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ENTROPY OF ELECTROENCEPHALOGRAM (EEG) SIGNALS CHANGES WITH SLEEP STATE

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ABSTRACT OF THESIS

ENTROPY OF ELECTROENCEPHALOGRAM (EEG) SIGNALS CHANGES   WITH SLEEP STATE

We hypothesized that temporal features of EEG are altered in sleep apnea subjects compared to normal subjects. The initial aim was to develop a measure to discriminate sleep stages in normals. The longer-term goal was to apply these methods to identify differences in EEG activity in sleep apnea subjects from normals. We analyzed the C3A2 EEG and an electrooculogram (EOG) recorded from 9 normal adults awake and in rapid eye movement (REM) and non-REM sleep. The EEG signals were filtered to remove EOG contamination. Two measures of the irregularity of EEG signals, Sample Entropy (SpEn) and Tsallis Entropy, were evaluated for their ability to discriminate sleep stages. SpEn changes with sleep state, being largest in Wake. Stage 3/4 had the smallest SpEn (0.57 ± 0.11) normalized to Wake values, followed by Stage 2 (0.72 ± 0.09), REM (0.75 ± 0.1) and Stage 1 (0.89 ± 0.05). This pattern was consistent in all the polysomnogram records analyzed. Similar pattern was observed in lead O1A2 as well. We conclude that SpEn may be useful as part of a montage for assessing sleep state. We analyzed data from sleep apnea subjects having obstructive and central apnea events and have made some preliminary observations; the SpEn values were more similar across sleep stages and also high correlation with oxygen saturation was observed.

KEYWORDS: EEG temporal features, EOG contamination, Sample Entropy, Tsallis Entropy, Apnea

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THESIS

Blesy Anu Mathew

The Graduate School

University of Kentucky

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STATE

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THESIS

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A thesis submitted in partial fulfillment
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By

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Lexington, Kentucky

Thesis Advisor: Dr. Eugene Bruce

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Chapter One: Introduction

This study is based on the hypothesis that temporal features of EEG signals are altered in subjects with sleep apnea compared to normal subjects. In sleep apnea, subjects have intermittent cessation of breathing during the night. We believe that the reason behind these altered EEG features is that certain brain centers or the communication between these centers are affected. Our first objective was to develop an EEG measure that could identify differences in these temporal EEG features among sleep stages in normal subjects. Our second objective was to determine whether this technique would be able to identify differences in temporal features of EEG signals between normal subjects and sleep apnea subjects and, if necessary, to modify the technique to achieve this goal. This second goal was only partly achieved in this study due to a delay in acquiring appropriate sleep apnea data. The sleep apnea data sent to us by two other sleep laboratories lacked information critical to our study. A large sleep apnea data set satisfying our criteria was obtained from the Sleep Heart Health Study only about 3 months before this thesis was submitted.

The interactions among the thalamus, cortex and the pons are responsible for EEG activity detected by EEG scalp electrodes. The interactions among these three brain regions vary among sleep stages and in this study a technique to quantify this variation in EEG among sleep stages in individual subjects has been developed.

The acetylcholinergic reticular activating system (RAS), which is a portion of the reticular formation, on activation passes nerve impulses to widespread areas of the cerebral cortex directly and via the thalamus. During wakefulness, the RAS inhibits the reticular nucleus and excites the neurons of the sensory thalamus. This activation results in an uninhibited flow of signal from the lower areas of the brain to the cerebral cortex. Two types of waves are associated with wake stage, beta waves and alpha waves. Beta waves are higher in frequency (> 13Hz) and lower in amplitude than alpha waves. Beta waves are not very regular, i.e. they are desynchronous in their pattern. The brain waves become slower and increase in amplitude during relaxed wakefulness. These alpha waves (> 8Hz to ≤ 13Hz) are more synchronous in their pattern. The transition from wake to Stage 1 is characterized by an increase in the rhythmicity or regularity of the EEG. This rhythmicity is dependent on interactions between the cortex and thalamus. The first stage of sleep is characterized by theta waves (> 4 Hz to ≤ 8 Hz), which are greater in

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amplitude than the alpha waves. In Stage 2, theta activity continues interspersed by two phenomena, sleep spindles, observed as a transient increase in frequency, and K complexes, observed as a transient increase in amplitude. The thalamus is very insensitive to sensory stimuli during deep sleep but when hyperpolarized in deep sleep, it shows slow intrinsic waves of activity. Thus Stage 3/4 is characterized by delta waves (≥ 0.5 to ≤ 4 Hz), which have a higher amplitude than alpha, beta, or theta waves. During REM sleep the acetylcholinergic RAS is again made active. The brain waves during REM are similar to wakefulness in that alpha and beta waves are predominant in both stages. The varying degree of regularity combined with the aperiodic interruptions in the lighter sleep stages, <u>which we will describe as the **complexity** of the EEG</u>, is diagnostic for clinical sleep staging.

Various measures have been used to quantify and better understand EEG complexity which differs not only among the various sleep stages, but also varies within a sleep stage. Spectral power calculation using Fourier transform has been used for sleep stage analysis [17]. Spectral power estimation has also been done to study changes in EEG frequency bands in sleep apnea subjects [23, 24, 29]. In these studies multiple frequency bands and their normalized band powers [24] and ratios of the frequency bands [29] are computed. The different frequency bands were normalized and/or ratios were taken due to lack of a reference threshold to detect any changes in frequency content. Approximate entropy (ApEn (m, r, N)) has been proposed as a measure for quantifying complexity. ApEn (m, r, N) measures the logarithmic likelihood that two data sequences of m contiguous observations that are pairwise close (within r), remain close (within the same tolerance width r) on subsequent comparisons of m+1 observations. A low value of ApEn indicates predictability and regularity in a time series whereas a high value indicates random variation. ApEn has been used in short and noisy data sets [3] and has also been applied in the analysis of sleep stages [4]. Acharya, et al. showed that the group means ApEn values in each sleep stage from 8 normal subjects differed among some sleep stages [4]. However, ApEn behavior during sleep stage analysis in the individual subjects was not addressed. The first goal of the present study was to develop a method sensitive enough to measure the difference in complexity of EEG signals among sleep stages in individual subjects. This goal was achieved.

Our approach also addresses the limitations of ApEn. ApEn requires each sequence on comparison to contribute a defined, non-zero probability. This requirement is met as the ApEn

algorithm counts each sequence as matching itself, avoiding the occurrence of ln (0) in the calculations [2]. This bias of ApEn makes it highly dependent on record length and is uniformly lower than expected for short records. Sample Entropy (SpEn (m, r, N)) calculates the negative logarithm of a probability associated with the time series as a whole, thereby avoiding the bias in ApEn.

One of the major challenges in EEG analysis and interpretation is the identification and removal of non-cerebral potentials from the EEG. Movement of the eyes causes the electric field around the eyes to change. As this field propagates over the scalp, it is picked up and appears in the EEG as artifacts. Various techniques have been used to remove these ocular artifacts from EEG signals [9, 10]. However, removal of ocular artifacts prior to entropy calculation has not been done [4, 6]. In this work we designed an optimal, least squares, noise cancellation filter to remove the component of EEG coherent with EOG [7].

In summary, the first objective of this study was to develop a technique to discriminate temporal changes in EEG activity among sleep stages. To accomplish this objective, it was also necessary to remove contamination by EOG and ECG signals that would affect EEG analysis. This objective was approached by analyzing EEG data from 9 normal subjects. The second objective was to identify any differences between apnea and normal subjects. This objective was approached by analyzing the data from a severely apneic subject followed by analysis of 7 sleep apnea subjects.

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Chapter Two: Background

EEG Basics:

EEG activity observed on the scalp is generated by the postsynaptic summated potentials of the underlying neurons. There are inhibitory and excitatory postsynaptic potentials. These potentials are caused by impulses arriving at the neurons from other nearby neurons. These impulses will cause release of neurotransmitters which will pass through the synaptic cleft to the receptor neurons. The interaction produces a change in the permeability of membranes to ions. During excitatory post synaptic potential (EPSP) the interaction reduces the resting potential (i.e. depolarizes the cells) and usually leads to increased permeability of ions. But in the case of an inhibitory post synaptic potential (IPSP), the interaction increases the resting potential thus hyperpolarizing the cells. The net contribution from these potentials arriving at the cortex is the recorded EEG.

Fisch suggested another mechanism in addition to postsynaptic potentials that might contribute to the recorded EEG [8]. Intrinsic cellular currents mediated by ionic currents can produce long duration, high amplitude extracellular potentials. These intrinsic currents are produced by neocortical cells which undergoes burst firing after a prolonged hyperpolarization. It is likely that these extracellular potential appear in the recorded scalp EEG.

The EEG activity recorded during the various stages of sleep vary in regularity. The thalamus, cortex and pons are the three main brain centers responsible for the EEG activity during sleep. The cerebrum consists of an outer layer of gray matter and deep inside the gray matter is the white matter. The outer rim of the gray matter is the cerebral cortex. The thalamus consists of a pair of oval masses of gray matter, organized into nuclei and interspersed with tracts of white matter [12]. The thalamus is the major relay station for most sensory impulses that reach the primary sensory areas of the cortex from the spinal cord, brain stem and midbrain. The thalamus contributes to the regulation of autonomic activities and the maintenance of consciousness. The axons that connect the thalamus to the cerebral cortex pass through an *internal capsule,* which is a thick band of white matter lateral to the thalamus. The internal medullary lamina divides the gray matter into the right and left sides of the thalamus. There are seven thalamic nuclei on

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each side of the thalamus depending on the position and function. For this study, the reticular nucleus that surrounds the lateral aspect of the thalamus is worth mentioning. This nucleus monitors, filters, and integrates activities of other thalamic nuclei. According to a study conducted by McCormick, et al., several neurotransmitters that are released from the brainstem, hypothalamus, basal forebrain and cortex depolarize the thalamocortical and thalamic reticular neurons leading to an enhanced excitability of the cortical pyramidal cells. These neurotransmitters include acetylcholine (ACh), norepinephrine, serotonin, histamine, and glutamate. [14]. This enhanced excitability suppresses sleep and leads to an active state. When the thalamocortical cells are depolarized, the recorded EEG activity has low amplitude and high frequency. But when these cells are hyperpolarized, delta oscillations (0.2 – 4 Hz) are more prominent. Delta oscillations are also synchronized; this is achieved by recruitment of thalamic cells. Figure 1 displays the different brain regions along with certain neurotransmitters [30].

The brainstem is composed of clusters of cell bodies (gray matter) interspersed with axons (white matter). The broad region of white matter and gray matter exhibits a netlike arrangement known as the reticular formation. This extends from the upper part of the spinal cord, throughout the brainstem, and into the lower part of the diencephalon. Neurons within the reticular formation have both sensory and motor functions. Part of the reticular formation called the reticular activating system (RAS), which consists of the sensory axons, projects to the cortex. The brainstem consists of three regions: 1) the medulla oblongata, 2) pons, and 3) midbrain.

The pons consists of nuclei and tracts and acts like a bridge that connects one part of the brain with one another. These connections are provided by bundles of axons. Some of these axons connect the left and right sides of the cerebellum while some are part of the ascending sensory tracts and descending motor tracts. The pons is also responsible for triggering REM sleep. The Pons-Geniculate-Occipital (PGO) waves send signals that activate eye movements. They also send signals to the spinal cord to inhibit motor activity associated with large muscles.

Sleep is divided into Wake, Stage 1, Stage 2, Stage 3/4 and REM stages. NREM is composed of Stage 1, Stage 2 and Stage 3/4. Sleep consists of alternating cycles of NREM-REM cycles. Wake EEG is highly desynchronous in its pattern and contains high

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frequency rhythms namely, beta waves (> 13 Hz) and alpha waves (> 8Hz to ≤ 13Hz). In Stage 1, alpha rhythm disappears and theta waves (> 4 Hz to ≤ 8 Hz) appear. Alpha waves may also recur briefly in this Stage 1 [8]. Stage 2 is characterized by theta waves interspersed with spindles and K complexes. Sleep Spindles (12- 14 Hz) are characterized by a transient increase in frequency while K complexes are characterized by a transient increase in amplitude. Stage 1 and Stage 2 are also known as lighter sleep stages. Stage 3 is characterized by very low frequency waves called delta waves in the 0.5 to ≤ 4 Hz range. These waves are the most regular and have the highest amplitude than the other waves. Stage 4 is similar to Stage 3 except that Stage 4 has more delta waves present. In this study, EEG recordings in Stage 3 and Stage 4 are grouped together and referred to as Stage 3/4. REM sleep is characterized by low voltage EEG activity, rapid eye movements and reduced muscle activity. Although the EEG activity in REM appears similar to that in Wake stage, it is difficult to arouse a person from REM, suggestive of a deeper sleep stage.

Sleep architecture refers to the relative amounts of time spent in the various sleep stages. Usually as sleep progresses, the duration spent in REM sleep increases while the duration spent in NREM decreases. Redline et al reported that sleep architecture varies with age, sex, ethnicity and sleep disordered breathing (SDB). They also found that men have lighter sleep compared to females and that older men have poorer sleep than older women [11].
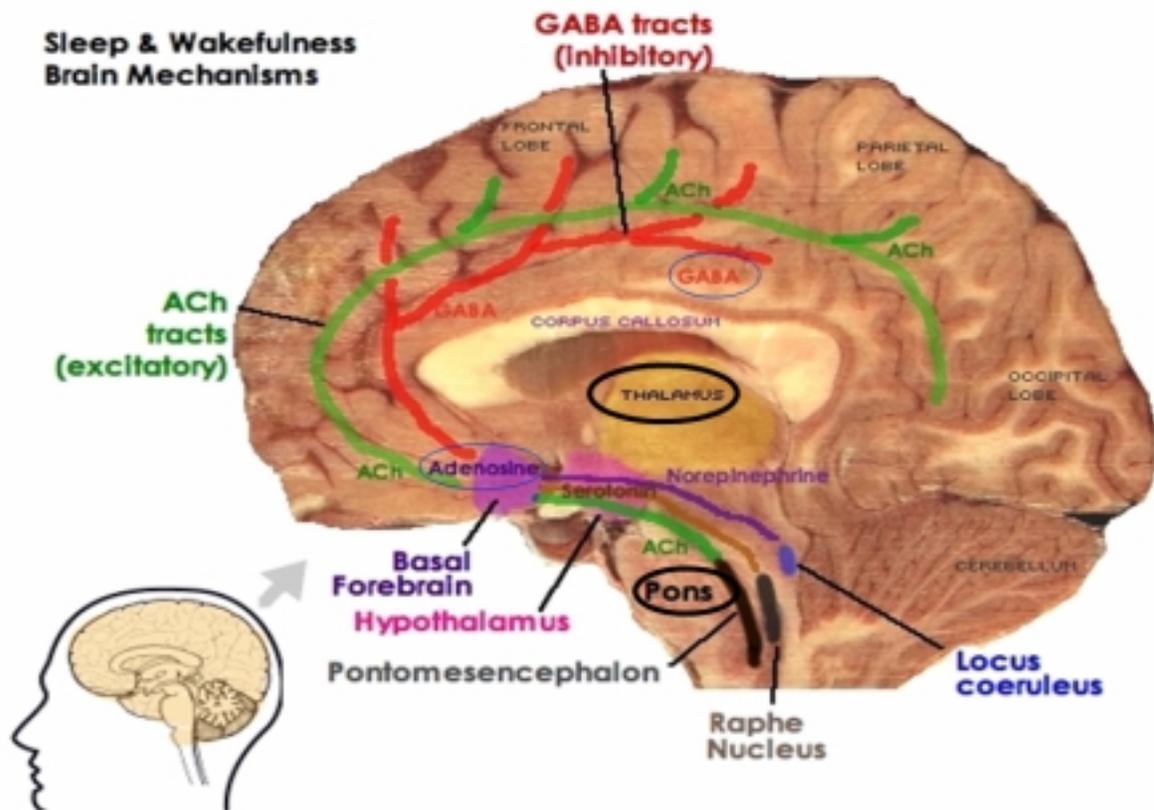
Figure 1: The Cortex, Thalamus and the Pons are the three main regions responsible for the different sleep stages

Polysomnogram and electrode placement:

A polysomnogram is an overnight test done to diagnose and evaluate sleep disorders. Various variables are recorded during this test including electroencephalogram (EEG), electrooculogram (EOG), chin electromyogram (EMG), respiratory movements (thorax and abdomen), nasal airflow, electrocardiogram (ECG), and measurements of oxygen saturation. Sleep stage classification is done using EEG, EOG, and EMG. C3A2 / C4A1 are the standard cerebral montages used for sleep stage classification. Sleep staging is done following the guidelines of Rechstchaffen and Kales [1].

For EEG recording, electrodes are placed on the scalp of the patient. The standard electrode placement system followed is the International 10-20 Electrode System [27]. Normally the frontal and/or the occipital electrodes are used for EEG recording during a polysomnogram along with the central electrodes. EEG can be recorded as a potential difference between two electrodes (known as bipolar EEG) or can be recorded at one electrode position with one or both ear electrodes as the reference.

For EOG recording, one electrode is placed above one eye while the other electrode is placed below the other eye, this is done in order to record both the horizontal and vertical eye movements.

Three electrodes are placed for recording the EMG activity, one in front and center of the chin and the other two underneath and on the jaw bone. This placement of electrodes gives information about the patient's movements and is also used in evaluating artifacts in other channels.

Contamination for other channels (e.g. EOG):

The recorded EEG is sometimes contaminated by other signals, namely ECG and/or EOG. The main contamination observed was EOG contamination. We need to first understand what the EOG is actually recording. The eye forms an electric dipole, in which case the cornea is positive and the retina is negative. When the eye moves, the electric field around the eye changes, producing an electric signal known as the EOG. As this signal propagates across the scalp, this signal appears in the recorded EEG as noise or artifacts. This contamination is a serious problem and affects EEG analysis and interpretations. Various methods have been developed to remove the ocular artifacts [9, 10]. He et al. describe a noise cancellation method based on adaptive filtering for removal of ocular artifacts. In this study a non-adaptive filter employing a least squares approach is used to remove the EOG contamination [9]. Jung et al. suggests using Independent Component analysis (ICA) for removal of eye artifacts. But in this study an optimal filter using minimum mean squared error (MMSE) approach worked satisfactorily in EOG contamination removal. Also in this study, cerebral montage C3A2 was used as the EEG recording and left EOG was used as the EOG recording for removal of contamination. These recordings were selected because C3A2 recordings were available in all the

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polysomnogram recordings and also since the electrode is on the left hemisphere, it is located closer to the left EOG and hence the contamination will be more compared to that from right EOG.

Entropy:

Entropy is a measure of rate of information generation; usually a high value corresponds to increased irregularity or unpredictability while a low value corresponds to high regularity.

In this study two types of entropy were computed, Sample entropy and Tsallis entropy. Sample entropy is a measure of the time correlation of a time series while Tsallis entropy is a measure of the probability distribution of the amplitude of a time series:

Sample Entropy

Richman, et al. define Sample entropy (SpEn(m, r, N)) as the negative natural logarithm of the conditional probability that two sequences similar for m points remain similar at the next point within a tolerance width r, where self matches are not included in the calculating the probability [2].

It is the bias involved in Approximate entropy (ApEn (m, r, N) computation that led to the development of Sample entropy. The calculation of ApEn (m, r, N) is done as follows [3]:

For a time series of N points, $\{u(j) : 1 \leq j \leq N\}$ form *N-m-1* vectors, x_m *(i)* for $\{i : 1 \leq i \leq N - m + 1\}$ where

x_m *(i)* = $\{u(i+k) : 0 \leq k \leq m-1\}$ is the vector of m data points from u (i) to u (i+m-1)

m is the length of the sequences to be compared, here m=2 is used

The distance between two such vectors is defined to be d[x(i), x(j)]=max{| u(i+k) − u(j+k) |:$0 \leq k \leq m$-1 }, which is the maximum difference between corresponding elements of the two vectors. Let x (i) be the template vector and since the conditional probability of x(j) falling within a tolerance width of x(i) is computed, we define x(j) as the conditional vector.

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Figure 2 gives an illustration of the steps above that are involved in ApEn calculation. Here, m=1 is used and we are considering i=260, so $x_1(260)$ is the template vector, indicated with a red circle. The conditional vector shown in the figure is indicated with a green circle (which corresponds to x (j)). The dashed line corresponds to r (which is 20% of standard deviation), and the lines above and below this line correspond to x(260)± r, respectively. Hence we compute the number of conditional vectors that fall within this tolerance width with respect to the template vector by taking the distance between the vectors.

We define $B_i{}^m(r)$ as:

[*Number of times x_m (i) within r of x_m (j) × (N-m+1)$^{-1}$*], In this project r was made equal to 20% of the standard deviation of the data set

And we define $A_i{}^m(r)$ as:

[*Number of times $x_{m+1}(i)$ within r of $x_{m+1}(j)$ × (N-m)$^{-1}$*],

And ApEn is defined as

$$ApEn = (N - m)^{-1} \sum_{i=1}^{N-m} -[\ln(A_i^m(r) / B_i^m(r))]$$

Each sequence is counted as matching itself in order to avoid the occurrence of ln (0) in the calculations.

Sample entropy was developed from ApEn to avoid this bias caused by ln (0) terms. Sample entropy is given by the following formula:

$$SpEn = -(N - m)^{-1} \ln\left[\sum_{i=1}^{N-m} (A_i^m(r) / B_i^m(r)) \right]$$

ApEn has been applied for EEG analysis in several studies [4, 5, 6]. In the study conducted by Diambra et al., ApEn was used to characterize different types of epileptic seizures (ES) [5]. In their study 8 subjects (6 males and 2 females) were studied. From the 8 subjects, 3 had a clinical history of partial seizure, 2 had generalized seizure and 3 had partial seizure turning into generalized seizure. They used data segments that were 1s long and concluded that ApEn is a good measure for temporal localization which decreased during ES, indicative of increased EEG regularity. And in the study conducted

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by Abasolo et al., ApEn was used in analyze EEG regularity in 10 Alzheimer's disease (AD) subjects [6]. They concluded that ApEn decreased (increased EEG regularity) in AD subjects on comparison with normal subjects. Acharya, et al., showed that the mean ApEn values in each sleep stage from 8 normal subjects differed among sleep stages [4]. Also in this study, various non-linear methods, Correlation Dimension (CD), Largest Lyapunov Exponent (LLE), Hurst exponent (H), and Fractal Dimension (FD), were computed for quantifying EEG complexity variation among sleep stages. They concluded that ApEn could be used as a measure of cortical activity in the various sleep stages. ApEn decreased from Wake stage to deeper sleep stage and increased in REM stage. However, ApEn behavior during sleep stage analysis in the individual subjects was not addressed.
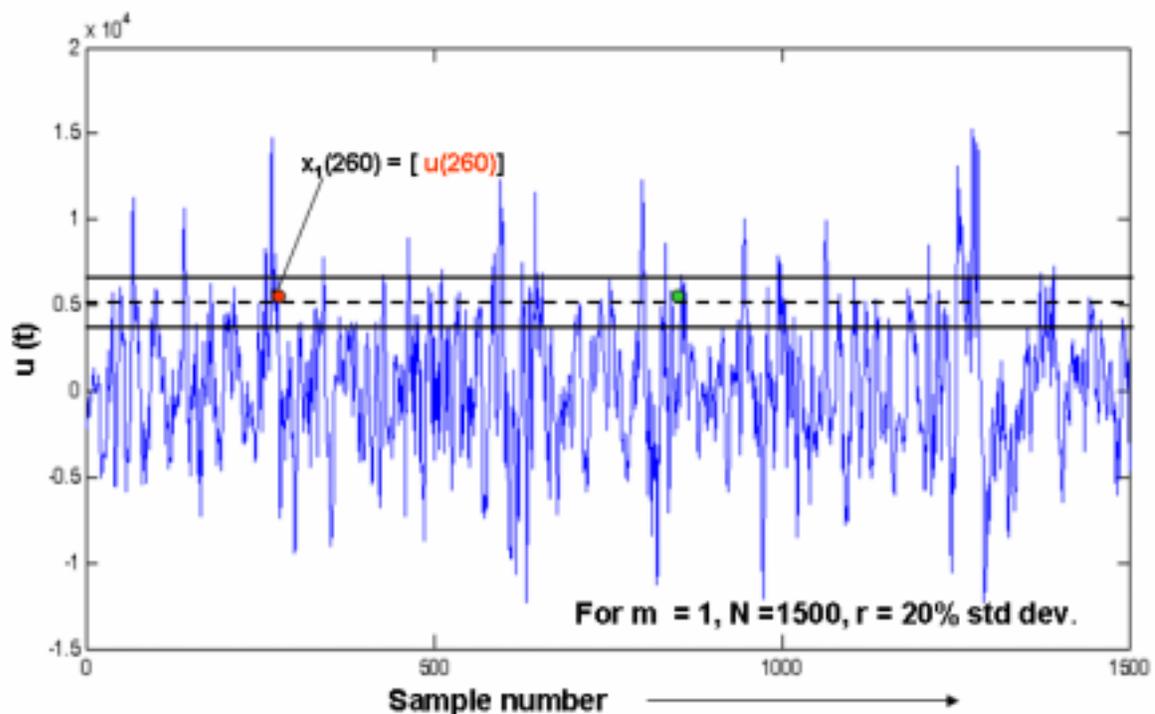
Figure 2. Illustration of the computation of Sample entropy using a template vector x(260) indicated with the red circle and the green circle indicates the conditional vector.

Tsallis Entropy

Tsallis Entropy calculation is described below [25]:

Let s(t) denote the temporal evolution of the EEG signals and consider a discrete-time set of amplitude values D={s(t)$_k$,k=1,2,....K}.   Let the amplitude domain D be partitioned into L equidistant boxes or disjoint amplitude intervals I$_v$(v=1,2,3,...L) covering the space between the maximum and minimum amplitude of the EEG segment. If

$$s_o = \min [D] = \min\{s (k), k=1, 2,....K\},$$
$$s_L = \max [D] = \max\{s (k), k=1, 2,....K\},$$
$$\text{and } s_o < s_1, s_2.... < s_L$$

Then there is set of disjoint boxes {I$_v$ = [s$_{v-1}$, s$_v$], v=1, 2,....L} such that

$$D = \overline{\bigcup_{v=1}^{L} I_v}$$

Then Tsallis entropy

$$TE = (q-1)^{-1}\left(1 - \sum_1^L \left[P(I)_v\right]^q\right)$$

Where $P(I)_v$ is the probability that s (k) is in interval I$_v$

The q parameter makes Tsallis entropy unique. A low value of q (q<1) focuses on long range rhythms while bursts or spikes are detected with high values of q (q >1). In this study we used q=2.

Bezerianos et al. used Tsallis entropy to study EEG activity following brain ischemia. Tsallis entropy was calculated with parameters M = 8 and q = 3. They concluded that this entropy measure is useful in characterizing local irregularity caused by spike during recovery from brain injury [26].

Sleep Apnea:

An apnea was defined by Redline et al. as a complete or almost complete cessation of airflow (<25% of baseline), lasting 10 seconds or longer, while hypopnea was defined as

a decrease in the amplitude of flow or volume to less than 70% of the baseline breathing for 10s or longer without meeting the criterion for an apnea [11].

Two studies have looked into EEG spectral changes in subjects with apnea. Dingle et al., [24] detected EEG spectral changes at the termination of an apnea/hypopnea. Power spectrum and power spectral density were calculated with Fourier transform using the Welch technique. They reported that theta power decreased at the termination of an apnea/hypopnea accompanied by an increase in high frequencies. In another study conducted by Svanborg et al, [23] EEG frequency changes during apnea were studied. They reported an increase in delta band 13 sec after onset of apnea in NREM while this was not seen in REM apneas.

Meadows et al., [28] reported that the response of the cerebral vasculature is drastically reduced in sleep apnea subjects compared to healthy subjects during sleep. Since hypoxia is characteristic of sleep apnea, the failure to increase cerebral blood flow in the face of hypoxia might lead to tissue hypoxia and neuronal injury. Since the scalp EEG is the net neuronal potential at the cortex, neuronal injury in sleep apnea would be expected to alter the EEG signals compared to those of normal subjects. In this study the goal is to develop a technique to discriminate any differences in the scalp EEG between normal and sleep apnea subjects.

Chapter Three: Methods

Subject description:

   This study used data from nine healthy subjects -- 7 young female subjects (21-34yrs), one older female (49yrs), and one middle-aged male (34 yrs) -- acquired from overnight polysomnography studies done in clinical sleep labs. In two of the female subjects, their polysomnograms (PSG) from two consecutive nights (nights one and two) were analyzed. This brings the total number of PSG records analyzed to 11. The EEG, EOG, electrocardiogram (ECG), chin electromyogram (EMG) and respiratory movements were recorded. Sleep staging was done at 30s intervals based on the Rechtschaffen and Kales criteria [1]. Part of the data was obtained from the control part of a 6-degree head-down bed rest (HDBR) NASA study at the University of Kentucky (UK). Sleep staging for this data set was done by a scorer in the Neurology Department at UK. The rest of the data was obtained from the Division of Sleep Disorders Medicine at Henry Ford Hospital, Detroit, MI. Sleep staging was already done upon receipt of this data set. Sleep apnea data also was received from the Sleep Heart Health Study (SHHS) for 108 subjects satisfying the following criteria: 1) females, 2) 40-50 yrs, 3) Caucasian, 4) Respiratory Disturbance Index at 4% oxygen desaturation = 15-30, 5) Body Mass Index < 30, and 6) no history of smoking or stoke.

Data:

   Cerebral montage C3A2 was used for EEG analysis with an additional simultaneous sampling of O1A2 from four of the 11 PSG records. EEG records that were visually free from respiratory or movement artifacts and noise and had minimal EMG activity were selected. Figure 3, displays a segment that has no visual artifacts and would be selected for analysis. Figure 4 displays a segment from a polysomnogram record, with the EMG, EKG, EEG, and the thorax (respiratory motion) channels, which includes a movement artifact. This artifact shows up in all the channels and is due to the subject moving in bed. During this artifact, we can observe activity in the EMG channel, an increased heart rate, some burst activity in the EEG and saturation of the respiration signal. During data selection, the section with the artifact would not be considered. Hence the EMG, EOG,

ECG, EEG, and thorax signals would be displayed as an aid in selection of appropriate data for analysis. For each subject, one or more 30s segments of simultaneous EEG and EOG were selected from each of the different sleep stages. In situations where ECG contamination was visible in the EEG, the ECG signal was also selected. The 30s segments were extracted until the end of the first REM stage of the night. All segments that we could possibly get without artifacts were selected. The EEG and EOG records were digitized at 50Hz. The digitized EEG and EOG records were then imported into MATLAB for further analysis. A total of 270 min of data were analyzed from 11 PSGs including 32 min from Wake, 18 min from stage 1, 111 min from stage 2, 74 min from stage 3/4 and 35 min from REM stage. The average data length per subject was 24.45 min.

Seven of the apnea subjects obtained from SHHS were analyzed. Segments not marked as an apnea event and with oxygen saturation >90 were selected.
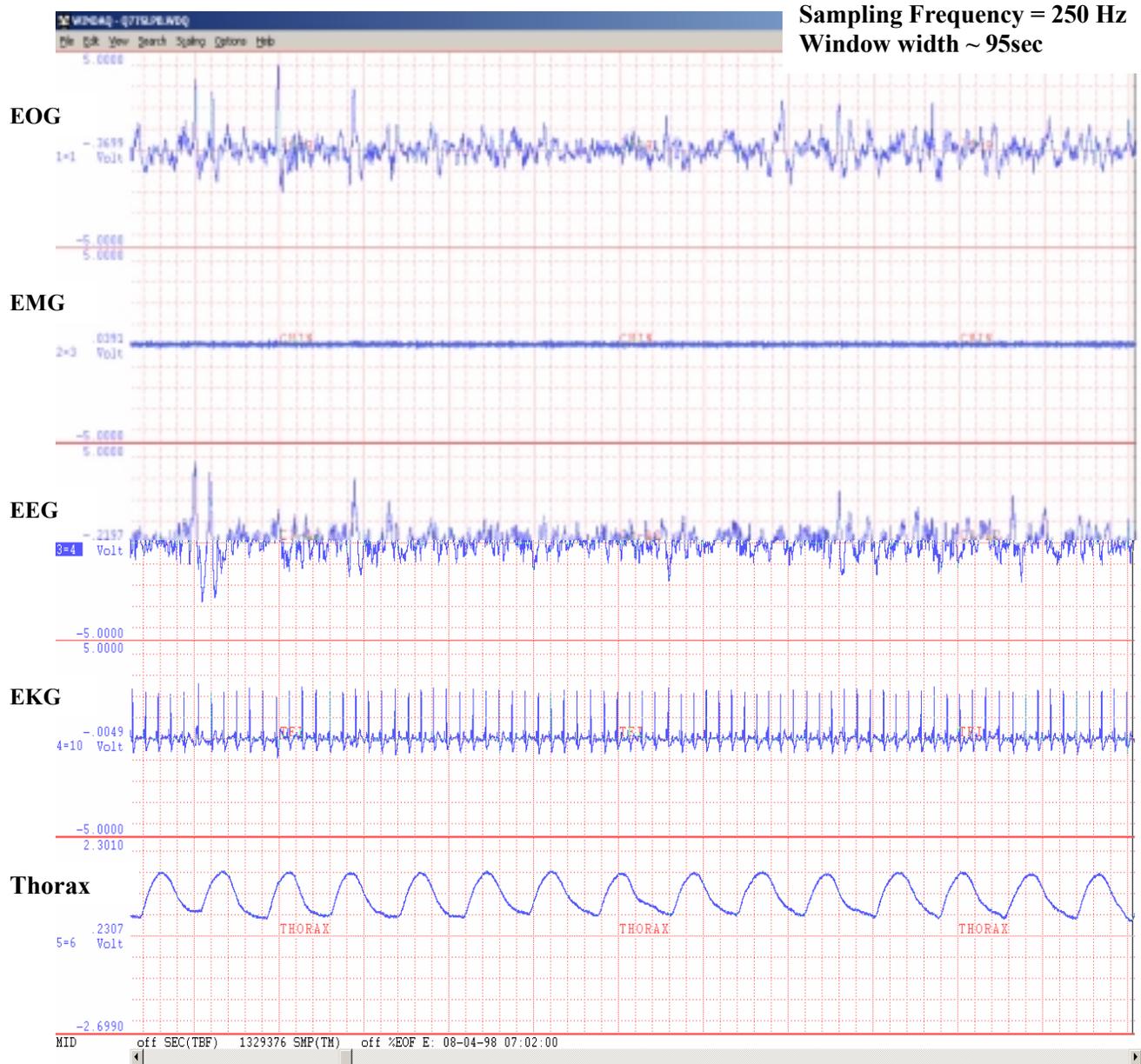
Figure 3: The selection of artifact-free data from a polysomnogram record. Five channels namely, EOG, EMG, C3A2 (EEG), EKG and Thorax are displayed for segment selection.
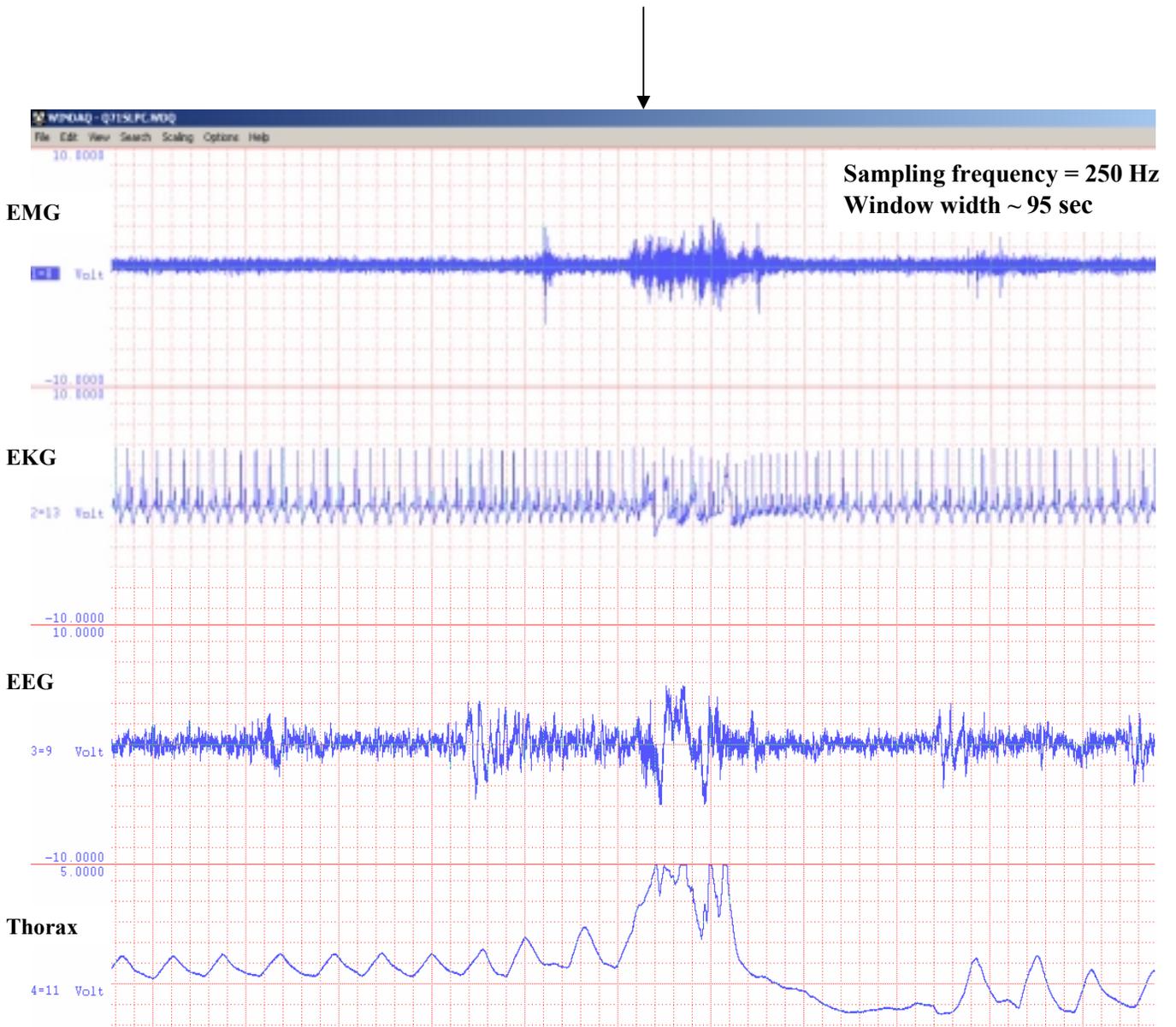
Figure 4: The identification of an artifact in data from a polysomnogram record. Notice the presence of a movement artifact which is evident in the EMG, EKG, EEG and Thorax channels.

Signal Analysis:

Preprocessing

Each 30s EEG and EOG segment (sampled at 50 Hz) was low pass filtered using a Hamming-window based finite impulse response filter with a cut off at 25 Hz. These

segments were then wavelet decomposed using Daubechies wavelet of order 4 (using the MATLAB Wavelet Toolbox). A MMSE filter for noise cancellation [7] was designed for removing EOG contamination of EEG as follows:

After wavelet decomposition, the EEG and EOG components below 3.125 Hz, which will be referred to as EEGF and EOGF respectively from now on, were extracted as the approximation components at the appropriate decomposition level. A non-adaptive optimal noise-removal filter with EOGF as input and EEGF as output (Figure 4) was designed using the following relation:

$$F = R^{-1} g$$

where F are the filter coefficients, let us consider the filter length as p,

so F= [f (0), f (1), f (2)……f (p-1)] ^{T}

Here, T stands for transpose, R is the autocorrelation matrix of EOGF, and g is the cross correlation vector between EEGF and EOGF. This was calculated for p+1 lags. Here elements in R and g are computed by generating a convolution matrix (provided by M. H. Hayes [22]). Each element in R and g is normalized by dividing by the total number of elements in the input signal.

The number of filter coefficients were chosen after considering a number of factors: firstly, the magnitude and phase response of the filter, again the main focus was on the magnitude and phase in the 0-3 Hz range; secondly, the filter impulse response, by checking that the values of the filter coefficients decreased as the number of the filter coefficients increased.; and lastly, the coherence plot, this was done to observe the extent of reduction of EOG-EEG coherence with the designed filter.

Coherence was estimated between:

        1) EEGF and EOGF

        2) EEGF and correlated EOG

        3) EOGF and Filtered EEG

where the correlated EOG is the EOG contamination signal that was removed from EEG.

Filtered EEG is the signal obtained after correlated EOG is subtracted from EEGF (Figure 5).

A coherence value of 0 corresponds to no temporal correlations between the two signals while a coherence value of 1 means maximum correlation. A low coherence value

is preferred between EOG-free EEG and EOGF after application of filter in the 0-3.125 Hz region.

The final EEG component (Filtered EEG) was added to the EEG detail components above 3.125 Hz to form the 30s data segment used for entropy calculation.
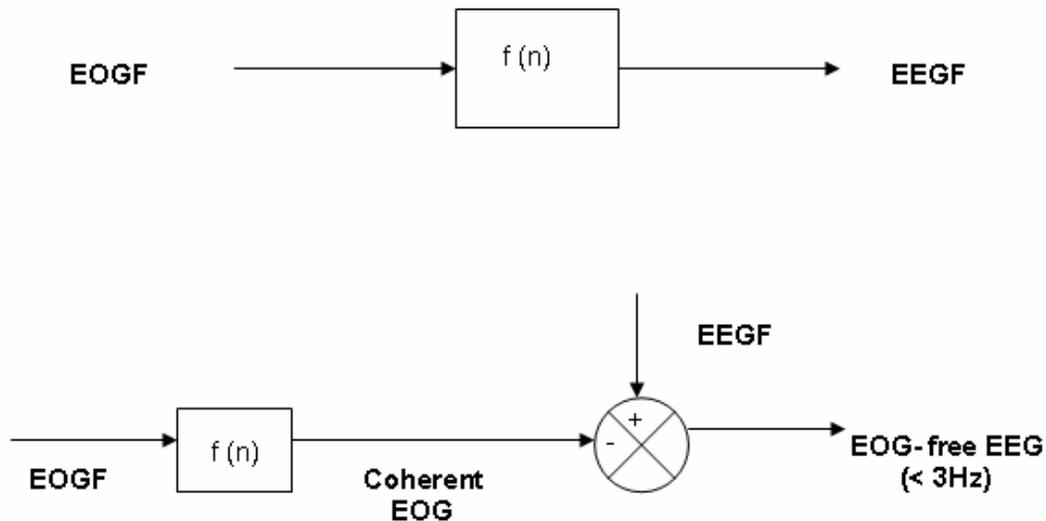
Figure 5. MMSE filter design

Wavelet decomposition was done with two motives in mind, firstly, to reduce the amount of relevant EEG signal being removed during the contamination removal process. For this purpose EOG and EEG signal components below 3.125 Hz were used and we assume that any correlations seen between the two signals above 3.125 Hz is due to EEG power in EOG and not the other way round. Secondly, wavelet decomposition performs orthonormal decomposition, thus making it easy to add the EEG signal component below 3.125 Hz back to the component above 3.125 Hz after contamination removal.

At times when ECG contamination was also present in the EEG signal, it was removed using the procedure similar to that for removing EOG contamination. However, wavelet decomposition of the ECG and EEG was not done at the 3.125 Hz level before removing it since the ECG contains components above 3.125 Hz..

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Entropy Calculation

There are no guidelines for choosing the values for m and r, however the number of matches for entropy calculation can be increased by reducing m (shorter template) and increasing r (wider tolerance), but there are penalties for relaxing these criteria. In many physiological studies [4, 6, 20], the values used for m and r were 1 or 2, and 0.1 to 0.25 times the standard deviation (SD), respectively. The parameter r is set as a fraction of the SD of the data, so this helps in comparing data sets of different amplitudes. We tested Sample entropy for different values of r, e.g., for r = 0.1, 0.15, and 0.2 of the SD, and decided on r = 0.2 for analyzing the data sets. SpEn (m, r, N) was computed with m = 2, r = 20% of the standard deviation of the 30s-long EOG-free EEG. For each subject, the SpEn values in a given sleep stage were averaged. From here on, $SpEn_A$ refers to the averaged SpEn value in a sleep state.

For Tsallis entropy, the maximum and minimum values for the interval (I) were defined using the maximum and minimum from the stage 3/4 data in each subject. Also, values of q=2 and M=6 were used. In the description of Tsallis entropy, it was mentioned that q>1 is to be used for observing frequent events. Since EEG is a complex signal with frequent events occurring (e.g. high frequency bursts), the parameter q was given a value >1. The parameter M was fixed after computing Tsallis entropy with varying values of M (ranging from 4 to ~100) applied to different sleep stages (e.g. Wake, REM, Stage2), and it was concluded that a value of M=6 was to be used since beyond that value for M, the Tsallis entropy of a given 30s segment stabilized .

Statistical Analysis

(i) ANOVA for inter stage comparisons:

Wake stage had the highest $SpEn_A$ value; therefore the $SpEn_A$ values from each stage were normalized to the Wake $SpEn_A$ value in each subject. When $SpEn_A$ is normalized to Wake $SpEn_A$, then it would be explicitly mentioned. Differences between sleep stages (i.e. Stage 1, Stage 2, Stage 3/4 and REM) were tested with analysis of variance (ANOVA) followed by a Tukey test. This was done using SYSTAT 9. Statistical significance was assessed for $p < 0.05$.

(ii) A 2 factor ANOVA was also done where one factor was the 2 groups of subjects (i.e. normals and apnea) and the other factor was the four sleep stages.

(iii) Paired Sample t-test for inter lead comparisons:

To test for statistical significance between the $SpEn_A$ derived from the two sets of EEG leads, C3A2 and O1A2, a paired sample t-test of the $SpEn_A$ values from four subjects was done. Statistical significance was tested for $p < 0.05$.

Analysis of Sleep Apnea data

The first data set received had no annotation information indicating any events (i.e. obstructive apnea (OA), central apnea (CA), or oxygen saturation information), neither was the sleep stage information provided at that point. Sample entropy for this data set was computed for 10 sec-long segments. A shorter EEG segment was used since events related to apnea occur at a smaller time scale than 30 sec. For an event to be termed as an apnea, at least 10 sec of cessation of breathing should occur [11].

Seven sleep apnea records were analyzed; these subjects (females: 46-49yrs) had a Respiratory Disturbance Index (RDI) at 5% oxygen desaturation ranging from 0 to 27.74. Entropy of the sleep apnea data from SHHS was analyzed following the same methods as used for analysis of 30sec segments from normals. The motive behind this analysis was to check for differences between sleep apnea data and control data. Sample entropy was also computed in 5 sec segments in various sleep stages in a subject to understand the entropy variations occurring during an apnea event.

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Chapter Four: Results

Tsallis entropy values:

Changes of Tsallis entropy with sleep state followed a pattern opposite to that followed by SpEn [Appendix A] and, in general, did not seem as consistent as SpEn. Also the results varied depending on the chosen values of M, q, and maximum and minimum of the interval. Hence, the Tsallis entropy computation was later discontinued and the values obtained will not be mentioned in the Results section.

 EOG contamination removal:

The MMSE noise cancellation filter performed well in the removal of EOG contamination. Figure 6 displays the coherence plot between the various signals. Here the number of filter coefficients used was 41. The number of filter coefficients varied from 5 to 47 (0.1 sec to 0.94 sec respectively) for the various data segments. The number of filter coefficients were based on:

1) the coherence plot: the coherence between Filtered EEG and EOGF must be low

2) the impulse response of the filter: when the filter coefficient's value decreases with increase of the number of coefficients then we can settle on the number of filter coefficients. When the number of filter coefficients sufficient to model the data has been reached, then increasing the number of filter coefficients will not contribute much and they will have values close to zero.

3) the frequency response of the filter: we need to check for a decreasing gain with frequency increase and minimal phase shift introduced in the 0-3 Hz range by the filter as we want to keep any distortion introduced by the filter to the minimum.

At times, though, deciding on the number of filter coefficients became difficult because the last filter coefficient was much greater than zero for all tested filter lengths. In certain segments, filter coefficients had numerous alternating cycles, and the number of filter coefficients was chosen where one period of the filter coefficients was completed. Data segments from two PSGs records had to be excluded due to the difficulty of adequate EOG contamination removal. Figure 7 displays EEGF, EOGF, Correlated EOG and Filtered EEG as a function of time. After EOG contamination

removal, the EEG segment was added to the remaining detail components and Sample entropy was computed.

Sample Entropy values:

Figure 8 exhibits single 30 sec segments of EEG signals from a subject in Wake, Stage 2, Stage 3/4 and REM, along with the corresponding Sample entropy values. Examination of all the 30 sec segments selected from a PSG data of any subject indicates that there is a systematic decrease in $SpEn_A$ values from Wake stage to NREM stages 1, 2, 3/4 followed by an increase in REM stage to a value close to Stage 2. Figure 9 displays the Sample entropy variations of the 30 sec segments selected from the various sleep states in one subject during one overnight recording.

The pattern followed by $SpEn_A$ (where $SpEn_A$ is the averaged SpEn value in each sleep stage) was consistent in all the 11 records. It was not possible to obtain more than 30 sec of artifact-free wake EEG and EOG signals from one female subject. Hence this subject was excluded for the statistical analysis. Also, due to the reported differences between sleep architecture of males and females [11], the male subject was excluded from the statistical analysis. The $SpEn_A$ values calculated from the remaining 9 data sets in each of the sleep stage were normalized to wake values for each subject. Figure 10 displays the normalized $SpEn_A$ variation in these 9 data sets. The means of the normalized $SpEn_A$ values in each of the sleep stages are as follows: NREM Stage 1: 0.89 ± 0.05; Stage 2: 0.72 ± 0.09; Stage 3/4: 0.57 ± 0.11; and REM: 0.75 ± 0.10. The individual values for each subject are presented in Appendix B.

Statistical analysis of SpEn values:

The analysis of variance of normalized $SpEn_A$ values of sleep stages indicated non-equal means among the sleep stages ($n=9$, $p<0.001$). Post-hoc testing showed that normalized $SpEn_A$ of Stage 3/4 was significantly lower than the other stages ($p < 0.01$). In addition, normalized $SpEn_A$ was greater in Stage 1 than in Stage 2 and REM ($p < 0.04$). However, Stage 2 was not significantly differently from REM.

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SpEn Interlead values:

For 4 subjects data were also available from O1A2 EEG leads. To determine whether the observed variations of $SpEn_A$ with sleep stage were unique to the C3A2 leads, $SpEn_A$ was compared between the 2 sets of leads. $SpEn_A$ values calculated from O1A2 leads also follow a systematic pattern similar to that observed in $SpEn_A$ values calculated from C3A2 (Figure 11). The slope and intercept of the regression line between the $SpEn_A$ values of the C3A2 and O1A2 leads were 1.07 and -0.04, respectively. The paired t-test indicated significant differences between the $SpEn_A$ values, implying that the two pairs of leads follow similar patterns ($p=0.816$) of SpEn variation with sleep stages.

Sample Entropy in Sleep apnea data:

The $SpEn_A$ (averaged entropy value in each sleep stage from each subject) values were normalized to W. The mean normalized $SpEn_A$ values are as follows Stage 1: 0.96 ± 0.1, Stage 2: 0.83 ± 0.06, Stage 3/4: 0.75 ± 0.06 and REM: 0.91 ± 0.04. Figure 12 displays the normalized $SpEn_A$ in each of the seven subjects along with the mean normalized $SpEn_A$. On comparing the mean normalized $SpEn_A$ values obtained from the normals and sleep apnea subjects, we notice that these values in sleep apneics are higher compared to normal subjects. The plots of the Sample entropy values in each of the 7 subjects are displayed in Appendix [C].

This technique was applied and entropy computed for shorter segments in: (1) a severe sleep apnea subject with periodic-breathing-with-apnea (Figure 13), and (2) a sleep apnea subject during Wake and Stage 2 (Figure 16). From Figure 11 it can be observed that the average entropy increases as ventilation goes from being periodic to periodic-breathing-with-apnea. Also, a slight periodicity resembling the periodicity in ventilation is seen in the entropy values calculated from the EEG. Figure 14 is a plot of the 10sec SpEn values along with the oxygen saturation values corresponding to that time. Figure 15 displays the cross correlation between SpEn and the simultaneously recorded oxygen saturation from Figure (14), for lags up to 30. This result indicates the presence of a periodicity in

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SpEn$_A$ that is correlated with the oscillation in oxygen saturation. Also to be mentioned here is that entropy was computed for 10s long segments. Figure 16 displays entropy values of 5s data segments in a sleep apnea subject obtained from SHHS. Here each cluster of bars is composed of at least one Obstructive apnea (OA) event lasting for a minimum of 20sec. In Figure 16 we notice that the average entropy values in Wake and Stage 2 are approximately the same. In normal subjects we noticed that Stage 2 entropy value was lower than in the Wake stage.

Statistical Analysis of results from normals and Sleep apnea data:

The analysis of variance of normalized SpEnA values from the two groups of subjects – normals and sleep apneics - indicated non-equal means among the two groups (p<0.001). Post-hoc testing showed that normalized SpEn$_A$ of Stage 3/4 and REM of the apnea data were statistically different from the normals. Table 1 gives the pair wise comparison probabilities between the two groups in the various sleep stages. In apnea data only Stage 3/4 was statistically different from REM and Stage 1.
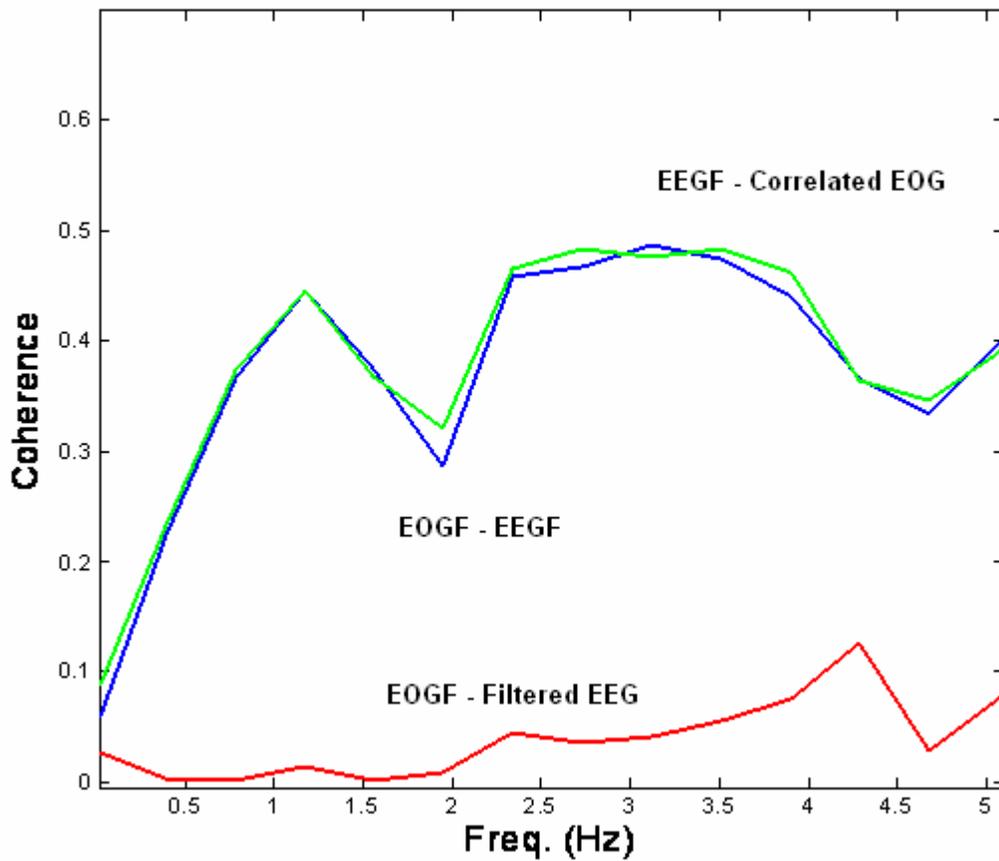
Figure 6: The coherence plot between EEGF and EOGF, EEGF and Correlated EOG and EOGF and filtered EEG. Notice that the coherence is reduced after EOG contamination has been removed and EEG was filtered. Here coherence between 0-5 hz has been displayed.
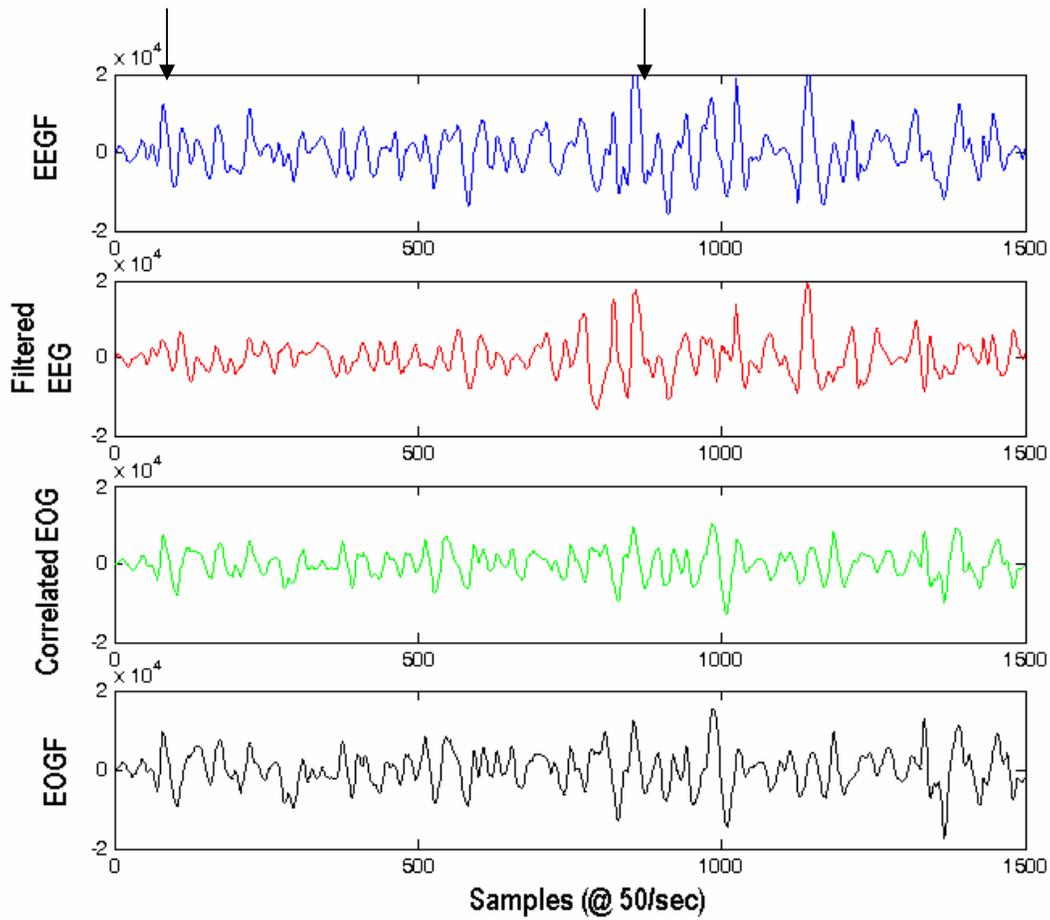
Figure 7: An example of signals before and after EOG contamination removal. Notice the EEGF and Filtered EEG with EOGF and Correlated EOG at the locations indicated by the arrows.
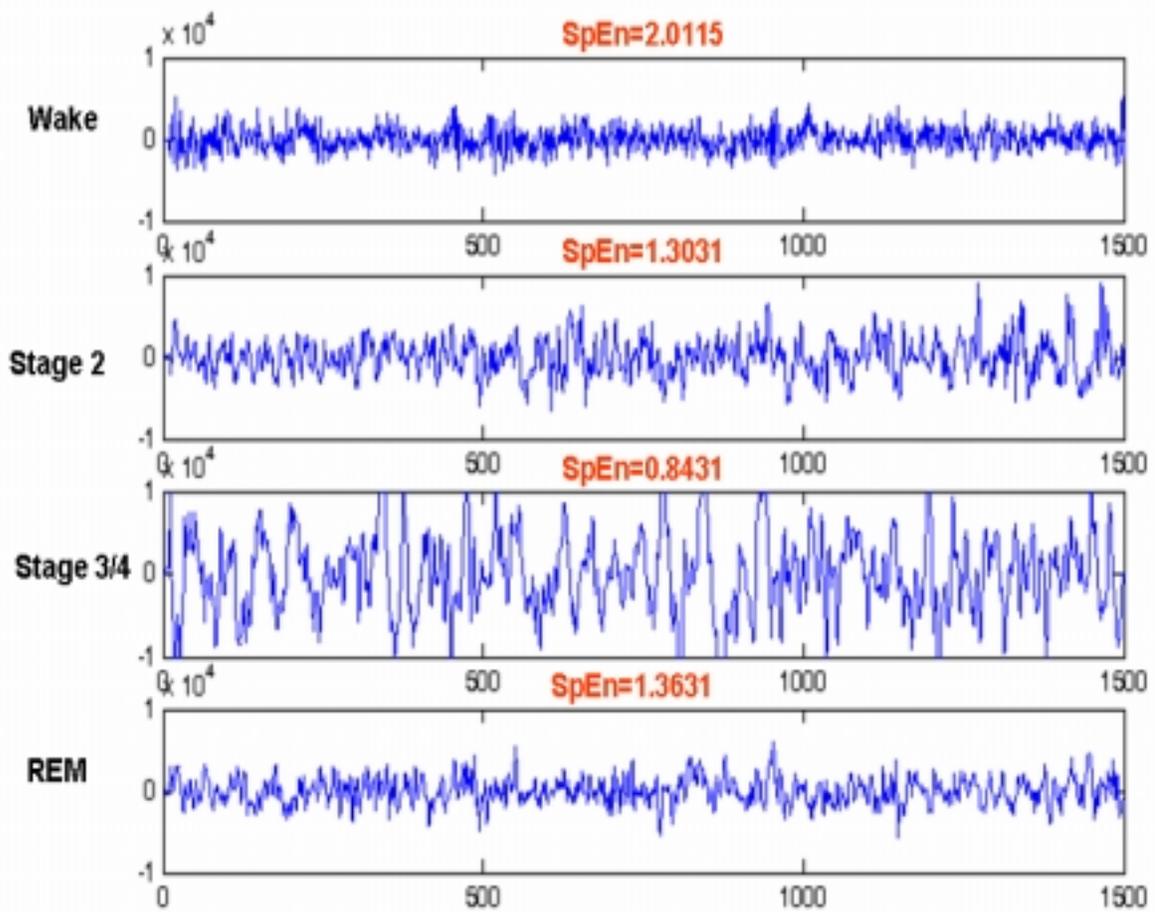
Figure 8: The Sample entropy value for 30s segments from a polysomnogram record after EOG contamination removal in the various sleep stages. All data jnnnare from one subject.
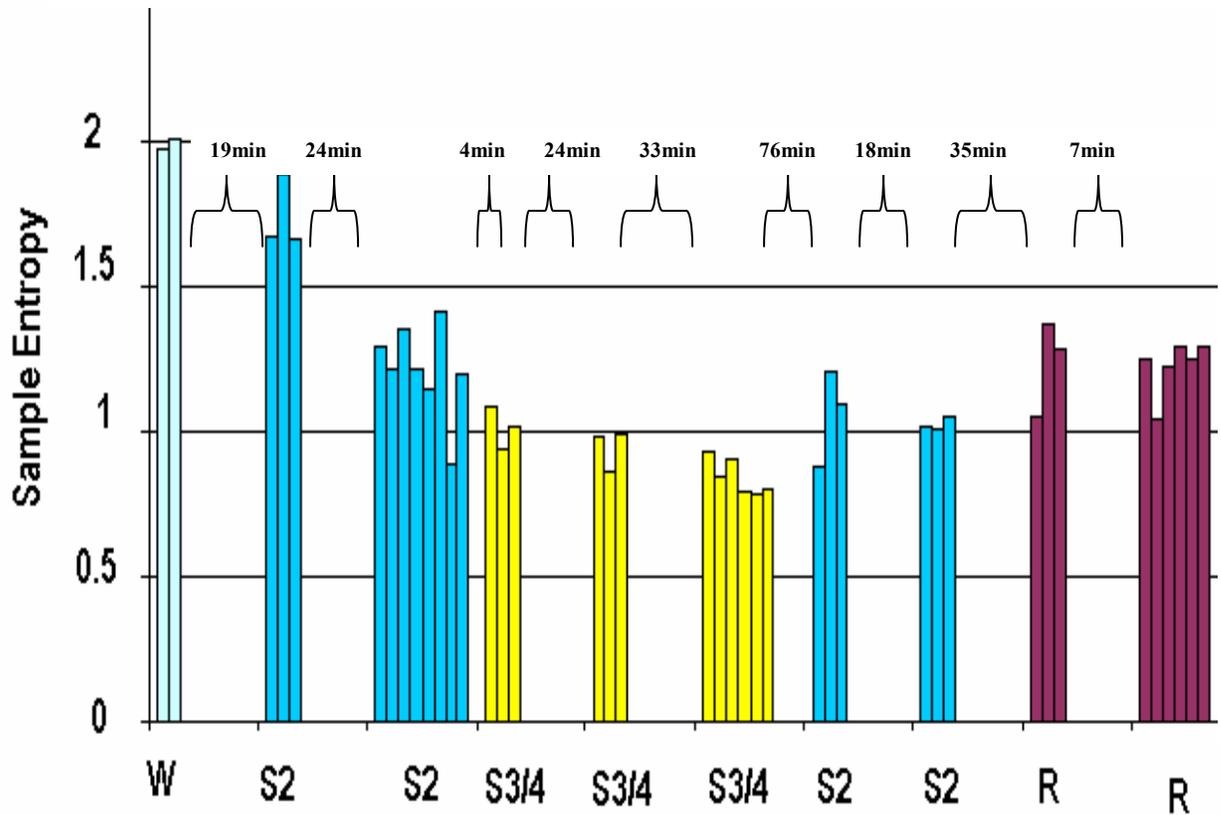
Figure 9: The Sample entropy values in the various sleep states from a single polysomnogram record. Each bar corresponds to 30s data segment. The bars that are plotted together are consecutive in time with a maximum separation of 7 mins while the separations in time of the gaps between the bars are indicated. W =Wake; R=REM.
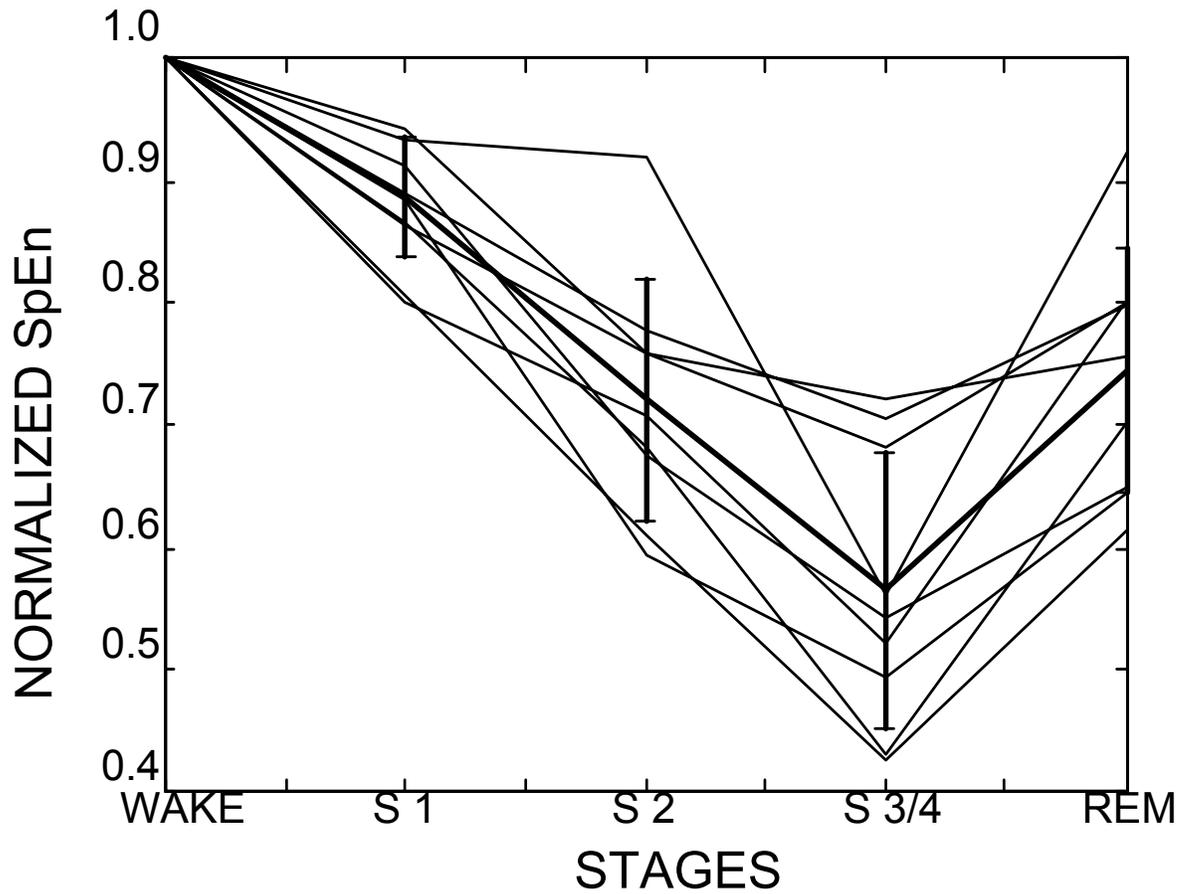
Figure 10: The individual normalized $SpEn_A$ values for each subject normalized to awake $SpEn_A$ values (thin lines) and the mean $SpEn_A$ values normalized to mean awake $SpEn_A$ values (solid line), are plotted as a function of sleep stages.
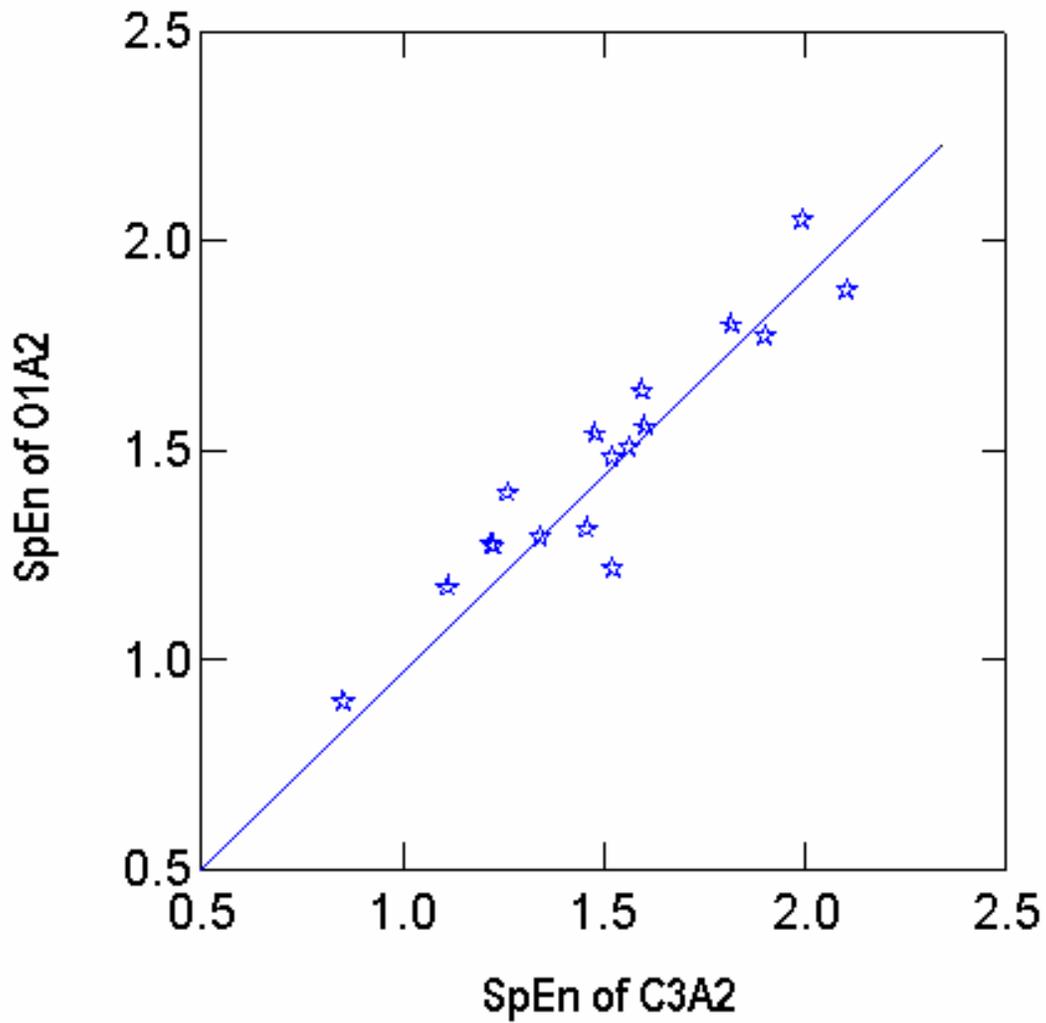
Figure 11: Plot of SpEnA of O1A2 and SpEn of C3A2. Solid line is the linear regression line. Each star symbol indicates average sample entropy from one of the 4 subjects in one sleep state.
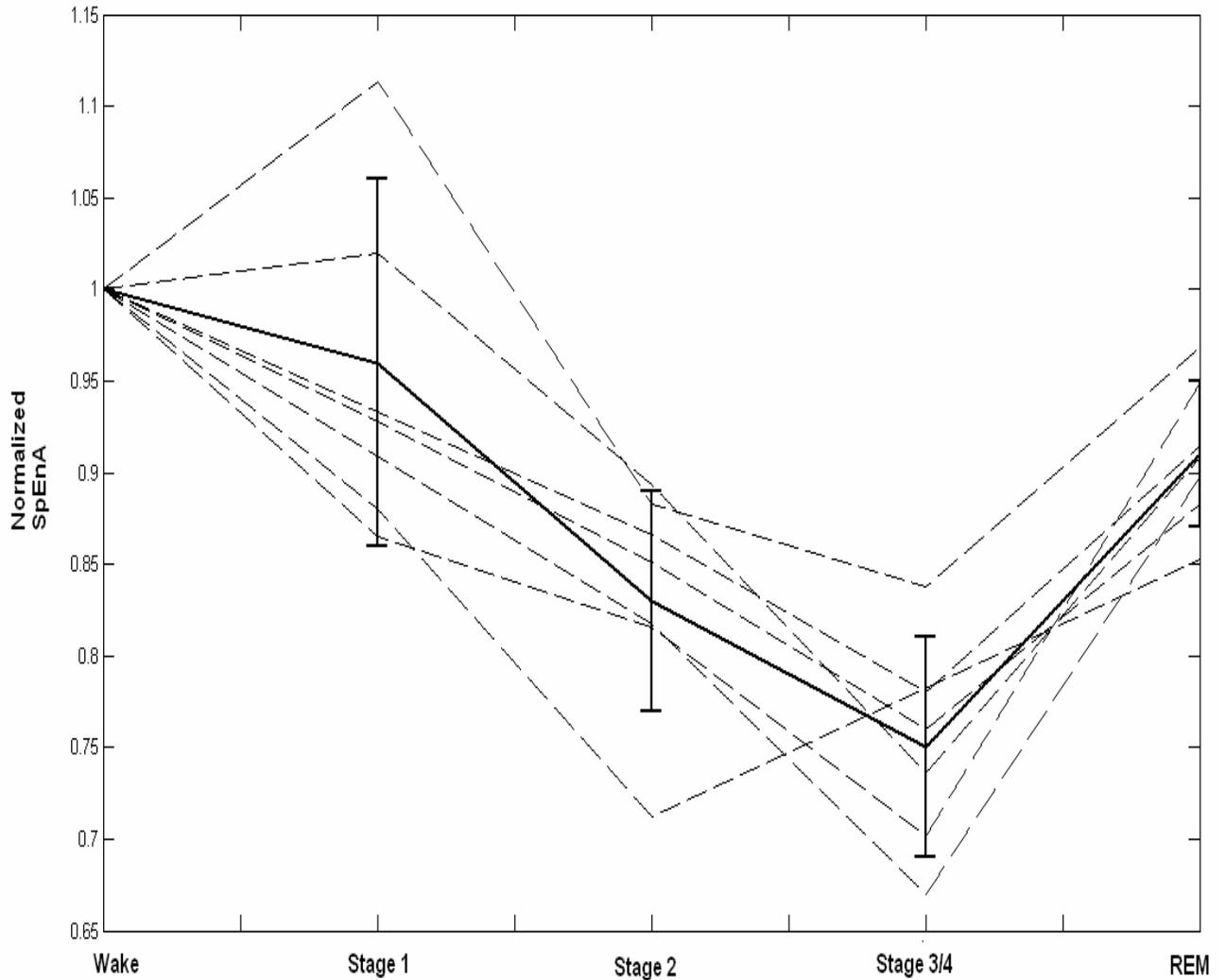
Figure 12: The individual normalized SpEn$_A$ values for each of the seven sleep apnea subjects normalized to awake SpEn$_A$ values (dashed lines) and the mean SpEn$_A$ values normalized to mean awake SpEn$_A$ values (solid line), are plotted as a function of sleep stages.
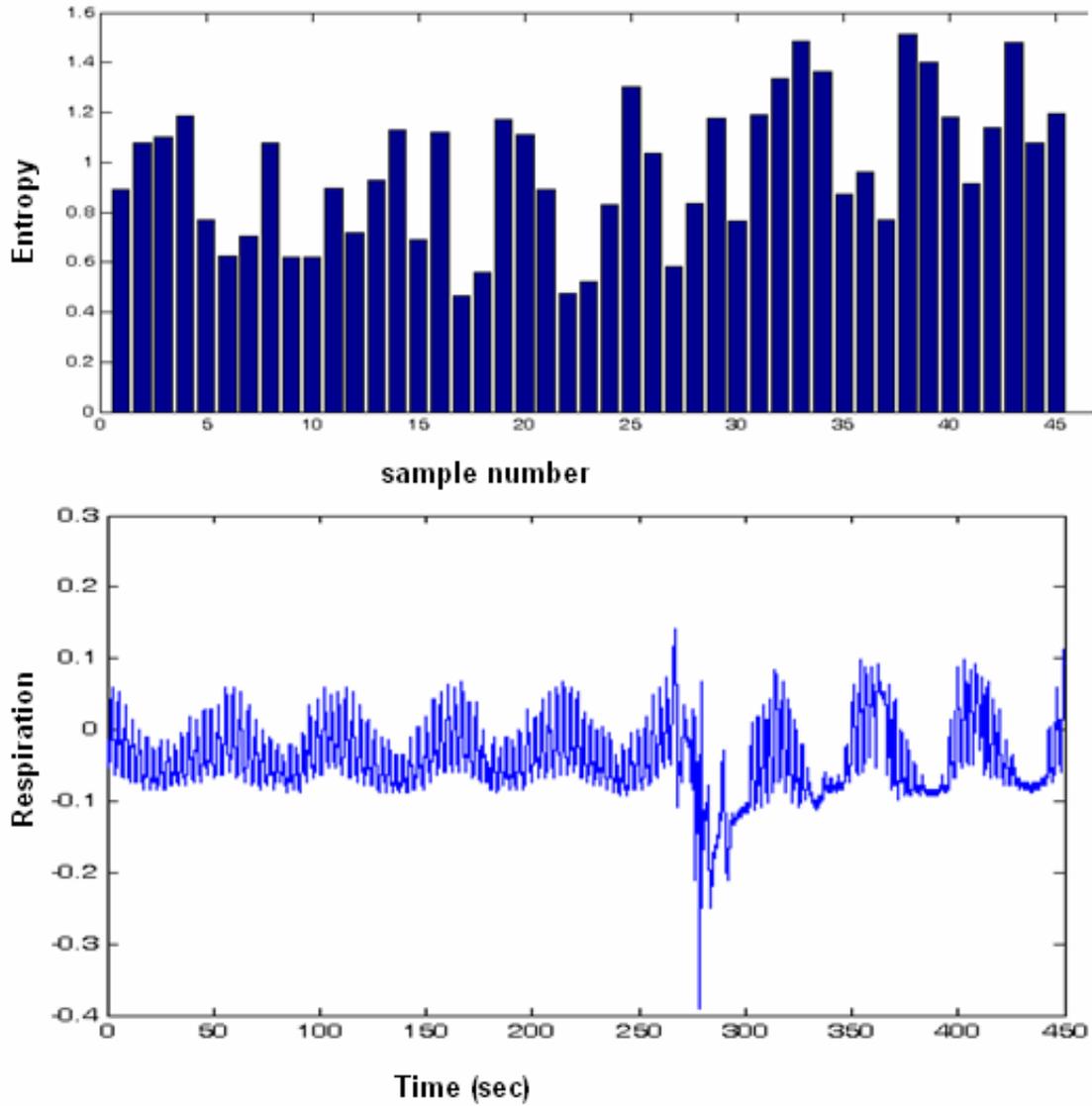
Figure 13: 10s Sample entropy computation on 450s of continuous EEG data in a subject with severe sleep apnea. Note the simultaneously recorded respiration signal with ~ 280s of periodic breathing followed by periodic-breathing-with-apnea.
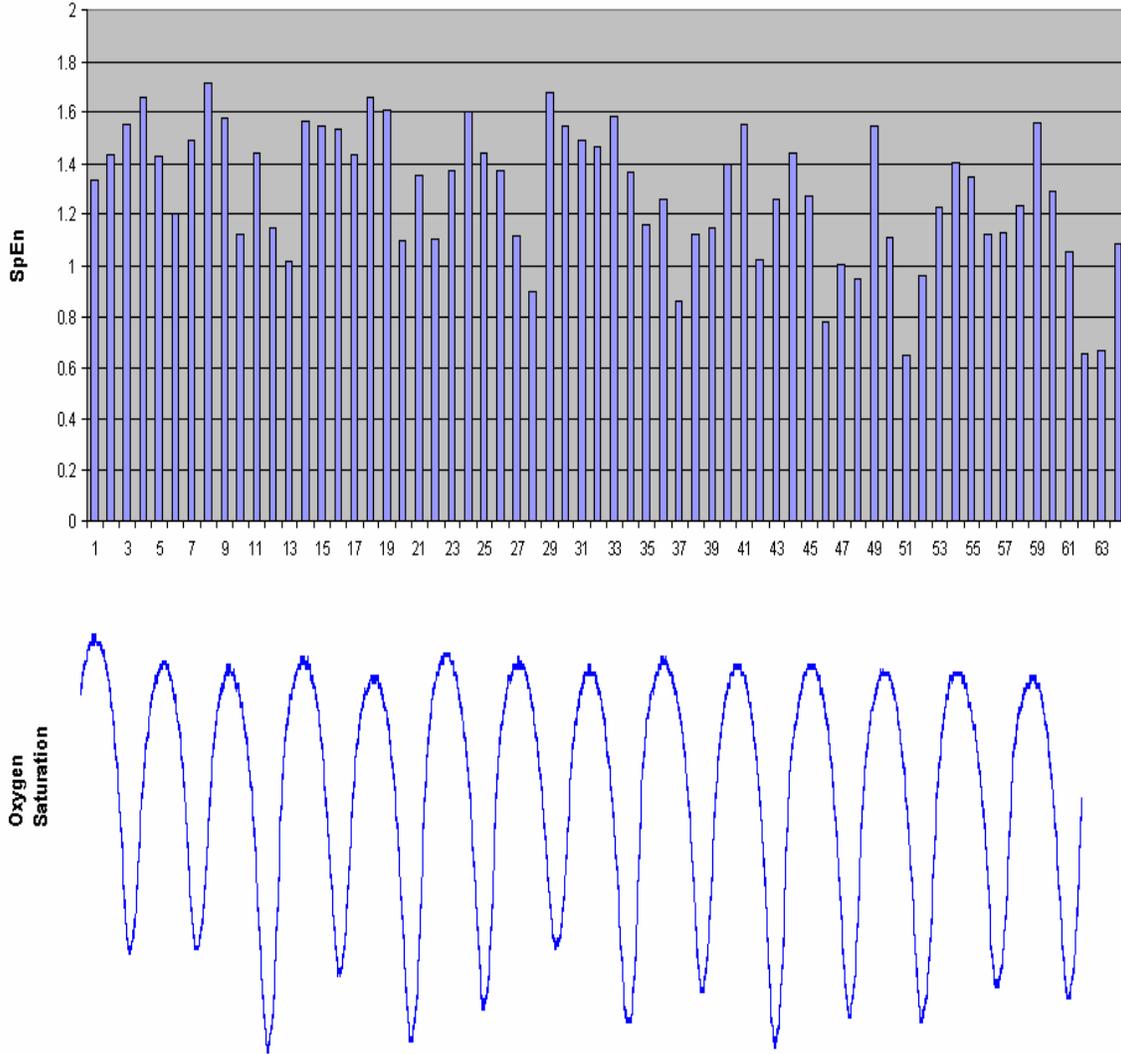
Figure 14. Displays the 10sec entropy values along with the corresponding oxygen saturation signal (uncalibrated).

Cross Correlation between SpEn and oxygen saturation

Lags
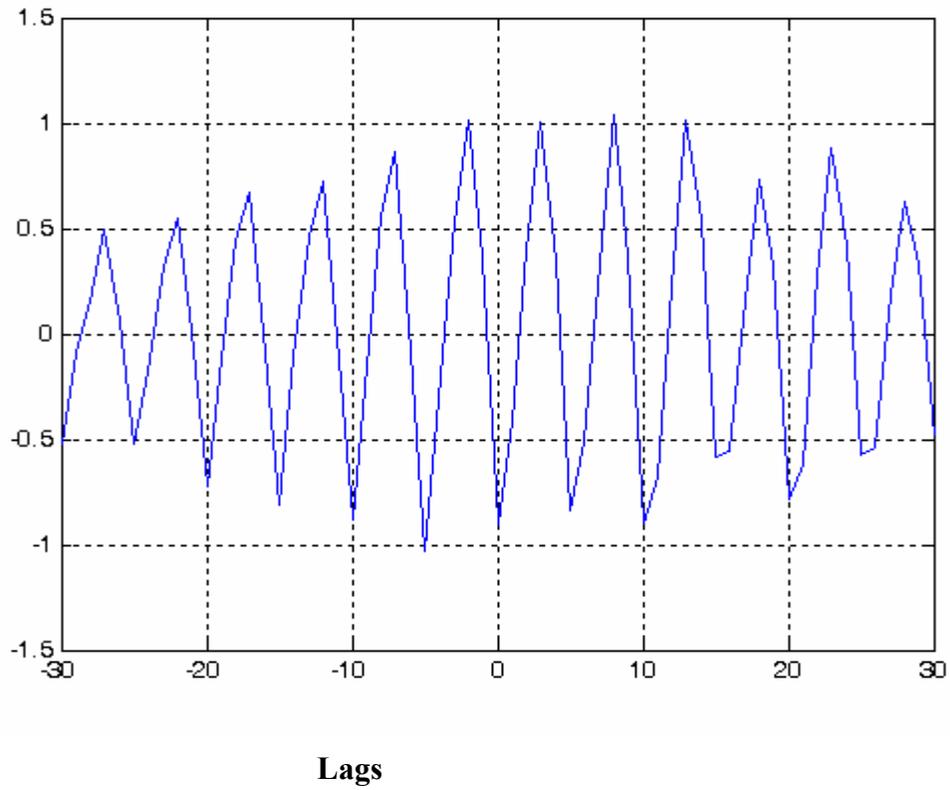
Figure 15: Notice the high, and periodic, normalized cross correlation between SpEn and oxygen saturation (in Figure 14)
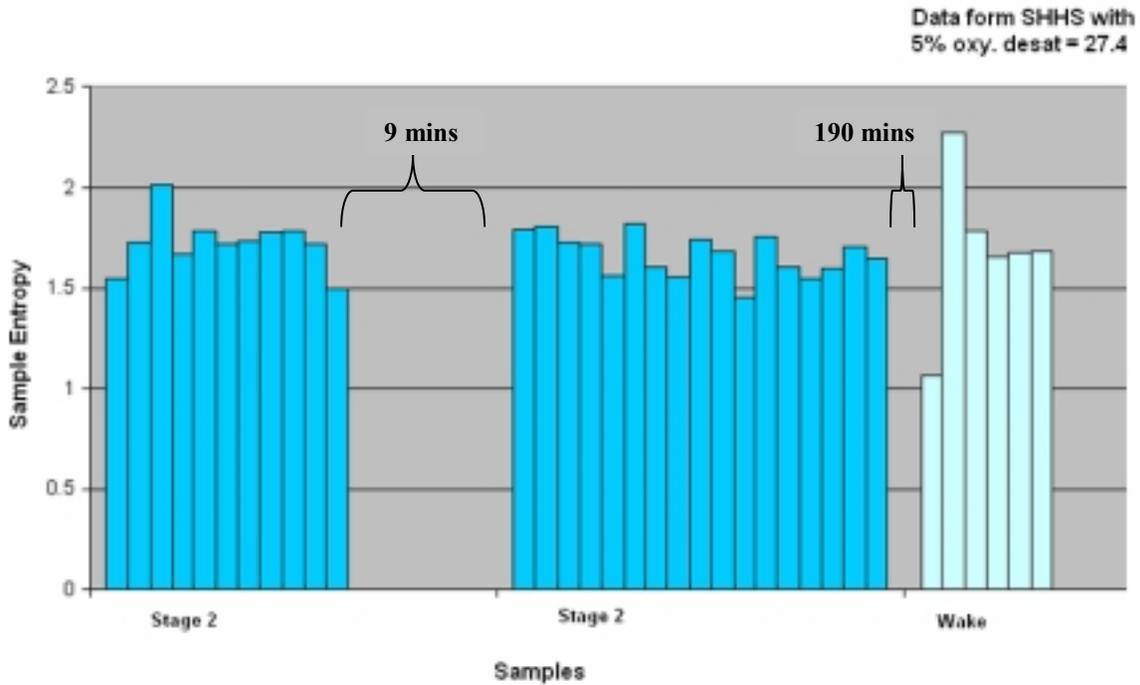
Figure 16: 5s Sample entropy computed on a subject with sleep apnea. Notice the comparable average value in Wake and Stage 2. The bars placed together are consecutive in time. Each cluster contains at least one OA event. 27.4 at 5% oxygen desaturation indicates the Respiratory Disturbance Index (RDI) value. RDI is the number of abnormal respiratory events /hr.

	RA	RN	S1A	S1N	S2A	S2N	S3A	S3N
RA	1.00							
RN	0.007	1.00						
S1A	0.968	0.001	1.00					
S1N	0.999	0.035	0.801	1.00				
S2A	0.7	0.441	0.196	0.941	1.00			
S2N	0.001	0.999	0.000	0.007	0.164	1.00		
S3A	0.023	1.00	0.003	0.085	0.600	0.999	1.00	
S3N	0.00	0.001	0.000	0.000	0.000	0.006	0.004	1.00

Figure 17, Table 1; The pairwise comparison probabilities between the various sleep stages from the two groups of data (9 normals and 7 sleep apnea records) are given. This is obtained from a post hoc test performed after ANOVA analysis (p<0.001) of the two groups. Here N refers to Normal subjects and A refers to Apnea subject. Notice that Stage 3/4 and REM are statistically different from the two groups.

Chapter Five: Discussion

In this chapter we will try to understand and interpret our results by providing physiological explanations. Also the limitations of this study will be discussed here.

The technique proposed in this study involving Sample entropy is shown to be sensitive to differences in the temporal structure of the EEG signals in the various sleep stages. Furthermore, the qualitative differences in SpEn among sleep stages were highly consistent in individual subjects after removing EOG contamination from the EEG signals. Although the data were not shown, this consistency was not seen without EOG removal. This systematic variation of SpEn among sleep stages was also observed in leads O1A2. Tsallis entropy did not vary with sleep state as consistently as Sample entropy, and its value was highly dependent on the values chosen for the parameters.

For a couple of reasons Tsallis entropy was not used in this study as a means to quantify EEG complexity. Firstly, the maximum and minimum values of the amplitude intervals used in calculating Tsallis entropy were fixed based on the largest and the lowest amplitudes respectively, obtained from the segments selected. These segments were processed and contamination removed prior to finding the maximum and minimum values. This fixing of the limits is known as a fixed partitioning approach [16]. An adaptive partitioning can also be done, during which the maximum and minimum would vary depending on each 30s segment. Fixed partitioning tracks the energy change in the segment while the adaptive partitioning tracks transient events [16]. Hence, the entropy value varied depending on the approach. Secondly, depending on q, burst activity or long range rhythms can be detected, so the value of q chosen had an influence on the result observed. For this study an integrative measure of the alteration of EEG complexity with sleep states is required. Hence, due to the above reasons, the interpretation of Tsallis entropy became difficult and was no longer used in this study.

Certain factors or limitations need to be mentioned before attempting to interpret the results in this study. Firstly, it was difficult at times to fix on the number of filter coefficients for the optimal filter; this made adequate removal of EOG contamination impossible. The number of filter coefficients varied from 5 to 47 (0.1 sec - 0.94sec).

However when EOG contamination was not able to be removed (decided by looking at coherence plot and filter response, etc.), the 30s segment was not considered for entropy computation. Secondly, the optimal noise cancellation filter designed here takes into consideration only the linear correlation between the EEG and EOG, so any nonlinear correlations will not be removed. Thirdly, here we are assuming that left EOG will have the maximum correlation with C3A2 as the leads are placed closer to the C3A2 electrodes than the right EOG electrodes are. Also, by not considering the right EOG for EOG contamination removal we are assuming that both the electrodes are equal in magnitude but opposite in direction considering the manner in which the EOG electrodes are placed. This linear relation between the two EOG electrodes might not be the case in reality. Fourthly, to avoid much of EEG power from being removed, EOG contamination removal was limited to 0-3.125 Hz range where the concentration of EOG power is highest. With this constraint, the EOG contamination at frequencies higher than 3.125 Hz is not considered for removal.

Fifthly, the data set from the HDBR study done at UK included both first night and second night PSG records. Curcio et. al conducted a study involving PSG from two consecutive nights to study the first night effect. They performed a spectral analysis of the EEG and concluded that there was a decreased sleep quality, with more Stage 1 and Wake in the first night sleep [19]. But, in another study conducted by Touissant et al., they reported that there are no differences between the first and second night and suggested that the first night data can be used for sleep analysis [21]. Curcio et al. also reported an increase in EEG complexity (increased delta power and beta power in the different brain locations) in the first night [19]. We believe that poor sleep quality is not reason enough for excluding the first night data from the analysis.

In Sample entropy the high entropy in Wake stage is mainly due to the desynchronous EEG activity. The EEG becomes more regular as the subject enters into deeper NREM sleep stages (i.e. Stage 1 to Stage 3/4) causing SpEn to fall. Stage 3/4, also known as deep sleep, had predominantly delta waveforms. EEG activity is most regular in Stage 3/4. This regularity of Stage 3/4 leads to a low entropy value that we obtain. This method

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was able to indicate a significant difference between REM and Stage 1. This difference hints at a possibility of some EEG signal component that is distinguishable between these stages. But, in this study no significant difference was obtained between REM and Stage 2. A possible explanation could be due to the fact that a REM cycle is almost always preceded by a Stage 2. Hence certain characteristics of Stage 2 might be present in REM which makes it difficult to find a statistical difference between them.

In a study conducted by Fell et al., eight different EEG measures were calculated: spectral measures such as relative delta power, spectral edge, spectral entropy and first spectral moment, and nonlinear measures such as correlation dimension (CD), largest Lyapunov exponent (LLE) and approximated Kolmogorov entropy (K2) [17]. They concluded that the nonlinear measures performed better in discriminating sleep Stage 1 and 2, whereas spectral measures discriminated Stage 2 and 3. Therefore, no measure alone, nonlinear or spectral, was able to differentiate among the sleep states. In another study conducted by Acharya, et al., various nonlinear measures such as CD, fractal dimension, LLE, ApEn, Hurst Exponent, phase space plots and recurrence plot were used to quantify cortical function in different sleep stages [4]. Their ApEn findings were similar to ours in the sense that average ApEn decreased during the transition from Wake to NREM 1, 2 and 3/4. However, these authors did not perform post-hoc testing to determine which sleep stages had different ApEn values, and the reproducibility of the mean responses in individual subjects was not discussed. Furthermore, EOG contamination was not removed from their EEG signals. In addition, the data segment in each subject from a sleep stage was as short as 8 sec, whereas we analyzed at least 30s of data from each subject in each sleep stage. Since SpEn variations are present within a sleep state, a longer segment would provide a better estimate of SpEn of the sleep state.

In a study conducted by Ferrara et al., topographical differences were found in EEG band powers between the frontal and occipital brain locations [18]. The EEG power over the time course in the first 30 min of sleep exhibited anterior-posterior gradient with maximal power at the frontal region. Normalizing each lead to itself can compensate for this sort of gradient difference. With the technique proposed in this study, this systematic

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variation of SpEn among sleep stages was also observed in leads O1A2 as well as C3A2, raising the possibility of observing similar patterns on other cerebral montages. Since Sample entropy is an integrative measure of the frequencies present, it is likely that changes in certain EEG bands might not affect the entropy computation much. It might be worth seeing how the frontal EEG leads behave on application of this technique.

Sample entropy variations are also seen within sleep states (Figure 9), implying that there are some brief transient alterations in the EEG properties which are picked up by Sample entropy. One possible explanation is that during a sleep state, though a net number of neurons are hyperpolarized or depolarized depending whether in sleep or wake stage respectively, there are transient changes brought about in neuron activation voltage. The mechanism(s) responsible for these transient changes is still not fully understood. It is also possible that alterations in these short-lived changes could be altered which might be indicative of some sleep disorder. This possibility is what led to the computation of Sample entropy for segments shorter than 30s in subjects with SDB.

The observations and discussions with sleep apnea data are preliminary but some tentative conclusions can be drawn based on the results of ANOVA analyses. Only Stage 3/4 was statistically different from REM and Stage 1; all other stages were statistically similar. Hence SpEn across sleep stages in sleep apnea subjects were more similar compared to normal subjects. Further validation of these results is necessary, as discussed later under the suggestions for future studies. An interpretation of the observations made from the 7 SHHS sleep apnea records analyzed is complicated by the following concerns: 1) though the subjects were apneics, initially no apnea events were present in the segments selected also oxygen saturation level was ≥ 90, hence a conclusion cannot be drawn with the results obtained from analyzing data from normal subjects, 2) the age difference between the two groups is large. Hence further analysis requires a control group in the age range (40-50yrs) and an apnea group with segments containing apnea events.

On applying this technique on a severely sleep apnea subject with segments of periodic breathing and periods of periodic-breathing-with-apnea, we noticed an increase in the

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average entropy value in the apnea segment. Now this increase was observed on comparing an EEG data segment corresponding to periodic breathing and with a segment corresponding to periodic-breathing-with-apnea within one subject. Another observation made in our study was a possible periodicity in entropy during the periodic-breathing-with-apnea. A possible explanation could be that, due to the activity of the respiratory center in the brainstem, during hyperventilation the neurons that project upwards towards the cortex are modulated. This modulation of the neurons shows up in the EEG activity measured at the cortex. It is still not clear whether ventilation drives the entropy changes or the EEG changes drive the ventilation. But it is also possible that a third signal drives them both. It would be interesting to see how entropy behaves on comparing sleep apnea subject with a healthy control subject. Abasolo et al., [6] studied EEG activity in Alzheimer's disease (AD) subjects and reported a decrease in ApEn in AD subjects compared to a (healthy) control group. Hence a neuronal disorder (due to AD) caused a change in the EEG activity recorded at the scalp and a decrease in ApEn. This decrease in ApEn observed in AD subjects might also be true for subjects with sleep apnea. Since hypoxia is characteristic of sleep apnea, a neuronal disorder might occur causing a similar change in the EEG activity observed. A significant difference was seen only at the parietal electrode. However, the variation of ApEn within a subject was not mentioned

Another possible explanation could be that the partial pressure of oxygen is affected as the oxygen saturation falls and rises during periodic-breathing-with-apnea. This affects the PO_2 (pressure of oxygen in a mixture) in the brain which then alters the firing of the neurons. Since the activation potentials of the brain neurons are affected, the EEG activity measured at the scalp is altered.

Also, on applying the techniques discussed in this work in a subject with occasional apnea but without periodic breathing (a less severe case of apnea), we observed an increase in the average entropy value such that both stages (Wake and Stage 2) had comparable SpEn. One possible explanation of this rise in average entropy value among sleep stages could be the following: In an apnea subject, the centers of the brain responsible for inducing deeper sleep and inhibiting high frequency EEG activity are

suppressed. This causes the brain to stay in an alert state and very rarely enters into deeper sleep stages. The lighter sleep stages (Stage 1 and Stage 2) occur when the sleep inducing centers attempt to get the patient into deep sleep but are not successful as its functions are still suppressed. This leads to an entropy value close to Wake stage.

To understand how this average entropy value described compares to a healthy subject, we hypothesize that a decrease in entropy might be seen in apnea subjects compared to normal subjects because of the following reason: apnea subjects rarely enter into deep sleep in night, hence they are drowsy and sleepy during daytime (a possible compensation mechanism due to the suppression of deep sleep in the night). This sleepiness and drowsiness appears in the EEG and causes the entropy to be lower compared to a normal subject's Wake stage (as they are more alert). Then in apnea subjects, the entropy of the remaining sleep stages averages closer to the Wake stage entropy value.

Chapter Six: Conclusions

1. Sample Entropy is sensitive to differences in the temporal structure of the EEG signals in the various sleep stages.

2. Sample Entropy follows a systematic pattern of variation with sleep state in individual normal subjects. As sleep progresses from Wake, there is a steady decrease in SpEn in Stage 1, through Stage 2, into Stage 3/4 and then an increase in REM to a value close to Stage 2

3. This pattern was also observed in EEG signals from O1A2 leads as well as C3A2 leads. It is possible that this pattern can be seen in other leads also.

4. SpEn in each sleep stage was statistically different from that in other sleep stages, except that SpEn in Stage 2 and REM were not different.

5. This technique can be used as an aid in sleep stage identification but SpEn would not be sufficient, by itself, to determine sleep stage.

6. Preliminary results from sleep apnea data show that SpEn is more similar across sleep stages in apneics and is correlated with oscillations in ventilation/oxygen saturation in a limited sample of subjects. Hence this technique can be used in further understanding EEG activity in apnea subjects

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Suggested Future Directions:

1) Intra stage variations within a sleep state were observed during analysis of normal records. Maybe these transient variations are not present or inhibited in subjects with apnea. Hence it would be of interest to understand or identify any pattern, if present, followed by sample entropy computed in shorter segments. I suggest further exploring Markov Modeling and its application in this purpose. Data from normal subjects and also subjects with sleep apnea might be used.

2) Based on the comparable average entropy value within a subject with sleep apnea between sleep Stage 2 and Wake, I suggest confirming whether this is observed in sleep apnea subjects in general. We could start by comparing average SpEn in the various sleep stage in a number of subjects. Since the subjects in SHHS are from a higher age group (40-50yrs), it is also essential to form a control group in the same age group for comparison.

3) Based on the rise of entropy within a subject when ventilation changed from periodic breathing to periodic-breathing-with-apnea, I would suggest confirming this rise in entropy by applying in more than one subject. We can check whether entropy is able to detect the alteration in EEG activity during all apnea events in at any levels of oxygen saturation.

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Appendix A

Sample and Tsallis entropy variations in the various sleep stages from a PSG record.

Notice the generally opposite pattern followed by the two entropies.
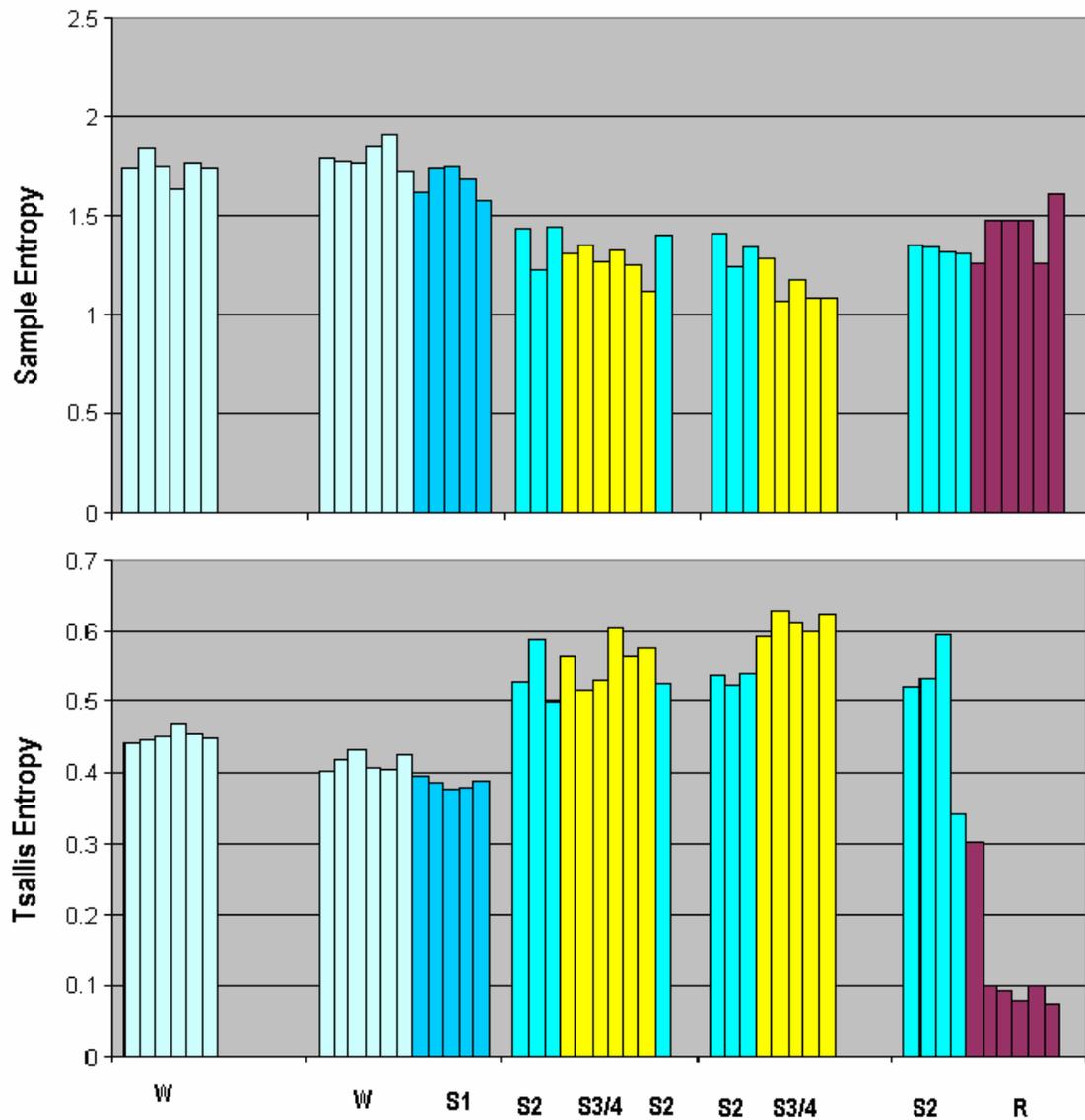
W = Wake, S1 = Stage 1, S2 = Stage 2, S 3/4 = Stage 3/4 , R = REM

Appendix B

The entropy variation in the various sleep stages in the data selected from 11 PSG recording are given below.

Record # 1, Q76A

Given below is the table containing the entropy values belonging to the various sleep stages. Also Cluster 1 is followed by Cluster 2 then Cluster 3, 4 and finally 5. The plot of the entropy values in given below the table

Cluster 1		Cluster 2		Cluster 3		Cluster 4		Cluster 5	
Stage	Ent	Stage	Ent	Stage	Ent	Stage	Ent	Stage	Ent
W	1.8904	S2	1.42	S2	1.3897	S3/4	1.5258	S3/4	1.24
W	1.896	S2	1.51	S2	1.3007	S3/4	1.6271	S3/4	1.21
W	1.9157	S2	1.39	S2	1.5147	S3/4	1.1537	S3/4	1.32
W	1.8822	S2	1.59	S2	1.3753	S3/4	1.1685	S2	1.4
W	1.8873	S2	1.32	S2	1.7061	S3/4	1.2295	S2	1.4
S2	1.4311	S2	1.66	S2	1.6242	S3/4	1.3156	S2	1.39
S2	1.5484	S3/4	1.3	S2	1.6084			R	1.42
S2	1.4605	S3/4	1.21	S2	1.5942			R	1.48
S2	1.6011	S3/4	1.51	S2	1.5268			R	1.57
S2	1.4747	S3/4	1.25	S2	1.4992			R	1.36
S2	1.5862	S3/4	1.33	S2	1.3864			R	1.65
S2	1.2261	S3/4	1.23	S2	1.353			R	1.63
S2	1.5666	W	2.01	S3/4	1.1938				
		W	1.96	S3/4	1.3507				
		W	1.78	S3/4	1.485				
		W	1.94	S3/4	1.373				
		W	1.81	S3/4	1.6593				
		W	1.94	S3/4	1.4513				
		W	1.83						
		W	1.83						
		W	1.79						
		W	1.93						
		W	1.99						
		W	2.01						

Sample Entropy of one subject PSG recording

Record # 2, COB0304

Cluster 1		Cluster 2		Cluster 3		Cluster 4		Cluster 5	
Stage	Ent	Stage	Ent	Stage	Ent	Stage	Ent	Stage	Ent
W	1.91	W	1.67	S1	1.5297	S2	1.6731	S2	1.69
W	1.8918	W	1.78	S1	1.5377	S2	1.6363	S2	1.57
W	1.8396	W	1.74	S1	1.7755	S2	1.8914	S2	1.46
W	1.93	W	1.76	S1	1.7226	S2	2.0005		
W	1.9315	W	1.84	S2	1.4654	S2	1.8824		
W	1.9462	S1	1.65	S2	1.4321	S2	1.8215		
		S1	1.82	S2	1.3893				
		S1	1.79	S2	1.7314				
		S1	1.93	S2	1.9291				
		S1	1.72	S2	1.8706				
		S1	1.74						

Cluster 6		Cluster 7		Cluster 8		Cluster 9	
Stage	Ent	Stage	Ent	Stage	Ent	Satge	Ent
S2	1.8653	S3/4	1.2997	S2	1.409	R	1.6216
S2	1.8745	S3/4	1.1838	S2	1.4363	R	1.753
S2	1.8388	S3/4	1.114			R	1.6397
		S3/4	0.9357			R	1.7806
		S3/4	1.0634			R	1.7501
		S3/4	0.9629			R	1.7413
		S3/4	0.9624			R	1.6326
		S3/4	0.898				
		S3/4	0.8656				

S1   S1
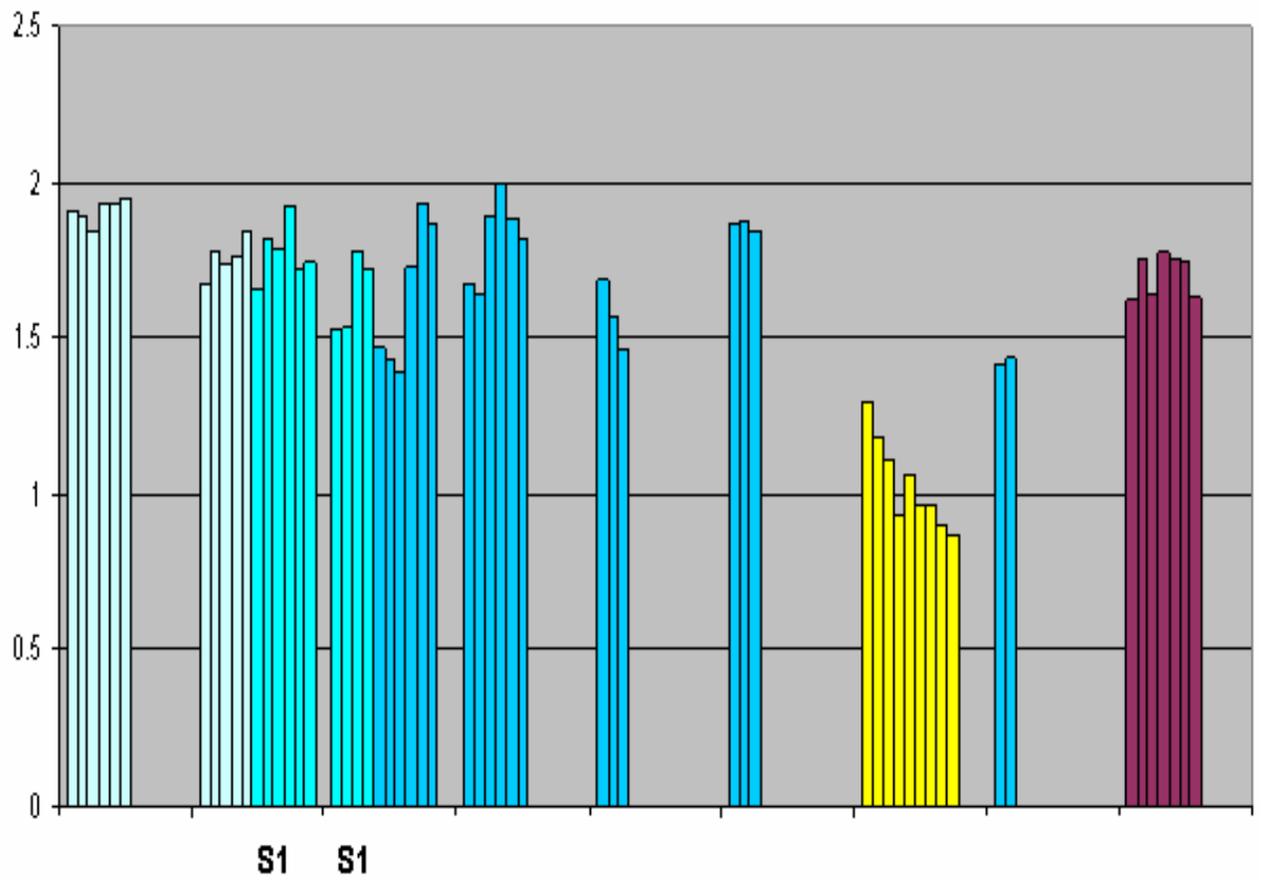
Record # 3, Q74A

Cluster 1		Cluster 2		Cluster 3		Cluster 4	
Stage	Ent	Stage	Ent	Stage	Ent	Stage	Ent
W	1.8084	S2	1.0094	S3/4	0.7951	S3/4	0.8535
S1	1.8267	S2	1.0513	S3/4	0.7983	S3/4	0.9257
S1	1.5842	S2	1.0642	S3/4	0.9206	S3/4	1.1303
S1	1.4432	S3/4	0.8708	S2	0.8992	S2	1.0217
S2	1.1613	S3/4	1.0709	S2	1.2996	S2	0.9998
S2	1.1076	S3/4	0.9573	S2	1.1695	S2	1.0654
S2	1.2927	S3/4	0.9387	S2	1.069	R	1.2597
S2	1.2036	S3/4	0.8826	S2	1.3092	R	1.0583
S2	1.3491	S3/4	0.8909	S2	1.173	R	1.2789
S2	1.3177	S3/4	0.9363	S3/4	1.0124	R	1.1334
		S3/4	0.9264	S3/4	1.1208	R	1.2822
		S3/4	0.874	S3/4	1.0197	R	1.0892
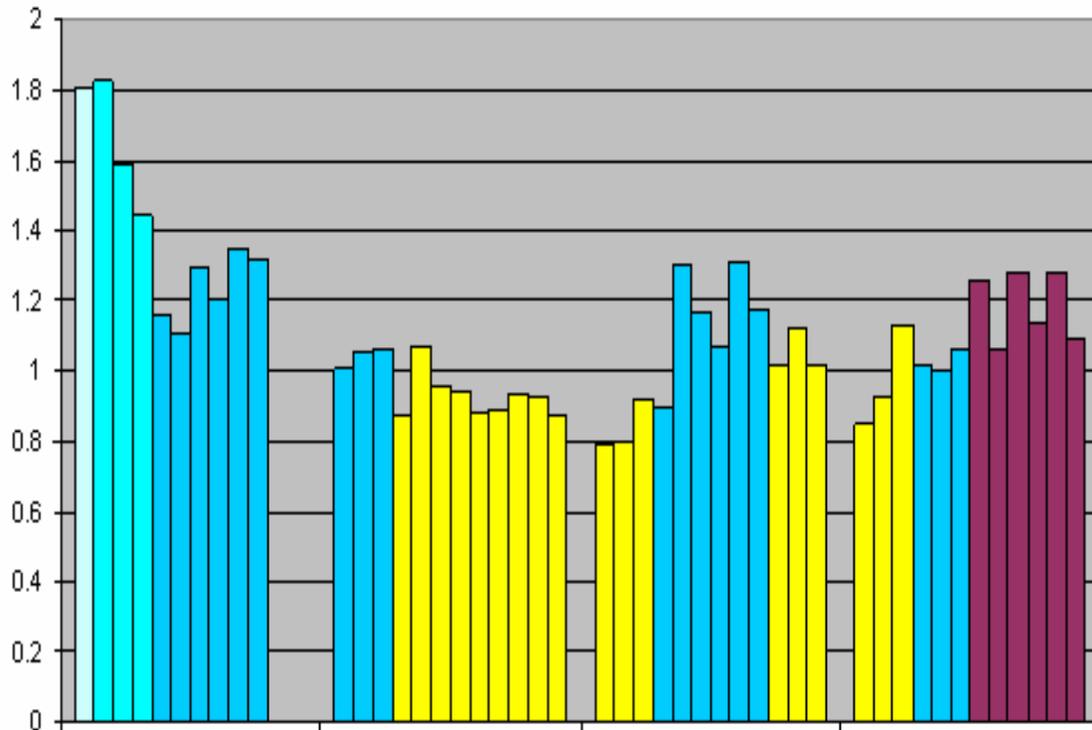
Record # 4, Q77B

Cluster 1		Cluster 2		Cluster 3		Cluster 4		Cluster 5	
Stage	Ent	Stage	Ent	Stage	Ent	Stage	Ent	Stage	Ent
W	1.972	S2	1.6664	S2	1.2926	S3/4	1.0872	S3/4	0.9848
W	2.0115	S2	1.8887	S2	1.2115	S3/4	0.9367	S3/4	0.8622
		S2	1.6602	S2	1.3501	S3/4	1.0145	S3/4	0.9947
				S2	1.2137				
				S2	1.1505				
				S2	1.4115				
				S2	0.8877				
				S2	1.197				

Cluster 6		Cluster 7		Cluster 8		Cluster 9		Cluster 10	
Stage	Ent	Stage	Ent	Stage	Ent	Stage	Ent	Stage	Ent
S3/4	0.9309	S2	0.8799	S2	1.0202	R	1.0509	R	1.2482
S3/4	0.8431	S2	1.2018	S2	1.0109	R	1.3631	R	1.0405
S3/4	0.8981	S2	1.0979	S2	1.0509	R	1.2801	R	1.2276
S3/4	0.7926							R	1.2965
S3/4	0.7868							R	1.2484
S3/4	0.7981							R	1.2911
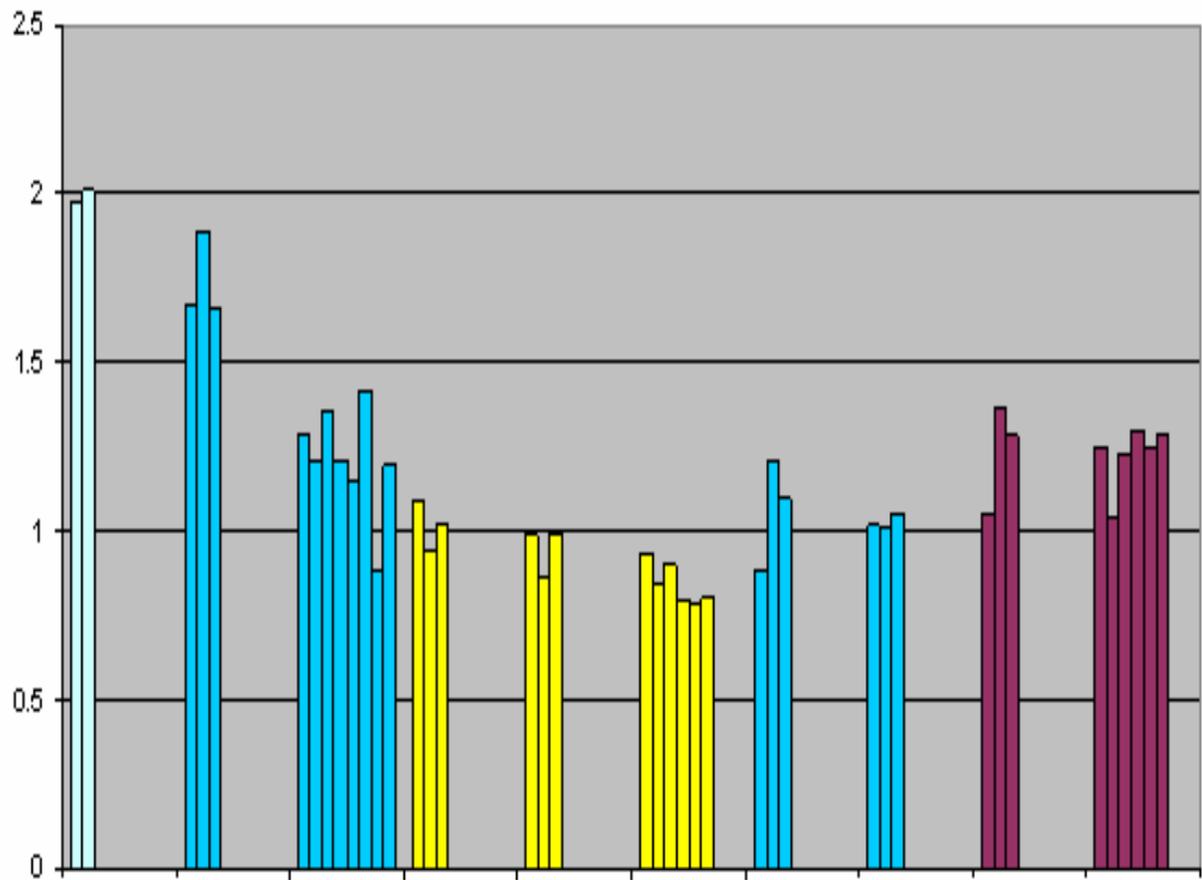
Record # 5, Q75B

Cluster 1		Cluster 2		Cluster 3		Cluster 4		Cluster 5	
Stage	Ent	Stage	Ent	Stage	Ent	Stage	Ent	Stage	Ent
W	1.5542	W	1.7974	S2	1.4004	S2	1.3733	S2	1.3152
W	1.7758	W	1.7703	S2	1.1618	S2	1.2118	S2	1.1876
W	1.7024	W	1.7725	S2	1.3465	S2	1.3248	S2	1.2277
W	1.7232	W	1.8673	S3/4	1.2765	S3/4	1.3733	S2	1.3733
W	1.7396	W	1.8387	S3/4	1.3268	S3/4	1.2118	R	1.2654
		W	1.6683	S3/4	1.1554	S3/4	1.1055	R	1.5006
		S1	1.6106	S3/4	1.1791	S3/4	1.076	R	1.4524
		S1	1.7691	S3/4	1.2073	S3/4	1.0446	R	1.4454
		S1	1.7389	S3/4	1.1569			R	1.2888
		S1	1.6516	S2	1.3493			R	1.5394
		S1	1.5603						
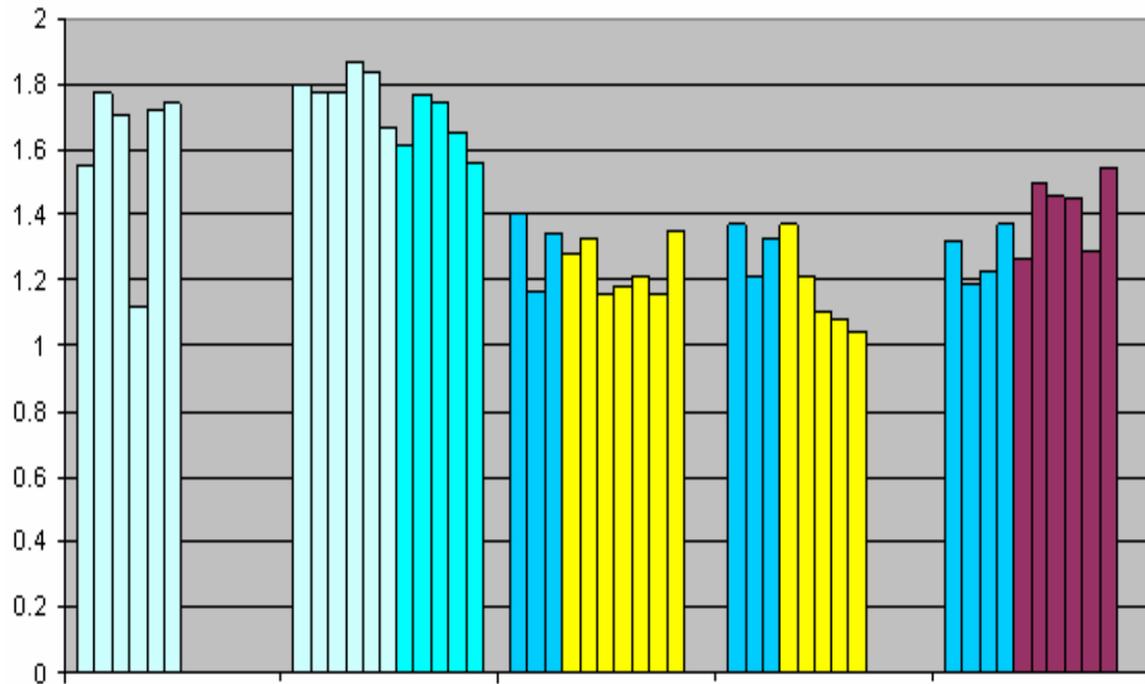
Record # 6, Q71B

Cluster 1		Cluster 2		Cluster 3		Cluster 4		Cluster 5	
Stage	Ent	Stage	Ent	Stage	Ent	Stage	Ent	Stage	Ent
S2	1.5151	S3/4	1.5761	S3/4	1.7826	S/34	1.2875	S2	1.5135
S2	1.5946	S3/4	1.5579	S3/4	1.5669	S3/4	1.2888		
S2	1.4198	S3/4	1.461	S3/4	1.5413	S3/4	1.4349		
S2	1.5793	S3/4	1.5658	S3/4	1.5772	S3/4	1.1833		
S2	1.5822	S3/4	1.549	S3/4	1.5669	S3/4	1.1488		
S2	1.5504	S3/4	1.6409	S3/4	1.698	S2	1.5155		
						S2	1.429		

Cluster 6		Cluster 7		Cluster 8		Cluster 9	
Stage	Ent	Stage	Ent	Stage	Ent	Satge	Ent
R	1.5142	R	1.6386	S2	1.4483	W	2.0369
R	1.595	R	1.6161	S2	1.6268	W	2.1222
R	1.557	R	1.5969	S2	1.5665	W	2.0651
R	1.5863			S2	1.5644	W	2.0655
R	1.5075					S1	1.9115
						S1	1.7976
						S1	1.8228
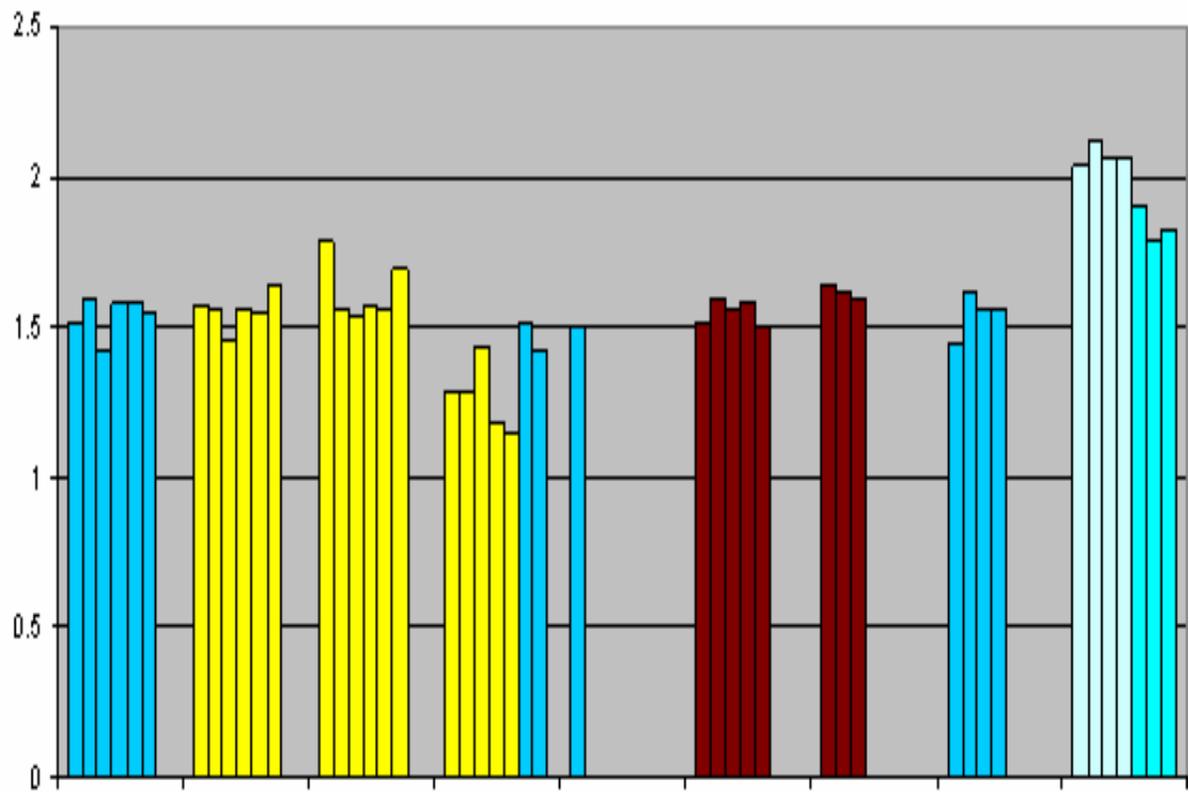
Record # 7, Q74B

Cluster 1		Cluster 2		Cluster 3		Cluster 4		Cluster 5	
Stage	Ent	Stage	Ent	Stage	Ent	Stage	Ent	Stage	Ent
W	1.7343	S2	1.1155	S2	0.9191	S2	1.4794	S2	1.0363
W	1.5336	S2	0.9461	S2	1.1899	S2	1.3307	S2	1.2336
W	1.682	S2	1.2592	S2	1.0863	S2	1.0053	S2	1.0831
S1	1.5919	S2	1.2221	S2	1.208	S2	1.1736		
S1	1.5061	S2	1.3394	S2	1.2889	S2	1.2576		
S1	1.5211					S2	1.2862		
S1	1.3605								

Cluster 6		Cluster 7		Cluster 8		Cluster 9	
Stage	Ent	Stage	Ent	Stage	Ent	Satge	Ent
S3/4	1.0004	S3/4	0.8435	S2	1.0505	R	1.1699
S3/4	0.9871			S2	1.1633	R	1.1968
S3/4	0.9382			S2	0.996	R	1.3172
S3/4	0.8973			S2	1.0759		
S3/4	0.9396						
S3/4	1.0291						
S3/4	0.8846						
S3/4	0.9422						
S3/4	0.8741						
S3/4	0.9199						
S3/4	0.9355						
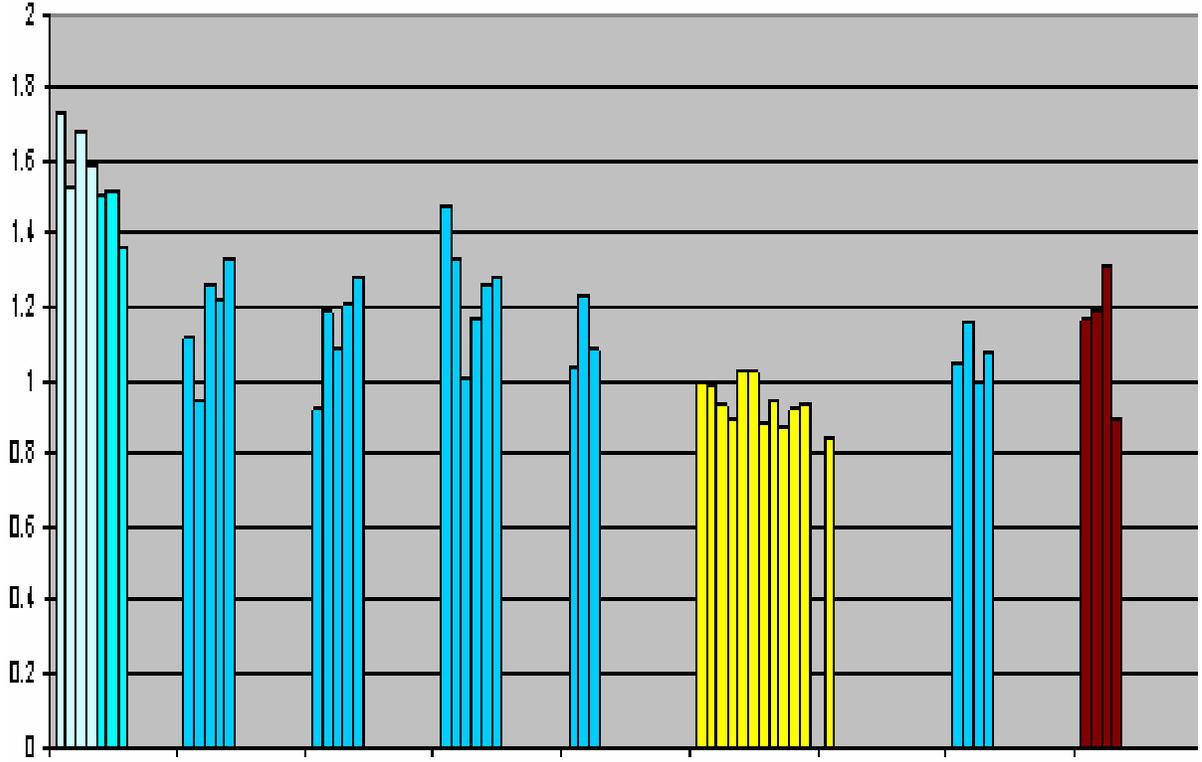
<u>Record # 8, Q78B</u>

Cluster 1		Cluster 2		Cluster 3		Cluster 4		Cluster 5		Cluster 6		Cluster 7	
Stage	Ent	Stage	Ent	Stage	Ent	Stage	Ent	Stage	Ent	Stage	Ent	Stage	Ent
W	1.49	S2	1.28	S2	0.99	S3/4	0.84	S2	0.9	S1	1.44	R	1.36
W	1.78	S2	1.17	S2	0.84	S3/4	1.05			S1	1.29	R	1.29
W	1.74	S2	1.5	S2	1.13	S3/4	0.93					R	1.42
W	1.76	S2	1.41	S3/4	0.97	S2	1.45					R	1.29
W	1.81	S2	1.25	S3/4	1.15	S2	1.29					R	1.39
		S2	1.26	S3/4	0.99	S2	1.31					R	1.52
				S3/4	0.85								
				S3/4	0.8								
				S3/4	0.97								
				S3/4	0.75								
				S3/4	0.69								
				S3/4	0.74								

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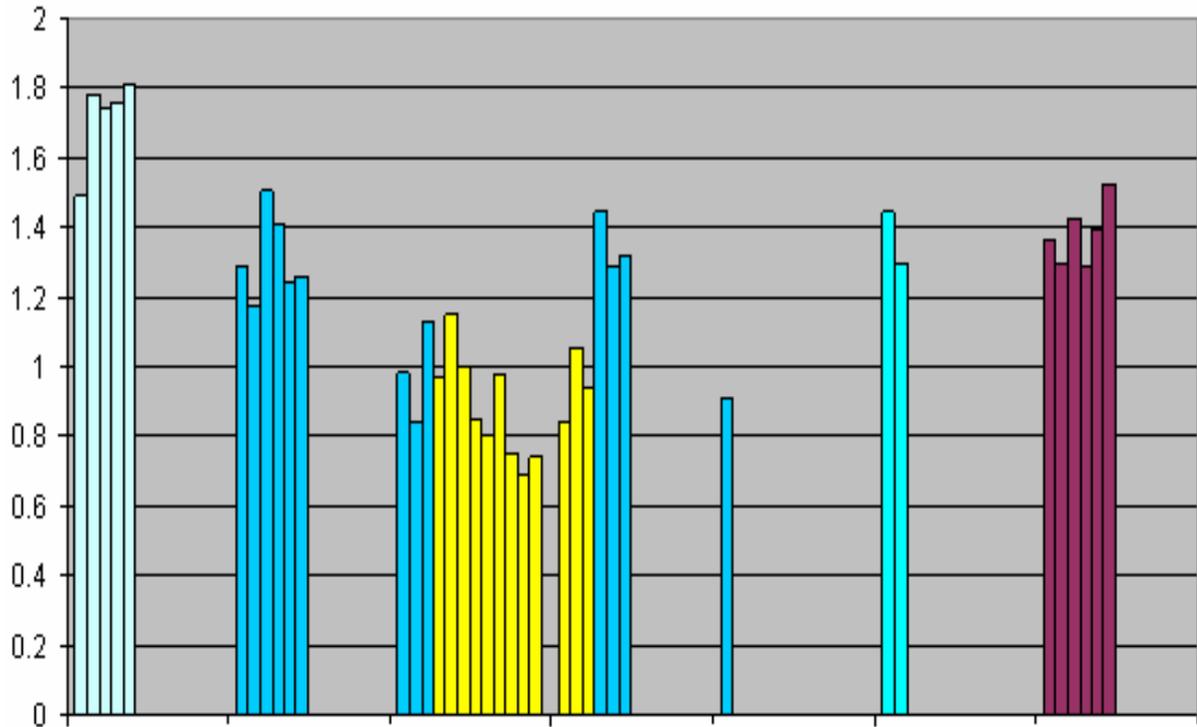
Record # 9, COBO321

Cluster 1		Cluster 2		Cluster 3		Cluster 4		Cluster 5		Cluster 6		Cluster 7	
Stage	Ent	Stage	Ent	Stage	Ent	Stage	Ent	Stage	Ent	Stage	Ent	Stage	Ent
W	1.8096	S2	1.07	S2	1.32	S3/4	0.9772	S2	0.84	S3/4	0.7446	S2	1.2137
W	1.7954	S2	1.42	S2	1.202	S3/4	0.9348	S2	0.99	S3/4	0.4943	S2	1.3759
W	1.6242	S2	1.36	S2	1.3783	S3/4	1.0966	S2	0.97	S3/4	0.5839	S2	1.144
W	1.5924	S2	1.22	S2	1.2052	S3/4	1.1036	S2	1.05	S3/4	0.4876	S2	1.1278
S1	1.5246	S2	1.01	S2	1.3139	S3/4	0.9865	S2	0.99	S3/4	0.4158	S2	1.18
S1	1.4309					S3/4	1.0546	S2	0.91	S3/4	0.4028	S2	0.8836
S2	1.4886					S3/4	0.9354			S3/4	0.4216	S2	0.7309
S2	1.2699									S3/4	0.6938	S2	0.5802
S2	1.3844									S3/4	0.4479	R	1.5979
S2	1.4642											R	1.1637
S2	1.4142											R	0.764
S2	1.3796											R	1.2834
												R	1.0835
												R	1.2874
												R	1.0722
												R	1.4178
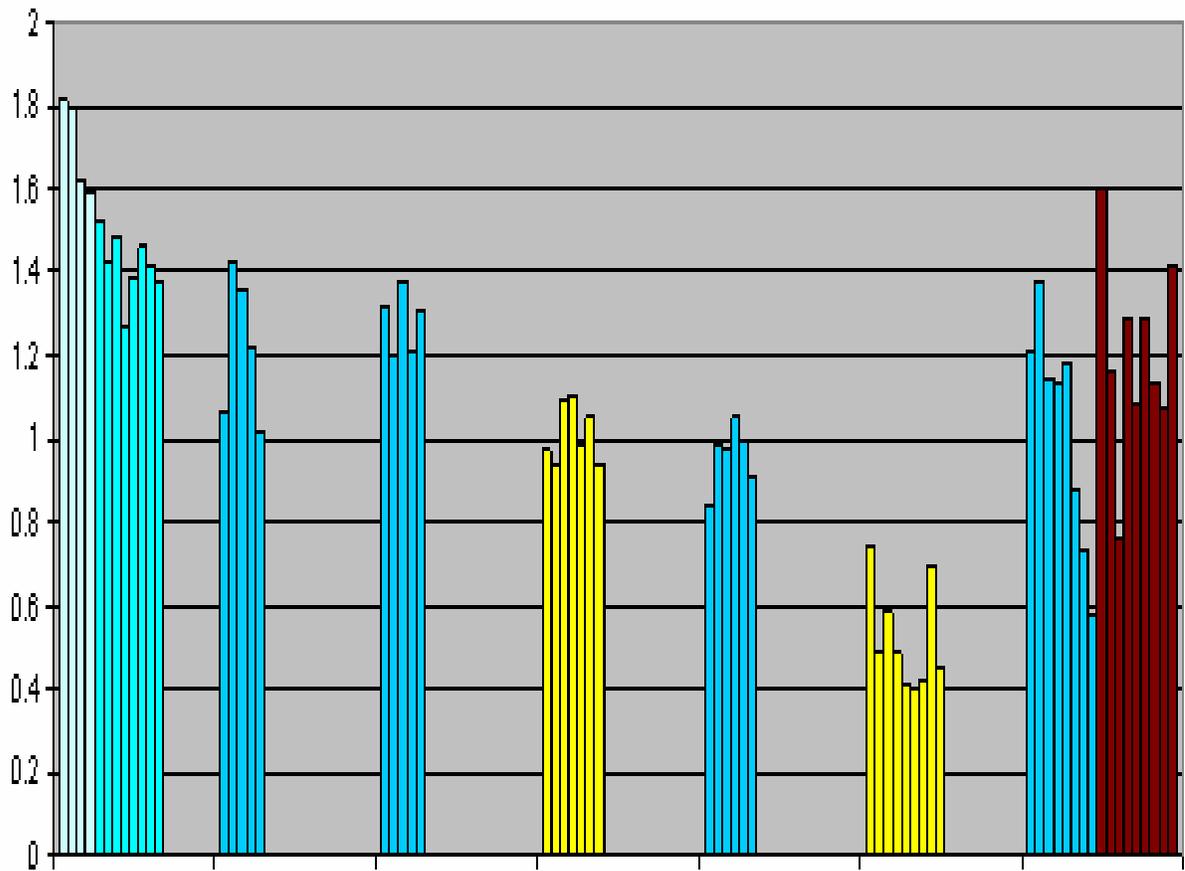
Record # 10, Q75A

Cluster 1		Cluster 2		Cluster 3		Cluster 4		Cluster 5		Cluster 6	
Stage	Ent	Stage	Ent	Stage	Ent	Stage	Ent	Stage	Ent	Stage	Ent
W	1.4555	S3/4	1.1029	S2	1.1549	S3/4	1.0489	S2	1.0909	R	1.317
S2	1.507	S3/4	1.3177	S2	1.1042	S3/4	1.2051	S2	1.1879	R	1.546
S2	1.3661	S3/4	1.1087	S2	1.1737	S3/4	1.0734	S2	1.1426	R	1.6116
S2	1.3293	S3/4	1.2314	S2	1.2569			S2	1.045	R	1.6177
S2	1.4821	S3/4	1.1821	S2	1.2662			S2	1.1494	R	1.693
S2	1.4028	S3/4	1.0842	S2	1.4551			S2	1.074	R	1.5716
S2	1.4223	S3/4	1.0104	S2	1.1226			S2	1.1753		
S2	1.5243	S3/4	0.975	S2	1.3039			S2	1.078		
S2	1.4973	S3/4	0.9761	S2	1.4253			S2	1.0014		
S2	1.4422			S2	1.1476						
S2	1.3309			S2	1.3788						
S2	1.2317			S2	1.0087						
S2	1.2375										
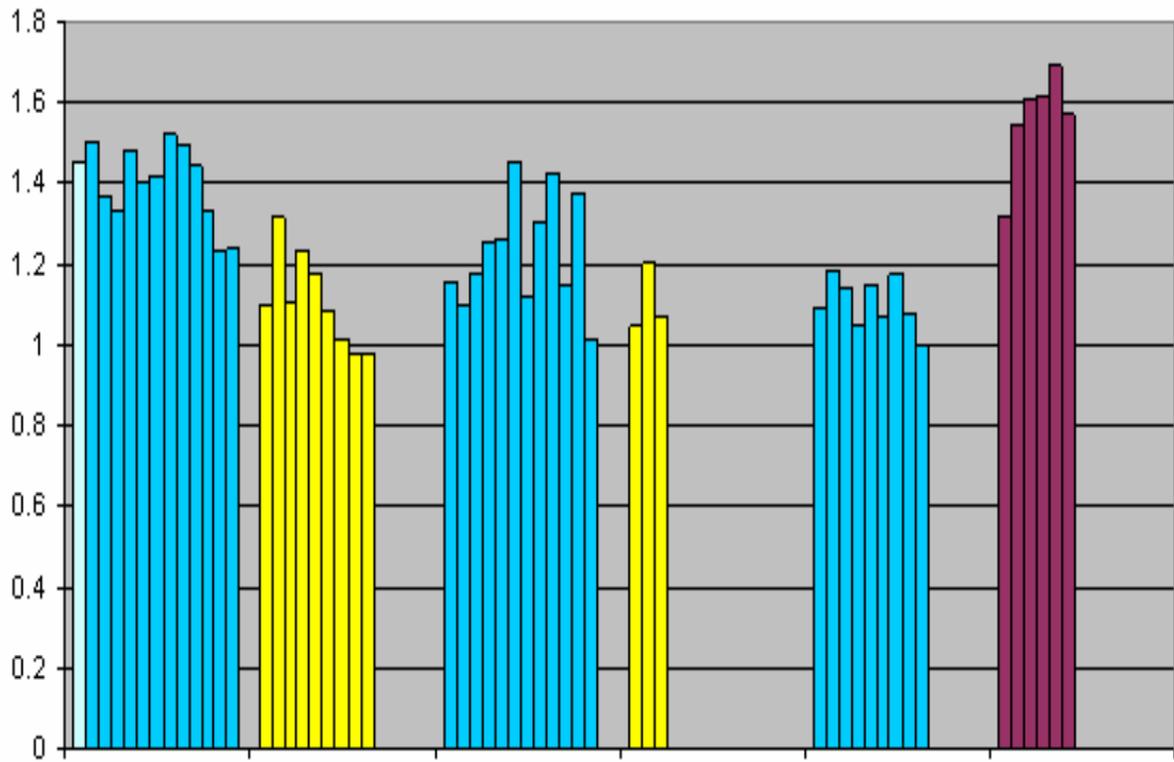
Record # 11, COB0311

Cluster 1		Cluster 2		Cluster 3		Cluster 4		Cluster 5	
Stage	Ent	Stage	Ent	Stage	Ent	Stage	Ent	Stage	Ent
W	1.3436	S2	1.0766	S2	1.3111	S2	1.3686	S2	1.3075
W	1.4702	S3/4	0.9095	S2	1.4153	S2	1.2524	S2	1.3687
W	1.4558	S3/4	1.0869	S2	1.3903	S2	1.2771	R	1.3518
W	1.4879	S3/4	1.27			S2	1.3669	R	1.4237
S2	1.5467	S3/4	1.3409			S2	1.142	R	1.3505
S2	1.4258	S3/4	1.2965			S3/4	1.1221		
S2	1.539					S3/4	1.3288		
S2	1.4439					S3/4	1.1034		
S2	1.6199					S2	1.3707		
S2	1.4434					S2	1.397		
						S2	1.3846		
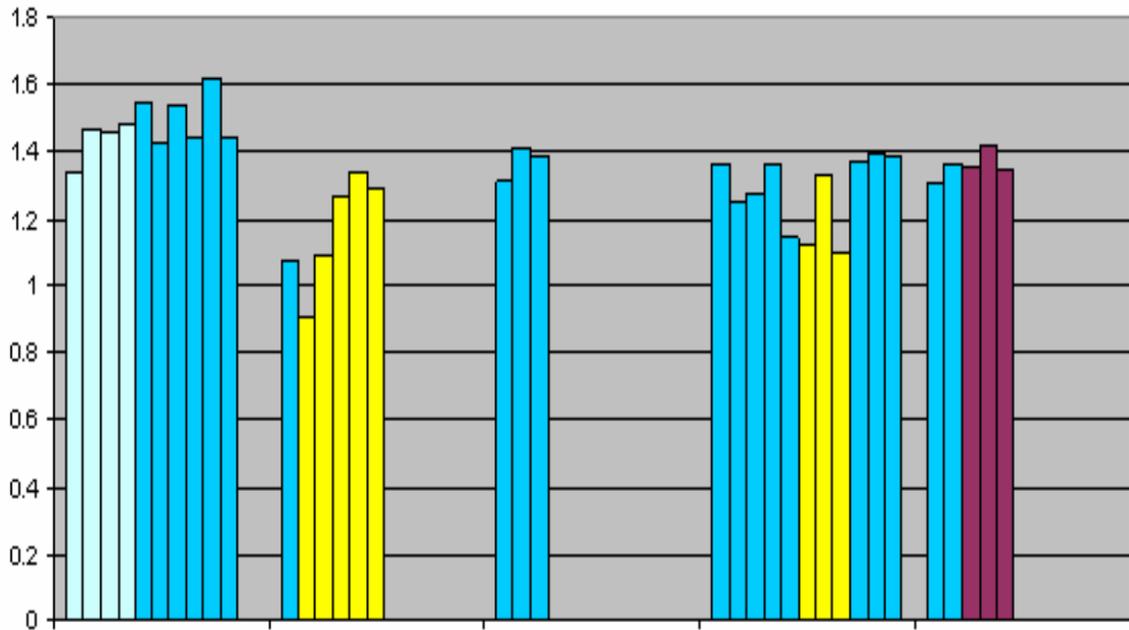
Appendix C

Analysis of Sleep apnea data from SHHS

Also given below each plot are the normalized SpEn$_A$ values

Record #1- 101580, Age=48yrs, RDI @5% oxy. Desat = 0.7832

Cluster 1, 2, 3, 4, 5, 6, 7 belong to the seven clusters of bars. Given below is a table, of the sleep stages and the corresponding entropy values

Cluster 1		Cluster 2		Cluster 3		Cluster 4		Cluster 5		Cluster 6		Cluster 7	
Stage	Ent	Stag	Ent	Stag	Ent	Stag	Ent	Stag	Ent	Stag	Ent	Stage	Ent
W	1.5499	S1	2.01	S2	1.713	S3/4	1.445	S2	1.35	S2	1.6064	R	1.6524
W	1.4868	S2	1.75			S3/4	1.578	S2	1.39	S2	1.5203	R	1.8265
W	1.7764	S2	1.77			S3/4	1.57	S2	1.5			R	1.8159
W	1.9272	S2	1.7			S3/4	1.566					R	1.6977
W	2.0623					S3/4	1.516						
W	2.0053					S3/4	1.524						
W	1.8296					S3/4	1.442						
						S3/4	1.609						
						S3/4	1.418						
						S3/4	1.45						
						S3/4	1.495						
						S3/4	1.457						
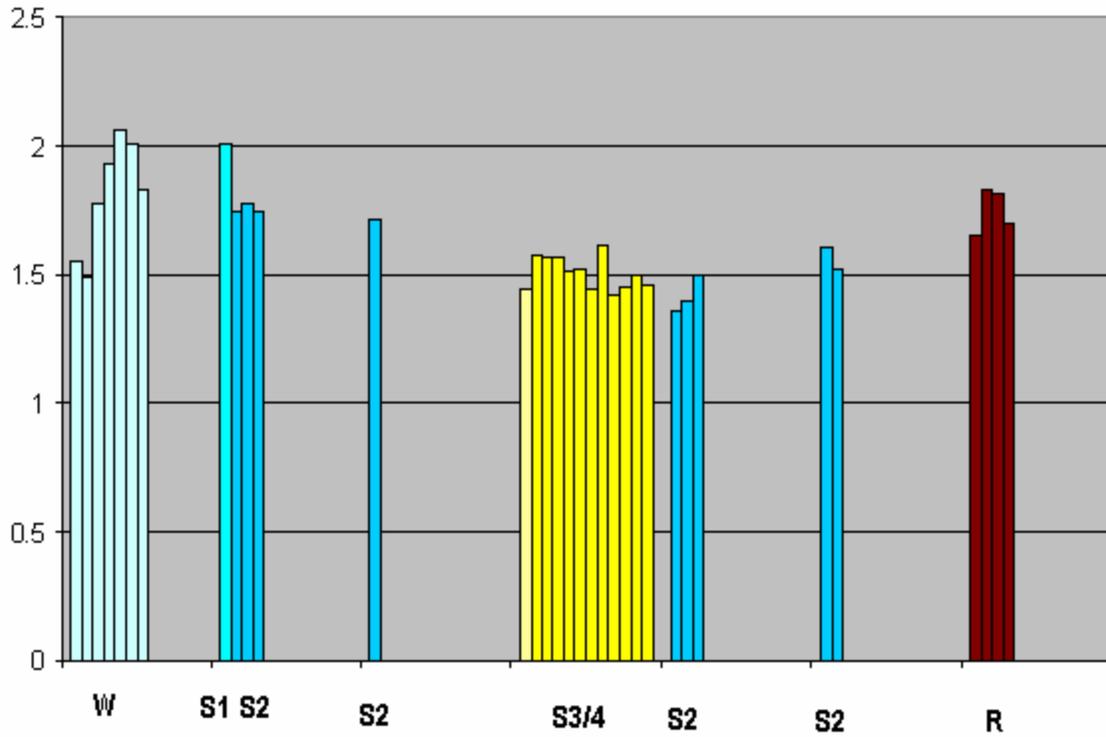
Here W=Wake, S1=Stage1, S2=Stage 2, S3/4=Stage 3/4, R=REM. The subsequent graphs have the corresponding stages in the same shades of gray.

S1	S2	S3/4	R
1.1129	0.8831	0.8373	0.9683

Record #2- 104630, Age=48yrs, RDI@5% oxy. Desat= 5.697

The plot of the sleep stages given below along with the entropy values are given in the next page. As a function of time Cluster 1 is followed by Cluster 2, then Cluster 3, Cluster 4 and finally Cluster 5.

Cluster 1		Cluster 2		Cluster 3		Cluster 4		Cluster 5	
Stage	Ent	Stage	Ent	Stage	Ent	Stage	Ent	Stage	Ent
W	1.955	W	1.8476	S3/4	1.5191	S3/4	1.3974	R	1.7025
W	1.91	W	1.7817	S3/4	1.3488	S3/4	1.3575	R	1.7479
W	1.997	S1	1.9171			W	1.8213	R	1.6853
S1	1.9747	S1	1.9013						
S1	1.919	S1	1.9633						
S2	1.959	S1	1.858						
S2	1.9545	S2	1.4744						
S2	1.7543	S3	1.4144						
S2	1.7336	S3	1.2644						
S2	1.7312	S3	1.3272						
S2	1.3549	S3	1.471						
S2	1.5149								
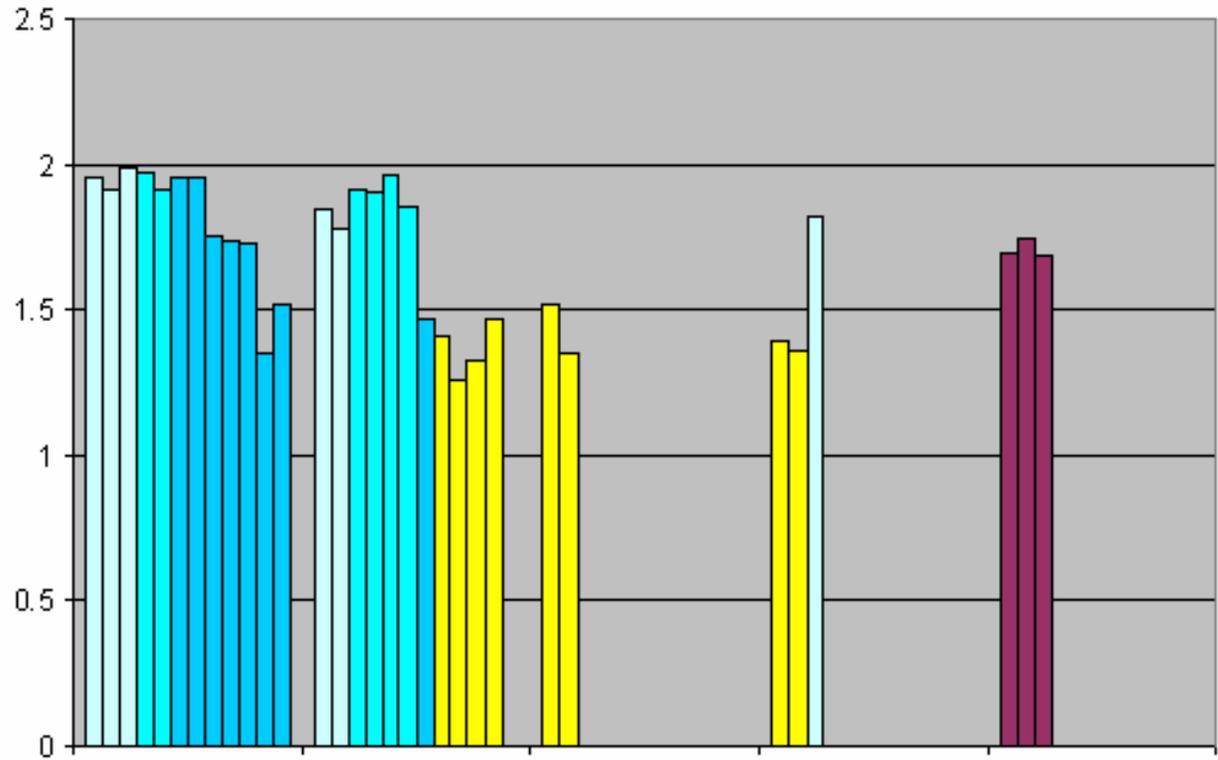
S1   S2   S3/4   R

1.0196   0.8935   0.7359   0.9080

Record #3- 104535, age=46, RDI @ 5% oxy. Desat= 5.69

Here there are 11 Clusters of bars and they are placed in 2 tables

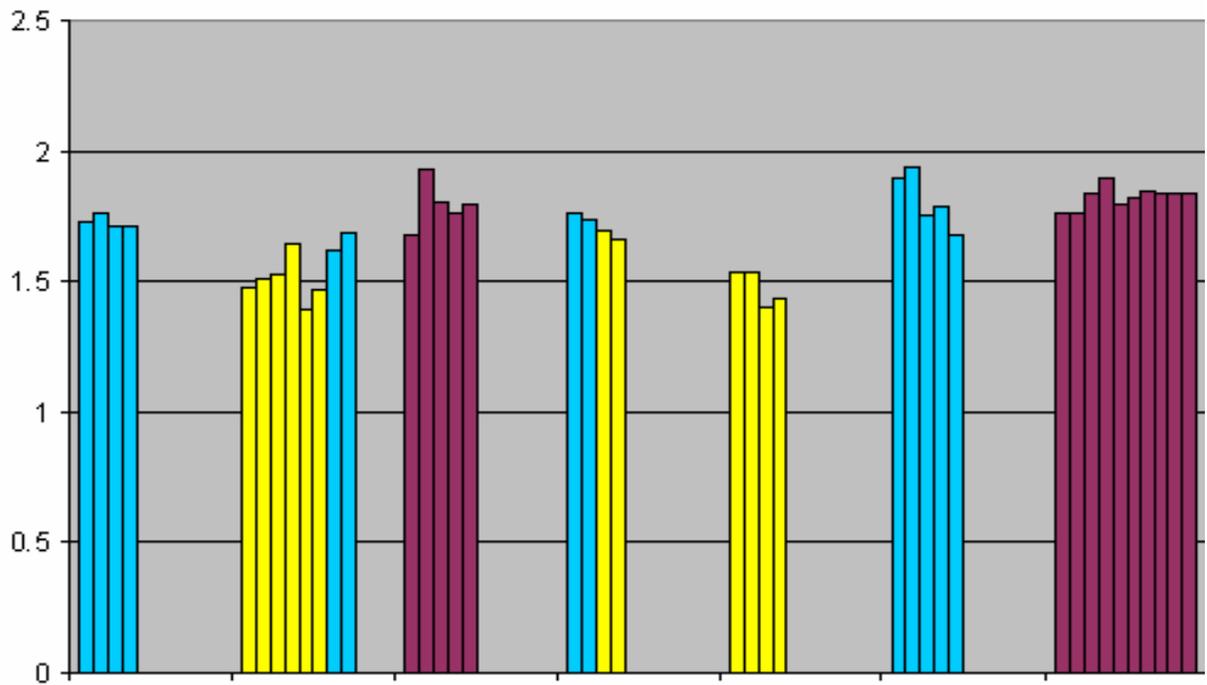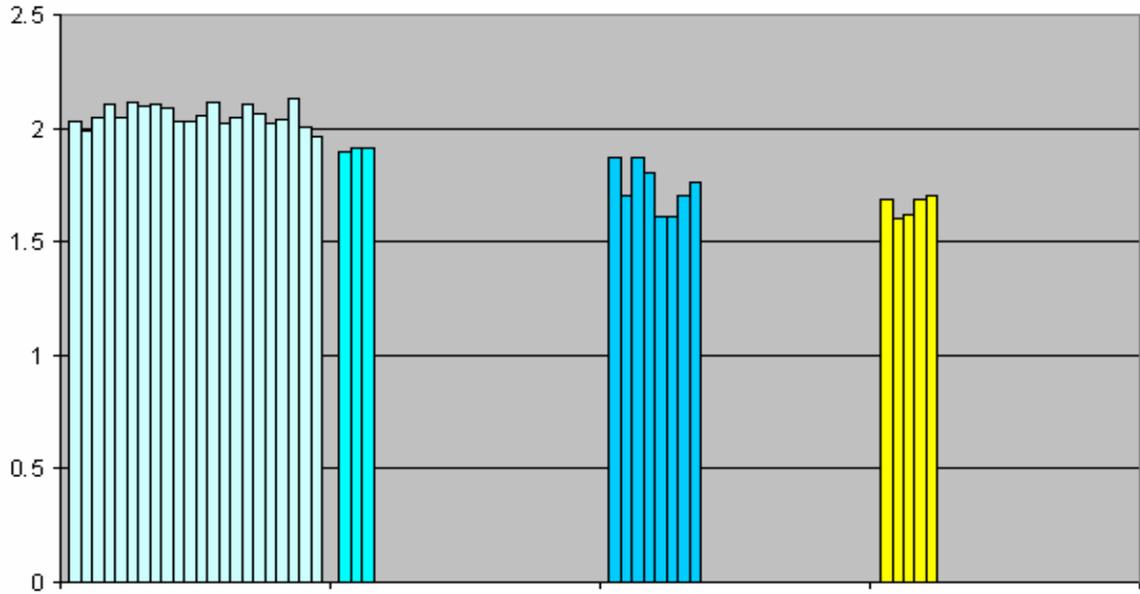| Cluster 1		Cluster 2		Cluster 3		Cluster 4	
Stage	Ent	Stage	Ent	Stage	Ent	Stage	Ent
W	2.0293	S1	1.895	S2	1.8758	S3/4	1.3974
W	1.9864	S1	1.9192	S2	1.7067	S3/4	1.6868
W	2.0432	S1	1.9151	S2	1.8719	S3/4	1.6027
W	2.1056			S2	1.8089	S3/4	1.6239
W	2.0476			S2	1.618	S3/4	1.6891
W	2.1147			S2	1.6179	S3/4	1.709
W	2.099			S2	1.7097		
W	2.1062			S2	1.7655		
W	2.0951						
W	2.028						
W	2.0298						
W	2.0651						
W	2.1134						
W	2.024						
W	2.0501						
W	2.1076						
W	2.0684						
W	2.0219						
W	1.961						

Cluster 5		Cluster 6		Cluster 7		Cluster 8		Cluster 9		Cluster 10		Cluster 11	
Stage	Ent	Stage	Ent	Stage	Ent	Stage	Ent	Stage	Ent	Stage	Ent	Stage	Ent
S2	1.7283	S3/4	1.48	R	1.6772	S2	1.7676	S3/4	1.54	S2	1.8987	R	1.7666
S2	1.7705	S3/4	1.51	R	1.9325	S2	1.7396	S3/4	1.53	S2	1.9378	R	1.7666
S2	1.7173	S3/4	1.52	R	1.8069	S3/4	1.6975	S3/4	1.41	S2	1.7553	R	1.8402
S2	1.7181	S3/4	1.64	R	1.7706	S3/4	1.6598	S3/4	1.44	S2	1.7915	R	1.8941
		S3/4	1.39	R	1.7975					S2	1.6747	R	1.7987
		S3/4	1.46									R	1.8184
		S2	1.63									R	1.8527
		S2	1.68									R	1.8352
												R	1.8384
												R	1.843

The sleep stages in the graph above is followed by the second graph placed below

S1	S2	S3/4	R
0.928	0.8511	0.7602	0.8824

Record #4- 105319, Age= 47, RDI @ 5 % oxy. Desat= 0

Cluster 1		Cluster 2		Cluster 3		Cluster 4	
Stage	Ent	Stage	Ent	Stage	Ent	Stage	Ent
W	1.8223	S3/4	1.6038	S3/4	1.3454	R	1.7637
W	2.0542	S3/4	1.4032	S3/4	1.4799	R	1.6768
W	1.9967	S3/4	1.3574	S3/4	1.2653	R	1.7213
W	1.8726	S3/4	1.528	S3/4	1.2522	R	1.8498
W	1.9846	S3/4	1.4966	S3/4	1.4121	R	1.5951
W	1.9377	S3/4	1.455	S3/4	1.1374	R	1.7796
W	2.0232	S3/4	1.3334	S3/4	1.2572	R	1.8456
W	2.0415	S3/4	1.4469	S3/4	1.311	R	1.7431
W	2.1241	S3/4	1.3542	S3/4	1.2542	R	1.8355
W	1.9994	S3/4	1.4196	S3/4	1.2696	R	1.8853
W	2.028	S2	1.4573	S3/4	1.2299	R	1.8558
W	1.8674	S2	1.5333	S3/4	1.2315	R	1.7341
W	2.1315			S3/4	1.2715	R	1.8326
S2	1.6452			S3/4	1.1172	R	1.8787
S2	1.6628			S3/4	1.1078	R	1.6899
S2	1.7024					R	1.8614
S2	1.6225					R	1.785
S2	1.6873					R	1.8056
S2	1.4057					R	1.8139
						R	1.7026
						R	1.8238
						R	1.8391
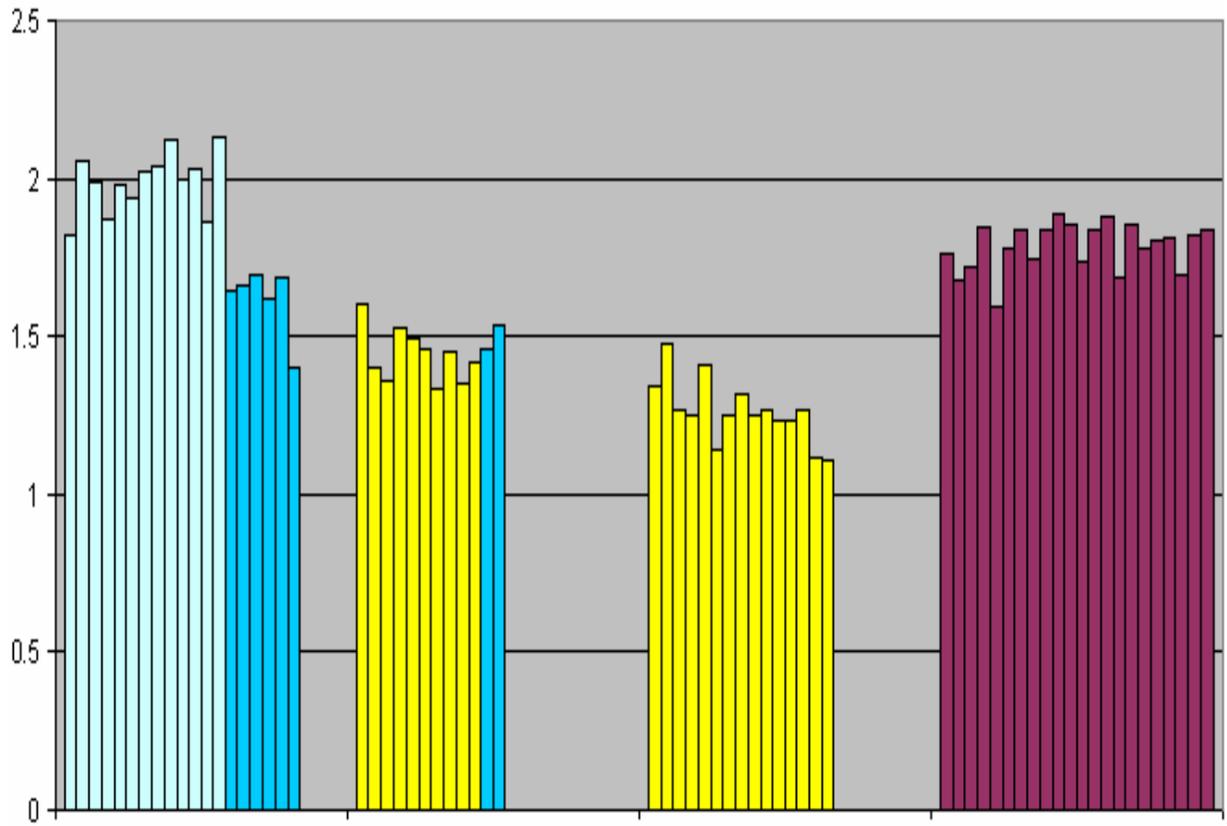
S1   S2   S3/4   R
0   0.8178   0.6698   0.8976

Record #5- 102702, Age= 49yrs, RDI @ 5% oxy. Desat=9.189

Cluster 1		Cluster 2		Cluster 3		Cluster 4		Cluster 5		Cluster 6	
Stage	Ent	Stage	Ent	Stage	Ent	Stage	Ent	Stage	Ent	Stage	Ent
W	2.1419	W	2.0269	S2	1.5198	S2	1.4174	R	1.8411	R	1.8299
W	2.1141	W	2.0888	S2	1.5191	S2	1.3617	R	1.6606	R	1.7237
		S1	1.9632	S2	1.3154	S2	1.4216			R	1.8512
		S1	1.7217	S2	1.4132	S2	1.2541			R	1.794
		S2	1.5945	S2	1.5018	S2	1.2379			R	1.7861
		S2	1.6526	S2	1.498	S2	1.345				
		S2	1.7219			S2	1.3269				
		S2	1.6688								
		S2	1.6269								
		S2	1.6838								
		S2	1.6323								
		S2	1.5923								
		S2	1.537								
		S2	1.6129								
		S2	1.513								
		S2	1.5411								
		S2	1.5531								
		S2	1.4967								
		S2	1.5112								
		S2	1.4943								
		S2	1.4919								
		S2	1.4839								
		S2	1.3951								
		S2	1.3723								
		S2	1.4464								
		S2	1.3954								
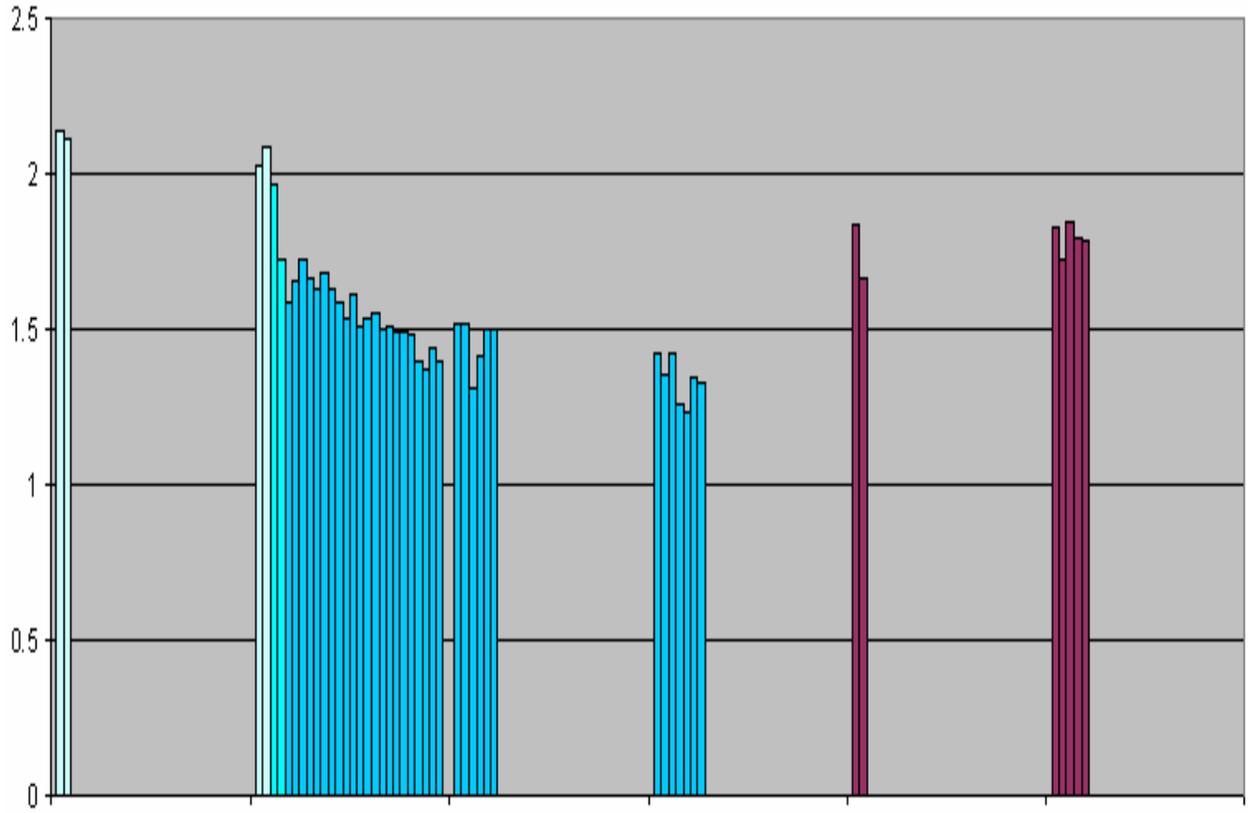
	S1	S2	S3/4	R
	0.8803	0.7119	0	0.8523

Record #6- 101028, Age=49yrs, RDI @5% oxy. Desat=0

Cluster 1		Cluster 2		Cluster 3		Cluster 3 (continued)	
Stage	Ent	Stage	Ent	Stage	Ent	Stage	Ent
W	1.8525	S2	1.6944	S2	1.6484	S3/4	1.3823
W	1.8866	S2	1.6445	S2	1.5981	S3/4	1.4218
W	1.9207	S2	1.6701	S2	1.5087	S3/4	1.3221
W	1.8965	S2	1.6471	S2	1.6141	S3/4	1.5011
W	1.8702	S2	1.7503	S2	1.5927	S3/4	1.4398
W	1.8611	S2	1.7558	S2	1.6604	S3/4	1.4151
W	1.8797			S2	1.6604	S3/4	1.5535
W	1.9807			S3/4	1.5343	S3/4	1.4489
W	1.9515			S3/4	1.5854	S3/4	1.4739
W	1.8042			S3/4	1.5737	S2	1.7198
W	1.7289			S3/4	1.5726	S2	1.5699
W	1.911			S3/4	1.5762	S2	1.7234
W	1.9733			S3/4	1.4571	R	1.7696
W	1.8533			S3/4	1.5508	R	1.7266
W	1.9555			S3/4	1.5433	R	1.8104
W	1.9321			S3/4	1.3905	R	1.6667
W	1.9961			S3/4	1.4341	R	1.7843
W	1.9354			S3/4	1.453	R	1.7026
W	1.8532			S2	1.6129	R	1.6896
				S2	1.6132	R	1.7252
				S2	1.5224		
				S3/4	1.5185		
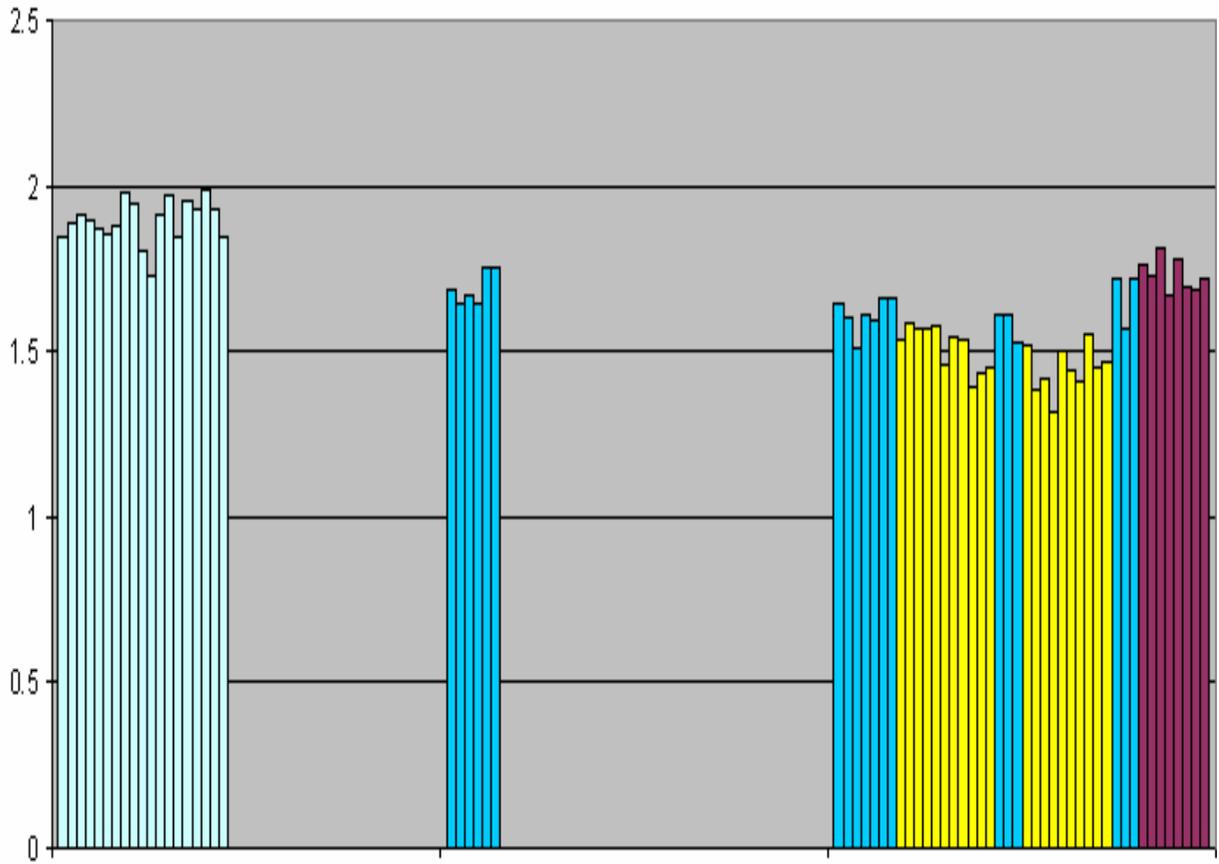
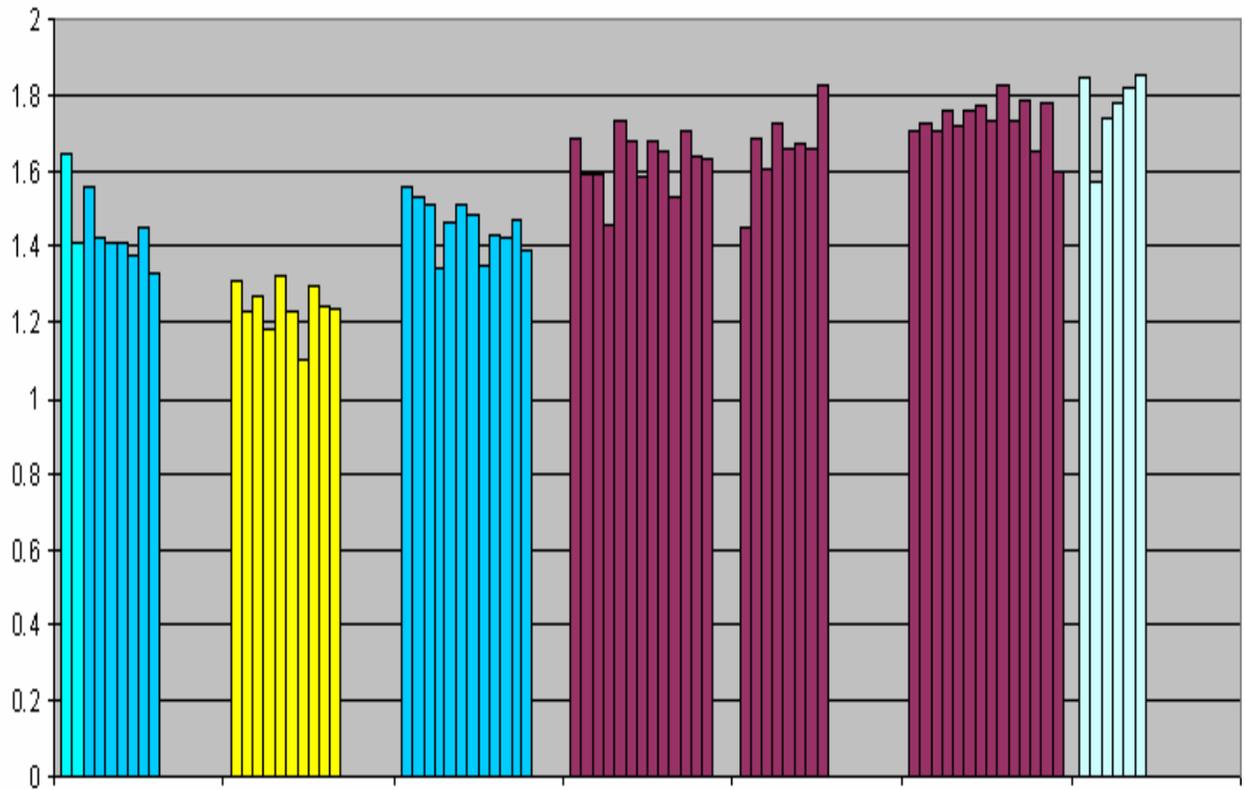|	S1	S2	S3/4	R
	0	0.8658	0.7806	0.9143

Record #7- 104698, age=45, RDI @ 5% oxy. Desat=27.741

Here normalization was done to a W stage after the first NREM/REM cycle, due to unavailability of W without an apnea event before the first cycle.

Cluster 1		Cluster 2		Cluster 3		Cluster 4		Cluster 5		Cluster 6		Cluster 7	
Stage	Ent	Stage	Ent	Stage	Ent	Stage	Ent	Stage	Ent	Stage	Ent	Stage	Ent
S1	1.6455	S3/4	1.31	S2	1.5594	R	1.6883	R	1.45	R	1.7073	W	1.8482
S1	1.4152	S3/4	1.23	S2	1.5288	R	1.5959	R	1.69	R	1.7261	W	1.5707
S2	1.5564	S3/4	1.27	S2	1.508	R	1.5959	R	1.61	R	1.7069	W	1.7401
S2	1.4265	S3/4	1.18	S2	1.3435	R	1.4552	R	1.73	R	1.7573	W	1.7828
S2	1.4068	S3/4	1.32	S2	1.461	R	1.7364	R	1.66	R	1.7247	W	1.8195
S2	1.4117	S3/4	1.22	S2	1.5103	R	1.6826	R	1.68	R	1.7587	W	1.8528
S2	1.3783	S3/4	1.1	S2	1.4858	R	1.5859	R	1.66	R	1.7761		
S2	1.4517	S3/4	1.3	S2	1.3532	R	1.6777	R	1.83	R	1.7337		
S2	1.3301	S3/4	1.25	S2	1.4306	R	1.6542			R	1.8315		
		S3/4	1.24	S2	1.4262	R	1.5313			R	1.7363		
				S2	1.4688	R	1.7121			R	1.7858		
				S2	1.3895	R	1.637			R	1.6556		
						R	1.6332			R	1.7826		
										R	1.6023		

	S1	S2	S3/4	R
	0.8651	0.8160	0.7019	0.9493

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