A Real-Time Classifier for Closed-Loop Sleep Modulation in Mice

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Sleep is essential for normal health, mediating processes such as memory consolidation, cognition, and homeostasis. Changes in sleep architecture are often clinically relevant, but identifying them requires the collection and analysis of a polysomnogram. Typically, this requires the subject to sleep in an unfamiliar setting and have a multitude of electrodes, wires, and sensors placed on their body. As a result, normal sleep behavior is nearly impossible to observe, and so animal models have come to be a widely acceptable surrogate for human sleep studies. However, a mutual bottleneck of all sleep research is identification of sleep structure through the current gold standard of manual scoring. While the advent of modern computing technologies and machine learning techniques have allowed for automated classification of sleep, there is still no current gold standard for use in sleep research – especially in real time applications. Here, we develop and validate a system that models baseline sleep dynamics in mice with essentially no supervision and classifies sleep stages in real-time thereafter – eventually be used as the basis for stimulation in sleep modulation studies.

Following IACUC-approved protocols, six C57BL/6 mice were instrumented with tethered headmount electrodes to acquire EEG/EMG signals. Data was sampled at 400 Hz and saved to a file to be manually scored by human raters. In parallel, signals were also routed to a custom LabVIEW program, which passed the incoming data through a hidden Markov Model to classify it as either Wake, REM, or Non-REM sleep in real time with 1-second resolution. Animal-specific models were built from prior 6-hour long recordings. Each animal underwent 24 hours of real-time classification, which was later compared to manual scores to assess performance. Classifier output yielded >90% overall agreement with manual scores, with mean Kappa of 81%. Furthermore, sensitivity, specificity, and positive prediction value (PPV) were all greater than 85%, with the exception of REM PPV, as is expected. When applied to the task of REM sleep restriction, classifier output triggered non-invasive, vibrational stimulation to effectively interrupt REM. Modified sleep did not significantly affect classifier performance.

Overall, the system presented here provides a versatile framework for sleep research in rodents. The method of hidden Markov modeling captures the essential dynamics of sleep, providing accurate estimates of sleep metrics while codifying sleep structure. In fact, the main parameters of the model (i.e. state transition probabilities) can be inspected to identify disordered sleep, and serve as a screening tool in genetic or pharmacological studies. Additional user-specific modules such as seizure detection, breathing regularity tracking, etc., can be easily added and also used to trigger various forms of output (e.g., sensory stimulation, optogenetic stimulation, etc.) to alter behavior in a controlled manner. Furthermore, by processing classifier output, various indicators of sleep quality can be estimated (e.g., sleep efficiency, REM-NREM ratio, etc.) and used as the basis for stimulation to modulate sleep quality. It is our hope that the further development of this system will address the deficiencies in currently available technologies, and facilitate closed-loop, dynamic experimentation to answer complex questions surrounding sleep, physiology, behavior, and medicine.

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