Automatic Sleep and Wake State Detection in Rats Using EEG

BY

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THESIS

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This thesis is dedicated to my family, friends and mentors

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SUMMARY

Epileptic seizures are believed to follow a circadian rhythm. There is an underlying relationship between Epilepsy and the sleep state. It is important to understand and evaluate the correlation between them. A robust algorithm to determine the sleep-wake states in the animals was developed and the sleep in the light and dark cycles for the epilepsy-induced animals vs the control animals was evaluated.

A quantitative study of the traditional EEG bands - delta, theta, alpha, beta and gamma were performed to understand their contribution in the sleep-wake states. The EEG band-power contribution in the epilepsy induced animal vs the control animal was evaluated in the sleep-wake states. A different set of frequency bands were evaluated to which proved more robust in differentiating the different sleep-wake states. A brute threshold algorithm and Machine learning algorithms – Logistic Regression & k-Nearest Neighbors were created to detect the sleep-wake states of the animals based on the set of EEG frequency bands.

The developed algorithms were compared for overall accuracy against the outcome of the manually marked EEG sleep segments from the Video-EEG recordings and it was observed that some of the Machine Learning algorithms outperformed the brute-threshold algorithm. Based on the detected sleep-wake states in the animals using the brute threshold algorithm, an evaluation was performed on the effect of induced epilepsy on the duration of the sleep-wake states of the animals. It was observed that the animals with induced epilepsy slept for longer durations in the light cycle as compared to the control animals. A comparative analysis was performed to determine the relationship between the sleep states in the disease-induced animals vs the control animals based on the light-dark cycle.

1 INTRODUCTION

Epilepsy is one of the most common and severe neurological disorder characterized by recurrent epileptic seizures (Karoly et al. 2016; Duncan et al. 2006). At present, more than 50 million people worldwide suffer from Epilepsy ("Epilepsy" 2019). There are different treatments available for Epilepsy, however, there is no current measure which can predict the occurrence of these epileptic seizures. Over the years, it has been discovered that there is an underlying relationship between the sleep-wake cycle and the occurrence of epileptic spikes and seizures nearly one-third of the patients suffer from seizures in the sleep state (Karoly et al. 2016; Méndez and Radtke 2001). There is a correlation between sleep-wake states and the occurrence of epileptic seizures and spikes as well as its relationship with sleep deprivation. (Janz 1962; Kellaway 1985; Malow 2004, 2007; Méndez and Radtke 2001; Kotagal and Yardi 2008). Considering the relationship between seizures and sleep, it is important to understand the underlying relationships between epileptic events and the sleep-wake patterns. Accurate characterization of the sleep-wake state is also essential to study the circadian patterns of sleep and its relationship to epileptic events. Longitudinal animal model of epilepsy often records data for months. Most often, video-EEG is used for continuous monitoring and is the gold standard for documenting the occurrence of Epileptic events in rodent models of epilepsy (Ono et al. 2018) along with identifying different sleep-wake stages. However, it is extremely cumbersome to identify the sleep-wake stage in the recorded EEG data manually and in a standardized format. This demands a robust and fast automated detection system that can independently detect sleep segments using EEG modality only.

The sleep-wake states are divided into three different stages, namely, Rapid Eye Movement (REM) sleep - indicated by presence of theta activity and a high frequency low amplitude EEG signal, Non-Rapid Eye Movement (NREM) sleep - indicated by the presence of high amplitude, low frequency EEG signal along with the presence of delta activity and the wake state or the active state - indicated by the presence of high frequency low amplitude EEG signals (Ono et al. 2018). Electromyography (EMG) along with EEG signals are used to differentiate between sleep state (REM + NREM) and the wake state of the animals (Vivaldi et al. 1984; Benington, Kodali, and Heller 1994; Hamrahi, Chan, and Horner 2001; van Luijtelaar and Coenen 1984; Robert, Guilpin, and Limoge 1999). EEG signals alone can also be used for the detection of these sleep-wake states (Robert, Guilpin, and Limoge 1999). It is essential to understand the role of the different frequency bands in the sleep-wake states and understand their alterations in the sleep-wake states of the epilepsy model of the animal vs the control animal. The sleep-wake cycle follows a circadian rhythm – basically a 24-hour internal clock between sleepiness and alertness at regular intervals which is regulated by the 24-hour light-dark cycle of the environment. (Mary A. Carskadon 2011; Czeisler et al. 1980) (Chouvet G 1974). Just like the sleep-wake states, it was observed that the both interictal spikes and seizures showed an existence of circadian rhythm over a period ranging from weeks to months (Karoly et al. 2016). This makes it essential to understand the correlation between the sleep state, the light-dark cycle and their relationship in the epileptic vs the control population. Investigating these relationships would help in understanding the association between sleep and epilepsy.

In the current study, we quantitatively evaluated the conventional EEG frequency bands such as alpha, beta, delta, theta and gamma in predicting the sleep EEG segments. We also evaluated a set of frequency bands which proved to be more robust in isolating sleep events from wake states. Using these new frequency bands, we compared the output of brute force threshold approach with machine learning algorithms. The outcome was also compared with the video recording to find the overall accuracy. Based on the detected sleep-wake states in the animals, we evaluated the effect of induced epilepsy on sleep patterns. We also quantify the sleep in diseased and naive animals during the light-dark cycle and performed a comparative analysis.

2 MATERIALS AND METHODS

2.1 Animals:

EEG Analysis was performed on two animal cohorts. Diseased cohort consisted of 4-Male Sprague Dawley Rats (2-4 months) injected with Tetanus toxin for inducing Epilepsy EEG data was collected. Naïve cohort consisted of 2-Male Sprague Dawley Rats (2-4 months), which were control animals used for EEG data collection. All the EEG recordings were 24-hour long, collected every alternate day, over the span of 3 months and were collected through a six-channel electrode system implanted on each animal. For our study, we used 552 hours of diseased animal data divided over a period of 15 consecutive days. Naïve animal data consisted of 48 hours of EEG data from 1-control animal. We used the same dataset for validation of the algorithm along with additional 480 hours of naïve animal data for one of the analysis. All the animals were singly housed in a soundproof glass cage maintained at a constant ambient temperature. A light-dark cycle was maintained with around 12-14 hours of light cycle and 10-12hours of dark cycle (lights off at 7.00 PM until 5 AM). Food and water were freely accessible by the animals in their cage. The experimental protocol was reviewed and approved by the Animal Care Committee (ACC) at the University of Illinois at Chicago administered through the Office of Animal Care and Institutional Biosafety (OACIB) for the Office of the Vice Chancellor of Research.

2.2 Electrode Implantation & Data Acquisition:

Craniotomy was performed on the diseased and naïve animals under general anesthesia which a combination of ketamine (100 mg/kg) and xylazine (13 mg/kg) with level administered every 15 minutes throughout the surgery. Each animal was implanted with a six-electrode system onto their scalp for recording and studying the EEG signals. The holes for the electrode placement were drilled relative to the Bregma for the rat brain. Three holes were drilled at a depth of 1.5mm in the skull over each hemisphere at +4mm, -1mm and -6mm relative to the bregma in the cranial-caudal axis and 3.5mm lateral. A seventh hole was drilled at the midline over the nasal sinus and was considered as a reference electrode. Diseased animals were injected with 1ul of 100 ng/ul tetanus toxin stock in PBS into a Hamilton syringe (0.4ul of prepared dilution of tetanus toxin + 0.6ul of cold PBS) into the somatosensory cortex at the electrode 2 position (Barkmeier and Loeb 2009).

2.3 Video EEG Monitoring and Analysis:

The six-channel system with one reference electrode was then connected to Stellate system for data acquisition from these animals at a sampling frequency of 1000 Hz. A continuous 24-hour video EEG monitoring system was set up for the purpose of data acquisition that recorded 4- diseased and 2-naïve animals at a single time.

Continuous Video-EEG recordings were used as a gold standard for detecting the sleep-wake states. The data was monitored on Harmonie Signal File Browser by Stellate. **Sleep** in the animals is defined as events that depicted no motor activity on the recorded video characterized by the presence of slow waves - low amplitude, high frequency delta waves and the presence of high frequency low amplitude signals. **Wake** state for the animal is defined as events where the video of the animals and compared for activities like grooming, chewing, moving etc. Change in the state of the animal was observed for each second. An event was considered as a sleep / wake state only when they were continuously occurring for a period longer than 40 sec. Any event duration shorter than 40 secs was disregarded and was considered as a part of the previous event. To avoid complications, we only made note of each sleep segments occurring throughout the day for an animal and marked the sleep and wake transitions.

2.4 Data Analysis & Feature Selection:

All the data was analyzed using MATLAB 2019a. We considered the total of all the 6-channels for our analyses. We normalized the powers of the individual frequency bands by dividing them with a power in the 0-50 Hz frequency band. We will refer to this power as normalized power throughout the document. We did our analyses on the absolute and normalized powers in the common reference montage and common average montage. We calculated the power spectral density using the frequency domain analysis of the signal. A short-time Fourier transform of the signal was calculated to obtain the power spectrum of the signal. The absolute power spectrum in the reference montage and the normalized power spectrum in the reference and average montage were calculated. A 10-sec window length was considered to determine the power spectrum for each sleep and wake state in an animal for a 24-hour long duration. The average band-power in the traditional EEG frequency bands: Delta (1-4Hz), Theta (4-7Hz), Alpha (7-12Hz), Beta (12-30Hz), Gamma (30-50Hz) was calculated using the power spectral density estimate of the signal plotted for the sleep and wake states individually from the manually marked data for 552 hours of diseased animal data and 48 hours of naïve animal data. Based on the power spectrum analysis while deciding EEG signature, differences were observed in the frequency bands between the sleep and wake states. The average band-power in the absolute reference montage and the normalized band-power in the average montage for 10-sec window lengths were calculated for the frequency bands: 0-1Hz, 3-5Hz, 4-7Hz, 4-10Hz, 5-12 Hz and 6-14Hz. These calculated powers were plotted for the individual sleep and wake states for entire 600-hour diseased and naive animal data.

2.5 Algorithm for State detection:

The Stellate files for EEG were extracted to readable EDF files on MATLAB. For a window length of 20 sec the absolute common reference montage power and normalized average montage power were calculated using the power spectral density estimate of the signals. The median of this calculated normalized power was considered as a threshold to detect the sleep and wake state. Depending on the frequency, the power in the sleep state for that frequency was either higher or lower than the median of the normalized power. Using this threshold, the data was divided into the sleep and wake state, with sleep = 1 and wake = 0. All the different outputs for each of the frequency band were summed to find the final output matrix such that if the sum is greater than or equal to 3 it was considered as sleep state = 1 and if it was less than 3 it was considered as wake state = 0. This output was then consolidated to disregard any events that are lower than 40 sec of length. This output was then converted to samples for marking the file onto the Stellate file on the Harmonie Signal File Browser for validation. MATLAB 2009a was used to mark the files on the Stellate file because of compatibility.

Using the 20 sec window length, the absolute reference montage power and normalized average montage power for the frequency bands were provided as features to Machine Learning Algorithms – k-Nearest Neighbors (Medium KNN; 10-nearest neighbors; Euclidean Distance), Support Vector Machine and Logistic Regression from the Classification Learner on MATLAB. The model was trained using 80% of the randomized data from the 600 hours and we used 20% of the remaining data to test it. The algorithm was then used to test the accuracy for the complete dataset of 600 hours. The output of the Machine Learning Algorithm was then used to mark files using the consolidation algorithm as used for Manual Thresholding and mark the data onto the Stellate file on the Harmonie Signal File Browser using MATLAB 2009a. On algorithm implementation, sleep durations in the dark and light cycle were calculated based on the markings using the manual thresholding algorithm. The individual sleep durations as well as the total sleep durations during each cycle and overall were calculated for comparative statistical analysis. 552 hours of diseased data and 288 hours of naïve data was considered for this analysis.

2.6 Statistical Analysis:

Receiver Operator Curve (ROC) for the Optimal Cut Off point was used to decide the best window length for average band-power calculations. Accuracy was defined as (True Positive + True Negative) / (True Positive + False Negative). Optimal Cut-Off Point distance was calculated using Euclidean Distance between the True Positive Rate = True Positive / (True Positive + False Negative) and False Positive Rate = False Positive / (True Positive + False Negative) and (1,0). All the comparative statistical analysis was performed using a paired t-test to validate the hypothesis and determine the p-value.

Flowchart: Brute Force Thresholding algorithm

Calculate Normalized Power - Average Montage for the different frequency bands; Window length

Calculate the median of the power for each frequency band

Threshold sleep = 1 and wake = 0 based on frequency bands using median

Sum the output for all the frequency bands

For sum greater than or equal to 3, threshold final output matrix as sleep = 1 and wake = 0

Consolidate the output matrix to disregard any events smaller than 40 s in length

Mark on video-EEG file

Test for accuracy against manually marked files

3 RESULTS

We analyzed 24 hours continuous video-EEG recordings from 5-animals (4-Diseased & 1-Naive) recorded over multiple days totaling 600 hours of EEG data. The goal of the research work was to develop an algorithm that automatically identifies the sleep and wake state of the animals using only EEG. Using this sleep and wake information, we further explored the relationship between sleep and epilepsy. We followed a two-step approach. First, using the video-EEG dataset, we manually marked the dataset with sleep and wake states, and then further analyzed the EEG for sleep signatures. Using the sleep EEG signature, we developed a simple frequency band-based power threshold approach to automatically detect sleep. We further implemented multiple machine learning algorithms to find sleep-wake states using the same feature set as previous, to verify the accuracy improvements of machine learning algorithms over brute force thresholding approach. As a next step, using the identified sleep-wake patterns in each animal we answered a set of scientific questions as follows: (a) Do diseased animals sleep for longer durations than naïve animals? (b) Is there any difference between average sleep duration between light and dark cycle and does it depend on the disease and (c) what is the average sleep duration per sleep event in naïve and diseased animals?

3.1 Delta and Theta band power is significantly higher compared to other frequency bands in sleep state

Video-EEG is the gold standard and is most used, to monitor and understand sleep-wake states in animal studies and corresponding EEG recordings. Using the 24 hours continuous video-EEG recordings, we manually marked sleep and wake segments in 600 hours of EEG data. Sleep was defined on basis of no motor activity on the video for a specific animal along, with the presence of higher amplitude waves in delta and theta frequency bands compared to other higher frequency bands where the amplitude was often low. Wake state was identified by movement, grooming, chewing and activity in general, accompanied by low amplitude high frequency activity EEG, along with presence of slow waves but not as much during sleep (fig.1a & 1b). These manually marked sleep-wake EEG segments were further used to investigate for specific EEG signatures in the frequency domain (fig. 1c & 1d). We observed distinct peaks

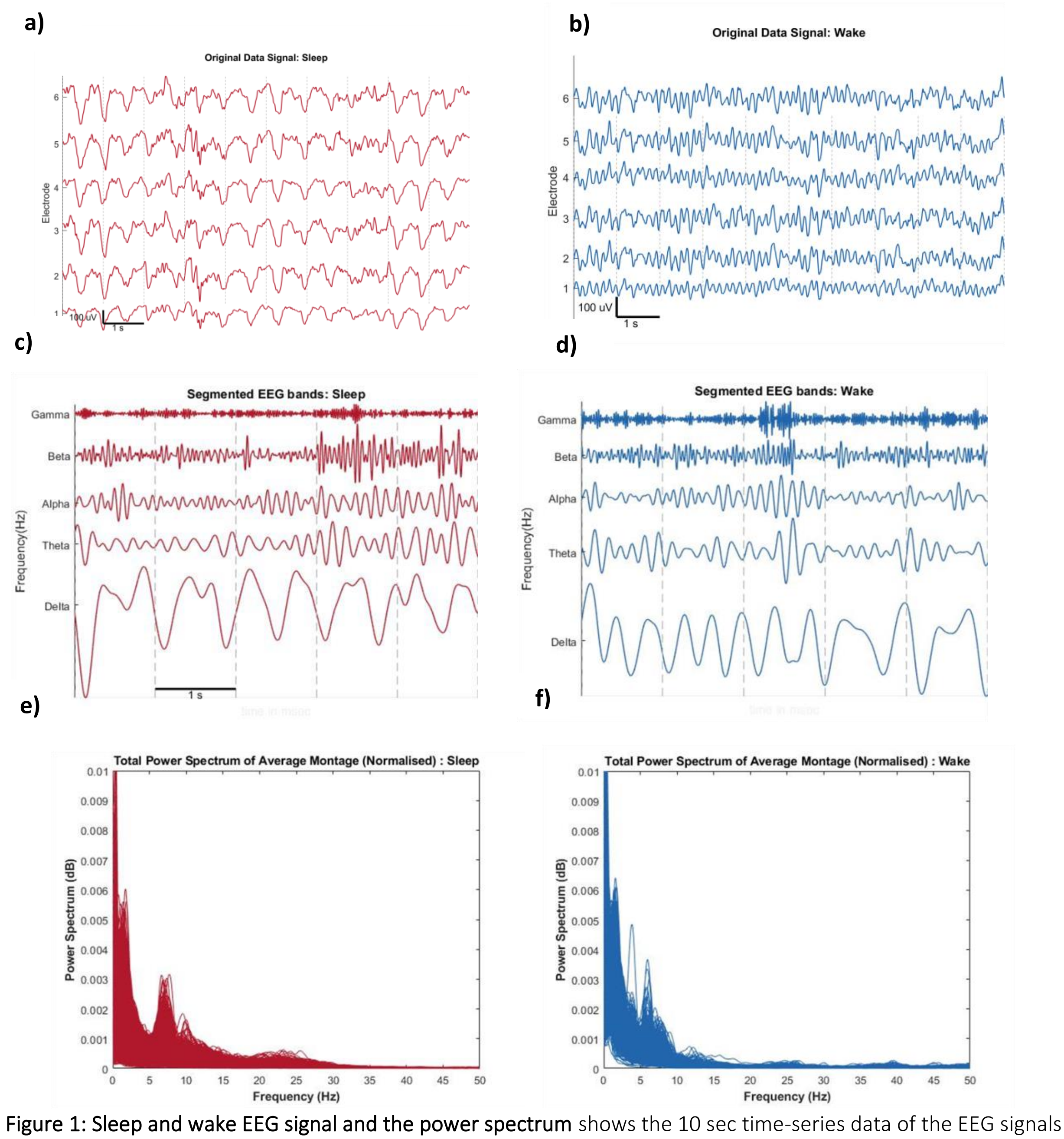

Figure 1: Sleep and wake EEG signal and the power spectrum shows the 10 sec time-series data of the EEG signals in the (A) sleep and (B) wake state of the animal. (C) and (D) shows 5 sec window of single channel sleep and wake signal split into different EEG frequency bands respectively. (E) and (F) shows the power spectrum normalized to total power in 0-50Hz in sleep and wake state. We can observe band specific peaks at 1Hz, 7Hz and power in 0-1Hz, 3-5Hz, 4-7Hz, 4-10Hz, 5-12Hz, 6-14Hz shows distinct difference between the sleep wake states.

at 1Hz and 7Hz in the power spectrum for sleep events, which were also present in wake state, however, were not prominent (fig.1e & 1f).

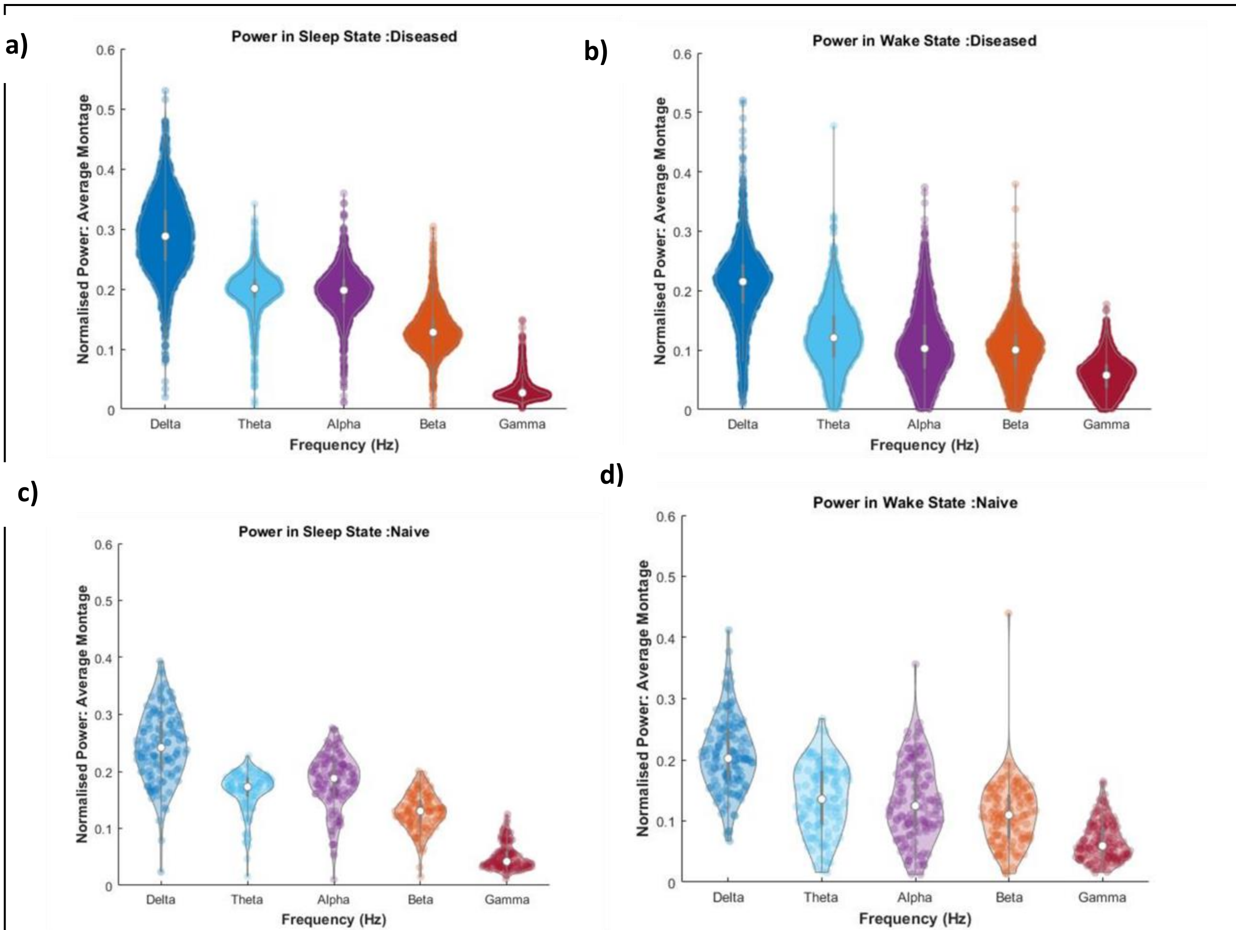

Figure 2: Sleep-Wake Delta & Theta power is higher than other frequencies The normalized average montage powers in the distinct EEG frequencies: Delta (1-4Hz), Theta (4-7Hz), Alpha (7-12 Hz), Beta (12-30 Hz), Gamma (30-50 Hz) were calculated for the sleep-wake segments in the animals. Figure 2 (A), (B) & (C), (D) show the power distribution in the different frequency bands for the sleep and wake states of diseased and naïve animals respectively. Statistical significance test shows that the delta and theta bands are significantly higher in both the sleep and wake state of the diseased animal ($p<0.05$). Similarly, in naïve animals, the delta and theta bands are significantly higher than other frequency bands in the sleep and wake states, except theta power is similar to the alpha power in the wake state with $p = 0.4932$. On comparing the powers in the frequency bands between the sleep and wake states, we observed a significant difference ($p<0.05$) between them in both diseased and naïve animals.

We considered both diseased and naïve animals, while evaluating the EEG features in the frequency bands Delta (1-4Hz), Theta (4-7Hz), Alpha (7-12Hz), Beta (12-30 Hz) and Gamma (30-50Hz) for analysis of sleep-wake states. We further calculated the band power for the above frequencies in common reference montage, common average montage, and the normalized power for the same bands in both the montage (normalized to the average band power in 0-50Hz). The normalized power in average montage was the best approach which provided distinct differences (fig.2). We observed that the normalized delta and theta band power in average montage during sleep was significantly higher compared to other frequency bands ($p<0.05$) which coincided with a similar observation in the wake state ($p<0.05$). These differences were observed in both naïve and diseased animals with slight alterations. The comparison of powers between the sleep and wake state showed that there was a statistically significant difference between all the frequency bands in both naïve and diseased animals. Apart from the conventional frequency bands, we also considered a separate set of frequency bands: 0-1Hz, 3-5Hz, 4-7Hz, 4-10Hz, 5-12Hz and 6-14Hz which were observed from the power spectrum in fig 1(e) & (f). The frequency band differences are as shown in

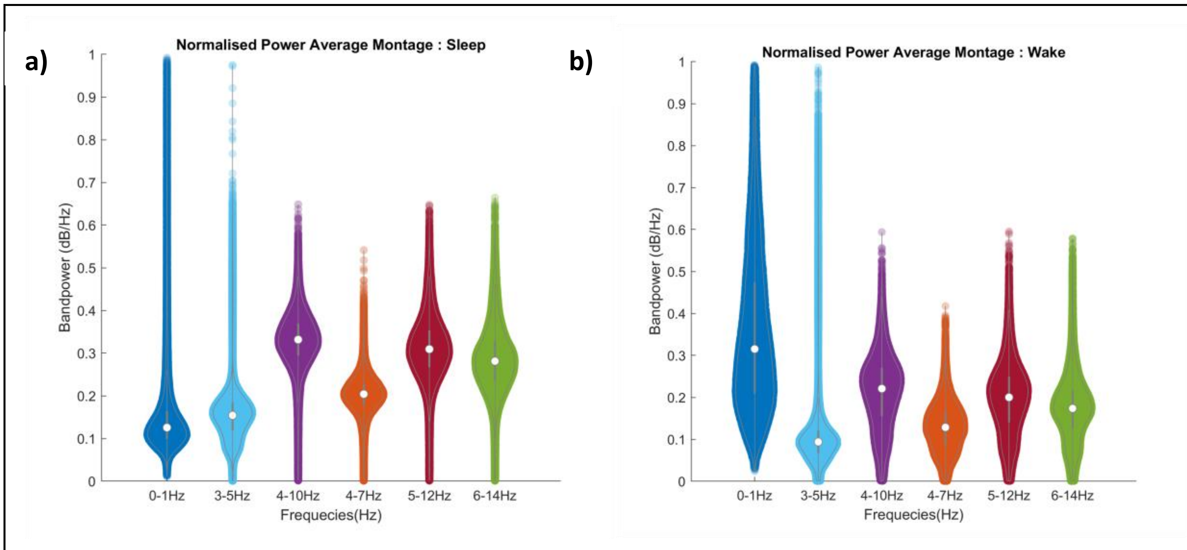

Figure 3: Median is a threshold for sleep-wake state detection in brute-force thresholding shows the violin plot of the normalized power of the average montage for the determined EEG signature frequencies. As seen from figure 3(a) and (b) there is a stark difference in frequency band-powers for the sleep and wake states. The median of the data served as a perfect linear threshold for separation of the sleep and wake states.

fig. 3. Since the frequency bands differences were more distinct compared to the conventional frequency bands, we used these frequency bands for further classification.

The detection algorithm used non overlapping small EEG data segments for the band power calculation. For this purpose, another parameter we investigated is the length of the data segment that is taken into consideration while performing the band power calculations. We observed that among different data lengths considered (5sec, 10 sec, 20 sec, 30 sec, and 60 sec), 5 second data segment was performing the worst, while the other segment lengths didn't have significant difference (p< 0.05) in terms of accuracy (fig. 4a). For our further calculation, we fixed the data segment length to 20 secs.

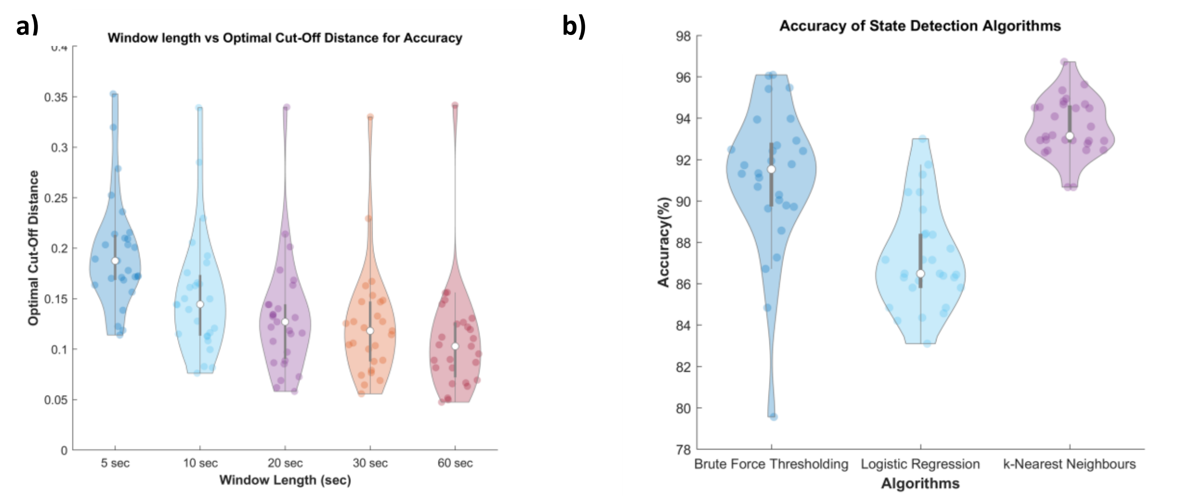

Figure 4: Machine learning algorithms are more accurate than brute force thresholding. (a) shows the optimal cut-off distance distribution for the manual thresholding algorithm for window lengths: 5 sec, 10 sec, 20 sec, 30 sec and 60 sec. The algorithm shows the best accuracy for a window length of 60 sec. However, there is no significant difference (p > 0.05) between the window lengths:10 sec, 20 sec, 30 sec and 60 sec for the optimal cut-off distance. Figure 4 (b) shows the accuracy of the state detection algorithms – Brute Force Thresholding & Machine Learning (Logistic Regression and KNN). Significant difference (p < 0.05) is observed in the accuracy of the Brute force thresholding algorithm and KNN, however Brute force threshold and logistic regression did not show a significant difference (p = 0.0945).

3.2 Machine learning algorithms outperform simple brute force thresholding algorithm using band-powers in automatically detecting sleep-wake states

We observed distinct power in the frequency bands which we further used for sleep-wake state detection. For the brute force thresholding approach, we used the median normalized band power for the frequency bands in the average montage. The brute force automatic sleep-wake detection was 90 - 95% accurate in both diseased and naïve animals. Further using the same parameters, we implemented KNN (Features: Absolute reference power and normalized average montage power, for 6 frequencies; Medium KNN; Euclidean Distance – 10 nearest neighbors ; Training Accuracy: 92.4%) and logistic regression (Training Accuracy: 87.6%) for supervised clustering of the sleep-wake events. The machine learning algorithms certainly outperformed brute force method for most cases.

The brute force detection method detected sleep-wake segments with 93% accuracy (91% - 95%), whereas the logistic regression had an accuracy of 87% and the KNN had an accuracy of 94%. The KNN was the best predictor of the sleep-wake states compared to the brute force method however the results it was observed that brute force median thresholding was better when compared to Logistic Regression (fig. 4b).

3.3 Diseased animals sleep for longer durations than Naïve animals

We had considered 4-diseased (23: 24-hour files) animals & 2-naïve (12: 24-hour files) animals for the analyses. Using brute force thresholding approach for state detection in animals, we studied the interdependence of the sleep-wake states with the dark and light cycle for naïve and diseased animals. We calculated the sleep durations & total sleep in minutes occurring within 24-hours in the corresponding light and dark cycles. Total sleep in the diseased animals was not statistically ($p = 0.3300$) different from the total sleep in naïve animals in a 24-hour period. Figure 5 shows the distribution of the sleep duration in minutes for the light and the dark cycles for both diseased and naive animals and the distribution of the total sleep duration of the animals in 24 hours. It was observed that the sleep durations in the light cycle are significantly higher than that in the dark cycle for both diseased & naive animals as seen in Figure 5 (a) & (b). It was observed from Figure 5 (c) & (d) that the total sleep of the diseased and naïve animals is higher during the light cycle as compared to the dark cycle. Total sleep duration of the diseased animals in the light were statistically higher than the naïve animals with the maximum sleep of up to 11 hours for the diseased animals in a 24-hour period. Naïve animals slept more during the dark cycle as compared to the diseased animals with up to 5 hours of total sleep in the dark cycle for a 24-hour period. Both diseased and naive animals slept for similar durations throughout the 24-hour period with approximate sleep of around 13 hours each day.

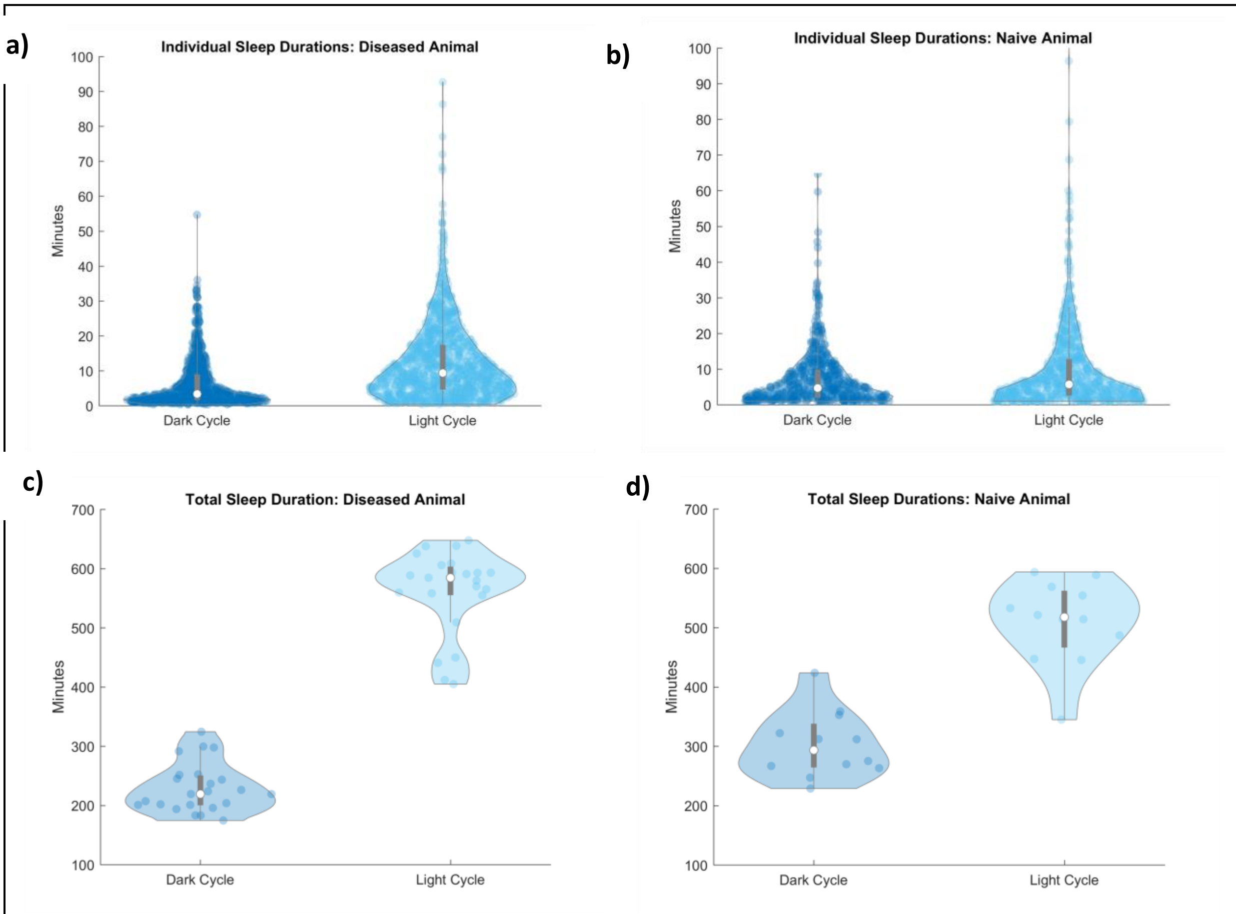

Figure 5: Diseased animals sleep for longer durations as compared to naïve animals in the light cycle. (a) & (b) shows the sleep-wake state durations of diseased & naïve animals in the dark and light cycles in 24-hour period. Diseased & naïve animals sleep for longer durations in the light cycle as compared to the dark cycle ($p < 0.05$). Sleep durations in the dark and light cycle for the diseased animals are statistically higher($p<0.05$) than naïve animals. Total sleep in the light cycle is higher than that in the dark cycle ($p<0.05$) as observed in Figure 5(c) & (d). Total sleep duration of the diseased animals compared to naïve animals, in a 24-hour period is higher in the light cycle and lower in the dark cycle with a statistical difference $p < 0.05$.

4 DISCUSSION

Our study highlights the high incidence of delta and theta band-powers in both sleep and wake states when compared to the other frequency bands. It helps identify the typical frequency bands involved in the detection of the sleep-wake states of the animals. A comparative study identifies that the Machine learning algorithms, especially k-nearest neighbors perform better than brute force median-thresholding to accurately detect the sleep-wake states of the animals – both diseased and naïve. The major outcome of the study was that the total sleep durations for the diseased animals were higher in the light cycle when compared to the naïve animals. This will help in deriving a potential relationship between sleep and Epilepsy.

Sleep is generally divided into Rapid Eye Movement and Non-Rapid Eye Movement states, each having their own characteristics. REM sleep is characterized by the presence of low amplitude high frequency activities like the wake EEG as well as the presence of the theta oscillations, whereas NREM sleep is a slow wave sleep characterized by the presence of the delta frequency (1 – 4Hz) in its power spectrum (Ono et al. 2018; Montgomery, Sirota, and Buzsaki 2008; Achermann and Borbély 2003). Our results show that delta and theta frequencies show higher powers as compared to other frequency bands in sleep state. The higher delta and theta power in the sleep state as observed, corresponds to the REM and NREM sleep states as defined. This presence of the delta and theta power in the sleep state re-iterates their contribution in the sleep state as observed in the literature.

Traditionally, the wake states were associated with high frequency and low amplitude signals (Bloom 1981; Steriade 2000). Our observations showed that, there was a significant increase in the delta and theta power even in the wake states of the diseased animals. Although the naïve animals showed similar characteristics, it was also observed that theta power in the wake state for these animals was similar when compared to the alpha power. The literature suggests that there is a presence of delta rhythm in the awake state of the animal, (Sachdev et al. 2015) and this may be considered as local sleep in the awake states of the rodents (Vyazovskiy et al. 2011). Like rodents, even humans have a presence of rhythmic delta waves during the wake states (Sachdev et. al.). The density of delta waves in the wake state quantifies the tendency to sleep and this response is generally caused due to sleep deprivation (Borbély, Tobler, and Hanagasioglu 1984; Mistlberger, Bergmann, and Waldenar 1983). Sleep deprivation also causes an enhanced theta power in awake state of the animal with an increase in the spectral density (Borbély, Tobler, and Hanagasioglu 1984).The presence of these prominent delta and theta frequencies in the wake states of animals means that our animals are sleep deprived and there is a likelihood for them to sleep more often. We analyzed both epileptic and naïve animals for their power content in the delta and theta bands. The potential factors resulting in sleep deprivation or disruption are the occurrences of seizures in the diseased animals. The electrode placement surgery also influences the sleep cycle of these animals, which eventually causes sleep disruption or deprivation. A longitudinal and in-depth analysis is required to understand the causes of sleep deprivation or disruption in these animals and understand specific markers for these increased delta and theta frequency powers in these animals.

The k-nearest neighbors (KNN) machine learning algorithm showed the best performance when used to classify the sleep-wake states of the animals. The machine learning algorithms outperformed the brute median thresholding algorithm for the purpose of classification. Machine learning algorithm classification is based on the properties learned from the predictive/training samples however, these algorithms come with a computational cost and may cause overfitting of the classification model (Al-Jarrah et al. 2015). The brute thresholding algorithm is computationally simple, however has less accuracy compared to the Machine learning algorithms. We had used Support Vector Machine (SVM) algorithm as well for the classification of the states. Although it provided a maximum accuracy of 97% while classification, the training of the algorithm consumed an extensive amount of time for training and computations of large data sets. This points out a potential trade-off between the computational cost and the accuracy of the classification system. As the machine learning algorithms are computationally extensive and require training samples, it becomes difficult to train them in real-time. Hence, we used the brute thresholding algorithm to detect the sleep-wake states in our animals.

Rats being nocturnal animals sleep during the day or the light cycle and are awake generally during the dark cycle. Our observations show that (a) there was no difference in the total sleep durations for the sleep in the diseased vs the naïve animals. This observation depicts that total sleep durations for these animals is the same irrespective of the type of the animal. (b) The total as well as individual sleep durations during the light cycle were higher than that in the dark cycle for both the diseased and naïve animals. Diseased animals however, slept for longer total durations as well had longer individual sleep durations among all the sleep events in the light cycle when compared to the naïve animals. This marks as a very important finding towards relating sleep and epilepsy. There is evidence that most of the seizures occur when the patient is sleeping (Kotagal and Yardi 2008) (National Sleep Foundation - Sleep Research & Education n.d.). The electrical discharges in the brain due to sleep are responsible for seizures, and sleep deprivation is one of the factors that leads to epileptic seizures (Frucht et al. 2000; Malow 2004; Rajna and Veres 1993) (National Sleep Foundation - Sleep Research & Education n.d.). As the diseased animals sleep for longer durations of time, there is a higher incidence of electrical discharges in the brain, which eventually lead to seizures. These occurrences of seizures eventually lead to sleep deprivation, which again adds to the possibility of increase in seizures. This observation also helps us quantify the previous result of increased delta and theta rhythm in the wake state of the diseased animals is due to sleep deprivation.

Although there is an evidence regarding higher sleep durations in the diseased animals, there is still no specific observation which can help us determine the ambiguity involved in the intimate relationship between sleep and Epilepsy. A longitudinal study is required to understand relationship between the durations of sleep in the light cycle and the occurrence of seizures and seizure like events over time. Although there is evidence regarding increased delta rhythm in the wake state due to sleep deprivation, more naïve and diseased animals should be studied to quantify the result and find the causes of the sleep deprivation. There are still some questions that remain to be answered, such as (a) why do the diseased animals sleep for longer durations during the light cycle? (b) why do they have smaller sleep durations in the dark cycle when compared to the naïve animals? The relationship between the sleep in the light and dark cycle of the animals is still unknown and needs to be evaluated in terms of the diseased model of Epilepsy. The current study can further be developed to understand the relationship between Epileptic spikes & seizures with sleep-wake states & circadian rhythm. This would answer a lot of questions regarding the occurrence of the epileptic seizures in the sleep state for both animals as well as humans. It will also help identifying the biomarkers for these epileptic seizures related to these sleep-wake events.

5 CONCLUSION

We created an algorithm to detect the sleep and wake states of the animals both diseased and naïve. KNN was the best predictor of sleep and wake states with 94% accuracy where the brute force was significantly similar accuracy (92%). Epileptic animals sleep for longer durations as compared to naïve animals in the light cycle. Both epileptic and naïve animals sleep for equal total duration throughout the day. There is a fragmented sleep of the epileptic and naïve animals in dark and light cycle.

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Academic Projects:

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- Studied the importance of RLS algorithm as compared to other algorithms of adaptive filtering and implemented RLS adaptive filtering on online EEG removing 90% artifacts

Risk Analysis of Electrocautery Device

- Studied the regulatory process involved in the Research and Development of a medical device
- Created DHF, PRD, RMP and performed FMEA for the medical device using the JAMA software following FDA standards

Effect of deformation on the propagation of Action Potential

- Compared the Action Potential Propagation through Active Axons and Passive Dendrites using Hodgkin-Huxley Neuron Model on MATLAB and studied the effect of deformation on the propagation of action potential

Epilepsy Detection using Artificial Intelligence

- Studied the different features of the human EEG data and developed a neural network based automated classification system with 90% accuracy to differentiate epileptic patients from healthy using EEG

Publications:

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