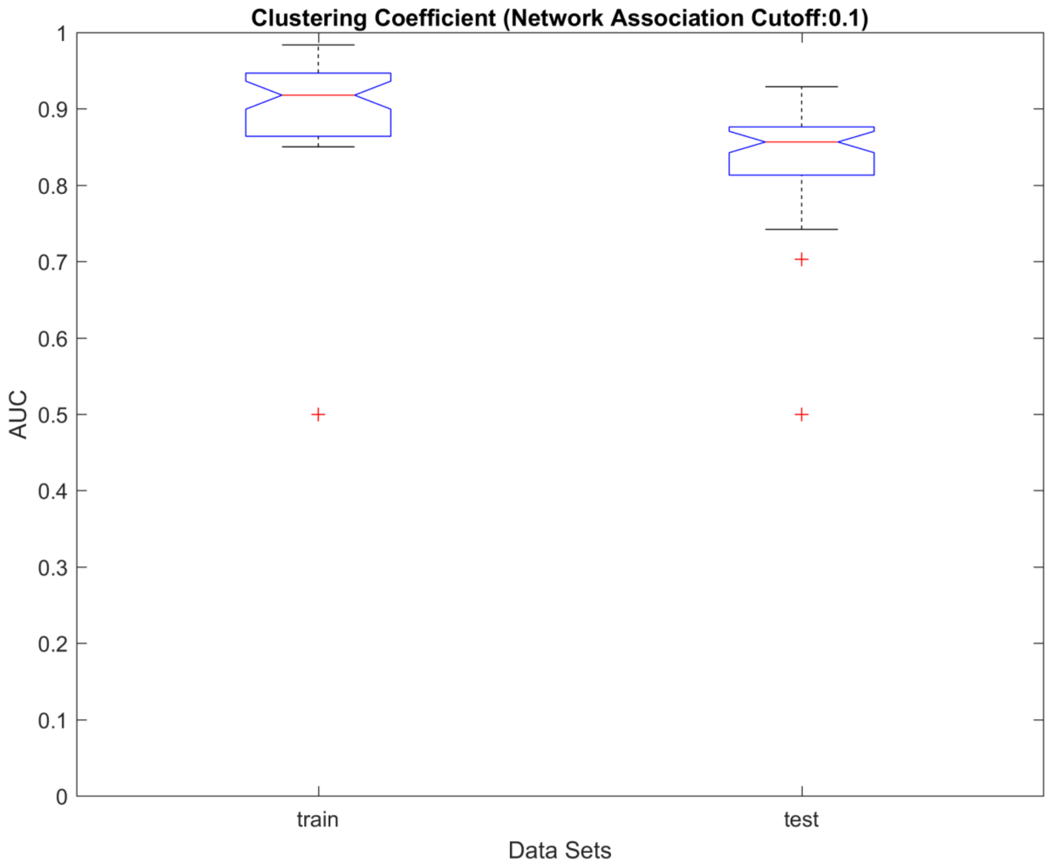

Figure 74. Training and test set classification performance of LASSO for EEG network constructed using Pearson correlation threshold of 0.1 over frequency range of 7-9 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.1)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.9179	0.8566	-0.0613	-6.68%
Mean	0.9008	0.8379	-0.0629	-6.98%
Standard Deviation	0.0713	0.0705	-0.0008	-1.11%

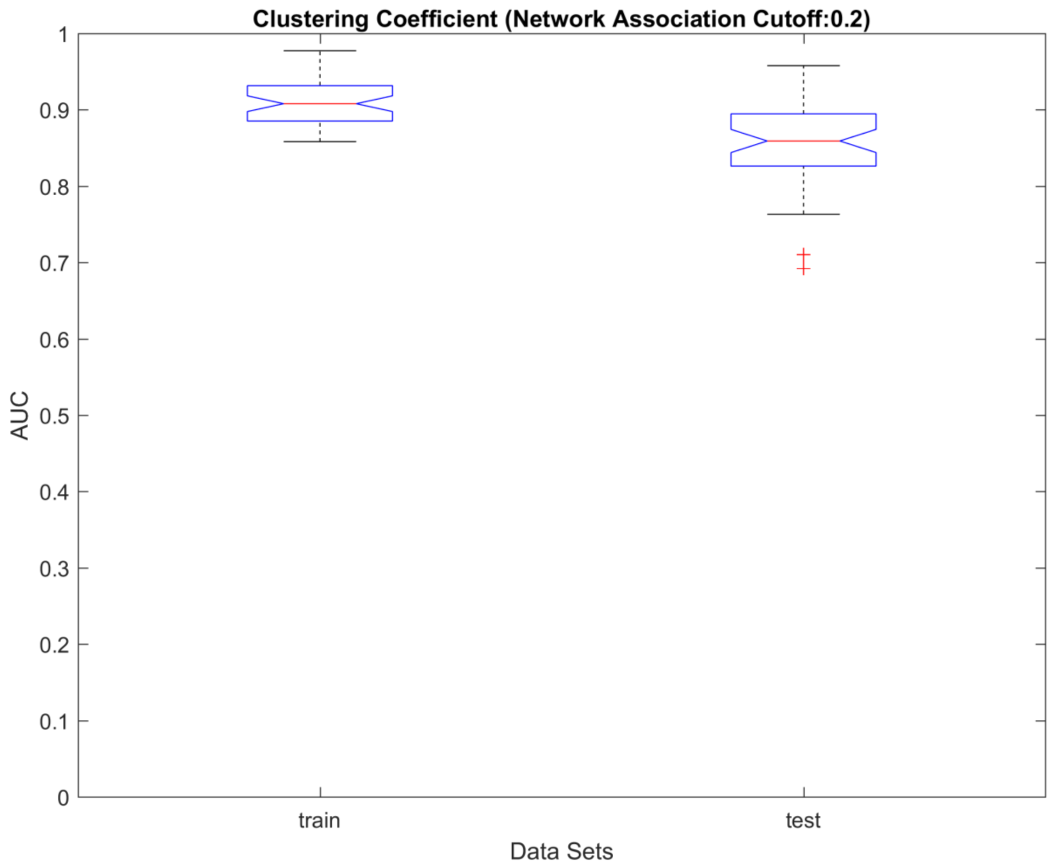

Figure 75. Training and test set classification performance of LASSO for EEG network constructed using Pearson correlation threshold of 0.2 over frequency range of 7-9 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.2)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.9081	0.8592	-0.0488	-5.38%
Mean	0.9094	0.8568	-0.0526	-5.79%
Standard Deviation	0.0291	0.0562	0.027	92.89%

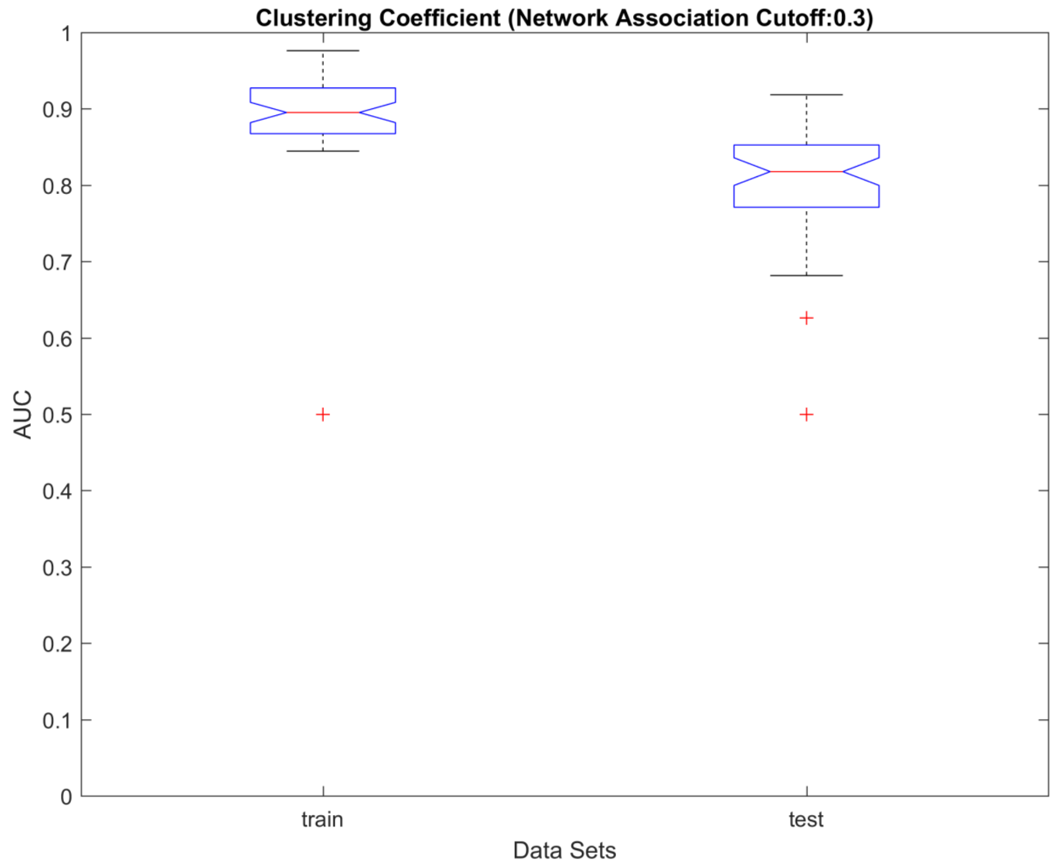

Figure 76. Training and test set classification performance of LASSO for EEG network constructed using Pearson correlation threshold of 0.3 over frequency range of 7-9 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.3)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.8952	0.8178	-0.0774	-8.65%
Mean	0.8918	0.807	-0.0848	-9.51%
Standard Deviation	0.0656	0.0753	0.0097	14.83%

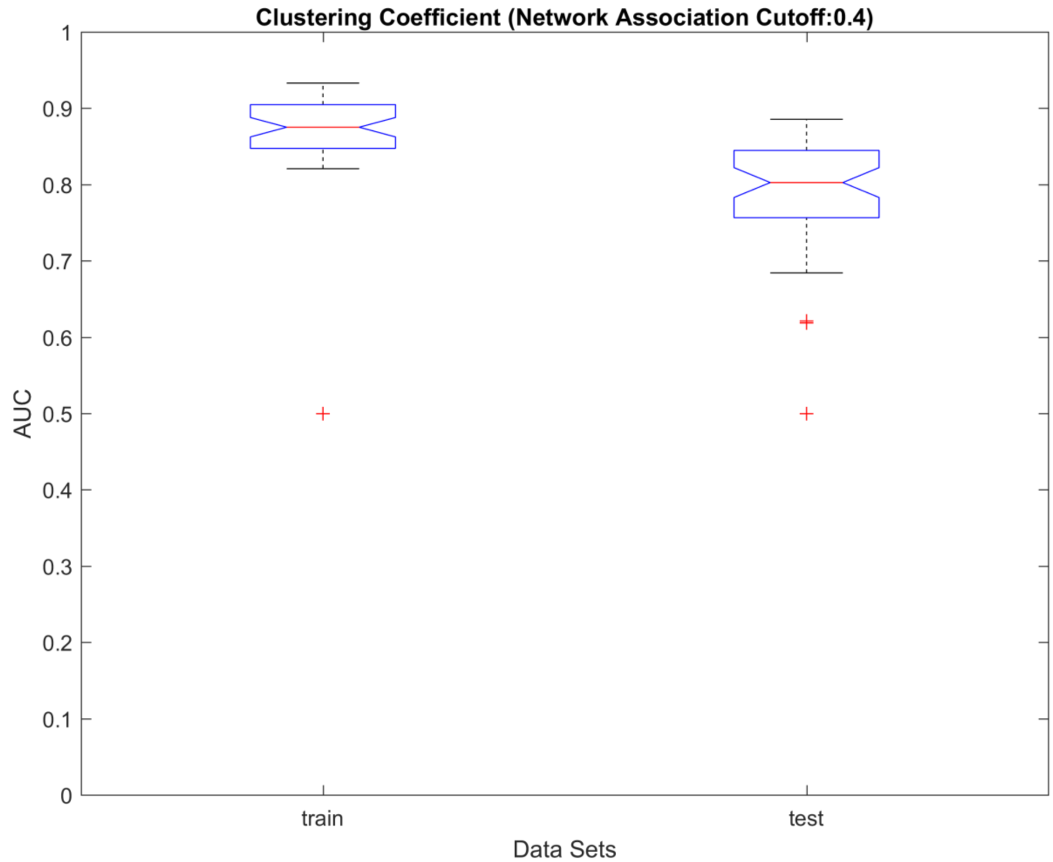

Figure 77. Training and test set classification performance of LASSO for EEG network constructed using Pearson correlation threshold of 0.4 over frequency range of 7-9 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.4)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.8752	0.8026	-0.0725	-8.29%
Mean	0.8685	0.7887	-0.0798	-9.19%
Standard Deviation	0.0616	0.0743	0.0127	20.63%

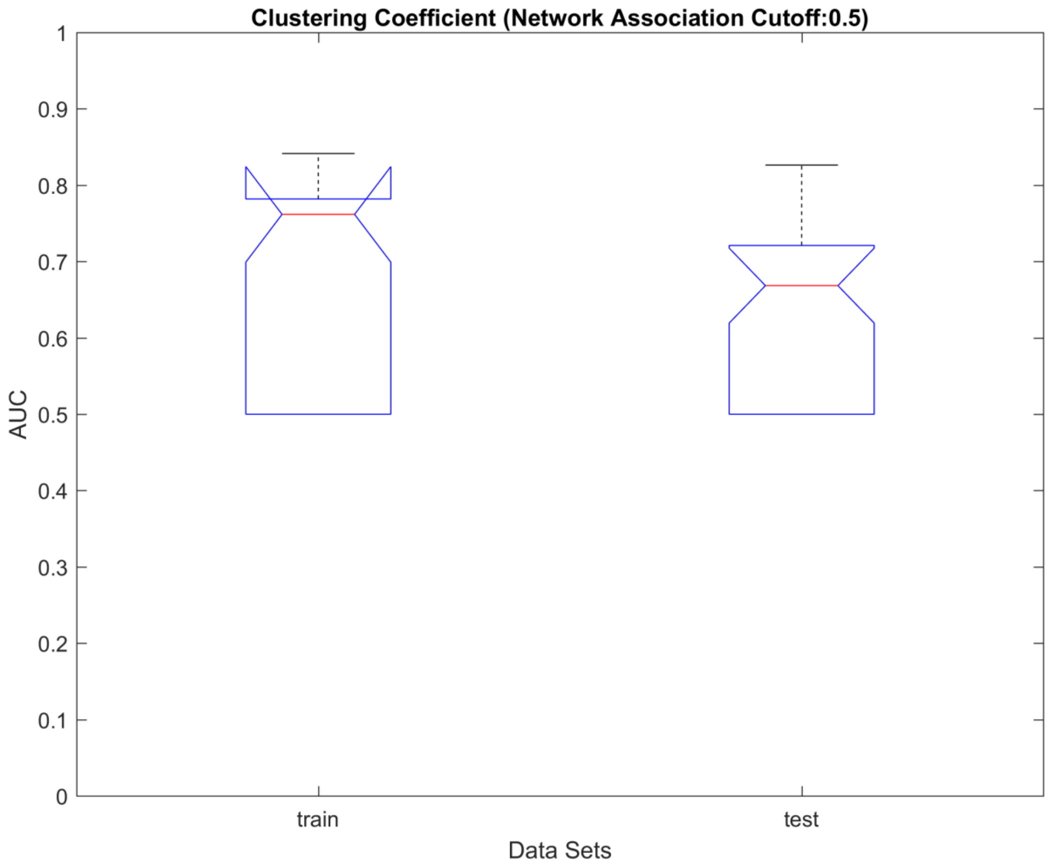

Figure 78. Training and test set classification performance of LASSO for EEG network constructed using Pearson correlation threshold of 0.5 over frequency range of 7-9 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.5)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.7617	0.6684	-0.0933	-12.25%
Mean	0.6937	0.6425	-0.0512	-7.38%
Standard Deviation	0.1303	0.1078	-0.0225	-17.27%

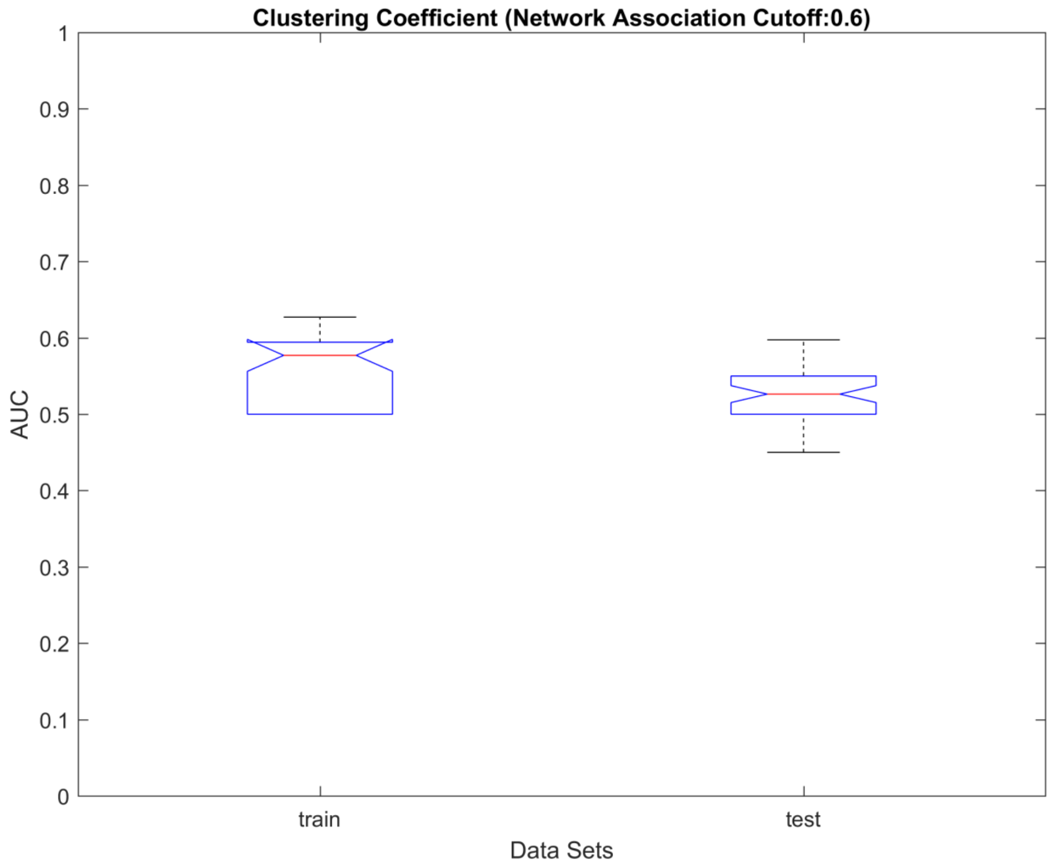

Figure 79. Training and test set classification performance of LASSO for EEG network constructed using Pearson correlation threshold of 0.6 over frequency range of 7-9 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.6)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5771	0.5263	-0.0508	-8.79%
Mean	0.5565	0.5321	-0.0245	-4.39%
Standard Deviation	0.0462	0.0377	-0.0085	-18.39%

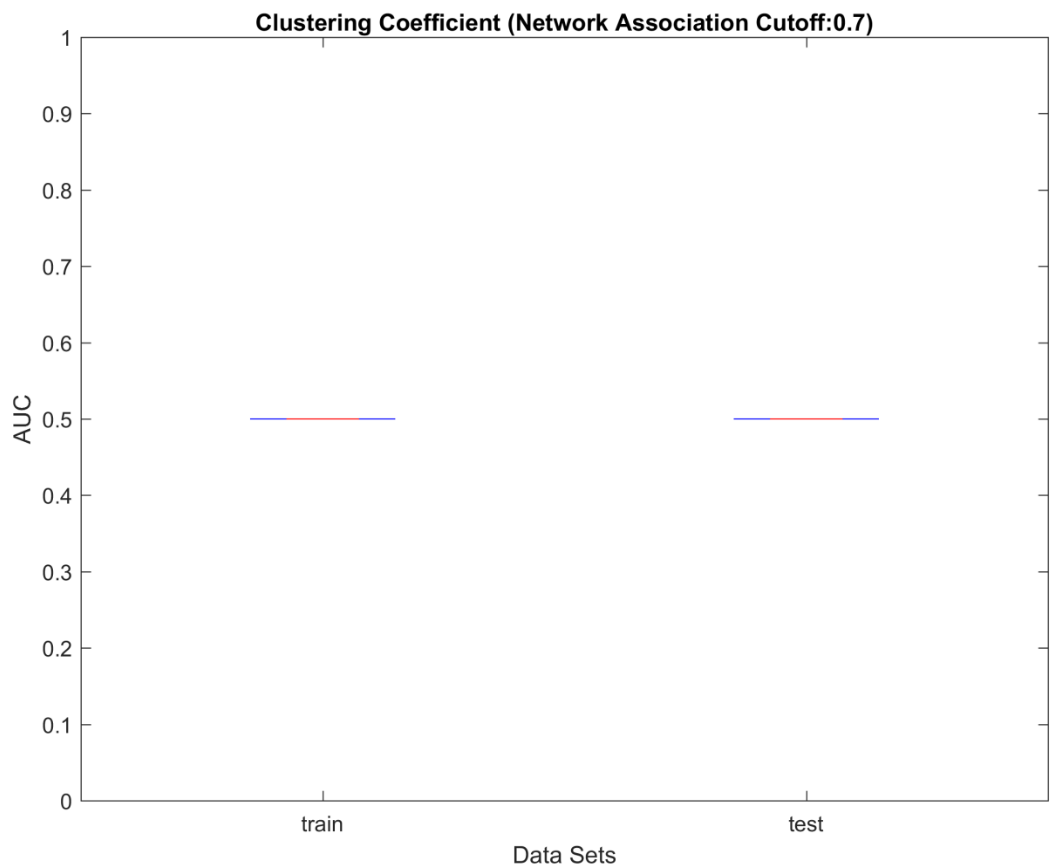

Figure 80. Training and test set classification performance of LASSO for EEG network constructed using Pearson correlation threshold of 0.7 over frequency range of 7-9 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.7)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5	0.5	0	0%
Mean	0.5	0.5	0	0%
Standard Deviation	0	0	0	0%

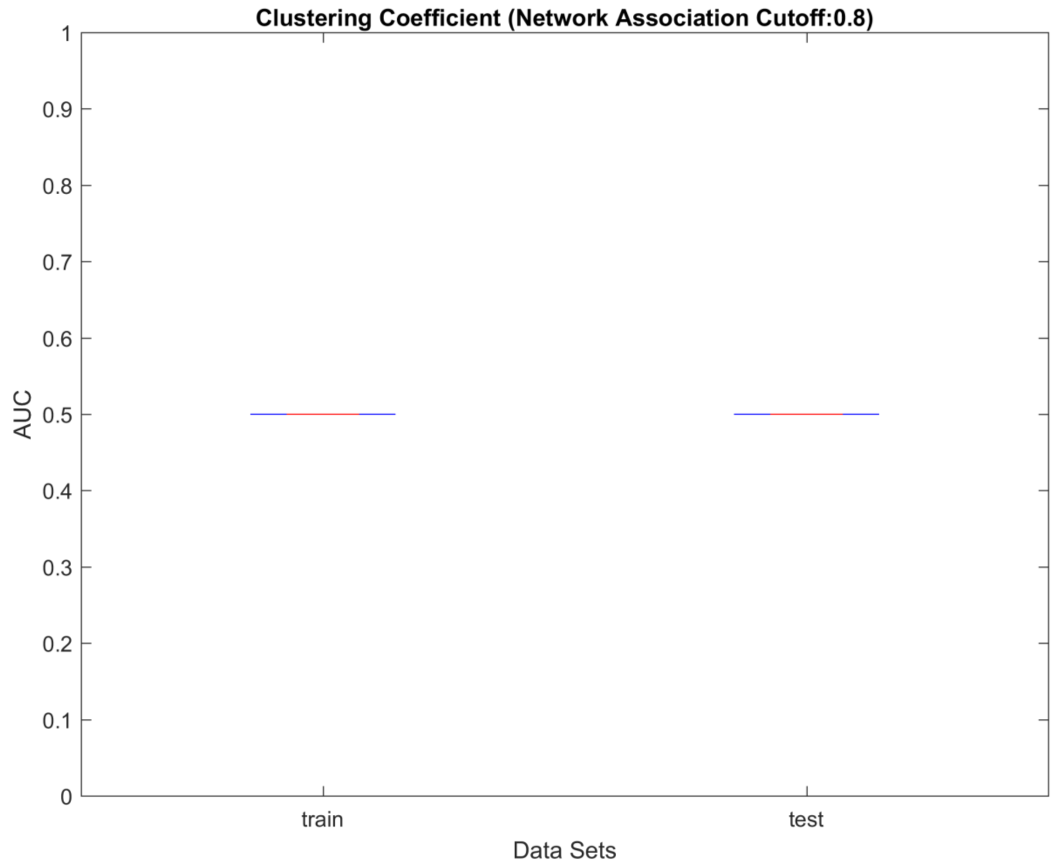

Figure 81. Training and test set classification performance of LASSO for EEG network constructed using Pearson correlation threshold of 0.8 over frequency range of 7-9 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.8)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5	0.5	0	0%
Mean	0.5	0.5	0	0%
Standard Deviation	0	0	0	0%

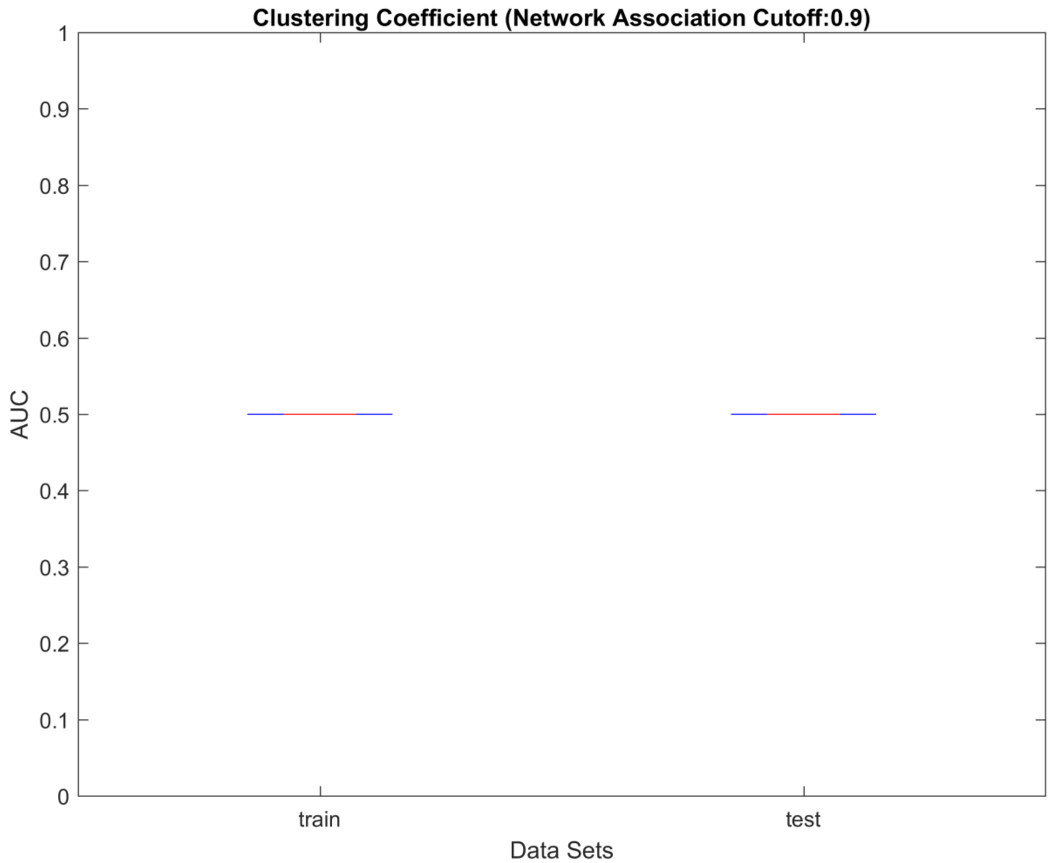

Figure 82. Training and test set classification performance of LASSO for EEG network constructed using Pearson correlation threshold of 0.9 over frequency range of 7-9 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.9)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5	0.5	0	0%
Mean	0.5	0.5	0	0%
Standard Deviation	0	0	0	0%

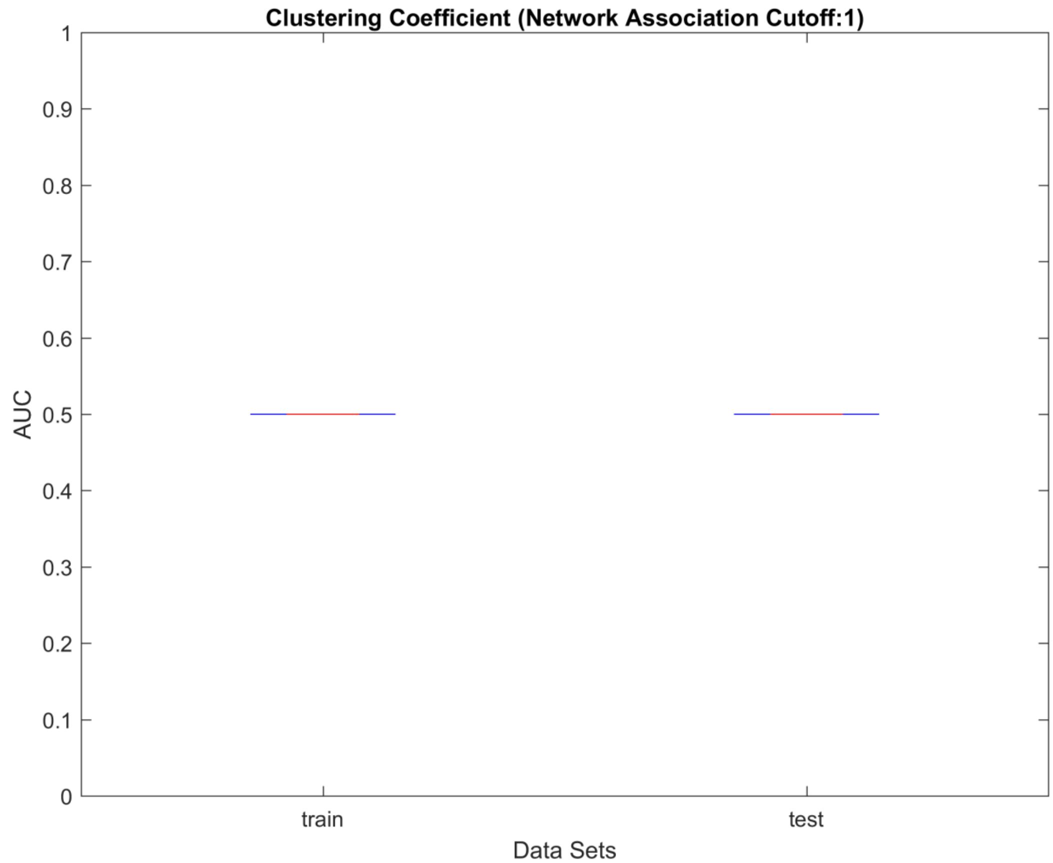

Figure 83. Training and test set classification performance of LASSO for EEG network constructed using Pearson correlation threshold of 1 over frequency range of 7-9 Hz.

	ROC Curve's AUC (Network Association Threshold: 1)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5	0.5	0	0%
Mean	0.5	0.5	0	0%
Standard Deviation	0	0	0	0%

7.3.5.2 Alpha Wave (11-13 Hz)

The summary result of classification performance in terms of ROC Curve’s AUC distribution for selected value of Pearson correlation coefficient used as thresholds to construct undirected EEG/brain network based on channel data for 11-13 Hz frequency range is shown Figure 84. For the detailed comparison classification performance of the training datasets and that of the test datasets focusing on only one Pearson correlation value, the distributions of corresponding ROC curve’s AUC for the 100 sampling iterations are show in Figure 85 to Figure 94. The Pearson correlations used to construct the EEG frequency network are 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9 and 1. Below each of the boxplots of AUC distributions for training and test sets, a table summarizes the median AUC and mean AUC of training and test set, difference and percentage of difference between test set’s median and mean AUC with respect to training set’s AUC is presented.

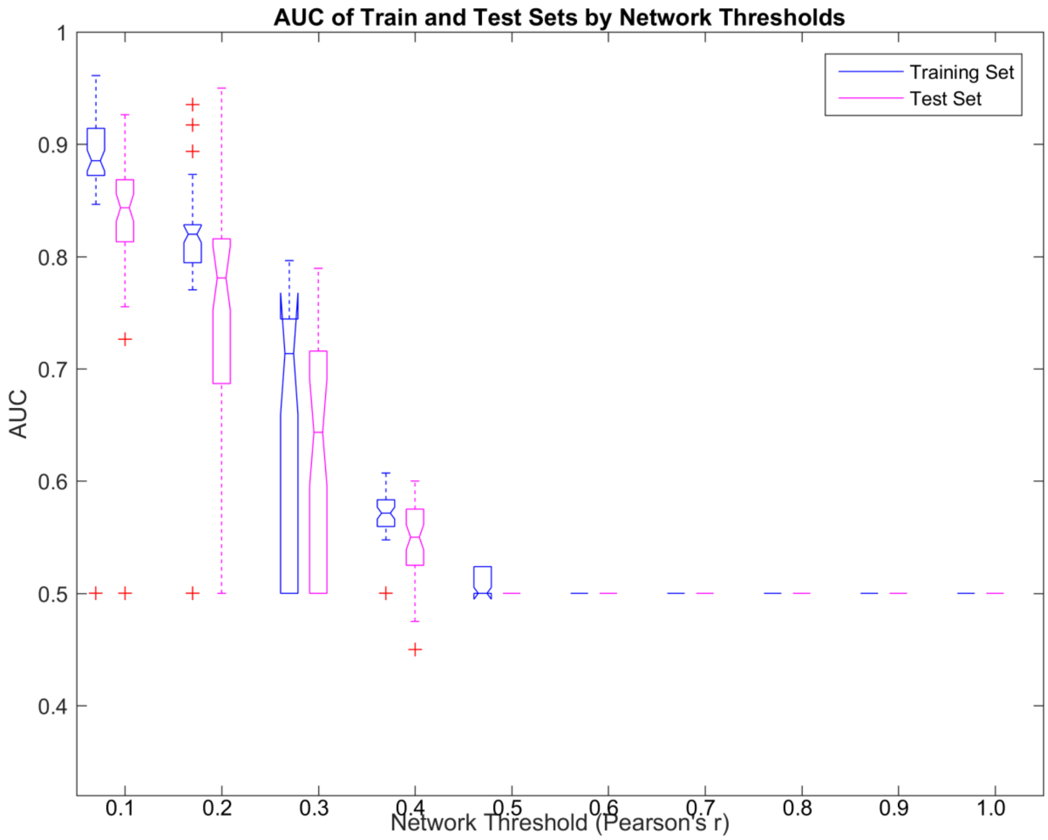

Figure 84. Training and test set classification performance of LASSO over range of Pearson correlations used to construct EEG network for frequency of 11-13 Hz.

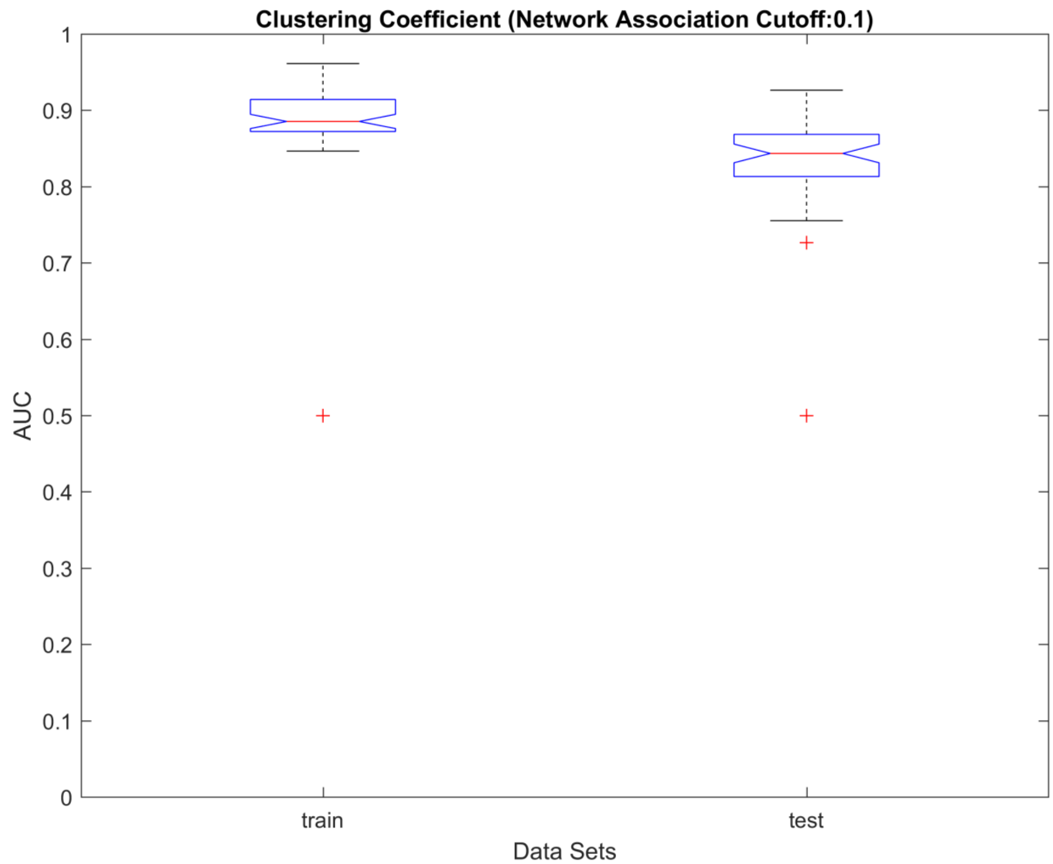

Figure 85. Training and test set classification performance of LASSO for EEG network constructed using Pearson correlation threshold of 0.1 over frequency range of 11-13 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.1)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.8853	0.8434	-0.0419	-4.73%
Mean	0.8765	0.8273	-0.0492	-5.62%
Standard Deviation	0.0824	0.0792	-0.0032	-3.88%

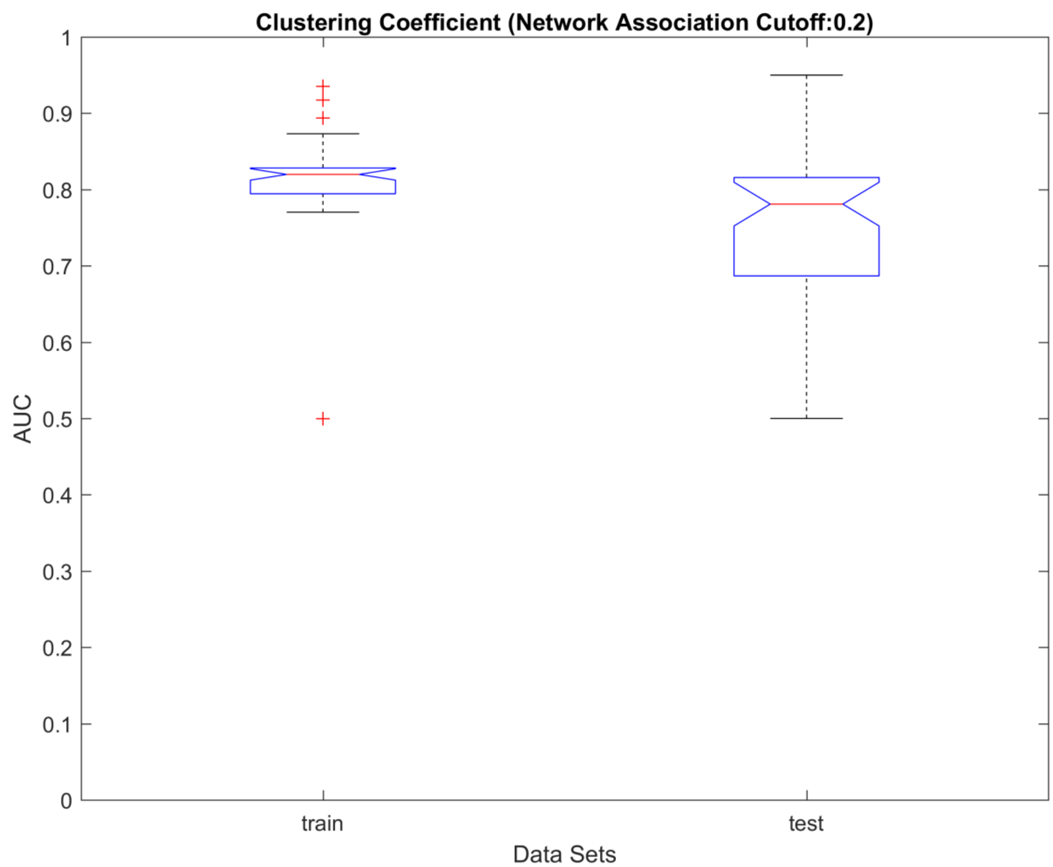

Figure 86. Training and test set classification performance of LASSO for EEG network constructed using Pearson correlation threshold of 0.2 over frequency range of 11-13 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.2)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.8199	0.7809	-0.0389	-4.75%
Mean	0.7799	0.7424	-0.0375	-4.81%
Standard Deviation	0.1181	0.1167	-0.0014	-1.17%

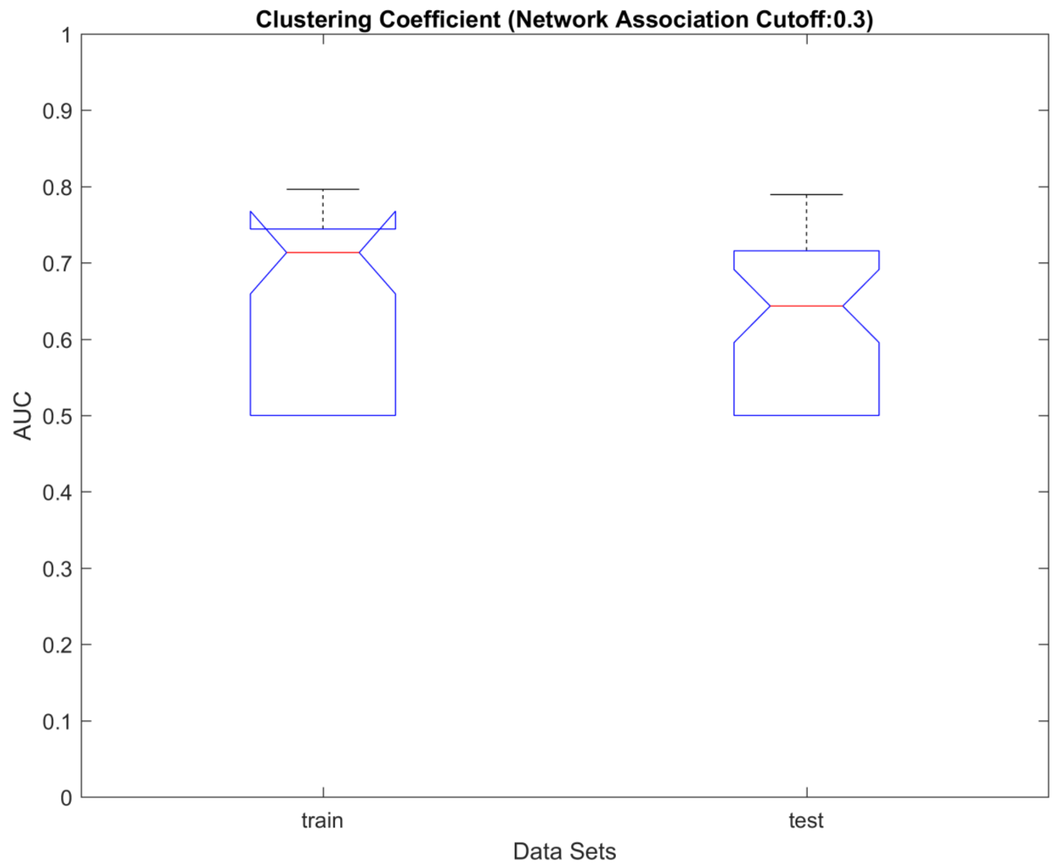

Figure 87. Training and test set classification performance of LASSO for EEG network constructed using Pearson correlation threshold of 0.3 over frequency range of 11-13 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.3)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.7135	0.6434	-0.0701	-9.82%
Mean	0.6657	0.6282	-0.0375	-5.63%
Standard Deviation	0.113	0.1	-0.013	-11.5%

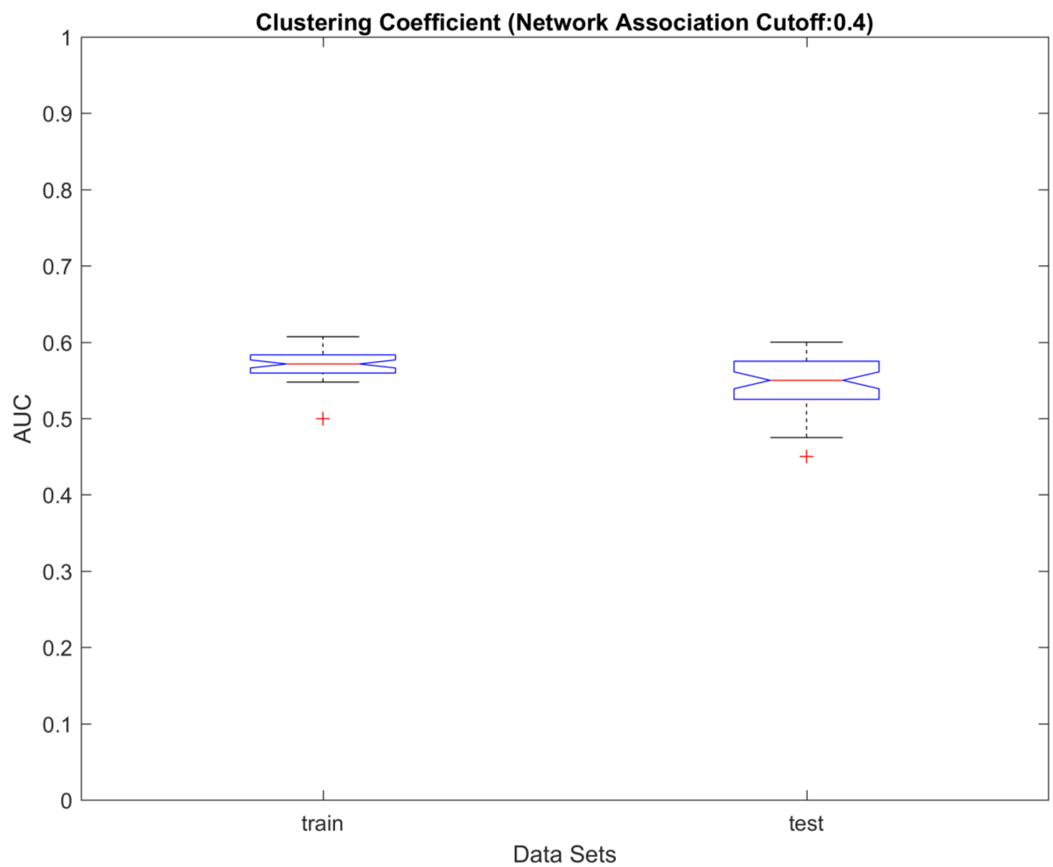

Figure 88. Training and test set classification performance of LASSO for EEG network constructed using Pearson correlation threshold of 0.4 over frequency range of 11-13 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.4)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5714	0.55	-0.0214	-3.75%
Mean	0.5634	0.5396	-0.0238	-4.23%
Standard Deviation	0.0329	0.0343	0.0014	4.28%

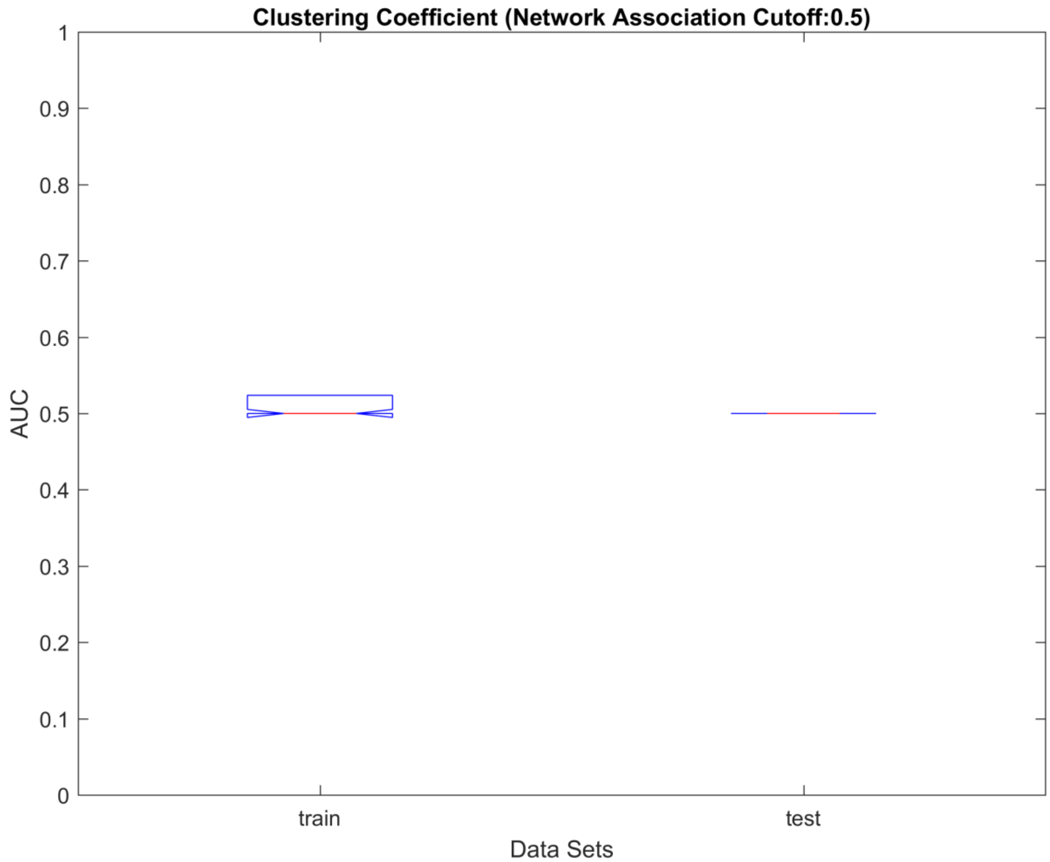

Figure 89. Training and test set classification performance of LASSO for EEG network constructed using Pearson correlation threshold of 0.5 over frequency range of 11-13 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.5)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5	0.5	0	0%
Mean	0.5095	0.5	-0.0095	-1.87%
Standard Deviation	0.0118	0	-0.0118	-100%

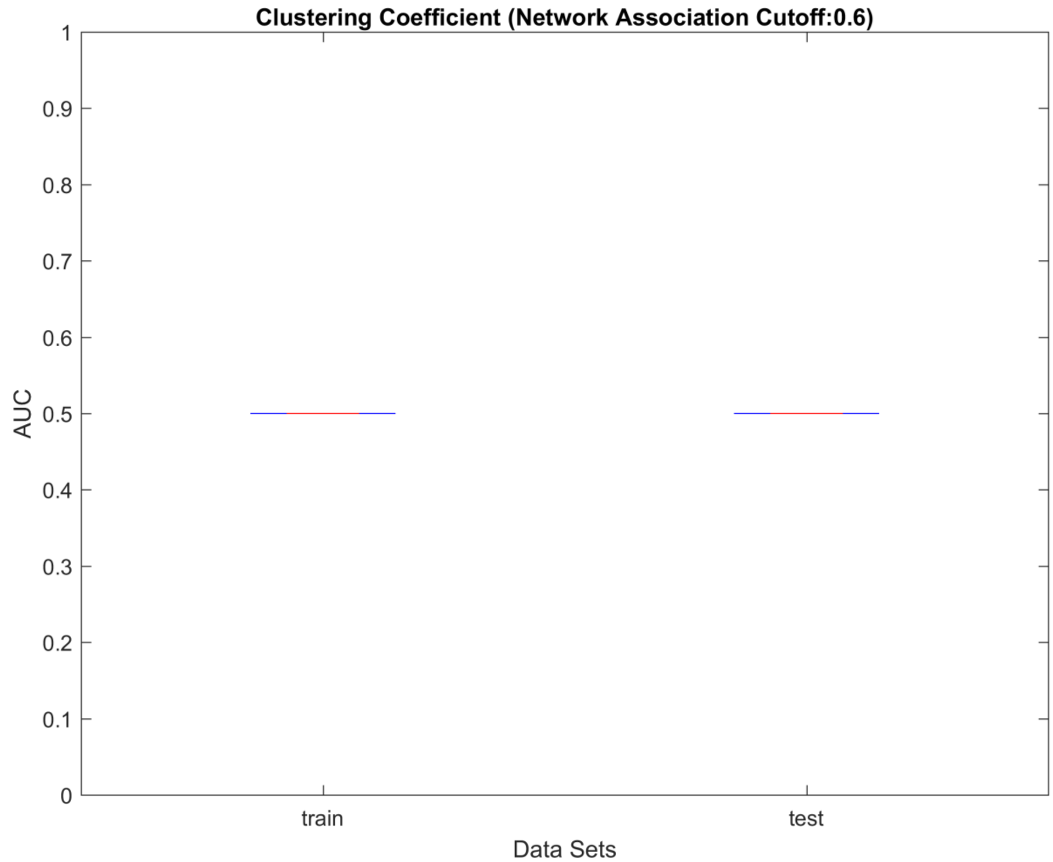

Figure 90. Training and test set classification performance of LASSO for EEG network constructed using Pearson correlation threshold of 0.6 over frequency range of 11-13 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.6)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5	0.5	0	0%
Mean	0.5	0.5	0	0%
Standard Deviation	0	0	0	0%

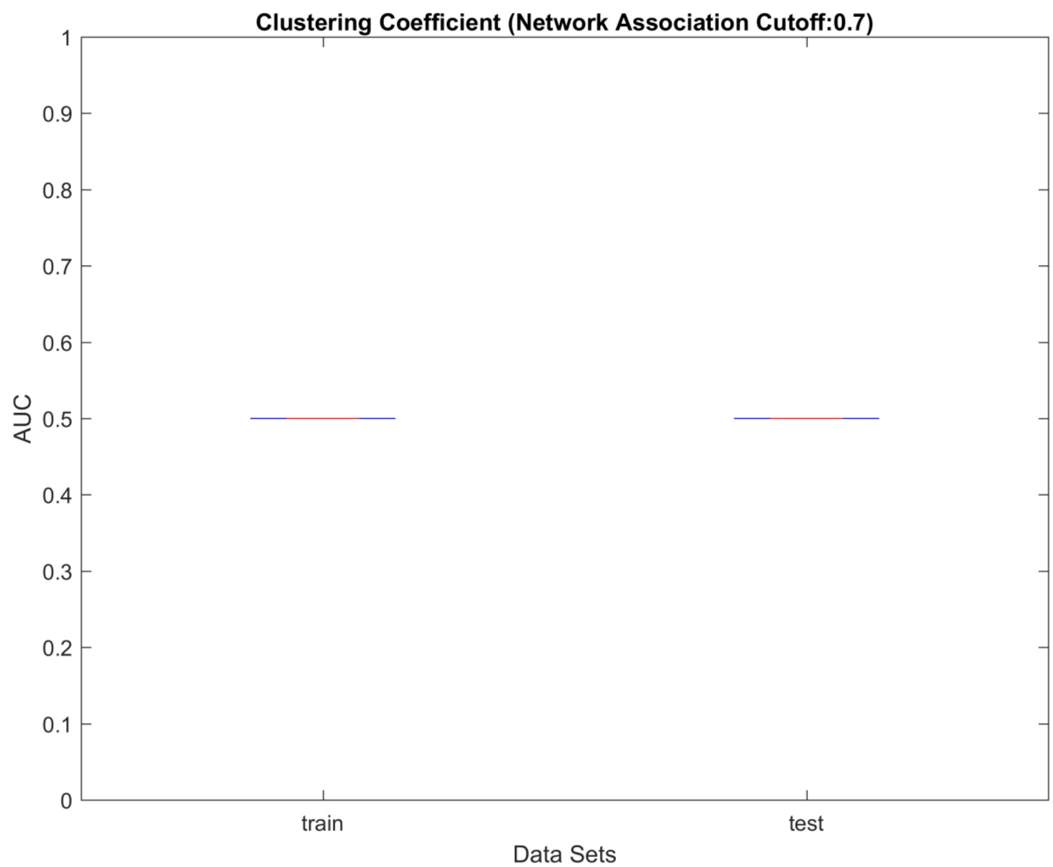

Figure 91. Training and test set classification performance of LASSO for EEG network constructed using Pearson correlation threshold of 0.7 over frequency range of 11-13 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.7)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5	0.5	0	0%
Mean	0.5	0.5	0	0%
Standard Deviation	0	0	0	0%

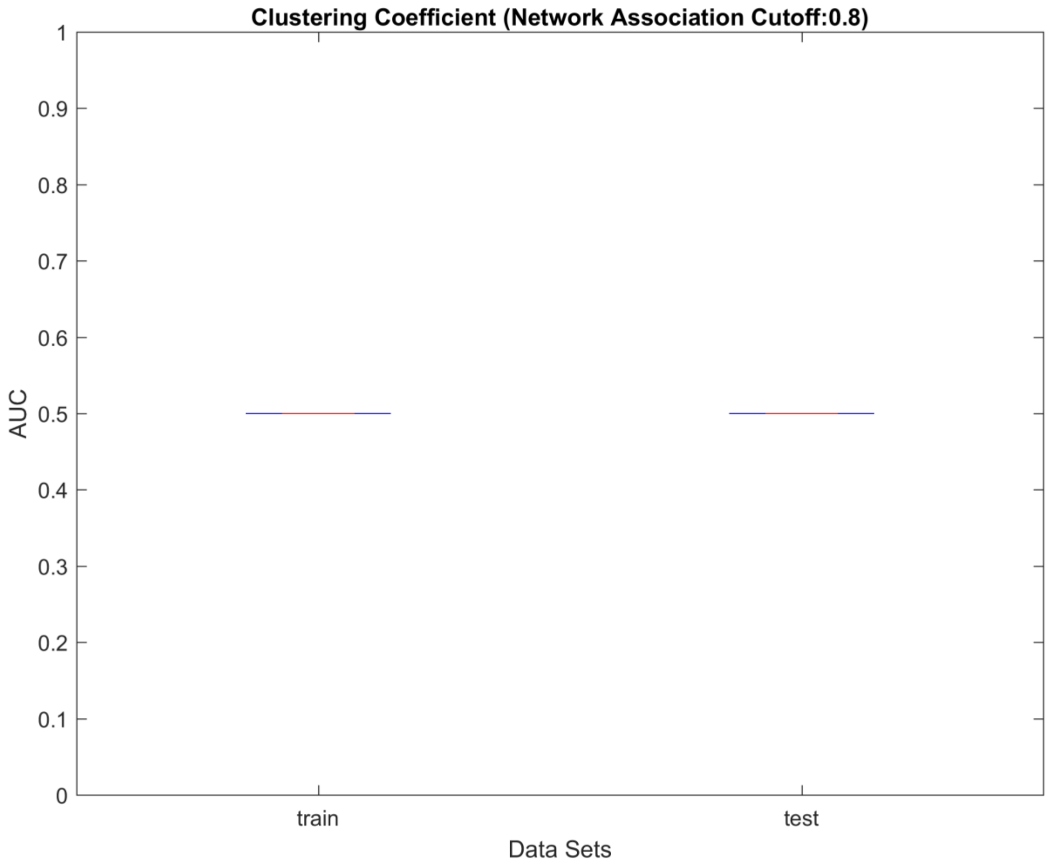

Figure 92. Training and test set classification performance of LASSO for EEG network constructed using Pearson correlation threshold of 0.8 over frequency range of 11-13 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.8)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5	0.5	0	0%
Mean	0.5	0.5	0	0%
Standard Deviation	0	0	0	0%

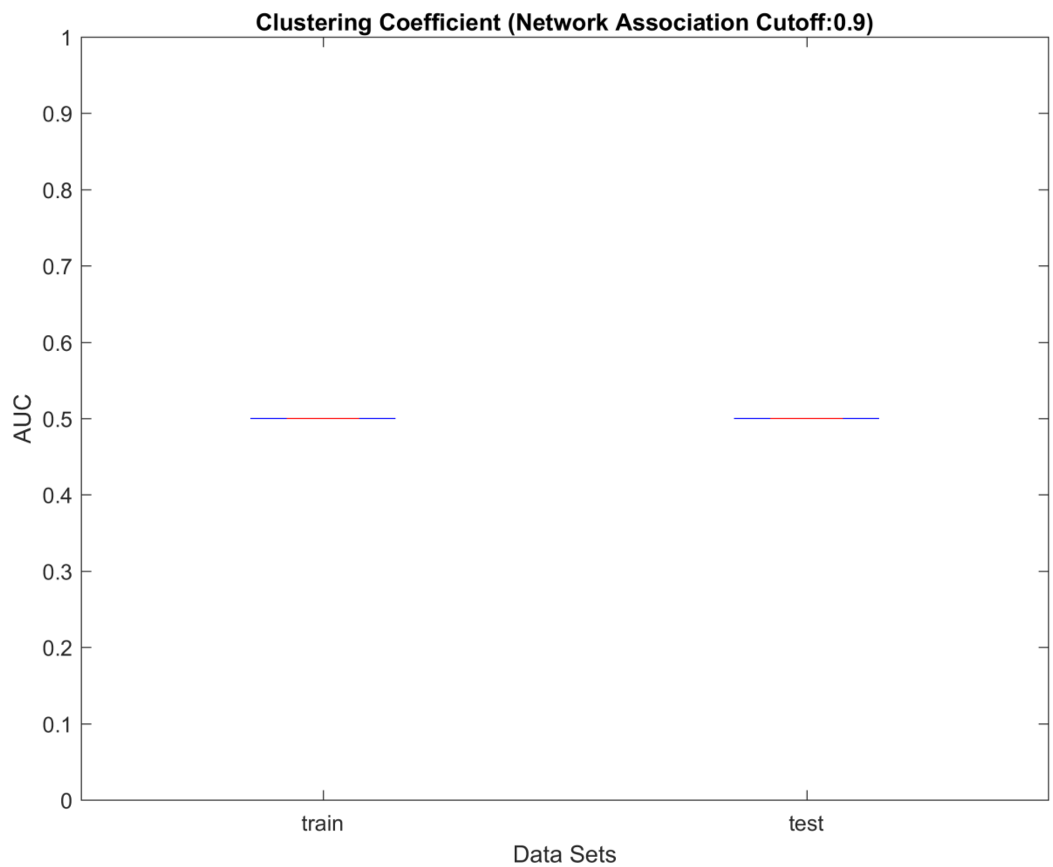

Figure 93. Training and test set classification performance of LASSO for EEG network constructed using Pearson correlation threshold of 0.9 over frequency range of 11-13 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.9)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5	0.5	0	0%
Mean	0.5	0.5	0	0%
Standard Deviation	0	0	0	0%

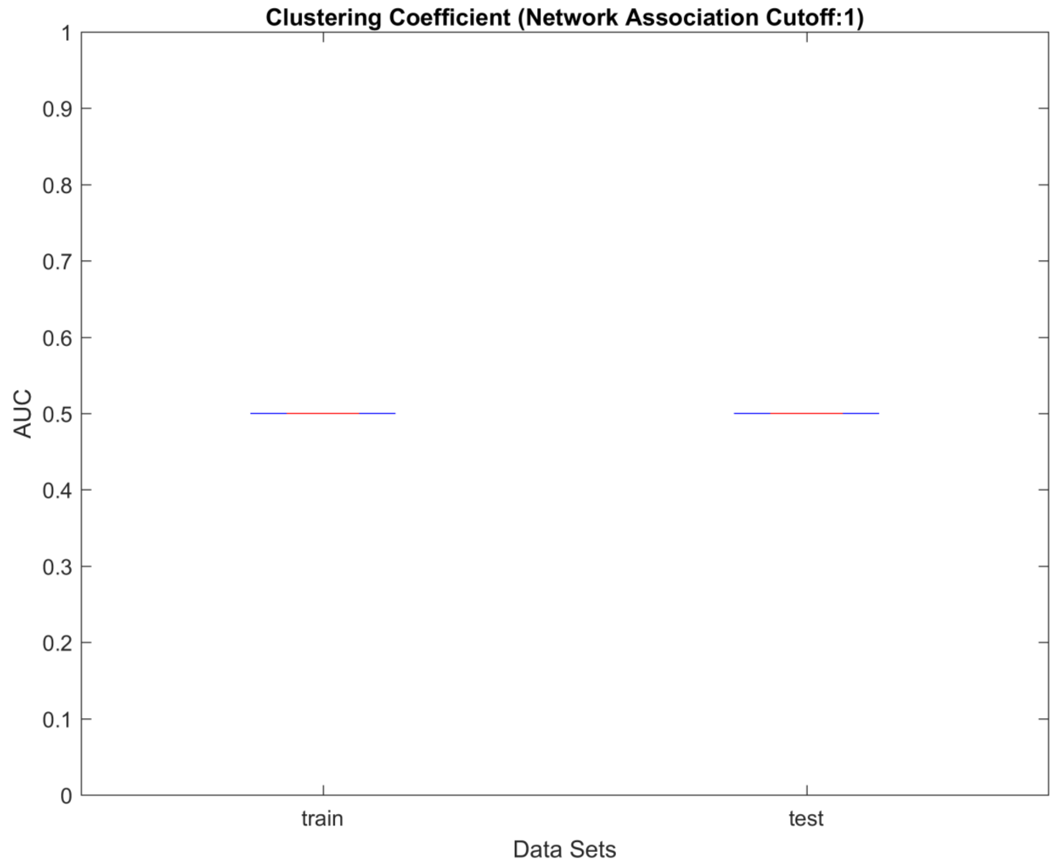

Figure 94. Training and test set classification performance of LASSO for EEG network constructed using Pearson correlation threshold of 1 over frequency range of 11-13 Hz.

	ROC Curve's AUC (Network Association Threshold: 1)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5	0.5	0	0%
Mean	0.5	0.5	0	0%
Standard Deviation	0	0	0	0%

7.3.5.3 Beta Wave (13-19 Hz)

The summary result of classification performance in terms of ROC Curve's AUC distribution for selected value of Pearson correlation coefficient used as thresholds to construct undirected EEG/brain network based on channel data for 13-19 Hz frequency range is shown in Figure 95. For the detailed comparison classification performance of the training datasets and that of the test datasets focusing on only one Pearson correlation value, the distributions of corresponding ROC curve's AUC for the 1,000 sampling iterations are show in Figure 96 to Figure 105. The Pearson correlations used to construct the EEG frequency network are 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9 and 1. Below each of the boxplots of AUC distributions for training and test sets, a table summarizes the median AUC and mean AUC of training and test set, difference and percentage of difference between test set's median and mean AUC with respect to training set's AUC is presented.

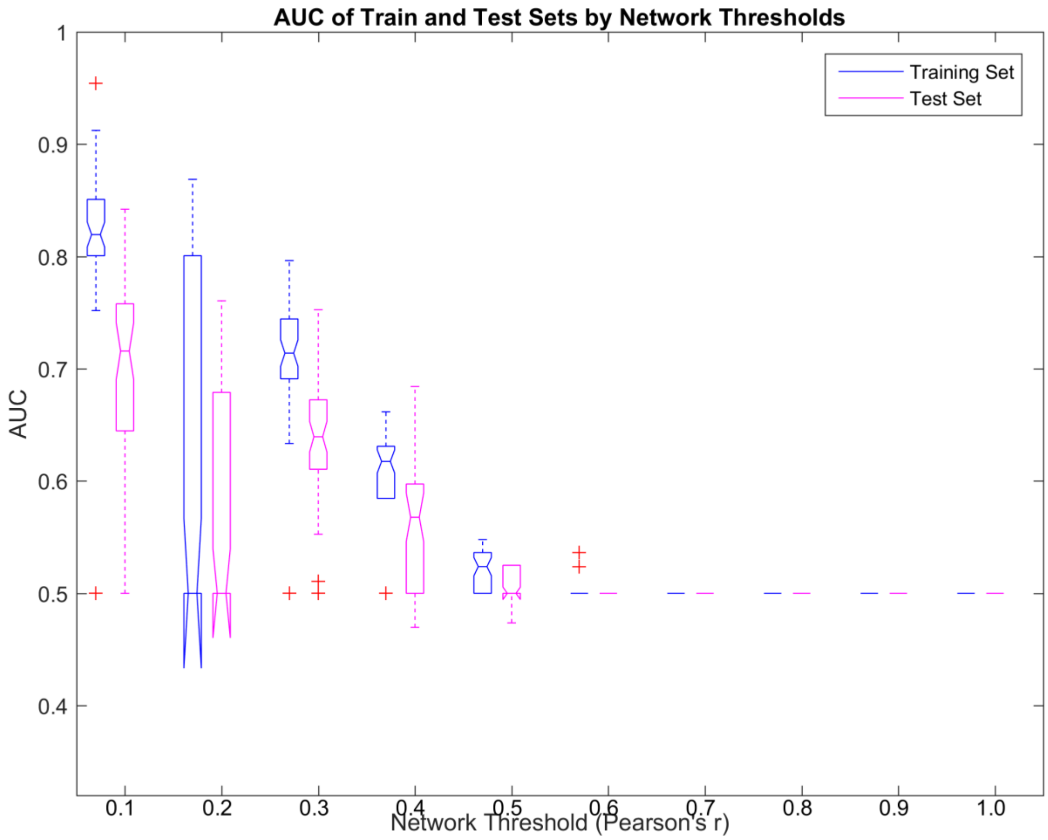

Figure 95. Training and test set classification performance of LASSO over range of Pearson correlations used to construct EEG network for frequency of 13-19 Hz.

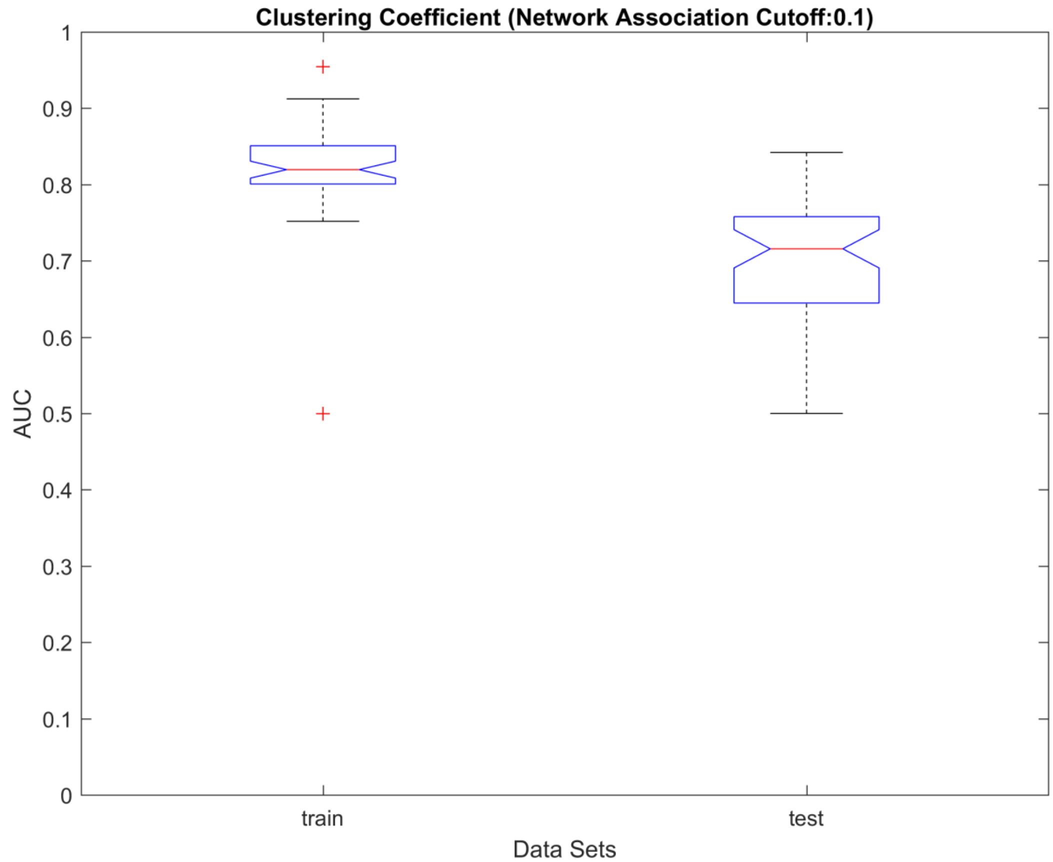

Figure 96. Training and test set classification performance of LASSO for EEG network constructed using Pearson correlation threshold of 0.1 over frequency range of 13-19 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.1)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.8195	0.7158	-0.1038	-12.66%
Mean	0.8110	0.6996	-0.1115	-13.74%
Standard Deviation	0.0872	0.0803	-0.0069	-7.87%

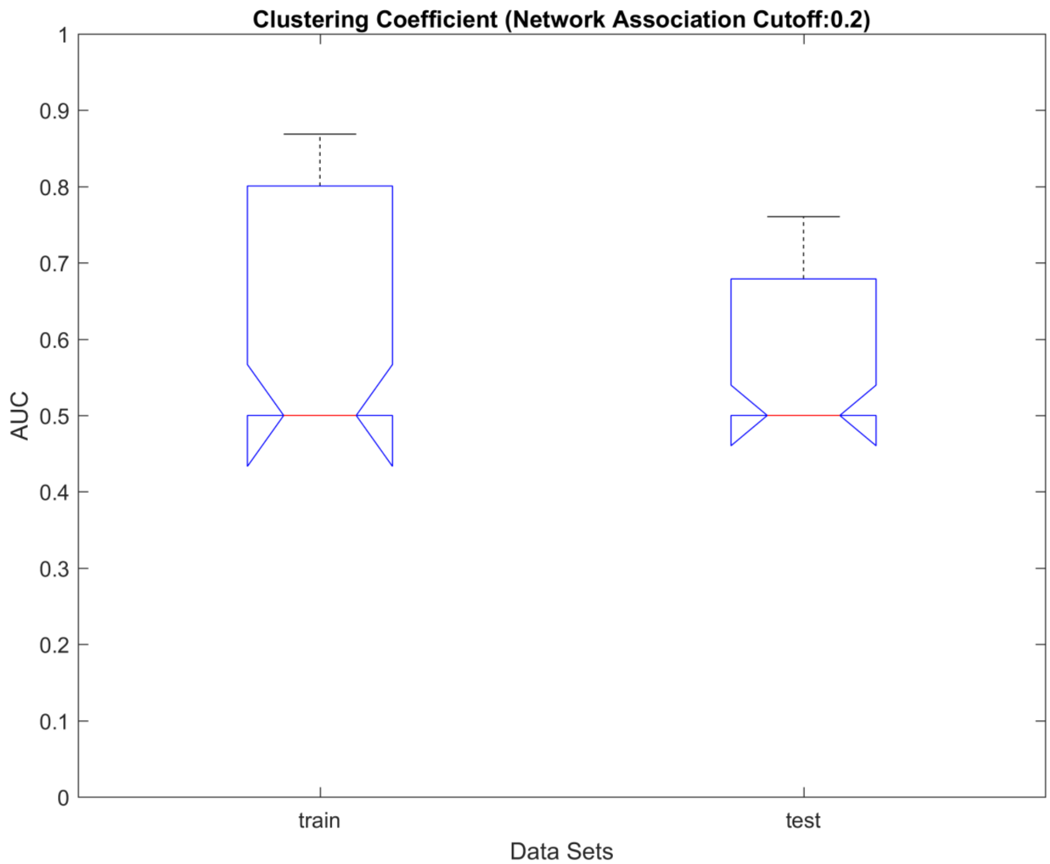

Figure 97. Training and test set classification performance of LASSO for EEG network constructed using Pearson correlation threshold of 0.2 over frequency range of 13-19 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.2)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5	0.5	0	0%
Mean	0.634	0.5767	-0.0574	-9.05%
Standard Deviation	0.1541	0.0943	-0.0598	-38.8%

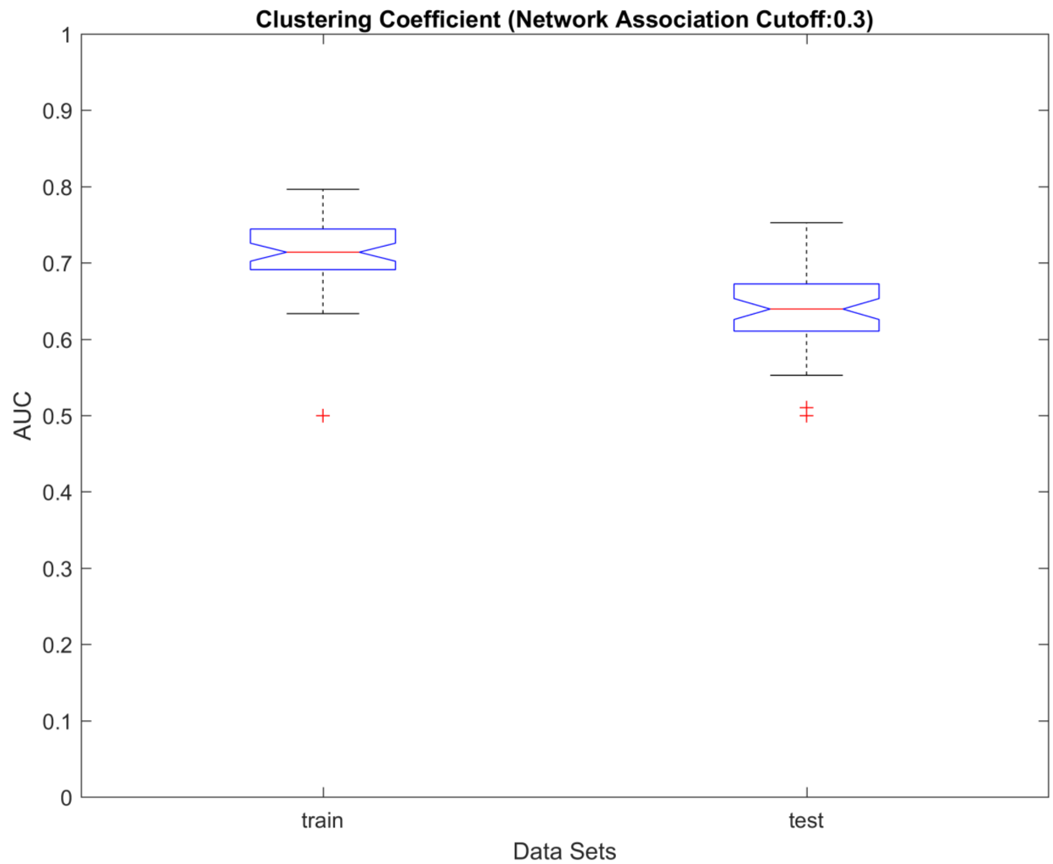

Figure 98. Training and test set classification performance of LASSO for EEG network constructed using Pearson correlation threshold of 0.3 over frequency range of 13-19 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.3)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.714	0.6395	-0.0745	-10.43%
Mean	0.7104	0.6394	-0.071	-9.995
Standard Deviation	0.0552	0.0587	0.0034	6.25%

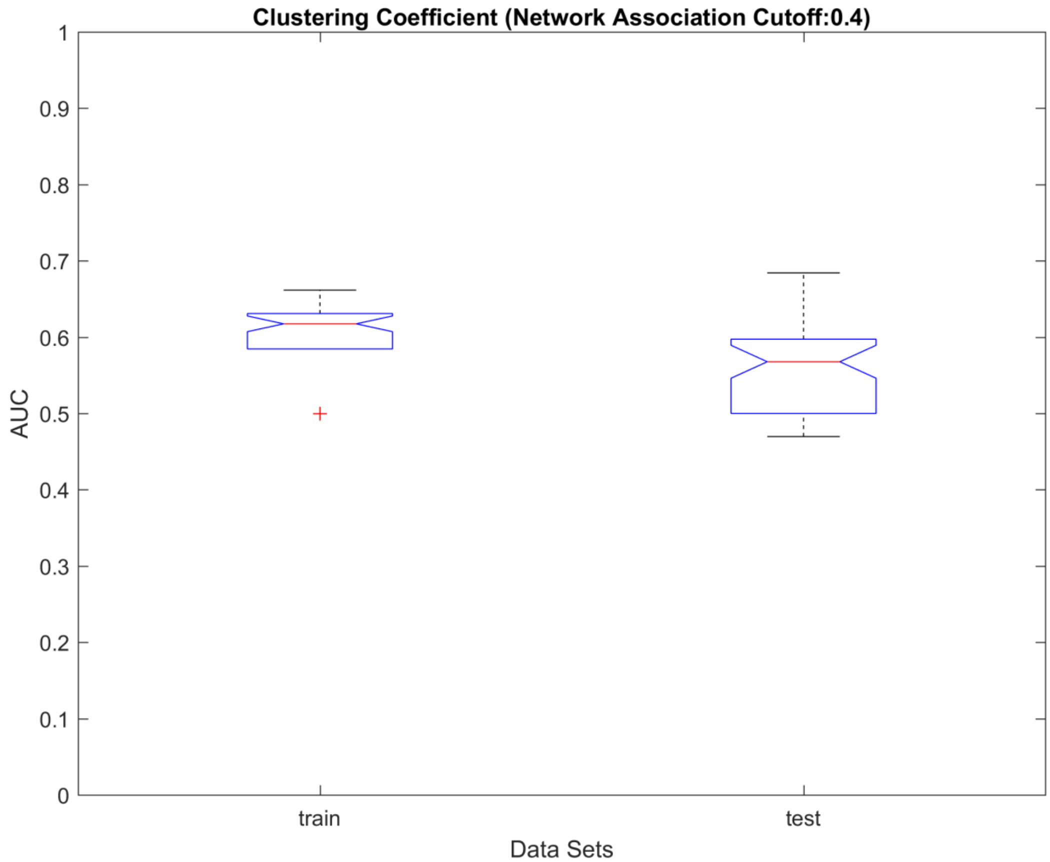

Figure 99. Training and test set classification performance of LASSO for EEG network constructed using Pearson correlation threshold of 0.4 over frequency range of 13-19 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.4)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.6175	0.5678	-0.0497	-8.05%
Mean	0.5946	0.5584	-0.0362	-6.09%
Standard Deviation	0.0559	0.0501	-0.0058	-10.42%

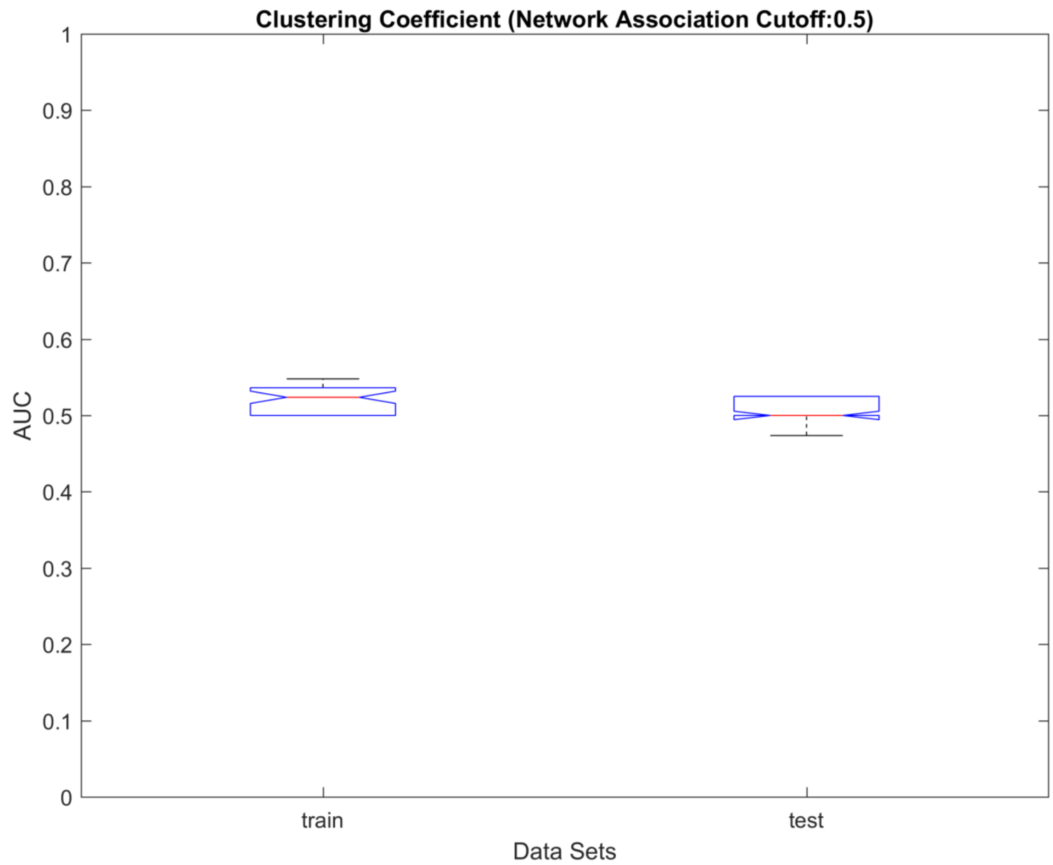

Figure 100. Training and test set classification performance of LASSO for EEG network constructed using Pearson correlation threshold of 0.5 over frequency range of 13-19 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.5)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5238	0.5	-0.0238	-4.55%
Mean	0.5194	0.5048	-0.0146	-2.81%
Standard Deviation	0.0178	0.0163	-0.0015	-8.58%

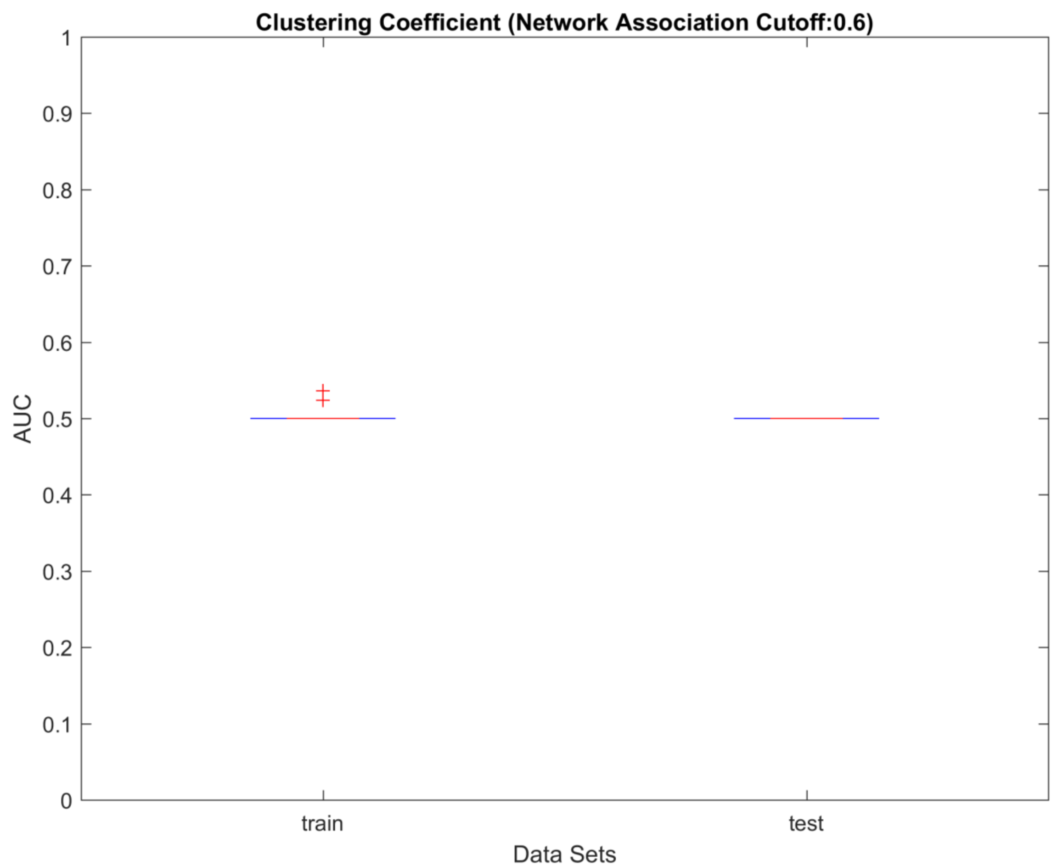

Figure 101. Training and test set classification performance of LASSO for EEG network constructed using Pearson correlation threshold of 0.6 over frequency range of 13-19 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.6)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5	0.5	0	0%
Mean	0.5012	0.5	-0.0012	-0.24%
Standard Deviation	0.0061	0	-0.0061	-100%

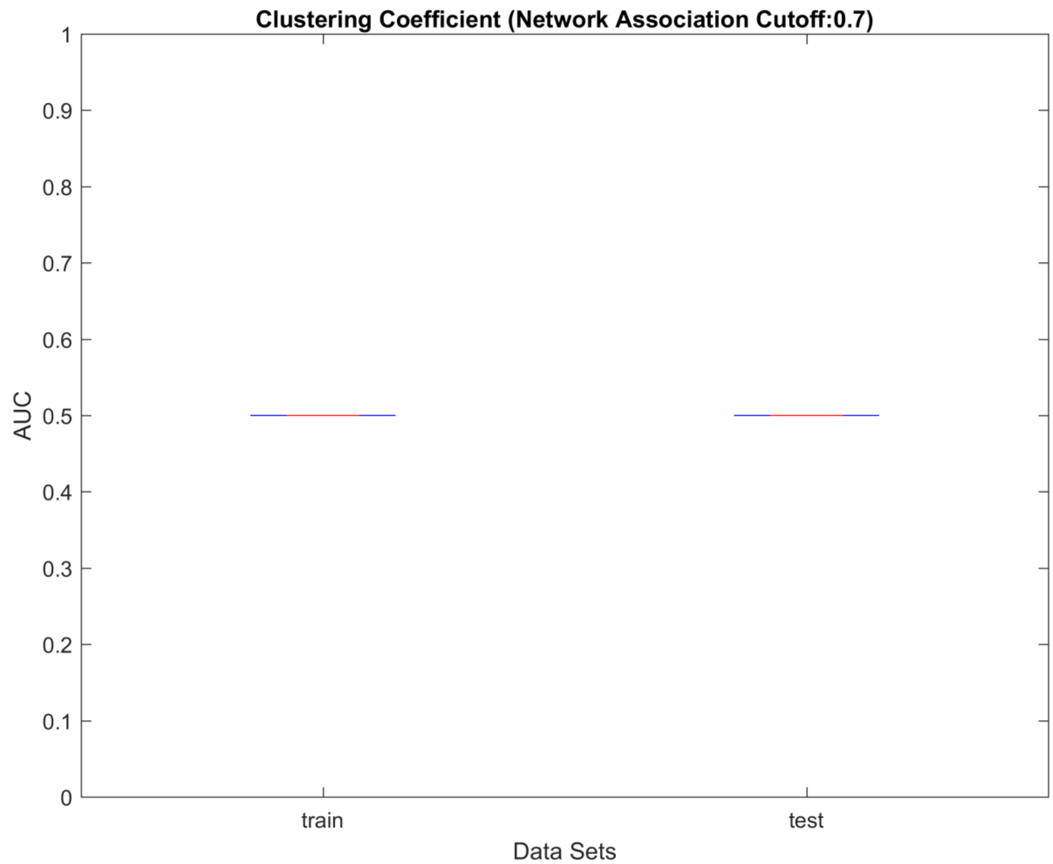

Figure 102. Training and test set classification performance of LASSO for EEG network constructed using Pearson correlation threshold of 0.7 over frequency range of 13-19 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.7)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5	0.5	0	0%
Mean	0.5	0.5	0	0%
Standard Deviation	0	0	0	0%

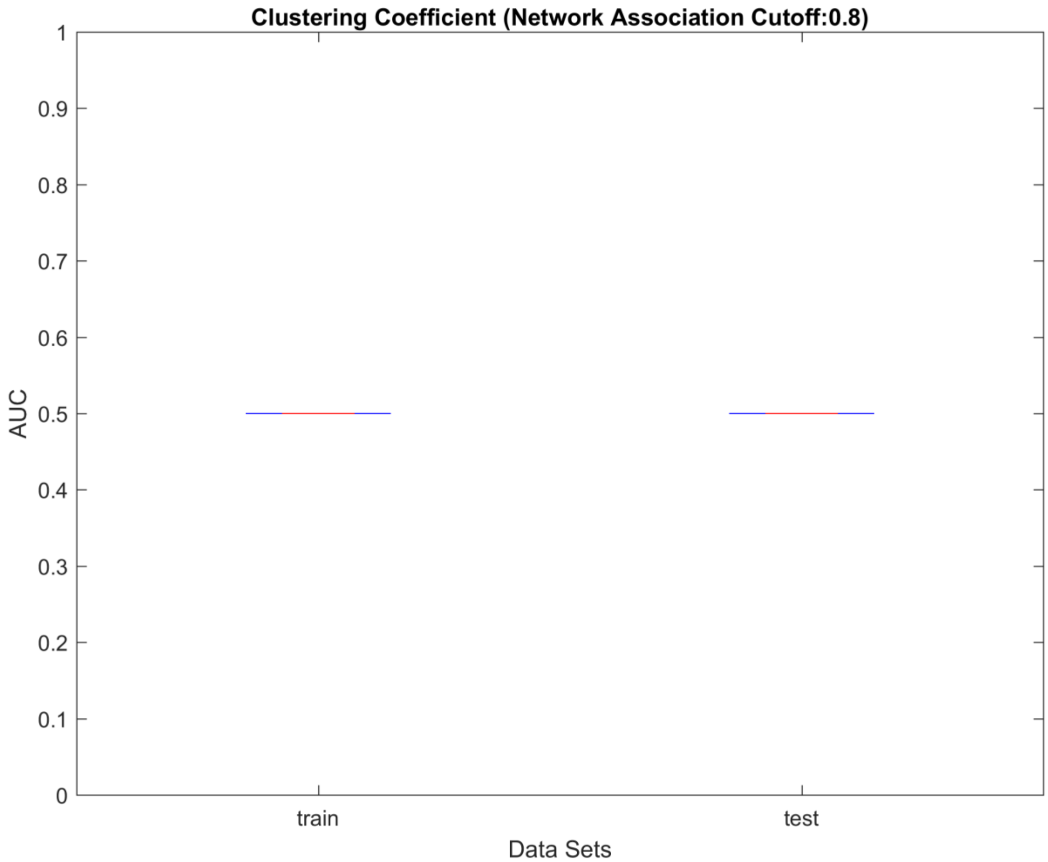

Figure 103. Training and test set classification performance of LASSO for EEG network constructed using Pearson correlation threshold of 0.8 over frequency range of 13-19 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.8)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5	0.5	0	0%
Mean	0.5	0.5	0	0%
Standard Deviation	0	0	0	0%

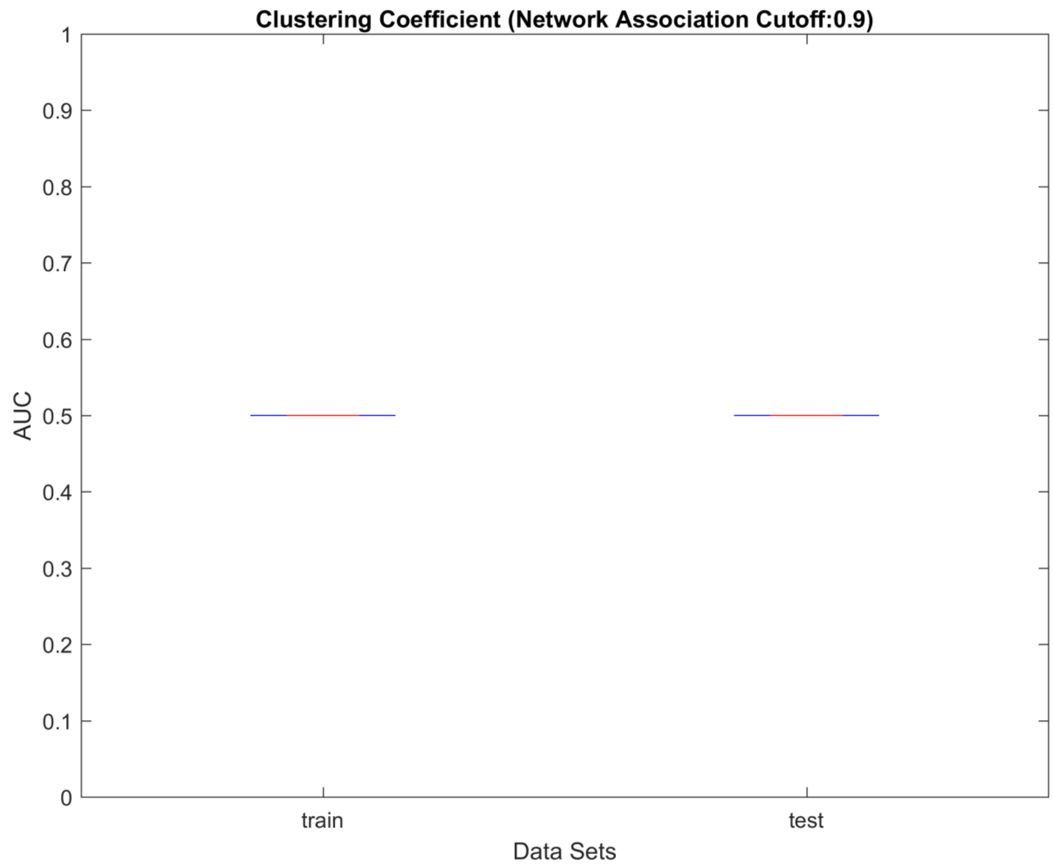

Figure 104. Training and test set classification performance of LASSO for EEG network constructed using Pearson correlation threshold of 0.9 over frequency range of 13-19 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.9)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5	0.5	0	0%
Mean	0.5	0.5	0	0%
Standard Deviation	0	0	0	0%

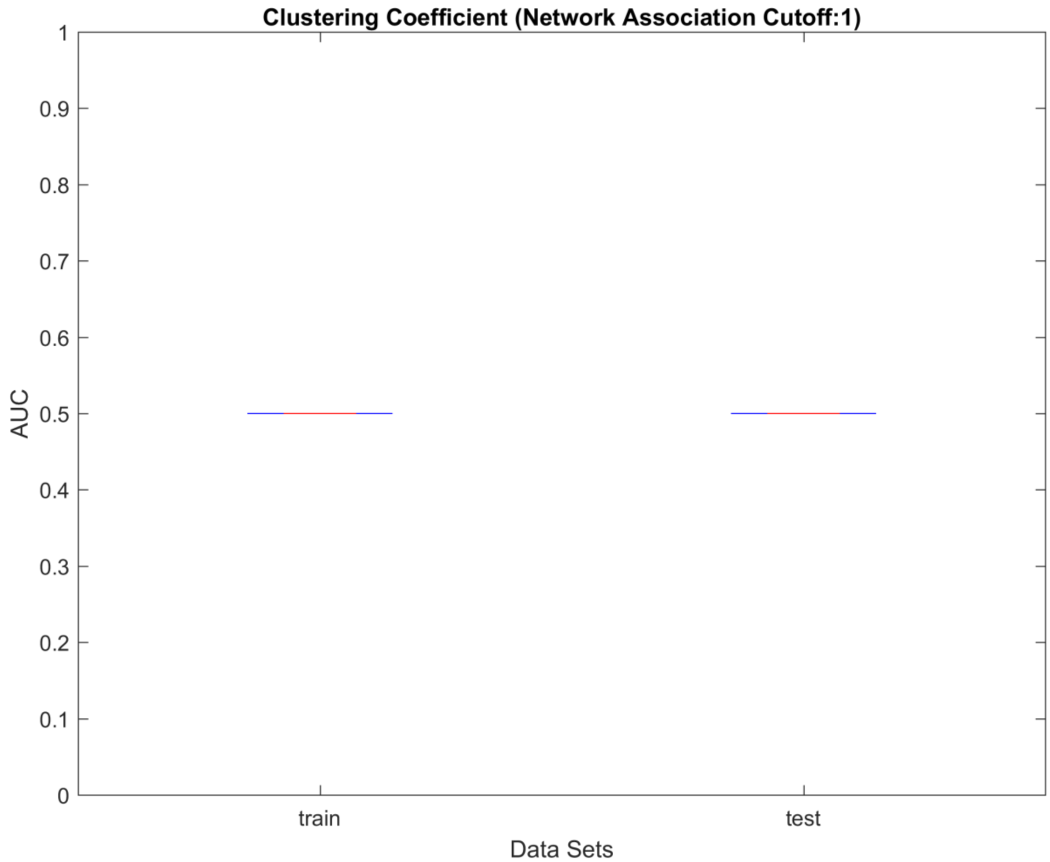

Figure 105. Training and test set classification performance of LASSO for EEG network constructed using Pearson correlation threshold of 1 over frequency range of 13-19 Hz.

	ROC Curve's AUC (Network Association Threshold: 1)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5	0.5	0	0%
Mean	0.5	0.5	0	0%
Standard Deviation	0	0	0	0%

7.3.5.4 Beta Wave (21-29 Hz)

The summary result of classification performance in terms of ROC Curve's AUC distribution for selected value of Pearson correlation coefficient used as thresholds to construct undirected EEG/brain network based on channel data for 21-29 Hz frequency range is shown in Figure 106 . For the detailed comparison classification performance of the training datasets and that of the test datasets focusing on only one Pearson correlation value, the distributions of corresponding ROC curve's AUC for the 1,000 sampling iterations are show in Figure 107 to Figure 116. The Pearson correlations used to construct the EEG frequency network are 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9 and 1. Below each of the boxplots of AUC distributions for training and test sets, a table summarizes the median AUC and mean AUC of training and test set, difference and percentage of difference between test set's median and mean AUC with respect to training set's AUC is presented.

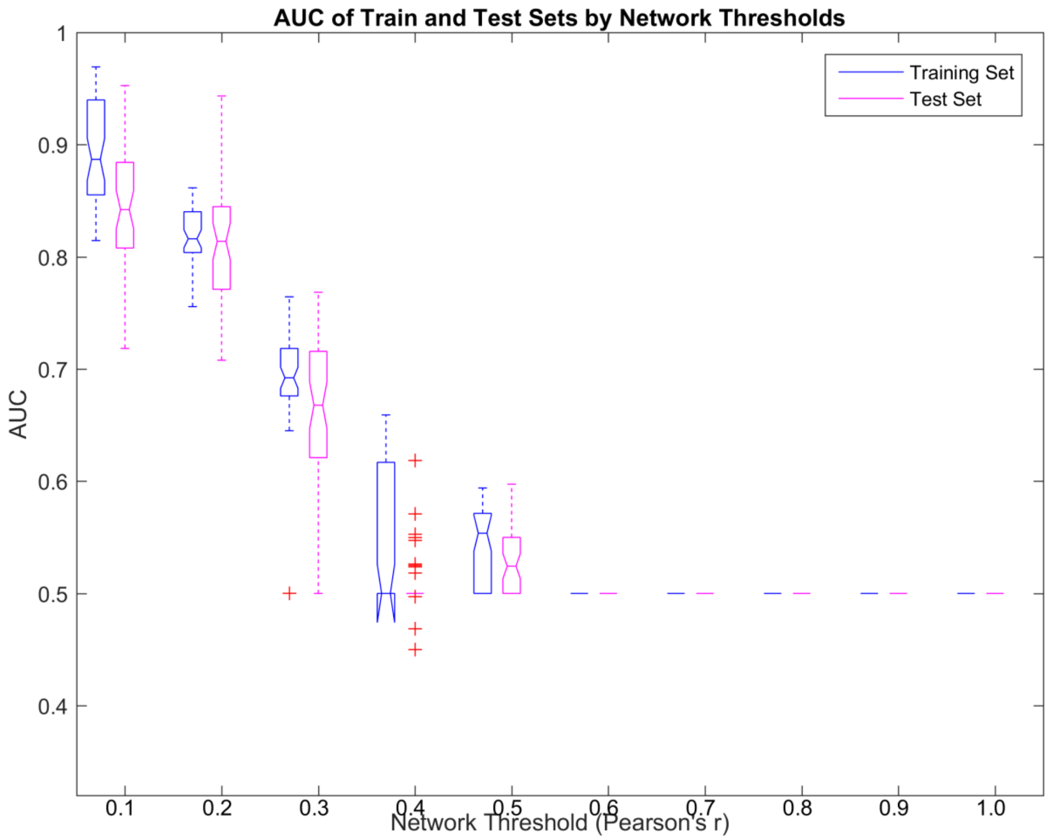

Figure 106. Training and test set classification performance of LASSO over range of Pearson correlations used to construct EEG network for frequency of 21-29 Hz.

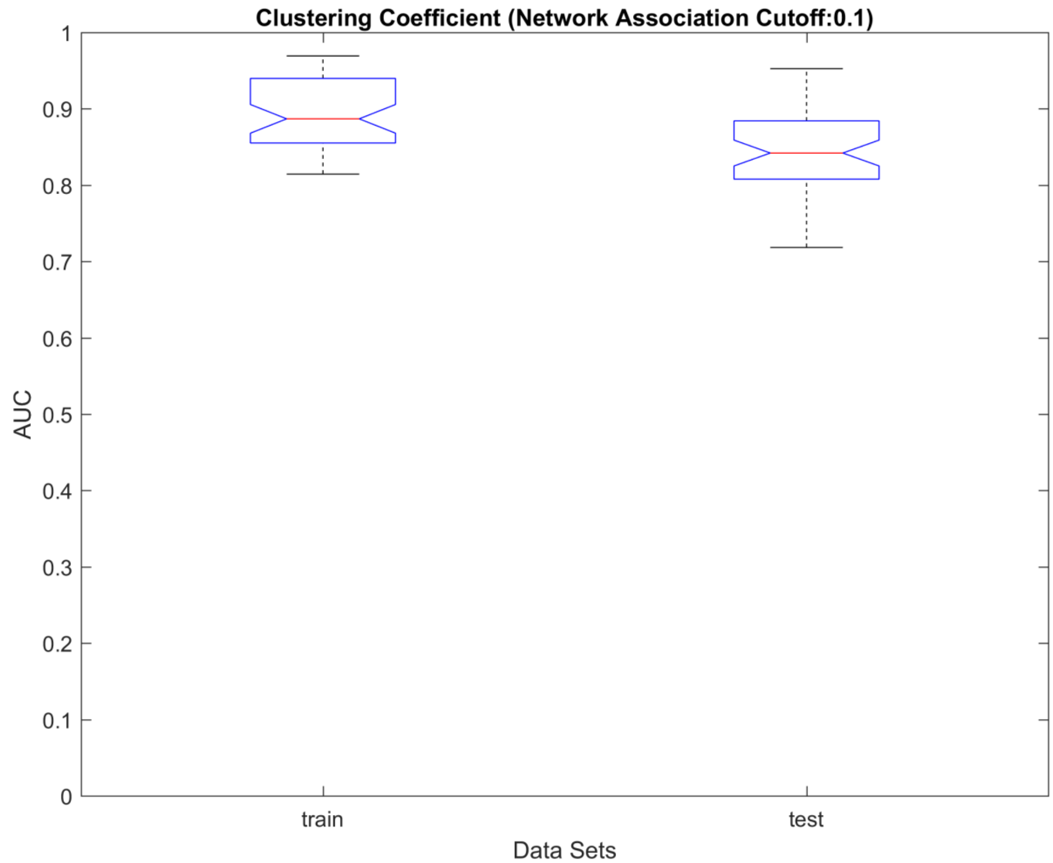

Figure 107. Training and test set classification performance of LASSO for EEG network constructed using Pearson correlation threshold of 0.1 over frequency range of 21-29 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.1)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.8869	0.8421	-0.0448	-5.05%
Mean	0.8943	0.8417	-0.0526	-5.88%
Standard Deviation	0.0451	0.0549	0.0098	21.70%

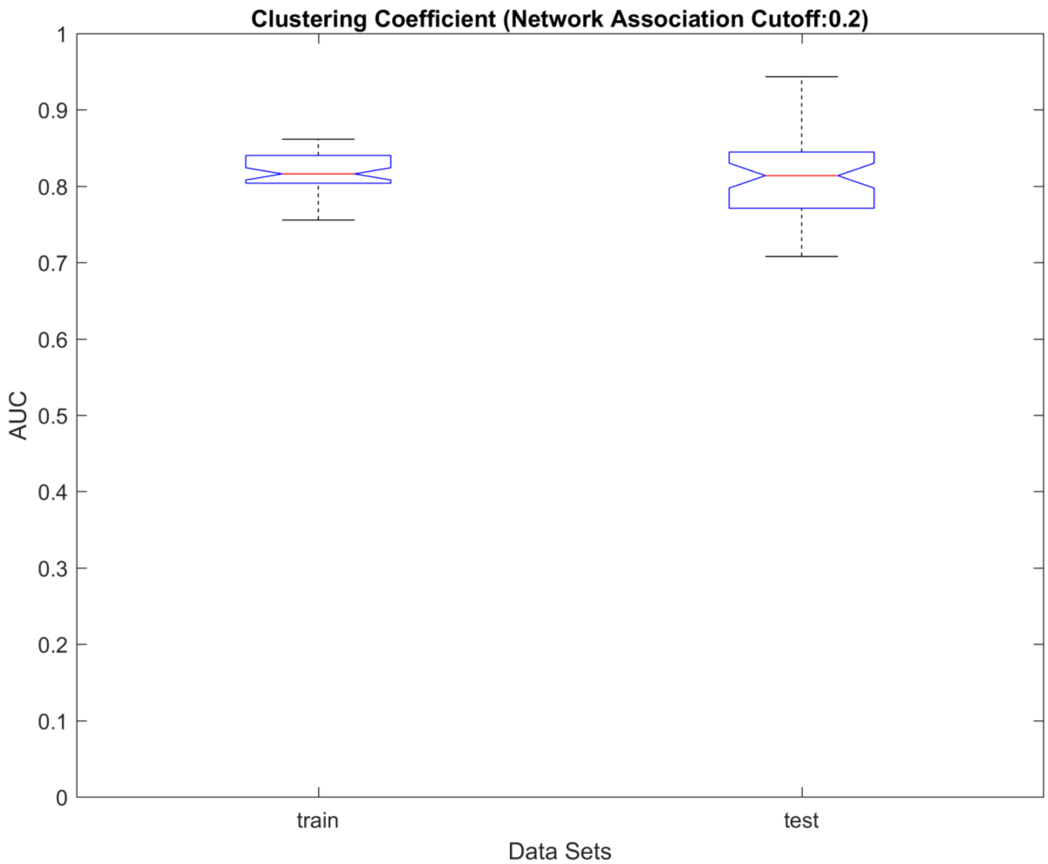

Figure 108. Training and test set classification performance of LASSO for EEG network constructed using Pearson correlation threshold of 0.2 over frequency range of 21-29 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.2)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.8161	0.8138	-0.0023	-0.28%
Mean	0.82	0.8079	-0.0122	-1.48%
Standard Deviation	0.0261	0.053	0.027	103.48%

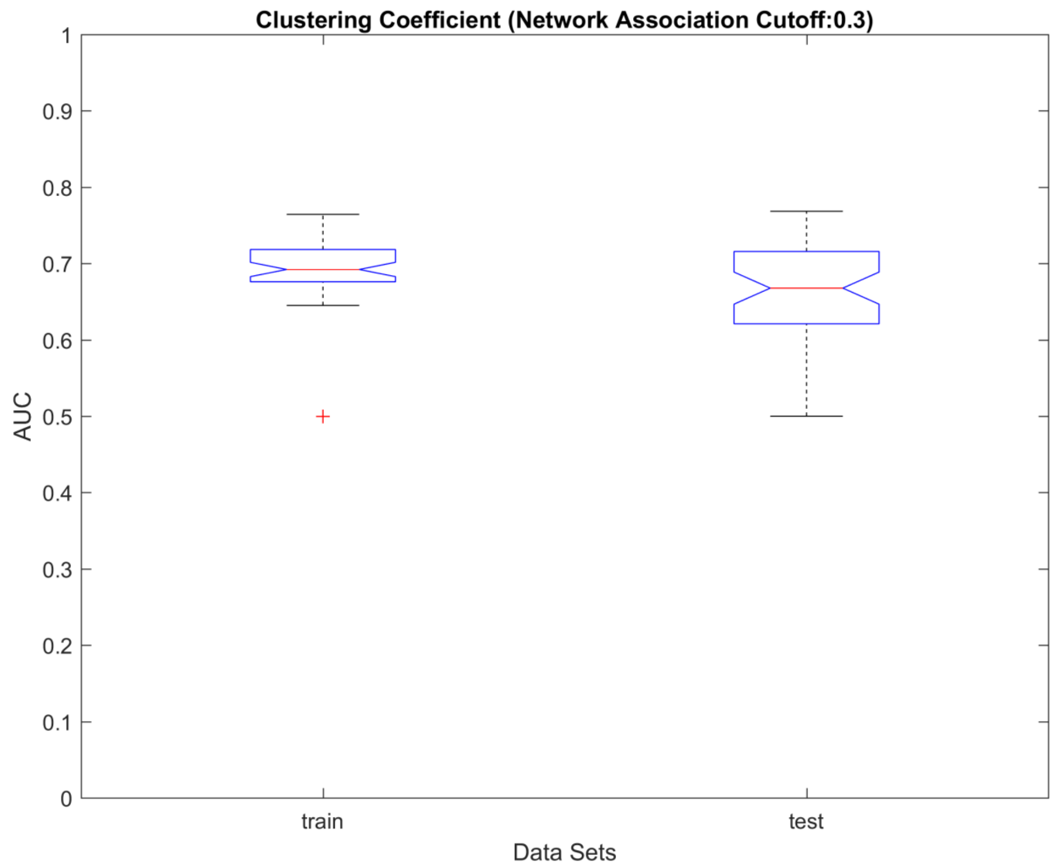

Figure 109. Training and test set classification performance of LASSO for EEG network constructed using Pearson correlation threshold of 0.3 over frequency range of 21-29 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.3)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.6922	0.6678	-0.0244	-3.53%
Mean	0.6766	0.6541	-0.0225	-3.33%
Standard Deviation	0.0707	0.0756	0.0049	6.90%

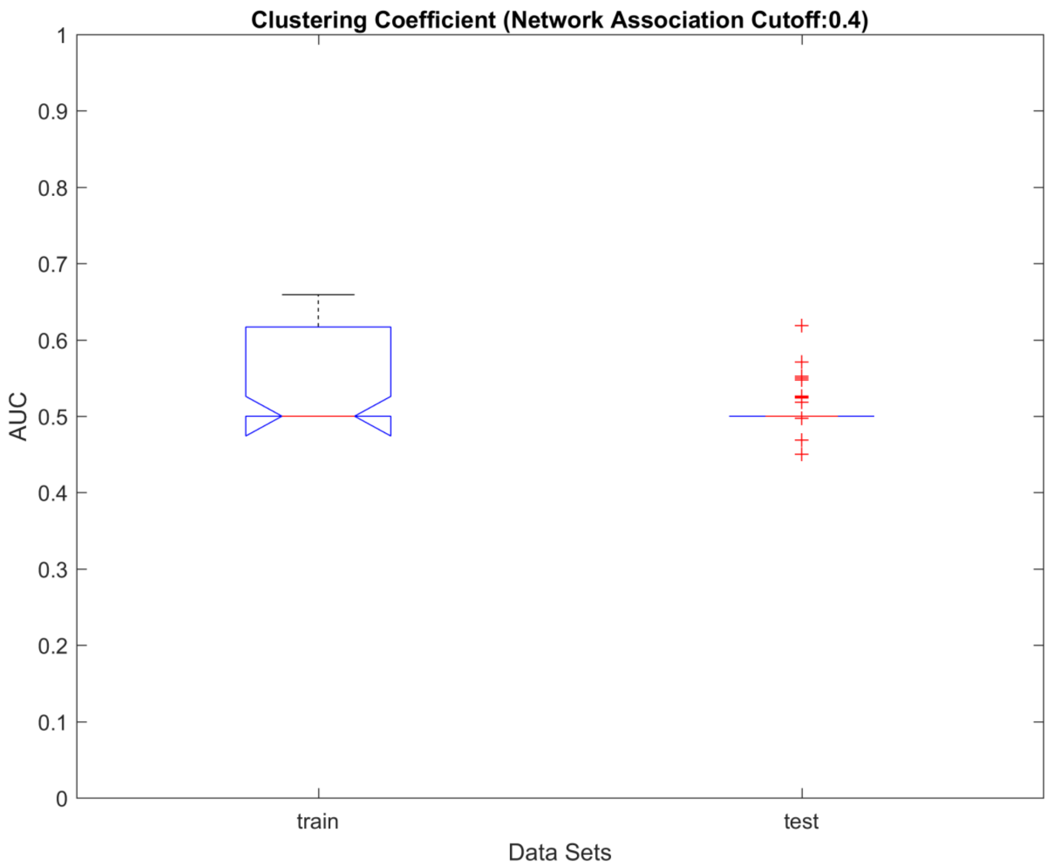

Figure 110. Training and test set classification performance of LASSO for EEG network constructed using Pearson correlation threshold of 0.4 over frequency range of 21-29 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.4)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5	0.5	0	0%
Mean	0.5414	0.5094	-0.032	-5.91%
Standard Deviation	0.0619	0.026	-0.0359	-58.05%

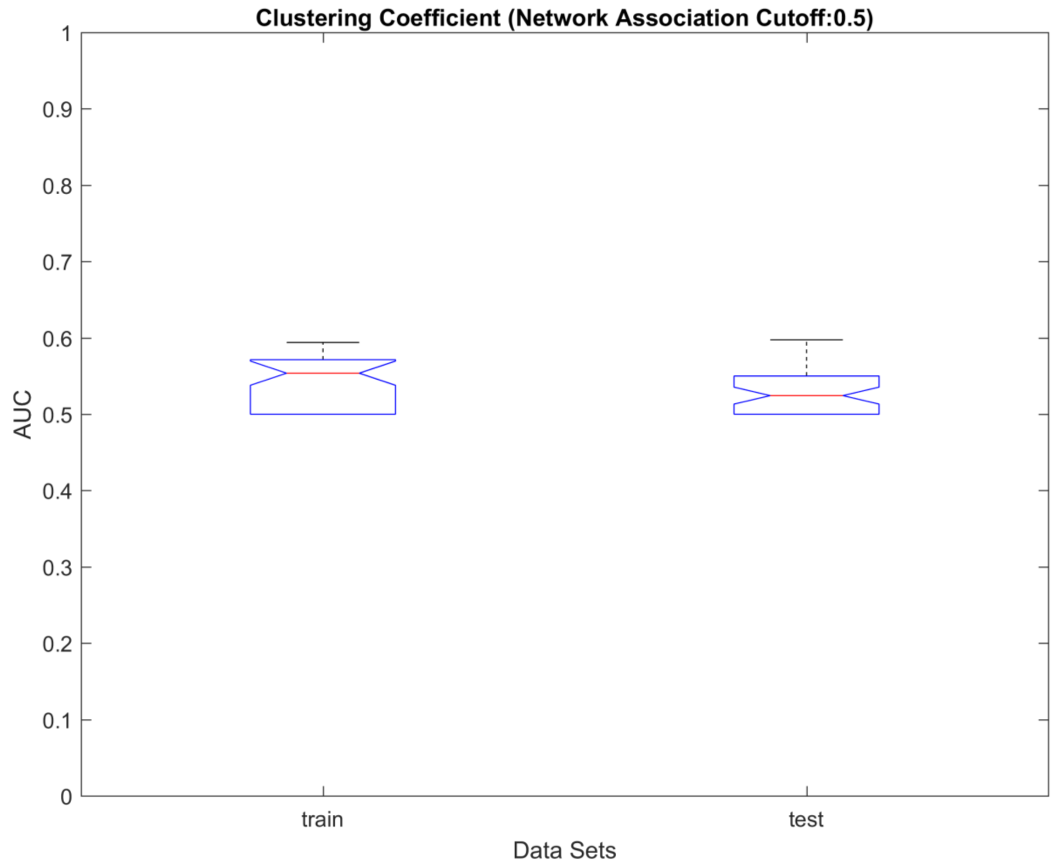

Figure 111. Training and test set classification performance of LASSO for EEG network constructed using Pearson correlation threshold of 0.5 over frequency range of 21-29 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.5)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5537	0.5243	-0.0294	-5.31%
Mean	0.542	0.5254	-0.0167	-3.08%
Standard Deviation	0.0354	0.0297	-0.0057	-16.09%

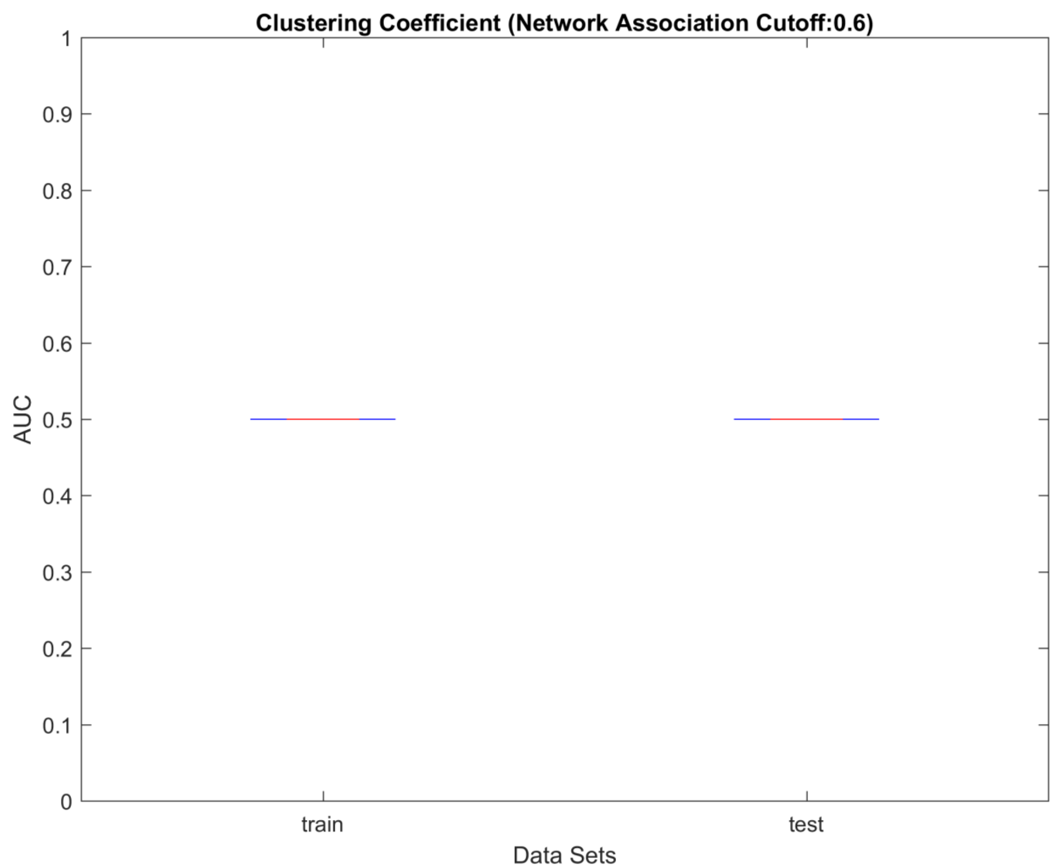

Figure 112. Training and test set classification performance of LASSO for EEG network constructed using Pearson correlation threshold of 0.6 over frequency range of 21-29 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.6)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5	0.5	0	0%
Mean	0.5	0.5	0	0%
Standard Deviation	0	0	0	0%

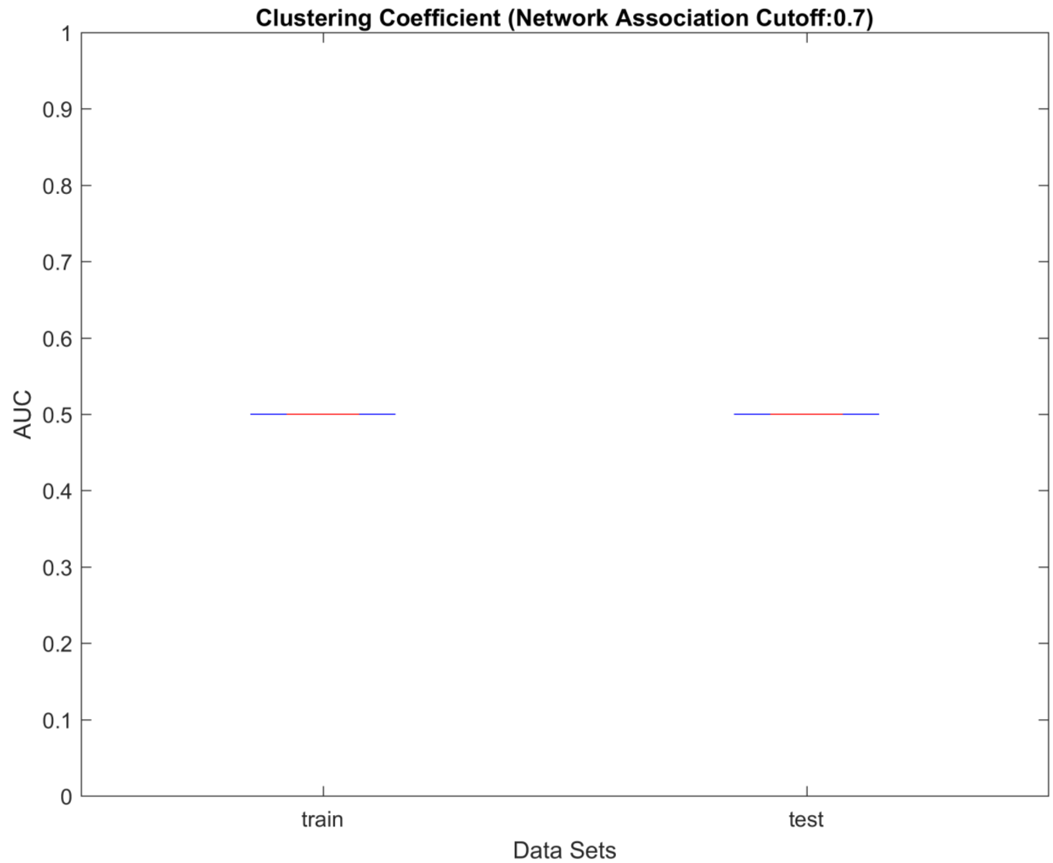

Figure 113. Training and test set classification performance of LASSO for EEG network constructed using Pearson correlation threshold of 0.7 over frequency range of 21-29 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.7)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5	0.5	0	0%
Mean	0.5	0.5	0	0%
Standard Deviation	0	0	0	0%

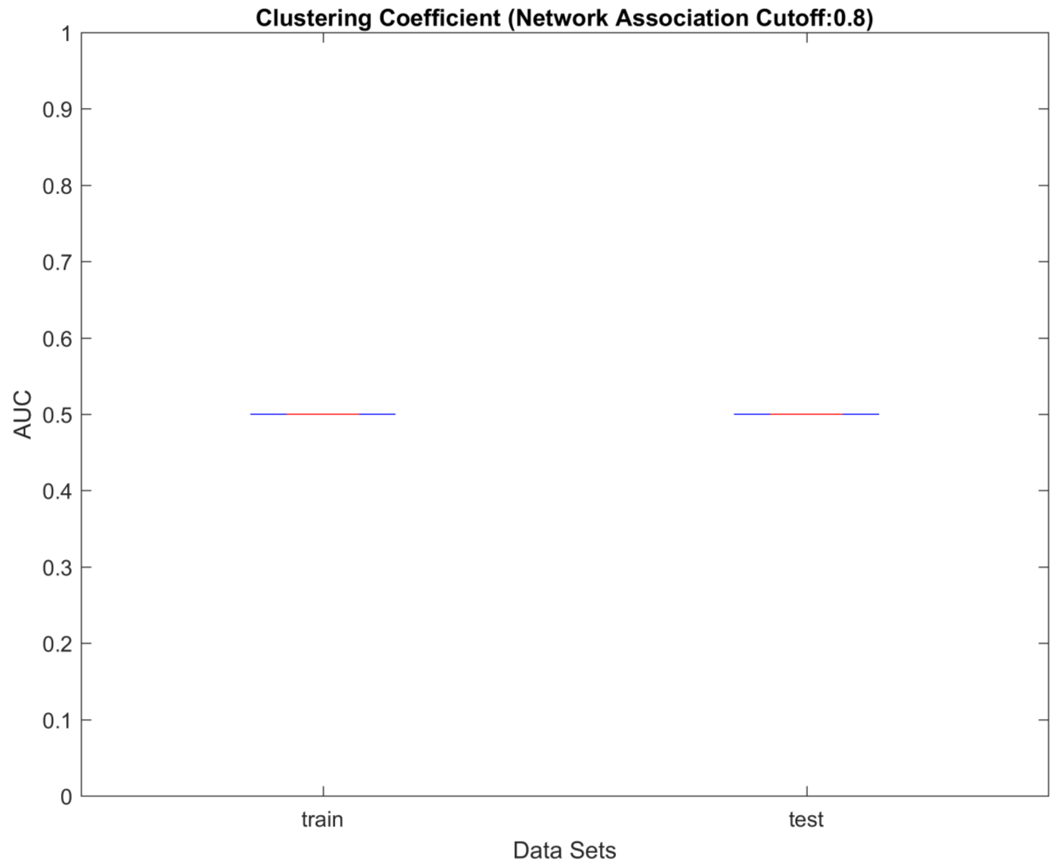

Figure 114. Training and test set classification performance of LASSO for EEG network constructed using Pearson correlation threshold of 0.8 over frequency range of 21-29 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.8)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5	0.5	0	0%
Mean	0.5	0.5	0	0%
Standard Deviation	0	0	0	0%

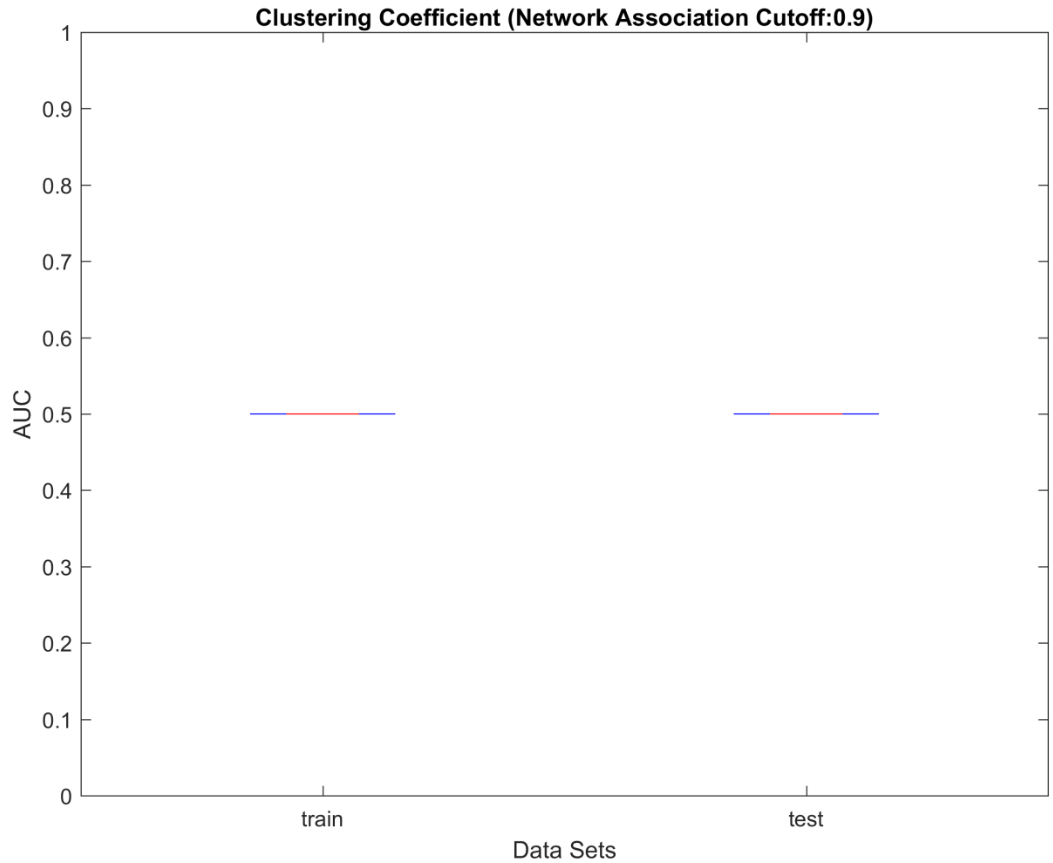

Figure 115. Training and test set classification performance of LASSO for EEG network constructed using Pearson correlation threshold of 0.9 over frequency range of 21-29 Hz.

	ROC Curve's AUC (Network Association Threshold: 0.9)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5	0.5	0	0%
Mean	0.5	0.5	0	0%
Standard Deviation	0	0	0	0%

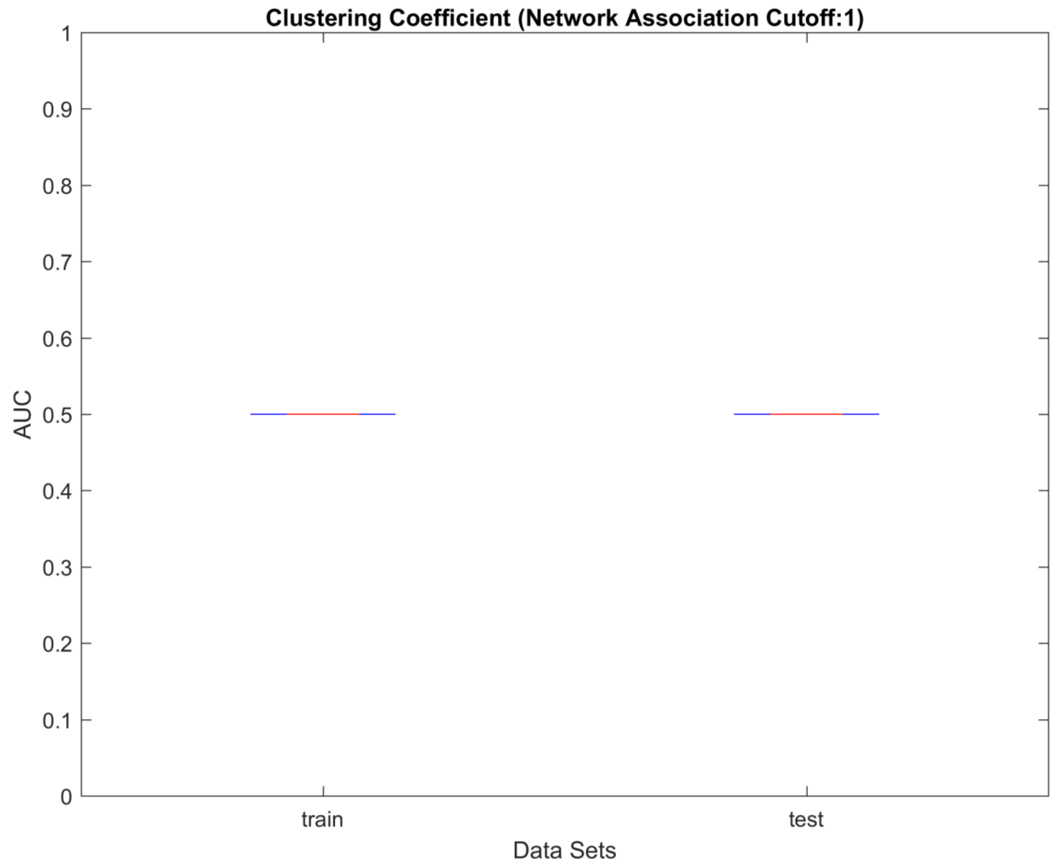

Figure 116. Training and test set classification performance of LASSO for EEG network constructed using Pearson correlation threshold of 1 over frequency range of 21-29 Hz.

	ROC Curve's AUC (Network Association Threshold: 1)			
	Training Set	Test Set	Difference (Test Set's AUC - Training Set's AUC)	% Change of Test Set's AUC
Median	0.5	0.5	0	0%
Mean	0.5	0.5	0	0%
Standard Deviation	0	0	0	0%

7.3.6 Comparison of Model Classification Performance Based on Clustering Coefficient: ROC Curve's AUC vs. Pearson Correlation (PCSSLR, LASSO, Logistic Regression)

The summary result of classification performance of LASSO, PCSSLR, and logistic regression in terms of ROC curve's AUC distribution for selected value of Pearson correlation coefficient used as thresholds to construct undirected EEG/brain network based on channel data are presented for four different physiological frequency ranges.

7.3.6.1 Alpha Wave (7-9 Hz)

The summary result of classification performance of LASSO, PCSSLR, and logistic regression in terms of ROC curve's AUC distribution for selected value of Pearson correlation coefficient used as thresholds to construct undirected EEG/brain network based on channel data for 7-9 Hz frequency range is shown in Figure 117 for training sets and Figure 118 for test sets. The VIFs of the clustering coefficient covariates are shown in Figure 119 to Figure 125.

7.3.6.1.1 AUC Comparison of Models – Training Sets

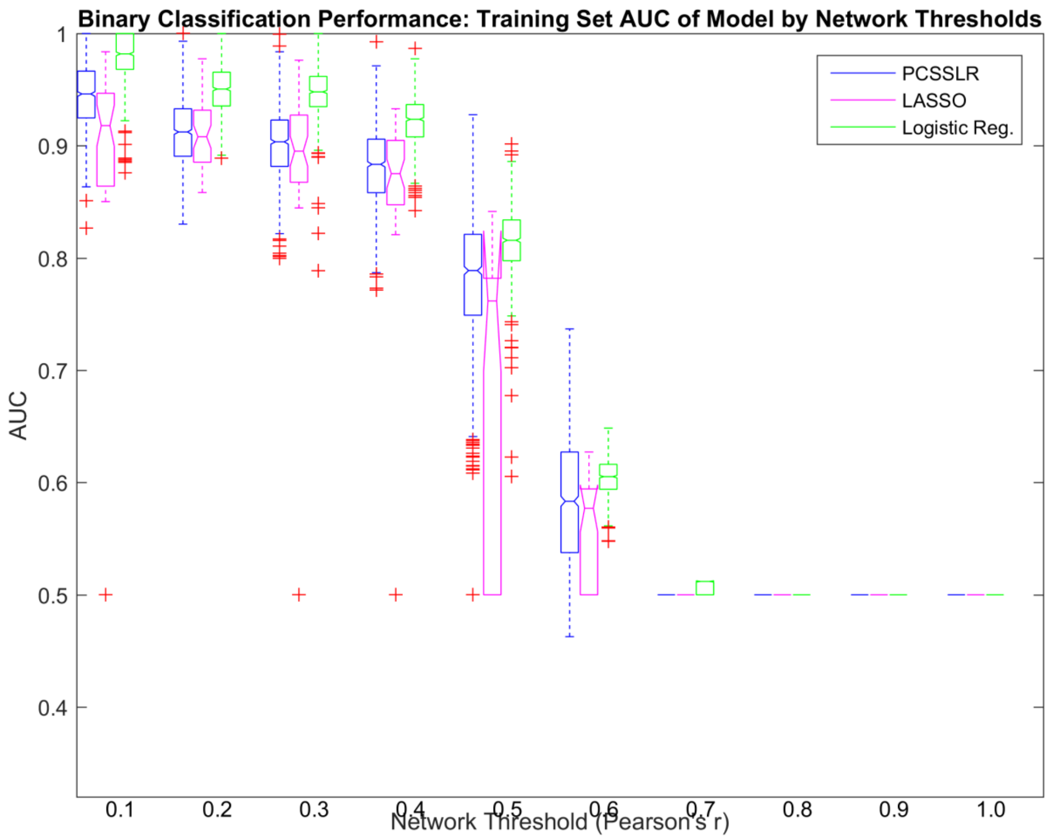

Figure 117. Training set DBS-on vs. DBS-off classification performance of PCSSLR, LASSO and logistic regression over range of Pearson correlations used to construct EEG network for frequency of 7-9 Hz.

7.3.6.1.2 AUC Comparison of Models – Test Sets

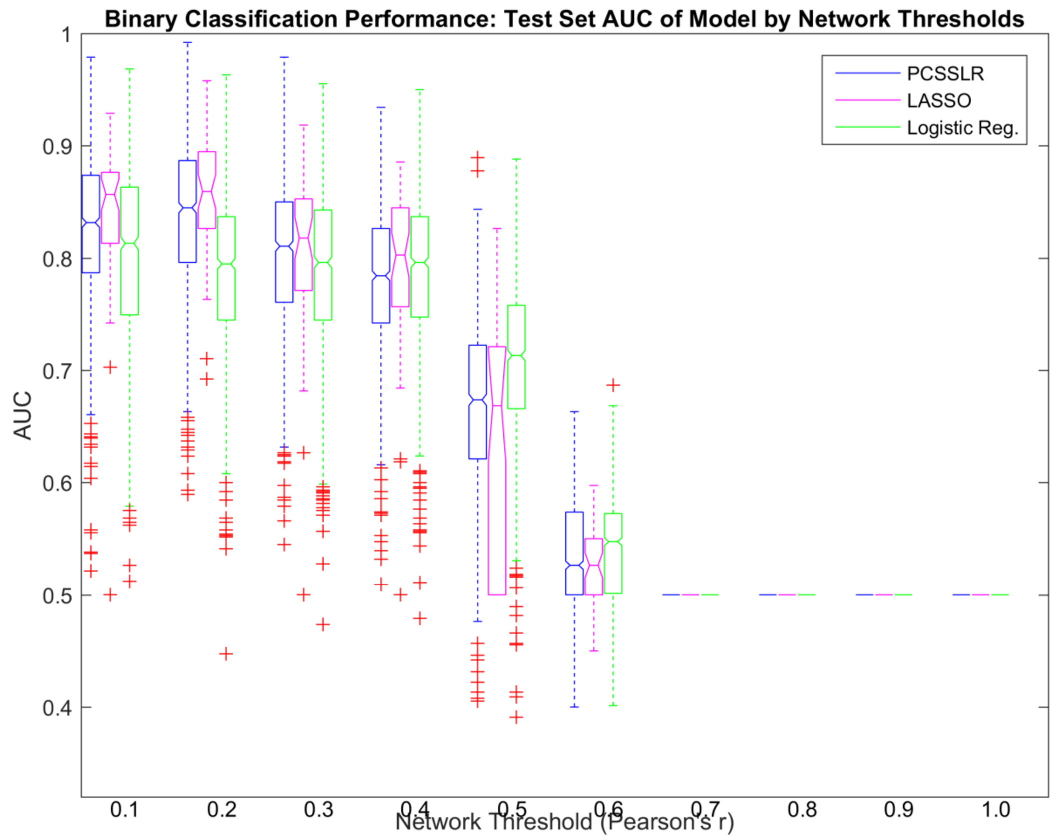

Figure 118. Test set DBS-on vs. DBS-off classification performance of PCSSLR, LASSO and logistic regression over range of Pearson correlations used to construct EEG network for frequency of 7-9 Hz.

7.3.6.1.3 Network Constructed Using Pearson's Correlation Cutoff: 0.1

7.3.6.1.3.1 Variance Inflation Factors (VIF)

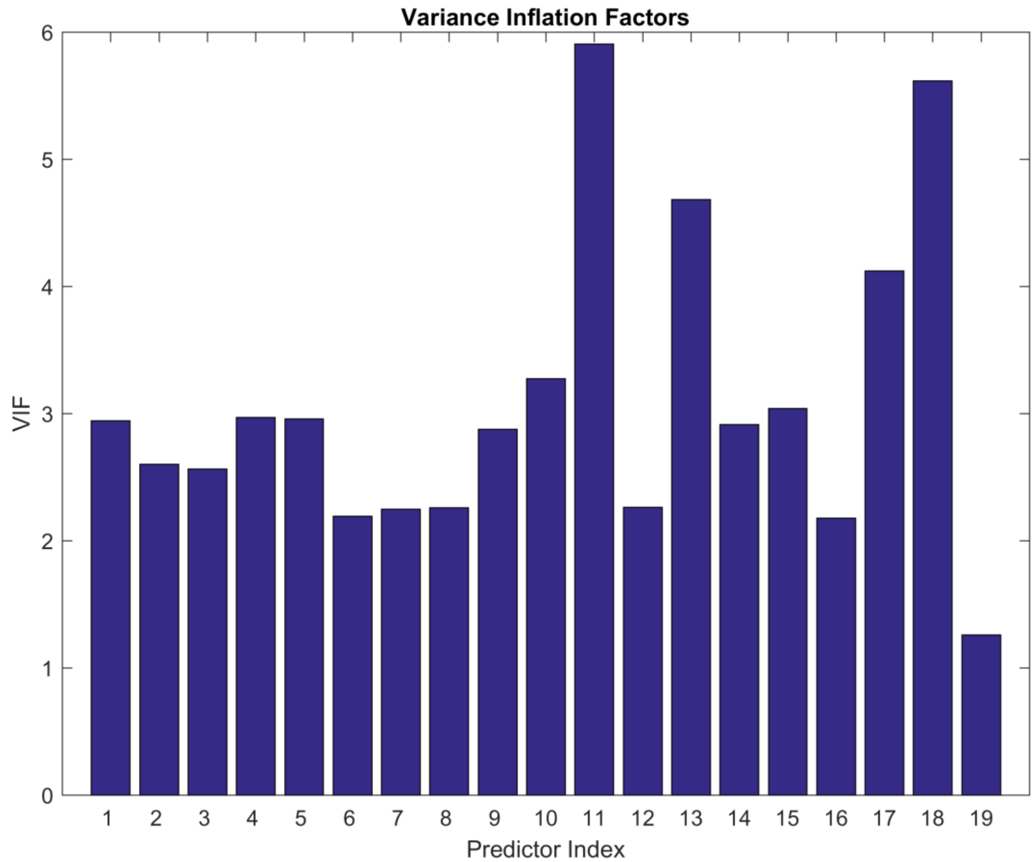

Figure 119. Variance inflation factors of 19 clustering coefficients for EEG network created with Pearson correlation of 0.1 as threshold and frequency range of 7-9 Hz.

The VIFs of the 19 clustering coefficients corresponding to 18 EEG channels and the EKG data. As seen from Figure 119, the covariates with index of 11 and 18 have VIFs > 5, indicating that the multidimensional data set exhibits strong multicollinearity.

The following table shows comparison of model classification performance.

	PCSSLR		LASSO		Logistic Regression	
	Training Set	Test Set	Training Set	Test Set	Training Set	Test Set
Median	0.9461	0.8316	0.9179	0.8566	0.9818	0.8132
Mean	0.9457	0.8259	0.9008	0.8379	0.9809	0.8035

7.3.6.1.4 Network Constructed Using Pearson's Correlation Cutoff: 0.2

7.3.6.1.4.1 Variance Inflation Factors (VIF)

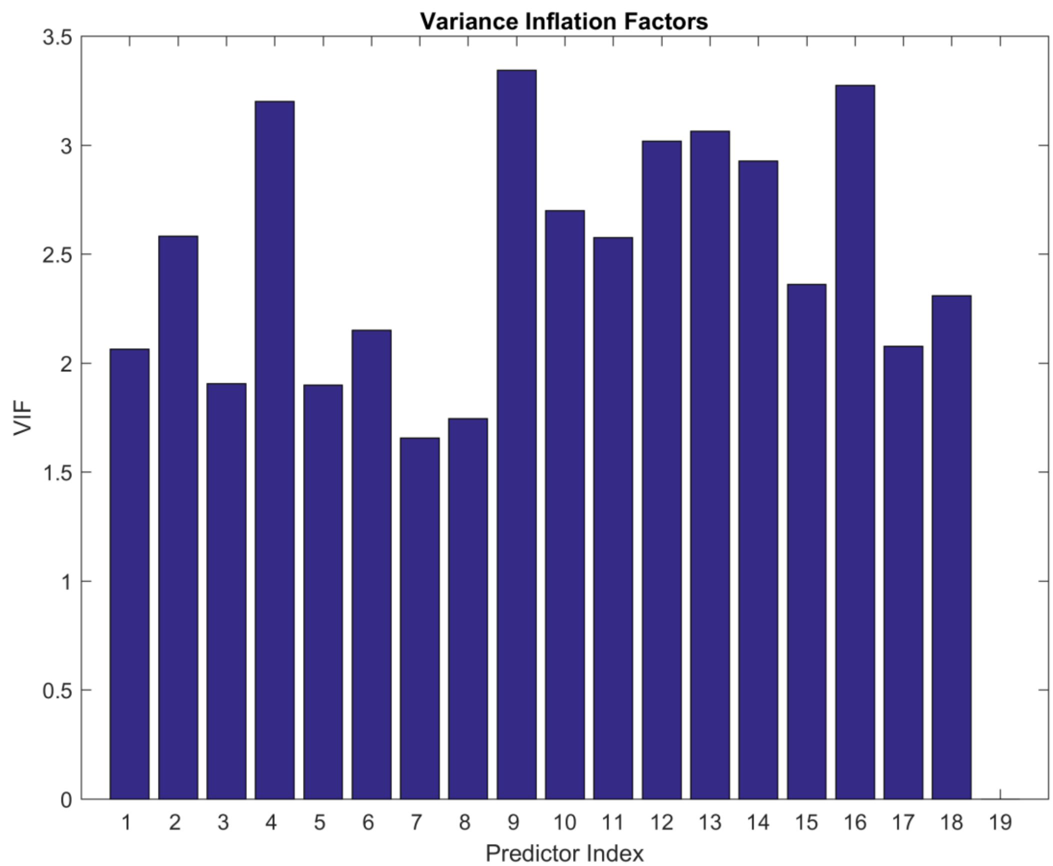

Figure 120. Variance inflation factors of 19 clustering coefficients for EEG network created with Pearson correlation of 0.2 as threshold and frequency range of 7-9 Hz.

The following table shows comparison of model classification performance.

	PCSSLR		LASSO		Logistic Regression	
	Training Set	Test Set	Training Set	Test Set	Training Set	Test Set
Median	0.9123	0.8447	0.9081	0.8592	0.9505	0.7947
Mean	0.9116	0.8384	0.9094	0.8568	0.9507	0.7875

7.3.6.1.5 Network Constructed Using Pearson's Correlation Cutoff: 0.3

7.3.6.1.5.1 Variance Inflation Factors (VIF)

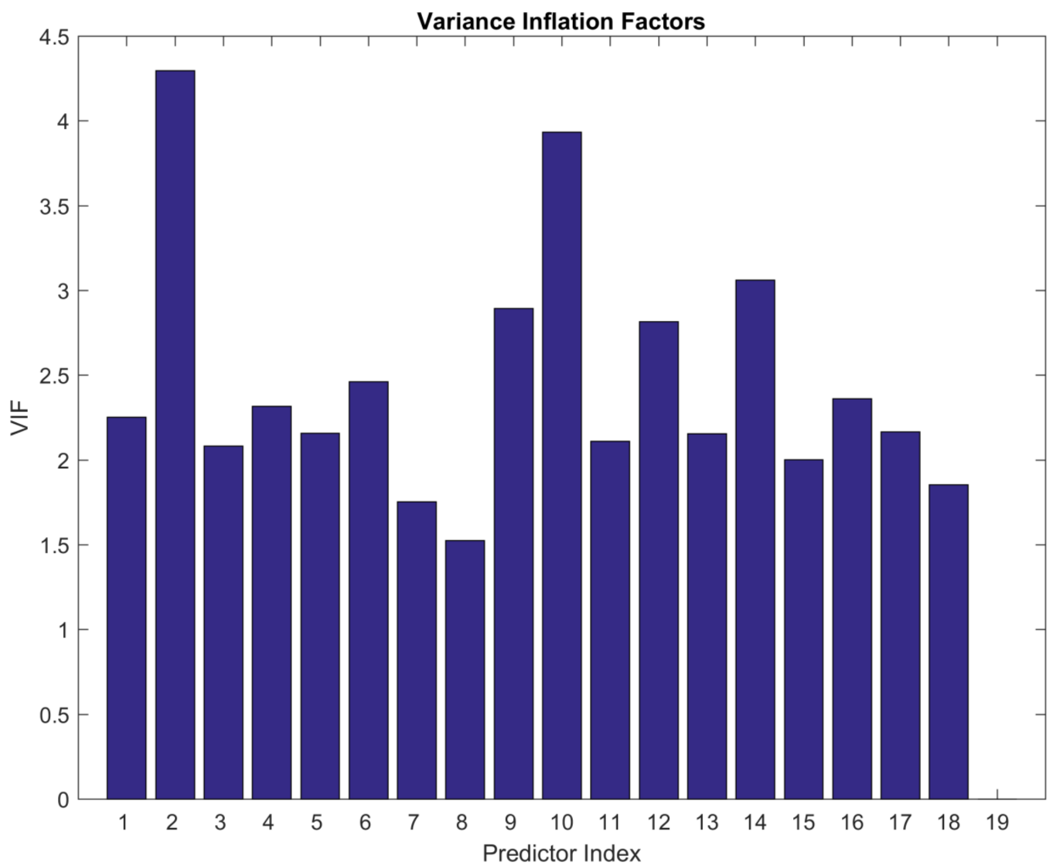

Figure 121. Variance inflation factors of 19 clustering coefficients for EEG network created with Pearson correlation of 0.3 as threshold and frequency range of 7-9 Hz.

The following table shows comparison of model classification performance.

	PCSSLR		LASSO		Logistic Regression	
	Training Set	Test Set	Training Set	Test Set	Training Set	Test Set
Median	0.9035	0.8105	0.8952	0.8178	0.9480	0.7961
Mean	0.9020	0.8025	0.8918	0.8070	0.9472	0.7911

7.3.6.1.6 Network Constructed Using Pearson's Correlation Cutoff: 0.4

7.3.6.1.6.1 Variance Inflation Factors (VIF)

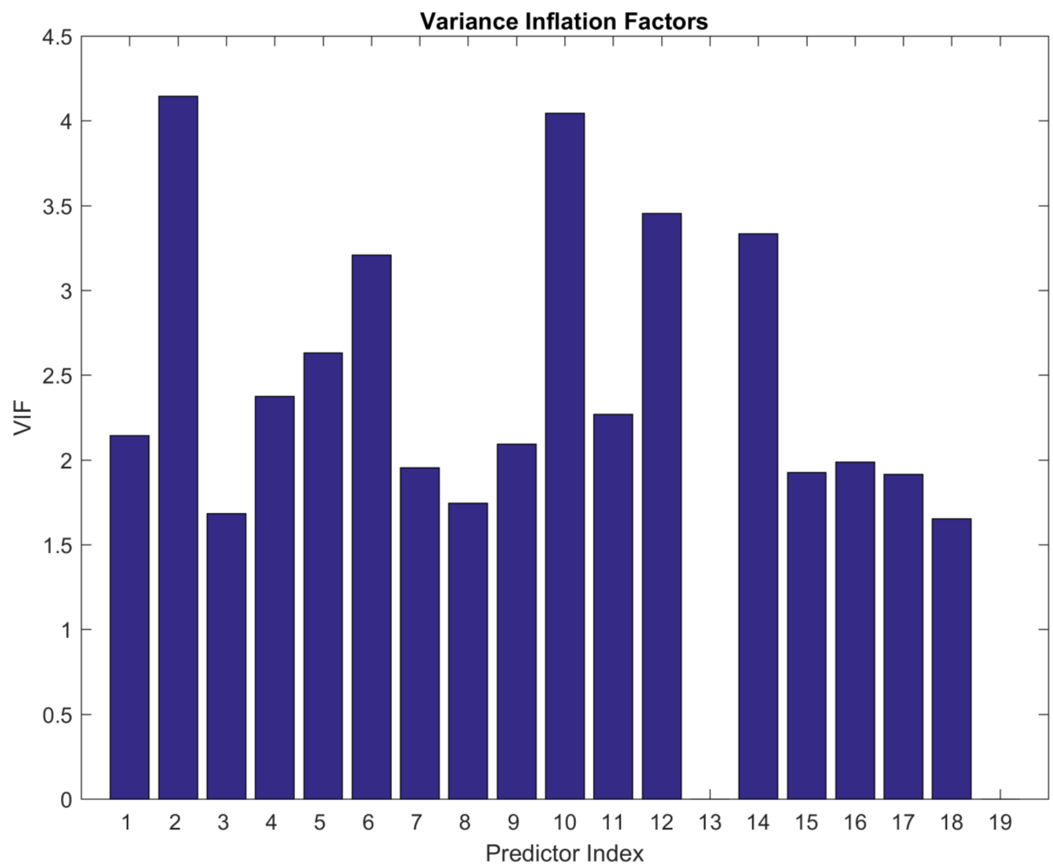

Figure 122. Variance inflation factors of 19 clustering coefficients for EEG network created with Pearson correlation of 0.4 as threshold and frequency range of 7-9 Hz.

The following table shows comparison of model classification performance.

	PCSSLR		**LASSO**		**Logistic Regression**	
	Training Set	Test Set	Training Set	Test Set	Training Set	Test Set
Median	0.8835	0.7842	0.8752	0.8026	0.9236	0.7961
Mean	0.8817	0.7800	0.8685	0.7887	0.9227	0.7896

7.3.6.1.7 Network Constructed Using Pearson's Correlation Cutoff: 0.5

7.3.6.1.7.1 Variance Inflation Factors (VIF)

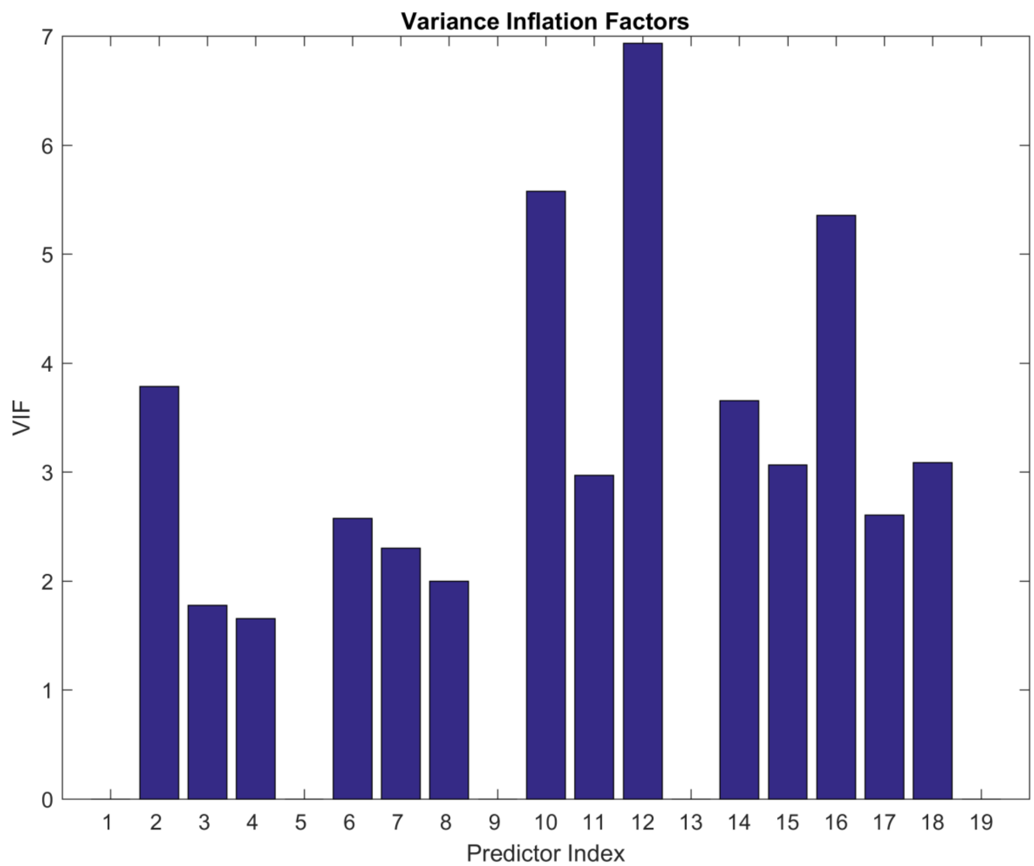

Figure 123. Variance inflation factors of 19 clustering coefficients for EEG network created with Pearson correlation of 0.5 as threshold and frequency range of 7-9 Hz.

The following table shows comparison of model classification performance.

	PCSSLR		LASSO		Logistic Regression	
	Training Set	Test Set	Training Set	Test Set	Training Set	Test Set
Median	0.7888	0.6737	0.7617	0.6684	0.8158	0.7132
Mean	0.7823	0.6679	0.6937	0.6425	0.8152	0.7088

7.3.6.1.8 Network Constructed Using Pearson's Correlation Cutoff: 0.6

7.3.6.1.8.1 Variance Inflation Factors (VIF)

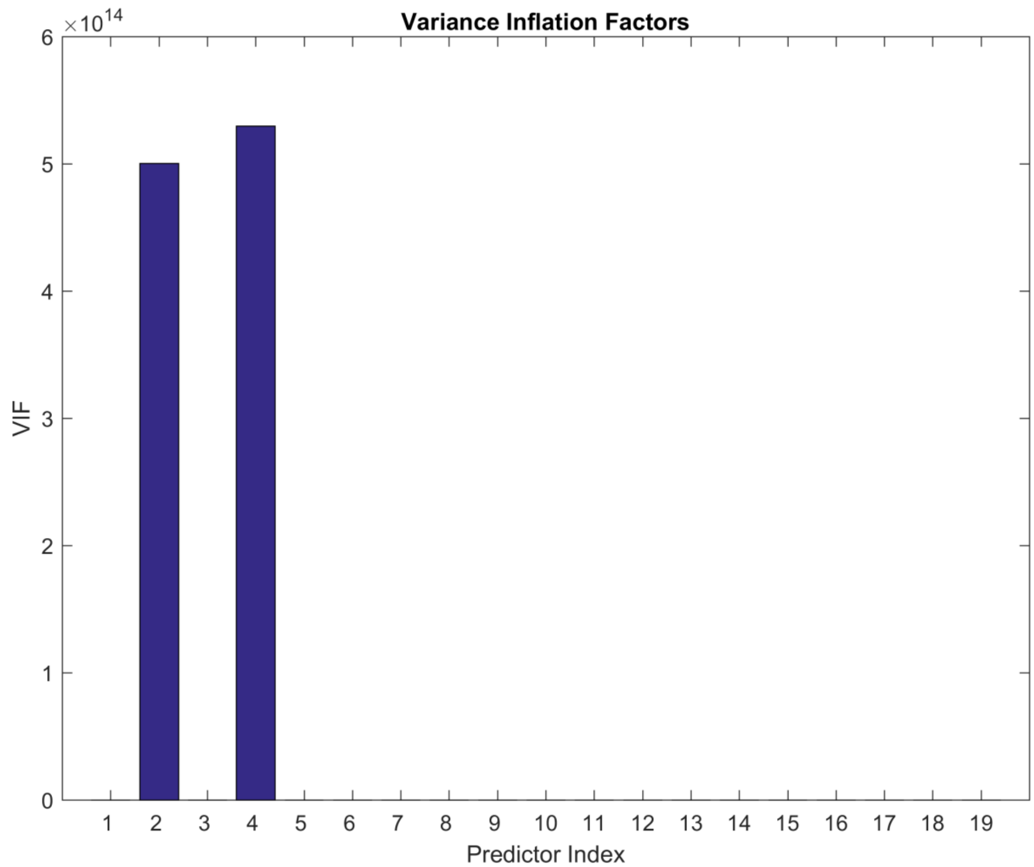

Figure 124. Variance inflation factors of 19 clustering coefficients for EEG network created with Pearson correlation of 0.6 as threshold and frequency range of 7-9 Hz.

The following table shows comparison of model classification performance.

	PCSSLR		LASSO		Logistic Regression	
	Training Set	Test Set	Training Set	Test Set	Training Set	Test Set
Median	0.5833	0.5263	0.5771	0.5263	0.6053	0.5474
Mean	0.5816	0.5384	0.5565	0.5321	0.6031	0.5391

7.3.6.1.9 Network Constructed Using Pearson's Correlation Cutoff: 0.7

7.3.6.1.9.1 Variance Inflation Factors (VIF)

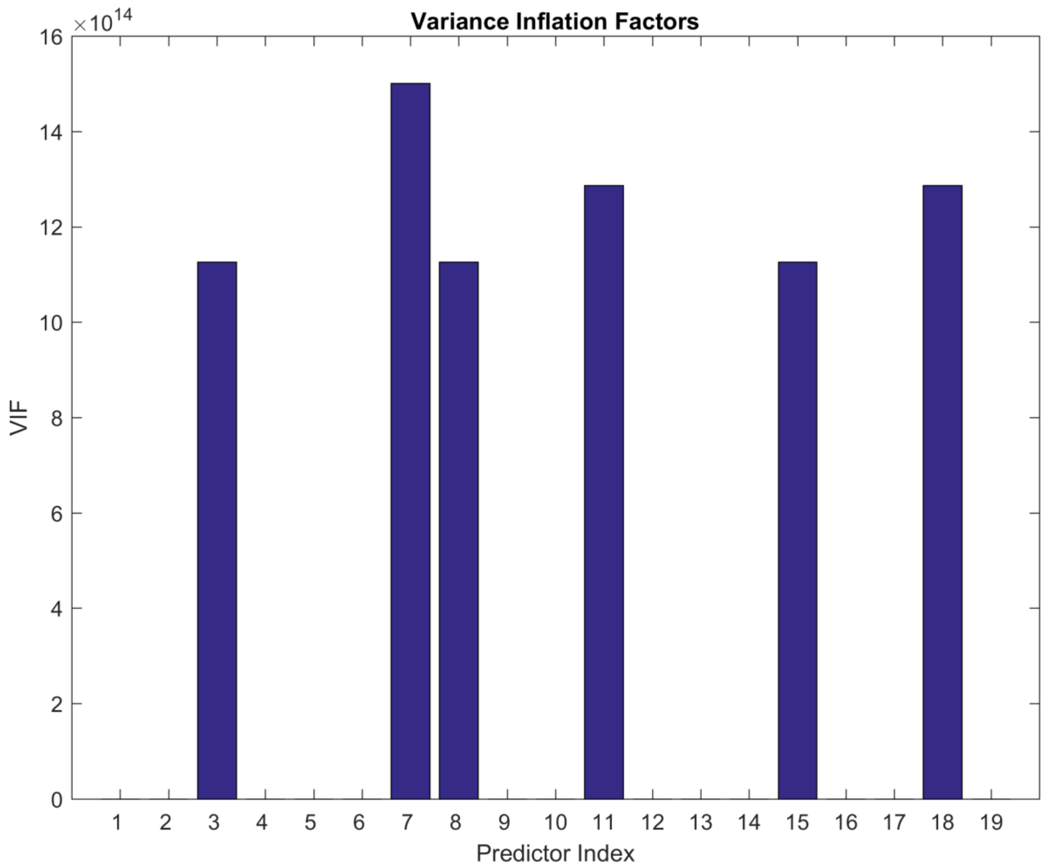

Figure 125. Variance inflation factors of 19 clustering coefficients for EEG network created with Pearson correlation of 0.7 as threshold and frequency range of 7-9 Hz.

The following table shows comparison of model classification performance.

	PCSSLR		**LASSO**		**Logistic Regression**	
	Training Set	Test Set	Training Set	Test Set	Training Set	Test Set
Median	0.5000	0.5000	0.5000	0.5000	0.5119	0.5000
Mean	0.5000	0.5000	0.5000	0.5000	0.5082	0.5000

7.3.6.1.10 Network Constructed Using Pearson's Correlation Cutoff: 0.8

7.3.6.1.10.1 Variance Inflation Factors (VIF)

All 19 predictor variables have VIF values exceed 10^{14}. The following table shows comparison of model classification performance.

	PCSSLR		LASSO		Logistic Regression	
	Training Set	Test Set	Training Set	Test Set	Training Set	Test Set
Median	0.5000	0.5000	0.5000	0.5000	0.5000	0.5000
Mean	0.5000	0.5000	0.5000	0.5000	0.5000	0.5000

7.3.6.1.11 Network Constructed Using Pearson's Correlation Cutoff: 0.9

All 19 predictor variables have VIF values exceed 10^{14}. The following table shows comparison of model classification performance.

	PCSSLR		LASSO		Logistic Regression	
	Training Set	Test Set	Training Set	Test Set	Training Set	Test Set
Median	0.5000	0.5000	0.5000	0.5000	0.5000	0.5000
Mean	0.5000	0.5000	0.5000	0.5000	0.5000	0.5000

7.3.6.1.12 Network Constructed Using Pearson's Correlation Cutoff: 1

All 19 predictor variables have VIF values exceed 10^{14}. The following table shows comparison of model classification performance.

	PCSSLR		LASSO		Logistic Regression	
	Training Set	Test Set	Training Set	Test Set	Training Set	Test Set
Median	0.5000	0.5000	0.5000	0.5000	0.5000	0.5000
Mean	0.5000	0.5000	0.5000	0.5000	0.5000	0.5000

7.3.6.2 Alpha Wave (11-13Hz)

The summary result of classification performance of LASSO, PCSSLR, and logistic regression in terms of ROC curve's AUC distribution for selected value of Pearson correlation coefficient used as thresholds to construct undirected EEG/brain network based on channel data for 11-13 Hz frequency range is shown in Figure 126 for training and Figure 127 for test sets. The VIFs of the clustering coefficient covariates are shown in Figure 128 to Figure 132.

7.3.6.2.1 AUC Comparison of Models – Training Sets

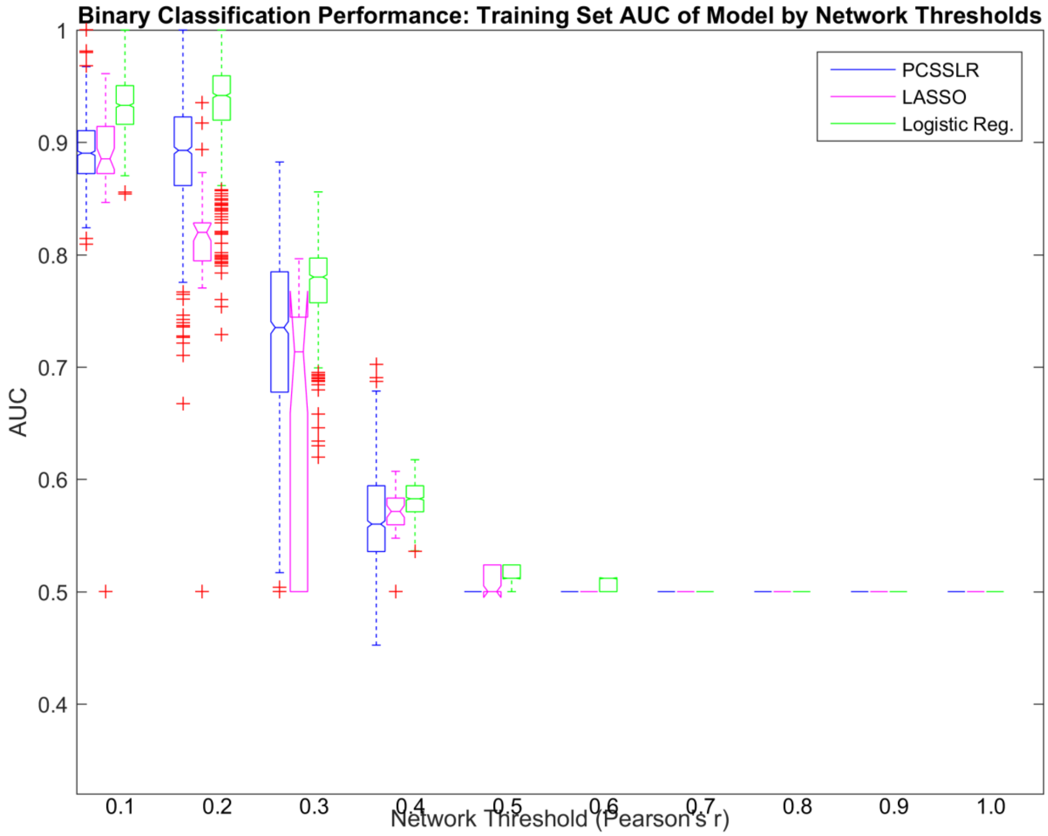

Figure 126. Training set DBS-on vs. DBS-off classification performance of PCSSLR, LASSO and logistic regression over range of Pearson correlations used to construct EEG network for frequency of 11-13 Hz.

7.3.6.2.2 AUC Comparison of Models – Test Sets

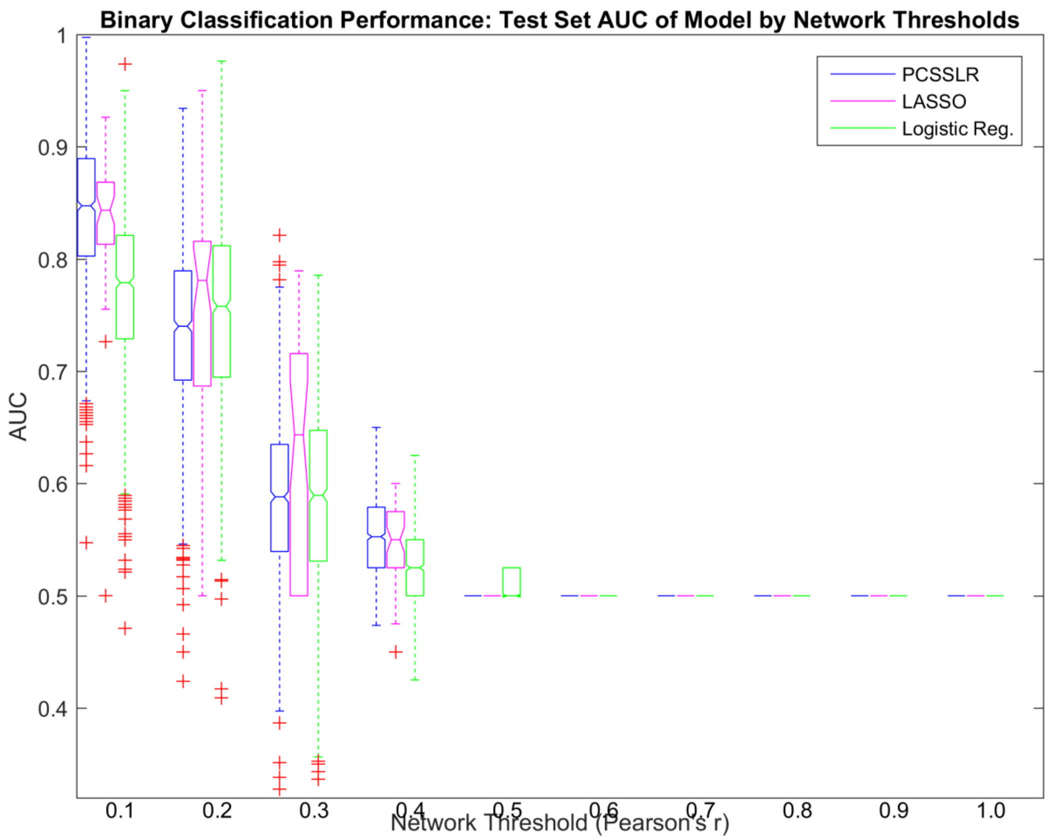

Figure 127. Test set DBS-on vs. DBS-off classification performance of PCSSLR, LASSO and logistic regression over range of Pearson correlations used to construct EEG network for frequency of 11-13 Hz.

7.3.6.2.3 11-13 Hz, AUC and Network Constructed Using Pearson's Correlation Cutoff: 0.1

7.3.6.2.3.1 Variance Inflation Factors (VIF)

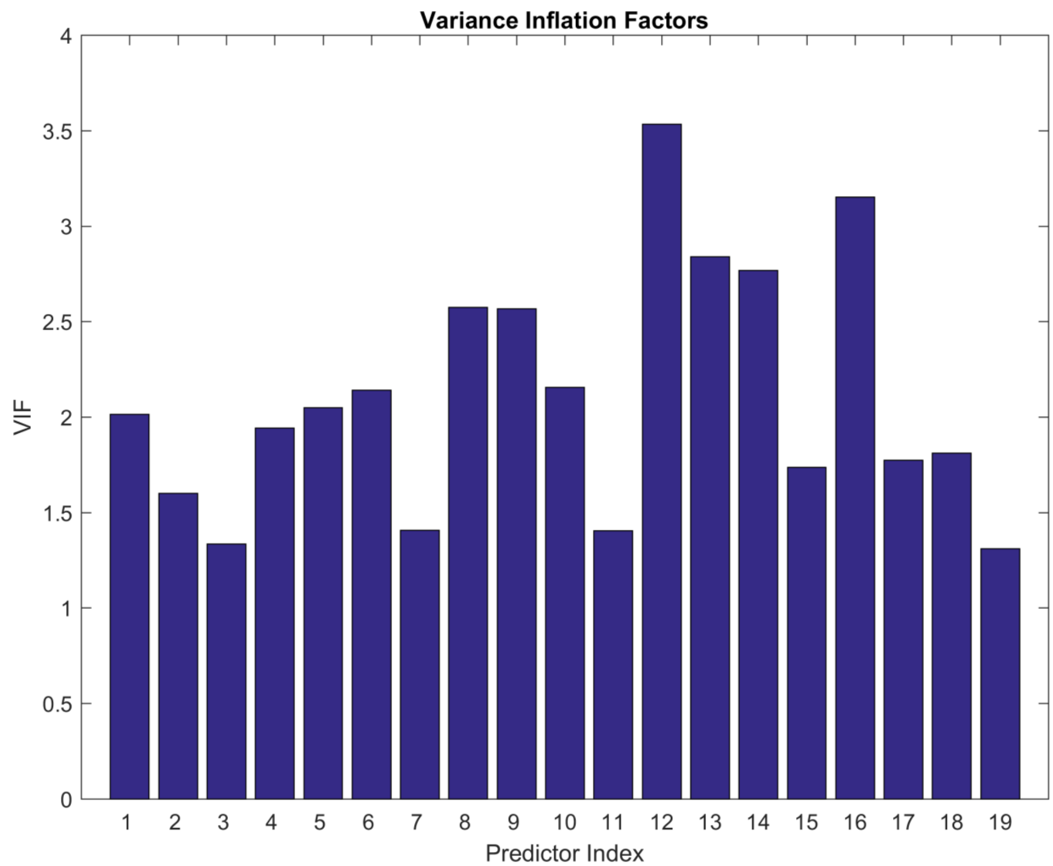

Figure 128. Variance inflation factors of 19 clustering coefficients for EEG network created with Pearson correlation of 0.1 as threshold and frequency range of 11-13 Hz.

The following table shows comparison of model classification performance.

	PCSSLR		**LASSO**		**Logistic Regression**	
	Training Set	Test Set	Training Set	Test Set	Training Set	Test Set
Median	0.8904	0.8474	0.8853	0.8434	0.9330	0.7789
Mean	0.8921	0.8446	0.8765	0.8273	0.9341	0.7703

7.3.6.2.4 Network Constructed Using Pearson's Correlation Cutoff: 0.2

7.3.6.2.4.1 Variance Inflation Factors (VIF)

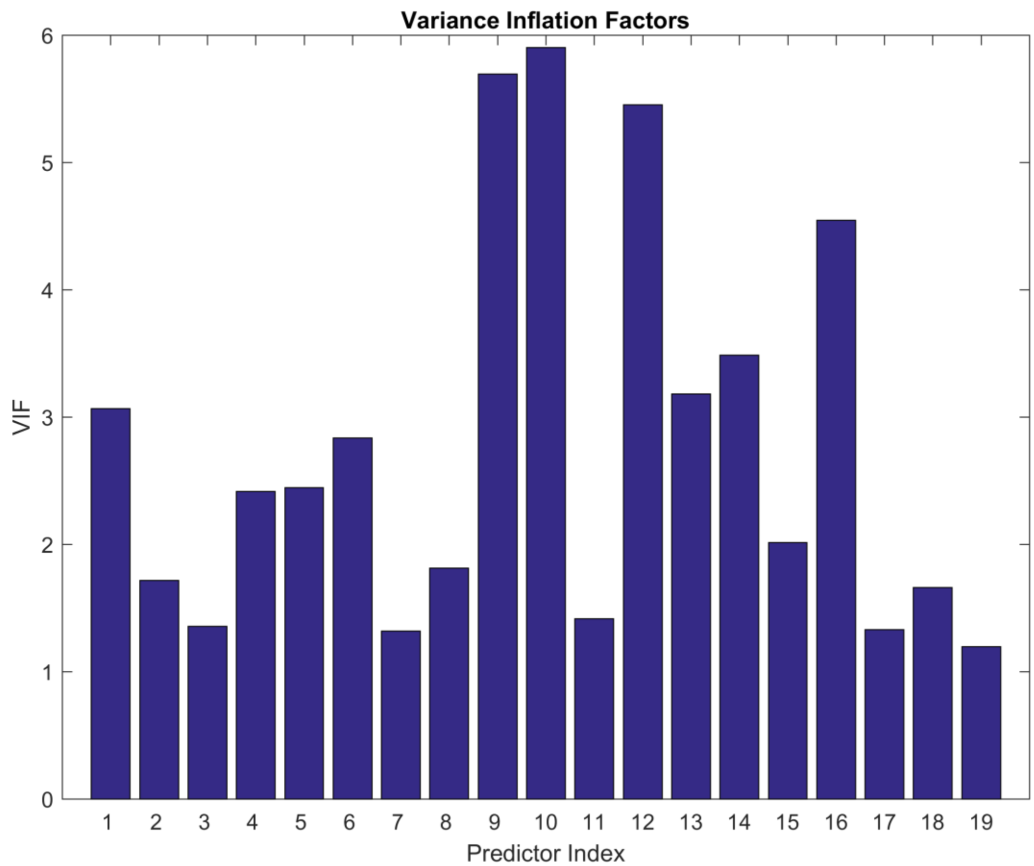

Figure 129. Variance inflation factors of 19 clustering coefficients for EEG network created with Pearson correlation of 0.2 as threshold and frequency range of 11-13 Hz.

The following table shows comparison of model classification performance.

	PCSSLR		**LASSO**		**Logistic Regression**	
	Training Set	Test Set	Training Set	Test Set	Training Set	Test Set
Median	0.8929	0.7401	0.8199	0.7809	0.9417	0.7579
Mean	0.8889	0.7374	0.7799	0.7424	0.9365	0.7520

7.3.6.2.5 Network Constructed Using Pearson's Correlation Cutoff: 0.3

7.3.6.2.5.1 Variance Inflation Factors (VIF)

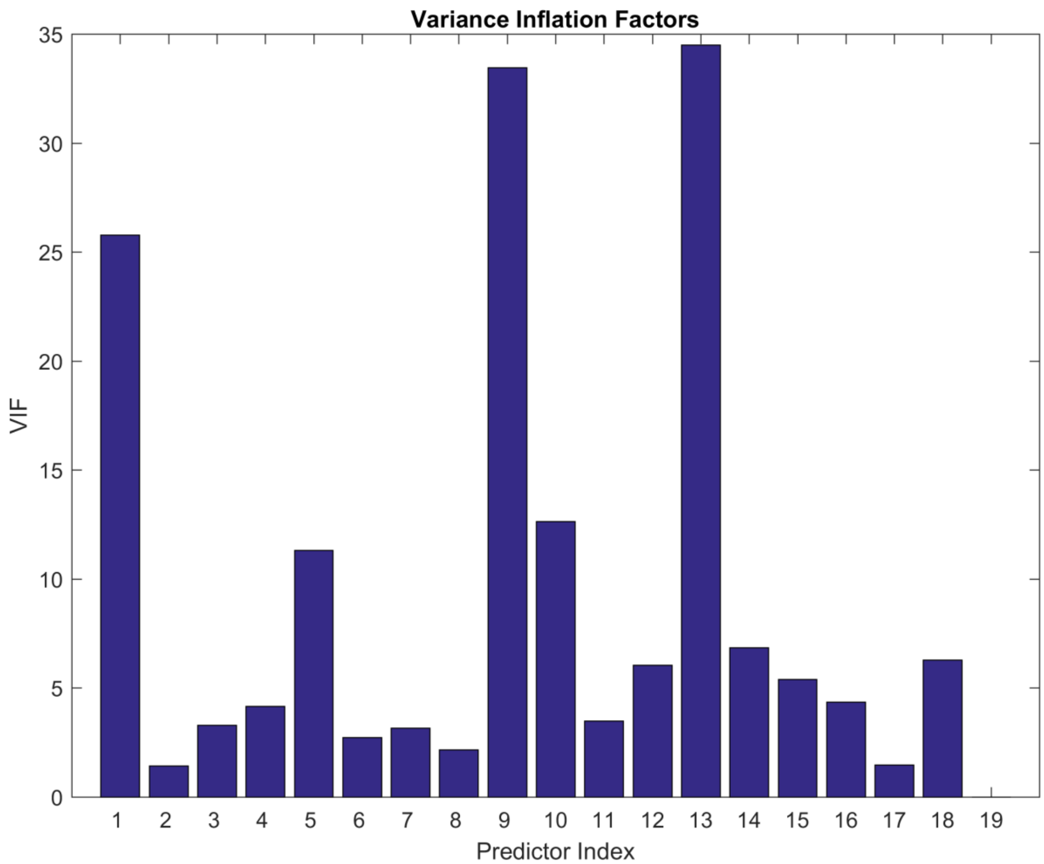

Figure 130. Variance inflation factors of 19 clustering coefficients for EEG network created with Pearson correlation of 0.3 as threshold and frequency range of 11-13 Hz.

The following table shows comparison of model classification performance.

	PCSSLR		LASSO		Logistic Regression	
	Training Set	Test Set	Training Set	Test Set	Training Set	Test Set
Median	0.7351	0.5882	0.7135	0.6434	0.7801	0.5895
Mean	0.7242	0.5864	0.6657	0.6282	0.7760	0.5858

7.3.6.2.6 Network Constructed Using Pearson's Correlation Cutoff: 0.4)

7.3.6.2.6.1 Variance Inflation Factors (VIF)

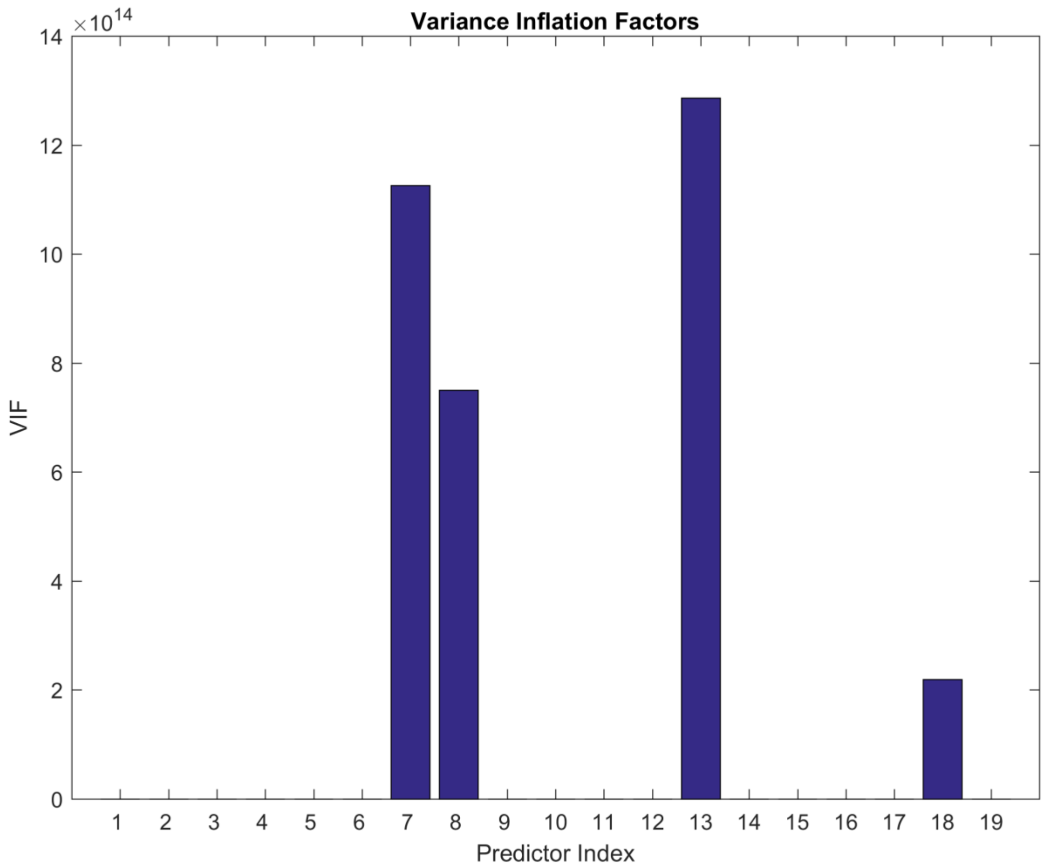

Figure 131. Variance inflation factors of 19 clustering coefficients for EEG network created with Pearson correlation of 0.4 as threshold and frequency range of 11-13 Hz.

The following table shows comparison of model classification performance.

	PCSSLR		**LASSO**		**Logistic Regression**	
	Training Set	Test Set	Training Set	Test Set	Training Set	Test Set
Median	0.5602	0.5526	0.5714	0.5500	0.5827	0.5250
Mean	0.5628	0.5564	0.5634	0.5396	0.5798	0.5322

7.3.6.2.7 Network Constructed Using Pearson's Correlation Cutoff: 0.5)

7.3.6.2.7.1 Variance Inflation Factors (VIF)

All 19 predictor variables have VIF values exceed 10^{14}. The following table shows comparison of model classification performance.

	PCSSLR		**LASSO**		**Logistic Regression**	
	Training Set	Test Set	Training Set	Test Set	Training Set	Test Set
Median	0.5000	0.5000	0.5000	0.5000	0.5119	0.5000
Mean	0.5000	0.5000	0.5095	0.5000	0.5161	0.5113

7.3.6.2.8 Network Constructed Using Pearson's Correlation Cutoff: 0.6

7.3.6.2.8.1 Variance Inflation Factors (VIF)

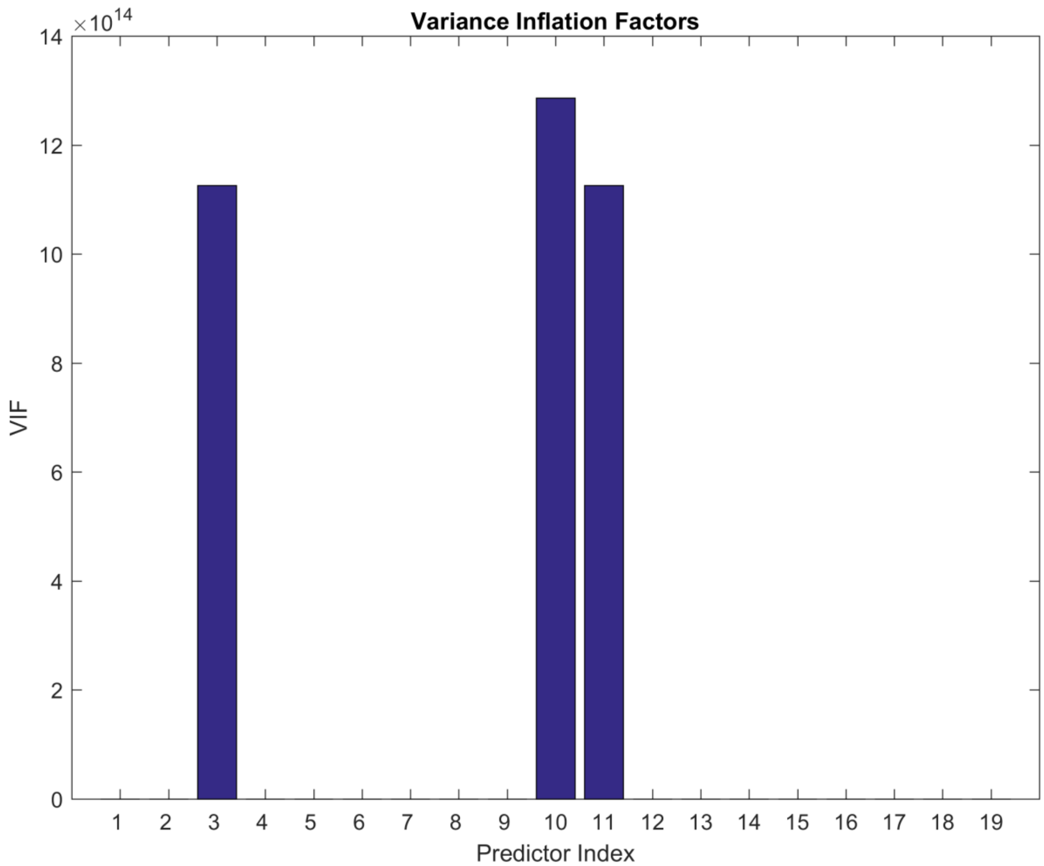

Figure 132. Variance inflation factors of 19 clustering coefficients for EEG network created with Pearson correlation of 0.6 as threshold and frequency range of 11-13 Hz.

The following table shows comparison of model classification performance.

	PCSSLR		LASSO		Logistic Regression	
	Training Set	Test Set	Training Set	Test Set	Training Set	Test Set
Median	0.5000	0.5000	0.5000	0.5000	0.5119	0.5000
Mean	0.5000	0.5000	0.5000	0.5000	0.5082	0.5000

7.3.6.2.9 Network Constructed Using Pearson's Correlation Cutoff: 0.7

7.3.6.2.9.1 Variance Inflation Factors (VIF)

All 19 predictor variables have VIF values exceed 10^{14}. The following table shows comparison of model classification performance.

	PCSSLR		**LASSO**		**Logistic Regression**	
	Training Set	Test Set	Training Set	Test Set	Training Set	Test Set
Median	0.5000	0.5000	0.5000	0.5000	0.5000	0.5000
Mean	0.5000	0.5000	0.5000	0.5000	0.5000	0.5000

7.3.6.2.10 11-13Hz Network (Pearson's Correlation Cutoff: 0.8)

7.3.6.2.10.1 Variance Inflation Factors (VIF)

All 19 predictor variables have VIF values exceed 10^{14}. The following table shows comparison of model classification performance.

	PCSSLR		**LASSO**		**Logistic Regression**	
	Training Set	Test Set	Training Set	Test Set	Training Set	Test Set
Median	0.5000	0.5000	0.5000	0.5000	0.5000	0.5000
Mean	0.5000	0.5000	0.5000	0.5000	0.5000	0.5000

7.3.6.2.11 11-13Hz Network (Pearson's Correlation Cutoff: 0.9)

7.3.6.2.11.1 Variance Inflation Factors (VIF)

All 19 predictor variables have VIF values exceed 10^{14}. The following table shows comparison of model classification performance.

	PCSSLR		**LASSO**		**Logistic Regression**	
	Training Set	Test Set	Training Set	Test Set	Training Set	Test Set
Median	0.5000	0.5000	0.5000	0.5000	0.5000	0.5000
Mean	0.5000	0.5000	0.5000	0.5000	0.5000	0.5000

7.3.6.2.12 11-13Hz Network (Pearson's Correlation Cutoff: 1)

7.3.6.2.12.1 Variance Inflation Factors (VIF)

All 19 predictor variables have VIF values exceed 10^{14}. The following table shows comparison of model classification performance.

	PCSSLR		**LASSO**		**Logistic Regression**	
	Training Set	Test Set	Training Set	Test Set	Training Set	Test Set
Median	0.5000	0.5000	0.5000	0.5000	0.5000	0.5000
Mean	0.5000	0.5000	0.5000	0.5000	0.5000	0.5000

7.3.6.3 Beta Wave (13-19Hz)

The summary result of classification performance of LASSO, PCSSLR, and logistic regression in terms of ROC curve's AUC distribution for selected value of Pearson correlation coefficient used as thresholds to construct undirected EEG/brain network based on channel data for 13-19 Hz frequency range is shown in Figure 133 for training sets and Figure 134 for test sets. The VIFs of the clustering coefficient covariates are shown in Figure 135 to Figure 140.

7.3.6.3.1 AUC Comparison of Models – Training Sets

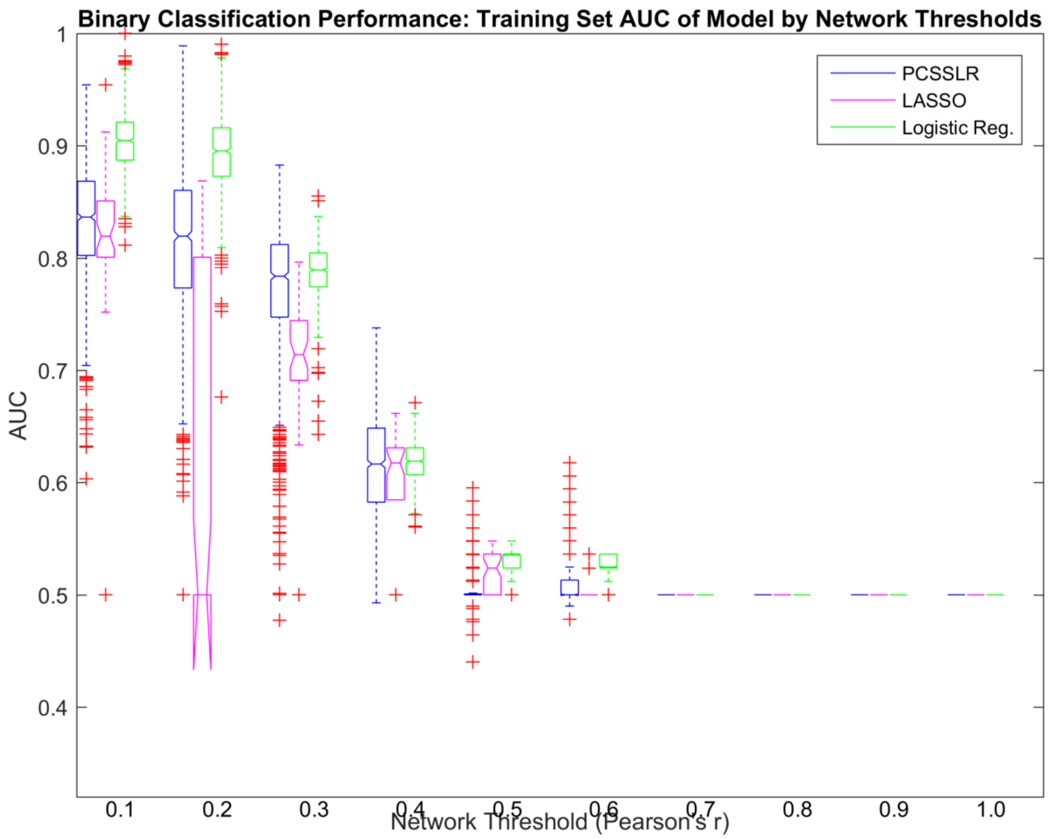

Figure 133. Training set DBS-on vs. DBS-off classification performance of PCSSLR, LASSO and logistic regression over range of Pearson correlations used to construct EEG network for frequency of 13-19 Hz.

7.3.6.3.2 AUC Comparison of Models – Test Sets

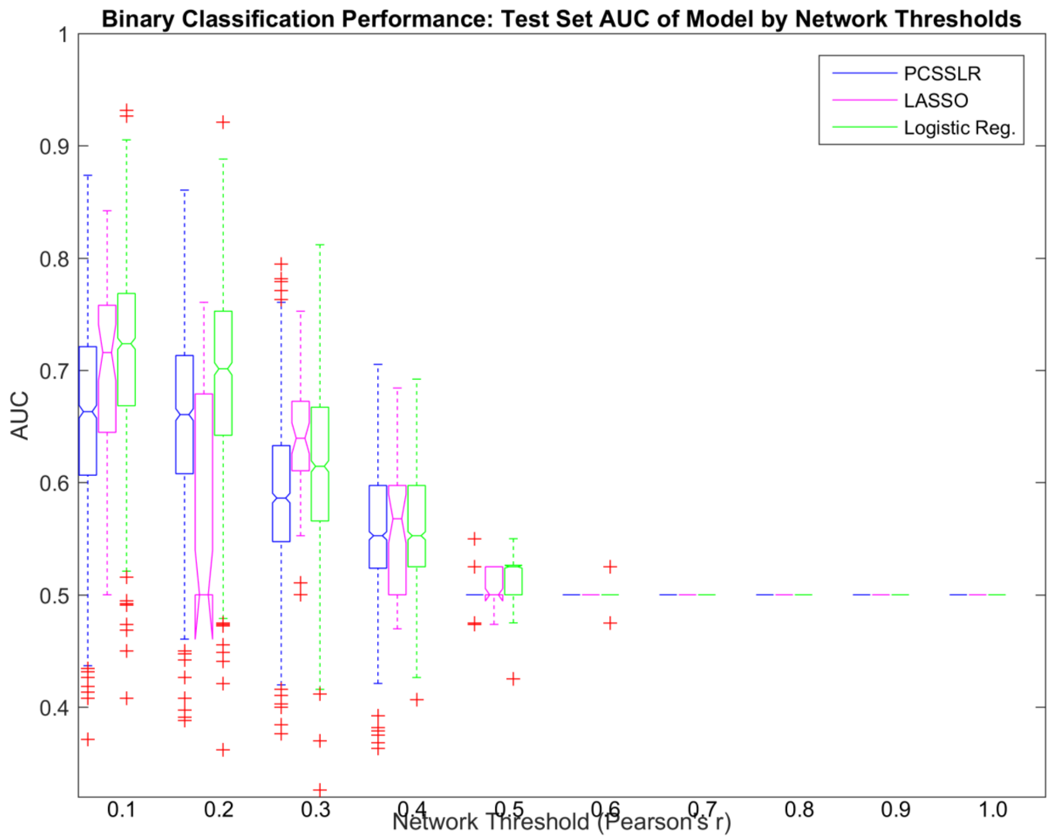

Figure 134. Test set DBS-on vs. DBS-off classification performance of PCSSLR, LASSO and logistic regression over range of Pearson correlations used to construct EEG network for frequency of 13-19 Hz.

7.3.6.3.3 Network Constructed Using Pearson's Correlation Cutoff: 0.1

7.3.6.3.3.1 Variance Inflation Factors (VIF)

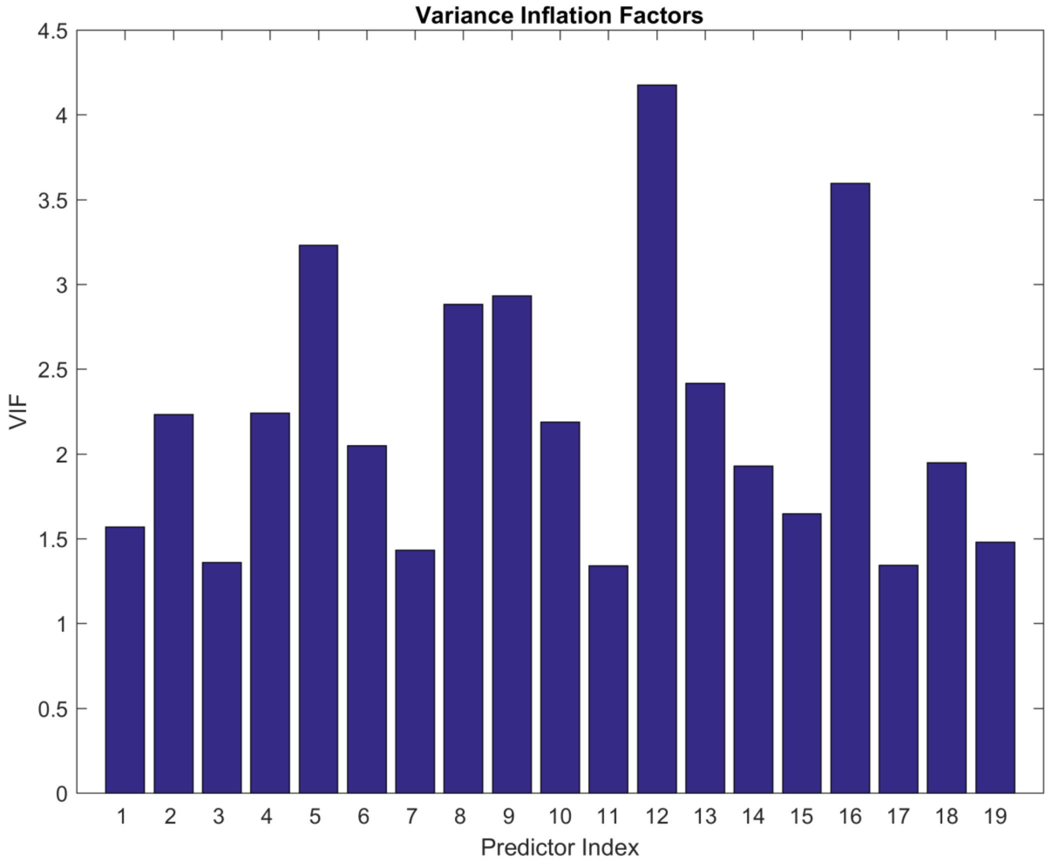

Figure 135. Variance inflation factors of 19 clustering coefficients for EEG network created with Pearson correlation of 0.1 as threshold and frequency range of 13-19 Hz.

The following table shows comparison of model classification performance.

	PCSSLR		LASSO		Logistic Regression	
	Training Set	Test Set	Training Set	Test Set	Training Set	Test Set
Median	0.8365	0.6632	0.8195	0.7158	0.9048	0.7237
Mean	0.8327	0.6600	0.8110	0.6996	0.9046	0.7163

7.3.6.3.4 Network Constructed Using Pearson's Correlation Cutoff: 0.2

7.3.6.3.4.1 Variance Inflation Factors (VIF)

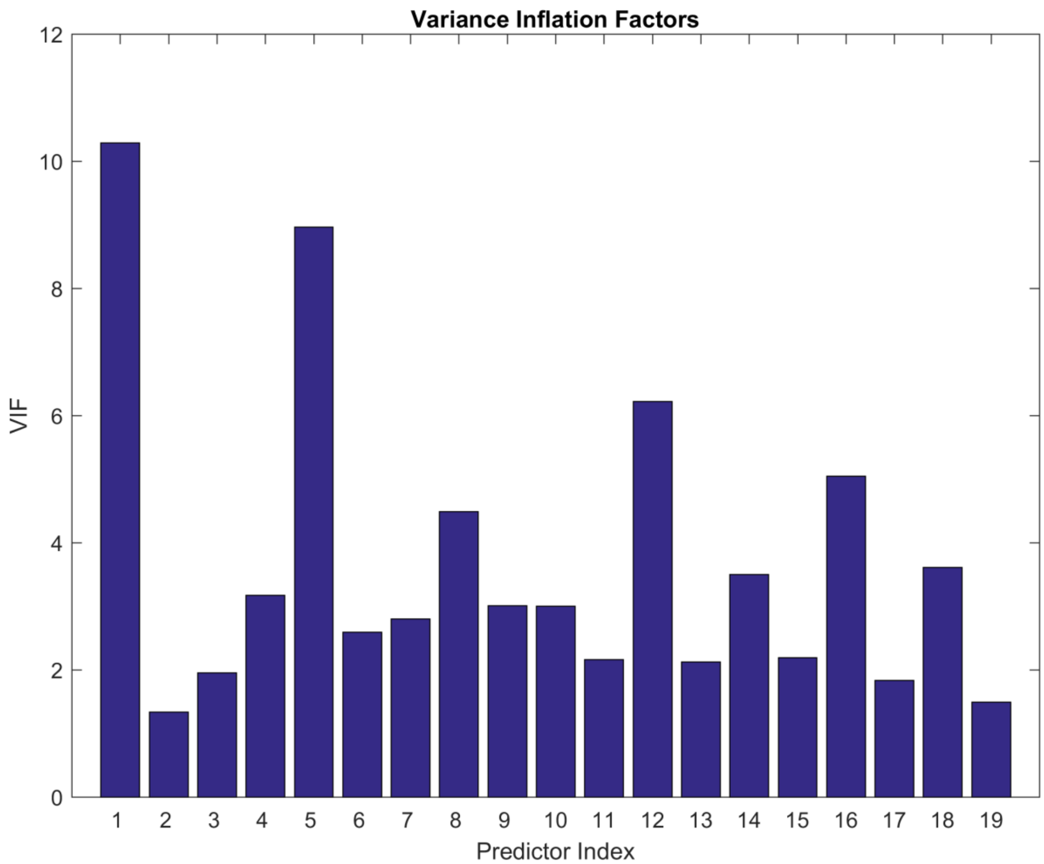

Figure 136. Variance inflation factors of 19 clustering coefficients for EEG network created with Pearson correlation of 0.2 as threshold and frequency range of 13-19 Hz.

The following table shows comparison of model classification performance.

	PCSSLR		LASSO		Logistic Regression	
	Training Set	Test Set	Training Set	Test Set	Training Set	Test Set
Median	0.8195	0.6605	0.5000	0.5000	0.8954	0.7013
Mean	0.8133	0.6577	0.6340	0.5767	0.8945	0.6944

7.3.6.3.5 Network Constructed Using Pearson's Correlation Cutoff: 0.3

7.3.6.3.5.1 Variance Inflation Factors (VIF)

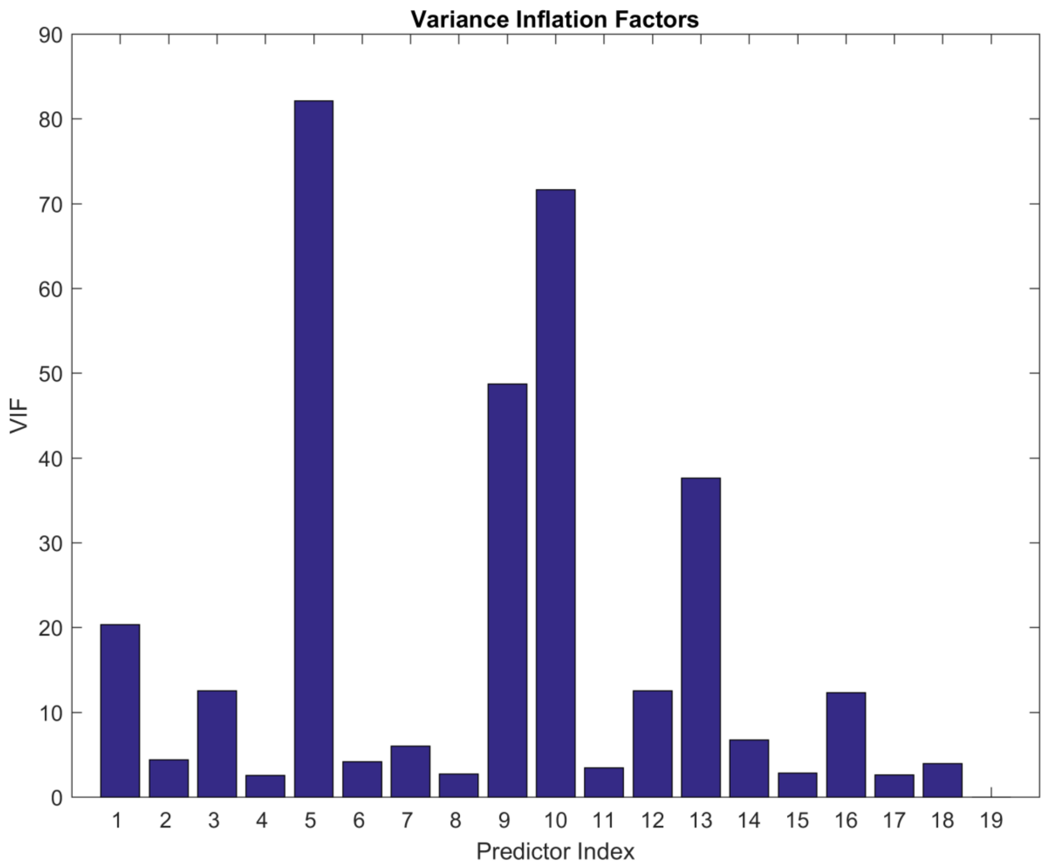

Figure 137. Variance inflation factors of 19 clustering coefficients for EEG network created with Pearson correlation of 0.3 as threshold and frequency range of 13-19 Hz.

The following table shows comparison of model classification performance.

	PCSSLR		LASSO		Logistic Regression	
	Training Set	Test Set	Training Set	Test Set	Training Set	Test Set
Median	0.7838	0.5862	0.7140	0.6395	0.7895	0.6145
Mean	0.7642	0.5899	0.7104	0.6394	0.7890	0.6131

7.3.6.3.6 Network Constructed Using Pearson's Correlation Cutoff: 0.4

7.3.6.3.6.1 Variance Inflation Factors (VIF)

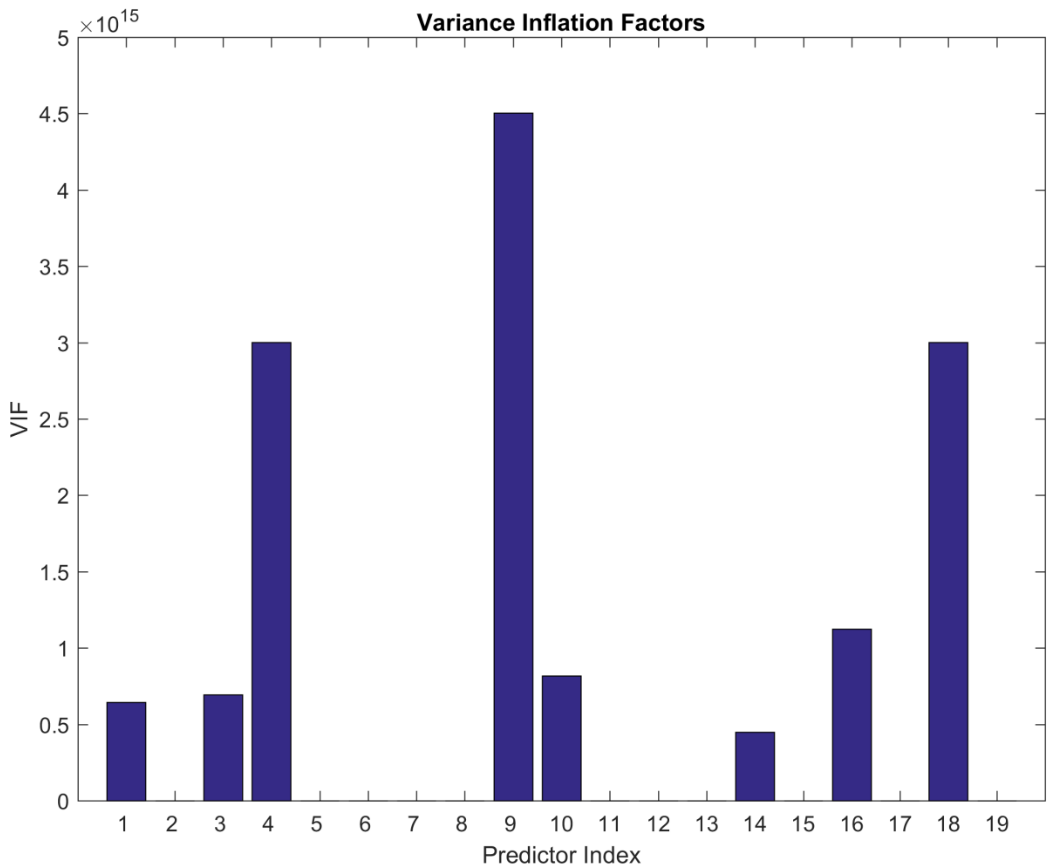

Figure 138. Variance inflation factors of 19 clustering coefficients for EEG network created with Pearson correlation of 0.4 as threshold and frequency range of 13-19 Hz.

The following table shows comparison of model classification performance.

	PCSSLR		LASSO		Logistic Regression	
	Training Set	Test Set	Training Set	Test Set	Training Set	Test Set
Median	0.6165	0.5526	0.6175	0.5678	0.6190	0.5526
Mean	0.6083	0.5585	0.5946	0.5584	0.6200	0.5592

7.3.6.3.7 Network Constructed Using Pearson's Correlation Cutoff: 0.5

7.3.6.3.7.1 Variance Inflation Factors (VIF)

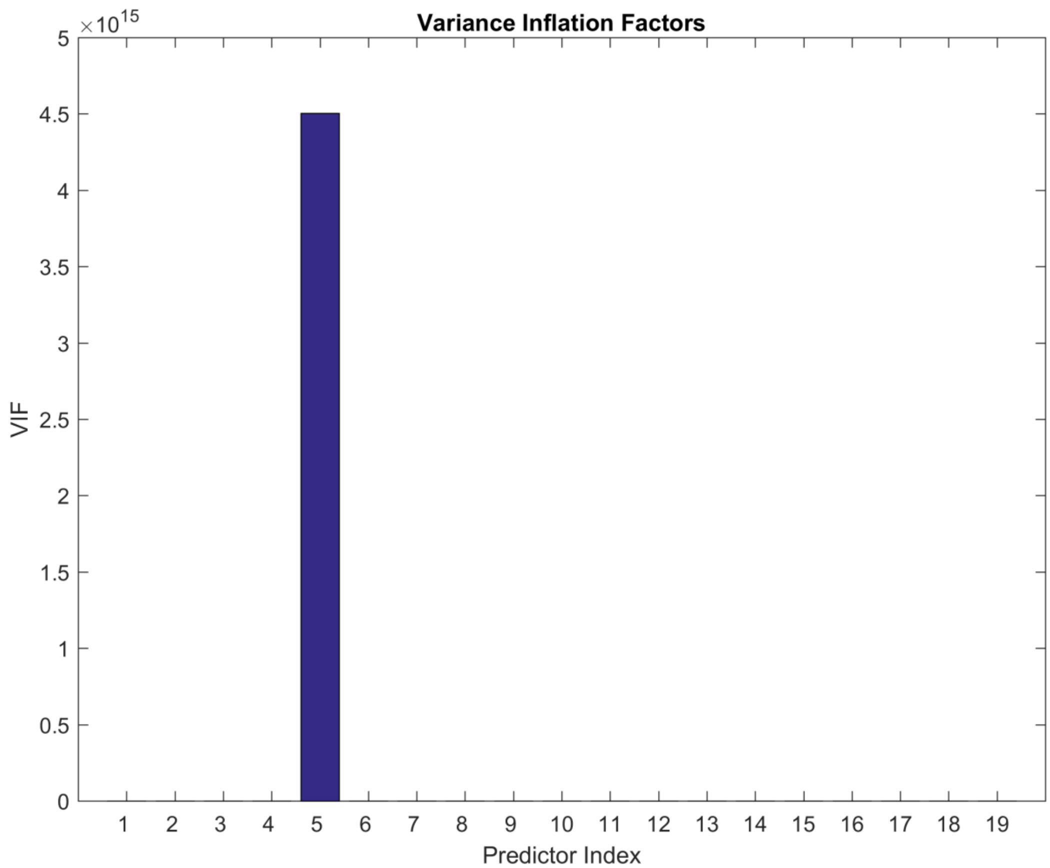

Figure 139. Variance inflation factors of 19 clustering coefficients for EEG network created with Pearson correlation of 0.5 as threshold and frequency range of 13-19 Hz.

The following table shows comparison of model classification performance.

	PCSSLR		**LASSO**		**Logistic Regression**	
	Training Set	Test Set	Training Set	Test Set	Training Set	Test Set
Median	0.5000	0.5000	0.5238	0.5000	0.5357	0.5250
Mean	0.5082	0.4969	0.5194	0.5048	0.5319	0.5183

7.3.6.3.8 Network Constructed Using Pearson's Correlation Cutoff: 0.6

7.3.6.3.8.1 Variance Inflation Factors (VIF)

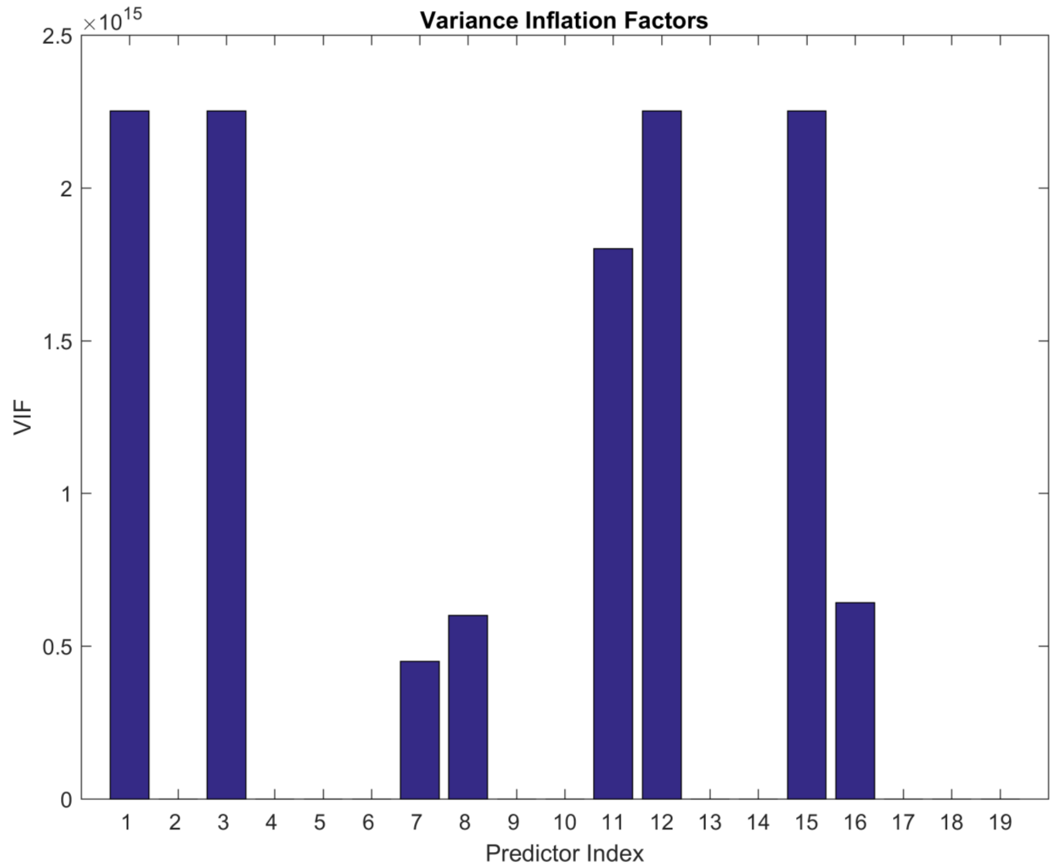

Figure 140. Variance inflation factors of 19 clustering coefficients for EEG network created with Pearson correlation of 0.6 as threshold and frequency range of 13-19 Hz.

The following table shows comparison of model classification performance.

	PCSSLR		LASSO		Logistic Regression	
	Training Set	Test Set	Training Set	Test Set	Training Set	Test Set
Median	0.5000	0.5000	0.5000	0.5000	0.5247	0.5000
Mean	0.5098	0.5000	0.5012	0.5000	0.5249	0.5038

7.3.6.3.9 Network Constructed Using Pearson's Correlation Cutoff: 0.7

7.3.6.3.9.1 Variance Inflation Factors (VIF)

All 19 predictor variables have VIF values exceed 10^{14}. The following table shows comparison of model classification performance.

	PCSSLR		**LASSO**		**Logistic Regression**	
	Training Set	Test Set	Training Set	Test Set	Training Set	Test Set
Median	0.5000	0.5000	0.5000	0.5000	0.5000	0.5000
Mean	0.5000	0.5000	0.5000	0.5000	0.5000	0.5000

7.3.6.3.10 Network Constructed Using Pearson's Correlation Cutoff: 0.8

All 19 predictor variables have VIF values exceed 10^{14}. The following table shows comparison of model classification performance.

	PCSSLR		**LASSO**		**Logistic Regression**	
	Training Set	Test Set	Training Set	Test Set	Training Set	Test Set
Median	0.5000	0.5000	0.5000	0.5000	0.5000	0.5000
Mean	0.5000	0.5000	0.5000	0.5000	0.5000	0.5000

7.3.6.3.11 Network Constructed Using Pearson's Correlation Cutoff: 0.9

All 19 predictor variables have VIF values exceed 10^{14}. The following table shows comparison of model classification performance.

	PCSSLR		**LASSO**		**Logistic Regression**	
	Training Set	Test Set	Training Set	Test Set	Training Set	Test Set
Median	0.5000	0.5000	0.5000	0.5000	0.5000	0.5000
Mean	0.5000	0.5000	0.5000	0.5000	0.5000	0.5000

7.3.6.3.12 Network Constructed Using Pearson's Correlation Cutoff: 1

All 19 predictor variables have VIF values exceed 10^{14}. The following table shows comparison of model classification performance.

	PCSSLR		LASSO		Logistic Regression	
	Training Set	Test Set	Training Set	Test Set	Training Set	Test Set
Median	0.5000	0.5000	0.5000	0.5000	0.5000	0.5000
Mean	0.5000	0.5000	0.5000	0.5000	0.5000	0.5000

7.3.6.4 Beta Wave (21-29Hz)

The summary result of classification performance of LASSO, PCSSLR, and logistic regression in terms of ROC curve's AUC distribution for selected value of Pearson correlation coefficient used as thresholds to construct undirected EEG/brain network based on channel data for 21-29 Hz frequency range is shown in Figure 141 for training sets and Figure 142 for test sets. The VIFs of the clustering coefficient covariates are shown in Figure 143 to Figure 149.

7.3.6.4.1 AUC Comparison of Models – Training Sets

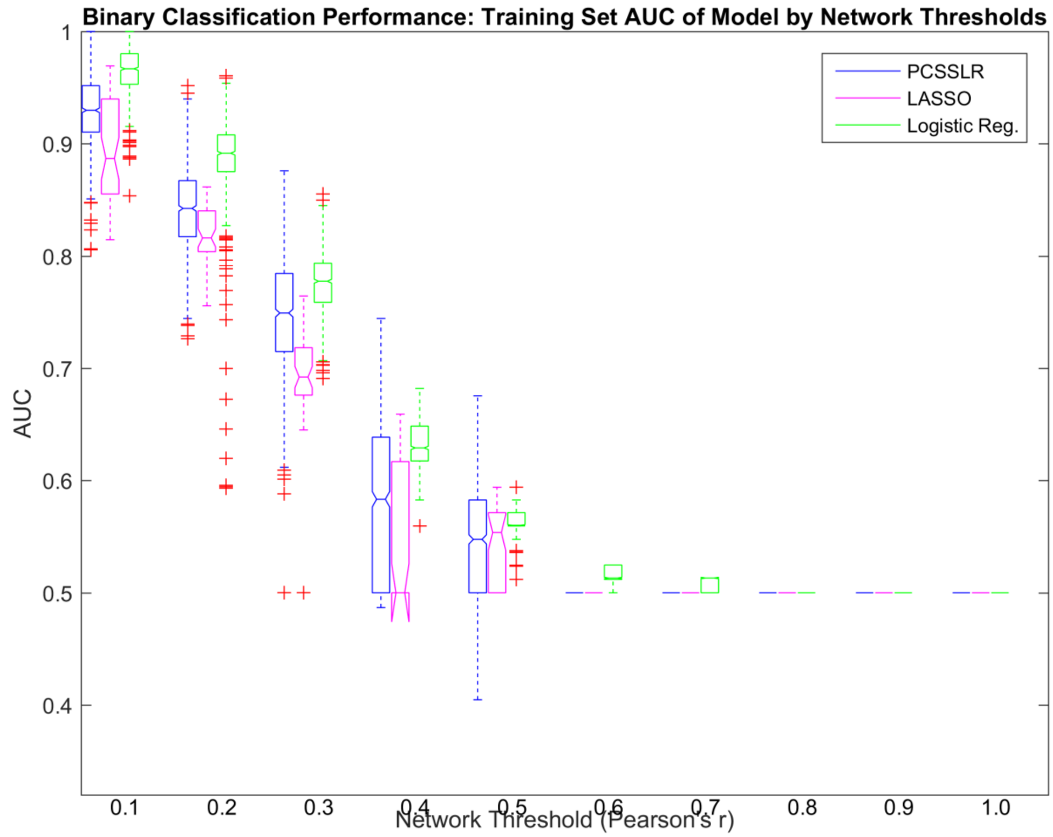

Figure 141. Training set DBS-on vs. DBS-off classification performance of PCSSLR, LASSO and logistic regression over range of Pearson correlations used to construct EEG network for frequency of 21-29 Hz.

7.3.6.4.2 AUC Comparison of Models – Test Sets

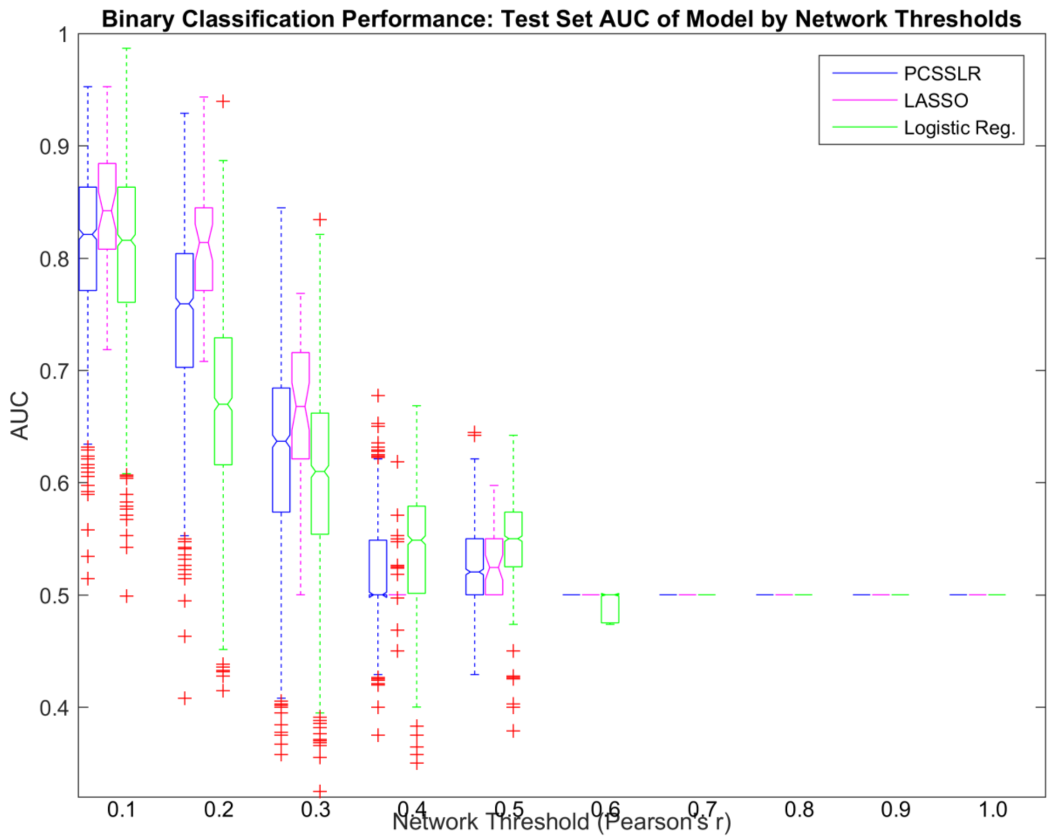

Figure 142. Test set DBS-on vs. DBS-off classification performance of PCSSLR, LASSO and logistic regression over range of Pearson correlations used to construct EEG network for frequency of 21-29 Hz.

7.3.6.4.3 Network Constructed Using Pearson's Correlation Cutoff: 0.1

7.3.6.4.3.1 Variance Inflation Factors (VIF)

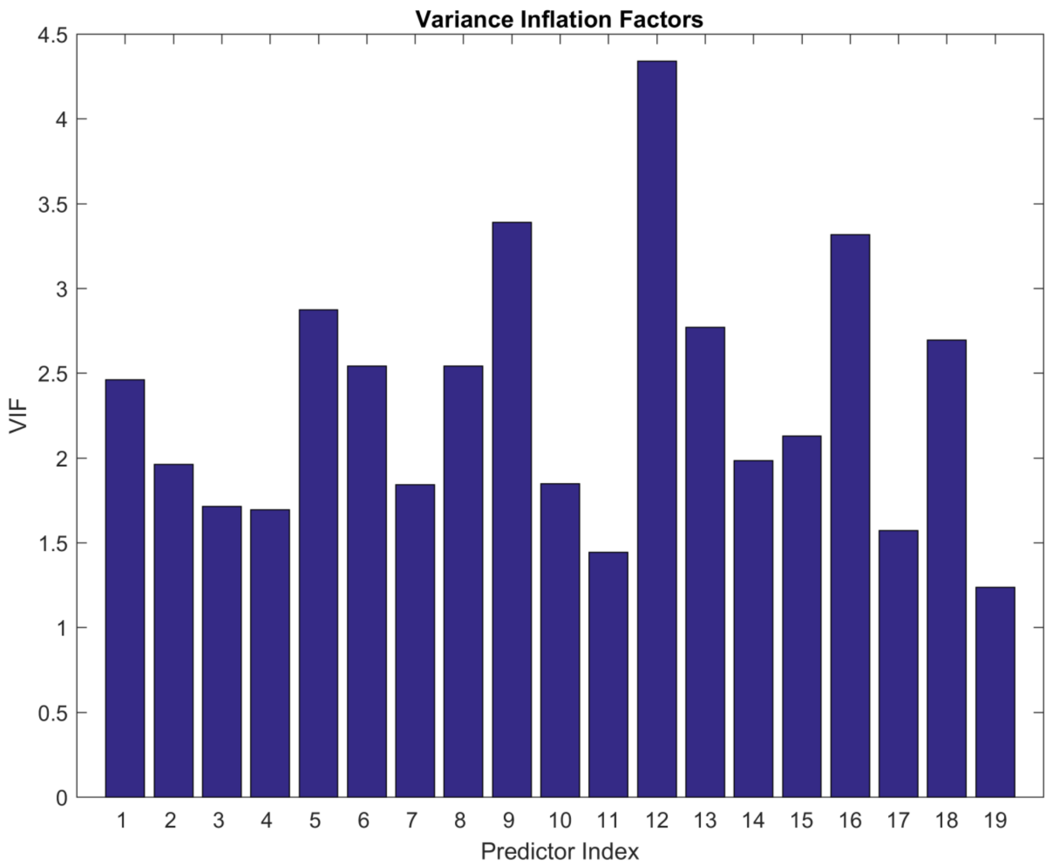

Figure 143. Variance inflation factors of 19 clustering coefficients for EEG network created with Pearson correlation of 0.1 as threshold and frequency range of 21-29 Hz.

The following table shows comparison of model classification performance.

	PCSSLR		**LASSO**		**Logistic Regression**	
	Training Set	Test Set	Training Set	Test Set	Training Set	Test Set
Median	0.9298	0.8211	0.8869	0.8421	0.9668	0.8158
Mean	0.9305	0.8112	0.8943	0.8417	0.9661	0.8067

7.3.6.4.4 Network Constructed Using Pearson's Correlation Cutoff: 0.2

7.3.6.4.4.1 Variance Inflation Factors (VIF)

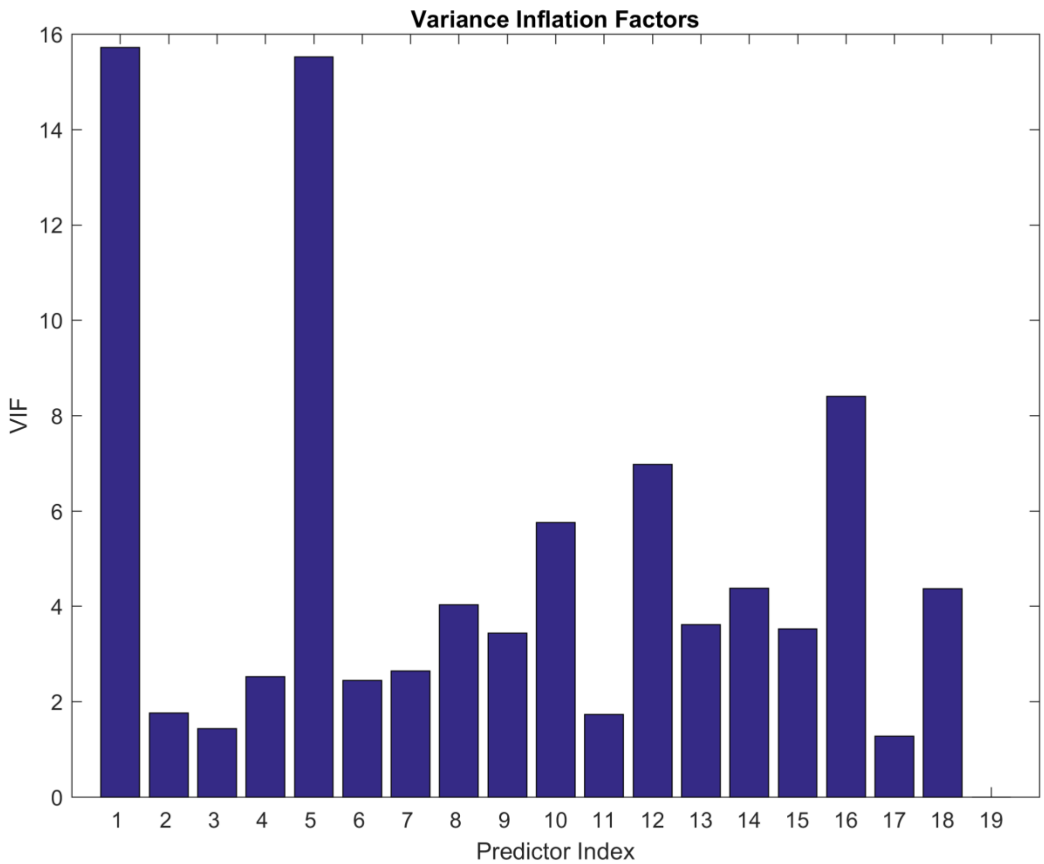

Figure 144. Variance inflation factors of 19 clustering coefficients for EEG network created with Pearson correlation of 0.2 as threshold and frequency range of 21-29 Hz.

The following table shows comparison of model classification performance.

	PCSSLR		LASSO		Logistic Regression	
	Training Set	Test Set	Training Set	Test Set	Training Set	Test Set
Median	0.8424	0.7592	0.8161	0.8138	0.8916	0.6697
Mean	0.8424	0.7505	0.8200	0.8079	0.8888	0.6694

7.3.6.4.5 Network Constructed Using Pearson's Correlation Cutoff: 0.3

7.3.6.4.5.1 Variance Inflation Factors (VIF)

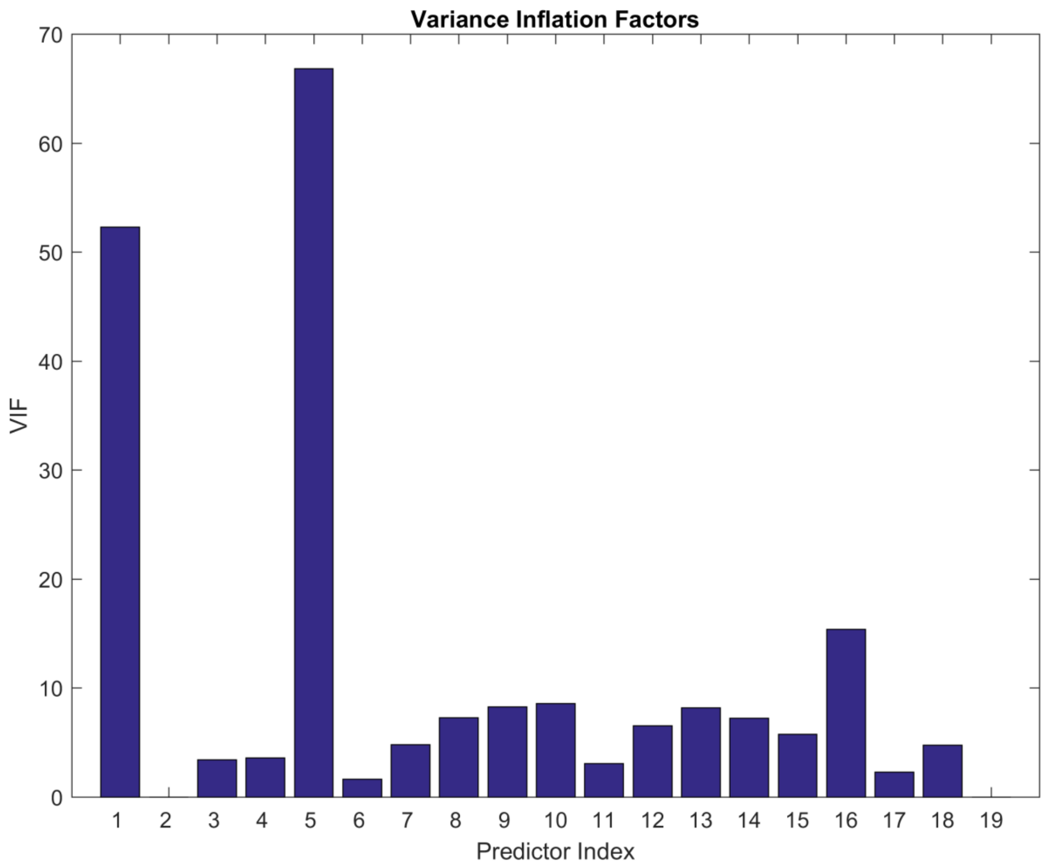

Figure 145. Variance inflation factors of 19 clustering coefficients for EEG network created with Pearson correlation of 0.3 as threshold and frequency range of 21-29 Hz.

The following table shows comparison of model classification performance.

	PCSSLR		**LASSO**		**Logistic Regression**	
	Training Set	Test Set	Training Set	Test Set	Training Set	Test Set
Median	0.7492	0.6368	0.6922	0.6678	0.7776	0.6099
Mean	0.7486	0.6248	0.6766	0.6541	0.7756	0.6049

7.3.6.4.6 Network Constructed Using Pearson's Correlation Cutoff: 0.4

7.3.6.4.6.1 Variance Inflation Factors (VIF)

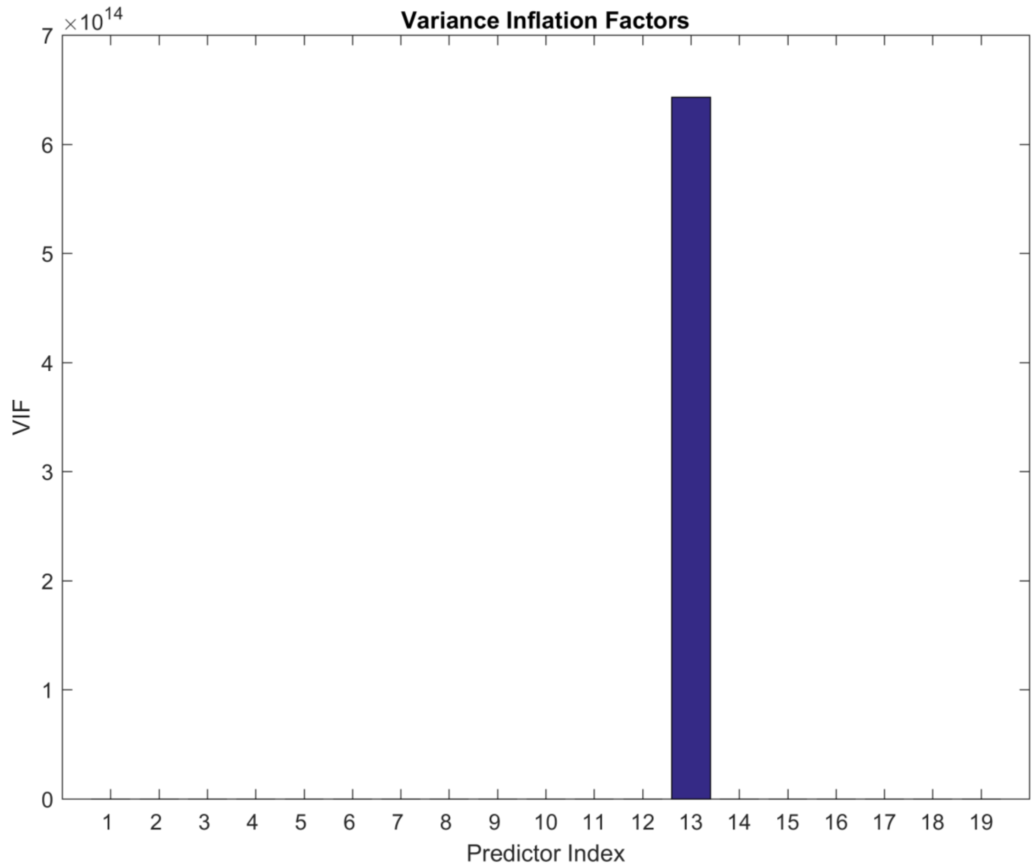

Figure 146. Variance inflation factors of 19 clustering coefficients for EEG network created with Pearson correlation of 0.4 as threshold and frequency range of 21-29 Hz.

The following table shows comparison of model classification performance.

	PCSSLR		**LASSO**		**Logistic Regression**	
	Training Set	Test Set	Training Set	Test Set	Training Set	Test Set
Median	0.5833	0.5000	0.5000	0.5000	0.6291	0.5487
Mean	0.5811	0.5214	0.5414	0.5094	0.6330	0.5446

7.3.6.4.7 Network Constructed Using Pearson's Correlation Cutoff: 0.5

7.3.6.4.7.1 Variance Inflation Factors (VIF)

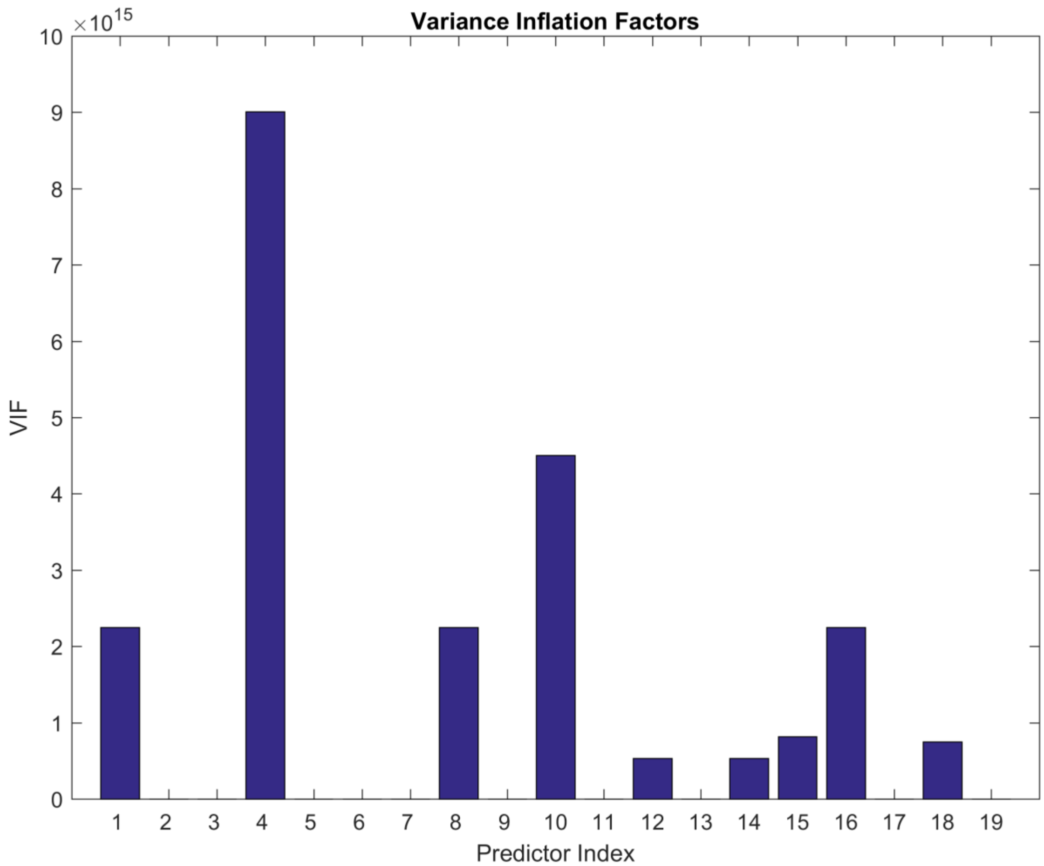

Figure 147. Variance inflation factors of 19 clustering coefficients for EEG network created with Pearson correlation of 0.5 as threshold and frequency range of 21-29 Hz.

The following table shows comparison of model classification performance.

	PCSSLR		**LASSO**		**Logistic Regression**	
	Training Set	Test Set	Training Set	Test Set	Training Set	Test Set
Median	0.5476	0.5204	0.5537	0.5243	0.5602	0.5500
Mean	0.5468	0.5239	0.5420	0.5254	0.5642	0.5426

7.3.6.4.8 Network Constructed Using Pearson's Correlation Cutoff: 0.6

7.3.6.4.8.1 Variance Inflation Factors (VIF)

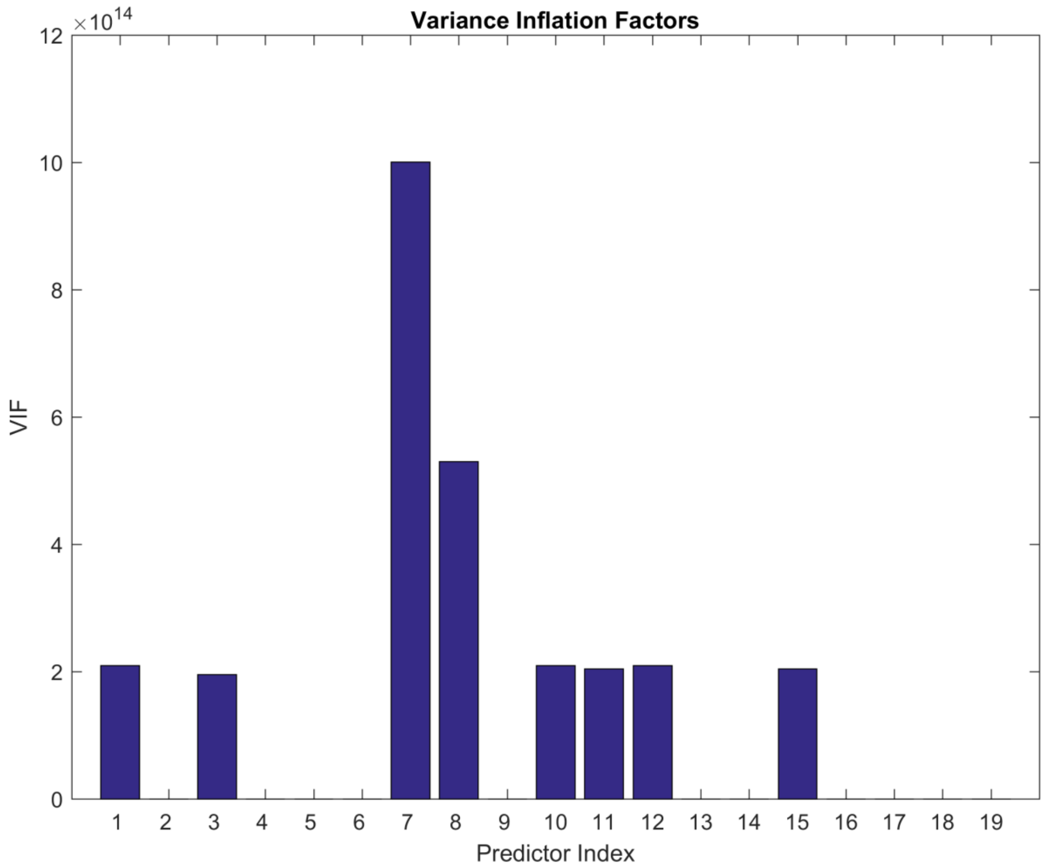

Figure 148. Variance inflation factors of 19 clustering coefficients for EEG network created with Pearson correlation of 0.6 as threshold and frequency range of 21-29 Hz.

The following table shows comparison of model classification performance.

	PCSSLR		LASSO		Logistic Regression	
	Training Set	Test Set	Training Set	Test Set	Training Set	Test Set
Median	0.5000	0.5000	0.5000	0.5000	0.5132	0.5000
Mean	0.5000	0.5000	0.5000	0.5000	0.5166	0.4892

7.3.6.4.9 Network Constructed Using Pearson's Correlation Cutoff: 0.7

7.3.6.4.9.1 Variance Inflation Factors (VIF)

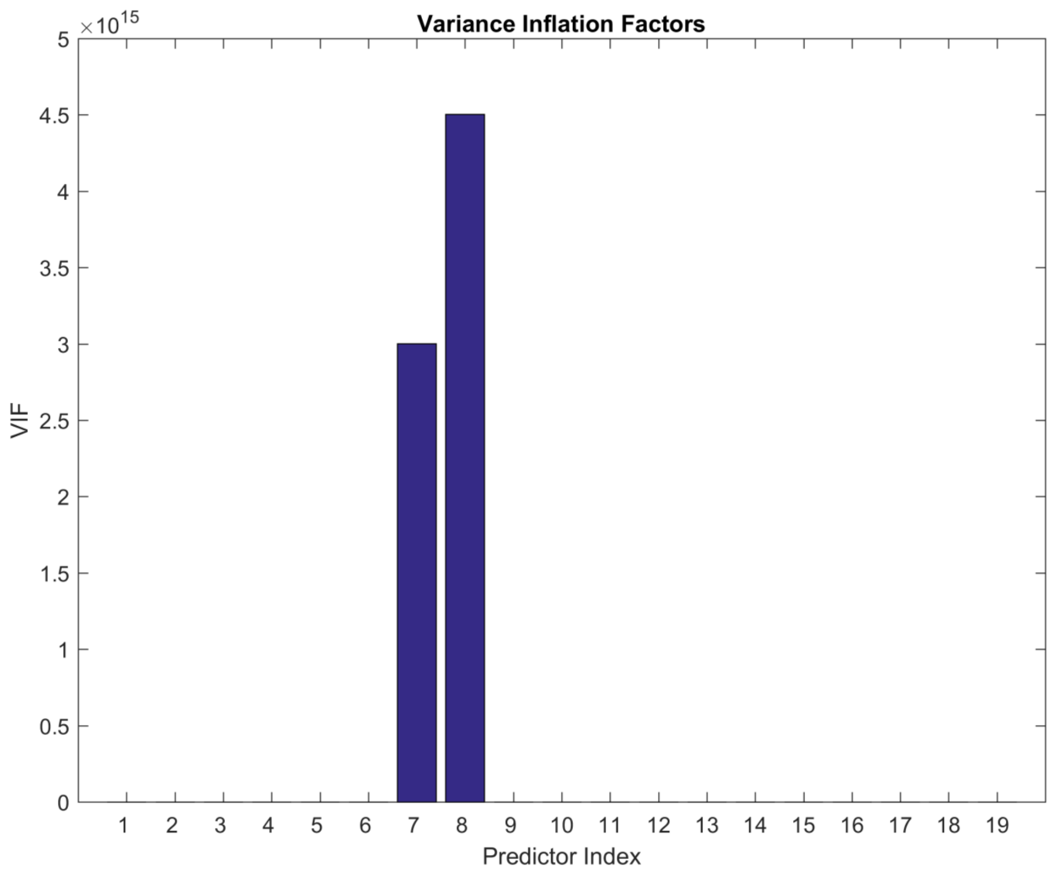

Figure 149. Variance inflation factors of 19 clustering coefficients for EEG network created with Pearson correlation of 0.7 as threshold and frequency range of 21-29 Hz.

The following table shows comparison of model classification performance.

	PCSSLR		**LASSO**		**Logistic Regression**	
	Training Set	Test Set	Training Set	Test Set	Training Set	Test Set
Median	0.5000	0.5000	0.5000	0.5000	0.5132	0.5000
Mean	0.5000	0.5000	0.5000	0.5000	0.5084	0.5000

7.3.6.4.10 Network Constructed Using Pearson's Correlation Cutoff: 0.8

7.3.6.4.10.1 Variance Inflation Factors (VIF)

All 19 predictor variables have VIF values exceed 10^{14}. The following table shows comparison of model classification performance.

	PCSSLR		LASSO		Logistic Regression	
	Training Set	Test Set	Training Set	Test Set	Training Set	Test Set
Median	0.5000	0.5000	0.5000	0.5000	0.5000	0.5000
Mean	0.5000	0.5000	0.5000	0.5000	0.5000	0.5000

7.3.6.4.11 Network Constructed Using Pearson's Correlation Cutoff: 0.9

All 19 predictor variables have VIF values exceed 10^{14}. The following table shows comparison of model classification performance.

	PCSSLR		LASSO		Logistic Regression	
	Training Set	Test Set	Training Set	Test Set	Training Set	Test Set
Median	0.5000	0.5000	0.5000	0.5000	0.5000	0.5000
Mean	0.5000	0.5000	0.5000	0.5000	0.5000	0.5000

7.3.6.4.12 Network Constructed Using Pearson's Correlation Cutoff: 1

All 19 predictor variables have VIF values exceed 10^{14}. The following table shows comparison of model classification performance.

	PCSSLR		LASSO		Logistic Regression	
	Training Set	Test Set	Training Set	Test Set	Training Set	Test Set
Median	0.5000	0.5000	0.5000	0.5000	0.5000	0.5000
Mean	0.5000	0.5000	0.5000	0.5000	0.5000	0.5000

7.3.7 Comparison of Physiological Frequency Range Classification Performance Based on Clustering Coefficients: ROC Curve's AUC vs. Physiological Frequency Range

The summary result of classification performance of LASSO, PCSSLR, and logistic regression in terms of ROC curve's AUC distribution for the four physiological frequency ranges (Alpha Wave (7-9 Hz), Alpha Wave (11-13 Hz), Beta Wave (13-19 Hz), Beta Wave (21-29 Hz) are presented. Because the binary classification of all three binary classifiers shows the best performance for the correlation threshold of 0.1, the comparison is conducted for correlation threshold value of 0.1.

7.3.7.1 Correlation Threshold of 0.1

The summary result of classification performance of the training sets in terms of ROC curve's AUC distribution for the four physiological frequency ranges is shown in Figure 150. The corresponding summary result of the test set is shown in Figure 151.

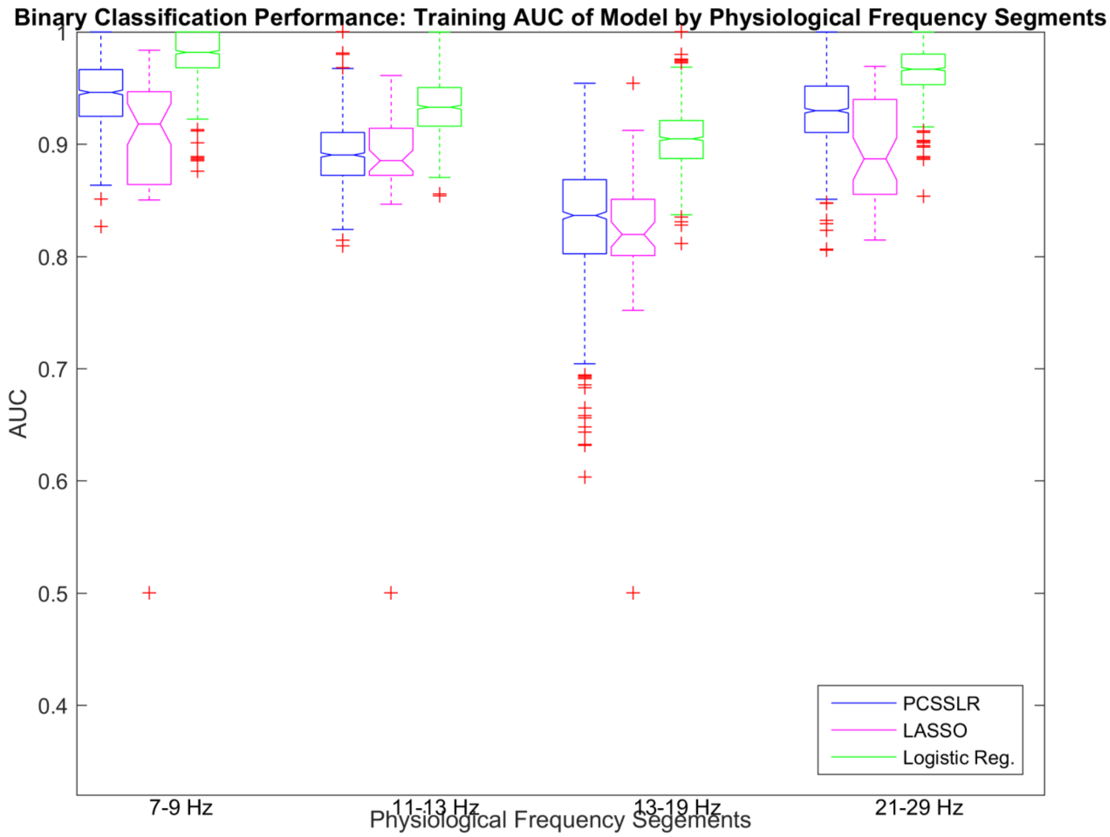

Figure 150. Training set classification performance of PCSSLR, LASSO and logistic regression for EEG network constructed using Pearson correlation threshold of 0.1 over four physiological frequency ranges of 7-9 Hz, 11-13 Hz, 13-19 Hz, and 21-29 Hz.

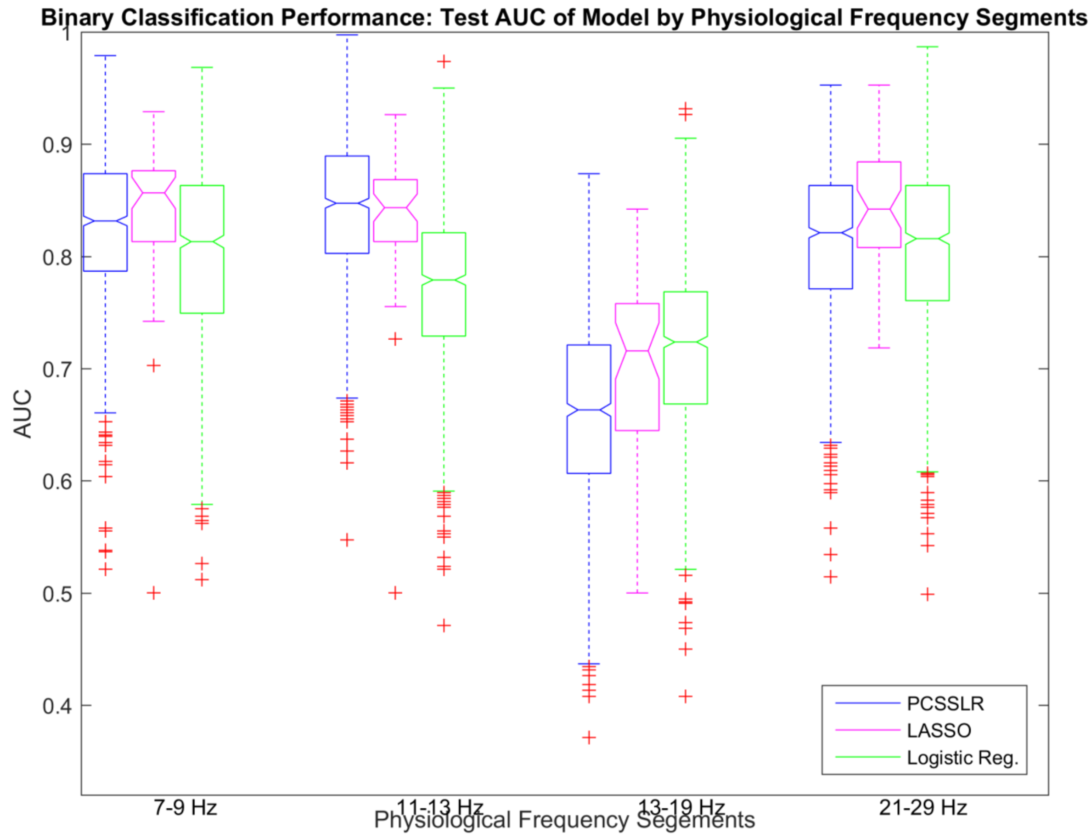

Figure 151. Test set classification performance of PCSSLR, LASSO and logistic regression for EEG network constructed using Pearson correlation threshold of 0.1 over four physiological frequency ranges of 7-9 Hz, 11-13 Hz, 13-19 Hz, and 21-29 Hz.

7.4 Brain Regions and EEG Channels Selected in Binary Classification Model

For binary classifier trained using LASSO method, a subset of covariates is selected to be used in the final model that is developed using all observations. LASSO regression coefficients are constrained to minimize difference between observed classes of the EEG data and the classes predicted by the LASSO model. As a result of the constraint, a subset of coefficients is set to zero. By forcing a subset of regression coefficients to be zero, LASSO effectively results in a model with only the covariates that are strongly associated with the DBS-on and DBS-off classes. In this study, these selected covariates are clustering coefficients of individual EEG channel which represents specific brain region.

7.4.1 Brain Regions and EEG Channels Selected by LASSO for Correlation Threshold of 0.1

Topographic map of EEG channels that are selected in the LASSO models with correlation threshold of 0.1 are presented. The topographic map is created based on non-zero regression coefficient weights of the LASSO model developed using all networks derived from original EEG data.

7.4.1.1 Beta Wave (21-29 Hz)

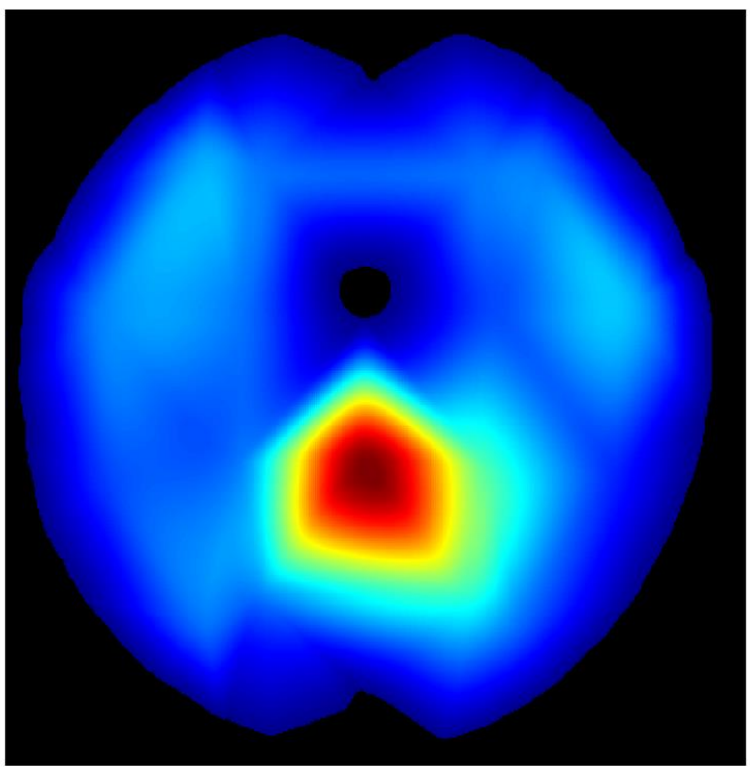

Figure 152. Topographic map of regression coefficient weights of LASSO model using EEG data from 21-29 Hz and correlation threshold of 0.1.

As seen in Figure 152, the selected regression coefficient weights of the LASSO model are highly concentrated around midline plane of the parietal lobe (Cz-Pz channel).

7.4.1.2 Beta Wave (13-19 Hz)

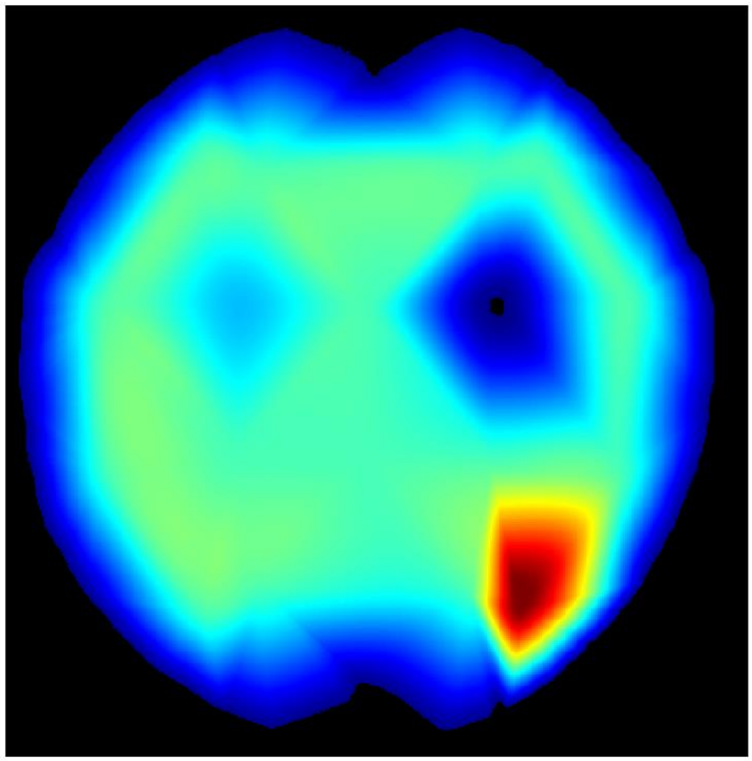

Figure 153. Topographic map of regression coefficient weights of LASSO model using EEG data from 13-19 Hz and correlation threshold of 0.1.

As seen in Figure 153, the selected regression coefficient weights of the LASSO model are mostly concentrated around the right temporal and occipital lobe regions (T6-O2 channel).

7.4.1.3 Alpha Wave (11-13 Hz)

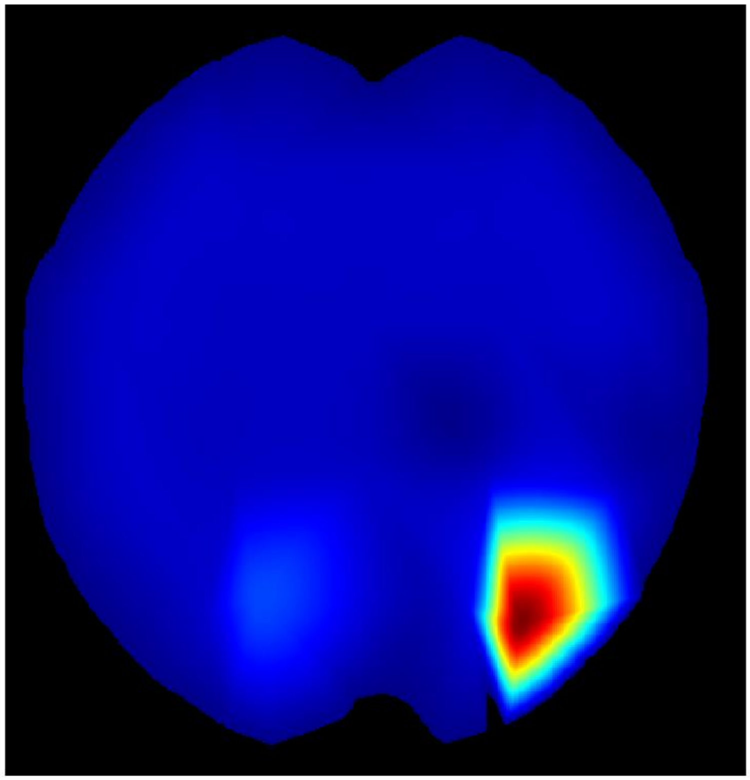

Figure 154. Topographic map of regression coefficient weights of LASSO model using EEG data from 11-13 Hz and correlation threshold of 0.1.

As seen in Figure 153, the selected regression coefficient weights of the LASSO model are mostly concentrated around the right temporal and occipital lobe regions (T6-O2 channel).

7.4.1.4 Alpha Wave (7-9 Hz)

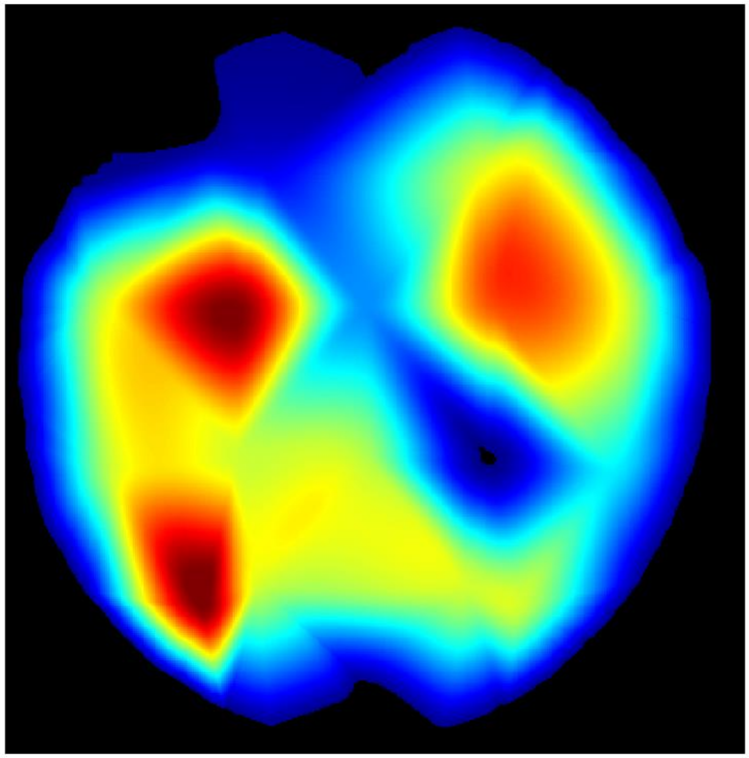

Figure 155. Topographic map of regression coefficient weights of LASSO model using EEG data from 7-9 Hz and correlation threshold of 0.1.

As seen in Figure 155, the selected regression coefficient weights of the LASSO model are more diffuse for the 7-9 Hz frequency range relative to the other three physiological frequency ranges. The regression coefficient mostly concentrated around the left frontal region near the left parasagittal plane (F3-C3 channel), the left temporal lobe region (T5-O1) and the right frontal lobe region (F8-T4 channel).

Chapter 8 Discussion

The binary classification framework that was developed in this study attempts to use only information of EEG channel data network to perform classification for EEG data. More specifically, the binary classification involves with distinguishing EEG data into either DBS-on class or DBS-off class by using inter-channel correlation of EEG recordings. In developing the classification framework, both prediction and interpretation of the results are important to practicing clinicians who are interested in analyzing the EEG dataset. Given binary classification models that shows sufficient classification performance, results that can be readily interpretable from a clinical point of view may more easily lead to identification of potential biomarkers of DBS effects.

8.1 Comparison of Classification Results of Training and Test Data Set with Different Network Association Cutoffs

As seen in section 7.3.4 and section 7.3.5, the classification performance as measured by ROC curve's AUC has an inverse relationship with Pearson correlation thresholds that are used to construct the EEG frequency network. The relationship makes sense given that fact that the value of Pearson correlation is used as cutoff to derive a binary network. For a relatively high value of Pearson correlation used as threshold (e.g. 0.9), relatively few channel pairwise correlations are selected as realized connections of the network because most of the underlying correlations of the pairwise EEG channel in frequency space are less than that the threshold. Given very few connections in the network, the interconnectivity network metric derived does not contain enough information to differentiate networks into either DBS-on or DBS-off state. As a result, the binary classifiers developed with a high value of Pearson's correlation threshold tend to have lower median ROC curve's AUC than the binary classifiers developed with a lower value of Pearson's correlation regardless the binary classifiers are trained based on PCSSLR, LASSO or simple logistic regression. From the series of binary classification results, it can also inferred that a Pearson correlation threshold of 0.1 generally results in the best classification results of EEG network with DBS on vs. DBS off for all four physiological frequency ranges defined in this study.

8.2 Comparison of Classification Performance of Different Models

Based on comparison shown in section 7.3.6, it can be seen that all three binary classifier modeling approaches have advantages and disadvantages.

The binary classification based on logistic regression tends to result in large percentage drop in median and mean AUC for the test dataset with respect to the AUC of the training set. This indicates that the binary classifier may over-fit the training data. The average percentage drop is 12.6% compared to 10.1% for PCSSLR and 8.3% for LASSO. As a result, the binary classifier developed based on simple logistic regression leads to relatively modest binary classification performance for the test dataset with respect to the training dataset. In addition, simple logistic regression model do not result in identification of subset of features that are important in separating the data into the DBS-on and DBS-off classes because no specific feature selection step is deployed within the context of developing a logistic regression model. An advantage of logistic regression is its relative ease of use in quickly developing a binary classifier. Thus, simple logistic regression is often a good modeling method to use as a first attempt to develop a binary classifier for a dataset as was done in this current study.

The binary classification based on LASSO tends to result in good binary classification performance. The average ROC curve's AUC of binary classifiers developed based on LASSO is approximately 0.7511 for the range of Pearson correlations defined in this study. In addition, the difference in percentage change of median AUC between the training set and test set models is only 8.3%. However, the LASSO method requires selecting the value of the parameter of λ, the choice of which has a large impact of the binary classification performance of the model developed. In addition, cross validation is needed to determine the relative merit of what value to use for λ which leads to increased time requirement to develop an appropriate LASSO model.

The binary classification based on PCSSLR tends to result in binary classification performance similar to the performance of binary classifier based on LASSO. The binary classifiers based on PCSSLR perform better than those based on LASSO with Pearson correlation of 0.1 for frequency range of 11-13 Hz. One disadvantage of PCSSLR is that the covariates need to be linearly transformed. These transformed variables of the original clustering coefficients of the EEG frequency networks may be more difficult to interpret because each of the transformed variables is a combination of all the original variables. As a result, the features selected by a PCSSLR binary classifier model requires more abstract interpretation with respect to the features selected by binary classifier developed based on LASSO.

8.3 Comparison of Physiological Frequency Range Classification Performance

Based on results from section 7.3.7, it can be seen that different physiological frequency range segments tend to results in different classification performance with respect to the binary classifier modeling methods used. Using median of the AUC distribution from the cross validation samples, it can be seen from Figure 151 that PCSSLR performs the best among the three binary classification methods for alpha wave of 11-13 Hz. LASSO performs the best among the three binary classification methods for alpha wave of 7-9 Hz and for beta wave of 21-29 Hz. Logistic regression performs the best among the three classification methods for beta wave of 13-19 Hz. It can also been seen from Figure 151 that beta wave of 13-19 Hz leads to an inferior binary classification with respect to other three defined physiological frequency ranges.

8.4 Potential Biomarkers: Brain Regions and EEG Channels Selected in Binary Classification Model

As shown in Figure 152 to Figure 155, different brain regions and EEG channels are selected in different physiological frequency ranges by the LASSO model developed using all EEG network-derived clustering coefficients. For 20-28 Hz of beta activity, the model coefficient weights are highly concentrated around the midline plane of the parietal lobe (Cz-Pz channel). This result is interesting in view of the fact that the target of the DBS treatment received by the patient in this study is the subthalamic nucleus (STN) and the horizontal plane location of the STN is approximately centered around anterior and posterior commissures [22]. In addition, elevated beta activity has been proposed to be associated with slowing of spontaneous movements in Parkinson’s disease

[23]. The channels selected in the model suggest that the clustering coefficients of these channels are highly associated with the DBS-on and DBS-off state. Since clustering coefficient of a node in a network measures the proportion of the connections among the neighboring nodes that are realized compared to all possible connections, the modeling results indicate that the proportion of realized connections among channels other than those selected channels may be significantly different while DBS is on related to while DBS is off.

In addition to the selected channels and brain regions for 21-29 Hz beta activity, the model also indicates another selected channel for beta activity of 13-19 Hz and alpha activity of 11-13 Hz. For these two physiological frequency ranges, the coefficient weights of the LASSO model are highly concentrated at T6-O2 channel corresponding to the right temporal and occipital lobe regions of the brain. For alpha activity of 7-9 Hz, the model has coefficient weights concentrated around F3-C3, T5-O1, and the F8-T4 channels.

Extract potentially new biomarkers using brain network data is an important challenge for a number of neurological disorders including Alzheimer's disease, multiple sclerosis and epilepsy [24]. The result of the this study indicates that it is possible to apply the modeling framework developed to extract potential biomarkers using only inter-channel correlation of EEG recordings to identify effects of treatment procedure such as deep brain stimulation and other physiological states including disorders such as Parkinson's disease.

8.5 Network Interpretation of Potential Biomarkers of DBS Effects

In this study, a framework is developed that can be used to develop binary classifier to select EEG segments into binary categories of DBS-on and DBS-off states. The binary classifier is trained based on only inter-channel correlation of pairwise EEG data. Binary classifiers that are developed using LASSO result in a subset of channels that are selected to be included in the classifier model. This subset of channels is hypothesized to be potential biomarkers related to the effects of deep brain stimulation (DBS).

An important issue in examining the study results and any potential biomarker is whether or not these selected channels and their clustering coefficients of the EEG network are biomarkers for the effects of DBS on EEG data or for therapeutic efficacy of DBS on reducing motor symptoms such as those associated with Parkinson's disease. Even though there are effects on the physiological range of brain waves uncovered based on the classification framework developed in this study, it is not clear within the context of this study the true nature of these effects. It is possible that the effects found are simply another set of artifacts that are not directly related to physiology of brain wave. On the other hand, it is also possible that the subtle difference in inter-channel frequency correlation of EEG data that seems to contain information to differentiate EEG data into DBS-on vs DBS-off state may have an underlying physiological basis that can be used for diagnostic and therapeutic purposes. This issue is outside the scope of the current study. In order to examine the direct therapeutic effects of DBS on motor symptoms associated with Parkinson's disease, it will be necessary to also acquire and analyze quantitative data from a patient population of sufficient size. In addition, the data would need to be used to measure severity of symptoms of Parkinson’s disease based on rating scale such as the unified Parkinson’s disease rating scale (UPDRS) [25].

Regardless the true nature of the potential biomarkers from this study, it can be determined based on the modeling framework investigation conducted in this study that a network approach can help gain insights into characteristics of EEG data that are not normally noticeable to neurologists and neurophysiologists. The modeling framework developed in this study can potentially help guide discovery of other EEG signal of interest in the future.

The potential biomarkers found in this study can be useful for future workflow of providing DBS treatment to patients and the design of new DBS devices. In order to properly use DBS to treat motor symptoms of Parkinson’s disease for a patient, it is necessary to adjust parameter settings over the course of a few months through interactions between clinicians and patients. The current approach requires multiple office visits which are costly, slow and inefficient. A closed loop, adaptive DBS system that can adjust itself automatically to be on or off based on a measureable biomarker from the patients would provide clinical benefits to both clinicians and patients. The potential biomarkers that are found in the current study may be used in such close loop system. More specifically, one or several of these EEG biomarkers can be used as a proxy of EEG effects of DBS and serve as the measureable variables for the closed loop adaptive system. Thus, these potential biomarkers may be useful as long as these variables can be measurable directly or indirectly from the patient by the use of EEG devices.

Moreover, the general classification framework developed in the study can be used to identify other potential biomarkers that may only become noticeable by examining the interrelationship of multiple EEG channel data as a whole. Thus, the classification framework can service as a good basis that allow researchers to examine network effects by using EEG data.

Chapter 9 Conclusion

In this study, a framework to combine inter-EEG-channel association measures and network features to train binary classifiers was developed to distinguish EEG data into either one of the two binary categories of DBS-on state and DBS-off state.

The comparison of AUC obtained using PCSSLR, LASSO and logistic regression shows the binary classification performance of the three methods are comparable over certain physiological frequency range. Each of these methods results in the best binary classification performance among the three methods for different physiological frequency range. Moreover, each method has advantages and disadvantages and it is prudent to employ multiple binary classification approaches to compare and confirm classification prediction results.

An advantage of using network characteristics such as clustering coefficient is that such network-based metric offers objective measures to quantify interactions of EEG recordings from all pairs of EEG channels. Based on result from current study, it is reasonable to conclude that characteristics of network constructed based on correlation among pairs of EEG channel data are suitable to be used as features to train classifier for DBS-on and DBS-off classification.

In addition, the general classification framework developed in this study can be used to identify potential biomarkers that may only become noticeable by examining the interrelationship of multiple EEG channel datasets as one whole system. These potential biomarkers can be further investigated for use in adaptive DBS feedback control system to improve DBS therapy for patients and clinicians. The classification framework established in this study can serve as a good basis to enable researchers to examine the network effects of EEG data and brain activity.

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