Real-time State of Vigilance Detection for Probing Seizure Mechanisms and Seizure Control

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Abstract

States of consciousness in the brain offer a metric for explaining and predicting behaviors. There is a well-known correlation between epileptic seizure susceptibility and state of vigilance. Our goal is to design a system for detecting state of vigilance in real time using invasive electroencephalography and measurements of head movement. We will use this to probe the relationship between state of vigilance and seizure mechanisms. This system has potential clinical applications for state-based seizure prediction and control.

Introduction

For neuroscientists in a span of disciplines, brain states offer a useful measurement of human consciousness. In the fields of Brain-Computer Interfaces (BCI), Behavioral Neuroscience, or Computational Neuroscience, researchers consider analyses of discrete brain states crucial for ongoing studies about characteristics of waking and sleep states. Some studies suggest correlations between sleep states and neurophysiologic behaviors like epilepsy or sleep disorders such as sleep apnea[1]. Traditionally, sleep state has been determined by an expert analysis of biopotentials following a standardized method[2]. These biopotentials typically include electroencephalography (EEG) and electromyography (EMG) signals, but contemporary studies also consist of accelerometers to further and more accurately distinguish sleep state [3]. Researchers analyze raw data from biopotentials through sleep staging/scoring, which is a classification system for measuring sleep states.

Sleep scoring is done by hand and it often takes many hours to accurately score a data set. For applications that rely on this data, scoring by hand frequently causes potential delays when researchers need to score large quantities of information. To resolve this issue, post-processing techniques of automating sleep scoring have been developed, but this limits any applications to identification or classification, with no possibility for real-time clinical treatment options. In our research group, we seek to probe the relationship between state of vigilance and seizure susceptibility. Using the offline post-processing techniques, a lot of conclusions can be drawn about the seizure-sleep state relationship, but these conclusions are purely diagnostic. We seek to probe the relationship between rates of seizures and state of vigilance using perturbative stimulation. A real-time state of vigilance detector allows us to track state of vigilance as it changes dynamically over time, and allows us the ability to automatically stimulate based on a threshold. By making that threshold a specific state of vigilance, we can explore the mechanisms of seizure generation and how they relate to the specific state of vigilance of interest. This system has applications in seizure control, as the perturbative stimulation can be introduced precisely at the onset of a seizure, disrupting it and preventing it from propagating through the brain.

Literature Review

Literature dating back to the 1960s suggests that sleep states have distinct characteristics that allow for a variety of automated detection methods [2], [4]. These states of vigilance have been chosen for this study with considerations of long term applications in the research group. These states are *NREM*, *REM*, and *Wake* (subclassified into $Wake_{\theta}$ and $Wake_{wb}$), and are characterized by different combinations of frequency and accelerometer channel data. In order to discern the incoming frequency of a signal, a power spectral analysis is done, which returns the value of the dominating frequency of a periodic signal[3], [5]. Due to the nature of the sleep scoring systems, a strict definition needs to be established for each of the frequency ranges, as they are not consistent between animal and human subjects, and can vary greatly between researchers in literature[6]. Recent studies in automatic sleep scoring systems use multiple definitions to account for the discrepancies between published work[3]. This allows for a more adaptable system where discrimination could be improved by using a different classification scheme. In general, the accepted standard spectral band limits of EEG are *Delta*, δ (0.5-4Hz); *Theta*, θ (4-8Hz); *Alpha*, α (8-13Hz); *Beta*, β (13-30Hz); and *Gamma*, γ (30-55Hz) [2], [7]. Each frequency band limit is closely related to a behavior or state of vigilance which, when coupled with EMG or accelerometer data, can be used to classify a state as a form of sleep or wake. The sleep states are characterized by immobile activity (low EMG or accelerometer) with oscillations <8Hz in EEG. *NREM* and *REM* can be differentiated by their EEG signature, since both are characterized by quiet accelerometer channels. *NREM* is characterized by oscillations in the δ(0.5-4Hz) band and *REM* is characterized by oscillations in the θ (4-8Hz) band in EEG signals. The wake states are characterized by accelerometer or EMG activity with higher frequency oscillations in EEG (>8Hz). $Wake_{\theta}$ is characterized by the same θ (4-8Hz) band as REM, but is able to be distinguished from REM by the quieter accelerometer/EMG channel data [7]. $Wake_{wb}$ is characterized by little to high accelerometer/EMG signal with a wide range of frequencies present in the signal, hence the name “wide band wake”.

Once the limits and definitions of these states are defined, a method of classifying data based on these spectral band limits is required. Manual scoring involves looking at windows of EEG and EMG/Accelerometer data and visually determining the sleep state. This is coupled with a power spectral density of the particular epoch to determine what the dominating frequency of biopotentials was during that specific epoch (small time window, usually 10-15 seconds). To make a determination of state, a “scorer” looks at the incoming data, decides whether it is a sleep or wake state, and then looks at the incoming frequency to determine which bin it fits under. For example, if the signal coming in had high accelerometer movement and showed a peak in the signal in the 4-8Hz range, it could be determined that the animal was in $Wake_{\theta}$ or “active wake”. Automated techniques of sleep scoring follow this theory of operation, but require discrete operations and data transformations in order to be able to classify sleep. Linear discriminant analysis (LDA) has proven useful for this as well as a variety of related tasks [8],

[9]. LDA takes a multi-dimensional, multi-variate system and breaks down the components to provide maximum separation between each of the variables while reducing the dimensionality. More simply, it looks for a specified number of characteristics (4 in our case – one for each state of vigilance), and separates them into groups. We feed the classifier all of the EEG and accelerometer information to build the classifier's "picture" of each of the four sleep states. This has proven useful for a variety of clinical and diagnostic applications, where discrimination of key states is crucial [10], [11].

Classifying sleep states has proven useful for a variety of disorders, particularly epilepsy. It has been suggested that sleep and state of vigilance have effects on rates of seizures in patients with epilepsy, and the need to explore that relationship further has necessitated a method of real-time state determination.

Methods

Data Collection

EEG, accelerometer, and video recordings of rats were continuously monitored using custom-made acquisition hardware and software written in LabView (Labview, National Instruments). A head-mounted preamplifier connects depth electrodes and cortical surface electrodes for EEG, located in the dorsal hippocampus and on Bregma-referenced coordinates, respectively [12]. The preamplifier also contains a biaxial MEMS accelerometer that detects motion in three dimensions. The EEG and acceleration signals are sampled at 2kHz and stored as word type (16-bit signed integer) binary data files in one-hour long continuous segments. The animals are located in isolation with a 12-hour light-dark cycle. Cameras with infrared capabilities allow monitoring during all hours to be used for better verification of state of vigilance.

Manual Expert Sleep Scoring

EEG and acceleration channels are scored visually by an expert (MSS) to label sleep state as *REM*, *NREM*, $Wake_{\theta}$(Active Wake), or $Wake_{wb}$(Quiet Wake). Epochs (small windows of data) of 10-15 seconds are chosen to match literature on sleep state scoring [7]. This epoch window aims to provide a long enough window to discern sleep state while being short enough to only contain one state.

To score sleep, each of the 10 second epoch windows is analyzed to determine the state in that window as sleep or wake. Subsequent analysis aims to further discern sleep as *REM* or *NREM*. If there is a transition to a different state or the animal had a state lasting less than 10s, that transition period is considered indeterminate and is not scored. To score sleep as one of the sleep states, EEG signals must be <8Hz and the accelerometer channels should be quiet, with little to no activity. *REM* is characterized by the θ frequency band, and NREM is characterized by the δ frequency band.The remaining two wake states are classified as *Quiet Wake* if EEG oscillations are in the $\alpha, \beta, or\ \gamma$ bands (all above 8-10Hz) with high accelerometer signals, and $Wake_{\theta}$ if the EEG oscillations are in the θ frequency band with some to high accelerometer signals.

Automated Post-Processing Scoring

To score data automatically, a classifier built on Fisher's linear discriminant analysis (LDA) is created. This classifier, when applied to raw EEG signals, separates the signals into groups based on what feature sets are desired. Using Matlab (Mathworks Ltd.), spectral power is computed for specific EEG channels and accelerometer channels that are chosen based on how noisy the signal is. The ideal signal is a clean one, with little to no background noise. To obtain spectral power we must first take non-overlapping 1s windows and convolve them using a Hamming window. A power spectral density (PSD) is computed for the resulting convolution and then averaged into 0.5Hz bins. This gives us the power of a wide array of incoming frequencies in 0.5Hz resolution. The results of the PSD are averaged for each 10s epoch window. In each of these windows, the power of each of the specific bands (θ, δ, etc.) was summed, and the results are used as input variables (known as features) for classification using LDA. In calculations, the $\log(x)$ of the power was taken to provide a more dynamic response, where a tolerance of $\log(x + \epsilon)$ was included to ensure that a logarithm of zero was avoided.

Pipeline Processing

Using the same theory of application as an offline sleep scorer, a real-time system is proposed that would be able to perform the same sleep state scoring in real-time. This pipeline process handles data continuously, and analysis can be done on incoming data in real time by using slightly different approaches to calculate feature sets. Once these feature sets are obtained, they can be compared against the manually scored data. By matching the spectral signatures of the working feature set to one of the states defined by the manually scored data, a decision can be made in real time to discern sleep/wake state.

In any signal processing, the spectral power can only be calculated in bins due to the nature of the power spectral density calculations. In offline analysis, this was accomplished by dividing the 60 minute file into 1s non-overlapping windows and convolved. The bins for our pipeline processing are accumulated over similar 10s epochs as the offline analysis, only instead of dividing 60 minutes of data, the program need only store the last 10 seconds of data that had been collected to perform its averaging. Since a convolution of data of this nature can be reduced to simple addition, the pipeline process needs only a working memory of summations of each of these spectral powers to generate a feature set. The streaming data from the pipeline can be filtered by applying the classifier built by LDA in offline analysis to it. This will essentially act as a preliminary filter for each of the frequency bins to give us a good "first guess" of the state of vigilance. The classifier built in offline analysis set up boundaries for feature discrimination that the pipeline feature can be compared against. By matching the spectral signatures of the classifier and the pipeline feature, the pipeline feature can be classified. Since this feature set is built from the past 10 seconds worth of data, it theoretically takes no more than 10 seconds to begin accurately scoring sleep with this pipeline system.

Using the features built in real-time, a determination of state can be made. Once this state is known, any number of actions can be done. For our purposes, we aim to implement a perturbative stimulation system that interrupts a certain sleep state, namely *REM*. The system designed will be able to detect *REM*, deliver controlled stimulation, and then continue to collect data for subsequent analysis as to the mechanics of the seizure generation and how it pertains to state of vigilance. Ideally, this would allow for not only an improved model of seizure generation, but also allow for state-based seizure control.

Preliminary Findings

A custom piece of software exists in our lab that generates features from previously recorded offline data files. These features are simply manipulations of the power spectral density of the signal and include numerical operations such as mean square, derivatives, and averages. These features are used an inputs into the MATLAB script that I have written to make a determination of state. This is akin to the offline methods we currently use, the difference being that this script takes into account the transition to pipeline processing and includes simple Boolean logic and structures that can be implemented into LabVIEW for the real-time state discrimination.

At this stage in the development process, the input variables are limited to accelerometer data. This is to simplify as well as guide the design of the program – accelerometer data is very easy to interpret by eye when looking at the raw data. A such, thresholds for state boundaries can be set accurately and adjusted with ease on accelerometer channels by looking at the data stream. Later, when hippocampal EEG is considered, the refinement to the accelerometer channels' discrimination variables will make it easier to fine tune the thresholds and boundaries for discriminating EEG.

Using the analysis paradigm I created, I was able to compare the program's efficacy of determining sleep or wake using just accelerometer data. Using accelerometer data alone renders it impossible to discern any state other than simple *sleep* or *wake*, because any further determination (REM, NREM, active wake) relies on frequency analysis of hippocampal EEG. Since manually scored data does discriminate between the sub-categories of *sleep* and *wake*, I had to lump the sleep and wake states together in order to provide a basis for comparison of my classifier. When compared to manually scored data, this analysis on accelerometer data alone considering just *Wake*versus *Sleep* shows an agreement percentage of 74 ± 5%. When coupled with the EEG data, it is anticipated that the agreement percentage will go up, as well as allow me to compare the efficacy of my classifier to discern the sub-categories of *Sleep* and *Wake*. Ideally, a rate of agreement between 79-87%is desired. Even between two or three experts manually scoring data, discrepancies exist because of the relatively subjective nature of manual sleep scoring. Typical values of user-user agreement are in the 83 ± 4% range for most states of vigilance, which is why a target agreement of the classifier is set at that range – the algorithm should at least be as effective as the system it is replacing.

I have written a piece of LabVIEW software that takes in raw data and computes a power spectral density on it in real time. From that power spectral density taken over a period of 10 seconds, features can be generated and subsequent analysis can be done on it. Using the logic implemented in my MATLAB script, a LabVIEW equivalent is being further developed to incorporate all of the parts that I have built into the final real-time state of vigilance detector.

Discussion

Scoring state of vigilance has been an important part of many research topics in a wide range of disciplines. Post-processing techniques offer a way to classify and explain behaviors but offer little flexibility in terms of feedback mechanisms. Analysis in post-processing is able to discern states, but offers virtually no way to provide feedback to the subject being recorded from. Real-time systems offer a method of disrupting a state at specific times. Because of this conditionality, systems can be designed to trigger different kinds of interference at different times. For our lab, we have found that there is a strong correlation between REM and seizures. Because of this relationship, we aim to design a system that responds to REM and disrupts it by providing a controlled stimulation at the onset of a REM bout to both test our hypothesis as well as test treatment methods. The decision to stimulate and the actual stimulation must be done in matters of milliseconds, so having a reliable real-time detection system is essential for this goal.

In designing the SOV detector, many considerations were made about what logic and features to use and whether or not they would be effective in the pipeline/real-time process. Since the first step was to generate a real-time power spectral analyzer using sound, it made sense to make determinations based on a specific frequency band and the time spent within that frequency band. When transitioning to the EEG and accelerometer data, this method of feature generation proved useful for accelerometer data but not EEG data. This is because there are a lot of other factors to consider when dealing with sleep states in hippocampal EEG. The transition from one rhythm to another is not a discrete jump – the signals slowly shift up or down the frequency spectrum both within a state as well as during a transition. These transition periods cause a lot of over-classification in the algorithms. Basically, if there are more signatures in the data than we are looking for, the algorithm will generalize these transitions and other erratic behaviors as one of the sleep states (REM, NREM, etc.). This decreases accuracy because transitions between states in the real-time signal could now be classified as something that they are not. To remedy this, an algorithm based around the LDA classification technique is being further developed to run in real-time. Time was a limiting factor in the implementation of this classification scheme during this project, but will be implemented in further work. This classifier will describe the features numerically, providing a filter for incoming data to be separated and classified into a specific group. This classifier relies on post-processing methods to be generated, but can be implemented in a real-time system once it is available. It is important to note that this classifier would need to be generated and trained for each test subject it is being applied to. No two brains are exactly alike, so no classifier is general enough to work for all subjects without some modification.

A major focus of this project was not only to obtain a working real-time state of vigilance detector, but also to improve the communication between the computer interface and the acquisition hardware to provide more reliable and accurate measurements. In our lab, data acquisition is the heart of all ongoing research, whether it is for designing the electrodes or performing analysis on data. As such, it is imperative that all recordings taken from animals are as accurate and reliable as possible. In order to make real-time measurements better, improvements to the fine details of operation of the acquisition hardware had to be made. These changes were made to both the firmware of the acquisition hardware as well as the software interface running on our computer acquisition systems. The robustness of this system is crucial for being able to transition to a system that is able to provide controlled stimulation at a moment’s notice. By improving the methods of interfacing with all aspects of the hardware, we can ensure that our decisions and analyses are as accurate and precise as possible moving forward, and that we can indeed add our desired functionality to our system.

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