Dynamic Phenotype Learning: A Novel Machine Learning Approach To Develop And Discover New OSA Sub-Types

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Introduction

The current paradigm for measuring sleep is predicated on several flawed assumptions; that there are only 5 distinct stages of sleep, that humans sleep in discrete thirty second segments, and encode only 3 to 4 different types of breathing. In the context of AI predictive modeling, this limited paradigm is further compressed to a point that it eliminates multiple orders of magnitude of data resolution that exists within waveform data. Application of this limited paradigm is further confined by the reality that manual scoring remains the current gold standard, resulting in a laborious, high-cost, and highly variable process for obtaining sleep quantification. In this work, we present initial evidence for a new, and fundamentally different approach to utilize Dynamic Phenotype Learning (DPL) as an innovative machine learning (ML) technique to identify new sleep and obstructive sleep apnea (OSA) subtypes that can better predict clinical risk and success with therapies. Furthermore, since the suggested approaches are specialty agnostic, the foundation laid by this research project can further impact electroencephalogram (EEG) processing in neurology, electrocardiogram (EKG) processing in cardiology, as well as enable new uses cases for wearable and consumer sleep technology data, disorder phenotyping, and waveform analysis more generally.

Research Objectives

- Validating reproducibility of prior DPL experimental performance on a diverse and comprehensive dataset and to further establish baseline efficacy of the method.
- Apply DPL methods to identify and study OSA phenotypes, biomarkers, and endotypes associated with adverse health outcome risks, insomnia and other sleep disorders, therapy personalization and success predictors, non-sleep conditions including comorbidities known to be particularly exacerbated by OSA, and other conditions in pediatric populations.
- Investigate underlying mechanics that result in identifiable subtype expression, including explainability, interpretability, methods for bias verification, generalizability, and uncertainty.
- Contribute to the state of scientific knowledge on influence of sleep on health and disease.

Dataset Description

- More than 234,000 subjects.
- Adult cohort analyses include men and women subjects ages 18 and older, including pregnant women due to the impact of OSA in the obstetric population.
- Pediatric cohort analyses include neonatal (0-28 days), infant (29 days-2 years), children (2 years-12 years), and adolescent (13 years-17 years).
- Types I, II, III, or IV de-identified sleep study data with polysomnography (PSG), home sleep apnea test (HSAT), and Multiple Sleep Latency Test (MSLT).
- Comprehensive de-identified electronic health record (EHR).
- PAP data.
- Sleep questionnaires.
- Additional patient reported data.
- Confounding condition variables for control include sleep disorders, mental health disorders, neurodegenerative disorders, neurodevelopmental disorders, seizure disorder, acquired and traumatic brain injuries, consciousness disorders, cardiovascular diseases, pulmonary diseases, and diabetes.
- Confounding medication variables for control include antidepressants, stimulants, anxiolytics, sleep aids, opiates/narcotics, cholesterol medications, antipsychotics, anticonvulsants, and alternative OSA therapies.
- Confounding demographics for control include age, sex, ethnic group, racial group, body mass index, height, weight, blood pressure, HDL/LDL cholesterol, STOP-BANG.

Methods

Autoencoders (AEs)

AEs are a type of artificial neural network architecture that allows for the encoding of highly dense data into a multi dimensional latent space in an unsupervised manner. See figure 1a for an illustration of the AE architecture.

Variational Autoencoders (VAEs)

VAEs are similar in concept to the AEs in that they both contain an encoder and a decoder, and can create multi-dimensional representations of the input data. However, instead of simply converting the input data to its latent dimension, VAEs can learn the continuous latent distribution (mean and standard deviation of each latent variable) that the input data originated from. See figure 1b for an illustration of the VAE architecture.

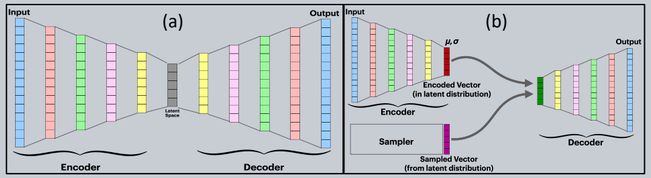

Figure 1. AE and VAE architectures. (a) The autoencoder contains two sub-models, an encoder and a decoder. During training, the model is optimized to output a result that is as close as possible to the input data. After training, the encoder part of the model can be used to down-sample the input data to its latent dimension which can then be used for additional dimensionality reduction algorithms and/or unsupervised algorithms for the exploratory data analysis of highly dense data. (b) During training, VAEs are optimized to output a result that is as close as possible to the input data. After training, the encoder part of the model can transform the input data into its approximated latent distribution. Exploratory data analysis can then be executed on the entire latent distribution rather than on single "snapshots" of the latent feature dimension of the input data.

t-Distributed Stochastic Neighbor Embedding (t-SNE)

t-SNE is a non-linear statistical dimensionality reduction method that is usually used in exploratory data analysis. The t-SNE algorithm transforms the features of high dimensional data into a 2- or 3-dimensional point such that similar samples are represented by nearby points and dissimilar samples are represented by distant points. This modeling is achieved utilizing a stochastic neighboring algorithm that can model the relationship between samples and embed them in a lower dimensional space. The algorithm enables high dimensionality data to be visualized in a more intuitive feature space (such as 2D or 3D space).

Hierarchical Density-Based Spatial Clustering of Applications with Noise (HDBSCAN)

HDBSCAN is an unsupervised clustering algorithm which can take a large amount of data samples with *m* number of features and find meaningful structures in the data thus, clustering them into *j* unique clusters. These clusters can then be associated with known characteristics of the analyzed data and allows for the samples to be gathered into meaningful groups based on their unique features.

Results

Re-Evaluating Sleep Epochs in the Latent Dimension

In order to explore the physiological characteristics of sleep epochs and their association with different sleep stages, we sampled sleep epochs from thousands of full night PSG studies where each sleep epoch contained 30 second recordings of an 8-channel EEG and electrooculogram (EOG) montage.

Initially, we looked at the t-SNE output of common, well know, time and frequency-based hand engineered features which can be seen in figure 2a. We have found that even though some clusters have emerged, non of them were highly correlated with any one of the 5 sleep stages. This demonstrates that the hand engineered features are lacking the resolution needed for accurately evaluating the sleep stages and the association between them.

We then trained an AE and encoded the sleep epochs into their latent dimension. The t-SNE output can be seen in figure 2b. We have observed that certain structures associated with the sleep stages have emerged when compared to the hand engineered features however, the 2D representation is still lacking the needed separation for the evaluation of the different sleep stages.

Next, we trained a VAE and encoded the sleep epochs into their latent distributions. The t-SNE output can be seen in figure 2c. This time, a clear separation has emerged between wake and the other 4 sleep stages which demonstrates VAEs' capabilities to model the electrophysiological latent distributions of sleep vs. wake.

Finally, we trained a sleep staging model to classify the sleep stage associated with each 30 seconds epoch. We then utilized the latent dimension of that model which contained 1024 uniquely learned features as inputs to the t-SNE algorithm. The t-SNE output can be seen in figure 2d. We have observed clear clusters associated with each one of the sleep stages. The distance between the clusters can demonstrate the similarity or dissimilarity between the different sleep stages and the lack of separation between some of the clusters may suggest that merging specific sleep stages together might result in more representative sleep quantification. Furthermore, we have observed that a certain amount of sleep epochs were associated with the "wrong" cluster. This might suggest that those sleep epochs have been misclassified during the manual sleep scoring process.

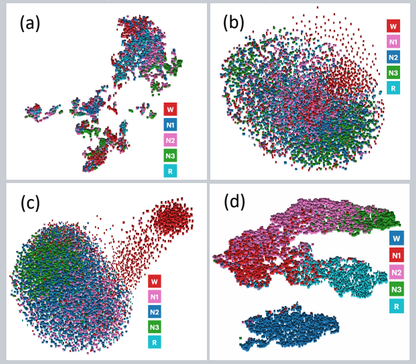

Figure 2. t-SNE visualization of 30 seconds sleep epochs. (a) t-SNE of hand engineered features. (b) t-SNE of the latent dimension obtained from an AE. (c) t-SNE of the latent distribution obtained from a VAE. (d) t-SNE of the latent features extracted from a sleep staging model.

Finding Structures in Age and Sex Models

For the further exploration of the physiological characteristics that exist within the 8-channel EEG and EOG montage recorded during full night PSG studies, we trained an age AI predictive model and a sex AI predictive model. We obtained a mean absolute error of 4.6 for the age model and an 80% accuracy for the sex model. The results of these models can be seen in figure 3a,b.

We then extracted the latent dimensions from each one of the models, each containing 1024 uniquely learned features, concatenated the features together, and utilized them as inputs to the t-SNE algorithm. The HDBSCAN algorithm was then used to locate clusters that exist within the extracted features. The t-SNE representation and clusters can be seen in figure 3c. Overall, 4 clusters have emerged (labeled in red, blue, green, and purple) along with several examples classified as noise (labeled in yellow). These clusters should be studied in the future in order to fully define the meaning of each cluster and their association with different characteristics that exist within the physiological signals.

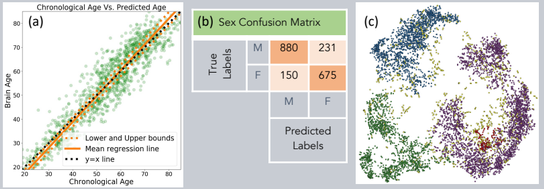

Figure 3. Regression plot of the age model, confusion matrix of the sex model, and the t-SNE representation of the combined latent dimensions. (a) Regression plot demonstrating the capabilities of the model to accurately predict the age of a patient from the 8-channel EEG and EOG montage recorded during full night PSG studies. (b) Confusion matrix demonstrating the capabilities of the model to accurately predict the sex (M-male, F-female) of a patient from the 8-channel EEG and EOG montage recorded during full night PSG studies. (c) t-SNE of the combined latent dimensions of the age and sex models, where each data point is color coded with the associated cluster detected by the HDBSCAN algorithm.

Conclusion

In this research project we presented initial evidence for the utilization of dynamic phenotype learning for exploratory data analysis of physiological characteristics that exist within the common 8-channel EEG and EOG montage recorded during full night PSG studies, and their association with the currently known five sleep stages, age, and sex. The relationship between the clusters that have emerged for the sleep stages demonstrate the similarity between them and challenges the definition of the currently analyzed five sleep stages. Furthermore, studying each sleep epoch in the latent dimension may reveal sleep epochs that have been misclassified during the manual sleep scoring process. In addition, clusters have emerged from the latent dimensions of the age and sex models. The physiological meaning of these clusters is not yet known but future research should be dedicated to uncover the underlying phenotypes associated with these clusters and their correlation with different patient conditions and outcomes. Overall, this preliminary research project reveals the potential of DPL as novel ML technique for the re-evaluation of current sleep events definitions and the formulation of new phenotypes that are based on features extracted from AI models trained to predict different patient related variables.